Essential Evidence Topics January 2018
North Dakota Academy of Family Physicians
Big Sky, Montana

Learning Objectives

Discuss recent research important to family physicians for updating their diagnostic and treatment approaches to musculoskeletal conditions, cardiovascular disease, hypertension, diabetes, diet, asthma, COPD, men's health, women's health, substance abuse, pediatrics and vitamin therapy. Objectives for each presentation are listed at the beginning of each talk. Each talk is based on a literature review of recent research studies. Evidence sources include PubMed, InfoPoems and Cochrane systematic reviews.

Faculty

Gary Ferenchick, MD, MS. is Professor of Medicine at Michigan State University College of Human Medicine, where he practices general internal medicine and is deeply involved in MSU-CHM major curriculum renovation. He earned his master's degree in human nutrition and medical degree from Michigan State University and completed his residency training in internal medicine at Michigan State University College of Human Medicine, where he has been a faculty member for over 25 year. Dr. Ferenchick is a Past-President of the Clerkship Directors in Internal Medicine. His research interest is the interface between medical education and information technology.

John Hickner, MD, MS. is Professor and Head of Family Medicine at the University of Illinois at Chicago and Editor-in-Chief of the *Journal of Family Practice*. After receiving his medical degree from Indiana University School of Medicine, Dr. Hickner completed his residency in family medicine at the Medical University of South Carolina and received a master's degree in Biostatistics and Research Design from the University of Michigan School of Public Health. His main research focus is patient safety, especially testing safety and medication safety in primary care practice.

William (Bill) Wadland, MD, MS. is Professor, former Chair of Family Medicine, and Senior Associate Dean Emeritus in the College of Human Medicine at Michigan State University. He received his MD from the University of Michigan School of Medicine and completed family medicine training at the Medical University of South Carolina. He was co-founder of the original Primary Care Medical Abstracts Courses on which the current Essentials Update Courses are modelled. His research focus is health promotion and disease prevention, especially tobacco control. He is the Deputy Editor of the *American Journal of Preventive Medicine* (AJPM).

Speaker and Faculty Disclosures

John Hickner disclosed no relevant financial relationship or interest with a proprietary entity producing health care goods or services.
Gary Ferenchick disclosed no relevant financial relationship or interest with a proprietary entity producing health care goods or services.
William Wadland disclosed no relevant financial relationship or interest with a proprietary entity producing health care goods or services.

Essential Evidence Schedule

Tuesday, January 16, 2018

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Wednesday, January 17, 2018

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Musculoskeletal: Backs and Knees

John Hickner, MD, MSc

Objectives

1. Discuss the findings of recent studies of the effectiveness or lack of effectiveness for treatments of knee osteoarthritis and low back pain

Low Back Pain

I thought there was nothing more to say about low back pain. I was wrong. Here are some new studies that may help you manage patients with back pain.

1. Diazepam adds little to NSAID treatment for acute low back pain

Clinical question: In patients with acute low back pain, does the addition of diazepam to analgesic treatment improve symptoms?
Study design: Randomized controlled trial (double-blinded)
Setting: Emergency department
Synopsis: These authors enrolled 114 patients who presented to an emergency department with uncomplicated low back pain that lasted less than 2 weeks and had a score of at least 5 (median = 18) on the Roland-Morris Low Back Pain and Disability Questionnaire. The 24-item disability questionnaire asked patients about daily activities that would be limited by back pain. The patients were randomized, allocation concealment uncertain, to receive naproxen 500 mg twice daily as needed for 1 week with either placebo or diazepam 5 mg, 1 or 2 tablets every 12 hours, as needed. Scores at 1 week by telephone interview had improved by an average 11 points on the disability scale in both groups. Moderate to severe pain was still reported in 32% of patients in the diazepam group and 22% of patients in the placebo group (P = NS) at 7 days. Other outcomes—length of time to return to work, desire to seek additional treatment, or desire to take the prescribed medicine (diazepam or placebo) again—were also not different. The study had 80% power to find a difference in scores of at least 5.
Bottom line: Diazepam (Valium) added to naproxen does not improve disability or pain scores in patients with acute low back pain more than naproxen alone. The dose was standard and most patients had significant relief regardless of whether they took diazepam or placebo in addition to analgesia.
Friedman BW, Irizarry E, Solorzano C, et al. Diazepam is no better than placebo when added to naproxen for acute low back pain. Ann Emerg Med 2017;70(2):169-176.

2. Lumbar fusion no better than exercise and therapy in the long term

Clinical question: Is lumbar fusion effective for patients with chronic low back pain?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (specialty)
Synopsis: This is an important question; one not without controversy. This study reports a mean 12.8 years of follow-up from a trial that randomized 294 persons with severe chronic low back pain in a 3:1 ratio to lumbar fusion or physical therapy. This report provides almost no detail about their methods, but a look at their earlier publication reveals that outcome assessors (and, obviously, patients) were not masked to treatment assignment. The earlier report, after 2 years of follow-up, showed generally favorable results for surgery. Approximately 20% of patients in each group died or were lost to follow-up. In the long-term results, using intention-to-treat analysis, there is no difference between groups for any outcome, including the patient's Global Assessment (GA) of back pain score, the Oswestry Disability index score, a visual analog scale for pain score, pain medication use, pain frequency, or employment status. The authors also report an "as treated" analysis, which counts the 19 of 72 patients who crossed over to surgery as if they had originally been assigned to surgery (they were not!), and they report a per-protocol analysis, which ignores patients who crossed over or were lost to follow-up. Both of these analyses found an improvement in the patient's GA score with surgery, but failed to find improvement in any other outcomes. On the basis of the single outcome of GA score in the more biased analyses, the authors' conclusion is that surgery should be considered effective. An accompanying editorial, which strongly disagrees with the authors, begins with the snide headline: Consensus at last... fusion is no better than nonoperative care in improving pain and disability in chronic low back pain.
Bottom line: This trial is a good example of how to do just about everything wrong in order to get the results you want. The authors did not conceal allocation, did not mask anyone in the study, used an unvalidated and subjective primary outcome, and downplayed the intention-to-treat analysis. Funding for the original study came from industry, and the authors have numerous conflicts of interest. Two other trials in the United Kingdom and Norway found no benefit to lumbar fusion, and the results of this study are consistent with those findings, despite what the authors conclude.
Hedlund R, Johansson C, Hagg O, et al. The long-term outcome of lumbar fusion in the Swedish lumbar spine study. Spine 2016;16(5):579-587.

3. Adding spinal fusion to decompression does not improve outcomes for lumbar stenosis and has harms

Clinical question: Does the addition of spinal fusion in patients with lumbar stenosis (with or without evidence of spondylolisthesis) improve outcomes?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (specialty)
Synopsis: Almost all US patients with lumbar stenosis and spondylolisthesis, and many without spondylolisthesis, undergo spinal fusion as well as decompression. In this study, 247 patients aged 50 to 80 years with lumbar stenosis and neuroclaudication for at least 6 months were randomized to decompression only or decompression plus spinal fusion. Fourteen patients did not receive the assigned intervention, leaving 233 in the per-protocol population. The mean age was 67 years, 98 patients had no evidence of spondylolisthesis while 135 did, and the patients with spondylolisthesis were more likely to be women. The primary outcome was a per-protocol analysis, which is probably acceptable in this case since relatively few patients assigned to surgery did not undergo it. At 2 years, there was no difference between groups with regard to pain and function scores or overall assessment of decreased back or leg pain. Approximately half of the patients without spondylolisthesis and approximately two thirds of those with spondylolisthesis reported satisfaction with the surgery, with no difference between groups by type of surgery. Harms of adding spinal fusion included a longer length of stay (7.4 vs 4.1 days), higher cost ($12,200 vs $5,400), a longer operative time, and greater blood loss.
Bottom line: Adding spinal fusion does not improve outcomes among patients with lumbar stenosis.
Forsth P, Olafsson G, Carlsson T, et al. A randomized, controlled trial of fusion surgery for lumbar spinal stenosis. N Engl J Med 2016;374(15):1413-1423.

4. Spinal fusion does not significantly improve outcomes for patients with lumbar stenosis and grade I spondylolisthesis

Clinical question: Does the addition of spinal fusion to decompressive laminectomy improve outcomes in patients with grade I degenerative spondylolisthesis and spinal stenosis?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (specialty)
Synopsis: Although lumbar decompression is often accompanied by spinal fusion in patients with spinal stenosis and degenerative spondylolisthesis, to date there have been no randomized controlled trials of this practice, only observational studies with conflicting results. In this study, 66 patients with grade I lumbar spondylolisthesis (3 mm to 14 mm of vertebral body displacement) and lumbar stenosis accompanied by symptoms of neurogenic claudication. Patients with instability or previous surgery, as well as those with major comorbidities, were excluded. A panel of 10 spine surgeons reviewed images and decided that each patient was suitable for randomization (clinical equipoise). This is good trial design and, according to the researchers, appeared to increase the likelihood that patients were willing to be included in the randomization, which was a problem in previous trials of spinal surgery. Approximately half the patients who were screened for inclusion agreed to be randomized to receive either decompression alone or decompression plus posterolateral-instrumented fusion at the level of the spondylolisthesis. The fusion is thought to stablize the spine and reduce the risk of recurrence. The patients had a mean age of 67 years, 80% were women, and they had a mean 6 mm of spondylolisthesis. Groups were balanced and analysis was by intention to treat. Patients were followed up for 4 years, and the primary outcome was the change in the physical component of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and the change in the ODI. The surgical group had a slightly greater improvement on both scales, which was statistically significant for the SF-36 but not for the ODI. However, the changes were small and unlikely to be clinically noticeable (~ 4 to 9 points on a 100-point scale). The rate of re-operation was lower for the fusion group (14% vs 34%; P = .05; number needed to treat = 5), but this may reflect the fact that surgeons knew patients in the decompression-only group had not undergone fusion, which might make them more likely to offer surgery as an option if symptoms recurred or worsened. There was more blood loss and longer hospital stays for patients in the fusion group. Loss to follow-up was relatively high after the first year, so estimates based on longer follow-up are unreliable.
Bottom line: Adding spinal fusion to lumbar decompression provides an increase in the physical component of quality of life, but no significant improvement on the more sensitive Oswestry Disability Index (ODI). An editorial in the same journal concluded--and I agree--that the small benefits of routinely adding spinal fusion to decompression in patients with lumbar stenosis and spondylolisthesis are probably not worth the additional costs and risks.
Ghogawala Z, Dziura J, Butler WE, et al. Laminectomy plus fusion versus laminectomy alone for lumbar spondylolisthesis. N Engl J Med 2016;374:1424-1434.

5. Does Operative or Nonoperative Treatment Achieve Better Results in A3 and A4 Spinal Fractures Without Neurological Deficit? - Systematic Literature Review With Meta-Analysis

STUDY DESIGN: Systematic literature review with meta-analysis.
OBJECTIVE: Thoracolumbar (TL) fractures can be treated conservatively or surgically. Especially, the treatment strategy for incomplete and complete TL burst fractures (A3 and A4, AOSpine classification) in neurologically intact patients remains controversial. The aim of this work was to collate the clinical evidence on the respective treatment modalities.
METHODS: Searches were performed in PubMed and the Web of Science. Clinical and radiological outcome data were collected. For studies comparing operative with nonoperative treatment, the standardized mean differences (SMD) for disability and pain were calculated and methodological quality and risk of bias were assessed.
RESULTS: From 1929 initial matches, 12 were eligible. Four of these compared surgical with conservative treatment. A comparative analysis of radiological results was not possible due to a lack of uniform reporting. Differences in clinical outcomes at follow-up were small, both between studies and between treatment groups. The SMD was 0.00 (95% CI -0.072, 0.72) for disability and -0.05 (95% CI -0.91, 0.81) for pain. Methodological quality was high in most studies and no evidence of publication bias was revealed.

CONCLUSIONS: We did not find differences in disability or pain outcomes between operative and nonoperative treatment of A3 and A4 TL fractures in neurologically intact patients. Notwithstanding, the available scores have been developed and validated for degenerative diseases; thus, their suitability in trauma may be questionable. Specific and uniform outcome parameters need to be defined and enforced for the evaluation of TL trauma.
Rometsch E, Spruit M, Härtl R, McGuire RA, Gallo-Kopf BS, Kalampoki V, Kandziora F. Does Operative or Nonoperative Treatment Achieve Better Results in A3 and A4 Spinal Fractures Without Neurological Deficit? - Systematic Literature Review With Meta-Analysis. Global Spine J. 2017 Jun;7(4):350-372.

6. ACP Recommendations for Care of Low Back Pain

Clinical question: What are the roles of the various interventions in the treatment of acute and chronic low back pain?
Study design: Practice guideline
Setting: Various (guideline)
Synopsis: This guideline is based on 2 systematic reviews, conducted by outside researchers, of drug and nondrug treatment of low back pain (doi: 10.7326/M16-2459 and doi: 10.7326/M16-2458). The guideline developers evaluated the effects of treatment on patient-oriented outcomes, graded the evidence, and minimized (but didn't eliminate) conflicts of interest. Their recommendations are as follows. For acute or subacute low back pain: Strong recommendation: Start with heat (moderate-quality evidence), massage, acupuncture, or spinal manipulation (low-quality evidence). Consider drug therapy with a nonsteroidal anti-inflammatory drug or skeletal muscle relaxant (moderate-quality evidence). For chronic low back pain: Strong recommendation: Start with any nondrug therapy that appeals to the patient exercise, rehabilitation, acupuncture, or mindfulness-based stress reduction (moderate-quality evidence); or tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation (low-quality evidence). Drug therapy is largely not effective. In patients with an inadequate response to these treatments, consider a nonsteroidal anti-inflammatory drug as first-line therapy, and tramadol (Ultram) or duloxetine (Cymbalta) as second-line therapy. Weak recommendation: Opioid treatment should be reserved for patients for whom nothing else works and only after a discussion of benefits, risks, and realistic expectations (moderate-quality evidence).
Bottom line: These guidelines recommend starting with nondrug approaches to the treatment of both acute low back pain and chronic low back pain, given the low evidence of benefit and the risks associated with medication. See the synopsis: There is evidence of some benefit for a wide variety of nondrug approaches, which allows patients to choose the one that makes the most sense for them.
Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2017 Feb 14. doi: 10.7326/M16-2367. [Epub ahead of print]

7. Placebo decreases chronic low back pain

Clinical question: Can simply telling patients that a medicine works, even if it is placebo, decrease pain and improve disability in patients with chronic low back pain?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (any)
Synopsis: These investigators, who conducted the study in Portugal, enrolled 83 patients who'd had low back pain for at least 3 months and responded to an advertisement. Most (87%) were taking analgesia, approximately 40% were taking adjuvant medication (eg, gabapentin or a muscle relaxant), and approximately 20% were taking an antidepressant. The authors excluded patients with severe fibromyalgia or rheumatoid arthritis and those who had received opioid treatment in the past. For 3 weeks patients were asked to continue their usual treatment. Using concealed allocation, half of the patients were also given 2 placebo tablets twice a day. They were told that it was an inactive placebo, but: (1) it could still have a powerful effect; (2) the body can automatically respond to placebo; (3) a positive attitude is helpful but not necessary; and, (4) the placebo must be taken faithfully. Knowingly taking placebo significantly decreased maximum reported pain, minimum reported pain, and usual pain as compared with usual therapy only. Back pain–related disability was also decreased with placebo. There were several problems with the study, however: unbalanced baseline pain, small numbers in each group, and the lack of a commercially available placebo.
Bottom line: Building on the received wisdom of Sir William Osler that, "The desire to take medicine is perhaps the greatest feature which distinguishes man from animals," these investigators gave twice daily placebo to patients with chronic back pain and told them it was placebo. They also told them that placebos can have a pronounced effect (which is true). The addition of placebo to usual care improved patients' pain and disability scores over the 3 weeks of the study. Although we probably won't start prescribing placebo, this study emphasizes the great value of conveying one's confidence in the treatment to bolster its effect
Carvalho C, Caetano JM, Cunha L, et al. Open-label placebo treatment in chronic low back pain: a randomized controlled trial. Pain 2016;157(12):2766-2772.

Knees

I see patients with painful knee osteoarthritis in my office every day. After pain medication, exercise and physical therapy and perhaps acupuncture, it appears that we have to jump to joint replacement and skip other invasive treatments such as injections and arthroscopic whittling, which now have strong evidence against effectiveness.

8. OA shoes no better than walking shoes for knee OA pain and function

Clinical question: Are special shoes more effective than conventional walking shoes to decrease the pain of knee osteoarthritis and improve physical function?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Some shoes are specifically designed to "unload" knees through modified midsoles that have variable stiffness and a lateral wedge to decrease the biomechanical load on the medial aspect of the knee. This study, conducted in Australia, enrolled 164 patients recruited through advertising who were at least 50 years old, had knee pain of at least 4 on a scale of 0 to 10 for most days, and radiographic evidence of medial knee osteoarthritis. The participants were randomly assigned, using concealed allocation, to wear either unloading shoes (Asics GEL-Melbourne OA) or neutral walking shoes (Asics GEL-Odyssey) for at least 4 hours a day for 6 months. Shoes for both groups were provided by the researchers. Pain scores changed from an average 5.7 to 6.0 before the start of the study to an average 4.2 in both groups on an 11-point scale (P = NS). Function also improved to a clinically significant degree (> 6 units on the Western Ontario and McMaster Universities Osteoarthritis Index) in both groups (function improved in 44% and 48% of patients in the unloading and neutral shoe groups, respectively).The study had 90% power to find a 2.5-unit difference in pain and a 10.5-unit difference in function. The results might be cause in part by an "acquiescence bias," in which people in both groups felt they needed to report improvement to researchers who gave them free shoes. It would have been great if this study had included a third group who stuck to their usual shoe-wearing habits.
Bottom line: A quick search of the Internet will yield many walking shoes targeted at the bad knees market. But specifically designed shoes with modified midsoles and a wedge to unload the medial aspect of the knee are no more effective than typical walking shoes at relieving pain and improving function in patients with documented knee osteoarthritis. In this study, patients in both groups improved, which either might be an artifact of the study or because any type of walking shoe improves pain and function.
Hinman RS, Wrigley TV, Metcalf BR, et al. Unloading shoes for self-management of knee osteoarthritis. A randomized trial. Ann Intern Med 2016;165(6):381-389.

9. Meta-analysis: acupuncture minimally decreases knee pain from DJD in the short term

Clinical question: Is acupuncture effective in alleviating knee pain in patients with degenerative joint disease?
Study design: Meta-analysis (randomized controlled trials)
Setting: Outpatient (any)
Synopsis: These researchers searched PubMed, EMBASE, and the Cochrane Registry of Controlled Trials to identify randomized trials that evaluated acupuncture in managing knee pain in patients with DJD. Two authors independently assessed studies for inclusion and resolved disagreements by discussion, reserving third-party consultation and voting for when discussion failed. They don't describe additional efforts to identify unpublished studies, but they report that they did not find evidence of significant publication bias. The authors evaluated the quality of each included study using the Cochrane Back Review Group criteria. Ultimately they included 10 studies (4 from the United States, 2 from the United Kingdom, and 1 each from Canada, Spain, Germany, and Australia) with 2007 patients (range 20 - 697). Most of the studies were of high quality. The studies assessed outcomes from 3 to 26 weeks after treatment. Seven used sham acupuncture. The researchers identified modest amounts of heterogeneity among the study results. In the short term, patients treated with acupuncture had an average improvement of 1.2 weighted mean difference in pain measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score (range 0 - 20 points). Additionally, patients treated with acupuncture had an average improvement in the WOMAC function score of 4.6 (range 0 - 68). Sensitivity analysis did not change results. Although these results are statistically significant, they are probably not clinically meaningful. The authors don't report on the proportion of patients experiencing the minimal clinically important difference in pain or function. Finally, long-term pain scores were comparable among the different treatment groups.
Bottom line: In this meta-analysis, patients with knee pain from degenerative joint disease (DJD) treated with acupuncture experienced minimal improvement in short-term pain and function compared with those who received sham acupuncture or usual care. The improvements are not likely to be clinically important.
Lin X, Huang K, Zhu G, Huang Z, Qin A, Fan S. The effects of acupuncture on chronic knee pain due to osteoarthritis: a meta-analysis. J Bone Joint Surg Am 2016;98(18):1578-1585.

10. Bone marrow aspirate injections equal saline in patients with knee DJD

Clinical question: Do injections of bone marrow aspirate concentrate improve pain in patients with mild to moderate knee degenerative joint disease?
Study design: Randomized controlled trial (single-blinded)
Setting: Outpatient (specialty)
Synopsis: The authors describe this as a pilot study comparing a novel therapy (bone marrow aspirate concentrate) with saline in 25 patients with bilateral knee DJD. They enrolled patients with 2 bad knees so that patients could serve as their own internal control and, of course, to spare control patients from sham bone marrow aspiration. Statistically, this means they didn't need as many patients. To be included, the patients had to have longstanding bilateral knee pain from mild to moderate bilateral osteoarthritis despite conventional treatments such as activity modification, weight loss, physical therapy, analgesics, nonsteroidal anti-inflammatory drugs, or injection therapy. The study staff concentrated patients' own bone marrow and then re-suspended it with platelet-poor plasma. Each patient's right knee received an injection of either bone marrow aspirate concentrate or saline and the left received the other therapy (the knees were randomized to avoid the possibility of differential treatment allocation based on severity). Patients experienced improved pain

scores in both knees 1 week, 3 months, and 6 months after treatment. However, there was no differences in the degree of relief between the knees.
Bottom line: In this study, patients with bilateral knee degenerative joint disease (DJD) experience comparable degrees of pain relief with saline injections or bone marrow aspirate concentrate injections.
Shapiro SA, Kazmerchak SE, Heckman MG, Zubair AC, O'Connor MI. A prospective, single-blind, placebo-controlled trial of bone marrow aspirate concentrate for knee osteoarthritis. Am J Sports Med 2017;45(1):82-90.

11. Steroid injection does not improve response to exercise therapy for knee OA

Clinical question: Does a steroid injection before the start of exercise therapy improve the response in patients with knee osteoarthritis?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (specialty)
Synopsis: The Danish researchers enrolled 100 patients with knee osteoarthritis (confirmed by radiography) and knee pain while walking who were not morbidly obese. The patients were randomized, using concealed allocation, to receive an injection of methylprednisolone 40 mg or saline (both with lidocaine). Two weeks later all participants started a 12-week supervised exercise program. At the 2-week visit (before starting exercise), pain scores had improved slightly in both groups. By the end of 3 months of exercise therapy, scores had improved significantly and similarly in both groups.
Bottom line: Unlike other study results, in this study a steroid injection given 2 weeks before the start of supervised exercise was no more effective than a placebo injection at improving pain scores 2 weeks later in patients with knee osteoarthritis. It also did not cause a greater improvement after 3 months of exercise.
Henriksen M, Christensen R, Klokker L, et al. Evaluation of the benefit of corticosteroid injection before exercise therapy in patients with osteoarthritis of the knee: A randomized clinical trial. JAMA Intern Med 2015;175(6):923-930.

12. Steroid injections ineffective for knee osteoarthritis

Clinical question: Do intra-articular corticosteroids improve pain and function and decrease cartilage loss in adults with osteoarthritis of the knee?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Although intra-articular corticosteroids are commonly used for the treatment of knee osteoarthritis, data are limited in terms of benefits and safety. The most recent Cochrane Review on this topic evaluated 27 randomized controlled trials (26 with a high risk of bias) and found minimal improvement in pain and function in the short-term with steroids compared with placebo. The only study with low risk of bias found no benefit from steroids (Jüni P, et al. Cochrane Database Syst Rev 2015;(10):CD005328). These investigators recruited 140 adults, 45 years or older, with knee osteoarthritis diagnosed using standard national criteria. Eligible patients randomly received (concealed allocation assignment) either ultrasound-guided intra-articular triamcinolone (40 mg) or saline injections every 3 months for 2 years. Patients, clinicians administering the injections, and outcome assessors remained masked to treatment group assignment. Pain and function assessments based on validated questionnaires and physical examination occurred regularly throughout the study. Periodic magnetic resonance imaging occurred at 0, 12, and 24 months to evaluate changes in knee cartilage volume over the 2-year period. Complete follow-up occurred for 95% of patients at 2 years. Using intention-to-treat analysis, pain and function scores did not significantly differ between the 2 groups. However, the rate of cartilage loss and damage was significantly greater in the triamcinolone treatment group. There were no significant group differences in serious adverse events. The authorship of this POEM is attributed to Emma J. Pace, MD, Fellow and Instructor, Department of Family Medicine, University of Virginia, Charlottesville, VA.
Bottom line: This well-done study found that regular three-month intra-articular injections of triamcinolone for two years resulted in no significant difference in pain and function assessments compared to saline. However, a significant increase in cartilage loss and damage did occur in patients receiving steroids compared to saline. This study confirms the findings of the only other published study with a low risk of bias (see Synopsis).
McAlindon TE, LaValley MP, Harvey WF, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. JAMA 2017;317(19):1967-1975.

13. Exercise = knee surgery for degenerative meniscal tear

Clinical question: Is arthroscopic surgery better than exercise therapy to treat symptoms associated with degenerative meniscal tears in middle-aged patients?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (specialty)
Synopsis: The researchers (orthopedists practicing in Norway) enrolled 140 patients (between the ages of 35 and 60 years) who were referred for care for unilateral knee pain with medial degenerative meniscal tear confirmed by magnetic resonance imaging. Most (96%) had no or minimal radiographic changes associated with osteoarthritis. Pain had to be present for at least 2 months without a history of major knee trauma. The patients were randomized, using concealed allocation, to receive either exercise therapy 2 or 3 times weekly for 3 months or arthroscopic meniscectomy. There were no sham treatments; patients assigned to exercise did not get arthroscopy without meniscal repair and patients undergoing surgery did not have additional sham or actual exercise. Patients reported on pain, function, knee-related quality of life, and other symptoms using the knee injury and osteoarthritis outcome score. Using intention-to-treat analysis at 2 years, there was no difference between the 2 groups. Approximately 1 in 5 (19%) patients who received exercise therapy

eventually underwent arthroscopic surgery without any additional benefit.
Bottom line: Despite a significant initial bump in benefit due to the placebo effect, arthroscopic meniscectomy in patients without a history of acute trauma and without a history of knee locking does not reduce pain and improve function after 2 years as compared with 3 months of exercise therapy. This study did not evaluate surgery with exercise versus exercise alone, but other studies have done so and found no additional benefit.
Kise NJ, Risberg MA, Stensrud S, Ranstam J, Engebretsen L, Roos EM. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up. BMJ 2016 July 20;354:i3740.

14. Arthroscopic meniscal surgery = nonoperative management

Clinical question: Is arthroscopy better than nonsurgical treatment for patients with meniscal tears?
Study design: Systematic review
Setting: Various (meta-analysis)
Synopsis: These authors searched multiple databases, including registries of clinical trials and the reference lists of retrieved studies, to identify randomized trials of systematic reviews published in English. Two authors independently decided which studies to include and determined the risk of bias in the included studies. They resolved disagreements through conversation and, when necessary, through third-party adjudication. Ultimately, they included 9 randomized trials and 8 systematic reviews. The clinical trials included 68 to 351 patients and the systematic reviews included 98 to 1374 patients. All the systematic reviews were published after 2012, so the variation in sample size is rather striking and reflects the inclusion criteria. For example, the largest systematic review evaluated case series, only slightly less biased than expert opinion in determining the effectiveness of an intervention. The main recurring problems with the randomized trials were the lack of adequate masking and the selective outcome reporting. Only 2 of the trials compared arthroscopy with sham surgery. The others used active comparisons (for example, resection, exercise, physical therapy, steroid injections, and bioabsorbable arrows). The follow-up duration for the studies ranged from 6 months to 5 years. The studies also used several different outcome assessments: repeat tear, radiographic findings, pain on a visual analog scale, Western Ontario and McMaster Universities Osteoarthritis Index score, Knee Injury and Osteoarthritis Outcome Score, and so forth. The authors, appropriately, decided not to pool the data and just summarize the findings. Most of the systematic reviews failed to identify clinically meaningful improvements and only one of the randomized trials found "marginal benefit" in patients treated arthroscopically. Since the systematic reviews included cohort and case-control study designs and the randomized trial flaws all tend to be biased in favor of intervention, the existing data strongly suggest that arthroscopy for meniscal injuries is ineffective. I find it remarkable that so many systematic reviews exist with only 9 clinical trials. This seems like overanalyzing the existing data. The authors seem disappointed, and no matter how many times the data demonstrate no advantage to arthroscopy they will likely call for more clinical trials. No, we do not have an urgent need for evidence—the existing evidence is plenty.
Bottom line: The existing research base, with biases that typically make interventions look better, is unable to demonstrate that arthroscopy for meniscal injuries is any better than nonoperative approaches. Since this is a costly intervention, and is being used more frequently, perhaps insurance companies should re-evaluate whether to continue paying for it.
Monk P, Garfjeld Roberts P, Palmer AJ, et al. The urgent need for evidence in arthroscopic meniscal surgery. Am J Sports Med 2017;45(4):965-973.

15. Knee surgery does not reduce knee catching or locking in patients with meniscal tear (FIDELITY)

Clinical question: Does partial meniscectomy fix mechanical symptoms -- knee catching or locking -- better than sham surgery?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (specialty)
Synopsis: This report is a substudy of a larger study investigating the effect of arthroscopic surgery on (relatively) young patients with meniscal tear but without signs of osteoarthritis. These Finnish investigators enrolled 146 patients, aged 35 to 65 years, who had knee pain for at least 3 months and evidence of a degenerative meniscal tear but did not respond to conservative treatment. They excluded patients with a verified locked knee (unable to straighten), though they included patients (n = 69) who had symptoms of "catching" or occasional or frequent locking. All patients underwent arthroscopic surgery, though slightly more than half were randomly assigned, using concealed allocation, to a group that did not have the tear addressed (sham surgery). In the surgery group, damaged and loose parts were removed; in the sham surgery group, diagnostic arthroscopy was performed and the surgeon simulated actual surgery (since patients were awake) without removing anything. In the subsequent 12 months, 23 (72%) in the surgery group and 22 (59%) in the sham surgery group with preoperative mechanical symptoms reported symptoms at least once. Only 9 of 32 patients (28%) in the surgery subgroup and 15 of 37 (41%) in the sham surgery subgroup reported complete resolution of their symptoms.
Bottom line: I guess it's time to stop the knee-jerk reaction of sending patients with occasional catches and locking to ortho for meniscal resection. Removing the torn bits of meniscus in middle-aged patients who have intermittent knee catches or locking does not decrease their likelihood of experiencing symptoms in the following year as compared with diagnostic arthroscopy (ie, looking but not touching). In general, meniscectomy does not improve knee pain, regardless of the symptoms (N Engl J Med 2013;369(26):2515-24).
Sihvonen R, Englund M, Turkiewicz A, Jarvinen TL, for the Finnish Degenerative Meniscal Lesion Study Group. Mechanical symptoms and arthroscopic partial meniscectomy in patients with degenerative meniscus tear: A secondary analysis of a randomized trial. Ann Intern Med. 2016;164(7):449-455.

16. Total knee replacement more effective for pain and function than nonsurgical treatment

Clinical question: Is total knee replacement better than nonsurgical treatment for patients with moderate to severe osteoarthritis?
Study design: Randomized controlled trial (single-blinded)
Setting: Outpatient (any)
Synopsis: It's about time. This is the first good-quality randomized controlled trial comparing total knee replacement with nonsurgical treatment of osteoarthritis. All patients had radiographically confirmed knee osteoarthritis classified as moderate to severe and were candidates for unilateral total knee replacement. Patients with previous knee replacement or pain worse than 60 on a 100-point visual analog scale were excluded. The patients' mean age was 66 years; 31% were women. Of the 127 who met the inclusion criteria, an impressive 100 were randomized (50 to each group). Half of the patients underwent total knee replacement, which was followed by 12 weeks of nonsurgical treatment that included education, exercise, dietary advice, custom insoles, and pain medications; the other half received only the 12 weeks of nonsurgical therapy. The authors reported both intention-to-treat and per-protocol analyses, with the latter including only patients who participated in at least 75% of the exercise sessions and who underwent the assigned treatment (ie, did not cross over). The primary outcomes—the total score and subscores for pain, symptoms, function, and quality of life on the Knee Injury and Osteoarthritis Outcome Scale (KOOS) at 12 months—were evaluated by a masked outcome assessor. Approximately 25% of the nonsurgical group crossed over to surgery before the 12 months were up, and overall only about half of the patients in each group met the criteria for the per-protocol analysis. At 12 months, the intention-to-treat analysis found that outcomes had improved significantly more in the surgical treatment group, and the differences were both clinically and statistically significant. Serious adverse events were more common in the surgery group (24 vs 6; P = .005) and in the affected knee, including 3 episodes of deep vein thrombosis, 3 of stiffness requiring mobilization under anesthesia, and 1 each of deep infection and supracondylar femur fracture. Unfortunately, the authors didn't ask the participants who had now been through surgery whether they would have chosen it, all things considered.
Bottom line: In patients with moderate to severe osteoarthritis, total knee replacement provides better symptomatic and functional improvement than nonsurgical care, but approximately half of the surgical patients experienced a serious adverse event, including 8 of 50 who had a serious adverse event that involved the affected limb.
Skou ST, Roos EM, Laursen M, et al. A randomized, controlled trial of total knee replacement. N Engl J Med 2015;373(17):1597-1606.

Diagnosis of Gout

17. Clinical diagnosis of gout okay unless you suspect septic joint

Clinical question: How should gout be diagnosed?
Study design: Practice guideline
Setting: Various (guideline)
Synopsis: This guideline is based on a systematic review and meta-analysis of various approaches to diagnosing gout, including various clinical criteria (eg, Rome Criteria), imaging, and aspiration of one or more joints. The authors found moderate-quality evidence that several clinical algorithms have good specificity and sensitivity (> 80%) for diagnosing gout compared with assessment of synovial fluid. The accompanying review has specifics for each set of diagnostic criteria (Ann Intern Med 2017;166:27-36). The authors found low-quality evidence that the use of either dual-energy computed tomography or ultrasound slightly improved diagnostic accuracy. The guideline development group consisted only of internal medicine physicians, included a methodologist, and they were all free of relevant conflicts of interest.
Bottom line: To aspirate or not to aspirate—that is the question. From the American College of Physicians: ". . . use synovial fluid analysis when clinical judgment indicates that diagnostic testing is necessary in patients with possible acute gout." Reading between the lines, it seems to me the common primary care practice of treating gout on the basis of clinical findings and elevated serum uric acid is just fine unless intuition makes you worry about a septic joint.
Qaseem A, McLean RM, Starkey M, Forciea MA, for the Clinical Guidelines Committee of the American College of Physicians. Diagnosis of acute gout: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2017;166:52-57.

Bottom lines

1. Don’t prescribe valium for acute low back pain.

2. Lumbar fusion does not appear to benefit patients with chronic low back pain.

3. Spinal stenosis decompression surgery is not better when lumber fusion is added.

4. Surgical management of spinal compression fracture does not lead to better outcomes than non-operative management.

5. Placebos can be effective for treating low back pain.

6. Special walking shoes for knee arthritis are no better than regular walking shoes.

7. Acupuncture may have a very small benefit for knee osteoarthritis (or may not) compared to sham acupuncture.

8. Steroid injections are not effective for chronic knee arthritis

9. Arthroscopic procedures are not effective for symptoms of knee osteoarthritis.

10. Joint replacement is, but about 15% of patients have complications.

Cardiovascular Update — Gary Ferenchick MD, MS

Objectives | Understand and apply

1. The 2016 and 2017 ACC/AHA CHF guidelines concerning recommendations on the use of new classes of medications including the ARNI valsartan/sacubitril and the use of biomarkers in HF
2. That NSAIDs can lead to heart failure
3. In patients with Heart Failure with reduced ejection fraction (HRrEF), CAD and EF of < 35%, Cabg is superior to medical therapy in terms of survival
4. Evidence on Vitamin D for CHF
5. Evidence for TAVI (transcatheter aortic-valve implantation)
6. Updates in the management of atrial fibrillation

A peptide, neprilysin, is a new target in the treatment of CHF. According to the background information in the article accompanying abstract #1, Neprilysin is a neutral endopeptidase that "degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling."

In 2016 the ACC/AHA updated their CHF Guidelines to include recommendations concerning the use of 2 new classes of medications for patients with Heart Failure with reduced ejection fraction (HRrEF). Note that the actual update was 5 pages long, and conflict of interest declarations for this update also went on for 5 pages (just saying!).

Updated ACC/AHA guidelines for patients with Stage 3 CHF with reduced ejection fraction (HFrEF)

First a word about the differences between the Stages of HF and the NYHA Classification

Stages of HF	
Stage A:	Patients at risk for heart failure who have *not yet developed structural heart changes* (i.e. those with diabetes, those with coronary disease without prior infarct)
Stage B:	Patients with *structural heart disease* (i.e. reduced ejection fraction, left ventricular hypertrophy, chamber enlargement) who have *not yet developed symptoms of heart failure*
Stage C:	Patients who have developed *clinical heart failure*
Stage D:	Patients with *refractory heart failure* requiring advanced intervention (i.e. biventricular pacemakers, left ventricular assist device, transplantation)

NYHA Classification | CHF Class	
Class	**Function**
I	Asymptomatic LV dysfunction
II	Dyspnea with ≥ ordinary activity
III	Dyspnea with < ordinary activity
IV	Dyspnea at rest

Second a word about the ACC/AHA guideline ratings

Class of Recommendation (COR) and Level of evidence (LOE) | ACC/AHA Guidelines

Class (Strength) of Recommendation (COR) Table

- **Class I (Benefit >>> Risk):** **Should be done | *Is* useful | (Strong)**
- Class IIa (Benefit >> Risk): Reasonable to do | *Can* be useful | (Moderate)
- Class IIb (Benefit ≥ Risk): May be considered | *Unknown* usefulness (Weak)
- Class III (No benefit or harm): Not helpful or harmful

Level (Quality) of Evidence (LOE)

- Level A:
  - High quality evidence from ≥ 1 RCT
  - Meta-analysis of high-quality RCTs
  - ≥ 1 RCT corroborated by high-quality registry studies
- Level B-R (Randomized):
  - Moderate quality evidence from ≥ 1 RCT
  - Meta-analyses of moderate quality RCTs
- Level B-NR (Non-randomized):
  - Moderate quality evidence from ≥ 1 high-quality nonrandomized/observational or registry studies
  - Meta-analyses of such studies
- Level C-LD
  - Randomized or nonrandomized/observational or registry studies with limitations of design or execution
  - Meta-analyses of such studies
  - Physiological or mechanistic studies in humans
- Level C-EO
  - Consensus opinion based upon clinical experience

The COR and LOE are determined independent of each other. Any COR can be paired with any LOE (notably LOE C does not imply the COR is weak)

New 2016 Recommendations | (paraphrased) for Stage C HF with Reduced Ejection Fraction

1. The clinical strategy of inhibition of the renin-angiotensin system with the following is recommended for patients with chronic HFrEF to reduce morbidity and mortality:
   - ACE inhibitors (COR 1 | Level of **Evidence: A**), OR
   - ARBs (COR 1 | Level of **Evidence: A**), OR
   - ARNI (COR 1 | Level of **Evidence: B-R**), in conjunction with evidence based
   - Beta blockers AND
   - Aldosterone antagonists in selected patients
2. "In patients with chronic symptomatic HFr EF NYHA class II or III *who tolerate an ACE inhibitor* or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality." (COR 1: LOE B-R)
   - This ARNI has recently been approved for patients with symptomatic HFrEF and is intended to be substituted for ACE inhibitors or ARBs.
   - HF effects and potential off-target effects may be complex with inhibition of the neprilysin enzyme, which has multiple biological targets
   - To facilitate initiation and titration, the approved ARNI is available in 3 doses that include a dose that was not tested in the HF trial; the target dose used in the trial was 97/103 mg twice daily
3. "ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor"

- Oral neprilysin inhibitors, used in combination with ACE inhibitors, can lead to angioedema and concomitant use is contraindicated and should be avoided
- An ARNI should not be administered within 36 hours of switching from or to an ACE inhibitor.
- ARNI should not be administered to patients with a history of angioedema

4. Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFr EF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (**COR 2a** | **LOE B-R**) (not covered in this chapter)

Benefit:

- All 3 classes are associated with ↓ morbidity and mortality in patients with CHF with reduced ejection fraction (HF/rEF)

Risk

- All 3 classes use with caution in patients with hypotension, renal insufficiency
- ACE and ARBS use with caution in patients with hyperkalemia
- ACE and ARNI also associated with angioedema
  - < 1% of patients on ACE get angioedema; more common in blacks and women
- ACE's also inhibit kinase and increase bradykinin (can therefore ↑ cough in ~ 20% of patients)

FROM ACC/AHA Guideline

- "Data suggest that there are no differences among available ACE inhibitors in their effects on symptoms or survival."
- "ACE inhibitors should be started at low doses and titrated upward to doses shown to reduce the risk of cardiovascular events in clinical trials" (See Appendix)
- **"**Abrupt withdrawal of ACE inhibition can lead to clinical deterioration and should be avoided."

#1: POEM: Valsartan/sacubitril reduces mortality more than enalapril 10 mg twice daily in patients with heart failure (PARADIGM-HF)

Clinical Question: Does inhibition of the both angiotensin and neprilysin offer benefits beyond those of angiotensin inhibition alone?
Bottom Line: The combination of an angiotensin receptor blocker (sacubitril) and neprilysin inhibitor (valsartan) reduces cardiovascular mortality more than an angiotensin-converting enzyme (ACE) inhibitor (enalapril) alone, with an acceptable safety and tolerability profile. The choice of dosage is concerning, however, as the study compared a fairly high dose of valsartan with a moderate dose of enalapril. (LOE = 1b)
Study Design: Randomized controlled trial (double-blinded) **Funding:** Industry
Allocation: Concealed **Setting:** Outpatient (any)
Synopsis: Neprilysin is an endopeptidase that breaks down vasoactive peptides such as natriuretic peptide, bradykinin, and adrenomedullin. Sacubitril inhibits this compound's activity, which has the effect of blocking the vasoconstruction, sodium retention, and cardiac remodeling that accompany more advanced stages of heart failure. A previous trial compared sacubitril with an ACE inhibitor, but angioedema was a problem. In the current trial, patients were randomized to receive the combination of sacubitril and the angiotensin receptor blocker valsartan or to receive enalapril, an older ACE inhibitor. All patients were adults with New York Heart Association (NYHA) class II, III, or IV heart failure; an ejection fraction no greater than 40% (later changed to 35%); and an elevated B-type natriuretic peptide level. The authors excluded those with hypotension, a glomerular filtration rate of less than 30 mL/min/1.73 m2, a serum potassium level greater than 5.2 mmol/L, or history of angioedema or other side effects of ACE inhibitors or angiotensin receptor blockers. The authors ultimately enrolled 10,513 patients. They then had to run a gauntlet of 2 separate run-in phases: 1102 patients left the study because they did not tolerate enalapril, 977 left because they did not tolerate the valsartan/sacubitril combination, and another 43 left primarily because of protocol violations. This meant a total of 8399 patients were randomized to receive valsartan/sacubitril 200 mg or enalapril 10 mg, each given twice daily. The dosage of valsartan is near the top of the recommended dosing range, while the dosage of enalapril is closer to the middle of the recommended range (10 to 40 mg per day) for that drug. Groups were balanced at the start of the study, with an average age of 63 years, 22% women, and the majority with NYHA class III (70%) or class III (24%) heart failure. Patients were followed up for a median of 27 months, at which time an independent data monitoring committee halted the trial. The primary outcome was a cardiovascular death or hospitalization for worsening heart failure. Obviously, this is an inappropriate composite, since they are very different outcomes. Looking at each outcome individually, however, there were fewer cardiovascular deaths in the intervention group (13.3% vs 16.5%; P < .001; number needed to treat [NNT] = 31) and fewer hospitalizations in the intervention group (12.8% vs 15.6%; P < .001; NNT = 36). All-cause mortality was also significantly lower in the intervention group (17% vs 19.8%; NNT = 36), as was a validated symptom score. There were no significant differences in rates of renal function decline or new onset atrial fibrillation. Subgroup analyses showed similar benefits by age, sex, race, and comorbidities. Significant hypotension was more common in the valsartan/sacubitril group (14.0% vs 9.2%; P < .001; number needed to treat to harm

[NNTH] = 21), while cough and elevated serum creatinine levels were more common in the enalapril group. The valsartan/sacubitril group had lower mean blood pressures, supporting concerns of a "straw man" comparison with the selected dose of enalapril.
Reference: McMurray JJ, Packer M, Desai AS, et al, for the PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371(11):993-1004.

#2: PubMed: Only 21% of HF patients meet the PARADIGM-HF inclusion criteria

AIMS: The PARADIGM-HF trial showed that sacubitril-valsartan, an ARB-neprilysin inhibitor, is more effective than enalapril for some patients with heart failure (HF). It is uncertain what proportion of patients with HF would be eligible for sacubitril-valsartan in clinical practice.
METHODS AND RESULTS: Between 2001 and 2014, 6131 patients consecutively referred to a community HF clinic with suspected HF were assessed. The criteria required to enter the randomized phase of PARADIGM-HF, including symptoms, NT-proBNP, and current treatment with or without target doses of ACE inhibitors or ARBs, were applied to identify the proportion of patients eligible for sacubitril-valsartan. Recognizing the diversity of clinical opinion and guideline recommendations concerning this issue, entry criteria were applied singly and in combination. Of
1396 patients with reduced left ventricular ejection fraction (≤40%, HFrEF) and contemporary measurement of NT-proBNP, 379 were on target doses of an ACE inhibitor or ARB at their initial visit and, of these, 172 (45%) fulfilled the
key entry criteria for the PARADIGM-HF trial. Lack of symptoms (32%) and NT-proBNP <600 ng/L (49%) were common reasons for failure to fulfil criteria. A further 122 patients became eligible during follow-up (n = 294, 21%). However, if background medication and doses were ignored, then 701 (50%) were eligible initially and a further 137 became eligible during follow-up.
CONCLUSIONS: Of patients with HFrEF referred to a clinic such as ours, only 21% fulfilled the PARADIGM-HF randomization criteria, on which the ESC Guidelines are based; this proportion rises to 60% if background medication is ignored.
REFERENCE: Pellicori P et al. What proportion of patients with chronic heart failure are eligible for sacubitril-valsartan? Eur J Heart Fail. 2017 Jun;19(6):768-778. Comment in JAMA. 2017 Aug 22;318(8):707-708.

New 2017 CHF Recommendations | (paraphrased)

In 2017 the ACC/AHA published a focused update to their 2013 guidelines for the management of HF. The update focused on 1) the use ARNI in patients with HFrEF (covered above); 2) the use of biomarkers; 3) Management of Stage C HF with preserved EF (HFpEF).

Below are the *new or modified recommendations* that have a moderate or strong class of recommendation (COR I or IIa) COR or a Class III (no benefit or harm) recommendation (see appendix). Recommendations with a IIb COR are not included

Biomarkers

According to this update, Natriuretic peptide biomarkers are used to track presence and severity of HF. BNP (B-type natriuretic peptide) and the NT-proBNP (N-terminal pro-B-type natriuretic peptide) both track similarly and both can be used. However do not use absolute values and cut points interchangeably. BNP is a substrate for neprilysn (but not NT-proBNP); therefore ARNI (e.g sacubritril or Entresto) will increase BNP levels.
Recommendations

Prevention:

- **NEW:** In patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team based care …. can be useful to prevent LV dysfunction or HF (IIa B-R)

Diagnosis

- **MODIFIED:** In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support or exclude a diagnosis of HF (1 | A)

Prognosis

- **MODIFIED:** Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF
- **NEW**: During a HF hospitalization, a predischarge natriuretic peptide biomarker level can be useful to establish post-discharge prognosis (IIA | B-NR)

#3: PubMed: NT-proBNP guided treatment adds nothing to usual care

Importance: The natriuretic peptides are biochemical markers of heart failure (HF) severity and predictors of adverse outcomes. Smaller studies have evaluated adjusting HF therapy based on natriuretic peptide levels ("guided therapy") with inconsistent results.
Objective: To determine whether an amino-terminal pro-B-type natriuretic peptide (NT-proBNP)-guided treatment strategy improves clinical outcomes vs usual care in high-risk patients with HF and reduced ejection fraction (HFrEF).
Design, Settings, and Participants: The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) study was a randomized multicenter clinical trial conducted between January 16, 2013, and September 20, 2016, at 45 clinical sites in the United States and Canada. This study planned to randomize 1100 patients with HFrEF (ejection fraction ≤40%), elevated natriuretic peptide levels within the prior 30 days, and a history of a prior HF event (HF hospitalization or equivalent) to either an NT-proBNP-guided strategy or usual care.
Interventions: Patients were randomized to either an NT-proBNP-guided strategy or usual care. Patients randomized to the guided strategy (n = 446) had HF therapy titrated with the goal of achieving a target NT-proBNP of less than 1000 pg/mL. Patients randomized to usual care (n = 448) had HF care in accordance with published guidelines, with emphasis on titration of proven neurohormonal therapies for HF. Serial measurement of NT-proBNP testing was discouraged in the usual care group.
Main Outcomes and Measures: The primary end point was the composite of time-to-first HF hospitalization or cardiovascular mortality. Prespecified secondary end points included all-cause mortality, total hospitalizations for HF, days alive and not hospitalized for cardiovascular reasons, the individual components on the primary end point, and adverse events.
Results: The data and safety monitoring board recommended stopping the study for futility when 894 (median age, 63 years; 286 [32%] women) of the planned 1100 patients had been enrolled with follow-up for a median of 15 months. The primary end point occurred in 164 patients (37%) in the biomarker-guided group and 164patients (37%) in the usual care group (adjusted hazard ratio [HR], 0.98; 95% CI,0.79-1.22; P = .88). Cardiovascular mortality was 12% (n = 53) in the biomarker-guided group and 13% (n = 57) in the usual care group (HR, 0.94; 95% CI; 0.65-1.37; P = .75). None of the secondary end points nor the decreases in the NT-proBNP levels achieved differed significantly between groups.
Conclusions and Relevance: In high-risk patients with HFrEF, a strategy of NT-proBNP-guided therapy was not more effective than a usual care strategy in improving outcomes.
REFERENCE: Felker GM, et al. Effect of Natriuretic Peptide-Guided Therapy on Hospitalization or Cardiovascular Mortality in High-Risk Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial.JAMA. 2017 Aug 22;318(8):713-720.

Treating HTN to reduce the incidence of HF

New Recommendations

1. In patients at increased risk, or with Stage A HF, the optimal BP in those with HTN should be <130/80 mm. (COR I | B-R)
2. In patients with HF with reduced ejection fraction (HFrEF) and HTN prescribe GDMT to attain a systolic BP of < 130 (COR I | C-EO)
3. In patients with HF with preserved ejection fraction (HFpEF) after management of volume overload, prescribe GDMT to attain a systolic BP of < 130 (COR I | C-LD)

Sleep disordered Breathing

1. In patients with NYHA class II-IV HF and suspicion of sleep disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable (COR IIa | C-LD)

#4: PubMed: CABG | better outcomes after 10 years in patients with CAD and LVEF < 35%

BACKGROUND: The survival benefit of a strategy of coronary-artery bypass grafting (CABG) added to guideline-directed medical therapy, as compared with medical therapy alone, in patients with coronary artery disease, heart failure, and severe left ventricular systolic dysfunction remains unclear.
METHODS: From July 2002 to May 2007, a total of 1212 patients with an ejection fraction of 35% or less and coronary artery disease amenable to CABG were randomly assigned to undergo CABG plus medical therapy (CABG group, 610 patients) or medical therapy alone (medical-therapy group, 602 patients). The primary outcome was death from any cause. Major secondary outcomes included death from cardiovascular causes and death from any cause or hospitalization for cardiovascular causes. The median duration of follow-up, including the current extended-follow-up study, was 9.8 years.
RESULTS: A primary outcome event occurred in 359 patients (58.9%) in the CABG group and in 398 patients (66.1%) in the medical-therapy group (hazard ratio with CABG vs. medical therapy, 0.84; 95% confidence interval [CI], 0.73 to 0.97; P=0.02 by log-rank test). A total of 247 patients (40.5%) in the CABG group and 297 patients (49.3%) in the medical-therapy group died from cardiovascular causes (hazard ratio, 0.79; 95% CI, 0.66 to 0.93; P=0.006 by log-rank test). Death from any cause or hospitalization for cardiovascular causes occurred in 467 patients (76.6%) in the CABG group and in 524 patients (87.0%) in the medical-therapy group (hazard ratio, 0.72; 95% CI, 0.64 to 0.82; P<0.001 by log-rank test).

CONCLUSIONS: In a cohort of patients with ischemic cardiomyopathy, the rates of death from any cause, death from cardiovascular causes, and death from any cause or hospitalization for cardiovascular causes were significantly lower over 10 years among patients who underwent CABG in addition to receiving medical therapy than among those who received medical therapy alone. (Funded by the National Institutes of Health; STICH [and STICHES] ClinicalTrials.gov number, NCT00023595.).
REERENCE: Velazquez EJ, et al. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. N Engl J Med. 2016 Apr 21;374(16):1511-20.

#5: PubMed: ICD | No mortality benefit in CHF patients with non-ischemic cardiomyopathy

Background The benefit of an implantable cardioverter-defibrillator (ICD) in patients with symptomatic systolic heart failure caused by coronary artery disease has been well documented. However, the evidence for a benefit of prophylactic ICDs in patients with systolic heart failure that is not due to coronary artery disease has been based primarily on subgroup analyses. The management of heart failure has improved since the landmark ICD trials, and many patients now receive cardiac resynchronization therapy (CRT).
Methods In arandomized, controlled trial, 556 patients with symptomatic systolic heart failure (left ventricular ejection fraction, ≤35%) not caused by coronary artery disease were assigned to receive an ICD, and 560 patients were assigned to receive usual clinical care (control group). In both groups, 58% of the patients received CRT. The primary outcome of the trial was death from any cause. The secondary outcomes were sudden cardiac death and cardiovascular death.
Results After a median follow-up period of 67.6 months, the primary outcome had occurred in 120 patients (21.6%) in the ICD group and in 131 patients (23.4%) in the control group (hazard ratio, 0.87; 95% confidence interval [CI], 0.68 to 1.12; P=0.28). Sudden cardiac death occurred in 24 patients (4.3%) in the ICD group and in 46 patients (8.2%) in the control group (hazard ratio, 0.50; 95% CI, 0.31 to 0.82; P=0.005). Device infection occurred in 27 patients (4.9%) in the ICD group and in 20 patients (3.6%) in the control group (P=0.29).
Conclusions: In this trial, prophylactic ICD implantation in patients with symptomatic systolic heart failure not caused by coronary artery disease was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care. (Funded by Medtronic and others; DANISH ClinicalTrials.gov number, NCT00542945 .).
Reference: Køber L et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med. 2016 Sep 29;375(13):1221-30.

#6: Center for Medical Education: Vit D has no effect in CHF on exercise capacity but is safe

BACKGROUND: Low vitamin D is a common finding in heart failure and is associated with a poor prognosis.
METHODS: These British authors report results of the randomized, double-blind VINDICATE study (Vitamin D Treating Patients with Chronic Heart Failure). Patients with optimally treated chronic heart failure with a left ventricular ejection fraction of 45% or lower and vitamin D deficiency (25[OH]D below 50nmol/L) were randomized to either vitamin D3 supplementation as cholecalciferol 4000 IU/day (n=80; mean age 68.5 years) or placebo (n=83; mean age 69.0 years). The primary outcome was the change in 6-minute walking test distance from baseline to one year compared between groups.
RESULTS: As expected, supplementation normalized vitamin D serum concentrations compared with placebo. Walking distance was not significantly different between the supplementation and placebo groups at one year (p=0.25). However, supplementation was associated with significantly greater improvements in cardiac function as determined by echocardiography, including LV ejection fraction (+7.7% versus +1.4%; p<0.0001), LV end-diastolic diameter (-2.5 mm versus -0.1 mm; p=0.002), and LV end-systolic diameter (-2.7 mm versus -1.0 mm; p=0.04). There were no cases of hypervitaminosis D, renal dysfunction or treatment-related adverse effects. The study was underpowered to detect a difference in the primary endpoint of walking distance, and the changes in LV function were secondary endpoints. A large number of patients originally enrolled (n=223) did not complete the study.
CONCLUSIONS: Vitamin D3 supplementation for one year did not increase exercise capacity, but was safe and improved left ventricular structure and function. 44 references (**k.k.witte@leeds.ac.uk** for reprints)
REFERENCE: Witte, K.K., et al. EFFECTS OF VITAMIN D ON CARDIAC FUNCTION IN PATIENTS WITH CHRONIC HF: THE VINDICATE STUDY. J Am Coll Cardiol 67(22):2593, June 7, 2016

#7: Center for Medical Education: Vit D no effect on clinical outcomes in CHF

BACKGROUND: Vitamin D deficiency has been associated with elevated risk for, and a poor prognosis of, cardiovascular diseases due to inflammation and endothelial dysfunction.
METHODS: These Chinese authors performed a systematic review and meta-analysis of seven randomized controlled trials of cardiovascular outcomes following vitamin D supplementation versus control treatment in 573 adults with chronic heart failure. The mean patient age was approximately 65, and 70% of the patients were male. The primary outcomes were left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, 6-minute walk distance, N-terminal pro-B-type natriuretic peptide (BNP), tumor necrosis factor-alpha (TNF-alpha), C-reactive protein (CRP), interleukin-10 (IL-10), parathyroid hormone (PTH), and renin.
RESULTS: Vitamin D doses ranged from 1000 to 50,000 IU/week, and follow-up lasted from six weeks to nine months. Vitamin D supplementation significantly reduced serum levels of inflammatory mediators TNF-alpha (weighted mean difference [WMD] -2.42 pg/mL) and CRP (WMD -0.72 mg/L), as well as serum PTH (WMD -13.44pg/mL) (all comparisons, p<0.05). When compared with conventional treatment, supplementation had no significant effect on IL-10, renin, LVEF, BNP or walking distance. The included trials are limited by deficiencies in methodology, small sample sizes, and heterogeneity.
CONCLUSIONS: These findings suggest that vitamin D supplementation decrease levels of serum PTH, TNF-alpha, and CRP in patients with chronic heart failure, but has no significant effect on LVEF, NYHA class, exercise tolerance, BNP, IL-10 or renin levels.
REFERENCE: Jiang, W.L., et al. VITAMIN D SUPPLEMENTATION IN THE TREATMENT OF CHRONIC HEART FAILURE: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. Clin Cardiol 39(1):56, January 2016

#8: PubMed: Telemonitoring | No effect on readmission for CHF

IMPORTANCE: It remains unclear whether telemonitoring approaches provide benefits for patients with heart failure (HF) after hospitalization.
OBJECTIVE: To evaluate the effectiveness of a care transition intervention using remote patient monitoring in reducing 180-day all-cause readmissions among a broad population of older adults hospitalized with HF.
DESIGN, SETTING, AND PARTICIPANTS: We randomized 1437 patients hospitalized for HF between October 12, 2011, and September 30, 2013, to the intervention arm (715 patients) or to the usual care arm (722 patients) of the Better Effectiveness After Transition-Heart Failure (BEAT-HF) study and observed them for 180 days. The dates of our study analysis were March 30, 2014, to October 1, 2015. The setting was 6 academic medical centers in California. Participants were hospitalized individuals 50 years or older who received active treatment for decompensated HF.
INTERVENTIONS: The intervention combined health coaching telephone calls and telemonitoring. Telemonitoring used electronic equipment that collected daily information about blood pressure, heart rate, symptoms, and weight. Centralized registered nurses conducted telemonitoring reviews, protocolized actions, and telephone calls.
MAIN OUTCOMES AND MEASURES: The primary outcome was readmission for any cause within 180 days after discharge. Secondary outcomes were all-cause readmission within 30 days, all-cause mortality at 30 and 180 days, and quality of life at 30 and 180 days.
RESULTS: Among 1437 participants, the median age was 73 years. Overall, 46.2% (664 of 1437) were female, and 22.0% (316 of 1437) were African American. The intervention and usual care groups did not differ significantly in readmissions for any cause 180 days after discharge, which occurred in 50.8% (363 of 715) and 49.2% (355 of 722) of patients, respectively (adjusted hazard ratio, 1.03; 95% CI, 0.88-1.20; P = .74). In secondary analyses, there were no significant differences in 30-day readmission or 180-day mortality, but there was a significant difference in 180-day quality of life between the intervention and usual care groups. No adverse events were reported.
CONCLUSIONS AND RELEVANCE: Among patients hospitalized for HF, combined health coaching telephone calls and telemonitoring did not reduce 180-day readmissions.
TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT01360203.
REFERENCE: Ong MK et al. Effectiveness of Remote Patient Monitoring After Discharge of Hospitalized Patients With Heart Failure: The Better Effectiveness After Transition – Heart Failure (BEAT-HF) Randomized Clinical Trial. JAMA Intern Med. 2016 Mar;176(3):310-8.

#9: PubMed: NSAIDS increase risk of hospitalization for CHF

OBJECTIVES: To investigate the cardiovascular safety of non-steroidal anti-inflammatory drugs (NSAIDs) and estimate the risk of hospital admission for heart failure with use of individual NSAIDs.
DESIGN: Nested case-control study.
SETTING: Five population based healthcare databases from four European countries (the Netherlands, Italy, Germany, and the United Kingdom).
PARTICIPANTS: Adult individuals (age ≥18 years) who started NSAID treatment in 2000-10. Overall, 92 163 hospital admissions for heart failure were identified and matched with 8 246 403 controls (matched via risk set sampling according to age, sex, year of cohort entry).
MAIN OUTCOME MEASURE: Association between risk of hospital admission for heart failure and use of 27 individual NSAIDs, including 23 traditional NSAIDs and four selective COX 2 inhibitors. Associations were assessed by multivariable conditional logistic regression models. The dose-response relation between NSAID use and heart failure risk was also assessed.
RESULTS: Current use of any NSAID (use in preceding 14 days) was found to be associated with a 19% increase of risk of hospital admission for heart failure (adjusted odds ratio 1.19; 95% confidence interval 1.17 to 1.22), compared with past use of any NSAIDs (use >183 days in the past). Risk of admission for heart failure increased for seven traditional NSAIDs (diclofenac, ibuprofen, indomethacin, ketorolac, naproxen, nimesulide, and piroxicam) and two COX 2 inhibitors (etoricoxib and rofecoxib). Odds ratios ranged from 1.16 (95% confidence interval 1.07 to 1.27) for naproxen to 1.83 (1.66 to 2.02) for ketorolac. Risk of heart failure doubled for diclofenac, etoricoxib, indomethacin, piroxicam, and rofecoxib used at very high doses (≥2 defined daily dose equivalents), although some confidence intervals were wide. Even medium doses (0.9-1.2 defined daily dose equivalents) of indomethacin and etoricoxib were associated with increased risk. There was no evidence that celecoxib increased the risk of admission for heart failure at commonly used doses.
CONCLUSIONS: The risk of hospital admission for heart failure associated with current use of NSAIDs appears to vary between individual NSAIDs, and this effect is dose dependent. This risk is associated with the use of a large number of individual NSAIDs reported by this study, which could help to inform both clinicians and health regulators.
REFERENCE: Arfè A et al. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. BMJ. 2016 Sep 28;354:i4857. doi: 10.1136/bmj.i4857.

#10: PubMed: PCI no different from placebo procedure in patients with single vessel stenosis (> 70%) and SIHD

BACKGROUND: Symptomatic relief is the primary goal of percutaneous coronary intervention (PCI) in stable angina and is commonly observed clinically. However, there is no evidence from blinded, placebo-controlled randomised trials to show its efficacy.
METHODS: ORBITA is a blinded, multicentre randomised trial of PCI versus a placebo procedure for angina relief that was done at five study sites in the UK. We enrolled patients with severe (≥70%) single-vessel stenoses. After enrolment, patients received 6 weeks of medication optimisation. Patients then had pre-randomisation assessments with cardiopulmonary exercise testing, symptom questionnaires, and dobutamine stress echocardiography. Patients were randomised 1:1 to undergo PCI or a placebo procedure by use

of an automated online randomisation tool. After 6 weeks of follow-up, the assessments done before randomisation were repeated at the final assessment. The primary endpoint was difference in exercise time increment between groups. All analyses were based on the intention-to-treat principle and the study population contained all participants who underwent randomisation. This study is registered with ClinicalTrials.gov, number NCT02062593.
FINDINGS: ORBITA enrolled 230 patients with ischaemic symptoms. After the medication optimisation phase and between Jan 6, 2014, and Aug 11, 2017, 200 patients underwent randomisation, with 105 patients assigned PCI and 95 assigned the placebo procedure. Lesions had mean area stenosis of 84·4% (SD 10·2), fractional flow reserve of 0·69 (0·16), and instantaneous wave-free ratio of 0·76 (0·22). There was no significant difference in the primary endpoint of exercise time increment between groups (PCI minus placebo 16·6 s, 95% CI -8·9 to 42·0, p=0·200). There were no deaths. Serious adverse events included four pressure-wire related complications in the placebo group, which required PCI, and five major bleeding events, including two in the PCI group and three in the placebo group.
INTERPRETATION: In patients with medically treated angina and severe coronary stenosis, PCI did not increase exercise time by more than the effect of a placebo procedure. The efficacy of invasive procedures can be assessed with a placebo control, as is standard for pharmacotherapy.
REFERENCE: Al-Lamee R et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial.Lancet. 2017 Nov 1. pii: [Epub ahead of print]

#11: PubMed: More exercise associated with lower mortality in patients with SIHD

BACKGROUND: Recommendations for physical activity in patients with stable coronary heart disease (CHD) are based on modest evidence.
OBJECTIVES: The authors analyzed the association between self-reported exercise and mortality in patients with stable CHD.
METHODS: A total of 15,486 patients from 39 countries with stable CHD who participated in the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) study completed questions at baseline on hours spent each week taking mild, moderate, and vigorous exercise. Associations between the volume of habitual exercise in metabolic equivalents of task hours/week and adverse outcomes during a median follow-up of 3.7 years were evaluated.
RESULTS: A graded decrease in mortality occurred with increased habitual exercise that was steeper at lower compared with higher exercise levels. Doubling exercise volume was associated with lower all-cause mortality (unadjusted hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.79 to 0.85; adjusting for covariates, HR: 0.90; 95% CI: 0.87 to 0.93). These associations were similar for cardiovascular mortality (unadjusted HR: 0.83; 95% CI: 0.80 to 0.87; adjusted HR: 0.92; 95% CI: 0.88 to 0.96), but myocardial infarction and stroke were not associated with exercise volume after adjusting for covariates. The association between decrease in mortality and greater physical activity was stronger in the subgroup of patients at higher risk estimated by the ABC-CHD (Age, Biomarkers, Clinical-Coronary Heart Disease) risk score (p for interaction = 0.0007).
CONCLUSIONS: In patients with stable CHD, more physical activity was associated with lower mortality. The largest benefits occurred between sedentary patient groups and between those with the highest mortality risk.
REFERENCE: Stewart RAH et al, for the STABILITY Investigators.Physical Activity and Mortality in Patients With Stable Coronary Heart Disease.J Am Coll Cardiol. 2017 Oct 3;70(14):1689-1700.

ATRIAL FIBRILATION

Most recommendations (51%) published in the ACC AHA atrial fibrillation guidelines are supported by C level “evidence” (e.g. expert opinion)

#12: PubMed: ACC AHA A Fib Guidelines 8.8% of recommendations Level A evidence

Importance: The joint American College of Cardiology (ACC), American Heart Association (AHA), and Heart Rhythm Society (HRS) guidelines on the management of atrial fibrillation (AF) are used extensively to guide patient care.
Objective: To describe the evidence base and changes over time in the AHA/ACC/HRS guidelines on AF with respect to the distribution of recommendations across classes of recommendations and levels of evidence.
Data Sources: Data from the AHA/ACC/HRS guidelines on AF from 2001, 2006, 2011,and 2014 were abstracted. A total of 437 recommendations were included.
Data Extraction and Synthesis: The number of recommendations and distribution of classes of recommendation (I, II, and III) and levels of evidence (A, B, and C) were determined for each guideline edition. Changes in recommendation class and level of evidence were analyzed using the 2001 and 2014 guidelines.
Results: From 2001 to 2014, the total number of AF recommendations increased from 95 to 113. Numerically, there was a nonsignificant increase in the use of level of evidence B (30.5% to 39.8%; P = .17) and a nonsignificant decrease in the use of level of evidence C (60.0% to 51.3%; P = .21), with limited changes in the use of level A evidence (8.4% to 8.8%; P = .92). In the 2014 guideline document, 10 of 113 (8.8%) recommendations were supported by level of evidence A, whereas 58 of 113 (51.3%) were supported by level of evidence C. Most recommendations were equally split among class I (49/113; 43.4%) and class IIa/IIb (49/113; 43.4%), with the minority (15/113; 13.3%) assigned as class III. Most class I recommendations were supported by level of evidence C (29/49; 59.2%), whereas only 6 of 49 (12.2%) were supported by level of evidence A. No rate control category recommendations were supported by level of evidence A.
Conclusions and Relevance: Some aspects of the quality of evidence underlying AHA/ACC/HRS AF guidelines have improved over time. However, the use of level of evidence A remains low and has not increased since 2001. These findings highlight the need for focused and pragmatic randomized studies on the clinical management of AF.
Reference: Barnett AS et al. Quality of Evidence Underlying the American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines on the Management of Atrial Fibrillation.JAMA Cardiol. 2016 Dec 14. doi: 10.1001/jamacardio.2016.4936.

#13: PubMed: NOACs | As good as warfarin in AF

OBJECTIVE: To study the effectiveness and safety of the non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) dabigatran, rivaroxaban, and apixaban compared with warfarin in anticoagulant naïve patients with atrial fibrillation.
DESIGN: Observational nationwide cohort study.
SETTING: Three Danish nationwide databases, August 2011 to October 2015.
PARTICIPANTS: 61 678 patients with non-valvular atrial fibrillation who were naïve to oral anticoagulants and had no previous indication for valvular atrial fibrillation or venous thromboembolism. The study population was distributed according to treatment type: warfarin (n=35 436, 57%), dabigatran 150 mg (n=12 701, 21%), rivaroxaban 20 mg (n=7192, 12%), and apixaban 5 mg (n=6349,10%).
MAIN OUTCOME MEASURES: Effectiveness outcomes defined a priori were ischaemic stroke; a composite of ischaemic stroke or systemic embolism; death; and a composite of ischaemic stroke, systemic embolism, or death. Safety outcomes were any bleeding, intracranial bleeding, and major bleeding.
RESULTS: When the analysis was restricted to ischaemic stroke, NOACs were not significantly different from warfarin. During one year follow-up, rivaroxaban was associated with lower annual rates of ischaemic stroke or systemic embolism (3.0% v 3.3%, respectively) compared with warfarin: hazard ratio 0.83 (95% confidence interval 0.69 to 0.99). The hazard ratios for dabigatran and apixaban (2.8% and 4.9% annually, respectively) were non-significant compared with warfarin. The annual risk of death was significantly lower with apixaban (5.2%) and dabigatran (2.7%) (0.65, 0.56 to 0.75 and 0.63, 0.48 to 0.82, respectively) compared with warfarin (8.5%), but not with rivaroxaban (7.7%). For the combined endpoint of any bleeding, annual rates for apixaban (3.3%) and dabigatran (2.4%) were significantly lower than for warfarin (5.0%) (0.62, 0.51 to 0.74). Warfarin and rivaroxaban had comparable annual bleeding rates (5.3%).
CONCLUSION: All NOACs seem to be safe and effective alternatives to warfarin in a routine care setting. No significant difference was found between NOACs and warfarin for ischaemic stroke. The risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran compared with warfarin.
REFERENCE: Larsen TB et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ. 2016 Jun 16;353:i3189

#14: PubMed: Bleeding risk score | ORBIT-AF better than HAS-BLED

BACKGROUND: Therapeutic decisions in atrial fibrillation (AF) are often influenced by assessment of bleeding risk. However, existing bleeding risk scores have limitations.
OBJECTIVES: We sought to develop and validate a novel bleeding risk score using routinely available clinical information to predict major bleeding in a large, community-based AF population.
METHODS: We analysed data from Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), a prospective registry that enrolled incident and prevalent AF patients at 176 US sites. Using Cox proportional hazards regression, we identified factors independently associated with major bleeding among patients taking oral anticoagulation (OAC) over a median follow-up of 2 years (interquartile range = 1.6-2.5). We also created a numerical bedside risk score that included the five most predictive risk factors weighted according to their strength of association with major bleeding. The predictive performance of the full model, the simple five-item score, and two existing risk scores (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly, HAS-BLED, and anticoagulation and risk factors in atrial fibrillation, ATRIA) were then assessed in both the ORBIT-AF cohort and a separate clinical trial population, Rivaroxaban Once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET-AF).
RESULTS: Among 7411 ORBIT-AF patients taking OAC, the rate of major bleeding was 4.0/100 person-years. The full continuous model (12 variables) and five-factor ORBIT risk score (older age [75+ years], reduced haemoglobin/haematocrit/history of anaemia, bleeding history, insufficient kidney function, and treatment with antiplatelet) both had good ability to identify those who bled vs. not (C-index 0.69 and 0.67, respectively). These scores both had similar discrimination, but markedly better calibration when compared with the HAS-BLED and ATRIA scores in an external validation population from the ROCKET-AF trial.
CONCLUSIONS: The five-element ORBIT bleeding risk score had better ability to predict major bleeding in AF patients when compared with HAS-BLED and ATRIA risk scores. The ORBIT risk score can provide a simple, easily remembered tool to support clinical decision making.
REFERENCE: O'Brien EC et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. Eur Heart J. 2015 Dec 7;36(46):3258-64.

Orbit Variables	Score
Older Age (> 74)	1
Reduced hemoglobin (men < 13 g/dL | women < 12 g/dL)	2
Bleeding tendency/predisposition*	2
Insufficienct kidney function (GFR < 60)	1
Treatment with antiplatelets	1
Low risk (0 – 2) | 2.4 bleeds/100 patient-years Medium risk (3) | 4.7 bleeds/patient-years High risk (≥ 4) | 8.1 bleeds/patient-years Reference: Eur Heart J (2015) 36 (46): 3258-3264.	

HAS-BLED	Score
Hypertension (systolic blood pressure >160 mm Hg)	1
Abnormal renal and liver function*	1 or 2
Stroke	1
Bleeding tendency/predisposition*	1
Labile INRs (if on warfarin)*	1
Elderly (e.g., age >65 y)	1
Drugs or alcohol (1 point each)*	1 or 2
Maximum score	9
Abnormal renal function is classified as the presence of chronic dialysis, renal transplantation, or serum creatinine ≥2.3 mg/dl. Abnormal liver function is defined as chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (bilirubin 2 to 3 times the upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase 3 times the upper limit normal, etc), history of bleeding or predisposition (anemia), labile INR (ie, time in therapeutic range <60%), concomitant antiplatelets or nonsteroidal anti-inflammatory drugs, or excess alcohol. High risk for bleeding ≥ 3	

#15: PubMed: NOACs | ~12% of US patients given off label doses → worse outcomes

BACKGROUND: Although non-vitamin K antagonist oral anticoagulants (NOACs) do not require frequent laboratory monitoring, each compound requires dose adjustments on the basis of certain clinical criteria.
OBJECTIVES: This study assessed the frequency of off-label NOAC doses among AF patients and the associations between off-label dose therapy and clinical outcomes in community practice.
METHODS: We evaluated 5,738 patients treated with a NOAC at 242 ORBIT-AF II (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation phase II) sites. NOAC doses were classified as either underdosed or overdosed, consistent with Food and Drug Administration labeling. Longitudinal outcomes (median follow-up: 0.99 years) included stroke or systemic embolism, myocardial infarction, major bleeding (International Society of Thrombosis and Haemostasis criteria), cause-specific hospitalization, and all-cause mortality.
RESULTS: Overall, 541 NOAC-treated patients (9.4%) were underdosed, 197 were overdosed (3.4%), and 5,000 were dosed according to U.S. labeling (87%). Compared with patients receiving the recommended dose, those who were receiving off-label doses were older (median: 79 and 80 years of age vs. 70 years of age, respectively; $p < 0.0001$), more likely female (48% and 67% vs. 40%, respectively; $p < 0.0001$), less likely to be treated by an electrophysiologist (18% and 19% vs.27%, respectively; $p < 0.0001$), and had higher CHA2DS2-VASc scores (96% and 97% ≥2 vs. 86%, respectively; $p < 0.0001$) and higher ORBIT bleeding scores (25% and 31% >4 vs. 11%, respectively; $p < 0.0001$). After dose adjustment, NOAC overdosing was associated with increased all-cause mortality compared with recommended doses (adjusted hazard ratio: 1.91; 95% confidence interval [CI]: 1.02 to 3.60; $p = 0.04$). Underdosing was associated with increased cardiovascular hospitalization (adjusted hazard ratio: 1.26; 95% CI: 1.07 to 1.50; $p = 0.007$).
CONCLUSIONS: A significant minority (almost 1 in 8) of U.S. patients in the community received NOAC doses inconsistent with labeling. NOAC over- and underdosing are associated with increased risk for adverse events.
(Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II [ORBIT-AF II]; NCT01701817).
REFERENCE: Steinberg BA et al. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry.J Am Coll Cardiol. 2016 Dec 20;68(24):2597-2604.

#16: Center for Medical Education: Monitoring NOACs

The authors, coordinated at the University of Toronto, present a practical evidence-based checklist for monitoring direct oral anticoagulants (DOACs) applied for stroke prevention in atrial fibrillation, such as apixaban, dabigatran, edoxaban, and rivaroxaban. The checklist for safety monitoring and risk factor modification contains the key categories A (adherence), B (bleeding), C (creatinine clearance), D (drug interactions), E (examination), and F (follow-up), and a reference table. In particular, concomitant use of aspirin or NSAIDs can increase risk of bleeding. Benefits vs. bleeding risk of concomitant antiplatelet therapy need to be evaluated, and the addition of aspirin to warfarin is discouraged. As low patient adherence can increase stroke risk, a target adherence rate of greater than 80% is suggested, and adherence should be checked and supported by patient education, and problem solving or counseling, as indicated. At a creatinine clearance between 30 and 50mL/min/1.73m2, oral factor Xa inhibitors are preferred over dabigatran due to its lower renal elimination rate, and DOACs should be avoided at a creatinine clearance below 30mL/min/1.73m2. Creatinine levels and glomerular filtration rate should be assessed at least every six to twelve months, and more often in those with dehydrating illnesses and a baseline borderline low creatinine clearance. Hypertension treatment and fall prevention aids should be provided as indicated. Follow-up and reassessment are recommended every six months, or every three months for high-risk patients. A useful monitoring checklist is available (free of charge) at http://thrombosiscanada.ca/?p=1400 .
REFERENCE: Gladstone DJ, et al. How to Monitor Patients Receiving Direct Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation: A Practice Tool Endorsed by Thrombosis Canada, the Canadian Stroke Consortium, the Canadian Cardiovascular Pharmacists Network, and the Canadian Cardiovascular Society. Ann Intern Med. 2015 Sep 1;163(5):382-5 PMID: 26121536

Monitoring Patients on Direct Oral Anticoagulants

Monitoring Patients on Direct Oral Anticoagulants	
Adherence	• "In an average week how many doses would you typically miss for 1 reason or another?"
Bleeding	• Message: Most CVAs associated with AF are disabling or fatal; whereas most bleeds associated with anticoagulation are not fatal
Creatinine clearance	• NOAs are renally cleared (dabigatran 80%, Xa inhibitors 25- 50%) • Check GFR 2x/year (more frequently with dehydrating illnesses, borderline low GFRs, or use of diuretics)
Drug interactions	• Avoid aspirin or NSAIDs
Examination	• Assess blood pressure for HTN AND orthostatic hypotension • Gait and balance assessment (? Need for canes)
Final assessment/follow up	• Q 6 months average risk • Q 3 months righ risk

REFERENCE: Gladstone DJ, et al. How to Monitor Patients Receiving Direct Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation: A Practice Tool Endorsed by Thrombosis Canada, the Canadian Stroke Consortium, the Canadian Cardiovascular Pharmacists Network, and the Canadian Cardiovascular Society. Ann Intern Med. 2015 Sep 1;163(5):382-5.

Access this URL for a useful table and free form for following patients on NOAs:

#17: PubMed: Modified Valsalva | Effective for SVT Termination

BACKGROUND: The Valsalva manoeuvre is an internationally recommended treatment for supraventricular tachycardia, but cardioversion is rare in practice (5-20%), necessitating the use of other treatments including adenosine, which patients often find unpleasant. We assessed whether a postural modification to the Valsalva manoeuvre could improve its effectiveness.
METHODS: We did a randomised controlled, parallel-group trial at emergency departments in England. We randomly allocated adults presenting with supraventricular tachycardia (excluding atrial fibrillation and flutter) in a 1:1 ratio to undergo a modified Valsalva manoeuvre (done semi-recumbent with supine
repositioning and passive leg raise immediately after the Valsalva strain), or a standard semi-recumbent Valsalva manoeuvre. A 40 mm Hg pressure, 15 s standardised strain was used in both groups. Randomisation, stratified by centre, was done centrally and independently, with allocation with serially numbered, opaque, sealed, tamper-evident envelopes. Patients and treating clinicians were not masked to allocation. The primary outcome was return to sinus rhythm at 1 min after intervention, determined by the treating clinician and electrocardiogram and confirmed by an investigator masked to treatment allocation. This study is registered with Current Controlled Trials (ISRCTN67937027).
FINDINGS: We enrolled 433 participants between Jan 11, 2013, and Dec 29, 2014. Excluding second attendance by five participants, 214 participants in each group were included in the intention-to-treat analysis. 37 (17%) of 214 participants assigned to standard Valsalva manoeuvre achieved sinus rhythm compared with 93 (43%) of 214 in the modified Valsalva manoeuvre group (adjusted odds ratio 3·7
(95% CI 2·3-5·8; p<0·0001). We recorded no serious adverse events.
INTERPRETATION: In patients with supraventricular tachycardia, a modified Valsalva manoeuvre with leg elevation and supine positioning at the end of the strain should be considered as a routine first treatment, and can be taught to patients.
FUNDING: National Institute for Health Research.

REFERENCE: Appelboam A et al. Postural modification to the standard Valsalva manoeuvre for emergency treatment of supraventricular tachycardias (REVERT): a randomised controlled trial. Lancet. 2015 Oct 31;386(10005):1747-53.

Key Points:

1) The ARN inhibitor Valsartan/sacubitril combination has received a Class 1 recommendation from the ACC/AHA in the treatment of Stage 3 (NYHA Class II or III) CHF with reduced ejection fraction (HFrEF)
2) In patients with coronary artery disease, heart failure, and severe left ventricular systolic dysfunction, CABG plus medical therapy is associated with better outcomes than medical therapy
3) Vitamin D is not associated with any patient orientated outcomes in patients with CHF
4) NSAIDS increase risk of hospitalization for CHF
5) NOACs are as good as warfarin in AF, but are given in off label doses ~ 12% of the time
6) The ORBIT risk score can provide a simple, easily remembered tool to support clinical decision making.
7) A modified Valsalva is effective in terminating SVT ~50% of the time

Appendix 1: Doses of HF meds achieved in clinical trials

Drug	Mean Doses Achieved in Clinical Trials
Captopril	122 mg/d
Enalapril	16 mg/d
Lisinopril	35 mg/d
Candesartan	24 mg/d
Losartan	129 mg/d
Valsartan	254 mg d
Carvedilol	37 mg /d
Metoprolol succinate	159 mg/d
Adapted from J Cardiac Failure 2017;23:628	

Appendix 2:

ACC/AHA AF 2014 Guidelines on Atrial Fibrillation

"The ACC/AHA practice guidelines are intended to assist clinicians in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. The guidelines attempt to define practices that meet the needs of most patients in most circumstances ... situations may arise in which deviations from these guidelines may be appropriate." The ACC/AHA recommendations are associated with various recommendation strengths:

Class of Recommendation Table

- **Class I (Benefit >>> Risk):** **Should be done**
- Class IIa (Benefit >> Risk): Reasonable to do
- Class IIb (Benefit > Risk): May be considered
- Class III (No benefit or harm): Not helpful or harmful

Estimate of certainty of treatment effect

- Level A: Multiple populations evaluated, Multiple RCTs or meta-analyses
- Level B: Limited populations evaluated, Single RCT or nonrandomized trials
- Level C: Very limited populations evaluated; Consensus opinion, Standard of care

Anticoagulant Recommendations		
Recommendation	**Class**	**LOE**
In patients with AF, antithrombotic therapy should be individualized based on shared decision making after discussion of the absolute and relative risks of stroke and bleeding and the patient's values and preferences.	I	C
Selection of antithrombotic therapy should be based on the risk of thromboembolism *irrespective of whether the AF pattern is paroxysmal, persistent, or permanent*	I	B
In patients with nonvalvular AF, the CHA2DS2-VASc score is recommended for assessment of stroke risk	I	B
For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a *CHA2DS2-VASc score of 2 or greater, oral anticoagulants are recommended.* Options include:	I	
• warfarin (INR 2.0 to 3.0)		A
• dabigatran		B
• rivaroxaban		B
• apixaban		B
Among patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable		A
For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor (dabigatran, rivaroxaban, or apixaban) is recommended		
Renal function should be evaluated before initiation of direct thrombin or factor Xa inhibitors and should be reevaluated when clinically indicated and at least annually		

Essentials Update on Women's Health William Wadland, MD

The following presentation is intended to be an update and not a comprehensive review. It is based on a selective search of the current Essentials data base, Cochrane reviews, and Pub Med. The update focuses on common conditions: osteoporosis, menopause, dysmenorrhea, sexual dysfunction, fibroids, vaginal atrophy, and contraception. Cancer screening and care is not included.

Objectives: after this presentation, participants should be able to:

1. Describe treatment recommendations for osteoporosis and menopausal symptoms
2. Describe interventions for common conditions: dysmenorrhea, sexual dysfunction, fibroids, and vaginal atrophy
3. Describe current studies on contraception

Osteoporosis

1. ACP clinical guidelines for osteoporosis treatment

Clinical question: Based on recent research, what changes to osteoporosis management are recommended by the American College of Physicians?
Study design: Practice guideline
Setting: Various (guideline)
Synopsis: This 2017 ACP guideline on the treatment of osteoporosis to prevent fractures in men and women is an update from the prior guideline in 2008, with endorsement from the American Academy of Family Physicians. The guideline is based on a systematic review of the literature and the focus of the recommendations is on improving patient-oriented outcomes (fractures, especially of the hip). The evidence is graded and the recommendations are labeled as either strong or weak. Neither the chair nor the majority of the development committee had conflicts of interest, and the committee included a methodologist. New or modified recommendations: • Treat women with osteoporosis with a bisphosphonate (alendronate, risendronate, or zolendronic acid) or a monoclonal antibody (denosumab). (strong recommendation, high-quality evidence) • Treat for only 5 years -- benefit beyond this duration has not been demonstrated. (weak recommendation, low-quality evidence) • Do not monitor bone mineral density while treating. (weak recommendation; low-quality evidence) • Treat men with osteoporosis with a bisphosphonate to decrease the risk of vertebral fracture. (weak recommendation, low-quality evidence) • The effect of calcium with vitamin D supplementation to prevent fracture is uncertain. • Citing greater risk than benefit, the group recommends against use of estrogens or raloxifene (Evista). (strong recommendation, moderate-quality evidence) • The group suggests discussing possible treatment with women 65 years or older who are osteopenic and at high risk for fracture.
Bottom line: The American College of Physicians (ACP) recommends treating women with osteoporosis with alendronate (Fosamax), risendronate (Actonel), zoledronic acid (Zometa), or denosumab (Prolia, Xgeva) for up to 5 years only, which makes sense since we don't have longer studies yet and because the bisphosphonates are sequestered in bone and slowly re-released. The guideline also suggests not monitoring bone density after the start of treatment. Menopausal estrogen therapy and selective estrogen receptor modulators (raloxifene) are no longer recommended. For men with osteoporosis, the ACP recommends bisphosphonate treatment, though this is a weak recommendation limited by low-quality evidence.
Qaseem A, Forciea MA, McLean RM, Denberg TD, for the Clinical Guidelines Committee of the American College of Physicians. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. Ann Intern Med 2017;166(11):818-839.

2. Vitamin D supplementation: good for bones and fall prevention, but little else

Clinical question: Is supplementation with vitamin D effective?
Study design: Systematic review
Setting: Uncertain
Synopsis: These authors searched the Cochrane Database of Systematic Reviews and PubMed to identify randomized controlled trials and systematic reviews/meta-analyses of studies that evaluated vitamin D for 10 common uses. Two researchers performed the searches and reviewed the research. The studies were compiled without formal explanation of how the authors included or excluded studies and they did not perform a quality analysis, analyze for publication bias, or try to combine the results via meta-analysis. In other words, this is a "trust us" type of review, which is okay in this case since the evidence that supports many common uses is sparse and not suitable for formal analysis. Vitamin D supplementation in older people (without regard to their vitamin D levels or risk of osteoporosis) may slightly reduce falls and the number of people who experience a fall. It also reduces hip fractures and other fractures by 10% to 15% in patients with osteoporosis, when given with calcium, though extremely high doses increase the risk. Vitamin D supplementation does not, however, affect the following: (1) respiratory tract infections in Western populations; (2) mental well-being scores in the general population without clear depression, even when vitamin D levels are low (data in patients with depression are conflicting and of poor quality); (3) rheumatoid arthritis, neither as prevention nor treatment; (4) multiple sclerosis symptoms; (5) overall

mortality; or (6) the likelihood of any cancer.
Bottom line: Vitamin D supplementation may reduce falls in older people and, given with calcium, will reduce the risk of hip fracture in women. It does not reduce respiratory tract infection risk, improve mental well-being, affect rheumatoid arthritis or multiple sclerosis, or prevent cancer. Vitamin D levels do not need to be checked in most patients.
Allan GM, Cranston L, Lindblad A, et al. Vitamin D: A narrative review examining the evidence for ten beliefs. J Gen Intern Med 31(7):780-791.

3. Treating low vitamin D levels is ineffective in postmenopausal women

Clinical question: Does vitamin D supplementation in women with low levels of the vitamin affect bone mineral density, muscle mass, strength, or falls risk?
Study design: Randomized Controlled Trials
Setting: Outpatient (any)
Synopsis: These investigators, through community advertising, enrolled a total of 230 postmenopausal women, 90% of whom were white, with an average age of 61 years and baseline vitamin D levels of 14 ng/mL through 27 ng/mL (39 - 67 nmol/L). A "low" 25-hydroxyvitamin D level is typically less than 30 ng/mL (75 nmol/L). The women had low-normal hip T scores of bone mineral density (average -1 SD). Using typical tests of balance and lower extremity strength, the women were at low risk of falls. The women were randomized, using concealed allocation, to receive either placebo, daily vitamin D3 800 IU (20 mcg), or twice- monthly vitamin D3 50,000 IU (125 mcg). The twice-monthly, high-dose group had their vitamin D levels monitored and the dose was increased if levels did not increase to at least 30 ng/mL (75 nmol/L). After 1 year, neither vitamin D treatment regimen changed bone mineral density, muscle mass, functional status, or physical activity. The number of women reporting at least one fall—almost of half of the women—was not different among the groups. The study was only 1 year in length, which should be long enough to see changes in vitamin D levels and muscle mass though perhaps not long enough to see changes in fall rates (if there is a difference). The US Preventive Services Task Force concludes there is insufficient evidence to recommend for or against screening for vitamin deficiency; the National Institute of Health and Care Excellences recommends vitamin D supplementation in members of high-risk groups.
Bottom line: "But her vitamin D level is low! I have to treat it." No, you don't, if your patient is a typical community-dwelling postmenopausal women younger than 75 years. The usual dose of vitamin D, 800 IU (20 mcg) daily, will not increase levels even after a year of therapy and has little effect on calcium absorption or bone mineral density. A high dosage -- 50,000 IU (125 mcg) twice monthly -- will raise levels but is similarly ineffective in improving minimally low bone mineral density, muscle strength, functional status, physical activity, or risk of falls. Not checking vitamin D levels will make it easier not to (ineffectively) treat low levels.
Hansen KE, Johnson RE, Chambers KR, et al. Treatment of vitamin D insufficiency in postmenopausal women: A randomized clinical trial. JAMA Intern Med. 2015;175(10):1612-1621.

3. Long-term use of bisphosphonates increases the risk of fractures in older women

Clinical question: Does long-term use of bisphosphonates increase the risk of fractures in older women?
Study design: Cohort (prospective)
Setting: Population-based
Synopsis: The Women's Health Initiative had 2 components, a randomized trial that busted a bunch of myths about hormone replacement therapy and an observational study with nearly 100,000 women that serves as the basis for this study. These authors pulled a subset of women who had taken an oral bisphosphonate for at least 2 years, had follow-up data, and who had a FRAX score placing their 5-year fracture risk at 1.5% or higher. Additionally the authors excluded women who took medications that affect bone metabolism (eg, calcitonin, parathyroid hormone, aromatase, inhibitors, and so forth). Ultimately, they included 5120 women. They then compared the rate of clinical fractures in women who had taken oral bisphosphonates for only 2 years with those who had taken them for 3 to 5 years, 6 to 9 years, and 10 to 13 years. It would have been helpful if they had included a group of women with no bisphosphonate exposure. The women were, on average, 80 years old. The women had an average of 4 years of follow-up data and reported 127 hip fractures, 159 wrist or forearm fractures, 235 clinical vertebral fractures, and a total of 1313 clinical fractures (presumably hip plus wrist plus forearm plus clinical vertebral plus all other fractures). After taking into account other factors that might influence the rate of fractures, 10 to 13 years of bisphosphonate use was associated with a higher risk of any clinical fracture (but not at any single specific site) than 2 years of use (hazard ratio = 1.29; 95% CI 1.07 - 1.57). There was no significant association between intermediate-term use of bisphosphonates and fracture risk. When the authors only looked at women with a fracture after age 54, the relationship between long-term bisphosphonate use and subsequent fracture remained.
Bottom line: In this cohort study, older women at a high risk of fractures who used oral bisphosphonates for 10 to 13 years had a higher risk of fractures than women who used bisphosphonates for only 2 years.
Drieling RL, LaCroix AZ, Beresford SAA, et al. Long-term oral bisphosphonate therapy and fractures in older women: The Women's Health Initiative. J Am Geriatr Soc 2017;65(9):1924-1931.
Menopause:

4. Transdermal estrogen and progestogen most effective to reduce menopausal vasomotor symptoms

Clinical question: What treatments are most effective for the relief of vasomotor symptoms among naturally menopausal women?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: This meta-analysis of 47 randomized controlled trials (RCTs) was conducted on behalf of the United Kingdom National Institute of Health and Care Excellence for the purpose of clinical guideline development. The authors used a technique called network

meta-analysis, which is suitable for decision-making when multiple treatments are being considered for one indication and the treatments have not been directly compared in the same trials. In this case, the question considered was the effectiveness of pharmacologic and nonpharmacologic treatment for VMS among naturally menopausal women (defined as amenorrhea for at least 12 consecutive months). Trials of nonpharmacological treatments had to be of at least 4 weeks duration and those to assess pharmacologic treatment had to be of at least 12 weeks. The authors considered 26 weeks to be the maximum follow-up time. There were 32 RCTs of 12 treatment classes that assessed the frequency of VMS at the end of treatment, the principal end point considered. Combination treatment with transdermal estrogen and progestogen (E+P) had the highest probability (69%) of being the most effective treatment. The combination of oral E+P had a point estimate suggesting it was similarly effective to transdermal E+P, but with a wide confidence interval. There was strong evidence that transdermal E+P was more effective for relief of VMS than raloxifene, SSRIs, SNRIs, isoflavones, and Chinese herbal medicine. Isoflavones and black cohosh were found to be better than placebo at reducing VMS. There were 21 RCTs that assessed treatment discontinuation. Non-oral E+P had significantly lower odds of discontinuation due to short-term adverse effects than placebo, while SSRIs and SNRIs had higher odds of discontinuation than placebo. The authors intended to assess the effect of treatments on vaginal bleeding, but data from the 5 included trials that assessed that outcome were insufficient to draw conclusions. Long-term adverse effects, such as cardiovascular events and breast cancer, were not assessed.
Bottom line: Transdermal estrogen plus progestogen or oral estrogen plus progestogen are the treatments most likely to effectively reduce the frequency of vasomotor symptoms (VMS) among menopausal women. Isoflavones and black cohosh were found to be better than placebo. Other treatments, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), were not likely to be beneficial and were more likely to be discontinued than placebo.
Sarri G, Pedder H, Dias S, Guo Y, Lumsden MA. Vasomotor symptoms resulting from natural menopause: a systematic review and network meta-analysis of treatment effects from the National Institute for Health and Care Excellence guideline on menopause. BJOG 2017;124(10):1514-1523.

5. Plant-based therapies with soy isoflavones may be effective for menopausal symptoms

Clinical question: Are plant-based therapies, including phytoestrogens, useful in the management of menopausal symptoms?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: Because of the concerns with using hormone replacement therapy many women use complementary therapies to treat menopausal symptoms. These investigators thoroughly searched multiple databases including MEDLINE, EMBASE, and the Cochrane CENTRAL registry for randomized trials that assessed the effects of plant-based therapy compared with placebo or no treatment in perimenopausal, menopausal, and postmenopausal women. Outcomes of interest included hot flashes, night sweats, and vaginal dryness. Two independent reviewers assessed individual studies for inclusion criteria and methodologic quality using standard risk-of-bias scoring tools. Disagreements were resolved by consensus discussion with a third independent reviewer. Overall, most of the studies showed a moderate to high risk of bias. A total of 62 studies (N = 6653) met the inclusion criteria, including 36 studies of phytoestrogens, 16 of black cohosh, and 10 of various medicinal herbs. Duration of interventions ranged from 4 weeks to 2 years. Overall, phytoestrogen use was associated with a significant reduction in the number of daily hot flashes (-1.31; 95% CI -2.01 to -0.61) and vaginal dryness (mean difference of change from baseline on a 4-point scale: -0.31; -0.52 to -0.10, with higher numbers indicating worse symptoms). There were no significant changes reported in night sweats with phytoestrogen use. In particular, soy isoflavone use alone or as a supplement replicated the findings of the combined analyses of phytoestrogens, whereas red clover did not significantly reduce hot flashes or vaginal dryness. Black cohosh use was also not significantly associated with changes in the number of daily hot flashes, vaginal dryness, or number of night sweats. Results were mixed regarding the use of evening primrose, flaxseed, St. John's wort, wheat germ, and Chinese medicinal herbs. A statistical analysis did show a significant amount of heterogeneity in the results between the different studies. Minimal, if any, evidence of publication bias existed for phytoestrogens.
Bottom line: This meta-analysis found some evidence that phytoestrogens, especially dietary and supplemental soy isoflavones, are significantly associated with improvement in daily hot flashes and vaginal dryness in women with menopausal symptoms. No evidence of a benefit was found for red clover or black cohosh. The overall quality of the evidence was poor, with a moderate to high risk of bias and significant hetereogeneity among the included studies.
Franco OH, Chowdhury R, Troup J, et al. Use of plant-based therapies and menopausal symptoms. A systematic review and meta-analysis. JAMA 2016;315(23):2554-263.

6. Duration of vasomotor symptoms can be quite long during menopause

Clinical question: How long can women expect the vasomotor symptoms associated with menopause to last?
Study design: Cohort (prospective)
Setting: Population-based
Synopsis: These investigators enrolled 1449 women identified at 7 sites across the United States. The women were between the ages of 42 and 52 years, reported a menstrual cycle in the 3 months before screening, and were not taking oral contraceptives or hormone therapy. The women were followed up for 13 years. The median duration of vasomotor symptoms was 7.4 years for all women. Women who were premenopausal or early perimenopausal when they first reported frequent vasomotor symptoms (occurring on at least 6 days over 2 weeks) had a median duration of more than 11.8 years, including a median 9.4 years following their final menstrual period. Some women continued to have symptoms at the end of the 13 years of study. Women who were postmenopausal at the onset of vasomotor symptoms experience these symptoms for a median 3.4 years. African-American women reported the longest total duration (median 10.1 years) and Japanese and Chinese women had the shortest total durations (median 4.8 - 5.4 years). For the 881 women for whom a final menstrual period could be determined, the median duration was 4.5 years following this final menstrual period. Perceived stress

and depressive symptoms were associated with an increase in vasomotor symptom duration (hazard ratio 0.75 and 0.66, respectively).
Bottom line: Vasomotor symptoms last a median 7.4 years in women progressing through menopause. Women who begin to have frequent symptoms early (during premenopause or perimenopause) will experience symptoms for a median of 11.8 years, including 9.4 years after their final menstrual period. African-American women will experience vasomotor symptoms longer (median 10.1 years), but symptoms disappear more quickly in Japanese and Chinese women (median ~5 years).
Avis NE, Crawford SL, Greendale G, et al, for the Study of Women's Health Across the Nation (SWAN). Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med. 2015;175(4):531-539.

7. Long-term hormone therapy for perimenopausal and postmenopausal women.

Background: Hormone therapy (HT) is widely provided for control of menopausal symptoms and has been used for the management and prevention of cardiovascular disease, osteoporosis and dementia in older women. This is an updated version of a Cochrane review first published in 2005.
Objectives: To assess effects of long-term HT (at least 1 year's duration) on mortality, cardiovascular outcomes, cancer, gallbladder disease, fracture and cognition in perimenopausal and postmenopausal women during and after cessation of treatment.
Search methods: We searched the following databases to September 2016: Cochrane Gynaecology and Fertility Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and PsycINFO. We searched the registers of ongoing trials and reference lists provided in previous studies and systematic reviews.
Selection criteria: We included randomised double-blinded studies of HT versus placebo, taken for at least 1 year by perimenopausal or postmenopausal women. HT included oestrogens, with or without progestogens, via the oral, transdermal, subcutaneous or intranasal route.
Data collection and analysis: Two review authors independently selected studies, assessed risk of bias and extracted data. We calculated risk ratios (RRs) for dichotomous data and mean differences (MDs) for continuous data, along with 95% confidence intervals (CIs). We assessed the quality of the evidence by using GRADE methods.
Main results: We included 22 studies involving 43,637 women. We derived nearly 70% of the data from two well-conducted studies (HERS 1998; WHI 1998). Most participants were postmenopausal American women with at least some degree of comorbidity, and mean participant age in most studies was over 60 years. None of the studies focused on perimenopausal women. In relatively healthy postmenopausal women (i.e. generally fit, without overt disease), combined continuous HT increased the risk of a coronary event (after 1 year's use: from 2 per 1000 to between 3 and 7 per 1000), venous thromboembolism (after 1 year's use: from 2 per 1000 to between 4 and 11 per 1000), stroke (after 3 years' use: from 6 per 1000 to between 6 and 12 per 1000), breast cancer (after 5.6 years' use: from 19 per 1000 to between 20 and 30 per 1000), gallbladder disease (after 5.6 years' use: from 27 per 1000 to between 38 and 60 per 1000) and death from lung cancer (after 5.6 years' use plus 2.4 years' additional follow-up: from 5 per 1000 to between 6 and 13 per 1000). Oestrogen-only HT increased the risk of venous thromboembolism (after 1 to 2 years' use: from 2 per 1000 to 2 to 10 per 1000; after 7 years' use: from 16 per 1000 to 16 to 28 per 1000), stroke (after 7 years' use: from 24 per 1000 to between 25 and 40 per 1000) and gallbladder disease (after 7 years' use: from 27 per 1000 to between 38 and 60 per 1000) but reduced the risk of breast cancer (after 7 years' use: from 25 per 1000 to between 15 and 25 per 1000) and clinical fracture (after 7 years' use: from 141 per 1000 to between 92 and 113 per 1000) and did not increase the risk of coronary events at any follow-up time.Women over 65 years of age who were relatively healthy and taking continuous combined HT showed an increase in the incidence of dementia (after 4 years' use: from 9 per 1000 to 11 to 30 per 1000). Among women with cardiovascular disease, use of combined continuous HT significantly increased the risk of venous thromboembolism (at 1 year's use: from 3 per 1000 to between 3 and 29 per 1000). Women taking HT had a significantly decreased incidence of fracture with long-term use. Risk of fracture was the only outcome for which strong evidence showed clinical benefit derived from HT (after 5.6 years' use of combined HT: from 111 per 1000 to between 79 and 96 per 1000; after 7.1 years' use of oestrogen-only HT: from 141 per 1000 to between 92 and 113 per 1000). Researchers found no strong evidence that HT has a clinically meaningful impact on the incidence of colorectal cancer. One trial analysed subgroups of 2839 relatively healthy women 50 to 59 years of age who were taking combined continuous HT and 1637 who were taking oestrogen-only HT versus similar-sized placebo groups. The only significantly increased risk reported was for venous thromboembolism in women taking combined continuous HT: Their absolute risk remained low, at less than 1/500. However, other differences in risk cannot be excluded, as this study was not designed to have the power to detect differences between groups of women within 10 years of menopause. For most studies, risk of bias was low in most domains. The overall quality of evidence for the main comparisons was moderate. The main limitation in the quality of evidence was that only about 30% of women were 50 to 59 years old at baseline, which is the age at which women are most likely to consider HT for vasomotor symptoms.
Authors' conclusions: Women with intolerable menopausal symptoms may wish to weigh the benefits of symptom relief against the small absolute risk of harm arising from short-term use of low-dose HT, provided they do not have specific contraindications. HT may be unsuitable for some women, including those at increased risk of cardiovascular disease, increased risk of thromboembolic disease (such as those with obesity or a history of venous thrombosis) or increased risk of some types of cancer (such as breast cancer, in women with a uterus). The risk of endometrial cancer among women with a uterus taking oestrogen-only HT is well documented. HT is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for prevention of deterioration of cognitive function in postmenopausal women. Although HT is considered effective for the prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk for whom non-oestrogen therapies are unsuitable. Data are insufficient for assessment of the risk of long-term HT use in perimenopausal women and in postmenopausal women younger than 50 years of age.
Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD004143. DOI: 10.1002/14651858.CD004143.pub5.

8. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials.

Objective: To examine total and cause-specific cumulative mortality, including during the intervention and extended post-intervention follow-up, of the 2 Women's Health Initiative hormone therapy trials.
Design, Setting, and Participants: Observational follow-up of US multiethnic postmenopausal women aged 50 to 79 years enrolled in 2 randomized clinical trials between 1993 and 1998 and followed up through December 31, 2014.
Interventions: Conjugated equine estrogens (CEE, 0.625 mg/d) plus medroxyprogesterone acetate (MPA, 2.5 mg/d) (n = 8506) vs placebo (n = 8102) for 5.6 years (median) or CEE alone (n = 5310) vs placebo (n = 5429) for 7.2 years (median).
Main Outcomes and Measures: All-cause mortality (primary outcome) and cause-specific mortality (cardiovascular disease mortality, cancer mortality, and other major causes of mortality) in the 2 trials pooled and in each trial individually, with prespecified analyses by 10-year age group based on age at time of randomization.
Results: Among 27 347 women who were randomized (baseline mean [SD] age, 63.4 [7.2] years; 80.6% white), mortality follow-up was available for more than 98%. During the cumulative 18-year follow-up, 7489 deaths occurred (1088 deaths during the intervention phase and 6401 deaths during postintervention follow-up). All-cause mortality was 27.1% in the hormone therapy group vs 27.6% in the placebo group (hazard ratio [HR], 0.99 [95% CI, 0.94-1.03]) in the overall pooled cohort; with CEE plus MPA, the HR was 1.02 (95% CI, 0.96-1.08); and with CEE alone, the HR was 0.94 (95% CI, 0.88-1.01). In the pooled cohort for cardiovascular mortality, the HR was 1.00 (95% CI, 0.92-1.08 [8.9 % with hormone therapy vs 9.0% with placebo]); for total cancer mortality, the HR was 1.03 (95% CI, 0.95-1.12 [8.2 % with hormone therapy vs 8.0% with placebo]); and for other causes, the HR was 0.95 (95% CI, 0.88-1.02 [10.0% with hormone therapy vs 10.7% with placebo]), and results did not differ significantly between trials. When examined by 10-year age groups comparing younger women (aged 50-59 years) to older women (aged 70-79 years) in the pooled cohort, the ratio of nominal HRs for all-cause mortality was 0.61 (95% CI, 0.43-0.87) during the intervention phase and the ratio was 0.87 (95% CI, 0.76-1.00) during cumulative 18-year follow-up, without significant heterogeneity between trials.
Conclusions and Relevance: *Among postmenopausal women, hormone therapy with CEE plus MPA for a median of 5.6 years or with CEE alone for a median of 7.2 years was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.*
Manson, J.E., Aragaki, A.K., Rossouw, J.E., Anderson, G.L., Prentice, R.L. (2017). Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the women's health initiative randomized trials. JAMA, 318 (10). 927-938.

Dysmenorrhea:

9. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea

Background: Dysmenorrhoea is a common gynaecological problem consisting of painful cramps accompanying menstruation, which in the absence of any underlying abnormality is known as primary dysmenorrhoea. Research has shown that women with dysmenorrhoea have high levels of prostaglandins, hormones known to cause cramping abdominal pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) are drugs that act by blocking prostaglandin production. They inhibit the action of cyclooxygenase (COX), an enzyme responsible for the formation of prostaglandins. The COX enzyme exists in two forms, COX-1 and COX-2. Traditional NSAIDs are considered 'non-selective' because they inhibit both COX-1 and COX-2 enzymes. More selective NSAIDs that solely target COX-2 enzymes (COX-2-specific inhibitors) were launched in 1999 with the aim of reducing side effects commonly reported in association with NSAIDs, such as indigestion, headaches and drowsiness.
Objectives: To determine the effectiveness and safety of NSAIDs in the treatment of primary dysmenorrhoea.
Search methods: We searched the following databases in January 2015: Cochrane Menstrual Disorders and Subfertility Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL, November 2014 issue), MEDLINE, EMBASE and Web of Science. We also searched clinical trials registers (ClinicalTrials.gov and ICTRP). We checked the abstracts of major scientific meetings and the reference lists of relevant articles.
Selection criteria: All randomised controlled trial (RCT) comparisons of NSAIDs versus placebo, other NSAIDs or paracetamol, when used to treat primary dysmenorrhoea.
Data collection and analysis: Two review authors independently selected the studies, assessed their risk of bias and extracted data, calculating odds ratios (ORs) for dichotomous outcomes and mean differences for continuous outcomes, with 95% confidence intervals (CIs). We used inverse variance methods to combine data. We assessed the overall quality of the evidence using GRADE methods.
Main results: We included 80 randomised controlled trials (5820 women). They compared 20 different NSAIDs (18 non-selective and two COX-2-specific) versus placebo, paracetamol or each other.
NSAIDs versus placebo: Among women with primary dysmenorrhoea, NSAIDs were more effective for pain relief than placebo (OR 4.37, 95% CI 3.76 to 5.09; 35 RCTs, I2 = 53%, low quality evidence). This suggests that if 18% of women taking placebo achieve moderate or excellent pain relief, between 45% and 53% taking NSAIDs will do so. However, NSAIDs were associated with more adverse effects (overall adverse effects: OR 1.29, 95% CI 1.11 to 1.51, 25 RCTs, I2 = 0%, low quality evidence; gastrointestinal adverse effects: OR 1.58, 95% CI 1.12 to 2.23, 14 RCTs, I2 = 30%; neurological adverse effects: OR 2.74, 95% CI 1.66 to 4.53, seven RCTs, I2 = 0%, low quality evidence). The evidence suggests that if 10% of women taking placebo experience side effects, between 11% and 14% of women taking NSAIDs will do so. NSAIDs versus other NSAIDs: When NSAIDs were compared with each other there was little evidence of the superiority of any individual NSAID for either pain relief or safety. However, the available evidence had little power to detect such differences, as most individual comparisons were based on very few small trials. Non-selective NSAIDs versus COX-2-specific selectors: Only two of the included studies utilised COX-2-specific inhibitors (etoricoxib and celecoxib). There was no evidence that COX-2-specific inhibitors were more effective or tolerable for the treatment of dysmenorrhoea than traditional NSAIDs;

however data were very scanty. NSAIDs versus paracetamol: NSAIDs appeared to be more effective for pain relief than paracetamol (OR 1.89, 95% CI 1.05 to 3.43, three RCTs, I2 = 0%, low quality evidence). There was no evidence of a difference with regard to adverse effects, though data were very scanty. Most of the studies were commercially funded (59%); a further 31% failed to state their source of funding.
Authors' conclusions: NSAIDs appear to be a very effective treatment for dysmenorrhoea, though women using them need to be aware of the substantial risk of adverse effects. There is insufficient evidence to determine which (if any) individual NSAID is the safest and most effective for the treatment of dysmenorrhoea. We rated the quality of the evidence as low for most comparisons, mainly due to poor reporting of study methods.
Marjoriebanks, J., Ayeleke, R.O., Farquhar, C., Proctor, M. (2015). Nonsteroidal anti-inflammatory drugs for dysmenorrhea. Cochrane Database of Systematic Reviews, 2015(7). Art. No.: CD001751. DOI: 10.1002/14651858.CD001751.pub3.

10. Effect of transcutaneous electrical nerve stimulation therapy for the treatment of primary dysmenorrheal.

Background:This study aimed to investigate the effect and safety of transcutaneous electrical nerve stimulation (TENS) therapy for relieving pain in women with primary dysmenorrhea (PD).
Methods: In this study, 134 participants with PD were randomly divided into the intervention group and the sham group, with 67 participants in each group. Participants in the intervention group received TENS, whereas those in the sham group received sham TENS. The primary outcome was measured by the Numeric Rating Scale (NRS). The secondary outcomes were measured by the duration of relief from dysmenorrheal pain, number of ibuprofen tablets taken, and the World Health Organization quality of life (WHOQOL)-BREF score, as well as the adverse events.
Results: A total of 122 participants completed the study. Compared to sham TENS, TENS showed a greater effect in pain relief with regard to the NRS (P<.01), duration of relief from dysmenorrheal pain (P<.01), and number of ibuprofen tablets taken (P<.01). However, no significant differences in the quality of life, measured by the WHOQOL-BREF score, were found between 2 groups. The adverse event profiles were also similar between 2 groups.
Conclusion: TENS was efficacious and safe in relieving pain in participants with PD.
Bai, H.Y., Bai, H.Y., Yang, Z.Q. (2017). Effect of transcutaneous electrical nerve stimulation therapy for the treatment of primary dysmenorrheal. Medicine (Baltimore), 96(36).

11. Dietary supplements for dysmenorrhea

Background: Dysmenorrhoea refers to painful menstrual cramps and is a common gynaecological complaint. Conventional treatments include non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptive pills (OCPs), which both reduce myometrial activity (contractions of the uterus). A suggested alternative approach is dietary supplements. We used the term 'dietary supplement' to include herbs or other botanical, vitamins, minerals, enzymes, and amino acids. We excluded traditional Chinese medicines.
Objectives: To determine the efficacy and safety of dietary supplements for treating dysmenorrhoea.
Search methods: We searched sources including the Cochrane Gynaecology and Fertility Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, AMED, PsycINFO (all from inception to 23 March 2015), trial registries, and the reference lists of relevant articles.
Selection criteria: We included randomised controlled trials (RCTs) of dietary supplements for moderate or severe primary or secondary dysmenorrhoea. We excluded studies of women with an intrauterine device. Eligible comparators were other dietary supplements, placebo, no treatment, or conventional analgesia.
Data collection and analysis: Two review authors independently performed study selection, performed data extraction and assessed the risk of bias in the included trials. The primary outcomes were pain intensity and adverse effects. We used a fixed-effect model to calculate odds ratios (ORs) for dichotomous data, and mean differences (MDs) or standardised mean differences (SMDs) for continuous data, with 95% confidence intervals (CIs). We presented data that were unsuitable for analysis either descriptively or in additional tables. We assessed the quality of the evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods.
Main results: We included 27 RCTs (3101 women). Most included studies were conducted amongst cohorts of students with primary dysmenorrhoea in their late teens or early twenties. Twenty-two studies were conducted in Iran and the rest were performed in other middle-income countries. Only one study addressed secondary dysmenorrhoea. Interventions included 12 different herbal medicines (German chamomile (*Matricaria chamomilla, M recutita, Chamomilla recutita)*, cinnamon (*Cinnamomum zeylanicum, C. verum)*, Damask rose (*Rosa damascena),* dill (*Anethum graveolens*), fennel (*Foeniculum vulgare*), fenugreek (*Trigonella foenum-graecum*), ginger (*Zingiber* officinale), guava (Psidium guajava), rhubarb (Rheum emodi), uzara (Xysmalobium undulatum), valerian (Valeriana officinalis), and zataria (Zataria multiflora)) and five non-herbal supplements (fish oil, melatonin, vitamins B1 and E, and zinc sulphate) in a variety of formulations and doses. Comparators included other supplements, placebo, no treatment, and NSAIDs. We judged all the evidence to be of low or very low quality. The main limitations were imprecision due to very small sample sizes, failure to report study methods, and inconsistency. For most comparisons there was only one included study, and very few studies reported adverse effects.
Effectiveness of supplements for primary dysmenorrhea: We have presented pain scores (all on a visual analogue scale (VAS) 0 to 10 point scale) or rates of pain relief, or both, at the first post-treatment follow-up.
Supplements versus placebo or no treatment: There was no evidence of effectiveness for vitamin E (MD 0.00 points, 95% CI −0.34 to 0.34; two RCTs, 135 women).There was no consistent evidence of effectiveness for dill (MD -1.15 points, 95% CI −2.22 to −0.08, one RCT, 46 women), guava (MD 0.59, 95% CI −0.13 to 1.31; one RCT, 151 women); one RCT, 73 women), or fennel (MD −0.34 points, 95% CI −0.74 to 0.06; one RCT, 43 women).There was very limited evidence of effectiveness for fenugreek (MD −1.71 points, 95% CI −2.35 to −1.07; one RCT, 101 women), fish oil (MD 1.11 points, 95% CI 0.45 to 1.77; one RCT, 120 women), fish oil plus vitamin B1

(MD −1.21 points, 95% CI −1.79 to −0.63; one RCT, 120 women), ginger (MD −1.55 points, 95% CI −2.43 to −0.68; three RCTs, 266 women; OR 5.44, 95% CI 1.80 to 16.46; one RCT, 69 women), valerian (MD −0.76 points, 95% CI −1.44 to −0.08; one RCT, 100 women), vitamin B1 alone (MD −2.70 points, 95% CI −3.32 to −2.08; one RCT, 120 women), zataria (OR 6.66, 95% CI 2.66 to 16.72; one RCT, 99 women), and zinc sulphate (MD −0.95 points, 95% CI −1.54 to −0.36; one RCT, 99 women).Data on chamomile and cinnamon versus placebo were unsuitable for analysis.
Supplements versus NSAIDS: There was no evidence of any difference between NSAIDs and dill (MD 0.13 points, 95% CI −1.01 to 1.27; one RCT, 47 women), fennel (MD −0.70 points, 95% CI −1.81 to 0.41; one RCT, 59 women), guava (MD 1.19, 95% CI 0.42 to 1.96; one RCT, 155 women), rhubarb (MD −0.20 points, 95% CI −0.44 to 0.04; one RCT, 45 women), or valerian (MD points 0.62 , 95% CI 0.03 to 1.21; one RCT, 99 women),
There was no consistent evidence of a difference between Damask rose and NSAIDs (MD −0.15 points, 95% CI −0.55 to 0.25; one RCT, 92 women). There was very limited evidence that chamomile was more effective than NSAIDs (MD −1.42 points, 95% CI −1.69 to −1.15; one RCT, 160 women).
Supplements versus other supplements: There was no evidence of a difference in effectiveness between ginger and zinc sulphate (MD 0.02 points, 95% CI −0.58 to 0.62; one RCT, 101 women). Vitamin B1 may be more effective than fish oil (MD −1.59 points, 95% CI −2.25 to −0.93; one RCT, 120 women).
Effectiveness of supplements for secondary dysmenorrhea: There was no strong evidence of benefit for melatonin compared to placebo for dysmenorrhoea secondary to endometriosis (data were unsuitable for analysis).
Safety of supplements: Only four of the 27 included studies reported adverse effects in both treatment groups. There was no evidence of a difference between the groups but data were too scanty to reach any conclusions about safety.
Authors' conclusions: There is no high quality evidence to support the effectiveness of any dietary supplement for dysmenorrhoea, and evidence of safety is lacking. However for several supplements there was some low quality evidence of effectiveness and more research is justified.

Sexual Dysfunction

12. Flibanserin ineffective for hypoactive sexual desire disorder in women

Clinical question: Is flibanserin a safe and effective treatment of hypoactive sexual desire disorder in premenopausal women?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: To assemble studies for inclusion, these authors searched 3 trial registries and 13 electronic databases, including the Cochrane Library, along with reference lists of retrieved articles to identify randomized studies. They included studies published in any language. Two researchers independently identified the studies for inclusion; data were extracted by one reviewer and checked by another. They included 5 published and 3 unpublished studies that enrolled a total of 5914 premenopausal and postmenopausal women. The overall study quality was low: many women dropped out, some authors shifted endpoints mid-study, and some authors used the "last observation carried forward." Benefit was statistically significant but clinically minimal for most outcomes. On average across the studies, treatment, as compared with placebo, resulted in one additional satisfying sexual event every 2 months. Diary scores for sexual desire increased from 1.7 to 2.30 points on a scale of 0 to 84 (4 studies) and scores on the female sexual function index increased an average of 0.2 to 0.4 on a scale of 1.2 to 6.0. There was either minimal or no change in the women's mean global impression of improvement. Patients who received treatment were twice as likely to drop out because of adverse effects, including dizziness, which was 4 times more likely in that group.
Bottom line: Flibanserin (Addyi) produces a minimal effect on sexual desire and minimally increases the number of satisfying sexual events in women (less than 1/2 an event per month increase). Many women will be unable to tolerate the side effects.
Jaspers L, Feys F, Bramer WM, Franco OH, Leusink P, Laan ET. Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder in women: A systematic review and meta-analysis. JAMA Intern Med 2016;176(4):453-462.

Fibroids

13. Imaging for Polyps and Leiomyomas in Women With Abnormal Uterine Bleeding: A Systematic Review.

Objective: To evaluate the accuracy of saline infusion sonohysterography in comparison with transvaginal ultrasonography for diagnosing polyps and submucosal leiomyomas in women with abnormal uterine bleeding.
Data sources: We searched the databases MEDLINE, EMBASE, CENTRAL, and ClinicalTrials.gov as well as citations and reference lists to the end of November 2015.
Methods of Study Selection: Two authors screened 5,347 citations for eligibility. We included randomized controlled trials or prospective cohort studies published in English, assessing the accuracy of saline infusion sonohysterography and transvaginal ultrasonography for diagnosing polyps and submucosal leiomyomas in women with abnormal uterine bleeding. We considered studies using histopathologic specimens obtained at either hysteroscopy or hysterectomy as criterion standard.
Tabulation, Integration, and Results: Twenty-five studies were eligible. Two authors extracted data and assessed the quality of included studies. Bivariate random-effects models were used to compare the different tests and evaluate sources of heterogeneity. Saline infusion sonohysterography was superior to transvaginal ultrasonography with pooled sensitivity and specificity of 0.92 and 0.89 compared with 0.64 and 0.90, respectively (P<.001). Transvaginal ultrasound sensitivity for diagnosing polyps was particularly low

(0.51). Saline infusion sonohysterography was also compared with hysteroscopy in seven studies and had similar sensitivity but inferior specificity (0.93 and 0.83 compared with 0.95 and 0.90, respectively, P=.007). All three procedures were well-tolerated by women. Saline infusion sonohysterography was successfully completed in 95% of women. Technical variations such as the use of balloon catheters were not found to affect diagnostic accuracy.
Conclusion: Transvaginal ultrasonography lacks sensitivity to be used alone to exclude the presence of polyps and leiomyomas in women with abnormal uterine bleeding. Although less specific than hysteroscopy, saline infusion sonohysterography offers a similar detection rate and permits concomitant visualization of the ovaries and myometrium. Cost, convenience, and tolerability of different imaging techniques require further evaluation.
Maheux-Lacroix, S., Li, F., Laberge, P,Y., Abbott, J. (2016) Imaging for polyps and leiomyomas in women with abnormal uterine bleeding: a systemic review. Obstet Gynecol 128(6). 1425-1436.

14. Uterine artery embolization for symptomatic uterine fibroids

Objectives: To review the benefits and risks of uterine artery embolization (UAE) versus other medical or surgical interventions for symptomatic uterine fibroids.
Search methods: We searched sources including the Cochrane Menstrual Disorders and Subfertility Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and trial registries. The search was last conducted in April 2014. We contacted authors of eligible randomised controlled trials to request unpublished data.
Selection criteria: Randomised controlled trials (RCTs) of UAE versus any medical or surgical therapy for symptomatic uterine fibroids. The primary outcomes of the review were patient satisfaction and live birth rate (among women seeking live birth).
Data collection and analysis: Two of the authors (AS and JKG) independently selected studies, assessed quality and extracted data. Evidence quality was assessed using GRADE methods.
Main results: Seven RCTs with 793 women were included in this review. Three trials compared UAE with abdominal hysterectomy, two trials compared UAE with myomectomy, and two trials compared UAE with either type of surgery (53 hysterectomies and 62 myomectomies).With regard to patient satisfaction rates, our findings were consistent with satisfaction rates being up to 41% lower or up to 48% higher with UAE compared to surgery within 24 months of having the procedure (odds ratio (OR) 0.94; 95% confidence interval (CI) 0.59 to 1.48, 6 trials, 640 women, I2 = 5%, moderate quality evidence). Findings were also inconclusive at five years of follow-up (OR 0.90; 95% CI 0.45 to 1.80, 2 trials, 295 women, I2 = 0%, moderate quality evidence). There was some indication that UAE may be associated with less favourable fertility outcomes than myomectomy, but it was very low quality evidence from a subgroup of a single study and should be regarded with extreme caution (live birth: OR 0.26; 95% CI 0.08 to 0.84; pregnancy: OR 0.29; 95% CI 0.10 to 0.85, 1 study, 66 women).Similarly, for several safety outcomes our findings showed evidence of a substantially higher risk of adverse events in either arm or of no difference between the groups. This applied to intra-procedural complications (OR 0.91; 95% CI 0.42 to 1.97, 4 trials, 452 women, I2 = 40%, low quality evidence), major complications within one year (OR 0.65; 95% CI 0.33 to 1.26, 5 trials, 611 women, I2 = 4%, moderate quality evidence) and major complications within five years (OR 0.56; CI 0.27 to 1.18, 2 trials, 268 women). However, the rate of minor complications within one year was higher in the UAE group (OR 1.99; CI 1.41 to 2.81, 6 trials, 735 women, I2 = 0%, moderate quality evidence) and two trials found a higher minor complication rate in the UAE group at up to five years (OR 2.93; CI 1.73 to 4.93, 2 trials, 268 women).UAE was associated with a higher rate of further surgical interventions (re-interventions within 2 years: OR 3.72; 95% CI 2.28 to 6.04, 6 trials, 732 women, I2 = 45%, moderate quality evidence; within 5 years: OR 5.79; 95% CI 2.65 to 12.65, 2 trials, 289 women, I2 = 65%). If we assumed that 7% of women will require further surgery within two years of hysterectomy or myomectomy, between 15% and 32% will require further surgery within two years of UAE.The evidence suggested that women in the UAE group were less likely to require a blood transfusion than women receiving surgery (OR 0.07; 95% CI 0.01 to 0.52, 2 trials, 277 women, I2 = 0%). UAE was also associated with a shorter procedural time (two studies), shorter length of hospital stay (seven studies) and faster resumption of usual activities (six studies) in all studies that measured these outcomes; however, most of these data could not be pooled due to heterogeneity between the studies.The quality of the evidence varied, and was very low for live birth, moderate for satisfaction ratings, and moderate for most safety outcomes. The main limitations in the evidence were serious imprecision due to wide confidence intervals, failure to clearly report methods, and lack of blinding for subjective outcomes.
Authors' conclusions: When we compared patient satisfaction rates at up to two years following UAE versus surgery (myomectomy or hysterectomy) our findings are that there is no evidence of a difference between the interventions. Findings at five year follow-up were similarly inconclusive. There was very low quality evidence to suggest that myomectomy may be associated with better fertility outcomes than UAE, but this information was only available from a selected subgroup in one small trial.We found no clear evidence of a difference between UAE and surgery in the risk of major complications, but UAE was associated with a higher rate of minor complications and an increased likelihood of requiring surgical intervention within two to five years of the initial procedure. If we assume that 7% of women will require further surgery within two years of hysterectomy or myomectomy, between 15% and 32% will require further surgery within two years of UAE. This increase in the surgical re-intervention rate may balance out any initial cost advantage of UAE. Thus although UAE is a safe, minimally invasive alternative to surgery, patient selection and counselling are paramount due to the much higher risk of requiring further surgical intervention.
Gupta, J.K., Sinha, A., Lumsden, M.A., Hickey, M. (2014). Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database of Systemic Reviews, 2014(12). CD005073. DOI: 10.1002/14651858.CD005073.pub4.

Vaginal atrophy

15. Local oestrogen for vaginal atrophy in postmenopausal women

Background: Vaginal atrophy is a frequent complaint of postmenopausal women; symptoms include vaginal dryness, itching, discomfort and painful intercourse. Systemic treatment for these symptoms in the form of oral hormone replacement therapy is not always necessary. An alternative choice is oestrogenic preparations administered vaginally (in the form of creams, pessaries, tablets and the oestradiol-releasing ring). This is an update of a Chochrane systematic review; the original version was first published in October 2006.
Objectives: The objective of this review was to compare the efficacy and safety of intra-vaginal oestrogenic preparations in relieving the symptoms of vaginal atrophy in postmenopausal women.
Search methods: We searched the following databases and trials registers to April 2016: Cochrane Gynaecology and Fertility Group Register of trials, The Cochrane Central Register of Controlled Trials (CENTRAL; 2016 issue 4), MEDLINE, Embase, PsycINFO, DARE, the Web of Knowledge, OpenGrey, LILACS, PubMed and reference lists of articles. We also contacted experts and researchers in the field.
Selection criteria: The inclusion criteria were randomised comparisons of oestrogenic preparations administered intravaginally in postmenopausal women for at least 12 weeks for the treatment of symptoms resulting from vaginal atrophy or vaginitis.
Data collection and analysis: Two review authors independently assessed trial eligibility and risk of bias and extracted the data. The primary review outcomes were improvement in symptoms (participant-assessed), and the adverse event endometrial thickness. Secondary outcomes were improvement in symptoms (clinician-assessed), other adverse events (breast disorders e.g. breast pain, enlargement or engorgement, total adverse events, excluding breast disorders) and adherence to treatment. We combined data to calculate pooled risk ratios (RRs) (dichotomous outcomes) and mean differences (MDs) (continuous outcomes) and 95% confidence intervals (CIs). Statistical heterogeneity was assessed using the I2 statistic. We assessed the overall quality of the evidence for the main comparisons using GRADE methods.
Main results: We included 30 RCTs (6235 women) comparing different intra-vaginal oestrogenic preparations with each other and with placebo. The evidence was low to moderate quality; limitations were poor reporting of study methods and serious imprecision (effect estimates with wide confidence intervals)
1. Oestrogen ring versus other regimens. Other regimens included oestrogen cream, oestrogen tablets and placebo. There was no evidence of a difference in improvement in symptoms (participant assessment) either between oestrogen ring and oestrogen cream (odds ratio (OR) 1.33, 95% CI 0.80 to 2.19, two RCTs, n = 341, I2 = 0%, low-quality evidence) or between oestrogen ring and oestrogen tablets (OR 0.78, 95% CI 0.53 to 1.15, three RCTs, n = 567, I2 = 0%, low-quality evidence). However, a higher proportion of women reported improvement in symptoms following treatment with oestrogen ring compared with placebo (OR 12.67, 95% CI 3.23 to 49.66, one RCT, n = 67). With respect to endometrial thickness, a higher proportion of women who received oestrogen cream showed evidence of increase in endometrial thickness compared to those who were treated with oestrogen ring (OR 0.36, 95% CI 0.14 to 0.94, two RCTs, n = 273; I2 = 0%, low-quality evidence). This may have been due to the higher doses of cream used. 2. Oestrogen tablets versus other regimens. Other regimens in this comparison included oestrogen cream, and placebo. There was no evidence of a difference in the proportions of women who reported improvement in symptoms between oestrogen tablets and oestrogen cream (OR 1.06, 95% CI 0.55 to 2.01, two RCTs, n = 208, I2 = 0% low-quality evidence). A higher proportion of women who were treated with oestrogen tablets reported improvement in symptoms compared to those who received placebo using a fixed-effect model (OR 12.47, 95% CI 9.81 to 15.84, two RCTs, n = 1638, I2 = 83%, low-quality evidence); however, using a random-effect model did not demonstrate any evidence of a difference in the proportions of women who reported improvement between the two treatment groups (OR 5.80, 95% CI 0.88 to 38.29). There was no evidence of a difference in the proportions of women with increase in endometrial thickness between oestrogen tablets and oestrogen cream (OR 0.31, 95% CI 0.06 to 1.60, two RCTs, n = 151, I2 = 0%, low-quality evidence).
3. Oestrogen cream versus other regimens. Other regimens identified in this comparison included isoflavone gel and placebo. There was no evidence of a difference in the proportions of women with improvement in symptoms between oestrogen cream and isoflavone gel (OR 2.08, 95% CI 0.08 to 53.76, one RCT, n = 50, low-quality evidence). However, there was evidence of a difference in the proportions of women with improvement in symptoms between oestrogen cream and placebo with more women who received oestrogen cream reporting improvement in symptoms compared to those who were treated with placebo (OR 4.10, 95% CI 1.88 to 8.93, two RCTs, n = 198, I2 = 50%, low-quality evidence). None of the included studies in this comparison reported data on endometrial thickness.
Authors' conclusions: There was no evidence of a difference in efficacy between the various intravaginal oestrogenic preparations when compared with each other. However, there was low-quality evidence that intra-vaginal oestrogenic preparations improve the symptoms of vaginal atrophy in postmenopausal women when compared to placebo. There was low-quality evidence that oestrogen cream may be associated with an increase in endometrial thickness compared to oestrogen ring; this may have been due to the higher doses of cream used. However there was no evidence of a difference in the overall body of evidence in adverse events between the various oestrogenic preparations compared with each other or with placebo.
Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD001500. DOI: 10.1002/14651858.CD001500.pub3.

Contraception:

16. Free contraception associated with reduced long-term pregnancy and birth rates in teens (CHOICE study)

Clinical question: Does education about contraceptive alternatives and the provision of free contraception, including long-acting reversible methods, reduce pregnancy and birth rates in teens?
Study design: Cohort (prospective)
Setting: Population-based
Synopsis: This was a cohort study that enrolled 1404 adolescents between the ages of 14 and 19 years between 2007 and 2011 in metropolitan St. Louis, Missouri. The patents were all sexually active and were either not currently using contraception or were interested in switching to a new, reversible method. Demographically, 63% were black, 30% white, and 8% another race. Almost half had low socioeconomic status, only 43% had private health insurance, and almost half had experienced a previous unintended pregnancy. They were educated about their contraceptive options in order from most effective to least effective, with an emphasis on long-acting reversible contraceptives (LARCs), such as intrauterine devices and implants. The benefits and harms of each method were described as part of the educational session, and the participant was able to choose her preferred method. In the absence of contraindications such as pregnancy, the LARC device was inserted on the same day. If a delay was needed, an alternative contraceptive was provided until it could be inserted. The chosen contraceptive method was IUD for 37% of patients, etonogestrel implant for 34%, oral contraceptive for 12%, depot medroxyprogesterone acetate injection for 9%, and another method for 7%. Thus, more than 70% chose a LARC method. Participants were followed up for up to 3 years via telephone calls every 6 months. The follow-up rate was 82% at 2 years and 75% at 3 years, which is decent for a cohort study of this kind. It is possible that self-selection bias could dampen the findings, if young women who were lost to follow-up were more likely to become pregnant or give birth than their adherent counterparts. Pregnancy, birth, and abortion rates were significantly lower for members of the study cohort (34.0, 19.4, and 9.7 per 1000 teens, respectively) than for a general US population sample of sexually experienced teens (158.5, 94.0, and 41.5 per 1000 teens) and lower than a general US population sample of all teens (57.4, 34.4, and 14.7 per 1000 teens). Results were similar when stratified for possible confounders such as race and age group. Most of the 56 participants who became pregnant were using either no method (25) or oral contraceptives (13). Failure rates for IUD and implant were approximately 5 per 1000 person-years (or ~ 0.5% per year). These results are probably affected to some extent by selection bias, as participants were responding to an advertisement offering free contraception or were referred for contraception. Pregnancy was self-reported, so there may have also been an ascertainment bias with regard to the primary outcome. Because the nationwide teen birth rate declined during the study period, comparing 2013 results to 2008 baseline data may somewhat overestimate the effect.
Bottom line: This prospective cohort study found that the provision of free, largely long-acting, contraception to sexually active teens was associated with lower rates of pregnancy, birth, and abortion.
Secura GM, Madden T, McNicholas C, et al. Provision of no-cost, long-acting contraception and teenage pregnancy. N Engl J Med 2014;371(14):1316-1323.

17. Long-acting contraceptive methods effective longer than approved duration

Clinical question: Do the etonogestrel implant and the levonorgestrel intrauterine device remain effective beyond the approved duration of use?
Study design: Cohort (prospective)
Setting: Outpatient (any)
Synopsis: In this observational study 500 women volunteered to continue to use beyond the stated expiration date a long-acting reversible contraceptive (LARC) method that was already in place. The majority of women enrolled were participants in a prior study designed to promote the use of LARC methods by eliminating barriers including cost, access, and knowledge deficits. There were an additional 58 participants recruited through local advertisements. The LARC methods used were etonogestrel implant (Nexplanon R) and levonorgestrel IUD (Mirena R). Participants were categorized into 3 categories of body mass index: less than 25.0, 25.0 to 29.9, and 30.0 or higher. Of the 237 implant users 123 had used it for at least 1 year beyond the 3-year approved duration and 34 used it for an additional 2 years (median extended duration = 12.5 months; range 5-40). Serum etonogestrel levels indicate that the implant contains adequate hormone levels for ovulation suppression at the end of both 3 years and 4 years of use. Of the 263 IUD users 108 had used it for at least 1 year beyond the approved 5-year duration (median extended duration = 12 months; range 5-36). There were no pregnancies among implant users. There was one pregnancy in an IUD user with conception estimated to be in the month prior to IUD expiration date and a physical examination that demonstrated partial expulsion of the device.
Bottom line: Both the etonogestrel implant and the levonorgestrel intrauterine device (IUD) remain highly effective for at least 1 year beyond the FDA-approved durations. This study adds to the evidence from a recent systematic review concluding that IUDs, including 52-mg levonorgestrel IUDs, could be safely used for up to 7 years.
McNicholas C, Maddipati R, Zhao Q, Swor E, Peipert JF. Use of etonogestrel implant and levonorgestrel intrauterine device beyond the US Food and Drug Administration–approved duration. Obstet Gynecol 2015;125(3):599-604.

18. Third-generation oral contraceptives associated with greater risk of PE, stroke, and MI

Clinical question: Which oral contraceptive combinations have the highest risk of cardiovascular effects?
Study design: Cohort (retrospective)
Setting: Population-based

Synopsis: This study, conducted in France, used the national health insurance database to identify all women who filled at least one prescription for an oral contraceptive between July 2010 and September 2012. The authors compared these data with the hospital discharge database to identify whether any of these women experienced an admission for pulmonary embolism, cancer, ischemic stroke, or myocardial infarction over the same period. They identified almost 5 million women with a total of 5,443,916 woman-years of oral contraceptive use. The risk of cardiovascular effects was very low: roughly 6 events per 10,000 woman-years, which is similar to other reports. However, the authors found some differences among products: After adjustment for progestogen and risk factors, stroke, pulmonary embolus, and myocardial infarction risk were all statistically lower with lower-dose estrogen (20 mcg vs 30-40 mcg). They also found, after adjustment, that progestogen mattered: desogestrel (in Desogen, Mircette) and gestodene (Gynera, Femoden, and many others) were associated with higher risk of pulmonary embolus than levonorgestrel. Norethisterone (in Loestrin, Microgestin, and others) was associated with lower pulmonary embolus risk. The combination of estrogen 20 mcg and levonorgestrel is associated with the lowest risk. These risks are still small (numbers needed to treat to harm are in the thousands). This study doesn't tell us about products that contain other estrogens or progestogens since these are the only combinations covered by French national health insurance. Also, the database doesn't allow for analysis by smoking status.
Bottom line: Although there is risk with any current oral contraceptive combination, those that contain lower doses of estrogen, and levonorgestrel instead of desogestrel or gestodene, are associated with the least risk of ischemic stroke, myocardial infarction, or pulmonary embolus. These safer products are older, so are often less expensive. This is not the first study to show this difference, but I think its enrollment of 5 million women makes it the largest.
Weill A, Dalichampt M, Raguideau F, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. BMJ 2016;353:i2002.

19. Progestin-only contraceptives: effects on weight.

Background: Progestin-only contraceptives (POCs) are appropriate for many women who cannot or should not take estrogen. POCs include injectables, intrauterine contraception, implants, and oral contraceptives. Many POCs are long-acting, cost-effective methods of preventing pregnancy. However, concern about weight gain can deter the initiation of contraceptives and cause early discontinuation among users.
Objectives: The primary objective was to evaluate the association between progestin-only contraceptive use and changes in body weight.
Search methods. Until 4 August 2016, we searched MEDLINE, CENTRAL, POPLINE, LILACS, ClinicalTrials.gov, and ICTRP. For the initial review, we contacted investigators to identify other trials.
Selection criteria: We considered comparative studies that examined a POC versus another contraceptive method or no contraceptive. The primary outcome was mean change in body weight or mean change in body composition. We also considered the dichotomous outcome of loss or gain of a specified amount of weight.
Data collection and analysis: Two authors extracted the data. Non-randomized studies (NRS) need to control for confounding factors. We used adjusted measures for the primary effects in NRS or the results of matched analysis from paired samples. If the report did not provide adjusted measures for the primary analysis, we used unadjusted outcomes. For RCTs and NRS without adjusted measures, we computed the mean difference (MD) with 95% confidence interval (CI) for continuous variables. For dichotomous outcomes, we calculated the Mantel-Haenszel odds ratio (OR) with 95% CI.
Main results: We found 22 eligible studies that included a total of 11,450 women. With 6 NRS added to this update, the review includes 17 NRS and 5 RCTs. By contraceptive method, the review has 16 studies of depot medroxyprogesterone acetate (DMPA), 4 of levonorgestrel-releasing intrauterine contraception (LNG-IUC), 5 for implants, and 2 for progestin-only pills. Comparison groups did not differ significantly for weight change or other body composition measure in 15 studies. Five studies with moderate or low quality evidence showed differences between study arms. Two studies of a six-rod implant also indicated some differences, but the evidence was low quality. Three studies showed differences for DMPA users compared with women not using a hormonal method. In a retrospective study, weight gain (kg) was greater for DMPA versus copper (Cu) IUC in years one (MD 2.28, 95% CI 1.79 to 2.77), two (MD 2.71, 95% CI 2.12 to 3.30), and three (MD 3.17, 95% CI 2.51 to 3.83). A prospective study showed adolescents using DMPA had a greater increase in body fat (%) compared with a group not using a hormonal method (MD 11.00, 95% CI 2.64 to 19.36). The DMPA group also had a greater decrease in lean body mass (%) (MD -4.00, 95% CI -6.93 to -1.07). A more recent retrospective study reported greater mean increases with use of DMPA versus Cu IUC for weight (kg) at years 1 (1.3 vs 0.2), 4 (3.5 vs 1.9), and 10 (6.6 vs 4.9). Two studies reported a greater mean increase in body fat mass (%) for POC users versus women not using a hormonal method. The method was LNG-IUC in two studies (reported means 2.5 versus -1.3; P = 0.029); (MD 1.60, 95% CI 0.45 to 2.75). One also studied a desogestrel-containing pill (MD 3.30, 95% CI 2.08 to 4.52). Both studies showed a greater decrease in lean body mass among POC users.
Authors' conclusions: We considered the overall quality of evidence to be low; more than half of the studies had low quality evidence. The main reasons for downgrading were lack of randomizations (NRS) and high loss to follow-up or early discontinuation.These 22 studies showed limited evidence of change in weight or body composition with use of POCs. Mean weight gain at 6 or 12 months was less than 2 kg (4.4 lb) for most studies. Those with multiyear data showed mean weight change was approximately twice as much at two to four years than at one year, but generally the study groups did not differ significantly. Appropriate counseling about typical weight gain may help reduce discontinuation of contraceptives due to perceptions of weight gain.
Lopez , L.M., Ramesh S, Chen M, Edelman A, Otterness C, Trussell J, Helmerhorst FM. Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD008815. DOI: 10.1002/14651858.CD008815.pub4.

20. Interventions for emergency contraception

Background: Emergency contraception (EC) is using a drug or copper intrauterine device (Cu-IUD) to prevent pregnancy shortly after unprotected intercourse. Several interventions are available for EC. Information on the comparative effectiveness, safety and convenience of these methods is crucial for reproductive healthcare providers and the women they serve. This is an update of a review previously published in 2009 and 2012.
Objectives: To determine which EC method following unprotected intercourse is the most effective, safe and convenient to prevent pregnancy.
Search methods: In February 2017 we searched CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, Popline and PubMed, The Chinese biomedical databases and UNDP/UNFPA/WHO/World Bank Special Programme on Human Reproduction (HRP) emergency contraception database. We also searched ICTRP and ClinicalTrials.gov as well as contacting content experts and pharmaceutical companies, and searching reference lists of appropriate papers.
Selection criteria: Randomised controlled trials including women attending services for EC following a single act of unprotected intercourse were eligible.
Data collection and analysis: We used standard methodological procedures recommended by Cochrane. The primary review outcome was observed number of pregnancies. Side effects and changes of menses were secondary outcomes.
Main results: We included 115 trials with 60,479 women in this review. The quality of the evidence for the primary outcome ranged from moderate to high, and for other outcomes ranged from very low to high. The main limitations were risk of bias (associated with poor reporting of methods), imprecision and inconsistency.Comparative effectiveness of different emergency contraceptive pills (ECP) Levonorgestrel was associated with fewer pregnancies than Yuzpe (estradiol-levonorgestrel combination) (RR 0.57, 95% CI 0.39 to 0.84, 6 RCTs, n = 4750, I2 = 23%, high-quality evidence). This suggests that if the chance of pregnancy using Yuzpe is assumed to be 29 women per 1000, the chance of pregnancy using levonorgestrel would be between 11 and 24 women per 1000.
Mifepristone (all doses) was associated with fewer pregnancies than Yuzpe (RR 0.14, 95% CI 0.05 to 0.41, 3 RCTs, n = 2144, I2 = 0%, high-quality evidence). This suggests that if the chance of pregnancy following Yuzpe is assumed to be 25 women per 1000 women, the chance following mifepristone would be between 1 and 10 women per 1000. Both low-dose mifepristone (less than 25 mg) and mid-dose mifepristone (25 mg to 50 mg) were probably associated with fewer pregnancies than levonorgestrel (RR 0.72, 95% CI 0.52 to 0.99, 14 RCTs, n = 8752, I2 = 0%, high-quality evidence; RR 0.61, 95% CI 0.45 to 0.83, 27 RCTs, n = 6052, I2 = 0%, moderate-quality evidence; respectively). This suggests that if the chance of pregnancy following levonorgestrel is assumed to be 20 women per 1000, the chance of pregnancy following low-dose mifepristone would be between 10 and 20 women per 1000; and that if the chance of pregnancy following levonorgestrel is assumed to be 35 women per 1000, the chance of pregnancy following mid-dose mifepristone would be between 16 and 29 women per 1000.Ulipristal acetate (UPA) was associated with fewer pregnancies than levonorgestrel (RR 0.59; 95% CI 0.35 to 0.99, 2 RCTs, n = 3448, I2 = 0%, high-quality evidence). Comparative effectiveness of different ECP doses. It was unclear whether there was any difference in pregnancy rate between single-dose levonorgestrel (1.5 mg) and the standard two-dose regimen (0.75 mg 12 hours apart) (RR 0.84, 95% CI 0.53 to 1.33, 3 RCTs, n = 6653, I2 = 0%, moderate-quality evidence). Mid-dose mifepristone was associated with fewer pregnancies than low-dose mifepristone (RR 0.73; 95% CI 0.55 to 0.97, 25 RCTs, n = 11,914, I2 = 0%, high-quality evidence). Comparative effectiveness of Cu-IUD versus mifepristone. There was no conclusive evidence of a difference in the risk of pregnancy between the Cu-IUD and mifepristone (RR 0.33, 95% CI 0.04 to 2.74, 2 RCTs, n = 395, low-quality evidence). Adverse effects. Nausea and vomiting were the main adverse effects associated with emergency contraception. There is probably a lower risk of nausea (RR 0.63, 95% CI 0.53 to 0.76, 3 RCTs, n = 2186 , I2 = 59%, moderate-quality evidence) or vomiting (RR 0.12, 95% CI 0.07 to 0.20, 3 RCTs, n = 2186, I2 = 0%, high-quality evidence) associated with mifepristone than with Yuzpe. levonorgestrel is probably associated with a lower risk of nausea (RR 0.40, 95% CI 0.36 to 0.44, 6 RCTs, n = 4750, I2 = 82%, moderate-quality evidence), or vomiting (RR 0.29, 95% CI 0.24 to 0.35, 5 RCTs, n = 3640, I2 = 78%, moderate-quality evidence) than Yuzpe. Levonorgestrel users were less likely to have any side effects than Yuzpe users (RR 0.80, 95% CI 0.75 to 0.86; 1 RCT, n = 1955, high-quality evidence). UPA users were more likely than levonorgestrel users to have resumption of menstruation after the expected date (RR 1.65, 95% CI 1.42 to 1.92, 2 RCTs, n = 3593, I2 = 0%, high-quality evidence). Menstrual delay was more common with mifepristone than with any other intervention and appeared to be dose-related. Cu-IUD may be associated with higher risks of abdominal pain than mifepristone (18 events in 95 women using Cu-IUD versus no events in 190 women using mifepristone, low-quality evidence).
Authors' conclusions: Levonorgestrel and mid-dose mifepristone (25 mg to 50 mg) were more effective than Yuzpe regimen. Both mid-dose (25 mg to 50 mg) and low-dose mifepristone(less than 25 mg) were probably more effective than levonorgestrel (1.5 mg). Mifepristone low dose (less than 25 mg) was less effective than mid-dose mifepristone. UPA was more effective than levonorgestrel. Levonorgestrel users had fewer side effects than Yuzpe users, and appeared to be more likely to have a menstrual return before the expected date. UPA users were probably more likely to have a menstrual return after the expected date. Menstrual delay was probably the main adverse effect of mifepristone and seemed to be dose-related. Cu-IUD may be associated with higher risks of abdominal pain than ECPs.
Shen J, Che Y, Showell E, Chen K, Cheng L. Interventions for emergency contraception. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD001324. DOI: 10.1002/14651858.CD001324.pub5.

Summary of Key Points

Osteoporosis:

1. Treat women with bisphosphonates or monoclonal antibody for only five years, long term increases fractures
2. Calcium with vitamin D to prevent fractures is uncertain
3. Treating low vitamin D levels is ineffective in post- menopausal women

Menopause:

1. Vasomotor symptoms can be quite long
2. Transdermal estrogen and progesterone are most effective in reducing vasomotor symptoms
3. Plant based therapies with soy isoflavones may be effective for menopausal symptoms
4. Long-term (> 1 year) use of HT increases absolute risk for CVD (heart attacks), venous thrombosis, strokes, breast cancer, and death from lung cancer. Balance risks and benefits per patient
5. USPSTF recommends against (D) the use of hormones (estrogen and progestin) for primary prevention of chronic conditions

Dysmenorrhea:

1. NSAIDs and TENs can be helpful
2. Acupuncture and dietary supplements showing inconsistent results or no evidence

Sexual Dysfunction:

1. Fibanserin (Addyi) –probably more harm than benefit for hypoactive sexual desire disorder (HSDD)
2. Costs-nearly $1000 per month

Fibroids:

1. Transvaginal ultrasound lacks sensitivity to be used alone to exclude polyps or leiomyomas with abnormal uterine bleeding
2. Uterine artery embolization is a treatment option

Contraception:

1. Free contraception is associated with more use and less pregnancy in teens
2. Third generation OCTs with more risk of PE, stroke, and MI than older combinations with low estrogen or levonorgestrel
3. Progestin only has little impact on weight
4. Emergency contraception with levonorgestrel and mifepristone is more effective than Yuzpe regimen (estradiol with levonorgestrel)

Objectives

1. Know the findings of recent studies regarding potential benefits and harms of screening for and treating prostate cancer

2. Know the findings of recent studies regarding understand the potential benefits and harms of testosterone therapy

Prostate Cancer

The landscape of prostate cancer screening and treatment has changed greatly during the past 5 years. Because most prostate cancer is relatively indolent, active surveillance of low grade (Gleason 6) prostate cancer has expanded dramatically, with about half of US men choosing active surveillance. This has caused the USPSTF to reconsider the D recommendation for PSA screening and reclassify as a C recommendation for men 55 to 69.

"The USPSTF recommends that clinicians inform men ages 55 to 69 years about the potential benefits and harms of prostate-specific antigen (PSA)–based screening for prostate cancer. The USPSTF recommends against PSA-based screening for prostate cancer in men age 70 years and older." (Draft 2017 recommendations.)

Here is some of the recently published evidence.

1. Prostate cancer screening: no mortality benefit after 15 years of follow-up (PLCO)

Clinical question: Does screening of asymptomatic men for prostate cancer improve mortality?
Study design: Randomized controlled trial (single-blinded)
Setting: Population-based
Synopsis: We have previously reported data from the original PLCO study (http://www.essentialevidenceplus.com/content/poem/110501) and its 13-year follow-up (http://www.essentialevidenceplus.com/content/poem/140343). In the original trial, more than 76,000 men between the ages of 55 years and 74 years at 10 centers were randomized to receive prostate cancer screening (annual prostate-specific antigen for 6 years plus digital rectal examination for 4 years) or no scheduled screening. This study reports additional follow-up (up to 19 years; median 15 years). The cumulative prostate cancer mortality rates were virtually identical (4.8 and 4.6 per 10,000 person-years, respectively). Additionally, there was no difference in all-cause mortality between the groups (173 and 177 per 10,000 person-years).
Bottom line: After nearly 2 decades of follow-up from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, there appears to be no mortality benefit to screening asymptomatic men for prostate cancer.
Pinsky PF, Prorok PC, Yu K, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer 2017;123(4):592-599.

2. Active surveillance for localized prostate CA: no increased mortality, but higher rates of clinical progression (ProtecT)

Clinical question: What is the best approach to the management of localized prostate cancer?
Study design: Randomized controlled trial (single-blinded)
Setting: Outpatient (specialty)
Synopsis: Clinically localized prostate cancer is defined as stage T1c or T2, and is confined to the prostate gland. In this study, 82,429 British men aged 50 to 69 years had a prostate-specific antigen (PSA) test. Of those, 2664 had grade T1c or T2 cancer, and 1643 agreed to be randomized to 1 of 3 groups: radical prostatectomy, radiotherapy, or a program of AS. AS consisted of frequent PSA tests (every 3 months in the first year and every 6 to 12 months after that), with a rise of 50% or more triggering an evaluation for possible biopsy, and treatment, if indicated. Approximately 80% of men assigned to surgery or radiotherapy received the assigned treatment during the first year following randomization. In the AS group, there was a steady increase in the percentage of men who received radiotherapy, prostatectomy, or another treatment with curative intent, from 20% at year 2, to 40% at year 5, to slightly more than 50% at year 10. There was no difference between groups in mortality due to prostate cancer, in prostate cancer–specific survival at 5 or 10 years, or in all-cause mortality. However, there was a greater likelihood of developing metastatic disease in the AS group, with approximately 3 more metastatic cancers detected per 1000 person-years than in the surgery or radiotherapy groups (P = .004). Clinical progression (defined as progression to T3 or T4 disease, urinary or rectal complications, or the use of androgen deprivation therapy) was also more common in the AS group, with approximately 13 additional patients progressing per 1000 person-years.

Stratification of patients by age, PSA result, Gleason score, or stage at diagnosis did not affect the results.
Bottom line: This landmark study compared active surveillance (AS) with radical prostatectomy or radiation therapy for patients with T1c or T2 prostate cancer. The benefits of AS include avoiding radical therapy in half the patients, with no effect on disease-specific survival or all-cause survival. The potential harms include a greater risk of metastatic disease (3 additional cases per 1000 person years, corresponding to 3 additional cases for 100 men followed up for 10 years) and a greater likelihood of clinical progression. An accompanying study (N Engl J Med 2016; 2016;375(15):1425-1437) discusses the effects on quality of life and complications of treatment.
Hamdy FC, Donovan JL, Lane JA, et al, for the ProtecT Study Group. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;375(15):1415-1424.

3. Prostatectomy for local prostate cancer does not significantly reduce mortality in up to 20 years of follow-up

Clinical question: For men with localized prostate cancer, does surgery improve long-term health outcomes?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (any)
Synopsis: This is a long-term follow-up of patients in the PIVOT trial, which compared radical prostatectomy with observation. Patients in each group saw a physician to assess progression of symptoms every 6 months and had bone scans every 5 years, although "active surveillance" was not practiced. All patients had localized (T1-G2NxM0) prostate cancer with a PSA level of less than 50 ng/mL, were younger than 75 years, and were expected to live at least 10 years. See our original review of the PIVOT trial for more details: http://www.essentialevidenceplus.com/content/poem/140901. In the current study, the authors report mortality data through 2014 (range: 12 years to 19.4 years), and provide additional details regarding disease progression and other health outcomes during the original study period (through 2010). Analyses were by intention to treat, and groups were balanced at the start of the study. There was a 5.5% absolute reduction in all-cause mortality and a 4% absolute reduction in prostate cancer–specific mortality at the end of follow-up. These differences were not statistically significant (P = .06 in both cases), but are potentially clinically significant. The absolute risk reductions were greater in patients younger than 65 years (12.2% vs 2.6%) and in those with an initial PSA level greater than 10 ng/mL, though these differences were not statistically significant due in part to small sample size for these subgroups. There was a statistically significant increase in all-cause mortality for patients in the intermediate-risk group based on the D'Amici risk score (in Essential Evidence at http://www.essentialevidenceplus.com/content/rules/304), but not in the low-risk or high-risk groups. The likelihood of disease progression was lower in the surgery group (33.0% vs 59.7%; P < .05; number needed to treat [NNT] = 4), although this was largely due to a greater likelihood of biochemical or local progression. Systemic progression (ie, metastasis) occurred less often in the radical surgery group (4.7% vs 8.7%; P < .05; NNT = 25), similar to the findings of the UK ProtecT trial (http://www.essentialevidenceplus.com/content/poem/181203). However, erectile dysfunction (14.6% vs 5.4%; P < .05; NNTH = 11) and incontinence (17.3% vs 4.4%, NNTH = 8) were also more common in the surgery group.
Bottom line: Radical prostatectomy has benefits and harms. There was a strong and consistent trend toward greater mortality in the PIVOT trial, which obtained a prostate-specific antigen (PSA) test every 6 months but left the subsequent follow-up to the individual physicians. But it is important to view this study in the context of the recent UK ProtecT trial, which used a more aggressive and structured active surveillance protocol. The UK study had higher rates of eventual treatment in the active surveillance arm than the PIVOT trial, and found no difference in mortality. Both studies found similar but small increases in rates of progression to metastatic disease, and much higher rates of erectile dysfunction and incontinence in the surgery group. The reduction in mortality was greatest in younger patients and in those with a PSA level greater than 10 ng/mL (though the reduction was not statistically significant because of the small numbers in these subgroups).
Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of prostatectomy versus observation for early prostate cancer. N Engl J Med 2017;377(2):132-142.

Testosterone Replacement Therapy

Because of several well done studies published in the past several years, we are getting closer to understanding potential benefits and harms of testosterone replacement therapy. Positive treatment effects appear relatively small. There does not appear to be risk of prostate cancer, but there is cardiovascular risk, at least for high risk men. In low risk men, benefits may outweigh potential cardiovascular harms.

4. Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis

OBJECTIVE: To review and quantify the association between endogenous and exogenous testosterone and prostate-specific antigen (PSA) and prostate cancer.
METHODS: Literature searches were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Prospective cohort studies that reported data on the associations between endogenous testosterone and prostate cancer, and placebo-controlled randomized trials of testosterone replacement therapy (TRT) that reported data on PSA and/or prostate cancer cases were retained. Meta-analyses were performed using random-effects models, with tests for publication

bias and heterogeneity.
RESULTS: Twenty estimates were included in a meta-analysis, which produced a summary relative risk (SRR) of prostate cancer for an increase of 5 nmol/L of testosterone of 0.99 (95% confidence interval [CI] 0.96, 1.02) without heterogeneity (I^2 = 0%). Based on 26 trials, the overall difference in PSA levels after onset of use of TRT was 0.10 ng/mL (-0.28, 0.48). Results were similar when conducting heterogeneity analyses by mode of administration, region, age at baseline, baseline testosterone, trial duration, type of patients and type of TRT. The SRR of prostate cancer as an adverse effect from 11 TRT trials was 0.87 (95% CI 0.30; 2.50). Results were consistent across studies.
CONCLUSIONS: Prostate cancer appears to be unrelated to endogenous testosterone levels. TRT for symptomatic hypogonadism does not appear to increase PSA levels nor the risk of prostate cancer development. The current data are reassuring, although some caution is essential until multiple studies with longer follow-up are available.
Boyle P, Koechlin A, Bota M, d'Onofrio A, Zaridze DG, Perrin P, Fitzpatrick J, Burnett AL, Boniol M. Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis. BJU Int. 2016 Nov;118(5):731-741.

5. Testosterone gel has little, if any, symptom benefit for older men with hypogonadism

Clinical question: Is testosterone replacement therapy safe and effective for older men with hypogonadism?
Study design: Randomized controlled trial (double-blinded)
Setting: Population-based
Synopsis: These researchers used mass mailings to recruit participants from the community, a strength of this particular study. Included patients were 65 years or older and had a mean serum testosterone level of less than 275 ng/dL. Three groups of men were recruited: (1) those with decreased libido on a standardized instrument and a partner willing to have sex at least twice a month, (2) those with difficulty climbing stairs or a speed of 1.2 m/sec on a 6-minute walk test, and (3) those with self-reported low vitality and fatigue. The authors used standardized, validated instruments to measure libido, physical function, and vitality/fatigue. Anyone with prostate cancer, depression, uncontrolled hypertension, cardiovascular disease, or symptoms of prostate enlargement was excluded. A total of 51,085 men were screened, of whom 1490 had 2 testosterone measurements with a mean value below the cutoff. Of those 1490 men, 790 met all of the other study criteria and were enrolled. They were randomized to receive testosterone gel 1% in an initial dose of 5 g daily (with the dose titrated to achieve a final value in the midpoint of the normal range for young men) or matching placebo. The mean age of participants was 72 years, 89% were white, 76% were married or living with a partner, and 52% were college graduates. Groups were balanced at baseline and analysis was by intention to treat, although how the allocation into groups was concealed is not reported. A total of 705 men completed the 12-month follow-up period. The only benefit with the testosterone was a small increase (0.58) in the Psychosexual Daily Questionnaire score compared with placebo. This is a 12-point scale, and patients in both groups had a baseline score of 1.4, so this is unlikely to be clinically significant. Another score measuring sexual desire showed a somewhat more impressive gain in the treatment group than in the control group: approximately 3 points higher than a baseline of about 12 points. However, both of these differences narrowed at 12 months. There was no significant difference in walking speed among the group of men specifically enrolled for that reason, but there was a small benefit (number needed to treat = 12 for one more man to walk 50 additional meters in 6 minutes) when you included all 790 patients. There was no difference between groups regarding measures of vitality or fatigue. There was no difference in harms, but the exclusion criteria were extensive and included anyone with or at risk for cardiovascular disease. Although the study was funded by the National Institutes of Health, the investigators report extensive conflicts of interest relevant to the study.
Bottom line: It's difficult to get too excited about these results. There are small, probably clinically insignificant changes on some measures of sexual desire, but the patient-oriented outcomes (more frequent and more satisfactory sex) were not reported. The change in physical function was small, there was no effect on mood or fatigue, and the study was too small to evaluate harms.
Snyder PJ, Bhasin S, Cunningham GR, et al, for the Testosterone Trials Investigators. Effects of testosterone treatment in older men. N Engl J Med 2016;374(7):611-624.

Testosterone and Cardiovascular Risk

Cardiovascular risk for testosterone therapy is real, but the degree of danger varies depending on baseline risk. For example, the first large study of testosterone replacement in older men was terminated early because of excessive cardiovascular events. On the other hand, some studies have shown no excess risk in younger, healthy men.

6. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels

BACKGROUND: Rates of testosterone therapy are increasing and the effects of testosterone therapy on cardiovascular outcomes and mortality are unknown. A recent randomized clinical trial of testosterone therapy in men with a high prevalence of cardiovascular diseases was stopped prematurely due to adverse cardiovascular events raising concerns about testosterone therapy safety.
OBJECTIVES: To assess the association between testosterone therapy and all-cause mortality, myocardial infarction (MI), or stroke among male veterans and to determine whether this association is modified by underlying coronary artery disease.
DESIGN, SETTING, AND PATIENTS: A retrospective national cohort study of men with low testosterone levels (<300 ng/dL) who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011.

MAIN OUTCOMES AND MEASURES: Primary outcome was a composite of all-cause mortality, MI, and ischemic stroke.
RESULTS: Of the 8709 men with a total testosterone level lower than 300 ng/dL, 1223 patients started testosterone therapy after a median of 531 days following coronary angiography. Of the 1710 outcome events, 748 men died, 443 had MIs, and 519 had strokes. Of 7486 patients not receiving testosterone therapy, 681 died, 420 had MIs, and 486 had strokes. Among 1223 patients receiving testosterone therapy, 67 died, 23 had MIs, and 33 had strokes. At 3 years after coronary angiography, the Kaplan-Meier estimated cumulative percentages with events were 19.9%in the no testosterone therapy group vs 25.7%in the testosterone therapy group, with an absolute risk difference of 5.8%(95%CI, -1.4%to 13.1%) [corrected].The Kaplan-Meier estimated cumulative percentages with events among the no testosterone therapy group vs testosterone therapy group at 1 year after coronary angiography were 10.1% vs 11.3%; at 2 years, 15.4% vs 18.5%; and at 3 years, 19.9% vs 25.7 [corrected].There was no significant difference in the effect size of testosterone therapy among those with and without coronary artery disease (test for interaction, P = .41).
CONCLUSIONS AND RELEVANCE: Among a cohort of men in the VA health care system who underwent coronary angiography and had a low serum testosterone level, the use of testosterone therapy was associated with increased risk of adverse outcomes. These findings may inform the discussion about the potential risks of testosterone therapy.
Vigen R, O'Donnell CI, Barón AE, Grunwald GK, Maddox TM, Bradley SM, Barqawi A, Woning G, Wierman ME, Plomondon ME, Rumsfeld JS, Ho PM. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA. 2013 Nov 6;310(17):1829-36.

7. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men

AIMS: There is a significant uncertainty regarding the effect of testosterone replacement therapy (TRT) on cardiovascular (CV) outcomes including myocardial infarction (MI) and stroke. The aim of this study was to examine the relationship between normalization of total testosterone (TT) after TRT and CV events as well as all-cause mortality in patients without previous history of MI and stroke.
METHODS AND RESULTS: We retrospectively examined 83 010 male veterans with documented low TT levels. The subjects were categorized into (Gp1: TRT with resulting normalization of TT levels), (Gp2: TRT without normalization of TT levels) and (Gp3: Did not receive TRT). By utilizing propensity score-weighted Cox proportional hazard models, the association of TRT with all-cause mortality, MI, stroke, and a composite endpoint was compared between these groups. The all-cause mortality [hazard ratio (HR): 0.44, confidence interval (CI) 0.42-0.46], risk of MI (HR: 0.76, CI 0.63-0.93), and stroke (HR: 0.64, CI 0.43-0.96) were significantly lower in Gp1 (n = 43 931, median age = 66 years, mean follow-up = 6.2 years) vs. Gp3 (n = 13 378, median age = 66 years, mean follow-up = 4.7 years) in propensity-matched cohort. Similarly, the all-cause mortality (HR: 0.53, CI 0.50-0.55), risk of MI (HR: 0.82, CI 0.71-0.95), and stroke (HR: 0.70, CI 0.51-0.96) were significantly lower in Gp1 vs. Gp2 (n = 25 701, median age = 66 years, mean follow-up = 4.6 years). There was no difference in MI or stroke risk between Gp2 and Gp3.
CONCLUSION: In this large observational cohort with extended follow-up, normalization of TT levels after TRT was associated with a significant reduction in all-cause mortality, MI, and stroke.
Sharma R, Oni OA, Gupta K, Chen G, Sharma M, Dawn B, Sharma R, Parashara D, Savin VJ, Ambrose JA, Barua RS. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J. 2015 Oct 21;36(40):2706-15.

8. Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men with Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial

IMPORTANCE: Testosterone use in older men is increasing, but its long-term effects on progression of atherosclerosis are unknown.
OBJECTIVE: To determine the effect of testosterone administration on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels.
DESIGN, SETTING, AND PARTICIPANTS: Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) was a placebo-controlled, double-blind, parallel-group randomized trial involving 308 men 60 years or older with low or low-normal testosterone levels (100-400 ng/dL; free testosterone <50 pg/mL), recruited at 3 US centers. Recruitment took place between September 2004 and February 2009; the last participant completed the study in May 2012.
INTERVENTIONS: One hundred fifty-six participants were randomized to receive 7.5 g of 1% testosterone and 152 were randomized to receive placebo gel packets daily for 3 years. The dose was adjusted to achieve testosterone levels between 500 and 900 ng/dL.
MAIN OUTCOMES AND MEASURES: Coprimary outcomes included common carotid artery intima-media thickness and coronary artery calcium; secondary outcomes included sexual function and health-related quality of life.
RESULTS: Baseline characteristics were similar between groups: patients were a mean age of 67.6 years; 42% had hypertension; 15%, diabetes; 15%, cardiovascular disease; and 27%, obesity. The rate of change in intima-media thickness was 0.010 mm/year in the placebo group and 0.012 mm/year in the testosterone group (mean difference adjusted for age and trial site, 0.0002 mm/year; 95% CI, -0.003 to 0.003, P = .89). The rate of change in the coronary artery calcium score was 41.4 Agatston units/year in the placebo group and 31.4 Agatston units/year in the testosterone group (adjusted mean difference, -10.8 Agatston units/year; 95% CI, -45.7 to 24.2; P = .54). Changes in intima-media thickness or calcium scores were not associated with change in testosterone levels among individuals assigned to receive testosterone. Sexual desire, erectile function, overall sexual function scores, partner intimacy, and health-related quality of life did not differ significantly between groups. Hematocrit and prostate-specific antigen levels increased more in testosterone group.
CONCLUSIONS AND RELEVANCE: Among older men with low or low-normal testosterone levels, testosterone administration for 3 years vs placebo did not result in a significant difference in the rates of change in either common carotid artery intima-media thickness or coronary artery calcium nor did it improve overall sexual function or health-related quality of life. Because this trial was only powered

to evaluate atherosclerosis progression, these findings should not be interpreted as establishing cardiovascular safety of testosterone use in older men.
Basaria S, Harman SM, Travison TG, Hodis H, Tsitouras P, Budoff M, Pencina KM, Vita J, Dzekov C, Mazer NA, Coviello AD, Knapp PE, Hally K, Pinjic E, Yan M, Storer TW, Bhasin S. Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial. JAMA. 2015 Aug 11;314(6):570-81.

9. Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone

IMPORTANCE: Recent studies have yielded conflicting results as to whether testosterone treatment increases cardiovascular risk.
OBJECTIVE: To test the hypothesis that testosterone treatment of older men with low testosterone slows progression of noncalcified coronary artery plaque volume.
DESIGN, SETTING, AND PARTICIPANTS: Double-blinded, placebo-controlled trial at 9 academic medical centers in the United States. The participants were 170 of 788 men aged 65 years or older with an average of 2 serum testosterone levels lower than 275 ng/dL (82 men assigned to placebo, 88 to testosterone) and symptoms suggestive of hypogonadism who were enrolled in the Testosterone Trials between June 24, 2010, and June 9, 2014.
INTERVENTION: Testosterone gel, with the dose adjusted to maintain the testosterone level in the normal range for young men, or placebo gel for 12 months.
MAIN OUTCOMES AND MEASURES: The primary outcome was noncalcified coronary artery plaque volume, as determined by coronary computed tomographic angiography. Secondary outcomes included total coronary artery plaque volume and coronary artery calcium score (range of 0 to >400 Agatston units, with higher values indicating more severe atherosclerosis).
RESULTS: Of 170 men who were enrolled, 138 (73 receiving testosterone treatment and 65 receiving placebo) completed the study and were available for the primary analysis. Among the 138 men, the mean (SD) age was 71.2 (5.7) years, and 81% were white. At baseline, 70 men (50.7%) had a coronary artery calcification score higher than 300 Agatston units, reflecting severe atherosclerosis. For the primary outcome, testosterone treatment compared with placebo was associated with a significantly greater increase in noncalcified plaque volume from baseline to 12 months (from median values of 204 mm3 to 232 mm3 vs 317 mm3 to 325 mm3, respectively; estimated difference, 41 mm3; 95% CI, 14 to 67 mm3; P = .003). For the secondary outcomes, the median total plaque volume increased from baseline to 12 months from 272 mm3 to 318 mm3 in the testosterone group vs from 499 mm3 to 541 mm3 in the placebo group (estimated difference, 47 mm3; 95% CI, 13 to 80 mm3; P = .006), and the median coronary artery calcification score changed from 255 to 244 Agatston units in the testosteronegroup vs 494 to 503 Agatston units in the placebo group (estimated difference, -27 Agatston units; 95% CI, -80 to 26 Agatston units). No major adverse cardiovascular events occurred in either group.
CONCLUSIONS AND RELEVANCE: Among older men with symptomatic hypogonadism, treatment with testosterone gel for 1 year compared with placebo was associated with a significantly greater increase in coronary artery noncalcified plaque volume, as measured by coronary computed tomographic angiography. Larger studies are needed to understand the clinical implications of this finding.
Budoff MJ, Ellenberg SS, Lewis CE, Mohler ER 3rd, Wenger NK, Bhasin S, Barrett-Connor E, et. al. Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone. JAMA. 2017 Feb 21;317(7):708-716.

10. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews

Given the conflicting evidence regarding the association between exogenous testosterone and cardiovascular events, we systematically assessed published systematic reviews for evidence of the association between exogenous testosterone and cardiovascular events. We searched PubMed, MEDLINE, Embase, Cochrane Collaboration Clinical Trials, ClinicalTrials.gov, and the US Food and Drug Administration website for systematic reviews of randomised controlled trials published up to July 19, 2016. Two independent reviewers screened 954 full texts from 29 335 abstracts to identify systematic reviews of randomised controlled trials in which the cardiovascular effects of exogenous testosterone on men aged 18 years or older were examined. We extracted data for study characteristics, analytic methods, and key findings, and applied the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist to assess methodological quality of each review. Our primary outcome measure was the direction and magnitude of association between exogenous testosterone and cardiovascular events. We identified seven reviews and meta-analyses, which had substantial clinical heterogeneity, differing statistical methods, and variable methodological quality and quality of data abstraction. AMSTAR scores ranged from 3 to 9 out of 11. Six systematic reviews that each included a meta-analysis showed no significant association between exogenous testosterone and cardiovascular events, with summary estimates ranging from 1·07 to 1·82 and imprecise confidence intervals. Two of these six meta-analyses showed increased risk in subgroup analyses of oral testosterone and men aged 65 years or older during their first treatment year. One meta-analysis showed a significant association between exogenous testosterone and cardiovascular events, in men aged 18 years or older generally, with a summary estimate of 1·54 (95% CI 1·09-2·18). Our optimal information size analysis showed that any randomised controlled trial aiming to detect a true difference in cardiovascular risk between treatment groups receiving exogenous testosterone and their controls (with a two-sided p value of 0·05 and a power of 80%) would require at least 17 664 participants in each trial group. Therefore, given the challenge of adequately powering clinical trials for rare outcomes, rigorous observational studies are needed to clarify the association between testosterone-replacement therapy and major adverse cardiovascular outcomes.
Onasanya O, Iyer G, Lucas E, Lin D, Singh S, Alexander GC. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. Lancet Diabetes Endocrinol. 2016 Nov;4(11):943-956.

Testosterone Replacement Therapy and Sexual Function

Although it is entirely reasonable to think that testosterone replacement would improve sexual function, it appears to have only a small effect on libido and no improvement in performance.

11. Low serum testosterone levels are poor predictors of sexual dysfunction

OBJECTIVE: To identify predictors of sexual dysfunction using baseline data from the reduction by dutasteride of prostate cancer events (REDUCE) study.
PATIENTS AND METHODS: REDUCE was a 4-year randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of once-daily dutasteride 0.5 mg in over 8000 men aged 50-75 years with a prostate-specific antigen (PSA) level of 2.5-10 ng/mL (50-60 years) or 3.0-10 ng/mL (>60 years) and a negative prostate biopsy within 6 months of enrolment. • Baseline values (mean serum testosterone, age, International Prostate Symptom Score [IPSS], total prostate volume [TPV], body mass index [BMI], and presence of diabetes/glucose intolerance) were compared in subjects with and without sexual dysfunction (sexual inactivity, impotence, decreased libido or a Problem Assessment Scale of the Sexual Function Index [PAS-SFI] score <9).
RESULTS: Multivariate logistic regression showed that baseline age and IPSS were significant predictors of all four sexual function criteria examined ($P < 0.0001$). • BMI was a significant predictor of decreased libido, impotence and a PAS-SFI score <9, while diabetes/glucose intolerance was a significant predictor of sexual inactivity, impotence and a PAS-SFI score <9. • Testosterone and TPV were not significant predictors of any sexual function criterion examined.
CONCLUSIONS: Age, IPSS, BMI and diabetes/glucose intolerance, but not serum testosterone or TPV, were significant independent predictors of sexual dysfunction in the REDUCE study population. • The lack of association between sexual dysfunction and serum testosterone questions the value of modestly reduced or low normal testosterone levels as criteria for choosing testosterone replacement in older men with sexual dysfunction.
Marberger M, Wilson TH, Rittmaster RS. Low serum testosterone levels are poor predictors of sexual dysfunction. BJU Int. 2011 Jul;108(2):256-62.

12. Testosterone Treatment and Sexual Function in Older Men with Low Testosterone Levels

CONTEXT: The Testosterone Trials are a coordinated set of seven trials to determine the efficacy of T in symptomatic men ≥65 years old with unequivocally low T levels. Initial results of the Sexual Function Trial showed that T improved sexual activity, sexual desire, and erectile function.
OBJECTIVE: To assess the responsiveness of specific sexual activities to T treatment; to relate hormone changes to changes in sexual function; and to determine predictive baseline characteristics and T threshold for sexual outcomes.
DESIGN: A placebo-controlled trial.
SETTING: Twelve academic medical centers in the United States.
PARTICIPANTS: A total of 470 men ≥65 years of age with low libido, average T <275 ng/dL, and a partner willing to have sexual intercourse at least twice a month.
METHODS: Men were assigned to take T gel or placebo for 1 year. Sexual function was assessed by three questionnaires every 3 months: the Psychosexual Daily Questionnaire, the Derogatis Interview for Sexual Function, and the International Index of Erectile Function.
RESULTS: Compared with placebo, T administration significantly improved 10 of 12 measures of sexual activity. Incremental increases in total and free T and estradiol levels were associated with improvements in sexual activity and desire, but not erectile function. No threshold T level was observed for any outcome, and none of the 27 baseline characteristics predicted responsiveness to T.
CONCLUSIONS: In older men with low libido and low T levels, improvements in sexual desire and activity in response to T treatment were related to the magnitude of increases in T and estradiol levels, but there was no clear evidence of a threshold effect.
Cunningham GR, Stephens-Shields AJ, Rosen RC, Wang C, Bhasin S, et. al. Testosterone Treatment and Sexual Function in Older Men With Low Testosterone Levels. J Clin Endocrinol Metab. 2016 Aug;101(8):3096-104.

Testosterone Replacement Therapy and Diabetes Mellitus

13. Effect of testosterone treatment on constitutional and sexual symptoms in men with type 2 diabetes: RCT

OBJECTIVE: The objective of the study was to assess the effect of T treatment on constitutional and sexual symptoms in men with type 2 diabetes (T2D).
DESIGN: This was a randomized double-blind, parallel, placebo-controlled trial.
SETTING: The study was conducted at a tertiary referral center.
PATIENTS: Men aged 35-70 years with T2D, a hemoglobin A1c less than 8.5%, and a total T level less than 12.0 nmol/L (346 ng/dL) with mild to moderate aging male symptoms and erectile dysfunction.
INTERVENTION: Eighty-eight participants were randomly assigned to 40 weeks of im T undecanoate (n = 45) or matching placebo (n = 43).
MAIN OUTCOME MEASURES: Constitutional symptoms using the aging male symptoms (AMS) score, sexual desire (question 17 AMS score), and erectile function (International Index of Erectile Function-5).
RESULTS: T treatment did not substantially improve aging male symptoms [mean adjusted difference (MAD) in change over 40 weeks

across the T and placebo groups in AMS total score, -0.9 (95% confidence interval [CI] -4.1, 2.2), P = .67] or sexual desire [MAD in question 17 AMS, -0.3 (95% CI -0.8, 0.2), P = .17]. Although compared with placebo, erectile function in men assigned to T was reduced [MAD in International Index of Erectile Function abridged version 5, -2.0 (95% CI -3.4, -0.6), P < .02], there was no significant difference between baseline and 40-week International Index of Erectile Function abridged version 5 scores if both groups were analyzed separately. At baseline, symptoms were worse in men with depression and microvascular complications but did not correlate with T levels.
CONCLUSIONS: In this trial, T treatment did not substantially improve constitutional or sexual symptoms in obese, aging men with T2D with mild to moderate symptoms and modest reduction in T levels typical for the vast majority of such men.
Gianatti EJ, Dupuis P, Hoermann R, Zajac JD, Grossmann M. Effect of testosterone treatment on constitutional and sexual symptoms in men with type 2 diabetes in a randomized, placebo-controlled clinical trial. J Clin Endocrinol Metab. 2014 Oct;99(10):3821-8.

14. Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the BLAST study

INTRODUCTION: The association between testosterone deficiency and insulin resistance in men with type 2 diabetes is well established and current endocrine society guidelines recommend the measurement of testosterone levels in all men with type 2 diabetes or erectile dysfunction.
AIM: We report the first double-blind, placebo-controlled study conducted exclusively in a male type 2 diabetes population to assess metabolic changes with long-acting testosterone undecanoate (TU).
METHODS: The type 2 diabetes registers of seven general practices identified 211 patients for a 30-week double-blind, placebo-controlled study of long-acting TU 1,000 mg followed by 52 weeks of open-label use. Because of the established impact of age, obesity, and depression on sexual function, these variables were also assessed for influence on metabolic parameters.
MAIN OUTCOME MEASURE: Changes in glycated hemoglobin (HbA1c) and the level of testosterone at which response are achieved.
RESULTS: Treatment with TU produced a statistically significant reduction in HbA1c at 6 and 18 weeks and after a further 52 weeks of open-label medication most marked in poorly controlled patients with baseline HbA1c greater than 7.5 where the reduction was 0.41% within 6 weeks, and a further 0.46% after 52 weeks of open-label use. There was significant reduction in waist circumference, weight, and body mass index in men without depression, and improvements were related to achieving adequate serum levels of testosterone. There were no significant safety issues.
CONCLUSIONS: Testosterone replacement therapy significantly improved HbA1c, total cholesterol, and waist circumference in men with type 2 diabetes. Improvements were less marked in men with depression at baseline, and therapeutic responses were related to achieving adequate serum testosterone levels. Current advice on 3- to 6-month trials of therapy may be insufficient to achieve maximal response. Patients reported significant improvements in general health.
Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P; BLAST Study Group. Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the BLAST study. J Sex Med. 2014 Mar;11(3):840-56.

Other Effects of Testosterone Replacement Therapy

15. Association of Testosterone Levels with Anemia in Older Men: A Controlled Clinical Trial

IMPORTANCE: In one-third of older men with anemia, no recognized cause can be found.
OBJECTIVE: To determine if testosterone treatment of men 65 years or older with unequivocally low testosterone levels and unexplained anemia would increase their hemoglobin concentration.
DESIGN, SETTING, AND PARTICIPANTS: A double-blinded, placebo-controlled trial with treatment allocation by minimization using 788 men 65 years or older who have average testosterone levels of less than 275 ng/dL. Of 788 participants, 126 were anemic (hemoglobin ≤12.7 g/dL), 62 of whom had no known cause. The trial was conducted in 12 academic medical centers in the United States from June 2010 to June 2014.
INTERVENTIONS: Testosterone gel, the dose adjusted to maintain the testosterone levels normal for young men, or placebo gel for 12 months.
MAIN OUTCOMES AND MEASURES: The percent of men with unexplained anemia whose hemoglobin levels increased by 1.0 g/dL or more in response to testosterone compared with placebo. The statistical analysis was intent-to-treat by a logistic mixed effects model adjusted for balancing factors.
RESULTS: The men had a mean age of 74.8 years and body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of 30.7; 84.9% were white. Testosterone treatment resulted in a greater percentage of men with unexplained anemia whose month 12 hemoglobin levels had increased by 1.0 g/dL or more over baseline (54%) than did placebo (15%) (adjusted OR, 31.5; 95% CI, 3.7-277.8; P = .002) and a greater percentage of men who at month 12 were no longer anemic (58.3%) compared with placebo (22.2%) (adjusted OR, 17.0; 95% CI, 2.8-104.0; P = .002). Testosterone treatment also resulted in a greater percentage of men with anemia of known cause whose month 12 hemoglobin levels had increased by 1.0 g/dL or more (52%) than did placebo (19%) (adjusted OR, 8.2; 95% CI, 2.1-31.9; P = .003). Testosterone treatment resulted in a hemoglobin concentration of more than 17.5 g/dL in 6 men who had not been anemic at baseline.
CONCLUSIONS AND RELEVANCE: Among older men with low testosterone levels, testosterone treatment significantly increased the hemoglobin levels of those with unexplained anemia as well as those with anemia from known causes. These increases may be of clinical value, as suggested by the magnitude of the changes and the correction of anemia in most men, but the overall health benefits remain to be established. Measurement of testosterone levels might be considered in men 65 years or older who have unexplained

anemia and symptoms of low testosterone levels.
Roy CN, Snyder PJ, Stephens-Shields AJ, Artz AS, Bhasin S, Cohen HJ, Farrar JT, et. al. Association of Testosterone Levels With Anemia in Older Men: A Controlled Clinical Trial. Intern Med. 2017 Apr 1;177(4):480-490. doi: 10.1001/jamainternmed.2016.9540.

16. Effects of Testosterone Supplementation for 3 Years on Muscle Performance and Physical Function in Older Men

Context: Findings of studies of testosterone's effects on muscle strength and physical function in older men have been inconsistent; its effects on muscle power and fatigability have not been studied.
Objective: To determine the effects of testosterone administration for 3 years in older men on muscle strength, power, fatigability, and physical function.
Design, Setting, and Participants: This was a double-blind, placebo-controlled, randomized trial of healthy men ≥60 years old with total testosterone levels of 100 to 400 ng/dL or free testosterone levels <50 pg/mL.
Interventions: Random assignment to 7.5 g of 1% testosterone or placebo gel daily for 3 years.
Outcome Measures: Loaded and unloaded stair-climbing power, muscle strength, power, and fatigability in leg press and chest press exercises, and lean mass at baseline, 6, 18, and 36 months.
Results: The groups were similar at baseline. Testosterone administration for 3 years was associated with significantly greater performance in unloaded and loaded stair-climbing power than placebo (mean estimated between-group difference, 10.7 W [95% confidence interval (CI), -4.0 to 25.5], P = 0.026; and 22.4 W [95% CI, 4.6 to 40.3], P = 0.027), respectively. Changes in chest-press strength (estimated mean difference, 16.3 N; 95% CI, 5.5 to 27.1; P < 0.001) and power (mean difference 22.5 W; 95% CI, 7.5 to 37.5; P < 0.001), and leg-press power were significantly greater in men randomized to testosterone than in those randomized to placebo. Lean body mass significantly increased more in the testosterone group.
Conclusion: Compared with placebo, testosterone replacement in older men for 3 years was associated with modest but significantly greater improvements in stair-climbing power, muscle mass, and power. Clinical meaningfulness of these treatment effects and their impact on disability in older adults with functional limitations remains to be studied.
Storer TW, Basaria S, Traustadottir T, Harman SM, Pencina K, Li Z, et. al. Effects of Testosterone Supplementation for 3 Years on Muscle Performance and Physical Function in Older Men. J Clin Endocrinol Metab. 2017 Feb 1;102(2):583-593. doi: 10.1210/jc.2016-2771.

17. Testosterone does not improve cognition in memory-impaired older men with low testosterone levels

Clinical question: Does supplemental testosterone improve cognitive function in memory-impaired older men with low testosterone levels?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (specialty)
Synopsis: These investigators recruited adult men, 65 years or older, with a mean of 2 morning serum testosterone concentrations of less than 275 ng/dL (9.54 nmol/L). Exclusion criteria included significant cognitive impairment (Mini-Mental State Examination score < 24) and severe depression. Age-associated memory impairment was classified as subjective memory complaints and relative memory impairment (defined as more than 1 standard deviation below the performance scores for men aged 20 years to 24 years, but not greater than 2 standard deviations below the scores of age-matched men) on a standard scoring tool. A total of 493 men randomly received (concealed allocation assignment) testosterone gel 1% concentration at an initial dose of 5 g daily or matched placebo. The dose of testosterone was adjusted by an unmasked study investigator to achieve a level within the mid-normal range for young men (500-800 ng/dL; 17.4-27.8 nmol/L). To maintain participant and treating-clinician masking, the dose of placebo gel was also adjusted simultaneously. Individuals masked to treatment group assignment assessed outcomes. Complete follow-up occurred for 97.3% of participants at 12 months. Using intention-to-treat analyses, there were no significant improvements between the testosterone and control group on measurements of delayed paragraph recall scores, visual memory, executive function, or spatial ability.
Bottom line: Testosterone supplementation for men 65 years or older with both age-associated memory impairment and a low baseline testosterone level was not associated with significant improvements in memory or other cognitive functions.
Resnick SM, Matsumoto AM, Stephens-Shields AJ, et al. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. JAMA 2017;317(7):717-727.

18. Effects of long-term testosterone administration on cognition in older men with low or low-to-normal testosterone concentrations

BACKGROUND: The effects of testosterone on cognitive function in older men are incompletely understood. We aimed to establish the effects of long-term testosterone administration on multiple domains of cognitive function in older men with low or low-to-normal testosterone concentrations.
METHODS: We did the randomised, double-blind, placebo-controlled, parallel-group TEAAM trial at three medical centres in Boston, Phoenix, and Los Angeles, USA. Men aged 60 years and older with low or low-to-normal testosterone concentrations (3·47-13·9 nmol/L, or free testosterone <173 pmol/L) were randomly assigned (1:1), via computer-generated randomisation, to receive either 7·5 g of 1% testosterone gel or placebo gel daily for 3 years. Randomisation was stratified by age (60-75 years vs >75 years) and study site. The testosterone dose was adjusted to achieve concentrations of 17·3-31·2 nmol/L. Participants and all study personnel were masked to treatment allocation. Multiple domains of cognitive function were assessed as prespecified secondary outcomes by use of

standardised tests at baseline and months 6, 18, and 36. We did analyses by intention to treat (in men who had baseline assessments of cognitive function) and per protocol (restricted to participants who completed the study drug and had both baseline and 36 month assessments of cognitive function). The TEAAM trial is registered with ClinicalTrials.gov, number NCT00287586.
FINDINGS: Between Sept 1, 2004, and Feb 12, 2009, we randomly assigned 308 participants to receive either testosterone (n=156) or placebo (n=152). 280 men had baseline cognitive assessments (n=140 per group). Mean follow-up time was 29·0 months (SD 11·5) in the testosterone group and 31·1 months (9·5) in the placebo group. The last participant completed the study on May 11, 2012. In the testosterone group, mean concentrations of serum total testosterone increased from 10·6 nmol/L (SD 2·2) to 19·7 nmol/L (9·2) and free testosterone concentrations increased from 222 pmol/L (62) to 364 pmol/L (222). In the placebo group, mean concentrations of serum total testosterone were 10·7 nmol/L (SD 2·3) at baseline and 11·1 nmol/L (3·2) post-intervention and free testosterone concentrations were 210 pmol/L (61) and 172 pmol/L (49), respectively. We recorded no between-group differences in changes in visuospatial ability (mean difference: Complex Figure Test -0·51, 95% CI -2·0 to 1·0), phonemic or category verbal fluency (phonemic fluency test 0·90, -1·3 to 3·1; categorical fluency test 1·1, -0·3 to 2·6), verbal memory (paragraph recall test 0·29, -1·2 to 1·8), manual dexterity (Grooved Pegboard Test 4·2, -1·3 to 9·7), and attention or executive function (Stroop Interference Test -2·6, -7·4 to 2·3) after adjustment for age, education, and baseline cognitive function. In both the intention-to-treat and per-protocol (n=86 per group) populations, changes in cognitive function scores were not related significantly to changes in total or free testosterone, or oestradiol concentrations.
INTERPRETATION: Testosterone administration for 36 months in older men with low or low-to-normal testosterone concentrations did not improve cognitive function. Future long-term trials are needed to investigate the efficacy of testosterone replacement in patients with impaired cognition, such as people with Alzheimer's disease.
Huang G, Wharton W, Bhasin S, Harman SM, Pencina KM, Tsitouras P, Li Z, Hally KA, Asthana S, Storer TW, Basaria S. Effects of long-term testosterone administration on cognition in older men with low or low-to-normal testosterone concentrations: a prespecified secondary analysis of data from the randomised, double-blind, placebo-controlled TEAAM trial. Lancet Diabetes Endocrinol. 2016 Aug;4(8):657-65.

Meta-analyses of Testosterone Replacement Therapy

19. Efficacy and safety of testosterone replacement therapy in men with hypogonadism: A meta-analysis study of placebo-controlled trials

Abstract: The purpose of the present meta-analysis was to evaluate the efficacy and safety of testosterone replacement therapy in men with hypogonadism. A search was conducted for appropriate randomized controlled trials and the data from 16 trials were pooled. The intended primary outcome of the present study was to determine the efficacy and safety of testosterone replacement therapy. The current data demonstrated that scores for Aging Male Symptoms (AMS) were significantly reduced following testosterone replacement therapy, with a mean decrease in AMS score of 1.52 [95% confidence interval (CI), 0.72 to 2.32; P=0.0002]. Testosterone replacement therapy increased lean body mass [mean difference (MD), 1.22; 95% CI, 0.33 to 2.11; P=0.007], reduced fat mass in a non-significantly manner (MD, -0.85; 95% CI, -1.74 to 0.04; P=0.06) and significantly reduced total cholesterol (MD, -0.16; 95% CI, -0.29 to -0.03; P=0.01). No significant differences were identified in body weight (MD, 0.09; 95% CI, -1.13 to 1.31; P=0.89), body mass index (MD, 0.10; 95% CI, -0.62 to 0.82; P=0.78) or bone mineral density (MD, -0.01; 95% CI, -0.03 to 0.02; P=0.60). Average prostate volume increased (MD, 1.58; 95% CI, 0.6 to 2.56; P=0.002) following testosterone replacement therapy, but the levels of prostate-specific antigen (PSA) (MD, 0.10; 95% CI, -0.03 to 0.22; P=0.14) and the International Prostate Symptom Scores (MD, 0.01; 95% CI, -0.37 to 0.39; P=0.96) did not change. In conclusion, testosterone replacement therapy improves quality of life, increases lean body mass, significantly decreases total cholesterol, and is well-tolerated and safe for men with hypogonadism who are exhibiting PSA levels of <4 ng/ml.
Guo C, Gu W, Liu M, Peng BO, Yao X, Yang B, Zheng J. Efficacy and safety of testosterone replacement therapy in men with hypogonadism: A meta-analysis study of placebo-controlled trials. Exp Ther Med. 2016 Mar;11(3):853-863.

20. Testosterone replacement therapy improves health-related quality of life for patients with late-onset hypogonadism: a meta-analysis of randomized controlled trials

Abstract: Although testosterone replacement therapy can restore serum testosterone concentrations to normal level in late-onset hypogonadism patients, whether it can improve patients' quality of life remains uncertain. Therefore, we perform a meta-analysis of randomized controlled trials on this issue. Five randomized controlled trials total 1,212 patients were included. Fixed-effect model was used to calculate the weighted mean difference of score of Aging Males' Symptom rating scale. Our result reveals that testosterone replacement therapy improves patients' health-related quality of life in terms of the decrease in the AMS total score [WMD = -2.96 (-4.21, -1.71), p < .00001] and the psychological [WMD = -0.89 (-1.41, -0.37), p = .0008], somatic [WMD = -0.89 (-1.41, -0.37), p = .0008] and sexual [WMD = -1.29 (-1.75, -0.83), p < .00001] subscale score.
Nian Y, Ding M, Hu S, He H, Cheng S, Yi L, Li Y, Wang Y. Testosterone replacement therapy improves health-related quality of life for patients with late-onset hypogonadism: a meta-analysis of randomized controlled trials. Andrologia. 2017 May;49(4).

21. Treatment of Men for "Low Testosterone": A Systematic Review

Testosterone products are recommended by some prescribers in response to a diagnosis or presumption of "low testosterone" (low-T) for cardiovascular health, sexual function, muscle weakness or wasting, mood and behavior, and cognition. We performed a systematic review of 156 eligible randomized controlled trials in which testosterone was compared to placebo for one or more of these conditions. We included studies in bibliographic databases between January 1, 1950 and April 9, 2016, and excluded studies involving

bodybuilding, contraceptive effectiveness, or treatment of any condition in women or children. Studies with multiple relevant endpoints were included in all relevant tables. Testosterone supplementation did not show consistent benefit for cardiovascular risk, sexual function, mood and behavior, or cognition. Studies that examined clinical cardiovascular endpoints have not favored testosterone therapy over placebo. Testosterone is ineffective in treating erectile dysfunction and controlled trials did not show a consistent effect on libido. Testosterone supplementation consistently increased muscle strength but did not have beneficial effects on physical function. Most studies on mood-related endpoints found no beneficial effect of testosterone treatment on personality, psychological well-being, or mood. The prescription of testosterone supplementation for low-T for cardiovascular health, sexual function, physical function, mood, or cognitive function is without support from randomized clinical trials.
Huo S, Scialli AR, McGarvey S, Hill E, Tügertimur B, Hogenmiller A, Hirsch AI, Fugh-Berman A. Treatment of Men for "Low Testosterone": A Systematic Review. PLoS One. 2016 Sep 21;11(9):e0162480.

22. 2016 Update on Medical Overuse: A Systematic Review

I**mportance:** Overuse of medical care is an increasingly recognized problem in clinical medicine.
Objective: To identify and highlight original research articles published in 2015 that are most likely to reduce overuse of medical care, organized into 3 categories: overuse of testing, overtreatment, and questionable use of services. The articles were reviewed and interpreted for their importance to clinical medicine.
Evidence Review: A structured review of English-language articles on PubMed published in 2015 and review of tables of contents of relevant journals to identify potential articles that related to medical overuse in adults.
Findings: Between January 1, 2015, and December 31, 2015, we reviewed 1445 articles, of which 821 addressed overuse of medical care. Of these, 112 were deemed most relevant based on their originality, methodologic quality, and number of patients potentially affected. The 10 most influential articles were selected by consensus using the same criteria. Findings included a doubling of specialty referrals and advanced imaging for simple headache (from 6.7% in 2000 to 13.9% in 2010); unnecessary hospital admission for low-risk syncope, often leading to adverse events; and overly frequent colonoscopy screening for 34% of patients. Overtreatment was common in the following areas: 1 in 4 patients with atrial fibrillation at low risk for thromboembolism received anticoagulation; **94% of testosterone replacement therapy was administered off guideline recommendations;** 91% of patients resumed taking opioids after overdose; and 61% of patients with diabetes were treated to potentially harmfully low hemoglobin A1c levels (<7%). Findings also identified medical practices to question, including questionable use of treatment of acute low-back pain with cyclobenzaprine and oxycodone/acetaminophen; of testing for Clostridium difficile with molecular assays; and serial follow-up of benign thyroid nodules.
Conclusions and Relevance: The number of articles on overuse of medical care nearly doubled from 2014 to 2015. The present review promotes reflection on the top 10 articles and may lead to questioning other non-evidence-based practices.
Morgan DJ, Dhruva SS, Wright SM, Korenstein S. 2016 Update on Medical Overuse: A Systematic Review. JAMA Intern Med. 2016 Nov 1;176(11):1687-1692.

Bottom Lines

1. Many more men with low grade prostate cancer are choosing active surveillance over surgery or radiation therapy, and the outcomes of active surveillance appear nearly as good with fewer side effects.

2. Since many men are choosing active surveillance, it is reasonable to screen for prostate cancer with PSA testing with shared decision making. The optimal screening protocol for prostate cancer screening with PSA is not known.

3. Testosterone replacement therapy has some small positive effects in some men, such as increased muscle strength and sense of well-being.

4. There is likely cardiovascular risk with TRT in patients at high risk of CAD. Cardiovascular risk in low risk men is uncertain.

5. TRT is not helpful for ED. It does increase desire in some men.

6. TRT raises the hemoglobin level about 1.0. The therapeutic benefit is uncertain.

Hypertension Update Gary Ferenchick, MD

Learning objectives | Understand:

1. The results of the Systolic Blood Pressure Intervention Trial (SPRINT) trial compared to the ACCORD BP Trial, and its relevance to cardiovascular disease prevention.
2. The results of the HOPE – 3 hypertension trial and its relevance to cardiovascular disease prevention.
3. Recent AAFP and ACP guidelines on intensive BP treatment for those > 60
4. Recent 2017 AHA ACC guideline on HTN

Blood pressure and macrovascular disease in the post–SPRINT era

#1: PubMed: The SPRINT Trial

BACKGROUND: The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.
METHODS: We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.
RESULTS: At 1 year, the mean systolic blood pressure was 121.4 mm Hg in the intensive-treatment group and 136.2 mm Hg in the standard-treatment group. The intervention was stopped early after a median follow-up of 3.26 years owing to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; hazard ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P<0.001). All-cause mortality was also significantly lower in the intensive-treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90; P=0.003). Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive-treatment group than in the standard-treatment group.
CONCLUSIONS: Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group.
REFERENCE: *SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26;373(22):2103-16. doi: 10.1056/NEJMoa1511939. Epub 2015 Nov 9. PMID: 26551272*

#2: PubMed: The ACCORD BP Trial

BACKGROUND: There is no evidence from randomized trials to support a strategy of lowering systolic blood pressure below 135 to 140 mm Hg in persons with type 2 diabetes mellitus. We investigated whether therapy targeting normal systolic pressure (i.e., <120 mm Hg) reduces major cardiovascular events in participants
with type 2 diabetes at high risk for cardiovascular events.
METHODS: A total of 4733 participants with type 2 diabetes were randomly assigned to intensive therapy, targeting a systolic pressure of less than 120 mm Hg, or standard therapy, targeting a systolic pressure of less than 140 mm Hg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years.
RESULTS: After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive-therapy group and 133.5 mm Hg in the standard-therapy group. The annual rate of the primary outcome was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (hazard ratio with intensive therapy, 0.88; 95% confidence interval [CI], 0.73 to 1.06; P=0.20). The annual rates of death from any cause were 1.28% and 1.19% in the two groups, respectively (hazard ratio, 1.07; 95% CI, 0.85 to 1.35; P=0.55). The annual rates of stroke, a prespecified secondary outcome, were 0.32% and 0.53% in the two groups, respectively (hazard ratio, 0.59; 95% CI, 0.39 to 0.89; P=0.01). Serious adverse events attributed to antihypertensive treatment occurred in 77 of the 2362 participants in the intensive-therapy group (3.3%) and 30 of the 2371 participants in the standard-therapy group (1.3%) (P<0.001).
CONCLUSIONS: In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events. (ClinicalTrials.gov number, NCT00000620.)
Reference*: ACCORD Study Group, Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010 Apr 29;362(17):1575-85. PMID: 20228401*

#3: PubMed: The Hope-3 Trial

BACKGROUND: Antihypertensive therapy reduces the risk of cardiovascular events among high-risk persons and among those with a systolic blood pressure of 160 mm Hg or higher, but its role in persons at intermediate risk and with lower blood pressure is unclear.
METHODS: In one comparison from a 2-by-2 factorial trial, we randomly assigned 12,705 participants at intermediate risk who did not have cardiovascular disease to receive either candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; the second coprimary outcome additionally included resuscitated cardiac arrest, heart failure, and revascularization. The median follow-up was 5.6 years.
RESULTS: The mean blood pressure of the participants at baseline was 138.1/81.9 mm Hg; the decrease in blood pressure was 6.0/3.0 mm Hg greater in the active-treatment group than in the placebo group. The first coprimary outcome occurred in 260 participants (4.1%) in the active-treatment group and in 279 (4.4%) in the placebo group (hazard ratio, 0.93; 95% confidence interval [CI], 0.79 to 1.10; P=0.40); the second coprimary outcome occurred in 312 participants (4.9%) and 328 participants (5.2%), respectively (hazard ratio, 0.95; 95% CI,0.81 to 1.11; P=0.51). In one of the three prespecified hypothesis-based subgroups, participants in the subgroup for the upper third of systolic blood pressure (>143.5 mm Hg) who were in the active-treatment group had significantly lower rates of the first and second coprimary outcomes than those in the placebo group; effects were neutral in the middle and lower thirds (P=0.02 and P=0.009, respectively, for trend in the two outcomes).
CONCLUSIONS: Therapy with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day was not associated with a lower rate of major cardiovascular events than placebo among persons at intermediate risk who did not have cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; ClinicalTrials.gov number, NCT00468923.).
REFERENCE: *Lonn EM, et al. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. N Engl J Med. 2016 May 26;374(21):2009-20.*

#4: PubMed: Baseline predicted CV risk equations for DP lowering decisions

BACKGROUND: We aimed to investigate whether the benefits of blood pressure-lowering drugs are proportional to baseline cardiovascular risk, to establish whether absolute risk could be used to inform treatment decisions for blood pressure-lowering therapy, as is recommended for lipid-lowering therapy.
METHODS: This meta-analysis included individual participant data from trials that randomly assigned patients to either blood pressure-lowering drugs or placebo, or to more intensive or less intensive blood pressure-lowering regimens. The primary outcome was total major cardiovascular events, consisting of stroke, heart attack, heart failure, or cardiovascular death. Participants were separated into four categories of baseline 5-year major cardiovascular risk using a risk prediction equation developed from the placebo groups of the included trials (<11%, 11-15%, 15-21%, >21%).
FINDINGS: 11 trials and 26 randomised groups met the inclusion criteria, and included 67,475 individuals, of whom 51,917 had available data for the calculation of the risk equations. 4167 (8%) had a cardiovascular event during a median of 4·0 years (IQR 3·4-4·4) of follow-up. The mean estimated baseline levels of 5-year cardiovascular risk for each of the four risk groups were 6·0% (SD 2·0), 12·1% (1·5), 17·7% (1·7), and 26·8% (5·4). In each consecutive higher risk group, blood pressure-lowering treatment reduced the risk of cardiovascular events relatively by 18% (95% CI 7-27), 15% (4-25), 13% (2-22), and 15% (5-24), respectively (p=0·30 for trend). However, in absolute terms, treating 1000 patients in each group with blood pressure-lowering treatment for 5 years would prevent 14 (95% CI 8-21), 20 (8-31), 24 (8-40), and 38 (16-61) cardiovascular events, respectively (p=0·04 for trend).
INTERPRETATION: Lowering blood pressure provides similar relative protection at all levels of baseline cardiovascular risk, but progressively greater absolute risk reductions as baseline risk increases. These results support the use of predicted baseline cardiovascular disease risk equations to inform blood pressure-lowering treatment decisions.
FUNDING: None.
REFERENCE: *Blood Pressure Lowering Treatment Trialists' Collaboration, Sundström J, et al. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014 Aug 16;384(9943):591-8.*

#5: PubMed: Meta-analysis: Intensive treatment for patients > 60

Background: Recent guidelines recommend a systolic blood pressure (SBP) goal of less than 150 mm Hg for adults aged 60 years or older, but the balance of benefits and harms is unclear in light of newer evidence.
Purpose: To systematically review the effects of more versus less intensive BP control in older adults.
Data Sources: Multiple databases through January 2015 and MEDLINE to September 2016.
Study Selection: 21 randomized, controlled trials comparing BP targets or treatment intensity, and 3 observational studies that assessed harms.
Data Extraction: Two investigators extracted data, assessed study quality, and graded the evidence using published criteria.
Data Synthesis: Nine trials provided high-strength evidence that BP control to less than 150/90 mm Hg reduces mortality (relative risk [RR], 0.90 [95% CI, 0.83 to 0.98]), cardiac events (RR, 0.77 [CI, 0.68 to 0.89]), and stroke (RR, 0.74 [CI, 0.65 to 0.84]). Six trials yielded low- to moderate-strength evidence that lower targets (≤140/85 mm Hg) are associated with marginally significant decreases in cardiac events (RR, 0.82 [CI, 0.64 to 1.00]) and stroke (RR, 0.79 [CI, 0.59 to 0.99]) and nonsignificantly fewer deaths (RR, 0.86 [CI, 0.69 to 1.06]). Low- to moderate-strength evidence showed that lower BP targets do not increase falls or cognitive impairment.
Limitation: Data relevant to frail elderly adults and the effect of multimorbidity are limited.
Conclusion: Treatment to at least current guideline standards for BP (<150/90 mm Hg) substantially improves health outcomes in older adults. There is less consistent evidence, largely from 1 trial targeting SBP less than 120 mm Hg, that lower BP targets are beneficial

for high-risk patients. Lower BP targets did not increase falls or cognitive decline but are associated with hypotension, syncope, and greater medication burden.
***Reference**: Weiss J et al Benefits and Harms of Intensive Blood Pressure Treatment in Adults Aged 60 Years or Older: A Systematic Review and Meta-analysis. Ann Intern Med doi:10.7326/M16-1754 published online January 17 2017.*
Primary Funding Source: U.S. Department of Veterans Affairs,Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. (PROSPERO 2015: CRD42015017677)

#6: Pubmed: AAFP/ACP: Practice guideline Intensive treatment for patients > 60

Description: The American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) jointly developed this guideline to present the evidence and provide clinical recommendations based on the benefits and harms of higher versus lower blood pressure targets for the treatment of hypertension in adults aged 60 years or older.
Methods: This guideline is based on a systematic review of published randomized, controlled trials for primary outcomes and observational studies for harms only (identified through EMBASE, the Cochrane Database of Systematic Reviews, MEDLINE,and ClinicalTrials.gov), from database inception through January 2015. The MEDLINE search was updated through September2016. Evaluated outcomes included all-cause mortality, morbidity and mortality related to stroke, major cardiac events (fatal and nonfatal myocardial infarction and sudden cardiac death), and harms. This guideline grades the evidence and recommendations using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) method.
Target Audience and Patient Population: The target audience for this guideline includes all clinicians, and the target patient population includes all adults aged 60 years or older with hypertension.
Recommendation 1: ACP and AAFP recommend that clinicians initiate treatment in adults aged 60 years or older with systolic blood pressure persistently at or above 150 mm Hg to achieve a target systolic blood pressure of less than 150 mm Hg to reduce the risk for mortality, stroke, and cardiac events. (Grade: strong recommendation, high-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.
Recommendation 2: ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in adults aged 60 years or older with a history of stroke or transient ischemic attack to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for recurrent stroke. (Grade: weak recommendation, moderate-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.
Recommendation 3: ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in some adults aged 60 years or older at high cardiovascular risk, based on individualized assessment, to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for stroke or cardiac events. (Grade: weak recommendation, low quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.
***Reference:** Qaseen A et al. Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher Versus Lower Blood Pressure Targets: A Clinical Practice Guideline From the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. doi:10.7326/M16-1785 Published online January 17 2017*

2107 ACC AHA Guidelines on HTN

In November of 2017 the American College of Cardiology/American Heart Association published a new guideline on the prevention, detection, evaluation, and management of high blood pressure in adults. The article was published online and is 401 pages, however the "meat" of the guideline was covered in only ~ 89 pages. Also the COI declarations covered 22 pages (on a quick review however most authors had no COI with industry). This guideline was heavily influenced by results of the SPRINT study. Broad sections included the following:

- BP and CVD risk
- Classification of the BP
- Measurement of BP
- Causes of HTN
- Patient Evaluation
- Treatment of High BP
- Hypertension in patients with comorbidities
- Special patient groups
- Other considerations (e.g. resistant HTN, hypertensive crises etc)

I'm including my determination of the items that most likely will have the highest impact on primary care providers. My Summary of key aspects of the New BP guidelines are below the numbering and emphases are mine

The New Normal

1. BP should be categorized as normal, elevated, or stage 1 or 2 hypertension to prevent and treat high BP (Table 6) (COR I | LOE B-NR)

The new normal is < 120 / < 80. In addition, a new category of "Elevated Blood Pressure" is included (and if present, non-pharmacological therapy is recommended). Hypertension is defined now as > 130 / > 80. Also returned from previous guidelines are stages of hypertension (Stage 1 and Stage 2). Note the checklist for accurate BP measurement from this guideline is in the appendix

BP Category	SBP		DBP
Normal	< 120	and	< 80
Elevated	120-129	and	< 80
Hypertension			
Stage 1	130-139	or	80 - 89
Stage 2	> 140	or	> 90

Out-of-office BP measurements recommended

2. Out-of-office BP measurements are recommended to confirm the diagnosis of hypertension and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions. (COR I | LOE A)

Take at least 2 readings 1 min apart in morning before taking medications and in evening before supper. Optimally, measure and record BP daily. Ideally, obtain weekly BP readings beginning 2 weeks after a change in the treatment regimen and during the week before a clinic visit. BP should be based on an average of readings on ≥2 occasions for clinical decision-making. The information above may be reinforced with videos available online: Monitoring Your Blood Pressure at Home

Treatment recommendations are a bit more nuanced

3. Use of BP-lowering medications is recommended for **secondary prevention** of recurrent CVD events in patients with clinical CVD and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher, and for **primary prevention** in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and an average SBP 130 mm Hg or higher or an average DBP 80 mm Hg or higher. (COR I | LOE A for SBP)
4. Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher. (COR I | LOE C-LD)

Use the ACC/AHA Pooled Cohort Equation to estimate 10-year risk of atherosclerotic CVD.
However – with one exception (as noted below) treatment should be initiated with a confirmed BP of ≥ 130 / ≥ 80. You will note that for most patients we are asked to calculated the 10-year ASCVD risk (much like we are asked to do for determining candidacy for statin therapy) to determine if the patients 10-year risk is > or < 10%

Summary of BP Thresholds and Goals for Pharmacologic Treatment		
Clinical Condition(s)	**BP Threshold, mm**	**Hg BP Goal, mm Hg**
General		

Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized,	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥130/80	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

5. For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs. (COR I | LOE A)
6. Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target. (COR I | LOE C-EO)

Special Circumstances

Stable ischemic Heart Dz (SIHD)

7. Adults with SIHD and hypertension (BP ≥130/80 mm Hg) should be treated with medications (e.g., GDMT beta blockers, ACE inhibitors, or ARBs) for compelling indications (e.g., previous MI, stable angina) as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension

Heart Failure with Preserved Ejection Fraction

8. Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta blockers titrated to attain SBP of less than 130 mm Hg. (COR I | C-LD)

Note that GDMT beta-blockers for BP control or relief of angina include carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol. Avoid beta-blockers with intrinsic sympathomimetic activity (e.g. pindolol, acebutolol). The beta-blocker atenolol should not be used because it is less effective than placebo in reducing cardiovascular events.

Diabetes

9. In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective (COR I | LOE A)
10. In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria (COR IIb | LOE B-NR)

African-Americans

11. In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. (COR I | B-R)

12. Two or more antihypertensive medications are recommended to achieve a BP target of less than 130/80 mm Hg in most adults with hypertension, especially in black adults with hypertension. (COR I | C-LD)

Elderly (> 65)

13. Treatment of hypertension with a SBP treatment goal of less than 130 mm Hg is recommended for noninstitutionalized ambulatory community dwelling adults (≥65 years of age) with an average SBP of 130 mm Hg or higher (COR I | LOE A)
14. For older adults (≥65 years of age) with hypertension and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. (COR IIa | LOE C-EO)

#7: PubMed: 13.7% more people in the US are now classified as having HTN

BACKGROUND: The 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults provides recommendations for the definition of hypertension, systolic and diastolic blood pressure (BP) thresholds for initiation of antihypertensive medication and BP target goals.
OBJECTIVE: Determine the prevalence of hypertension, implications of recommendations for antihypertensive medication and prevalence of BP above the treatment goal among US adults using criteria from the 2017 ACC/AHA and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) guidelines.
METHODS: We analyzed data from the 2011-2014 National Health and Nutrition Examination Survey (N=9,623). **NHANES** participants completed study interviews and an examination. For each participant, blood pressure was measured three times following a standardized protocol and averaged. Results were weighted to produce
US population estimates.
RESULTS: According to the 2017 ACC/AHA and JNC7 guidelines, the overall crude prevalence of hypertension among US adults was 45.6% (95% confidence interval [CI] 43.6%,47.6%) and 31.9% (95%CI 30.1%, 33.7%), respectively, and antihypertensive medication was recommended for 36.2% (95%CI 34.2%, 38.2%) and 34.3% (32.5%, 36.2%) of US adults, respectively. Compared to US adults recommended antihypertensive medication by JNC7, those recommended treatment by the 2017 ACC/AHA guideline but not JNC7 had higher CVD risk. Non-pharmacological intervention is advised for the 9.4% of US adults with hypertension according to the 2017 ACC/AHA guideline who are not recommended antihypertensive medication. Among US adults taking antihypertensive medication, 53.4% (95%CI 49.9%, 56.8%) and 39.0% (95%CI 36.4%, 41.6%) had BP above the treatment goal according to the 2017 ACC/AHA and JNC7 guidelines, respectively. Overall, 103.3 (95%CI 92.7,114.0) million US adults had hypertension according to the 2017 ACC/AHA guideline of whom 81.9 (95%CI 73.8, 90.1) million were recommended antihypertensive medication.
CONCLUSION: Compared with the JNC 7 guideline, the 2017 ACC/AHA guideline results in a substantial increase in the prevalence of hypertension but a small increase in the percentage of U.S. adults recommended antihypertensive medication. A substantial proportion of US adults taking antihypertensive medication is recommended more intensive BP lowering under the 2017 ACC/AHA guideline.
REFERENCE*: Muntner P et al. Potential U.S. Population Impact of the 2017 American College of Cardiology/American Heart Association High Blood Pressure Guideline.J Am Coll Cardiol. 2017 Nov 6.(PMID: 29146532)*

Key Points

1. The SPRINT trial demonstrated that targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, in *non-diabetic high risk patients*, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause
2. The HOPE-3 trial demonstrated that in average risk patients with a mean baseline BP of136/82; the addition of candesartan PLUS hydrochlorothiazide for ~5.6 years was not associated with better macrovascular outcomes
3. The ACP and AAFP recommend that clinicians initiate blood pressure treatment in adults aged 60 years or older with systolic blood pressure persistently at or above 150 mm Hg
4. The ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in adults aged 60 years or older with a history of stroke or transient ischemic attack to achieve a target systolic blood pressure of less than 140 mm Hg
5. The new ACC AHA guidelines are “hot off the press” and could have a dramatic effect on BP management in the next several years

6. As a result of these new guidelines, 13.7% more people in the US are now classified as having HTN

Appendix 1: The SPRINT Trial

The SPRINT trial compared the outcomes of treating systolic blood pressure to a target of 120 mm Hg compared to a target of 140. SPRINT inclusion criteria included all of the following:

- Age ≥ 50
- Systolic blood pressure of 130 -180 (note there was no diastolic BP inclusion criteria)
- Increased risk of cardiovascular events, as defined by ≥ 1 of the following:
    - A 10-year risk of cardiovascular disease of > 15% using the Framingham score
    - Clinical or subclinical cardiovascular disease other than CVA (defined in the appendix)
    - Chronic kidney disease (excluding polycystic kidney disease) as defined by:
        - Estimated GFR of 20 - 60 ml/min
    - Age > 75

Importantly the exclusion criteria included patients with diabetes (more later) and those with a prior stroke (other important exclusion criteria are in the appendix).

Treatment algorithms included 2 or 3 drug therapy using a combo of:

- Thiazide diuretic (or loop-diuretic if advanced CKD) , and or
- ACE or ARB (not both), and/or
- CCB

Use of beta-blockers or other antihypertensives (e.g. vasodilators, alpha 2 agonists, alpha-agonists) were allowed "as appropriate for compelling reasons".

The primary outcome was a composite of:

- MI
- ACS
- Stroke
- Acute decompensated CHF
- Death from CV causes

Secondary outcomes included:

- Individual components of the composite outcome
- Overall mortality
- Composite of primary outcome AND death.
- Renal outcomes were also assessed.

Finally the study included analysis of pre-specified subgroups:

- CKD at baseline (yes vs no)
- Sex
- Race (black vs non-black)
- Age (<75 > 75)
- Baseline SBP (< 132; 132 - 145; > 145).

SPRINT Results

There were 4678 randomized to the intensive Rx group and 4683 randomized to the standard Rx group. The median follow up 3.26 years.

Blood pressure results

- At 1-yr the mean SBP was 121 vs 136 (Δ 14.8 mmHg) and the mean DBP 68.7 vs 76.3 (Δ 7.6 mmHg).
- For the entire 3.26 years of f/u the mean SBP averaged 121.5 vs 134.6 (Δ 13.1 mmHg)
- The mean # of BP meds was 2.8 vs 1.8.

Primary outcome results:

- The primary outcome occurred in 1.65%/yr in the intensively treated group vs 2.19%/yr.
- The NNT to prevent one primary outcome in one year was 185.
- Over the 3.26 years of the study duration the NNT was:

- 61 to prevent one primary outcome; the separation in primary outcome was seen in 1 year
- 90 to prevent one death from any cause; the separation in mortality was seen in 2 years
- 173 to prevent one death from a CV cause

- The results for the primary outcome and total mortality were consistent across the pre-specified subgroups

Renal outcomes

- If CKD at baseline: no between group differences.
- If no CKD at baseline: a decrease in GFR of > 30% OR a decrease in the GFR to a value of < 60 ml/minute was higher in intensive Rx group (1.2. vs 0.35% per year: NNH = 117)

Serious Adverse Events:

- 4.7% intensive vs 2.5% standard (mostly: Hypotension, Syncope, Electrolyte abnormality, AKI/AKF: NNH = 45 – see appendix)
    - No major difference in those > 75 compared to the total population

SPRINT Exclusion Criteria

Among the exclusions, included:
• Patients with diabetes or prior stroke were excluded.
• Other exclusions:
  ○ Orthostatic BP of < 110
  ○ Proteinuria > 1 gram/d
  ○ GFR < 20
  ○ CV event or procedure within the past 3 months
  ○ Symptomatic heart failure within past 6 months or LVEF < 35%
  ○ Dementia

Inclusion criteria:
Clinical CVD (other than stroke) • Previous myocardial infarction (MI), percutaneous coronary intervention (PCI), • coronary artery bypass grafting (CABG), carotid endarterectomy (CE), carotid • stenting • Peripheral artery disease (PAD) with revascularization • Acute coronary syndrome with or without resting ECG change, ECG changes on a graded exercise test (GXT), or positive cardiac imaging study • At least a 50% diameter stenosis of a coronary, carotid, or lower extremity artery • Abdominal aortic aneurysm (AAA) ≥5 cm with or without repair Sub clinical CVD • Coronary artery calcium score ≥ 400 Agatston units within the past 2 years. • Ankle brachial index (ABI) ≤0.90 within the past 2 years. • Left ventricular hypertrophy (LVH) by ECG (based on computer reading), echocardiogram report, or other cardiac imaging procedure report within the past 2 years

Appendix 2: ACC AHA Guideline Rating Scheme

Class of Recommendation (COR) and Level of evidence (LOE) | ACC/AHA Guidelines

Class (Strength) of Recommendation (COR) Table

- **Class I (Benefit >>> Risk):** **Should be done | *Is* useful | (Strong)**
- Class IIa (Benefit >> Risk): Reasonable to do | *Can* be useful | (Moderate)
- Class IIb (Benefit ≥ Risk): May be considered | *Unknown* usefulness (Weak)
- Class III (No benefit or harm): Not helpful or harmful

Level (Quality) of Evidence (LOE)

- Level A:
  - High quality evidence from ≥ 1 RCT
  - Meta-analysis of high-quality RCTs
  - ≥ 1 RCT corroborated by high-quality registry studies
- Level B-R (Randomized):
  - Moderate quality evidence from ≥ 1 RCT
  - Meta-analyses of moderate quality RCTs
- Level B-NR (Non-randomized):
  - Moderate quality evidence from ≥ 1 high-quality nonrandomized/observational or registry studies
  - Meta-analyses of such studies
- Level C-LD
  - Randomized or nonrandomized/observational or registry studies with limitations of design or execution
  - Meta-analyses of such studies
  - Physiological or mechanistic studies in humans
- Level C-EO
  - Consensus opinion based upon clinical experience

The COR and the LOE are determined independent of each other. Any COR can be paired with any LOE (notably LOE C does not imply the COR is weak)

Appendix 3: Key Steps for accurate BP measurement in the office

Key Steps for Proper BP Measurements	Specific Instructions
Step 1: Properly prepare the patient	1. Have the patient relax, sitting in a chair (feet on floor, back supported) for >5 min. 2. The patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement. 3. Ensure patient has emptied his/her bladder. 4. Neither the patient nor the observer should talk during the rest period or during the measurement. 5. Remove all clothing covering the location of cuff placement. 6. Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria.
Step 2: Use proper technique for BP measurements	1. Use a BP measurement device that has been validated, and ensure that the device is calibrated periodically.* 2. Support the patient's arm (e.g., resting on a desk). 3. Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum). 4. Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used. 5. Either the stethoscope diaphragm or bell may be used for auscultatory readings.
Step 3: Take the proper measurements needed for diagnosis and treatment of elevated BP/hypertension	1. At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings. 2. Separate repeated measurements by 1–2 min. 3. For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff 20–30 mm Hg above this level for an auscultatory determination of the BP level. 4. For auscultatory readings, deflate the cuff pressure 2 mm Hg per second, and listen for Korotkoff sounds.
Step 4: Properly document accurate BP readings	1. Record SBP and DBP. If using the auscultatory technique, record SBP and DBP as onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even number. 2. Note the time of most recent BP medication taken before measurements.
Step 5: Average the readings	Use an average of ≥2 readings obtained on ≥2 occasions to estimate the individual's level of BP.
Step 6: Provide BP readings to patient	Provide patients the SBP/DBP readings both verbally and in writing.

Appendix 4: Nonpharmacological interventions for BP management (all with a COR 1 | LOE A)

	Nonpharmacological Intervention	Dose	Approximate Impact on SBP
			Hypertension
Weight loss	Weight/body fat	Best goal is ideal body weight, but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight.	- 5 mm Hg
Diet	DASH Diet	Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.	- 11 mm Hg
↓ Sodium		Optimal goal is <1500 mg/d, but aim for at least a 1000-mg/d reduction in most adults.	- 5 mm Hg
↑ Dietary Potassium		Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium.	- 5 mm Hg
Alcohol		Men: ≤2 drinks daily Women: ≤1 drink daily	- 4 mm Hg
Exercise	Aerobic	90–150 min/wk 65%–75% heart rate reserve	- 5 mm Hg
	Resistance	90–150 min/wk 50%–80% 1 rep maximum 6 exercises, 3 sets/exercise, 10 repetitions/set	- 4 mm Hg

Essentials Update on Substance Abuse — William Wadland, MD

The following presentation is intended to be an update and not a comprehensive review. It is based on a selective search of the current Essentials data base, Cochrane Reviews, and PubMed. The update focuses on interventions relevant to primary care practice concerning tobacco use, drugs of abuse (including prescription drugs), and alcohol abuse.

Objectives: after this presentation, participants should be able to:

1. Describe current interventions (behavioral and pharmacologic) for smoking cessation
2. Advise patients on the pros and cons of ENDs
3. Describe the DSM 5 criteria for substance abuse disorders and simple questions to identify patients at risk
4. Describe current interventions (behavioral and pharmacologic) for substance abuse disorder
5. Review effective brief interventions for risky drinking and alcohol abuse
6. Review pharmacologic interventions for acute alcohol withdrawal syndrome (AWS)

Tobacco Abuse

1. USPSTF: Stay the course on addressing smoking

Clinical question: What are the current recommendations from the U.S. Preventive Services Task Force regarding screening for and the treatment of nicotine and tobacco use?
Study design: Practice guideline
Setting: Various (guideline)
Synopsis: Based on an updated review of evidence, the USPSTF continues to recommend that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and pharmacotherapy (A recommendation). Unlike some other guideline-espousing groups, they do not suggest asking about electronic nicotine delivery systems (e-cigarettes) in the screening process. They find the evidence insufficient to recommend e-cigarettes as a path to smoking cessation (I statement).
Bottom line: In this update to their 2009 recommendations, the U.S. Preventive Services Task Force (USPSTF) continues to conclude that clinicians should ask all adult patients about tobacco use (they don't address whether e-cigarettes should be included) and advise them to stop. The authors do not find the research on e-cigarettes persuasive and continue to suggest other forms of nicotine replacement or usual treatments to aid patients who wish to quit.
Siu AL; U.S. Preventive Services Task Force. Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2015;163(8):622-634.

2. Reward-based financial incentives are effective for smoking cessation

Clinical question: What is the most effective approach to implementing financial rewards to incentivize smoking cessation?
Study design: Randomized controlled trial (double-blinded)
Setting: Population-based
Synopsis: Economists will tell you that behavior is aligned with incentives, and previous studies have indeed shown that financial incentives can increase the rate of smoking cessation. This study looked at different approaches to implementing such a program. The authors recruited 2538 CVS Caremark (a pharmacy chain) employees and randomized them into 1 of 5 groups: (1) usual care, (2) individual reward, (3) collaborative reward, (4) individual deposit, or (5) collaborative deposit. All participants received access to smoking cessation resources, including free access to nicotine replacement and a behavioral modification program. The individual reward program provided $200 payments for successfully being nicotine free at certain intervals (up to $800), while the deposit program put $150 of the employee's money at risk and they only got the money back (along with $450 per employee in matching funds from the employer) if they quit. Group programs created incentives to support one another and collaborate to encourage cessation in groups of 6. Patients were randomized to one of the groups, and then had the opportunity to participate or not participate in the assigned program. Because there were different rates of accepting the programs, the authors used an adaptive algorithm that assigned more employees to less popular programs to achieve a similar number in each group. The median age of participants was 33 years, 63% were women, and 80% were white. Approximately, 75% had a median household income of less than $60,000 per year, which meant that the incentives were financially meaningful. The median number of cigarettes smoked per day by participants was 15, with an interquartile range of 10 to 20. The groups were balanced at the beginning of the study, and analysis was by intention to treat. There were 3 key findings. First, participants were much more likely to choose a reward-based program over one that put $150 of their own money at risk (94.8% vs 12.6% for the individual-based programs; $P < .001$). There was also little difference between individual-based and group-based reward or deposit programs. The groups were not physically in the same location, and were only linked via computer, so it is still possible that group incentives may have more impact when you work alongside the members of the group. Finally, among persons who were willing to accept a deposit-based program, their quit rates were actually higher than those in the reward programs

(52.3% vs 17.1% at 6 months; P < .001; number needed to treat = 3).
Bottom line: Patients are more likely to participate in reward-based smoking cessation programs, with quit rates of 9.4% vs 16.0% for the programs compared with 6.0% for usual care. Individual reward-based programs had the highest quit rates, largely due to a much greater acceptance rate of these programs.
*Halpern SD, French B, Small DS, et al. Randomized trial of four financial-incentive programs for smoking cessation. N Engl J Med 2015;372(22):2108-2117.*Poem 2014-11-24:

3. Postdischarge tobacco cessation intervention results in higher quit rates for hospitalized smokers

Clinical question: For hospitalized smokers interested in quitting tobacco, does a postdischarge intervention including automated phone calls and free tobacco cessation medications increase smoking cessation rates?
Study design: Randomized controlled trial (nonblinded)
Setting: Inpatient (any location) with outpatient follow-up
Synopsis: Smokers who were hospitalized and were interested in quitting smoking upon discharge were enrolled in this trial. Using concealed allocation, investigators randomized 198 patients to the intervention, which consisted of a free supply of tobacco cessation medication for up to 3 months, as well as 5 automated phone calls during the first 90 days after discharge providing advice and support messages with an opportunity to call a counselor if needed for additional support. The tobacco cessation medication included nicotine replacement therapy, buproprion, and/or varenicline. The standard care group (n = 199) received only a recommendation for a postdischarge tobacco cessation medication and information for a free telephone quit line. Both groups received smoking cessation counseling in the hospital by trained counselors. Follow-up at 6 months included 81% of the smokers, with no significant difference between intervention and control groups. At baseline, the 2 groups had similar characteristics, with a mean age of 53 years and a mean daily cigarette count of 17. Nicotine replacement therapy was the favored medication, recommended to 96% of participants in both groups. Overall, the intervention group had a higher rate of use of tobacco cessation treatment, including both pharmacotherapy and counseling, throughout the 6 months following discharge. In the intervention group, the rate of biochemically confirmed past 7-day tobacco abstinence at the 6-month follow-up was almost double that of the standard care group (26% vs 15%; relative risk 1.71; 95% CI 1.13 - 2.56; number needed to treat = 9). Of note, the biochemical test used was a mailed saliva sample for cotinine and not a random test, thus patients could presumably show a negative result if they abstained for a week prior to testing even if they smoked at other times. The investigators calculated that the hospital's estimated cost per patient in delivering this intervention was $540 for year 1 and $294 for subsequent years. This included the cost of personnel time, medications, and office space, as well as the cost of building the telephone system and training the staff during the first year.
Bottom line: A postdischarge intervention that included interactive voice-response phone calls, opportunities for counseling, and a free supply of tobacco cessation medications resulted in higher quit rates than standard care at 6 months for hospitalized smokers interested in quitting. You would need to treat 9 patients with this intervention at an estimated cost of $300 to $500 per patient to have one additional person quit smoking.
Rigotti NA, Regan S, Levy DE, et al. Sustained care intervention and postdischarge smoking cessation among hospitalized adults. JAMA 2014;312(7):719-728.

4. Smoking cessation: abrupt quitting more effective than a gradual approach

Clinical question: Should patients stop smoking abruptly on their quit date or gradually reduce their smoking before attempting smoking cessation?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (primary care)
Synopsis: Participants in this study were recruited from 31 general practices in England. The practices sent letters to patients who smoke asking them to participate in a study on quitting. In other words, the 697 patients in this study were interested in quitting. The participants were assigned (allocation concealment unclear) to 2 groups, differing only in the initial approach to cessation. All patients were asked to set a quit day 2 weeks after enrollment and were given nicotine patches (21 mg per day) to use during those 2 weeks. Patients in the "abrupt cessation group" were asked to stop smoking on their quit day. Participants in the "gradual cessation group" were also given short-acting nicotine products (gum, lozenges, nasal spray, sublingual tablets, inhalator, or mouth spray) and asked to reduce smoking to half of the baseline amount by the end of the first week and to a quarter of the baseline amount at the end of the second week. All participants were given extensive behavior support by a research nurse weekly for 2 weeks before their quit day, the day before their quit day, weekly for 4 weeks after quitting, and at 8 weeks after the quit day. At both 1 month and 6 months, validated abstinence rates were higher in the abrupt cessation group: 49.0% vs 39.2% at 1 month (relative risk [RR] 0.80; 95% CI 0.66 to 0.93) and 22.0% vs 15.5% (RR 0.71; 0.46 to 0.91) at 6 months. At 1 month, one additional patient will be successful for every 13 patients who abruptly stop instead of stopping gradually (number needed to treat [NNT] = 12.8; 7.5 - 38.4). At 6 months, the benefit is not quite as large (NNT = 22.2; 11.9 - 71.7). Withdrawal symptoms and urge intensity reports were similar in both groups. The study was set up as a noninferiority trial, but inferiority (less than a 19-percentage-point difference) was not met.
Bottom line: For motivated patients, quitting abruptly on a set date, preceded by 2 weeks of nicotine replacement via a patch, is more effective than doing the same preparation but gradually cutting down before stopping, even when each omitted cigarette is replaced with a hit of nicotine. All of the patients in this study received extensive behavior support before quitting and during the first few months, which likely added to the success rates in both groups.
Lindson-Hawley N, Banting M, West R, Michie S, Shinkins B, Aveyard P. Gradual versus abrupt smoking cessation. A randomized, controlled noninferiority trial. Ann Intern Med 2016;164(9):585-592.

5. Long-term nicotine replacement no more effective

Clinical question: What is the best duration of nicotine replacement therapy in patients who also receive extensive counseling?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (any)
Synopsis: These investigators enrolled 525 smokers who responded to advertisements for a smoking cessation study. All participants received 12 counseling sessions, beginning with an in-person session 2 weeks before their quit date and continuing via telephone over the course of the next year. All patients received nicotine replacement via patch, randomized (allocation concealment uncertain) to a duration of 8, 24, or 52 weeks. Using intention-to-treat analysis, at 6 months 21.7% to 27.2% of patients were abstinent (as confirmed by expired carbon monoxide levels). By one year, abstinence rates were still greater than 20% in all 3 groups with no additional benefit to ongoing treatment.
Bottom line: In motivated smokers who receive ongoing telephone counseling, extended nicotine replacement beyond 8 weeks does little, on average, to increase cessation rates. Advise patients that they may follow the standard 8-week protocol for nicotine patches or continue to use the patch for longer than 8 weeks, if they so desire.
Schnoll RA, Goelz PM, Veluz-Wilkins A, et al. Long-term nicotine replacement therapy: a randomized clinical trial. JAMA Intern Med 2015;175(4):504-511.

6. Varenicline effective for smokers preferring to "cut down" rather than quit "cold turkey"

Clinical question: Is varenicline effective treatment for adult smokers preferring to "cut down" rather than to quit "cold turkey"?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Many smokers prefer to quit gradually (“cut down”) rather than immediately ("cold turkey"). These investigators recruited adult smokers (N = 1510), 18 years or older, who were interested in quitting smoking but preferred to cut down gradually. Eligible patients smoked an average of 10 or more cigarettes per day and were willing to reduce smoking and make a quit attempt within the next 3 months. Exclusion criteria included suicidal behavior or attempts for the 2 years before enrollment. Participants randomly received (concealed allocation assignment) varenicline (initially 0.5 mg once daily for 3 days, increasing to 0.5 mg twice daily for days 4 to 7, and then 1 mg twice daily) or matched placebo for 24 weeks. Standard smoking cessation counseling occurred for all participants. Patients, investigators, and individuals assessing outcomes (through measurement of exhaled carbon monoxide levels) remained masked to treatment group assignment. Complete follow-up occurred for approximately 70% of participants at 52 weeks. Patients who dropped out and were lost to follow-up were treated as persistent smokers in the data analysis. Using intention-to-treat analysis, patients in the varenicline group achieved significantly higher continuous abstinence rates from weeks 21 through 52 than those in the control group (27.0% vs 9.9%; NNT= 5.8, 4.8-7.5). Drop-out rates due to adverse events were similar between the varenicline and control groups (8.4% vs 7.0%, respectively).
Bottom line: Varenicline (Chantix) therapy for 24 weeks is effective in helping adult smokers who prefer to gradually reduce cigarette smoking rather than quit immediately achieve continuous tobacco abstinence at one year (number needed to treat [NNT] = 5.8, 95% CI 4.8-7.5).
Ebbert JO, Hughes JR, West RJ, et al. Effect of varenicline on smoking cessation through smoking reduction. A randomized clinical trial. JAMA 2015;313(7):687-694.

7. Overview of electronic nicotine delivery systems: a systematic review

Context: Rapid developments in e-cigarettes, or electronic nicotine delivery systems (ENDS), and the evolution of the overall tobacco product marketplace warrant frequent evaluation of the published literature. The purpose of this article is to report updated findings from a comprehensive review of the published scientific literature on ENDS.
Evidence acquisition: The authors conducted a systematic review of published empirical research literature on ENDS through May 31, 2016, using a detailed search strategy in the PubMed electronic database, expert review, and additional targeted searches. Included studies presented empirical findings and were coded to at least one of nine topics: (1) Product Features; (2) Health Effects; (3) Consumer Perceptions; (4) Patterns of Use; (5) Potential to Induce Dependence; (6) Smoking Cessation; (7) Marketing and Communication; (8) Sales; and (9) Policies; reviews and commentaries were excluded. Data from included studies were extracted by multiple coders (October 2015 to August 2016) into a standardized form and synthesized qualitatively by topic.
Evidence synthesis: There were 687 articles included in this systematic review. The majority of studies assessed patterns of ENDS use and consumer perceptions of ENDS, followed by studies examining health effects of vaping and product features.
Conclusions: Studies indicate that ENDS are increasing in use, particularly among current smokers, pose substantially less harm to smokers than cigarettes, are being used to reduce/quit smoking, and are widely available. More longitudinal studies and controlled trials are needed to evaluate the impact of ENDS on population-level tobacco use and determine the health effects of longer-term vaping
Glasser, A.M., Collins, L., Pearson, J.L., Abudayyeh, H., Niaura, R.S., Abrams, D.B., & Villanti, A.C. (2017). American Journal of Preventative Medicine, 52(2). 33-66.

Cochrane Reviews:

8. Internet-based interventions for smoking cessation

Background: Tobacco use is estimated to kill 7 million people a year. Nicotine is highly addictive, but surveys indicate that almost 70% of US and UK smokers would like to stop smoking. Although many smokers attempt to give up on their own, advice from a health professional increases the chances of quitting. As of 2016 there were 3.5 billion Internet users worldwide, making the Internet a potential platform to help people quit smoking.
Objectives: To determine the effectiveness of Internet-based interventions for smoking cessation, whether intervention effectiveness is altered by tailoring or interactive features, and if there is a difference in effectiveness between adolescents, young adults, and adults.
Search methods:We searched the Cochrane Tobacco Addiction Group Specialised Register, which included searches of MEDLINE, Embase and PsycINFO (through OVID). There were no restrictions placed on language, publication status or publication date. The most recent search was conducted in August 2016.
Selection criteria: We included randomised controlled trials (RCTs). Participants were people who smoked, with no exclusions based on age, gender, ethnicity, language or health status. Any type of Internet intervention was eligible. The comparison condition could be a no-intervention control, a different Internet intervention, or a non-Internet intervention. To be included, studies must have measured smoking cessation at four weeks or longer.
Data collection and analysis: Two review authors independently assessed and extracted data. We extracted and, where appropriate, pooled smoking cessation outcomes of six-month follow-up or more, reporting short-term outcomes narratively where longer-term outcomes were not available. We reported study effects as a risk ratio (RR) with a 95% confidence interval (CI).We grouped studies according to whether they (1) compared an Internet intervention with a non-active control arm (e.g. printed self-help guides), (2) compared an Internet intervention with an active control arm (e.g. face-to-face counselling), (3) evaluated the addition of behavioural support to an Internet programme, or (4) compared one Internet intervention with another. Where appropriate we grouped studies by age.
Main results: We identified 67 RCTs, including data from over 110,000 participants. We pooled data from 35,969 participants. There were only four RCTs conducted in adolescence or young adults that were eligible for meta-analysis. Results for trials in adults: Eight trials compared a tailored and interactive Internet intervention to a non-active control. Pooled results demonstrated an effect in favour of the intervention (RR 1.15, 95% CI 1.01 to 1.30, n = 6786). However, statistical heterogeneity was high (I2 = 58%) and was unexplained, and the overall quality of evidence was low according to GRADE. Five trials compared an Internet intervention to an active control. The pooled effect estimate favoured the control group, but crossed the null (RR 0.92, 95% CI 0.78 to 1.09, n = 3806, I2 = 0%); GRADE quality rating was moderate. Five studies evaluated an Internet programme plus behavioural support compared to a non-active control (n = 2334). Pooled, these studies indicated a positive effect of the intervention (RR 1.69, 95% CI 1.30 to 2.18). Although statistical heterogeneity was substantial (I2 = 60%) and was unexplained, the GRADE rating was moderate. Four studies evaluated the Internet plus behavioural support compared to active control. None of the studies detected a difference between trial arms (RR 1.00, 95% CI 0.84 to 1.18, n = 2769, I2 = 0%); GRADE rating was moderate. Seven studies compared an interactive or tailored Internet intervention, or both, to an Internet intervention that was not tailored/interactive. Pooled results favoured the interactive or tailored programme, but the estimate crossed the null (RR 1.10, 95% CI 0.99 to 1.22, n = 14,623, I2 = 0%); GRADE rating was moderate. Three studies compared tailored with non-tailored Internet-based messages, compared to non-tailored messages. The tailored messages produced higher cessation rates compared to control, but the estimate was not precise (RR 1.17, 95% CI 0.97 to 1.41, n = 4040), and there was evidence of unexplained substantial statistical heterogeneity (I2 = 57%); GRADE rating was low. Results should be interpreted with caution as we judged some of the included studies to be at high risk of bias.
Authors' conclusions: The evidence from trials in adults suggests that interactive and tailored Internet-based interventions with or without additional behavioural support are moderately more effective than non-active controls at six months or longer, but there was no evidence that these interventions were better than other active smoking treatments. However some of the studies were at high risk of bias, and there was evidence of substantial statistical heterogeneity. Treatment effectiveness in younger people is unknown.
Taylor, G.M.J, Dalili, M.N., Semwal, M., Civljak, M., Sheikh, A., Car, J. (2017). Internet-based interventions for smoking cessation. Cochrane Database of Systematic Reviews, (9). Art. No.: CD007078. DOI: 10.1002/14651858.CD007078.pub5.

9. Mobile phone-based interventions for smoking cessation

Background: Access to mobile phones continues to increase exponentially globally, outstripping access to fixed telephone lines, fixed computers and the Internet. Mobile phones are an appropriate and effective option for the delivery of smoking cessation support in some contexts. This review updates the evidence on the effectiveness of mobile phone-based smoking cessation interventions.
Objectives: To determine whether mobile phone-based smoking cessation interventions increase smoking cessation in people who smoke and want to quit.
Search methods: For the most recent update, we searched the Cochrane Tobacco Addiction Group Specialised Register in April 2015. We also searched the UK Clinical Research Network Portfolio for current projects in the UK, and the ClinicalTrials.gov register for ongoing or recently completed studies. We searched through the reference lists of identified studies and attempted to contact the authors of ongoing studies. We applied no restrictions on language or publication date.
Selection criteria: We included randomised or quasi-randomised trials. Participants were smokers of any age who wanted to quit. Studies were those examining any type of mobile phone-based intervention for smoking cessation. This included any intervention aimed at mobile phone users, based around delivery via mobile phone, and using any functions or applications that can be used or sent via a mobile phone.
Data collection and analysis: Review authors extracted information on risk of bias and methodological details using a standardised

form. We considered participants who dropped out of the trials or were lost to follow-up to be smoking. We calculated risk ratios (RR) and 95% confidence intervals (CI) for each included study. Meta-analysis of the included studies used the Mantel-Haenszel fixed-effect method. Where meta-analysis was not possible, we presented a narrative summary and descriptive statistics.
Main results: This updated search identified 12 studies with six-month smoking cessation outcomes, including seven studies completed since the previous review. The interventions were predominantly text messaging-based, although several paired text messaging with in-person visits or initial assessments. Two studies gave pre-paid mobile phones to low-income human immunodeficiency virus (HIV)-positive populations - one solely for phone counselling, the other also included text messaging. One study used text messages to link to video messages. Control programmes varied widely. Studies were pooled according to outcomes - some providing measures of continuous abstinence or repeated measures of point prevalence; others only providing 7-day point prevalence abstinence. All 12 studies pooled using their most rigorous 26-week measures of abstinence provided an RR of 1.67 (95% CI 1.46 to 1.90; I2 = 59%). Six studies verified quitting biochemically at six months (RR 1.83; 95% CI 1.54 to 2.19).
Authors' conclusions: The current evidence supports a beneficial impact of mobile phone-based smoking cessation interventions on six-month cessation outcomes. While all studies were good quality, the fact that those studies with biochemical verification of quitting status demonstrated an even higher chance of quitting further supports the positive findings. However, it should be noted that most included studies were of text message interventions in high-income countries with good tobacco control policies. Therefore, caution should be taken in generalising these results outside of this type of intervention and context.
Whittaker, R., McRobbie, H., Bullen, C., Rodgers, A., Gu, Y. (2016). Mobile-phone based interventions for smoking cessation. Cochrane Database of Systematic Reviews, (4). Art. No.: CD006611. DOI: 10.1002/14651858.CD006611.pub4.

10. Motivational interviewing for smoking cessation

Background: Motivational Interviewing (MI) is a directive patient-centred style of counselling, designed to help people to explore and resolve ambivalence about behaviour change. It was developed as a treatment for alcohol abuse, but may help people to a make a successful attempt to quit smoking.
Objectives: To determine whether or not motivational interviewing (MI) promotes smoking cessation.
Search methods: We searched the Cochrane Tobacco Addiction Group Specialized Register for studies using the term motivat* NEAR2 (interview* OR enhanc* OR session* OR counsel* OR practi* OR behav*) in the title or abstract, or motivation* as a keyword. Date of the most recent search: August 2014.
Selection criteria: Randomized controlled trials in which motivational interviewing or its variants were offered to tobacco users to assist cessation.
Data collection and analysis: We extracted data in duplicate. The main outcome measure was abstinence from smoking after at least six months follow-up. We used the most rigorous definition of abstinence in each trial, and biochemically validated rates where available. We counted participants lost to follow-up as continuing smoking or relapsed. We performed meta-analysis using a fixed-effect Mantel-Haenszel model.
Main results: We identified 28 studies published between 1997 and 2014, involving over 16,000 participants. MI was conducted in one to six sessions, with the duration of each session ranging from 10 to 60 minutes. Interventions were delivered by primary care physicians, hospital clinicians, nurses or counsellors. Our meta-analysis of MI versus brief advice or usual care yielded a modest but significant increase in quitting (risk ratio (RR) 1.26; 95% confidence interval (CI) 1.16 to 1.36; 28 studies; N = 16,803). Subgroup analyses found that MI delivered by primary care physicians resulted in an RR of 3.49 (95% CI 1.53 to 7.94; 2 trials; N = 736). When delivered by counsellors the RR was smaller (1.25; 95% CI 1.15 to 1.63; 22 trials; N = 13,593) but MI still resulted in higher quit rates than brief advice or usual care. When we compared MI interventions conducted through shorter sessions (less than 20 minutes per session) to controls, this resulted in an RR of 1.69 (95% CI 1.34 to 2.12; 9 trials; N = 3651). Single-session treatments might increase the likelihood of quitting over multiple sessions, but both regimens produced positive outcomes. Evidence is unclear at present on the optimal number of follow-up calls. There was variation across the trials in treatment fidelity. All trials used some variant of motivational interviewing. Critical details in how it was modified for the particular study population, the training of therapists and the content of the counselling were sometimes lacking from trial reports.
Authors' conclusions: Motivational interviewing may assist people to quit smoking. However, the results should be interpreted with caution, due to variations in study quality, treatment fidelity, between-study heterogeneity and the possibility of publication or selective reporting bias.
Lindson-Hawley, N., Thompson, T.P., Begh, R. (2015). Motivational interviewing for smoking cessation. Cochrane Database of Systematic Reivews, (3). Art. No.: CD006936. DOI: 10.1002/14651858.CD006936.pub3.

Substance Abuse (including prescription drugs)

USPSTF has no recommendations on substance abuse screening. Last systematic search was done in 2006. Presentlty taking recommendations on new search strategy.

DSM 5 Criteria for Substance Abuse Disorder: Opioid Use Disorder Criteria:

A minimum of 2-3 criteria is required for a mild substance us disorder diagnosis, while 4-5 is moderate, and 6-7 is severe (APA, 2013). Opioid Use Disorder is specified instead of Substance Use Disorder, if opioids are the drug of abuse. (check list version available for practice setting)

1. Taking the opioid in larger amounts and for longer than intended.
2. Wanting to cut down or quit but not being able to do it.
3. Spending a lot of time obtaining the opioid.
4. Craving or a desire to us opioids.
5. Repeatedly unable to carry out major obligations at work, school, or home due to opioid use.
6. Continued use despite persistent or recurring social or interpersonal problems caused or made worse by opioid use.
7. Stopping or reducing important social, occupational, or recreational activities due to opioid use.
8. Recurrent use of opioids in physically hazardous situations.
9. Consistent use of opioids despite acknowledgement of persistent or recurrent physical or psychological difficulties from using opioids.
10. Tolerance as defined by either a need for markedly increased amounts to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount. (does not apply under medical supervision).
11. Withdrawal manifesting as either characteristic syndrome or the substance is used to avoid withdrawal (does not apply under medical supervision).

11. Updated CDC guidelines for opioid prescribing for chronic pain

Clinical question: How should primary care clinicians handle opioid prescribing for adults with chronic pain not caused by cancer?
Study design: Practice guideline
Setting: Various (guideline)
Synopsis: Prescription opioid use has increased significantly over the last decade and decreasing opioid-related morbidity is an important public health goal. These authors collected the available evidence on opioid treatment for chronic noncancer pain to answer questions about opioid initiation and follow up, opioid selection and continuation, and opioid harms. The evidence search, along with input from topic experts, professional societies, and federal advisory committees, generated a list of best practice recommendations. The overall quality of evidence was poor. Salient points from the guideline include: (1) Recommending nonpharmacologic therapies (eg, exercise therapy) and nonopioid pharmacologic therapies (NSAIDs, antidepressants, and anticonvulsants) as first-line therapies for chronic pain; (2) establishing realistic goals for improvements in pain and function prior to initiation; (3) discussing known risks and benefits of opioids prior to initiation; (4) initiating therapy with immediate-release preparations and avoiding extended-release preparations; (5) using the lowest effective daily dose with careful reexamination of the risks and benefits of continued therapy (preferably with the help of a pain specialist) when doses exceed 50 to 90 morphine milligram equivalents per day; (6) ensuring close follow-up (1-4 weeks) after initiation and dosing changes, with periodic evaluation (1-3 months) for patients taking stable doses; and (7) using risk mitigation tools, including prescription-drug monitoring programs (all patients), urine drug screens, and naloxone education for patients at increased risk of adverse outcomes. Most studies of opioid effectiveness have been limited to study periods of 6 weeks to 3 months and no studies have evaluated effectiveness for longer than 1 year. Please attribute the authorship of this POEM to Patrick L. Turner, MD, Fellow, Department of Family Medicine, The University of Virginia, Charlottesville, VA.
Bottom line: Based on low-quality evidence, primary care clinicians should carefully weigh the decision to initiate chronic opioid therapy and establish realistic treatment goals focused not on pain relief but on functional improvement. The lowest effective dose should be used concomitantly with risk mitigation strategies to minimize adverse outcomes. Multidisciplinary treatment teams are highly encouraged for patients with an increased risk of adverse events. However, time constraints will likely make effective implementation difficult in current real-world clinical environments.
Dowell D, Haegerich T, Chou R. CDC guideline for prescribing opioids for chronic pain - United States, 2016. JAMA 2016;315(15):1624-1645.

12. Clonidine beneficial as adjuvant therapy for opioid dependence

Clinical question: Does adjunctive treatment with clonidine improve abstinence rates during buprenorphine treatment for opioid dependence?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (specialty)
Synopsis: This randomized controlled trial among opioid-dependent outpatient volunteers compared clonidine with placebo as adjuvant treatment to buprenorphine. The authors enrolled 208 physically dependent patients aged 18 to 60 years and then randomized the 118 who remained in the program at the end of week 6. Patients were excluded from the study if they had a current psychotic disorder or major depression, a history of bipolar disorder or schizophrenia, current dependence on alcohol or sedatives, cognitive impairment that would preclude consent or self-report, medical conditions that would compromise participation, or the use of contraindicated medications. Buprenorphine treatment began at enrollment with daily dosing observed at the clinic 7 days a week. The

patients also received individual counseling once weekly and provided urine and breath samples under observation thrice weekly for drug and alcohol testing. Participants who were abstinent in weeks 5 and 6 were included in the randomization. Clonidine was provided in the clinic once daily with a starting dose of 0.1 mg and increased weekly by 0.1 mg daily to 0.3 mg. Clonidine (or placebo) could be increased or decreased weekly at the discretion of a physician masked to treatment assignment. During the following 12 weeks patients used an electronic diary 4 times daily based on randomly timed prompts to record level of stress, craving, mood, and drug-related environmental cues. Thereafter, the clonidine was tapered off over a period of 14 days and after a total of 28 weeks buprenorphine was also tapered off (or the patient was transferred to another treatment program). Dropouts were relatively high at 28%, without differences between groups and those considered not abstinent. Patients in the clonidine group had higher average duration of consecutive days of abstinence (34.8 days [SD = 3.7] vs 25.5 days [SD = 2.7]), which was statistically significant in the subgroup of patients with no or low cocaine use documented during the baseline period. The diaries documented a buffering in opioid craving related to daily-life stresses, with overall reports of craving in 6.3% of instances of stress in the clonidine group versus reports of craving in 11.8% in the placebo group ($P < .001$). The decoupling in craving related to stress was not observed in relationship to drug cues. Clonidine was well tolerated.

Bottom line: Clonidine is a promising drug when used as adjuvant treatment to buprenorphine for maintaining abstinence from opioids. These authors documented longer duration of abstinence with clonidine as compared with placebo. They also credibly documented that patients in the clonidine-treated group experienced less craving when confronted with life stresses.

Kowalczyk WJ, Phillips KA, Jobes ML, et al. Clonidine maintenance prolongs opioid abstinence and decouples stress from craving in daily life: A randomized controlled trial with ecological momentary assessment. Am J Psychiatry 2015;172(8):760-767.

Cochrane reviews:

13. Psychosocial interventions for cannabis use disorder

Background: Cannabis use disorder is the most commonly reported illegal substance use disorder in the general population; although demand for assistance from health services is increasing internationally, only a minority of those with the disorder seek professional assistance. Treatment studies have been published, but pressure to establish public policy requires an updated systematic review of cannabis-specific treatments for adults.

Objectives: To evaluate the efficacy of psychosocial interventions for cannabis use disorder (compared with inactive control and/or alternative treatment) delivered to adults in an out-patient or community setting.

Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 6), MEDLINE, EMBASE, PsycINFO, the Cumulaive Index to Nursing and Allied Health Literature (CINAHL) and reference lists of articles. Searched literature included all articles published before July 2015.

Selection criteria: All randomised controlled studies examining a psychosocial intervention for cannabis use disorder (without pharmacological intervention) in comparison with a minimal or inactive treatment control or alternative combinations of psychosocial interventions.

Data collection and analysis: We used standard methodological procedures as expected by The Cochrane Collaboration.

Main results: We included 23 randomised controlled trials involving 4045 participants. A total of 15 studies took place in the United States, two in Australia, two in Germany and one each in Switzerland, Canada, Brazil and Ireland. Investigators delivered treatments over approximately seven sessions (range, one to 14) for approximately 12 weeks (range, one to 56). Overall, risk of bias across studies was moderate, that is, no trial was at high risk of selection bias, attrition bias or reporting bias. Further, trials included a large total number of participants, and each trial ensured the fidelity of treatments provided. In contrast, because of the nature of the interventions provided, participant blinding was not possible, and reports of researcher blinding often were unclear or were not provided. Half of the reviewed studies included collateral verification or urinalysis to confirm self report data, leading to concern about performance and detection bias. Finally, concerns of other bias were based on relatively consistent lack of assessment of non-cannabis substance use or use of additional treatments before or during the trial period. A subset of studies provided sufficient detail for comparison of effects of any intervention versus inactive control on primary outcomes of interest at early follow-up (median, four months). Results showed moderate-quality evidence that approximately seven out of 10 intervention participants completed treatment as intended (effect size (ES) 0.71, 95% confidence interval (CI) 0.63 to 0.78, 11 studies, 1424 participants), and that those receiving psychosocial intervention used cannabis on fewer days compared with those given inactive control (mean difference (MD) 5.67, 95% CI 3.08 to 8.26, six studies, 1144 participants). In addition, low-quality evidence revealed that those receiving intervention were more likely to report point-prevalence abstinence (risk ratio (RR) 2.55, 95% CI 1.34 to 4.83, six studies, 1166 participants) and reported fewer symptoms of dependence (standardised mean difference (SMD) 4.15, 95% CI 1.67 to 6.63, four studies, 889 participants) and cannabis-related problems compared with those given inactive control (SMD 3.34, 95% CI 1.26 to 5.42, six studies, 2202 participants). Finally, very low-quality evidence indicated that those receiving intervention reported using fewer joints per day compared with those given inactive control (SMD 3.55, 95% CI 2.51 to 4.59, eight studies, 1600 participants). Notably, subgroup analyses found that interventions of more than four sessions delivered over longer than one month (high intensity) produced consistently improved outcomes (particularly in terms of cannabis use frequency and severity of dependence) in the short term as compared with low-intensity interventions.The most consistent evidence supports the use of cognitive-behavioural therapy (CBT), motivational enhancement therapy (MET) and particularly their combination for assisting with reduction of cannabis use frequency at early follow-up (MET: MD 4.45, 95% CI 1.90 to 7.00, four studies, 612 participants; CBT: MD 10.94, 95% CI 7.44 to 14.44, one study, 134 participants; MET + CBT: MD 7.38, 95% CI 3.18 to 11.57, three studies, 398 participants) and severity of dependence (MET: SMD 4.07, 95% CI 1.97 to 6.17, two studies, 316 participants; MET + CBT: SMD 7.89, 95% CI 0.93 to 14.85, three studies, 573 participants), although no particular intervention was consistently effective at nine-month follow-up or later. In addition, data from five out of six studies supported the utility of adding voucher-based incentives for cannabis-negative urines to enhance treatment effect on cannabis use frequency. A

single study found contrasting results throughout a 12-month follow-up period, as post-treatment outcomes related to overall reduction in cannabis use frequency favoured CBT alone without the addition of abstinence-based or treatment adherence-based contingency management. In contrast, evidence of drug counselling, social support, relapse prevention and mindfulness meditation was weak because identified studies were few, information on treatment outcomes insufficient and rates of treatment adherence low. In line with treatments for other substance use, abstinence rates were relatively low overall, with approximately one-quarter of participants abstinent at final follow-up. Finally, three studies found that intervention was comparable with treatment as usual among participants in psychiatric clinics and reported no between-group differences in any of the included outcomes.
Authors' conclusions: Included studies were heterogeneous in many aspects, and important questions regarding the most effective duration, intensity and type of intervention were raised and partially resolved. Generalisability of findings was unclear, most notably because of the limited number of localities and homogeneous samples of treatment seekers. The rate of abstinence was low and unstable although comparable with treatments for other substance use. Psychosocial intervention was shown, in comparison with minimal treatment controls, to reduce frequency of use and severity of dependence in a fairly durable manner, at least in the short term. Among the included intervention types, an intensive intervention provided over more than four sessions based on the combination of MET and CBT with abstinence-based incentives was most consistently supported for treatment of cannabis use disorder.
Gates, P.J., Sabioni, P., Copeland, J. Le Foll B., Gowing, L. (2015). Psychosocial interventions for cannabis use disorder. Cochrane Database of Systematic Reviews, (5). Art. No.: CD005336. DOI: 10.1002/14651858.CD005336.pub4.

14. Buprenorphine for managing opioid withdrawal

Background: Managed withdrawal is a necessary step prior to drug-free treatment or as the endpoint of substitution treatment.
Objectives: To assess the effects of buprenorphine versus tapered doses of methadone, alpha2-adrenergic agonists, symptomatic medications or placebo, or different buprenorphine regimens for managing opioid withdrawal, in terms of the intensity of the withdrawal syndrome experienced, duration and completion of treatment, and adverse effects.
Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 11, 2016), MEDLINE (1946 to December week 1, 2016), Embase (to 22 December 2016), PsycINFO (1806 to December week 3, 2016), and the Web of Science (to 22 December 2016) and handsearched the reference lists of articles.
Selection criteria: Randomised controlled trials of interventions using buprenorphine to modify the signs and symptoms of withdrawal in participants who were primarily opioid dependent. Comparison interventions involved reducing doses of methadone, alpha2-adrenergic agonists (clonidine or lofexidine), symptomatic medications or placebo, and different buprenorphine-based regimens.
Data collection and analysis: We used standard methodological procedures expected by Cochrane.
Main results: We included 27 studies involving 3048 participants. The main comparators were clonidine or lofexidine (14 studies). Six studies compared buprenorphine versus methadone, and seven compared different rates of buprenorphine dose reduction. We assessed 12 studies as being at high risk of bias in at least one of seven domains of methodological quality. Six of these studies compared buprenorphine with clonidine or lofexidine and two with methadone; the other four studies compared different rates of buprenorphine dose reduction. For the comparison of buprenorphine and methadone in tapered doses, meta-analysis was not possible for the outcomes of intensity of withdrawal or adverse effects. However, information reported by the individual studies was suggestive of buprenorphine and methadone having similar capacity to ameliorate opioid withdrawal, without clinically significant adverse effects. The meta-analyses that were possible support a conclusion of no difference between buprenorphine and methadone in terms of average treatment duration (mean difference (MD) 1.30 days, 95% confidence interval (CI) −8.11 to 10.72; N = 82; studies = 2; low quality) or treatment completion rates (risk ratio (RR) 1.04, 95% CI 0.91 to 1.20; N = 457; studies = 5; moderate quality). Relative to clonidine or lofexidine, buprenorphine was associated with a lower average withdrawal score (indicating less severe withdrawal) during the treatment episode, with an effect size that is considered to be small to moderate (standardised mean difference (SMD) −0.43, 95% CI −0.58 to −0.28; N = 902; studies = 7; moderate quality). Patients receiving buprenorphine stayed in treatment for longer, with an effect size that is considered to be large (SMD 0.92, 95% CI 0.57 to 1.27; N = 558; studies = 5; moderate quality) and were more likely to complete withdrawal treatment (RR 1.59, 95% CI 1.23 to 2.06; N = 1264; studies = 12; moderate quality). At the same time there was no significant difference in the incidence of adverse effects, but dropout due to adverse effects may be more likely with clonidine (RR 0.20, 95% CI 0.04 to 1.15; N = 134; studies = 3; low quality). The difference in treatment completion rates translates to a number needed to treat for an additional beneficial outcome of 4 (95% CI 3 to 6), indicating that for every four people treated with buprenorphine, we can expect that one additional person will complete treatment than with clonidine or lofexidine. For studies comparing different rates of reduction of the buprenorphine dose, meta-analysis was possible only for treatment completion, with separate analyses for inpatient and outpatient settings. The results were diverse, and we assessed the quality of evidence as being very low. It remains very uncertain what effect the rate of dose taper has on treatment outcome.
Authors' conclusions: Buprenorphine is more effective than clonidine or lofexidine for managing opioid withdrawal in terms of severity of withdrawal, duration of withdrawal treatment, and the likelihood of treatment completion. Buprenorphine and methadone appear to be equally effective, but data are limited. It remains possible that the pattern of withdrawal experienced may differ and that withdrawal symptoms may resolve more quickly with buprenorphine. It is not possible to draw any conclusions from the available evidence on the relative effectiveness of different rates of tapering the buprenorphine dose. The divergent findings of studies included in this review suggest that there may be multiple factors affecting the response to the rate of dose taper. One such factor could be whether or not the initial treatment plan includes a transition to subsequent relapse prevention treatment with naltrexone. Indeed, the use of buprenorphine to support transition to naltrexone treatment is an aspect worthy of further research. Most participants in the studies included in this review were male. None of the studies reported outcomes on the basis of sex, preventing any exploration of differences related to this variable. Consideration of sex as a factor influencing response to withdrawal treatment would be relevant research for selecting the most appropriate type of intervention for each individual.

Gowing, L., Ali, R., White, J.M., Mbewe, D. (2017). Buprenorphine for managing opioid withdrawal. Cochrane Database of Systematic Reviews, (2). No.: CD002025. DOI: 10.1002/14651858.CD002025.pub5.

15. Alpha2-adrenergic agonists for the management of opioid withdrawal

Background: Withdrawal is a necessary step prior to drug-free treatment or as the endpoint of long-term substitution treatment.
Objectives: To assess the effectiveness of interventions involving the use of alpha2-adrenergic agonists compared with placebo, reducing doses of methadone, symptomatic medications, or an alpha2-adrenergic agonist regimen different to the experimental intervention, for the management of the acute phase of opioid withdrawal. Outcomes included the withdrawal syndrome experienced, duration of treatment, occurrence of adverse effects, and completion of treatment.
Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1946 to November week 2, 2015), EMBASE (January 1985 to November week 2, 2015), PsycINFO (1806 to November week 2, 2015), Web of Science, and reference lists of articles.
Selection criteria: Randomised controlled trials comparing alpha2-adrenergic agonists (clonidine, lofexidine, guanfacine, tizanidine) with reducing doses of methadone, symptomatic medications or placebo, or comparing different alpha2-adrenergic agonists to modify the signs and symptoms of withdrawal in participants who were opioid dependent.
Data collection and analysis: We used standard methodological procedures expected by The Cochrane Collaboration.
Main results: We included 26 randomised controlled trials involving 1728 participants. Six studies compared an alpha2-adrenergic agonist with placebo, 12 with reducing doses of methadone, four with symptomatic medications, and five compared different alpha2-adrenergic agonists. We assessed 10 studies as having a high risk of bias in at least one of the methodological domains that were considered. We found moderate-quality evidence that alpha2-adrenergic agonists were more effective than placebo in ameliorating withdrawal in terms of the likelihood of severe withdrawal (risk ratio (RR) 0.32, 95% confidence interval (CI) 0.18 to 0.57; 3 studies; 148 participants). We found moderate-quality evidence that completion of treatment was significantly more likely with alpha2-adrenergic agonists compared with placebo (RR 1.95, 95% CI 1.34 to 2.84; 3 studies; 148 participants). Peak withdrawal severity may be greater with alpha2-adrenergic agonists than with reducing doses of methadone, as measured by the likelihood of severe withdrawal (RR 1.18, 95% CI 0.81 to 1.73; 5 studies; 340 participants; low quality), and peak withdrawal score (standardised mean difference (SMD) 0.22, 95% CI -0.02 to 0.46; 2 studies; 263 participants; moderate quality), but these differences were not significant and there is no significant difference in severity when considered over the entire duration of the withdrawal episode (SMD 0.13, 95% CI -0.24 to 0.49; 3 studies; 119 participants; moderate quality). The signs and symptoms of withdrawal occurred and resolved earlier with alpha2-adrenergic agonists. The duration of treatment was significantly longer with reducing doses of methadone (SMD -1.07, 95% CI -1.31 to -0.83; 3 studies; 310 participants; low quality). Hypotensive or other adverse effects were significantly more likely with alpha2-adrenergic agonists (RR 1.92, 95% CI 1.19 to 3.10; 6 studies; 464 participants; low quality), but there was no significant difference in rates of completion of withdrawal treatment (RR 0.85, 95% CI 0.69 to 1.05; 9 studies; 659 participants; low quality). There were insufficient data for quantitative comparison of different alpha2-adrenergic agonists. Available data suggest that lofexidine does not reduce blood pressure to the same extent as clonidine, but is otherwise similar to clonidine.
Authors' conclusions: Clonidine and lofexidine are more effective than placebo for the management of withdrawal from heroin or methadone. We detected no significant difference in efficacy between treatment regimens based on clonidine or lofexidine and those based on reducing doses of methadone over a period of around 10 days, but methadone was associated with fewer adverse effects than clonidine, and lofexidine has a better safety profile than clonidine.
Gowing, L., Farrell, M., Ali, R., White, J.M. (2016). Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database of Systematic Reviews, (2016). Issue 5. Art. No.: CD002024. DOI: 10.1002/14651858.CD002024.pub5.

16. Psychostimulant drugs for cocaine dependence

Background: Cocaine dependence is a severe disorder for which no medication has been approved. Like opioids for heroin dependence, replacement therapy with psychostimulants could be an effective therapy for treatment.
Objectives: To assess the effects of psychostimulants for cocaine abuse and dependence. Specific outcomes include sustained cocaine abstinence and retention in treatment. We also studied the influence of type of drug and comorbid disorders on psychostimulant efficacy.
Search methods: This is an update of the review previously published in 2010. For this updated review, we searched the Cochrane Drugs and Alcohol Group Trials Register, CENTRAL, MEDLINE, Embase and PsycINFO up to 15 February 2016. We handsearched references of obtained articles and consulted experts in the field.
Selection criteria: We included randomised parallel group controlled clinical trials comparing the efficacy of a psychostimulant drug versus placebo.
Data collection and analysis: We used standard methodological procedures expected by Cochrane.
Main results: We included 26 studies involving 2366 participants. The included studies assessed nine drugs: bupropion, dexamphetamine, lisdexamfetamine, methylphenidate, modafinil, mazindol, methamphetamine, mixed amphetamine salts and selegiline. We did not consider any study to be at low risk of bias for all domains included in the Cochrane 'Risk of bias' tool. Attrition bias was the most frequently suspected potential source of bias of the included studies. We found very low quality evidence that psychostimulants improved sustained cocaine abstinence (risk ratio (RR) 1.36, 95% confidence interval (CI) 1.05 to 1.77, P = 0.02), but they did not reduce cocaine use (standardised mean difference (SMD) 0.16, 95% CI −0.02 to 0.33) among participants who continued to use it. Furthermore, we found moderate quality evidence that psychostimulants did not improve retention in treatment (RR 1.00, 95% CI 0.93 to 1.06). The proportion of adverse event-induced dropouts and cardiovascular adverse event-induced dropouts was similar for psychostimulants and placebo (RD 0.00, 95% CI −0.01 to 0.01; RD 0.00, 95% CI −0.02 to 0.01, respectively). When we included the

type of drug as a moderating variable, the proportion of patients achieving sustained cocaine abstinence was higher with bupropion and dexamphetamine than with placebo. Psychostimulants also appeared to increase the proportion of patients achieving sustained cocaine and heroin abstinence amongst methadone-maintained, dual heroin-cocaine addicts. Retention to treatment was low, though, so our results may be compromised by attrition bias. We found no evidence of publication bias.
Authors' conclusions: This review found mixed results. Psychostimulants improved cocaine abstinence compared to placebo in some analyses but did not improve treatment retention. Since treatment dropout was high, we cannot rule out the possibility that these results were influenced by attrition bias. Existing evidence does not clearly demonstrate the efficacy of any pharmacological treatment for cocaine dependence, but substitution treatment with psychostimulants appears promising and deserves further investigation.
Castells, X., Cunill, R., Perez-Mana, C., Vidal, X., Capella, D. (2016). Psychostimulant drugs for cocaine dependence. Cochrane Database of Systematic Reviews, (9). Art. No.: CD007380. DOI: 10.1002/14651858.CD007380.pub4.

17. Antipsychotic medications for cocaine dependence

Background: Cocaine dependence is a public health problem characterised by recidivism and a host of medical and psychosocial complications. Cocaine dependence remains a disorder for which no pharmacological treatment of proven efficacy exists.
Objectives: To evaluate the efficacy and the acceptability of antipsychotic medications for cocaine dependence.
Search methods: This review is an update of a previous Cochrane review published in 2007. We searched up to 15 July 2015 in Cochrane Drugs and Alcohol Group Specialised Register (searched in CRSLive); the Cochrane Library (including the Cochrane Central Register of Controlled Trials (CENTRAL); the Database of Abstracts of Reviews of Effects (DARE)); PubMed; EMBASE; CINAHL and Web of Science. All searches included non-English language literature.
Selection criteria: All randomised controlled trials and controlled clinical trials with focus on the use of any antipsychotic medication for the treatment of cocaine dependence.
Data collection and analysis: We used standard methodological procedures expected by Cochrane.
Main results: We included 14 studies (719 participants). The antipsychotic drugs studied were risperidone, olanzapine, quetiapine, lamotrigine, aripiprazol, haloperidol and reserpine. Comparing any antipsychotic drugs versus placebo, we found that antipsychotics reduced dropout: eight studies, 397 participants, risk ratio (RR) 0.75 (95% confidence interval (CI) 0.57 to 0.97), moderate quality of evidence. We found no significant differences for any of the other primary outcomes considered: number of participants using cocaine during the treatment, two studies, 91 participants: RR 1.02 (95% CI 0.65 to 1.62); continuous abstinence, three studies, 139 participants: RR 1.30 (95% CI 0.73 to 2.32); side effects, six studies, 291 participants: RR 1.01 (95% CI 0.93 to 1.10); and craving, four studies, 240 participants: RR 0.13 (-1.08 to 1.35). For all of these comparisons we rated the quality of evidence as low. Comparisons of single drug versus placebo or versus another drug are conducted in few trials with small sample sizes, limiting the reliability of the results. Among these comparisons, only quetiapine seemed to outperform placebo in reducing cocaine use, measured by grams per week: mean difference (MD) -0.54 (95% CI -0.92 to -0.16), by US dollars spent per week: MD -53.80 (95% CI -97.85 to -9.75), and by craving: MD -1.23 (95% CI -2.19 to -0.27), but results came from one study with 60 participants. The major limitations of the studies were the high risk of attrition bias (40% of the included studies) and low quality of reporting, mainly for the risk of selection bias, performance and detection bias, that we rated as being at unclear risk for 75% to 80% of the studies. Furthermore, most of the included studies did not report results on important outcomes such as side effects, or use of cocaine during treatment and craving, which prevented the possibility of including them in statistical synthesis.
Authors' conclusions: At present, there is no evidence supporting the clinical use of antipsychotic medications in the treatment of cocaine dependence, although results come from only 14 trials, with small sample sizes and moderate to low quality of evidence.
Indave, B.I., Minozzi, S., Pani, P.P., Amato, L. (2016). Antipsychotic medications for cocaine dependence. Cochrane Database of Systematic Reviews, (3). Art. No.: CD006306. DOI: 10.1002/14651858.CD006306.pub3.

18. Collaborative Care for Opioid and Alcohol Use Disorders in Primary Care: The SUMMIT Randomized Clinical Trial.

Objective: To determine whether CC for OAUD improves delivery of evidence-based treatments for OAUD and increases self-reported abstinence compared with usual primary care.
Design, Setting, and Participants: A randomized clinical trial of 377 primary care patients with OAUD was conducted in 2 clinics in a federally qualified health center. Participants were recruited from June 3, 2014, to January 15, 2016, and followed for 6 months.
Interventions: Of the 377 participants, 187 were randomized to CC and 190 were randomized to usual care; 77 (20.4%) of the participants were female, of whom 39 (20.9%) were randomized to CC and 38 (20.0%) were randomized to UC. The mean (SD) age of all respondents at baseline was 42 (12.0) years, 41(11.7) years for the CC group, and 43 (12.2) yearsfor the UC group. Collaborative care was a system-level intervention, designed to increase the delivery of either a 6-session brief psychotherapy treatment and/or medication-assisted treatment with either sublingual buprenorphine/naloxone for opioid use disorders or long-acting injectable naltrexone for alcohol use disorders. Usual care participants were told that the clinic provided OAUD treatment and given a number for appointment scheduling and list of community referrals.
Main Outcomes and Measures: The primary outcomes were use of any evidence-based treatment for OAUD and self-reported abstinence from opioids or alcohol at 6 months. The secondary outcomes included the Healthcare Effectiveness Data and Information Set (HEDIS) initiation and engagement measures, abstinence from other substances, heavy drinking, health-related quality of life, and consequences from OAUD.
Results: At 6 months, the proportion of participants who received any OAUD treatment was higher in the CC group compared with usual care (73 [39.0%] vs 32 [16.8%]; logistic model adjusted OR, 3.97; 95% CI, 2.32-6.79; $P < .001$). A higher proportion of CC participants reported abstinence from opioids or alcohol at 6 months (32.8% vs 22.3%); after linear probability model adjustment for covariates ($\beta = 0.12$; 95% CI, 0.01-0.23; $P = .03$). In secondary analyses, the proportion meeting the HEDIS initiation and engagement

measures was also higher among CC participants (initiation, 31.6% vs 13.7%; adjusted OR, 3.54; 95% CI, 2.02-6.20; P < .001; engagement, 15.5% vs 4.2%; adjusted OR, 5.89; 95% CI, 2.43-14.32; P < .001) as was abstinence from opioids, cocaine, methamphetamines, marijuana, and any alcohol (26.3% vs 15.6%; effect estimate, β = 0.13; 95% CI, 0.03-0.23; P = .01).
Conclusions and Relevance: Among adults with OAUD in primary care, the SUMMIT collaborative care intervention resulted in significantly more access to treatment and abstinence from alcohol and drugs at 6 months, than usual care.
Watkins, K.E., Ober, A.J., Lamp, K., Lind, M., Setodji, C., Osilla, K.C., Hunger, S.B., McCullough, C.M., Becker, K., Iyiewuare, P.O., Diamant, A., Heinzerling, K., Pincus, H.A. (2017). Collaborative care for opioid and alcohol use disorders in primary care: the summit randomized clinical trial. JAMA Internal Med, 177(10). 1480-1488.

Alcohol Abuse

USPSTF recommends screening adults 18 and older for alcohol misuse including risky and hazardous drinking with brief behavioral counseling to reduce misuse (B, recommendation).

USPSTF states there is insufficient information to assess benefits or harms for screening of children or adolescents. American Academy of Pediatrics recommends screening.

Simple screening questions for Risky Drinking: For healthy adults in general, drinking more than these amounts in a single day or weekly limits is considered at risk for 'heavy drinking.' Men: More than 4 drinks on any day or 14 per week. Women: more than 3 drinks on any day or 7 per week.

Second level screening: CAGE, AUDIT-C (3-item), AUDIT (10-item), MAST.

19. Brief interventions for heavy alcohol users admitted to general hospital wards

Background: Brief interventions involve a time-limited intervention focusing on changing behaviour. They are often motivational in nature using counselling skills to encourage a reduction in alcohol consumption.
Objectives: To determine whether brief interventions reduce alcohol consumption and improve outcomes for heavy alcohol users admitted to general hospital inpatient units.
Search methods: We searched the Cochrane Drug and Alcohol Group Register of Trials (March 2011) the Cochrane Central Register of Controlled Trials (The Cochrane Library March 2011), MEDLINE January 1966-March 2011, CINAHL 1982-March 2011, EMBASE 1980-March 2011 and www.clinicaltrials.gov to April 2011 and performed some relevant handsearching.
Selection criteria: All prospective randomised controlled trials and controlled clinical trials were eligible for inclusion. Participants were adults and adolescents (16 years or older) admitted to general inpatient hospital care for any reason other than specifically for alcohol treatment and received brief interventions (of up to 3 sessions) compared to no or usual care.
Data collection and analysis: Three reviewers independently selected the studies and extracted data. Where appropriate random effects meta-analysis and sensitivity analysis were performed.
Main results: fourteen studies involving 4041 mainly male participants were included. Our results demonstrate that patients receiving brief interventions have a greater reduction in alcohol consumption compared to those in control groups at six month, MD -69.43 (95% CI -128.14 to -10.72) and nine months follow up, MD -182.88 (95% CI -360.00 to -5.76) but this is not maintained at one year. Self reports of reduction of alcohol consumption at 1 year were found in favour of brief interventions, SMD -0.26 (95% CI -0.50 to -0.03). In addition there were significantly fewer deaths in the groups receiving brief interventions than in control groups at 6 months, RR 0.42 (95% CI 0.19 to 0.94) and one year follow up, RR 0.60 (95% CI 0.40 to 0.91). Furthermore screening, asking participants about their drinking patterns, may also have a positive impact on alcohol consumption levels and changes in drinking behaviour.
Authors' conclusions: The main results of this review indicate that there are benefits to delivering brief interventions to heavy alcohol users admitted to general hospital wards in terms of reduction in alcohol consumption and death rates. However, these findings are based on studies involving mainly male participants. Further research is required determine the optimal content and treatment exposure of brief interventions within general hospital settings and whether they are likely to be more successful in patients with certain characteristics.
McQueen, J., Howe, T.E., Allan, L., Manis, D., Hardy, V. (2011). Brief interventions for heavy alcohol users admitted to general hospital wards. Cochrane Database of Systematic Reviews, (8). Art. No.: CD005191. DOI: 10.1002/14651858.CD005191.pub3.

20. Variance in the Efficacy of Brief Interventions to Reduce Hazardous and Harmful Alcohol Consumption Between Injury and Noninjury Patients in Emergency Departments: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.

Study Objective: We adopt a comparative framework to measure the extent to which variance in the efficacy of alcohol brief interventions to reduce hazardous and harmful drinking at less than or equal to 5-, 6-, and 12-month follow-up in emergency department settings can be determined by differences between study populations (targeted injury and noninjury specific).
Methods: A systematic review and meta-analysis of randomized controlled trials published before September 2016 was undertaken. Twenty-three high-quality and methodologically similar randomized controlled trials were eligible, with a total number of 15,173 participants included. Primary outcome measure was efficacy of brief intervention compared with a control group in reducing quantity of alcohol consumed. An inverse variance model was applied to measure the effect of treatment in standard mean differences for brief intervention and control groups.
Results: At 6-month follow-up, an effect in favor of brief intervention over control was identified for targeted injury studies (standardized mean difference=-0.10; 95% confidence interval [CI] -0.17 to -0.02; I^2=0%). For pooled noninjury-specific studies, small benefits of brief intervention were evident at less than or equal to 5-month follow-up (standardized mean difference=-0.15; 95% CI -0.24 to -0.07; I^2=0%), at 6-month follow-up (standardized mean difference=-0.08; 95% CI -0.14 to -0.01; I^2=1%), and at 12-month follow-up (standardized mean difference=-0.08; 95% CI -0.15 to -0.01; I^2=0%).
Conclusion: Meta-analysis identified noninjury-specific studies as associated with better response to brief intervention than targeted injury studies. However, the inclusion of injured patients with noninjured ones in the experimental and control groups of noninjury-specific studies limited the interpretation of this finding.
Elzerbi, C., Donoqhue, K., Boniface, S., Drummond, C. (2017). Variance in the efficacy of brief interventions to reduce hazardous and harmful alcohol consumption between injury and noninjury patients in emergency departments: a systematic review and meta-analysis of randomized controlled trials. Annals of Emergency Medicine, 70(5). 714-723.

21. The emergency medicine management of severe alcohol withdrawal.

Introduction: Alcohol use is widespread, and withdrawal symptoms are common after decreased alcohol intake. Severe alcohol withdrawal may manifest with delirium tremens, and new therapies may assist in management of this life-threatening condition.
Objective: To provide an evidence-based review of the emergency medicine management of alcohol withdrawal and delirium tremens.
Discussion: The underlying pathophysiology of alcohol withdrawal syndrome (AWS) is central nervous system hyperexcitation. Stages of withdrawal include initial withdrawal symptoms, hallucinations, seizures, and delirium tremens. Management focuses on early diagnosis, resuscitation, and providing medications with gamma-aminobutyric acid (GABA) receptor activity. Benzodiazepines with symptom-triggered therapy have been the predominant medication class utilized and should remain the first treatment option with rapid escalation of dosing. Treatment resistant withdrawal warrants the use of phenobarbital or propofol, both demonstrating efficacy in management. Propofol can be used as an induction agent to decrease the effects of withdrawal. Dexmedetomidine does not address the underlying pathophysiology but may reduce the need for intubation. Ketamine requires further study. Overall, benzodiazepines remain the cornerstone of treatment. Outpatient management of patients with minimal symptoms is possible.
Conclusions: Alcohol withdrawal syndrome can result in significant morbidity and mortality. Physicians must rapidly diagnose these conditions while evaluating for other diseases. Benzodiazepines are the predominant medication class utilized, with adjunctive treatments including propofol or phenobarbital in patients with withdrawal resistant to benzodiazepines. Dexmedetomidine and ketamine require further study.
Long, D., Long, B., Koyfman, A. (2017). The emergency medicine management of severe alcohol withdrawal. American Journal of Emergency Medicine, 35(7). 1005-1011.

22. Collaborative Care for Opioid and Alcohol Use Disorders in Primary Care: The SUMMIT Randomized Clinical Trial.

Objective: To determine whether CC for OAUD improves delivery of evidence-based treatments for OAUD and increases self-reported abstinence compared with usual primary care.
Design, Setting, and Participants: A randomized clinical trial of 377 primary care patients with OAUD was conducted in 2 clinics in a federally qualified health center. Participants were recruited from June 3, 2014, to January 15, 2016, and followed for 6 months.
Interventions: Of the 377 participants, 187 were randomized to CC and 190 were randomized to usual care; 77 (20.4%) of the participants were female, of whom 39 (20.9%) were randomized to CC and 38 (20.0%) were randomized to UC. The mean (SD) age of all respondents at baseline was 42 (12.0) years, 41(11.7) years for the CC group, and 43 (12.2) years for the UC group. Collaborative care was a system-level intervention, designed to increase the delivery of either a 6-session brief psychotherapy treatment and/or medication-assisted treatment with either sublingual buprenorphine/naloxone for opioid use disorders or long-acting injectable naltrexone for alcohol use disorders. Usual care participants were told that the clinic provided OAUD treatment and given a number for appointment scheduling and list of community referrals.
Main Outcomes and Measures: The primary outcomes were use of any evidence-based treatment for OAUD and self-reported abstinence from opioids or alcohol at 6 months. The secondary outcomes included the Healthcare Effectiveness Data and Information

Set (HEDIS) initiation and engagement measures, abstinence from other substances, heavy drinking, health-related quality of life, and consequences from OAUD.
Results: At 6 months, the proportion of participants who received any OAUD treatment was higher in the CC group compared with usual care (73 [39.0%] vs 32 [16.8%]; logistic model adjusted OR, 3.97; 95% CI, 2.32-6.79; P < .001). A higher proportion of CC participants reported abstinence from opioids or alcohol at 6 months (32.8% vs 22.3%); after linear probability model adjustment for covariates (β = 0.12; 95% CI, 0.01-0.23; P = .03). In secondary analyses, the proportion meeting the HEDIS initiation and engagement measures was also higher among CC participants (initiation, 31.6% vs 13.7%; adjusted OR, 3.54; 95% CI, 2.02-6.20; P < .001; engagement, 15.5% vs 4.2%; adjusted OR, 5.89; 95% CI, 2.43-14.32; P < .001) as was abstinence from opioids, cocaine, methamphetamines, marijuana, and any alcohol (26.3% vs 15.6%; effect estimate, β = 0.13; 95% CI, 0.03-0.23; P = .01).
Conclusions and Relevance: Among adults with OAUD in primary care, the SUMMIT collaborative care intervention resulted in significantly more access to treatment and abstinence from alcohol and drugs at 6 months, than usual care.
Watkins, K.E., Ober, A.J., Lamp, K., Lind, M., Setodji, C., Osilla, K.C., Hunter, S.B., McCullough, C.M., Becker, K., Iyiewuare, P.O., Diamant, A., Heinzerling, K., Pincus, H.A. (2017). Collaborative care for opioid and alcohol use disorders in primary care: the summit randomized clinical trial. JAMA Internal Medicine, 177(10). 1480-1488.

Summary: Key Points

Tobacco Use

1. Stay the course with screening (use 5 A's)
2. Long-term (>8 weeks) of NRT no more effective
3. Varenicline is effective in smokers who want to 'cut down'
4. Abruptly quitting more effective than taper down
5. Post hospital, financial incentives, mobile phone, internet, and motivational interviewing interventions are all effective for smoking cessation in RCTs
6. E-cigarettes or ENDs are less harmful than combustible tobacco products and may or may not help in reduction or smoking cessation
7. Adolescents should not start ENDs due to risk of addiction, toxic exposure, and possible progression to poly-tobacco use

Substance Abuse

1. Understand benefits and limits of the CDC guidelines on opioid prescribing
2. Buprenorphine is more effective than clonidine or lofexidine for managing opioid withdrawal (severity, duration, and completion)
3. Clonidine is beneficial as an adjuvant to buprenorphine
4. Opioid antagonists (naloxone and naltrexone) with alpha2 adrenergic medications (clonidine and lofexidine) induces more withdrawal symptoms
5. Little or no efficacy for interventions for cocaine or cannabis reported
6. Advocate for a collaborative approach in primary care for substance and alcohol abuse disorders

Alcohol Use Disorders

1. Brief screening in adults recommended
2. Brief counseling interventions effective in outpatient and inpatient settings
3. Benzodiazepams remain the cornerstones of acute alcohol withdrawal syndrome (AWS)
4. Advocate for a collaborative approach in primary care for substance and alcohol abuse disorders

Asthma and COPD Update — John Hickner, MD, MSc

Objectives

1. Know recent new developments in the diagnosis and treatment of asthma
2. Know recent developments in the diagnosis and treatment of COPD
3. Understand the benefits of newer therapies for asthma and COPD

There remains a high level of research in asthma and COPD, and some studies are pertinent to primary care. Following are new research studies and meta-analyses published in the past 2 years that will have an impact on our practices. The first abstract may contain the most important finding.

1. One third of adults with diagnosed asthma can be weaned off all asthma meds

Clinical question: How many adults with physician-diagnosed asthma can safely taper off their asthma medications?
Study design: Cohort (prospective)
Setting: Population-based
Synopsis: These investigators randomly dialed both landline and cellular phones in Canada to identify a true cohort of adults, 18 years or older, with physician-diagnosed asthma within the previous 5 years. Exclusion criteria included pregnancy, smoking history greater than 10 pack-years, or the use of long-term oral steroids. Review of medical records allowed collection of data on the determination of the original diagnosis of asthma. All participants (N = 701) underwent assessment with baseline spirometry and continued symptom monitoring using standard tools, as well as serial bronchial challenge testing. Patients using daily medications and not confirmed to have asthma with either baseline spirometry or serial bronchial challenge testing had their medications gradually tapered off over 4 study visits. Patients with continued negative test results for asthma were followed up clinically and with repeated bronchial challenges over 1 year. Two pulmonologists independently reviewed all medical records to determine agreement with the final diagnosis for all participants. Discrepancies were resolved by consensus agreement with a third reviewer. A total of 613 patients (87.4%) completed the study assessment procedures. Of these, 203 (33.1%) had a diagnosis of current asthma ruled out. Patients ruled out for current asthma were less likely to be using asthma medications or daily asthma-controlling medications and less likely to have spirometry or bronchial challenge testing performed at the initial time of initial diagnosis. After 1 year of follow-up, 6 patients (2.9%) in the group who were ruled out for current asthma and tapered off their asthma medications presented with respiratory symptoms and resumed treatment. In 12 patients, a serious alternative respiratory diagnosis—including ischemic heart disease, subglottic stenosis, and bronchiectasis—was diagnosed.
Bottom line: This study found that current asthma was ruled out after repeated testing in one third of adults with physician-diagnosed asthma. Patients ruled out for current asthma were less likely to be using asthma medications or daily-controlling medications and less likely to have undergone testing for airflow limitation at the time of initial diagnosis. After 1 year of follow-up, 2.9% of the patients who tapered off their asthma medications presented with respiratory symptoms and resumed treatment.
Aaron SD, Vandemheen KL, FitzGerald JM, et al, for the Canadian Respiratory Research Network. Reevaluation of diagnosis in adults with physician-diagnosed asthma. JAMA 2017:317(3):269-279.

Asthma in Children

Reducing environmental exposure is one of the pillars of asthma treatment. Mite-impermeable covers provide benefits, but reducing mouse infestation in housing does not. A comprehensive community based intervention including allergy testing and environmental control was somewhat effective in reducing asthma symptom days in high risk low income children. Consider a single dose of dexamethasone instead of 3 days of prednisone for asthma exacerbations in children and adults.

2. Mite-impermeable covers decreases hospital visits in kids with asthma

Clinical question: Can mite-impermeable bedding decrease asthma exacerbations in children with asthma who are sensitive to mites?
Study design: Randomized controlled trial (double-blinded)
Setting: Inpatient (any location) with outpatient follow-up
Synopsis: House dust mites are a common allergen associated with asthma. This United Kingdom study included children with physician-diagnosed asthma who visited the hospital for an exacerbation (emergency department or admission). After the exacerbation had cleared, the researchers skin tested the children for house dust mite, cat, dog, pollen, and other allergens. They randomized children who had a wheal at least 3 mm larger than the negative control to receive mite-impermeable bedding covers (n = 146) or identical but non-impermeable bedding covers (n = 138) to use at home. The researchers gave all participants the same instructions on the care of the bedding covers and none were given instructions on mite avoidance. In the event that a second child from the same family entered the study, the researchers assigned them to the same intervention. Interviewers unaware of group assignment

interviewed the child's primary caregiver 1, 4, 8, and 12 months after enrollment to ascertain exacerbations, unscheduled medical care, medication use, and quality of life. Additionally, the researchers vacuumed the child's bedroom floor at baseline and at the end of the study to estimate the mite load in the room. At the end of 1 year, 23 children in the mite-impermeable bedding group dropped out compared with 20 in the control group. Although this 15% drop-out rate is not a major problem, it is still a bit worrisome. At the end of a year, 29% of children in the mite-impermeable bedding group had exacerbations leading to a hospital visit compared with 42% of the control group (number needed to treat = 9; 95% CI 5 - 512). However, approximately half the children in each group used oral corticosteroids during the year. Approximately 25% of the children complained that the special bedding covers were uncomfortable and thought about removing them, as did fewer than 3% of the children with the regular covers. These mite-impermeable bedding covers cost approximately US$200.
Bottom line: In children with house dust mite allergies and asthma, the use of mite-impermeable bedding decreases the frequency of asthma exacerbations.
Murray CS, Foden P, Sumner H, Shepley E, Custovic A, Simpson A. Preventing severe asthma exacerbations in children. A randomized trial of mite-impermeable bedcovers. Am J Respir Crit Care Med 2017;196(2):150-158.

3. Intensive intervention to reduce mouse infestation does not improve asthma morbidity in children

Clinical question: Does a professionally delivered pest management intervention reduce asthma morbidity among mouse-sensitized and exposed children and adolescents with asthma?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (primary care)
Synopsis: It is currently unknown if reducing mouse allergen exposure reduces asthma morbidity among mouse-sensitized children and adolescents. These investigators enrolled children and adolescents, aged 5 to 17 years, with persistent asthma and known mouse sensitization based on either a positive skin test result or an elevated mouse urine–specific IgE level. After a home visit, those patients with an elevated mouse allergen concentration on their bed or bedroom floor (N = 361) randomly received assignment (uncertain allocation concealment) to either a professionally delivered integrated pest management (IPM) intervention plus pest management education (PME) or PME alone. The IPM intervention was performed by licensed pest management experts and included cleaning to remove allergen reservoirs, placement of traps and rodenticide, sealing holes and cracks, installation of allergen-proof mattresses and pillow encasements, and placement of portable air purifiers. PME included written materials about setting mouse traps, sealing holes and cracks, and housekeeping practices. Infestation was assessed every 3 months and additional IPM was delivered as needed up to a total of 4 treatments. Asthma-related outcomes were assessed at clinic visits and via telephone calls every 3 months for a total of 12 months. The authors do not state whether the individuals who assessed outcomes remained masked to treatment group assignments. Complete follow-up occurred for 88% of participants at 12 months. Using intention-to-treat analyses, the authors found no significant difference between the 2 groups in the primary outcome of maximal number of days with symptoms in the 2 weeks prior to a clinical visit or telephone call. Similarly, they found no significant group differences in measured secondary outcomes, including rescue medication use, urgent health care clinic visits, emergency department use, hospitalizations, or reductions of 75% or 90% of mouse allergen levels. A decrease of at least 50% of mouse allergen levels was significantly associated with reduced asthma morbidity in both groups. The study was 90% powered to detect a predetermined clinically significant group difference.
Bottom line: An intensive year-long professionally delivered pest management intervention in the homes of mouse-sensitized and exposed children and adolescents with asthma was no more effective than written pest management education alone for reducing asthma morbidity.
Matsui EC, Perzanowski M, Peng R, et al. Effect of an integrated pest management intervention on asthma symptoms among mouse-sensitized children and adolescents with asthma. A randomized clinical trial. JAMA 2017;317(10):1027-1036.

4. Effectiveness of evidence-based asthma Interventions in high risk, low income children

BACKGROUND AND OBJECTIVES: Researchers often struggle with the gap between efficacy and effectiveness in clinical research. To bridge this gap, the Community Healthcare for Asthma Management and Prevention of Symptoms (CHAMPS) study adapted an efficacious, randomized controlled trial that resulted in evidence-based asthma interventions in community health centers.
METHODS: Children (aged 5-12 years; *N* = 590) with moderate to severe asthma were enrolled from 3 intervention and 3 geographically/capacity-matched control sites in high-risk, low-income communities located in Arizona, Michigan, and Puerto Rico. The asthma intervention was tailored to the participant's allergen sensitivity and exposure, and it comprised 4 visits over the course of 1 year. Study visits were documented and monitored prospectively via electronic data capture. Asthma symptoms and health care utilization were evaluated at baseline, and at 6 and 12 months.
RESULTS: A total of 314 intervention children and 276 control children were enrolled in the study. Allergen sensitivity testing (96%) and home environmental assessments (89%) were performed on the majority of intervention children. Overall study activity completion (eg, intervention visits, clinical assessments) was 70%. Overall and individual site participant symptom days in the previous 4 weeks were significantly reduced compared with control findings (control, change of -2.28; intervention, change of -3.27; difference, -0.99; $P < .001$), and this result was consistent with changes found in the rigorous evidence-based interventions.
CONCLUSIONS: Evidence-based interventions can be successfully adapted into primary care settings that serve impoverished, high-risk populations, reducing the morbidity of asthma in these high-need populations.
Pediatrics. 2017 Jun;139(6).

5. Salmeterol appears safe in children, but no benefit regarding exacerbations

Clinical question: Does adding salmeterol to fluticasone increase the likelihood of serious asthma related events or reduce the likelihood of exacerbations?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: This is another in a series of FDA-mandated, industry-sponsored trials to sort out the pros and cons of using a long-acting beta agonist (LABA) in addition to an inhaled corticosteroid in people with persistent asthma and frequent exacerbations. In this case, the drug is salmeterol and the population is children aged 4 to 11 years with a history of an asthma exacerbation in the past 1 to 12 months. The mean age was 7.6 years, 62% were boys, and 65% were white. A total of 6250 children were randomized to receive either fluticasone plus salmeterol or fluticasone alone; the dose of the fluticasone was either 100 mcg or 250 mcg, depending on disease severity. The groups were balanced at the start of the study, analysis was by intention to treat, and both patients and outcome assessors were masked to treatment assignment during the 6-month trial period. The authors designed this is a noninferiority trial with regard to serious asthma-related events (hospitalization, intubation, or asthma death), with a fairly generous margin. Basically, if the upper bound for the 95% confidence interval of the hazard ratio was less than 2.675, everything was just fine. They found 27 asthma-related hospitalizations in the combination therapy group and 21 in the fluticasone-only group, which met their criteria for noninferiority. There was no difference in the likelihood of experiencing a severe exacerbation (8.5% vs 10.0%; hazard ratio 0.86; 95% CI 0.73-1.01). They also examined the likelihood of exacerbations stratified by the previous therapy, and found a small benefit only for those who had originally been taking the combination of a glucocorticoid and a LABA (7.5% vs 9.9%; P < .05; number needed to treat = 42).
Bottom line: The addition of salmeterol to fluticasone was found to be safe in terms of serious asthma-related events (in this study, that meant hospitalizations) when using generous margins for "noninferiority." There was no significant difference in the number of severe exacerbations, though.
Stempel DA, Szefler SJ, Pedersen S, et al. Safety of adding salmeterol to fluticasone propionate in children with asthma. N Engl J Med 2016; 375: 840-9.

6. Inhaled steroids are effective prevention for wheezing preschoolers

Clinical question: In preschoolers with recurrent wheeze, do "controller" treatments decrease recurrences?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: The researchers searched 3 databases, including Cochrane CENTRAL, to identify randomized studies of children 6 years or younger with asthma or recurrent wheeze (at least 2 episodes in the past year) that compared inhaled corticosteroids, given daily or intermittently, with placebo or montelukast to prevent exacerbations requiring systematic steroids. The studies were selected and the data abstracted independently by 2 researchers. They found 22 studies enrolling a total of 4550 patients. The studies for the most part were of high quality, and heterogeneity was not significant. Most of the studies (n = 15, 3278 patients) compared daily inhaled corticosteroids with placebo. On average, the exacerbations were decreased by 30% (risk ratio [RR] = .70; 95% CI .61 - .79), with one fewer exacerbation for every 9 children treated. Results were better in patients with persistent asthma. In a single study of 202 patients, treatment with daily inhaled corticosteroids was more effective than with montelukast at preventing exacerbation (RR = .59; .38 - .92). Daily versus intermittent inhaled corticosteroids were found to be equal in 2 studies, but the number of patients (and events) was too small to draw firm conclusions. Though not formally a part of this analysis, height was slightly (.7 - 1.1 cm) affected by treatment with inhaled corticosteroids but growth differences resolved following discontinuation.
Bottom line: Daily moderate-dose inhaled corticosteroids can decrease episodes of wheezing that require oral corticosteroid treatment in kids 6 years or younger, especially if they have persistent asthma. Intermittent treatment is likely effective, too, and reduces the total inhaled steroid dose. Inhaled corticosteroid treatment is more effective than montelukast (Singulair).
Kaiser SV, Huynh T, Bacharier LB, et al. Preventing exacerbations in preschoolers with recurrent wheeze: a meta-analysis. Pediatrics. 2016;137(6):e20154496.

7. Single-dose dexamethasone = 3 days of steroids in children with acute asthma

Clinical question: In children with acute exacerbation of asthma, is a single dose of corticosteroid as effective as 3 days of treatment?
Study design: Randomized controlled trial (nonblinded)
Setting: Emergency department
Synopsis: These Irish investigators enrolled 226 children (for a total of 245 enrollments; some were enrolled twice) between the ages of 2 and 16 years with an acute exacerbation of asthma. The children were randomized (concealed allocation unknown) to receive either a single dose of oral dexamethasone (0.3 mg/kg) or 3 days of oral prednisolone (1 mg/kg/day) in addition to usual therapy. None of the patients, their parents, or the investigators were masked to treatment assignment, though the outcome assessor was unaware of treatment at the time of evaluation, which was 4 days after presentation. The Pediatric Respiratory Assessment Measure (PRAM) was used to measure symptoms. It consists of measuring suprasternal and scalene muscle contraction, air entry, wheezing, and oxygen saturation, with a maximum score of 12. At 4 days, PRAM scores were similar among the 2 groups (0.91 vs 0.91). Hospital admission rates were also similar between the 2 groups, as were days lost from school and parental workdays missed. Return visits were similar between the 2 groups, though more children receiving the single dose required further steroid treatment within the following 2 weeks (13% vs 4%). Vomiting occurred more often with prednisolone.
Bottom line: In addition to usual beta-agonist treatment, a single dose of oral dexamethasone is as effective as 3 days of prednisolone (with less vomiting) in decreasing respiratory symptoms without increasing hospitalizations, follow-up visits, and days lost from school.

Additional treatment with a steroid was more common in the group receiving the single dose of dexamethasone.
Cronin JJ, McCoy S, Kennedy U, et al. A randomized trial of single-dose oral dexamethasone versus multidose prednisolone for acute exacerbations of asthma in children who attend the emergency department. Ann Emerg Med. 2016;67(5):593-601.

Asthma in Adults

Single dose dexamethasone is about as effective as 5 days of prednisone for adults with asthma exacerbations. Although azithromycin 3 times a week reduces the frequency of asthma exacerbations, a short course for exacerbations is not helpful. Adding LABAs to inhaled steroids provides modest benefit in reducing exacerbations. Anti-IL5 monoclonal antibody therapies for asthma are somewhat effective in reducing prednisone dose and exacerbations in patients with severe asthma and are very expensive.

8. Single-dose dexamethasone an option for acute adult asthma

Clinical question: Is a single dose of dexamethasone as effective as 5 days of prednisone for acute exacerbations of asthma?
Study design: Randomized controlled trial (double-blinded)
Setting: Emergency department
Synopsis: These investigators enrolled 456 adults younger than 56 years who presented with acute asthma to an emergency department and required at least one treatment with a beta-agonist. The patients were randomly assigned, using concealed allocation, to receive treatment with prednisone 60 mg daily for 5 days or a single dose of dexamethasone 12 mg followed by 4 days of placebo. Treatment was started in the emergency department. Of the 456 people initially enrolled, 376 could be evaluated; 16 were admitted before leaving the emergency department and 73 could not be contacted (more in the dexamethasone group). Over the subsequent 2 weeks, 12.1% of the dexamethasone group and 9.8% of prednisone group had a relapse that required additional treatment (difference 2.3%; 95% CI -4.1% to 8.6%). This difference did not meet the researcher's threshold for noninferiority of 8%, meaning that treatment with dexamethasone was slightly less effective. The hospitalization rate was low (3%) and did not differ between treatment groups. Side effects were more common in the prednisone group.
Bottom line: A single dose of 12 mg dexamethasone, which has a longer duration of action than prednisone, is almost as effective as 5 days of 60 mg prednisone for the prevention of relapse in adults with acute asthma treated in an emergency department. It is a reasonable option for treatment in the emergency department, given its fewer side effects. In this study, patients who received the single dose also took placebo for 4 days; further research is needed to determine whether patients are comfortable with taking just a single dose.
Rehrer MW, Liu B, Rodriguez M, Lam J, Alter HJ. A randomized controlled noninferiority trial of single dose of oral dexamethasone versus 5 days of oral prednisone in acute adult asthma. Ann Emerg Med 2016;68(5):608-613.

9. Azithromycin reduces frequency of exacerbations in adults with persistent asthma

Clinical question: Does the regular use of azithromycin decrease the frequency of exacerbations in adults with persistent asthma?
Study design: Randomized controlled trial (double-blinded)
Setting: Uncertain
Synopsis: In this multicenter study, after a 2-week run-in period to establish stability and general adherence to an asthma care regimen, the researchers randomly assigned adults with symptomatic persistent asthma despite the use of inhaled corticosteroids and long-acting beta-agonists to receive azithromycin (500 mg 3 times per week; n = 213) or placebo (n = 207) for 48 weeks. The research team frequently evaluated the participants' exacerbations, medication use, adherence, and adverse events through office visits and telephone calls. The researchers evaluated the 2 primary end points (exacerbations and quality of life) using intention to treat. Unlike many studies that don't include the patients who withdraw, these authors conducted a true intention-to-treat analysis. The patients treated with azithromycin had fewer exacerbations (1.07 per year; 95% CI 0.85 - 1.29) than those treated with placebo (1.86; 1.54 - 2.18). Additionally, 44% of azithromycin-treated patients had at least one exacerbation compared with 61% of the placebo-treated patients (number needed to treat = 6; I 4 - 13). Azithromycin was effective in reducing the frequency of exacerbations in several planned subgroups of patients: those with sputum eosinophilia, frequent exacerbations, chronic cough, or bacterial pathogens on baseline sputum. There was no difference in the rate of severe adverse events or withdrawals due to side effects. More azithromycin-treated patients experienced diarrhea (34%) than placebo-treated patients (19%; number needed to treat to harm = 7; 5 - 16).
Bottom line: In this well-done government-funded study of adults with persistent asthma who use inhaled corticosteroids and long-acting beta-agonists, adding 500 mg azithromycin 3 times a week reduced the frequency of exacerbations. For every one exacerbation avoided, however, one patient will experience diarrhea.
Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet 2017;390(10095):659-668.

10. No benefit to azithromycin for acute asthma exacerbations

Clinical question: For patients with acute asthma exacerbations, does the addition of azithromycin improve the resolution of symptoms?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Along with its antimicrobial activity, azithromycin may have anti-inflammatory and antiviral properties that could potentially help resolve an acute asthma exacerbation. To test this theory, investigators in the United Kingdom enrolled adult patients who presented with symptoms and signs of acute asthma exacerbation that required systemic steroids. This was done in order to exclude patients with mild exacerbations. Of the 4582 eligible patients, 4383 were excluded (!), mainly because they were currently taking antibiotics or had taken antibiotics within 28 days of enrollment. The remaining 199 patients were randomized to receive either azithromycin 500 mg daily or matching placebo for 3 days along with standard care. The 2 groups were balanced at baseline: mean age was 40 years, two thirds were women, and baseline asthma symptom scores were similar. Patients recorded their symptoms in a diary and were assessed at days 5 and 10 after the initiation of treatment. For the primary outcome of mean asthma symptom scores at day 10, no difference was detected between the 2 groups. Additionally, there were no differences in quality-of-life scores or on any measure of lung function during the entire study. Of note, patients in this study had a low likelihood of concurrent respiratory infections; sputum samples and nasal/throat swabs indicated only 10% had bacterial infections and 18% had viral infections.
Bottom line: These data show no improved outcomes with the addition of azithromycin to standard treatment for patients with acute asthma exacerbations requiring systemic steroids. However, the recruitment for this study was difficult, as half the eligible patients were excluded because of current or recent use of antibiotics, which resulted in a very underpowered study that only reached half its recruitment target. For each person included, more than 10 were excluded. Beyond its impact on the study results, the recruitment difficulty suggests that antibiotic use for asthma exacerbation is widespread despite current treatment guidelines that recommend otherwise.
Johnston SL, Szigeti M, Cross M, et al, for the AZALEA Trial Team. Azithromycin for acute exacerbations of asthma: the AZALEA randomized clinical trial. JAMA Intern Med 2016 Sep 19.

11. Adding formoterol to budesonide for asthma: no significantly increased harms; minimal benefits

Clinical question: Does adding the long-acting beta agonist formoterol to budesonide increase the risk of serious adverse events in persons with persistent asthma?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (any)
Synopsis: This is one of several studies mandated by the FDA to assess the safety of LABAs in persons with asthma. This trial, sponsored by AstraZeneca, identified patients 12 years and older with persistent asthma (between 1 and 4 exacerbations in the previous year) who were taking a daily asthma medication, and had no previous life-threatening exacerbations. Their mean age was 43 years, 15% were current or former smokers, and 82% had experienced only 1 exacerbation in the previous year. A daily inhaled glucocorticoid was used by 90% at the time of recruitment, with half using a moderate dose. Based on the severity of their asthma, each patients was assigned to either a low dose of budesonide (160 mcg daily) or high dose of budesonide (320 mcg daily). They were then randomized to receive that dose of budesonide with or without formoterol in open-label fashion. A total of 11,693 persons were randomized, with approximately 80% receiving the high-dose budesonide. Patients were followed up for 26 weeks, with approximately 12% dropping out during that time (kind of a large number for such a short trial). Groups were balanced at the start of the study, and the primary analysis was by intention to treat. There was no significant difference between groups regarding serious asthma-related events, defined as hospitalization, intubation, or death. In the high-dose budesonide group, there were 37 serious asthma-related events in the formoterol group, including 2 deaths, compared with 32 events and no deaths in the budesonide-only group. The percentage of participants who experienced at least one exacerbation was slightly reduced in the combination therapy group (9.2 vs 10.8%; P = .002; number needed to treat = 63). However, the open-label design and apparent failure to mask the outcome assessors could easily bias the results.
Bottom line: I'm not convinced that adding formoterol will result in significant benefits, given its modest impact on exacerbations and the open-label design of this study. Formoterol appears to be safe, though the most important safety events (death or intubation) were very rare in this short trial, so it is important to combine these results with those from other trials of long-acting beta agonists (LABAs) in a meta-analysis.
Peters SP, Bleecker ER, Canonica GW, et al. Serious asthma events with budesonide plus formoterol vs. budesonide alone. N Engl J Med 2016;375(9):850-860.

12. Inhaled fluticasone-salmeterol better than fluticasone alone for moderate to severe asthma

Clinical question: Is the combination of a long-acting beta-agonist and an inhaled corticosteroid as safe and effective as an inhaled corticosteroid alone?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: This study was performed by GlaxoSmithKline at the behest of the FDA because of enduring concerns about the safety of long-acting beta-agonists. The authors identified patients with moderate to severe asthma who had experienced at least one exacerbation in the previous year that required systemic steroids or hospitalization (but no such episode in the previous month). The 11,751 included patients from 694 centers were randomized to receive fluticasone-salmeterol or fluticasone alone. The dose of

fluticasone alone was stratified into 3 subgroups based on disease severity: 100 mcg, 250 mcg, and 500 mcg. In the combination treatment group, salmeterol 50 mcg was combined with fluticasone at 100 mcg, 250 mcg, and 500 mcg, again according to disease severity. All medications were given twice daily. Patients were 12 years and older (mean age = 43 years) and most patients were from North America or Europe. Groups were balanced at the beginning of the study and analysis was by intention to treat. Outcomes were adjudicated by members of the research team who were masked to treatment assignment. The primary efficacy endpoint was the first severe asthma exacerbation, defined as the use of systemic steroids for at least 3 days, asthma-related hospitalization, or an emergency department visit resulting in systemic steroid administration. There were fewer severe asthma exacerbations in the fluticasone-salmeterol group than in the group that received fluticasone alone (8% vs 10%; P < .001; NNT = 50 over 26 weeks). The primary safety outcome (a composite of asthma-related deaths, asthma-related intubations, and asthma-related hospitalizations) was similar between groups: 36 events in the fluticasone-salmeterol group and 38 events in the fluticasone-only group. There were 3 deaths in the fluticasone-salmeterol group and 6 in the fluticasone-only group, none of which were adjudicated as being related to asthma.
Bottom line: The combination of fluticasone and salmeterol, with the steroid dose adjusted for disease severity, reduces the number of severe asthma exacerbations more than fluticasone alone (number needed to treat [NNT] = 50 over 26 weeks), with no difference in terms of potential harms such as intubation or asthma-related death.
Stempel DA, Raphiou I, Kral KM, et al, for the AUSTRI Investigators. Serious asthma events with fluticasone plus salmeterol versus fluticasone alone. N Engl J Med 2016;374(19):1822-1830.

13. Benralizumab reduces daily oral prednisone dose for severe asthma from 10 mg to 5 mg

Clinical question: Does benralizumab improve outcomes in patients with severe asthma who are receiving long-term systemic glucocorticoids?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Benralizumab is a human monoclonal antibody against the interleukin-5 receptor that gives it anti-inflammatory properties. This trial enrolled patients with severe asthma and an elevated blood eosinophil count who were taking a moderate-dose to high-dose inhaled steroid, a long-acting beta-agonist, and a daily dose of an oral steroid for at least 6 months. They initially recruited 369 patients, of whom 220 ultimately met the eligibility criteria after a run-in period during which their oral glucocorticoid dose was reduced to the minimum effective dose and at least 70% compliance with their current medications was ensured. These 220 were then randomized to receive either (1) benralizumab 30 mg by subcutaneous injection every 4 weeks for 28 weeks, (2) benralizumab 30 mg subcutaneously every 4 weeks for 3 months, and then every 8 weeks for the remaining 16 weeks, or (3) placebo injection every 4 weeks. All patients underwent a concerted effort during the 28-week study period to reduce their oral steroid dose, and the primary outcome was how much the steroid could be reduced. Groups were balanced at the start of the study, and analysis was by intention to treat. The mean age of participants was 50 years, with a median prednisone dose of 10 mg at baseline, and a forced expiratory volume in 1 second of approximately 60% of predicted. Asthma exacerbations were defined as requiring an increase in the steroid dose for 3 or more days, a visit to the emergency department (ED), or hospitalization. Patients in both of the active treatment groups saw a statistically significant reduction in the median daily oral dose of prednisone—from 10 mg to 5 mg—compared with no change in the placebo group. Approximately half the patients in the active treatment group were able to discontinue using their steroid. Patients in the active treatment groups were less likely to have any asthma exacerbation during the study period (17% to 19% vs 39%; P = .001; number needed to treat = 5 over 28 weeks). The annualized rate of exacerbations was lower for the active treatment groups (0.55 for benralizumab every 8 weeks, 0.82 for benralizumab every 4 weeks, 1.80 for placebo; P = .003). More serious exacerbations (resulting in a visit to the ED or hospitalization) were slightly less likely for the group dosed every 8 weeks (0.02 vs 0.32; P = 0.02), but not the group dosed every 4 weeks. There were small improvements in quality of life scores, but they were not clinically significant (eg, 0.45 points on a 12-point scale). Adverse events were similar between groups. In their article, the authors overemphasize the more dramatic-sounding relative reductions rather than the absolute reductions for all outcomes, something that the editors of the journal should not have tolerated.
Bottom line: The addition of the monoclonal antibody benralizumab reduced the median dose of prednisone from 10 mg to 5 mg, and resulted in a small decrease in serious exacerbations in one of the active treatment groups but not the other. Although this drug has not yet been approved by the US Food and Drug Administration, a similar drug, omalizumab (Zolair), is currently priced at approximately $1000 per month in the United States and $750 in Canada. It is unclear whether the modest benefits are worth the drug's high cost.
Nair P, Wenzel S, Rabe KF, et al, for the ZONDA Trial Investigators. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med 2017;376(25):2448-2458.

14. Anti-IL5 therapies for asthma are somewhat effective

BACKGROUND: This review is the first update of a previously published review in The Cochrane Library (Issue 7, 2015). Interleukin-5 (IL-5) is the main cytokine involved in the activation of eosinophils, which cause airway inflammation and are a classic feature of asthma. Monoclonal antibodies targeting IL-5 or its receptor (IL-5R) have been developed, with recent studies suggesting that they reduce asthma exacerbations, improve health-related quality of life (HRQoL) and lung function. These are being incorporated into asthma guidelines.
OBJECTIVES: To compare the effects of therapies targeting IL-5 signaling (anti-IL-5 or anti-IL-5Rα) with placebo on exacerbations, health-related qualify of life (HRQoL) measures, and lung function in adults and children with chronic asthma, and specifically in those with eosinophilic asthma refractory to existing treatments.
SEARCH METHODS: We searched the Cochrane Airways Trials Register, clinical trials registries, manufacturers' websites, and reference lists of included studies. The most recent search was March 2017.

SELECTION CRITERIA: We included randomised controlled trials comparing mepolizumab, reslizumab and benralizumab versus placebo in adults and children with asthma.
DATA COLLECTION AND ANALYSIS: Two authors independently extracted data and analysed outcomes using a random-effects model. We used standard methods expected by Cochrane.
MAIN RESULTS: Thirteen studies on 6000 participants met the inclusion criteria. Four used mepolizumab, four used reslizumab, and five used benralizumab. One study in benralizumab was terminated early due to sponsor decision and contributed no data. The studies were predominantly on people with severe eosinophilic asthma, which was similarly but variably defined. Eight included children over 12 years but these results were not reported separately. We deemed the risk of bias to be low, with all studies contributing data being of robust methodology. We considered the quality of the evidence for all comparisons to be high overall using the GRADE scheme, with the exception of intravenous mepolizumab because this is not currently a licensed delivery route. All of the anti-IL-5 treatments assessed reduced rates of 'clinically significant' asthma exacerbation (defined by treatment with systemic corticosteroids for three days or more) by approximately half in participants with severe eosinophilic asthma on standard of care (at least medium-dose inhaled corticosteroids (ICS)) with poorly controlled disease (either two or more exacerbations in the preceding year or Asthma Control Questionnaire (ACQ) 1.5 or more). Non-eosinophilic participants treated with benralizumab also showed a significant reduction in exacerbation rates, but no data were available for non-eosinophilic participants, and mepolizumab or reslizumab.

We saw modest improvements in validated HRQoL scores with all anti-IL-5 agents in severe eosinophilic asthma. However these did not exceed the minimum clinically important difference for ACQ and Asthma Quality of Life Questionnaire (AQLQ), with St. George's Respiratory Questionnaire (SGRQ) only assessed in two studies. The improvement in HRQoL scores in non-eosinophilic participants treated with benralizumab, the only intervention for which data were available in this subset, was not statistically significant, but the test for subgroup difference was negative. All anti-IL-5 treatments produced a small but statistically significant improvement in mean pre-bronchodilator forced expiratory flow in one second (FEV1) of between 0.08 L and 0.11 L.

There were no excess serious adverse events with any anti-IL-5 treatment, and indeed a reduction in favour of mepolizumab that could be due to a beneficial effect on asthma-related serious adverse events. There was no difference compared to placebo in adverse events leading to discontinuation with mepolizumab or reslizumab, but significantly more discontinued benralizumab than placebo, although the absolute numbers were small (36/1599 benralizumab versus 9/998 placebo).Mepolizumab, reslizumab and benralizumab all markedly reduced blood eosinophils, but benralizumab resulted in almost complete depletion, whereas a small number remained with mepolizumab and reslizumab. The implications for efficacy and/or adverse events are unclear.
AUTHORS' CONCLUSIONS: Overall our study supports the use of anti-IL-5 treatments as an adjunct to standard of care in people with severe eosinophilic asthma and poor control. These treatments roughly halve the rate of asthma exacerbations in this population. There is limited evidence for improved HRQoL scores and lung function, which may not meet clinically detectable levels. There were no safety concerns regarding mepolizumab or reslizumab, and no excess serious adverse events with benralizumab, although there remains a question over adverse events significant enough to prompt discontinuation. Further research is needed on biomarkers for assessing treatment response, optimal duration and long-term effects of treatment, risk of relapse on withdrawal, non-eosinophilic patients, children (particularly under 12 years), and comparing anti-IL-5 treatments to each other and, in people eligible for both, to anti-immunoglobulin E. For benralizumab, future studies should closely monitor rates of adverse events prompting discontinuation.
Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. Cochrane Database Syst Rev. 2017 Sep 21;9:CD010834.

15. Adjusting medications based on sputum eosinophils versus clinical symptoms reduces asthma exacerbations in adults

Background. Asthma severity and control can be measured both subjectively and objectively. Sputum analysis for evaluation of percentage of sputum eosinophilia directly measures airway inflammation, and is one method of objectively monitoring asthma. Using sputum analysis to adjust or tailor asthma medications is potentially superior to traditional methods based on symptoms and spirometry.
Objectives. To evaluate the efficacy of tailoring asthma interventions based on sputum analysis in comparison to traditional methods (usually symptom-based with or without spirometry/peak flow) for asthma-related outcomes in children and adults.
Search methods. We searched the Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, trials' registries, and reference lists of articles. The last search was conducted in February 2017.
Selection criteria. All randomised controlled comparisons of adjustment of asthma therapy based on sputum eosinophils compared to traditional methods (primarily clinical symptoms and spirometry/peak flow).
Data collection and analysis. Results of searches were reviewed against pre-determined criteria for inclusion. In this update, two reviewers selected relevant studies, independently assessed trial quality and extracted the data. We contacted authors for further information when relevant. We analysed data as 'treatment received' and performed sensitivity analyses.
Main results. Three new studies were added in this update, resulting in a total of six included studies (five in adults and one involving children/adolescents). These six studies were clinically and methodologically heterogeneous (use of medications, cut-off for percentage of sputum eosinophils and definition of asthma exacerbation). Of 374 participants randomised, 333 completed the trials. In the meta-analysis, there was a significant reduction in the occurrence of any exacerbations when treatment was based on sputum eosinophil counts, compared to that based on clinical symptoms with or without lung function; pooled odds ratio (OR) was 0.57 (95% confidence interval (CI) 0.38 to 0.86). The risk of having one or more exacerbations over 16 months was 82% in the control arm and 62% (95% CI 49% to 74%) in the sputum strategy arm, resulting in a number needed to treat to benefit (NNTB) of 6 (95% CI 4 to 13).There were also differences between the groups in the rate of exacerbation (any exacerbation per year) and severity of exacerbations defined by requirement for use of oral corticosteroids and hospitalisations: the risk of one or more hospitalisations over 16 months was 24% in controls compared to 8% (95% CI 3% to 21%) in the sputum arm. Data for clinical symptoms, quality of life and spirometry were not significantly different between groups. The mean dose of inhaled corticosteroids per day was also similar in both groups. However sputum induction was not always possible. The included studies did not record any adverse events. One study was not blinded and thus was considered to have a high risk of bias. However, when this study was removed in a sensitivity analysis, the difference between the groups for the primary outcome (exacerbations) remained statistically significant between groups. The GRADE quality of the

evidence ranged from moderate (for the outcomes 'Occurrence of any exacerbation' and 'Hospitalisation') to low (for the outcome 'Mean dose of inhaled corticosteroids per person per day') due to the inconsistency in defining exacerbations and the small number of hospital admissions.
Authors' conclusions. In this updated review, tailoring asthma interventions based on sputum eosinophils is beneficial in reducing the frequency of asthma exacerbations in adults with asthma. Adults with frequent exacerbations and severe asthma may derive the greatest benefit from this additional monitoring test, although we were unable to confirm this through subgroup analysis. There is insufficient data available to assess tailoring asthma medications based on sputum eosinophilia in children. Further robust RCTs need to be undertaken and these should include participants with different underlying asthma severities and endotypes.
Reference. *Petsky HL, Li A, Chang AB. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD005603. DOI: 10.1002/14651858.CD005603.pub3.*

COPD

16. Screening for Chronic Obstructive Pulmonary Disease Not Recommended: Evidence Report and Systematic Review for the US Preventive Services Task Force

IMPORTANCE: Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States.
OBJECTIVE: To systematically review literature on the accuracy of screening questionnaires and office-based screening pulmonary function testing and the efficacy and harms of treatment of screen-detected COPD.
DATA SOURCES: MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials for relevant English-language studies published through January 2015.
STUDY SELECTION: Two reviewers independently screened abstracts and studies. The search yielded 13,141 unique citations; 465 full-text articles were reviewed, and 33 studies met the inclusion criteria.
DATA EXTRACTION AND SYNTHESIS: Two reviewers rated the quality of each study using USPSTF criteria.
MAIN OUTCOMES AND MEASURES: Diagnostic accuracy (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]; treatment efficacy (COPD exacerbations, all-cause mortality, quality of life, and dyspnea); and treatment harms.
RESULTS: All screening questionnaires were based on symptoms as well as risk factors such as age and smoking history. The COPD Diagnostic Questionnaire was the most extensively studied (5 studies, n = 3048), with moderate overall performance for COPD detection: area under the receiver operating characteristic curve (AUC), 0.65 to 0.72; sensitivity, 80% to 93%; and specificity, 24% to 49%, at a threshold of greater than 16.5. Positive predictive value and NPV ranged from 17% to 45% and 76% to 98%, respectively. For pulmonary function-based screening tools, FEV1/FEV6 was the best studied (3 studies, n = 1587), with AUC ranging from 0.84 to 0.85. Sensitivity ranged from 51% to 80%. Specificity (range, 90%-95%) and PPV (range, 63%-75%) appeared better than questionnaires. There was not strong evidence to support that screening and supplying smokers with spirometry results improves smoking cessation rates. Treatment trials were unavailable for screen-detected patients. Trials that reported outcomes in patients with mild to moderate COPD included 2 trials of long-acting β-agonists (LABAs) (n = 3174), 1 RCT of LABAs and inhaled corticosteroids (ICS) (n = 1097), 5 RCTs of the long-acting muscarinic antagonist tiotropium (n = 4592), and 6 RCTs of ICS (n = 3983). They suggested no benefit in all-cause mortality, but a decrease in annual rates of exacerbations with pharmacologic treatments. Few trials reported harms for any individual drug class. Adverse effects were generally mild (eg, dry mouth and cough).
CONCLUSIONS AND RELEVANCE: There was no direct evidence available to determine the benefits and harms of screening asymptomatic adults for COPD using questionnaires or office-based screening pulmonary function testing or to determine the benefits of treatment in screen-detected populations. Indirect evidence suggests that the COPD Diagnostic Questionnaire has moderate overall performance for COPD detection. Among patients with mild to moderate COPD, the benefit of pharmacotherapy for reducing exacerbations was modest.
Guirguis-Blake JM, Senger CA, Webber EM, Mularski RA, Whitlock EP. Screening for Chronic Obstructive Pulmonary Disease: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2016 Apr 5;315(13):1378-93

17. Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease

BACKGROUND: Patients with mild or moderate chronic obstructive pulmonary disease (COPD) rarely receive medications, because they have few symptoms. We hypothesized that long-term use of tiotropium would improve lung function and ameliorate the decline in lung function in patients with mild or moderate COPD.
METHODS: In a multicenter, randomized, double-blind, placebo-controlled trial that was conducted in China, we randomly assigned 841 patients with COPD of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 (mild) or 2 (moderate) severity to receive a once-daily inhaled dose (18 μg) of tiotropium (419 patients) or matching placebo (422) for 2 years. The primary end point was the between-group difference in the change from baseline to 24 months in the forced expiratory volume in 1 second (FEV_1) before bronchodilator use. Secondary end points included the between-group difference in the change from baseline to 24 months in the FEV_1 after bronchodilator use and the between-group difference in the annual decline in the FEV_1 before and after bronchodilator use from day 30 to month 24.
RESULTS: Of 841 patients who underwent randomization, 388 patients in the tiotropium group and 383 in the placebo group were included in the full analysis set. The FEV_1 in patients who received tiotropium was higher than in those who received placebo throughout the trial (ranges of mean differences, 127 to 169 ml before bronchodilator use and 71 to 133 ml after bronchodilator use; $P<0.001$ for all comparisons). There was no significant amelioration of the mean (±SE) annual decline in the FEV_1 before bronchodilator use: the decline was 38±6 ml per year in the tiotropium group and 53±6 ml per year in the placebo group (difference, 15 ml per year; 95% confidence interval [CI], -1 to 31; $P=0.06$). In contrast, the annual decline in the FEV_1 after bronchodilator use was significantly less in the tiotropium group than in the placebo group (29±5 ml per year vs. 51±6 ml per year; difference, 22 ml per year [95% CI, 6 to

37]; P=0.006). The incidence of adverse events was generally similar in the two groups.
CONCLUSIONS: Tiotropium resulted in a higher FEV1 than placebo at 24 months and ameliorated the annual decline in the FEV1 after bronchodilator use in patients with COPD of GOLD stage 1 or 2. (Funded by Boehringer Ingelheim and others; Tie-COPD ClinicalTrials.gov number, NCT01455129).
Zhou Y, Zhong NS, Li X, Chen S, Zheng J, Zhao D, Yao W, et al. Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease. N Engl J Med. 2017 Sep 7;377(10):923-935.

18. Physician assessment of COPD doesn't match spirometry results

Clinical question: How accurate are physician assessments of the severity of chronic obstructive pulmonary disease?
Study design: Cross-sectional
Setting: Outpatient (primary care)
Synopsis: The study included 899 patients with COPD who were randomly selected from the practices of 83 primary care physicians (63% family medicine docs and 37% general internists). The physicians had been in practice an average of 22 years and most had in-office spirometry available before this study. At one visit both the physician and the patient rated the patient's pulmonary disease severity at that time on a 5-point scale, ranging from 1 (no clinical symptoms or disease impact/mild symptoms) to 5 (very severe). Following this assessment the patient immediately underwent in-office spirometry, though only 75% were able to produce at least 1 high-quality result. Overall, there was poor correlation among physician assessment, patient assessment, and spirometry results. Physicians underestimated severity in 41% of patients and overestimated severity in 29% of patients using the spirometry results as the reference standard. Correlation wasn't much better with the patients' own estimates, with physicians underestimating severity in 42% of patients and overestimating severity in 18% as compared with those patients' self-assessments. Overall, physician ratings were accurate for only 30% of patients. More important, the physicians in this study recommended treatment changes for 37% of patients after reviewing spirometry results.
Bottom line: Using immediate, in-office spirometry results as the gold standard, seasoned physicians accurately identified chronic obstructive pulmonary disease (COPD) severity in approximately 1 in 3 patients, underestimating severity in 41% of patients and overestimating severity in 29% of patients. This mismatch seems to be important since the physicians participating in this study changed their treatment plans for 37% of patients after reviewing the spirometry results. A second issue in this study: Even though most of the physicians in the study had a spirometer in their office, they (or their staff) were unable to get usable spirometry results in 25% of their patients.
Mapel DW, Dalal AA, Johnson P, Becker L, Hunter AG. A clinical study of COPD severity assessment by primary care physicians and their patients compared with spirometry. Am J Med 2015;128(6):629-637.

19. Supplemental oxygen ineffective for COPD with moderate hypoxemia

Clinical question: Is long-term supplemental oxygen effective for patients with stable chronic obstructive pulmonary disease and moderate resting or exertional hypoxemia?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (any)
Synopsis: Although there is good evidence that oxygen supplementation reduces mortality for patients with chronic obstructive pulmonary disease and severe resting hypoxemia, many patients are prescribed oxygen for moderate resting hypoxemia (a resting oxygen saturation of 89% to 93%) or moderate exertional hypoxemia (oxygen saturation of at least 80% for at least 5 minutes of a 6-minute walk test, but less than 90% for at least 10 seconds). Of the 738 patients in this study, 133 had moderate resting hypoxemia only, 319 had moderate exertional hypoxemia only, and 286 had both. Their mean age was 69 years, 73% were male, and their mean resting oxygen saturation on room air was 93%. Patients were randomized to receive oxygen supplementation or no oxygen supplementation. Of those randomized to receive oxygen supplementation, those with resting hypoxemia were told to use it 24 hours a day and those with exertional hypoxemia were told to use it during sleep and exercise. The "dose" was 2 liters of oxygen per minute, adjusted higher during exercise if necessary to maintain an oxygen saturation of at least 90%. Enrollment at the 42 participating centers was slow (it took 5 years). Patients were followed up for a median of 18 months (range 12 months to 6 years). Crossover rates were lower than expected: 12% to supplemental oxygen and 3% to no supplemental oxygen. Allocation was not concealed and the study was not masked, which would tend to bias in favor of the intervention. However, in the intention-to-treat analysis no difference was seen between groups with regard to death or first hospitalization; secondary outcomes, such as quality of life, psychological outcomes, and functional outcomes were also unaffected. There were 51 adverse events attributed to supplemental oxygen use, including 23 reports of tripping over equipment (2 that required hospitalization) and 5 reports of fires or burns (1 that required hospitalization).
Bottom line: In patients with moderate resting or exertional hypoxemia, supplemental oxygen does not reduce mortality or prevent hospitalizations. The groups were slightly imbalanced at the beginning of the study, with a lower BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index in the supplemental oxygen group, which is associated with lower mortality. However, this imbalance, as well as the failure to conceal allocation or mask the study, would bias the results in favor of supplemental oxygen, if bias occurred.
The Long Term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. N Engl J Med 2016;375(17):1617-1627.

20. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease improves outcomes

Background. Guidelines have provided positive recommendations for pulmonary rehabilitation after exacerbations of chronic obstructive pulmonary disease (COPD), but recent studies indicate that postexacerbation rehabilitation may not always be effective in patients with unstable COPD.
Objectives. To assess effects of pulmonary rehabilitation after COPD exacerbations on hospital admissions (primary outcome) and other patient-important outcomes (mortality, health-related quality of life (HRQL) and exercise capacity).
Search methods. We identified studies through searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PEDro (Physiotherapy Evidence Database) and the Cochrane Airways Review Group Register of Trials. Searches were current as of 20 October 2015, and handsearches were run up to 5 April 2016.
Selection criteria. Randomised controlled trials (RCTs) comparing pulmonary rehabilitation of any duration after exacerbation of COPD versus conventional care. Pulmonary rehabilitation programmes had to include at least physical exercise (endurance or strength exercise, or both). We did not apply a criterion for the minimum number of exercise sessions a rehabilitation programme had to offer to be included in the review. Control groups received conventional community care without rehabilitation.
Data collection and analysis. We expected substantial heterogeneity across trials in terms of how extensive rehabilitation programmes were (i.e. in terms of number of completed exercise sessions; type, intensity and supervision of exercise training; and patient education), duration of follow-up (< 3 months vs ≥ 3 months) and risk of bias (generation of random sequence, concealment of random allocation and blinding); therefore, we performed subgroup analyses that were defined before we carried them out. We used standard methods expected by Cochrane in preparing this update, and we used GRADE for assessing the quality of evidence.
Main results. For this update, we added 11 studies and included a total of 20 studies (1477 participants). Rehabilitation programmes showed great diversity in terms of exercise training (number of completed exercise sessions; type, intensity and supervision), patient education (from none to extensive self-management programmes) and how they were organised (within one setting, e.g. pulmonary rehabilitation, to across several settings, e.g. hospital, outpatient centre and home). In eight studies, participants completed extensive pulmonary rehabilitation, and in 12 studies, participants completed pulmonary rehabilitation ranging from not extensive to moderately extensive. Eight studies involving 810 participants contributed data on hospital readmissions. Moderate-quality evidence indicates that pulmonary rehabilitation reduced hospital readmissions (pooled odds ratio (OR) 0.44, 95% confidence interval (CI) 0.21 to 0.91), but results were heterogenous (I2 = 77%).

Extensiveness of rehabilitation programmes and risk of bias may offer an explanation for the heterogeneity, but subgroup analyses were not statistically significant (P values for subgroup effects were between 0.07 and 0.11). Six studies including 670 participants contributed data on mortality. The quality of evidence was low, and the meta-analysis did not show a statistically significant effect of rehabilitation on mortality (pooled OR 0.68, 95% CI 0.28 to 1.67). Again, results were heterogenous (I2 = 59%). Subgroup analyses showed statistically significant differences in subgroup effects between trials with more and less extensive rehabilitation programmes and between trials at low and high risk for bias, indicating possible explanations for the heterogeneity. Hospital readmissions and mortality studies newly included in this update showed, on average, significantly smaller effects of rehabilitation than were seen in earlier studies.

High-quality evidence suggests that pulmonary rehabilitation after an exacerbation improves health-related quality of life. The eight studies that used St George's Respiratory Questionnaire (SGRQ) reported a statistically significant effect on SGRQ total score, which was above the minimal important difference (MID) of four points (mean difference (MD) -7.80, 95% CI -12.12 to -3.47; I2 = 64%). Investigators also noted statistically significant and important effects (greater than MID) for the impact and activities domains of the SGRQ. Effects were not statistically significant for the SGRQ symptoms domain.

Again, all of these analyses showed heterogeneity, but most studies showed positive effects of pulmonary rehabilitation, some studies showed large effects and others smaller but statistically significant effects. Trials at high risk of bias because of lack of concealment of random allocation showed statistically significantly larger effects on the SGRQ than trials at low risk of bias. High-quality evidence shows that six-minute walk distance (6MWD) improved, on average, by 62 meters (95% CI 38 to 86; I2 = 87%). Heterogeneity was driven particularly by differences between studies showing very large effects and studies showing smaller but statistically significant effects. For both health-related quality of life and exercise capacity, studies newly included in this update showed, on average, smaller effects of rehabilitation than were seen in earlier studies, but the overall results of this review have not changed to an important extent compared with results reported in the earlier version of this review.
Reference: *Puhan MA, Gimeno-Santos E, Cates CJ, Troosters T. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD005305. DOI: 10.1002/14651858.CD005305.pub4.*

21. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease

BACKGROUND: Patients with chronic obstructive pulmonary disease (COPD) with an eosinophilic phenotype may benefit from treatment with mepolizumab, a monoclonal antibody directed against interleukin-5.
METHODS: We performed two phase 3, randomized, placebo-controlled, double-blind, parallel-group trials comparing mepolizumab (100 mg in METREX, 100 or 300 mg in METREO) with placebo, given as a subcutaneous injection every 4 weeks for 52 weeks in patients with COPD who had a history of moderate or severe exacerbations while taking inhaled glucocorticoid-based triple maintenance therapy. In METREX, unselected patients in the modified intention-to-treat population with an eosinophilic phenotype were stratified according to blood eosinophil count (≥150 per cubic millimeter at screening or ≥300 per cubic millimeter during the previous year). In METREO, all patients had a blood eosinophil count of at least 150 per cubic millimeter at screening or at least 300 per cubic millimeter during the previous year. The primary end point was the annual rate of moderate or severe exacerbations. Safety was also assessed.
RESULTS: In METREX, the mean annual rate of moderate or severe exacerbations in the modified intention-to-treat population with an eosinophilic phenotype (462 patients) was 1.40 per year in the mepolizumab group versus 1.71 per year in the placebo group (rate

ratio, 0.82; 95% confidence interval [CI], 0.68 to 0.98; adjusted P=0.04); no significant between-group differences were found in the overall modified intention-to-treat population (836 patients) (rate ratio, 0.98; 95% CI, 0.85 to 1.12; adjusted P>0.99). In METREO, the mean annual rate of moderate or severe exacerbations was 1.19 per year in the 100-mg mepolizumab group, 1.27 per year in the 300-mg mepolizumab group, and 1.49 per year in the placebo group. The rate ratios for exacerbations in the 100-mg and 300-mg mepolizumab groups versus the placebo group were 0.80 (95% CI, 0.65 to 0.98; adjusted P=0.07) and 0.86 (95% CI, 0.70 to 1.05; adjusted P=0.14), respectively. A greater effect of mepolizumab, as compared with placebo, on the annual rate of moderate or severe exacerbations was found among patients with higher blood eosinophil counts at screening. The safety profile of mepolizumab was similar to that of placebo.
CONCLUSIONS: Mepolizumab at a dose of 100 mg was associated with a lower annual rate of moderate or severe exacerbations than placebo among patients with COPD and an eosinophilic phenotype. This finding suggests that eosinophilic airway inflammation contributes to COPD exacerbations. (Funded by GlaxoSmithKline; METREX and METREO ClinicalTrials.gov numbers, NCT02105948 and NCT02105961 .).
Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, Martinot JB, Sagara H, Albers FC, Bradford ES, Harris SS, Mayer B, Rubin DB, Yancey SW, Sciurba FC. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. N Engl J Med. 2017 Oct 26;377(17):1613-1629.

Bottom Lines

1. Re-evaluate your asthma patients with spirometry. Many do not have asthma.

2. Dust mite impermeable mattress covers improve symptom control in children with asthma and dust mite sensitivity.

3. Consider using a single dose of dexamethasone in children and adults who have an asthma exacerbation requiring steroids.

4. Adding long acting beta agonists to inhaler corticosteroids appears to be safe and provides very modest benefit compared to the steroid alone for patients with asthma.

5. Supplemental oxygen does not prolong life or reduce hospitalizations in COPD patients with moderate hypoxia.

6. Pulmonary rehab improves outcomes for COPD patients.

7. Tiotropium may be useful in slowing the decline in lung function in COPD patients.

8. Physicians are not very accurate in predicting severity of COPD based on signs and symptoms.

9. Monoclonal antibody medications for asthma and COPD are proliferating, modestly effective and very expensive.

Diet and Nutrition — Gary Ferenchick MD MS

Learning objectives | Understand:

1. The DGAC conclusions on low cholesterol diets
2. Evidence on the percentage of calories consumed from ultra-processed foods in the US
3. The basic elements of the AHA/ACC and the US Department of Agriculture Dietary Guidelines for Americans
4. Understand the evidence on low carbohydrate vs low fat diets
5. The evidence on the Mediterranean Diet for Long-Term Weight Loss and cardiovascular risk reduction

The 2015 *Dietary Guidelines for Americans*

Every 5 years the US Department of Agriculture and Department of Health and Human Services jointly release the *Dietary Guidelines for Americans*. Dietary Guidelines Advisory Committee (DGAC) report; highlights of the 2015 report (https://health.gov/dietaryguidelines/2015-scientific-report/) included:

- "In the new DGAC report, one widely noticed revision *was the elimination of dietary cholesterol as a "nutrient of concern*."
- "A less noticed … change was the absence of an upper limit on total fat consumption"
- "The DGAC report *neither listed total fat as a nutrient of concern nor proposed restricting its consumption.* Rather, it concluded, "Reducing total fat (replacing total fat with overall carbohydrates) does not lower CVD [cardiovascular disease] risk.… Dietary advice should put the emphasis on *optimizing types of dietary fat and not reducing total fat*."
    - "*Limiting total fat was also not recommended for obesity prevention*; instead, the focus was placed on healthful food-based diet patterns that include more vegetables, fruits, whole grains, seafood, legumes, and dairy products and include less meats, sugar-sweetened foods and drinks, and refined grains."
- "With these quiet statements, the DGAG report reverses nearly 4 decades of nutrition policy that placed a priority on reducing total fat consumption throughout the population"
- "Most importantly, the policy focus on fat reduction did not account for the harms of highly processed carbohydrate (eg, refined grains, potato products, and added sugar)—consumption of which is inversely related to that of dietary fat."
- "The 2015 DGAC report tacitly acknowledges the lack of convincing evidence to recommend low-fat–high-carbohydrate diets for the general public in the prevention or treatment of any major health outcome, including heart disease, stroke, cancer, diabetes, or obesity."
- "*The DGAC report highlights that more than 70% of the US population consumes too many refined grain products*. Many of these foods enjoy a lingering health halo or at least a benign reputation, based on years of government guidelines and industry promotion. Recognizing this widespread misunderstanding, the 2015 DGAC report specifies that, "consumption of 'low-fat' or 'nonfat' products with high amounts of refined grains and added sugars should be discouraged."
- "Based on years of inaccurate messages about total fat, a 2014 Gallup poll shows that a majority of US residents are still actively trying to avoid dietary fat, while eating far too many refined carbohydrates."
- It is time for the US Department of Agriculture and Department of Health and Human Services to ... help people understand that limiting total fat does not produce any meaningful health benefits and that increasing healthful fats, including more than 35% of calories, has documented health benefits.

Quotes from (JAMA 2015;313:2421)

Recovered data from the Minnesota Coronary Experiment (MCE) was published in 2016. This RCT followed 9423 "patients" (residents of a mental health facility) for 4.5 years and tested the hypothesis that replacing dietary saturated fat with an omega-6 polyunsaturated fat (linoleic acid) would reduce coronary heart related and all-cause mortality. The intervention group had a 13% reduction in total serum cholesterol (vs 1% in the control arm) but a higher mortality (22% ↑ in mortality for each 30 mg/dl decrease in serum cholesterol)

#1: PubMed: Replacement of saturated fats in diet not associated with lower risk of death

OBJECTIVE: To examine the traditional diet-heart hypothesis through recovery and analysis of previously unpublished data from the Minnesota Coronary Experiment (MCE) and to put findings in the context of existing diet-heart randomized controlled trials through a systematic review and meta-analysis.
DESIGN: The MCE (1968-73) is a double blind randomized controlled trial designed to test whether replacement of saturated fat with vegetable oil rich in linoleic acid reduces coronary heart disease and death by lowering serum cholesterol. Recovered MCE unpublished documents and raw data were analyzed according to hypotheses prespecified by original investigators. Further, a systematic review and meta-analyses of randomized controlled trials that lowered serum cholesterol by providing vegetable oil rich in linoleic acid in place of saturated fat without confounding by concomitant interventions was conducted.
SETTING: One nursing home and six state mental hospitals in Minnesota, United States.
PARTICIPANTS: Unpublished documents with completed analyses for the randomized cohort of 9423 women and men aged 20-97; longitudinal data on serum cholesterol for the 2355 participants exposed to the study diets for a year or more; 149 completed autopsy files.
INTERVENTIONS: Serum cholesterol lowering diet that replaced saturated fat with linoleic acid (from corn oil and corn oil polyunsaturated margarine). Control diet was high in saturated fat from animal fats, common margarines, and shortenings.
MAIN OUTCOME MEASURES: Death from all causes; association between changes in serum cholesterol and death; and coronary atherosclerosis and myocardial infarcts detected at autopsy.
RESULTS: The intervention group had significant reduction in serum cholesterol compared with controls (mean change from baseline -13.8%v-1.0%; P<0.001). Kaplan Meier graphs showed no mortality benefit for the intervention group in the full randomized cohort or for any prespecified subgroup. There was a 22% higher risk of death for each 30 mg/dL (0.78 mmol/L) reduction in serum cholesterol in covariate adjusted Cox regression models (hazard ratio 1.22, 95% confidence interval 1.14 to 1.32; P<0.001). There was no evidence of benefit in the intervention group for coronary atherosclerosis or myocardial infarcts. Systematic review identified five randomized controlled trials for inclusion (n=10,808). In meta-analyses, these cholesterol lowering interventions showed no evidence of benefit on mortality from coronary heart disease (1.13, 0.83 to 1.54) or all-cause mortality (1.07, 0.90 to 1.27).
CONCLUSIONS: Available evidence from randomized controlled trials shows that replacement of saturated fat in the diet with linoleic acid effectively lowers serum cholesterol but does not support the hypothesis that this translates to a lower risk of death from coronary heart disease or all causes. Findings from the Minnesota Coronary Experiment add to growing evidence that incomplete publication has contributed to overestimation of the benefits of replacing saturated fat with vegetable oils rich in linoleic acid.
Reference: *Ramsden CE et al. Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73). BMJ. 2016 Apr 12;353:i1246.*

#2: PubMed: Saturated fats are not associated with all-cause mortality, CHD, ischemic stroke

OBJECTIVE: To systematically review associations between intake of saturated fat and trans unsaturated fat and all-cause mortality, cardiovascular disease (CVD) and associated mortality, coronary heart disease (CHD) and associated mortality, ischemic stroke, and type 2 diabetes.
DESIGN: Systematic review and meta-analysis.
DATA SOURCES: Medline, Embase, Cochrane Central Registry of Controlled Trials, Evidence-Based Medicine Reviews, and CINAHL from inception to 1 May 2015, supplemented by bibliographies of retrieved articles and previous reviews.
ELIGIBILITY CRITERIA FOR SELECTING STUDIES: Observational studies reporting associations of saturated fat and/or trans unsaturated fat (total, industrially manufactured, or from ruminant animals) with all-cause mortality, CHD/CVD mortality, total CHD, ischemic stroke, or type 2 diabetes.
DATA EXTRACTION AND SYNTHESIS: Two reviewers independently extracted data and assessed study risks of bias. Multivariable relative risks were pooled. Heterogeneity was assessed and quantified. Potential publication bias was assessed and subgroup analyses were undertaken. The GRADE approach was used to evaluate quality of evidence and certainty of conclusions.
RESULTS: For saturated fat, three to 12 prospective cohort studies for each association were pooled (five to 17 comparisons with 90,501-339,090 participants). Saturated fat intake was not associated with all-cause mortality (relative risk 0.99, 95% confidence interval 0.91 to 1.09), CVD mortality (0.97, 0.84 to 1.12), total CHD (1.06, 0.95 to 1.17), ischemic stroke (1.02, 0.90 to 1.15), or type 2 diabetes (0.95, 0.88 to 1.03). There was no convincing lack of association between saturated fat and CHD mortality (1.15, 0.97 to 1.36; P=0.10). For trans fats, one to six prospective cohort studies for each association were pooled (two to seven comparisons with 12,942-230,135 participants). Total trans fat intake was associated with all-cause mortality (1.34, 1.16 to 1.56), CHD mortality (1.28, 1.09 to 1.50), and total CHD (1.21, 1.10 to 1.33) but not ischemic stroke (1.07, 0.88 to 1.28) or type 2 diabetes (1.10, 0.95 to 1.27). Industrial, but not ruminant, trans fats were associated with CHD mortality (1.18 (1.04 to 1.33) v 1.01 (0.71 to 1.43)) and CHD (1.42 (1.05 to 1.92) v 0.93 (0.73 to 1.18)). Ruminant trans-palmitoleic acid was inversely associated with type 2 diabetes (0.58, 0.46 to 0.74). The certainty of associations between saturated fat and all outcomes was "very low." The certainty of associations of trans fat with CHD outcomes was "moderate" and "very low" to "low" for other associations.
CONCLUSIONS: Saturated fats are not associated with all-cause mortality, CVD, CHD, ischemic stroke, or type 2 diabetes, but the evidence is heterogeneous with methodological limitations. Trans fats are associated with all-cause mortality, total CHD, and CHD mortality, probably because of higher levels of intake of industrial trans fats than ruminant trans fats. Dietary guidelines must carefully consider the health effects of recommendations for alternative macronutrients to replace trans fats and saturated fats.
REFERENCE: *de Souza RJ et al. Intake of saturated and trans unsaturated fatty acids and risk of all-cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ. 2015 Aug 11;351:h3978.*

#3: PubMed: No evidence for guidelines on reducing dietary fat

INTRODUCTION: National dietary guidelines were introduced in 1977 and 1983, by the US and UK governments, with the aim of reducing coronary heart disease (CHD) mortality. The 2 specific dietary fat recommendations were to reduce total fat and saturated fat consumption to 30% and 10% of total energy intake, respectively.
METHODS: 4 systematic reviews (3 with meta-analysis) were undertaken to examine the evidence for these dietary fat guidelines: (1) randomised controlled trial (RCT) and (2) prospective cohort (PC) evidence at the time the guidelines were introduced; and (3) RCT and (4) PC evidence currently available. This narrative review examines all evidence collated.
RESULTS: The RCT and PC evidence available to the dietary committees did not support the introduction of the dietary fat guidelines. The RCT and PC evidence currently available does not support the extant recommendations. Furthermore, the quality of the evidence is so poor that it could not be relied on had it provided support.
CONCLUSIONS: Dietary fat guidelines have prevailed for almost 40 years. The evidence base at the time of their introduction has been examined for the first time and found lacking. Evidence currently available provides no additional support. Public health opinion differed when the guidelines were introduced. Opposition to the guidelines is becoming more strident. Substantial increases in diet-related illness over the past four decades, particularly obesity and type 2 diabetes, indicate that a review of dietary advice is warranted.
***Reference**: Harcombe Z. Dietary fat guidelines have no evidence base: where next for public health nutritional advice? Br J Sports Med. 2017 May;51(10):769-774.*

#4: High carbohydrate intake associated with higher risk of total mortality

BACKGROUND: The relationship between macronutrients and cardiovascular disease and mortality is controversial. Most available data are from European and North American populations where nutrition excess is more likely, so their applicability to other populations is unclear.
METHODS: The Prospective Urban Rural Epidemiology (PURE) study is a large,epidemiological cohort study of individuals aged 35-70 years (enrolled between Jan 1, 2003, and March 31, 2013) in 18 countries with a median follow-up of 7·4 years (IQR 5·3-9·3). Dietary intake of 135 335 individuals was recorded using validated food frequency questionnaires. The primary outcomes were total mortality and major cardiovascular events (fatal cardiovascular disease, non-fatal myocardial infarction, stroke, and heart failure). Secondary outcomes were all myocardial infarctions, stroke, cardiovascular disease mortality, and non-cardiovascular disease mortality. Participants were categorised into quintiles of nutrient intake (carbohydrate, fats, and protein) based on percentage of energy provided by nutrients. We assessed the associations between consumption of carbohydrate, total fat, and each type of fat with cardiovascular disease and total mortality. We calculated hazard ratios (HRs) using amultivariable Cox frailty model with random intercepts to account for centre clustering.
FINDINGS: During follow-up, we documented 5796 deaths and 4784 major cardiovascular disease events. Higher carbohydrate intake was associated with an increased risk of total mortality (highest [quintile 5] vs lowest quintile [quintile 1] category, HR 1·28 [95% CI 1·12-1·46], ptrend=0·0001) but not with the risk of cardiovascular disease or cardiovascular disease mortality. Intake of total fat and each type of fat was associated with lower risk of total mortality (quintile 5 vs quintile 1, total fat: HR 0·77 [95% CI 0·67-0·87], ptrend<0·0001; saturated fat, HR 0·86 [0·76-0·99], ptrend=0·0088; monounsaturated fat: HR 0·81 [0·71-0·92], ptrend<0·0001; and polyunsaturated fat: HR 0·80 [0·71-0·89],ptrend<0·0001). Higher saturated fat intake was associated with lower risk of stroke (quintile 5 vs quintile 1, HR 0·79 [95% CI 0·64-0·98], ptrend=0·0498).Total fat and saturated and unsaturated fats were not significantly associated with risk of myocardial infarction or cardiovascular disease mortality.
INTERPRETATION: High carbohydrate intake was associated with higher risk of total mortality, whereas total fat and individual types of fat were related to lower total mortality. Total fat and types of fat were not associated with cardiovascular disease, myocardial infarction, or cardiovascular disease mortality, whereas saturated fat had an inverse association with stroke. Global dietary guidelines should be reconsidered in light of these findings.
***REFERENCE:** Dehghan M, et. al. for the Prospective Urban Rural Epidemiology (PURE) study investigators.Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet. 2017 Nov 4;390(10107):2050-2062*

#5: Replacing saturated fats with carbohydrates adversely effects blood lipids.

BACKGROUND: The relation between dietary nutrients and cardiovascular disease risk markers in many regions worldwide is unknown. In this study, we investigated the effect of dietary nutrients on blood lipids and blood pressure, two of the most important risk factors for cardiovascular disease, in low-income,middle-income, and high-income countries.
METHODS: We studied 125 287 participants from 18 countries in North America, South America, Europe, Africa, and Asia in the Prospective Urban Rural Epidemiology (PURE) study. Habitual food intake was measured with validated food frequency questionnaires. We assessed the associations between nutrients (total fats, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, carbohydrates, protein, and dietary cholesterol) and cardiovascular disease risk markers using multilevel modelling. The effect of isocaloric replacement of saturated fatty acids with other fats and carbohydrates was determined overall and by levels of intakes by use of nutrient density models. We did simulation modelling in which we assumed that the effects of saturated fatty acids on cardiovascular disease events was solely related to their association through an individual risk marker, and then compared these simulated risk marker-based estimates with directly observed associations of saturated fatty acids with cardiovascular disease events.
FINDINGS: Participants were enrolled into the study from Jan 1, 2003, to March 31, 2013. Intake of total fat and each type of fat was associated with higher concentrations of total cholesterol and LDL cholesterol, but also with higher HDL cholesterol and apolipoprotein A1 (ApoA1), and lower triglycerides, ratio of total cholesterol to HDL cholesterol, ratio of triglycerides to HDL cholesterol, and ratio of apolipoprotein B (ApoB) to ApoA1 (all ptrend<0·0001). Higher
carbohydrate intake was associated with lower total cholesterol, LDL cholesterol,and ApoB, but also with lower HDL cholesterol and ApoA1, and higher triglycerides, ratio of total cholesterol to HDL cholesterol, ratio of triglycerides to HDL cholesterol, and ApoB-to-

ApoA1 ratio (all ptrend<0·0001, apart from ApoB [ptrend=0·0014]). Higher intakes of total fat, saturated fatty acids, and carbohydrates were associated with higher blood pressure, whereas higher protein intake was associated with lower blood pressure. Replacement of saturated fatty acids with carbohydrates was associated with the most adverse effects on lipids, whereas replacement of saturated fatty acids with unsaturated fats improved some risk markers (LDL cholesterol and blood pressure), but seemed to worsen others (HDL cholesterol and triglycerides). The observed associations between saturated fatty acids and cardiovascular disease events were approximated by the simulated associations mediated through the effects on the ApoB-to-ApoA1 ratio, but not with other lipid markers including LDL cholesterol.
INTERPRETATION: Our data are at odds with current recommendations to reduce total fat and saturated fats. Reducing saturated fatty acid intake and replacing it with carbohydrate has an adverse effect on blood lipids. Substituting saturated fatty acids with unsaturated fats might improve some risk markers, but might worsen others. Simulations suggest that ApoB-to-ApoA1 ratio probably provides the best overall indication of the effect of saturated fatty acids on cardiovascular disease risk among the markers tested. Focusing on a single lipid marker such as LDL cholesterol alone does not capture the net clinical effects of nutrients on cardiovascular risk.
REFERENCE*: Mente A et al.Prospective Urban Rural Epidemiology (PURE) study investigators.Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study. Lancet Diabetes Endocrinol. 2017 Oct;5(10):774-787.*

#6: PubMed: Sugar industry and coronary heart disease research

Early warning signals of the coronary heart disease (CHD) risk of sugar (sucrose) emerged in the 1950s. We examined Sugar Research Foundation (SRF) internal documents, historical reports, and statements relevant to early debates about the dietary causes of CHD and assembled findings chronologically into a narrative case study. The SRF sponsored its first CHD research project in 1965, a literature review published in the New England Journal of Medicine, which singled out fat and cholesterol as the dietary causes of CHD and downplayed evidence that sucrose consumption was also a risk factor. The SRF set the review's objective, contributed articles for inclusion, and received drafts. The SRF's funding and role was not disclosed. Together with other recent analyses of sugar industry documents, our findings suggest the industry sponsored a research program in the 1960s and 1970s that successfully cast doubt about the hazards of sucrose while promoting fat as the dietary culprit in CHD. Policymaking committees should consider giving less weight to food industry-funded studies and include mechanistic and animal studies as well as studies appraising the effect of added sugars on multiple CHD biomarkers and disease development.
Reference: *Kearns CE et al. Sugar Industry and Coronary Heart Disease Research: A Historical Analysis of Internal Industry Documents.1. JAMA Intern Med. 2016 Nov 1;176(11):1680-1685.*

Abstracts #4 and #5 “Ultra processed foods are food that include formulations of several ingredients which, besides salt, sugar, oils and fats, include *food substances not used in culinary preparations, in particular, flavours, colours, sweeteners, emulsifiers and other additives* used to imitate sensorial qualities of unprocessed or minimally processed foods and their culinary preparations or to disguise undesirable qualities of the final product.” Such foods make up ~ 60% of the US daily dietary caloric intake. The most common ultra processed foods include: soft drinks (17.1% of US intake of added sugars); fruit drinks (13.9%); milk-based drinks (4.6%); cakes, cookies and pies (11.2%); breads (7.6%); desserts (7.3%); sweet snacks (7.1%); breakfast cereals (6.4%); ice creams and ice pops (5.9%).

#7: PubMed: News Flash # 1 | Americans have lousy diets

OBJECTIVES: To investigate the contribution of ultra-processed foods to the intake of added sugars in the USA. Ultra-processed foods were defined as industrial formulations which, besides salt, sugar, oils and fats, include substances not used in culinary preparations, in particular additives used to imitate sensorial qualities of minimally processed foods and their culinary preparations.
DESIGN: Cross-sectional study.
SETTING: National Health and Nutrition Examination Survey 2009-2010.
PARTICIPANTS: We evaluated 9317 participants aged 1+ years with at least one 24 h dietary recall.
MAIN OUTCOME MEASURES: Average dietary content of added sugars and proportion of individuals consuming more than 10% of total energy from added sugars.
DATA ANALYSIS: Gaussian and Poisson regressions estimated the association between consumption of ultra-processed foods and intake of added sugars. All models incorporated survey sample weights and adjusted for age, sex, race/ethnicity, family income and educational attainment.
RESULTS: Ultra-processed foods comprised 57.9% of energy intake, and contributed 89.7% of the energy intake from added sugars. The content of added sugars in ultra-processed foods (21.1% of calories) was eightfold higher than in processed foods (2.4%) and fivefold higher than in unprocessed or minimally processed foods and processed culinary ingredients grouped together (3.7%). Both in unadjusted and adjusted models, each increase of 5 percentage points in proportional energy intake from ultra-processed foods increased the proportional energy intake from added sugars by 1 percentage point. Consumption of added sugars increased linearly across quintiles of ultra-processed food consumption: from 7.5% of total energy in the lowest quintile to 19.5% in the highest. A total of 82.1% of Americans in the highest quintile exceeded the recommended limit of 10% energy from added sugars, compared with 26.4% in the lowest.
CONCLUSIONS: Decreasing the consumption of ultra-processed foods could be an effective way of reducing the excessive intake of added sugars in the USA.
REFERENCE: *Martínez Steele E et al. Ultra-processed foods and added sugars in the US diet: evidence from a nationally representative cross-sectional study. BMJ Open. 2016 Mar 9;6(3):e009892.*

#8: PubMed: Newsflash #2 | Canadians aren't much better

This study describes food consumption patterns in Canada according to the types of food processing using the Nova classification and investigates the association between consumption of ultra-processed foods and the nutrient profile of the diet. Dietary intakes of 33,694 individuals from the 2004 Canadian Community Health Survey aged 2 years and above were analyzed. Food and drinks were classified using Nova into unprocessed or minimally processed foods, processed culinary ingredients, processed foods and ultra-processed foods. Average consumption (total daily energy intake) and relative consumption (% of total energy intake) provided by each of the food groups were calculated. Consumption of ultra-processed foods according to sex, age, education, residential location and relative family revenue was assessed. Mean nutrient content of ultra-processed foods and non-ultra-processed foods were compared, and the average nutrient content of the overall diet across quintiles of dietary share of ultra-processed foods was measured. In 2004, 48% of calories consumed by Canadians came from ultra-processed foods. Consumption of such foods was high amongst all socioeconomic groups, and particularly in children and adolescents. As a group, ultra-processed foods were grossly nutritionally inferior to non-ultra-processed foods. After adjusting for covariates, a significant and positive relationship was found between the dietary share of ultra-processed foods and the content in carbohydrates, free sugars, total and saturated fats and energy density, while an inverse relationship was observed with the dietary content in protein, fiber, vitamins A, C, D, B6 and B12, niacin, thiamine, riboflavin, as well as zinc, iron, magnesium, calcium, phosphorus and potassium. Lowering the dietary share of ultra-processed foods and raising consumption of hand-made meals from unprocessed or minimally processed foods would substantially improve the diet quality of Canadian.

Reference: *Moubarac JC et al. Consumption of ultra-processed foods predicts diet quality in Canada.Appetite. 2017 Jan 1;108:512-520.*

At the end of 2016, the AHA/ACC published recommendation for dietary patterns to reduce CV risk. Implementation strategies presented in the report target nutrient-dense foods that contain cardiopreventive types of fats while avoiding excessive energy intake. (http://circ.ahajournals.org/content/134/22/e505.long#T2)

Importantly, they endorsed many options that in general advocate for vegetables, fruits, and whole grains; include low-fat or fat-free dairy products, poultry, fish, legumes, nontropical (not coconut or palm kernel oil) vegetable oils, and nuts; and limit intake of sweets, sugar-sweetened beverages (SSBs), salty or highly processed foods, and fatty or processed meats (choose lean or extra-lean meats instead).

These recommendations have evolved from nutrient-based ("eat less fat") to food-based ("follow the DASH diet") dietary patterns, as these are more easily translated for counseling patients/clients.

The report specifically endorsed:

- The Dietary Approaches to Stop Hypertension (DASH) dietary pattern | Emphasizes fruits, vegetables, and low-fat dairy products; includes whole grains, poultry, fish, and nuts; and is reduced in SFAs, red meat, sweets, and beverages containing added sugars.
- A traditional Mediterranean-style diet | This pattern was characterized as being "generous in fruits and vegetables, whole grains and fatty fish." Other characteristics often include lean meat, skim or low-fat dairy products, and sources of monounsaturated fatty acids, including olive, canola oil, nuts (walnuts, almonds, and hazelnuts), and soft margarine spreads. Modest consumption of alcohol, specifically wine, is also featured but without recommended frequency or amounts.
- The AHA dietary pattern | Emphasizing an eating pattern low in SFAs and sodium and moderate in unsaturated and total fat.
- A vegetarian dietary pattern comprises predominantly plant-based foods without (vegan) and with dairy products, eggs (lacto-ovo vegetarian), or fish (pesco-vegetarian). These patterns include predominantly vegetables, fruits, whole grains, legumes, seeds, and nuts.

#9: PubMed: 2016 ACC AHA Dietary Recommendations

In 2013, the American Heart Association and American College of Cardiology published the "Guideline on Lifestyle Management to Reduce Cardiovascular Risk," which was based on a systematic review originally initiated by the National Heart, Lung, and Blood Institute. The guideline supports the American Heart Association's 2020 Strategic Impact Goals for cardiovascular health promotion and disease reduction by providing more specific details for adopting evidence-based diet and lifestyle behaviors to achieve those goals. In addition, the 2015-2020 Dietary Guidelines for Americans issued updated evidence relevant to reducing cardiovascular risk and provided additional recommendations for adopting healthy diet and lifestyle approaches. This scientific statement, intended for healthcare providers, summarizes relevant scientific and translational evidence and offers practical tips, tools, and dietary approaches to help patients/clients adapt these guidelines according to their sociocultural, economic, and taste preferences.

Reference*: Van Horn L et al. Recommended Dietary Pattern to Achieve Adherence to the American Heart Association/American*

College of Cardiology (AHA/ACC) Guidelines: A Scientific Statement From the American Heart Association. Circulation. 2016 Nov 29;134(22):e505-e529. Epub 2016 Oct 27.

#10: PubMed: The Mediterranean diet ↓ the risk of major CV events

BACKGROUND: Observational cohort studies and a secondary prevention trial have shown an inverse association between adherence to the Mediterranean diet and cardiovascular risk. We conducted a randomized trial of this diet pattern for the primary prevention of cardiovascular events.
METHODS: In a multicenter trial in Spain, we randomly assigned participants who were at high cardiovascular risk, but with no cardiovascular disease at enrollment, to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat). Participants received quarterly individual and group educational sessions and, depending on group assignment, free provision of extra-virgin olive oil, mixed nuts, or small nonfood gifts. The primary end point was the rate of major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes). On the basis of the results of an interim analysis, the trial was stopped after a median follow-up of 4.8 years.
RESULTS: A total of 7447 persons were enrolled (age range, 55 to 80 years); 57% were women. The two Mediterranean-diet groups had good adherence to the intervention, according to self-reported intake and biomarker analyses. A primary end-point event occurred in 288 participants. The multivariable-adjusted hazard ratios were 0.70 (95% confidence interval [CI], 0.54 to 0.92) and 0.72 (95% CI, 0.54 to 0.96) for the group assigned to a Mediterranean diet with extra-virgin olive oil (96 events) and the group assigned to a Mediterranean diet with nuts (83 events), respectively, versus the control group (109 events). No diet-related adverse effects were reported.
CONCLUSIONS: Among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events. (Funded by the Spanish government's Instituto de Salud Carlos III and others; Controlled-Trials.com number, ISRCTN35739639.).
Reference: *Estruch R et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013 Apr 4;368(14):1279-90.*

#11: PubMed: The Mediterranean diet associated with weight loss in overweight patients

BACKGROUND: Although the long-term health benefits of the Mediterranean diet are well established, its efficacy for weight loss at ≥12 months in overweight or obese individuals is unclear. We therefore conducted a systematic review of randomized controlled trials (RCTs) to determine the effect of the Mediterranean diet on weight loss and cardiovascular risk factor levels after ≥12 months.
METHODS: We systematically searched MEDLINE, EMBASE, and the Cochrane Library of Clinical Trials for RCTs published in English or French and with follow-up ≥12 months that examined the effect of the Mediterranean diet on weight loss and cardiovascular risk factor levels in overweight or obese individuals trying to lose weight.
RESULTS: Five RCTs (n = 998) met our inclusion criteria. Trials compared the Mediterranean diet to a low-fat diet (4 treatment arms), a low-carbohydrate diet (2 treatment arms), and the American Diabetes Association diet (1 treatment arm). The Mediterranean diet resulted in greater weight loss than the low-fat diet at ≥12 months (range of mean values: -4.1 to -10.1 kg vs 2.9 to -5.0 kg), but produced similar weight loss as other comparator diets (range of mean values:-4.1 to -10.1 kg vs -4.7 to -7.7 kg). Moreover, the Mediterranean diet was generally similar to comparator diets at improving other cardiovascular risk factor levels, including blood pressure and lipid levels.
CONCLUSION: Our findings suggest that the Mediterranean diet results in similar weight loss and cardiovascular risk factor level reduction as comparator diets in overweight or obese individuals trying to lose weight.
Reference: *Mancini JG et al. Systematic Review of the Mediterranean Diet for Long-Term Weight Loss. Am J Med. 2016 Apr;129(4):407-415*

#12: PubMed: Diets lower in CHO reduce BP, and estimated CV risk

CONTEXT: Reduced intake of saturated fat is widely recommended for prevention of cardiovascular disease. The type of macronutrient that should replace saturated fat remains uncertain.
OBJECTIVE: To compare the effects of 3 healthful diets, each with reduced saturated fat intake, on blood pressure and serum lipids.
DESIGN, SETTING, AND PARTICIPANTS: Randomized, 3-period, crossover feeding study (April 2003 to June 2005) conducted in Baltimore, Md, and Boston, Mass. Participants were 164 adults with prehypertension or stage 1 hypertension. Each feeding period lasted 6 weeks and body weight was kept constant.
INTERVENTIONS: A diet rich in carbohydrates; a diet rich in protein, about half from plant sources; and a diet rich in unsaturated fat, predominantly monounsaturated fat.
MAIN OUTCOME MEASURES: Systolic blood pressure and low-density lipoprotein cholesterol.
RESULTS: Blood pressure, low-density lipoprotein cholesterol, and estimated coronary heart disease risk were lower on each diet compared with baseline. Compared with the carbohydrate diet, the protein diet further decreased mean systolic blood pressure by 1.4 mm Hg (P = .002) and by 3.5 mm Hg (P = .006) among those with hypertension and decreased low-density lipoprotein cholesterol by 3.3 mg/dL (0.09 mmol/L; P = .01), high-density lipoprotein cholesterol by 1.3 mg/dL (0.03 mmol/L; P = .02), and triglycerides by 15.7 mg/dL (0.18 mmol/L; P<.001). Compared with the carbohydrate diet, the unsaturated fat diet decreased systolic blood pressure by 1.3 mm Hg (P = .005) and by 2.9 mm Hg among those with hypertension (P = .02), had no significant effect on low-density lipoprotein cholesterol, increased high-density lipoprotein cholesterol by 1.1 mg/dL (0.03 mmol/L; P = .03), and lowered triglycerides by 9.6 mg/dL (0.11 mmol/L; P = .02). Compared with the carbohydrate diet, estimated 10-year coronary heart disease risk was lower and similar on the protein and unsaturated fat diets.
CONCLUSION: In the setting of a healthful diet, partial substitution of carbohydrate with either protein or monounsaturated fat can further lower blood pressure, improve lipid levels, and reduce estimated cardiovascular risk.
Clinical Trials Registration ClinicalTrials.gov Identifier: NCT00051350.

***Reference**: Appel LJ et al. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. JAMA. 2005 Nov 16;294(19):2455-64.*

#13: PubMed: Paleo diet improves weight loss and A1c in DM at 12 weeks

BACKGROUND: Means to reduce future risk for cardiovascular disease in subjects with type 2 diabetes are needed.
METHODS: Thirty-two patients with type 2 diabetes (age 59 ± 8 years) followed a Paleolithic diet for 12 weeks. Participants were randomized to either standard care exercise recommendations (PD) or 1-h supervised exercise sessions (aerobic exercise and resistance training) three times per week (PD-EX).
RESULTS: For the within group analyses, fat mass decreased by 5.7 kg (IQR: -6.6, -4.1; $p < 0.001$) in the PD group and by 6.7 kg (-8.2, -5.3; $p < 0.001$) in the PD-EX group. Insulin sensitivity (HOMA-IR) improved by 45% in the PD ($p < 0.001$) and PD-EX ($p < 0.001$) groups. HbA1c decreased by 0.9% (-1.2, -0.6; $p < 0.001$) in the PD group and 1.1% (-1.7, -0.7; $p < 0.01$) in the PD-EX group. Leptin decreased by 62% ($p < 0.001$) in the PD group and 42% ($p < 0.001$) in the PD-EX group. Maximum oxygen uptake increased by 0.2 L/min (0.0, 0.3) in the PD-EX group, and remained unchanged in the PD group ($p < 0.01$ for the difference between intervention groups). Male participants decreased lean mass by 2.6 kg (-3.6, -1.3) in the PD group and by 1.2 kg (-1.3, 1.0) in the PD-EX group ($p < 0.05$ for the difference between groups).
CONCLUSIONS: A Paleolithic diet improves fat mass and metabolic balance including insulin sensitivity, glycemic control, and leptin in subjects with type 2 diabetes. Supervised exercise training may not enhance the effects on these outcomes, but preserves lean mass in men and increases cardiovascular fitness.
***REFERENCE:** Otten J(1), et al. Benefits of a Paleolithic diet with and without supervised exercise on fat mass, insulin sensitivity, and glycemic control: a randomized controlled trial in individuals with type 2 diabetes. Diabetes Metab Res Rev. 2017 Jan;33:e2828.*

#14: PubMed: Low CHO diet improves CV risks at 52 weeks

BACKGROUND: Low-carbohydrate diets are popular for weight loss, but their cardiovascular effects have not been well-studied, particularly in diverse populations.
OBJECTIVE: To examine the effects of a low-carbohydrate diet compared with a low-fat diet on body weight and cardiovascular risk factors.
DESIGN: A randomized, parallel-group trial. (ClinicalTrials.gov: NCT00609271).
SETTING: A large academic medical center.
PARTICIPANTS: 148 men and women without clinical cardiovascular disease and diabetes.
INTERVENTION: A low-carbohydrate (<40 g/d) or low-fat (<30% of daily energy intake from total fat [<7% saturated fat]) diet. Both groups received dietary counseling at regular intervals throughout the trial.
MEASUREMENTS: Data on weight, cardiovascular risk factors, and dietary composition were collected at 0, 3, 6, and 12 months.
RESULTS: Sixty participants (82%) in the low-fat group and 59 (79%) in the low-carbohydrate group completed the intervention. At 12 months, participants on the low-carbohydrate diet had greater decreases in weight (mean difference in change, -3.5 kg [95% CI, -5.6 to -1.4 kg]; P = 0.002), fat mass (mean difference in change, -1.5% [CI, -2.6% to -0.4%]; P = 0.011), ratio of total-high-density lipoprotein (HDL) cholesterol (mean difference in change, -0.44 [CI, -0.71 to -0.16]; P = 0.002), and triglyceride level (mean difference in change, -0.16 mmol/L [-14.1 mg/dL] [CI, -0.31 to -0.01 mmol/L {-27.4 to -0.8 mg/dL}]; P = 0.038) and greater increases in HDL cholesterol level (mean difference in change, 0.18 mmol/L [7.0 mg/dL] [CI, 0.08 to 0.28 mmol/L {3.0 to 11.0 mg/dL}]; P < 0.001) than those on the low-fat diet.
LIMITATION: Lack of clinical cardiovascular disease end points.
CONCLUSION: The low-carbohydrate diet was more effective for weight loss and cardiovascular risk factor reduction than the low-fat diet. Restricting carbohydrate may be an option for persons seeking to lose weight and reduce cardiovascular risk factors.
***REFERENCE**: Bazzano LA, et al. Effects of low-carbohydrate and low-fat diets: a randomized trial. Ann Intern Med. 2014 Sep 2;161(5):309-18.*

Appendix:

What about low carbohydrate diets for weight loss?

#15: PubMed: Low CHO vs balanced weight-loss diets | No diff in weight loss

BACKGROUND: Some popular weight loss diets restricting carbohydrates (CHO) claim to be more effective, and have additional health benefits in preventing cardiovascular disease compared to balanced weight loss diets.
METHODS AND FINDINGS: We compared the effects of low CHO and isoenergetic balanced weight loss diets in overweight and obese adults assessed in randomised controlled trials (minimum follow-up of 12 weeks), and summarised the effects on weight, as well as cardiovascular and diabetes risk. Dietary criteria were derived from existing macronutrient recommendations. We searched Medline, EMBASE and CENTRAL (19 March 2014). Analysis was stratified by outcomes at 3-6 months and 1-2 years, and participants with diabetes were analysed separately. We evaluated dietary adherence and used GRADE to assess the quality of evidence. We calculated mean differences (MD) and performed random-effects meta-analysis.Nineteen trials were included (n=3209); 3 had adequate allocation concealment. In non-diabetic participants, our analysis showed little or no difference in mean weight loss in the two groups at 3-6 months (MD 0.74 kg, 95%CI -1.49 to 0.01 kg; I2=53%; n=1745, 14 trials; moderate quality evidence) and 1-2 years (MD 0.48 kg, 95%CI -1.44 kg to 0.49 kg; I2=12%; n=1025; 7 trials, moderate quality evidence). Furthermore, little or no difference was detected at 3-6 months and 1-2 years for blood pressure, LDL, HDL and total cholesterol, triglycerides and fasting blood glucose (>914 participants). In diabetic participants, findings showed a similar pattern.
CONCLUSIONS: Trials show weight loss in the short-term irrespective of whether the diet is low CHO or balanced. There is probably little or no difference in weight loss and changes in cardiovascular risk factors up to two years of follow-up when overweight and obese adults, with or without type 2 diabetes, are randomized to low CHO diets and isoenergetic balanced weight loss diets.
***REFERENCE**: Naude CE et al. Low carbohydrate versus isoenergetic balanced diets for reducing weight and cardiovascular risk: a systematic review and meta-analysis. PLoS One. 2014 Jul 9;9(7):e100652.*

#16: PubMed: Low CHO Diets decrease weight but increase LDA

The effects of low-carbohydrate (LC) diets on body weight and cardiovascular risk are unclear, and previous studies have found varying results. Our aim was to conduct a meta-analysis of randomised controlled trials (RCT), assessing the effects of LC diets v. low-fat (LF) diets on weight loss and risk factors of CVD. Studies were identified by searching MEDLINE, Embase and Cochrane Trials. Studies had to fulfil the following criteria: a RCT; the LC diet was defined in accordance with the Atkins diet, or carbohydrate intake of <20% of total energy intake; twenty subjects or more per group; the subjects were previously healthy; and the dietary intervention had a duration of 6 months or longer. Results from individual studies were pooled as weighted mean difference (WMD) using a random effect model. In all, eleven RCT with 1369 participants met all the set eligibility criteria. Compared with participants on LF diets, participants on LC diets experienced a greater reduction in body weight (WMD -2·17 kg; 95% CI -3·36,-0·99) and TAG (WMD -0·26 mmol/l; 95% CI -0·37, -0·15), but a greater increase in HDL-cholesterol (WMD 0·14 mmol/l; 95% CI 0·09, 0·19) and LDL-cholesterol (WMD 0·16 mmol/l; 95% CI 0·003, 0·33). This meta-analysis demonstrates opposite change in two important cardiovascular risk factors on LC diets--greater weight loss and increased LDL-cholesterol. Our findings suggest that the beneficial changes of LC diets must be weighed against the possible detrimental effects of increased LDL-cholesterol.
***Reference:** Mansoor N et al. Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials. Br J Nutr. 2016 Feb 14;115(3):466-79.*

#17: PubMed: Low CHO vs low fat weight-loss diets

BACKGROUND: Reduced calorie, low fat diet is currently recommended diet for overweight and obese adults. Prior data suggest that low carbohydrate diets may also be a viable option for those who are overweight and obese.
PURPOSE: Compare the effects of low carbohydrate versus low fats diet on weight and atherosclerotic cardiovascular disease risk in overweight and obese patients.
DATA SOURCES: Systematic literature review via PubMed (1966-2014).
STUDY SELECTION: Randomized controlled trials with ≥8 weeks follow up, comparing low carbohydrate (≤120gm carbohydrates/day) and low fat diet (≤30% energy from fat/day).
DATA EXTRACTION: Data were extracted and prepared for analysis using double data entry. Prior to identification of candidate publications, the outcomes of change in weight and metabolic factors were selected as defined by Cochrane Collaboration. Assessment of the effects of diets on predicted risk of atherosclerotic cardiovascular disease risk was added during the data collection phase.
DATA SYNTHESIS: 1797 patients were included from 17 trials with <1 year follow up in 12. Compared with low fat diet, low carbohydrate was associated with significantly greater reduction in weight (Δ = -2.0 kg, 95% CI: -3.1, -0.9) and significantly lower predicted risk of atherosclerotic cardiovascular disease events (p<0.03). Frequentist and Bayesian results were concordant. The probability of greater weight loss associated with low carbohydrate was >99% while the reduction in predicted risk favoring low carbohydrate was >98%.
LIMITATIONS: Lack of patient-level data and heterogeneity in dropout rates and outcomes reported.
CONCLUSIONS: This trial-level meta-analysis of randomized controlled trials comparing LoCHO diets with LoFAT diets in strictly adherent populations demonstrates that each diet was associated with significant weight loss and reduction in predicted risk of ASCVD events. However, LoCHO diet was associated with modest but significantly greater improvements in weight loss and predicted ASCVD risk in studies from 8 weeks to 24 months in duration. These results suggest that future evaluations of dietary guidelines should consider low carbohydrate diets as effective and safe intervention for weight management in the overweight and obese, although long-term effects require further investigation.

***REFERENCE**: Sackner-Bernstein J et al. Dietary Intervention for Overweight and Obese Adults: Comparison of Low-Carbohydrate and Low-Fat Diets. A Meta-Analysis. PLoS One. 2015 Oct 20;10(10):e0139817.*

#18: PubMed: Low CHO vs low fat weight-loss diets

BACKGROUND: The effectiveness of low-fat diets for long-term weight loss has been debated for decades, with many randomised controlled trials (RCTs) and recent reviews giving mixed results. We aimed to summarise the large body of evidence from RCTs to determine whether low-fat diets contribute to greater weight loss than participants' usual diet, low-carbohydrate diets, and other higher-fat dietary interventions.
METHODS: We did a systematic review and random effects meta-analysis of RCTs comparing the long-term effect (≥1 year) of low-fat and higher-fat dietary interventions on weight loss by searching MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews to identify eligible trials published from database inception up until July 31, 2014. We excluded trials if one intervention group included a non-dietary weight loss component but the other did not, and trials of dietary supplements or meal replacement drink interventions. Data including the main outcome measure of mean difference in weight change between interventions, and whether interventions were intended to lead to weight loss, weight maintenance, or neither, were extracted from published reports. We estimated the pooled weighted mean difference (WMD) with a DerSimonian and Laird random effects method.
FINDINGS: 3517 citations were identified by the search and 53 studies met our inclusion criteria, including 68 128 participants (69 comparisons). In weight loss trials, low-carbohydrate interventions led to significantly greater weight loss than did low-fat interventions (18 comparisons; WMD 1·15 kg [95% CI 0·52 to 1·79]; I(2)=10%). Low-fat interventions did not lead to differences in weight change compared with other higher-fat weight loss interventions (19 comparisons; WMD 0·36 kg [-0·66 to 1·37; I(2)=82%), and led to a greater weight decrease only when compared with a usual diet (eight comparisons; -5·41 kg [-7·29 to -3·54]; I(2)=68%). Similarly, results of non-weight-loss trials and weight maintenance trials, for which no low-carbohydrate comparisons were made, showed that low-fat versus higher-fat interventions have a similar effect on weight loss, and that low-fat interventions led to greater weight loss only when compared with usual diet. In weight loss trials, higher-fat weight loss interventions led to significantly greater weight loss than low-fat interventions when groups differed by more than 5% of calories obtained from fat at follow-up (18 comparisons; WMD 1·04 kg [95% CI 0·06 to 2·03]; I(2)=78%), and when the difference in serum triglycerides between the two interventions at follow-up was at least 0·06 mmol/L (17 comparisons; 1·38 kg [0·50 to 2·25]; I(2)=62%).
INTERPRETATION: These findings suggest that the long-term effect of low-fat diet intervention on bodyweight depends on the intensity of the intervention in the comparison group. When compared with dietary interventions of similar intensity, evidence from RCTs does not support low-fat diets over other dietary interventions for long-term weight loss.
FUNDING: National Institutes of Health and American Diabetes Association.
***REFERENCE:** Tobias DK et al. Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis.Lancet Diabetes Endocrinol. 2015 Dec;3(12):968-79.*

#19: PubMed: Low CHO diet safe and efficacious option

Low-carbohydrate high-fat (LCHF) diets are a highly contentious current topic in nutrition. This narrative review aims to provide clinicians with a broad overview of the effects of LCHF diets on body weight, glycaemic control and cardiovascular risk factors while addressing some common concerns and misconceptions. Blood total cholesterol and LDL-cholesterol concentrations show a variable, highly individual response to LCHF diets, and should be monitored in patients adhering to this diet. In contrast, available evidence from clinical and preclinical studies indicates that LCHF diets consistently improve all other markers of cardiovascular risk-lowering elevated blood glucose, insulin, triglyceride, ApoB and saturated fat (especially palmitoleic acid) concentrations, reducing small dense LDL particle numbers, glycated haemoglobin (HbA1c) levels, blood pressure and body weight while increasing low HDL-cholesterol concentrations and reversing non-alcoholic fatty liver disease (NAFLD). This particular combination of favourable modifications to all these risk factors is a benefit unique to LCHF diets. These effects are likely due in part to reduced hunger and decreased ad libitum calorie intake common to low-carbohydrate diets, allied to a reduction in hyperinsulinaemia, and reversal of NAFLD. Although LCHF diets may not be suitable for everyone, available evidence shows this eating plan to be a safe and efficacious dietary option to be considered. LCHF diets may also be particularly beneficial in patients with atherogenic dyslipidaemia, insulin resistance, and the frequently associated NAFLD.
***Reference:** Noakes TD et al. Evidence that supports the prescription of low-carbohydrate high-fat diets: a narrative review. Br J Sports Med. 2017 Jan;51(2):133-139.*

#20: PubMed: Skipping breakfast tied to ASCVD

BACKGROUND: Daily habits, including the number and quality of eating occasions, are potential targets for primary prevention strategies with large health impacts. Skipping breakfast is considered a frequent and unhealthy habit associated with an increased cardiovascular (CV) risk.
OBJECTIVES: The study sought to explore the association between different breakfast patterns and CV risk factors and the presence, distribution, and extension of subclinical atherosclerosis.
METHODS: Cross-sectional analysis was performed within the PESA (Progression of Early Subclinical Atherosclerosis) study, a prospective cohort of asymptomatic (free of CV events at baseline) adults 40 to 54 years of age. Lifestyle and multivascular imaging data along with clinical covariates were collected from 4,052 participants. Multivariate logistic regression models were used in the analysis.
RESULTS: Three patterns of breakfast consumption were studied: high-energy breakfast, when contributing to >20% of total daily energy intake (27% of the population); low-energy breakfast, when contributing between 5% and 20% of total daily energy intake (70% of the population); and skipping breakfast, when consuming <5% of total daily energy (3% of the population). Independent of the presence of traditional and dietary CV risk factors, and compared with

high-energy breakfast, habitual skipping breakfast was associated with a higher prevalence of noncoronary (odds ratio: 1.55; 95% confidence interval: 0.97 to 2.46) and generalized (odds ratio: 2.57; 95% confidence interval: 1.54 to 4.31) atherosclerosis. **CONCLUSION:** Skipping breakfast is associated with an increased odds of prevalent noncoronary and generalized atherosclerosis independently of the presence of conventional CV risk factors. (Progression of Early Subclinical Atherosclerosis [PESA]; NCT01410318).
***REFERENCE**: Uzhova I(1), et al. The Importance of Breakfast in Atherosclerosis Disease: Insights From the PESA Study. J Am Coll Cardiol. 2017 Oct 10;70(15):1833-1842.*

Conclusions

1. According to the USDA, dietary cholesterol is no longer a nutrient of concern and advice on dietary fat should emphasize *optimizing the types of dietary fat and not reducing total fat*."
2. Replacing saturated fats in the diet with linoleic acid (a polyunsaturated fat) lowers cholesterol but does not support the hypothesis that this translates to a lower risk of death from coronary heart disease or all causes.
3. The consumption of ultra-processed foods is the norm in this country and in Canada
4. The 2016 AHA/ACC dietary recommendations have evolved from nutrient-based ("eat less fat") to food-based ("follow the DASH diet") dietary patterns, as these are more easily translated for counseling patients/clients
5. The Mediterranean Diet is associated with fewer macrovascular events
6. Low carbohydrate diets appear to be a reasonable option for weight management and possibly CV risk modification

Editor's Choice

1. Cost-effectiveness of confirmatory testing before treatment of onychomycosis

Clinical question: Is confirmatory diagnostic testing cost-effective for the management of clinically suspected onychomycosis?
Bottom line: The most cost-effective approach to the patient with clinically suspected onychomycosis is empiric therapy with oral terbinafine. The chance of liver injury is estimated to be only 1 in 50,000 to 1 in 120,000, so testing to confirm the diagnosis would cost tens of millions of dollars per case of liver injury avoided. If you plan to prescribe the much more expensive topical solution efinaconazole 10% (Jublia), then confirmatory testing with periodic acid-Schiff (PAS) reduces costs (LOE = 2a)
Study design: Decision analysis
Funding source: Unknown/not stated
Setting: Outpatient (any)
Synopsis: An annoyance of clinical practice is the requirement by many insurance companies to perform confirmatory diagnostic testing prior to initiating treatment for patients with clinically suspected onychomycosis. This was based on analyses done 15 years ago, when terbinafine was significantly more expensive. Terbinafine is now affordable (approximately $10 for a full 12-week course), but the topical solution efinaconazole 10% provides a new, more expensive option (more than $500 for each 4-mL bottle in the United States). These authors performed a decision analysis that compared 3 strategies: (1) treat all patients empirically; (2) if in-office potassium hydroxide testing result is positive, treat; if negative, order PAS stain and treat if positive; or (3) order PAS stain on all patients and treat only if positive. They assumed, on the basis of previous studies, that between 65% and 95% of patients presenting with clinical nail dystrophy have a fungal infection, and that the cost of a course of treatment was $2307 for efinaconazole and $53 for terbinafine (including monitoring liver function). They concluded that if you are going to prescribe terbinafine, empiric therapy without confirmatory testing is the preferred strategy (and the least expensive overall) with a very low risk of serious adverse effects. If you are going to prescribe efinaconazole, then confirmatory testing with PAS is preferred. However, this is a much more expensive treatment option.
Mikailov A, Cohen J, Joyce C, Mostaghimi A. Cost-effectiveness of confirmatory testing before treatment of onychomycosis. JAMA Dermatol 2016;152(3):276-281.

2. AAN Guideline on managing patients with restless leg syndrome

Clinical question: How should clinicians manage restless leg syndrome?
Bottom line: The American Academy of Neurology recommends using dopamine agonists to treat patients with moderate to severe restless leg syndrome (RLS). Second-line treatments include long-acting opioid/naltrexone combinations or iron supplements (in patients with a ferritin level < 75 mcg/L). For patients who prefer nonpharmaceutical treatment, pneumatic compression appears to be the most studied alternative. (LOE = 5)
Study design: Practice guideline
Funding source: Foundation
Setting: Outpatient (any)
Synopsis: This committee of the American Academy of Neurology, staffed by members who had multiple ties to industry, systematically assessed multiple studies to develop guidance on managing patients with RLS. Before reviewing the studies, the committee decided to use a change of 3 points on the International Restless Legs Syndrome Study Group rating scale (IRLS) as clinically meaningful. Additionally, the authors established criteria for meaningful findings on polysomnography (periodic leg movement index, total sleep time, sleep efficiency, sleep latency, wake after sleep onset), as well as measures of sleep outcomes. Finally, when making their treatment recommendations, the committee suggested that establishing qualifying criteria is not necessary before treating patients with moderate to severe RLS. Many of the agents in question are also used in treating Parkinson's disease, yet the number of high-quality studies on treating patients with RLS are limited. Most studies are of short duration (approximately 12 weeks), rarely evaluate individual agents head-to-head, and I suspect from my experience in reviewing studies that they also tend to underreport the harms of treatment. Most of the existing data are on the use of dopamine agonists: ropinorole (Requip), pramipexole (Mirapex), rotigotine (Neupro), cabergoline (Cabaser, Dostinex), and levodopa. Each appears effective in managing various symptoms, though cabergoline has not been rigorously studied in RLS and the data on levodopa are mixed. Additionally, dopamine agonists have the potential problem of augmentation—gradual worsening of symptoms after treatment that often requires changing medication or adding a new agent. Gabapentin (Neurontin) and pregabalin (Lyrica) also improve the IRLS score but less clearly decrease periodic limb movements. Iron, oral and parenteral, also improves the IRLS score. Long-acting opioid/naltrexone combinations improve the IRLS score and improve sleep quality in patients with poor response to other agents. Very limited data suggest that the following clinical interventions are also likely to be effective: near-infrared spectroscopy, pneumatic compression, transcranial direct current stimulation, repetitive transcranial magnetic stimulation, and vibrating pads.
Winkelman JW, Armstrong MJ, Allen RP, et al. Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2016;87(24):2585-2593.

3. Meta-analysis: alpha blockers effective for kidney stones

Clinical question: In patients with kidney stones (ureteric calculi), is treatment with an alpha blocker effective in improving passage rate and decreasing pain?
Bottom line: Although a recent large study found no benefit to alpha blocker treatment (Lancet 2015;386:341-49), this meta-analysis of 55 studies found a benefit to using alpha blockers to increase the likelihood of stone passage, decrease surgical intervention, and decrease episodes of pain. These findings support European and US guidelines that recommend their use. Patients with larger (at least 5 mm) stones are more likely to benefit. (LOE = 1a-)
Study design: Randomized controlled trial (single-blinded) **Funding source:** Self-funded or unfunded

Allocation: Concealed **Setting:** Population-based
Synopsis: To conduct this study, the authors searched 5 databases (including Cochrane CENTRAL), a previous systematic review, reference lists of other reviews, and clinical trial registries. Two researchers independently selected randomized controlled trials that compared alpha blockers with placebo or no treatment in patients with ureteric stones. Two researchers independently extracted the data from 55 studies enrolling a total of 5990 patients. Stone passage, which occurs in approximately half of patients without intervention, is 50% greater with treatment (number needed to treat [NNT] = 3.74) and will occur an average 9.5 days after presentation as compared with 13.3 days without treatment. Episodes of pain will also be decreased. The need for surgery will decrease by approximately half (NNT = 6.17) and hospital admissions will decrease approximately 60% (NNT = 10.6) Patients with larger stones (at least 5 mm) are more likely to benefit. There was some evidence of publication bias; for some outcomes, results were calculated only using data from the larger studies. There was significant heterogeneity among the studies regarding stone passage rate.
Hollingsworth JM, Canales BK, Rogers MA, et al. Alpha blockers for treatment of ureteric stones: systematic review and meta-analysis. BMJ 2016;355:i6112.

4. Better outcomes for hospitalized patients treated by female physicians

Clinical question: Are there differences in outcomes for hospitalized patients who are treated by female physicians versus male physicians?
Bottom line: Patients hospitalized for medical conditions who are treated by female physicians are less likely to die or be readmitted within 30 days than those treated by male physicians. Although the effects shown in this study were modest, at less than a percentage point reduction for both outcomes, the difference may be clinically meaningful when applied to more than 10 million annual Medicare hospitalizations. (LOE = 2b)
Study design: Cross-sectional **Funding source:** Government
Allocation: Uncertain **Setting:** Inpatient (any location) with outpatient follow-up
Synopsis: These authors analyzed a 20% sample of Medicare patients who had a nonelective hospitalization for a medical condition between 2011 and 2014. The main physician caring for the patient during the hospitalization was identified as the physician who garnered the highest amount of Medicare Part B spending, which includes professional fees as well as other fees determined by the physician. The analysis was restricted only to those hospitalizations in which the main physician was identified as a general internist. More than 1.5 million hospitalizations treated by almost 58,000 physicians were included in the sample. The characteristics of patients treated by female physicians and those treated by male physicians were well-balanced, with a mean age of 81 years and similar comorbidities across the 2 groups. The overall 30-day mortality rate and 30-day readmission rates were 11.32% and 15.42%, respectively. After adjusting for patient, hospital, and physician factors, patients treated by female physicians had a lower 30-day mortality than those treated by male physicians (11.07% vs 11.49%; P < .001; number needed to treat [NNT] = 233). Similarly, 30-day readmission rates were lower in the group treated by female physicians (15.02% vs 15.57%; P < .001; NNT = 182). When the sample was restricted to patients treated by hospitalists only, the findings remained the same with lower mortality and readmission rates for patients treated by female hospitalists. Furthermore, the results were consistent when analyzed across specific medical conditions and different categories of severity of illness.
Tsugawa Y, Jena AB, Figueroa JF, Orav EJ, Blumenthal DM, Jha AK. Comparison of hospital mortality and readmission rates for Medicare patients treated by male vs. female physicians. JAMA Intern Med 2017;177(2):206-213.

5. Type 2 diabetes: metformin first, other treatments second

Clinical question: What should we use as the primary treatment of type 2 diabetes mellitus?
Bottom line: The American College of Physicians recommends treating patients with type 2 diabetes with metformin first, then adding a second oral treatment (a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor) if needed for glycemic control. The group saves advice about when to initiate treatment, treatment goals, use of insulin, and when to add the second treatment for another guideline. (LOE = 5)
Study design: Practice guideline
Funding source: Foundation
Setting: Various (guideline)
Synopsis: These guidelines, developed by the American College of Physicians, were based on a systematic review (doi:10.7326/M15-2650). The committee represented a single primary care specialty and members had no reported financial conflicts of interest. The recommendations focus on improving patient-oriented outcomes and are based on graded evidence, but they are a bit fuzzy. The authors recommend prescribing metformin "when pharmacologic therapy is needed to improve glycemic control" (strong recommendation, moderate-quality evidence), implying that there should be a specific goal for glycemic control but not stating what it should be. Metformin remains the cornerstone of treatment on the basis of its effectiveness in reducing cardiovascular mortality as compared with sulfonylurea treatment, its effectiveness in reducing glycemic levels, its association with weight loss, low risk of hypoglycemic, and cost. When additional glycemic control is needed (again, no guidance regarding when that would be), the authors suggest using either a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor in addition to metformin (weak recommendation, moderate-quality evidence). The authors focused only on oral therapy here and did not give recommendations regarding insulin.
Qaseem A, Barry M, Humphrey LL, Forciea MA, for the Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians. Ann Intern Med 2017;166(4):279-290.

6. No added benefit with higher doses of ketorolac for treatment of acute pain in the ED

Clinical question: Are lower doses of ketorolac as effective as standard doses for acute pain control in patients presenting to the emergency department?

Bottom line: A 10-mg dose of ketorolac is as effective as higher doses for the short-term treatment of acute pain for emergency department (ED) patients. (LOE = 1b)
Study design: Randomized controlled trial (double-blinded) **Funding source:** Government
Allocation: Concealed **Setting:** Emergency department
Synopsis: Ketorolac is a nonsteroidal anti-inflammatory drug available in parenteral form for the treatment of acute pain. Although higher doses are often used, ketorolac may have a therapeutic ceiling of 10 mg. To investigate the efficacy of lower doses of ketorolac, these investigators used a convenience sample of patients presenting to the ED on weekdays between 8 AM and 8 PM to enroll patients with acute flank, abdominal, musculoskeletal, or headache pain rated at least 5 on a 0 to 10 numeric rating scale. The authors excluded patients with unstable vitals, active peptic ulcer disease or gastrointestinal bleeding, history of liver or renal disease, and those who were pregnant or breastfeeding. Using concealed allocation, investigators randomized 240 patients to receive either a 10-mg, 15-mg, or 30-mg dose of ketorolac. Patients who still required pain medication after 30 minutes of administration of the study drug received intravenous morphine at a dose of 0.1 mg per kg. The 3 groups were similar at baseline: They all had a mean age of approximately 40 years, two-thirds were female, and the baseline pain score was between 7 and 8. Analysis was by intention to treat. The primary outcome was a reduction of pain scores at 30 minutes after administration of the study drug. In all 3 groups, there was a significant decrease in pain scores from baseline to 30 minutes by at least 2 points. However, there were no significant differences in reduction of pain scores across the 3 groups at 30 minutes, or at subsequent time points of 60, 90, and 120 minutes. Further, there were no differences in the use of rescue morphine analgesia between the 3 groups. The most common adverse effects reported were dizziness, nausea, and headache, and again, were similar in all 3 groups.
Motov S, Yasavolian M, Likourezos A et al. Comparison of intravenous ketorolac at three single-dose regimens for treating acute pain in the emergency department. 2016 Dec 16 [Epub ahead of print].

7. Two-year outcomes better with endovascular stroke treatment in selected patients (MR CLEAN follow-up)

Clinical question: Does mechanical thrombectomy using a stent retriever improve long-term outcomes in patients with acute stroke?
Bottom line: Mechanical thrombectomy using a stent retriever appears to have some functional benefits, with a greater likelihood that patients have no more than slight disability (number needed to treat [NNT] = 7). There was a trend toward reduced all-cause mortality, but this was not significant, and the loss of more than 20% of patients to follow-up is concerning. (LOE = 1b-)
Study design: Randomized controlled trial (single-blinded) **Funding source:** Industry + govt
Allocation: Concealed **Setting:** Inpatient (any location) with outpatient follow-up
Synopsis: This is a follow-up study to the original MR CLEAN trial, which compared usual care with mechanical thrombectomy using a stent retriever in patients within 6 hours of the onset of acute stroke. The original trial, funded by industry and a foundation, found that the intervention improved 90-day outcomes. This follow-up study was funded by the Dutch government. Of the original 500 patients enrolled in the study, 391 were included in the follow-up study of function and quality of life. The authors evaluated function using a modified Rankin Scale (0 to 6 points, where lower scores are better) every 6 months for up to 2 years following the original intervention. The patients' quality of life was also evaluated, and the vital status was assessed even for patients not giving consent. A modified Rankin score of 0, 1, or 2 was more likely in the intervention group (37% vs 24%, NNT = 7 over 2 years), and the quality of life score was also significantly but modestly better in the intervention group (effect size 0.1). However, all-cause mortality was not significantly different (26% vs 31%; P = .46; adjusted hazard ratio 0.9; 95% CI 0.6 - 1.2). Patients in the follow-up study were more likely to have been in the intervention group, and they had a lower incidence of atrial fibrillation and a shorter time from stroke to randomization.
van den Berg LA, Dijkgraaf MG, Berkhemer OA, et al, for the MR CLEAN Investigators. Two-year outcome after endovascular treatment for acute ischemic stroke. N Engl J Med 2017;376(14):1341-1349.

8. Children with appendicitis do fairly well with antibiotic treatment!

Clinical question: Do children with appendicitis treated with antibiotics do as well as those treated with surgery?
Bottom line: The existing data are limited to a few small studies. While surgery is clearly better at improving short term and long-term outcomes, it is expensive and patients need to recover. Most children treated with antibiotics will do well, but about 1 in 4 will undergo surgery within a year. This is the perfect place for shared decision-making. (LOE = 2a)
Study design: Meta-analysis (randomized controlled trials)
Funding source: Unknown/not stated
Setting: Various (meta-analysis)
Synopsis: These authors searched multiple databases and a trial registry to identify trials comparing antibiotics and surgery in children with acute uncomplicated appendicitis. Two authors independently evaluated each potential paper for inclusion and assessed each included paper's risk of bias. They included five small studies with 404 children; 168 were treated with antibiotics and 236 were treated surgically. Only one of the trials was randomized. Three studies reported one year follow up and one followed the children for 4.3 years. One planned one year of follow up but only reported a median of 4.7 months. The range of patients not available after one year ranged from 0% to 23% and was similar among those treated surgically or with antibiotics. The included studies also used different diagnostic approaches. In the children treated with antibiotics, 9.5% failed initial treatment - resolution of symptoms without needing surgery within 48 hours or recurrence of appendicitis 1 month after antibiotics while all 236 of those treated surgically had confirmed appendicitis and only one needed reoperation. In other words, about 90% of children treated with antibiotics will do well initially. Forty-five of the antibiotic-treated children (26.8%), however, underwent appendectomy within the following year, 8 of whom had normal appendices on histopathology. Children treated with antibiotics had 8 days of disability compared with 21 in those treated surgically. Four studies reported data on children with an appendicolith, three of which reported that its presence was associated with a 50% rate of antibiotic failure.
Huang L, Yin Y, Yang L, Wang C, Li Y, Zhou Z. Comparison of Antibiotic Therapy and Appendectomy for Acute Uncomplicated Appendicitis in Children: A Meta-analysis. JAMA Pediatr. 2017;171(5):426-434.

9. Medication reminder gizmos don't help adherence

Clinical question: Do medication reminder devices improve adherence to chronic disease medication?
Bottom line: William Osler believed that "the desire to take medicine is perhaps the greatest feature which distinguishes man from animals." Well, perhaps we like the idea more than the practice. None of 3 different devices improved adherence to chronic disease medication as measured by prescription refill rates. I'm waiting for the study in which they give the participants Apple Watches to improve adherence; I'd sign up for that one. (LOE = 1b)
Study design: Randomized controlled trial (single-blinded) **Funding source:** Industry
Allocation: Uncertain **Setting:** Population-based
Synopsis: These researchers enrolled 53,480 participants with an average age of 45 years who were identified through a pharmacy benefits manager. The patients took 1 to 3 chronic medications but did not take them regularly. The researchers randomized patients (allocation concealment unknown) to receive 1 of 3 reminder systems: (1) a strip to be attached to a prescription bottle with toggles to keep track of dosing; (2) a digital timer cap that displays the elapsed time since the previous dose, or (3) a standard pillbox. A fourth group did not receive any device. Over 12 months, only approximately 15% of the patients in each of the 4 groups took at least 80% of their chronic medicine, according to prescription records. Similar results were found in patients who were prescribed antidepressants. Analysis was by intention to treat. The researchers simply mailed the devices to patients. Perhaps direct delivery of the device by prescribers or pharmacists would result in better results; the added aspect of "I'm watching you" might have benefit. Reminders delivered via text have been shown to be effective in studies of mixed adherers and nonadherers (JAMA Intern Med 2016;176(3):340-349).
Choudhry NK, Krumme AA, Ercole PM, et al. Effect of reminder devices on medication adherence: The REMIND randomized clinical trial. JAMA Intern Med 2017;177(5):624-631.

10. Umbrellas alone do not provide adequate sun protection

Clinical question: Which provides better sun protection, sunscreen or a beach umbrella?
Bottom line: This study had a number of important limitations: industry sponsorship, small size, uncertain clinical significance of "sunburn scores," and a somewhat contrived set of study conditions (who doesn't get in the water when you're at the beach on a hot day?). Nevertheless, I think the authors are correct in concluding that an umbrella alone does not provide complete protection from the reflected and diffused ultraviolet (UV) rays that reach the shaded person. This makes some sense since it isn't pitch black under an umbrella. So, slather on that sunscreen, even if you plan to stay under an umbrella. (LOE = 2b)
Study design: Randomized controlled trial (single-blinded) **Funding source:** Industry
Allocation: Uncertain **Setting:** Population-based
Synopsis: These researchers recruited 81 patients, all of whom spent 3.5 hours at a beach in Texas. The participants are not described at all, an important deficiency in the study, other than that all but one had Fitzpatrick skin type II or III (moderately pale, either European Scandinavian or southern/central European). Half were randomized to receive a standard-sized beach umbrella (just over 6 feet in diameter) and half received an application of sunscreen with a sun protection factor of 100. Participants in the sunscreen group reapplied it an average of twice during the study period. Those under the umbrella were told to stay there, and could only leave it for a total of 30 minutes and only after covering up. Neither group was allowed to enter the water, which seems cruel. The investigators evaluated the exposed areas 24 hours later for the presence of redness or sunburn using a 4-point sunburn score, where 0 indicated no sunburn, 2 indicated defined redness clearly caused by UV rays, and 4 meant edema and/or blisters. The global sunburn score was more likely to increase (worsen) in the umbrella group, and there were more sunburned body sites in the umbrella group than in the sunscreen group (142 vs 17). This study was sponsored and conducted by Johnson & Johnson, the manufacturer of Neutrogena sunscreens and skin care products.
Ou-Yang H, Jiang LI, Meyer K, Wang SQ, Farberg AS, Rigel DS. Sun protection by beach umbrella vs sunscreen with a high sun protection factor: a randomized controlled trial. JAMA Dermatol 2017;153(3):304-308.

11. Treatment of subclinical hypothyroidism ineffective in older adults

Clinical question: Is there a clinical benefit to treating subclinical hypothyroidism in older adults?
Bottom line: Treatment of patients with a minimally elevated thyrotropin (thyroid-stimulating hormone) level did not result in any improvement in symptoms. If patients present with a thyrotropin level between 4.6 mIU and 10 mIU per liter, repeat the test as the levels often normalize (this occurred in 60% of the patients initially referred for the study). Only consider treatment if levels increase to above 10.0 mIU/L. (LOE = 1b)
Study design: Randomized controlled trial (double-blinded) **Funding source:** Government
Allocation: Concealed **Setting:** Outpatient (any)
Synopsis: Whether to treat patients with subclinical hypothyroidism (slightly elevated thyrotropin, normal T4, and no or minimal symptoms) remains controversial. The authors of this study recruited 737 such adults, 65 years and older, and randomized them to receive thyroid replacement or matching placebo. The mean baseline thyrotropin level was 6.4 mIU/L (normal range: 0.4 to 4.59 mIU/L), and few had a value greater than 10.0 mIU/L. The groups were balanced, allocation was appropriately concealed, and analysis was by intention to treat. Patients were followed up for 1 year, and the primary outcomes were the 4-item ThyPRO thyroid symptom score and a 7-item Tiredness Score. The treatment dose of levothyroxine was started at 50 mcg daily for most patients, and gradually increased until the thyrotropin was in the normal range (the placebo group had sham titration of their "dose"). The final achieved average thyrotropin level was just over 3.0, which is a bit higher than the target 2.5 mIU/L recommended by some guidelines (Eur Thyroid J 2013;2:215-28). At the end of the study period, there was no difference in any clinical outcomes. A subset of slightly more than half the patients in each group had extended follow-up for a median of 2 years, and at that time there was a slightly greater improvement in the Tiredness Score in the levothyroxine group, but this was of marginal clinical and statistical significance. There was no difference in harms, including cardiovascular events, although the study was not powered to detect a difference if there was one.
Stott DJ, Rodondi N, Kearney PM, et al, for the TRUST Study Group. Thyroid hormone therapy for older adults with subclinical hypothyroidism. N Engl J Med 2017;376(26):2534-2544.

12. "Bendopnea"—dyspnea in heart failure patients when bending forward—predicts adverse outcomes

Clinical question: What is bendopnea and what does it tell us?
Bottom line: Unlike "'Twas brillig, and the slithy toves did gyre and gimble in the wabe," bendopnea is not a nonsense word but a neologism used to describe the shortness of breath experienced by some patients with heart failure. Bendopnea is defined as becoming dyspneic within 20 seconds of leaning forward while seated in a chair as if to tie a shoelace. It seems to be predictive of a worse prognosis; at the very least it's another marker for worsening symptoms. Patients experiencing bendopnea were more likely to have New York Heart Association (NYHA) class IV heart failure, were more likely to have a subsequent hospitalization within 3 months, and might have a worse long-term prognosis. We'll need to wait for research that compares patients with similar heart failure symptoms to determine how much additional prognosis value this has. (LOE = 1b)
Study design: Cohort (prospective)
Funding source: Self-funded or unfunded
Setting: Outpatient (specialty)
Synopsis: Don't know about bendopnea? It is a recently described observation that occurs in approximately 20% of patients with heart failure and associated with higher ventricular filling pressures, especially in patients with a low cardiac index. For this study, the researchers enrolled a convenience sample (ie, not randomized) of 179 patients in a heart failure clinic. The patients were an average 57 years old, there were slightly more men than women, and approximately 60% were white. Patients with bendopnea were more likely to have NYHA class IV heart failure. Higher body mass index was not associated with bendopnea, and other studies have not shown an association with abdominal circumference and bendopnea. The patients were followed up for 1 year. Those with bendopnea were at increased risk of experiencing death, admission for heart failure, inotrope use, left ventricular assist device implantation, and cardiac transplantation—though none of these outcomes was individually significantly more likely. Patients were more likely to be admitted for heart failure treatment within 3 months.
Thibodeau JT, Jenny BE, Maduka JO, et al. Bendopnea and risk of adverse clinical outcomes in ambulatory patients with systolic heart failure. Am Heart J 2017;183:102-107.

13. No mortality benefit and higher costs with early goal-directed therapy for septic shock

Clinical question: Does early goal-directed therapy improve outcomes when treating septic shock?
Bottom line: Early goal-directed therapy (EGDT)—a 6-hour resuscitation protocol using central venous monitoring to administer fluids, vasopressors, inotropes, and as-needed transfusions for early treatment of septic shock—does not improve mortality and can lead to longer intensive care unit stays and higher hospitalization costs. Even patients at the highest risk of mortality did not benefit from EGDT in this analysis. Notably, another study in the same journal of the timing of more basic care for septic shock in the emergency department, including drawing blood cultures, measuring lactate levels, and administering antibiotics within 3 hours, showed that longer times were associated with higher in-hospital mortality. (LOE = 1a)
Study design: Meta-analysis (randomized controlled trials)
Funding source: Government
Allocation: Concealed
Setting: Inpatient (any location)
Synopsis: The ProCESS, ARISE, and ProMISe trials were multi-center randomized controlled trials that compared EGDT with usual care for the management of septic shock. Each trial revealed a lack of mortality benefit with the use of EGDT. The investigators planned a prospective meta-analysis prior to the enrollment of the first patient into the first trial with the goal of pooling patient-level data from all 3 trials (N = 3723). Patients in the EGDT group and the usual care group were balanced at baseline. For the primary outcome of 90-day mortality, the 2 groups had similar mortality rates (24.9% in the EGDT group vs 25.4% in the usual care group). Additionally, the EGDT group had longer intensive care unit stays, higher costs, and required more cardiovascular support. Subgroup analyses showed no benefit of EGDT in patients with greater severity of illness or those with a higher intensity of underlying care. A separate restrospective study looked at New York's mandated emergency care for the treatment of severe sepsis and septic shock. In this study, a delay in timing of the delivery of a 3-hour bundle, consisting of obtaining blood cultures prior to starting antibiotics, measuring serum lactate, and administering broad-spectrum antibiotics, was associated with higher in-hospital mortality with each incremental hour until the completion of the 3-hour bundle (odds ratio of death until completion of 3-hour bundle: 1.04 per hour; 95% CI 1.02 - 1.05).
The PRISM Investigators, Rowan KM, Angus DC, et al. Early, goal-directed therapy for septic shock—a patient-level meta-analysis. N Engl J Med 2017;376(23):2223-2234. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med 2017;376(23):2235-2244.

14. Pathologists disagree with each other and themselves on melanoma diagnoses

Clinical question: How accurate are pathologists' evaluations of skin lesions for melanoma?
Bottom line: Pathologists use a wide variety of descriptors to report biopsy results. Even so, a diagnosis of normal (nevus or mild atypia) can be trusted most of the time. But pathologists often disagree with one another (and themselves): They disagree with one another on moderate atypia (only 25% agreement), severe atypia (40% agreement), and early melanoma (43% agreement). Approximately 8% of all cases will be overinterpreted and 9% will be underinterpreted. (LOE = 1c)
Study design: Diagnostic test evaluation
Funding source: Government
Setting: Other
Synopsis: These investigators enrolled 187 US pathologists who interpret melanocytic lesions for this study. To test the pathologists' interpretive skills, the investigators assembled slides from 240 shave, punch, and excisional specimens. The cases represented more atypia than is commonly encountered, with approximately 75% of cases representing from severe atypia to invasive melanoma (class III - class V). Each pathologist randomly received 1 of 5 sets of 48 cases and were asked to evaluate them and provide recommendations. Eight or more months later they received the same slides again. Given the slippery nature of identification, the researchers used 3

reference standards: (1) a panel of 3 dermatopathologists, (2) the most common diagnosis by the board-certified and/or fellowship–trained participants in the study, and (3) the most frequent diagnosis by all participants. Participants were given case information but were unaware of the reference diagnosis or the prevalence distribution of the cases. In the first phase, an average of 10 different diagnostic terms were applied to each case. The pathologists agreed with one another at either extreme: 92% of the time for class I (nevus or mild atypia) and 72% of the time for class V (T1b invasive melanoma or higher). However, they only agreed with one another 25% of the time for class II (moderate atypia), 40% for class III (severe atypia or melanoma in situ); and 43% for class IV (early invasive melanoma). These numbers translate into 8.0% overinterpreted and 9% underinterpreted. When asked to re-read the same slides, the pathologists agreed with themselves most of the time for class I (76.7%) and class V (82.6%); agreement was lower for class II (35.2%), III (59.5%), and IV (63.2%). Pathologists in this study are aware of the problem, with 96% describing interpretation of melanocytic lesions as challenging.
Elmore JG, Barnhill RL, Elder DE, et al. Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study. BMJ 2017;357:j2813.

15. Treating sleep apnea with positive airway pressure does not reduce adverse CV outcomes or mortality

Clinical question: Does positive airway pressure for adults with sleep apnea reduce cardiovascular disease morbidity and mortality?
Bottom line: The use of positive airway pressure (PAP) for adults with sleep apnea does not reduce adverse cardiovascular events or mortality. Patients who experience daytime fatigue at baseline benefit from reduced sleepiness and improved physical and mental well-being. Order sleep testing only in patients with signs or symptoms of sleep apnea who also experience clinically significant symptoms of daytime fatigue. No one else will benefit. (LOE = 1a)
Study design: Meta-analysis (randomized controlled trials)
Funding source: Government
Setting: Various (meta-analysis)
Synopsis: These investigators thoroughly searched multiple databases including MEDLINE, EMBASE, and the Cochrane Library, as well as reference lists from clinical trials, review articles, conference abstracts, and the clinicaltrials.gov website. Eligible studies included randomized clinical trials that assessed the use of PAP compared with standard care or sham PAP among adults, 18 years or older, with either obstructive sleep apnea (OSA) or central sleep apnea (CSA). No language restrictions were applied. Two individuals independently assessed studies for inclusion criteria and for methodologic quality using a standard risk of bias assessment tool. Disagreements were resolved by consensus. A total of 10 studies that assessed the use of PAP in adults (N = 7266) with OSA and CSA met the inclusion criteria—9 evaluated continuous positive airway pressure and 1 evaluated adaptive servo-ventilation. The overall risk of bias was low to medium; all studies concealed allocation assignment and masked outcomes assessment. No significant associations occurred between the use of PAP and major adverse cardiovascular events, cardiovascular mortality, or all-cause mortality in patients with both OSA and CSA. In addition, there was no significant association with length of follow-up, adherence with using PAP, and baseline apnea-hypopnea index. The use of PAP was significantly associated with improvements in sleepiness and quality of life. A formal analysis found no evidence of publication bias and minimal heterogeneity of assessed outcomes.
Yu J, Zhou Z, McEvoy D, et al. Association of positive airway pressure with cardiovascular events and death in adults with sleep apnea. A systematic review and meta-analysis. JAMA 2017;318(2):156-166.

16. Personal sound amplification works as well as a hearing aid for understanding speech at 20% of the cost

Clinical question: Are personal sound amplification devices useful for improving speech understanding in noisy environments?
Bottom line: The mean cost of a pair of hearing aids ($4700) is out of reach for most adults and not currently covered by Medicare. This study found that 3 of 5 commercially available personal sound amplification products (PSAPs) improved speech understanding in noisy environments as well as hearing aids. The most expensive of these is still less than one-fifth the cost of a conventional hearing aid. Hmmm… this sounds like useful information for our Medicare patients. (LOE = 2b)
Study design: Cohort (prospective)
Funding source: Foundation
Setting: Outpatient (specialty)
Synopsis: Understanding what a friend is saying from across the table in a noisy restaurant can be a frustrating experience, especially as one ages (as I know from personal experience). For most adults, the price of 2 hearing aids (mean cost $4700) is way out of their budget. These investigators identified 42 adults, aged 60 to 85 years, with mild to moderate hearing loss (20 - 55 dB HL) with no history of prior amplification use or cognitive impairment. Participants completed a standard sentence-in-noise hearing test used to measure speech understanding and functional hearing in the presence of background noise under 7 conditions: unaided, with a standard hearing aid, and with each of 5 commercially available PSAPs. The primary outcome was speech accuracy, defined as the percentage of words repeated correctly. The mean unaided accuracy was 76.5%. Hearing aids improved speech understanding accuracy to 88.4% (absolute improvement 11.9%; 95% CI 9.8 - 14.0%). Three PSAPs improved accuracy by a similar absolute improvement amount: Sound World Solutions C550+ (11%; 8.8% - 13.1%), Soundhawk (10.2%; 8.0% - 12.3%), and Etymotic BEAN (7.7%; 5.5% - 9.8%). The Tweak Focus improved hearing but to a lesser degree than the other 3 (4.9%; 2.8% - 7.0%). One PSAP resulted in significantly worse speech accuracy (MSA 30X, accuracy 65%; absolute difference -11.2%; -15.2 to -7.3%). Among this sample, performance correlated with price: The 2 best are $350 and the worst is $30.
Reed NS, Betz J, Kendig N, Korczak M, Lin FR. Personal sound amplification products vs a conventional hearing aid for speech understanding in noise. JAMA 2017;318(1):89-90.

17. Price transparency doesn't change clinicians' ordering of inpatient lab tests (PRICE)

Clinical question: Does displaying the prices for inpatient laboratory tests in the electronic health record influence clinician ordering?
Bottom line: Displaying fees at the point of order entry did not affect the number of inpatient laboratory tests ordered. The fees displayed in this study were Medicare reimbursement rates rather than actual costs to patients. (LOE = 1b)
Study design: Randomized controlled trial (nonblinded) **Funding source:** Other
Allocation: Concealed **Setting:** Inpatient (any location)
Synopsis: To evaluate the effect of price transparency on clinical ordering, these investigators randomly assigned 60 groups of inpatient laboratory tests to either display the Medicare allowable fees in the electronic health record (intervention) or to not display the fees (control). The laboratory test groups were composed of tests that could be ordered both individually or within a panel. For example, the basic metabolic panel and all its individual components were in the same group. Randomization was stratified with attention to high-volume tests and more expensive tests so that there was an equal representation in the tests that displayed fees and those that did not. Any clinician who was able to place orders in the electronic health record was able to see the prices of the intervention tests at the time of order entry during the intervention period. The primary outcome was number of tests ordered per patient-day. An adjusted analysis, which took into account patient demographics and comorbidities, showed no significant change in the number of tests ordered from either the intervention group or the control group from a 1-year pre-intervention period to a 1-year postintervention period. Additionally, there were no changes in associated laboratory fees per patient-day over time. These findings suggest that displaying prices did not alter clinician behavior when ordering tests. Alert fatigue or one-time ordering of repeat daily labs (which would eliminate the daily price reminder) may have contributed to the lack of effect.
Sedrak MS, Myers JS, Small DS, et al. Effect of a price transparency intervention in the electronic health record on clinician ordering of inpatient laboratory tests: The PRICE randomized clinical trial. JAMA Intern Med 2017;177(7):939-945.

18. Guideline on managing adults with primary Sjogren's syndrome

Clinical question: How should clinicians manage the symptoms of adults with primary Sjogren's syndrome?
Bottom line: Primary care physicians can manage the bulk of symptoms experienced by patients with Sjogren's syndrome by using simple measures to improve local dryness: lubricants, sugar-free gum, and pilocarpine. (LOE = 5)
Study design: Practice guideline
Funding source: Other
Setting: Various (guideline)
Synopsis: The National Institute for Health and Care Excellence accredited the process used by the British Society for Rheumatology for this study. Although the society reported they received no funding to support the guideline, several authors had ties to industry. The authors searched several databases for studies published since 1990 and then used a formal Delphi process to develop this guideline; its target audience includes rheumatologists, primary care clinicians, and other specialists. The guideline covers management of the eye and mouth manifestations, xerosis, and systemic disease. Virtually all of the recommendations are based on expert opinion and other lower-quality evidence. Sicca syndrome is among the most bothersome of Sjogren's manifestations and all patients should be offered symptomatic treatment. Patients with mild eye symptoms can be managed with lubricants; those with moderately severe symptoms should also receive topical steroids or antibiotics (if blepharitis is present). Additionally, patients with moderate to severe symptoms benefit from punctal plugs or secretagogues such as pilocarpine. Patients with more severe eye problems should be referred to an ophthalmologist. You should not be surprised that the focus on xerostomia similarly focuses on moisture: room air humidification; the avoidance of medications that cause dry mouth; and the use of sugar-free chewing gum, anhydrous crystalline maltose, and pilocarpine. Additionally, the guideline recommends fastidious dental hygiene, the use of fluoride, and so forth because of the higher rate of dental caries associated with xerostomia. Additionally, since these patients often experience oral candida and cheilitis, the panel recommends topical antifungals when these occur. In patients who experience parotid enlargement, the panel recommends ultrasound to assess for stones, the use of massage, and treatment with systemic corticosteroids when inflamed. Systemic dryness, manifested as chronic cough and vaginal dryness, should be treated with local products, and with pilocarpine when the symptoms are more severe. The panel recommends immunomodulating agents (methotrexate, azathioprine, hydroxychloroquine, mycophenolate, biologics, and the like) and corticosteroids in patients with systemic disease. Mucosal lymphoma (salivary and gastrointestinal) occurs more frequently in patients with Sjogren's syndrome, especially those with lymphadenopathy, parotid enlargement, palpable purpura, low serum C4 levels, and cryoglobulins. The panel recommends the use of ultrasound and biopsy to evaluate patients with firm, palpable parotid swelling given the increased risk of lymphoma. Lymphoma can also be present in the orbits, thyroid, airways, and gastrointestinal tract, so symptoms in those areas may necessitate further evaluation.
Price EJ, Rauz S, Tappuni AR, et al, for the British Society for Rheumatology Standards, Guideline and Audit Working Group. The British Society for Rheumatology guideline for the management of adults with primary Sjogren's syndrome. Rheumatology (Oxford). 2017;56(10):e24-e48.

19. Patent foramen ovale closure in cryptogenic stroke reduces recurrence rate compared with antiplatelet agents

Clinical question: In patients with a patent foramen ovale and a history of cryptogenic stroke, does closure followed by antiplatelet therapy improve outcomes compared with antiplatelet therapy alone?
Bottom line: After closure, patients with a patent foramen ovale (PFO) and a cryptogenic stroke and had a reduced risk of recurrent stroke over a 5.4-year mean follow-up period (number needed to treat [NNT] = 16), though atrial fibrillation was a common complication, occurring in 4.6%. A second study in the same journal compared PFO closure followed by at least 6 months of antiplatelet therapy with anticoagulation or antiplatelet therapy alone in 980 patients, and found that PFO closure was more effective than antiplatelet therapy, especially for patients with a large shunt or an atrial septal aneurysm. However, that study did not find a benefit when compared with anticoagulation. Finally, a third study that randomized 664 patients to PFO closure plus antiplatelet therapy versus antiplatelet therapy alone found similar results to this study by Mas and colleagues. (LOE = 1b)

Study design: Randomized controlled trial (nonblinded) **Funding source:** Government
Allocation: Concealed **Setting:** Outpatient (specialty)
Synopsis: Previous studies (http://www.essentialevidenceplus.com/content/poem/140501, http://www.essentialevidenceplus.com/content/poem/150507) have not found a benefit to PFO closure in patients with a cryptogenic stroke (that is, a stroke in patients with no clear underlying cause such as atrial fibrillation or coronary artery disease). However, these studies showed trends in favor of intervention, and they may have been underpowered. The current study identified patients aged 16 to 60 years who had suffered an acute ischemic stroke in the past 6 months, had at least 30 microbubbles in the left atrium within 3 cardiac cycles on a bubble test, and had no alternative cause of stroke based on a standardized set of tests. This study was larger than previous trials and also included patients with lower vascular risk, making a recurrent stroke due to other vascular causes less likely. The mean age of patients was 44 years and they had few cardiovascular risk factors (10% hypertension, 3% diabetes mellitus, and 14% hyperlipidemia). In the primary comparison, 524 patients were randomized to receive either PFO closure plus antiplatelet therapy (aspirin plus clopidogrel for 3 months, followed by one of the drugs from then on), to antiplatelet therapy alone, or to anticoagulation alone. Patients with a contraindication to PFO closure (n = 10) were randomized to receive antiplatelet therapy or anticoagulation, and those with a contraindication to oral anticoagulants (n= 129) were randomized to PFO closure plus antiplatelet therapy or antiplatelet therapy alone. For the comparison of PFO closure plus antiplatelet therapy versus antiplatelet therapy alone, at 4.4 years of follow-up the likelihood of recurrent stroke was 0.0% in the former and 6.0% in the latter (hazard ratio [HR] 0.02; 95% CI 0.0 - 0.26; NNT = 16). The risk of the composite of stroke, transient ischemic stroke, or thromboembolic event was also lower in the PFO group (3.4% vs 8.9%; P = .01; NNT = 18). The risk of major or fatal complications (largely atrial fibrillation or flutter, supraventricular tachycardia, air embolism, or hypothermia) in the PFO group was 5.9%. For the comparison of anticoagulation with antiplatelet therapy, there was a nonsignificant trend favoring anticoagulation (HR 0.44; 0.11 - 1.48) for the outcome of recurrent stroke. There was only 1 death in the study (in a patient assigned to anticoagulation). Disabling strokes were rare, with no more than 1 occurring in each treatment group.
Mas JL, Derumeaux G, Guillon B, et al, for the CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med 2017;377(11):1011-1021.

20. Care by general internists who trained outside of US superior to that of US trained physicians

Objective To determine whether patient outcomes differ between general internists who graduated from a medical school outside the United States and those who graduated from a US medical school.
Design Observational study.
Setting Medicare, USA.
Participants 20% national sample of data for Medicare fee-for-service beneficiaries aged 65 years or older admitted to hospital with a medical condition in 2011-14 and treated by international or US medical graduates who were general internists. The study sample for mortality analysis included 1 215 490 admissions to the hospital treated by 44 227 general internists.
Main outcome measures Patients' 30 day mortality and readmission rates, and costs of care per hospital admission, with adjustment for patient and physician characteristics and hospital fixed effects (effectively comparing physicians within the same hospital). As a sensitivity analysis, we focused on physicians who specialize in the care of patients admitted to hospital ("hospitalists"), who typically work in shifts and whose patients are plausibly quasi-randomized based on the physicians' work schedules.
Results Compared with patients treated by US graduates, patients treated by international graduates had slightly more chronic conditions. After adjustment for patient and physician characteristics and hospital fixed effects, patients treated by international graduates had lower mortality (adjusted mortality 11.2% *v* 11.6%; adjusted odds ratio 0.95, 95% confidence interval 0.93 to 0.96; P<0.001) and slightly higher costs of care per admission (adjusted costs $1145 (£950; €1080) *v* $1098; adjusted difference $47, 95% confidence interval $39 to $55, P<0.001). Readmission rates did not differ between the two types of graduates. Similar differences in patient outcomes were observed among hospitalists. Differences in patient mortality were not explained by differences in length of stay, spending level, or discharge location.
Conclusions Data on older Medicare patients admitted to hospital in the US showed that patients treated by international graduates had lower mortality than patients cared for by US graduates.
Tsugawa Y, Jena AB, Orav EJ, Jha AK. Quality of care delivered by general internists in US hospitals who graduated from foreign versus US medical schools: observational study. BMJ 2017; 356 doi: https://doi.org/10.1136/bmj.j273 (Published 03 February 2017)Cite this as: BMJ 2017;356:j273

21. Scribes improve physician satisfaction and charting accuracy and efficiency: RCT

PURPOSE: Scribes are increasingly being used in clinical practice despite a lack of high-quality evidence regarding their effects. Our objective was to evaluate the effect of medical scribes on physician satisfaction, patient satisfaction, and charting efficiency.
METHODS: We conducted a randomized controlled trial in which physicians in an academic family medicine clinic were randomized to 1 week with a scribe then 1 week without a scribe for the course of 1 year. Scribes drafted all relevant documentation, which was reviewed by the physician before attestation and signing. In encounters without a scribe, the physician performed all charting duties. Our outcomes were physician satisfaction, measured by a 5-item instrument that included physicians' perceptions of chart quality and chart accuracy; patient satisfaction, measured by a 6-item instrument; and charting efficiency, measured by time to chart close.
RESULTS: Scribes improved all aspects of physician satisfaction, including overall satisfaction with clinic (OR = 10.75), having enough face time with patients (OR = 3.71), time spent charting (OR = 86.09), chart quality (OR = 7.25), and chart accuracy (OR = 4.61) (all *P* values <.001). Scribes had no effect on patient satisfaction. Scribes increased the proportion of charts that were closed within 48 hours (OR =1.18, *P*=.028).
CONCLUSIONS: To our knowledge, we have conducted the first randomized controlled trial of scribes. We found that scribes produced significant improvements in overall physician satisfaction, satisfaction with chart quality and accuracy, and charting efficiency without

detracting from patient satisfaction. Scribes appear to be a promising strategy to improve health care efficiency and reduce physician burnout.

Gidwani R, Nguyen C, Kofoed A, Carragee C, Rydel T, Nelligan I, Sattler A, Mahoney M, Lin S. Impact of Scribes on Physician Satisfaction, Patient Satisfaction, and Charting Efficiency: A Randomized Controlled Trial. Ann Fam Med. 2017 Sep;15(5):427-433.

Pediatric Potpourri 2018 — William Wadland, MD

Written by: Steven R. Brown, MD

Objectives

1. Summarize clinical approaches to fever in a pediatric patient
2. Discuss updates in well-child preventive care including vision screening and screening for hip dysplasia
3. Review evidence for use of tympanostomy tubes

What is a reasonable approach to the febrile infant? Is clinical diagnosis reliable? Are any blood tests helpful?

#1: Clinical diagnosis of serious infection in children is difficult

Clinical question: How reliable is the history and physical in determining if a child has a serious infection?

Study design: Meta-analysis (other) **Funding source:** Government

Setting: Various (meta-analysis)

Synopsis: These authors searched several databases looking for studies in ambulatory settings that evaluated clinical features of children (1 month to 18 years of age) with suspected serious infection. The studies had to include an appropriate spectrum of illness severity and a reference standard. The authors defined serious infection as sepsis (including bacteremia), meningitis, pneumonia, osteomyelitis, cellulitis, gastroenteritis with dehydration, complicated urinary tract infection (positive urine culture and systemic signs such as fever), and viral respiratory tract infections complicated by hypoxia (eg, bronchiolitis). One can argue about whether some of these are truly serious. Two authors independently assessed the quality of each study, finding most only fair to poor. They found 30 studies evaluating clinical features. The studies included from 72 to 3981 children! The positive likelihood ratios (LR+) for individual elements of the history ranged from 1 to 23 and the negative likelihood ratios (LR-) ranged from 0.26 to 1.3. (Remember: Tests with likelihood ratios of 1 provide no useful information and that an LR+ near 10 and an LR- near 0.1 have the greatest discriminatory capacity.) In most of the studies, the value of the history and physical ranged widely on the basis of the rate of illness in the sick children (less than 5%, 5% to 20%, or more than 20%). Among all of the tested history and physical findings, 4 were predictive for serious infections: cyanosis (LR+ range = 2.66 - 52.2); rapid breathing (LR+ range = 1.26 - 9.78); poor peripheral perfusion (LR+ range = 2.39 - 38.8); and petechial rash (LR+ range = 6.18 - 83.7). In one primary care study, parental concern and clinician instinct were also strong red flags. The negative likelihood ratios, however, were too high to be useful to rule out serious infection. Clinical decision rules, such as the Yale Observational Scale, were also quite variable with the LR+ ranging from 1.1 to 7 and the LR- from 0.2 to 1. There are a couple of "Aunt Fannie" findings in this study (everyone has an Aunt Fannie who can be recognized from 100 feet away because of her easily recognized and eccentric manner of dress). For example, the presence of petechiae, nuchal rigidity, or coma had a LR+ of 395. I think most of us would recognize that a comatose child is seriously ill!

Bottom line: In this systematic review, each element of the history and physical has a wide enough range of reliability that they should not be used independently to evaluate sick children. Specifically, they are not reliable enough to rule out serious infection. (LOE = 1a-)

Reference: *Van den Bruel A, Haj-Hassan T, Thompson M, Buntinx F, Mant D; European Research Network on Recognising Serious Infection investigators. Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: a systematic review. Lancet 2010;375(9717):834-845.*

#2: Pediatric SIRS criteria not accurate for predicting which children will require critical care

Clinical question: How useful are pediatric SIRS vital signs in predicting which children require critical care resuscitation?

Study design: Cohort (retrospective) **Funding source:** Unknown/not stated

Setting: Emergency department

Synopsis: Pediatric SIRS vital signs require the presence of 2 or more of the following criteria, one of which must be abnormal temperature or leukocyte count: Core temperature less than 36C or greater than 38.5C, tachycardia (or bradycardia in infants), tachypnea, abnormal leukocyte count for age, or greater than 10% immature neutrophils. Despite consensus agreement on these criteria, their effectiveness as a screening test for detecting critically ill children is unknown. These investigators retrospectively analyzed data from all visits by patients younger than 18 years to the emergency department (ED) of a tertiary academic pediatric hospital between April 2011 and March 2012. Eligible patients (N = 40,356) included those presenting to the ED for the first time within

the preceding 72 hours with nontrauma-related diagnoses and for whom SIRS vital signs were recorded. A temperature-heart rate correction was performed: For each 1 degree Celsius above 38.5C, 10 beats per minute was subtracted from the heart rate. Outcomes included requirement for critical care within 24 hours of ED arrival, intensive care unit admission, 30-day in-hospital mortality, 72-hour readmission, ED laboratory evaluation, and ED intravenous therapy. A total of 6122 patients (15.2%) met SIRS criteria. Of these, 4993 (81.6%) were discharged from the ED without the need for intravenous therapy and without 72-hour readmission. Only 99 children (0.25%) required critical care within the first 24 hours, including 23 patients with and 76 without SIRS vital signs. Those children meeting SIRS criteria had a significantly increased risk of critical care requirement, intensive care unit admission, and intravenous therapy, but the sensitivity of meeting the SIRS criteria for critical care requirement was only 23.2% (95% CI 15.3%-32.8%). The pair of SIRS vital signs with the highest positive likelihood ratio was temperature and corrected heart rate (LR+ = 2.74; 95% CI 1.87-4.01). Positive likelihood ratios of less than 5 are generally felt not to be clinically useful. No differences in results were detected in any specific age subgroups.

Bottom line: Pediatric systemic inflammatory response syndrome (SIRS) vital signs are minimally, if at all, accurate in predicting which acutely ill children will require critical care resuscitation. (LOE = 2c)

Reference: *Scott HF, Deakyne SJ, Woods JM, Bajaj L. The prevalence and diagnostic utility of systemic inflammatory response syndrome vital signs in a pediatric emergency department. Acad Emerg Med 2015:22(4):382-389.*

#3: Useful signs and symptoms for diagnosing pneumonia in children younger than 5 years

Clinical question: Are there useful signs and symptoms for diagnosing pneumonia in children younger than 5 years?

Study design: Other **Funding source**: Unknown/not stated

Setting: Population-based

Synopsis: These investigators sourced MEDLINE and Embase, as well as pertinent references for articles evaluating the accuracy of the medical history and physical examination for the diagnosis of pneumonia in children younger than 5 years. Additional eligibility criteria included the use of chest radiography as the reference standard for diagnosis. Two individuals evaluated potential articles for study inclusion and assessed methodologic quality using a standard scoring tool. Disagreements were resolved by consensus discussion with a third reviewer. Only studies of medium or high quality were included. A total of 23 prospective cohort studies (N = 13,833 patients) met inclusion criteria. The presence of chest pain was the only symptom with a positive likelihood ratio approximating at least 2.0 (LR+ = 1.9; 95% CI 1.1 - 3.4). Cough, difficulty breathing, vomiting, and diarrhea all had positive likelihood ratios that were not useful (95% CI that included 1.0). Absence of cough was the only finding with a negative likelihood ratio of less than 0.5 (LR- = 0.47; 0.24 - 0.70). The finding of hypoxemia varied with oxygen saturation thresholds: hypoxemia at 96% or less (LR+ = 2.8; 2.1 - 3.6) and hypoxemia at 95% or less (LR+ = 3.5; 2.0 - 6.4). More severe hypoxemia (oxygen saturation < 90%) was actually less useful (LR+ = 1.5; 1.1 - 1.9). A normal oxygenation saturation (> 96%) was useful for ruling out pneumonia (LR- = 0.47; 0.32 - 0.67). The presence of fever was not useful for ruling in pneumonia, but the absence of fever decreased the likelihood of pneumonia (LR- range = 0.17 - 0.37). Tachypnea (respiratory rate at least 40 breaths per minute), the physicians general assessment of the presence or absence of tachypnea, and tachypnea defined by age-specific rates all had positive likelihood rates of less than 2.0 or with 95% CI that included 1.0 or less). However, a respiratory rate less than or equal to 40 breaths per minute decreased the likelihood of pneumonia (LR- = 0.41; 0.17 - 0.99). No auscultatory findings—including crackles, rales, crepitations, wheeze and rhonchi—were useful in ruling pneumonia in or out. Signs of increased work of breathing were the most useful physical examination findings, including grunting (LR+ = 2.7; 1.5 - 5.1), nasal flaring (LR+ = 2.2; 1.3 - 3.1), and chest retractions (LR+ = 1.9; 1.2 - 2.5).

Bottom line: No single symptom or physical examination finding is reliably useful (positive likelihood ratio [LR+] > 10.0; negative likelihood ratio [LR-] < 0.1) for diagnosing pneumonia in children younger than 5 years. Hypoxia (oxygen saturation < 96%) and physical findings of increased work of breathing (grunting, nasal flaring, and chest retractions) are the most useful for the diagnosis of pneumonia. Tachypnea and auscultation are not useful. (LOE = 3a)

Reference: *Shah SN, Bachur RG, Simel DL, Neuman MI. Does this child have pneumonia? The rational clinical examination systematic review. JAMA 2017;318(5):462-471.*

#4: Clinical signs and symptoms of pneumonia unreliable in children

Clinical question: Which clinical features are useful for the accurate diagnosis of pneumonia in children younger than 5 years?

Study design: Systematic review **Funding source:** Government

Setting: Various (meta-analysis)

Synopsis: These investigators searched multiple databases including MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews, as well as performed manual searches of reference lists from eligible articles, for studies evaluating the diagnostic accuracy of clinical signs and symptoms of pneumonia in children aged between 2 months and 6 years. Studies included otherwise healthy children with acute respiratory infections from both the ambulatory and inpatient hospital settings. No language restrictions were applied. Two reviewers used standard risk of bias assessment tools to independently assess articles for inclusion criteria and methodological quality. Disagreements were resolved by consensus discussion. Chest radiography served as the reference standard for the diagnosis of pneumonia. Of the 18 studies that met the inclusion criteria, most were of low to moderate risk of bias. No clinical signs or symptoms reached the level for commonly accepted clinical usefulness (positive likelihood ratio [LR+] > 5 or negative likelihood ratio [LR?] < 0.2). The most useful signs and symptoms for ruling in pneumonia included respiratory rate higher than 50 breaths per minute (LR+ = 1.90; 95% CI 1.45-2.48); grunting (LR+ = 1.78; 1.10-2.88), chest retractions (LR+ = 1.76; 0.86-3.58), and nasal flaring (LR+ = 1.75; 1.20-2.56). The most useful signs and symptoms (when absent) for excluding the diagnosis of pneumonia included cough (LR? = 0.30; 0.09-0.96), history of fever (LR? = 0.53; 0.41-0.69), and respiratory rate higher than 40 breaths per minute (LR? = 0.43; 0.23-0.83).

Bottom line: Standard clinical signs and symptoms are minimally useful in accurately diagnosing pneumonia in children younger than 5 years. The most useful signs and symptoms for ruling in pneumonia included a respiratory rate higher than 50 breaths per minute, grunting, chest retractions, and nasal flaring. The most useful signs and symptoms (when absent) for excluding the diagnosis of pneumonia included cough, history of fever, and a respiratory rate higher than 40 breaths per minute. (LOE = 2a)

Reference: *Rambaud-Althaus C, Althaus F, Genton B, D'Acremont V. Clinical features for diagnosis of pneumonia in children younger than 5 years: A systematic review and meta-analysis. Lancet Infect Dis 2015;15(4):439-450.*

#5: Gut feelings have good negative predictive value for serious infection in children

Clinical question: What is the accuracy of a clinician's gut feelings about the seriousness of illness in children without overt symptoms of serious infection?

Study design: Diagnostic test evaluation **Funding source**: Foundation

Setting: Outpatient (primary care)

Synopsis: Cognitive researchers have found that experienced clinicians make diagnoses using 2 different approaches: either a slow, logical, step-by-step reasoning process, or (more often) a fast, intuitive approach based on recognition of patterns of illness seen in previous cases. This study, conducted in Belgium, evaluated the role of the latter approach, which they called "gut feeling," in the diagnosis of children with possible serious infections. The researchers evaluated 3890 consecutive children aged 0 to 16 years presenting to primary care physicians with acute illness. For each child the doctors recorded clinical features along with their overall clinical impression and whether the doctor had a gut feeling, based on intuition, suggesting the child had something more serious than was suggested by the clinical features. The report doesn't tell us anything about the clinicians but they all seem to be practicing in primary care. After this initial assessment the children were cared for in the usual manner. Serious infection -- defined as requiring hospitalization for pneumonia, sepsis, meningitis, or other infections -- occurred in 21 children (0.54%). Physicians' gut feeling of seriousness was present in 62% of these children but also in 2.7% of children without a serious illness, resulting in a sensitivity of 61.9% and a specificity of 97%. Given the low likelihood of serious infection in the group, though, the positive predictive value was only 10.8% and the negative predictive value was 99.8%. An accurate gut feeling of seriousness was present for 2 the 6 seriously ill children whose clinical features suggested a nonserious illness (positive predictive value = 4.4%; negative predictive value = 99.8%). Individual clinical features strongly associated with a gut feeling of serious illness were the child's lack of responsiveness, abnormal breathing, weight loss, convulsions, and parents' concern.

Bottom line: An intuitive feeling that the objective clinical assessment of a sick child misrepresents the seriousness of his or her illness usually overidentifies serious infection. But, in some cases, this gut feeling is correct. In this study, a parent's concern and nonspecific symptoms in the child (such as drowsiness, abnormal breathing, weight loss, and convulsions) were linked to clinicians' gut feelings of a more serious illness. The authors suggest that you can hone the accuracy of these gut feelings by reflecting on the triggers in the clinical presentation that make you suspicious of something more serious. (LOE = 1c)

Reference: Van den Bruel A, Thompson M, Buntinx F, Mant D. Clinicians' gut feelings about serious infections in children: observational study. BMJ 2012;345:e6144.

#6: CRP and procalcitonin best for dx in febrile children

Clinical question: What is the diagnostic value of laboratory tests for the diagnosis of serious infections in febrile children?

Study design: Meta-analysis (other) **Funding source:** Government

Setting: Outpatient (any)

Synopsis: To conduct this systematic review, the authors searched 4 databases, including DARE, to find studies that evaluated the diagnostic accuracy of tests in febrile outpatient children at least 30 days of age. They identified 14 studies, all of moderate quality or low quality. The prevalence of serious infection ranged from 4.5% to 29.3%. The tests best at ruling in serious infection were C-reactive protein, using a cut-off of 80 mg/L (positive likelihood ratio [LR+] = 8.4; 95% CI, 5.1 - 14.1), and procalcitonin greater than 2 ng/mL (LR+ [from 2 studies] = 3.6 and 13.7; 95% CIs, 7.4 - 25.3 and 1.4 - 8.9). Using a C-reactive protein cutoff of 20 mg/L (negative likelihood ratio [LR-] = .19 - .25) and a procalcitonin cutoff of .5 ng/mL (LR- = .08 - .25) is effective in ruling out serious infection. An elevated white blood cell count is not effective at ruling in or ruling out disease. Combinations of tests did not appreciably improve diagnostic accuracy.

Bottom line: C-reactive protein and procalcitonin are the most effective laboratory tests for ruling in or ruling out serious infections in febrile children. Both tests are better at ruling out than ruling in disease. A white blood cell count is not useful, and other markers of inflammation do not provide good sensitivity or specificity. (LOE = 2a)

Reference: *Van den Bruel A, Thompson MJ, Haj-Hassan T, et al. Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review. BMJ 2011;342:d3082.*

From the authors:

What this study adds

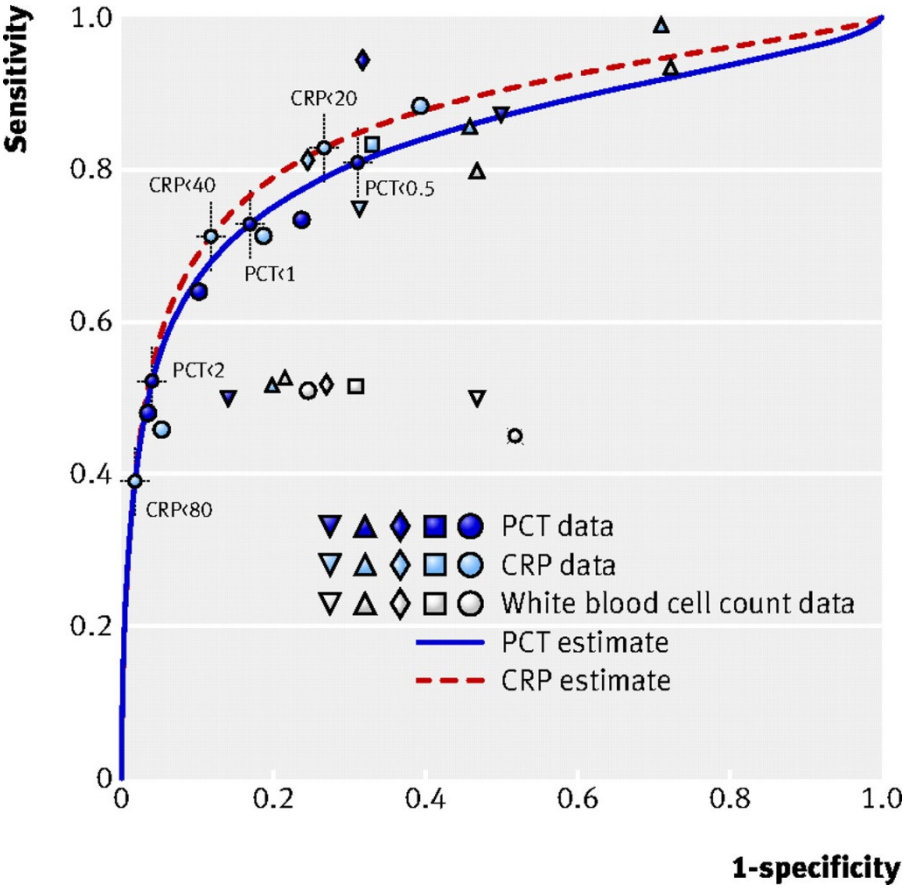
C reactive protein and procalcitonin may be useful measures, but different cut-off values should be used for ruling in or ruling out serious infections

White blood cell counts are less useful

MAJOR CAVEATS:

No evidence from primary care was identified

No studies of high methodologic quality



#7: Risk-based use of CRP preferred for acutely ill children

Clinical question: Should C-reactive protein be used for all acutely ill children, or only for those at high risk of serious infection?

Study design: Randomized controlled trial (nonblinded) **Funding source:** Government

Allocation: Unconcealed **Setting:** Outpatient (primary care)

Synopsis: CRP is an inflammatory biomarker available as a rapid point-of-care test in many countries (it is not CLIA-waived in the United States, though). It has been shown in previous studies to be a good predictor of pneumonia, acute sinusitis, and other bacterial infections. In this study, 133 general practitioners in 78 practices in Belgium were randomized to use universal or selective CRP for acutely ill children. Children aged 1 month to 16 years were eligible for the study if they had been sick for less than 5 days, and if the illness was not due to a traumatic, neurologic, or psychiatric condition, or to poisoning or intoxication. The universal group always ordered a CRP, while the selective group only ordered a CRP when one of the following was present: shortness of breath, fever 40 ℃ or higher, diarrhea (in children 12 to 30 months old), or "physician concern." The primary outcome was whether the child was hospitalized for a serious infection between 1 and 5 days after the index visit. In the selective testing group, 285 of 1417 patients met the criteria for testing, of whom 30 were referred to the hospital and 4 had a serious infection. In the comparison group, 50 were referred to the hospital, of whom 7 had a serious infection. These small differences between groups were not statistically significant. In the selective testing group, a cutoff of 5 mg/L or higher would not have missed any serious infections, but would have resulted in a 57% false positive rate. Among the 24 children with a CRP of less than 5 mg/L who were referred to the hospital, 13 received a final diagnosis of viral upper respiratory tract infection, 3 had a urinary tract infection, and 8 had viral gastroenteritis. Only one of these 24 children were admitted.

Bottom line: Restricting the use of C-reactive protein (CRP) to children with shortness of breath, fever of 40 ℃ or higher, or diarrhea (in 12- to 30-month-olds), or because of "physician concern" is a safe strategy. Of the 24 children who met these criteria and had a CRP level of less than 5 mg/L, 3 had a urinary tract infection and the remainder had a self-limited viral infection. (LOE = 1b-)

Reference: *Verbakel JY, Lemiengre MB, De Burghgraeve T, et al. Should all acutely ill children in primary care be tested with point-of-care CRP: a cluster randomised trial. BMC Medicine 2016;14(1)131.*

What's new with the well child exam?

#8: American Academy of Pediatrics guidelines for hip dysplasia screening and treatment

Clinical question: How should infants be screened and treated for hip dysplasia?

Study design: Practice guideline **Funding source:** Foundation

Setting: Various (guideline)

Synopsis: These guidelines, largely in line with guidelines from the Canadian Task Force and other groups, recommend screening for developmental hip dysplasia through physical examination that includes leg length comparison, examination for asymmetric thigh/gluteal creases, the Ortolani maneuver around the time of birth, and observation for limited abduction after 3 months of age. Though they recommend against universal ultrasonography, they suggest that it be considered between the ages of 6 weeks and 6 months for "high-risk" infants without positive physical findings (though they go on to say that most hip dysplasia occurs in children without risk factors). Evaluation for possible hip dislocation should be performed by an orthopedist. The authors also suggest counseling parents to swaddle the infant in a way that does not restrict hip motion. The guideline developers acknowledge these guidelines are very conservative and err on the side of overdiagnosis; the US Preventive Services Task Force has concluded there is insufficient evidence to support screening. If you find a click or clunk on examination, remember that only 1 in 8 children with positive findings will have dysplasia (Arch Dis Child Fetal Neonatal Ed 2005;90:F25-30).

Bottom line: The American Academy of Pediatrics continues to recommend physical examination for the screening of newborns for developmental hip dysplasia, reserving ultrasound screening for infants at "high risk." A video showing an abnormal Barlow-Ortolani test result can be downloaded at www2.aap.org/sections/ortho/BarlowOrtolani.avi. The authors also suggest counseling parents to swaddle infants in a way that does not restrict hip motion. (LOE = 5)

Reference: Shaw BA, Segal LS, SECTION ON ORTHOPAEDICS. Evaluation and referral for developmental dysplasia of the hip in infants. Pediatrics 2016;138(6):e20163107.

#9: USPSTF 2017 recommends vision screening for all children aged 3 years to 5 years

Clinical question: Should primary care clinicians screen for vision abnormalities in children younger than 6 years?

Study design: Practice guideline **Funding source:** Government

Setting: Population-based

Synopsis: In this updated review the USPSTF evaluated current evidence that assessed the accuracy of vision screening tests and the benefits and harms of vision screening and treatment in children younger than 6 years. The prevalence of amblyopia or its risk factors in this age group is 1% to 6%. No eligible randomized clinical trials directly compared screening with no screening. In addition, no studies evaluated patient-oriented outcomes, such as school performance or quality of life. The task force found adequate evidence that vision-screening tools are accurate for detecting vision abnormalities. Treatment of amblyopia is associated with improved visual acuity in children aged 3 to 5 years. Potential harms of screening include psychosocial problems due to labeling and anxiety (eg, if wearing a patch or eyeglasses is necessary), unnecessary referrals due to false-positive results, and unnecessary treatments. Overall, the task force considered the potential harms of screening and subsequent treatment as small. Trials that examined the benefits and harms of treatment did not enroll children younger than 3 years. The Academy of Pediatrics and Ophthalmology recommend vision assessment in children aged 6 months to 3 years. The American Academy of Family Physicians recommends vision screening in all children at least once between the age of 3 years and 5 years.

Bottom line: The US Preventive Services Task Force (USPSTF) recommends that primary care clinicians perform visual screening at least once for all children aged 3 to 5 years to detect amblyopia or its risk factors (B recommendation). Current evidence is insufficient to assess the benefits and harms of vision screening in children younger than 3 years (I statement). This updated recommendation is essentially unchanged from the previous recommendation in 2011. (LOE = 2b)

Reference: US Preventive Services Task Force, Grossman DC, Curry SJ, et al. Vision screening in children aged 6 months to 5 years. US Preventive Services Task Force recommendation statement. JAMA 2017;318(9):836-844.

#10: Screening for and treating iron deficiency in children: no evidence of benefit or harm

Clinical question: Is there a benefit to screening for iron deficiency in infants and children and in subsequently giving supplements to those found to be deficient?

Study design: Systematic review

Funding source: Government **Setting:** Various (meta-analysis)

Synopsis: Here's the logic trail: Iron deficiency can be identified in approximately 8% of infants and toddlers in the United States; approximately one-third of these children (and 1% to 2% of all children) will have iron-deficiency anemia. However, there is no research that demonstrates either the harm or the benefit of treating iron deficiency or anemia. The researchers searched Medline and the Cochrane databases, as well as reference lists of systematic reviews, to identify English-language clinical trials and observational studies performed in developed countries regarding the screening for iron deficiency and the benefits and harms of iron supplementation in children aged 6 to 24 months. Two investigators evaluated identified studies for inclusion and 2 investigators evaluated included research for quality. They found no studies that evaluated the effect of screening on growth, development, mortality, or quality of life. Iron supplementation had an inconsistent effect on hematologic measures (10 studies). No studies of iron supplementation evaluated the effect on neurodevelopment. Five of 6 weak studies found no clear benefit on growth. No studies have evaluated the harm of iron supplementation.

Bottom line: There is no evidence to support screening for iron deficiency or iron-deficiency anemia in infants and toddlers, and no good research showing a benefit to iron supplementation in identified children. Limited evidence does not show significant harm with supplementation. In both cases -- benefit and harm -- absence of proof is not proof of absence. It would be great to have research that explores these common interventions in children. (LOE = 1a)

Reference: *McDonagh MS, Blazina I, Dana T, Cantor A, Bougatsos C. Screening and routine supplementation for iron deficiency anemia: a systematic review. Pediatrics 2015;135(4):723-733.*

#11: USPSTF: Prevention of dental caries in children

DESCRIPTION: Update of the 2004 US Preventive Services Task Force (USPSTF) recommendation on prevention of dental caries in preschool-aged children.

METHODS: The USPSTF reviewed the evidence on prevention of dental caries by primary care clinicians in children 5 years and younger, focusing on screening for caries, assessment of risk for future caries, and the effectiveness of various interventions that have possible benefits in preventing caries.

POPULATION: This recommendation applies to children age 5 years and younger.

RECOMMENDATION: The USPSTF recommends that primary care clinicians prescribe oral fluoride supplementation starting at age 6 months for children whose water supply is deficient in fluoride. (B recommendation) The USPSTF recommends that primary care clinicians apply fluoride varnish to the primary teeth of all infants and children starting at the age of primary tooth eruption. (B recommendation) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of routine screening examinations for dental caries performed by primary care clinicians in children from birth to age 5 years. (I Statement).

Moyer VA; US Preventive Services Task Force. Prevention of dental caries in children from birth through age 5 years: US Preventive Services Task Force recommendation statement. Pediatrics. 2014 Jun;133(6):1102-11.

#12: USPSTF: Screening for speech and language delay and disorders

BACKGROUND: This report is an update of the US Preventive Services Task Force (USPSTF) 2006 recommendation on screening for speech and language delay in preschool-aged children.

METHODS: The USPSTF reviewed the evidence on screening for speech and language delay and disorders in children aged 5 years or younger, including the accuracy of screening in primary care settings, the role of surveillance by primary care clinicians, whether screening and interventions lead to improved outcomes, and the potential harms associated with screening and interventions.

POPULATION: This recommendation applies to asymptomatic children aged 5 years or younger whose parents or clinicians do not have specific concerns about their speech, language, hearing, or development.

RECOMMENDATION: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for speech and language delay and disorders in children aged 5 years or younger (I statement).

Siu AL; US Preventive Services Task Force. Screening for Speech and Language Delay and Disorders in Children Aged 5 Years or Younger: US Preventive Services Task Force Recommendation Statement. Pediatrics. 2015 Aug;136(2):e474-81.

#13: USPSTF: Screening for autism spectrum disorder in young children

DESCRIPTION: New US Preventive Services Task Force (USPSTF) recommendation on screening for autism spectrum disorder (ASD) in young children.

METHODS: The USPSTF reviewed the evidence on the accuracy, benefits, and potential harms of brief, formal screening instruments for ASD administered during routine primary care visits and the benefits and potential harms of early behavioral treatment for young children identified with ASD through screening.

POPULATION: This recommendation applies to children aged 18 to 30 months who have not been diagnosed with ASD or developmental delay and for whom no concerns of ASD have been raised by parents, other caregivers, or health care professionals.

RECOMMENDATION: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for ASD in young children for whom no concerns of ASD have been raised by their parents or a clinician. (I statement).

Siu AL; US Preventive Services Task Force (USPSTF), Screening for Autism Spectrum Disorder in Young Children: US Preventive Services Task Force Recommendation Statement. JAMA. 2016 Feb 16;315(7):691-6.

#14: Editorial: What to Do at Well-Child Visits: The AAFP's Perspective

Evidence supports the following clinical interventions:

Newborns	Congenital hypothyroidism, screening
	Hearing loss, screening
	Ocular gonorrhea infection, preventive medication
	Phenylketonuria, screening
	Sickle cell disease, screening
Children six months and older	Fluoride supplementation in areas where the primary water source is deficient in fluoride
Children three to five years of age	Visual impairment, screening
School-aged children	Tobacco use, counseling to prevent initiation
Children six years and older	Obesity, screening
Children 10 years and older	Skin cancer, counseling to reduce risk
Children 12 years and older	Depression, screening
Sexually active adolescents	Sexually transmitted infections, counseling to reduce risk
Sexually active adolescent females	Gonorrhea and chlamydia infections, screening
Children at high risk of infection	Hepatitis B virus, screening

“The current AAP Bright Futures guideline includes three screening tests that were not recommended for all children in previous versions: autism screening at 18 and 24 months of age, cholesterol screening between nine and 11 years of age, and annual screening for high blood pressure beginning at three years of age.”

“Time is a precious clinical resource. Clinicians who spend time delivering unproven or ineffective interventions at health maintenance visits risk “crowding out” effective services. For example, a national survey of family and internal medicine physicians regarding adult well-male examination practices found that physicians spent an average of five minutes discussing prostate-specific antigen screening

(a service that the AAFP and the USPSTF recommend against because the harms outweigh the benefits), but one minute or less each on nutrition and smoking cessation counseling. Similarly, family physicians have limited time at well-child visits and therefore should prioritize preventive services that have strong evidence of net benefit."

KENNETH W. LIN, MD, MPH, : Editorial: What to Do at Well-Child Visits: The AAFP's Perspective. Am Fam Physician. 2015 Mar 15;91(6):362-364.

When are tympanostomy tubes recommended for otitis media with effusion? How strong is the evidence they are beneficial?

#15: AHRQ: Otitis Media With Effusion: Comparative Effectiveness of Treatments

Objectives: To compare benefits and harms of strategies currently in use for managing otitis media with effusion (OME). Treatment for OME may include single approaches alone or combinations of two or more approaches. We compared benefits and harms among these treatments: tympanostomy tubes (TT), myringotomy (myr), adenoidectomy (adenoid), autoinflation (auto), oral or nasal steroids, complementary and alternative medicine (CAM), and watchful waiting (WW). We included comparisons of treatment effectiveness in subgroups of patients with OME, and whether outcome differences were related to factors affecting health care delivery or the receipt of pneumococcal vaccine inoculation.

Data sources: We identified five recent systematic reviews a priori and searched MEDLINE, Embase, the Cochrane Library, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), from root through August 13, 2012, for additional studies. Eligible studies included randomized controlled trials (RCTs), nonrandomized trials, and cohort studies.

Review methods: Eligible studies included at least two arms comparing the treatments described above. Pairs of reviewers independently selected, extracted data from, and rated the risk of bias of relevant studies; they graded the strength of evidence using established criteria. We incorporated meta-analyses from the earlier reviews and synthesized additional evidence qualitatively.

Results: We identified 59 studies through the earlier reviews and our independent searches. Generally, studies examined interventions in otherwise healthy, noninfant children. We did not find any eligible studies covering CAM. Findings are reported for clinical and functional outcomes, and harms. Variation in length of TT retention corresponded to whether TT were designed to be short versus long term, but variation in TT type was not related to improved OME and hearing outcomes. TT decreased OME for 2 years compared with WW or myr, and improved hearing for 6 months compared with WW. OME resolution was more likely with adenoid than no treatment at 12 months. Adenoid and myr were superior to myr alone in relation to OME and hearing outcomes at 24 months. Adenoid and TT were superior to WW for hearing outcomes at 24 months. Auto was superior to standard treatment at improving OME at 1 month. We found no benefits from oral steroids at 2 months, or topical steroids at 9 months. In relation to functional outcomes, TT and WW did not differ in long-term language, cognitive or academic outcomes. Tympanosclerosis and otorrhea were more common in ears with TT. Adenoid increased the risk of postsurgical hemorrhage. In one study of a subgroup, adults receiving auto were more likely to recover from OME than those in the control group at one month. We found no studies examining the influence of any health care factors on treatment effectiveness.

Conclusions: There is evidence that both TT and adenoid reduce OME and improve hearing in the short term, but both treatments also have associated harms. Large, well-controlled studies could help resolve the risk-benefit ratio by measuring AOM recurrence, functional outcomes, quality of life measures, and long-term outcomes. Finally, additional research is needed to support treatment decisions in subpopulations, particularly those with comorbidities and those who have received a pneumococcal vaccine inoculation.Reference: Berkman ND, Wallace IF, Steiner MJ, Harrison M, Greenblatt AM, Lohr KN, Kimple A, Yuen A. Otitis Media With Effusion: Comparative Effectiveness of Treatments. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 May. Report No.: 13-EHC091-EF. AHRQ Comparative Effectiveness Reviews.

#16: Clinical practice guideline: Tympanostomy tubes in children.

Objective: Insertion of tympanostomy tubes is the most common ambulatory surgery performed on children in the United States. Tympanostomy tubes are most often inserted because of persistent middle ear fluid, frequent ear infections, or ear infections that persist after antibiotic therapy. Despite the frequency of tympanostomy tube insertion, there are currently no clinical practice guidelines in the United States that address specific indications for surgery. This guideline is intended for any clinician involved in managing children, aged 6 months to 12 years, with tympanostomy tubes or being considered for tympanostomy tubes in any care setting, as an intervention for otitis media of any type.

Purpose: The primary purpose of this clinical practice guideline is to provide clinicians with evidence-based recommendations on patient selection and surgical indications for and management of tympanostomy tubes in children. The development group broadly discussed indications for tube placement, perioperative management, care of children with indwelling tubes, and outcomes of tympanostomy tube surgery. Given the lack of current published guidance on surgical indications, the group focused on situations in

which tube insertion would be optional, recommended, or not recommended. Additional emphasis was placed on opportunities for quality improvement, particularly regarding shared decision making and care of children with existing tubes.

ACTION STATEMENTS: The development group made a strong recommendation that clinicians should prescribe topical antibiotic eardrops only, without oral antibiotics, for children with uncomplicated acute tympanostomy tube otorrhea. The panel made recommendations that (1) clinicians should not perform tympanostomy tube insertion in children with a single episode of otitis media with effusion (OME) of less than 3 months' duration; (2) clinicians should obtain an age-appropriate hearing test if OME persists for 3 months or longer (chronic OME) or prior to surgery when a child becomes a candidate for tympanostomy tube insertion; (3) clinicians should offer bilateral tympanostomy tube insertion to children with bilateral OME for 3 months or longer (chronic OME) and documented hearing difficulties; (4) clinicians should reevaluate, at 3- to 6-month intervals, children with chronic OME who did not receive tympanostomy tubes until the effusion is no longer present, significant hearing loss is detected, or structural abnormalities of the tympanic membrane or middle ear are suspected; (5) clinicians should not perform tympanostomy tube insertion in children with recurrent acute otitis media (AOM) who do not have middle ear effusion in either ear at the time of assessment for tube candidacy; (6) clinicians should offer bilateral tympanostomy tube insertion to children with recurrent AOM who have unilateral or bilateral middle ear effusion at the time of assessment for tube candidacy; (7) clinicians should determine if a child with recurrent AOM or with OME of any duration is at increased risk for speech, language, or learning problems from otitis media because of baseline sensory, physical, cognitive, or behavioral factors; (8) in the perioperative period, clinicians should educate caregivers of children with tympanostomy tubes regarding the expected duration of tube function, recommended follow-up schedule, and detection of complications; (9) clinicians should not encourage routine, prophylactic water precautions (use of earplugs, headbands; avoidance of swimming or water sports) for children with tympanostomy tubes. The development group provided the following options: (1) clinicians may perform tympanostomy tube insertion in children with unilateral or bilateral OME for 3 months or longer (chronic OME) and symptoms that are likely attributable to OME including, but not limited to, vestibular problems, poor school performance, behavioral problems, ear discomfort, or reduced quality of life and (2) clinicians may perform tympanostomy tube insertion in at-risk children with unilateral or bilateral OME that is unlikely to resolve quickly as reflected by a type B (flat) tympanogram or persistence of effusion for 3 months or longer (chronic OME).

Reference: Rosenfeld RM[1], Schwartz SR, Pynnonen MA, Tunkel DE, Hussey HM, Fichera JS, Grimes AM, Hackell JM, Harrison MF, Haskell H, Haynes DS, Kim TW, Lafreniere DC, LeBlanc K, Mackey WL, Netterville JL, Pipan ME, Raol NP, Schellhase KG.*Clinical practice guideline: Tympanostomy tubes in children.* Otolaryngol Head Neck Surg. *2013 Jul;149(1 Suppl):S1-35. doi: 10.1177/0194599813487302.*

#17: Prompt tympanostomy tube insertion doesn't improve 9 yr outcomes

Clinical question: Does the delayed insertion of tympanostomy tubes impair the long-term outcomes in children with persistent middle-ear effusion?
Study design: Randomized controlled trial (single-blinded) **Setting:** Outpatient (any)
Synopsis: Many parents and clinicians still believe that there is a significant risk of permanent harm if tympanostomy tubes are not promptly inserted for children with persistent middle-ear effusion. In this study, which is a follow-up to a previously published POEM (N Engl J Med 2005;353:576), 429 children between the ages of 2 months and 3 years with middle-ear effusion for at least 90 days (bilateral) or 135 days (unilateral) were randomized to receive either prompt or delayed tympanostomy tube insertion. The delay was 6 months for bilateral effusion and 9 months for unilateral effusion. Allocation was concealed, groups were balanced at the start of the study, and analysis was by intention to treat. The researchers did an excellent job of following up: 195 of 216 in the early treatment group and 196 of 213 in the delayed treatment group underwent developmental testing between the ages of 9 years and 11 years. At the time of this final evaluation, 86% in the early treatment group had received tympanostomy tubes compared with only 49% in the delayed treatment group. There was no differences between groups in the results of a broad range of tests including evaluation of hearing, reading, oral fluency, auditory processing, phonological processing, behavior, or intelligence. There was also no difference between these groups and a group of children with ear problems that weren't bad enough to qualify them for the study.
Bottom line: Delayed tympanostomy tube insertion successfully helps many children avoid tubes and does not result in any developmental or other impairment. (LOE = 1b)
Reference: *Paradise JL, Feldman HM, Campbell TF, et al. Tympanostomy tubes and developmental outcomes at 9 to 11 years of age. N Engl J Med 2007;356:248-261.*

There is evidence that tympanostomy tubes are substantially overused. According to a 2008 cohort study in the BMJ (Keyhani, et al, Oct 3 2008), only 30% of tube insertions met criteria based on any guideline in the New York City metropolitan area. The authors concluded:

"A significant majority of tympanostomy tube insertions in the largest and most populous metropolitan area in the United States were inappropriate according to the explicit criteria and not recommended according to both guidelines. Regardless of whether current practice represents a substantial overuse of surgery or the guidelines are overly restrictive, the persistent discrepancy between guidelines and practice cannot be good for children or for people interested in improving their health care."

#18: Tubes ineffective for treating otitis media in children

Clinical question: In children with recurrent otitis media or chronic effusion, do tympanostomy tubes decrease further episodes, improve hearing, or improve language acquisition?

Study design: Meta-analysis (other) **Funding source:** Government

Setting: Various (meta-analysis)

Synopsis: These researchers searched 4 databases, including Cochrane CENTRAL, to find randomized controlled trials and other comparative research studies that evaluated the effectiveness of tympanostomy tubes. They included research written in any language. Citations were selected by 2 independent researchers. Study details were abstracted by one researcher and checked by a second researcher. In 16 randomized controlled trials of treating children with otitis media with effusion, the insertion of tubes with or without adenoidectomy decreased (improved) hearing threshold within the first 1 month to 3 months by an average 9.1 dB to 10.0 dB as compared with no treatment. However, there was no effect on hearing thresholds at 12 months to 24 months for tympanostomy alone or combined with adenoidectomy, prophylactic antibiotic treatment, or myringotomy as compared with no treatment. Overall, there was no effect on cognitive, language, and behavioral outcomes. In 3 small studies of children with recurrent acute otitis media the effect of tympanostomy tubes was inconsistent regarding recurrences. This analysis was a Bayesian network analysis, a statistical approach that still has some kinks in it, and the study report itself was somewhat incomplete, as is the evidence base for this common intervention.

Bottom line: Tympanostomy tubes, with or without other interventions, do not produce sustained improved hearing as compared with no treatment, and has not been shown to improve language acquisition, cognitive development, or behavior measures. There might be a small reduction in the recurrence of acute otitis media, but there is little research in this area. Another study of tubes found no long-term (6 years to 9 years) benefit on development (N Engl J Med 2007;356:248-261). (LOE = 1a-)

Reference: *Steele DW, Adam GP, Di M, Halladay CW, Balk EM, Trikalinos TA. Effectiveness of tympanostomy tubes for otitis media: a meta-analysis. Pediatrics 2017;139(6):e20170125*

#19: Surface swimming all right with tympanostomy tubes

Clinical question: What precautions, if any, are required to decrease the incidence of otorrhea in children with tympanostomy tubes?
Study design: Non-randomized controlled trial **Setting:** Outpatient (any)
Synopsis: Five hundred thirty-three children who were undergoing placement of tympanostomy tubes were enrolled in the study. Of those enrolled, only 399 had comprehensive follow-up. Clinical examination occurred two weeks after the procedure and then every 3 months until the tubes were extruded. Parents were asked to recall the number of episodes of otorrhea for their children and the relationship of otorrhea to swimming, bathing, and upper respiratory infections (URIs). The authors report only the total percentage of subjects who developed otorrhea. A child who swam once and developed otorrhea was counted the same as a child who went swimming on multiple occasions and developed otorrhea once. It was not possible therefore to calculate the risk of otorrhea based on the amount of exposure. Parents self-selected one of four interventions for their children: 1) swimming allowed with no precautions, 2) swimming allowed with no precautions, but on days with water exposure three drops of a suspension of polymyxin B sulfate, neomycin sulfate, and hydrocortisone were instilled into each ear before bedtime, 3) swimming allowed only with custom-molded ear plugs, and 4) swimming not allowed. Diving or swimming more than 180 cm (approximately 6 feet) below the surface was discouraged for all subjects. The groups differed by age (mean age of 29, 31, 60, and 26 months for groups 1, 2, 3, and 4, respectively). No other comparisons between the groups were given such as gender or the performance of simultaneous tonsillectomy or adenoidectomy. No reason was given for subjects that were lost to follow-up (25%). There were no comparisons between those in the study and those lost to follow-up. No power calculations were performed so it is uncertain if there were sufficient subjects in each group to show a statistically significant difference between the groups, if one truly existed. Most episodes of otorrhea were related to URIs and not to swimming. There was no difference between the three swimming groups with respect to swimming-related, URIs-related or bathing-related otorrhea. Although not statistically significant, swimming children using ear molds were nearly twice as likely to report otorrhea compared with children using no precautions (20 percent vs. 11 percent). Nonswimmers had a lower overall incidence of otorrhea (59%) than the swimming groups (68%), but this difference was not statistically significant. The place of swimming (pool, ocean, lake, river) did not make a significant difference on the incidence of swimming-related otorrhea.
Bottom line: Preventing children from swimming during the hot summer months may cause considerable family strife and should not be mandated without clear evidence of harm. Allowing surface swimming without specific precautions for children with tubes is a reasonable approach until there is evidence to the contrary. (LOE = 3b)
Reference: *Salata JA, Derkay CS. Water precautions in children with tympanostomy tubes. Arch Otolaryngol Head Neck Surg 1996;122:276-80.*

#20: Antibiotic/steroid drops best treatment for otorrhea in afebrile kids with tympanostomy tubes

Clinical question: In children with tympanostomy tubes, what is the best treatment for acute otorrhea?
Study design: Randomized controlled trial (double-blinded) **Setting:** Outpatient (any)
Synopsis: These researchers identified children with TT who had at least 7 days of otorrhea symptoms; excluded were any kids with temperature > 38.5 C, and any with recent TT placement, recent episode of otorrhea, recent antibiotics, or secondary cause such as immunodeficiency or craniofacial abnormality. Patients were recruited, and either immediately enrolled in the trial if currently

symptomatic or the parents were asked to call in if the child became symptomatic. Of 1133 children who were registered for the study, 886 did not report an episode of otorrhea and 247 had home visits for otorrhea. After excluding those with fever, 230 children were randomized to 1 of 3 groups: (1) hydrocortisone-bacitracin-colistin eardrops -- 5 drops given 3 times daily for 7 days; (2) oral amoxicillin-clavulanate -- 30 mg/7.5 mg per kilogram divided into 3 daily doses for 7 days; or (3) observation only for 2 weeks. The patients' mean age was 4.5 years, 58% were male, and 17% had bilateral symptoms. Patients or parents kept a symptom diary for 6 months, and the children were examined in their home by a study physician at 2 weeks and at 6 months. Adherence to to the assigned treatment, or lack thereof, was best for eardrops (93%), then for oral antibiotics (88%), and least for observation (79%); analysis was by intention to treat. The primary outcome was persistent otorrhea at 2 weeks, and was much less common with the eardrops than with oral antibiotics or observation (5% vs 44% vs 55%; P < .05; number needed to treat = 2). The median duration of otorrhea was 4 days with eardrops, 5 days with antibiotics, and 12 days with observation. There was also a median of 1 fewer recurrence in the eardrop group than in the oral antibiotic group (P = 0.03). Gastrointestinal symptoms were fairly common in children receiving an oral antibiotic, and pain with eardrop administration was also common. No complications or serious adverse events were reported. Note that the specific antibiotic combination studied is only available in Europe. Also, the dose of amoxicillin used was lower than typically used in the United States (30 mg/kg divided 3 times a day instead of 80 to 90 mg/kg divided 3 times a day).
Bottom line: For nonfebrile children aged 1 year to 10 years with tympanostomy tubes (TT) and at least 1 week of otorrhea symptoms, a combination hypdrocortisone-bacitracin-colistin eardrop is the best initial therapy. (LOE = 1b)
Reference: *van Dongen TM, van der Heijden GJ, Venekamp RP, Rovers MM, Schilder AG. A trial of treatment for acute otorrhea in children with tympanostomy tubes. N Engl J Med 2014;370(8):723-733.*

Bottom Lines

1. Clinical signs and symptoms of serious infection can be unreliable in children; your "gut feeling" may be the most useful
2. There may be a limited role for CRP in diagnosing serious infection in children, but there are no high quality studies in primary care settings.
3. Well child exams should be evidence based; there is insufficient evidence for many interventions currently recommended by experts
4. Evidence to support tympanostomy tubes in children with otitis media with effusion is weak, but they may be indicated in children with effusion and 3 months of hearing loss.

Vitamins: to take or not to take, that is the question

John Hickner MD, MSc

Objectives

1. Know the value of a variety of vitamins for prevention and disease treatment

2. Know the conditions for which Vitamin D supplementation is effective or ineffective or unknown

Vitamin supplementation other than Vitamin D

Vitamins are a multi-billion dollar business. Unfortunately, solid evidence from RCTs for effectiveness of vitamin therapy is scarce. Here are a few studies about vitamins published in the past few years. There is not a whole lot that is new, other than Vitamin D, which is the current darling child of vitamin researchers.

1. B vitamins produce small increase in sustained depression remission

Clinical question: Does B vitamin supplementation enhance response to antidepressants?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Drawing on epidemiologic research that found a relationship between B vitamin deficiency and anemia with depression, the authors of this Australian study tested a B vitamin supplement on 153 patients. The patients were referred by their primary care physician or were drawn from a survey of adults who were found to have moderate depression but were not yet being treated. The patients were randomly assigned, using concealed allocation, to treatment with citalopram plus a combination of 0.5 mg vitamin B12, 2 mg folic acid, and 25 mg vitamin B6, or to citalopram plus placebo. Citalopram doses were adjusted to a maximum of 40 mg daily. Citalopram was continued, or the antidepressant was changed, for 9 months in patients who achieved remission, at the discretion of the treating physician, and B vitamin or placebo was continued. Remission (resolution of depression scores) within 3 months occurred in approximately 78% of patients in both groups. However, more patients who were taking the supplement were in remission after 1 year (85.5% vs 75.8%). A few caveats: The study was small, patients had more severe depression than typically seen in primary care, and the response to the antidepressant in both groups was higher than is typical.
Bottom line: The addition of B vitamins -- cyanocobalamin, thiamine, and folate -- to antidepressant medication in patients with moderate depression does not improve the initial response rate but increases the percentage of patients in remission after 1 year. This effect was more pronounced in patients with higher baseline homocysteine levels, a marker of low B vitamin status. The effect in this study was small, but given their low expense and low risk B vitamin supplements could be tried in some patients.
Almeida OP, Ford AH, Hirani, V, et al. B vitamins to enhance treatment response to antidepressants in middle-aged and older adults: results from the B-VITAGE randomised, double-blind, placebo-controlled trial. Br J Psychiatry 2014;205(6):450-457. doi: 10.1192/bjp.bp.114.145177.

2. Nicotinamide reduces recurrent non-melanoma skin cancers in high-risk patients

Clinical question: Does nicotinamide reduce the likelihood of new nonmelanoma skin cancers in high-risk patients?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (specialty)
Synopsis: Previous studies have shown that nicotinamide (vitamin B3) may improve cell repair and can reduce the likelihood of actinic keratoses. In this Australian study (Australia, with its combination of pale inhabitants and lots of sun, is the epicenter of skin cancer), 386 adults with at least 2 previous nonmelanoma skin cancers (NMSC) were randomized to receive nicotinamide 500 mg twice daily or matching placebo. Patients who were immunosuppressed, pregnant, who had significant comorbidities, or were currently taking medications for actinic keratosis (eg, fluorouracil) were excluded. The patients' mean age at enrollment was 66 years, 63% were men, and 47% were never smokers. These folks had a lot of skin cancers: a mean of 8 NMSC (6 basal cell and 2 squamous cell) in the previous 5 years. Clearly, this was a very high-risk group. They were evaluated every 3 months by dermatologists masked to treatment assignment, and followed up for 12 months. The mean number of new NMSC during the year of active treatment was lower with nicotinamide (1.8 vs 2.4; P = .02), with a trend toward both fewer basal cell cancers (1.3 vs 1.7; P = .12) and squamous cell cancers (0.5 vs 0.7; P = .05). The relative reduction was 23%. During the 6 months after the intervention the benefit went away, with no differences between groups. There was no difference between groups in melanomas or serious adverse events.
Bottom line: For patients at very high risk of nonmelanoma skin cancers (NMSC), with a mean of 8 such cancers in the previous 5 years, nicotinamide 500 mg twice daily provides a modest reduction of 0.6 fewer lesions in 12 months of treatment.
Chen AC, Martin AJ, Choy B, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. N Engl J Med 2015;373(17):1618-1626.

3. Carotenoids and omega-3 fatty acids do not effect rate of cognitive function decline

Clinical question: Can an increased dietary intake of carotenoids (lutein plus zeaxanthin), omega-3 fatty acids, or both, reduce the rate of cognitive function decline in adults with age-related macular degeneration?
Study design: Systematic review
Setting: Outpatient (specialty)
Synopsis: Previous studies from the Age-Related Eye Disease Study (AREDS) reported that adding the carotenoids lutein and zeaxanthin and/or omega-3 fatty acids as daily oral supplements to standard antioxidant vitamins and minerals did not further reduce the risk of advanced AMD. As part of the AREDS these investigators identified adults, aged 50 to 85 years, at high risk for progression to advanced AMD with either bilateral large drusen or large drusen in one eye and advanced AMD in the other eye. Consenting patients (N = 3741) eligible for an add-on cognitive function study randomly received assignment (concealed allocation assignment) to 1 of 4 treatment groups: (1) omega-3 fatty acids (1g), (2) the carotenoids lutein (10 mg) and zeaxanthin (2 mg), (3) both the omega-3s and the carotenoids, or (4) matched placebo. All patients were also given varying combinations of vitamins C, E, beta carotene, and zinc. Individuals who assessed outcomes using a standard cognitive function battery test remained masked to treatment group assignment. Testing occurred 3 months after randomization and then approximately every 2 years. Follow-up with at least 2 interviews occurred for 93% of participants. Using intention-to-treat analysis, the authors found no significant differences between the treatment groups in the rate of cognitive function decline for a mean of 4.9 years. Similarly, no significant difference in cognitive function decline occurred in high-zinc versus low-zinc groups nor in groups with or without beta carotene. Multiple analyses were performed to adjust for potential confounding factors, including age, sex, race, education, depression, and history of hypertension. No clinically significant differences in reported serious adverse events occurred. The study was adequately powered to have a 85% chance of detecting a pre-determined clinically significant difference between the treatment groups.
Bottom line: Adding the carotenoids lutein and zeaxanthin and/or omega-3 fatty acids as daily oral supplements to standard antioxidant vitamins and minerals did not reduce the rate of cognitive function decline in adults with advanced age-related macular degeneration (AMD). A similar study in the same issue also found no benefit to moderate-intensity physical activity in reducing cognitive function decline in the elderly.
Chew EY, Clemons TE, Agron E, et al, for the Age-Related Eye Disease Study 2 (AREDS2) Research Group. Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function. The AREDS2 randomized clinical trial. JAMA 2015;314(8):791-801.

4. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration: Cochrane

Background: It has been proposed that antioxidants may prevent cellular damage in the retina by reacting with free radicals that are produced in the process of light absorption. Higher dietary levels of antioxidant vitamins and minerals may reduce the risk of progression of age-related macular degeneration (AMD).
Objectives: The objective of this review was to assess the effects of antioxidant vitamin or mineral supplementation on the progression of AMD in people with AMD.
Search methods: We searched CENTRAL (2017, Issue 2), MEDLINE Ovid (1946 to March 2017), Embase Ovid (1947 to March 2017), AMED (1985 to March 2017), OpenGrey (System for Information on Grey Literature in Europe, the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 29 March 2017.
Selection criteria: We included randomised controlled trials (RCTs) that compared antioxidant vitamin or mineral supplementation (alone or in combination) to placebo or no intervention, in people with AMD.
Data collection and analysis: Both review authors independently assessed risk of bias in the included studies and extracted data. One author entered data into RevMan 5; the other author checked the data entry. We graded the certainty of the evidence using GRADE.
Main results: We included 19 studies conducted in USA, Europe, China, and Australia. We judged the trials that contributed data to the review to be at low or unclear risk of bias.Nine studies compared multivitamins with placebo (7 studies) or no treatment (2 studies) in people with early and moderate AMD. The duration of supplementation and follow-up ranged from nine months to six years; one trial followed up beyond two years. Most evidence came from the Age-Related Eye Disease Study (AREDS) in the USA. People taking antioxidant vitamins were less likely to progress to late AMD (odds ratio (OR) 0.72, 95% confidence interval (CI) 0.58 to 0.90; 2445 participants; 3 RCTs; moderate-certainty evidence). In people with very early signs of AMD, who are at low risk of progression, this would mean that there would be approximately 4 fewer cases of progression to late AMD for every 1000 people taking vitamins (1 fewer to 6 fewer cases). In people at high risk of progression (i.e. people with moderate AMD) this would correspond to approximately 8 fewer cases of progression for every 100 people taking vitamins (3 fewer to 13 fewer). In one study of 1206 people, there was a lower risk of progression for both neovascular AMD (OR 0.62, 95% CI 0.47 to 0.82; moderate-certainty evidence) and geographic atrophy (OR 0.75, 95% CI 0.51 to 1.10; moderate-certainty evidence) and a lower risk of losing 3 or more lines of visual acuity (OR 0.77, 95% CI 0.62 to 0.96; 1791 participants; moderate-certainty evidence). Low-certainty evidence from one study of 110 people suggested higher quality of life scores (National Eye Institute Visual Function Questionnaire) in treated compared with the non-treated people after 24 months (mean difference (MD) 12.30, 95% CI 4.24 to 20.36). Six studies compared lutein (with or without zeaxanthin) with placebo. The duration of supplementation and follow-up ranged from six months to five years. Most evidence came from the AREDS2 study in the USA. People taking lutein or zeaxanthin may have similar or slightly reduced risk of progression to late AMD (RR 0.94, 95% CI 0.87 to 1.01; 6891 eyes; low-certainty evidence), neovascular AMD (RR 0.92, 95% CI 0.84 to 1.02; 6891 eyes; low-certainty evidence), and geographic atrophy (RR 0.92, 95% CI 0.80 to 1.05; 6891 eyes; low-certainty evidence). A similar risk of progression to visual loss of 15

or more letters was seen in the lutein and control groups (RR 0.98, 95% CI 0.91 to 1.05; 6656 eyes; low-certainty evidence). Quality of life (measured with Visual Function Questionnaire) was similar between groups in one study of 108 participants (MD 1.48, 95% -5.53 to 8.49, moderate-certainty evidence). One study, conducted in Australia, compared vitamin E with placebo. This study randomised 1204 people to vitamin E or placebo, and followed up for four years. Participants were enrolled from the general population; 19% had AMD. The number of late AMD events was low (N = 7) and the estimate of effect was uncertain (RR 1.36, 95% CI 0.31 to 6.05, very low-certainty evidence). There were no data on neovascular AMD or geographic atrophy.There was no evidence of any effect of treatment on visual loss (RR 1.04, 95% CI 0.74 to 1.47, low-certainty evidence). There were no data on quality of life. Five studies compared zinc with placebo. The duration of supplementation and follow-up ranged from six months to seven years. People taking zinc supplements may be less likely to progress to late AMD (OR 0.83, 95% CI 0.70 to 0.98; 3790 participants; 3 RCTs; low-certainty evidence), neovascular AMD (OR 0.76, 95% CI 0.62 to 0.93; 2442 participants; 1 RCT; moderate-certainty evidence), geographic atrophy (OR 0.84, 95% CI 0.64 to 1.10; 2442 participants; 1 RCT; moderate-certainty evidence), or visual loss (OR 0.87, 95% CI 0.75 to 1.00; 3791 participants; 2 RCTs; moderate-certainty evidence). There were no data reported on quality of life.Very low-certainty evidence was available on adverse effects because the included studies were underpowered and adverse effects inconsistently reported.
Authors' conclusions: People with AMD may experience some delay in progression of the disease with multivitamin antioxidant vitamin and mineral supplementation. This finding was largely drawn from one large trial, conducted in a relatively well-nourished American population. We do not know the generalisability of these findings to other populations. Although generally regarded as safe, vitamin supplements may have harmful effects. A systematic review of the evidence on harms of vitamin supplements is needed. Supplements containing lutein and zeaxanthin are heavily marketed for people with age-related macular degeneration but our review shows they may have little or no effect on the progression of AMD.
Reference: Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database of Systematic Reviews 2017, Issue 7. Art. No.: CD000254.

5. Vitamin E for Alzheimer's dementia and mild cognitive impairment

Background: Vitamin E occurs naturally in the diet. It has several biological activities, including functioning as an antioxidant to scavenge toxic free radicals. Evidence that free radicals may contribute to the pathological processes behind cognitive impairment has led to interest in the use of vitamin E supplements to treat mild cognitive impairment (MCI) and Alzheimer's disease (AD). This is an update of a Cochrane Review first published in 2000, and previously updated in 2006 and 2012.
Objectives: To assess the efficacy of vitamin E in the treatment of MCI and dementia due to AD.
Search methods: We searched the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (ALOIS), the Cochrane Library, MEDLINE, Embase, PsycINFO, CINAHL, LILACS as well as many trials databases and grey literature sources on 22 April 2016 using the terms: "Vitamin E", vitamin-E, alpha-tocopherol.
Selection criteria: We included all double-blind, randomised trials in which treatment with any dose of vitamin E was compared with placebo in people with AD or MCI.
Data collection and analysis: We used standard methodological procedures according to the *Cochrane Handbook for Systematic Reviews of Interventions*. We rated the quality of the evidence using the GRADE approach. Where appropriate we attempted to contact authors to obtain missing information.
Main results: Four trials met the inclusion criteria, but we could only extract outcome data in accordance with our protocol from two trials, one in an AD population (n = 304) and one in an MCI population (n = 516). Both trials had an overall low to unclear risk of bias. It was not possible to pool data across studies owing to a lack of comparable outcome measures. In people with AD, we found no evidence of any clinically important effect of vitamin E on cognition, measured with change from baseline in the Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog) over six to 48 months (mean difference (MD) -1.81, 95% confidence interval (CI) -3.75 to 0.13, P = 0.07, 1 study, n = 272; moderate quality evidence). There was no evidence of a difference between vitamin E and placebo groups in the risk of experiencing at least one serious adverse event over six to 48 months (risk ratio (RR) 0.86, 95% CI 0.71 to 1.05, P = 0.13, 1 study, n = 304; moderate quality evidence), or in the risk of death (RR 0.84, 95% CI 0.52 to 1.34, P = 0.46, 1 study, n = 304; moderate quality evidence). People with AD receiving vitamin E showed less functional decline on the Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory than people receiving placebo at six to 48 months (mean difference (MD) 3.15, 95% CI 0.07 to 6.23, P = 0.04, 1 study, n = 280; moderate quality evidence). There was no evidence of any clinically important effect on neuropsychiatric symptoms measured with the Neuropsychiatric Inventory (MD -1.47, 95% CI -4.26 to 1.32, P = 0.30, 1 study, n = 280; moderate quality evidence). We found no evidence that vitamin E affected the probability of progression from MCI to probable dementia due to AD over 36 months (RR 1.03, 95% CI 0.79 to 1.35, P = 0.81, 1 study, n = 516; moderate quality evidence). Five deaths occurred in each of the vitamin E and placebo groups over the 36 months (RR 1.01, 95% CI 0.30 to 3.44, P = 0.99, 1 study, n = 516; moderate quality evidence). We were unable to extract data in accordance with the review protocol for other outcomes. However, the study authors found no evidence that vitamin E differed from placebo in its effect on cognitive function, global severity or activities of daily living . There was also no evidence of a difference between groups in the more commonly reported adverse events.
Authors' conclusions: We found no evidence that the alpha-tocopherol form of vitamin E given to people with MCI prevents progression to dementia, or that it improves cognitive function in people with MCI or dementia due to AD. However, there is moderate quality evidence from a single study that it may slow functional decline in AD. Vitamin E was not associated with an increased risk of serious adverse events or mortality in the trials in this review. These conclusions have changed since the previous update, however they are still based on small numbers of trials and participants and further research is quite likely to affect the results.
***Reference**: Farina N, Llewellyn D, Isaac MGEKN, Tabet N. Vitamin E for Alzheimer's dementia and mild cognitive impairment. Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD002854. DOI: 10.1002/14651858.CD002854.pub5.*

6. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial

CONTEXT: Multivitamin preparations are the most common dietary supplement, taken by at least one-third of all US adults. Observational studies have not provided evidence regarding associations of multivitamin use with total and site-specific cancer incidence or mortality.
OBJECTIVE: To determine whether long-term multivitamin supplementation decreases the risk of total and site-specific cancer events among men.
DESIGN, SETTING, AND PARTICIPANTS: A large-scale, randomized, double-blind, placebo controlled trial (Physicians" Health Study II) of 14 641 male US physicians initially aged 50 years or older (mean [SD] age, 64.3 [9.2] years), including 1312 men with a history of cancer at randomization, enrolled in a common multivitamin study that began in 1997 with treatment and follow-up through June 1, 2011.
INTERVENTION: Daily multivitamin or placebo.
MAIN OUTCOME MEASURES: Total cancer (excluding nonmelanoma skin cancer), with prostate, colorectal, and other site-specific cancers among the secondary end points.
RESULTS: During a median (interquartile range) follow-up of 11.2 (10.7-13.3) years, there were 2669 men with confirmed cancer, including 1373 cases of prostate cancer and 210 cases of colorectal cancer. Compared with placebo, men taking a daily multivitamin had a statistically significant reduction in the incidence of total cancer (multivitamin and placebo groups, 17.0 and 18.3 events, respectively, per 1000 person-years; hazard ratio [HR], 0.92; 95% CI, 0.86-0.998; P=.04). There was no significant effect of a daily multivitamin on prostate cancer (multivitamin and placebo groups, 9.1 and 9.2 events, respectively, per 1000 person-years; HR, 0.98; 95% CI, 0.88-1.09; P=.76), colorectal cancer (multivitamin and placebo groups, 1.2 and 1.4 events, respectively, per 1000 person-years; HR, 0.89; 95% CI, 0.68-1.17; P=.39), or other site-specific cancers. There was no significant difference in the risk of cancer mortality (multivitamin and placebo groups, 4.9 and 5.6 events, respectively, per 1000 person-years; HR, 0.88; 95% CI, 0.77-1.01; P=.07). Daily multivitamin use was associated with a reduction in total cancer among 1312 men with a baseline history of cancer (HR, 0.73; 95% CI, 0.56-0.96; P=.02), but this did not differ significantly from that among 13 329 men initially without cancer (HR, 0.94; 95% CI, 0.87-1.02; P=.15; P for interaction=.07).
CONCLUSION: In this large prevention trial of male physicians, daily multivitamin supplementation modestly but significantly reduced the risk of total cancer.
***Reference**: Gaziano JM1, Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, Schvartz M, Manson JE, Glynn RJ, Buring JE. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA. 2012 Nov 14;308(18):1871-80.*

7. Vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer: U.S. Preventive services Task Force recommendation statement

DESCRIPTION: Update of the 2003 U.S. Preventive Services Task Force (USPSTF) recommendation on vitamin supplementation to prevent cardiovascular disease and cancer.
METHODS: The USPSTF reviewed the evidence on the efficacy of multivitamin or mineral supplements in the general adult population for the prevention of cardiovascular disease and cancer.
POPULATION: This recommendation applies to healthy adults without special nutritional needs (typically aged 50 years or older). It does not apply to children, women who are pregnant or may become pregnant, or persons who are chronically ill or hospitalized or have a known nutritional deficiency.
RECOMMENDATION: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of multivitamins for the prevention of cardiovascular disease or cancer. (I statement). The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of single- or paired-nutrient supplements (except β-carotene and vitamin E) for the prevention of cardiovascular disease or cancer. (I statement). The USPSTF recommends against β-carotene or vitamin E supplements for the prevention of cardiovascular disease or cancer. (D recommendation).
***Reference**: Moyer VA; U.S. Preventive Services Task Force. Vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer: U.S. Preventive services Task Force recommendation statement. Ann Intern Med. 2014 Apr 15;160(8):558-64.*

Vitamin D as a Medication

Vitamin D's popularity as a therapy is booming. A PubMed search of "vitamin D supplementation" in December of 2017 yielded 5,776 clinical studies and 683 systematic reviews. The good news is that, although the benefits are small, there is evidence that Vitamin D therapy is useful for more than bone health. Following are some of the new findings, both positive and negative. These studies are not so much about achieving an adequate vitamin D level ("adequate level" is controversial) but about using vitamin D as a medication to improve outcomes of specific conditions. There is hardly an affliction that affects humans for which Vitamin D has not been tested. I have not included all the negative trials,

such as those for liver disease (no effects). Vitamin D therapy for vascular disease and cancer has not yet been adequately studied, but most RCTs to date have been negative. The very large trial underway should have definitive results in about 5 years. Vitamin D combined with calcium has very modest effects on fracture prevention, but we will not present data about bones in this chapter.

Respiratory Tract Infections and Asthma

8. Bolus dosing of Vitamin D does not prevent ARTI or asthma exacerbation in vitamin D–deficient patients

Clinical question: Does vitamin D supplementation improve asthma symptoms?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Ah, vitamin D. You are such a good marker of bad health, yet supplementing you seems to have so little effect. For example, lots of observational studies have found an association between low vitamin D levels and a high rate of acute respiratory tract infections (ARTI). This is the first randomized trial to test the hypothesis that vitamin D supplementation would reduce the likelihood of ARTI or asthma exacerbation in adults with corticosteroid-treated asthma. The authors identified 590 patients with asthma: 297 were then screened for inclusion and 250 met the inclusion criteria. All were between the ages of 16 and 80 years, had smoked less than 15 pack-years, were using an inhaled corticosteroid, and had evidence of reversible airway obstruction. The 250 participants were randomized to receive either 120,000 IU vitamin D every 2 months for 1 year, or matching placebo. The mean age of participants was 48 years, 44% were male, most had received a flu vaccine, and most had moderately severe asthma. Most (82%) had a low vitamin D level at enrollment (serum 25(OH)D level < 75 nmol/L [30 ng/mL]). Unfortunately, the intervention had no effect. The intervention group experienced a significant increase in vitamin D levels (23 nmol/L [10 ng/mL]), but there was no difference between groups in the time to first exacerbation or time to first ARTI. The study was powered to detect a 60-day difference in the time to event.
Bottom line: Vitamin D supplementation does nothing to prevent exacerbations or improve clinical outcomes in a group of adults with asthma, most of whom were also vitamin D deficient.
Martineau AR, MacLaughlin BD, Hooper RL, et al. Double-blind randomised placebo-controlled trial of bolus-dose vitamin D3 supplementation in adults with asthma (ViDiAs). Thorax 2015;70(5): 451-457.

9. High-dose vitamin D does not reduce wintertime URIs in healthy children

Clinical question: Does high-dose vitamin D reduce the incidence of wintertime upper respiratory infections in otherwise healthy children?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (primary care)
Synopsis: Vitamin D increases the synthesis of antimicrobial peptides in respiratory epithelium and may thus reduce viral replication and subsequent URIs. These investigators enrolled 703 healthy children, 1 year to 5 years old, who presented for a scheduled well-child visit prior to the wintertime viral season in Toronto, Ontario, Canada. Eligible children randomly received (concealed allocation assignment) liquid vitamin D in a standard dose (400 IU daily) or a high-dose (2000 IU daily). Drops were identical in taste, volume, and color. Throughout the winter months parents completed a symptom checklist and collected viral nasal swabs for suspected URIs. The individuals who assessed outcomes remained masked to treatment group assignment. Follow-up occurred for 99.4% of participants for approximately 6 months (winter lasts a LONG time up there). Mean baseline serum 25-hydroxyvitamin D levels were comparable in the standard-dose and high-dose groups (36.9 ng/mL and 35.9 ng/mL, respectively). Using intention-to-treat analysis, no significant differences occurred between the 2 groups in the mean number of infections per child based on both parent-reported URIs and laboratory confirmed upper respiratory virus infections from nasal smears. There was a statistically significant difference in serum 25-hydroxyvitamin D levels between the standard-dose and high-dose groups after treatment (36.8 ng/mL vs 48.7 ng/mL, respectively). The study was 90% powered to detect a reduction of at least 1 URI per winter season between the 2 treatment groups.
Bottom line: Daily administration of high-dose vitamin D (2000 IU) did not reduce the incidence of wintertime upper respiratory infections (URIs) compared with standard dose vitamin D (400 IU) in otherwise healthy children residing in Toronto, Canada.
Aglipay M, Birken CS, Parkin PC, et al, for the TARGet Kids! Collaboration. Effect of high-dose vs standard-dose wintertime vitamin D supplementation on viral upper respiratory tract infections in young healthy children. JAMA 2017;318(3):245-255.

10. Vitamin D does not reduce URIs in children age 1 to 5

IMPORTANCE: Epidemiological studies support a link between low 25-hydroxyvitamin D levels and a higher risk of viral upper respiratory tract infections. However, whether winter supplementation of vitamin D reduces the risk among children is unknown.
OBJECTIVE: To determine whether high-dose vs standard-dose vitamin D supplementation reduces the incidence of wintertime upper respiratory tract infections in young children.
DESIGN, SETTING, AND PARTICIPANTS: A randomized clinical trial was conducted during the winter months between September 13, 2011, and June 30, 2015, among children aged 1 through 5 years enrolled in TARGet Kids!, a multisite primary care practice-based research network in Toronto, Ontario, Canada.
INTERVENTIONS: Three hundred forty-nine participants were randomized to receive 2000 IU/d of vitamin
D oral supplementation (high-dose group) vs 354 participants who were randomized to receive 400 IU/d (standard-dose group) for a

minimum of 4 months between September and May.
MAIN OUTCOME MEASURES: The primary outcome was the number of laboratory-confirmed viral upper respiratory tract infections based on parent-collected nasal swabs over the winter months. Secondary outcomes included the number of influenza infections, noninfluenza infections, parent-reported upper respiratory tract illnesses, time to first upper respiratory tract infection, and serum 25-hydroxyvitamin D levels at study termination.
RESULTS: Among 703 participants who were randomized (mean age, 2.7 years, 57.7% boys), 699 (99.4%) completed the trial. The mean number of laboratory-confirmed upper respiratory tract infections per child was 1.05 (95% CI, 0.91-1.19) for the high-dose group and 1.03 (95% CI, 0.90-1.16) for the standard-dose group, for a between-group difference of 0.02 (95% CI, -0.17 to 0.21) per child. There was no statistically significant difference in number of laboratory-confirmed infections between groups (incidence rate ratio [RR], 0.97; 95% CI, 0.80-1.16). There was also no significant difference in the median time to the first laboratory-confirmed infection: 3.95 months (95% CI, 3.02-5.95 months) for the high-dose group vs 3.29 months (95% CI, 2.66-4.14 months) for the standard-dose group, or number of parent-reported upper respiratory tract illnesses between groups (625 for high-dose vs 600 for standard-dose groups, incidence RR, 1.01; 95% CI, 0.88-1.16). At study termination, serum 25-hydroxyvitamin D levels were 48.7 ng/mL (95% CI, 46.9-50.5 ng/mL) in the high-dose group and 36.8 ng/mL (95% CI, 35.4-38.2 ng/mL) in the standard-dose group.
CONCLUSIONS AND RELEVANCE: Among healthy children aged 1 to 5 years, daily administration of 2000 IU compared with 400 IU of vitamin D supplementation did not reduce overall wintertime upper respiratory tract infections. These findings do not support the routine use of high-dose vitamin D supplementation in children for the prevention of viral upper respiratory tract infections.
Aglipay M, Birken CS, Parkin PC, Loeb MB, Thorpe K, Chen Y, Laupacis A, Mamdani M, Macarthur C, Hoch JS, Mazzulli T, Maguire JL; TARGet Kids! Collaboration. Effect of High-Dose vs Standard-Dose Wintertime Vitamin D Supplementation on Viral Upper Respiratory Tract Infections in Young Healthy Children. JAMA. 2017 Jul 18;318(3):245-254.

11. No Effect of Vitamin D3 Supplementation on Respiratory Tract Infections in Healthy Individuals

OBJECTIVE: Vitamin D supplementation may be a simple preventive measure against respiratory tract infections (RTIs) but evidence from randomized controlled trials is inconclusive. We aimed to systematically summarize results from interventions studying the protective effect of vitamin D supplementation on clinical and laboratory confirmed RTIs in healthy adults and children.
METHODS: Medline, EMBASE, CENTRAL, and CINAHL were screened from inception until present (last updated in January 2016) completed by a search of the grey literature, clinical trial registers and conference abstracts. We included randomized trials comparing vitamin D versus placebo or no treatment. Two independent reviewers were responsible for study selection and data extraction. Cochrane's risk of bias tool and the GRADE approach were used for quality assessment. Estimates were pooled with random-effects models. Heterogeneity was explored by sub-group and meta-regression analyses.
RESULTS: Of 2627 original hits, 15 trials including 7053 individuals were ultimately eligible. All used oral cholecalciferol. We found a 6% risk reduction with vitamin D3 supplementation on clinical RTIs, but the result was not statistically significant (RR 0.94; 95% CI 0.88 to 1.00). Heterogeneity was large (I-square 57%) and overall study quality was low. There were too few studies to reliably assess a potential risk reduction of laboratory confirmed RTI. Evidence was insufficient to demonstrate an association between vitamin D supplementation and risk of clinical RTI in sub-groups with vitamin D deficiency.
CONCLUSIONS: In previously healthy individuals vitamin D supplementation does not reduce the risk of clinical RTIs. However, this conclusion is based on a meta-analysis where the included studies differed with respect to population, baseline vitamin D levels and study length. This needs to be considered when interpreting the results. Future trials should focus on vitamin D deficient individuals and apply more objective and standardized outcome measurements.
Vuichard Gysin D, Dao D, Gysin CM, Lytvyn L, Loeb M. Effect of Vitamin D3 Supplementation on Respiratory Tract Infections in Healthy Individuals: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS One. 2016 Sep 15;11(9):e0162996.

12. Vitamin D reduces the frequency of respiratory tract infections

Objectives To assess the overall effect of vitamin D supplementation on risk of acute respiratory tract infection, and to identify factors modifying this effect.
Design Systematic review and meta-analysis of individual participant data (IPD) from randomised controlled trials.
Data sources Medline, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov, and the International Standard Randomised Controlled Trials Number registry from inception to December 2015.
Eligibility criteria for study selection Randomised, double blind, placebo controlled trials of supplementation with vitamin D_3 or vitamin D_2 of any duration were eligible for inclusion if they had been approved by a research ethics committee and if data on incidence of acute respiratory tract infection were collected prospectively and prespecified as an efficacy outcome.
Results 25 eligible randomised controlled trials (total 11 321 participants, aged 0 to 95 years) were identified. IPD were obtained for 10 933 (96.6%) participants. Vitamin D supplementation reduced the risk of acute respiratory tract infection among all participants (adjusted odds ratio 0.88, 95% confidence interval 0.81 to 0.96; P for heterogeneity <0.001). In subgroup analysis, protective effects were seen in those receiving daily or weekly vitamin D without additional bolus doses (adjusted odds ratio 0.81, 0.72 to 0.91) but not in those receiving one or more bolus doses (adjusted odds ratio 0.97, 0.86 to 1.10; P for interaction=0.05). Among those receiving daily or weekly vitamin D, protective effects were stronger in those with baseline 25-hydroxyvitamin D levels <25 nmol/L (adjusted odds ratio 0.30, 0.17 to 0.53) than in those with baseline 25-hydroxyvitamin D levels ≥25 nmol/L (adjusted odds ratio 0.75, 0.60 to 0.95; P for interaction=0.006). Vitamin D did not influence the proportion of participants experiencing at least one serious adverse event (adjusted odds ratio 0.98, 0.80 to 1.20, P=0.83). The body of evidence contributing to these analyses was assessed as being of high quality.
Conclusions Vitamin D supplementation was safe and it protected against acute respiratory tract infection overall. Patients who were very vitamin D deficient and those not receiving bolus doses experienced the most benefit.

Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC, Grant CC, Griffiths CJ, Janssens W, Laaksi I, Manaseki-Holland S, Mauger D, Murdoch DR, Neale R, Rees JR, Simpson S Jr, Stelmach I, Kumar GT, Urashima M, Camargo CA Jr. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017 Feb 15;356:i6583.

13. Vitamin D supplementation during pregnancy does not prevent wheezing in the infant

Clinical question: Does vitamin D supplementation during pregnancy reduce the risk of asthma or recurrent wheezing in children up to 3 years of age?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: These investigators identified 623 consenting and eligible Danish women within pregnancy weeks 22 through 26 with no history of endocrine, cardiovascular, or nephrological disorders. Patients randomly received (concealed allocation assignment) a daily dose of 2400 IU vitamin D3 supplementation or matching placebo from pregnancy week 24 to postpartum week 1. All women also took an additional 400 IU per day of vitamin D3 supplementation. Participating clinicians masked to treatment group assignment assessed children at periodic scheduled visits for a total of 36 months. Parents, also masked to treatment group, assessed their children's daily symptom burden between scheduled visits using daily diary cards. Complete follow-up occurred for 94% of children at 3 years. The authors used intention-to-treat analysis and found that, although the intervention resulted in a significant increase in maternal serum vitamin D levels in the treatment group, no significant differences occurred between the 2 groups in the risk of the primary outcome: persistent wheeze in offspring during the first 3 years of life. No confounding effect was found after controlling for sex, season of birth, or maternal vitamin D3 level at baseline. A secondary analysis found a significant reduction in episodes of "troublesome lung symptoms" in the vitamin D group, but no significant differences occurred in the risk of asthma diagnosis, upper or lower respiratory tract infections, or eczema diagnoses. The study was underpowered (< 80%) to detect a clinically significant effect in the primary end point of wheezing.
Bottom line: Vitamin D supplementation (2800 IU/day) during the third trimester of pregnancy compared with a standard prenatal dose of 400 IU per day in average-risk women did not significantly reduce the risk of wheezing-related illness in offspring through the age of 3 years. A similar study of supplementation with a higher vitamin D dose (4400 IU/day) in pregnant women at high risk of allergic disease also reported no reduced risk of wheezing-related illness in offspring through age 3 years (Litonjua AA, et al. JAMA 2016;315(4):362-370).
Chawes BL, Bonnelykke K, Stokholm J. Effect of vitamin D3 supplementation during pregnancy on risk of persistent wheeze in the offspring. A randomized clinical trial. JAMA 2016;315(4):353-361.

14. Prenatal vitamin D supplementation reduces risk of asthma/recurrent wheeze in early childhood

BACKGROUND: We recently published two independent randomized controlled trials of vitamin D supplementation during pregnancy, both indicating a >20% reduced risk of asthma/recurrent wheeze in the offspring by 3 years of age. However, neither reached statistical significance.
OBJECTIVE: To perform a combined analysis of the two trials and investigate whether maternal 25-hydroxy-vitamin D (25(OH)D) level at trial entry modified the intervention effect.
METHODS: VDAART (N = 806) and COPSAC2010. (N = 581) randomized pregnant women to daily high-dose vitamin D3 (4,000 IU/d and 2,400 IU/d, respectively) or placebo. All women also received a prenatal vitamin containing 400 IU/d vitamin D3. The primary outcome was asthma/recurrent wheeze from 0-3yrs. Secondary end-points were specific IgE, total IgE, eczema and lower respiratory tract infections (LRTI). We conducted random effects combined analyses of the treatment effect, individual patient data (IPD) meta-analyses, and analyses stratified by 25(OH)D level at study entry.
RESULTS: The analysis showed a 25% reduced risk of asthma/recurrent wheeze at 0-3yrs: adjusted odds ratio (aOR) = 0.74 (95% CI, 0.57-0.96), p = 0.02. The effect was strongest among women with 25(OH)D level ≥30ng/ml at study entry: aOR = 0.54 (0.33-0.88), p = 0.01, whereas no significant effect was observed among women with 25(OH)D level <30ng/ml at study entry: aOR = 0.84 (0.62-1.15), p = 0.25. The IPD meta-analyses showed similar results. There was no effect on the secondary end-points.
CONCLUSIONS: This combined analysis shows that vitamin D supplementation during pregnancy results in a significant reduced risk of asthma/recurrent wheeze in the offspring, especially among women with 25(OH)D level ≥ 30 ng/ml at randomization, where the risk was almost halved. Future studies should examine the possibility of raising 25(OH)D levels to at least 30 ng/ml early in pregnancy or using higher doses than used in our studies.
Wolsk HM, Chawes BL, Litonjua AA, Hollis BW, Waage J, Stokholm J, Bønnelykke K, Bisgaard H, Weiss ST. Prenatal vitamin D supplementation reduces risk of asthma/recurrent wheeze in early childhood: A combined analysis of two randomized controlled trials. PLoS One. 2017 Oct 27;12(10):e0186657.

15. Vitamin D Reduces the Risk of Asthma Exacerbations

BACKGROUND: A previous aggregate data meta-analysis of randomised controlled trials showed that vitamin
D supplementation reduces the rate of asthma exacerbations requiring treatment with systemic corticosteroids. Whether this effect is restricted to patients with low baseline vitamin D status is unknown.
METHODS: For this systematic review and one-step and two-step meta-analysis of individual participant data, we searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science for double-blind, placebo-controlled, randomised controlled trials of vitamin D_3 or vitamin D_2 supplementation in people with asthma that reported incidence of asthma exacerbation, published between database inception and Oct 26, 2016. We analysed individual participant data requested from the principal

investigator for each eligible trial, adjusting for age and sex, and clustering by study. The primary outcome was the incidence of asthma exacerbation requiring treatment with systemic corticosteroids. Mixed-effects regression models were used to obtain the pooled intervention effect with a 95% CI. Subgroup analyses were done to determine whether effects of vitamin D on risk of asthma exacerbation varied according to baseline 25-hydroxyvitamin D (25[OH]D) concentration, age, ethnic or racial origin, body-mass index, vitamin D dosing regimen, use of inhaled corticosteroids, or end-study 25(OH)D levels; post-hoc subgroup analyses were done according to sex and study duration. This study was registered with PROSPERO, number CRD42014013953.
FINDINGS: Our search identified 483 unique studies, eight of which were eligible randomised controlled trials (total 1078 participants). We sought individual participant data for each and obtained it for seven studies (955 participants). Vitamin D supplementation reduced the rate of asthma exacerbation requiring treatment with systemic corticosteroids among all participants (adjusted incidence rate ratio [aIRR] 0·74, 95% CI 0·56-0·97; p=0·03; 955 participants in seven studies; high-quality evidence). There were no significant differences between vitamin D and placebo in the proportion of participants with at least one exacerbation or time to first exacerbation. Subgroup analyses of the rate of asthma exacerbations treated with systemic corticosteroids revealed that protective effects were seen in participants with baseline 25(OH)D of less than 25 nmol/L (aIRR 0·33, 0·11-0·98; p=0·046; 92 participants in three studies; moderate-quality evidence) but not in participants with higher baseline 25(OH)D levels (aIRR 0·77, 0·58-1·03; p=0·08; 764 participants in six studies; moderate-quality evidence; $p_{interaction}$=0·25). p values for interaction for all other subgroup analyses were also higher than 0·05; therefore, we did not show that the effects of this intervention are stronger in any one subgroup than in another. Six studies were assessed as being at low risk of bias, and one was assessed as being at unclear risk of bias. The two-step meta-analysis did not reveal evidence of heterogeneity of effect (I^2=0·0, p=0·56).
INTERPRETATION: Vitamin D supplementation reduced the rate of asthma exacerbations requiring treatment with systemic corticosteroids overall. We did not find definitive evidence that effects of this intervention differed across subgroups of patients.
Jolliffe DA, Greenberg L, Hooper RL, Griffiths CJ, Camargo CA Jr, Kerley CP, Jensen ME, Mauger D, Stelmach I, Urashima M, Martineau AR. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. Lancet Respir Med. 2017 Nov;5(11):881-890.

Pain

16. Vitamin D does not reduce pain in adults with symptomatic knee osteoarthritis

Clinical question: Does vitamin D supplementation reduce pain in adults with symptomatic knee osteoarthritis and low vitamin D levels?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (primary care)
Synopsis: These investigators identified adults, aged 50 to 79 years, in otherwise good health with at least 6 months of symptomatic knee osteoarthritis (based on standard diagnostic criteria) and a pain score of 20 mm to 80 mm on a 100-mm visual analog scale. Eligibility criteria also included a low serum 25-hydroxyvitamin D level (12.5 nmol/L to 60 nmol/L). Study patients randomly received (concealed allocation assignment) a monthly capsule of 50,000 IU vitamin D3 or identical placebo for 24 months. The primary outcomes of knee pain and tibial cartilage volume were assessed using standard evaluation tools by individuals masked to treatment group assignment. Complete follow-up occurred for 82.4% of participants at 24 months. Serum 25-hydroxyvitamin D levels increased significantly more in the vitamin D group than in the placebo group, with 79% versus 43% of patients, respectively, who reached a 25-hydroxyvitamin D level of greater than 60 nmol/L at month 3. Although pain scores significantly decreased from baseline over 24 months in both groups, there was no difference in change of pain scores from baseline to 24 months between the 2 groups using intention-to-treat and per-protocol analyses. Tibial cartilage volume loss also occurred similarly between both groups. The study was 80% powered to detect predetermined clinically significant differences in pain scores and cartilage loss.
Bottom line: Vitamin D supplementation did not significantly reduce pain or prevent cartilage loss compared with placebo in adults with symptomatic knee osteoarthritis and low vitamin D levels over 2 years.
Jin X, Jones G, Cicuttini F, et al. Effect of vitamin D supplementation on tibial cartilage volume and knee pain among patients with symptomatic knee osteoarthritis. A randomized clinical trial. JAMA 2016;315(10):1005-1013.

17. Maintaining Vitamin D Sufficiency Is Associated with Improved Structural and Symptomatic Outcomes in Knee Osteoarthritis

BACKGROUND: The aim of this study was to describe whether maintaining sufficient serum vitamin D levels in people with knee osteoarthritis and baseline vitamin D insufficiency has an association with change in knee structures and symptoms over 2 years.
METHODS: Participants (n = 413, mean age 63.2 years) with symptomatic knee osteoarthritis and vitamin D insufficiency were enrolled in a clinical trial. In all, 340 participants (82.3%) completed the study, with 25-hydroxyvitamin D [25(OH)D] measurements at baseline and months 3 and 24. Participants were classified as consistently insufficient [serum 25(OH)D ≤50 nmol/L at months 3 and 24, n = 45], fluctuating [25(OH)D >50 nmol/L at either point, n = 68), and consistently sufficient [25(OH)D >50 nmol/L at months 3 and 24, n = 226] groups. Knee cartilage volume, cartilage defects, bone marrow lesions, and effusion-synovitis volume were assessed using MRI at baseline and month 24. Knee symptoms were assessed at baseline and months 3, 6, 12, and 24 using the Western Ontario and McMaster Universities Arthritis Index.
RESULTS: The consistently sufficient group had significantly less loss of tibial cartilage volume (β 2.1%; 95% confidence interval [CI], 0.3%, 3.9%), less increase in effusion-synovitis volume (β -2.5 mL; 95 CI%, -4.7, -0.2 mL), and less loss of Western Ontario and McMaster Universities Arthritis Index physical function (β -94.2; 95% CI, -183.8, -4.5) compared with the consistently insufficient group

in multivariable analyses. In contrast, there were no significant differences in these outcomes between the fluctuating and consistently insufficient groups. Changes in cartilage defects, bone marrow lesions, and knee pain were similar between groups.
CONCLUSION: This post hoc analysis suggests beneficial effects of maintaining vitamin D sufficiency on cartilage loss, effusion-synovitis, and physical function in people with knee osteoarthritis.
***Reference**: Am J Med. Zheng S1, Jin X1, Cicuttini F2, Wang X1, Zhu Z1, Wluka A2, Han W3, Winzenberg T4, Antony B1, Aitken D1, Blizzard L1, Jones G1, Ding C5. Maintaining Vitamin D Sufficiency Is Associated with Improved Structural and Symptomatic Outcomes in Knee Osteoarthritis. 2017 Oct;130(10):1211-1218. doi: 10.1016/j.amjmed.2017.04.038. Epub 2017 May 24.*

18. Vitamin D for the treatment of chronic painful conditions in adults

Background: This review is an update of a previously published review in the Cochrane Database of Systematic Reviews (Issue 1, 2010) on 'Vitamin D for the treatment of chronic painful conditions in adults'. Vitamin D is produced in the skin after exposure to sunlight and can be obtained through food. Vitamin D deficiency has been linked with a range of conditions, including chronic pain. Observational and circumstantial evidence suggests that there may be a role for vitamin D deficiency in the aetiology of chronic painful conditions.
Objectives: To assess the efficacy and safety of vitamin D supplementation in chronic painful conditions when tested against placebo or against active comparators.
Search methods: For this update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE to February 2015. This was supplemented by searching the reference lists of retrieved articles, reviews in the field, and online trial registries.
Selection criteria: We included studies if they were randomised double-blind trials of vitamin D supplementation compared with placebo or with active comparators for the treatment of chronic painful conditions in adults.
Data collection and analysis: Two review authors independently selected the studies for inclusion, assessed methodological quality, and extracted data. We did not undertake pooled analysis due to the heterogeneity of the data. Primary outcomes of interest were pain responder outcomes, and secondary outcomes were treatment group average pain outcomes and adverse events.
Main results: We included six new studies (517 participants) in this review update, bringing the total of included studies to 10 (811 participants). The studies were heterogeneous with regard to study quality, the chronic painful conditions that were investigated, the dose of vitamin D given, co-interventions, and the outcome measures reported. Only two studies reported responder pain outcomes; the other studies reported treatment group average outcomes only. Overall, there was no consistent pattern that vitamin D treatment was associated with greater efficacy than placebo in any chronic painful condition (low quality evidence). Adverse events and withdrawals were comparatively infrequent, with no consistent difference between vitamin D and placebo (good quality evidence).
Authors' conclusions: The evidence addressing the use of vitamin D for chronic pain now contains more than twice as many studies and participants than were included in the original version of this review. Based on this evidence, a large beneficial effect of vitamin D across different chronic painful conditions is unlikely. Whether vitamin D can have beneficial effects in specific chronic painful conditions needs further investigation.
Straube S, Derry S, Straube C, Moore RA. Vitamin D for the treatment of chronic painful conditions in adults. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD007771. DOI: 10.1002/14651858.CD007771.pub3.

19. Vitamin D supplementation improves pain symptoms in patients with chronic widespread pain (aka fibromyalgia)

Chronic non-specific widespread pain (CWP) including fibromyalgia (FMS) is characterized by widespread pain, reduced pain threshold, and multiple tender points on examination, causing disability and decreased quality of life. Vitamin D has been proposed as an associated factor in CWP. This meta-analysis aimed to explore the benefit of vitamin D supplementation in the management of CWP. A comprehensive search of the CENTRAL, MEDLINE, and Embase databases was performed from inception through January 2017. The inclusion criterion was the randomized clinical trials' evaluating the effects of vitamin D treatment in adult subjects with CWP or FMS. CWP was defined as chronic recurrent musculoskeletal pain without secondary causes; FMS patients met the American College of Rheumatology criteria for FMS. Study outcome was assessed using visual analog scale (VAS) of pain intensity. Pooled mean difference (MD) of VAS and 95% confidence interval (CI) were calculated using a random-effect meta-analysis. Meta-regression analysis using a random-effects model was performed to explore the effects of change in vitamin D in the treatment group on difference in the mean of VAS. Sensitivity analysis was performed to evaluate the robustness of results. The between-study heterogeneity of effect size was quantified using the Q statistic and I 2. Data were extracted from four randomized controlled trials involving 287 subjects. Pooled result demonstrated a significantly lower VAS in CWP patients who received vitamin D treatment compared with those who received placebo (MD = 0.46; 95% CI 0.09-0.89, I 2 = 48%). Meta-regression analysis revealed no significant relationship between the changes of vitamin D and VAS (coefficient = 0.04 (95% CI -0.01 to 0.08), p = 0.10). In this meta-analysis, we conclude that vitamin D supplementation is able to decrease pain scores and improve pain despite no significant change in VAS after increasing serum vitamin D level. Further studies need to be conducted in order to explore the improvement of functional status, quality of life, and the pathophysiological change that improves chronic widespread pain.
Yong WC, Sanguankeo A, Upala S. Effect of vitamin D supplementation in chronic widespread pain: a systematic review and meta-analysis. Clin Rheumatol. 2017 Dec;36(12):2825-2833.

20. The Effect of Improved Serum 25-Hydroxyvitamin D Status on Glycemic Control in Diabetic Patients: A Meta-Analysis

Background: Type 2 diabetes is a global health concern, with an increased prevalence and high cost of treatment.
Objective: The aim of this systematic review and meta-analysis was to determine the effect of vitamin D supplementation and improved vitamin D status on glycemia and insulin resistance in type 2 diabetic patients.
Data Source: We searched PUBMED/Medline, Cumulative Index to Nursing and Allied Health, and Cochrane Library (until January 2017).
Study Selection: Prospective clinical trials were selected evaluating the impact of vitamin D supplementation on glycosylated hemoglobin (HbA1c), serum fasting plasma glucose (FPG), and homeostatic model assessment of insulin resistance (HOMA-IR) in diabetic patients. Data Extraction and Synthesis: We used a random-effects model to synthesize quantitative data, followed by a leave-one-out method for sensitivity analysis. The systematic review registration was CRD42017059555. From a total of 844 entries identified via literature search, 24 controlled trials (1528 individuals diagnosed with type 2 diabetes) were included. The meta-analysis indicated a significant reduction in HbA1c [mean difference: -0.30%; 95% confidence interval (CI): -0.45 to -0.15, P < 0.001], FPG [mean difference: -4.9 mg/dL (-0.27 mmol/L); 95% CI: -8.1 to -1.6 (-0.45 to -0.09 mmol/L), P = 0.003], and HOMA-IR (mean difference: -0.66; 95% CI: -1.06 to -0.26, P = 0.001) following vitamin D supplementation and significant increase in serum 25-hydroxyvitamin D levels [overall increase of 17 ± 2.4 ng/mL (42 ± 6 nmol/L)].
Conclusions: Vitamin D supplementation, a minimum dose of 100 µg/d (4000 IU/d), may significantly reduce serum FPG, HbA1c, and HOMA-IR index, and helps to control glycemic response and improve insulin sensitivity in type 2 diabetic patients.
***Reference**: Mirhosseini N1, Vatanparast H2, Mazidi M3,4, Kimball SM1,5. The Effect of Improved Serum 25-Hydroxyvitamin D Status on Glycemic Control in Diabetic Patients: A Meta-Analysis. J Clin Endocrinol Metab. 2017 Sep 1;102(9):3097-3110. doi: 10.1210/jc.2017-01024.*

21. Vitamin D does not improve symptoms of bipolar disorder

OBJECTIVE: Bipolar depression is difficult to treat. Vitamin D supplementation is well tolerated and may improve mood via its neurotransmitter synthesis regulation, nerve growth factor enhancement and antioxidant properties. Vitamin D adjunct reduces unipolar depression, but has not been tried in bipolar depression.
METHODS: 18-70yos with DSM IV bipolar depression and Vitamin D deficiency (<30 ng/ml) were randomized in a controlled double blind trial of 5000IU Vitamin D_3 po qday supplementation versus placebo for twelve weeks. Change in Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A), Young Mania Rating Scale (YMRS), medication, and tolerance were assessed q2weeks.
RESULTS: 16 VitD vs 17 placebo subjects did not differ in baseline characteristics (mean = 44 yo, SD = 13), VitD level (19.2 ± 65.8 g/ml vs 19.3 ± 5.5 ng/ml respectively) or mood ratings (MADRS 21.3 ± 6.4 vs 22.8 ± 6.9 respectively). At 12wks, the placebo group VitD levels remained unchanged, while the VitD group levels increased to 28 ng/ml. MADRS score decreased significantly in both placebo (mean = 6.42 (95% CI [2.28 to 10.56]) and VitD groups (mean = 9.54 (95% CI[3.51 to 15.56]) (p = 0.031), but there were no differences between treatment groups (time by treatment interaction estimate: 0.29, $t_{(23)} = 0.14$, p = 0.89); VitD and placebo groups had similar reductions in YMRS and HAM-A. Vitamin D_3 was well tolerated.
CONCLUSIONS: In this small study, despite a greater rise in Vitamin D levels in the VitD supplementation group, there was no significant difference reduction in depressive symptoms. However both groups' VitD levels remained deficient. Vitamin D_3 supplementation vs placebo did not improve reduction in mood elevation or anxiety symptoms.
Marsh WK, Penny JL, Rothschild AJ. Vitamin D supplementation in bipolar depression: A double blind placebo controlled trial. J Psychiatr Res. 2017 Dec;95:48-53.

22. Vitamin D plus calcium does not reduce cancer risk in postmenopausal women

Clinical question: Does dietary supplementation with vitamin D and calcium reduce the risk of cancer in postmenopausal women?
Study design: Randomized controlled trial (double-blinded)
Setting: Population-based
Synopsis: These investigators enrolled 2303 postmenopausal women, 55 years and older, who consented to random (concealed) allocation to either the treatment group (2000 IU vitamin D3 once daily and 500 mg calcium carbonate 3 times daily) or identical placebos. Individuals masked to treatment group assignments assessed cancer diagnosis outcomes (excluding nonmelanoma skin cancer) using medical records and death certificates. The mean baseline serum 25-hydroxyvitamin D level for all women was 32.8 ng/mL (81.8 nmol/L) and the values did not differ significantly between groups. Complete follow-up occurred for 89.6% of patients at 4 years. Using intention-to-treat analysis, the authors found no significant difference between the treatment group and the control group in the incidence of cancers diagnosed (3.89% vs 5.58%, respectively, difference not significant). In particular, there was no significant difference in the incidence of breast cancer diagnoses, with all other individual cancers occurring too infrequently to analyze separately. All serum 25-hydroxyvitamin D levels after baseline were significantly higher in the treatment group than in the control group. No serious adverse events occurred more frequently in the treatment group, including renal calculi. The study was 94.4% powered to detect a 50% reduction in cancer incidence, assuming an annual incidence rate of 2% in the control group.
Bottom line: Among healthy postmenopausal women, 55 years and older, with normal baseline serum vitamin D levels, supplementation with vitamin D3 and calcium did not significantly reduce the risk of all-type cancers at 4 years.
Lappe J, Watson P, Travers Gustafson D, et al. Effect of vitamin D and calcium supplementation on cancer incidence in older women. A randomized clinical trial. JAMA 2017;317(12):1234-1243.

23. High Dose Bolus Vitamin D does NOT prevent cardiovascular disease

IMPORTANCE: Cohort studies have reported increased incidence of cardiovascular disease (CVD) among individuals with low vitamin D status. To date, randomized clinical trials of vitamin D supplementation have not found an effect, possibly because of using too low a dose of vitamin D.
OBJECTIVE: To examine whether monthly high-dose vitamin D supplementation prevents CVD in the general population.
DESIGN, SETTING, AND PARTICIPANTS: The Vitamin D Assessment Study is a randomized, double-blind, placebo-controlled trial that recruited participants mostly from family practices in Auckland, New Zealand, from April 5, 2011, through November 6, 2012, with follow-up until July 2015. Participants were community-resident adults aged 50 to 84 years. Of 47 905 adults invited from family practices and 163 from community groups, 5110 participants were randomized to receive vitamin D3 (n = 2558) or placebo (n = 2552). Two participants retracted consent, and all others (n = 5108) were included in the primary analysis.
INTERVENTIONS: Oral vitamin D3 in an initial dose of 200 000 IU, followed a month later by monthly doses of 100 000 IU, or placebo for a median of 3.3 years (range, 2.5-4.2 years).
MAIN OUTCOMES AND MEASURES: The primary outcome was the number of participants with incident CVD and death, including a prespecified subgroup analysis in participants with vitamin D deficiency (baseline deseasonalized 25-hydroxyvitamin D [25(OH)D] levels <20 ng/mL). Secondary outcomes were myocardial infarction, angina, heart failure, hypertension, arrhythmias, arteriosclerosis, stroke, and venous thrombosis.
RESULTS: Of the 5108 participants included in the analysis, the mean (SD) age was 65.9 (8.3) years, 2969 (58.1%) were male, and 4253 (83.3%) were of European or other ethnicity, with the remainder being Polynesian or South Asian. Mean (SD) baseline deseasonalized 25(OH)D concentration was 26.5 (9.0) ng/mL, with 1270 participants (24.9%) being vitamin D deficient. In a random sample of 438 participants, the mean follow-up 25(OH)D level was greater than 20 ng/mL higher in the vitamin D group than in the placebo group. The primary outcome of CVD occurred in 303 participants (11.8%) in the vitamin D group and 293 participants (11.5%) in the placebo group, yielding an adjusted hazard ratio of 1.02 (95% CI, 0.87-1.20). Similar results were seen for participants with baseline vitamin D deficiency and for secondary outcomes.
CONCLUSIONS AND RELEVANCE: Monthly high-dose vitamin D supplementation does not prevent CVD. This result does not support the use of monthly vitamin D supplementation for this purpose. The effects of daily or weekly dosing require further study.
Scragg R, Stewart AW, Waayer D, Lawes CMM, Toop L, Sluyter J, Murphy J, Khaw KT, Camargo CA Jr. Effect of Monthly High-Dose Vitamin D Supplementation on Cardiovascular Disease in the Vitamin D Assessment Study : A Randomized Clinical Trial. JAMA Cardiol. 2017 Jun 1;2(6):608-616.

Slow S, Florkowski CM, Chambers ST, Priest PC, Stewart AW, Jennings LC, Livesey JH, Camargo CA Jr, Scragg R, Murdoch DR. Effect of monthly vitamin D3 supplementation in healthy adults on adverse effects of earthquakes: randomized controlled trial. BMJ. 2014 Dec 15;349:g7260.

Sorry; Vitamin D did not help earthquake survivors

Bottom Lines

1. Consider augmenting depression treatment with a multi-B vitamin.

2. Prescribe nicotinamide for patients with multiple non-melanoma skin cancers.

3. People with acute macular degeneration may experience some delay in progression of the disease with multivitamin antioxidant vitamin and mineral supplementation.

4. Vitamin E may slow cognitive decline in patients with Alzheimer's dementia but does not prevent cardiovascular disease.

5. The jury is out on whether any vitamins reduce risk of cancer or cardiovascular disease. So are there is no strong evidence to support benefit.

6. Vitamin D decreases frequency of acute respiratory infections, though not in young children.

7. Vitamin D decreases asthma exacerbations requiring steroids, but not the rate of exacerbations.

8. Vitamin D does not reduce pain from knee arthritis but does decrease the pain of chronic widespread pain syndrome.

9. Vitamin D decreases A1C slightly in type 2 diabetes; the clinical significance is unknown

10. Vitamin D does not decrease symptoms of manic depression.

Diabetes Gary Ferenchick, MD

Learning objectives: Understand:

1. USPSTF screening recommendations and the ADA recommendations for glycemic targets in type II diabetes in 2017
2. Where "tight control" is in 2017 for most patients with DM-II.
3. That empagliflozin, liraglutide and semaglutide use are associated with improved macrovascular outcomes in patients with long standing DM-II *and established vascular disease*
4. Understand metformin remains the primary recommended option for DM-II, and cautions on its use have been relaxed
5. Hypoglycemia remains a major limiting feature associated with diabetic medications
6. Incretin based therapies and sulphonylureas are not associated with excess CV risk
7. Replacing diet beverages with water in diabetics associated with weight loss

The USPSTF

- The USPSTF recommends screening for abnormal blood glucose as part of cardiovascular risk assessment in adults aged 40 to 70 years who are overweight or obese. Clinicians should offer or refer patients with abnormal blood glucose to intensive behavioral counseling interventions to promote a healthful diet and physical activity. (B)

#1: PLOS One | Death attributable to diabetes is severely underestimated

Objective: The goal of this research was to identify the fraction of deaths attributable to diabetes in the United States.
Research Design and Methods: We estimated population attributable fractions (PAF) for cohorts aged 30–84 who were surveyed in the National Health Interview Survey (NHIS) between 1997 and 2009 (N = 282,322) and in the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2010 (N = 21,814). Cohort members were followed prospectively for mortality through 2011. We identified diabetes status using self-reported diagnoses in both NHIS and NHANES and using HbA1c in NHANES. Hazard ratios associated with diabetes were estimated using Cox model adjusted for age, sex, race/ethnicity, educational attainment, and smoking status.
Results: We found a high degree of consistency between data sets and definitions of diabetes in the hazard ratios, estimates of diabetes prevalence, and estimates of the proportion of deaths attributable to diabetes. The proportion of deaths attributable to diabetes was estimated to be 11.5% using self-reports in NHIS, 11.7% using self-reports in NHANES, and 11.8% using HbA1c in NHANES. Among the sub-groups that we examined, the PAF was highest among obese persons at 19.4%. The proportion of deaths in which diabetes was assigned as the underlying cause of death (3.3–3.7%) severely understated the contribution of diabetes to mortality in the United States.
Conclusion: Diabetes may represent a more prominent factor in American mortality than is commonly appreciated, reinforcing the need for robust population-level interventions aimed at diabetes prevention and care.
Reference: *Stokes A, Preston SH (2017) Deaths Attributable to Diabetes in the United States: Comparison of Data Sources and Estimation Approaches. PLoS ONE 12(1): e0170219. doi:10.1371/journal.pone.0170219*

ADA Glycemic Targets 2017

- "A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol)." (A)
- "Providers might reasonably suggest more stringent A1C goals (such as <6.5% [48 mmol/mol]) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment (i.e., polypharmacy). Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease." (C)
- "Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin." (B)

#2: PubMed: ACCORD Follow up | No macrovascular benefit for *tight control* after 9 years

OBJECTIVE: In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, ~4 years of intensive versus standard glycemic control in participants with type 2 diabetes and other cardiovascular risk factors had a neutral effect on the composite cardiovascular outcome, increased cardiovascular and total mortality, and reduced nonfatal myocardial infarction. Effects of the intervention during prolonged follow-up were analyzed.
RESEARCH DESIGN AND METHODS: All surviving ACCORD participants were invited to participate in the ACCORD Follow-on (ACCORDION) study, during which participants were treated according to their health care provider's judgment. Cardiovascular and other health-related outcomes were prospectively collected and analyzed using an intention-to-treat approach according to the group to which participants were originally allocated.
RESULTS: A total of 8,601 people, representing 98% of those who did not suffer a primary outcome or death during the ACCORD trial, were monitored for a median of 8.8 years and a mean of 7.7 years from randomization. Intensive glucose lowering for a mean of 3.7 years had a neutral long-term effect on the primary composite outcome (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death), death from any cause, and an expanded composite outcome that included all-cause death. Moreover, the risk of cardiovascular mortality noted during the active phase (hazard ratio 1.49; 95% CI 1.19, 1.87; P < 0.0001) decreased (HR 1.20; 95% CI 1.03, 1.39; P = 0.02).
CONCLUSIONS: In high-risk people with type 2 diabetes monitored for 9 years, a mean of 3.7 years of intensive glycemic control had a neutral effect on death and nonfatal cardiovascular events but increased cardiovascular-related death.
REFERENCE: *ACCORD Study Group. Nine-Year Effects of 3.7 Years of Intensive Glycemic Control on Cardiovascular Outcomes. Diabetes Care. 2016 May;39(5):701-8.*

We know that targeting an HbA1c of ~ 7% is *not* associated with improved macrovascular outcomes compared to an A1c of ~8% (brief review in the appendix). We also know that metformin is associated with improved macrovascular outcomes *independent* of HbA1c (UKPDS). To my knowledge no other class of drugs has been associated with improved macrovascular outcomes, in spite of the fact that all of them are proven to reduce A1c levels by 0.5 – 1.0%. Indeed, most of the recently approved GLP-1 agents have been approved because they have been proven *to not increase* major cardiovascular events.

According to the ADA "Atherosclerotic cardiovascular disease (ASCVD) …. is the leading cause of morbidity and mortality for individuals with diabetes and is the largest contributor to the direct and indirect costs of diabetes" (Diabetes Care 2017 Jan; 40(Supplement 1): S75-S87.) Since macrovascular disease (including coronary disease) is the primary process affecting diabetics, AND since glucose lowering therapies (e.g. insulin, GLP-1 agonists, DDP-IV inhibitors, sulphonylureas, glitazones, etc) have not been associated with improved macrovascular outcomes (except metformin) and several may have adverse effects on macrovascular outcomes, abstract #3 caught my eye this past year; is there a new (albeit much more expensive!) metformin for some of our diabetic patients? Given this, the industry sponsored EMPA-REG trial (Abstract #3) also deserves a more in-depth analysis. This drug was initially FDA approved for glycemic management in 2014, and in December of 2016 was approved to decrease the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease.

Pharmacologic Therapy for DM II

The updated ADA guidelines (Appendix | Figure 2) on pharmacologically treating DM – II state in part

- "Metformin …is the preferred initial pharmacologic agent for the treatment of type 2 diabetes."
    - "...periodic measurement of vitamin B12 levels should be considered in metformin-treated patients..."
    - "Metformin may be safely used in patients with estimated glomerular filtration rate (eGFR) as low as 30 mL/min/1.73 m2"
- "In patients with *long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease*, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes."

Note that the patient populations in studies demonstrating improved macrovascular outcomes of all three drugs were older, predominantly male with long standing diabetes AND established vascular disease (Appendix)

The EMPA-Reg, Leader and Sustain-3 trials | Abstracts 3 – 5

Baseline characteristics of patients enrolled in the EMPA-Reg, Leader and Sustain-3 trials

Patient Features	Empaglifozin	Liraglutide	Semaglutide
Study	Empa-Reg	Leader	Sustain-6
Mean Follow up (yrs)	3.1	3.8	2.1
Mean age	63	64	65
Male	70%	64%	60%
Race			
• White	72%	NR	83%
• Asian	21%		8%
• Black/African-American	5%		7%
DM Duration	**57% > 10 years**	**13 years**	**14 yrs**
Coronary artery disease	**75%**	**81%**	
• Coronary artery disease	47%		**60%**
• CVA	23%	16%	14%
• PAD	20%		
• Cabg	25%	39%	
• MI hx	46%	34%	32%
Microabluminuria	33%	11%	
Macroalbuminuria	10%		
Heart failure	10%	18%	23%
Average HbA1c	8%	8.7	8.7%
Anti-hypertensive meds	95%	92%	94%
Lipid lowering therapy	80%	75%	76%
Anti-coagulants (mostly antiplatelet agents)	90%	67%	75%

EMPA-Reg Trial Results | 3.1 year follow up					
	Placebo (n=2333)	**Empa (n=4687)**	**ARR**	**NNT**	**p-value**
Primary outcome (composite) • CV death • Nonfatal MI • Nonfatal CVA	12.1%	10.5%	1.6	**62**	.04
All-cause mortality	8.3	5.7	2.6	**38**	<.001
CV mortality	5.9	3.7	2.2	**45**	<.001
Hosp for heart failure	4.1	2.7	1.4	**71**	.003
Hosp for heart failure or CV death (excluding fatal CVA)	30.1	19.7			<.001
End-of-study HbA1c	~8.1	~7.7			
Empagliflozin, **Cardiovascular Outcomes**, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28.					

Leader Trial Results | 3.8 year follow-up					
	Placebo (n=4672)	**Liraglutide (n=4668)**	**ARR**	**NNT**	**p-value**
	Rate/1000 patient-years				
Primary outcome (composite) • CV death • Nonfatal MI • Nonfatal CVA	14.9	13.0	1.9	**53**	0.01
MI	6.3	7.3	1	**100**	.046
All-cause mortality	9.6	8.2	1.4	**71**	.02
CV mortality	6.0	4.70	1.3	**77**	.007
Hosp for heart failure	4.7	5.3			.14
End-of-study HbA1c	~8.1	~7.7			
Liraglutide and **Cardiovascular Outcomes** in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):311-22.					

Sustain-3 Trial Results | 2.1 year follow-up					
	Placebo (n=1649)	**Semaglutide (n=1648)**	**ARR (%)**	**NNT**	**p-value**
Primary Composite Outcome • CV Death • Non-fatal MI • Non-fatal CVA	8.9%	6.6%	2.3	**43**	0.02
Nonfatal CVA	2.7	1.6	1.1	**90**	0.04
Nonfatal MI	3.9%	2.9%			0.12
All-cause mortality	3.6	3.8			0.79
CV mortality	2.8	2.7			0.92
Hosp for heart failure	3.3	3.6			0.57
End of study HbA1c	8.3%	7.3 – 7.6%			
Semaglutide and **Cardiovascular Outcomes** in Patients with Type 2 Diabetes. N Engl J Med. 2016 Nov 10;375(19):1834-1844.					

3: PubMed: Empagliflozin (Jardiance®) is associated with ↓ CV events & all-cause mortality in DM-II

BACKGROUND: The effects of empagliflozin, an inhibitor of sodium-glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.
METHODS: We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.
RESULTS: A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no significant between-group difference in the key secondary outcome (P=0.08 for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events.
CONCLUSIONS: Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care. (Funded by Boehringer Ingelheim and Eli Lilly; EMPA-REG OUTCOME ClinicalTrials.gov number, NCT01131676.).
***REFERENCE**: Zinman B, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28. doi: 10.1056/NEJMoa1504720. Epub 2015 Sep 17. PMID: 26378978 [PubMed - indexed for MEDLINE]*

Two other drugs for DM-II (both GLP-1 agonists) are on the horizon (one already approved) which also ↓ macrovascular disease

#4: PubMed: Liraglutide (Victoza®) decreases cardiovascular events and all-cause mortality in DM-II

BACKGROUND: The cardiovascular effect of liraglutide, a glucagon-like peptide 1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown.
METHODS: In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.
RESULTS: A total of 9340 patients underwent randomization. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group than in the placebo group.
CONCLUSIONS: In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo. (Funded by Novo Nordisk and the National Institutes of Health; LEADER ClinicalTrials.gov number, NCT01179048.).
REFERENCE: *Marso SP, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):311-22.*

#5: PubMed: Semaglutide decreases cardiovascular death, MI and CVA in DM-II

Background Regulatory guidance specifies the need to establish cardiovascular safety of new diabetes therapies in patients with type 2 diabetes in order to rule out excess cardiovascular risk. The cardiovascular effects of semaglutide, a glucagon-like peptide 1 analogue with an extended half-life of approximately 1 week, in type 2 diabetes are unknown.
Methods We randomly assigned 3297 patients with type 2 diabetes who were on a standard-care regimen to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. We hypothesized that semaglutide would be noninferior to placebo for the primary outcome. The noninferiority margin was 1.8 for the upper boundary of the 95% confidence interval of the hazard ratio.
Results At baseline, 2735 of the patients (83.0%) had established cardiovascular disease, chronic kidney disease, or both. The primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and in 146 of 1649 patients (8.9%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95; P<0.001 for noninferiority). Nonfatal myocardial infarction occurred in 2.9% of the patients receiving semaglutide and in 3.9% of those receiving placebo (hazard ratio, 0.74; 95% CI, 0.51 to 1.08; P=0.12); nonfatal stroke occurred in 1.6% and 2.7%, respectively (hazard ratio, 0.61; 95% CI, 0.38 to 0.99; P=0.04). Rates of death from cardiovascular causes were similar in the two groups. Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) were significantly higher (hazard ratio, 1.76; 95% CI, 1.11 to 2.78; P=0.02). Fewer serious adverse events occurred in the semaglutide group, although more patients discontinued treatment because of adverse events, mainly gastrointestinal.
Conclusions In patients with type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, an outcome that confirmed the noninferiority of semaglutide. (Funded by Novo Nordisk; SUSTAIN-6 ClinicalTrials.gov number, NCT01720446 .).
Reference: *Marso SP et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016 Nov 10;375(19):1834-1844.*

Other effects of empagliflozin …

6. PubMed: Empagliflozin (Jardiance®) is associated with ↓ CHF event

AIMS: We previously reported that in the EMPA-REG OUTCOME(®) trial, empagliflozin added to standard of care reduced the risk of 3-point major adverse cardiovascular events, cardiovascular and all-cause death, and hospitalization for heart failure in patients with type 2 diabetes and high cardiovascular risk. We have now further investigated heart failure outcomes in all patients and in subgroups, including patients with or without baseline heart failure.
METHODS AND RESULTS: Patients were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo. Seven thousand and twenty patients were treated; 706 (10.1%) had heart failure at baseline. Heart failure hospitalization or cardiovascular

death occurred in a significantly lower percentage of patients treated with empagliflozin [265/4687 patients (5.7%)] than with placebo [198/2333 patients (8.5%)] [hazard ratio, HR: 0.66 (95% confidence interval: 0.55-0.79); P < 0.001], corresponding to a number needed to treat to prevent one heart failure hospitalization or cardiovascular death of 35 over 3 years. Consistent effects of empagliflozin were observed across subgroups defined by baseline characteristics, including patients with vs. without heart failure, and across categories of medications to treat diabetes and/or heart failure. Empagliflozin improved other heart failure outcomes, including hospitalization for or death from heart failure [2.8 vs. 4.5%; HR: 0.61 (0.47-0.79); P < 0.001] and was associated with a reduction in all-cause hospitalization [36.8 vs. 39.6%; HR: 0.89 (0.82-0.96); P = 0.003]. Serious adverse events and adverse events leading to discontinuation were reported by a higher proportion of patients with vs. without heart failure at baseline in both treatment groups, but were no more common with empagliflozin than with placebo.
CONCLUSION: In patients with type 2 diabetes and high cardiovascular risk, empagliflozin reduced heart failure hospitalization and cardiovascular death, with a consistent benefit in patients with and without baseline heart failure.
REFERENCE: *Fitchett D et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur Heart J. 2016 Jan 26. pii: ehv728. [Epub ahead of print] PMID: 26819227*

7. PubMed: Empagliflozin (Jardiance®) is associated with ↓ renal events

BACKGROUND: Diabetes confers an increased risk of adverse cardiovascular and renal events. In the EMPA-REG OUTCOME trial, empagliflozin, a sodium-glucose cotransporter 2 inhibitor, reduced the risk of major adverse cardiovascular events in patients with type 2 diabetes at high risk for cardiovascular events. We wanted to determine the long-term renal effects of empagliflozin, an analysis that was a prespecified component of the secondary microvascular outcome of that trial.
METHODS: We randomly assigned patients with type 2 diabetes and an estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m(2) of body-surface area to receive either empagliflozin (at a dose of 10 mg or 25 mg) or placebo once daily. Prespecified renal outcomes included incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) and incident albuminuria.
RESULTS: Incident or worsening nephropathy occurred in 525 of 4124 patients (12.7%) in the empagliflozin group and in 388 of 2061 (18.8%) in the placebo group (hazard ratio in the empagliflozin group, 0.61; 95% confidence interval, 0.53 to 0.70; P<0.001). Doubling of the serum creatinine level occurred in 70 of 4645 patients (1.5%) in the empagliflozin group and in 60 of 2323 (2.6%) in the placebo group, a significant relative risk reduction of 44%. Renal-replacement therapy was initiated in 13 of 4687 patients (0.3%) in the empagliflozin group and in 14 of 2333 patients (0.6%) in the placebo group, representing a 55% lower relative risk in the empagliflozin group. There was no significant between-group difference in the rate of incident albuminuria. The adverse-event profile of empagliflozin in patients with impaired kidney function at baseline was similar to that reported in the overall trial population.
CONCLUSIONS: In patients with type 2 diabetes at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care. (Funded by the Boehringer Ingelheim and Eli Lilly and Company Diabetes
Alliance; EMPA-REG OUTCOME ClinicalTrials.gov number, NCT01131676.).
REFERENCE: *Wanner C et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes.N Engl J Med. 2016 Jul 28;375(4):323-34.*

FDA APPROVAL ALERT: DIABETES COMBINATION APPROVED | On December 12, 2016 the FDA approved Synjardy XR (empagliflozin and metformin hydrochloride extended-release tablets; Boehringer Ingelheim and Eli Lilly) tablets for adults with type 2 diabetes. Cost for a one-month supply is $426 on googdrx.com

Note a cousin of empagliflozin (canagliflozin sold as Invokana® and Invokamet®) has an FDA warning on bone fracture risk and decreased bone mineral density.
www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm461876.htm

#8. PubMed: AAFP/ACP Guideline | Metformin for most patients with DM-II needing pharmacotherapy

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on oral pharmacologic treatment of type 2 diabetes in adults. This guideline serves as an update to the 2012 ACP guideline on the same topic. This guideline is endorsed by the American Academy of Family Physicians.
Methods: This guideline is based on a systematic review of randomized, controlled trials and observational studies published through December 2015 on the comparative effectiveness of oral medications for type 2 diabetes. Evaluated interventions included metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium–glucose cotransporter-2 (SGLT-2) inhibitors. Study quality was assessed, data were extracted, and results were summarized qualitatively on the basis of the totality of evidence identified by using several databases. Evaluated outcomes included intermediate outcomes of hemoglobin A1c, weight, systolic blood pressure, and heart rate; all-cause mortality; cardiovascular and cerebrovascular morbidity and mortality; retinopathy, nephropathy, and neuropathy; and harms. This guideline grades the recommendations by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.
Target Audience and Patient Population: The target audience for this guideline includes all clinicians, and the target patient population includes adults with type 2 diabetes.

Recommendation 1: ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. (Grade: strong recommendation; moderate-quality evidence)
Recommendation 2: ACP recommends that clinicians consider adding either a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered. (Grade: weak recommendation; moderate-quality evidence.) ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.
Reference: *Qaseem A, et al. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med 2017; Jan 3. doi: 10.7326/M16-1860. [Epub ahead of print]*

#9. PubMed: Metformin is safe in patients who historically had contraindications

Background: Recent changes to the U.S. Food and Drug Administration boxed warning for metformin will increase its use in persons with historical contraindications or precautions. Prescribers must understand the clinical outcomes of metformin use in these populations.
Purpose: To synthesize data addressing outcomes of metformin use in populations with type 2 diabetes and moderate to severe chronic kidney disease (CKD), congestive heart failure (CHF), or chronic liver disease (CLD) with hepatic impairment.
Data Sources: MEDLINE (via PubMed) from January 1994 to September 2016, and Cochrane Library, EMBASE, and International Pharmaceutical Abstracts from January 1994 to November 2015.
Study Selection: English-language studies that: 1) examined adults with type 2 diabetes and CKD (with estimated glomerular filtration rate less than 60 mL/min/1.73 m2), CHF, or CLD with hepatic impairment; 2) compared diabetes regimens that included metformin with those that did not; and 3) reported all-cause mortality, major adverse cardiovascular events, and other outcomes of interest.
Data Extraction: 2 reviewers abstracted data and independently rated study quality and strength of evidence.
Data Synthesis: On the basis of quantitative and qualitative syntheses involving 17 observational studies, metformin use is associated with reduced all-cause mortality in patients with CKD, CHF, or CLD with hepatic impairment, and with fewer heart failure readmissions in patients with CKD or CHF.
Limitations: Strength of evidence was low, and data on multiple outcomes of interest were sparse. Available studies were observational and varied in follow-up duration.
Conclusion: Metformin use in patients with moderate CKD, CHF, or CLD with hepatic impairment is associated with improvements in key clinical outcomes. Our findings support the recent changes in metformin labeling.
Primary Funding Source: U.S. Department of Veterans Affairs. (PROSPERO: CRD42016027708).
Reference: *Crowley MJ et al. Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease: A Systematic Review.Ann Intern Med. 2017 Jan 3. doi: 10.7326/M16-1901. [Epub ahead of print]*

#10: PubMed: 5 diabetic agents among 15 most common drugs → ED visits

Importance: The Patient Protection and Affordable Care Act of 2010 brought attention to adverse drug events in national patient safety efforts. Updated, detailed, nationally representative data describing adverse drug events can help focus these efforts.
Objective: To describe the characteristics of emergency department (ED) visits for adverse drug events in the United States in 2013-2014 and describe changes in ED visits for adverse drug events since 2005-2006.
Design, Setting, and Participants: Active, nationally representative, public health surveillance in 58 EDs located in the United States and participating in the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project.
Exposures: Drugs implicated in ED visits.
Main Outcomes and Measures: National weighted estimates of ED visits and subsequent hospitalizations for adverse drug events.
Results: Based on data from 42 585 cases, an estimated 4.0 (95% CI, 3.1-5.0) ED visits for adverse drug events occurred per 1000 individuals annually in 2013 and 2014 and 27.3% (95% CI, 22.2%-32.4%) of ED visits for adverse drug events resulted in hospitalization. An estimated 34.5% (95% CI, 30.3%-38.8%) of ED visits for adverse drug events occurred among adults aged 65 years or older in 2013-2014 compared with an estimated 25.6% (95% CI, 21.1%-30.0%) in 2005-2006; older adults experienced the highest hospitalization rates (43.6%; 95% CI, 36.6%-50.5%). Anticoagulants, antibiotics, and diabetes agents were implicated in an estimated 46.9% (95% CI, 44.2%-49.7%) of ED visits for adverse drug events, which included clinically significant adverse events, such as hemorrhage (anticoagulants), moderate to severe allergic reactions (antibiotics), and hypoglycemia with moderate to severe neurological effects (diabetes agents).Since 2005-2006, the proportions of ED visits for adverse drug events from anticoagulants and diabetes agents have increased, whereas the proportion from antibiotics has decreased. Among children aged 5 years or younger, antibiotics were the most common drug class implicated (56.4%; 95% CI, 51.8%-61.0%). Among children and adolescents aged 6 to 19 years, antibiotics also were the most common drug class implicated (31.8%; 95% CI, 28.7%-34.9%) in ED visits for adverse drug events, followed by antipsychotics (4.5%; 95% CI, 3.3%-5.6%). Among older adults (aged ≥65 years), 3 drug classes (anticoagulants, diabetes agents, and opioid analgesics) were implicated in an estimated 59.9% (95% CI, 56.8%-62.9%) of ED visits for adverse drug events; 4 anticoagulants (warfarin, rivaroxaban, dabigatran, and enoxaparin) and 5 diabetes agents (insulin and 4 oral agents) were among the 15 most common drugs implicated. Medications to always avoid in older adults according to Beers criteria were implicated in 1.8% (95% CI, 1.5%-2.1%) of ED visits for adverse drug events.
Conclusions and Relevance: The prevalence of emergency department visits for adverse drug events in the United States was estimated to be 4 per 1000 individuals in 2013 and 2014. The most common drug classes implicated were anticoagulants, antibiotics, diabetes agents, and opioid analgesics.

REFERENCE: *Shehab N et al. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014.JAMA. 2016 Nov 22;316(20):2115-2125.*

#11: PubMed: Prevalence of hypoglycemia in diabetic patients not on insulin

IMPORTANCE: Intensive glucose-lowering treatment among patients with non-insulin-requiring type 2 diabetes may increase the risk of hypoglycemia.
OBJECTIVES: To estimate the prevalence of intensive treatment and the association between intensive treatment, clinical complexity, and incidence of severe hypoglycemia among adults with type 2 diabetes who are not using insulin.
DESIGN, SETTING, AND PARTICIPANTS: Retrospective analysis of administrative, pharmacy, and laboratory data from the OptumLabs Data Warehouse from January 1, 2001, through December 31, 2013. The study included nonpregnant adults 18 years or older with type 2 diabetes who achieved and maintained a hemoglobin A1c (HbA1c) level less than 7.0% without use of insulin and had no episodes of severe hypoglycemia or hyperglycemia in the prior 12 months.
MAIN OUTCOMES AND MEASURES: Risk-adjusted probability of intensive treatment and incident severe hypoglycemia, stratified by patient clinical complexity. Intensive treatment was defined as use of more glucose-lowering medications than recommended by practice guidelines at specific index HbA1c levels. Severe hypoglycemia was ascertained by ambulatory, emergency department, and hospital claims for hypoglycemia during the 2 years after the index HbA1c test. Patients were categorized as having high vs low clinical complexity if they were 75 years or older, had dementia or end-stage renal disease, or had 3 or more serious chronic conditions.
RESULTS: Of 31 542 eligible patients (median age, 58 years; interquartile range, 51-65 years; 15 483 women [49.1%]; 18 188 white [57.7%]), 3910 (12.4%) had clinical complexity. The risk-adjusted probability of intensive treatment was 25.7% (95% CI, 25.1%-26.2%) in patients with low clinical complexity and 20.8% (95% CI, 19.4%-22.2%) in patients with high clinical complexity. In patients with low clinical complexity, the risk-adjusted probability of severe hypoglycemia during the subsequent 2 years was 1.02% (95% CI, 0.87%-1.17%) with standard treatment and 1.30% (95% CI, 0.98%-1.62%) with intensive treatment (absolute difference, 0.28%; 95% CI, -0.10% to 0.66%). In patients with high clinical complexity, intensive treatment significantly increased the risk-adjusted probability of severe hypoglycemia from 1.74% (95% CI, 1.28%-2.20%) with standard treatment to 3.04% (95% CI, 1.91%-4.18%) with intensive treatment (absolute difference, 1.30%; 95% CI, 0.10%-2.50%).
CONCLUSIONS AND RELEVANCE: More than 20% of patients with type 2 diabetes received intensive treatment that may be unnecessary. Among patients with high clinical complexity, intensive treatment nearly doubles the risk of severe hypoglycemia.
REFERENCE: *McCoy RG et al. Intensive Treatment and Severe Hypoglycemia Among Adults With Type 2 Diabetes. JAMA Intern Med. 2016 Jul 1;176(7):969-78*

#12: PubMed: Hypoglycemia risk ↑ 50% with DPP-IV inhibitors and sulphonylureas

OBJECTIVE: To quantify the risk of hypoglycaemia associated with the concomitant use of dipeptidyl peptidase-4 (DPP-4) inhibitors and sulphonylureas compared with placebo and sulphonylureas.
DESIGN: Systematic review and meta-analysis.
DATA SOURCES: Medline, ISI Web of Science, SCOPUS, Cochrane Central Register of Controlled Trials, and clinicaltrial.gov were searched without any language restriction.
STUDY SELECTION: Placebo controlled randomised trials comprising at least 50 participants with type 2 diabetes treated with DPP-4 inhibitors and sulphonylureas.
REVIEW METHODS: Risk of bias in each trial was assessed using the Cochrane Collaboration tool. The risk ratio of hypoglycaemia with 95% confidence intervals was computed for each study and then pooled using fixed effect models (Mantel Haenszel method) or random effect models, when appropriate. Subgroup analyses were also performed (eg, dose of DPP-4 inhibitors). The number needed to harm (NNH) was estimated according to treatment duration.
RESULTS: 10 studies were included, representing a total of 6546 participants (4020 received DPP-4 inhibitors plus sulphonylureas, 2526 placebo plus sulphonylureas). The risk ratio of hypoglycaemia was 1.52 (95% confidence interval 1.29 to 1.80). The NNH was 17 (95% confidence interval 11 to 30) for a treatment duration of six months or less, 15 (9 to 26) for 6.1 to 12 months, and 8 (5 to 15) for more than one year. In subgroup analysis, no difference was found between full and low doses of DPP-4 inhibitors: the risk ratio related to full dose DPP-4 inhibitors was 1.66 (1.34 to 2.06), whereas the increased risk ratio related to low dose DPP-4 inhibitors did not reach statistical significance (1.33, 0.92 to 1.94).
CONCLUSIONS: Addition of DPP-4 inhibitors to sulphonylurea to treat people with type 2 diabetes is associated with a 50% increased risk of hypoglycaemia and to one excess case of hypoglycaemia for every 17 patients in the first six months of treatment. This highlights the need to respect recommendations for a decrease in sulphonylureas dose when initiating DPP-4 inhibitors and to assess the effectiveness of this risk minimisation strategy.
REFERENCE: *Salvo F et al. Addition of dipeptidyl peptidase-4 inhibitors to sulphonylureas and risk of hypoglycaemia: systematic review and meta-analysis. BMJ. 2016 May 3;353:i2231*

Glucagon like peptide–1 (GLP-1) acts to increase insulin secretion in response to food. GLP-1 is an incretin based therapy [i.e. Intestinal secretion of insulin (Incretin]. GLP-1 is diminished or absent in many with DM-II. GLP-1 agonists act as “replacement therapy” whereas Dipeptidyl peptidase-4 inhibitors (DPP-IV inhibitors) inhibit the endogenous enzyme that breaks down endogenous GLP-1 (thereby increasing endogenous GLP-1)

#13: PubMed: Incretin based therapies not associated with risk of hospitalization for CHF

BACKGROUND: There is concern that antidiabetic incretin-based drugs, including dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) analogues, can increase the risk of heart failure. Ongoing clinical trials may not have large enough samples to effectively address this issue.
METHODS: We applied a common protocol in the analysis of multiple cohorts of patients with diabetes. We used health care data from four Canadian provinces, the United States, and the United Kingdom. With the use of a nested case-control analysis, we matched each patient who was hospitalized for heart failure with up to 20 controls from the same cohort; matching was based on sex, age, cohort-entry
date, duration of treated diabetes, and follow-up time. Cohort-specific hazard ratios for hospitalization due to heart failure among patients receiving incretin-based drugs, as compared with those receiving oral antidiabetic-drug combinations, were estimated by means of conditional logistic regression and pooled across cohorts with the use of random-effects models.
RESULTS: The cohorts included a total of 1,499,650 patients, with 29,741 hospitalized for heart failure (incidence rate, 9.2 events per 1000 persons per year). The rate of hospitalization for heart failure did not increase with the use of incretin-based drugs as compared with oral antidiabetic-drug combinations among patients with a history of heart failure (hazard ratio, 0.86; 95% confidence interval [CI], 0.62 to 1.19) or among those without a history of heart failure (hazard ratio, 0.82; 95% CI, 0.67 to 1.00). The results were similar for DPP-4 inhibitors and GLP-1 analogues.
CONCLUSIONS: In this analysis of data from large cohorts of patients with diabetes, incretin-based drugs were not associated with an increased risk of hospitalization for heart failure, as compared with commonly used combinations of oral antidiabetic drugs. (Funded by the Canadian Institutes of Health Research; ClinicalTrials.gov number, NCT02456428.).
***REFERENCE**: Filion KB et al. A Multicenter Observational Study of Incretin-based Drugs and Heart Failure. N Engl J Med. 2016 Mar 24;374(12):1145-54.*

#14: PubMed: Sulphonylureas <u>are not</u> associated with risk of all-cause/CV mortality

BACKGROUND: Sulfonylureas are an effective and inexpensive treatment for type 2 diabetes. There is conflicting data about the safety of these drugs regarding mortality and cardiovascular outcomes. The objective of the present study was to evaluate the safety of the sulfonylureas most frequently used and to use trial sequential analysis (TSA) to analyze whether the available sample was powered enough to support the results.
METHODS AND FINDINGS: Electronic databases were reviewed from 1946 (Embase) or 1966 (MEDLINE) up to 31 December 2014. Randomized clinical trials (RCTs) of at least 52 wk in duration evaluating second- or third-generation sulfonylureas in the treatment of adults with type 2 diabetes and reporting outcomes of interest were included. Primary outcomes were all-cause and cardiovascular mortality. Additionally, myocardial infarction and stroke events were evaluated. Data were summarized with Peto odds ratios (ORs), and the reliability of the results was evaluated with TSA. Forty-seven RCTs with 37,650 patients and 890 deaths in total were included. Sulfonylureas were not associated with all-cause (OR 1.12 [95% CI 0.96 to 1.30]) or cardiovascular mortality (OR 1.12 [95% CI 0.87 to 1.42]). Sulfonylureas were also not associated with increased risk of myocardial infarction (OR 0.92 [95% CI 0.76 to 1.12]) or stroke (OR 1.16 [95% CI 0.81 to 1.66]). TSA could discard an absolute difference of 0.5% between the treatments, which was considered the minimal clinically significant difference. The major limitation of this review was the inclusion of studies not designed to evaluate safety outcomes.
CONCLUSIONS: Sulfonylureas are not associated with increased risk for all-cause mortality, cardiovascular mortality, myocardial infarction, or stroke. Current evidence supports the safety of sulfonylureas; an absolute risk of 0.5% could be firmly discarded.
REVIEW REGISTRATION: PROSPERO CRD42014004330.
***REFERENCE:** Varvaki Rados D et al. The Association between Sulfonylurea Use and All-Cause and Cardiovascular Mortality: A Meta-Analysis with Trial Sequential Analysis of Randomized Clinical Trials. PLoS Med. 2016 Apr 12;13(4):e1001992.*

#15: PubMed: Sulphonylureas <u>are</u> associated with risk of all-cause/CV mortality

AIM: To conduct a systematic review and meta-analysis to determine the risk of cardiovascular events and all-cause mortality associated with sulphonylureas (SUs) vs other glucose lowering drugs in patients with T2DM (T2DM).
MATERIALS AND METHODS: A systematic review of Medline, Embase, Cochrane and clinicaltrials.gov was conducted for studies comparing SUs with placebo or other antihyperglycaemic drugs in patients with T2DM. A cloglog model was used in the Bayesian framework to obtain comparative hazard ratios (HRs) for the different interventions. For the analysis of observational data, conventional fixed-effect pairwise meta-analyses were used.
RESULTS: The systematic review identified 82 randomized controlled trials (RCTs) and 26 observational studies. Meta-analyses of RCT data showed an increased risk of all-cause mortality and cardiovascular-related mortality for SUs compared with all other treatments combined (HR 1.26, 95% confidence interval [CI] 1.10-1.44 and HR 1.46, 95% CI 1.21-1.77, respectively). The risk of myocardial infarction was significantly higher for SUs compared with dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose co-transporter-2 inhibitors (HR 2.54, 95% CI 1.14-6.57 and HR 41.80, 95% CI 1.64-360.4, respectively). The risk of stroke was significantly higher for SUs than for DPP-4 inhibitors, glucagon-like peptide-1 agonists, thiazolidinediones and insulin.
CONCLUSIONS: The present meta-analysis showed an association between SU therapy and a higher risk of major cardiovascular disease-related events compared with other glucose lowering drugs. Results of ongoing RCTs, which should be available in 2018, will provide definitive results on the risk of cardiovascular events and all-cause mortality associated with SUs vs other antihyperglycaemic drugs.

REFERENCE: *Bain S et al. Cardiovascular events and all-cause mortality associated with sulphonylureas compared with other antihyperglycaemic drugs: A Bayesian meta-analysis of survival data. Diabetes Obes Metab. 2016 Nov 14. doi: 10.1111/dom.12821. [Epub ahead of print]*

#16: PubMed: Moderate alcohol improves cardiometabolic risk

BACKGROUND: Recommendations for moderate alcohol consumption remain controversial, particularly in type 2 diabetes mellitus (T2DM). Long-term randomized, controlled trials (RCTs) are lacking.
OBJECTIVE: To assess cardiometabolic effects of initiating moderate alcohol intake in persons with T2DM and whether the type of wine matters.
DESIGN: 2-year RCT (CASCADE [CArdiovaSCulAr Diabetes & Ethanol] trial). (ClinicalTrials.gov: NCT00784433).
SETTING: Ben-Gurion University of the Negev-Soroka Medical Center and Nuclear Research Center Negev, Israel.
PATIENTS: Alcohol-abstaining adults with well-controlled T2DM.
INTERVENTION: Patients were randomly assigned to 150 mL of mineral water, white wine, or red wine with dinner for 2 years. Wines and mineral water were provided. All groups followed a Mediterranean diet without caloric restriction.
MEASUREMENTS: Primary outcomes were lipid and glycemic control profiles. Genetic measurements were done, and patients were followed for blood pressure, liver biomarkers, medication use, symptoms, and quality of life.
RESULTS: Of the 224 patients who were randomly assigned, 94% had follow-up data at 1 year and 87% at 2 years. In addition to the changes in the water group (Mediterranean diet only), red wine significantly increased high-density lipoprotein cholesterol (HDL-C) level by 0.05 mmol/L (2.0 mg/dL) (95% CI, 0.04 to 0.06 mmol/L [1.6 to 2.2 mg/dL]; P < 0.001) and apolipoprotein(a)1 level by 0.03 g/L (CI, 0.01 to 0.06 g/L; P = 0.05) and decreased the total cholesterol-HDL-C ratio by 0.27 (CI, -0.52 to -0.01; P = 0.039). Only slow ethanol metabolizers (alcohol dehydrogenase alleles [ADH1B*1] carriers) significantly benefited from the effect of both wines on glycemic control (fasting plasma glucose, homeostatic model assessment of insulin resistance, and hemoglobin A1c) compared with fast ethanol metabolizers (persons homozygous for ADH1B*2). Across the 3 groups, no material differences were identified in blood pressure, adiposity, liver function, drug therapy, symptoms, or quality of life, except that sleep quality
improved in both wine groups compared with the water group (P = 0.040). Overall, compared with the changes in the water group, red wine further reduced the number of components of the metabolic syndrome by 0.34 (CI, -0.68 to -0.001; P = 0.049).
LIMITATION: Participants were not blinded to treatment allocation.
CONCLUSION: This long-term RCT suggests that initiating moderate wine intake, especially red wine, among well-controlled diabetics as part of a healthy diet is apparently safe and modestly decreases cardiometabolic risk. The genetic interactions suggest that ethanol plays an important role in glucose metabolism, and red wine's effects also involve nonalcoholic constituents.
PRIMARY FUNDING SOURCE: European Foundation for the Study of Diabetes.
REFERENCE: *Gepner Y, et al. Effects of Initiating Moderate Alcohol Intake on Cardiometabolic Risk in Adults With Type 2 Diabetes: A 2-Year Randomized, Controlled Trial. Ann Intern Med. 2015 Oct 20;163(8):569-79.*

#17: PubMed: Replacing diet beverages with water associated with weight reduction in diabetics

AIMS: To compare the effect of replacing diet beverages (DBs) with water or continuing to drink DBs in patients with type 2 diabetes during a 24-week weight loss program. The primary endpoint was the effect of intervention on weight over a 24-week period. The main secondary endpoints included anthropometric measurement and glucose and fat metabolism during the 24-week period.
METHODS: A total of 81 overweight and obese women with type 2 diabetes, who usually consumed DBs in their diet, were asked to either substitute water for DBs or continue drinking DBs five times per week after lunch for 24 weeks (DBs group) during a weight loss program.
RESULTS: Compared with the DBs group, the water group had a greater decrease in weight (water, -6.40 ± 2.42 kg; DBs, -5.25 ± 1.60 kg; P = .006), in BMI (water,-2.49 ± 0.92 kg/m(2) ; DBs, -2.06 ± 0.62 kg/m(2) ; P = .006), in FPG (water, -1.63 ± 0.54 mmol/L; DBs, -1.29 ± 0.48 mmol/L, P = .005), in fasting insulin (water, -5.71 ± 2.30 m IU/mL; DBs, -4.16 ± 1.74 m IU/mL, P = .011), in HOMA IR (water, -3.20 ± 1.17; DBs, -2.48 ± 0.99, P = 003) and in 2 hour postprandial glucose (water, -1.67 ± 0.62 mmol/L; DBs, -1.35 ± 0.39 mmol/L; P = 0.027) over the 24-week period. However, there was no significant time × group interaction for waist circumference, lipid profiles and HbA1c within both groups over the 24-week period.
CONCLUSION: Replacement of DBs with water after the main meal in obese adult women with type 2 diabetes may lead to more weight reduction during a weight loss program.
REFERENCE*: Madjd A et al. Beneficial effects of replacing diet beverages with water on type 2 diabetic obese women following a hypo-energetic diet: A randomized, 24-week clinical trial. Diabetes Obes Metab. 2017 Jan;19(1):125-132.*

Bottom Lines

1. Diabetes related mortality is estimated to be ~ 12% in the US
2. A 9 year follow up to the ACCORD trial continue to demonstrate no mortality benefit AND an increase in CV related deaths
3. For appropriately selected patients, empagliflozin therapy is associated with improved macrovascular outcomes and decreased all-cause mortality.
4. Liraglutide and semaglutide use is also associated with improved macrovascular outcomes in DM-II

5. Metformin is safe in patients who historically had contraindications
6. The prevalence of hypoglycemia in patients with DM-II is not insubstantial
7. The association between Sulfonylureas and macrovascular outcomes amongst patients with DM-II is still not known
8. Moderate alcohol intake (red wine) in well controlled diabetics is associated with a slight improvement in metabolic risk
9. Replacing diet beverages with water associated with weight reduction in diabetics

Appendix 1

References

1. American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment. Diabetes Care 2017 Jan; 40(Supplement 1): S64-S74.
2. American Diabetes Association. Glycemic Targets. Diabetes Care 2017 Jan; 40(Supplement 1): S48-S56

Appendix 2

Tight Control

Brief Overview of the major trials testing the hypothesesis on targeting and A1c ~ 7 vs and A1c ~8

- The ACCORD trial tested this hypothesis in about 10,000 patients with a mean age of 62 with already established cardiovascular disease (35% of the study population) or those with risk factors for CV disease. Within 4 months the authors noted
    - A 1.1% separation in the target an A1C between the intervention group (6.4%) and the control group (7.5%).
    - At the end of 3.5 years, death from any cause was 5% in the intervention group and 4% in the control group. The study was terminated early.
- The ADVANCE trial tested this hypothesis in about 11,000 patients with a mean age of 66, 32% of whom had macrovascular disease. The authors noted:
    - A 0.8% separation in the targeted A1C between the treatment group (6.5%) and the control group (7.3%).
    - After 5 years, the major outcome in the study were:
        - Slightly lower risk of developing macroalbuminuria (2.9% in the intervention group vs. 4.1% in the control group).
        - So you'd have to treat 83 patients to an A1C of 6.5% for 5 years to prevent a single case of macroalbuminuria.
        - No between group differences in macrovascular outcomes were noted.
- The VDAT trail tested this hypothesis in about 1,800 patients with a mean age of 60 (40% with known ASCVD). The authors noted:
    - A 1.5% separation (6.9% vs. 8.4%) in A1c levels.
    - After 5.6 years of follow up, no between group differences were noted in any macrovascular outcome.

What each of these studies did demonstrate was an excess of hypoglycemia in the "intensive" group (3.2x higher in ACCORD; 1.4X higher in ADVANCE; and 3.6 x higher in the VDAT trial) an outcome that is associated with a higher risk of dementia in diabetics over the age of 65. Taken in sum, these studies suggest that targeting an A1C of ~ 7.0 (vs. ~ 8.0) for 3 – 5 years is at best associated with a slightly lower risk of albuminuria, at the cost of a slightly higher risk of mortality and much higher risk of hypoglycemia.

You may remember the UKPDS study from the late 1980's. This 15-year study also assessed the effect of intensive glycemic control in *newly diagnosed* type II diabetics. This non-blinded study produced a between group A1C difference of 0.9% (7.0 v 7.9%) and demonstrated that intensive treatment (either insulin or sulfonylurea or, in obese patients, metformin) vs. diet, lowered diabetes-related endpoints ~ 12%, almost all due to a decreased need for retinal photocoagulation (it should be noted that there were no between group differences in visual acuity, blindness or other markers of microvascular disease including microabluminuria). Also, as in the above-mentioned studies, the intensive treatment group demonstrated no between group differences in macrovascular disease, death from CVD or all-cause mortality, and hypoglycemia was much more common in the intensive treatment group vs. diet (11-36% vs. 1.2%). Subgroup analysis demonstrated that within the intensive treatment group, those obese patients taking metformin alone had a reduction in mortality and myocardial infarction, an effect not seen in the intensive treatment group receiving insulin or sulfonylureas, suggesting a beneficial effect of metformin, and not of "intensive treatment" per se.

A follow up to the UKPDS was published in 2008. About three quarters of the original patients were followed for 10 years *after* the study finished (note this is ~ 25 years after the study started). No attempt was made to keep the previously randomized treatments (the differences in A1C levels were lost within a year). Patients originally randomized to the insulin-sulfonylurea group demonstrated a 2.8% absolute risk reduction in MI and a 3.5% decrease in overall mortality, patients in the metformin group demonstrated an absolute decrease of 6.3% in MI and a 7.2% decrease in all-cause mortality. These results raise the possibly of a legacy effect (a delayed effect of early glucose control).

Recall the results of 3 major randomized controlled trails published over the past few years concluded tight (A1C target 6–7%) vs less tight (A1c 7-8%) demonstrated no benefit on macrovascular outcomes, minimal benefit on microvascular outcomes, and higher rates of hypoglycemia.

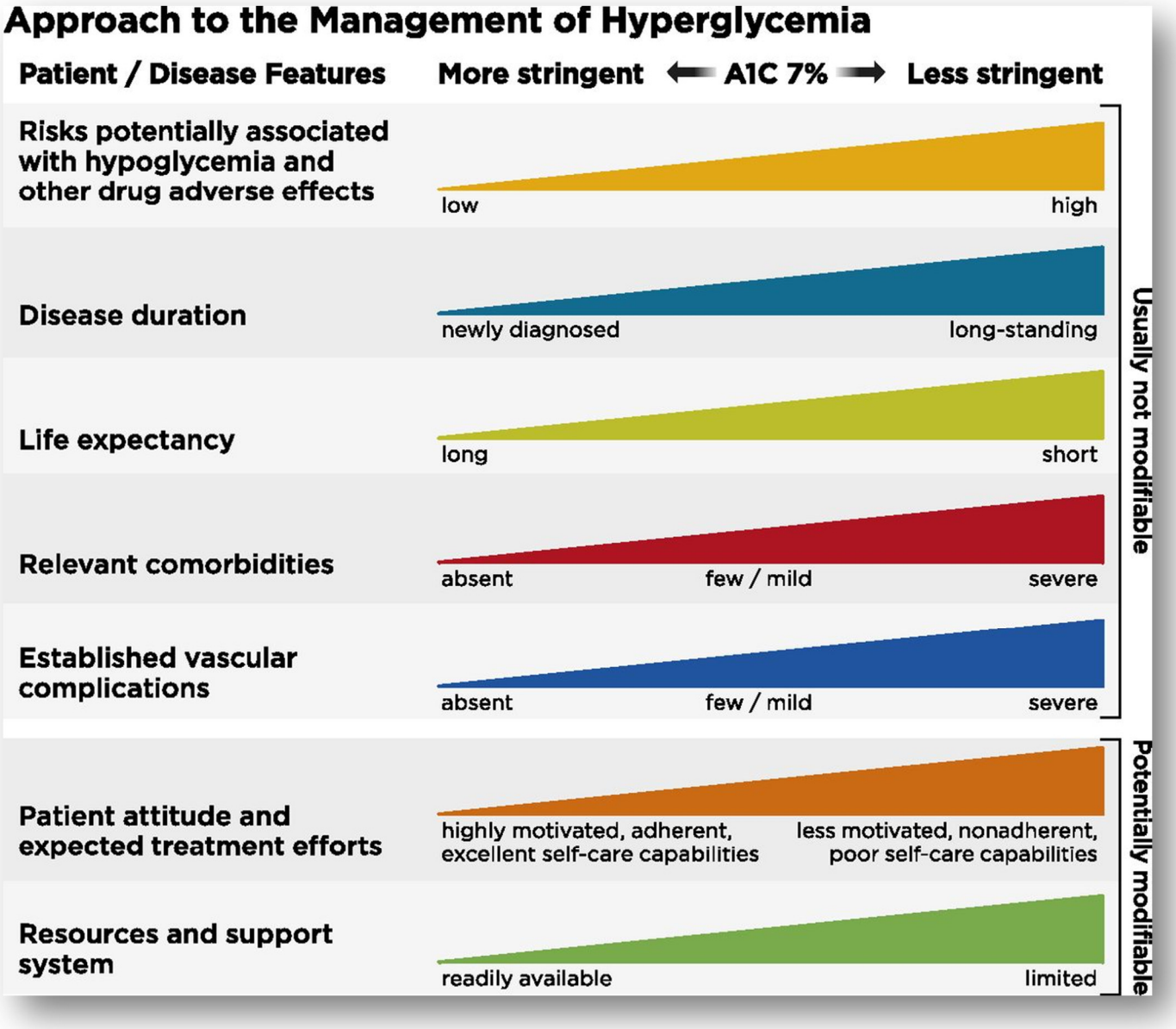
Also as part of their annual update, the ADA published "Standards of medical care in diabetes – 2015" (Diabetes Care 2015;38(suppl 1):S33-S40)

Among their recommendations/statement on tight control include ver batim:

- "Mortality findings in ACCORD and subgroup analyses of the VADT suggested that the potential risks of intensive glycemic control may outweigh its benefits in some patients."
- "Those with long duration of diabetes, known history of severe hypoglycemia, advanced atherosclerosis, or advanced age/frailty may benefit from less aggressive targets."
- "Severe hypoglycemia was significantly more likely in participants in all three trials randomized to the intensive glycemic control arm."
    - "Severe or frequent hypoglycemia is an absolute indication for the modification of treatment regimens, including setting higher glycemic goals."
- "Less stringent A1C goals (such as < 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advance microvascular or macrovascular complications and extensive co-morbid conditions …"
- "…individualization of treatment is the cornerstone of success"
- "Our recommendations are less prescriptive than and not as algorithmic as prior guidelines"
- "Importantly, utilizing the percent of diabetic patients who are achieving an HbA1c < 7.0% as a quality indicator, as promulgated by various health care organizations, is inconsistent with the emphasis on individualization of treatment goals"

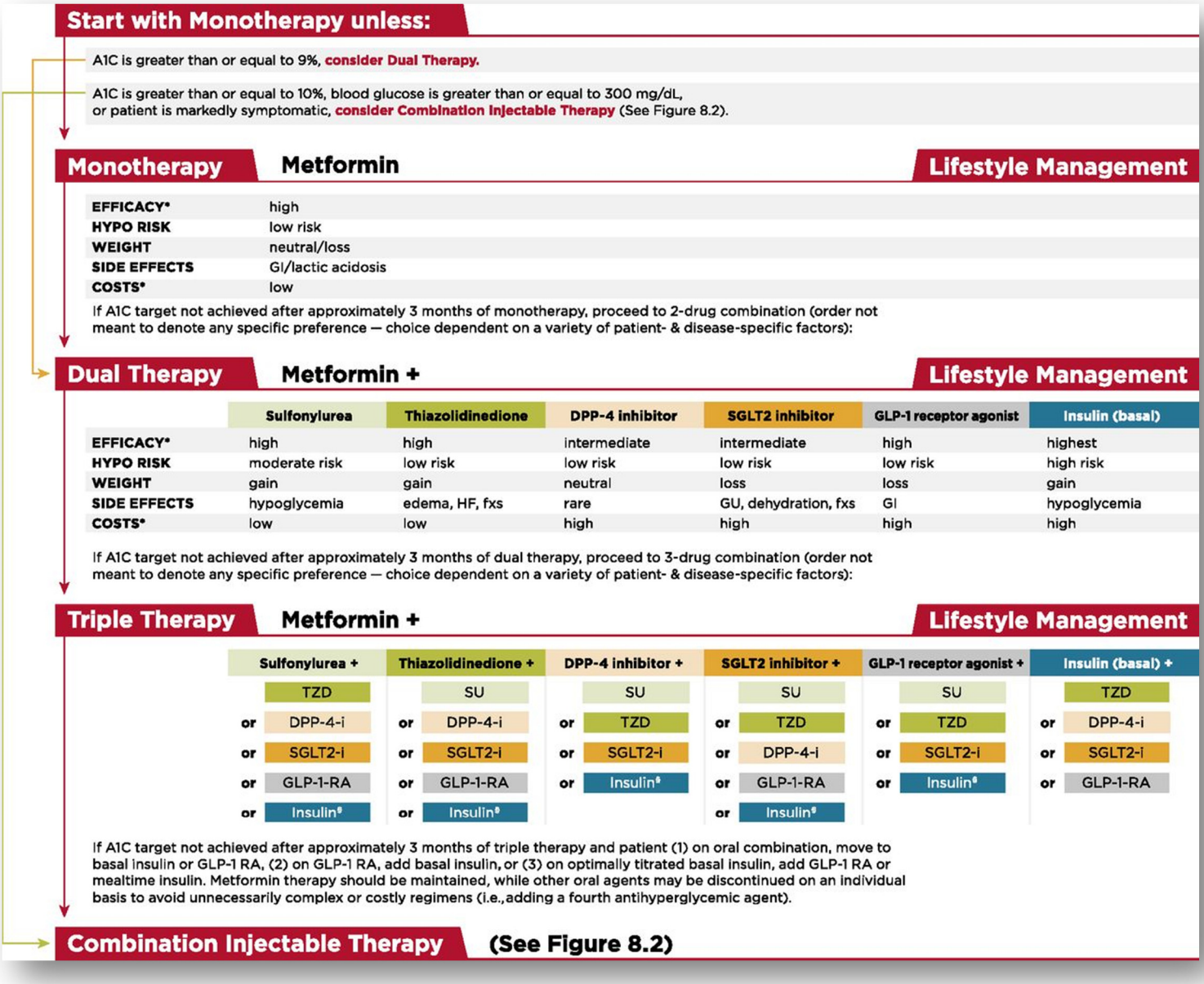
Appendix 3

Clinical Decision making for glycemic targets in DM - II



Appendix 4

General Recommendations for pharmacotherapy for DM-II



General Recommendations: The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference.

Appendix 5

Bonus Abstracts

PubMed: ASA for primary prevention in diabetics, not all upside

AIMS: To evaluate the benefits and harms of aspirin for the primary prevention of cardiovascular disease and all-cause mortality events in people with diabetes by conducting a systematic review and meta-analysis.
METHODS: Randomized controlled trials of aspirin compared with placebo (or notreatment) in people with diabetes with no history of cardiovascular disease were identified from MEDLINE, EMBASE, Web of Science, the Cochrane Library and a manual search of bibliographies to November 2015. Study-specific relative risks with 95% CIs were aggregated using random effects models.
RESULTS: A total of 10 randomized trials were included in the review. There was a significant reduction in risk of major adverse cardiovascular events in groups taking aspirin compared with placebo or no treatment. Limited subgroup analyses suggested that the effect of aspirin on major adverse cardiovascular events *differed by baseline cardiovascular disease risk*, medication compliance and sex (P for interaction for all > 0.05). There was no significant reduction in the risk of myocardial infarction, coronary heart disease, stroke, cardiovascular mortality or all-cause mortality. Aspirin significantly reduced the risk of myocardial infarction for a treatment duration of ≤ 5 years. There were differences in the effect of aspirin by dosage and treatment duration on overall stroke outcomes (P for interaction for all < 0.05). There was an increase in risk of major or gastrointestinal bleeding events, but estimates were imprecise and not significant.
CONCLUSIONS: The emerging data do not clearly support guidelines that encourage the use of aspirin for the primary prevention of cardiovascular disease in adults with diabetes who are at increased cardiovascular disease risk.
REFERENCE*: Kunutsor SK et al. Aspirin for primary prevention of cardiovascular and all-cause mortality events in diabetes: updated meta-analysis of randomized controlled trials. Diabet Med. 2016 Apr 17. doi: 10.1111/dme.13133. [Epub ahead of print]*

PubMed: Excessive testing for A1c → over treatment

STUDY QUESTION: What is the extent and effect of excessive testing for glycated hemoglobin (HbA1c) among adults with controlled type 2 diabetes?
METHODS: A retrospective analysis of data from a national administrative claims database included commercially insured individuals in the USA, 2001-13. Study patients were aged 18 years or older, had type 2 diabetes with stable glycemic control (two consecutive tests showing HbA1c<7.0% within 24 months), did not use insulin, had no history of severe hypoglycemia or hyperglycemia, and were not pregnant. HbA1c testing frequency was measured within 24 months after the second (index) HbA1c test, and classified as guideline recommended (≤ 2 times/year),frequent (3-4 times/year), and excessive (≥ 5 times/year). Changes in treatment regimen were ascertained within three months of the index test.
STUDY ANSWER AND LIMITATIONS: Of 31,545 patients in the study cohort (mean age 58 years; mean index HbA1c 6.2%), HbA1c testing frequency was excessive in 6% and frequent in 55%. Despite good glycemic control at baseline, treatment was further intensified by addition of glucose lowering drugs or insulin in 8.4% of patients (comprising 13%, 9%, and 7% of those tested excessively, frequently, and per guidelines, respectively; P<0.001). Compared with guideline recommended testing, excessive testing was associated with treatment intensification (odds ratio 1.35 (95% confidence interval 1.22 to 1.50)). Excessive testing rates remained unchanged in 2001-08, but fell significantly after 2009. The odds of excessive testing was 46% lower in 2011 than in 2001-02. The study population is not representative of all US patients with type 2 diabetes because it was restricted to commercially insured adults with stable and controlled diabetes not receiving insulin treatment. The study design did not capture the underuse of HbA1c testing.
WHAT THIS STUDY ADDS: In this US cohort of adults with stable and controlled type 2 diabetes, more than 60% received too many HbA1c tests, a practice associated with potential overtreatment with hypoglycemic drugs. Excessive testing contributes to the growing problem of waste in healthcare and increased patient burden in diabetes management.
FUNDING, COMPETING INTERESTS, DATA SHARING: NDS and RGM are funded partly by the Agency for Healthcare Research and Quality (R18HS18339) and AcademyHealth Delivery System Science Fellowship (2013), respectively. No competing interests declared. Additional data are available from mccoy.rozalina@mayo.edu.
REFERENCE: *McCoy RG, et al. HbA1c overtesting and overtreatment among US adults with controlled type 2 diabetes, 2001-13: observational population based study. BMJ. 2015 Dec 8;351:h6138.*

Poem: Older patients with diabetes have higher fall risk, especially if using insulin

Clinical question: Are older patients with diabetes at increased risk of falls?
Study design: Meta-analysis (other)
Setting: Various (meta-analysis)
Synopsis: Because of inconsistent findings in individual studies, these authors searched two databases to identify prospective cohort studies that evaluated falls in patients older than 60 years with diabetes. In addition to the databases, the authors supplemented the search by combing through the reference lists of included studies and relevant reviews. They don't describe searching registries for unpublished studies. Two reviewers independently extracted data and assessed the quality of the studies. Ultimately, they included 6 studies with nearly 15,000 patients followed from 10 months to 10 years. Two of the studies included only women, and 3 reported whether patients received insulin. The range of quality scores of the studies ranged from 6 to 8 (of a maximum of 9). Over the course of

the studies, the overall rate of falls was 25% in patients with diabetes and 18% in patients without diabetes (relative risk [RR] 1.64; 95% CI 1.27 - 2.11). Although the increased risk persisted across many subgroups (eg, follow-up duration, sex, and body weight), the rate was especially higher in patients using insulin (32% vs 21%; RR 1.94; 1.42 - 2.63). The authors don't report on the annual rate of falls nor did they formally assess the potential for publication bias. Finally, the authors reported significant heterogeneity in the rate of falls across the studies.

Bottom line: This limited meta-analysis of high-quality prospective cohort studies found that older patients with diabetes, especially those using insulin, have a higher rate of falls than older patients without diabetes and those not using insulin.

***Reference**: Yang Y, Hu X, Zhang Q, Zou R. Diabetes mellitus and risk of falls in older adults: a systematic review and meta-analysis. Age Ageing 2016;45(6):761-767*.