Learning Objectives

Discuss recent research critical to family physicians for updating their diagnostic and treatment approaches to musculoskeletal conditions, cardiovascular disease, primary care prevention, pneumonia and influenza, atrial fibrillation, allergic conditions, exercise and rehab, skin diseases, GI and liver problems and pain management. 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

Mark H. Ebell MD, MS. is a Professor in the College of Public Health at The University of Georgia. Dr. Ebell is Deputy Editor of American Family Physician and Editor-in-Chief of Essential Evidence. He is a graduate of the University of Michigan School of Medicine, a former RWJ Generalist Physician Faculty Scholar, and is former editor of the Journal of Family Practice. Dr. Ebell is author of 7 books and over 300 peer reviewed articles. From 2012 to 2016 he was a member of the USPSTF.

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.

Mark, John and Gary have been teaching evidence based medicine for over 20 years, and they are delighted to return to Big Sky for the 40th Annual Conference.

Speaker and Faculty Disclosures

Mark Ebell is the Editor-in-Chief of Essential Evidence, a publication of John Wiley and Sons, Inc. 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.

“Essential Evidence” and all content in this handout is copyright by John Wiley and Sons, Inc, 2014. This syllabus may not be reproduced without permission from the publisher.
http://www.essentialevidence.com
# Essential Evidence Schedule for Big Sky, 2017

## Monday, January 16th

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:30</td>
<td>DVT and PE</td>
<td>Ebell</td>
<td>3</td>
</tr>
<tr>
<td>8:00</td>
<td>Cardiovascular disease</td>
<td>Ferenchick</td>
<td>13</td>
</tr>
<tr>
<td>8:30</td>
<td>Musculoskeletal update</td>
<td>Hickner</td>
<td>23</td>
</tr>
<tr>
<td>9:00</td>
<td>Pneumonia and influenza</td>
<td>Ebell</td>
<td>31</td>
</tr>
<tr>
<td>9:30</td>
<td>Atrial fibrillation and NOAs</td>
<td>Ferenchick</td>
<td>40</td>
</tr>
</tbody>
</table>

**Ski Break**

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:30</td>
<td>Allergy Update</td>
<td>Hickner</td>
<td>54</td>
</tr>
<tr>
<td>5:00</td>
<td>Prevention</td>
<td>Ebell</td>
<td>61</td>
</tr>
<tr>
<td>5:30</td>
<td>Exercise and rehab</td>
<td>Ferenchick</td>
<td>72</td>
</tr>
<tr>
<td>6:00</td>
<td>Editor’s Choice</td>
<td>All</td>
<td>126</td>
</tr>
</tbody>
</table>

## Tuesday, January 17th

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:30</td>
<td>Skin diseases</td>
<td>Hickner</td>
<td>87</td>
</tr>
<tr>
<td>8:00</td>
<td>Upper GI problems</td>
<td>Ebell</td>
<td>96</td>
</tr>
<tr>
<td>8:30</td>
<td>Liver and GI Update</td>
<td>Ferenchick</td>
<td>106</td>
</tr>
<tr>
<td>9:00</td>
<td>Pain management</td>
<td>Hickner</td>
<td>115</td>
</tr>
<tr>
<td>9:30</td>
<td>Editor’s Choice</td>
<td>All</td>
<td>126</td>
</tr>
</tbody>
</table>
Objectives

1. Review the latest ACCP guideline recommendations
2. Learn about age-adjusting the d-dimer test result to improve its accuracy
3. Learn about the role (if any) for compression stockings, fibrinolysis for PE, and retrievable IVC filters
4. Discuss when we should extend anticoagulation beyond 3 months

The ACCP guidelines, a pretty reasonable source of evidence-based recommendations, were recently updated. They do a really nice job of summarizing the evidence, and present results in terms of absolute effects. Nice. Here are some key takeaways, mostly consistent with what we’ve been saying in POEMs for the past 5 years or so:

1) NOA’s are now recommended over warfarin due to less bleeding (5 fewer/1000), although it’s important to note that there is more recurrences (3/1000) and no change in ACM.
2) LMWH preferred for VTE in cancer patients
3) Consider > 3 months of treatment if unprovoked VTE and/or d-dimer remains elevated at 3 months
4) Just do surveillance if subsegmental PE, no proximal DVT in legs, and not otherwise at high risk of recurrence
5) Thrombolitics only as a last resort

Here are their summary tables for NOA vs vitamin K antagonists (VKA, i.e. warfarin). Each comparison is warfarin vs NOA:

<table>
<thead>
<tr>
<th></th>
<th>All cause mortality</th>
<th>Recurrent VTE</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>19 vs 15/1000 (NS)</td>
<td>27 vs 23/1000 (NS)</td>
<td>18 vs 5/1000 (RR 0.31, 95% CI 0.17-0.55)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>18 vs 18/1000 (NS)</td>
<td>22 vs 25/1000 (NS)</td>
<td>20 vs 15/1000 (NS)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>24 vs 23/1000 (NS)</td>
<td>23 vs 21/1000 (NS)</td>
<td>17 vs 9/1000 (p = NS)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>31 vs 33/1000 (NS)</td>
<td>35 vs 29/1000 (NS)</td>
<td>16 vs 14/1000 (NS)</td>
</tr>
</tbody>
</table>

As you can see, only 1 significant difference, which was lower risk of major bleeding with apixaban.

1. ACCP 2016: updated guidelines for VTE

Clinical question: What is the best way to manage venous thromboembolism?
Study design: Practice guideline
Setting: Various (guideline)
Synopsis: This is the latest update to the guidelines from the ACCP on the use of antithrombotic therapy. The guideline panel based their recommendations on the results of systematic reviews, graded the strength of evidence, disclosed financial conflicts of interests, and prohibited members with a significant conflict of interest from voting. It's surprising there was anyone left to vote, as they had a long, long list of conflicts of interest. Perhaps the most important change is that they now recommend the use of a novel oral anticoagulant over warfarin for patients with VTE, based on lower rates of major bleeding (5 fewer bleeds per 1000 patients; range = 10 fewer to 2 more), although the same studies found no difference in all-cause mortality and a higher risk of recurrent VTE (3 more recurrences per 1000 patients; range = 5 fewer to 13 more). For patients with VTE and cancer, a low-molecular-weight heparin is the
preferred agent. Therapy for more than 3 months is an option for patients with unprovoked VTE, especially if they have an elevated D-dimer level 1 month after stopping anticoagulation. For those who stop anticoagulation at 3 months, aspirin is recommended to reduce the likelihood of recurrence. Another big change is that for patients with a subsegmental PE, no proximal deep vein thrombosis in the legs, and who are not at high risk for recurrence (and especially if bleeding risk is high), clinical surveillance is recommended over anticoagulation. Thrombolytics are only recommended for patients with PE if they are hypotensive and do not have a high bleeding risk, or if they are deteriorating after anticoagulation is initiated and have a low bleeding risk.

**Bottom line:** According to the American College of Chest Physicians (ACCP), novel oral anticoagulants are now recommended as the preferred drugs for the treatment of venous thromboembolism (VTE), low-molecular-weight heparin is preferred for patients with VTE and cancer, and selected patients with subsegmental pulmonary embolism (PE) do not require anticoagulation. See the full article for a comprehensive list of recommendations.


What about longer courses of therapy for unprovoked VTE? You get strong trend toward higher all-cause mortality with longer duration (41 vs 57 deaths/1000, 95% CI 4 fewer to 46 more deaths), more major bleeding (12 vs 21/1000, 95% CI 1 fewer to 27 more bleeds) but fewer recurrences (128 vs 110/1000, 95% CI 40 fewer to 8 more). So be VERY thoughtful about continuing, and only in patients who are at low bleeding risk or VERY high VTE risk.

2. Optimal treatment of acute venous thromboembolism

**Clinical question:** What is the optimal treatment strategy for acute venous thromboembolism?

**Study design:** Meta-analysis (randomized controlled trials)

**Setting:** Various (meta-analysis)

**Synopsis:** These investigators performed a complicated meta-analysis comparing the clinical outcomes and safety associated with 8 different treatment regimens for acute venous thromboembolism, including deep vein thrombosis or pulmonary embolism. Multiple databases were searched, including MEDLINE, EMBASE, the Cochrane Registry, the Health Technology Assessment, and references of included studies, for randomized trials that compared at least 2 of any of the 8 various regimens to each other, but not to placebo. No language restrictions were applied. Two individuals independently evaluated potential studies for inclusion and assessed methodologic quality using a standard risk-of-bias scoring tool. Differences were resolved by consensus agreement. The primary outcomes measured included recurrent venous thromboembolism events and major bleeding episodes of clinical significance. A total of 45 articles (N = 44,989 patients) met study inclusion criteria, including 22 trials that compared a UFH–vitamin K antagonist combination with a LMWH–vitamin K antagonist combination, 12 that compared a UFH–vitamin K antagonist combination with LMWH alone, 3 that compared an LMWH–vitamin K antagonist combination with LMWH alone, 2 that compared a fondaparinux–vitamin K antagonist combination with an LMWH–vitamin K antagonist combination or an UFH–vitamin K antagonist combination, and 6 that compared an LMWH–vitamin K antagonist combination with one of the direct oral anticoagulants: 2 with dabigatran, 1 with apixaban, 1 with edoxaban, and 2 with rivaroxaban. Follow-up occurred for a median of 3 months. Compared with an LMWH–vitamin K antagonist combination, all treatment strategies except an UFH–vitamin K antagonist combination resulted in a similarly lower rate of recurrent venous thromboembolism events. The UFH–vitamin K antagonist combination was actually associated with a significantly increased rate of recurrent venous thromboembolism events (number needed to treat to harm = 188) compared with an LMWH–vitamin K antagonist combination. Compared with an LMWH–vitamin K antagonist combination, the risk of a major bleeding episode was statistically less with rivaroxaban (number needed to treat [NNT] = 258) and apixaban (NNT = 165). All of the other treatment regimens were associated with a similar risk of adverse bleeding events compared with an LMWH–vitamin K antagonist combination. Apixaban was associated with the greatest overall probability of being the least harmful therapy, although it was only evaluated in one manufacturer-sponsored trial.

**Bottom line:** This complex network meta-analysis of 8 different treatment regimens for acute venous thromboembolism found that a combination of unfractionated heparin (UFH) and vitamin K antagonists is associated with the least effective strategy with the highest risk of recurrent events. Oral rivaroxaban and apixaban may be associated with the lowest risk of bleeding, but no overall significant differences occurred for efficacy and safety compared with the combination of low-molecular-weight heparin (LMWH) and vitamin K antagonists. Rivaroxaban and apixaban have only been compared head-to-head with the traditional LMWH–vitamin K antagonist combination in 3 manufacturer-sponsored clinical trials (2 of rivaroxaban; 1 of apixaban).


3. Pulmonary embolism common in patients with first episode of syncope (PESIT)

**Clinical question:** What is the prevalence of pulmonary embolism among patients hospitalized for syncope?

**Study design:** Cross-sectional

**Setting:** Inpatient (any location)

**Synopsis:** Although PE is a known cause of syncope, evaluation for PE in patients presenting with syncope is not common. In this Italian study, physicians at 11 hospitals enrolled patients who were hospitalized for an initial episode of syncope, defined as loss of consciousness for less than 1 minute with no obvious cause (such as stroke, seizure, or trauma). All patients underwent a standard evaluation that included an assessment of the Wells score for PE and a d-dimer test. No further evaluation was done if the patient was...
at low risk and had a normal d-dimer result (~ 60% of patients). Otherwise they underwent either computed tomography angiography or a ventilation perfusion scan. Of the 2584 patients presenting to the hospital, 1867 were not admitted. Of the 717 admitted, 157 didn’t provide informed consent, were already anticoagulated, or it wasn’t their first episode. That left 560 patients in the study, most of whom were older than 70 years (mean age 76 years), and 39% were men. Most had a potential explanation for the episode; for example, it could have been neurally mediated (30%), had a cardiovascular origin (17%), or been due to orthostatic hypotension (20%). Of the 560 hospitalized syncope patients in the study, 97 had a PE (17.3%; 95% CI 14.2% - 20.5%). Most were clinically significant, in either the pulmonary artery, a lobar artery, or a segmental artery. Only 7% were subsegmental.

**Bottom line:** Among patients hospitalized for a first episode of syncope, pulmonary embolism (PE) was commonly detected. It is likely causal, as most of the PEs were clinically important. The overall prevalence in all patients with syncope is likely lower, as these hospitalized patients were probably sicker and had more comorbidities that nonhospitalized patients.


### 4. Age-adjusted D-dimer cutoff levels more accurate for PE diagnosis (ADJUST-PE)

Age-adjusting is easy. The cutoff for elevated d-dimer is 500 mcg/L up to age 50, and after that it is age x 10. So my cutoff is 550, Steve’s is 500, and Gary and John’s are, well, higher than mine!

**Clinical question:** Is the age-adjusted D-dimer cutoff level accurate for diagnosing pulmonary embolus?

**Study design:** Diagnostic test evaluation

**Setting:** Emergency department

**Synopsis:** D-dimer levels increase with age and thus may affect the clinical usefulness of the test. These investigators wished to prospectively validate the value of a progressive D-dimer cutoff adjusted to patient’s age multiplied by 10 in patients 50 years or older. Eligible patients included consecutive outpatients presenting to the emergency department of participating hospitals with clinical suspicion of PE without another obvious etiology. Previously validated clinical decision tools (Geneva or Wells) assessed the initial clinical probability of PE and patients with a high or a likely probability proceeded directly to CT pulmonary angiography (CTPA). Patients with a low/intermediate or unlikely clinical probability underwent D-dimer testing. Patients with a positive D-dimer result (> 500 mcg/L in patients younger than 50 years, and > age multiplied by 10 in patients 50 years or older) also underwent CTPA. Patients with a positive CTPA result received anticoagulant therapy. Individuals who were masked to the criteria used to rule out PE at inclusion reviewed the medical records and adjudicated all suspected VTEs and deaths. Complete follow-up occurred for 3 months. The authors note that the false negative rate of pulmonary angiography for diagnosing PE is 3%, so 3% is the accepted criterion for the validation of diagnostic strategies for PE. Of the 3324 eligible patients, clinical probability was not high in 2898 (87.2%). Of these, 1154 (39.8%) patients had a negative D-dimer result as defined by the study criteria. The use of the age-adjusted cutoff resulted in an 11.6% absolute increase in the proportion of negative D-dimer results. The overall prevalence of PE in the study was 19.0%. During the 3-month follow-up period, of the 817 patients with a D-dimer level lower than 500 mcg/L, only one adjudicated confirmed nonfatal PE occurred (0.1%; 95% CI, 0.0% - 0.7%). Of the 337 patients with a D-dimer level between 500 mcg/L and their age-adjusted cutoff, only one adjudicated confirmed nonfatal PE occurred (0.3%, 0.1% - 1.7%). In the 1539 patients with an elevated D-dimer level or with a high or likely clinical probability but with a negative CTPA result, 7 adjudicated confirmed VTEs occurred, resulting in a false negative CTPA rate of 0.5% (0.2% - 1.0%). Of the 195 patients 75 years or older with a negative D-dimer result, none had a confirmed VTE during follow-up (0.0%; 0.0% - 1.9%).

**Bottom line:** Using the age-adjusted D-dimer cutoff level (< 500 mcg/L in patients younger than 50 years and < age multiplied by 10 in patients 50 years or older) combined with probability assessment using the Geneva score or Wells score accurately ruled out the diagnosis of pulmonary embolism (PE) in the emergency department and was associated with a low likelihood of subsequent symptomatic venous thromboembolic events (VTEs). In addition, the age-adjusted D-dimer cutoff level results in an increased proportion of patients in whom the diagnosis could be accurately excluded, thus avoiding unnecessary and costly additional imaging testing.


### 5. Wells score plus age-adjusted d-dimer rules out more PEs

**Clinical question:** When added to the Wells score, how does age-adjusted d-dimer testing compare with fixed d-dimer testing to rule out pulmonary embolism?

**Study design:** Practice guideline

**Setting:** Outpatient (any)

**Synopsis:** These investigators searched MEDLINE and EMBASE for studies that prospectively evaluated a diagnostic strategy that uses the Wells rule and d-dimer testing to guide the management of patients with suspected PE in an emergency department or inpatient ward. Two authors independently selected studies and assessed each study for the potential of bias. The authors of the 6 selected studies provided individual patient data to the study investigators for the meta-analysis. The efficiency of the diagnostic strategy was defined as the proportion of patients with suspected PE who had a Wells score of 4 or less and a negative d-dimer result, thus ruling out PE. The failure rate of the diagnostic strategy was defined as the proportion of patients who were ruled out for PE (based on a Wells score of 4 or less and a negative d-dimer result) but were subsequently found to have a PE or symptomatic deep venous thrombosis during a 3-month follow-up. A safe diagnostic strategy for PE is one that has a failure rate of less than 3%. Two thresholds were used to establish a negative d-dimer result: a fixed threshold of 500 mcg/L and an age-adjusted threshold defined as the age of patients times 10 mcg/L in those older than 50 years. Of the 7288 patients in the meta-analysis, 21% had diagnosed PE at baseline.
Using the fixed d-dimer threshold, PE was ruled out in 28% of patients, with a failure rate of 0.65% and no deaths. Using the age-adjusted d-dimer threshold, PE was ruled out in 33% of patients, with a failure rate of 0.94% and 1 death. In subgroup analyses, the age-adjusted d-dimer strategy was more efficient in patients older than 75 years and in those with chronic obstructive pulmonary disease, and less so in hospitalized patients, patients with active cancer, and those with previous history of venous thromboembolism. Since this study involved patients in a secondary care setting (emergency department or inpatient ward), these results are not generalizable to an outpatient population.

**Bottom line:** As compared with a fixed d-dimer threshold, using an age-adjusted d-dimer threshold plus the Wells score for patients with suspected pulmonary embolism (PE) improves the ability of this diagnostic algorithm to rule out PE without increasing the failure rate.


The Wells score isn’t always helpful. Remember that it excludes pregnant patients, and it turns out that it isn’t very good in hospitalized patients either:

### 6. Wells score not helpful in hospitalized patients with suspected DVT

**Clinical question:** How useful is the Wells score for risk-stratifying hospitalized patients with suspected deep vein thrombosis?

**Study design:** Diagnostic test evaluation

**Setting:** Inpatient (any location)

**Synopsis:** The Wells score has been previously validated to risk-stratify outpatients with suspected DVT but its utility in the inpatient setting is unknown. These investigators evaluated 1135 hospitalized patients with suspected DVT who underwent a lower extremity ultrasound study in the hospital. When ordering these studies, clinicians were required to enter information regarding clinical predictors in order to calculate an individual patient’s Wells score. The patients were divided into 3 Wells score categories that determined their pre-test probability for DVT (low risk = 0 or lower, moderate risk = 1 or 2, high risk = 3 or higher). Baseline characteristics for the patients in the study showed that 71% were recently bedridden or had recent major surgery and almost 40% had active cancer. Overall, 12% of patients in the study had proximal DVT confirmed by a lower extremity ultrasound study. When classified by Wells score categories, the incidence of proximal DVT was 5.9%, 9.5%, and 16.4% in low, moderate, and high pre-test probability groups, respectively. The area under the receiving operating characteristics curve for the Wells score as a diagnostic test was 0.60. This indicates that the ability of the Wells score to discriminate between the presence and absence of DVT in hospitalized patients was only slightly better than chance. The authors postulate that the reason for this is that hospitalized patients are inherently different from outpatients: they have a higher prevalence of immobilization and/or have active cancer; they receive routine DVT prophylaxis; and they are more likely to have other comorbidities that increase DVT risk, such as heart failure and chronic obstructive pulmonary disease — risk factors that are not accounted for in the Wells score calculation. As such, the Wells score is less meaningful in this population.

**Bottom line:** The Wells score is not helpful in the inpatient setting to predict the presence or absence of deep vein thrombosis (DVT). Based on this study, if a hospitalized patient has a low Wells score, the risk of having DVT is still relatively high (6%). If a patient has a moderate or high score, however, the risk of having DVT is fairly low (10% to 16%). In all 3 categories, a patient would need further testing with ultrasound to evaluate for DVT.


### 7. Routine CT scans for occult malignancy not useful in patients with unprovoked VTE

**Clinical question:** Is routine computed tomography of the abdomen and pelvis in patients with an initial unprovoked episode of venous thromboembolism helpful?

**Study design:** Randomized controlled trial (single-blinded)

**Setting:** Outpatient (specialty)

**Synopsis:** Patients with an unprovoked episode of deep vein thrombosis (DVT) or pulmonary embolism (PE) are at increased risk of occult malignancy. However, the best approach to evaluate patients for cancer is unclear. In this trial, adults with a first diagnosis of an episode of DVT or PE at 1 of 9 Canadian centers were randomized to receive either a basic evaluation for occult malignancy (history and physical, basic blood tests, chest x-ray, mammogram for women older than 50 years, Pap test for sexually active women aged 18 to 70 years, and prostate cancer screening for men older than 40 years) or the same evaluation plus a comprehensive CT of the abdomen and pelvis. Patients with impaired renal function or allergy to contrast media, and those who could not easily comply with a CT scan, were excluded. A total of 3186 patients were evaluated for eligibility, 862 were randomized, and 854 were included in the intention-to-treat analysis. The mean age of the included patients was 53 years, 67% had a DVT, 33% PE, and 12% had both. Overall, 33 patients (3.9%) had a new diagnosis of cancer during the first year of follow-up: 14 in the basic screening group, and 19 in the group that also received a CT scan. The mean time to a new cancer diagnosis was 4.2 months for the patients who received basic screening, and 4 months for those who also received CT.

**Bottom line:** There is no advantage to adding computed tomography (CT) of the abdomen and pelvis to a basic screening protocol for occult malignancy in patients with unprovoked venous thromboembolism.

Compressions stockings for DVT prevention and treatment

First, are they helpful for prevention? Only at 40,000 feet, apparently:

8. IPC safer and as effective as medical prophylaxis; much better than TEDS

Clinical question: How effective is intermittent pneumatic compression for the prevention of venous thromboembolism in hospitalized patients?
Study design: Meta-analysis (randomized controlled trials)
Setting: Inpatient (any location)
Synopsis: The authors performed a careful search for randomized trials comparing IPC with either no treatment, TEDS, or pharmacotherapy in hospitalized patients to prevent DVT or PE. They also looked for studies comparing IPC plus pharmacotherapy with IPC alone. The search included PubMed, Embase (a European database), and the Cochrane Controlled Trials Register. Overall, the authors found 70 trials with a total of 16,164 patients, mostly in surgical and postoperative populations. Most trials included patients undergoing orthopedic surgery, major abdominal surgery, urologic surgery, or neurosurgery. The overall quality of studies was fair, with approximately half failing to adequately report allocation concealment or blindly assess outcomes. IPC was more effective than doing nothing in preventing PE (relative risk [RR] = 0.48; 95% CI, 0.33 - 0.69) and DVT (RR = 0.43; 0.36 - 0.52). IPC was also more effective than TEDS at preventing DVT (95% CI = 0.61; 0.39 - 0.93) but not PE (RR = 0.64; 0.21 - 1.95). Not surprisingly, when compared with medical thromboprophylaxis (usually with unfractionated or low-molecular-weight heparin), patients randomized to receive IPC had less systemic bleeding or bleeding complications (RR = 0.41; 0.25 - 0.65). The overall likelihood of DVT and PE was similar between patients given IPC or medical thromboprophylaxis, but there was considerable heterogeneity of results for the studies of DVT. There was no significant difference in mortality when medical thromboprophylaxis was added to IPC or when medical thromboprophylaxis was compared with IPC. Finally, adding medical thromboprophylaxis to IPC further reduced the risk of DVT but did not significantly reduce the likelihood of PE. As for TEDS, the relative risk was similar for prevention of DVT and PE, but because PE is much less common, the sample size may have been insufficient to demonstrate a significant reduction even if one actually existed.
Bottom line: Intermittent pneumatic compression (IPC) is more effective than doing nothing or using thromboembolic deterrent stockings (TEDS), and is similarly effective to medical thromboprophylaxis for the prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). It is also safer than anticoagulants. The authors pool the studies to determine absolute risk reductions and numbers needed to treat but this is inappropriate when the baseline risk of DVT, PE, and bleeding varies so much between studies. Using a more statistically correct approach of applying the relative risk from the meta-analysis to the baseline risk of events, I found a number needed to treat to prevent one bleed of 40 for IPC compared with medical thromboprophylaxis, and a number needed to treat of 22 to prevent one DVT by using IPC instead of TEDS.


9. Cochrane: Compression stockings for preventing deep vein thrombosis in airline passengers

Background: Air travel might increase the risk of deep vein thrombosis (DVT). It has been suggested that wearing compression stockings might reduce this risk. This is an update of the review first published in 2006.
Objectives: To assess the effects of wearing compression stockings versus not wearing them for preventing DVT in people travelling on flights lasting at least four hours.
Search methods: For this update the Cochrane Vascular Information Specialist (CIS) searched the Specialised Register (10 February 2016). In addition, the CIS searched the Cochrane Register of Studies (CENTRAL (2016, Issue 1)).
Selection criteria: Randomised trials of compression stockings versus no stockings in passengers on flights lasting at least four hours. Trials in which passengers wore a stocking on one leg but not the other, or those comparing stockings and another intervention were also eligible.
Data collection and analysis: Two review authors independently selected trials for inclusion and extracted data. We sought additional information from trialists where necessary.
Main results: One new study that fulfilled the inclusion criteria was identified for this update. Eleven randomised trials (n = 2906) were included in this review: nine (n = 2821) compared wearing graduated compression stockings on both legs versus not wearing them; one trial (n = 50) compared wearing graduated compression tights versus not wearing them; and one trial (n = 35) compared wearing a graduated compression stocking on one leg for the outbound flight and on the other leg on the return flight. Eight trials included people judged to be at low or medium risk of developing DVT (n = 1598) and two included high-risk participants (n = 1273). All flights had a duration of more than five hours.
Fifty of 2637 participants with follow-up data available in the trials of wearing compression stockings on both legs had a symptomless DVT; three wore stockings, 47 did not (odds ratio (OR) 0.10, 95% confidence interval (CI) 0.04 to 0.25, P < 0.001; high-quality evidence). There were no symptomless DVTs in three trials. Sixteen of 1804 people developed superficial vein thrombosis, four wore stockings, 12 did not (OR 0.45, 95% CI 0.18 to 1.13, P = 0.09; moderate-quality evidence). No deaths, pulmonary emboli or symptomatic DVTs were reported. Wearing stockings had a significant impact in reducing oedema (mean difference (MD) −4.72, 95% CI −4.91 to −4.52; based on six trials; low-quality evidence). A further two trials showed reduced oedema in the stockings group but could not be included in the meta-analysis as they used different methods to measure oedema. No significant adverse effects were reported.
Authors’ conclusions: There is high-quality evidence that airline passengers similar to those in this review can expect a substantial reduction in the incidence of symptomless DVT and low-quality evidence that leg oedema is reduced if they wear compression stockings. Quality was limited by the way that oedema was measured. There is moderate-quality evidence that superficial vein
thrombosis may be reduced if passengers wear compression stockings. We cannot assess the effect of wearing stockings on death, pulmonary embolism or symptomatic DVT because no such events occurred in these trials. Randomised trials to assess these outcomes would need to include a very large number of people.


What about in patients who have a DVT, to prevent post-thrombotic syndrome?

10. Compression stockings ineffective after DVT

Clinical question: Should patients who have experienced a deep vein thrombosis wear elastic compression stockings?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: To perform this systematic review these authors searched 7 databases to identify randomized controlled trials that evaluated the effectiveness of elastic compression stockings worn after deep vein thrombosis (DVT). Two authors independently screened articles for inclusion and extracted the data. Five of the 6 included studies were unblinded and of low quality. Heterogeneity was very high among the studies of postthrombotic syndrome. Publication bias could not be assessed because of the small number of studies. All studies evaluated the effect of elastic compression stockings that produced at least 20 mmHg of increased pressure following a first-time DVT. Using pooled data from a total of 1418 patients, the stockings did not significantly reduce the likelihood of developing postthrombotic syndrome. Similarly, stockings did not reduce mortality, the likelihood of recurrence, or (in the single study evaluating it) pain.
Bottom line: Elastic compression stockings do not relieve pain or prevent postthrombotic syndrome or its recurrence in patients who have experienced venous thromboembolism. They will, however, give you that "I've just been in the hospital" look.


11. Compression stockings = placebo stockings in preventing post-thrombotic syndrome (SOX)

Clinical question: Are compression stockings effective in preventing post-thrombotic syndrome in patients with deep vein thrombosis?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: In this multicenter study, patients with their first proximal DVT were randomized to 2 years of compression stockings (30 to 40 mmHg gradient; n = 410) or placebo stockings (5 mmHg; n = 396). The stockings were given within 2 weeks of the DVT and were replaced every 6 months (sooner if they were worn, got torn, or the patient's leg changed size). The researchers evaluated the patients at baseline and 1, 6, 12, 18, and 24 months. The patients did not wear their stockings to these visits (scheduled for the afternoon) to facilitate the evaluation of signs of post-thrombotic syndrome. The authors defined post-thrombotic syndrome as ipsilateral pain and swelling that lasted at least 1 month that was worse at the end of the day or with prolonged sitting or standing and better in the morning or with leg elevation. Overall, the rate of post-thrombotic syndrome was not statistically different in patients treated with compression stockings than in patients treated with placebo stockings (14.2% vs 12.7%; P = 0.6). These findings are strengthened in light of the potential bias introduced by the authors' analytic approach.
Bottom line: Compression stockings are no better than placebo stockings in preventing post-thrombotic syndrome in patients after their first proximal deep vein thrombosis (DVT).


Treatment of pulmonary embolism

Thrombolysis is of limited value, and is only recommended by ACCP guidelines for patients with PE if they are hypotensive and do not have a high bleeding risk, or if they are deteriorating after anticoagulation is initiated and have a low bleeding risk. Here's why they say that:

12. Fibrinolysis for intermediate-risk PE: increased bleeding, no mortality effect

Clinical question: Does the use of fibrinolytic therapy improve mortality and morbidity in normotensive patients with acute pulmonary embolism who are at intermediate risk for adverse outcomes?
Study design: Randomized controlled trial (nonblinded)
Setting: Inpatient (any location)
Synopsis: These authors enrolled adult patients with acute PE who were hemodynamically stable and were considered to have an intermediate risk for adverse outcomes as indicated by right ventricular dysfunction or myocardial injury. Right ventricular dysfunction was confirmed by either echocardiography or chest computed tomography, and myocardial injury was confirmed by a positive troponin test result. Using concealed allocation, investigators randomized these patients (N = 1006) to receive either fibrinolysis with tenecteplase at a weight-based dose or matching placebo. Both groups also received full anticoagulation with unfractionated heparin. Baseline characteristics were similar in the 2 groups and analysis was by intention to treat. Fewer patients in the tenecteplase group experienced the primary outcome of death or hemodynamic decompensation at 7 days (2.6% vs 5.6%; odds ratio = 0.44; 95% CI, 0.23-0.74) but the difference was not statistically significant (P = 0.08). The mortality rate was 2.0% in the fibrinolysis group compared with 4.0% in the placebo group (OR = 0.49; 95% CI, 0.23-1.05). These results support the ACCP guidelines, but do not refute the need for further research on fibrinolysis for intermediate-risk PE.

13. Thrombolysis for PE reduces rate of all-cause mortality but increases risk of major bleeding

Clinical question: Is thrombolytic therapy beneficial in the treatment of adults with pulmonary embolism?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: Two investigators independently searched multiple databases including the Cochrane Library, MEDLINE, EMBASE, EBSCO, and others without language restrictions for randomized trials evaluating thrombolytic therapy in patients with PE. Standard rating scales were applied for evaluating study appropriateness, methodologic quality, and risk of bias. Disagreements were resolved by consensus. Data analysis included the presence or absence of RV dysfunction as assessed by reported abnormalities on echocardiogram, abnormalities of troponin and brain natriuretic peptide, or both. Sixteen randomized controlled trials (N = 2125) met inclusion criteria, including 210 patients (9.9%) with low-risk PE (hemodynamically stable without objective evidence of RV dysfunction), 1499 (70.5%) with intermediate-risk PE (hemodynamically stable with objective evidence of RV dysfunction), and 31 (1.5%) with high-risk PE (hemodynamically unstable and/or documented systolic blood pressure < 90 mmHg), and 385 (18.1%) without risk-classified PE. Thrombolytic therapy was associated with a significantly decreased risk of all-cause mortality (number needed to treat = 59; 95% CI, 31-380) compared with standard anticoagulant therapy. Thrombolytic therapy also significantly increased the risk of major bleeding and intracranial hemorrhage (number needed to treat to harm [NNTH] = 18, 13-27) compared with anticoagulant therapy (NNTH = 78; 48-206). Statistical analysis found no evidence of significant heterogeneity in the results or evidence of publication bias. In the subgroup of patients 66 years or older, there was a significantly greater risk of major bleeds without a significant decrease in all-cause mortality. No increased risk of major bleeding occurred in patients 65 years or younger. Thrombolysis was similarly beneficial and risky in those trials specifically enrolling only patients who were hemodynamically stable with evidence of RV dysfunction. The majority of the benefit of thrombolysis occurred in patients with intermediate-risk PE and it is uncertain whether thrombolysis is beneficial in patients with low-risk PE and no RV dysfunction.
Bottom line: Thrombolytic therapy is associated with a reduced risk of all-cause mortality but an increased risk of major bleeding and intracerebral hemorrhage in adults with pulmonary embolism (PE), including those who are hemodynamically stable with right ventricle (RV) dysfunction. The majority of the benefit of thrombolysis occurred in patients with intermediate-risk PE and it is uncertain if it is beneficial in patients with low-risk PE and no RV dysfunction. Thrombolysis was most beneficial in patients 65 years or younger.

14. Temporary IVC filter added to anticoagulation does not decrease risk of PE recurrence

Clinical question: Does the insertion of a retrievable inferior vena cava filter in addition to anticoagulation prevent the recurrence of pulmonary embolism in high-risk patients?
Study design: Randomized controlled trial (nonblinded)
Setting: Inpatient (any location) with outpatient follow-up
Synopsis: The utility of retrievable IVC filters added to anticoagulation for the prevention of recurrent PE is unknown. This study included adults who were hospitalized for acute PE associated with lower extremity venous thrombosis and had one additional criterion for severity (older than 75 years, active cancer, chronic cardiopulmonary conditions, recent stroke with leg paralysis, iliocaval or bilateral venous thromboses, or evidence of right ventricular dysfunction or myocardial injury). The patients were randomized, using concealed allocation, to receive a filter plus anticoagulation or anticoagulation alone. Both groups were anticoagulated for at least 6 months and filters were retrieved at 3 months. More patients in the filter group had chronic respiratory failure at baseline but the groups were otherwise well matched. Analysis was by intention to treat. At 3 months, the rate of recurrent PE did not differ between the 2 groups (3% in filter group vs 1.5% in control group; P = .50; RR with filter 2.00; 95% CI 0.51-7.89). Additionally, there were no differences detected in venous thromboembolism recurrence, major bleeding, or death at either 3 or 6 months. Complications in the filter group included access site hematomas, filter thromboses, and filter retrieval failures. The authors based their analysis on an expected PE recurrence rate of 8% in the control group but the actual rate was much lower. Although this results in an underpowered study, the authors note that the point estimate of the relative risk still favors the control group and if filters did confer a small advantage it would likely not be clinically meaningful.
Bottom line: For patients with pulmonary embolism (PE) who are at high risk of recurrence or who have poor cardiopulmonary reserve, the addition of a retrievable inferior vena cava (IVC) filter plus anticoagulation does not decrease the risk of recurrent PE as compared with anticoagulation alone. Although this study was underpowered to detect a difference if one truly exists, the authors postulate that
such a difference would likely be small and thus clinically irrelevant.


Secondary Prevention of VTE

The ACC guidelines recommend LMWH for patients with cancer and VTE to prevent recurrence. But not so fast – this study shows that warfarin is just as good (and of course, way cheaper):

15. Tinzaparin no better than warfarin in preventing recurrent VTE in adults with cancer

Clinical question: Is the low-molecular-weight heparin tinzaparin more effective and safer than warfarin for preventing recurrent venous thromboembolism in adults with active cancer?

Study design: Randomized controlled trial (single-blinded)

Setting: Outpatient (any)

Synopsis: Clinical guidelines generally recommend treating VTE in adults with active cancer with low-molecular-weight heparin rather than vitamin K antagonists. These investigators enrolled 900 adults, 18 years or older, with active cancer and acute symptomatic proximal deep vein thrombosis, pulmonary embolism, or both. Eligible patients randomly received (concealed allocation assignment) tinzaparin 175 IU/kg subcutaneously once daily for 6 months or the same dose of tinzaparin for the first 5 to 10 days and then standard-protocol warfarin for 6 months. INR testing occurred at least once every week to maintain a therapeutic range (2.0 - 3.0). Although patients and their clinicians knew treatment group assignment (open label), individuals masked to treatment group assignment assessed all outcomes, including recurrent VTE, bleeding events, and causes of death. Complete follow-up occurred for 91% of patients at 180 days. Using intention-to-treat and per-protocol analyses, there were no significant differences between the 2 treatment groups in the rate of VTE recurrence. Similarly, there were also no significant group differences in major bleeding events or all-cause mortality. Nonmajor bleeding events that were not fatal, did not occur in a critical area (eg, intracranial) or in an organ, or led to a blood transfusion of 2 or more units occurred significantly less often in the tinzaparin group than in the warfarin group (number needed to treat = 23). There were no group differences in drug discontinuation due to adverse events. The study was 90% powered to detect predetermined clinically significant difference between the groups.

Bottom line: In adults with active cancer and acute symptomatic venous thromboembolism (VTE), daily therapy with tinzaparin (Innohep) for 6 months was not superior to standard warfarin therapy for 6 months in preventing recurrent VTE or reducing major bleeding and all-cause mortality.


16. Continuing warfarin for 18 months after unprovoked PE reduces risk of recurrent VTE

Clinical question: Does continuing warfarin for 18 months after an unprovoked pulmonary embolism reduce the risk of recurrent venous thrombotic events?

Study design: Randomized controlled trial (double-blinded)

Setting: Inpatient (any location) with outpatient follow-up

Synopsis: Patients with unprovoked VTE have a higher risk of recurrence than those with a provoked event. This is the first study to evaluate extended anticoagulation beyond 6 months for patients with unprovoked pulmonary embolism. The authors enrolled adults (N = 371), 18 years or older, who received 6 months of therapy with a vitamin K antagonist following their first episode of symptomatic unprovoked pulmonary embolism. Patients randomly continued to receive (concealed allocation assignment) warfarin (target international normalized ratio [INR] = 2 - 3) or placebo for 18 months. The investigators maintained double-blinding with the use of sham INR tests and results for the placebo group. Individuals who assessed outcomes remained masked to treatment group assignment. Complete follow-up occurred for 97.8% of patients at 18 months and for 76.3% at 42 months. Using intention-to-treat analysis, 3 of 184 patients in the warfarin group and 25 of 187 in the placebo group developed a symptomatic recurrent VTE during the 18-month treatment period (number needed to treat = 8.5, 95% Cl 5.7-15.2). During the same period, 4 of 184 patients in the warfarin group and 1 of 187 patients in the placebo group suffered a major bleed (number needed to treat to harm = 61). After discontinuation of therapy at 18 months, the risk of symptomatic recurrent VTE in the warfarin group increased so that over the course of the entire study period (42 months) there was not a significant difference in the number of symptomatic recurrent VTEs between treatment groups. Thus, extending anticoagulation with warfarin beyond 6 months after an unprovoked VTE reduces the risk of recurrence, but only during the time of anticoagulation. Please attribute the authorship of this POEM to Kristina Gern Johnson, MD, Assistant Professor, Department of Family Medicine, The University of Virginia, Charlottesville, VA.

Bottom line: Continuing warfarin therapy for 18 months after an unprovoked pulmonary embolism reduces the risk of recurrent symptomatic venous thromboembolism (VTE). However, benefit after 18 months is not maintained after the warfarin is discontinued.


17. Patients with initial unprovoked DVT or PE benefit from long-term low-dose aspirin (INSPIRE)

Clinical question: Does aspirin reduce the likelihood of recurrent venous thromboembolism when used after the discontinuation of anticoagulation?
Study design: Meta-analysis (randomized controlled trials)

Setting: Outpatient (any)

Synopsis: This was an individual patient meta-analysis. In most meta-analyses, authors are limited to using published, aggregated data, but by combining data from different studies at the individual patient level, there is greater statistical power to detect important clinical effects. The authors of this report combined data from 2 previous trials: WARFASA with 403 patients and ASPIRE with 822. The trials had similar designs and populations (nonpregnant adults with a first unprovoked deep vein thrombosis or pulmonary embolism). There were 56 withdrawals from these studies before the end of the study period because of revoked consent (31), no qualifying VTE episode (12), and loss to follow-up (13). The WARFASA study followed patients for up to 2 years, and ASPIRE for up to 4 years. The intervention in each study was aspirin 100 mg given once daily or matching placebo, and analysis was by intention to treat. The anticoagulation protocol was low-molecular-weight heparin initially followed by warfarin for most patients. The rate of recurrent VTE was approximately one third lower in the aspirin group (5.1% vs 7.5% per year; P = .008; number needed to treat [NNT] = 42 per year), with a similar hazard ratio of 0.66 for deep vein thrombosis and pulmonary embolism. The rate of myocardial infarction, stroke, or cardiovascular death was also lower (5.7% vs 8.7% per year; P = .002; NNT = 33 per year), and there was no difference in the risk of major bleeding (0.4% per year in the placebo group versus 0.5% in the aspirin group). The combined outcome of any bad thing (major vascular event, major bleeding, or death from any cause) was lower in the aspirin group as well (6.5% vs 9.8% per year; P = .002; NNT = 30). Aspirin's benefit was greatest in the first year, but a consistent and significant benefit was seen in years 2 through 4.

Bottom line: Aspirin improves long-term cardiovascular and thrombotic outcomes in patients who have had an initial unprovoked episode of venous thromboembolism (VTE). The risk of bleeding was no higher in the aspirin group, perhaps because those at risk for bleeding were "uncovered" during the initial period of anticoagulation.


Using a higher estrogen dose roughly doubles the risk of PE, stroke, or MI, as does use of something other than levonorgestrel for the progestogen.

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.


Absolute risks are relatively small, though. Unadjusted incidence rates are shown below per 100,000 woman-years:

<table>
<thead>
<tr>
<th></th>
<th>PE</th>
<th>Stroke</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen dose 20 mcg vs 30 to 40 mcg</td>
<td>31.9 vs 33.5</td>
<td>13.6 vs 20.6</td>
<td>3.1 vs 8.6</td>
</tr>
<tr>
<td>Levonorgestrel vs desogestrel vs gestodene</td>
<td>27.9 vs 46.9 vs 39.5</td>
<td>20.3 vs 14.2 vs 17.9</td>
<td>8.4 vs 4.4 vs 2.7</td>
</tr>
</tbody>
</table>
Bottom Lines

1) Age-adjust your d-dimer to do a better job of ruling out PE

2) Compression stockings aren’t very helpful except perhaps in airline passengers on long-haul flights

3) Prolonged anticoagulation is recommended for selected patients; aspirin may also be helpful.

4) Thrombolysis for PE should only be used selectively and as a last resort, and retrievable IVC filters add nothing to anticoagulation
Cardiovascular Disease

Gary Ferenchick, MD, MS

Objectives

1. Understand the many categories and specific recommendations on CV disease detection and prevention published by the USPSTF.
2. Understand the results of the Systolic Blood Pressure Intervention Trial (SPRINT) trial compared to the ACCORD BP Trial, and its relevance to cardiovascular disease prevention.
3. Understand the results of the EMPA-REG OUTCOME trial and its relevance to cardiovascular disease prevention in diabetics.
4. Understand that PCI PLUS optimal medical therapy is offers no survival benefit over optimal medical therapy alone in patients with stable CAD
5. Understand that DAPT (ASA PLUS clopidogrel) is not associated with a mortality benefit in patients at high risk for CAD

USPSTF Update

The USPSTF has at least a dozen recommendations applying to different populations on CV disease detection and/or prevention.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade (see Table in appendix)</th>
<th>Last update</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Aortic Aneurysm: Screening with a single US</td>
<td></td>
<td>2014</td>
</tr>
<tr>
<td>Men 65-75 who have ever smoked</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Men 65-75 who have never smoked</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Women 65-75 who have ever smoked</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Women who have never smoked</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: Preventive Medication</td>
<td></td>
<td>2016</td>
</tr>
<tr>
<td>Adults aged 50 to 59 years with a ≥10% 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Adults aged 60 to 69 years with a ≥10% 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Adults younger than 50 years</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Adults aged 70 years or older</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Blood Pressure in Children and Adolescents (Hypertension): Screening</td>
<td>I</td>
<td>2013</td>
</tr>
<tr>
<td>Carotid Artery Stenosis: Screening</td>
<td>D</td>
<td>2014</td>
</tr>
</tbody>
</table>
**Coronary Heart Disease: Screening Using Non-Traditional Risk Factors**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2009*</td>
</tr>
</tbody>
</table>

**Coronary Heart Disease: Screening with Electrocardiography**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2012*</td>
</tr>
</tbody>
</table>

**Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults With Cardiovascular Risk Factors: Behavioral Counseling**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>2014</td>
</tr>
</tbody>
</table>

**Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults: Behavioral Counseling**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2012*</td>
</tr>
</tbody>
</table>

**High Blood Pressure in Adults: Screening**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2015</td>
</tr>
</tbody>
</table>

**Lipid Disorders in Adults (Cholesterol, Dyslipidemia): Screening**

<table>
<thead>
<tr>
<th>Sex and Age</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men 35 and older</td>
<td>A</td>
</tr>
<tr>
<td>Men 20-35 at Increased Risk for CHD</td>
<td>B</td>
</tr>
<tr>
<td>Women 45 and Older at Increased Risk for CHD</td>
<td>A</td>
</tr>
<tr>
<td>Women 20-45 at Increased Risk for CHD</td>
<td>B</td>
</tr>
</tbody>
</table>

**Lipid Disorders in Children and Adolescents: Screening**

<table>
<thead>
<tr>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
</tr>
</tbody>
</table>

**Peripheral Arterial Disease (PAD) and CVD in Adults: Risk Assessment with Ankle Brachial Index**

<table>
<thead>
<tr>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013*</td>
</tr>
</tbody>
</table>

**Vitamin Supplementation to Prevent Cancer and CVD: Counseling**

<table>
<thead>
<tr>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
</tr>
</tbody>
</table>

**Use of Multivitamins to Prevent Cardiovascular Disease or Cancer**

<table>
<thead>
<tr>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
</tr>
</tbody>
</table>

**Single- or Paired-Nutrient Supplements for Prevention of Cardiovascular Disease or Cancer**

<table>
<thead>
<tr>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
</tr>
</tbody>
</table>

**Use of β-carotene or Vitamin E for Prevention of Cardiovascular Disease or Cancer**

<table>
<thead>
<tr>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
</tr>
</tbody>
</table>

* update in progress as of 9/7/2016

---

**Hypertension**

It is uncommon to have 2 two potential landmark articles relevant to the day-to-day practice of primary care published in the same issue of a journal at the same time. The November 26 New England Journal of Medicine edition included two such articles: the Systolic Blood Pressure Intervention Trial (SPRINT) trial (abstract #1) and the EMPA-REG OUTCOME trial (abstract #3). Both of these trials warrant a close look as they have the potential to change our practices.

In February of 2014 the JNC VIII published the "2014 evidence-based guideline for the management of high blood pressure in adults. This was the first time in the JNC series where randomized trial evidence was heavily used to develop the final recommendations. In part, the new recommendations recommended only treating systolic blood pressures of ≥ 140 (for those < 60) or ≥ 150 (for those ≥ 60). These recommendations were, in part, informed by the results of the ACCORD BP Trial (abstract #2), which provide an important caveat to the
application of the SPRINT results. As with any guideline, the research continues to evolve and we need to adapt our practices accordingly. Parenthetically, this is one of many reasons why quality metrics and payment incentive programs built upon guidelines need to be carefully assessed.

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 and many other important exclusion criteria.

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 was seen in 1 year
  - 90 to prevent one death from any cause; the separation 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)
  o No major difference in those > 75 compared to the total population

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.


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.)


Diabetes and macrovascular disease

We know that targeting an HbA1c of ~7% is not associated with improved macrovascular outcomes compared to an A1c of ~8%. We also know that metformin is associated with improved macrovascular outcomes independent of HbA1c (UKPDS). No other class of drugs has been associated with improved macrovascular outcomes, in spite of the fact that all of them 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 “Cardiovascular disease is the major cause of morbidity and mortality for individuals with diabetes”. 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, the EMPA-REG Trial garnered lots of attention. Is there a new (albeit much more expensive!) metformin? Given this, the industry sponsored EMPA-REG trial also deserves a more in-depth analysis.

The patients enrolled in EMPA-REG were an especially high risk group. Nearly half the patients had a history of myocardial infarction, and about three quarters had evidence of coronary artery disease, a quarter had previous stroke, and a fifth had peripheral vascular disease. A majority of the patients had more than a 10-year history of type 2 diabetes, a third had microalbuminuria, and a tenth had macroalbuminuria. Not surprisingly, most patients were taking multiple medications for hyperglycemia, more than 95% were taking antihypertensive agents, and 80% were taking lipid-lowering drugs. Unfortunately, the vast majority of the patients were white, which makes the results difficult to generalize to black and Hispanic patients.

The appendix includes specific data and estimates of the number needed to treat over 3 years for one person to benefit. As with many studies, the reporting of harms is not very robust and important and uncommon events take much longer and many more patients before they are identified. Additionally, this is the first study showing such a benefit. History has taught us that subsequent studies often fail to demonstrate the same effects and many important journals, especially Lancet and the New England Journal of Medicine, publish many industry-sponsored studies that subsequently are disproven. The risk–benefit profile for this drug class will need further elucidation (particularly for adverse events), and the ultimate position of empagliflozin among multiple drugs in the management of patients with type 2 diabetes is still undefined.

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.).


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

4. 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.


5: PubMed: Vildagliptin (a DPP-IV inhibitor) not associated with ↑ CHF rates

AIMS: To report the cardiovascular (CV) safety profile and heart failure (HF) risk of vildagliptin from a large pool of studies, including trials in high-risk patients with type 2 diabetes mellitus (T2DM), such as those with congestive HF and/or moderate/severe renal impairment.

METHODS: We conducted a retrospective meta-analysis of prospectively adjudicated CV events. Patient-level data were pooled from 40 double-blind, randomized controlled phase III and IV vildagliptin studies. The primary endpoint was occurrence of major adverse CV events (MACEs; myocardial infarction, stroke, and CV death). Assessments of the individual MACE components and HF events (requiring hospitalization or new onset) were secondary endpoints. The risk ratio (RR) of vildagliptin (50 mg once- and twice-daily combined) versus comparators (placebo and all non-vildagliptin treatments) was calculated using the Mantel-Haenszel (M-H) method.

RESULTS: Of the 17,446 patients, 9,599 received vildagliptin (925.1 subject-years of exposure) and 7,847 received comparators (7317.0 subject-years of exposure). The mean age of the patients was 57 years, body mass index 30.5 kg/m(2) (nearly 50% obese), glycated haemoglobin concentration 8.1% and T2DM duration 5.5 years. A MACE occurred in 83 (0.86%) vildagliptin-treated patients and 85 (1.20%) comparator-treated patients, with an M-H RR of 0.82 [95% confidence interval (CI) 0.61-1.11]. Similar RRs were observed for the individual events. Confirmed HF events were reported in 41 (0.43%) vildagliptin-treated patients and 32 (0.45%) comparator-treated patients, with an M-H RR 1.08 (95% CI 0.68-1.70).

CONCLUSIONS: This large meta-analysis indicates that vildagliptin is not associated with an increased risk of adjudicated MACEs relative to comparators. Moreover, this analysis did not find a significant increased risk of HF in vildagliptin-treated patients.


6: PubMed: Sitagliptin (another DPP-IV inhibitor) not associated with ↑ MACE rates

BACKGROUND: Data are lacking on the long-term effect on cardiovascular events of adding sitagliptin, a dipeptidyl peptidase 4 inhibitor, to usual care in patients with type 2 diabetes and cardiovascular disease.

METHODS: In this randomized, double-blind study, we assigned 14,671 patients to add either sitagliptin or placebo to their existing therapy. Open-label use of antihyperglycemic therapy was encouraged as required, aimed at reaching individually appropriate glycemic targets in all patients. To determine whether sitagliptin was noninferior to placebo, we used a relative risk of 1.3 as the marginal upper boundary. The primary cardiovascular outcome was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina.

RESULTS: During a median follow-up of 3.0 years, there was a small difference in glycated hemoglobin levels (least-squares mean difference for sitagliptin vs. placebo, -0.29 percentage points; 95% confidence interval [CI], -0.32 to -0.27). Overall, the primary outcome occurred in 839 patients in the sitagliptin group (11.4%; 4.06 per 100 person-years) and 851 patients in the placebo group (11.6%; 4.17 per 100 person-years). Sitagliptin was noninferior to placebo for the primary composite cardiovascular outcome (hazard ratio, 0.98; 95% CI, 0.88 to 1.09; P=0.001). Rates of hospitalization for heart failure did not differ between the two groups (hazard ratio, 1.00; 95% CI, 0.83 to 1.20; P=0.98). There were no significant between-group differences in rates of acute pancreatitis (P=0.07) or pancreatic cancer (P=0.32).

CONCLUSIONS: Among patients with type 2 diabetes and established cardiovascular disease, adding sitagliptin to usual care did not appear to increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events. (Funded by Merck Sharp & Dohme; TECOS ClinicalTrials.gov number, NCT00790205.)

Coronary Artery Disease

7: POEM: No survival advantage to PCI vs optimal medical therapy (COURAGE)

Clinical Question: Does a percutaneous coronary intervention, when added to optimal medical therapy, improve survival in patients with stable coronary artery disease?
Study Design: Randomized controlled trial (single-blinded)
Funding: Government
Allocation: Uncertain
Setting: Outpatient (any)
Synopsis: The original COURAGE trial identified 2287 adults with chronic stable angina, defined as typical ECG findings and symptoms accompanied by at least a 70% stenosis of one coronary artery. Most had class II or class III angina that had been diagnosed a mean of 2 years previously; approximately two-thirds had multivessel disease. The patients were randomized to receive a percutaneous coronary intervention (chosen by their cardiologist) plus optimal medical therapy, or optimal medical therapy alone. Medical therapy had targets of 70 mg/dL for low-density lipoprotein cholesterol and 130/85 for blood pressure. The original study had a median follow-up of 4.6 years and found no difference in clinical outcomes between groups. At the time of enrollment, where not forbidden by human subjects committees (Canada and some non-VA hospitals), patients were asked for their Social Security number so mortality could be tracked over the long term. Social Security numbers were obtained for slightly more than half of the patients in each original study group (613 in the PCI group and 598 in the medical therapy group). The extended follow-up period was a median of 11.9 years, and the researchers found no difference in all-cause mortality between the 2 groups (24% vs 25%). PMID: 26559572
Bottom Line: This extended follow-up of the largest trial comparing percutaneous coronary intervention (PCI) with medical therapy still found no survival advantage of PCI plus optimal medical therapy over optimal medical therapy alone. (LOE = 1b)

8: PubMed: PPI not associated with increased risk of CV events in patients on clopidogrel

BACKGROUND: Dual antiplatelet therapy is the standard of care after coronary stent placement but increases the bleeding risk. The effects of proton pump inhibitors (PPIs) on clopidogrel metabolism have been described, but the clinical significance is not yet definitive. We aimed to do an updated meta-analysis comparing outcomes in patients receiving clopidogrel with and without PPIs.
METHODS: We systematically searched PubMed, Scopus and the Cochrane Central Register of Controlled Trials for randomised controlled trials (RCTs) and controlled observational studies in patients taking clopidogrel stratified by concomitant PPI use. Heterogeneity was examined with the Cochran Q test and I(2) statistics; p values inferior to 0.10 and I(2) >25% were considered significant for heterogeneity.
RESULTS: We included 39 studies with a total of 214 851 patients, of whom 73 731 (34.3%) received the combination of clopidogrel and a PPI. In pooled analysis, all-cause mortality, myocardial infarction, stent thrombosis and cerebrovascular accidents were more common in patients receiving both drugs. However, among 23 552 patients from eight RCTs and propensity-matched studies, there were no significant differences in mortality or ischaemic events between groups. The use of PPIs in patients taking clopidogrel was associated with a significant reduction in the risk of gastrointestinal bleeding.
CONCLUSIONS: The results of our meta-analysis suggest that PPIs are a marker of increased cardiovascular risk in patients taking clopidogrel, rather than a direct cause of worse outcomes. The pharmacodynamic interaction between PPIs and clopidogrel most likely has no clinical significance. Furthermore, PPIs have the potential to decrease gastrointestinal bleeding in clopidogrel users.

9: POEM: FDA: Clopidogrel/aspirin (DAPT) does not decrease overall mortality

Clinical Question: Is clopidogrel/aspirin treatment effective in decreasing overall mortality in patients with acute coronary syndrome or in patients at risk of coronary artery disease?
Study Design: Meta-analysis (randomized controlled trials)
Funding: Government
Setting: Various (meta-analysis)
Synopsis: Following the publication of the Dual Antiplatelet Therapy trial in 2014, which showed a significantly increased risk of death associated with clopidogrel plus aspirin following percutaneous coronary intervention and the placement of a drug-eluting stent, the FDA conducted a meta-analysis of 12 trials enrolling a total of 56,799 patients. Overall, there was no decrease—or increase—in mortality due to any cause in patients with CAD treated with clopidogrel/aspirin (6.7% vs 6.6%). There was also no difference in mortality in patients who are at risk of CAD. Although the FDA is not in the comparative treatment business, they suggest “prescribers should consider that prasugrel and ticagrelor have been shown to be superior to clopidogrel when used in this patient population.”
Bottom Line: The U.S. Food and Drug Administration (FDA) concludes that clopidogrel (Plavix), when added to aspirin, does not change the overall risk of death in patients with, or at risk for, coronary artery disease (CAD). The official labeling of clopidogrel will be changed to reflect this conclusion. They suggest prasugrel (Effient) or ticagrelor (Brilinta) following coronary stent implantation, and ticagrelor for patients with a history of myocardial infarction. (LOE = 1a)
10: POEM: The effect of totally eliminating 5 leading risk factors for CV mortality?

**BACKGROUND:** Impressive decreases in cardiovascular mortality have been achieved through risk factor reduction and clinical intervention, yet cardiovascular disease remains a leading cause of death nationally.

**OBJECTIVE:** To estimate up-to-date preventable fractions of cardiovascular mortality associated with elimination and reduction of 5 leading risk factors nationally and by state in the United States.

**DESIGN:** Cross-sectional and cohort studies.

**SETTING:** Nationally representative and state-representative samples of the U.S. population.

**PARTICIPANTS:** Adults aged 45 to 79 years.

**MEASUREMENTS:** Self-reported risk factor status in the BRFSS (Behavioral Risk Factor Surveillance System) 2009-2010 was corrected to approximate clinical definitions. The relative hazards of cardiovascular death (International Classification of Diseases, 10th Revision, codes I00 to I99) associated with risk factors were estimated using data from NHANES (National Health and Nutrition Examination Survey) (1988-1994 and 1999-2004, followed through 2006).

**RESULTS:** The preventable fraction of cardiovascular mortality associated with complete elimination of elevated cholesterol levels, diabetes, hypertension, obesity, and smoking was 54.0% for men and 49.6% for women in 2009 to 2010. When the more feasible target of reducing risk factors to the best achieved levels in the states was considered, diabetes (1.7% and 4.1%), hypertension (3.8% and 7.3%), and smoking (5.1% and 4.4%) were independently associated with the largest preventable fractions among men and women, respectively. With both targets, southern states had the largest preventable fractions, and western states had the smallest.

**LIMITATION:** Self-reported state data; mortality hazards relied on baseline risk factor status.

**CONCLUSION:** Major modifiable cardiovascular risk factors collectively accounted for half of cardiovascular deaths in U.S. adults aged 45 to 79 years in 2009 to 2010. Fewer than 10% of cardiovascular deaths nationally could be prevented if all states were to achieve risk factor levels observed in the best-performing states.

**PRIMARY FUNDING SOURCE:** Robert Wood Johnson Foundation.


Coronary Artery Calcification (CAC) Anatomic Testing

11: PubMed: CAC predicts 15 year mortality in asymptomatic persons

**BACKGROUND:** The extent of coronary artery calcification (CAC) and near-term adverse clinical outcomes are strongly related through 5 years of follow-up.

**OBJECTIVE:** To describe the ability of CAC scores to predict long-term mortality in persons without symptoms of coronary artery disease.

**DESIGN:** Observational cohort.

**SETTING:** Single-center, outpatient cardiology laboratory.

**PATIENTS:** 9715 asymptomatic patients.

**MEASUREMENTS:** Coronary artery calcification scoring and binary risk factor data were collected. The primary end point was time to all-cause mortality (median follow-up, 14.6 years). Univariable and multivariable Cox proportional hazards models were used to compare survival distributions. The net reclassification improvement statistic was calculated.

**RESULTS:** In Cox models adjusted for risk factors for coronary artery disease, the CAC score was highly predictive of all-cause mortality (P < 0.001). Overall 15-year mortality rates ranged from 3% to 28% for CAC scores from 0 to 1000 or greater (P < 0.001). The relative hazard for all-cause mortality ranged from 1.68 for a CAC score of 1 to 10 (P < 0.001) to 6.26 for a score of 1000 or greater (P < 0.001). The categorical net reclassification improvement using cut points of less than 7.5% to 22.5% or greater was 0.21 (95% CI, 0.16 to 0.32).

**LIMITATIONS:** Data collection was limited to a single center with generalizability limitations. Only binary risk factor data were available, and CAC was only measured once.

**CONCLUSION:** The extent of CAC accurately predicts 15-year mortality in a large cohort of asymptomatic patients. Long-term estimates of mortality provide a unique opportunity to examine the value of novel biomarkers, such as CAC, in estimating important patient outcomes.

**PRIMARY FUNDING SOURCE:** None.


12: PubMed: CAC in symptomatic persons not better than functional testing

**BACKGROUND:** Many patients have symptoms suggestive of coronary artery disease (CAD) and are often evaluated with the use of diagnostic testing, although there are limited data from randomized trials to guide care.

**METHODS:** We randomly assigned 10,003 symptomatic patients to a strategy of initial anatomical testing with the use of coronary computed tomographic angiography (CTA) or to functional testing (exercise electrocardiography, nuclear stress testing, or stress...
echoangiography). The composite primary end point was death, myocardial infarction, hospitalization for unstable angina, or major procedural complication. Secondary end points included invasive cardiac catheterization that did not show obstructive CAD and radiation exposure.

RESULTS: The mean age of the patients was 60.8±8.3 years, 52.7% were women, and 87.7% had chest pain or dyspnea on exertion. The mean pretest likelihood of obstructive CAD was 53.3±21.4%. Over a median follow-up period of 25 months, a primary end-point event occurred in 164 of 4996 patients in the CTA group (3.3%) and in 151 of 5007 (3.0%) in the functional-testing group (adjusted hazard ratio, 1.04; 95% confidence interval, 0.83 to 1.29; P=0.75). CTA was associated with fewer catheterizations showing no obstructive CAD than was functional testing (3.4% vs. 4.3%, P=0.02), although more patients in the CTA group underwent catheterization within 90 days after randomization (12.2% vs. 8.1%). The median cumulative radiation exposure per patient was lower in the CTA group than in the functional-testing group (10.0 mSv vs. 11.3 mSv), but 32.6% of the patients in the functional-testing group had no exposure, so the overall exposure was higher in the CTA group (mean, 12.0 mSv vs. 10.1 mSv; P<0.001).

CONCLUSIONS: In symptomatic patients with suspected CAD who required noninvasive testing, a strategy of initial CTA, as compared with functional testing, did not improve clinical outcomes over a median follow-up of 2 years. (Funded by the National Heart, Lung, and Blood Institute; PROMISE ClinicalTrials.gov number, NCT01174550.)


Resistant HTN

13: POEM: Spironolactone most effective add-on for patients with resistant hypertension (PATHWAY-2)

Clinical Question: In patients with resistant hypertension (poor control despite the maximum dosages of 3 drugs), what is the most effective add-on medication?

Study Design: Cross-over trial (randomized)

Funding: Government

Allocation: Concealed

Setting: Outpatient (any)

Synopsis: Many guidelines recommend the A+C+D approach to managing patients with hypertension: start with an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, add a calcium channel blocker, then a diuretic.* Once patients are taking maximum dosages of all 3 drugs, then what? These authors enrolled 335 such patients in a randomized cross-over trial to see which of the following was more effective in lowering blood pressure: spironolactone, doxazosin, or bisoprolol. To be eligible, the patients had to be aged between 18 and 79 years, have systolic blood pressure (SBP) 140 mm Hg or greater in the office plus home SBP 130 mm Hg or greater in spite of maximum dosages of all 3 drugs. This was a 12-month study that began with all patients receiving a placebo during the first month followed by 6 weeks of low dosages of either spironolactone (25 mg daily), doxazosin (4 mg daily), or bisoprolol (5 mg daily) followed by 6 weeks of double doses (if tolerated). In most cross-over studies, there is a washout period between each treatment interval to minimize the potential for carryover effect of the previous treatment. These authors did not include washout intervals but tried to account for this by doing a sensitivity analysis comparing individual active treatment periods with the initial placebo period. The primary outcome was the average of 18 home SBP readings ascertained on 4 consecutive days. Unfortunately, 21 patients never "played at all" and only 234 patients completed all of the treatment cycles. However, the researchers reported having at least 274 patients for any single treatment period. Compared with the other drugs, the average reductions in SBP for spironolactone, doxazosin, and bisoprolol were 9 mm Hg, 4 mm Hg, and 4 mm Hg, respectively (P < .001). Compared with placebo, the reductions were 13 mm Hg, 9 mm Hg, and 8 mm Hg, respectively. The rate of serious adverse events was comparable in each group (2%-3%) as was the rate of all adverse events (15%-23%).

*The Eighth Joint National Committee gives equal weight to each of 3 strategies: (1) push drugs to maximum dosage before adding an additional drug, (2) add a second agent before pushing initial agent to maximum dosage, and (3) start with 2 medications then titrate to maximum dosage. It also gives no preference to initial medication choice among "A, C, or D."

Bottom Line: In the short term, spironolactone is most effective at lowering blood pressure in patients with resistant hypertension. Whether this will result in better long-term control or decrease the rate of clinically important outcomes—such as stroke, congestive heart failure, kidney failure, and so forth—is unknown. (LOE = 2b)


Communicating with patients about statins

14: PubMed: Communicating statin evidence to support shared decision-making

BACKGROUND:
The practice of clinical medicine rests on a foundation of ethical principles as well as scientific knowledge. Clinicians must artfully balance the principle of beneficence, doing what is best for patients, with autonomy, allowing patients to make their own well-informed health care decisions. The clinical communication process is complicated by varying degrees of confidence in scientific evidence
regarding patient-oriented benefits, and by the fact that most medical options are associated with possible harms as well as potential benefits.

DISCUSSION:
Evidence-based clinical guidelines often neglect patient-oriented issues involved with the thoughtful practice of shared decision-making, where individual values, goals, and preferences should be prioritized. Guidelines on the use of statin medications for preventing cardiovascular events are a case in point. Current guidelines endorse the use of statins for people whose 10-year risk of cardiovascular events is as low as 7.5%. Previous guidelines set the 10-year risk benchmark at 20%. Meta-analysis of randomized trials suggests that statins can reduce cardiovascular event rates by about 25%, bringing 10-year risk from 7.5 to 5.6%, for example, or from 20 to 15%. Whether or not these benefits should justify the use of statins for individual patients depends on how those advantages are valued in comparison with disadvantages, such as side effect risks, and with inconveniences associated with taking a pill each day and visiting clinicians and laboratories regularly.

CONCLUSIONS:
Whether or not the overall benefit-harm balance justifies the use of a medication for an individual patient cannot be determined by a guidelines committee, a health care system, or even the attending physician. Instead, it is the individual patient who has a fundamental right to decide whether or not taking a drug is worthwhile. Researchers and professional organizations should endeavor to develop shared decision-making tools that provide up-to-date best evidence in easily understandable formats, so as to assist clinicians in helping their patients to make the decisions that are right for them.

A nice tool to help guide this discussion is at the Mayo Clinic: [https://statindecisionaid.mayoclinic.org/](https://statindecisionaid.mayoclinic.org/)

**Bottom Lines**

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. Among patients with type 2 diabetes at high risk for cardiovascular events, empagliflozin, as compared with placebo, was associated with lower rates of cardiovascular outcomes and of death from any cause, compared to standard care.
3. In patients with stable CAD, PCI with medical therapy is not associated with a survival advantage compared to optimal medical therapy after 12 years.
4. The use of PPI’s in patients on clopidogrel is not associated with significant differences in mortality or ischemic events compared to those on clopidogrel alone.
5. Clopidogrel/aspirin (DAPT) does not decrease overall mortality in patients post PCI or in high risk patients.
6. Totally eliminating the 5 major modifiable cardiovascular risk factors would prevent 50% of all CV deaths among adults in the US, more achievable levels of risk reduction are associated with < 10% in cardiovascular deaths.
7. Although CAC is a prognostic factor for 15 year all-cause mortality in asymptomatic adult patients, it does not perform better than functional testing for symptomatic patients in predicting outcomes.
8. Among patients with resistant hypertension, spironolactone is most effective at lowering blood pressure; however, its effect on decreasing the rate of clinically important outcomes in such patients is unknown.
Musculoskeletal

John Hickner, MD, MS

Objectives

1. Review recent RCT and meta-analyses regarding evidence for effective and ineffective treatments for acute and chronic back pain

2. Review recent RCT and meta-analyses regarding evidence for effective and ineffective treatments for knee osteoarthritis

Back

1. Few red flags associated with low back pain actually predict fracture or malignancy

Clinical question: How accurate are the typical "red flags" to screen for fracture or malignancy in patients with low back pain?

Study design: Systematic review

Setting: Various (meta-analysis)

Synopsis: The authors searched 4 databases, as well as reference lists of identified articles, and identified 14 studies that compared red flag signs and symptoms with a reference standard in patients presenting for primary, secondary, or tertiary care. Four authors independently selected research for inclusion, and 3 authors extracted the data. They found quite a bit of heterogeneity in the study methods and results so were unable to combine some studies. Older age, prolonged corticosteroid use, severe trauma, and presence of a contusion or abrasion increased the likelihood of a fracture, especially when more than one was present, especially prolonged steroid use. Other warning signs were associated with trivial increases in the likelihood of fracture. Among the typical red flags listed as predictors of malignancy, only "history of cancer" has been studied, which increases the posttest probability of malignancy to 7% in primary care (95% CI, 3% - 16%) and to 33% (22% - 46%) in the emergency department.

Bottom line: Older age, prolonged corticosteroid use, severe trauma, and the presence of a contusion or abrasion are the only typical red flags associated with an increase in the likelihood of fracture in patients with low back pain. Of the long list of warning signs for cancer, only "history of cancer" has been evaluated, which predicts cancer in 1 in 14 patients in primary care and 1 in 3 patients presenting to an emergency department.


2. Early imaging for low back pain in elderly raises costs without improving quality

Clinical question: Does early imaging of older adults with back pain improve outcomes?

Study design: Cohort (prospective)

Setting: Outpatient (primary care)

Synopsis: Early imaging (before 6 weeks) of adults with back pain is associated with increased costs and worse outcomes (Ann Intern Med 2011;154(3):181-189). However, most studies have included few, if any, adults 65 years or older. These investigators prospectively enrolled 5239 adults, 65 years or older, who presented to a participating primary care clinician for a new episode of back pain. Of these, 1264 patients (26%) received early back imaging (within 6 weeks of the initial visit), including 1174 who underwent plain film radiography and 349 who underwent either computed tomography or magnetic resonance imaging. Case patients were propensity-matched when possible for multiple variables, including sex, race/ethnicity, age, education, smoking, comorbidities, back pain, leg pain, and various quality-of-life and function scoring tools, with similar control patients not undergoing early imaging (approximately 93% match rate). Outcomes were assessed at 3, 6, and 12 months using validated back pain–related disability and quality-of-life scoring tools. Complete follow-up occurred for approximately 90% of patients at 12 months. Although fractures were detected more often in the early imaging group, no statistically significant differences in disability or quality of life occurred between the early-imaging group and the control group at any points in the evaluation process. In addition, no differences occurred in the proportion of patients with cancer diagnoses. Overall costs were approximately 30% higher in the early-imaging group.

Bottom line: Among adults, 65 years or older, who present to primary care clinicians for a new episode of back pain, early imaging (before 6 weeks) resulted in no improved outcomes at 1 year, but increased overall health care costs by almost 30%. Indications for early imaging include major risk factors for cancer, signs of cauda equina syndrome, severe neurologic deficits, and fever with a history of intravenous drug use or recent infection.


3. Naproxen alone may be best for acute low back pain

Clinical question: What is the optimal medication regimen for treating adults with acute low back pain?

Study design: Randomized controlled trial (double-blinded)

Setting: Emergency department

Synopsis: Clinicians frequently treat acute LBP with a combination of nonsteroidal anti-inflammatory drugs, muscle relaxants, and opioids. These investigators identified adults (N = 323), aged 21 to 64 years, presenting to the emergency department for LBP clinically
diagnosed as acute musculoskeletal LBP, defined as pain between the lower border of the scapulae and the upper gluteal folds. Exclusion criteria included radicular pain below the gluteal folds, direct trauma to the back within the previous month, pain duration longer than 2 weeks, and recent history of more than one LBP episode per month. Eligible patients randomly received (concealed allocation assignment) naproxen (500 mg twice daily for 10 days) plus either (1) placebo; (2) 5 mg cyclobenzaprine; or (3) 5 mg oxycodone / 32 mg acetaminophen, all taken as 1 or 2 tablets every 8 hours. Individuals masked to treatment group assignment assessed pain and functional outcomes at 7 days and at 3 months after emergency department discharge using a validated scoring tool. Complete follow-up occurred for 96% of participants at 7 days and 87% at 3 months. Using intention-to-treat analysis, there were no significant differences in pain and function scores between the 3 treatment groups at both 7 days and 3 months of follow-up. Use of additional health care resources was infrequent but not significantly different between the 3 groups. Adverse effects, including drowsiness, dizziness, dyspepsia, and nausea or vomiting were, however, significantly increased compared with naproxen plus placebo for both oxycodone/acetaminophen (number needed to treat to harm [NNTH] = 5.3; 95% CI 3-14) and cyclobenzaprine (NNTH=7.8; 4-129).

**Bottom line:** Naproxen alone is as effective as naproxen plus oxycodone/acetaminophen or naproxen plus cyclobenzaprine in reducing pain and improving function in adults with acute musculoskeletal low back pain (LBP) without radicular symptoms. Adverse events were significantly more common in patients additionally treated with either muscle relaxants or opioids. Be sure to note the exclusion criteria in the synopsis.


### 4. Acetaminophen (paracetamol) minimally effective for back pain and osteoarthritis

**Clinical question:** Is acetaminophen (paracetamol) effective for the treatment of low back pain or osteoarthritis?

**Study design:** Meta-analysis (randomized controlled trials)

**Setting:** Various (meta-analysis)

**Synopsis:** To identify all randomized controlled trials the authors searched 9 databases, including the Cochrane Registry. Two investigators independently selected articles for inclusion and extracted the data. Two investigators evaluated the quality of the 13 research studies, most of which were of good quality. Most of the studies used full dosages (3900 mg - 4000 mg daily). There was no evidence of publication bias. For patients with low back pain, high-quality research in more than 1000 patients found a lack of effectiveness on pain and disability in either the immediate (< 2 weeks) or short-term (2 weeks - 3 months) follow-up periods. For hip or knee osteoarthritis, acetaminophen produced a statistically significant but clinically unimportant effect on pain and disability over the immediate or short terms. The research results were homogeneous except for immediate-term disability. Adverse effects were minimal. Patients receiving acetaminophen were more likely to have higher liver function test results (>1.5 times normal) than patients receiving placebo.

**Bottom line:** Although acetaminophen was hoped to be a safer alternative to nonsteroidal anti-inflammatory drugs and opioids for the treatment of common musculoskeletal problems, on average it only provides minimal pain relief and improvement in function for patients with low back pain or osteoarthritis. Some people may benefit with full dosages but most will not.


### 5. Oral steroids minimally improve function but do not reduce pain or need for surgery for herniated lumbar disk

**Clinical question:** Does a short course of tapering oral steroids improve outcomes in adults with acute radiculopathy from a herniated lumbar disk?

**Study design:** Randomized controlled trial (double-blinded)

**Setting:** Outpatient (primary care)

**Synopsis:** Oral steroids are commonly used to treat acute low back but their effectiveness is uncertain. These investigators enrolled adults (N = 269) aged 18 to 70 years with leg pain extending below the knee in a nerve root distribution and a herniated disk confirmed by magnetic resonance imaging. Exclusion criteria included onset of radicular pain more than 3 months prior to enrollment. Patients randomly received (concealed allocation assignment) either oral prednisone (60 mg daily for 5 days, 40 mg daily for 5 days, and 20 mg daily for 5 days) or matched placebo. NSAIDs were not allowed for 3 weeks after randomization. Patients masked to treatment group assignment self-reported outcomes using previously validated pain and function rating tools, including the Oswestry Disability Index (ODI). The primary outcome was a minimal 7-point predetermined clinically important difference between treatment and control on the ODI. Complete follow-up occurred for 99.3% of participants at 3 weeks and 87.0% at 52 weeks. Using intention-to-treat analysis, at 3 weeks patients in the prednisone-treated group showed a statistically significant (but not clinically relevant) reduction in ODI scores compared with the placebo group (mean difference 6.4 points; 95% CI 1.9-10.9). At 52 weeks, patients in the prednisone-treated group showed a statistically significant and minimally clinically relevant reduction in ODI scores compared with the placebo group (mean difference 7.4 points; 2.2-12.5). Patients in the prednisone-treated group were significantly more likely to report a 50% improvement in ODI scores than the placebo group at 3 weeks and at 52 weeks (numbers needed to treat = 7.6 and 5.5, respectively). No statistically significant differences occurred between groups in pain scores at either 3 weeks or at 52 weeks, and there was no significant group difference in the likelihood of undergoing spinal surgery.

**Bottom line:** A short course of tapering oral steroids minimally improves clinical function in adults with acute radiculopathy from a herniated lumbar disk. However, oral steroids were no better than placebo at reducing pain scores or the need for subsequent spinal surgery. Patients in the placebo group were not allowed to take nonsteroidal anti-inflammatory drugs (NSAIDs) for 3 weeks, so any benefit of steroids compared with standard clinical practice may be overestimated.
6. Gabapentin = epidural steroid for radicular pain

Clinical question: Is an epidural steroid injection or gabapentin more effective for pain relief in patients with lumbosacral radicular pain due to a herniated disc or spinal stenosis?

Study design: Randomized controlled trial (double-blinded)

Setting: Outpatient (specially)

Synopsis: Patients enrolled in this study were recruited from 8 hospitals in different areas of the United States and from a U.S. military facility in Europe. The 145 patients (74% men) had lumbosacral radicular pain due to a herniated disc or spinal stenosis for less than 4 years in duration and the leg pain was as severe or more severe than back pain. The patients were randomly assigned, using concealed allocation to receive either gabapentin (titrated to between 1800 and 3600 mg per day in 3 doses for 3 months) or to receive a single epidural injection of depomethylprednisolone 60 mg with a local anesthetic. To mask patients to their treatment, thereby minimizing the placebo effect of the procedure or the daily medication use, all patients took daily medicine and all patients received an injection, with the patients in the gabapentin group receiving a saline injection. After 1 month, pain scores had decreased similarly in both groups. Patients receiving steroid had a slightly better response to a reduction in their "worst leg pain" scores (a decrease of 3 points vs 2 points; P = .04) and were more likely to report a positive successful outcome (number needed to treat = 5). By 3 months, though, improvement was similar in both groups.

Bottom line: After controlling for the placebo effect that may accompany an epidural steroid injection, treatment with gabapentin is as effective as the injection in reducing radicular leg pain in the short term (3 months). A placebo bump in response, if present, is likely to be transient.


7. Epidural steroid not better than placebo injection for sciatica and spinal stenosis pain and function

Clinical question: Is epidural corticosteroid injection effective to reduce pain and improve function in patients with radicular low back pain or spinal stenosis?

Study design: Meta-analysis (randomized controlled trials)

Setting: Various (meta-analysis)

Synopsis: To conduct this review, the authors searched 2 databases, including the Cochrane Database, as well as reference lists and a trial registry. Two investigators independently reviewed studies for inclusion, considering randomized trials of epidural corticosteroid injection versus placebo, other steroid, or other injection techniques for patients with radicular low back pain ("sciatica") or spinal stenosis of any duration. They included periradicular injections. One investigator extracted the studies and a second checked the results for accuracy. Of the 63 studies, most (n = 40) were of fair quality and 5 studies were rated as high quality. In 6 studies of 701 patients, steroid injection provided, on average, immediate pain relief and functional improvement that was not clinically different from placebo treatment. There was no difference in pain and function at short-term (2 weeks - 3 months) or intermediate-term (3 months - 1 year) follow-ups. There was no effect on symptoms of spinal stenosis. Pain scores were reduced to a greater degree, initially, with steroid but patients who received the placebo reported pain improvement at short-, intermediate-, and long-term follow-ups, essentially "catching up" with steroid-treated patients; for function, scores initially improved with steroid but then regressed.

Bottom line: It's hard to figure out what to do with these results. On the one hand, steroid injection did not provide a significant benefit as compared with placebo injection in patients with either radicular pain or spinal stenosis. However, part of the reason for this may be the significant and sustained improvement of pain scores seen with the placebo injection. This improvement might reflect natural history, but it may reflect the ability of patients treated with either injection to reframe the pain, since short-term improvement in function was (unlike pain relief) quickly lost in patients treated with steroid or placebo injection.


8. Early physical therapy for adults with acute low back pain is minimally effective

Clinical question: Is early physical therapy more effective than usual care in treating adults with acute low back pain?

Study design: Randomized controlled trial (single-blinded)

Setting: Outpatient (primary care)

Synopsis: These investigators conducted a randomized controlled trial of early physical therapy (n = 108) vs usual care (n = 112) for adults presenting to a primary care physician with recent-onset LBP. Eligibility criteria included adults, aged 18 to 60 years, with uncomplicated LBP for less than 16 days and with an Oswestry Disability Index (ODI) score of 20 or higher (scores range from 0 to 100 with higher scores indicating greater disability). The ODI is a validated, 10-item measure of function in patients with LBP. Patients were excluded if their pain had extended below the knee in the past 72 hours, or if they had been treated for LBP in the past 6 months. All patients received education about the favorable prognosis of LBP, advice to remain active, and a booklet providing information consistent with standard LBP education guidelines. The usual care control group received no further intervention. The intervention group underwent four physical therapy sessions, beginning within 72 hours of the primary care visit and continuing for 3 weeks. Physical therapy included an assessment followed by spinal manipulation and instructions to perform daily home exercises focusing on both spinal range-of-motion and trunk-strengthening. Individuals masked to treatment group assignment assessed the primary outcome using changes in ODI scores. The authors assessed several secondary outcomes (including physical activity, return to work, and
quality of life) at 4 weeks, at 3 months, and at 1 year using additional scoring tools. Complete follow-up occurred for 94% of participants at 1 year of follow-up. The mean baseline ODI score of study participants was 41. Using intention-to-treat analysis, a statistically significant reduction in ODI scores occurred in the physical therapy group at 3 months compared with the usual care group (mean difference -3.2; 95% CI -5.9 to -0.47). However, this difference did not meet the predetermined minimally clinically important difference in ODI score of 6. In addition, the group difference in ODI scores was no longer significant at 1 year. The authors found statistically significant improvements in some, but not all, secondary outcomes at 4 weeks, 3 months, and 1 year, but these differences were modest at best.

**Bottom line:** Early referral to physical therapy (within 72 hours of study enrollment) compared with usual care for adults with recent-onset low back pain (LBP) is minimally, if at all, effective for reducing measures of disability and pain or for improving quality of life. Fritz JM, Magel JS, McFadden M, et al. Early physical therapy vs usual care in patients with recent-onset low back pain: A randomized clinical trial. JAMA 2015;314(14):1459-1467.

9. Spinal manipulation more effective than exercise advice alone for back-related leg pain

**Clinical question:** In patients with leg pain related to back pain, is spinal manipulation with home exercise more effective than home exercise alone?

**Study design:** Randomized controlled trial (nonblinded)

**Setting:** Outpatient (any)

**Synopsis:** The researchers conducting this study recruited 192 patients with low back pain and pain radiating into the proximal or distal leg with or without neurologic signs for at least 4 weeks. They excluded patients with only back pain or with neurologic deficits, spinal stenosis or fracture, or cauda equina syndrome. All patients received four 1-hour one-on-one visits with a healthcare provider for pain management and prevention recurrence advice and daily exercise instructions. The exercises were aimed at enhancing mobility and increasing core strength. Half of the patients were randomized, using concealed allocation, to also receive chiropractic spinal manipulation therapy aimed at mobilizing the lumbar vertebral or sacroiliac joints, adjusted to each patient depending on symptoms. Patients could receive up to 20 sessions with the chiropractor. At 3 months, the percent of patients with at least a 50% reduction in leg pain was significantly higher in patients also receiving spinal manipulation (60% vs 44%; number needed to treat [NNT] = 6.3; 95% CI 3.4 - 62.5). At 1 year, though, the results were similar. However, patients’ estimate of global improvement and their satisfaction with care were both significantly higher in patients receiving spinal manipulation.

**Bottom line:** In patients with back-related leg pain, including those with neurologic signs, chiropractic spinal manipulation results in more patients achieving better pain relief at 4 months, but similar effects at 1 year, compared with intense home exercise and advice alone.


10. Generic activity advice approximately equal to structured exercise for sciatica

**Clinical question:** Do patients with sciatica who perform supervised structured exercise get better faster than patients given generic advice?

**Study design:** Systematic review

**Setting:** Outpatient (any)

**Synopsis:** These authors searched several databases and reference lists to identify randomized trials comparing supervised structured exercise with generic advice to stay active in patients with uncomplicated sciatica. They don’t describe evaluating registries or other attempts to identify unpublished studies. Although the authors don’t say much about the mechanics of selecting which papers to include, they report that 2 authors independently assessed the methodologic quality and extracted the data. Ultimately, they included 6 trials with slightly more than 600 patients aged 18 to 65 years. Five of the studies provided enough data for pooling results. Four of the studies were considered high quality and the other 2 were of moderate quality. The small handful of common outcomes between studies limited the ability to perform robust analyses. Finally, the authors failed to adequately address the role of publication bias. In the first 6 weeks of follow-up, the data showed no difference in disability between the treatments, but there was a tendency toward less leg pain intensity in the patients treated with supervised structure exercise. However, during the 6-week to 12-week interval, there was no difference in treatment outcomes. Finally, after 1 year there was still no difference in these outcomes. There is a curious absence of narrative about other relevant outcomes such as return to work, function, and so forth.

**Bottom line:** If these authors have found all the relevant studies, patients with uncomplicated sciatica treated with supervised structured exercise have minimally less leg pain in the first 6 weeks, but overall are no better than patients given generic advice to stay active. The data are of good quality but are not very robust. The authors don’t report on other important outcomes. The good news is that it’s pretty easy to tell patients to stay as active as possible within their comfort level.


11. Walking program effective for chronic low back pain

**Clinical question:** For adults with chronic low back pain, is a prescribed walking program as effective as physical therapy?

**Study design:** Randomized controlled trial (nonblinded)

**Setting:** Outpatient (specialty)

**Synopsis:** These Irish researchers enrolled 246 patients referred for physical therapy for the treatment of low back pain that was either chronic (at least 3 months) or recurrent (3 or more episodes in the past year). Patients also reported low levels of physical activity and
76% were overweight or obese. The patients were randomized, using concealed allocation, to receive 1 of 3 interventions for up to 8 weeks: (1) standard tailored physical therapy; (2) a weekly exercise class specifically aimed at patients with back pain; or (3) a tailored graduated program of walking. The patients in the walking program were given a walking diary and a pedometer and asked to walk at least 4 days per week. Patients started with at least a 10-minute walk (1200 steps daily) with the goal of achieving 30 minutes of moderate-intensity physical activity (such as a brisk walk) 5 days per week. They were supported by weekly telephone calls. All patients also were given a booklet that explains back pain. Using intention-to-treat analysis, pain and function as measured by the Oswestry Disability Index similarly improved an average 6 points in all groups (from an average 35 points of a possible 100). Significantly more walkers, though, achieved a clinically important difference in the score. Scores were higher in all 3 groups in the patients who adhered to treatment. Patient satisfaction with treatment was similar among the groups. Cost was lowest for the walking program and sustained adherence with treatment was highest. Time lost from work was similar among the 3 groups. These were likely highly motivated patients

**Bottom line:** Giving patients a pedometer, a walking diary, and instructions to walk at least 4 days per week then gradually increase the walk’s duration and intensity (see synopsis) results in improvement in pain and disability similar to usual physical therapy or a group exercise program. Patient satisfaction and days lost from work are similar, and patients are more likely to continue treatment for at least 1 year. In our office, many clinicians wear a pedometer and we have a box of inexpensive ($1) ones available to give to patients with low back pain and other problems that would benefit from some get-up-and-go.


### 12. Mindfulness-based stress reduction training effective for chronic low back pain

**Clinical question:** Is mindfulness-based stress reduction training useful in the treatment of chronic low back pain in adults?

**Study design:** Randomized controlled trial (single-blinded)

**Setting:** Population-based

**Synopsis:** MBSR training focuses on increasing awareness and acceptance of moment-to-moment life experiences. These investigators identified adults, aged 20 to 70 years, with nonspecific low back pain persisting for at least 3 months. Eligible patients were randomly assigned (concealed allocation) to 1 of 3 groups: (1) usual care consisting of a $50 stipend and recommendation to seek whatever treatment, if any, they choose; (2) MBSR training; or (3) CBT. The MBSR and CBT training included 2 hours of instruction sessions per week for 8 weeks and an optional 6-hour retreat for the MBSR program only. MBSR classes included mindfulness practice (body scan, yoga, and meditation focusing on awareness of the present moment). CBT training focused on education about chronic pain, relationships between the body and mind and physical reactions, sleep hygiene, practice in changing dysfunctional thoughts, and pain-coping strategies. Individuals masked to treatment group assignment assessed outcomes by telephone interviews using validated pain and function scoring tools. Complete follow-up occurred for approximately 90% of participants at 52 weeks. Using intention-to-treat analyses, an overall clinically meaningful improvement (a greater than or equal to 30% improvement from baseline in functional limitations and self-reported back pain) occurred significantly more often in patients who received either MBSR training or CBT than in patients who received usual care (60.5% and 57.7% vs 44.1%; numbers needed to treat = 6 and 7). There were no significant differences in outcomes between the MBSR and CBT groups. However, the benefit of functional improvement and pain reduction compared with usual care seen at 26 weeks was maintained at 52 weeks for MBSR but not CBT. The study was 80% powered to detect a predetermined clinically meaningful difference in the MBSR and CBT groups.

**Bottom line:** Both mindfulness-based stress reduction (MBSR) training and cognitive behavior therapy (CBT) are superior to usual care alone in reducing pain and improving function in adults with chronic low back pain. The difference in effectiveness, if any, between MBSR and CBT is minimal.


### 13. Effect of Primary Care-Based Education on Reassurance in Patients With Acute Low Back Pain: Systematic Review and Meta-analysis

**IMPACTANCE:** Reassurance is a core aspect of daily medical practice, yet little is known on how it can be achieved.

**OBJECTIVE:** To determine whether patient education in primary care increases reassurance in patients with acute or subacute low back pain (LBP).

**DATA SOURCES:** Medline, EMBASE, Cochrane Central Register for Controlled Trials, and PsychINFO databases were searched to June 2014.

**DESIGN:** Systematic review and meta-analysis of randomized and nonrandomized clinical trials.

**STUDY SELECTION:** To be eligible, studies needed to be controlled trials of patient education for LBP that were delivered in primary care and measured reassurance after the intervention. Eligibility criteria were applied, and studies were selected by 2 independent authors.

**MAIN OUTCOMES AND MEASURES:** The primary outcomes were reassurance in the short and long term and health care utilization at 12 months.

**DATA EXTRACTION AND SYNTHESIS:** Data were extracted by 2 independent authors and entered into a standardized form. A random-effects meta-analysis tested the effects of patient education compared with usual care on measures of reassurance. To investigate the effect of study characteristics, we performed a preplanned subgroup analysis. Studies were stratified according to duration, content, and provider of patient education.

**RESULTS:** We included 14 trials (n=4872) of patient education interventions. Trials assessed reassurance with questionnaires of fear,
worry, anxiety, catastrophization, and health care utilization. There is moderate- to high-quality evidence that patient education increases reassurance more than usual care/control education in the short term (standardized mean difference [SMD], -0.21; 95% CI, -0.35 to -0.06) and long term (SMD, -0.15; 95% CI, -0.27 to -0.03). Interventions delivered by physicians were significantly more reassuring than those delivered by other primary care practitioners (eg, physiotherapist or nurse). There is moderate-quality evidence that patient education reduces LBP-related primary care visits more than usual care/control education (SMD, -0.14; 95% CI, -0.28 to -0.00 at a 12-month follow-up). The number needed to treat to prevent 1 LBP-related visit to primary care was 17.

CONCLUSIONS AND RELEVANCE: There is moderate- to high-quality evidence that patient education in primary care can provide long-term reassurance for patients with acute or subacute LBP.


IMPORTANCE: Existing guidelines and systematic reviews lack clear recommendations for prevention of low back pain (LBP).

OBJECTIVE: To investigate the effectiveness of interventions for prevention of LBP.

DATA SOURCES: MEDLINE, EMBASE, Physiotherapy Evidence Database Scale, and Cochrane Central Register of Controlled Trials from inception to November 22, 2014.

STUDY SELECTION: Randomized clinical trials of prevention strategies for nonspecific LBP.

DATA EXTRACTION AND SYNTHESIS: Two independent reviewers extracted data and assessed the risk of bias. The Physiotherapy Evidence Database Scale was used to evaluate the risk-of-bias. The Grading of Recommendations Assessment, Development, and Evaluation system was used to describe the quality of evidence.

MAIN OUTCOMES AND MEASURES: The primary outcome measure was an episode of LBP, and the secondary outcome measure was an episode of sick leave associated with LBP. We calculated relative risks (RRs) and 95% CIs using random-effects models.

RESULTS: The literature search identified 6133 potentially eligible studies; of these, 23 published reports (on 21 different randomized clinical trials including 30,850 unique participants) met the inclusion criteria. With results presented as RRs (95% CIs), there was moderate-quality evidence that exercise combined with education reduces the risk of an episode of LBP (0.55 [0.41-0.74]) and low-quality evidence of no effect on sick leave (0.74 [0.44-1.26]). Low- to very low-quality evidence suggested that exercise alone may reduce the risk of both an LBP episode (0.65 [0.50-0.86]) and use of sick leave (0.22 [0.06-0.76]). For education alone, there was moderate- to very low-quality evidence of no effect on LBP (1.03 [0.83-1.27]) or sick leave (0.87 [0.47-1.60]). There was low- to very low-quality evidence that back belts do not reduce the risk of LBP episodes (1.01 [0.71-1.44]) or sick leave (0.87 [0.47-1.60]). There was low-quality evidence of no protective effect of shoe insoles on LBP (1.01 [0.74-1.40]).

CONCLUSION AND RELEVANCE: The current evidence suggests that exercise alone or in combination with education is effective for preventing LBP. Other interventions, including education alone, back belts, and shoe insoles, do not appear to prevent LBP. Whether education, training, or ergonomic adjustments prevent sick leave is uncertain because the quality of evidence is low.


Knees

15. Chondroitin/glucosamine = celecoxib for knee OA (MOVES)

Clinical question: Is combined chondroitin/glucosamine as effective as celecoxib in reducing pain and improving function in patients with painful knee osteoarthritis?

Study design: Randomized controlled trial (double-blinded)

Setting: Outpatient (specialty)

Synopsis: The 606 patients in this study were enrolled by 1 of 42 rheumatologists practicing in France, Germany, Poland, or Spain. The patients were an average of 63 years of age, most were women (84%), and almost all were white (99%). They all had radiographic evidence of knee osteoarthritis and had severe pain as measured by a score higher than 300 (of a possible 500) on the Western Ontario and McMaster osteoarthritis (WOMAC) index, which is the standard research scale used to evaluate pain, stiffness, and function. The patients were randomized (concealed allocation unknown) to receive 400 mg chondroitin sulfate/500 mg glucosamine hydrochloride 3 times a day or 200 mg celecoxib every day for 6 months (both with matched placebo). The glucosamine/chondroitin dose is a little higher than is typically recommended and studied. At 6 months, using a modified intention-to-treat analysis that only included 94% of enrolled patients, WOMAC pain scores were decreased by 50% in both groups, stiffness scores decreased 46.9% with the combination versus 49.2% with celecoxib (P = NS), and function improved similarly (decreased in 45.5% vs 46.4%; P = NS).

Bottom line: For patients with painful knee osteoarthritis, a high-dose combination of glucosamine hydrochloride 1500 mg and chondroitin 1200 mg was as effective in lessening pain and stiffness and improving function as celecoxib (Celebrex) 200 mg. Other studies have not found benefit. It's time for someone (not me) to really analyze all the studies of chondroitin/glucosamine to determine who is most likely to benefit.


16. Hyaluronic acid = sham injections in patients with knee DJD

Clinical question: Do hyaluronic acid injections in patients with knee degenerative joint disease improve pain and function?

Study design: Meta-analysis (randomized controlled trials)
Setting: Outpatient (specially)

Synopsis: These authors searched multiple databases and a clinical trial registry to identify randomized trials comparing hyaluronic acid injections with control treatments in patients with knee degenerative joint disease. Studies had to include at least 30 patients in each group, include pain and function scales for which minimal clinically important differences are established, and have at least 4 weeks of follow up. The authors don’t describe the process of article inclusion. Ultimately, they included 19 studies with nearly 4500 patients: 14 used sham injections as the comparator; 2 used usual care; 3 used injections combined with some other active treatment. The authors did not find any statistically significant potential for publication bias. In the studies using sham injections, hyaluronic acid was slightly better at improving pain and function, but the improvement was not clinically important. Similarly, the improvements in double-blind trials were also not clinically significant. Among the other studies with designs at higher risk of bias, the magnitude of improvement in pain and function were really impressive. We have seen this story before: The stuff looks really effective until the studies are done correctly. In the meantime, all the placebo responders are writing testimonials about how their “lives were saved.”

Bottom line: The highest quality studies, which are now fairly plentiful, show that hyaluronic acid injections are only minimally better than sham injections in improving pain and function in patients with knee degenerative joint disease.


17. 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.


BACKGROUND: Non-steroidal anti-inflammatory drugs (NSAIDs) are the backbone of osteoarthritis pain management. We aimed to assess the effectiveness of different preparations and doses of NSAIDs on osteoarthritis pain in a network meta-analysis.

METHODS: For this network meta-analysis, we considered randomised trials comparing any of the following interventions: NSAIDs, paracetamol, or placebo, for the treatment of osteoarthritis pain. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) and the reference lists of relevant articles for trials published between Jan 1, 1980, and Feb 24, 2015, with at least 100 patients per group. The prespecified primary and secondary outcomes were pain and physical function, and were extracted in duplicate for up to seven timepoints after the start of treatment. We used an extension of multivariable Bayesian random effects models for mixed multiple treatment comparisons with a random effect at the level of trials. For the primary analysis, a random walk of first order was used to account for multiple follow-up outcome data within a trial. Preparations that used different total daily dose were considered separately in the analysis. To assess a potential dose-response relation, we used preparation-specific covariates assuming linearity on log relative dose.

FINDINGS: We identified 8973 manuscripts from our search, of which 74 randomised trials with a total of 58,556 patients were included in this analysis. 23 nodes concerning seven different NSAIDs or paracetamol with specific daily dose of administration or placebo were considered. All preparations, irrespective of dose, improved point estimates of pain symptoms when compared with placebo. For six interventions (diclofenac 150 mg/day, etoricoxib 30 mg/day, 60 mg/day, and 90 mg/day, and rofecoxib 25 mg/day and 50 mg/day), the probability that the difference to placebo is at or below a prespecified minimum clinically important effect for pain reduction (effect size [ES] -0·37) was at least 95%. Among maximally approved daily doses, diclofenac 150 mg/day (ES -0·57, 95% credibility interval [CrI] -0·69 to -0·46) and etoricoxib 60 mg/day (ES -0·58, -0·73 to -0·43) had the highest probability to be the best intervention, both with 100% probability to reach the minimum clinically important difference. Treatment effects increased as drug dose increased, but corresponding tests for a linear dose effect were significant only for celecoxib (p=0·030), diclofenac (p=0·031), and naproxen (p=0·026). We found no evidence that treatment effects varied over the duration of treatment. Model fit was good, and between-trial heterogeneity and inconsistency were low in all analyses. All trials were deemed to have a low risk of bias for blinding of patients. Effect estimates did not change in sensitivity analyses with two additional statistical models and accounting for methodological quality criteria in meta-regression analysis.

INTERPRETATION: On the basis of the available data, we see no role for single-agent paracetamol for the treatment of patients with
osteoarthritis irrespective of dose. We provide sound evidence that diclofenac 150 mg/day is the most effective NSAID available at present, in terms of improving both pain and function. Nevertheless, in view of the safety profile of these drugs, physicians need to consider our results together with all known safety information when selecting the preparation and dose for individual patients.

**FUNDING:** Swiss National Science Foundation (grant number 405340-104762) and Arco Foundation, Switzerland.


19. **Moxibustion Treatment for Knee Osteoarthritis: A Systematic Review and Meta-Analysis**

To determine whether the administration of moxibustion is an effective treatment for knee osteoarthritis (KOA). We conducted a search of relevant articles using Medline, EMBASE, the Web of Science, and the Cochrane Library published before October 2015. The Western Ontario and McMaster Universities’ Osteoarthritis Index (WOMAC scale) and the short form 36 questionnaire (SF-36 scale) were assessed. Evidence grading was evaluated according to the Grading of Recommendations, Assessment, Development and Evaluation system. Four studies containing 746 participants fulfilled the inclusion criteria in the final analysis. In terms of quality of life (QOL), the meta-analysis of 2 randomized clinical trials (RCTs) showed significantly effects of moxibustion only in bodily pain (BP) compared with those in the control group (n=348; weighted mean difference [WMD], 4.36; 95% confidence intervals [CIs], 2.27-6.44; P<0.0001; heterogeneity: χ²=1.53, P=0.22, I²=34%) in all of the subcategories of the SF-36 scale, with moderate quality. The meta-analysis of the 2 included trials showed that there was not a statistically significant difference in the pain or function subscale for the WOMAC scale when the 2 groups were compared (n=322; WMD, 17.63; 95% CI, -23.15-58.41; P=0.40; heterogeneity: χ²=19.42, P<0.0001, I²=95%), with low or moderate quality separately. The administration of moxibustion can to some extent alleviate the symptoms of KOA. More rigorous, randomized controlled trials are required in the future.


**Bottom Lines**

1. Older age, prolonged corticosteroid use, severe trauma, and the presence of a contusion or abrasion are the only typical red flags associated with fracture in patients with low back pain. History of cancer is a somewhat useful red flag for cancer.

2. Early imaging is not indicated for most patients with acute low back pain, with or without sciatica.

3. Naproxen is a decent pain reliever for acute low back pain; about equal to oxycodone or oxycodone plus cyclobenzaprine.

4. Acetaminophen is not so good for acute or chronic back pain and osteoarthritis for most patients.

5. Gabapentin = epidural steroid for chronic radicular pain.

6. On the other hand, epidural steroids appear no better than placebo injections for chronic back pain.

7. Early PT is not all that helpful for acute low back pain.

8. Spinal manipulation can help relieve leg symptoms in patients with sub-acute low back pain.

9. Walking is good for patients with back pain.

10. Chondroitin/glucosamine is as effective as celecoxib for knee osteoarthritis pain.

11. Hyaluronic acid injections are not that helpful for painful knee arthritis.

12. When all else fails, try moxibustion!
Pneumonia and Influenza

Mark H. Ebell MD, MS

Objectives

1. To review the latest evidence regarding diagnosis of pneumonia and flu
2. To be able to identify patients at low risk for pneumonia who do not require antibiotics.
3. To understand the evidence regarding treatment of influenza and pneumonia, including the role of corticosteroids for pneumonia.

Diagnosis of pneumonia and influenza

So, what causes CAP in adults? This is the best, most recent data:

1. Most common identified causes of community-acquired pneumonia are viruses

Clinical question: What is the epidemiology of community-acquired pneumonia in adults who require hospitalization?
Study design: Cohort (prospective)
Setting: Inpatient (any location)
Synopsis: This Centers for Disease Control study attempted to determine the etiology of CAP in 3 Chicago hospitals and 2 Nashville hospitals. CAP was defined as acute respiratory symptoms, accompanied by fever, altered mental status, chills, or leukocytosis or leukopenia; and an infiltrate consistent with pneumonia on a chest radiograph. The authors excluded patients who had been hospitalized in the previous 4 weeks, lived in a nursing home, had a clear alternative diagnosis, or who were immunosuppressed. Of the 3634 eligible patients admitted during the study period (January 1, 2010, to June 30, 2012), 2488 could be enrolled, of whom 2320 (93%) had radiographic evidence of pneumonia and 2259 had complete evaluation for bacterial and viral causes of pneumonia. The last group had bacterial cultures and PCR assays of sputum for a range of bacterial causes, and nasopharyngeal swabs for a variety of viral causes of respiratory infection. The median age of the population was 57 years, and the median length of stay was 3 days. Approximately 1 in 5 patients were admitted to the intensive care unit (ICU), about 1 in 16 required mechanical ventilation, and 1 in 50 died during the hospitalization. Overall, at least 1 pathogen was detected in only 38%: 1 or more viruses in 23%, one or more bacteria in 11%, at least 1 virus and bacteria in 3%, and fungi or mycobacteria in 1%. Thus, 62% had no pathogen detected despite a careful search. The most common pathogens were human rhinovirus (9%), influenza A or B (6%), strep pneumoniae (5%), human metapneumovirus (4%), respiratory syncytial virus (3%), coronavirus (3%), mycoplasma pneumoniae (2%), staph aureus (2%), adenovirus (1.5%), legionella pneumophila (1.5%), enterobacteriaceae (1.5%), and other (3.5%). The majority of patients had a single pathogen. Strep pneumoniae, staph aureus, and enterobacteriaceae were all more common among the presumably sicker patients in the ICU than in non-ICU patients. The incidence of hospitalization for CAP increased with age, from 6.7/10,000/year in those aged 18 to 49 years, to 26.3/10,000/year for those 50 to 64 years old, 63.0/10,000/year for those 65 to 79 years old, and 164/10,000/year for those 80 years and older.

Bottom line: The 3 key messages from this study: (1) Most patients did not have a pathogen identified, so choosing an appropriate initial empiric antibiotic is important; (2) human rhinovirus, influenza, and metapneumovirus are among the most commonly identified viral causes of pneumonia; and (3) the incidence of community-acquired pneumonia (CAP) increases substantially with increasing age.


Most useful for ruling in pneumonia are RR > 50, grunting, retractions, and nasal flaring. Best at ruling out are absence of cough, absence of fever, and RR < 40. None are terribly accurate alone, so consider the full picture.

2. Clinical signs and symptoms of pneumonia 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
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.


There are some new technologies and tests on the horizon, some of which are already widely used in other settings such as the ED or other countries.

3. Lung ultrasound reduces need for CXR in children with suspected pneumonia

**Clinical question:** Does the use of lung ultrasound safely reduce the need for chest radiography in children?

**Study design:** Randomized controlled trial (single-blinded)

**Setting:** Emergency department

**Synopsis:** A recent meta-analysis concluded that lung ultrasound was highly accurate for diagnosing pneumonia in children (96% sensitive, 93% specific, positive likelihood ratio = 15, negative likelihood ratio = .06). This study looked at whether its use was safe in children and whether it affected process outcomes. The authors randomized 191 children and adolescents with clinically suspected pneumonia to receive either CXR always followed by lung ultrasound (LUS), or initial LUS followed by CXR only if the clinician had residual uncertainty or otherwise requested it. The study had an 80% power to detect a 15% or greater reduction in CXR use. The median patient age was 3 years, and cough, difficulty breathing and fever were the most common symptoms. The authors appeared to track return visits for up to 2 weeks, although how this was done is not clearly described. Patients in the initial LUS group had fewer CXRs, with 40 of 103 patients not receiving one (NNT = 2.5 to prevent one CXR). The authors claim no missed pneumonias in either group, although I'm not convinced that the follow-up was good enough to guarantee that. There was also no difference in unscheduled healthcare visits or antibiotic use, and there was a nonsignificant 27-minute reduction in emergency department stay in the initial LUS group. Results looked even better with more experienced sonologists.

**Bottom line:** Handheld ultrasound is making its way into clinical practice, and this study shows that it can safely reduce the use of chest radiography (CXR) in children with clinically suspected pneumonia and may make care more efficient.


4. Procalcitonin rules out pneumonia in patients with dyspnea in the emergency department

**Clinical question:** Is procalcitonin testing useful for patients with dyspnea who present for emergency care?

**Study design:** Cohort (prospective)

**Setting:** Emergency department

**Synopsis:** This is not the cleanest study, but that's what you get when existing data are repurposed to answer a different question. These investigators used data from 2 studies in which procalcitonin levels were determined for patients with dyspnea in an (accident and) emergency department. The majority of the patients (n = 365) were drawn from a study of patients who presented with dyspnea to a single emergency department (ED); an additional 88 patients were drawn from a study of patients whose admitting ED physician was sure that the patient's dyspnea was due to heart failure. A substantial number of the original patients from both studies were excluded from this analysis because procalcitonin levels were not drawn. Overall, 13% of the 453 patients had pneumonia, 47% had a final diagnosis of heart failure, 6.6% had pneumonia, and 6.6% of the patients with heart failure had a secondary diagnosis of pneumonia. Procalcitonin levels were higher in patients with pneumonia (0.38 ng/mL vs 0.06 ng/mL; P < .001). In patients with possible pneumonia or heart failure, procalcitonin had a sensitivity of 78% and a specificity of 80%; it was better at ruling out pneumonia (negative predictive value = 96%) than identifying patients with pneumonia (positive predictive value = 39%). It was even better at ruling out pneumonia as the clinical suspicion of heart failure increased, with a 99% negative predictive value in patients with likely heart failure.

**Bottom line:** In patients with dyspnea who present to an emergency department with a typical likelihood of pneumonia (13%), a negative procalcitonin result (< 0.1 ng/mL) will correctly rule out pneumonia 96% of the time. However, pneumonia is present in only approximately 40% of patients with positive results. Adding procalcitonin to the initial work-up of suitable patients with dyspnea may decrease the number of patients with heart failure who are treated with antibiotics.


In primary care, we want to know who needs a chest x-ray and who doesn't. These rules help us identify low risk patients who don't.

5. Validation of a rule for ruling out pneumonia

**Background:** We recently reported the derivation of a diagnostic aid to rule out pneumonia in adults presenting with new onset of cough or worsening of chronic cough and increased body temperature. The aim of the present investigation was to validate the diagnostic aid in a new sample of primary care patients.
**Methods:** From two group practices in Zurich, we included 110 patients with the main symptoms of cough and subjective feeling of increased body temperature, and C-reactive protein levels below 50 μg/ml, no dyspnea, and not daily feeling of increased body temperature since the onset of cough. We excluded patients who were prescribed antibiotics at their first consultation. Approximately two weeks after inclusion, practice assistants contacted the participants by phone and asked four questions regarding the course of their complaints. In particular, they asked whether a prescription of antibiotics or hospitalization had been necessary within the last two weeks.

**Results:** In 107 of 110 patients, pneumonia could be ruled out with a high degree of certainty, and no prescription of antibiotics was necessary. Three patients were prescribed antibiotics between the time of inclusion in the study and the phone interview two weeks later. Acute rhinosinusitis was diagnosed in one patient, and antibiotics were prescribed to the other two patients because their symptoms had worsened and their CRP levels increased. Use of the diagnostic aid could have missed these two possible cases of pneumonia. These observations correspond to a false negative rate of 1.8% (95% confidence interval: 0.50%-6.4%).

**Conclusions:** This diagnostic aid is helpful to rule out pneumonia in patients from a primary care setting. After further validation application of this aid in daily practice may help to reduce the prescription rate of unnecessary antibiotics in patients with respiratory tract infections.


**Low risk rule:** CRP < 10 mg/L OR CRP < 50 mg/L (mcg/ml), no dyspnea, and no subjective fever daily since onset of cough.

6. **Large primary care trial incorporating CRP to rule out pneumonia**

**Objectives:** To quantify the diagnostic accuracy of selected inflammatory markers in addition to symptoms and signs for predicting pneumonia and to derive a diagnostic tool.

**Design:** Diagnostic study performed between 2007 and 2010. Participants had their history taken, underwent physical examination and measurement of C reactive protein (CRP) and procalcitonin in venous blood on the day they first consulted, and underwent chest radiography within seven days.

**Setting:** Primary care centres in 12 European countries.

**Participants:** Adults presenting with acute cough.

**Main outcome measures:** Pneumonia as determined by radiologists, who were blind to all other information when they judged chest radiographs.

**Results:** Of 3106 eligible patients, 286 were excluded because of missing or inadequate chest radiographs, leaving 2820 patients (mean age 50, 40% men) of whom 140 (5%) had pneumonia. Re-assessment of a subset of 1675 chest radiographs showed agreement in 94% (κ 0.45, 95% confidence interval 0.36 to 0.54). Six published “symptoms and signs models” varied in their discrimination (area under receiver operating characteristics curve (ROC) ranged from 0.55 (95% confidence interval 0.50 to 0.61) to 0.71 (0.66 to 0.76)). The optimal combination of clinical prediction items derived from our patients included absence of runny nose and presence of breathlessness, crackles and diminished breath sounds on auscultation, tachycardia, and fever, with an ROC area of 0.70 (0.65 to 0.75). Addition of CRP at the optimal cut off of >30 mg/L increased the ROC area to 0.77 (0.73 to 0.81) and improved the diagnostic classification (net reclassification improvement 28%). In the 1556 patients classified according to symptoms, signs, and CRP >30 mg/L as “low risk” (<2.5%) for pneumonia, the prevalence of pneumonia was 2%. In the 132 patients classified as “high risk” (>20%), the prevalence of pneumonia was 31%. The positive likelihood ratio of low, intermediate, and high risk for pneumonia was 0.4, 1.2, and 8.6 respectively. Measurement of procalcitonin added no relevant additional diagnostic information. A simplified diagnostic score based on symptoms, signs, and CRP >30 mg/L resulted in proportions of pneumonia of 0.7%, 3.8%, and 18.2% in the low, intermediate, and high risk group respectively.

**Conclusions:** A clinical rule based on symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough performed best in patients with mild or severe clinical presentation.

Van Vugt S, et al. Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough: diagnostic study. BMJ 2013;346:f2450

<table>
<thead>
<tr>
<th>Sign or symptoms</th>
<th>Points</th>
<th>Score</th>
<th>Pneumonia/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of runny nose</td>
<td>1</td>
<td>0</td>
<td>4/572 (0.7%)</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>1</td>
<td>1-2</td>
<td>73/1902 (3.8%)</td>
</tr>
<tr>
<td>Crackles on auscultation</td>
<td>1</td>
<td>3+</td>
<td>63/346 (18.2%)</td>
</tr>
<tr>
<td>Diminished sounds on auscultlation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP &gt; 30 mg/L</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7. Targeted approach for kids with CAP decreases costs and testing, with low rate of missed bacteremia

**Clinical question:** In children hospitalized for community acquired pneumonia, is a targeted approach to obtaining blood cultures from only those at high risk for bacteremia more efficient than a universal strategy?

**Study design:** Cost-effectiveness analysis

**Setting:** Inpatient (any location)

**Synopsis:** Current guidelines recommend that all children admitted for CAP who are moderately or severely ill have blood cultures performed, but the recommendations are based on low-quality evidence. This aspect of care has been questioned because of the low yield of blood cultures (less than 10%). These researchers wanted to evaluate the clinical utility and cost-effectiveness of a targeted approach compared with universal testing. In the targeted approach, blood cultures would be performed only on children at high risk for bacteremia based on any one of the following: younger than 6 months; not fully immunized; presence of a central line; immunocompromised; toxic appearance; admission to an intensive care unit; the presence of a chronic medical condition; or the presence of an effusion or empyema on chest radiographs. The authors used published data to determine the rate of key events in their model (ie, rates of bacteremia for the aforementioned clinical situations). Additionally, they assigned costs from the hospital’s perspective using published charge data. The authors assumed that children would be admitted for 2 days. They also assumed that children would receive narrow-spectrum penicillins. They performed sensitivity analyses to test the robustness of the model and its assumptions, then ran their model over 1000 simulations and analyzed the results. In the targeted approach, for every 100 children there would be 0.07 missed episodes of bacteremia with treatment failure. In the universal approach, there would be 1 episode of bacteremia for every 118 cultures. The targeted approach would cost slightly less than $2000 per 100 patients compared with more than $5000 per 100 patients with universal testing. The sensitivity analyses did not change the outcomes.

**Bottom line:** In this cost-effectiveness analysis of children hospitalized with community-acquired pneumonia (CAP), restricting blood cultures to only those at high risk for bacteremia appears to be clinically effective and cost effective. This approach should now be subjected to rigorous prospective studies.


**Prevention of pneumonia and influenza**

Flu vaccination is still the best strategy for preventing flu. Fancy N-95’s are no better than facemasks, and antibiotics aren’t indicated post-stroke to prevent pneumonia.

8. Flu vaccine for surgical inpatients not associated with higher health care use in the immediate postdischarge period

**Clinical question:** Does the influenza vaccination during the perioperative period for hospitalized surgical patients lead to higher rates of health care use following discharge?

**Study design:** Cohort (retrospective)

**Setting:** Inpatient (ward only)

**Synopsis:** The rate of influenza vaccination in the surgical inpatient population is low and may be due to perceptions that vaccine-associate adverse events such as fever and myalgia could be misinterpreted as surgical complications, in turn affecting postsurgical care. To identify an association between influenza vaccination and the rates of post-discharge healthcare use in surgical patients, these investigators obtained data from the Kaiser Permanente Southern California health care system database. All patients 6 months and older who underwent an inpatient surgery within a span of 3 years and were eligible for an influenza vaccination during their hospitalization were included in the study (N = 81,647 surgeries). Exposed patients were those who received the vaccination during their hospitalization; unexposed patients were those who were either unvaccinated or received an influenza vaccination more than one week after discharge. The primary outcomes were the number of outpatient visits, ED visits, or readmissions in the 7 days following discharge. The exposed patients were more likely to be older, male, have one or more ED or inpatient stays in the 6 months prior to surgery, have higher Charlson Comorbidity Index scores, and have longer lengths of stay during their surgery hospitalizations. A propensity score analysis was used to balance these and other factors between the 2 groups. Adjusted analyses revealed no significant differences between the 2 groups in the rates of inpatient hospitalizations or ED visits within 7 days of discharge. Additionally, vaccinated patients did not have an increased risk of fever or a higher rate of laboratory work-ups for infection during the 7 days following discharge. The vaccinated group did have a slightly higher rate of outpatient visits (relative risk 1.05; 95% CI 1.00 - 1.10). Although this finding was statistically significant, the increase in risk was small and may not be clinically significant. Further, the authors did not differentiate between planned and unplanned outpatient visits.

**Bottom line:** Giving the flu vaccine to surgical inpatients during the perioperative period is not associated with increased risk of emergency department (ED) visits, re-hospitalizations, fevers, or laboratory work-ups for infection in the week following discharge. Although a small increase in outpatient visits was detected, it was minimal and does not appear to be clinically important.

9. Cochrane: Influenza vaccines for preventing cardiovascular disease

**Background:** This is an update of the original review published in 2008. The risk of adverse cardiovascular outcomes is increased with influenza-like infection, and vaccination against influenza may improve cardiovascular outcomes.

**Objectives:** To assess the potential benefits of influenza vaccination for primary and secondary prevention of cardiovascular disease.

**Search methods:** We searched the following electronic databases on 18 October 2013: The Cochrane Library (including Cochrane Central Register of Controlled Trials [CENTRAL], Database of Abstracts of Reviews of Effects [DARE], Economic Evaluation Database [EED] and Health Technology Assessment database [HTA]), MEDLINE, EMBASE, Science Citation Index Expanded, Conference Proceedings Citation Index – Science and ongoing trials registers (www.controlled-trials.com/ and www.clinicaltrials.gov). We examined reference lists of relevant primary studies and systematic reviews. We performed a limited PubMed search on 2 February 2015, just before publication.

**Selection criteria:** Randomised controlled trials (RCTs) of influenza vaccination compared with placebo or no treatment in participants with or without cardiovascular disease, assessing cardiovascular death or non-fatal cardiovascular events.

**Data collection and analysis:** We used standard methodological procedures as expected by The Cochrane Collaboration. We carried out meta-analyses only for cardiovascular death, as other outcomes were reported too infrequently. We expressed effect sizes as risk ratios (RRs), and we used random-effects models.

**Main results:** We included eight trials of influenza vaccination compared with placebo or no vaccination, with 12,029 participants receiving at least one vaccination or control treatment. We included six new studies (n = 11,251), in addition to the two included in the previous version of the review. Four of these trials (n = 10,347) focused on prevention of influenza in the general or elderly population and reported cardiovascular outcomes among their safety analyses; four trials (n = 1682) focused on prevention of cardiovascular events in patients with established coronary heart disease. These populations were analysed separately. Follow-up continued between 42 days and one year. Five RCTs showed deficits in at least three of the risk of bias criteria assessed. When reported (seven studies), vaccination provided adequate immunogenicity or protection against influenza. Cardiovascular mortality was reported by four secondary prevention trials and was significantly reduced by influenza vaccination overall (risk ratio [RR] 0.45, 95% confidence interval [CI] 0.26 to 0.76; P value 0.003) with no significant heterogeneity between studies, and by three trials reporting cardiovascular mortality as part of their safety analyses when the numbers of events were too small to permit conclusions. In studies of patients with coronary heart disease, composite outcomes of cardiovascular events tended to be decreased with influenza vaccination compared with placebo.

**Authors’ conclusions:** In patients with cardiovascular disease, influenza vaccination may reduce cardiovascular mortality and combined cardiovascular events. However, studies had some risk of bias, and results were not always consistent, so additional high-quality evidence is necessary to confirm these findings. Not enough evidence was available to establish whether influenza vaccination has a role to play in the primary prevention of cardiovascular disease.


10. Overuse alert: Prophylactic abx don't prevent poststroke pneumonia in patients with dysphagia

**Clinical question:** Do prophylactic antibiotics prevent pneumonia in patients with acute stroke and dysphagia?

**Study design:** Randomized controlled trial (single-blinded)

**Setting:** Inpatient (any location)

**Synopsis:** These researchers randomized patients from 48 British stroke units into an intervention or a control group. The intervention consisted of the administration of 1 week of prophylactic antibiotics (a choice of amoxicillin or amoxicillin-clavulanate, together with clarithromycin in the absence of local preference) plus dysphagia care; the control group was provided only dysphagia care. The research protocol called for sequential assessment (including respiratory rate, temperature, chest symptoms and signs, white blood cell count, and C-reactive protein level) of each patient at baseline and again on days 2, 4, 7, 10, and 14. Additionally, the researchers assessed mortality, function, and quality of life at 90 days and newly diagnosed pneumonia at any time from 2 weeks to 90 days. Finally, the researchers tested patients with diarrhea for methicillin-resistant Staphylococcus aureus (MRSA) or Clostridium difficile. In addition to physician-diagnosed pneumonia, the main outcome was adjudicated by researchers unaware of treatment allocation. The rate of rate poststroke pneumonia was actually higher in the intervention group than in the control group (13% vs 10%), but this difference was not statistically significant. The rate of MRSA was similar in each group (~ 2%) as was the rate of C. difficile (< 1%).

**Bottom line:** Even in this study, with its biases that tend to make interventions look more effective (such as single blinding and a high drop-out rate), prophylactic antibiotics given to patients with dysphagia after acute stroke did not prevent pneumonia.


11. No evidence that N95 respirators are better than surgical masks

**Clinical question:** Are N95 respirators superior to surgical masks at preventing transmission of respiratory infections?

**Study design:** Systematic review

**Setting:** Various (meta-analysis)

**Synopsis:** Guidelines from the Centers for Disease Control (CDC) and the World Health Organization recommend N95 respirators for high-risk patients with seasonal flu, and the CDC recommends that the N95 respirators be used for all patients with pandemic influenza. However, evidence regarding their benefits over conventional surgical masks is lacking. This systematic review identified both randomized controlled trials (RCTs) and observational studies of healthcare workers that compared the effectiveness of surgical masks
with N95 respirators. The authors identified a total of 29 studies for the systematic review, of which 6 could be used in the quantitative meta-analysis. The strongest evidence came from 3 RCTs (2 studies with 3110 participants including nurses, doctors, and ward clerks from Beijing and 1 study with 446 nurses from Canada), which found no significant differences in the likelihood of laboratory-confirmed respiratory infection (odds ratio [OR] 0.89; 95% CI 0.64 - 1.24) or influenzalike illness (OR 0.51; 0.19 - 1.41). Surrogate exposure studies on healthy volunteers and mannequins exposed to artificial aerosols showed less filter penetration, less face-seal leakage, and less total inward leakage with N95 masks. The studies were at low risk of bias for all quality domains other than the masking of participants to the intervention (which would be understandably hard to do!). One study masked outcome assessors, the other 2 did not. The authors do not discuss statistical power, and the existing evidence base may be too small to detect a small but clinically important benefit.  

**Bottom line:** Although N95 respirators have theoretical advantages over surgical masks, in practice there is no evidence to support better healthcare outcomes. There were nonsignificant trends in favor of the respirators; additional studies using masked outcome assessors are needed.  


## Treatment of CAP

Abstract #12 is a well done systematic review of CAP treatment. Start antibiotics early, use a fluoroquinolone or a beta-lactam + macrolide, and switch to oral when patients are stable.

### 12. No surprises in the management of hospitalized patients with CAP

**Clinical question:** What is the best antibiotic strategy to improve outcomes in patients hospitalized with community-acquired pneumonia?  
**Study design:** Systematic review  
**Setting:** Inpatient (ward only)  
**Synopsis:** These investigators searched MEDLINE, EMBASE, and the Cochrane databases to identify studies that evaluated outcomes for patients hospitalized with CAP with regard to optimal timing of antibiotic initiation, initial antibiotic selection, and criteria for transition from intravenous to oral antibiotic therapy. Two authors independently reviewed studies for inclusion and assessed study quality. Of 8 low-quality observational studies, 4 showed a significant association between initiating antibiotic therapy within 4 hours to 8 hours of hospital arrival and reduced mortality. When comparing 2 different antibiotic strategies, 6 of 8 observational studies showed mortality benefit with the use of beta-lactams plus macrolides as compared with beta-lactam monotherapy, though the 2 recent high-quality randomized trials had conflicting results. All 3 observational studies that compared fluoroquinolones with beta-lactam monotherapy for the treatment of CAP showed an association with fluoroquinolone use and decreased mortality. Finally, one high-quality trial showed that transitioning patients to oral antibiotics once they meet clinical criteria for stability (stable vital signs, lack of confusion, ability to tolerate oral medications) leads to a shorter length of stay.  
**Bottom line:** For patients hospitalized with community-acquired pneumonia (CAP), start antibiotics early, use either fluoroquinolone monotherapy or beta-lactam/macrolide combination therapy, and switch to oral antibiotics as soon as patients are hemodynamically stable and can take oral medications. Although the evidence is mostly of low quality, this review reaffirms what we already do.  


The next two look at steroids in patients with pneumonia.

### 13. Prednisone speeds recovery, shortens stay in patients hospitalized with CAP

**Clinical question:** Does adding prednisone to antibiotics improve outcomes in adults hospitalized with community-acquired pneumonia?  
**Study design:** Randomized controlled trial (double-blinded)  
**Setting:** Inpatient (any location)  
**Synopsis:** In this Swiss study, patients admitted to the hospital with CAP randomly received 50 mg prednisone daily for 7 days (n = 402) or placebo (n = 400). Each day, a researcher unaware of treatment assignment assessed the patients' clinical status. Patients treated with prednisone reached clinical stability (at least 24 hours of stable vital signs: afebrile, no tachycardia or tachypnea, normotensive, normal mental status, no hypoxia) approximately 1.5 days faster than patients treated with placebo. The average length of stay was 1 day longer in the placebo-treated patients. The prednisone-treated patients were more likely to have hyperglycemia treated with insulin.  
**Bottom line:** Among patients hospitalized with community-acquired pneumonia (CAP), adjunctive prednisone speeds time to recovery by 1.5 days and shortens hospital length of stay by approximately 1 day, but produces no difference in pneumonia complications at 30 days.  


### 14. Steroids beneficial as adjunctive treatment for community-acquired pneumonia

**Clinical question:** Should steroids be used as adjunctive therapy for patients with community-acquired pneumonia?
Study design: Meta-analysis (randomized controlled trials)
Setting: Inpatient (any location)
Synopsis: These authors searched MEDLINE, EMBASE, and the Cochrane Register to find randomized controlled trials that compared the use of steroids with placebo in adults with CAP. Two reviewers independently evaluated studies for eligibility, extracted data, and assessed the included studies for risk of bias. Five of the 13 included studies, whose population made up 70% of the total sample population, had low risk of bias. The treatment groups in the individual studies received different steroid preparations, routes of administration, dosages, and duration of treatment. All groups otherwise received antibiotics and usual care for CAP. High-quality evidence showed that the use of steroids decreased hospital length of stay by 1 day (3 studies: mean difference: -1.0 day; 95% CI -1.79 to -0.21 days) and decreased time to clinical stability by 1.22 days (5 studies, mean difference: -1.22 days; -2.08 to -0.35 days). Moderate-quality evidence showed that the use of steroids decreased the need for mechanical ventilation (5 studies: relative risk [RR] = 0.45; 0.26-0.79) and the incidence of acute respiratory distress syndrome (4 studies: RR = 0.24; 0.10-0.56). Finally, data from the 12 trials that assessed all-cause mortality revealed a trend toward decreased risk of death in the steroid group. The difference between the 2 groups for this end point became statistically significant when only the trials that met the criteria for severe pneumonia were included (6 studies: RR = 0.39; 0.20-0.77). Although steroid use, not surprisingly, increased the risk of significant hyperglycemia (6 studies: RR = 1.49; 1.01-2.19), there were no differences detected in the rates of gastrointestinal bleeds, severe neuropsychiatric complications, or rehospitalizations.

Bottom line: Moderate-quality to high-quality evidence suggests that steroids, when added to antibiotics and usual care, can improve outcomes in the treatment of community-acquired pneumonia (CAP). Benefits include reduced hospital length of stay, decreased time to clinical stability, and lower rates of mechanical ventilation and acute respiratory distress syndrome. Steroids may also play a role in preventing deaths, especially in patients with severe CAP; however, the certainty of this evidence is not as clear. Given varying treatment regimens used in the individual studies, the appropriate steroid formulation, dose, and duration of steroids cannot be elucidated from the current set of data.


The next two address the duration of antibiotics for CAP. More isn’t always better.

15. A shorter course of antibiotics based on clinical stability is safe and effective for CAP

Clinical question: Are shorter courses of antibiotics based on clinical criteria effective in treating patients with community-acquired pneumonia?

Study design: Randomized controlled trial (nonblinded)
Setting: Inpatient (any location) with outpatient follow-up
Synopsis: For patients with CAP, IDSA/ATS guidelines recommend a minimum of 5 days of antibiotic treatment with discontinuation of antibiotics if the patient is afebrile for at least 48 hours and otherwise has no signs of hemodynamic instability. To validate this, these investigators randomized patients hospitalized with CAP into either an intervention group that followed these guidelines or into a control group that allowed bedside physicians to determine antibiotic duration. The authors excluded patients who were immunosuppressed, admitted to the intensive care unit, or had complicated pneumonia. Baseline characteristics of both groups were similar: two thirds of patients were male, mean age was in the mid-60s, and approximately 40% had Pneumonia Severity Index scores of IV or V. The majority of patients were treated with quinolones. The primary outcomes were symptom severity at day 5 and day 10 (as assessed by an 18-item CAP symptom questionnaire) and clinical success rates at day 10 and day 30 (defined as resolution or improvement of signs and symptoms of CAP without further antibiotics). There were no significant differences detected in any of these outcomes by either intention-to-treat or per-protocol analyses. Success rates were approximately 50% to 60% in both groups at day 10 and 88% to 94% at day 30. Moreover, the control group had longer median duration of antibiotic use than the intervention group (10 days vs 5 days; P < .001), although the length of intravenous antibiotic use was similar. Overall, 70% of patients in the intervention group received only 5 days of antibiotics as compared with 3% of patients in the control group. Other secondary outcomes including mortality, in-hospital complications, recurrence of symptoms, and length of hospital stay were similar in the 2 groups. Of note, the control group had a higher 30-day readmission rate (6.6% vs 1.4%; P = .02).

Bottom line: As recommended by guidelines from the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS), a minimum of 5 days of antibiotic therapy with discontinuation of antibiotics based on clinical stability is an appropriate strategy for the treatment of community-acquired pneumonia (CAP).


16. Cochrane: Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults

Background: Pneumonia is the most common hospital-acquired infection affecting patients in the intensive care unit (ICU). However, current national guidelines for the treatment of hospital-acquired pneumonia (HAP) are several years old and the diagnosis of pneumonia in mechanically ventilated patients (VAP) has been subject to considerable recent attention. The optimal duration of antibiotic therapy for HAP in the critically ill is uncertain.

Objectives: To assess the effectiveness of short versus prolonged-course antibiotics for HAP in critically ill adults, including patients with VAP.

Selection criteria: We considered all randomised controlled trials (RCTs) comparing a fixed 'short' duration of antibiotic therapy with a 'prolonged' course for HAP (including patients with VAP) in critically ill adults.

Data collection and analysis: Two review authors conducted data extraction and assessment of risk of bias. We contacted trial authors for additional information.

Main results: We identified six relevant studies involving 1088 participants. This included two new studies published after the date of our previous review (2011). There was substantial variation in participants, in the diagnostic criteria used to define an episode of pneumonia, in the interventions and in the reported outcomes. We found no evidence relating to patients with a high probability of HAP who were not mechanically ventilated. For patients with VAP, overall a short seven- or eight-day course of antibiotics compared with a prolonged 10- to 15-day course increased 28-day antibiotic-free days (two studies; N = 431; mean difference (MD) 4.02 days; 95% confidence interval (CI) 2.26 to 5.78) and reduced recurrence of VAP due to multi-resistant organisms (one study; N = 110; odds ratio (OR) 0.44; 95% CI 0.21 to 0.95), without adversely affecting mortality and other recurrence outcomes. However, for cases of VAP specifically due to non-fermenting Gram-negative bacilli (NF-GNB), recurrence was greater after short-course therapy (two studies, N = 176; OR 2.18; 95% CI 1.14 to 4.16), though mortality outcomes were not significantly different. One study found that a three-day course of antibiotic therapy for patients with suspected HAP but a low Clinical Pulmonary Infection Score (CPIS) was associated with a significantly lower risk of superinfection or emergence of antimicrobial resistance, compared with standard (prolonged) course therapy.

Authors' conclusions: On the basis of a small number of studies and appreciating the lack of uniform definition of pneumonia, we conclude that for patients with VAP not due to NF-GNB a short, fixed course (seven or eight days) of antibiotic therapy appears not to increase the risk of adverse clinical outcomes, and may reduce the emergence of resistant organisms, compared with a prolonged course (10 to 15 days). However, for patients with VAP due to NF-GNB, there appears to be a higher risk of recurrence following short-course therapy. These findings do not differ from those of our previous review and are broadly consistent with current guidelines. There are few data from RCTs comparing durations of therapy in non-ventilated patients with HAP, but on the basis of a single study, short-course (three-day) therapy for HAP appears not to be associated with worse clinical outcome, and may reduce the risk of subsequent infection or the emergence of resistant organisms when there is low probability of pneumonia according to the CPIS.


Note: Non-fermenting Gram neg bacilli include pseudomonas and Acinetobacter.

And what about mycoplasma pneumonia treatment in kids? We still don’t know.

17. POEM: Evidence lacking regarding treatment of mycoplasma pneumonia in children

Clinical question: In children with confirmed mycoplasma pneumonia, is treatment effective in decreasing duration of symptoms?

Study design: Meta-analysis (other)

Setting: Various (meta-analysis)

Synopsis: The authors of this meta-analysis searched PubMed for observational and randomized trials evaluating antibiotic treatment of confirmed lower respiratory tract infections caused by M. pneumoniae in children. They searched bibliographies of identified studies, but did not search other databases and thus may have missed applicable articles. They did not include unpublished studies, but included studies published in any language. Since most of the studies enrolled children with pneumonia due to any cause who were given antibiotics effective against several organisms, the authors had to do a bit of statistical jujutsu to produce relevant results for just the children with mycoplasma. Study quality was assessed but the assessment focused on various selection and reporting biases rather than on indicators of study conduct as is typically done in meta-analysis. In their analysis of the 5 randomized controlled studies (N = 2233), the authors found no evidence to support or refute treatment. Individually, 4 of the 5 studies found no benefit, though there was heterogeneity among the studies and also a risk of publication bias.

Bottom line: After all these years of knowing about Mycoplasma pneumoniae as a cause of lower respiratory tract infections and the effectiveness of various antibiotics against it in a Petri dish, we still don't know whether the treatment of it in kids is effective. This study doesn't tell us to stop testing and treating, but it doesn't tell us to start, either.


Bottom Lines

1. In kids, the most useful signs and symptoms for ruling in pneumonia are RR higher than 50 breaths per minute, grunting, chest retractions, and nasal flaring. Absence of cough, fever, and a RR < 40 bpm were best at ruling out pneumonia.

2. Clinical decision rules and c-reactive protein can help identify patients at low risk for radiographic pneumonia.

3. Consider corticosteroids in patients with moderate to severe CAP.
4. For hospitalized patients with CAP, start antibiotics early, give a fluoroquinolone OR macrolide + beta-lactam, and switch to oral antibiotics as soon as the patient is hemodynamically stable and can take oral meds.

5. For patients with ventilator acquired pneumonia, 7 or 8 days are as good as 10 to 15 days for non-pseudomonas infections.
Atrial Fibrillation: Anticoagulation focus on NOAs and novel treatments

Gary Ferenchick, MD, MS

Objectives

1. Understand the evidence on the tradeoffs for Left Atrial Appendage Closure (LAAC) vs oral anticoagulation in patients with non-valvular atrial fibrillation
2. Understand that the CHA2DS-Vasc score is recommended by the AHA/ACC for risk stratification in AF patients, and that application of this risk score substantially increases the number of patients newly qualified for oral anticoagulants.
3. Understand contemporary evidence of the risk/benefit of using newer oral anticoagulants vs warfarin in AF patients
4. Understand how to monitor patients on NOAs, and that a reversal agent for dabigitran has been studied
5. Understand the risks associated with ablation therapy for AF
6. Understand the bridging anticoagulation is less effective than no bridging in AF patients undergoing procedures.

Left Atrial Appendage Closure (LAAC)

Atrial fibrillation is the most common significant arrhythmia (estimated prevalence of > 3 million by 2020), and ~ 15% of all strokes in the US are attributable to AF. Anticoagulation reduces the risk of CVA by ~ 66%, and is the standard of care for stroke prevention in most patients with AF. Bleeding risk, medical compliance, costs and interactions, and in some the risk of bleeding is prohibitive.

In pts with non-valvular AF, up to 91% of left atrial thrombi are localized in the LAA (see image in the appendix 1). LAAC is an alternative approach to chronic oral anticoagulation therapy in patients with AF, therefore mechanical closure of the LAA may be an alternative to systemic anticoagulation. The Watchman device (picture in the appendix) has been approved by the FDA for patients with non-valvular AF at increased risk of CVA. One editorialist state in part the following “No other device for LAA closure has been studied as rigorously” and that it “…should be considered on a selective basis for high-risk patients with non-valvular AF who cannot tolerate long-term warfarin therapy” and that more observation is required before LAA closure becomes a regular consideration for patients with non-valvular atrial fibrillation. (JACC: Cardiovascular Interventions, Volume 8, Issue 15, 28 December 2015, Pages 1925-1932). In 2014 the ACC/AHA

1: PubMed: LAAC non-inferior to warfarin for stroke prevention improves outcomes vs warfarin in patients with NV atrial fib

BACKGROUND: In the PROTECT AF (Watchman Left Atrial Appendage Closure Technology for Embolic Protection in Patients With Atrial Fibrillation) trial that evaluated patients with nonvalvular atrial fibrillation (NVAF), left atrial appendage (LAA) occlusion was noninferior to warfarin for stroke prevention, but a periprocedural safety hazard was identified. OBJECTIVES: The goal of this study was to assess the safety and efficacy of LAA occlusion for stroke prevention in patients with NVAF compared with long-term warfarin therapy.

METHODS: This randomized trial further assessed the efficacy and safety of the Watchman device. Patients with NVAF who had a CHADS2 (congestive heart failure, hypertension, age >75 years, diabetes mellitus, and previous stroke/transient ischemic attack) score ≥2 or 1 and another risk factor were eligible. Patients were randomly assigned (in a 2:1 ratio) to undergo LAA occlusion and subsequent discontinuation of warfarin (intervention group, n = 269) or receive chronic warfarin therapy (control group, n = 138). Two efficacy and 1 safety coprimary endpoints were assessed. RESULTS: At 18 months, the rate of the first coprimary efficacy endpoint (composite of stroke, systemic embolism [SE], and cardiovascular/unexplained death) was 0.064 in the device group versus 0.063 in the control group (rate ratio 1.07 [95% credible interval (CrI): 0.57 to 1.89]) and did not achieve the prespecified criteria noninferiority (upper boundary of 95% CrI ≥1.75). The rate for the second coprimary efficacy endpoint (stroke or SE >7 days’ postrandomization) was 0.0253 versus 0.0200 (risk difference 0.0053 [95% CrI::0.0190 to 0.0273]), achieving noninferiority. Early safety events occurred in 2.2% of the
Watchman arm, significantly lower than in PROTECT AF, satisfying the pre-specified safety performance goal. Using a broader, more inclusive definition of adverse effects, these still were lower in PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial than in PROTECT AF (4.2% vs. 8.7%; p = 0.004). Pericardial effusions requiring surgical repair decreased from 1.6% to 0.4% (p = 0.027), and those requiring pericardiocenteses decreased from 2.9% to 1.5% (p = 0.36), although the number of events was small. **CONCLUSIONS:** In this trial, LAA occlusion was noninferior to warfarin for ischemic stroke prevention or SE >7 days' post-procedure. Although noninferiority was not achieved for overall efficacy, event rates were low and numerically comparable in both arms. Procedural safety has significantly improved. This trial provides additional data that LAA occlusion is a reasonable alternative to warfarin therapy for stroke prevention in patients with NVAF who do not have an absolute contraindication to short-term warfarin therapy.


2: PubMed: Meta-analysis: LAAC improves outcomes vs warfarin in patients with NV atrial fib

**BACKGROUND:** The risk-benefit ratio of left atrial appendage closure (LAAC) versus systemic therapy (warfarin) for prevention of stroke, systemic embolism, and cardiovascular death in nonvalvular atrial fibrillation (NVAF) requires continued evaluation.

**OBJECTIVES:** This study sought to assess composite data regarding left atrial appendage closure (LAAC) in 2 randomized trials compared to warfarin for prevention of stroke, systemic embolism, and cardiovascular death in patients with nonvalvular AF.

**METHODS:** Our meta-analysis included 2,406 patients with 5,931 patient-years (PY) of follow-up from the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) and PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trials, and their respective registries (Continued Access to PROTECT AF registry and Continued Access to PREVAIL registry).

**RESULTS:** With mean follow-up of 2.69 years, patients receiving LAAC with the Watchman device had significantly fewer hemorrhagic strokes (0.15 vs. 0.96 events/100 patient-years [PY]; hazard ratio [HR]: 0.22; p = 0.004), cardiovascular/unexplained death (1.1 vs. 2.3 events/100 PY; HR: 0.48; p = 0.006), and nonprocedural bleeding (6.0% vs. 11.3%; HR: 0.51; p = 0.006) compared with warfarin. All-cause stroke or systemic embolism was similar between both strategies (1.75 vs. 1.87 events/100 PY; HR: 1.02; 95% CI: 0.62 to 1.7; p = 0.94). There were more ischemic strokes in the device group (1.6 vs. 0.9 and 0.2 vs. 1.0 events/100 PY; HR: 1.95 and 0.22, respectively; p = 0.05 and 0.004, respectively). Both trials and registries identified similar event rates and consistent device effect in multiple subsets.

**CONCLUSIONS:** In patients with NVAF at increased risk for stroke or bleeding who are candidates for chronic anticoagulation, LAAC resulted in improved rates of hemorrhagic stroke, cardiovascular/unexplained death, and nonprocedural bleeding compared to warfarin.


3: PubMed: Percutaneous left atrial appendage closure non-inferior → superior compared to warfarin in patients with atrial fibrillation.

**IMPORTANCE:** While effective in preventing stroke in patients with atrial fibrillation (AF), warfarin is limited by a narrow therapeutic profile, a need for lifelong coagulation monitoring, and multiple drug and diet interactions.

**OBJECTIVE:** To determine whether a local strategy of mechanical left atrial appendage (LAA) closure was noninferior to warfarin.

**DESIGN, SETTING, AND PARTICIPANTS:** PROTECT AF was a multicenter, randomized (2:1), unblinded, Bayesian-designed study conducted at 59 hospitals of 707 patients with nonvalvular AF and at least 1 additional stroke risk factor (CHADS2 score ≥1). Enrollment occurred between February 2005 and June 2008 and included 4-year follow-up through October 2012. Noninferiority required a posterior probability greater than 97.5% and superiority a probability of 95% or greater; the noninferiority margin was a rate ratio of 2.0 comparing event rates between treatment groups.

**INTERVENTIONS:** Left atrial appendage closure with the device (n = 463) or warfarin (n = 244; target international normalized ratio, 2-3).

**MAIN OUTCOMES AND MEASURES:** A composite efficacy end point including stroke, systemic embolism, and cardiovascular/unexplained death, analyzed by intention-to-treat.

**RESULTS:** At a mean (SD) follow-up of 3.8 (1.7) years (2621 patient-years), there were 39 events among 463 patients (8.4%) in the device group for a primary event rate of 2.3 events per 100 patient-years, compared with 34 events among 244 patients (13.9%) for a primary event rate of 0.8 events per 100 patient-years with warfarin (rate ratio, 0.60; 95% credible interval, 0.41-1.05), meeting prespecified criteria for both noninferiority (posterior probability, >99.9%) and superiority. Patients in the device group demonstrated lower rates of both cardiovascular mortality (1.0 events per 100 patient-years for the device group [17/463 patients, 3.7%] vs 2.4 events per 100 patient-years with warfarin [22/244 patients, 9.0%]; hazard ratio [HR], 0.40; 95% CI, 0.21-0.75; P = .005) and all-cause mortality (3.2 events per 100 patient-years for the device group [57/466 patients, 12.3%] vs 4.8 events per 100 patient-years with warfarin [44/244 patients, 18.0%]; HR, 0.66; 95% CI, 0.45-0.98; P = .04).

**CONCLUSIONS AND RELEVANCE:** After 3.8 years of follow-up among patients with nonvalvular AF at elevated risk for stroke, percutaneous LAA closure met criteria for both noninferiority and superiority, compared with warfarin, for preventing the combined outcome of stroke, systemic embolism, and cardiovascular death, as well as superiority for cardiovascular and all-cause mortality.

**TRIAL REGISTRATION:** clinicaltrials.gov Identifier: NCT00129545.

The protocol for the use of the LAAC requires warfarin PLUS 81 mg ASA for 45 days post implantation, followed DAPT with ASA 325 and clopidogrel for 6 months then indefinite ASA 325 mg. The following shows that the overall rates of bleed are similar after 3 years.

4: PubMed: Rate of bleeding similar with LAA closure and warfarin for AF

OBJECTIVES: The purpose of this study was to compare the relative risk of major bleeding with left atrial appendage (LAA) closure compared with long-term warfarin therapy.

BACKGROUND: LAA closure is an alternative approach to chronic oral anticoagulation for the prevention of thromboembolism in patients with atrial fibrillation (AF).

METHODS: We conducted a pooled, patient-level analysis of the 2 randomized clinical trials that compared WATCHMAN (Boston Scientific, Natick, Massachusetts) LAA closure with long-term warfarin therapy in AF.

RESULTS: A total of 1,114 patients were included, with a median follow-up of 3.1 years. The overall rate of major bleeding from randomization to the end of follow-up was similar between treatment groups (3.5 events vs. 3.6 events per 100 patient-years; rate ratio [RR]: 0.96; 95% confidence interval [CI]: 0.66 to 1.40; p = 0.84). LAA closure significantly reduced bleeding >7 days post-randomization (1.8 events vs. 3.6 events per 100 patient-years; RR: 0.49; 95% CI: 0.32 to 0.75; p = 0.001), with the difference emerging 6 months after randomization (1.0 events vs. 3.5 events per 100 patient-years; RR: 0.28; 95% CI: 0.16 to 0.49; p < 0.001), when patients assigned to LAA closure were able to discontinue adjunctive oral anticoagulation and antiplatelet therapy. The reduction in bleeding with LAA closure was directionally consistent across all patient subgroups.

CONCLUSIONS: There was no difference in the overall rate of major bleeding in patients assigned to LAA closure compared with extended warfarin therapy over 3 years of follow-up. However, LAA closure significantly reduced bleeding beyond the procedural period, particularly once adjunctive pharmacotherapy was discontinued. The favorable effect of LAA closure on long-term bleeding should be considered when selecting a stroke prevention strategy for patients with nonvalvular AF. (WATCHMAN Left Atrial Appendage System for Embolic PROTECTION in Patients With Atrial Fibrillation; NCT00129545; and Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy [PREVAIL]; NCT01182441).


CHADS2-VASC Score

The 2014 AF guidelines by the ACC/AHA gave a class 1 recommendation to the use of the CHA2DS2-VASC score (Appendix 2) for risk stratification in patients with AF (vs using the CHADS2 score). This change increased the number of patients “newly qualified” for oral anticoagulants by 1 million.

5: Center for Medical Education: Applying the CHA2DS2-VASC score → ~ 1 million newly qualified for oral anticoagulants

BACKGROUND: The 2014 update of the AHA/ACC guidelines for the use of oral anticoagulants in patients with atrial fibrillation (AF) substituted the CHA2DS2-VASC score for risk stratification in place of the CHADS2 score as recommended in the 2011 guideline, and also revised the threshold for initiation of oral anticoagulation.

METHODS: The authors, coordinated at Duke Clinical Research Institute, compared the percentage of patients with AF for whom oral anticoagulation would be recommended under the 2011 and the 2014 guidelines, based on data from 10,132 adults with AF included in the ORBIT-AF national database.

RESULTS: Application of the revised guidelines would increase the number of patients for whom oral anticoagulation would be recommended from 71.8% (per the 2011 guideline) to 90.8%. A recommendation for anticoagulation increased from 43.1% to 60.6% for patients below the age of 65, from 79.1% to 98.5% for older patients, and from 76.7% to 97.7% for women. Among patients for whom anticoagulation would be newly recommended under the revised guideline, vascular disease was a factor that contributed to reclassification for 35.1%, female gender was contributory for 46.8%, and age was contributory for 81.4%. Extrapolating these data to the broader population of patients with AF in the US, it was determined that application of the revised guidelines could result in a new recommendation for oral anticoagulation in 988,500 patients.

CONCLUSIONS: Use of the 2014 revision of the AHA/ACC guidelines would substantially increase the number of patients with atrial fibrillation for whom oral anticoagulation would be recommended. 6 references


Newer oral anticoagulants (NOAs)

In the appendix is a brief table summarizing the 4 major studies that led to the approval of the 4 major newer oral anticoagulants in the treatment of AF (dabigatran Pradaxa®, rivaroxaban Xarelto®, apixaban Eliquis®, edoxaban Savaysa®) (appendix 3), and the current (2014) ACC/AHA recommendations on oral anticoagulants in AF (appendix 4).
Note that in each of these sentinel studies, the differences between warfarin and the NOA are extremely small (NNT’s of ~ 200 – 300 for prevention of embolization, mortality and bleeding risk/appendix 3). Subsequent systematic reviews (using 13 RCTs combining AF and VTE patients) demonstrated a larger net benefit vs warfarin for many outcomes (abstract #6). Be careful, however. Most studies don’t address the effectiveness of NOAs compared with patients who are *adequately anticoagulated* on warfarin. Abstract #7, in a manufacturers supported study demonstrated that although initial pharmacy costs are higher with dabigatran, overall health care utilization costs are lower in a retrospective analysis of 1102 patients started in either. Since the relative “safety” of these agents, and the lack of need for monitoring, are major driver for their use; Appendix 5 contains two references to articles in the BMJ outlining concerns about the results of two of these sentinel studies a) inaccurate INR monitoring in the Rocket-AF trial, and b) withholding data about the potential safety benefit of measuring plasma dabigatran levels. (Stay tuned)

Regardless, these agents are being used at an increasing frequency, Abstract # 8 (and the table and other resources in the appendix 6) provide a reasonable way to monitor and risk assess patients on NOAs.

**6: PubMed: NOAs associate with improved mortality vs warfarin in patients with AF/VTE**

**BACKGROUND:** Direct oral anticoagulants (DOACs) are widely used as an alternative for warfarin. However, the impact of DOACs on mortality outcomes compared with warfarin remains unclear. **OBJECTIVE:** To estimate the mortality outcomes in patients treated with DOACs vs. warfarin (or another vitamin K antagonist). **METHODS:** MEDLINE, EMBASE and CENTRAL databases (inception to September 2014), conference abstracts and www.clinicaltrials.gov, were searched, without language restriction. Studies were selected if there were phase III, randomized trials comparing DOACs with warfarin in patients with non-valvular atrial fibrillation or venous thromboembolism. **RESULTS:** Thirteen randomized controlled trials involving 102 707 adult patients were included in the analysis. The case-fatality rate of major bleeding was 7.57% (95% CI, 6.53-8.68; I(2) = 0%) in patients taking DOACs and 11.04% (95% CI,9.16-13.07; I(2) = 33.3%) in patients taking warfarin. The rate of fatal bleeding in adult patients receiving DOACs was 0.16 per 100 patient-years (95% CI, 0.12-0.20; (2) = 36.5%). When compared with warfarin, DOACs were associated with significant reductions in fatal bleeding (RR, 0.53; 95% CI, 0.43-0.64; I2(2) = 0%), cardiovascular mortality (RR, 0.88; 95% CI, 0.82-0.94; I2(2) = 0%) and all-cause mortality (RR, 0.91; 95% CI, 0.87-0.96; I2(2) = 0%). **CONCLUSIONS:** The use of DOACs compared with warfarin is associated with a lower rate of fatal bleeding, case-fatality rate of major bleeding, cardiovascular mortality and all-cause mortality. **REFERENCE:** Chai-Adisaksopha C, et al. Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials. J Thromb Haemost. 2015 Nov;13(11):2012-20

**7: PubMed: Healthcare utilization costs lower with dabigatran vs warfarin**

**PURPOSE:** Real-world healthcare resource utilization and costs were compared among patients with non-valvular atrial fibrillation (NVAF) receiving either dabigatran or warfarin. **METHODS:** A retrospective cohort study was conducted using administrative claims data from the United States Department of Defense (DOD) Military Health System. Patients with newly diagnosed AF initiated on dabigatran or warfarin were identified using ICD-9 diagnosis, procedure and drug codes. Patients were observed for 3 months prior to treatment initiation to ascertain a diagnosis of valvular heart disease and 12 months for exclusion of those with a history of anticoagulation therapy. Propensity score matching was used to balance baseline characteristics between the two treatment cohorts. Medical and pharmacy utilization and costs were compared between the dabigatran and warfarin treatment groups for 3 and 12 months following treatment initiation. **RESULTS:** A total of 1102 patients with newly diagnosed NVAF initiated on dabigatran were matched with corresponding warfarin-treated patients. In the 12 months following initiation of anticoagulation, the mean medical costs for patients initiated on dabigatran were significantly lower than for patients initiated on warfarin (-$6299, p < 0.001), largely due to fewer hospitalizations (-0.162, p = 0.009). While pharmacy costs were higher ($4369, p < 0.001) for dabigatran, overall healthcare costs were significantly lower compared with patients on warfarin (12 months: -$1940, p < 0.001). Mean hospital length of stay between these two groups were similar (6.033 days for dabigatran vs 6.318 days for warfarin, p = 0.139). **CONCLUSION:** Despite higher pharmacy costs for NVAF patients initiated on dabigatran vs warfarin, this was more than offset by lower utilization of medical care resources. **REFERENCE:** Francis K, et al. Healthcare utilization and costs associated with dabigatran compared to warfarin treatment in newly diagnosed patients with non-valvular atrial fibrillation. Curr Med Res Opin. 2015 Dec;31(12):2189-95. PMID: 26359333

**8: Center for Medical Education: Monitoring NOAs**

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.


**9: PubMed: Idarucizumab: A new reversal agent for dabigatran**

**BACKGROUND:** Specific reversal agents for non-vitamin K antagonist oral anticoagulants are lacking. Idarucizumab, an antibody fragment, was developed to reverse the anticoagulant effects of dabigatran.

**METHODS:** We undertook this prospective cohort study to determine the safety of 5 g of intravenous idarucizumab and its capacity to reverse the anticoagulant effects of dabigatran in patients who had serious bleeding (group A) or required an urgent procedure (group B). The primary end point was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab, on the basis of the determination at a central laboratory of the dilute thrombin time or ecarin clotting time. A key secondary end point was the restoration of hemostasis.

**RESULTS:** This interim analysis included 90 patients who received idarucizumab (51 patients in group A and 39 in group B). Among 68 patients with an elevated dilute thrombin time and 81 with an elevated ecarin clotting time at baseline, the median maximum percentage reversal was 100% (95% confidence interval, 100 to 100). Idarucizumab normalized the test results in 88 to 98% of the patients, an effect that was evident within minutes. Concentrations of unbound dabigatran remained below 20 ng per milliliter at 24 hours in 79% of the patients. Among 35 patients in group A who could be assessed, hemostasis, as determined by local investigators, was restored at a median of 11.4 hours. Among 36 patients in group B who underwent a procedure, normal intraoperative hemostasis was reported in 33, and mildly or moderately abnormal hemostasis was reported in 2 patients and 1 patient, respectively. One thrombotic event occurred within 72 hours after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated.

**CONCLUSIONS:** Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes. (Funded by Boehringer Ingelheim; RE-VERSE AD)


**Ablation**

Appendix 7 includes the current (2014) ACC/AHA recommendations for rate vs rhythm control strategies are listed along with several (verbatim) statements on both strategies. Of note they state that “RCTs comparing outcomes of a rhythm-control strategy using antiarrhythmic drugs with a rate-control strategy in patients with AF failed to show a superiority of rhythm control on mortality for either strategy.” … and that “Catheter ablation has not been studied in this context”.

**10: PubMed: Incidence of serious adverse events post is ~ 3% post ablation in AF**

**BACKGROUND:** The aim of this study was to assess the overall incidence of complications in a large sample of consecutive patients having undergone pulmonary vein (PV) isolation, evaluating also the rate of complications in radiofrequency (RF) and cryoballoon (CB) ablation technologies.

**METHODS AND RESULTS:** From January 2008 to December 2014, 1352 consecutive PV isolation procedures were performed in our center; a total amount of 1233 AF ablation procedures fulfilling inclusion criteria was finally taken into consideration for our analysis. A total of 642 procedures were performed using RF ablation technology and 591 using CB system. Serious adverse events occurred in 36 procedures (2.9%): specifically, vascular complications in 14 (1.1%); cardiac tamponade in 13 (1.0%); a thromboembolic event in 4 (0.3%); and atrial-esophageal fistula, PV intramural hematoma, retroperitoneal hematoma, pleural hematoma and persisting phrenic nerve palsy all occurred in 1 patient individually (0.1%). No deaths related to the procedure occurred. The complication rate did not significantly differ in the RF and CB groups (respectively, 3.6% vs 2.2%; p=0.1). Complication rates considerably decreased over the study period from 4.67% in 2008 to 1.55% in 2014. Interestingly, each 1-point increase in the CHA2DS2-VASc score was found to increase by 51% the likelihood of a serious adverse event.

**CONCLUSIONS:** The incidence of serious adverse events following AF ablation procedures was 2.9%. Vascular complications were the most frequent complication followed by tamponade and thromboembolic events. The rate of complications considerably decreased over time. CHA2DS2-VASc score was found to be associated with higher risk of complications.

Bridging anticoagulation

11: PubMed: Forgoing bridging anticoagulation was noninferior to perioperative bridging with low-molecular-weight heparin

**Background** It is uncertain whether bridging anticoagulation is necessary for patients with atrial fibrillation who need an interruption in warfarin treatment for an elective operation or other elective invasive procedure. We hypothesized that forgoing bridging anticoagulation would be noninferior to bridging with low-molecular-weight heparin for the prevention of perioperative arterial thromboembolism and would be superior to bridging with respect to major bleeding. **Methods** We performed a randomized, double-blind, placebo-controlled trial in which, after perioperative interruption of warfarin therapy, patients were randomly assigned to receive bridging anticoagulation therapy with low-molecular-weight heparin (100 IU of dalteparin per kilogram of body weight) or matching placebo administered subcutaneously twice daily, from 3 days before the procedure until 24 hours before the procedure and then for 5 to 10 days after the procedure. Warfarin treatment was stopped 5 days before the procedure and was resumed within 24 hours after the procedure. Follow-up of patients continued for 30 days after the procedure. The primary outcomes were arterial thromboembolism (stroke, systemic embolism, or transient ischemic attack) and major bleeding. **Results** In total, 1884 patients were enrolled, with 950 assigned to receive no bridging therapy and 934 assigned to receive bridging therapy. The incidence of arterial thromboembolism was 0.4% in the no-bridging group and 0.3% in the bridging group (risk difference, 0.1 percentage points; 95% confidence interval [CI], -0.6 to 0.8; P=0.01 for noninferiority). The incidence of major bleeding was 1.3% in the no-bridging group and 3.2% in the bridging group (relative risk, 0.41; 95% CI, 0.20 to 0.78; P=0.005 for superiority). **Conclusions** In patients with atrial fibrillation who had warfarin treatment interrupted for an elective operation or other elective invasive procedure, forgoing bridging anticoagulation was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism and decreased the risk of major bleeding. (Funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health; BRIDGE ClinicalTrials.gov number, NCT00786474.). **Reference:** Douketis JD, Spyropoulos AC, Kaatz S, et al. BRIDGE Investigators. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. N Engl J Med. 2015 Jun 22. [Epub ahead of print]

**Bottom Lines**

1. Left Atrial Appendage Closure (LAAC) is a potentially promising new treatment in patients with AF.
2. The CHA2DS-Vasc score significantly increases the number of AF patients who are newly qualified for oral anticoagulants.
3. The risk/benefit of using newer oral anticoagulants vs warfarin in AF patients continues to evolve with new data. The 2014 ACC/AHA guidelines endorse a Level 1 recommendation for both classes, but the level of certainty is A for warfarin and B for newer agents.
4. An evidence based protocol exists for monitoring patients on NOAs.
5. A reversal agent for dabigatran has been studied. Its effect on clinical outcomes is not known.
6. Ablation therapy for AF is associated with ~3% adverse event rate.
7. Bridging anticoagulation is less effective than no bridging in AF patients undergoing procedures.
Appendix 1

Left Atrial Appendage (LAA)

The LAA probably functions as a “decompression chamber” during periods of high left atrial pressure (e.g. left ventricular systole). Thrombus has a predilection to form in the LAA in patients with atrial fibrillation (up to 91% of left atrial thrombi are located in the LAA in patients with nonvalvular AF), mitral valve disease, and other conditions, likely due to relative stasis occurring in the appendage owing to its shape and other features. Obliteration or amputation of the LAA may help to reduce the risk of thromboembolism, but this may result in undesirable physiological sequelae such as reduced atrial compliance and a reduced capacity for ANF secretion in response to pressure and volume overload.

Additionally, LAA is an endocrine organ, the concentration of Atrial natriuretic peptide is 40 x higher in the LAA than the rest of the atrial wall and the ventricular endocardium. The long term effects of LAA closure on atrial release of ANP is not known.

NIH: [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1760793/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1760793/)

Image used with permission "Heart left atrial appendage tee view" by Patrick J. Lynch, medical illustrator Licensed under CC BY 2.5 via Wikimedia Commons.
Appendix 2

CHA2DS2-VASc Score (0-9 points)

<table>
<thead>
<tr>
<th>C</th>
<th>CHF</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>HTN</td>
<td>1</td>
</tr>
<tr>
<td>A2</td>
<td>Age ≥ 75</td>
<td>2</td>
</tr>
<tr>
<td>D</td>
<td>DM</td>
<td>1</td>
</tr>
<tr>
<td>S2</td>
<td>Stroke or TIA</td>
<td>2</td>
</tr>
<tr>
<td>V</td>
<td>Vascular dz – (e.g. CAD, PAD or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Age 65 – 74</td>
<td>1</td>
</tr>
<tr>
<td>Sc</td>
<td>Sex category - Female</td>
<td>1</td>
</tr>
</tbody>
</table>

Total:

<table>
<thead>
<tr>
<th>CHA2DS2-VASc Points</th>
<th>Annual Stroke Risk (% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1.3%</td>
</tr>
<tr>
<td>2</td>
<td>2.2%</td>
</tr>
<tr>
<td>3</td>
<td>3.2%</td>
</tr>
<tr>
<td>4</td>
<td>4.0%</td>
</tr>
<tr>
<td>5</td>
<td>6.7%</td>
</tr>
<tr>
<td>6</td>
<td>9.8%</td>
</tr>
<tr>
<td>7</td>
<td>9.6%</td>
</tr>
<tr>
<td>8</td>
<td>6.7%</td>
</tr>
<tr>
<td>9</td>
<td>15.2%</td>
</tr>
</tbody>
</table>
Appendix 3:
Comparisons between warfarin and 4 NOAs for atrial fibrillation

<table>
<thead>
<tr>
<th>Study Comparisons</th>
<th>Rely</th>
<th>Rocket</th>
<th>Aristotle</th>
<th>Engage-AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Warfarin vs Dabigatran</td>
<td>NNT</td>
<td>Δ Warfarin vs Rivaroxaban</td>
<td>NNT</td>
<td>Δ Warfarin vs Apixaban</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVA or Systemic Embolism/yr</td>
<td>0.58%</td>
<td>172</td>
<td>0.5%</td>
<td>200</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.49%</td>
<td>204</td>
<td>0.4%</td>
<td>250</td>
</tr>
<tr>
<td>Major Bleed/yr</td>
<td>0.25%</td>
<td>400</td>
<td>0.2%</td>
<td>500</td>
</tr>
</tbody>
</table>

Data from:
Appendix 4:

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

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF pattern is paroxysmal, persistent, or permanent</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with nonvalvular AF, the CHA2DS2-VASc score is recommended for assessment of stroke risk</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>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:</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>• warfarin (INR 2.0 to 3.0)</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>• dabigatran</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>• rivaroxaban</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>• apixaban</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>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</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>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</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>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</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>For patients with atrial flutter, use the same risk profile for antithrombotic therapy as AF</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>
Appendix 5:

Cohen D. Rivaroxaban: can we trust the evidence? BMJ. 2016 Feb 3;352:i575. PMID: 26843102 (much of the following is taken verbatim from this article)

In an investigative article in the BMJ in Feb 2016, the BMJ found that a defective point of care device was used in the warfarin arm of the trial, and that the validity of the trial (in which rivaroxaban was found to be non-inferior to warfarin in multiple outcomes in AF patients -- the Rocket-AF trial - see appendix) "is in question" until an independent analysis is completed. The concern, according to the article is that the care for the warfarin control arm patient appears to have been compromised, in that the point-of-care device used to track the INR in the warfarin patients, had a class 1 recall by the FDA in December of 2014, over concern that the devices delivered INR results clinically significantly lower than laboratory derived INRs. According to the article the defect was known to the device company dating back to 2002 (before the Rocket-AF trial was started). The results meant that patient could have had their warfarin levels unnecessarily increased, producing a greater risk of bleeding and making "rivaroxaban seem safer than it was in terms of the risk of bleeding and throws doubt on outcomes use to support the use of the worlds best selling new oral anticoagulant"; and that "the study should be considered of uncertain validity until a more thorough review can be done". Furthermore according to this article, "Currently, there is little public information about which diagnostic point of care devices are used in any of the direct oral anticoagulant trials (box)" and "Any changes to the ROCKET-AF trial will have a broader effect on the literature."

Cohen D. Dabigatran: how the drug company withheld important analyses. BMJ. 2014 Jul 23;349:g4670 PMID: 25055829 (much of the following is taken verbatim from this article)

"The company (Boehringer Ingelheim) found that if the plasma levels of the drug were measured and the dose was adjusted accordingly major bleeds could be reduced by 30-40% compared with well controlled warfarin. The adjustment would have little or no effect on the risk of ischaemic stroke. It has also identified the plasma levels at which the dose adjustment should occur to reduce the risk of a major bleed. The conclusion of the analyses was: “Optimally used (=titrated) dabigatran has the potential to provide patients an even better efficacy and safety profile than fixed dose dabigatran and also a better safety and efficacy profile than a matched warfarin group.” Internal emails released during litigation perhaps show that some within the company did not want these conclusions to be known. During internal email discussions about the potential merits of drug plasma monitoring one Boehringer employee, whose name has been redacted, said: “This may not be a onetime test and could result in a more complex message (regular monitoring) and a weaker value proposition.” Even as employees expressed concerns that elderly patients were being harmed, the company did not share these analyses with the regulators. However, the company said that the emails made public had been selected to show it in a bad light and restated its claim that the anticoagulant activity or plasma concentrations of dabigatran do not need to be monitored.

"The analysis did not provide a reliable prediction of patient outcomes, and therefore we did not share the simulation with FDA or EMA,” a spokesperson told The BMJ.

“Our scientists determined, and the FDA concurred, that the research does not support making dosage decisions based on plasma concentrations—a conclusion based solely on science and patient welfare,” he said.
Appendix 6:

Monitoring Patients on Direct Oral Anticoagulants

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


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

Appendix 7:

ACC/AHA Recommendations on rate vs rhythm control for AF include the following:

**Rate Control**

**Class 1**
Control of the ventricular rate using a beta blocker or nondihydropyridine calcium channel antagonist is recommended for patients with paroxysmal, persistent, or permanent AF. (Level of Evidence: B)

**Class IIA**
A heart rate control (resting heart rate <80 beats per minute [bpm]) strategy is reasonable for symptomatic management of AF. (Level of Evidence: B)

**Class IIB**
A lenient rate-control strategy (resting heart rate <110 bpm) may be reasonable as long as patients remain asymptomatic and left ventricular systolic function is preserved. (Level of Evidence: B)
Rhythm Control

Class I
AF catheter ablation is useful for symptomatic paroxysmal AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication \emph{when a rhythm-control strategy is desired}. (Level of Evidence: A)

Class IIa
AF catheter ablation is reasonable for some patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication. (Level of Evidence: A)

In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm-control strategy before therapeutic trials of antiarrhythmic drug therapy, after weighing the risks and outcomes of drug and ablation therapy. (Level of Evidence: A)

Class IIb
AF catheter ablation may be considered for symptomatic long-standing (>12 months) persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication \emph{when a rhythm-control strategy is desired}. (Level of Evidence: B)

AF catheter ablation may be considered before initiation of antiarrhythmic drug therapy with a class I or III antiarrhythmic medication for symptomatic persistent AF \emph{when a rhythm-control strategy is desired}. (Level of Evidence: C)

AF catheter ablation to restore sinus rhythm should not be performed with the sole intent of obviating the need for anticoagulation. (Level of Evidence: C)

In their content they make the following statements concerning rate vs rhythm control strategies:

- "RCTs comparing outcomes of a rhythm-control strategy using antiarrhythmic drugs with a rate-control strategy in patients with AF failed to show a superiority of rhythm control on mortality for either strategy."
- "Furthermore, when applied in patients who are candidates for both treatment strategies (rhythm or rate control), a rhythm-control strategy results in more hospitalizations. Therefore, the routine use of a rhythm-control strategy is not warranted for some patients. Catheter ablation has not been studied in this context."
- "Persistent symptoms associated with AF remain the most compelling indication for a rhythm-control strategy. Other factors that may favor attempts at rhythm control include difficulty in achieving adequate rate control, younger patient age, tachycardia-mediated cardiomyopathy, first episode of AF, AF precipitated by an acute illness, and patient preference."
- "AF progresses from paroxysmal to persistent in many patients and subsequently results in electrical and structural remodeling that becomes irreversible with time."
- "For this reason, acceptance of AF as permanent in a patient may render future rhythm-control therapies less effective. This may be more relevant for a younger patients"
Atrial fibrillation (AF) is a significant health care problem for patients with obstructive sleep apnea (OSA). Continuous positive airway pressure (CPAP) as a therapy for OSA is underused, and it is unknown if CPAP might reduce rates of AF. We systematically reviewed published reports on CPAP use and risk of AF. MEDLINE, EMBASE, CINAHL, Web of Science, meeting abstracts, and Cochrane databases were searched from inception to June 2015. Studies needed to report the rates of AF in participants who were and were not on CPAP. Data were extracted by 2 authors. A total of 8 studies on OSA were identified (1 randomized controlled trial) with 698 CPAP users and 549 non-CPAP users. In a random effects model, patients treated with CPAP had a 42% decreased risk of AF (pooled risk ratio, 0.58; 95% confidence interval, 0.47 to 0.70; p <0.001). There was low heterogeneity in the results (I² = 30%). In metaregression analysis, benefits of CPAP were stronger for younger, obese, and male patients (p <0.05). An inverse relationship between CPAP therapy and AF recurrence was observed. Results suggest that more patients with AF also should be tested for OSA.


The WATCHMAN left atrial appendage closure (LAAC) technology is a percutaneously delivered permanent cardiac implant placed in the LAA. This device is designed to reduce the risk of stroke and systemic embolism in warfarin-eligible patients with nonvalvular atrial fibrillation. The first circulatory system device panel reviewed the Embolic Protection in Patients With Atrial Fibrillation (PROTECT AF) study in 2009, and a "not approvable" letter was issued by the US Food and Drug Administration (FDA) based on safety concerns. Subsequently, the FDA, collaboratively with the sponsor, designed a new Prospective Randomized Evaluation of the WATCHMAN LAAC Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy (PREVAIL) trial to address the earlier study limitations. A second panel was convened in December 2013 to review the results of PREVAIL and additional long-term follow-up data from PROTECT AF. The second panel voted favorably 13 to 1 that the benefits of the WATCHMAN LAAC therapy do outweigh the risks for use in patients who meet the criteria specified in the proposed indication. Subsequently, and during the premarket approval review, updated data from the PREVIAL study revealed more ischemic strokes in the WATCHMAN group, corresponding to a total of 13 ischemic strokes in the WATCHMAN group versus 1 in the control group. As a result of these strokes, the FDA called for a third panel to assess the benefit-risk profile of the WATCHMAN device. This summary aims to describe the discussions and recommendations made during the panel meetings.

REFERENCE: Waksman R, Pendyala LK. Overview of the Food and Drug Administration circulatory system devices panel meetings on WATCHMAN left atrial appendage closure therapy. Am J Cardiol. 2015 Feb 1;115(3):378-84.
Allergy Update

John Hickner, MD, MS

Objectives

1. Describe the natural history of childhood milk, egg and peanut allergies

2. Discuss the evidence for the effectiveness of several interventions for food allergies, especially peanuts.

3. Review miscellaneous recent studies regarding allergic conditions commonly seen by family physicians and other primary care clinicians

Allergic conditions are one of the most common issues confronting primary care clinicians. This chapter is not intended as a comprehensive review of allergies, but it provides a summary of the most recent published studies regarding childhood food allergies and several other important allergy updates. It is important to understand the natural history of allergic conditions before one can judge the effectiveness of treatments.

What is the natural history of milk, egg and peanut allergies in children?

1. The natural history of milk allergy in an observational cohort

OBJECTIVE: There are few studies on the natural history of milk allergy. Most are single-site and not longitudinal, and these have not identified a means for early prediction of outcomes.

METHODS: Children aged 3 to 15 months were enrolled in an observational study with either: (1) a convincing history of egg allergy, milk allergy, or both with a positive skin prick test (SPT) response to the trigger food and/or (2) moderate-to-severe atopic dermatitis (AD) and a positive SPT response to milk or egg. Children enrolled with a clinical history of milk allergy were followed longitudinally, and resolution was established by means of successful ingestion.

RESULTS: The cohort consists of 293 children, of whom 244 were given a diagnosis of milk allergy at baseline. Milk allergy has resolved in 154 (52.6%) subjects at a median age of 63 months and a median age at last follow-up of 66 months. Baseline characteristics that were most predictive of resolution included milk-specific IgE level, milk SPT wheal size, and AD severity (all P < .001). Baseline milk-specific IgG4 level and milk IgE/IgG4 ratio were not predictive of resolution and neither was expression of cytokine-inducible SH2-containing protein, forkhead box protein 3, GATA3, IL-10, IL-4, IFN-γ, or T-bet by using real-time PCR in CD25-selected, casein-stimulated mononuclear cells. A calculator to estimate resolution probabilities using baseline milk IgE level, SPT response, and AD severity was devised for use in the clinical setting.

CONCLUSIONS: In this cohort of infants with milk allergy, approximately one half had resolved over 66 months of follow-up. Baseline milk-specific IgE level, SPT wheal size, and AD severity were all important predictors of the likelihood of resolution.


2. The natural history of egg allergy in an observational cohort

BACKGROUND: There are few studies on the natural history of egg allergy, and most are single-site and non-longitudinal and have not identified early predictors of outcomes.

OBJECTIVE: We sought to describe the natural course of egg allergy and to identify early prognostic markers.

METHODS: Children age 3 to 15 months were enrolled in a multicenter observational study with either (1) a convincing history of an immediate allergic reaction to egg, milk, or both with a positive skin prick test (SPT) response to the trigger food and/or (2) moderate-to-severe atopic dermatitis and a positive SPT response to egg or milk. Children enrolled with a clinical history of egg allergy were followed longitudinally, and resolution was established based on successful ingestion.

RESULTS: The cohort with egg allergy consists of 213 children followed to a median age of 74 months. Egg allergy resolved in 105 (49.3%) children at a median age of 72 months. Factors that were most predictive of resolution included milk-specific IgE level, milk SPT wheal size, atopic dermatitis severity, IgG4 level, and IL-4 response (all P < .05). Numerous additional baseline clinical and demographic factors and laboratory assessments were not associated with resolution. Multivariate analysis identified baseline egg-specific IgE levels and initial reaction characteristics as strongly associated with resolution; a calculator to estimate resolution probabilities using these variables was established.

CONCLUSIONS: In this cohort of infants with egg allergy, approximately one half had resolved over 74 months of follow-up. Baseline egg-specific IgE levels and initial reaction characteristics were important predictors of the likelihood of resolution.


3. The natural history and clinical predictors of egg allergy in the first 2 years of life: a prospective, population-based cohort study
BACKGROUND: There is a paucity of data examining the natural history of and risk factors for egg allergy persistence, the most common IgE-mediated food allergy in infants.

OBJECTIVE: We aimed to assess the natural history of egg allergy and identify clinical predictors for persistent egg allergy in a population-based cohort.

METHODS: The HealthNuts study is a prospective, population-based cohort study of 5276 infants who underwent skin prick tests to 4 allergens, including egg. Infants with a detectable wheal were offered hospital-based oral food challenges (OFCs) to egg, irrespective of skin prick test wheal sizes. Infants with challenge-confirmed raw egg allergy were offered baked egg OFCs at age 1 year and follow-up at age 2 years, with repeat OFCs to raw egg.

RESULTS: One hundred forty infants with challenge-confirmed egg allergy at age 1 year participated in the follow-up. Egg allergy resolved in 66 (47%) infants (95% CI, 37 to 56%) by 2 years of age; however, resolution was lower in children with baked egg allergy at age 1 year compared with baked egg tolerance (13% and 56%, respectively; adjusted odds ratio, 5.27; 95% CI, 1.36-20.50; P = .02). In the subgroup of infants who were tolerant to baked egg at age 1 year, frequent ingestion of baked egg (≥5 times per month) compared with infrequent ingestion (0-4 times per month) increased the likelihood of tolerance (adjusted odds ratio, 3.52; 95% CI, 1.38-8.98; P = .009). Mutation in the filaggrin gene was not associated with the resolution of either egg allergy or egg sensitization at age 2 years.

CONCLUSION: Phenotyping of egg allergy (baked egg tolerant vs allergic) should be considered in the management of this allergy because it has prognostic implications and eases dietary restrictions. Randomized controlled trials for egg oral immunotherapy should consider stratifying at baseline by the baked egg subphenotype to account for the differential rate of tolerance development.


4. Peanut allergy resolves in approximately 1 in 5 children in the first 4 years of life

Clinical question: What is the natural history of peanut allergy in the first 4 years of life?

Study design: Cohort (prospective)

Setting: Population-based

Synopsis: In conjunction with the Australian HealthNuts study, these investigators analyzed data obtained from 5276 twelve-month-old infants who underwent skin prick test screening to 4 common food allergens, including peanut. Infants with a detectable skin prick test response (equal to or greater than 1 mm) were referred for a formal OFC. Individuals masked to skin prick test results performed the OFCs and classified the results as positive or negative, based on standard diagnostic criteria. All children with a positive OFC result at age 1 year were assessed again, if possible, at 4 years of age. Follow-up included both a parental questionnaire and a repeat OFC. Of the original cohort of 12-month-old children with a positive OFC (n = 156), 139 (89%) had parents who completed the evaluation questionnaire and 103 (66%) of the children underwent repeat OFC testing at 4 years. Of these, 22 children had a negative OFC result. In the group of 36 children not undergoing formal OFC testing, 6 parents reported a history of peanut tolerance in their child, defined as an absence of adverse symptoms with regular ingestion of peanuts in the child's diet. Thus, a total of 28 children from the original cohort (18%) had either a parental history of tolerating regular ingestion of peanuts or a negative OFC result. A history of tree nut and house dust mite sensitization, coexisting food allergies, eczema, and asthma were not predictive of persistent peanut allergy.

Bottom line: In this study, 18% of children with a positive oral food challenge (OFC) result to peanuts at 1 year of age showed no evidence of persistent peanut allergy at 4 years of age.


What interventions are effective for peanut and egg allergy and general food allergies?

5. Sublingual immunotherapy for peanut allergy: Long-term follow-up of a randomized multicenter trial

BACKGROUND: We previously reported the initial results of the first multicenter, randomized, double-blind, placebo-controlled clinical trial of peanut sublingual immunotherapy (SLIT), observing a favorable safety profile associated with modest clinical and immunologic effects in the first year.

OBJECTIVE: We sought to provide long-term (3-year) clinical and immunologic outcomes for our peanut SLIT trial. Key end points were (1) percentage of responders at 2 years (ie, could consume 5 g of peanut powder or a 10-fold increase from baseline), (2) percentage reaching desensitization at 3 years, (3) percentage attaining sustained unresponsiveness after 3 years, (4) immunologic end points, and (5) assessment of safety parameters.

METHODS: Response to treatment was evaluated in 40 subjects aged 12 to 40 years by performing a 10-g peanut powder oral food challenge after 2 and 3 years of daily peanut SLIT therapy. At 3 years, SLIT was discontinued for 8 weeks, followed by another 10-g oral food challenge and an open feeding of peanut butter to assess sustained unresponsiveness.

RESULTS: Approximately 98% of the 18,165 doses were tolerated without adverse reactions beyond the oropharynx, with no severe symptoms or uses of epinephrine. A high rate (>50%) discontinued therapy. By study's end, 4 (10.8%) of 37 SLIT-treated participants were fully desensitized to 10 g of peanut powder, and all 4 achieved sustained unresponsiveness. Responders at 2 years showed a significant decrease in peanut-specific basophil activation and skin prick test titration compared with nonresponders.

CONCLUSIONS: Peanut SLIT induced a modest level of desensitization, decreased immunologic activity over 3 years in responders, and had an excellent long-term safety profile. However, most patients discontinued therapy by the end of year 3, and only 10.8% of subjects achieved sustained unresponsiveness.

6. Randomized trial of peanut consumption in infants at risk for peanut allergy

**BACKGROUND:** The prevalence of peanut allergy among children in Western countries has doubled in the past 10 years, and peanut allergy is becoming apparent in Africa and Asia. We evaluated strategies of peanut consumption and avoidance to determine which strategy is most effective in preventing the development of peanut allergy in infants at high risk for the allergy.

**METHODS:** We randomly assigned 640 infants with severe eczema, egg allergy, or both to consume or avoid peanuts until 60 months of age. Participants, who were at least 4 months but younger than 11 months of age at randomization, were assigned to separate study cohorts on the basis of preexisting sensitivity to peanut extract, which was determined with the use of a skin-prick test--one consisting of participants with no measurable wheal after testing and the other consisting of those with a wheal measuring 1 to 4 mm in diameter. The primary outcome, which was assessed independently in each cohort, was the proportion of participants with peanut allergy at 60 months of age.

**RESULTS:** Among the 530 infants in the intention-to-treat population who initially had negative results on the skin-prick test, the prevalence of peanut allergy at 60 months of age was 13.7% in the avoidance group and 1.9% in the consumption group (P<0.001). Among the 98 participants in the intention-to-treat population who initially had positive test results, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group (P=0.004). There was no significant between-group difference in the incidence of serious adverse events. Increases in levels of peanut-specific IgG4 antibody occurred predominantly in the consumption group; a greater percentage of participants in the avoidance group had elevated titers of peanut-specific IgE antibody. A larger wheal on the skin-prick test and a lower ratio of peanut-specific IgG4:IgE were associated with peanut allergy.

**CONCLUSIONS:** The early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts.


7. Effect of Avoidance on Peanut Allergy after Early Peanut Consumption

**BACKGROUND:** In a randomized trial, the early introduction of peanuts in infants at high risk for allergy was shown to prevent peanut allergy. In this follow-up study, we investigated whether the rate of peanut allergy remained low after 12 months of peanut avoidance among participants who had consumed peanuts during the primary trial (peanut-consumption group), as compared with those who had avoided peanuts (peanut-avoidance group).

**METHODS:** At the end of the primary trial, we instructed all the participants to avoid peanuts for 12 months. The primary outcome was the percentage of participants with peanut allergy at the end of the 12-month period, when the participants were 72 months of age.

**RESULTS:** We enrolled 556 of 628 eligible participants (88.5%) from the primary trial; 550 participants (98.9%) had complete primary-outcome data. The rate of adherence to avoidance in the follow-up study was high (90.4% in the peanut-avoidance group and 69.3% in the peanut-consumption group). Peanut allergy at 72 months was significantly more prevalent among participants in the peanut-avoidance group than among those in the peanut-consumption group (18.6% [52 of 280 participants] vs. 4.8% [13 of 270], P<0.001). Three new cases of allergy developed in each group, but after 12 months of avoidance there was no significant increase in the prevalence of allergy among participants in the consumption group (3.6% [10 of 274 participants] at 60 months and 4.8% [13 of 270] at 72 months, P=0.25). Fewer participants in the peanut-consumption group than in the peanut-avoidance group had high levels of Ara h2 (a component of peanut protein)-specific IgE and peanut-specific IgE; in addition, participants in the peanut-consumption group continued to have a higher level of peanut-specific IgG4 and a higher peanut-specific IgG4:IgE ratio.

**CONCLUSIONS:** Among children at high risk for allergy in whom peanuts had been introduced in the first year of life and continued until 5 years of age, a 12-month period of peanut avoidance was not associated with an increase in the prevalence of peanut allergy. Longer-term effects are not known.


8. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants

**BACKGROUND:** The age at which allergenic foods should be introduced into the diet of breast-fed infants is uncertain. We evaluated whether the early introduction of allergenic foods in the diet of breast-fed infants would protect against the development of food allergy.

**METHODS:** We recruited, from the general population, 1303 exclusively breast-fed infants who were 3 months of age and randomly assigned them to the early introduction of six allergenic foods (peanut, cooked egg, cow’s milk, sesame, whitefish, and wheat; early-introduction group) or to the current practice recommended in the United Kingdom of exclusive breast-feeding to approximately 6 months of age (standard-introduction group). The primary outcome was food allergy to one or more of the six foods between 1 year and 3 years of age.

**RESULTS:** In the intention-to-treat analysis, food allergy to one or more of the six intervention foods developed in 7.1% of the participants in the standard-introduction group (42 of 595 participants) and in 5.6% of those in the early-introduction group (32 of 567) (P=0.32). In the per-protocol analysis, the prevalence of any food allergy was significantly lower in the early-introduction group than in the standard-introduction group (2.4% vs. 7.3%, P=0.01), as was the prevalence of peanut allergy (0% vs. 2.5%, P=0.003) and egg
allergy (1.4% vs. 5.5%, P=0.009); there were no significant effects with respect to milk, sesame, fish, or wheat. The consumption of 2 g per week of peanut or egg-white protein was associated with a significantly lower prevalence of these respective allergies than was less consumption. The early introduction of all six foods was not easily achieved but was safe.

**CONCLUSIONS** The trial did not show the efficacy of early introduction of allergenic foods in an intention-to-treat analysis. Further analysis raised the question of whether the prevention of food allergy by means of early introduction of multiple allergenic foods was dose-dependent.


9. **Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy**

**BACKGROUND** We previously reported the results of a randomized placebo-controlled study of egg oral immunotherapy (eOIT) in which 27.5% of subjects achieved sustained unresponsiveness (SU) after 2 years. Here we report the results of treatment through 4 years and long-term follow-up.

**OBJECTIVE** We sought to evaluate the efficacy and safety of eOIT in participants treated up to 4 years.

**METHODS** Children with egg allergy (5-18 years old) received eOIT (n = 40) for up to 4 years or placebo (n = 15) for 1 year or less. The key outcome was the percentage of subjects achieving SU by year 4. Safety and immunologic assessments were performed, and long-term follow-up questionnaires (LFQs) were administered after study conclusion (LFQ-1) and 1 year later (LFQ-2).

**RESULTS** Of 40 eOIT-treated subjects, 20 (50.0%) of 40 demonstrated SU by year 4. For those subjects still dosing during years 3 and 4, mild symptoms were present in 12 (54.5%) of 22 subjects. At the time of the LFQ, more subjects receiving eOIT (LFQ-1, 23/34 [68%]; LFQ-2, 21/33 [64%]) were consuming unbaked and baked egg versus placebo (LFQ-1, 2/11 [18%], P = .006; LFQ-2, 3/12 [25%], P = .04). Of subjects achieving SU, 18 (90%) of 20 completed the LFQ, with 18 (100%) of 18 reporting consumption of all forms of egg. When compared with subjects not achieving SU, subjects achieving SU had higher IgG4 values (P = .001) and lower egg skin prick test scores (P = .0002) over time and a lower median baseline ratio of egg-specific IgE to total IgE (1.1% vs 2.7%, P = .04).

**CONCLUSIONS** SU after eOIT is enhanced with longer duration of therapy and increases the likelihood of tolerating unbaked egg in the diet.


**Are probiotics effective for preventing allergies?**

10. **Probiotics for the prevention of allergy: A systematic review and meta-analysis of randomized controlled trials**

**BACKGROUND** Allergic diseases are considered a health burden because of their high and constantly increasing prevalence, high direct and indirect costs, and undesirable effects on quality of life. Probiotics have been suggested as an intervention to prevent allergic diseases.

**OBJECTIVE** We sought to synthesize the evidence supporting use of probiotics for the prevention of allergies and inform World Allergy Organization guidelines on probiotic use.

**METHODS** We performed a systematic review of randomized trials assessing the effects of any probiotic administered to pregnant women, breast-feeding mothers, and/or infants.

**RESULTS** Of 2403 articles published until December 2014 identified in Cochrane Central Register of Controlled Trials, MEDLINE, and Embase, 29 studies fulfilled a priori specified inclusion criteria for the analyses. Probiotics reduced the risk of eczema when used by women during the last trimester of pregnancy (relative risk [RR], 0.71; 95% CI, 0.60-0.84), when used by breast-feeding mothers (RR, 0.57; 95% CI, 0.47-0.69), or when given to infants (RR, 0.80; 95% CI, 0.68-0.94). Evidence did not support an effect on other allergies, nutrition status, or incidence of adverse effects. The certainty in the evidence according to the Grading of Recommendation Assessment Development and Evaluation approach is low or very low because of the risk of bias, inconsistency and imprecision of results, and indirectness of available research.

**CONCLUSION** Probiotics used by pregnant women or breast-feeding mothers and/or given to infants reduced the risk of eczema in infants; however, the certainty in the evidence is low. No effect was observed for the prevention of other allergic conditions.


11. **Probiotics for Prevention of Atopy and Food Hypersensitivity in Early Childhood: A PRISMA-Compliant Systematic Review and Meta-Analysis of Randomized Controlled Trials**

Most studies investigated probiotics on food hypersensitivity, not on oral food challenge confirmed food allergy in children. The authors systematically reviewed the literature to investigate whether probiotic supplementation prenatally and/or postnatally could reduce the risk of atopy and food hypersensitivity in young children. PubMed, Embase, the Cochrane Central Register of Controlled Trials, and 4 main Chinese literature databases (Wan Fang, VIP, China National Knowledge Infrastructure, and SinoMed) were searched for
randomized controlled trials regarding the effect of probiotics on the prevention of allergy in children. The last search was conducted on July 11, 2015. Seventeen trials involving 2947 infants were included. The first follow-up studies were analyzed. Pooled analysis indicated that probiotics administered prenatally and postnatally could reduce the risk of atopy (relative risk [RR] 0.78; 95% confidence interval [CI] 0.66-0.92; I²=0%), especially when administered prenatally to pregnant mother and postnatally to child (RR 0.71; 95% CI 0.57-0.89; I²=0%), and the risk of food hypersensitivity (RR 0.77; 95% CI 0.61-0.98; I²=0%). When probiotics were administered either only prenatally or only postnatally, no effects of probiotics on atopy and food hypersensitivity were observed. Probiotics administered prenatally and postnatally appears to be a feasible way to prevent atopy and food hypersensitivity in young children. The long-term effects of probiotics, however, remain to be defined in the follow-up of existing trials. Still, studies on probiotics and confirmed food allergy, rather than surrogate measure of food hypersensitivity, are warranted.


Other recent randomized trials/meta-analyses of allergy treatment and prevention

12. RCT: Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy for Adults With Allergic Asthma

BACKGROUND: The house dust mite (HDM) sublingual allergen immunotherapy (SLIT) tablet is a potential novel treatment option for HDM allergy-related asthma.

OBJECTIVES: To evaluate the efficacy and adverse events of the HDM SLIT tablet vs placebo for asthma exacerbations during an inhaled corticosteroid (ICS) reduction period.

DESIGN, SETTINGS, AND PARTICIPANTS: Double-blind, randomized, placebo-controlled trial conducted between August 2011 and April 2013 in 109 European trial sites. The trial included 834 adults with HDM allergy-related asthma not well controlled by ICS or combination products, and with HDM allergy-related rhinitis. Key exclusion criteria were FEV1 less than 70% of predicted value or hospitalization due to asthma within 3 months before randomization. Efficacy was assessed during the last 6 months of the trial when ICS was reduced by 50% for 3 months and then completely withdrawn for 3 months.

INTERVENTIONS: 1:1:1 randomization to once-daily treatment with placebo (n = 277) or HDM SLIT tablet (dosage groups: 6 SQ-HDM [n = 275] or 12 SQ-HDM [n = 282]) in addition to ICS and the short-acting β2-agonist salbutamol.

MAIN OUTCOMES AND MEASURES: Primary outcome was time to first moderate or severe asthma exacerbation during the ICS reduction period. Secondary outcomes were deterioration in asthma symptoms, change in allergen-specific immunoglobulin G4 (IgG4), change in asthma control or asthma quality-of-life questionnaires, and adverse events.

RESULTS: Among 834 randomized patients (mean age, 33 years [range, 17-83]; women, 48%), 693 completed the study. The 6 SQ-HDM and 12 SQ-HDM doses both significantly reduced the risk of a moderate or severe asthma exacerbation compared with placebo (hazard ratio [HR]: 0.72 [95% CI, 0.52-0.99] for the 6 SQ-HDM group, P = .045, and 0.69 [95% CI, 0.50-0.96] for the 12 SQ-HDM group, P = .03). The absolute risk differences based on the observed data (full analysis set) in the active groups vs the placebo group were 0.09 (95% CI, 0.01-0.15) for the 6 SQ-HDM group and 0.10 (95% CI, 0.02-0.16) for the 12 SQ-HDM group. There was no significant difference between the 2 active groups. Compared with placebo, there was a reduced risk of an exacerbation with deterioration in asthma symptoms (HR, 0.72 [95% CI, 0.49-1.02] for the 6 SQ-HDM group, P = .11, and 0.64 [95% CI, 0.42-0.96] for the 12 SQ-HDM group, P = .03) and a significant increase in allergen-specific IgG4. However, there was no significant difference for change in asthma control questionnaire or asthma quality-of-life questionnaire for either dose. There were no reports of severe systemic allergic reactions. The most frequent adverse events were mild to moderate oral pruritus (13% for the 6 SQ-HDM group, 20% for the 12 SQ-HDM group, and 3% for the placebo group), mouth edema, and throat irritation.

CONCLUSIONS AND RELEVANCE: Among adults with HDM allergy-related asthma not well controlled by ICS, the addition of HDM SLIT to maintenance medications improved time to first moderate or severe asthma exacerbation during ICS reduction, with an estimated absolute reduction at 6 months of 9 to 10 percentage points; the reduction was primarily due to an effect on moderate exacerbations. Treatment-related adverse events were common at both active doses. Further studies are needed to assess long-term efficacy and safety.


13. Oral therapy for grass pollen allergy only marginally effective

Clinical question: Is the sublingual administration of grass pollen extract more effective than placebo in diminishing symptoms in patients with grass pollen allergy?

Study design: Meta-analysis (randomized controlled trials)

Setting: Various (meta-analysis)

Synopsis: These researchers searched, without language restriction, 4 databases, including the Cochrane Library, and identified 13 published randomized trials comparing the effect on symptoms of sublingual administration of grass pollen extract with placebo in 4659 patients with documented allergy to grass pollen. The studies evaluated the effectiveness of both available products, timothy grass pollen extract (Grastek [Grazax in Europe]) and 5-grass extract (Oralair). Two reviewers independently extracted the data, which were checked by 2 other reviewers. All studies were of good quality (using Jadad criteria). They didn't locate any unpublished data, but didn't find any evidence of publication bias. As compared with placebo, there was a small difference in clinical symptoms (standardized mean difference [SMD] -0.28; 95% CI -0.37 to -0.19; P < .001) and in the medication score (SMD -0.24; -0.31 to -0.17; P < .001). As compared with baseline scores, though, there was no difference between placebo and active treatment. The studies performed in Europe showed

58
a greater benefit in symptom scores than the studies in North America, though not by much. Side effects were reported by 60% of the patients, including several episodes of anaphylaxis that required epinephrine.

**Bottom line:** Neither available sublingual grass pollen extract produced a profound effect on symptoms. Itchy eyes and runny noses were still common, as was the use of medication to control symptoms. Side effects were reported by 60% of the patients using the grass pollen extract.


### 14. Topical steroids for nasal polyps

**Background.** Chronic rhinosinusitis with nasal polyps (CRSwNP) represents inflammatory changes throughout the nose and sinuses from a group of disorders which all lead to swelling and overgrowth of the nasal mucosa. Topical corticosteroids have been the most widely used treatment, with each clinician using different regimes, at different doses, in different settings and with or without sinus surgery. CRSwNP requires ongoing medical management to prevent recurrence.

**Objectives.** To assess the effects of topical corticosteroids on CRSwNP and to analyse various subgroups, including patients who had sinus surgery immediately prior to the delivery of the corticosteroids, surgery any time prior to the topical corticosteroids or patients who had never had previous surgery. Also, to assess the most effective dose and delivery methods for topical corticosteroids.

**Search methods.** We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of the search was 10 April 2012.

**Selection criteria.** Randomised controlled trials studying topical corticosteroids for patients with CRSwNP.

**Data collection and analysis.** At least two authors reviewed the search results and selected trials meeting the eligibility criteria, obtaining full texts and contacting authors. We documented our justification for the exclusion of studies. At least two authors extracted data using a pre-determined, standardised data form.

**Main results.** Forty studies (3624 patients) met the inclusion criteria. The trials were at low (21 trials), medium (13 trials) and high (six trials) risk of bias. The primary outcomes were sino-nasal symptoms, polyp size and polyp recurrence after surgery. When compared to placebo, topical corticosteroids improved overall symptom scores (standardised mean difference (SMD) -0.46; 95% confidence interval (CI) -0.65 to -0.27, P < 0.00001; seven trials, n = 445) and had a higher proportion of patients whose symptoms improved (responders) (risk ratio (RR) 1.71; 95% CI 1.29 to 2.26, P = 0.0002; four trials, n = 234). Topical corticosteroids also decreased the polyp score (SMD -0.73; 95% CI -1.00 to -0.46, P = 0.0001; three trials, n = 237) and had a greater proportion of patients with a reduction in polyp size (responders) (RR 2.09; 95% CI 1.65 to 2.64, P < 0.00001; eight trials, n = 785) when compared to placebo. Topical corticosteroids also prevented polyp recurrence after surgery (RR 0.59; 95% CI 0.45 to 0.79, P = 0.0004; six trials, n = 437). Subgroup analyses by sinus surgery status revealed a greater benefit in reduction of polyp score when topical steroid was administered any time after sinus surgery (SMD -1.19; 95% CI -1.54 to -0.83) compared to patients who had never had surgery (SMD -0.13; 95% CI -0.53 to 0.28, P < 0.00001). There was no difference between groups in terms of adverse events.

**Authors’ conclusions.** Topical corticosteroids are a beneficial treatment for CRSwNP and the adverse effects are minor, with benefits outweighing the risks. They improve symptoms, reduce polyp size and prevent polyp recurrence after surgery. Patients having sinus surgery may have a greater response to topical corticosteroids but further research is required.


### 15. Hand washing children’s dishes associated with fewer allergies

**Clinical question:** Can the way dishes are washed affect the development of allergies in children?

**Study design:** Cross-sectional

**Setting:** Population-based

**Synopsis:** The goal of this wide-ranging study was to see whether exposure to microbes early in life affected the development of allergies. The Swedish investigators sent questionnaires to parents of 1029 children, aged 7 to 8 years, in a single city, asking about the child’s history of allergy, including any diagnosis of eczema, asthma, or allergic rhinoconjunctivitis, as well as asking about eating habits. To test for dietary microbes, the researchers asked parents about how they washed their dishes (using a dishwasher or by hand); their use of farm-purchased milk, eggs, or unpasteurized milk; whether their diet included fermented foods (e.g., sauerkraut) or home-cooked foods; and the duration of their breastfeeding. Most of the children attended daycare and one third had a pet, but only 6% lived in a household in which a parent reported they smoked inside. After analyzing all these factors to look for associations, hand dishwashing, which occurred in only 12% of households, was associated with the greatest reduced risk of allergic disease development (odds ratio 0.57, 95% CI 0.37-0.85). The risk was further reduced in a dose-response pattern if the children were also served fermented food and if the family bought food directly from farms. The associations remained after adjusting for socioeconomic factors.

**Bottom line:** This study might cause one to quip, “Cleanliness is next to atomicity.” These results add further credence to the idea that the gastrointestinal system plays a big role in the development of our immune system (the “hygiene hypothesis”). Washing children’s bottles and eating utensils by hand instead of using an automatic dishwasher was associated with a lower risk of developing an allergic disorder. The authors stop short of recommending low hygienic standards, but they suggest that fastidiousness might not allow the immune system to learn how to self-modulate.

**Bottom Lines**

1. Half of children with milk allergy will not be allergic to milk by age 5.
2. Half of children with egg allergy will not be allergic to egg by 2 to 5 years of age.
3. One in five children with peanut allergy will not be allergic to peanuts by age 4.
4. Early exposure to peanuts in allergy prone children greatly reduced the prevalence of peanut allergy.
5. Early exposure to peanut and egg protein (3 mo.) in breast fed infants cuts the rate of food allergy significantly.
6. Probiotics given to pregnant mothers and their infants reduces the prevalence of eczema.
7. Oral immunotherapies for asthma (house dust mite) and allergic rhinitis (grass) reduce symptoms only slightly.
8. Nasal steroids are effective for nasal polyps.
9. Exposure to dirt aint all bad!
Prevention

Mark H. Ebell MD, MS

Aspirin

The most recent USPSTF guidelines on aspirin give it a “B” for adults age 50 to 59 with at least a 10% 10 year CV risk, for a moderate net benefit.

The recommendation is a C for persons age 60 to 69 years, indicating a small net benefit.

The benefit may be even greater in those under age 50 based on modeling, but in the absence of direct trial evidence that age group got an “I”. What’s new is that this recommendation looked at CV risk reduction, cancer risk reduction, and harms all at once. VERY COMPLICATED.

At right is a graph showing the importance of the duration of aspirin use and cancer death. Longer is better, and 5 to 7.5 years is the minimum for benefit.

1. Low-dose aspirin not effective for primary prevention of CV events (again) and increases risk of serious bleeding

Clinical question: Is low-dose aspirin beneficial for the primary prevention of cardiovascular disease in high-risk older adults with atherosclerotic risk factors?

Study design: Randomized controlled trial (single-blinded)

Setting: Outpatient (primary care)

Synopsis: These investigators identified consecutive adults, aged 60 to 85 years, presenting to their local health clinic in Japan with a history of hypertension, dyslipidemia, or diabetes, but with no history of atherosclerotic disease, including coronary artery disease, cerebrovascular disease (including transient ischemic attack), vascular disease requiring surgery or intervention, or atrial fibrillation. Patients with a history of gastrointestinal bleeding or bleeding diathesis were excluded. Eligible patients (N = 14,658) received standard treatment for cardiac risk factors and randomly received (concealed allocation assignment) 100 mg enteric-coated aspirin daily or no aspirin in an open-label fashion. Individuals who assessed outcomes remained masked to treatment group assignment. Complete follow-up occurred for nearly 90% of patients at 5 years. Using intention-to-treat analysis, no significant differences occurred between the 2 groups in the primary end point of the composite of death from cardiovascular causes, nonfatal stroke, and nonfatal myocardial infarction. The individual outcomes of nonfatal myocardial infarction and transient ischemic attack were significantly lower in the aspirin group, but gastrointestinal bleeding events and serious extracranial hemorrhage requiring hospitalization were also significantly increased with daily aspirin use. No overall significant differences occurred for all-cause mortality between groups. Finally, no differences were detected between the 2 groups when doing subgroup analyses for specific risk factors, including hypertension, dyslipidemia, diabetes, male sex, aged at least 70 years, body mass index, smoking, or family history of CVD.

Bottom line: A systematic review/meta-analysis published in 2011 (Am Heart J 2011;162(1):115-124.e2) based on 9 studies of more than 100,000 patients found no overall benefit to aspirin for the primary prevention of cardiovascular events in patients without clinical cardiovascular disease (CVD). This recent study of high-risk older adults in Japan similarly found no benefit to low-dose aspirin,
including in the subgroups of hypertension, hyperlipidemia, diabetes, obesity, male gender, smoking, and family history of CVD. The risks of major gastrointestinal bleeding and brain hemorrhage were significantly increased. It's time to let this one go.


2. USPSTF: Some adults should take aspirin to prevent CVD, colorectal cancer

Clinical question: Should adults take aspirin to lower the risk of cardiovascular disease and colorectal cancer?

Study design: Practice guideline

Setting: Various (guideline)

Synopsis: Citing 5 new studies of aspirin to prevent CVD and additional analysis of data on colorectal cancer, the USPSTF has updated and refined its recommendations for recommending aspirin to decrease the likelihood of both CVD and colorectal cancer. They conclude that for adults aged 50 to 59 years there is a moderate chance of a reduction in risk of myocardial infarction and ischemic stroke after 10 years of use and, with long-term use, a reduced incidence of colorectal cancer. In contrast, there is a small risk of gastrointestinal bleeding in this age group. The group suggests the use of the American College of Cardiology/American Heart Association risk calculator (see Essential Evidence Plus or http://tools.acc.org/ASCVD-Risk-Estimator/), though this calculator is likely to overestimate risk—and, therefore, the benefit of aspirin in many people (see J Am Coll Cardiol 2016;67:2118-2130). For patients aged 60 to 69 years with a 10% or greater CVD risk, the USPSTF suggests the decision be based on the desires of the patient (C recommendation). The evidence is insufficient regarding the use of aspirin for people younger than 50 years or older than 70 years of age (I recommendation).

Bottom line: The U.S. Preventive Services Task Force (USPSTF) recommends that adults aged 50 years to 59 years take 81 mg aspirin per day to prevent both cardiovascular disease (CVD) and colorectal cancer if they meet the following criteria: (1) 10% or greater CVD risk, (2) no increased risk for bleeding, (3) a life expectancy of at least 10 years, and (4) a willingness to continue treatment for at least 10 years. This is a B recommendation (should be offered to individuals meeting the criteria).

But what are, for example, 71.6 QALY per 1000 persons. Distributed evenly, that is 26 days per person.

3. USPSTF: Use aspirin to prevent preeclampsia in at-risk women

Clinical question: Should low-dose aspirin be used to prevent preeclampsia?
Study design: Practice guideline
Setting: Various (guideline)
Synopsis: Citing evidence of substantial net benefit to prevent preeclampsia, preterm birth, and intrauterine growth retardation, the USPSTF recommends aspirin (60 - 150 mg/day) starting between 12 and 28 weeks of gestation in women with at least one of the following risk factors: history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or type 2 diabetes, renal disease, or an autoimmune disease. This is a B recommendation and should be provided to most women at risk. Women with several moderate risk factors can consider using aspirin. This recommendation is an update from the 1996 recommendation, which concluded that evidence was insufficient to recommend for or against the routine use of aspirin.

Bottom line: The United States Preventive Services Task Force (USPSTF) recommends low-dose aspirin (81 mg/day) after 12 weeks of gestation in women who are at high risk for preeclampsia. (B recommendation).

Sexually transmitted infections

4. Suppressive treatment results in zero HIV transmission in serodifferent couples reporting condomless sex

Clinical question: Is the use of suppressive antiretroviral therapy associated with low HIV transmission rates to HIV-seronegative partners during condomless sex?
Study design: Cohort (prospective)
Setting: Population-based
Synopsis: Although ART reduces the risk of sexual transmission in HIV-positive people, the risk of transmission specifically from sex without a condom remains uncertain. These investigators recruited serodifferent couples from 14 European countries who reported regular penetrative sex without using condoms. All of the HIV-positive partners, 18 years or older, were taking continuous ART. Eligibility criteria included that the latest plasma HIV-1 RNA load in the positive partner to be less than 200 copies/mL. The HIV-negative partner underwent testing for evidence of HIV seroconversion every 6 to 12 months, while the HIV-positive partner underwent plasma HIV-1 RNA measurement every 6 to 12 months. A total of 888 couples (548 heterosexual and 340 MSM) contributed 1238 eligible couple-years of follow-up. Median eligible follow-up per couple was 1.3 years. Overall, 94% of the follow-up occurred during periods of very low plasma HIV-1 RNA load (< 50 copies/mL) with the other 6% occurring during periods with HIV-1 RNA loads between 50 and 200 copies/mL. The majority of HIV-positive patients had CD4 cell counts greater than 350 mm3 at baseline. Although 11 of the originally HIV-negative partners acquired HIV during follow-up, none of the cases occurred with viral genetic sequences than were phylogenetically linked transmissions with the original HIV-positive partner. Of these 11, 10 were MSM and 1 was heterosexual; 8 reported that they had had recent condomless sex with someone other than their study partner.

Bottom line: In this study of serodifferent couples with the HIV-positive partner using continuous antiretroviral therapy (ART) and reporting regular condomless sex, no documented cases of within-couple HIV transmission occurred during a median follow-up of 1.3...
years per couple. This included both heterosexual couples and men having sex with men (MSM). The study is ongoing for the cohort of MSM and further results are forthcoming.


It’s of course best to use condoms. But not everyone adheres to that recommendation. There is now good evidence that Truvada can reduce the risk of transmission in high risk HIV negative men:

5. Preexposure prophylaxis with tenofovir/emtricitabine prevents HIV infection in men who have unprotected anal intercourse

Clinical question: Among men who have unprotected anal intercourse, does the combination of tenofovir and emtricitabine taken before and after intercourse reduce the risk of HIV infection?

Study design: Randomized controlled trial (double-blinded)

Setting: Population-based

Synopsis: These researchers identified 400 HIV-negative men who had unprotected anal intercourse with at least 2 men in the previous 6 months. Those with impaired renal function, hepatitis B, or hepatitis C were excluded. The patients were randomized to receive tenofovir 300 mg and emtricitabine 200 mg (Truvada) or matching placebo. They were told to take 2 pills between 2 and 24 hours before intercourse, and a third and fourth pill at 24 and 48 hours after the first 2 pills were taken. The median age of participants was 35 years, 92% were white, and 73% were not currently in a relationship. The groups were balanced at the beginning of the study, and analysis was by intention to treat. Patients had regular clinic visits and were followed up for a median of 9.3 months. Follow-up was good, with a similar number (23, 26) lost to follow-up in each group. Adherence was also good, with more than 80% having serologic evidence of having taken the drugs in the previous week. Patients in the intervention group were less likely to develop HIV during the study period than those in the placebo group (14 vs 2 infections, or 6.6 vs 0.91 per 100 person-years of follow-up; P = .002, NNT = 17 per year). Gastrointestinal adverse effects were more common in the intervention group (14% vs 5%; P = .002), but otherwise the medication was safe and well-tolerated.

Bottom line: Pre-exposure prophylaxis in high-risk men who have unprotected anal intercourse reduces the likelihood of developing HIV (number needed to treat [NNT] = 17 per year). Participants averaged 15 pills per month, which costs approximately $700 per month ($8400/year). That kind of money would buy a lot of condoms, which would be a much more cost-effective way to prevent HIV infection (although condoms were not compared with medications in this study).


Exercise and diet

The next 3 abstracts show that exercise is good for pregnant women: it reduces weight gain, the likelihood of cesarean delivery and GDM (all of which may be associated):

6. Structured exercise in pregnancy reduces cesarean delivery

Clinical question: Do structured exercise programs during pregnancy reduce rates of cesarean delivery?

Study design: Meta-analysis (randomized controlled trials)

Setting: Outpatient (any)

Synopsis: This was a meta-analysis of randomized controlled trials of structured exercise programs during pregnancy, including 16 studies with 3359 participants. The women were of any age, parity, and body mass index and all had a singleton pregnancy. Exercise programs had to include at least one session weekly of supervised resistance and/or aerobic exercise. Studies with interventions limited to pelvic floor strengthening, stretching, and relaxation were excluded. Interventions started from the end of the first trimester to the end of the second trimester, allowing for a variable number of weeks of intervention and hours of exercise. Data were reported for 3037 participating women; a cumulative 9.7% dropout rate. In many studies mode of delivery was not a primary outcome of interest and in some cases (eg, primary vs repeat cesarean) the indication for cesarean delivery was not reported. The exercise groups had a significantly lower cesarean delivery rate than the control groups (14.2% vs 17.8%; relative risk [RR] 0.85; 95% CI 0.73 - 0.99; number needed to treat = 33). Subgroup analysis of the 7 studies with more than 50 hours of planned supervised exercise showed greater effect (RR 0.76, 95% CI 0.58 - 0.99). There was no difference in instrumental delivery rate in the 8 studies (n = 2083 participants) reporting this outcome. Women in the exercise groups had significantly lower gestational weight gain (mean =1.13 kg; 95% CI ?1.49 to ?0.78). Mean birthweight in the exercise groups was 35 g less, which was not statistically significant.

Bottom line: Women assigned to exercise groups during pregnancy had significantly lower risk of cesarean delivery and less gestational weight gain. Infant birthweights were not significantly affected.


7. Physical activity interventions in pregnancy decrease weight gain and risk of GDM

Clinical question: Do interventions to increase physical activity during pregnancy reduce the risks of excessive weight gain and gestational diabetes?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: For this meta-analysis of programs of physical activity during pregnancy the authors selected 13 unmasked randomized controlled trials (N = 2873 women). Studies were included if the participants were healthy women with singleton pregnancies whose physical activity level was fewer than 20 minutes 3 times weekly, the control group did not receive an exercise program, and the considered outcomes included GDM and maternal weight gain. The exercise interventions varied markedly in number, duration, and content. In all but 1 study the programs were supervised; the program was home-based in the remaining study. The methodology for the meta-analysis was thoroughly described and well-executed. Of the included studies 11 had adherence rates of greater than 85%. Drop-outs were also low overall, with 12 studies reporting rates of less than 20%. Only 2 studies were conducted in the United States. Only 4 studies provided intention-to-treat analysis. The calculated relative risk (RR) for GDM among the intervention groups was 0.69 (95% CI 0.52-0.91; P = .009). The weighted mean difference for weight gain was -1.14 kg (95% CI -1.5 to -0.78 kg; P < .001). In planned subgroup analyses the authors found that there was a lower risk of GDM when the program was implemented throughout the pregnancy than when it began in second trimester (RR 0.64, 95% CI 0.36-0.98; P = .038), without a corresponding effect on weight gain. There was also a lower risk of GDM with combined exercise programs that included aerobic exercise and resistance or strength training (RR 0.69, 95% CI 0.48-0.99; P = .043).

Bottom line: Structured programs of moderate physical activity decreased the risk of gestational diabetes mellitus (GDM) and decreased maternal weight gain among otherwise healthy sedentary women. Programs that were continuous throughout the pregnancy had more benefit that those started in the second trimester. Programs that combined aerobic exercise and resistance or strength training were also more beneficial.


8. Regular, moderately intense exercise during pregnancy is beneficial

Clinical question: Does a supervised exercise program during pregnancy reduce the risks of pregnancy complications?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (primary care)
Synopsis: In this randomized controlled trial healthy pregnant women (N = 840) either participated in a supervised exercise program or received standard care. Women were included if they had an uncomplicated singleton pregnancy, no prior preterm birth, and no contraindications to exercise. The exercise intervention included three 50- to 55-minute sessions weekly from 9 to 11 weeks' gestation to 38 to 39 weeks' gestation (approximately 85 total sessions) conducted by a fitness professional at the hospital where the women received care. Each session included aerobic, resistance, and stretching exercises and consisted of a warm-up and cool-down of 10 minutes each and vigorous exercise for 25 to 30 minutes. Women in the control group were encouraged to exercise and would have been excluded if they reported regular exercise for more than 20 minutes daily (which no one did). Loss to follow-up was similar between groups. Preterm birth was similar between groups and those women were excluded from analysis. Compliance was high, which may not be true of other populations. Women in the exercise group were less likely to develop hypertension (2.1% vs 5.7%; P = .009; number needed to treat [NNT] = 27, 95% CI 15-113) or to develop gestational diabetes (2.4% vs 5.5%; P = .03; NNT = 32, 16-290). Although mean weight gain was similar between groups, women in the exercise group were less likely to gain excessive weight (26% vs 34%; P = .03; NNT = 13, 7-80). Mean infant birth weight was not significantly different between groups, but the incidence of macrosomia (> 4000 g) was lower in the intervention group (1.8% vs 4.7%; P = .03; NNT = 35, 18-320). There were no differences in other secondary outcomes including gestational age at delivery, low birth weight, type of delivery, Apgar scores, or umbilical artery pH of the newborn at birth.

Bottom line: Healthy Spanish women who participated in a supervised exercise program from late first trimester until term were less likely to develop hypertension or gestational diabetes, to gain excess weight, or to give birth to a macrosomic infant. Similar interventions should be tested in other populations to determine whether these results are generalizable.


Does a systematic approach to measuring the BMI in kids in the primary care office, and counseling those who are overweight, have any benefit?

9. Brief interventions for weight management in kids are not effective

Clinical question: Should children and adolescents be screened for body mass index and be given brief counseling if overweight?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: These investigators searched 5 databases, including the Cochrane CENTRAL Library, as well as reference lists of retrieved studies and review articles, to identify 10 randomized studies and 2 quasi-experimental studies that evaluated the effect of brief interventions to reduce BMI in children between the ages of 2 years and 18 years. They looked at any primary care weight-management interventions (eg, lifestyle modification education, BMI feedback and lifestyle counseling, and motivational interviewing). Two reviewers independently selected articles and abstracted the data. The quality of the research was not good. Brief interventions produced a very small reduction in the BMI z score, which is the measure of the relative weight adjusted for the child's age and sex.
(effect size as compared with usual care - .04; 95% CI - .08 to - .01), with good agreement across the studies. A change of .5 to .6 is necessary to be sure of a clear reduction in fat and associated health benefit. Body satisfaction scores were similar between treatment group and control group patients, as were child- and parent-reported quality of life and self worth scores, though there was significant heterogeneity among these results. Adverse effects were not measured in most studies.

**Bottom line:** Calculating the body mass index (BMI) of children and adolescents in primary care practices and counseling those who are overweight is ineffective to reduce BMI in children over several years of follow-up.


This next one was a bit surprising and counter-intuitive…

10. **Wearable technology (eg, Fitbit) combined with lifestyle intervention = LESS weight loss**

**Clinical question:** Compared with standard behavioral weight-loss programs, does a technology-enhanced weight-loss intervention, including a wearable device, result in greater long-term weight loss in adults?

**Study design:** Randomized controlled trial (single-blinded)  
**Setting:** Outpatient (any)

**Synopsis:** Many commercial technologies, including wearable devices, are available to provide feedback on physical activity and diet. However, there are limited data on the long-term effectiveness of these technologies. These investigators identified adults, aged 18 to 35 years, with a body mass index (BMI) of 25.0 to 39.9. Eligible participants (N = 470) randomly received assignment (concealed) to either a standard behavioral weight-loss intervention group or the technology-enhanced weight-loss group. Both groups received behavioral weight loss education on diet and exercise for 6 months, and at 6 months both groups also received weekly telephone counseling sessions, weekly text message prompts, and access to study materials on a website. After 6 months, participants in the standard group initiated self-monitoring of diet and physical activity, while those in the technology-enhanced group began using a wearable device along with a web-based interface (FITCore; Body Media) to monitor physical activity and diet. Individuals who assessed outcomes remained masked to treatment group assignment. Complete follow-up occurred for 74.5% of participants at 24 months. Intention-to-treat analysis showed that participants in the enhanced-intervention group lost significantly less weight at 24 months that those in the standard-intervention group (mean loss = 3.5 kg; 95% CI 2.6 - 4.5 vs mean loss = 5.9 kg; 5.0 - 6.8; mean difference = 2.4 kg; 1.0 - 3.7). The percent weight loss was also significantly less in the enhanced-intervention group than in the standard-intervention group (3.6% vs 6.4% at 24 months). No significant group differences occurred for fat mass, lean mass, percent body fat, bone mineral density, or cardiorespiratory fitness.

**Bottom line:** This study found that a weight-loss program for adults, aged 18 to 35 years, that included technology-enhanced weight-loss interventions (a wearable device and a web-based interface) resulted in LESS weight loss than standard weight-loss education focusing on dietary changes and increased physical activity. Here’s how I think it went down: Should I eat that yummy piece of chocolate cake? Those in the standard group said “Nope” (because they figured they shouldn’t). Those in the technology-enhanced group, however, said, “Let me look at my device. I’ve walked a lot today, so I’m eating the cake!”


11. **PubMed: Exercise improves CV, metabolic, fitness, cognitive, and QOL outcomes in those > 70**

Aging is intrinsically associated with a progressive decline in muscle strength and mass, and aerobic capacity. This contributes to reduced mobility and impaired quality of life (QoL) among seniors. Regular physical activity, and more particularly aerobic training (AT), has demonstrated benefits on adults’ health. The aim of this review was to assess the current level of evidence regarding the health benefits of AT in the population aged 70 years and over. A comprehensive, systematic database search for manuscripts was performed. Two reviewers independently assessed interventional studies for potential inclusion. Cardiovascular, metabolic, functional, cognitive, and QoL outcomes were targeted. Fifty-three studies were included totalling 2051 seniors aged 70 years and over. Studies selected were divided into 5 categories according to their main outcomes: cardiovascular function (34 studies), metabolic outcomes (26 studies), functional fitness (19 studies), cognitive functions (8 studies), and QoL (3 studies). With a good level of evidence but a wide heterogeneity among these results. A change of .5 to .6 is necessary to be sure of a clear reduction in fat and associated health benefit. Body satisfaction scores were similar between treatment group and control group patients, as were child- and parent-reported quality of life and self worth scores, though there was significant heterogeneity among these results. Adverse effects were not measured in most studies.

**Clinical question:** Does exercise training, vitamin D, or the combination of both, decrease the number of falls in older women?

**Study design:** Randomized controlled trial (single-blinded)  
**Setting:** Outpatient (any)

**Setting:** Outpatient (any)

This study found that a weight-loss program for adults, aged 18 to 35 years, that included technology-enhanced weight-loss interventions (a wearable device and a web-based interface) resulted in LESS weight loss than standard weight-loss education focusing on dietary changes and increased physical activity. Here’s how I think it went down: Should I eat that yummy piece of chocolate cake? Those in the standard group said “Nope” (because they figured they shouldn’t). Those in the technology-enhanced group, however, said, “Let me look at my device. I’ve walked a lot today, so I’m eating the cake!”


11. **PubMed: Exercise improves CV, metabolic, fitness, cognitive, and QOL outcomes in those > 70**

Aging is intrinsically associated with a progressive decline in muscle strength and mass, and aerobic capacity. This contributes to reduced mobility and impaired quality of life (QoL) among seniors. Regular physical activity, and more particularly aerobic training (AT), has demonstrated benefits on adults’ health. The aim of this review was to assess the current level of evidence regarding the health benefits of AT in the population aged 70 years and over. A comprehensive, systematic database search for manuscripts was performed. Two reviewers independently assessed interventional studies for potential inclusion. Cardiovascular, metabolic, functional, cognitive, and QoL outcomes were targeted. Fifty-three studies were included totalling 2051 seniors aged 70 years and over. Studies selected were divided into 5 categories according to their main outcomes: cardiovascular function (34 studies), metabolic outcomes (26 studies), functional fitness (19 studies), cognitive functions (8 studies), and QoL (3 studies). With a good level of evidence but a wide heterogeneity among these results. A change of .5 to .6 is necessary to be sure of a clear reduction in fat and associated health benefit. Body satisfaction scores were similar between treatment group and control group patients, as were child- and parent-reported quality of life and self worth scores, though there was significant heterogeneity among these results. Adverse effects were not measured in most studies.

**Clinical question:** Does exercise training, vitamin D, or the combination of both, decrease the number of falls in older women?

**Study design:** Randomized controlled trial (single-blinded)  
**Setting:** Outpatient (any)

Oh, vitamin D. We had so much hope for you! What a disappointing little vitamin…

12. **Exercise, but not vitamin D, decreases the risk of falls that cause injury in older women**

**Clinical question:** Does exercise training, vitamin D, or the combination of both, decrease the number of falls in older women?

**Study design:** Randomized controlled trial (single-blinded)  
**Setting:** Outpatient (any)
Synopsis: These Finnish investigators enrolled 409 home-dwelling women 70 to 80 years old with at least 1 fall during the previous year who were not taking vitamin D supplements. The women were randomly assigned (concealed allocation unknown), to a group receiving 800 IU vitamin D per day, twice-weekly group exercise classes, both vitamin D and exercise, or placebo vitamin D and no exercise. All participants kept logs recording any falls. Exercise improved measures of muscle strength, balance, and mobility. Exercise did not improve—and vitamin D worsened—scores on the “timed up and go test,” which is a predictor of falls and consists of the time required for a person to rise from sitting from a standard arm chair, walk 3 meters, turn, walk back to the chair, and sit down. Using intention-to-treat analysis, the number of falls was not different among the 4 groups over 2 years. However, exercise, with or without vitamin D, halved the number of patients who experienced falls that required medical care, including bruises, sprains, and head injuries (hazard ratio [HR] 0.47; 95% CI .23 - .99 for exercise alone and HR .38; .17-.83 for vitamin D and exercise together). A recent Cochrane review has also shown a decrease in falls with group exercise.

Bottom line: Group exercise sessions twice a week for the first year and once a week for the second year, did not decrease the number of falls among older women but halved the likelihood of a fall resulting in an injury. Vitamin D was ineffective.


Some POEMs from the past year addressing vitamin D have found that it doesn’t prevent ARTI or asthma exacerbation (Thorax 2015;70(5): 451-457), doesn’t reduce pain in knee OA (JAMA 2016;315(10):1005-1013), and doesn’t reduce wheezing in offspring when given prenatally (JAMA 2016;315(4):353-361).

Miscellaneous

13. Small changes to adult immunization recommendations

Clinical question: What recommendations have changed regarding immunizations for adults?

Study design: Practice guideline

Setting: Various (guideline)

Synopsis: The latest recommendations from the U.S. Centers for Disease Controls Advisory Committee on Immunization Practices have updated a few recommendations for immunizing adults. For the prevention of human papillomavirus (HPV), the nine-valent HPV vaccine can be used for women instead of the bivalent or quadrivalent options and for males instead of the quadrivalent vaccine. The recommendations give no guidance regarding the use of the 9-valent vaccine in patients who previously have received a series of one of the other vaccines. Meningitis vaccine (eg, Menactra) should be administered to college freshman living in residents halls if they haven’t been vaccinated since they were 16 years of age. HIV is not an indication for routine vaccination with meningococcus quadrivalent or type B vaccine. For the pneumococcal vaccines, the 13-valent vaccine (Prevnar 13) should be followed by the 23-valent vaccine (Pneumovax 23) by at least 1 year in all adults 65 years and older. The complete immunization schedule is available at: http://www.cdc.gov/vaccines/schedules/hcp/adult.html.

Bottom line: The Advisory Committee on Immunization Practices has made a few new recommendations regarding immunization of adults: (1) Nine-valent human papillomavirus vaccine (Gardasil) can be used for the routine vaccination of male and female adolescents and adults; (2) people with human immunodeficiency virus (HIV) do not require vaccination against meningococcus, either quadrivalent or type B; and (3) the 13-valent and 23-valent pneumococcal vaccines should be administered at least 1 year apart in adults 65 years and older. See the Synopsis for greater detail. (LOE = 5)


So: 9-valent HPV is an option; meningitis vaccine to freshmen if they haven’t been vaccinated since 16; and give Pneumovax 23 one year after Prevnar 13.

14. USPSTF: Offer medication to prevent breast cancer to women at risk

Clinical question: Should women at increased risk of breast cancer be offered medication to reduce their risk?

Study design: Practice guideline

Setting: Various (guideline)

Synopsis: This recommendation is an update of the 2002 guideline of the USPSTF. It applies to asymptomatic women at least 35 years of age without a prior diagnosis of breast cancer, ductal carcinoma in situ, or lobular carcinoma in situ. Separate guidelines are available for women with the BRCA gene mutation. The USPSTF recommends, following discussion, tamoxifen or raloxifene for women at increased risk of developing breast cancer and at low risk for adverse effects (B recommendation; moderate certainty of moderate benefit). Women at an increase risk of adverse effects are those with a history of thromboembolic events. Overall, the incidence of invasive breast cancer will be decreased by 7 to 9 women for every 1000 treated. Risk can be assessed using the Gail Risk tool (a tool is available at www.cancer.gov/bcrisktool). In women at low risk for adverse effects, between 4 and 7 women out of every 1000 treated will experience a thromboembolic event. The Task Force recommends against offering preventive treatment for women at low or average risk of breast cancer (D recommendation).

Bottom line: Based on a moderate certainty of a moderate effect, the United States Preventive Services Task Force (USPSTF) recommends offering either tamoxifen or raloxifene to women (without the BRCA gene mutation) who are at increased risk of developing breast cancer. For every 1000 women taking this preventive therapy, 7 to 9 breast cancers will be prevented and 4 to 7 thromboembolic events will occur. This recommendation is unchanged from their 2002 statement. The task force suggests not offering preventive therapy for women at average (typical) risk.
15. USPSTF: I recommendation for autism screening in children aged 18-30 months

Clinical question: Should we screen for autism spectrum disorder in children aged 18 to 30 months?

Study design: Practice guideline

Setting: Outpatient (any)

Synopsis: The USPSTF found evidence that currently available screening tests can detect ASD among children aged 18 to 30 months. However, citing a lack of direct evidence on the benefits of screening for ASD in toddlers and preschool-aged children for whom no concerns of ASD have been raised by family members, other caregivers, or health care professionals, the USPSTF concludes there is insufficient evidence to recommend screening for this population. The task force also found that the harms of screening for ASD and subsequent interventions are likely to be small; thus the I statement (the balance of benefits and harms cannot be determined and patients should understand the uncertainty). The American Academy of Pediatrics continues to recommend universal screening for ASD in all children at ages 18 and 24 months along with developmental surveillance and monitoring. The American Academy of Family Physicians concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for ASD in children for whom no concerns of ASD have been raised.

Bottom line: The U.S. Preventive Services Task Force (USPSTF) concludes that there is insufficient evidence to determine whether the benefits outweigh the risks of screening for autism spectrum disorder (ASD) in children aged 18 months to 30 months (I statement) for whom no concerns of ASD have been raised by their parents or care providers.


Bottom Lines

1. Aspirin is recommended for adults at high risk of CV disease over the age of 50.
2. Pre-exposure prophylaxis is useful in HIV positive patients.
3. Exercise is beneficial in pregnancy, and probably reduces risk of injurious falls.
4. Telling kids they are overweight and providing brief advice is not helpful.
5. Think about raloxifene in women at high risk for breast cancer
6. Autism screening is not proven to be beneficial, but be alert for symptoms, especially when parents may not be clued in.
Worksheet for Screening and Prevention of Breast Cancer

1. Is there a significant family history? Assign points for every family member with breast or ovarian cancer, including 2nd and 3rd degree relatives. For example, a woman with a sister diagnosed at age 45 (4 points), an aunt at age 55 (3 points) and a grandmother at age 60 (3 points) would get 10 points total. If 8 or more points, chance of BRCA mutation is 10% or higher, so consider referral for genetic counseling.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer at age 50+ years</td>
<td>3</td>
</tr>
<tr>
<td>Breast cancer at age &lt; 50 years</td>
<td>4</td>
</tr>
<tr>
<td>Ovarian cancer at any age</td>
<td>5</td>
</tr>
<tr>
<td>Male breast cancer at any age</td>
<td>8</td>
</tr>
<tr>
<td>Ashkenazi Jewish heritage</td>
<td>4</td>
</tr>
</tbody>
</table>


3. Finally, use 5 year risk, age, race, and uterine status to assess net benefit of breast cancer chemoprevention:

White (non-Hispanic) women with uterus
### White (non-Hispanic) women without uterus

<table>
<thead>
<tr>
<th>5-Year Projected Risk of IBC (%)</th>
<th>Tamoxifen v Placebo (without uterus)</th>
<th>Raloxifene v Placebo (without uterus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>2.0</td>
<td>31</td>
<td>49</td>
</tr>
<tr>
<td>2.5</td>
<td>57</td>
<td>71</td>
</tr>
<tr>
<td>3.0</td>
<td>84</td>
<td>92</td>
</tr>
<tr>
<td>3.5</td>
<td>111</td>
<td>114</td>
</tr>
<tr>
<td>4.0</td>
<td>138</td>
<td>134</td>
</tr>
<tr>
<td>4.5</td>
<td>164</td>
<td>156</td>
</tr>
<tr>
<td>5.0</td>
<td>191</td>
<td>178</td>
</tr>
<tr>
<td>5.5</td>
<td>218</td>
<td>199</td>
</tr>
<tr>
<td>6.0</td>
<td>244</td>
<td>220</td>
</tr>
<tr>
<td>6.5</td>
<td>270</td>
<td>242</td>
</tr>
<tr>
<td>7.0</td>
<td>297</td>
<td>262</td>
</tr>
</tbody>
</table>

5-year projected risk of IBC is ≥ 1.67%.

- Using BCPT data and WHI baseline rates
- Combining RR from BCPT and STAR using WHI baseline rates

### Black women with uterus

<table>
<thead>
<tr>
<th>5-Year Projected Risk of IBC (%)</th>
<th>Tamoxifen v Placebo (with uterus)</th>
<th>Raloxifene v Placebo (with uterus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>-144</td>
<td>-25</td>
</tr>
<tr>
<td>2.0</td>
<td>-117</td>
<td>-3</td>
</tr>
<tr>
<td>2.5</td>
<td>-89</td>
<td>19</td>
</tr>
<tr>
<td>3.0</td>
<td>-62</td>
<td>41</td>
</tr>
<tr>
<td>3.5</td>
<td>-36</td>
<td>62</td>
</tr>
<tr>
<td>4.0</td>
<td>-9</td>
<td>83</td>
</tr>
<tr>
<td>4.5</td>
<td>18</td>
<td>105</td>
</tr>
<tr>
<td>5.0</td>
<td>45</td>
<td>126</td>
</tr>
<tr>
<td>5.5</td>
<td>72</td>
<td>147</td>
</tr>
<tr>
<td>6.0</td>
<td>98</td>
<td>169</td>
</tr>
<tr>
<td>6.5</td>
<td>124</td>
<td>190</td>
</tr>
<tr>
<td>7.0</td>
<td>151</td>
<td>211</td>
</tr>
</tbody>
</table>

5-year projected risk of IBC is ≥ 1.67%.

- Using BCPT data and WHI baseline rates
- Combining RR from BCPT and STAR using WHI baseline rates
Black women without uterus

<table>
<thead>
<tr>
<th>5-Year Projected Risk of IBC (%)</th>
<th>Tamoxifen v Placebo (without uterus)</th>
<th>Raloxifene v Placebo (without uterus)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50-59</td>
<td>60-69</td>
</tr>
<tr>
<td>1.5</td>
<td>-67</td>
<td>-111</td>
</tr>
<tr>
<td>2.0</td>
<td>-40</td>
<td>-84</td>
</tr>
<tr>
<td>2.5</td>
<td>-12</td>
<td>-56</td>
</tr>
<tr>
<td>3.0</td>
<td>15</td>
<td>-29</td>
</tr>
<tr>
<td>3.5</td>
<td>42</td>
<td>-3</td>
</tr>
<tr>
<td>4.0</td>
<td>69</td>
<td>25</td>
</tr>
<tr>
<td>4.5</td>
<td>95</td>
<td>51</td>
</tr>
<tr>
<td>5.0</td>
<td>122</td>
<td>78</td>
</tr>
<tr>
<td>5.5</td>
<td>149</td>
<td>104</td>
</tr>
<tr>
<td>6.0</td>
<td>175</td>
<td>131</td>
</tr>
<tr>
<td>6.5</td>
<td>201</td>
<td>157</td>
</tr>
<tr>
<td>7.0</td>
<td>228</td>
<td>183</td>
</tr>
</tbody>
</table>

5-year projected risk of IBC is \( \geq 1.67\% \).

- Using BCPT data and WHI baseline rates
- Combining RR from BCPT and STAR using WHI baseline rates

- Strong evidence of benefits outweighing risks
- Moderate evidence of benefits outweighing risks
- Benefits do not outweigh risks
Exercise and rehabilitation

Gary Ferenchick MD, MS

Objectives

1. Understand the relationship of exercise to cardiovascular risk, cancer & mortality
2. Understand the concerns raised about CV risk associated with “too much exercise”
3. Understand that exercise is safe for older adults with knee pain attributable to OA
4. Understand recent evidence on associations between exercise and cancer survival, cognitive function and glucose control
5. Understand the effect of rehabilitative exercise on hand osteoarthritis and low back pain

As you sit here quietly listening to this talk, your energy expenditure is ~ 1.2 kcal/minute. If you are an average 70-kg human then in the next hour you will expend 84 calories doing this “activity”. Stated another way, doing this same “activity” you are consuming ~ 3.5 milliliters of oxygen/kg of body weight/min. This number is also referred to as 1 MET, and METS are a common way to quantify exercise.

In the appendix is a table from the CDC and the American College of Sports Medicine that groups all kinds of physical activity into Moderate Intensity (3.5 to 7 kcal/minute OR 3.0 to 6.0 METs) and Vigorous Activity (> 7 kcal/minute OR > 6.0 METs). The US Department of Health and Human Services recommends 150 minutes/week of moderate-intensity (~ 22 minutes per day) exercise, or 75 minutes per weeks of vigorous-intensity exercise for all US adults.

The following table identifies several common moderate- and vigorous-intensity exercises.

<table>
<thead>
<tr>
<th>Examples of moderate- and vigorous-intensity exercises</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate-intensity aerobic exercise</td>
</tr>
<tr>
<td>(&gt; 150 minutes/week; average ~ 22 minutes/day)</td>
</tr>
<tr>
<td>Stationary cycling – moderate effort</td>
</tr>
<tr>
<td>Hiking</td>
</tr>
<tr>
<td>Water aerobics</td>
</tr>
<tr>
<td>Yoga</td>
</tr>
<tr>
<td>Tennis - doubles</td>
</tr>
<tr>
<td>Golf - walking</td>
</tr>
<tr>
<td>Vigorous-intensity aerobic exercise</td>
</tr>
<tr>
<td>(&gt; 75 minutes/week; average ~ 11 minutes/day)</td>
</tr>
<tr>
<td>Stationary cycling – vigorous effort</td>
</tr>
<tr>
<td>Jogging/running</td>
</tr>
<tr>
<td>Step aerobics</td>
</tr>
<tr>
<td>Stair climber at a fast pace</td>
</tr>
<tr>
<td>Tennis -singles</td>
</tr>
<tr>
<td>Handball/racquetball/squash</td>
</tr>
</tbody>
</table>

In early 2016, the American College of Cardiology published a clinical perspective entitled “The amount of exercise to reduce cardiovascular events” aimed at reviewing “the published data on the volume and intensity of aerobic exercise required for favorable cardiovascular health”.

#1: PubMed: The amount of exercise to ↓ CV events

Habitual physical activity and regular exercise training improve cardiovascular health and longevity. A physically active lifestyle is, therefore, a key aspect of primary and secondary prevention strategies. An appropriate volume and intensity are essential to maximally benefit from exercise interventions. This document summarizes available evidence on the relationship between the exercise volume and risk reductions in cardiovascular morbidity and mortality. Furthermore, the risks and benefits of moderate-versus high-intensity exercise interventions are compared. Findings are presented for the general population and cardiac patients eligible for cardiac rehabilitation. Finally, the controversy of excessive volumes of exercise in the athletic population is discussed.


Clinical pearls from this article on exercise in primary prevention include the following:
The greatest change in CV risk associated with exercise is from inactive to mild-moderate activity (Figure 1 in the appendix); further increases in exercise volume (although still beneficial) yield smaller changes in CV risk.

What is the minimum volume of aerobic physical activity that produces health benefits?

- Standing > 2 hours/day (vs < 2 hours/day) associated with 10% ↓ in all-cause mortality (independent of health status, and other variables);
  - More hours of standing associated with lower CV risk
- Running 51 to 92 minutes per week (average 7 - 13 minutes/day; vs non-runners or inactive peers) associated with 10 - 55% ↓ in CV mortality and 14 - 30% ↓ in all-cause mortality

What is the theoretical maximum volume of aerobic physical activity that is associated with health benefits?

- Estimated maximum volume of aerobic exercise to that is associated with maximum improvement in CV outcomes is 547 minutes/week (~ 78 minutes/day) of moderate-intensity exercise (@ 4.5 METs), or 289 minutes per week of vigorous activity (@ 8.5 METs)
  - Note that exceeding this exercise volume was not associated with additional CV outcomes (also note this means there is no evidence for adverse CV outcomes when exceeding this threshold, more later)

Is there a difference between moderate-intensity continuous exercise (i.e. 3 – 6 METs/min) vs vigorous-intensity interval training (i.e. > 6 METs/min)

- Comparing groups with:
  - < 30 % total exercise time in vigorous-intensity vs groups with only moderate-intensity exercise is associated with a 9% ↓ in mortality
  - > 30 % total exercise time in vigorous-intensity vs only moderate-intensity exercise is associated with a 13% ↓ in mortality

# 2: PubMed: < 150 min/week of moderate-to-vigorous-intensity physical activity (MVPA) associated with 22% mortality benefit

BACKGROUND: The health benefits of 150 min a week of moderate-to-vigorous-intensity physical activity (MVPA) in older adults, as currently recommended, are well established, but the suggested dose in older adults is often not reached.

OBJECTIVES: We aimed to determine whether a lower dose of MVPA was effective in reducing mortality, in participants older than 60 years.

METHODS: The PubMed and Embase databases were searched from inception to February 2015. Only prospective cohorts were included. Risk ratios of death were established into four doses based on weekly Metabolic Equivalent of Task (MET)-minutes, defined as inactive (reference), low (1-499), medium (500-999) or high (≥1000). Data were pooled and analysed through a random effects model using comprehensive meta-analysis software.

RESULTS: Of the 835 reports screened, nine cohort studies remained, totaling 122 417 participants, with a mean follow-up of 9.8±2.7 years and 18 122 reported deaths (14.8%). A low dose of MVPA resulted in a 22% reduction in mortality risk (RR=0.78 (95% CI 0.71 to 0.87) p<0.0001). MVPA beyond this threshold brought further benefits, reaching a 28% reduction in all-cause mortality in older adults who followed the current recommendations (RR=0.72 (95% CI 0.65 to 0.80) p<0.0001) and a 35% reduction beyond 1000 MET-min per week (RR=0.65 (95% CI 0.61 to 0.70) p<0.0001).

CONCLUSIONS: A dose of MVPA below current recommendations reduced mortality by 22% in older adults. A further increase in physical activity dose improved these benefits in a linear fashion. Older adults should be encouraged to include even low doses of MVPA in their daily lives.


Abstracts # 3 and #4 remind us that although the risk of sudden cardiac death is marginally higher during, and for 30 minutes after exercise, cardiorespiratory fitness reduces overall cardiac event rates
# 3: PubMed: 5% of sudden deaths occur during exercise

**BACKGROUND:** Sports-associated sudden cardiac arrests (SCAs) occur mostly during middle age. We sought to determine the burden, characteristics, and outcomes of SCA during sports among middle-aged residents of a large US community.

**METHODS AND RESULTS:** Patients with SCA who were 35 to 65 years of age were identified in a large, prospective, population-based study (2002-2013), with systematic and comprehensive assessment of their lifetime medical history. Of the 1247 SCA cases, 63 (5%) occurred during sports activities at a mean age of 51.1±8.8 years, yielding an incidence of 21.7 (95% confidence interval, 1.35-3.13) per 1 million per year. The incidence varied significantly by sex, with a higher incidence among men (relative risk, 18.68; 95% confidence interval, 2.50-139.56) for sports SCAs compared with all other SCAs (relative risk 2.58; 95% confidence interval, 2.12-3.13). Sports SCA was also more likely to be a witnessed event (87% versus 53%; P<0.001) with cardiopulmonary resuscitation (44% versus 25%; P=0.001) and ventricular fibrillation (84% versus 51%; P<0.0001). Survival to hospital discharge was higher for sports-associated SCA (23.2% versus 13.6%; P=0.04). Sports SCA cases presented with known preexisting cardiac disease in 16% and =1 cardiovascular risk factors in 56%, and overall, 36% of cases had typical cardiovascular symptoms during the week preceding the SCA.

**CONCLUSIONS:** Sports-associated SCA in middle age represents a relatively small proportion of the overall SCA burden, reinforcing the idea of the high-benefit, low-risk nature of sports activity. Especially in light of current population aging trends, our findings emphasize that targeted education could maximize both safety and acceptance of sports activity in the older athlete.

**REFERENCE:** Marijon E, et al. Sudden cardiac arrest during sports activity in middle age. Circulation. 2015 Apr 21;131(16):1384-91. PMID: 25847988

# 4: PubMed: Cardiorespiratory fitness (CRF) reduces CHD Risk

**OBJECTIVE:** To examine the association of cardiorespiratory fitness (CRF) with risk of coronary heart disease (CHD) while controlling for an individual's Framingham Risk Score (FRS)-predicted CHD risk.

**PATIENTS AND METHODS:** The study included 29,854 men from the Aerobics Center Longitudinal Study, who received a baseline examination from January 1, 1979, to December 31, 2002. Coronary heart disease events included self-reported myocardial infarction or revascularization or CHD death. Multivariable survival analysis investigated the association between CRF, FRS, and CHD. Cardiorespiratory fitness was analyzed as both a continuous and a categorical variable. The population was stratified by "low" and "moderate or high" risk of CHD to test for differences in the FRS stratified by CRF.

**RESULTS:** Compared with men without incident CHD, men with incident CHD were older (mean age, 51.6 years vs 44.6 years), had lower average maximally achieved fitness (10.9 metabolic equivalent of tasks vs 12.0 metabolic equivalent of tasks [METs]), and were more likely to have moderate or high 10-year CHD risk (P<.001). Cardiorespiratory fitness, defined as maximal METs, exhibited a 20% lower risk of CHD (hazard ratio, 0.80; 95% CI, 0.77-0.83) for each 1-unit MET increase. Among men in the low CRF strata, individuals with moderate or high 10-year CHD risk, according to the FRS, had a higher CHD risk (hazard ratio, 6.55; 95% CI, 3.64-11.82) than men with low risk according to the FRS.

**CONCLUSION:** Clinicians should promote physical activity to improve CRF so as to reduce CHD risk, even to patients with otherwise low CHD risk.


# 5: PubMed: Sedentary behavior and low CRF associated with ↑ mortality

**BACKGROUND:** Sedentary behavior is related to increased mortality risk. Whether such elevated risk can be offset by enhanced physical activity has not been examined using accelerometer data.

**MATERIALS AND METHODS:** We examined the relations of sedentary time and physical activity to mortality from any cause using accelerometer data among 1,677 women and men aged 50 years or older from the National Health and Nutrition Examination Survey (NHANES) 2003-2004 cycle with follow-up through December 31, 2006.

**RESULTS:** During an average follow-up of 34.67 months and 4,845.42 person-years, 112 deaths occurred. In multivariate Cox proportional hazard models, greater sedentary time (≥ median of 8.60 hours/day) was associated with increased risk of mortality from any cause (relative risk (RR) = 2.03; 95% confidence interval (CI) = 1.09-3.81). Low level of moderate to vigorous physical activity (< median of 6.60 minutes/day) was also related to enhanced all-cause mortality risk (RR = 3.30; 95% CI = 6.55; 95% CI, 3.64-11.82) than men with low CRF according to the FRS.

**CONCLUSIONS:** Both high levels of sedentary time and low levels of moderate to vigorous physical activity are strong and independent predictors of early death from any cause. Whether a high physical activity level removes the increased risk of all-cause mortality related to sedentariness requires further investigation.


We have historically used the body mass index as a proxy for obesity. Abstract # 3 indicates that adding cardiorespiratory fitness to risk stratify obese patients is more accurate in determining all-cause mortality than using a combination of the BMI plus waist circumference alone. The diagnostic accuracy of the BMI for
determining obesity is not optimal, as it does not take into account the distribution of fat (e.g. adipose tissue in the legs and buttocks likely has no deleterious effect on glucose metabolism vs central obesity); abstract #4 demonstrates that normal weight individuals with central obesity have a higher mortality rate compared to normal fat distribution regardless of BMI.

# 6: PubMed: Cardiorespiratory fitness (CRF) improves estimation of mortality risk

**BACKGROUND:** Guidelines for identification of obesity-related risk stratify disease risk using specific combinations of body mass index and waist circumference. Whether the addition of cardiorespiratory fitness, an independent predictor of disease risk, provides better risk prediction of all-cause mortality within current body mass index and waist circumference categories is unknown.

**OBJECTIVE:** To determine whether the addition of cardiorespiratory fitness improves prediction of all-cause mortality risk classified by the combination of body mass index and waist circumference.

**METHODS:** We performed a prospective observational study using data from the Aerobics Center Longitudinal Study (ACLS). A total of 31,267 men (mean age 43.9 [SD, 9.4] years) who completed a baseline medical examination during 1974-2002. The main outcome measure was all-cause mortality. Participants were grouped using body mass index- and waist circumference-specific threshold combinations: Normal body mass index: 18.5-24.9 kg/m², waist circumference threshold of 90 cm; overweight body mass index: 25.0-29.9 kg/m², waist circumference threshold of 100 cm, and obese body mass index: 30.0-34.9 kg/m², waist circumference threshold of 110 cm. Participants were classified using cardiorespiratory fitness as unfit or fit, where unfit was the lowest fifth of the age-specified distribution of maximal exercise test time on treadmill among the entire ACLS population.

**RESULTS:** 1,399 deaths occurred over a follow-up of 14.1 ± 7.4 years, for a total of 439, 991 person-years of observation. Males who were unfit and normal body mass index with waist circumference <90 cm and =90 cm had 95% (1.95, 1.34-2.83) [Hazard ratio, 95% confidence interval] and 163% (2.63, 1.58-4.40) higher mortality risk than males who were fit, respectively (p<.05). Males who were unfit and overweight had 41% (1.41, 1.04-1.90) higher mortality risk with a waist circumference <100 cm (p<.05), but were at no greater risk (1.30, 0.92-1.84) if their waist circumference was =100 cm (p=.14). Males who were unfit and obese were not at increased mortality risk (1.37, 0.90-2.09) with a waist circumference <110 cm (p=.14), but were at 111% (2.11, 1.31-3.42) increased risk with a waist circumference =110 cm (p<.05).

**CONCLUSIONS:** For most of the body mass index and waist circumference categories, inclusion of cardiorespiratory fitness allowed for improved identification of males at increased mortality risk.


# 7: PubMed: Normal weight, normal BMI central obesity associated with ↑ mortality

**BACKGROUND:** The relationship between central obesity and survival in community-dwelling adults with normal body mass index (BMI) is not well-known.

**OBJECTIVE:** To examine total and cardiovascular mortality risks associated with central obesity and normal BMI.

**DESIGN:** Stratified multistage probability design.

**SETTING:** NHANES III (Third National Health and Nutrition Examination Survey).

**PARTICIPANTS:** 15 184 adults (52.3% women) aged 18 to 90 years.

**MEASUREMENTS:** Multivariable Cox proportional hazards models were used to evaluate the relationship of obesity patterns defined by BMI and waist-to-hip ratio (WHR) and total and cardiovascular mortality risk after adjustment for confounding factors.

**RESULTS:** Persons with normal-weight central obesity had the worst long-term survival. For example, a man with a normal BMI (22 kg/m²) and central obesity had greater total mortality risk than one with similar BMI but no central obesity (hazard ratio [HR], 1.87 [95% CI, 1.53 to 2.29]), and this man had twice the mortality risk of participants who were overweight or obese according to BMI only (HR, 2.24 [CI, 1.52 to 3.32]) and 2.42 [CI, 1.30 to 4.53], respectively). Women with normal-weight central obesity also had a higher mortality risk than those with similar BMI but no central obesity (HR, 1.48 [CI, 1.35 to 1.62]) and those who were obese according to BMI only (HR, 1.32 [CI, 1.15 to 1.51]). Expected survival estimates were consistently lower for those with central obesity when age and BMI were controlled for.

**LIMITATIONS:** Body fat distribution was assessed based on anthropometric indicators alone. Information on comorbidities was collected by self-report.

**CONCLUSION:** Normal-weight central obesity defined by WHR is associated with higher mortality than BMI-defined obesity, particularly in the absence of central fat distribution.

**PRIMARY FUNDING SOURCE:** National Institutes of Health, American Heart Association, European Regional Development Fund, and Czech Ministry of Health.


# 8: PubMed: Exercise intensity associated with better 2-hour glucose control, not abdominal obesity

**BACKGROUND:** Exercise reduces obesity and related glucose tolerance, but whether increasing exercise intensity offers additional benefit at fixed exercise amounts is unknown.

**OBJECTIVE:** To determine the separate effects of exercise amount and intensity on abdominal obesity and glucose tolerance.

**DESIGN:** 24-week, single-center, parallel-group trial from 2009 to 2013. (ClinicalTrials.gov: NCT00955071).

**SETTING:** Kingston, Ontario, Canada.
PARTICIPANTS: 300 abdominally obese adults.

INTERVENTION: Control (no exercise) (n = 75) or 5 weekly sessions of low-amount, low-intensity exercise (LALI) (180 and 300 kcal/session for women and men, respectively, at 50% of maximum oxygen consumption [Vo2peak]) (n = 73); high-amount, low-intensity exercise (HALI) (360 and 600 kcal/session, respectively, at 50% of Vo2peak) (n = 76); or high-amount, high-intensity exercise (HAHI) (360 and 600 kcal/session, respectively, at 75% of Vo2peak) (n = 76). Daily unsupervised physical activity and sedentary time were measured by accelerometer.

MEASUREMENTS: Waist circumference and 2-hour glucose level (primary outcomes) and cardiorespiratory fitness and measures of insulin action (secondary measurements).

RESULTS: 217 participants (72.3%) completed the intervention. Mean exercise time in minutes per session was 31 (SD, 4.4) for LALI, 58 (SD, 7.6) for HALI, and 40 (SD, 6.2) for HAHI. Daily unsupervised physical activity and sedentary time did not change in any exercise group versus control (P > 0.33). After adjustment for age and sex in a linear mixed model, reductions in waist circumference were greater in the LALI group (Δ-3.9 cm [95% CI, -5.6 to -2.3 cm]; P < 0.001), HALI (Δ-4.6 cm [CI, -6.2 to -3.0 cm]; P < 0.001), and HAHI (Δ-4.6 cm [CI, -6.3 to -2.9 cm]; P < 0.001) groups than the control group but did not differ among the exercise groups (P > 0.43). After adjustment for covariates, reductions in 2-hour glucose level were greater in the HAHI group (Δ-0.7 mmol/L [-12.5 mg/dL] [CI, -1.3 to -0.1 mmol/L [-23.5 to -1.5 mg/dL]]; P = 0.027) than the control group but did not differ for the LALI or HALI group versus the control group (P > 0.159). Weight loss was greater in all exercise groups than the control group (P < 0.001); however, reduction in body weight did not differ among the exercise groups (P > 0.182).

LIMITATION: The clinical importance of reducing 2-hour glucose level in nondiabetic adults remains undetermined.

CONCLUSION: Fixed amounts of exercise independent of exercise intensity resulted in similar reductions in abdominal obesity. Reduction in 2-hour glucose level was restricted to high-intensity exercise.


# 9: PubMed: Midlife CRF inversely assoc with risk of lung cancer and CRC

IMPORTANCE: Cardiorespiratory fitness (CRF) as assessed by formalized incremental exercise testing is an independent predictor of numerous chronic diseases, but its association with incident cancer or survival following a diagnosis of cancer has received little attention.

OBJECTIVE: To assess the association between midlife CRF and incident cancer and survival following a cancer diagnosis.

DESIGN, SETTING, AND PARTICIPANTS: This was a prospective, observational cohort study conducted at a preventive medicine clinic. The study included 13?949 community-dwelling men who had a baseline fitness examination. All men completed a comprehensive medical examination, a cardiovascular risk factor assessment, and incremental treadmill exercise test to evaluate CRF. We used age- and sex-specific distribution of treadmill duration from the overall Cooper Center Longitudinal Study population to define fitness groups as those with low (lowest 20%), moderate (middle 40%), and high (upper 40%) CRF groups. The adjusted multivariable model included age, examination year, body mass index, smoking, total cholesterol level, systolic blood pressure, diabetes mellitus, and fasting glucose level. Cardiorespiratory fitness levels were assessed between 1971 and 2009, and incident lung, prostate, and colorectal cancer using Medicare Parts A and B claims data from 1999 to 2009; the analysis was conducted in 2014.

MAIN OUTCOMES AND MEASURES: The main outcomes were (1) incident prostate, lung, and colorectal cancer and (2) all-cause mortality and cause-specific mortality among men who developed cancer at Medicare age (=65 years).

RESULTS: Compared with men with low CRF, the adjusted hazard ratios (HRs) for incident lung, colorectal, and prostate cancers among men with high CRF were 0.45 (95% CI, 0.29-0.68), 0.56 (95% CI, 0.36-0.87), and 1.22 (95% CI, 1.02-1.46), respectively. Among those diagnosed as having cancer at Medicare age, high CRF in midlife was associated with an adjusted 32% (HR, 0.68; 95% CI, 0.47-0.98) risk reduction in all cancer-related deaths and a 68% reduction in cardiovascular disease mortality following a cancer diagnosis (HR, 0.32; 95% CI, 0.16-0.64) compared with men with low CRF in midlife.

CONCLUSIONS AND RELEVANCE: There is an inverse association between midlife CRF and incident lung and colorectal cancer but not prostate cancer. High midlife CRF is associated with lower risk of cause-specific mortality in those diagnosed as having cancer at Medicare age.


# 10: PubMed: Physical activity is not associated with improved cognitive performance

IMPORTANCE: Epidemiological evidence suggests that physical activity benefits cognition, but results from randomized trials are limited and mixed.

OBJECTIVE: To determine whether a 24-month physical activity program results in better cognitive function, lower risk of mild cognitive impairment (MCI) or dementia, or both, compared with a health education program.

DESIGN, SETTING, AND PARTICIPANTS: A randomized clinical trial, the Lifestyle Interventions and Independence for Elders (LIFE) study, enrolled 1635 community-living participants at 8 US centers from February 2010 until December 2011. Participants were sedentary adults aged 70 to 89 years who were at risk for mobility disability but able to walk 400 m.

INTERVENTIONS: A structured, moderate-intensity physical activity program (n=7818) that included walking, resistance training, and flexibility exercises or a health education program (n=7817) of educational workshops and upper-extremity stretching.

MAIN OUTCOMES AND MEASURES: Prespecified secondary outcomes of the LIFE study included cognitive function measured by the Digit Symbol Coding (DSC) task subtest of the Wechsler Adult Intelligence Scale (score range: 0-133; higher scores indicate better function) and the revised Hopkins Verbal Learning Test (HVLT-R; 12-item word list recall test) assessed in 1476 participants (90.3%). Tertiary outcomes included global and executive cognitive function and incident MCI or dementia at 24 months.
RESULTS: At 24 months, DSC task and HVLT-R scores (adjusted for clinic site, sex, and baseline values) were not different between groups. The mean DSC task scores were 46.26 points for the physical activity group vs 46.28 for the health education group (mean difference, -0.01 points [95% CI, -0.80 to 0.77 points], P=.97). The mean HVLT- R delayed recall scores were 7.22 for the physical activity group vs 7.25 for the health education group (mean difference, -0.03 words [95% CI, -0.29 to 0.24 words], P=.84). No differences for any other cognitive or composite measures were observed. Participants in the physical activity group who were 80 years or older (n=?707) and those with poorer baseline physical performance (n=?328) had better changes in executive function composite scores compared with the health education group (P=.01 for interaction for both comparisons). Incident MCI or dementia occurred in 98 participants (13.2%) in the physical activity group and 91 participants (12.1%) in the health education group (odds ratio, 1.08 [95% CI, 0.80 to 1.46]).

CONCLUSIONS AND RELEVANCE: Among sedentary older adults, a 24-month moderate-intensity physical activity program compared with a health education program did not result in improvements in global or domain-specific cognitive function.


Are high volumes of aerobic exercise (think endurance athletes who run marathons, cycle the Tour de France, do tri-athlelons and competitive cross country-skiing, etc) as bad for CVD outcomes as physical inactivity???

Of course, concerns about too much exercise are not an issue for most patients. However, for some, it might be.

Abstract #11 (summarized below) reviews the world’s literature on strenuous endurance exercise.

#11: PubMed: Too much exercise???

Prolonged strenuous endurance exercise (SEE) such as marathon running has recently been associated with potential deleterious cardiac effects, particularly increased risk of atrial fibrillation (AF). This topic is medically important due to the increasing number of participants in SEE events lasting several hours, including older people. The aim of this narrative review is to provide a summary of the evidence available on SEE and related issues such as cardiovascular mortality, AF, potential cardiac remodeling, cardiovascular events during exertion, or the need for pre- participation screening (with a special focus on beginners). This type of information can help physicians giving advice to their patients and the general public regarding safe SEE practice.


- **Fact #1: Post-exercise troponins increase**: Post-exercise troponin increases to above the upper limit of normal (ULN) reference range for acute myocardial infarction (AMI) in 50% of endurance athletes
  - However, the troponins are only modestly elevated and they normalize within 72 hours (vs AMI patients with elevations up to 50x ULN, which take 4 – 10 days to normalize)
  - Hypothesis that this represents an exercise induced ↑ in membrane permeability

- **Fact #2: Evidence of myocardial fibrosis**: 12 – 50% of endurance athletes have evidence of myocardial fibrosis (assessed by gadolinium enhancement (GE) during a cardiac MRI).
  - However the fibrosis is frequently found in areas that are rarely observed in patients with ischemic events (e.g. insertion point of the right ventricle to the septum); suggesting a non-ischemic etiology of the fibrosis.
  - Hypothesis this this represents fibrosis from increased mechanical stress of the RV during exercise (i.e. RV’s forced to produce ↑ increased pressures to meet metabolic demands).
  - Runners with subendocardial regions of GE (vs mid myocardial regions) had 3 coronary events vs 1 coronary event in a runner without GE among adults (age 50 - 72) followed for 21 months after a cardiac MRI (Radiology. 2009 Apr;251(1):50-7)

- **Fact #3: Transient post-exercise ↓ in ventricular function (right > left)**
  - This can occur for up to 48 hours after exercise in some endurance athletes.
  - The clinical importance of this (specifically with regards to arrhythmias) is not known
Fact #4: The incidence of atrial fibrillation is higher in endurance athletes
   - The association between exercise and AF is likely U shaped, with moderate amounts of exercise decreasing, and larger volumes of exercising increasing AF risk.
   - The risk of AF among endurance athletes may be high as 1.3 to 5.2 x compared to the general population.
   - The long-term consequences and medical manageability of strenuous activity associated AF is yet to be determined.

Fact #5: Coronary artery calcification may be greater in endurance trained athletes vs controls.
   - Coronary calcifications scores were noted to be 3x higher in German marathon runners vs controls (matched for age and Framingham risk score).
   - Hypothesis that higher CAC density is associated with plaque stabilization (note CAC density has been noted to be “protective” vs CAC volume which is associated with increased CV risk) (JAMA 2014;311:271).

#12: Primary Care Medical Abstracts: Do patients need “medical clearance” before starting an exercise program?
Several studies have suggested that the risk of sudden death is much greater in non-exercisers and when sedentary. The ACSM and others recommend undergoing medical consultation before starting an exercise program. Barry Franklin, in the next abstract, suggests that patients choosing to become sedentary need medical clearance.

PREVENTING EXERCISE-RELATED CARDIOVASCULAR EVENTS: IS A MEDICAL EXAMINATION MORE URGENT FOR PHYSICAL ACTIVITY OR INACTIVITY?
Physical inactivity contributes to the development of cardiovascular disease. Exercise is protective but is also associated with a risk of myocardial infarction and sudden cardiac death. The author, from William Beaumont Hospital in Royal Oak, MI, comments on efforts to identify individuals at risk for complications of vigorous physical activity. He notes that self-screening to identify adults who should seek medical clearance before exercising using the instrument developed by the American Heart Association/American College of Sports Medicine would likely be impractical, as one study found that more than 90% of individuals would be advised to consult a physician using this instrument. Recent studies suggest that the risks of exercise are inversely proportional to the habitual level of physical activity. The American College of Sports Medicine suggests that medical clearance is not necessary for low-risk individuals (asymptomatic with fewer than two risk factors) planning to initiate moderate to vigorous exercise, while a medical assessment is advised for moderate-risk individuals (asymptomatic with two or more risk factors) and high-risk persons (symptomatic or with known cardiovascular, pulmonary, renal or metabolic disease). Exercise testing is advised for patients with known cardiovascular disease planning on initiating vigorous exercise. However, data to support these recommendations are limited. The author notes that the evidence suggests that the net benefits of regular exercise appear to outweigh the risks for most adults. He concludes that medical evaluation might, therefore, be more urgent for individuals who plan to remain inactive than for those intending to become physically fit. 25 references (bfranklin@beaumont.edu for correspondence)
Copyright 2014 by Primary Care Medical Abstracts – All Rights Reserved 11/14 - #4

#13: PubMed: Long-term exercise is safe for older adults with OA associated knee pain
The next abstract asks, “Is long-term physical activity safe for older adults with knee pain attributable to osteoarthritis”. Concerns over the safety of PA include PA will lead to more damage to “wear and tear” arthritis, that pain during an activity is an indicator of harm (“pain = harm”). Fear of falling leads to decreased PA. The systematic review concludes that “therapeutic” exercise was consistently safe across a broad range of types and intensities of interventions. And as importantly the “The long-term exercise safety profile and risk of serious adverse events appears favorable when compared to common pharmacological treatment options such as paracetamol and NSAIDs”

OBJECTIVE: To determine whether long-term physical activity is safe for older adults with knee pain.
DESIGN: A comprehensive systematic review and narrative synthesis of existing literature was conducted using multiple electronic databases from inception until May 2013. Two reviewers independently screened, checked data extraction and carried out quality assessment. Inclusion criteria for study designs were randomised controlled trials (RCTs), prospective cohort studies or case control studies, which included adults of mean age over 45 years old with knee pain or osteoarthritis (OA), undertaking physical activity over at least 3 months and which measured a safety related outcome (adverse events, pain, physical functioning, structural OA imaging progression or progression to total knee replacement (TKR)).
RESULTS: Of the 8614 unique references identified, 49 studies were included in the review, comprising 48 RCTs
and one case control study. RCTs varied in quality and included an array of low impact therapeutic exercise interventions of varying cardiovascular intensity. There was no evidence of serious adverse events, increases in pain, decreases in physical function, progression of structural OA on imaging or increased TKR at group level. The case control study concluded that increasing levels of regular physical activity was associated with lower risk of progression to TKR.

CONCLUSIONS: Long-term therapeutic exercise lasting 3 to 30 months is safe for most older adults with knee pain. This evidence supports current clinical guideline recommendations. However, most studies investigated selected, consenting older adults carrying out low impact therapeutic exercise which may affect result generalizability.

REFERENCE: Quicke JG et al. Is long-term physical activity safe for older adults with knee pain?: a systematic review Osteoarthritis Cartilage. 2015 Sep;23(9):1445-56.

#14: PubMed: Hand exercises improve outcomes in hand osteoarthritis

BACKGROUND: Hand exercises are recommended for patients with hand osteoarthritis (HOA), though evidence for their effect is conflicting.

OBJECTIVE: To evaluate, in a randomised controlled trial, the effect of HOA information plus home-based hand exercises (exercise group) compared with information only (control group) in women with HOA.

METHODS: Interventions were delivered by two occupational therapists. Exercise group participants received eight follow-up calls over the 3-month study and recorded adherence, pain after exercises and adverse events in a diary. Primary outcome was activity performance measured after 3 months by the Patient-Specific Functional Scale (PSFS), with a range of 0-10. Secondary outcomes included changes in the ODI score at 4-, 3-month, and 1-year follow-up, and change in pain intensity, Pain Catastrophizing Scale (PCS) score, fear-avoidance beliefs, quality of life, patient-reported success, and health care utilization at 4-week, 3-month, and 1-year follow-up.

RESULTS: Of 80 women randomised (40:40) (mean age (SD) 60.8 years (7.0)), follow-up was 89% (n=71). An intention-to-treat analysis was performed. The adjusted mean difference for the exercise versus control group was 1.4 points (95% CI 0.6 to 2.2, effect size 1.0) for the PSFS score. Thirteen patients in the exercise group versus three participants in the control group reached a positive minimal clinical important difference of 2.2 points in the PSFS total score, while none versus two, respectively, had a negative change (p=0.007). For secondary outcomes, significant mean differences were found in grip strength and thumb web space, in fatigue, joint pain and the Functional Index for HOA activity performance scores. Sixteen exercise-group participants fulfilled the OMERACT-OARSI response criteria versus two control-group participants (p<0.001).

CONCLUSIONS: Hand exercises were well tolerated and significantly improved activity performance, grip strength, pain and fatigue in women with HOA.


#15: PubMed: Early PT marginally helpful for patients with acute LBP

IMPORTANCE: Low back pain (LBP) is common in primary care. Guidelines recommend delaying referrals for physical therapy.

OBJECTIVE: To evaluate whether early physical therapy (manipulation and exercise) is more effective than usual care in improving disability for patients with LBP fitting a decision rule.

DESIGN, SETTING, AND PARTICIPANTS: Randomized clinical trial with 220 participants recruited between March 2011 and November 2013. Participants with no LBP treatment in the past 6 months, aged 18 through 60 years (mean age, 37.4 years [SD, ?10.3]), an Oswestry Disability Index (ODI) score of 20 or higher, symptom duration less than 16 days, and no symptoms distal to the knee in the past 72 hours were enrolled following a primary care visit. INTERVENTIONS: All participants received education. Early physical therapy (n=108) consisted of 4 physical therapy sessions. Usual care (n=112) involved no additional interventions during the first 4 weeks.

MAIN OUTCOMES AND MEASURES: Primary outcome was change in the ODI score (range: 0-100; higher scores indicate greater disability; minimum clinically important difference, 6 points) at 3 months. Secondary outcomes included changes in the ODI score at 4-week and 1-year follow-up, and change in pain intensity, Pain Catastrophizing Scale (PCS) score, fear-avoidance beliefs, quality of life, patient-reported success, and health care utilization at 4-week, 3-month, and 1-year follow-up.

RESULTS: One-year follow-up was completed by 207 participants (94.1%). Using analysis of covariance, early physical therapy showed improvement relative to usual care in disability after 3 months (mean ODI score: early physical therapy group, 41.3 [95% CI, 38.7 to 44.0] at baseline to 6.6 [95% CI, 4.7 to 8.5] at 3 months; usual care group, 40.9 [95% CI, 38.6 to 43.1] at baseline to 9.8 [95% CI, 7.9 to 11.7] at 3 months; between-group difference, -3.2 [95% CI, -5.9 to -0.47], P?=?.02). A significant difference was found between groups for the ODI score after 4 weeks (between-group difference, -3.5 [95% CI, -6.8 to -0.08], P=?.045), but not at 1-year follow-up (between-group difference, -2.0 [95% CI, -5.0 to 1.0], P?=?.19). There was no improvement in pain intensity at 4-week, 3-month, or 1-year follow-up (between-group difference, -0.42 [95% CI, -0.90 to 0.02] at 4-week follow-up; -0.38 [95% CI, -0.84 to 0.09] at 3-month follow-up; and -0.17 [95% CI, -0.62 to 0.27] at 1-year follow-up). The PCS scores improved at 4 weeks and 3 months but not at 1-year follow-up (between-group difference, -2.7 [95% CI, -4.6 to -0.85] at 4-week follow-up; -2.2 [95% CI, -3.9 to -0.49] at 3-month follow-up; and -0.92 [95% CI, -2.7 to 0.61] at 1-year follow-up). There were no differences in health care utilization at any point.

CONCLUSIONS AND RELEVANCE: Among adults with recent-onset LBP, early physical therapy resulted in statistically significant improvement in disability, but the improvement was modest and did not achieve the minimum clinically important difference compared with usual care.

Bottom Lines

1. Exercise and cardiorespiratory fitness is associated with improved CHD, mortality and cancer outcomes; but not cognitive outcomes in sedentary 70 – 90 year olds.
2. Prolonged strenuous endurance exercise (SEE) is associated with several theoretically pathologic changes to the cardiac system, however actual harm associated with these changes are yet to be determined.
3. Long-term exercise is safe for older adults with OA associated knee pain.
4. Rehabilitative exercise is marginally effective for acute low back pain and is effective for hand osteoarthritis.
Appendix:

Figure 1: Effect of exercise on CV risk: Increases in exercise volume produce smaller relative risk reductions

From J Am Coll Cardiol. 2016 Jan 26;67(3):316-29
General Physical Activities Defined by Level of Intensity

The following is in accordance with CDC and ACSM guidelines.

<table>
<thead>
<tr>
<th><strong>Moderate activity</strong>&lt;sup&gt;+&lt;/sup&gt;</th>
<th><strong>Vigorous activity</strong>&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.0 to 6.0 METs</strong>&lt;sup&gt;*&lt;/sup&gt; (3.5 to 7 kcal/min)</td>
<td><strong>Greater than 6.0 METs</strong>&lt;sup&gt;*&lt;/sup&gt; (more than 7 kcal/min)</td>
</tr>
<tr>
<td>Walking at a moderate or brisk pace of 3 to 4.5 mph on a level surface inside or outside, such as x Walking to class, work, or the store; x Walking for pleasure; x Walking the dog; or x Walking as a break from work.</td>
<td>Racewalking and aerobic walking—5 mph or faster Jogging or running Wheeling your wheelchair Walking and climbing briskly up a hill Backpacking Mountain climbing, rock climbing, rapelling Roller skating or in-line skating at a brisk pace</td>
</tr>
<tr>
<td>Racewalking downstairs or down a hill</td>
<td>Bicycling more than 10 mph or bicycling on steep uphill terrain Stationary bicycling—using vigorous effort</td>
</tr>
<tr>
<td>Using crutches Hiking Roller skating or in-line skating at a leisurely pace</td>
<td>Aerobic dancing—high impact Step aerobics Water jogging Teaching an aerobic dance class</td>
</tr>
<tr>
<td>Bicycling 5 to 9 mph, level terrain, or with few hills Stationary bicycling—using moderate effort</td>
<td>Calisthenics—light Yoga Gymnastics General home exercises, light or moderate effort, getting up and down from the floor Jumping on a trampoline Using a stair climber machine at a light-to-moderate pace Using a rowing machine—with moderate effort</td>
</tr>
<tr>
<td>Calisthenics—push-ups, pull-ups, vigorous effort Karate, judo, tae kwon do, jujitsu Jumping rope Performing jumping jacks Using a stair climber machine at a fast pace Using an arm cycling machine—with vigorous effort</td>
<td></td>
</tr>
<tr>
<td>Aerobic dancing—high impact Water aerobics</td>
<td>Using a stair climber machine at a fast pace</td>
</tr>
<tr>
<td>Using a rowing machine—with moderate effort</td>
<td>Circuit weight training</td>
</tr>
<tr>
<td>Weight training and bodybuilding using free weights, Nautilus- or Universal-type weights</td>
<td>Boxing—punching bag</td>
</tr>
<tr>
<td>Box—ing—in the ring, sparring Wrestling—competitive</td>
<td>Professional ballroom dancing—energetically Square dancing—energetically Folk dancing—energetically Clogging</td>
</tr>
<tr>
<td>Yoga</td>
<td>Most competitive sports Football game Basketball game Wheelchair basketball Soccer Rugby Kickball Field or rollerblade hockey Lacrosse</td>
</tr>
<tr>
<td>General home exercises, light or moderate effort, getting up and down from the floor</td>
<td>Table tennis—competitive Tennis—doubles Wheelchair tennis</td>
</tr>
<tr>
<td>Golf, wheeling or carrying clubs</td>
<td>Square dancing</td>
</tr>
<tr>
<td>Ballroom dancing</td>
<td>Folk dancing—energetically</td>
</tr>
<tr>
<td>Line dancing</td>
<td>Clogging</td>
</tr>
<tr>
<td>Square dancing</td>
<td>Using a rowing machine—with vigorous effort</td>
</tr>
<tr>
<td>Folk dancing</td>
<td>Most competitive sports Football game Basketball game Wheelchair basketball Soccer Rugby Kickball Field or rollerblade hockey Lacrosse</td>
</tr>
<tr>
<td>Modern dancing, disco</td>
<td>Coaching children’s or adults’ sports</td>
</tr>
<tr>
<td>Competitive Sports</td>
<td>Beach Sports</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>----------------------------------------------------</td>
</tr>
<tr>
<td>Volleyball</td>
<td>Beach volleyball</td>
</tr>
<tr>
<td>Playing Frisbee</td>
<td>Handball</td>
</tr>
<tr>
<td>Juggling</td>
<td>General or team</td>
</tr>
<tr>
<td>Curling</td>
<td>Racquetball</td>
</tr>
<tr>
<td>Cricket—batting and bowling</td>
<td>Squash</td>
</tr>
<tr>
<td>Badminton</td>
<td></td>
</tr>
<tr>
<td>Archery (nonhunting)</td>
<td></td>
</tr>
<tr>
<td>Fencing</td>
<td></td>
</tr>
<tr>
<td>Downhill skiing—light effort</td>
<td>Downhill skiing—racing or vigorous effort</td>
</tr>
<tr>
<td>Ice skating at a leisurely pace (9 mph or less)</td>
<td>Ice-skating—fast pace or speedskating</td>
</tr>
<tr>
<td>Snowmobiling</td>
<td>Cross-country skiing</td>
</tr>
<tr>
<td>Ice sailing</td>
<td>Sledding Toboggan</td>
</tr>
<tr>
<td>Swimming—recreational</td>
<td>Playing ice hockey</td>
</tr>
<tr>
<td>Treading water—slowly, moderate effort</td>
<td></td>
</tr>
<tr>
<td>Diving—springboard or platform</td>
<td></td>
</tr>
<tr>
<td>Aquatic aerobics</td>
<td></td>
</tr>
<tr>
<td>Waterskiing</td>
<td></td>
</tr>
<tr>
<td>Snorkeling</td>
<td></td>
</tr>
<tr>
<td>Surfing, board or body</td>
<td></td>
</tr>
<tr>
<td>Canoeing or rowing a boat at less than 4 mph</td>
<td>Canoeing or rowing—4 or more mph</td>
</tr>
<tr>
<td>Rafting—whitewater</td>
<td>Kayaking in whitewater rapids</td>
</tr>
<tr>
<td>Sailing—recreational or competition</td>
<td></td>
</tr>
<tr>
<td>Paddle boating</td>
<td></td>
</tr>
<tr>
<td>Kayaking—on a lake, calm water</td>
<td></td>
</tr>
<tr>
<td>Washing or waxing a powerboat or the hull of a sailboat</td>
<td></td>
</tr>
<tr>
<td>Fishing while walking along a riverbank or</td>
<td></td>
</tr>
<tr>
<td>while wading in a stream—wearing waders</td>
<td></td>
</tr>
<tr>
<td>Hunting deer, large or small game</td>
<td></td>
</tr>
<tr>
<td>Pheasant and grouse hunting</td>
<td></td>
</tr>
<tr>
<td>Hunting with a bow and arrow or crossbow—walking</td>
<td></td>
</tr>
<tr>
<td>Horseback riding—general</td>
<td>Horseback riding—trotting, galloping, jumping, or</td>
</tr>
<tr>
<td>Saddling or grooming a horse</td>
<td>in competition</td>
</tr>
<tr>
<td>Playing on school playground equipment,</td>
<td></td>
</tr>
<tr>
<td>moving about, swinging, or climbing</td>
<td>Running</td>
</tr>
<tr>
<td>Playing hopscotch, 4-square, dodgeball, T-ball,</td>
<td>Skipping</td>
</tr>
<tr>
<td>or tetherball</td>
<td></td>
</tr>
<tr>
<td>Skateboarding</td>
<td>Jumping rope</td>
</tr>
<tr>
<td>Roller-skating or in-line skating—leisurely pace</td>
<td>Performing jumping jacks</td>
</tr>
<tr>
<td>Playing instruments while actively moving;</td>
<td>Roller-skating or in-line skating—fast pace</td>
</tr>
<tr>
<td>playing in a marching band; playing guitar or drums in</td>
<td></td>
</tr>
<tr>
<td>a rock band</td>
<td></td>
</tr>
<tr>
<td>Twirling a baton in a marching band</td>
<td></td>
</tr>
<tr>
<td>Singing while actively moving about—as on stage or in</td>
<td></td>
</tr>
<tr>
<td>church</td>
<td></td>
</tr>
<tr>
<td>Gardening and yard work: raking the lawn, bagging</td>
<td>Gardening and yard work: heavy or rapid shovel</td>
</tr>
<tr>
<td>grass or leaves, digging, hoeing, light shoveling</td>
<td>shoveling (more than 10 lbs per minute), digging</td>
</tr>
<tr>
<td>(less than 10 lbs per minute), or weeding while</td>
<td>ditches, or carrying heavy loads</td>
</tr>
<tr>
<td>standing or bending</td>
<td>Felling trees, carrying large logs, swinging an ax,</td>
</tr>
<tr>
<td>Planting trees, trimming shrubs and trees,</td>
<td>hand-splitting logs, or climbing and</td>
</tr>
<tr>
<td>hauling branches, stacking wood</td>
<td>trimming trees</td>
</tr>
<tr>
<td>Pushing a power lawn mower or tiller</td>
<td>Pushing a nonmotorized lawn mower</td>
</tr>
<tr>
<td>Shoveling light snow</td>
<td>Shoveling heavy snow</td>
</tr>
<tr>
<td>Moderate housework: scrubbing the floor or</td>
<td>Heavy housework: moving or pushing heavy</td>
</tr>
<tr>
<td>Pushing a nonmotorized lawn mower</td>
<td></td>
</tr>
<tr>
<td>Gardening and yard work:      heavy or rapid shovel</td>
<td></td>
</tr>
<tr>
<td>Gardening and yard work: moving or pushing heavy</td>
<td></td>
</tr>
<tr>
<td>General household tasks requiring considerable effort</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Bathtub while on hands and knees, hanging laundry on a clothesline, sweeping an outdoor area, cleaning out the garage, washing windows, moving light furniture, packing or unpacking boxes, walking and putting household items away, carrying out heavy bags of trash or recyclables (e.g., glass, newspapers, and plastics), or carrying water or firewood</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furniture (75 lbs or more), carrying household items weighing 25 lbs or more up a flight or stairs, or shoveling coal into a stove</td>
</tr>
<tr>
<td>Standing, walking, or walking down a flight of stairs while carrying objects weighing 50 lbs or more</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putting groceries away—walking and carrying especially large or heavy items less than 50 lbs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrying several heavy bags (25 lbs or more) of groceries at one time up a flight of stairs</td>
</tr>
<tr>
<td>Grocery shopping while carrying young children and pushing a full grocery cart, or pushing two full grocery carts at once</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actively playing with children—walking, running, or climbing while playing with children</td>
</tr>
<tr>
<td>Walking while carrying a child weighing less than 50 lbs</td>
</tr>
<tr>
<td>Walking while pushing or pulling a child in a stroller or an adult in a wheelchair</td>
</tr>
<tr>
<td>Carrying a child weighing less than 25 lbs up a flight of stairs</td>
</tr>
<tr>
<td>Child care: handling uncooperative young children (e.g., chasing, dressing, lifting into car seat), or handling several young children at one time</td>
</tr>
<tr>
<td>Bathing and dressing an adult</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigorously playing with children—running longer distances or playing strenuous games with children</td>
</tr>
<tr>
<td>Racewalking or jogging while pushing a stroller designed for sport use</td>
</tr>
<tr>
<td>Carrying an adult or a child weighing 25 lbs or more up a flight of stairs</td>
</tr>
<tr>
<td>Standing or walking while carrying an adult or a child weighing 50 lbs or more</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal care: shoveling grain, feeding farm animals, or grooming animals</td>
</tr>
<tr>
<td>Playing with or training animals</td>
</tr>
<tr>
<td>Manually milking cows or hooking cows up to milking machines</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal care: forking bales of hay or straw, cleaning a barn or stables, or carrying animals weighing over 50 lbs</td>
</tr>
<tr>
<td>Handling or carrying heavy animal-related equipment or tack</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home repair: cleaning gutters, caulking, refinishing furniture, sanding floors with a power sander, or laying or removing carpet or tiles</td>
</tr>
<tr>
<td>General home construction work: roofing, painting inside or outside of the house, wall papering, scraping, plastering, or remodeling</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home repair or construction: very hard physical labor, standing or walking while carrying heavy loads of 50 lbs or more, taking loads of 25 lbs or more up a flight of stairs or ladder (e.g., carrying roofing materials onto the roof), or concrete or masonry work</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outdoor carpentry, sawing wood with a powersaw</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand-sawing hardwoods</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automobile bodywork</td>
</tr>
<tr>
<td>Hand washing and waxing a car</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pushing a disabled car</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>~Occupations that require extended periods of walking, pushing or pulling objects weighing less than 75 lbs, standing while lifting objects weighing less than 50 lbs, or carrying objects of less than 25 lbs up a flight of stairs</td>
</tr>
<tr>
<td>Tasks frequently requiring moderate effort and considerable use of arms, legs, or occasional total body movements.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>For example:</td>
</tr>
<tr>
<td>x Briskly walking on a level surface while carrying a suitcase or load weighing up to 50 lbs</td>
</tr>
<tr>
<td>x Maid service or cleaning services</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>~Occupations that require extensive periods of running, rapid movement, pushing or pulling objects weighing 75 lbs or more, standing while lifting heavy objects of 50 lbs or more, walking while carrying heavy objects of 25 lbs or more</td>
</tr>
<tr>
<td>Tasks frequently requiring strenuous effort and extensive total body movements.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General household tasks requiring considerable effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>For example:</td>
</tr>
<tr>
<td>x Running up a flight of stairs while carrying a suitcase or load weighing 25 lbs or more</td>
</tr>
<tr>
<td>x Teaching a class or skill requiring</td>
</tr>
<tr>
<td>x</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>x</td>
</tr>
<tr>
<td>x</td>
</tr>
<tr>
<td>x</td>
</tr>
<tr>
<td>x</td>
</tr>
<tr>
<td>x</td>
</tr>
<tr>
<td>x</td>
</tr>
<tr>
<td>x</td>
</tr>
<tr>
<td>x</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>active and strenuous participation, such as aerobics or physical education instructor</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>Firefighting</td>
</tr>
<tr>
<td>x</td>
<td>Masonry and heavy construction work</td>
</tr>
<tr>
<td>x</td>
<td>Coal mining</td>
</tr>
<tr>
<td>x</td>
<td>Manually shoveling or digging ditches</td>
</tr>
<tr>
<td>x</td>
<td>Using heavy nonpowered tools</td>
</tr>
<tr>
<td>x</td>
<td>Most forestry work</td>
</tr>
<tr>
<td>x</td>
<td>Farming—forking straw, baling hay, cleaning barn, or poultry work</td>
</tr>
<tr>
<td>x</td>
<td>Moving items professionally</td>
</tr>
<tr>
<td>x</td>
<td>Loading and unloading a truck</td>
</tr>
</tbody>
</table>
The ratio of exercise metabolic rate. One MET is defined as the energy expenditure for sitting quietly, which, for the average adult, approximates 3.5 ml of oxygen uptake per kilogram of body weight per minute (1.2 kcal/min for a 70-kg individual). For example, a 2-MET activity requires two times the metabolic energy expenditure of sitting quietly. For an average person, defined here as 70 kilograms or 154 pounds. The activity intensity levels portrayed in this chart are most applicable to men aged 30 to 50 years and women aged 20 to 40 years. For older individuals, the classification of activity intensity might be higher. For example, what is moderate intensity to a 40-year-old man might be vigorous for a man in his 70s. Intensity is a subjective classification.

Data for this chart were available only for adults. Therefore, when children’s games are listed, the estimated intensity level is for adults participating in children’s activities.

To compute the amount of time needed to accumulate 150 kcal, do the following calculation: 150 kcal divided by the MET level of the activity equals the minutes needed to expend 150 kcal. For example:

\[ 150 \div 7 = 21.4 \text{ minutes} \]

Generally, activities in the moderate-intensity range require 25-50 minutes to expend a moderate amount of activity, and activities in the vigorous-intensity range would require less than 25 minutes to achieve a moderate amount of activity. Each activity listed is categorized as light, moderate, or vigorous on the basis of current knowledge of the overall level of intensity required for the average person to engage in it, taking into account brief periods when the level of intensity required for the activity might increase or decrease considerably.

Persons with disabilities, including motor function limitations (e.g., quadriplegia) may wish to consult with an exercise physiologist or physical therapist to properly classify the types of physical activities in which they might participate, including assisted exercise. Certain activities classified in this listing as moderate might be vigorous for persons who must overcome physical challenges or disabilities.

~Note: Almost every occupation requires some mix of light, moderate, or vigorous activities, depending on the task at hand. To categorize the activity level of your own position, ask yourself: How many minutes each working day do I spend doing the types of activities described as light, moderate, or vigorous? To arrive at a total workday caloric expenditure, multiply the minutes spent doing activities within each intensity level by the kilocalories corresponding to each level of intensity. Then, add together the total kilocalories spent doing light, moderate, and vigorous activities to arrive at your total energy expenditure in a typical day.
Skin Diseases

John Hickner, MD, MS

Objectives

1. Review recent evidence for screening and prevention of skin cancers
2. Review evidence for the use of antibiotics for MRSA skin infections
3. Review evidence for effectiveness of treatments for fungal skin infections
4. Review recent RCT and meta-analysis evidence for treatments of other skin conditions presenting in primary care

Screening and Prevention of Skin Cancers

1. Screening for Skin Cancer in Adults: Updated Evidence Report and Systematic Review for the US Preventive Services

IMPORTANCE: Skin cancer, primarily melanoma, is a leading cause of morbidity and mortality in the United States.

OBJECTIVE: To provide an updated systematic review for the US Preventive Services Task Force regarding clinical skin cancer screening among adults.

DATA SOURCES: MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials were searched for relevant studies published from January 1, 1995, through June 1, 2015, with surveillance through February 16, 2016.

STUDY SELECTION: English-language studies conducted in asymptomatic populations 15 years and older at general risk for skin cancer.

DATA EXTRACTION AND SYNTHESIS: Relevant data were abstracted, and study quality was rated.

MAIN OUTCOMES AND MEASURES: Melanoma incidence and mortality, harms from cancer screening, diagnostic accuracy, and stage distribution.

RESULTS: No randomized clinical trials were identified. There was limited evidence on the association between skin cancer screening and mortality. A German ecologic study (n = 360,288) found a decrease of 0.8 per 100,000 melanoma deaths in a region with population-based skin cancer screening compared with no change or slight increases in comparison regions. The number of excisions needed to detect 1 skin cancer from clinical visual skin examinations varied by age and sex; for example, 22 for women 65 years or older compared with 41 for women aged 20 to 34 years. In 2 studies of performing visual skin examination, sensitivity to detect melanoma was 40.2% and specificity was 86.1% when conducted by primary care physicians (n = 16,383). Sensitivity was 49.0% and specificity was 97.6% when skin examinations were performed by dermatologists (n = 7436). In a case-control study of melanoma (n = 7586), cases diagnosed with thicker lesions (>0.75 mm) had an odds ratio of 0.86 (95% CI, 0.75-0.98) for receipt of a physician skin examination in the prior 3 years compared with controls. Eight cohort studies (n = 236,485) demonstrated a statistically significant relationship between the degree of disease involvement at diagnosis and melanoma mortality, regardless of the characterization of the stage or lesion thickness. Tumor thickness greater than 4.0 mm was associated with increased melanoma mortality compared with thinner lesions, and late stage at diagnosis was associated with increased all-cause mortality.

CONCLUSIONS AND RELEVANCE: Only limited evidence was identified for skin cancer screening, particularly regarding potential benefit of skin cancer screening on melanoma mortality. Future research on skin cancer screening should focus on evaluating the effectiveness of targeted screening in those considered to be at higher risk for skin cancer.


2. Total-Body Examination vs Lesion-Directed Skin Cancer Screening

IMPORTANCE: Skin cancer is the most frequent cancer type. It remains unknown if and how screening programs can be organized in a cost-effective manner.

OBJECTIVE: To compare the 2 screening strategies of systematic total-body examination (TBE) and lesion-directed screening (LDS), with a focus on the participation rate, detection rate, anxiety, and cost.

DESIGN, SETTING, AND PARTICIPANTS: Population-based cross-sectional screenings by a team of 6 dermatologists were organized in 2 sociodemographically similar regions. The TBE was organized in a community of 9325 inhabitants 18 years and older (Wichelen, East Flanders, Belgium) during a 5-day screening (March 14-18, 2014). The LDS was organized in a sociodemographically comparable community (Nevele, East Flanders, Belgium) of 9484 adult inhabitants during a 4-day screening (April 22 and 25-27, 2014).

The first population received a personal invitation for a standard TBE. In the second population, individuals were invited for an LDS if they had a lesion meeting 1 or more of the following criteria: ABCD rule (A, asymmetry; B, borders; C, colors; and D, differential structures), ugly duckling sign, new lesion lasting longer than 4 weeks, or red nonhealing lesions.
3. Complete skin examination is essential in the assessment of dermatology patients: findings from 483 patients

BACKGROUND: Dermatological teaching has traditionally stressed that complete skin examination is essential in the assessment of patients with potential skin disease.

OBJECTIVES: To determine whether complete skin examination results in increased diagnoses of skin malignancies that would not have been discovered otherwise.

METHODS: New patients (n = 483) attending a dermatology clinic in a university teaching hospital and private dermatology practice had a complete skin examination, as is our normal practice. These patients were seen over a 9-month period (January-September 2009). All patients were examined by the same consultant dermatologist. Data were collected on patients' sex, age, presenting complaint and findings on complete skin examination.

RESULTS: Two nodular malignant melanomas with mean Breslow thickness of 0.6 mm (0.4%) and one melanoma in situ were identified at sites distant from the patient's presenting complaint. Sixteen patients (3.3%) had a basal cell carcinoma that would not have been discovered if the presenting lesion alone had been examined. Thirty-three patients (6.8%) had actinic keratoses or squamous cell carcinoma in situ and nine (1.9%) had dysplastic naevi. A further 21 patients (4.3%) had a suspicious lesion biopsied or excised with subsequent benign histology. Seventy-three patients (15.1%) had other benign dermatological diagnoses requiring treatment or investigation.

CONCLUSIONS: In a 9-month period, in a sample of 483 new patients, three patients (0.6%) had potentially lethal skin malignancies identified that would not have been diagnosed without a complete skin examination. Sixteen (3.3%) patients had basal cell carcinomas that would have been missed without complete skin examination. This study confirms the traditional teaching that complete skin examination has the potential to reduce morbidity and mortality from cutaneous malignancy.


4. Targeted melanoma prevention intervention: a cluster randomized controlled trial

BACKGROUND: Targeted interventions to reduce the risk and increase the early detection of melanoma have the potential to save lives. We aimed to assess the effect of such an intervention on patient prevention behavior.

METHODS: We conducted a pilot clustered randomized controlled trial, comparing a targeted screening and education intervention with a conventional information-based campaign in 20 private surgeries in western France. In the intervention group, 10 general practitioners identified patients at elevated risk for melanoma with a validated assessment tool, the Self-Assessment Melanoma Risk Score (SAMScore), examined their skin, and counseled them using information leaflets. In the control group, 10 general practitioners displayed a poster and the leaflets in their waiting room and examined patients' skin at their own discretion. The main outcome measures were sunbathing and skin self-examinations among patients at elevated risk, assessed 5 months later with a questionnaire.

RESULTS: Analyses were based on 173 patients. Compared with control patients, intervention patients were more likely to remember the campaign (81.4% vs 50.0%, P = .0001) and to correctly identify their elevated risk of melanoma (71.1% vs 42.1%, P = .001). Furthermore, intervention patients had higher levels of prevention behaviors: they were less likely to sunbathe in the summer (24.7% vs 40.8%, P = .048) and more likely to have performed skin self-examinations in the past year (52.6% vs 36.8%, P = .029). The intervention was not associated with any clear adverse effects, although there were trends whereby intervention patients were more likely to worry about melanoma and to consult their general practitioner again about the disease.

CONCLUSIONS: The combination of use of the SAMScore and general practitioner examination and counseling during consultations is an efficient way to promote patient behaviors that may reduce melanoma risk. Extending the duration of follow-up and demonstrating an impact on morbidity and mortality remain major issues for further research.

OBJECTIVE: To test the impact of a theory-based, SMS (text message)-delivered behavioural intervention (Healthy Text) targeting sun protection or skin self-examination behaviours compared to attention control.

METHOD: Overall, 546 participants aged 18-42 years were randomised using a computer-generated number list to the skin self-examination (N=176), sun protection (N=187), or attention control (N=183) text messages group. Each group received 21 text messages about their assigned topic over 12 months (12 weekly messages for 3 months, then monthly messages for the next 9 months). Data were collected via telephone survey at baseline, 3, and 12 months across Queensland from January 2012 to August 2013.

RESULTS: One year after baseline, the sun protection (mean change 0.12; P=0.030) and skin self-examination groups (mean change 0.12; P=0.035) had significantly greater improvement in their sun protection habits (SPH) index compared to the attention control group (reference mean change 0.02). The increase in the proportion of participants who reported any skin self-examination from baseline to 12 months was significantly greater in the skin self-examination intervention group (103/163; 63%; P<0.001) than the sun protection (83/173; 48%) or attention control (65/165; 36%) groups. There was no significant effect of the intervention for participants’ self-reported whole-body skin self-examination, sun tanning, or sunburn behaviours.

CONCLUSION: The Healthy Text intervention was effective in inducing significant improvements in sun protection and any type of skinself-examination behaviours.

TRIAL REGISTRATION: The Australian and New Zealand Clinical Trials register (ACTRN12612000577819).


MRSA Skin Infections

6. Placebo = antibiotics for skin abscesses in children

Clinical question: In children with drained skin abscesses, is no treatment as effective as antibiotic treatment?

Study design: Randomized controlled trial (double-blinded)

Setting: Emergency department

Synopsis: The treatment of skin abscesses with antibiotic following incision and drainage (called by some the "Keflex-reflex") has not previously been subjected to controlled study. The authors of this study enrolled 161 children ages 3 months to 18 years with an ultrasound-confirmed skin abscess requiring drainage. Half the children were younger than 5 years. They excluded children with systemic symptoms -- including a temperature greater than 38 degrees C -- and children with chronic disease, with recent antibiotic use, or receiving oral corticosteroid. The majority of infections (80%) were due to community-acquired methicillin-resistant Staphylococcus aureus, with all strains being susceptible to trimethoprim-sulfamethoxazole. Following drainage, the children were randomly assigned, using concealed allocation, to receive a standard dose of trimethoprim-sulfamethoxazole or matched placebo twice daily for 10 days. Patients, on average, took only 66% of the total dose, which is similar to rates found in other studies of antibiotic use. Failure, defined as erythema, warmth, induration, fluctuance, tenderness, or drainage after 10 days of treatment, occurred in 4% to 5% of children in both groups, the difference not being significant. However, 8 children were lost to follow-up in the placebo group and 4 children were lost in the treatment group. If we assume a worst case scenario -- that all these children failed treatment -- antibiotic treatment would have been superior. Significantly more children treated with placebo developed new lesions during treatment (25% vs 12.3%; number needed to treat = 8), but new lesion rates were similar at 90 days although the authors lost contact with 35% of the enrolled patients.

Bottom line: No treatment produces similar resolution rates as antibiotic treatment in children who have had skin abscesses drained. Antibiotic treatment may prevent new lesions in the short term.


7. Outpatient pediatric skin infections resolve without MRSA coverage

Clinical question: In children with uncomplicated skin infections due to community-associated methicillin-resistant Staphylococcus aureus, is clindamycin more effective than cephalaxin?

Study design: Randomized controlled trial (double-blinded)

Setting: Outpatient (primary care)

Synopsis: The investigators enrolled 200 children with uncomplicated purulent skin and soft-tissue infection -- such as an abscess, furuncle, or cellulitis -- who were initially evaluated in a pediatric outpatient clinic or a pediatric emergency department. Children were excluded if they were younger than 6 months, had immune deficiency, were deemed to require inpatient treatment, or had an infection due to a surgical wound. The infections were drained and packed as necessary. All infections were cultured; 69% were positive for MRSA. The children were then randomized, using concealed allocation, to receive either cephalaxin (40 mg/kg/day) or clindamycin (20 mg/kg/day) for 1 week. By 48 hours and 72 hours, 94% to 97% of children were improved, and by 7 days all children had improved, with complete resolution reported in 94% to 97% of children, with no differences between the groups. The presence of fever and being younger than 1 year were associated with treatment failure, regardless of antibiotic used, though the degree of erythema did not predict response. These results are similar to those from a study comparing antibiotic treatment to placebo for pediatric skin abscess, with antibiotic treatment conferring no benefit (Ann Emerg Med 2010;55(5):401-407).

Bottom line: Incision and drainage of an abscess, regardless of the degree of surrounding erythema or induration, is the key to curing
skin infections in children. Even though almost 70% of the children in this study had methicillin-resistant Staphylococcus aureus (MRSA) infections, their response to treatment was similar whether they received clindamycin or cephalaxin, which does not have activity against MRSA: 95% improved after 2 to 3 days, and a similar proportion was cured within 7 days. 


8. Trimethoprim-Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess

BACKGROUND: U.S. emergency department visits for cutaneous abscess have increased with the emergence of methicillin-resistant Staphylococcus aureus (MRSA). The role of antibiotics for patients with a drained abscess is unclear.

METHODS: We conducted a randomized trial at five U.S. emergency departments to determine whether trimethoprim-sulfamethoxazole (at doses of 320 mg and 1600 mg, respectively, twice daily, for 7 days) would be superior to placebo in outpatients older than 12 years of age who had an uncomplicated abscess that was being treated with drainage. The primary outcome was clinical cure of the abscess, assessed 7 to 14 days after the end of the treatment period.

RESULTS: The median age of the participants was 35 years (range, 14 to 73); 45.3% of the participants had wound cultures that were positive for MRSA. In the modified intention-to-treatment population, clinical cure of the abscess occurred in 507 of 630 participants (80.5%) in the trimethoprim-sulfamethoxazole group versus 454 of 617 participants (73.6%) in the placebo group (difference, 6.9 percentage points; 95% confidence interval [CI], 2.1 to 11.7; P=0.005). In the per-protocol population, clinical cure occurred in 487 of 524 participants (92.9%) in the trimethoprim-sulfamethoxazole group versus 457 of 533 participants (85.7%) in the placebo group (difference, 7.2 percentage points; 95% CI, 3.2 to 11.2; P<0.001). Trimethoprim-sulfamethoxazole was superior to placebo with respect to most secondary outcomes in the per-protocol population, resulting in lower rates of subsequent surgical drainage procedures (3.4% vs. 8.6%; difference, -5.2 percentage points; 95% CI, -8.2 to -2.2), skin infections at new sites (3.1% vs. 10.3%; difference, -7.2 percentage points; 95% CI, -10.4 to -4.1), and infections in household members (1.7% vs. 4.1%; difference, -2.4 percentage points; 95% CI, -4.6 to -0.2) 7 to 14 days after the treatment period. Trimethoprim-sulfamethoxazole was associated with slightly more gastrointestinal side effects (mostly mild) than placebo. At 7 to 14 days after the treatment period, invasive infections had developed in 2 of 524 participants (0.4%) in the trimethoprim-sulfamethoxazole group and in 2 of 533 participants (0.4%) in the placebo group; at 42 to 56 days after the treatment period, an invasive infection had developed in 1 participant (0.2%) in the trimethoprim-sulfamethoxazole group.

CONCLUSIONS: In settings in which MRSA was prevalent, trimethoprim-sulfamethoxazole treatment resulted in a higher cure rate among patients with a drained cutaneous abscess than placebo. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT00729937.).


What Treatments are Effective for Fungal Skin Infections?

9. Tavaborole (Kerydin) minimally, if at all, effective for toenail onychomycosis

Clinical question: Is tavaborole topical solution safe and effective for the treatment of toenail onychomycosis?

Study design: Randomized controlled trial (double-blinded)

Setting: Outpatient (specialty)

Synopsis: In 2 separate but similarly designed studies these investigators randomly assigned (uncertain allocation concealment) adults (N = 1198 divided between 2 studies), 18 years or older, with distal subungual toenail onychomycosis involving 20% to 60% of at least one infected great toenail to daily application of tavaborole topical solution or a placebo vehicle solution for 48 weeks. Eligibility criteria included a positive potassium hydroxide wet mount and culture for dermatophytes, greater than or equal to 3-mm clear nail measured from the proximal nail fold to the most proximal visible mycotic border, and distal nail thickness 3 mm or less. The authors do not state whether outcomes were assessed by individuals masked to treatment group assignment. The primary end point was a completely clear nail and negative mycology at 52 weeks. Complete follow-up occurred for 97% of participants at 52 weeks. Using intention-to-treat analysis, significantly more patients in the tavaborole group achieved complete cure at week 52 compared with the vehicle group in both study 1 and study 2 (6.5% vs 0.5%, number needed to treat [NNT] = 16.7 and 9.1% vs 1.5%, NNT=13.2). Adverse events were minimal and discontinuation rates due to side effects were similar in all treatment groups.

Bottom line: Two studies found minimal benefit to the treatment of toenail onychomycosis with tavaborole topical solution (Kerydin). At best, 1 in 11 patients can expect completely clear nails and a negative fungal culture after 1 full year of treatment.


10. Oral treatments for fungal infections of the skin of the foot

Background. About 15% of the world population have fungal infections of the feet (tinea pedis or athlete's foot). There are many clinical presentations of tinea pedis, and most commonly, tinea pedis is seen between the toes (interdigital) and on the soles, heels, and sides of the foot (plantar). Plantar tinea pedis is known as moccasin foot. Once acquired, the infection can spread to other sites including the nails, which can be a source of re-infection. Oral therapy is usually used for chronic conditions or when topical treatment has failed.
Objectives. To assess the effects of oral treatments for fungal infections of the skin of the foot (tinea pedis).

Search methods. For this update we searched the following databases to July 2012: the Cochrane Skin Group Specialised Register, CENTRAL in The Cochrane Library, MEDLINE (from 1946), EMBASE (from 1974), and CINAHL (from 1981). We checked the bibliographies of retrieved trials for further references to relevant trials, and we searched online trials registers.

Selection criteria. Randomised controlled trials of oral treatments in participants who have a clinically diagnosed tinea pedis, confirmed by microscopy and growth of dermatophytes (fungi) in culture.

Data collection and analysis. Two review authors independently undertook study selection, ‘Risk of bias’ assessment, and data extraction.

Main results. We included 25 studies (N = 4449); 4 studies (N = 2637) were new to this update. Terbinafine for four weeks and griseofulvin for eight weeks showed similar efficacy for the primary outcome of complete (i.e. clinical and mycological) cure in three studies involving 328 participants with Trichophyton species infections (84.2% versus 79.0%; risk ratio (RR) 1.06, 95% confidence interval (CI) 0.98 to 1.15; low quality evidence). Complete cure with itraconazole (two to six weeks) and griseofulvin (six weeks) was similar in two studies (83.6% versus 91.0%; RR 0.92, 95% CI 0.81 to 1.05; N = 134; very low quality evidence). In two studies, there was no difference between itraconazole and terbinafine for two to three weeks treatment (73.8% versus 78.8%; RR 0.93, 95% CI 0.72 to 1.19; N = 160; low quality evidence). In three studies, there was a similar proportion achieving complete cured with two to four weeks of fluconazole or six weeks of griseofulvin (41.4% versus 52.7%; RR 0.92, 95% CI 0.81 to 1.05; N = 615; moderate quality evidence). Current evidence for ketoconazole versus griseofulvin was limited. One study favoured griseofulvin (12 weeks) because ketoconazole (12 weeks) appeared less effective for complete cure (RR 0.76, 95% CI 0.62 to 0.94; low quality evidence). However, their effects appeared to be similar when the treatment lasted 26 weeks (RR 0.95, 95% CI 0.83 to 1.07; low quality evidence). Another study indicated that complete cure was similar for ketoconazole (12 weeks) and griseofulvin (12 weeks) (RR 0.89, 95% CI 0.57 to 1.39; low quality evidence). For one trial, there was no significant difference for complete cure between fluconazole (for two to three weeks) and terbinafine (for two to three weeks) (82.0% versus 94.0%; RR 0.87, 95% CI 0.75 to 1.01; N = 100; low quality evidence). For complete cure, we did not find a significant difference between fluconazole (for two to three weeks) and itraconazole (for two to three weeks) (82.0% versus 82.0%; RR 1.00, 95% CI 0.83 to 1.20; low quality evidence). All of the included studies were at either high or unclear risk of bias in at least one domain. Using GRADE to rate the overall quality of the evidence, lower quality evidence resulted in lower confidence in the estimate of effect.

Authors' conclusions. Newer treatments including terbinafine, itraconazole and fluconazole are at least similar to griseofulvin in children with tinea capitis caused by Trichophyton species. Limited evidence suggests that terbinafine, itraconazole and fluconazole have similar effects, whereas ketoconazole may be less effective than griseofulvin in children infected with Trichophyton. With some interventions the proportion achieving complete clinical cure was in excess of 90% (e.g. one study of terbinafine or griseofulvin for Trichophyton infections), but in many of the comparisons tested, the proportion cured was much lower. New evidence from this update suggests that terbinafine is more effective than griseofulvin in children with T. tonsurans infection. However, in children with Microsporum infections, new evidence suggests that the effect of griseofulvin is better than terbinafine. Not all treatments for tinea capitis are available in paediatric formulations but all have reasonable safety profiles.


11. Systemic antifungal therapy for tinea capitis in children

Background. Tinea capitis is a common contagious fungal infection of the scalp in children. Systemic therapy is required for treatment and to prevent spread. This is an update of the original Cochrane review.

Objectives. To assess the effects of systemic antifungal drugs for tinea capitis in children.

Search methods. We updated our searches of the following databases to November 2015: the Cochrane Skin Group Specialised Register, CENTRAL (2015, Issue 10), MEDLINE (from 1946), EMBASE (from 1974), LILACS (from 1982), and CINAHL (from 1981). We included 25 studies (N = 4449); 4 studies (N = 2637) were new to this update. Terbinafine for four weeks and griseofulvin for eight weeks showed similar efficacy for the primary outcome of complete (i.e. clinical and mycological) cure in three studies involving 328 participants with Trichophyton species infections (84.2% versus 79.0%; risk ratio (RR) 1.06, 95% confidence interval (CI) 0.98 to 1.15; low quality evidence). Complete cure with itraconazole (two to six weeks) and griseofulvin (six weeks) was similar in two studies (83.6% versus 91.0%; RR 0.92, 95% CI 0.81 to 1.05; N = 134; very low quality evidence). In two studies, there was no difference between itraconazole and terbinafine for two to three weeks treatment (73.8% versus 78.8%; RR 0.93, 95% CI 0.72 to 1.19; N = 160; low quality evidence). In three studies, there was a similar proportion achieving complete cured with two to four weeks of fluconazole or six weeks of griseofulvin (41.4% versus 52.7%; RR 0.92, 95% CI 0.81 to 1.05; N = 615; moderate quality evidence). Current evidence for ketoconazole versus griseofulvin was limited. One study favoured griseofulvin (12 weeks) because ketoconazole (12 weeks) appeared less effective for complete cure (RR 0.76, 95% CI 0.62 to 0.94; low quality evidence). However, their effects appeared to be similar when the treatment lasted 26 weeks (RR 0.95, 95% CI 0.83 to 1.07; low quality evidence). Another study indicated that complete cure was similar for ketoconazole (12 weeks) and griseofulvin (12 weeks) (RR 0.89, 95% CI 0.57 to 1.39; low quality evidence). For one trial, there was no significant difference for complete cure between fluconazole (for two to three weeks) and terbinafine (for two to three weeks) (82.0% versus 94.0%; RR 0.87, 95% CI 0.75 to 1.01; N = 100; low quality evidence). For complete cure, we did not find a significant difference between fluconazole (for two to three weeks) and itraconazole (for two to three weeks) (82.0% versus 82.0%; RR 1.00, 95% CI 0.83 to 1.20; low quality evidence). All of the included studies were at either high or unclear risk of bias in at least one domain. Using GRADE to rate the overall quality of the evidence, lower quality evidence resulted in lower confidence in the estimate of effect.

Authors' conclusions. Newer treatments including terbinafine, itraconazole and fluconazole are at least similar to griseofulvin in children with tinea capitis caused by Trichophyton species. Limited evidence suggests that terbinafine, itraconazole and fluconazole have similar effects, whereas ketoconazole may be less effective than griseofulvin in children infected with Trichophyton. With some interventions the proportion achieving complete clinical cure was in excess of 90% (e.g. one study of terbinafine or griseofulvin for Trichophyton infections), but in many of the comparisons tested, the proportion cured was much lower. New evidence from this update suggests that terbinafine is more effective than griseofulvin in children with T. tonsurans infection. However, in children with Microsporum infections, new evidence suggests that the effect of griseofulvin is better than terbinafine. Not all treatments for tinea capitis are available in paediatric formulations but all have reasonable safety profiles.
Treatments for other common skin conditions

12. Meta-analysis: Interventions for vitiligo

**Background.** Vitiligo is a chronic skin disorder characterised by patchy loss of skin color. Some people experience itching before the appearance of a new patch. It affects people of any age or ethnicity, more than half of whom develop it before the age of 20 years. There are two main types: generalised vitiligo, the common symmetrical form, and segmental, affecting only one side of the body. Around 1% of the world’s population has vitiligo, a disease causing white patches on the skin. Several treatments are available. Some can restore pigment but none can cure the disease.

**Objectives.** To assess the effects of all therapeutic interventions used in the management of vitiligo.

**Search methods.** We updated our searches of the following databases to October 2013: the Cochrane Skin Group Specialised Register, CENTRAL in *The Cochrane Library* (2013, Issue 10), MEDLINE, Embase, AMED, PsycINFO, CINAHL and LILACS. We also searched five trials databases, and checked the reference lists of included studies for further references to relevant randomised controlled trials (RCTs).

**Selection criteria.** Randomised controlled trials (RCTs) assessing the effects of treatments for vitiligo.

**Data collection and analysis.** At least two review authors independently assessed study eligibility and methodological quality, and extracted data.

**Main results.** This update of the 2010 review includes 96 studies, 57 from the previous update and 39 new studies, totaling 4512 participants. Most of the studies, covering a wide range of interventions, had fewer than 50 participants. All of the studies assessed repigmentation, however only five reported on all of our three primary outcomes which were quality of life, > 75% repigmentation and adverse effects. Of our secondary outcomes, six studies measured cessation of spread but none assessed long-term permanence of repigmentation resulting from treatment at two years follow-up. Most of the studies assessed combination therapies which generally reported better results. New interventions include seven new surgical interventions. We analysed the data from 25 studies which assessed our primary outcomes.

Nine analyses from eight studies reported >75% repigmentation. In the following studies the repigmentation was better in the combination therapy group: calcipotriol plus PUVA (psoralen with UVA light) versus PUVA (paired OR 4.25, 95% CI 1.43 to 12.64, one study, N = 27); hydrocortisone-17-butyrate plus excimer laser versus excimer laser alone (RR 2.57, 95% CI 1.20 to 5.50, one study, N = 84); oral minipulse of prednisolone (OMP) plus NB-UVB (narrowband UVB) versus OMP alone (RR 7.41, 95% CI 1.03 to 53.26, one study, N = 47); azathioprine with PUVA versus PUVA alone (RR 17.77, 95% CI 1.08 to 291.82, one study, N = 58) and 8-Methoxy psoralen (8-MOP) plus sunlight versus psoralen (RR 2.50, 95% CI 1.06 to 5.91, one study, N = 168). In these three studies *ginkgo biloba* was better than placebo (RR 4.40, 95% CI 1.08 to 17.95, one study, N = 47); clobetasol propionate was better than PUVA (PUVA with sunlight) (RR 4.70, 95% CI 1.14 to 19.39, one study, N = 45); split skin grafts with PUVA sal was better than minipunch grafts with PUVA sal (RR 1.89, 95% CI 1.25 to 2.85, one study, N = 64). We performed one meta-analysis of three studies, in which we found a non-significant 60% increase in the proportion of participants achieving >75% repigmentation in favour of NB-UVB compared to PUVA (RR 1.60, 95% CI 0.74 to 3.45; I² = 0%).

**Authors’ conclusions.** This review has found some evidence from individual studies to support existing therapies for vitiligo, but the usefulness of the findings is limited by the different designs and outcome measurements and lack of quality of life measures. There is a need for follow-up studies to assess permanence of repigmentation as well as high-quality randomised trials using standardised measures which also address quality of life.


13. Meta-analysis: Interventions for photodamaged skin

**Background.** Photodamage describes skin changes such as fine and coarse wrinkles, roughness, freckles and pigmentation changes that occur as a result of prolonged exposure to the sun. Many treatments are available to reverse the damage, but it is unclear which work and at what cost in terms of unwanted side effects.

**Objectives.** To assess the effects of topically applied treatments, tablet treatments, laser and surgical procedures for photodamaged skin.

**Search methods.** We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, Issue 1 2002, MEDLINE (1966-June 2002), EMBASE (1974-June 2002), Health Periodicals (1976-June 2002). We also searched five trials databases, and checked the reference lists of included studies for further references to relevant randomised controlled trials (RCTs).

**Selection criteria.** Randomised controlled trials which compared drug or surgical interventions with no treatment, placebo or another drug, in adults with mild, moderate or severe photodamage of the face or forearms.

**Data collection and analysis.** Two reviewers independently extracted data and assessed trial quality.

**Main results** Thirty studies of variable quality were included. Eight trials showed that topical tretinoin cream, in concentrations of 0.02% or higher, was superior to placebo for participants with mild to severe photodamage on the face and forearms. For example, the relative risk of improvement for 0.05% tretinoin cream, compared to placebo (3 studies), at 24 weeks, was 1.73 (95% confidence interval 1.39 to 2.14). A dose-response relationship was evident for both effectiveness and skin irradiation. One small within-patient study showed
benefit from topical ascorbic acid compared with placebo. Tazarotene (0.01% to 0.1%) and isotretinoin (0.1%) both showed significant improvement over placebo for moderate photodamage (one study each). There is limited evidence (one trial), to show that the effectiveness of 0.05% tretinoin, is equivalent to the effects of 0.05% and 0.1% tazarotene. One small study showed greater improvement in upper lip wrinkles with CO2 laser technique compared to Baker's phenol chemical peel, at six months. Three small RCTs comparing CO2 laser with dermabrasion found no difference in wrinkle score at four to six months. The effectiveness of other interventions such as hydroxy acids and natural polysaccharides was not clear.

**Authors' conclusions.** There is conclusive evidence that topical tretinoin improves the appearance of mild to moderate photodamage on the face and forearms, in the short-term. However erythema, scaling/dryness, burning/stinging and irritation may be experienced initially. There is limited evidence that tazarotene and isotretinoin benefit patients with moderate photodamage on the face: both are associated with skin irritation and erythema. The effectiveness of other interventions remains uncertain.


14. Meta-analysis: Histamine H2-receptor antagonists for urticaria

**Background.** Urticaria is a common skin disease characterised by itching weals or hives, which can occur almost anywhere on the body. There are a number of different subtypes and a range of available treatment options. There is lack of agreement on the efficacy of H2-receptor antagonists used in the treatment of urticaria.

**Objectives.** To assess the safety and effectiveness of H2-receptor antagonists in the treatment of urticaria.

**Search methods.** We searched the following databases up to 7 October 2011: the Cochrane Skin Group Specialised Register, CENTRAL in The Cochrane Library (2011, Issue 4), MEDLINE (from 2005), EMBASE (from 2007), and LILACS (from 1982). We also searched online trials registries for ongoing trials.

**Selection criteria.** Randomised controlled trials of H2-receptor antagonists in people with a clinical diagnosis of urticaria of any duration or of any subtype. Studies including H1-antihistamines for chronic urticaria are the topic of a separate Cochrane review; thus, they were not included in this review.

**Data collection and analysis.** Two reviewers independently assessed trial quality and extracted and analysed data.

**Main results.** Four studies of a relatively small size, involving 144 participants, were included in this review. A combination of ranitidine with diphenhydramine was more effective at improving the resolution of urticaria than diphenhydramine administered alone (risk ratio (RR) 1.59, 95% confidence interval (CI) 1.07 to 2.36). Although there was a similar improvement in itching, weal size, and intensity, cimetidine provided no statistically significant greater overall improvement in symptoms of urticaria when compared to diphenhydramine. However, a combination of these medications was more effective than diphenhydramine alone (RR 2.02, 95% CI 1.03 to 3.94). Adverse events were reported with several of the interventions, i.e. ranitidine and diphenhydramine, causing drowsiness and sedation, but there was no significant difference in the level of sedation from baseline with either famotidine or diphenhydramine.

**Authors’ conclusions.** The very limited evidence provided by this review was based on a few old studies of a relatively small size, which we categorised as having high to unclear risk of bias. Thus, at present, the review does not allow confident decision-making about the use of H2-receptor antagonists for urticaria. Although some of these studies have reported a measure of relief of symptoms of urticaria and rather minimal clinical improvement in some of the participants, the evidence was weak and unreliable. We have emphasised the lack of precision and limitations in the reported data where appropriate in this review.


15. Meta-analysis: H1-antihistamines for chronic spontaneous urticaria

**BACKGROUND:** Chronic spontaneous urticaria is characterized by recurrent itchy wheals. First-line management is with H1-antihistamines.

**OBJECTIVE:** To conduct a Cochrane Review of H1-antihistamines in the treatment of chronic spontaneous urticaria.

**METHODS:** A systematic search of major databases for randomized controlled trials was conducted.

**RESULTS:** We included 73 studies with 9759 participants; 34 studies provided outcome data for 23 comparisons. Compared with placebo, cetirizine 10 mg daily in the short and intermediate term (RR 2.72; 95% confidence interval [CI] 1.51-4.91) led to complete suppression of urticaria. Levocetirizine 20 mg daily was effective for short-term use (RR 20.87; 95% CI 1.37-317.60) as was 5 mg for intermediate-term use (RR 52.88; 95% CI 3.31-843.81). Desloratadine 20 mg was effective for the short term (RR 15.97; 95% CI 1.04-245.04) as was 5 mg in the intermediate term (RR 37.00; 95% CI 2.31-593.70). There was no evidence to suggest difference in adverse event rates between treatments.

**LIMITATIONS:** Some methodological limitations were observed. Few studies for each comparison reported outcome data that could be incorporated in meta-analyses.

**CONCLUSIONS:** At standard doses, several antihistamines are effective and safe in complete suppression of chronic spontaneous urticaria. Research on long-term treatment using standardized outcome measures and quality of life scores is needed.


16. Oral doxycycline, tetracycline, isotretinoin, and topical metronidazole and ivermectin all options for acne rosacea
Clinical question: What are the most effective treatments for acne rosacea?

Study design: Meta-analysis (randomized controlled trials)

Setting: Various (meta-analysis)

Synopsis: This systematic review updated a previous review, identifying nearly twice as many patients. All told, this time the authors identified 106 randomized controlled trials with a total of 13,831 patients with acne rosacea, including those comparing 2 active treatments and those comparing an active treatment to placebo. Only 12 studies were judged to be at low risk of bias; the remainder were either at unclear (n = 57) or high (n = 37) risk of bias. Regarding older antibiotic therapies: (1) doxycycline and tetracycline are effective; (2) a doxycycline dose of 40 mg may be as effective as the 100 mg dose, but with fewer side effects; and (3) oral tetracycline is similar to topical metronidazole in terms of effectiveness for papulopustular rosacea. So what's new? The topical alpha adrenergic agonist brimonidine 0.33% gel reduces redness for up to 12 hours after use, and has been studied in 2 good-quality randomized controlled trials with 553 patients. There was good evidence of effectiveness compared with a vehicle control (relative risk [RR] 2.0 - 2.2 in the 2 trials) for patient-assessed improvement in redness. Topical ivermectin is another novel therapy that also showed evidence of patient-assessed improvement compared with placebo (RR 1.8 - 1.9 in the 2 included trials), and was shown in one study to be similarly effective to metronidazole. Finally, a study at low risk of bias compared isotretinoin 0.3 mg/kg with doxycycline 100 mg for papulopustular rosacea in 261 patients, and concluded that isotretinoin was more effective (number needed to treat = ~7) with no significant difference in adverse events.

Bottom line: In addition to the old standbys (doxycycline, tetracycline, and topical metronidazole), other drugs that may be effective for acne rosacea include isotretinoin and topical ivermectin. Topical brimonidine reduces redness temporarily.

17. Guidelines of care for the management of acne vulgaris

Acne is one of the most common disorders treated by dermatologists and other health care providers. While it most often affects adolescents, it is not uncommon in adults and can also be seen in children. This evidence-based guideline addresses important clinical questions that arise in its management. Issues from grading of acne to the topical and systemic management of the disease are reviewed. Suggestions on use are provided based on available evidence.


18. Two Phase 3 Trials of adalimumab for hidradenitis suppurativa

BACKGROUND: Hidradenitis suppurativa is a painful, chronic inflammatory skin disease with few options for effective treatment. In a phase 2 trial, adalimumab, an antibody against tumor necrosis factor α, showed efficacy against hidradenitis suppurativa.

METHODS: PIONEER I and II were similarly designed, phase 3 multicenter trials of adalimumab for hidradenitis suppurativa, with two double-blind, placebo-controlled periods. In period 1, patients were randomly assigned in a 1:1 ratio to 40 mg of adalimumab weekly or matching placebo for 12 weeks. In period 2, patients were reassigned to adalimumab at a weekly or every-other-week dose or to placebo for 24 weeks. The primary end point was a clinical response, defined as at least a 50% reduction from baseline in the abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula counts, at week 12.

RESULTS: We enrolled 307 patients in PIONEER I and 326 in PIONEER II. Clinical response rates at week 12 were significantly higher for the groups receiving adalimumab weekly than for the placebo groups: 41.8% versus 26.0% in PIONEER I (P=0.003) and 58.9% versus 27.6% in PIONEER II (P<0.001). Patients receiving adalimumab had significantly greater improvement than the placebo groups in rank-ordered secondary outcomes (lesions, pain, and the modified Sartorius score for disease severity) at week 12 in PIONEER II only. Serious adverse events in period 1 (excluding worsening of underlying disease) occurred in 1.3% of patients receiving adalimumab and 1.3% of those receiving placebo in PIONEER I and in 1.8% and 3.7% of patients, respectively, in PIONEER II. In period 2, the rates of serious adverse events were 4.6% or less in all the groups in both studies, with no significant between-group differences.

CONCLUSIONS: Treatment with adalimumab (40 mg weekly), as compared with placebo, resulted in significantly higher clinical response rates in both trials at 12 weeks; rates of serious adverse events were similar in the study groups. (Funded by AbbVie; ClinicalTrials.gov numbers, NCT01468207 and NCT01468233 for PIONEER I and PIONEER II, respectively.).


19. Natural course of cutaneous warts among primary schoolchildren: a prospective cohort study

PURPOSE: Because cutaneous warts resolve spontaneously and available treatments often fail, family physicians and patients may consider a wait-and-see policy. We examined the natural course of cutaneous warts and treatment decisions in a prospective observational cohort of primary schoolchildren.

METHODS: We inspected the hands and feet of children aged 4 to 12 years from 3 Dutch primary schools for the presence of warts at baseline and after a mean follow-up of 15 months. Parental questionnaires at follow-up provided information on inconvenience caused by warts and any treatments used.

RESULTS: Of the 1,134 eligible children, 1,099 (97%) participated, of whom 366 (33%) had cutaneous warts at baseline. Among these
children with warts, loss to follow-up was 9% and the response rate to the parental questionnaires was 83%. The complete resolution rate was 52 per 100 person-years at risk (95% CI, 44-60). Younger age (hazard ratio = 1.1 per year decrease; 95% CI, 1.0-1.2) and non-Caucasian skin type (hazard ratio = 2.0; 95% CI, 1.3-2.9) increased the likelihood of resolution. During follow-up, 38% of children with warts at baseline treated their warts: 18% used over-the-counter treatment only, 15% used a family physician-provided treatment only, and 5% used both. Children were more likely to initiate treatment if the warts measured at least 1 cm in diameter (odds ratio = 3.2; 95% CI, 1.9-5.3) and especially if parents reported that the warts caused inconvenience (odds ratio = 38; 95% CI, 16-90).

CONCLUSIONS: One-half of primary schoolchildren with warts will be free of warts within 1 year. Young age and non-Caucasian skin type enhance resolution. Children with large or inconvenient warts are more likely to start treatment. These findings will be useful in the process of shared decision making with parents and children.


Bottom Lines

1. There is insufficient evidence to support regular skin screening for detection and prevention of skin cancer.
2. Dermatologist are likely to discover more potentially treatable skin lesions on complete skin exam of referred patients. It is unclear if this leads to better outcomes, but it does lead to more scars.
3. Educational interventions can improve patients’ sun exposure protection behaviors.
4. Trimethoprin/sulfamethoxazole improves outcome slightly when used as an adjunct to incision and drainage for skin abscesses. However, I and D is not necessary in children.
5. Tavaborole (Kerydin) is not cost-effective for onychomycosis.
6. Several oral agents are about equally effective for tinea infections of the foot and scalp. The comparative data is not high quality.
7. H-1 antihistamines are effective for symptoms of chronic urticaria; H-2 antihistamines not so much.
8. Tretinoin and tazarotene are effective topical treatment for photo-damaged skin.
9. Oral doxycycline, tetracycline, isotretinoin, and topical metronidazole and ivermectin are all reasonable options for treating acne rosacea.
First, an overview of some key points regarding my take on the management of UGI problems after reading and writing POEMs on this topic for over 20 years:

1) There isn’t much difference between PPIs for GERD. Nothing has been shown to be better than 20 to 40 mg omeprazole.

2) Test for the presence of HP in patients with dyspepsia or ulcer symptoms, and eradicate it if present (“test and treat”)

3) Patients 50 and older, and anyone with a red flag symptoms, need endoscopy

4) If you suspect GERD, treat it. Scope patients with risk factors such as prolonged or severe symptoms, anemia, hematemesis, weight loss, anemia, or dysphagia.

5) The likelihood of progression to cancer in patients with Barrett’s is 0.12% per year. The risk is greatest in patients with dysplasia or long-segment involvement. There is no evidence that surveillance of these patients, particularly those at low risk, is helpful.

Diagnosis in primary care

How likelihood are various conditions in primary care practice?

1. Differential diagnosis of abdominal pain in primary care

Clinical question: What is the differential diagnosis of abdominal pain in the primary care setting?

Study design: Meta-analysis (other)

Setting: Outpatient (primary care)

Synopsis: The starting point for a diagnostic evaluation is the pretest probability of each item in the differential diagnosis: How common are the possible causes of a symptom? But this information is often not available, and has been poorly studied, especially in primary care. These authors do a nice job of reviewing the evidence regarding the differential diagnosis of abdominal pain. They first searched the literature for all studies of abdominal pain in the primary care setting that reported prevalence or incidence of different causes. Qualitative studies and studies of children only were excluded. Of 2540 studies initially identified, 14 met the inclusion criteria. These studies were published between 1982 and 2010, and 12 were from the United States, Europe, Australia, or New Zealand (that is, countries with well-developed primary care systems). The quality of studies was often poor, and most relied on the physician's final clinical diagnosis rather than a standard evaluation or reference standard test for the final diagnosis. The authors performed a meta-analysis, combining data from studies to come up with an overall estimate of the likelihood of each diagnosis. This was expressed as a "prediction interval"; there is a 95% probability that if one more study is done, the point estimate from that study will fall in the prediction interval. Typically, prediction intervals are broader and more conservative than confidence intervals. The prediction intervals for important diagnosis in the primary care setting include: appendicitis 1.5% - 2.4%, cancer 0.3% - 2.9%, ulcer 1.0% - 11.9%, gallbladder or pancreas disease 2.4% - 6.6%, inflammatory bowel disease 0.2% - 1.5%, gastroenteritis 7.2% - 18.7%, irritable bowel syndrome 2.6% - 13.2%, urologic cause 4.1% - 6.9%, and constipation 3.1% - 6.2%. Some conditions such as "no diagnosis" and dyspepsia or reflux had very broad prediction intervals, indicating large variability between studies.

Bottom line: This study provides a starting point for primary care physicians who are evaluating a patient with abdominal pain. Overall, approximately 10% of patients had a serious, potentially surgical diagnosis. The most common diagnoses were gastroenteritis, irritable bowel syndrome, gastritis, or a urologic cause for the pain. The evidence these researchers found has important limitations; much more (and better) research is needed in this area.


Just what are those red flags? Here is some new evidence in the next two abstracts.
2. Six clinical variables in patients with dysphagia identify decreased esophageal cancer risk

**Clinical question:** Can clinical variables be used to identify patients with dysphagia who are at low risk of esophageal cancer?

**Study design:** Decision rule (validation)

**Setting:** Outpatient (specialty)

**Synopsis:** These authors used a standardized clinical assessment form to systematically evaluate all patients referred to their dysphagia center. They compared these variables with endoscopic findings to identify clinical factors that were correlated with a finding of esophageal cancer. To develop a prediction model, they used data from 394 patients referred between August 2005 and August 2006. This prediction model, the Edinburgh Dysphagia Score (EDS), was then independently validated on a cohort of 180 patients referred to their center between January 2007 and July 2007. Six factors make up the EDS: age*, weight loss exceeding 3 kg (2 points), sex (male = 0 points, female = -1 point); location of dysphagia sensation in neck (-2 points); presence of reflux (-1 point); symptom duration at least 6 months (-1.5 points). Based on the development cohort, a total score of 3.5 or more identifies the patient as high risk of esophageal cancer (overall accuracy = 83%). In the validation cohort, 26 patients had cancer and the score identified all of them, but also predicted cancer in 100 patients who didn't have it (overall accuracy = 71%). In the validation cohort, the EDS was 100% sensitive and 35% specific (positive likelihood ratio = 1.5; negative likelihood ratio = 0.05). The primary goal of the EDS is to identify patients at low risk of cancer so that invasive diagnostic testing could be deferred. Based on the likelihood ratios, having a score less than 3.5 is very reassuring. However, since having a likelihood ratio near 1 provides no useful information, having a score above 3.5 tells us nothing about the patient's cancer risk. Finally, since the diagnostic accuracy in the validation cohort was much lower than in the development cohort, it is unclear how well this score will perform in primary care settings. *Patients 39 years and younger receive 0 points. For those aged 40 to 49 years, 4 points are assigned, and then 1 additional point is assigned for each additional decade of life.

**Bottom line:** Six clinical factors combined into a single score can identify patients referred to a dysphagia center who are at low risk of having esophageal cancer: age, weight loss, sex, dysphagia location, and reflux. It is not clear how well this score will perform in primary care settings.


3. Alarm symptoms for dyspepsia increase risk of CA

**Clinical question:** What is the predictive value of "alarm" symptoms in patients with dyspepsia?

**Study design:** Cohort (prospective)

**Setting:** Outpatient (primary care)

**Synopsis:** Most guidelines for the management of dyspepsia emphasize that patients with "alarm" symptoms (anemia, black stools, bloody stools, dysphagia, jaundice, or weight loss) should undergo endoscopic evaluation. But what is the predictive value of these symptoms in primary care? In this study, 93 general practitioners in Denmark systematically collected data for 3 years on over 7000 patients presenting with dyspepsia. At the end of the study period, they returned a survey that reported what had happened to these patients. This is a limitation of the study -- it is certainly possible that patients were treated empirically for an ulcer and never had it formally diagnosed endoscopically, since not all patients underwent endoscopy. The data for cancer as a diagnosis are probably more reliable. They used a random sample of 988 patients from different diagnostic groups with and without alarm symptoms to determine the predictive value of alarm symptoms. Overall, 11% (n=105) of this group had one or more alarm symptoms; the most common were weight loss (46), dysphagia (35), black stools (24) and blood in stools (14). The positive predictive value of any alarm symptom for cancer was 3% and for ulcer was 10%; negative predictive values were 99% and 97%, respectively. The risk of cancer during the follow-up period was increased in those with dyspepsia and alarm symptoms as compared with the general population (OR 6.3, 95% CI 3.6-11.0).

**Bottom line:** Alarm symptoms for dyspepsia such as anemia, evidence of gastrointestinal bleeding, jaundice, weight loss, and dysphagia, are associated with an increased risk of cancer. This supports current recommendations for more aggressive evaluation of these patients.


From Essential Evidence, here is the accuracy of some signs and symptoms for common conditions:

<table>
<thead>
<tr>
<th>Symptom → diagnosis</th>
<th>Sign or symptom</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abd pain → acute cholecystitis</td>
<td>Murphy’s sign</td>
<td>5.0</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>2.6</td>
<td>0.9</td>
</tr>
<tr>
<td>RUQ pain</td>
<td>2.5</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Palpable GB</td>
<td>2.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia → peptic ulcer</td>
<td>Food reduces pain</td>
<td>3.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Symptom</td>
<td>Score</td>
<td>Probability</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>-------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>Night waking + food relief</td>
<td>2.8</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Episodic pain</td>
<td>2.3</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>GERD suspected → GERD</td>
<td>Relief with high dose PPI for 1-2 weeks</td>
<td>1.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Heartburn</td>
<td>1.4</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Overall physician impression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GERD</td>
<td>3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncertain</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abd pain → choledolithias</td>
<td>Biliary colic</td>
<td>3.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Radiating pain</td>
<td>1.6</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Use of analgesics</td>
<td>1.6</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Fat intolerance</td>
<td>1.3</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Overall physician impression</td>
<td>8.3</td>
<td>0.7</td>
<td></td>
</tr>
</tbody>
</table>

### Esophageal problems

A large Danish registry study found 193 incident cancers during an average of 6 years of surveillance in 11,028 patients with BE, of which 2/3 (131) were found in the first year. These were probably missed on the original scope. After that, the overall rate of progression was 0.12% per year (N Engl J Med 2011; 365(15): 1375-83). Progression was more likely in patients with low grade dysplasia on the initial scope, but was still low (0.5% per year).

Here are the recommendations from Cancer Control Alberta’s guidelines, which seem reasonable (Alberta Provincial Gastrointestinal Tumour Team. Management of patients with early esophageal cancer, dysplastic and non-dysplastic Barrett’s esophagus. Edmonton (Alberta): CancerControl Alberta; 2014 Mar. 19 p. (Clinical practice guideline; no. GI-011):

- For patients with no dysplasia and a Barrett's esophagus segment ≤3 cm, endoscopic surveillance is recommended every 5 years; for patients with no dysplasia and a Barrett's esophagus segment >3 cm, endoscopic surveillance is recommended every 3 years, with 4-quadrant biopsies every 2 cm.
- Patients with biopsies that are indefinite for dysplasia should have a repeat endoscopy every 3 to 6 months, with 4-quadrant biopsies every 1 cm.
- For patients with low-grade dysplasia, endoscopic surveillance is recommended every 6 to 12 months, with the goal of detecting potential progression to high-grade dysplasia or esophageal adenocarcinoma early.
- Patients with high-grade dysplasia, early esophageal cancer, or invasive cancer should be referred to a tertiary centre for further evaluation.

Other guidelines recommend that radiofrequency ablation be considered for patients with low grade dysplasia (see below).

### 4. Evidence-based Delphi process for Barrett's esophagus management
Clinical question: What is the best approach to the detection and management of Barrett's esophagus?

Study design: Practice guideline

Synopsis: This guideline—funded by a consortium of gastroenterology societies, as well as the National Institutes of Health—was created using an "evidence-based Delphi process" with the following steps: (1) identify the experts, (2) identify the questions, (3) systematically review the literature, (4) draft statements, and (5) do 3 rounds of anonymous voting and feedback, plus 3 additional rounds of voting after peer review. At the end of the voting rounds, 15 statements had at least 80% agreement by the participants. The participants agreed on a common definition of BE (US and European researchers had previously used different definitions): BE is now defined by the presence of columnar mucosa in the esophagus, and it should be stated whether intestinal metaplasia is present above the gastroesophageal junction. The guideline recommends against population screening, but suggests the screening of high-risk individuals (men older than 60 years who have had gastroesophageal reflux disease for at least 10 years). This was a conditional recommendation based on very-low-quality evidence. Risk factors other than age and male sex include central obesity, smoking, and greater length of BE. The quality of evidence is very low for surveillance, and the risk of malignant transformation is only 0.12% per year, so no definitive recommendations can be made regarding surveillance. The authors note that the diagnosis of dysplasia is challenging; many patients initially thought to have dysplasia do not have that diagnosis confirmed when the specimen is reviewed by a specialist pathologist. Patients with dysplasia and high-risk features or with visible lesions may wish to consider ablation or endoscopic resection.

Bottom line: Experts agree: We don't know much about screening, surveillance, or treatment of Barrett's esophagus (BE). Much more research is needed, but for now primary care physicians should not refer patients for screening unless they are considered high risk (men older than 60 years with prolonged or severe gastroesophageal reflux disease).


5. Radiofrequency ablation reduces risk of neoplastic progression with BE and low-grade dysplasia

Clinical question: Is radiofrequency ablation superior to endoscopic surveillance in reducing morbidity or mortality in adults with Barrett esophagus and low-grade dysplasia?

Study design: Randomized controlled trial (single-blinded)

Setting: Outpatient (specially)

Synopsis: The optimal management of Barrett esophagus with low-grade dysplasia is uncertain. These investigators identified 136 eligible patients (mean age = 63 years) who had previously undergone upper endoscopy and biopsy within the previous 18 months that confirmed low-grade dysplasia. Eligible patients randomly received (by concealed allocation) either endoscopic radiofrequency ablation or surveillance only. The ablation group received sessions every 3 months until complete endoscopic and histological eradication of Barrett esophagus or a maximum of 2 circumferential and 3 focal sessions. Subsequent endoscopy and 4-quadrant surveillance biopsies occurred annually for a total of 3 years. Patients in the surveillance-only group received endoscopy and 4-quadrant biopsies at 6 months and 12 months initially, and then annually for a total of 3 years. Individuals masked to group assignment assessed histologic and clinical outcomes. Complete follow-up occurred for all patients at 3 years. Using intention-to-treat analysis, patients in the ablation group were significantly less likely to progress to high-grade dysplasia or adenocarcinoma, but also significantly more likely to develop esophageal stricture requiring dilation than patients in the control group (11.8% vs 0.0%). The trial was terminated by the monitoring committee before any additional patient-oriented outcomes were evaluated. The progression to high-grade dysplasia/adenocarcinoma was noted to be directly related to the presence of circumferential Barrett esophagus, age, time since diagnosis of Barrett esophagus, and dysplasia noted on multiple endoscopies. No predictors of spontaneous resolution of the low-grade dysplasia in the control group could be discerned to help guide the choice of ablation therapy over surveillance in patients.

Bottom line: Unfortunately, this study was terminated before the important clinical questions about mortality and morbidity could be answered. Radiofrequency ablation reduced the risk of neoplastic progression in adults with Barrett esophagus and low-grade dysplasia (compared with endoscopic surveillance). But it also caused significantly more adverse events, including the need for dilation for esophageal stricture in nearly 12% of patients. I understand the concerns of monitoring committees, but we truly need overall patient-oriented evidence to most accurately guide our clinical decisions. If a monitoring committee had stopped the clinical trial of intravenous lidocaine in the setting of acute myocardial infarction because of a concern for life-threatening cardiac arrhythmias in the placebo group, we would never know that lidocaine actually increased mortality by 10%. The optimal management of Barrett esophagus with low-grade dysplasia will remain uncertain.


Achalasia is an esophageal motility disorder characterized by failure of smooth muscle to relax, and failure of the lower esophageal sphincter to open. The next 2 abstracts update us on treatment:

6. Optimal treatment for achalasia

Clinical question: What is the optimal management of adults with achalasia?

Study design: Systematic review
**Objectives:** To assess the benefits and harms of laparoscopic fundoplication versus medical treatment for people with gastro-oesophageal reflux disease (GORD) in adults.

**Background:** Gastro-oesophageal reflux disease (GORD) is a common condition with 3% to 33% of people from different parts of the world suffering from GORD. There is considerable uncertainty about whether people with GORD should receive an operation or medical treatment for controlling the condition.

**Objectives:** Medical treatment for controlling the condition. There is considerable uncertainty about whether people with GORD should receive an operation or medical management.

**Setting:** Various (meta-analysis)

**Synopsis:** Patients with achalasia usually present with complaints of pain and difficulty swallowing secondary to esophageal dysmotility. These investigators thoroughly searched multiple databases including MEDLINE, EMBASE, the Cochrane Register of Controlled Trials, and the Science Citation Index, as well as abstracts from relevant national meetings, and retrieved article reference lists for English language-only randomized trials evaluating treatments for achalasia. Two individuals independently reviewed potential articles for inclusion and methodologic quality using standard criteria. Any differences were resolved by consensus. A total of 17 studies (N = 761) met inclusion criteria, including the evaluation of botulinum toxin injection, pneumatic dilation, laparoscopic and thoracic myotomy, and pharmacologic treatment with nifedipine. The various clinical trials were of moderate to high methodologic quality. The remission and relapse rates for pneumatic dilation was significantly superior to botulinum toxin injection. Laparoscopic and thoracic myotomy were general similar in efficacy but statistically more efficacious than both botulinum toxin injection and pneumatic dilation. Excellent or good results occurred for more than 75% of patients treated with sublingual nifedipine. Complications for botulinum toxin injection included dysphagia and chest pain. The risks of pneumatic dilation and myotomy included dysphagia, heartburn, and esophageal perforation.

**Bottom line:** Sublingual nifedipine results in excellent or good clinical results in approximately 75% of adults with mild to moderate achalasia. For those patients not responding to pharmacotherapy, laparoscopic or thoracic myotomy is more effective than either botulinum toxin injection or pneumatic dilation.


**7. Cochrane: Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia**

**Background:** Achalasia is an oesophageal motility disorder, of unknown cause, which results in increased lower oesophageal sphincter (LOS) tone and symptoms of difficulty swallowing. Treatments are aimed at reducing the LOS tone. Current endoscopic therapeutic options include pneumatic dilation (PD) or botulinum toxin (BTX) injection.

**Objectives:** To undertake a systematic review comparing the efficacy and safety of two endoscopic treatments, PD and intraspincteric BTX injection, in the treatment of oesophageal achalasia.

**Search methods:** Trials were initially identified by searching MEDLINE (1966 to August 2008), EMBASE (1980 to September 2008), ISI Web of Science (1955 to September 2008), The Cochrane Library Issue 3, 2008. Searches in all databases were conducted in October 2005 and updated in September 2008 and April 2014. The Cochrane highly sensitive search strategy for identifying randomised trials in MEDLINE, sensitivity maximising version in the Ovid format, was combined with specific search terms to identify randomised controlled trials in MEDLINE. The MEDLINE search strategy was adapted for use in the other databases that were searched.

**Selection criteria:** Randomised controlled trials comparing PD to BTX injection in individuals with primary achalasia.

**Data collection and analysis:** Two review authors independently performed study quality assessment and data extraction.

**Main results:** Seven studies involving 178 participants were included. Two studies were excluded from the meta-analysis of remission rates on the basis of clinical heterogeneity of the initial endoscopic protocols. There was no significant difference between PD or BTX treatment in remission within four weeks of the initial intervention; with a risk ratio of remission of 1.11 (95% CI 0.97 to 1.27). There was also no significant difference in the mean oesophageal pressures between the treatment groups; with a weighted mean difference for PD of -0.77 (95% CI -2.44 to 0.91, P = 0.37). Data on remission rates following the initial endoscopic treatment were available for three studies at six months and four studies at 12 months. At six months 46 of 57 PD participants were in remission compared to 29 of 56 in the BTX group, giving a risk ratio of 1.57 (95% CI 1.19 to 2.08, P = 0.0015); whilst at 12 months 55 of 75 PD participants were in remission compared to 27 of 72 BTX participants, with a risk ratio of 1.88 (95% CI 1.35 to 2.61, P = 0.0002). No serious adverse outcomes occurred in participants receiving BTX, whilst PD was complicated by perforation in three cases.

**Authors’ conclusions:** The results of this meta-analysis suggest that PD is the more effective endoscopic treatment in the long term (greater than six months) for patients with achalasia.


This recently updated Cochrane review looks at 4 RCTs with 1160 patients randomized to lap fundoplication vs medical management.

**8. Cochrane: Laparoscopic fundoplication surgery versus medical management for gastro-oesophageal reflux disease (GORD) in adults**

**Background:** Gastro-oesophageal reflux disease (GORD) is a common condition with 3% to 33% of people from different parts of the world suffering from GORD. There is considerable uncertainty about whether people with GORD should receive an operation or medical treatment for controlling the condition.

**Objectives:** To assess the benefits and harms of laparoscopic fundoplication versus medical treatment for people with gastro-oesophageal reflux disease.
Data collection and analysis:

Main results:

A total of 1160 participants in the four RCTs were either randomly assigned to laparoscopic fundoplication (589 participants) or medical treatment in people with GORD irrespective of language, blinding, or publication status for inclusion in the review.

Selection criteria:

We considered only randomised controlled trials (RCT) comparing laparoscopic fundoplication with medical treatment in people with GORD irrespective of language, blinding, or publication status for inclusion in the review. Data collection and analysis: Two review authors independently identified trials and independently extracted data. We calculated the risk ratio (RR) or standardised mean difference (SMD) with 95% confidence intervals (CI) using both fixed-effect and random-effects models with RevMan 5 based on available case analysis.

Main results:

Four studies met the inclusion criteria for the review, and provided information on one or more outcomes for the review. A total of 1160 participants in the four RCTs were either randomly assigned to laparoscopic fundoplication (589 participants) or medical treatment with proton pump inhibitors (571 participants). All the trials included participants who had had reflux symptoms for at least six months and had received long-term acid suppressive therapy. All the trials included only participants who could undergo surgery if randomised to the surgery arm. All of the trials were at high risk of bias. The overall quality of evidence was low or very low. None of the trials reported long-term health-related quality of life (HRQoL) or GORD-specific quality of life (QoL).

The difference between laparoscopic fundoplication and medical treatment was imprecise for overall short-term HRQOL (SMD 0.14, 95% CI -0.02 to 0.30; participants = 605; studies = 3), medium-term HRQOL (SMD 0.03, 95% CI -0.19 to 0.24; participants = 323; studies = 2), medium-term GORD-specific QoL (SMD 0.28, 95% CI -0.27 to 0.84; participants = 994; studies = 3), proportion of people with adverse events (surgery: 7/43 (adjusted proportion = 14.0%); medical: 0/40 (0.0%); RR 13.98, 95% CI 0.82 to 237.07; participants = 83; studies = 1), long-term dysphagia (surgery: 27/118 (adjusted proportion = 22.9%); medical: 28/110 (25.5%); RR 0.90, 95% CI 0.57 to 1.42; participants = 228; studies = 1), and long-term reflux symptoms (surgery: 29/118 (adjusted proportion = 24.6%); medical: 41/115 (35.7%); RR 0.69, 95% CI 0.46 to 1.03; participants = 233; studies = 1).

The short-term GORD-specific QoL was better in the laparoscopic fundoplication group than in the medical treatment group (SMD 0.58, 95% CI 0.46 to 0.70; participants = 1160; studies = 4).

The proportion of people with serious adverse events (surgery: 60/331 (adjusted proportion = 18.1%); medical: 38/306 (12.4%); RR 1.46, 95% CI 1.01 to 2.11; participants = 637; studies = 2), short-term dysphagia (surgery: 44/331 (adjusted proportion = 12.9%); medical: 11/306 (3.6%); RR 3.58, 95% CI 1.91 to 6.71; participants = 637; studies = 2), and medium-term dysphagia (surgery: 29/288 (adjusted proportion = 10.2%); medical: 5/266 (1.9%); RR 5.36, 95% CI 2.1 to 13.64; participants = 554; studies = 1) was in the laparoscopic fundoplication group than in the medical treatment group.

The proportion of people with heartburn at short term (surgery: 29/288 (adjusted proportion = 10.0%); medical: 59/266 (22.2%); RR 0.45, 95% CI 0.30 to 0.69; participants = 554; studies = 1), medium term (surgery: 12/288 (adjusted proportion = 4.2%); medical: 59/266 (22.2%); RR 0.19, 95% CI 0.10 to 0.34; participants = 554; studies = 1), long term (surgery: 46/111 (adjusted proportion = 41.2%); medical: 78/106 (73.6%); RR 0.56, 95% CI 0.44 to 0.72; participants = 217; studies = 1) and those with reflux symptoms at short-term (surgery: 6/288 (adjusted proportion = 2.0%); medical: 53/266 (19.9%); RR 0.10, 95% CI 0.05 to 0.24; participants = 554; studies = 1) was in the laparoscopic fundoplication group than in the medical treatment group.

Authors’ conclusions:

There is considerable uncertainty in the balance of benefits versus harms of laparoscopic fundoplication compared to long-term medical treatment with proton pump inhibitors. Further RCTs of laparoscopic fundoplication versus medical management in patients with GORD should be conducted with outcome-assessor blinding and should include all participants in the analysis. Such trials should include long-term patient-orientated outcomes such as treatment-related adverse events (including severity), quality of life, and also report on the social and economic impact of the adverse events and symptoms.


What about treatment of heartburn in pregnancy? A Cochrane review found 3 studies with a total of 286 women looking at IM prostigmine, an antacid, and an antacid + ranitidine. All three worked, but all were compared against placebo. (Neilson JP. Interventions for heartburn in pregnancy. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD007065)

Helicobacter pylori

Maybe eradicating HP does more than treat ulcers. The most accurate test is the urea breath test, although stool antigen tests are also very accurate. Avoid office-based blood tests or serum tests for HP antigen, they are less accurate and cannot be used as a test of cure.

9. Some new regimens slightly more effective for H. pylori eradication.

Clinical question: What is the best treatment regimen for eradication of Helicobacter pylori?

Study design: Meta-analysis (randomized controlled trials)

Setting: Various (meta-analysis)
Synopsis: To perform this systematic review, the authors searched 3 databases, including the Cochrane Library, to find randomized controlled trials published in any language. Although H. pylori was only discovered in 1982, the authors identified a whopping 15,565 studies evaluating treatments to eradicate it. From these, the authors identified 143 studies comparing 14 kinds of treatment versus standard triple treatment [PPI plus clarithromycin plus metronidazole or amoxicillin]. Three researchers independently selected articles for inclusion and 2 authors independently extracted the data and assessed the study quality. The studies, as is usually the case, were of varying quality, though more than half of them were not double-blinded. Also, they were conducted in countries around the world where antibiotic resistance rates may differ from your local patterns. Trying to make sense of these data gets a little tricky so the authors did the analysis 2 ways: they performed meta-analyses, where possible, comparing one treatment regimen to another, and they used a Bayesian network analysis to rank the relative benefit of one regimen against another even when they weren't directly compared. All regimens are effective, though 3 had higher rates of eradication: 7 to 14 days of PPI plus amoxicillin plus clarithromycin plus metronidazole/tinadazole (90%-94% eradication), 10 to 14 days of standard triple therapy plus probiotics (90%), and 10 to 14 days of PPI plus levofloxacin plus another antibiotic (90%). All treatments were tolerated.

Bottom line: All treatment regimens to eradicate Helicobacter pylori are fairly effective. The 3 regimens that are at least 90% effective are: (1) 7 to 14 days of a proton pump inhibitor (PPI) plus amoxicillin plus clarithromycin plus metronidazole/tinadazole (90%-94% eradication), (2) 10 to 14 days of standard triple therapy plus probiotics (90%), and (3) 10 to 14 days of PPI plus levofloxacin plus another antibiotic (90%).


10. Eradicating HP may reduce GERD symptoms

Clinical question: Does the eradication of Helicobacter pylori improve symptoms of gastroesophageal disease?

Study design: Meta-analysis (randomized controlled trials)

Setting: Various (meta-analysis)

Synopsis: We know that eradicating HP is good for peptic ulcer disease, but it is less clear whether it is beneficial for patients with nonulcer dyspepsia or GERD. In fact, the decreasing rates of HP infection and simultaneously increasing rates of GERD have caused some experts to suspect that eradicating HP may actually worsen GERD. These authors did a careful search and identified 10 randomized controlled trials that compared HP eradication therapy with no eradication in patients with GERD but without functional dyspepsia. Only 5 studies confirmed eradication. The authors do not give details about other interventions used in those studies; we must assume that there were no other differences between groups. Similarly, we are not given the outcome scales or measures used to evaluate symptom improvement. The 10 studies included 2943 patients, with eradication of HP confirmed in 2132 patients. The investigators found no significant symptomatic benefit of eradication in the entire group of 2943 patients (odds ratio [OR] = 0.81; 95% CI, 0.56 - 1.27). However, when only considering the per-protocol group with confirmed eradication of HP, there was a significant symptomatic benefit (13.8% vs 24.9%; OR = 0.55; P < .01). There was no difference in the likelihood of reflux esophagitis after treatment. The authors found no evidence of publication bias (that is, failure to publish negative trials). Although the authors explain how they evaluated the quality of included studies using the Jadad score, they don't bother to report those findings in the article. There was quite a bit of heterogeneity between studies, as well.

Bottom line: This somewhat poorly reported meta-analysis supports the notion that eradication of Helicobacter pylori (HP) may improve symptoms of gastroesophageal disease (GERD), with a number needed to treat of approximately 9. However, we are not given a lot of detail about the magnitude of symptomatic benefit, and the benefit was only seen in the per-protocol analysis, not in the intention-to-treat analysis.


11. H. pylori eradication decreases functional dyspepsia symptoms (HEROES)

Clinical question: Is Helicobacter pylori eradication in H. pylori-positive patients more effective than placebo to decrease symptoms of functional dyspepsia?

Study design: Randomized controlled trial (double-blinded)

Setting: Outpatient (any)

Synopsis: The Brazilian investigators conducting this study recruited patients from primary care clinics as well via media advertisements. This is the first major study that enrolled patients from primary care practices rather than specialty clinics. The 404 patients in this study (79% women) were positive for H. pylori and were had functional dyspepsia, defined as postprandial fullness, early satiety, and epigastric pain or burning for at least 6 months without evidence of structural disease established via endoscopy before enrollment. The authors excluded patients with heartburn or symptoms of other illnesses and those who had previous treatment for H. pylori or recent acid suppression therapy. The patients were randomized, using concealed allocation, to receive omeprazole combined either with placebo or with H. pylori eradication therapy consisting of amoxicillin and clarithromycin for 10 days. The primary outcome was a 50% decrease in symptoms at 12 months, which was reported by 49.0% of treated patients as compared with 36.5% of placebo-treated patients (P = .01). This difference translates into a number needed to treat of 8 (95% CI, 4.6 - 38.8). Using a global assessment, 78.1% of treated patients reported being symptomatically better as compared with 67.5% of untreated patients (P = .02).

Bottom line: It might make sense to test more patients with functional dyspepsia for H. pylori and give antibiotic therapy to those patients with positive results. These authors enrolled primary care patients with functional dyspepsia symptoms who were positive for H. pylori (as is
half the adult population), and they found better symptom improvement with eradication therapy than with placebo, though the benefit is not nearly as significant as with peptic ulcer disease. For every 8 patients treated with eradication therapy instead of placebo, one additional patient will have a 50% improvement in symptoms 1 year later. However, the range of this estimate is quite large (4.6 - 38.8). Mazzoleni LE, Sander GB, Francesconi CF, et al. Helicobacter pylori eradication in functional dyspepsia. HEROES trial. Arch Intern Med 2011;171(21):1929-1936

12. Cochrane: Eradication of Helicobacter pylori for non-ulcer dyspepsia

**BACKGROUND:** Helicobacter pylori (H pylori) is the main cause of peptic ulcer disease. The role of H pylori in non-ulcer dyspepsia is less clear.

**OBJECTIVES:** To determine the effect of H pylori eradication on dyspepsia symptoms in patients with non-ulcer dyspepsia.

**SEARCH STRATEGY:** Trials were identified through electronic searches of the Cochrane Controlled Trials Register (CCTR), MEDLINE, EMBASE, CINAHL and SIGLE, using appropriate subject headings and keywords, searching bibliographies of retrieved articles, and through contacts with experts in the fields of dyspepsia and with pharmaceutical companies.

**SELECTION CRITERIA:** All parallel group randomised controlled trials (RCTs) comparing drugs to eradicate H pylori with placebo or other drugs known not to eradicate H pylori for patients with non-ulcer dyspepsia.

**DATA COLLECTION AND ANALYSIS:** Data were collected on individual and global dyspeptic symptom scores, quality of life measures and adverse effects. Dyspepsia outcomes were dichotomised into minimal/resolved versus same/worse symptoms.

**MAIN RESULTS:** Twenty one randomised controlled trials were included in the systematic review. Eighteen trials compared antisecretory dual or triple therapy with placebo antibiotics +/- antisecretory therapy, and evaluated dyspepsia at 3-12 months. Seventeen of these trials gave results as dichotomous outcomes evaluating 3566 patients and there was no significant heterogeneity between the studies. There was a 10% relative risk reduction in the H pylori eradication group (95% CI = 6% to 14%) compared to placebo. The number needed to treat to cure one case of dyspepsia = 14 (95% CI = 10 to 25). A further three trials compared Bismuth based H pylori eradication with an alternative pharmacological agent. These trials were smaller and had a shorter follow-up but suggested H pylori eradication was more effective than either H2 receptor antagonists or sucralfate in treating non-ulcer dyspepsia.

**AUTHORS’ CONCLUSIONS:** H pylori eradication therapy has a small but statistically significant effect in H pylori positive non-ulcer dyspepsia. An economic model suggests this modest benefit may still be cost-effective but more research is needed.


**Duodenal and gastric ulcers**

The next two abstracts look at how to treat patients with bleeding peptic ulcers.

13. Intermittent PPI = continuous-infusion PPI for high-risk bleeding ulcers

**Clinical question:** Is intermittent proton pump inhibitor (PPI) therapy comparable with continuous-infusion PPI for the treatment of patients with high-risk bleeding ulcers who have undergone endoscopic therapy?

**Study design:** Meta-analysis (randomized controlled trials)

**Setting:** Inpatient (ward only)

**Synopsis:** Current guidelines recommend that patients with bleeding ulcers and endoscopic evidence of active bleeding, nonbleeding visible vessels, and adherent clots should receive an intravenous bolus dose of PPI followed by a continuous PPI infusion for 72 hours to prevent rebleeding. In this study, investigators searched multiple databases including MEDLINE, EMBASE, and the Cochrane Register to find randomized clinical trials that evaluated this continuous PPI regimen versus the use of intermittent PPIs for the treatment of these high-risk bleeding ulcers. The intermittent PPI regimens differed in both dosage and administration, from pantoprazole 40 mg given orally every 12 hours to pantoprazole 80 mg given intravenously once, followed by 40 mg intravenously every 6 hours. Two authors independently performed the search, selected studies for inclusion, extracted data, and assessed the risk of bias for included studies. Ten of the 13 selected studies reported on the primary outcome of recurrent bleeding within 7 days and found that intermittent PPI use was noninferior to continuous-infusion PPI therapy, with the noninferiority margin predefined as an absolute risk difference of 3%. Noninferiority criteria were also met for the secondary outcomes, including rebleeding at 3 days or 30 days, mortality, need for surgical intervention, need for transfusion, and hospital length of stay. No publication or reporting biases were detected.

**Bottom line:** For patients with high-risk bleeding ulcers who have been treated endoscopically, treatment with intermittent proton pump inhibitor (PPI) therapy is as effective as continuous infusion of PPIs for the prevention of rebleeding. This systematic review, however, was not able to determine the most optimal intermittent PPI regimen for this purpose because the included studies included used various dosing schedules and administration routes.


14. Restrictive transfusion strategy improves outcomes in acute upper GI bleeding

**Clinical question:** In patients with acute upper gastrointestinal bleeding, does a restrictive transfusion strategy improve mortality?
**Study design:** Randomized controlled trial (nonblinded)

**Setting:** Inpatient (any location)

**Synopsis:** Using concealed allocation, these investigators randomized patients with acute upper gastrointestinal bleeding to either a restrictive (n = 461) or liberal (n = 460) transfusion strategy. Patients with exsanguinating bleeding or those at low risk of rebleeding were excluded. Randomization was stratified by the presence or absence of cirrhosis. In the restrictive strategy group, patients were transfused throughout the hospitalization at a hemoglobin level of less than 7g/dL, with a posttransfusion hemoglobin goal of 9g/dL to 10g/dL. In the liberal strategy group, the transfusion threshold was 9g/dL, with a posttransfusion goal of 9g/dL to 11g/dL. Transfusions were also administered to patients who were symptomatic from anemia. All patients underwent endoscopy with intervention as needed in the first 6 hours of presentation. Baseline characteristics were similar in the 2 groups: The mean admission hemoglobin level was 9.6g/dL and approximately 50% of patients in both groups were bleeding because of peptic ulcer disease. Analysis was by intention to treat. Overall, 85% of the patients in the liberal strategy group received transfusions as compared with only 49% of the patients in the restrictive strategy group. The primary outcome of all-cause mortality at 45 days was lower in the restrictive group (5% vs 9%; P = .02). After adjusting for baseline risk factors of mortality, the risk of death remained lower in the restrictive group (hazard ratio = 0.55; 95% CI, 0.33-0.92). In addition, patients in the restrictive group had a decreased rate of further bleeding (10% vs 16%; P = .01) and a shorter hospital stay (9.6 days vs 11.5 days; P = .01). In the subgroup of cirrhotic patients with bleeding esophageal varices, the restrictive strategy resulted in decreased need for rescue therapies, such as balloon tamponade or transjugular intrahepatic portosystemic shunt. Finally, adverse events such as transfusion reactions and cardiac complications were less likely to occur in the restrictive group (40% vs 48%; P = .02). The authors postulate that increased bleeding events in patients who receive more transfusions may be related to transfusion-related impairment of hemostasis.

**Bottom line:** A restrictive transfusion strategy using a hemoglobin transfusion threshold of less than 7g/dL results in decreased mortality, shorter hospital stays, and fewer adverse events in patients with acute upper gastrointestinal bleeding.


## Gallbladder disease

**Clinical question:** Are nonsteroidal antiinflammatory drugs as effective as opioids to treat pain and decrease complications in patients with biliary colic?

**Study design:** Meta-analysis (randomized controlled trials)

**Setting:** Inpatient (any location)

**Synopsis:** These Italian authors searched several databases, including the Cochrane Register, and identified 11 randomized controlled trials comparing NSAIDs with no treatment, placebo, or other drugs in patients with biliary colic. All the authors independently selected articles for inclusion; 2 authors extracted the data and determined methodologic quality. They included studies with or without masking, published or not, in any language. There was no evidence of publication bias. NSAIDs administered in the emergency department (injectable diclofenac was the most commonly studied) resulted in significantly more patients being pain-free within 2 hours than did placebo (relative risk [RR] = 3.77; 95% CI, 1.65 - 8.61) and also decreased the risk of cholecystitis by approximately half, again as compared with placebo (RR = 0.52; 31 - 89). Ketorolac (Toradol) and flurbiprofen (Ansaid) given intramuscularly were as effective as meperidine at various doses. The quality of the included studies was fair and there was significant heterogeneity among the studies, but it makes sense to start with an injectable NSAID, following up with opioid treatment if pain is not quelled.

**Bottom line:** Injectable nonsteroidal antiinflammatory drugs (NSAIDs), primarily diclofenac (Voltaren) in these studies, decreased cholecystitis and produced pain relief equivalent to meperidine in patients with acute biliary pain due to cholelithiasis.


**Clinical question:** Do patients who suffer from mild pancreatitis due to gallstones have fewer complications when they undergo early surgery rather than delayed surgery?

**Study design:** Randomized controlled trial (nonblinded)

**Setting:** Inpatient (any location) with outpatient follow-up

**Synopsis:** The PONCHO (Pancreatitis of biliary origin: Optimal timiNg of CHOlecystectomy—a particularly tortured acronym) study investigators recruited patients with mild gallstone-associated pancreatitis to undergo surgery on the index admission (n = 129) or to delayed surgery (n = 137). They defined mild pancreatitis based on the absence of organ failure 48 hours after admission and the absence of local complications such as necrosis or peripancreatic fluid collections on computed tomography. The study team did not randomize patients until they were stable and their hospital discharge was anticipated within 2 days. It took approximately 2.5 years and 23 centers to complete this small study. Only one patient in each group was not included in the final analysis. Prior to randomization, approximately one quarter of the patients undergoing surgery on the same day as the index admission had undergone endoscopic sphincterotomy compared with one third of the control patients. Six (5%) of the patients undergoing early surgery experienced a gallstone-related complication or died compared with 23 (17%) of those undergoing delayed surgery (number needed to treat [NNT] = 9; 95% CI 6 - 22). Additionally, 3 (2%) of the same-day surgery patients experienced recurrent pancreatitis compared with 12 (9%) of...
the delayed surgery group (NNT = 16; 8 - 128).

**Bottom line:** In this study, patients with mild gallstone-associated pancreatitis who had cholecystectomy on the index admission day had fewer complications than those who delayed the surgery.


17. **No harm in stopping antibiotics after cholecystectomy for acute cholecystitis**

**Clinical question:** Does stopping antibiotic treatment after cholecystectomy for mild to moderate acute calculous cholecystitis affect outcomes?

**Study design:** Randomized controlled trial (nonblinded)

**Setting:** Inpatient (any location) with outpatient follow-up

**Synopsis:** Using concealed allocation, these investigators randomized 414 adult patients who presented to an emergency department with mild or moderate acute calculous cholecystitis requiring cholecystectomy into 2 groups: (1) continue taking antibiotics or (2) stop taking antibiotics during the postoperative period. Those with severe cholecystitis, defined as concomitant dysfunction of other organ systems, were excluded, as were those with acute pancreatitis, cholangitis, biliary peritonitis, or cirrhosis. All study patients received amoxicillin plus clavulanic acid 3 times a day from admission to day of surgery. The treatment group continued the same antibiotic regimen for 5 days after surgery, while the nontreatment group received no further antibiotics. The 2 groups were well balanced, with a mean age of 56 years and mean duration of preoperative antibiotics of 2 days. Approximately half the patients in each group had mild cholecystitis. For the primary outcome of postoperative surgical site or distant site infections at 4 weeks, there was no significant difference detected between the 2 groups in either the intention-to-treat or per-protocol analyses (intention-to-treat: 17% for nontreatment vs 15% for antibiotic group; per-protocol: 13% for both groups). This held true when the outcomes were analyzed according to severity of cholecystitis or duration of preoperative antibiotic use.

**Bottom line:** Stopping antibiotic treatment after cholecystectomy for mild to moderate acute cholecystitis does not increase postoperative infection rates compared with a strategy of 5 days of postoperative antibiotics.


**Bottom Lines**

1. Remember to ask about red flags in patients with GERD and dyspepsia

2. Nifedipine is effective for achalasia, although pneumatic dilation may be necessary.

3. Eradicating HP may do more than cure ulcers.

4. NSAIDs are similar to opiates for acute biliary pain, and post-operative antibiotics for mild to moderate acute chole are not needed.

5. BE progresses slowly. Ablation in patients with low grade dysplasia is an option, and it’s definitely recommended for those with high-grade dysplasia.
Liver and GI Update

Gary Ferenchick MD, MS

Objectives

1. Understand and apply the recent consensus recommendations on *H pylori* associated gastritis
2. Understand and apply the recent American College of Gastroenterology recommendations on screening for Barrett’s Esophagus
3. Understand updated epidemiological data on *C difficile* and current recommendations for treatment
4. Understand recent evidence suggesting high viral eradication rates but also concerns about hepatocellular carcinoma associated with Hepatitis C treatment.

In September of 2015, a global report on *H Pylori* gastritis was published (Abstract #1) with the objectives of developing a consensus on:

1. Classification of chronic gastritis/duodenitis
2. Clinical distinction of dyspepsia caused by *H pylori* from functional dyspepsia
3. Appropriate diagnostic assessment of gastritis
4. When, whom and how to treat *H Pylori* gastritis

Note that PUD guidelines unanimously recommend eradication therapy as primary treatment for those with positive *H pylori* tests. This report focuses on recommendations for *H pylori* associated gastritis.

**Bottom line:** All *H. pylori* infections should be considered pathogenic and be eradicated.

Pertinent statements related to *H Pylori* gastritis discussed in this report (some reproduced verbatim and some summarized), include the following:

- “No global consensus has been published on when to recommend eradication therapy of *H pylori* gastritis and how to follow up after eradication”
- "*H. pylori* causes a chronic infection, similar to asymptomatic syphilis or tuberculosis; and the final outcome for any individual cannot be predicted.
- “*H. pylori* gastritis may remain clinically unapparent or evolve into severe complications.
- *H. pylori* leads to chronic active gastritis of varying severity in virtually all infected subjects and causes progressive damage to the gastric mucosa, leading to: peptic ulcer disease (gastric and duodenal), gastric adenocarcinoma and gastric MALT (mucosa-associated lymphoid tissue) lymphoma
- “The rate of progression is unpredictable and "...most patients with chronic gastritis may remain asymptomatic until the appearance of severe complications."
- Implicitly then, *H pylori* is a known carcinogen and 78% of all cases of gastric cancer are attributed to chronic *H pylori* infection.
- Importantly not all patients with dyspeptic symptoms are infected with HP, and not all HP infected patients are symptomatic
- The risk for gastric cancer among patients chronically infected with *H pylori* is related to severity and extent of atrophic gastritis (and not symptoms), and the extent of atrophic changes is a function of the duration of the infection.
  - Gastric precancerous lesions include atrophic gastritis, intestinal metaplasia and dysplasia/intraepithelial neoplasia, and on average are associated with a 2–3% ten-year risk of cancer, varying with the stage of lesion: 0.8% for atrophic gastritis, 1.8% for intestinal metaplasia, 3.9% for mild-to-moderate dysplasia and 32.7% for severe dysplasia

Given all of this

1) Should we screen for HP?
   a. "Depending on the epidemiological context, it is appropriate to search and screen for *H pylori* gastritis at an age before development of atrophic gastritis and intestinal metaplasia."
b. “H pylori infection is mainly acquired in childhood, up to the age of 12 years, in developed countries mostly by intrafamilial transmission. The bacterium and associated gastritis persist lifelong, unless treated by eradication therapy, or unless end-stage widespread atrophic gastritis and intestinal metaplasia occur.”

c. “Against this background, it is appropriate to search and screen for H pylori gastritis at an age when new infections become less likely (>12 years) and before development of atrophic gastritis and intestinal metaplasia.” “This all depends on the geographical location and epidemiological context, taking into account the prevalence of infection and age-related cancer incidence.”

2) Should all H pylori-positive individuals receive eradication therapy?

a. “H pylori-infected individuals should be offered eradication therapy, unless there are competing considerations.”

3) Optimal timing of eradication in asymptomatic subjects

a. Maximal benefit is obtained before gastric atrophic changes occur (risk stratification based upon histology and not age)

b. However, eradication therapy always confers benefit by halting progressive gastric mucosal damage and reducing the reservoir of H pylori-infected people

4) The outcome of eradication therapy should always be assessed, preferably non-invasively (urea breath test, stool antigen test) or histologically

5) For those diagnosed with H pylori non-invasively, offer histological assessment

6) Offer surveillance after eradication depending on the extent and severity of atrophic gastritis

H Pylori


OBJECTIVE: To present results of the Kyoto Global Consensus Meeting, which was convened to develop global consensus on (1) classification of chronic gastritis and duodenitis, (2) clinical distinction of dyspepsia caused by Helicobacter pylori from functional dyspepsia, (3) appropriate diagnostic assessment of gastritis and (4) when, whom and how to treat H. pylori gastritis.

DESIGN: Twenty-three clinical questions addressing the above-mentioned four domains were drafted for which expert panels were asked to formulate relevant statements. A Delphi method using an anonymous electronic system was adopted to develop the consensus, the level of which was predefined as ≥80%. Final modifications of clinical questions and consensus were achieved at the face-to-face meeting in Kyoto.

RESULTS: All 24 statements for 22 clinical questions after extensive modifications and omission of one clinical question were achieved with a consensus level of >80%. To better organize classification of gastritis and duodenitis based on aetiology, a new classification of gastritis and duodenitis is recommended for the 11th international classification. A new category of H.pylori-associated dyspepsia together with a diagnostic algorithm was proposed. The adoption of grading systems for gastric cancer risk stratification, and modern image-enhancing endoscopy for the diagnosis of gastritis, were recommended. Treatment to eradicate H. pylori infection before preneoplastic changes develop, if feasible, was recommended to minimize the risk of more serious complications of the infection.

CONCLUSIONS: A global consensus for gastritis was developed for the first time, which will be the basis for an international classification system and for further research on the subject.


2: POEM: Some new regimens slightly more effective for H. pylori eradication.

Clinical question: What is the best treatment regimen for eradication of Helicobacter pylori?

Bottom line: All treatment regimens to eradicate Helicobacter pylori are fairly effective. The 3 regimens that are at least 90% effective are: (1) 7 to 14 days of a proton pump inhibitor (PPI) plus amoxicillin plus clarithromycin plus metronidazole/tinidazole (90%-94% eradication), (2) 10 to 14 days of standard triple therapy plus probiotics (90%), and (3) 10 to 14 days of PPI plus levofloxacin plus another antibiotic (90%). (LOE = 1a)


Study design: Meta-analysis (randomized controlled trials)

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

Synopsis: To perform this systematic review, the authors searched 3 databases, including the Cochrane Library, to find randomized controlled trials published in any language. Although H. pylori was only discovered in 1982, the authors identified a whopping 15,565 studies evaluating treatments to eradicate it. From these, the authors identified 143 studies comparing 14 kinds of treatment versus standard triple treatment [PPI plus clarithromycin plus metronidazole or amoxicillin]. Three researchers independently selected articles for inclusion and 2 authors independently extracted the data and assessed the study quality. The studies, as is usually the case, were of varying quality, though more than half of them were not double-blinded. Also, they were conducted in countries around the world.
where antibiotic resistance rates may differ from your local patterns. Trying to make sense of these data gets a little tricky so the authors did the analysis 2 ways: they performed meta-analyses, where possible, comparing one treatment regimen to another, and they used a Bayesian network analysis to rank the relative benefit of one regimen against another even when they weren't directly compared. All regimens are effective, though 3 had higher rates of eradication: 7 to 14 days of PPI plus amoxicillin plus clarithromycin plus metronidazole/tinadazole (90%-94% eradication), 10 to 14 days of standard triple therapy plus probiotics (90%), and 10 to 14 days of PPI plus levofloxacin plus another antibiotic (90%). All treatments were tolerated.

3: PubMed: H Pylori Antibiotic resistance

BACKGROUND & AIMS: The most recent information published on resistance of Helicobacter pylori to antibiotics in a large population in the United States is more than 10 years old. We assessed the susceptibility of H pylori to antibiotics among patients in a large metropolitan hospital, as well as demographic, clinical, and lifestyle factors associated with antimicrobial resistance.

METHODS: We performed a cross-sectional study of a random sample of 656 patients (90.2% men) from a cohort of 1559 undergoing esophagogastroduodenoscopy with collection of gastric biopsies from 2009 through 2013 at the Houston Veterans Affairs Medical Center. We performed culture analyses of gastric tissues to detect H pylori. The minimum inhibitory concentrations of amoxicillin, clarithromycin, metronidazole, levofloxacin, and tetracycline were determined by the Epsilometer test. Logistic regression analysis was performed to estimate the association between risk factors and antimicrobial resistance.

RESULTS: Biopsies from 135 subjects (20.6%) tested positive for H pylori; 128 of these were from men (94.8%). Only 65 strains were susceptible to all 5 antibiotics. The prevalence of resistance to levofloxacin was 31.3% (95% confidence interval [CI], 23.1%-39.4%), to metronidazole it was 20.3% (95% CI, 13.2%-27.4%), to clarithromycin it was 16.4% (95% CI, 9.9%-22.9%), and to tetracycline it was 0.8% (95% CI, 0.0%-2.3%). No isolate was resistant to amoxicillin. Clarithromycin resistance increased from 9.1% in 2009-2010 to 24.2% in 2011-2013. In multivariate analysis, prior treatment of H pylori infection and use of fluoroquinolones were significantly associated with clarithromycin and levofloxacin resistance, respectively.

CONCLUSIONS: H pylori resistance to clarithromycin increased between 2009 and 2013; resistance to metronidazole remains high in infected men in the United States. The high frequency of resistance to levofloxacin is a new and concerning finding.


GERD/Barrett's

4: PubMed: The risk of esophageal carcinoma with Barrett's is low

The clinical value of screening women with GERD for BE has been likened to the value of theoretical routine screening for breast cancer in men.

BACKGROUND & AIMS: Published estimates for the rate of progression from Barrett's esophagus (BE) to esophageal adenocarcinoma (EAC) vary. We used simulation modeling to reconcile published data and more accurately estimate the incidence of EAC among people with BE.

METHODS: We calibrated the ERASMUS/UW model (a collaboration between Erasmus Medical Center, Rotterdam, the Netherlands and the University of Washington, Seattle) for EAC to match the 0.18% annual rate of progression from population-based studies. This model was then used to simulate the design of prospective studies, introducing more endoscopic surveillance. We used the model to predict rates of progression for both types of studies and for different periods of follow-up, and compared the predicted rates with published data.

RESULTS: For the first 5 years of follow-up, the model reproduced the 0.19% mean annual rate of progression observed in population-based studies; the same disease model predicted a 0.36% annual rate of progression in studies with a prospective design (0.41% reported in published articles). After 20 years, these rates each increased to 0.63% to 0.65% annually, corresponding with a 9.1% to 9.5% cumulative cancer incidence. Between these periods, the difference between the progression rates of both study designs decreased from 91% to 5%.

CONCLUSIONS: In the first 5 years after diagnosis, the rate of progression from BE to EAC is likely to more closely approximate the lower estimates reported from population-based studies than the higher estimates reported from prospective studies in which EAC is detected by surveillance. Clinicians should use this information to explain to patients their short-term and long-term risks if no action is taken, and then discuss the risks and benefits of surveillance.


5: PubMed: ACG Barrett’s Guideline

Barrett's esophagus (BE) is among the most common conditions encountered by the gastroenterologist. In this document, the American College of Gastroenterology updates its guidance for the best practices in caring for these patients. These guidelines continue to endorse screening of high-risk patients for BE; however, routine screening is limited to men with reflux symptoms and multiple other risk
factors. Acknowledging recent data on the low risk of malignant progression in patients with nondysplastic BE, endoscopic surveillance intervals are attenuated in this population; patients with nondysplastic BE should undergo endoscopic surveillance no more frequently than every 3-5 years. Neither routine use of biomarker panels nor advanced endoscopic imaging techniques (beyond high-definition endoscopy) is recommended at this time. Endoscopic ablative therapy is recommended for patients with BE and high-grade dysplasia, as well as T1a esophageal adenocarcinoma. Based on recent level 1 evidence, endoscopic ablative therapy is also recommended for patients with BE and low-grade dysplasia, although endoscopic surveillance continues to be an acceptable alternative. Given the relatively common recurrence of BE after ablation, we suggest postablation endoscopic surveillance intervals. Although many of the recommendations provided are based on weak evidence or expert opinion, this document provides a pragmatic framework for the care of the patient with BE.


**C difficile**

*Clostridium difficile* is the most common health-care associated infection in the US. In 2011, ~500,000 cases of *C difficile* occurred in the US and 29,000 deaths were attributed to *C diff* and almost 50% were either hospital acquired or nursing home acquired. Other risks for *C diff* include female gender (↑1.26), white race (↑1.76) and age ≥ 65 (↑8.6). Recurrence rates for community acquired infection were 14% 30 days after the initial diagnosis with a 1% mortality rate, vs 21% and 9% for health-care associated *C diff*.

**6: PubMed: 500,000 cases and 29,000 deaths attributable to *C Difficile***

**BACKGROUND:** The magnitude and scope of *Clostridium difficile* infection in the United States continue to evolve.

**METHODS:** In 2011, we performed active population- and laboratory-based surveillance across 10 geographic areas in the United States to identify cases of *C difficile* infection (stool specimens positive for *C difficile* on either toxin or molecular assay in residents ≥ 1 year of age). Cases were classified as community-associated or health care-associated. In a sample of cases of *C difficile* infection, specimens were cultured and isolates underwent molecular typing. We used regression models to calculate estimates of national incidence and total number of infections, first recurrences, and deaths within 30 days after the diagnosis of *C difficile* infection.

**RESULTS:** A total of 15,461 cases of *C difficile* infection were identified in the 10 geographic areas; 65.8% were health care-associated, but only 24.2% had onset during hospitalization. After adjustment for predictors of disease incidence, the estimated number of incident *C difficile* infections in the United States was 453,000 (95% confidence interval [CI], 397,100 to 508,500). The incidence was estimated to be higher among females (rate ratio, 1.26; 95% CI, 1.25 to 1.27), whites (rate ratio, 1.72; 95% CI, 1.56 to 2.0), and persons 65 years of age or older (rate ratio, 8.65; 95% CI, 8.16 to 9.31). The estimated number of first recurrences of *C difficile* infection was 83,000 (95% CI, 57,000 to 108,900), and the estimated number of deaths was 29,300 (95% CI, 16,500 to 42,100). The North American pulsed-field gel electrophoresis type 1 (NAP1) strain was more prevalent among health care-associated infections than among community-associated infections (30.7% vs. 18.8%, P<0.001).

**CONCLUSIONS:** *C difficile* was responsible for almost half a million infections and was associated with approximately 29,000 deaths in 2011.


**7: PubMed: 8% of patients admitted to hospital are colonized with *C Difficile***

**OBJECTIVES:** It has been suggested that colonization with *C difficile* protects from infection. Nevertheless, the association between carriage of toxinogenic strains and ensuing *C difficile* infections (CDIs) has not been studied.

**METHODS:** We searched PubMed and EMBASE databases up to 20 June 2014, using the term "difficile". Our primary outcomes of interest included the prevalence of isolation of toxinogenic *C difficile* or its toxins from asymptomatic patients on hospital admission through stool or rectal swab testing and the risk of ensuing infection among colonized and noncolonized patients. Data on previous hospitalization, antibiotic, and proton pump inhibitor (PPI) use and prior CDIs among colonized and noncolonized patients were also extracted.

**RESULTS:** Nineteen out of 26,081 studies on 8,725 patients were included. The pooled prevalence of toxinogenic *C difficile* colonization was 8.1% (95% confidence interval [CI] 5.7-11.1%), with an increasing trend over time (P<0.003), and 10.0% (95% CI 7.1-13.4%) among North American studies. Patients colonized upon hospital admission had a 5.9 times higher risk of subsequent CDIs compared with noncolonized patients (relative risk [RR] 5.86; 95% CI 4.21-8.16). The risk of CDI for colonized patients was 21.8% (95% CI 7.9-40.1%), which was significantly higher than that of noncolonized patients (3.4%; 95% CI 1.5-6.6%; P=0.03), with an attributable risk of 18.4%. History of hospitalization during the previous 3 months was associated with a higher risk of colonization (RR 1.63; 95% CI 1.13-2.34), as opposed to previous antibiotic (RR 1.07; 95% CI 0.75-1.53) and PPI use (RR 1.44; 95% CI 0.94-2.23), as well as history of CDI (RR 1.45; 95% CI 0.66-3.18) that had no impact.
CONCLUSIONS: Over 8% of admitted patients are carriers of toxinogenic C. difficile with an almost 6 times higher risk of infection. These findings update current knowledge regarding the contribution of colonization in CDI epidemiology and stress the importance of preventive measures toward colonized patients.


8: PubMed: C Difficile current evidence for diagnosis and treatment

IMPORTANCE: Since 2000, the incidence and severity of Clostridium difficile infection (CDI) have increased.

OBJECTIVE: To review current evidence regarding best practices for the diagnosis and treatment of CDI in adults (age ≥ 18 years).

EVIDENCE REVIEW: Ovid MEDLINE and Cochrane databases were searched using keywords relevant to the diagnosis and treatment of CDI in adults. Articles published between January 1978 and October 31, 2014, were selected for inclusion based on targeted keyword searches, manual review of bibliographies, and whether the article was a guideline, systematic review, or meta-analysis published within the past 10 years. Of 4682 articles initially identified, 196 were selected for full review. Of these, the most pertinent 116 articles were included. Clinical trials, large observational studies, and more recently published articles were prioritized in the selection process.

FINDINGS: Laboratory testing cannot distinguish between asymptomatic colonization and symptomatic infection with C difficile.

Diagnostic approaches are complex due to the availability of multiple testing strategies. Multistep algorithms using polymerase chain reaction (PCR) for the toxin gene(s) or single-step PCR on liquid stool samples have the best test performance characteristics (for multistep: sensitivity was 0.68-1.00 and specificity was 0.92-1.00; and for single step: sensitivity was 0.86-0.92 and specificity was 0.94-0.97). Vancomycin and metronidazole are first-line therapies for most patients, although treatment failures have been associated with metronidazole in severe or complicated cases of CDI. Recent data demonstrate clinical success rates of 66.3% for metronidazole vs 78.5% for vancomycin for severe CDI. Newer therapies show promising results, including fidaxomicin (similar clinical cure rates to vancomycin, with lower recurrence rates for fidaxomicin, 15.4% vs vancomycin, 25.3%; P = .005) and fecal microbiota transplantation (response rates of 83%-94% for recurrent CDI).

CONCLUSIONS AND RELEVANCE: Diagnostic testing for CDI should be performed only in symptomatic patients. Treatment strategies should be based on disease severity, history of prior CDI, and the individual patient's risk of recurrence. Vancomycin is the treatment of choice for severe or complicated CDI, with or without adjunctive therapies. Metronidazole is appropriate for mild disease. Fidaxomicin is a therapeutic option for patients with recurrent CDI or a high risk of recurrence. Fecal microbiota transplantation is associated with symptom resolution of recurrent CDI but its role in primary and severe CDI is not established.

Non-alcoholic steatohepatitis (NASH)

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of hepatic steatosis (hepatocyte fat deposition) ranging from simple steatosis to steatosis with inflammation, without an identifiable secondary cause such as excess of alcohol intake. Without inflammation this condition is called non-alcoholic fatty liver disease (NAFLD) and is generally thought to be benign; with inflammation this condition is called non-alcoholic steatohepatitis (NASH). NASH can be present with or without fibrosis. NASH can progress to more advanced stages of liver disease. ~20% of patients with NASH progress to cirrhosis.

Abstract #4 is a systematic review of 9 RCT's on Vitamin E, pioglitazone, pentoxifylline and obeticholic acid on NASH. (Note: results of several of the primary trials are listed in the appendix). Abstract #5 is a recent study on obeticholic acid and #6 & #7 look at the effects of the glucagon-like peptide-1 (GLP-1) analogue liraglutide and bariatric surgery on NASH histology.

9: PubMed: Meds for NASH

We performed a Bayesian network meta-analysis combining direct and indirect treatment comparisons to assess the comparative effectiveness of pharmacological agents for the treatment of nonalcoholic steatohepatitis (NASH). Through systematic literature review, we identified nine randomized, controlled trials (RCTs) including 964 patients with biopsy-proven NASH, comparing vitamin E, thiazolidinediones (TZDs), pentoxifylline, or obeticholic acid to one another or placebo. The primary outcome was improvement in fibrosis stage; secondary outcomes were improvement in ballooning degeneration, lobular inflammation, and steatosis. We reported relative risks (RRs) and 95% confidence intervals (CIs) from direct meta-analysis and 95% credible intervals (CrIs) from Bayesian network meta-analysis, and used Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria to appraise quality of evidence. Moderate-quality evidence supports the use of pentoxifylline (RR, 0.26; 95% CrI: 0.05-1.00) and obeticholic acid (RR, 0.81; 95% CI: 0.70-0.95) over placebo in improving fibrosis. High-quality evidence supports the effect of vitamin E, TZDs, and obeticholic acid over placebo in improving ballooning degeneration. All four interventions seemed to have at least moderate-quality evidence over placebo to improve steatosis. Moderate-quality evidence supports that TZDs, pentoxifylline, and obeticholic acid decrease lobular inflammation. All the head-to-head comparisons were supported by very-low-quality evidence except for superiority of TZDs over vitamin E on improving steatosis and lobular inflammation, which had moderate-quality evidence.
CONCLUSIONS: Based on direct and network meta-analysis, pentoxifylline and obeticholic acid improve fibrosis, and vitamin E, TZDs, and obeticholic acid improve ballooning degeneration in patients with NASH. Future comparative trials of combination therapies targeting distinct histological features are warranted.


10: PubMed: Obeticholic acid improved the histological features of NASH

BACKGROUND: The bile acid derivative 6-ethylchenodeoxycholic acid (obeticholic acid) is a potent activator of the farnesoid X nuclear receptor that reduces liver fat and fibrosis in animal models of fatty liver disease. We assessed the efficacy of obeticholic acid in adult patients with non-alcoholic steatohepatitis.

METHODS: We did a multicentre, double-blind, placebo-controlled, parallel group, randomised clinical trial at medical centres in the USA in patients with non-cirrhotic, non-alcoholic steatohepatitis to assess treatment with obeticholic acid given orally (25 mg daily) or placebo for 72 weeks. Patients were randomly assigned 1:1 using a computer-generated, centrally administered procedure, stratified by clinical centre and diabetes status. The primary outcome measure was improvement in centrally scored liver histology defined as a decrease in non-alcoholic fatty liver disease activity score by at least 2 points without worsening of fibrosis from baseline to the end of treatment. A planned interim analysis of change in alanine aminotransferase at 24 weeks undertaken before end-of-treatment (72 weeks) biopsies supported the decision to continue the trial (relative change in alanine aminotransferase -24%, 95% CI -45 to -3). A planned interim analysis of the primary outcome showed improved efficacy of obeticholic acid (p=0·0024) and supported a decision not to do end-of-treatment biopsies and end treatment early in 64 patients, but to continue the trial to obtain the 24-week post-treatment measures. Analyses were done by intention-to-treat. This trial was registered with ClinicalTrials.gov, number NCT01265498.

FINDINGS: Between March 16, 2011, and Dec 3, 2012, 141 patients were randomly assigned to receive obeticholic acid and 142 to placebo. 50 (45%) of 110 patients in the obeticholic acid group who were meant to have biopsies at baseline and 72 weeks had improved liver histology compared with 23 (21%) of 109 such patients in the placebo group (relative risk 1·9, 95% CI 1·3 to 2·8; p=0·0002). 33 (23%) of 141 patients in the obeticholic acid developed pruritus compared with nine (6%) of 142 in the placebo group.

INTERPRETATION: Obeticholic acid improved the histological features of non-alcoholic steatohepatitis, but its long-term benefits and safety need further clarification.


11: PubMed: Liraglutide (Victoza®) and NASH

BACKGROUND: Glucagon-like peptide-1 (GLP-1) analogues reduce hepatic steatosis, concentrations of liver enzymes, and insulin resistance in murine models of fatty liver disease. These analogues are licensed for type 2 diabetes, but their efficacy in patients with non-alcoholic steatohepatitis is unknown. We assessed the safety and efficacy of the long-acting GLP-1 analogue, liraglutide, in patients with non-alcoholic steatohepatitis.

METHODS: This multicentre, double-blinded, randomised, placebo-controlled phase 2 trial was conducted in four UK medical centres to assess subcutaneous injections of liraglutide (1·8 mg daily) compared with placebo for patients who are overweight and show clinical evidence of non-alcoholic steatohepatitis. Patients were randomly assigned (1:1) using a computer-generated, centrally administered procedure, stratified by trial centre and diabetes status. The trial was designed using A'Hern's single-group method, which required eight (38%) of 21 successes in the liraglutide group for the effect of liraglutide to be considered clinically significant. Patients, investigators, clinical trial site staff, and pathologists were masked to treatment assignment throughout the study. The primary outcome measure was resolution of definite non-alcoholic steatohepatitis with no worsening in fibrosis from baseline to end of treatment (48 weeks), as assessed centrally by two independent pathologists. Analysis was done by intention-to-treat analysis, which included all patients who underwent end-of-treatment biopsy. The trial was registered with ClinicalTrials.gov, number NCT01237119.

FINDINGS: Between Aug 1, 2010, and May 31, 2013, 26 patients were randomly assigned to receive liraglutide and 26 to placebo. Nine (39%) of 23 patients who received liraglutide and underwent end-of-treatment liver biopsy had resolution of definite non-alcoholic steatohepatitis compared with two (9%) of 22 such patients in the placebo group (relative risk 4·3 [95% CI 1·0-17·7]; p=0·019). Two (9%) of 23 patients in the liraglutide group versus eight (36%) of 22 patients in the placebo group had progression of fibrosis (0·2 [0·1-1·0]; p=0·04). Most adverse events were grade 1 (mild) to grade 2 (moderate) in severity, transient, and similar in the two treatment groups for all organ classes and symptoms, with the exception of gastrointestinal disorders in 21 (81%) of 23 patients in the liraglutide group and 17 (65%) of 22 patients in the placebo group, which included diarrhoea (ten [38%] patients in the liraglutide group vs five [19%] in the placebo group), constipation (seven [27%] vs none), and loss of appetite (eight [31%] vs two [8%]).

INTERPRETATION: Liraglutide was safe, well tolerated, and led to histological resolution of non-alcoholic steatohepatitis, warranting extensive, longer-term studies.


12: PubMed: Bariatric surgery and NASH
**BACKGROUND & AIDS:** The effects of bariatric surgery in patients with nonalcoholic fatty liver disease (NASH) are not well established. We performed a prospective study to determine the biological and clinical effects of bariatric surgery in patients with NASH.

**METHODS:** From May 1994 through May 2013, one hundred and nine morbidly obese patients with biopsy-proven NASH underwent bariatric surgery at the University Hospital of Lille, France (the Lille Bariatric Cohort). Clinical, biological, and histologic data were collected before and 1 year after surgery.

**RESULTS:** One year after surgery, NASH had disappeared from 85% of the patients (95% confidence interval [CI]: 75.8%-92.2%). Compared with before surgery, patients had significant reductions in mean ± SD body mass index (BMI, from 49.3 ± 8.2 to 37.4 ± 7) and level of alanine aminotransferase (from 52.1 ± 25.7 IU/L to 25.1 ± 20 IU/L); mean levels of γ-glutamyltranspeptidase were reduced from 51 IU/L before surgery (interquartile range [IQR], 34-87 IU/L) to 23 IU/L afterward (IQR, 14-33 IU/L) and mean insulin resistance index values were reduced from 3.6 ± 0.5 to 2.9 ± 0.5 (P < .01 for each comparison). NASH disappeared from a higher proportion of patients with mild NASH before surgery (94%) than severe NASH (70%) (P < .05) according to Brunt score. In histologic analysis, steatosis was detected in 60% of the tissue before surgery (IQR, 40%-80%) but only 10% 1 year after surgery (IQR, 2.5%-21.3%); the mean nonalcoholic fatty liver disease score was reduced from 5 (IQR, 4-5) to 1 (IQR, 1-2) (each P < .001). Hepatocellular ballooning was reduced in 84.2% of samples (n = 69; 95% CI: 74.4-91.3) and lobular inflammation in 67.1% (n = 55; 95% CI: 55.8-77.1). According to Metavir scores, fibrosis was reduced in 33.8% of patients (95% CI: 23.6%-45.2%). Patients whose NASH persisted 1 year after surgery (n = 12) had lost significantly less weight (change in BMI, 9.1 ± 1.5) than those without NASH (change in BMI, 12.3 ± 0.6) (P = .005). Patients who underwent laparoscopic gastric banding lost less weight (change in BMI, 6.4 ± 0.7) than those who underwent gastric bypass (change in BMI, 14.0 ± 0.5) (P < .0001), and a higher proportion had persistent NASH (30.4% vs 7.6% of those with gastric bypass; P = .015).

**CONCLUSIONS:** Bariatric surgery induced the disappearance of NASH from nearly 85% of patients and reduced the pathologic features of the disease after 1 year of follow-up. It could be a therapeutic option for appropriate morbidly obese patients with NASH who do not respond to lifestyle modifications. More studies are needed to determine the long-term effects of bariatric surgery in morbidly obese patients with NASH.


**Hepatitis C**

HCV (a single stranded RNA virus) has 6 major genotypes (Types 1 – 6), and infects up to 3.5 million in the US and 170 million worldwide. Chronic HCV is associated with 700,000 deaths worldwide annually primarily from cirrhosis and hepatocellular carcinoma. (NEJM 2015; 373:2678). Effective regimens for the treatment of HCV infection have been available for several years, but the choice of agents has been complicated by knowledge of the HCV genotype, stage of fibrosis, patterns of antiviral resistance and the patient’s treatment history. Currently approved treatments for chronic HCV are not effective across all genotypes. The following 3 reference-supported companion articles were simultaneously published in the NEJM in December 2015, and identify high efficacy for a single combination regimen of sofosbuvir-velpatasvir for 12 weeks with very high cure rates (83 – 100%) in patients regardless of genotype, the presence of cirrhosis, prior treatment failure. Additionally, baseline anti-viral resistance patterns were not associated with treatment failure.

**13: PubMed:** Sofosbuvir-velpatasvir highly effective for HCV genotypes 1,2,4,5,6

**BACKGROUND:** A simple treatment regimen that is effective in a broad range of patients who are chronically infected with the hepatitis C virus (HCV) remains an unmet medical need.

**METHODS:** We conducted a phase 3, double-blind, placebo-controlled study involving untreated and previously treated patients with chronic HCV genotype 1, 2, 4, 5, or 6 infection, including those with compensated cirrhosis. Patients with HCV genotype 1, 2, 4, or 6 were randomly assigned in a 5:1 ratio to receive the nucleotide polymerase inhibitor sofosbuvir and the NS5A inhibitor velpatasvir in a once-daily, fixed-dose combination tablet or matching placebo for 12 weeks. Because of the low prevalence of genotype 5 in the study regions, patients with genotype 5 did not undergo randomization but were assigned to the sofosbuvir-velpatasvir group. The primary end point was a sustained virologic response at 12 weeks after the end of therapy.

**RESULTS:** Of the 624 patients who received treatment with sofosbuvir-velpatasvir, 34% had HCV genotype 1a, 19% genotype 1b, 17% genotype 2, 19% genotype 4, 6% genotype 5, and 7% genotype 6. A total of 8% of patients were black, 19% had cirrhosis, and 32% had been previously treated for HCV. The rate of sustained virologic response among patients receiving sofosbuvir-velpatasvir was 99% (95% confidence interval, 98 to >99). Two patients receiving sofosbuvir-velpatasvir, both with HCV genotype 1, had a virologic relapse. None of the 116 patients receiving placebo had a sustained virologic response. Serious adverse events were reported in 15 patients (2%) in the sofosbuvir-velpatasvir group and none in the placebo group.

**CONCLUSIONS:** Once-daily sofosbuvir-velpatasvir for 12 weeks provided high rates of sustained virologic response among both previously treated and untreated patients infected with HCV genotype 1, 2, 4, 5, or 6, including those with compensated cirrhosis. (Funded by Gilead Sciences; ClinicalTrials.gov number, NCT02201940.).

14: PubMed: Sofosbuvir-velpatasvir highly effective for HCV genotypes 2,3

**BACKGROUND:** In phase 2 trials, treatment with the combination of the nucleotide polymerase inhibitor sofosbuvir and the NS5A inhibitor velpatasvir resulted in high rates of sustained virologic response in patients chronically infected with hepatitis C virus (HCV) genotype 2 or 3.

**METHODS:** We conducted two randomized, phase 3, open-label studies involving patients who had received previous treatment for HCV genotype 2 or 3 and those who had not received such treatment, including patients with compensated cirrhosis. In one trial, patients with HCV genotype 2 were randomly assigned in a 1:1 ratio to receive sofosbuvir-velpatasvir, in a once-daily, fixed-dose combination tablet (134 patients), or sofosbuvir plus weight-based ribavirin (132 patients) for 12 weeks. In a second trial, patients with HCV genotype 3 were randomly assigned in a 1:1 ratio to receive sofosbuvir-velpatasvir for 12 weeks (277 patients) or sofosbuvir-ribavirin for 24 weeks (275 patients). The primary end point for the two trials was a sustained virologic response at 12 weeks after the end of therapy.

**RESULTS:** Among patients with HCV genotype 2, the rate of sustained virologic response in the sofosbuvir-velpatasvir group was 99% (95% confidence interval [CI], 96 to 100), which was superior to the rate of 94% (95% CI, 88 to 97) in the sofosbuvir-ribavirin group (P=0.02). Among patients with HCV genotype 3, the rate of sustained virologic response in the sofosbuvir-velpatasvir group was 95% (95% CI, 92 to 98), which was superior to the rate of 80% (95% CI, 75 to 85) in the sofosbuvir-ribavirin group (P<0.001). The most common adverse events in the two studies were fatigue, headache, nausea, and insomnia.

**CONCLUSIONS:** Among patients with HCV genotype 2 or 3 with or without previous treatment, including those with compensated cirrhosis, 12 weeks of treatment with sofosbuvir-velpatasvir resulted in rates of sustained virologic response that were superior to those with standard treatment with sofosbuvir-ribavirin. (Funded by Gilead Sciences; ASTRAL-2 ClinicalTrials.gov number, NCT02220998; and ASTRAL-3, NCT02201953.)


15: PubMed: Sofosbuvir-velpatasvir effective for HCV associated decompensated cirrhosis

**BACKGROUND:** As the population that is infected with the hepatitis C virus (HCV) ages, the number of patients with decompensated cirrhosis is expected to increase.

**METHODS:** We conducted a phase 3, open-label study involving both previously treated and previously untreated patients infected with HCV genotypes 1 through 6 who had decompensated cirrhosis (classified as Child-Pugh-Turcotte class B). Patients were randomly assigned in a 1:1:1 ratio to receive the nucleotide polymerase inhibitor sofosbuvir and the NS5A inhibitor velpatasvir once daily for 12 weeks, sofosbuvir-velpatasvir plus ribavirin for 12 weeks, or sofosbuvir-velpatasvir for 24 weeks. The primary end point was a sustained virologic response at 12 weeks after the end of therapy.

**RESULTS:** Of the 267 patients who received treatment, 78% had HCV genotype 1, 4% genotype 2, 15% genotype 3, 3% genotype 4, and less than 1% genotype 6; no patients had genotype 5. Overall rates of sustained virologic response were 83% (95% confidence interval [CI], 74 to 90) among patients who received 12 weeks of sofosbuvir-velpatasvir, 94% (95% CI, 87 to 98) among those who received 12 weeks of sofosbuvir-velpatasvir plus ribavirin, and 86% (95% CI, 77 to 92) among those who received 24 weeks of sofosbuvir-velpatasvir. Post hoc analysis did not detect any significant differences in rates of sustained virologic response among the three study groups. Serious adverse events occurred in 19% of patients who received 12 weeks of sofosbuvir-velpatasvir, 16% of those who received 12 weeks of sofosbuvir-velpatasvir plus ribavirin, and 18% of those who received 24 weeks of sofosbuvir-velpatasvir. The most common adverse events were fatigue (29%), nausea (23%), and headache (22%) in all patients and anemia (31%) in the patients receiving ribavirin.

**CONCLUSIONS:** Treatment with sofosbuvir-velpatasvir with or without ribavirin for 12 weeks and with sofosbuvir-velpatasvir for 24 weeks resulted in high rates of sustained virologic response in patients with HCV infection and decompensated cirrhosis. (Funded by Gilead Sciences; ASTRAL-4 ClinicalTrials.gov number, NCT02201901.)


Unanswered: How well does sustained viral response correlate with clinical outcomes such as prevention of cirrhosis, reduction in hepatocellular carcinoma, improved quality of life, survival, etc.? We now have the first known report of a significant harm associated with anti-HCV treatment (abstract 16). This suggests that we need to stay tuned to get the long-term effects of these aggressive HCV-eradication campaigns.

16: UNEXPECTED TUMOR RECURRENCE IN PATIENTS WITH HEPATITIS C VIRUS-RELATED HEPATOCELLULAR CARCINOMA UNDERGOING THERAPY

**BACKGROUND:** The success of direct-acting antivirals (DAA) against hepatitis C is a major breakthrough in hepatology. Until now, however, there are very few data on the effect of hepatitis C virus (HCV) eradication in patients who have already developed
hepatocellular carcinoma.

METHODS: The study included patients with HCV infection and prior history of treated hepatocellular carcinoma who achieved complete response and lacked 'non-characterized nodules' at the time they underwent anti-HCV treatment with all-oral DAAs in 4 hospitals. Patients receiving interferon as part of the antiviral regimen were excluded. The baseline characteristics, laboratory and radiologic tumor response were registered in all patients before starting antiviral therapy and during the follow-up according to the clinical practice policy.

RESULTS: Between 2014 and 2015, 103 patients with prior hepatocellular carcinoma received DAA, 58 of them met the inclusion criteria. After a median follow-up of 5.7 months, 3 patients died and 16 developed radiologic tumor recurrence (27.6%). The pattern of recurrence was: intrahepatic growth (3 patients), new intrahepatic lesion (1 nodule in 5 patients, up to 3 nodules less or equal to 3cm in 4 cases and multifocal in one patient) and infiltrative ill-defined hepatocellular carcinoma and/or extra-hepatic lesions in 3 patients.

CONCLUSIONS: Our data show an unexpected high rate and pattern of tumor recurrence coinciding with HCV clearance and, although based in a very small cohort of patients, should be taken as a note of caution and prime a large scale assessment that exceeds the individual investigators capacity.


Bottom Lines

1. Recent consensus recommendations on *H pylori* associated gastritis recommend enhanced screening and that all *H pylori* infections should be considered pathogenic and should be eradicated
2. Screen for BE in men with sx of heartburn or regurgitation if: a) Chronic (> 5 years), OR b) Frequent (≥ weekly), AND if > 2 of the following: i) Age > 50; ii) Caucasian race, iii) Central obesity, iv) Smoking hx (current or past). Consider screening women with multiple risk factors.
3. C difficile is associated with close to 30,000 deaths/year. Metronidazole is appropriate for mild disease and vancomycin is the treatment of choice for severe or complicated CDI.
4. Recent evidence suggests high cure rates (83 – 100%) associated with a 12 week course of once-daily sofosbuvir-velpatasvir in a wide-spectrum of patients chronically infected chronically Hepatitis C
Pain Management

John Hickner, MD, MS

Objectives

1. Briefly review the 2016 CDC opioid prescribing guidelines
2. Present evidence for the effectiveness/lack of effectiveness of opioids for treatment of chronic pain
3. Present several novel interventions to improve pain control and reduce opioid use by patients with chronic pain.

Perhaps no medical topic received more press in 2016 than the epidemic of overdose deaths from narcotics in the United States, the world’s leading consumer of opioids. Since 2000, the rate of deaths from drug overdoses has increased 137%, including a 200% increase in the rate of overdose deaths involving opioids (opioid pain relievers and heroin). During 2014, 47,055 drug overdose deaths occurred in the United States. In contrast, in 2014, 32,675 people died in motor vehicle traffic crashes in the United States, a 0.7-percent decrease from the 32,894 fatalities in 2013.

FIGURE 1. Age-adjusted rate* of drug overdose deaths† and drug overdose deaths involving opioids§,¶ — United States, 2000–2014


This chapter is intended to provide some of the evidence for and against the effectiveness of opioids for treatment of patients who have chronic, non-cancer pain and to provide some suggestions for primary care physicians who help manage these patients’ medical and psychological care.

What is the evidence that opioids are effective for chronic pain?

1. Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee

The efficacy and safety of a once-daily extended-release formulation of tramadol hydrochloride (tramadol ER) was evaluated in patients with moderate to severe chronic pain of osteoarthritis (OA). This was a randomized, double-blind, placebo-controlled, parallel-group, 12-week study. Eligible patients with radiographically confirmed OA of the knee meeting the American College of Rheumatology diagnostic criteria, defined by knee pain and presence of osteophytes, plus at least age >50 years, morning stiffness <30 minutes in duration, and/or crepitus, entered a 2-7 day washout period during which all analgesics were discontinued. When pain at the index knee joint reached > or =40 mm (0-100 mm VAS), patients were randomized to tramadol ER or placebo. Tramadol ER was initiated at 100
mg QD and increased to 200 mg QD by the end of 1 week of treatment. After the first week, further increases to tramadol ER 300 mg or 400 mg QD were allowed. Outcome measures included Arthritis Pain Intensity Visual Analogue Scale (VAS), Western Ontario and McMaster Universities Arthritis Scale (WOMAC) Pain, Stiffness, Physical Function VAS subscales, Patient and Physician Global Assessment of Therapy, Sleep, dropouts due to insufficient therapeutic effect, and adverse events. Two hundred forty-six patients were randomized (tramadol ER 124, placebo 122). There were no baseline differences between the two treatments. The mean age was 61 years, mean duration of OA 12.9 years, and the mean tramadol ER dose was 276 mg QD. All efficacy outcome measures favored tramadol ER over placebo. On the primary outcome variable of average change from baseline in Arthritis Pain Intensity VAS over 12 weeks, tramadol ER was superior to placebo (least squares mean change from baseline: 30.4 mm vs. 17.7 mm, \( P < 0.001 \)). Significant differences from placebo were evident at week 1, the first post-treatment visit. Similarly, outcomes on the WOMAC Pain, Stiffness and Physical Function subscales, the WOMAC Composite Scale, dropouts due to insufficient therapeutic effect, Patient and Physician Global Assessment of Therapy, and Sleep were all significantly better with tramadol ER than placebo (\( P < 0.001 \) to \( < 0.05 \)). Treatment with tramadol ER results in statistically significant and clinically important and sustained improvements in pain, stiffness, physical function, global status, and sleep in patients with chronic pain. A once-a-day formulation of tramadol has the potential to provide patients increased control over the management of their pain, fewer interruptions in sleep and improved compliance.


---

### 2. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase.

**BACKGROUND:** Buprenorphine is a mixed-activity, partial mu-opioid agonist. Its lipid solubility makes it well suited for transdermal administration.

**OBJECTIVE:** This study assessed the efficacy and safety profile of a 7-day buprenorphine transdermal system (BTDS) in adult (age \( >18 \)) years) patients with moderate to severe chronic low back pain previously treated with \( > or = 1 \) tablet daily of an opioid analgesic.

**METHODS:** This was a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. After a 2- to 7-day washout of previous opioid therapy, eligible patients were randomized to receive BTDS 10 microg/h or matching placebo patches. The dose was titrated weekly using 10- and 20-microg/h patches (maximum, 40 microg/h) based on efficacy and tolerability. After 4 weeks, patients crossed over to the alternative treatment for another 4 weeks. Patients who completed the double-blind study were eligible to enter the 6-month open-label phase. Rescue analgesia was provided as acetaminophen 325 mg to be taken as 1 or 2 tablets every 4 to 6 hours as needed. The primary outcome assessments were daily pain intensity, measured on a 100-mm visual analog scale (VAS), from no pain to exacerbating pain, and a 5-point ordinal scale, from 0 = none to 4 = exacerbating. Secondary outcome assessments included the Pain and Sleep Questionnaire (100-mm VAS, from never to always), Pain Disability Index (ordinal scale, from 0 = no disability to 11 = total disability), Quebec Back Pain Disability Scale (categorical scale, from 0 = no difficulty to 5 = unable to do), and the 36-item Short Form Health Survey (SF-36). Patients and investigators assessed overall treatment effectiveness at the end of each phase; they assessed treatment preference at the end of double-blind treatment. After implementation of a precautionary amendment, the QTc interval was measured 3 to 4 days after randomization and after any dose adjustment. All assessments performed during the double-blind phase were also performed every 2 months during the open-label extension. Adverse events were collected by non-directed questioning throughout the study.

**RESULTS:** Of 78 randomized patients, 52 (66.7%) completed at least 2 consecutive weeks of treatment in each study phase without major protocol violations (per-protocol [PP] population: 32 women, 20 men; mean [SD] age, 51.3 [11.4] years; mean weight, 85.5 [19.5] kg; 94% white, 4% black, 2% other). The mean (SD) dose of study medication during the last week of treatment was 29.8 (12.1) microg/h for BTDS and 32.9 (10.7) microg/h for placebo (\( P = NS \)). During the last week of treatment, BTDS was associated with significantly lower mean (SD) pain intensity scores compared with placebo on both the VAS (45.3 [21.3] vs 53.1 [24.3] mm, respectively; \( P = 0.022 \)) and the 5-point ordinal scale (1.9 [0.7] vs 2.2 [0.8]; \( P = 0.044 \)). The overall Pain and Sleep score was significantly lower with BTDS than with placebo (177.6 [125.5] vs 232.9 [131.9]; \( P = 0.027 \)). There were no treatment differences on the Pain Disability Index, Quebec Back Pain Disability Scale, or SF-36; however, BTDS was associated with significant improvements compared with placebo on 2 individual Quebec Back Pain Disability Scale items (get out of bed: \( P = 0.042 \); sit in a chair for several hours: \( P = 0.022 \)). Of the 48 patients/physicians in the PP population who rated the effectiveness of treatment, 64.6% of patients (\( n = 31 \)) rated BTDS moderately or highly effective, as did 62.5% of investigators (\( n = 30 \)). Among the 50 patients in the PP population who answered the preference question, 66.0% of patients (\( n = 33 \)) preferred the phase in which they received BTDS and 24.0% (\( n = 12 \)) preferred the phase in which they received placebo (\( P = 0.001 \)), with the remainder having no preference; among investigators, 60.0% (\( n = 30 \)) and 28.0% (\( n = 14 \)) preferred the BTDS and placebo phases, respectively (\( P = 0.008 \)), with the remainder having no preference. The mean placebo-adjusted change from baseline in the QTc interval ranged from -0.8 to +3.8 milliseconds (\( P = NS \)). BTDS treatment was associated with a significantly higher frequency of nausea (\( P < 0.001 \)), dizziness (\( P < 0.001 \)), vomiting (\( P = 0.008 \)), somnolence (\( P = 0.020 \)), and dry mouth (\( P = 0.003 \)), but not constipation. Of the 49 patients completing 8 weeks of double-blind treatment, 40 (81.6%) entered the 6-month, open-label extension study and 27 completed it. Improvements in pain scores achieved during the double-blind phase were maintained in these patients.

**CONCLUSIONS:** In the 8-week, double-blind portion of this study, BTDS 10 to 40 microg/h was effective compared with placebo in the management of chronic, moderate to severe low back pain in patients who had previously received opioids. The improvements in pain scores were sustained throughout the 6-month, open-label extension. (Current Controlled Trials identification number: ISRCTN 06013881.)

3. Efficacy and safety of buprenorphine transdermal system (BTDS) for chronic moderate to severe low back pain: a randomized, double-blind study

In this enriched design study, 1,160 opioid-experienced patients with chronic, moderate to severe low back pain entered an open-label run-in period; 660 demonstrated analgesic benefit from and tolerability to buprenorphine transdermal system 20 mcg/hour (BTDS 20) treatment and were randomized to receive either BTDS 20, BTDS 5 mcg/hour (BTDS 5), or the active control (immediate release oxycodone 40-mg/day) during an 84-day double-blind phase. The primary endpoint, "average pain in the last 24 hours" during double-blind weeks 4, 8, and 12, was significantly lower for patients receiving BTDS 20 compared with patients receiving BTDS 5 (P < .001, treatment difference of -.67). A treatment difference of -.75 in favor of oxycodone 40 mg/day versus BTDS 5 (P < .001) indicated the assay sensitivity of the study. Four sensitivity analyses, secondary, and exploratory analyses supported the results of the primary analysis. Incidences of treatment-emergent adverse events were 56% during the open-label period, and 59, 77, and 73% for the BTDS 5, BTDS 20, and oxycodone 40 mg/day treatment groups, respectively, during the double-blind phase. One death considered unrelated to study treatment occurred in a patient receiving BTDS 10 during the run-in period. BTDS 20 treatment was demonstrated to be efficacious and generally well tolerated.

PERSPECTIVE: This article presents results of a pivotal Phase 3 study that assesses a new treatment for the management of chronic low back pain: a transdermal patch containing the opioid buprenorphine (BTDS). In this active controlled, superiority study with an enriched design, BTDS 20 was found to be efficacious and generally well tolerated.


4. Controlled-release oxycodone and naloxone in the treatment of chronic low back pain: a placebo-controlled, randomized study

BACKGROUND: For Canadian regulatory purposes, an analgesic study was required to complement previously completed, pivotal studies on bowel effects and analgesia associated with controlled-release (CR) oxycodone/CR naloxone.

OBJECTIVES: To compare the analgesic efficacy and safety of CR oxycodone/CR naloxone versus placebo in patients with chronic low back pain.

METHODS: Patients requiring opioid therapy underwent a two- to seven-day opioid washout before being randomly assigned to receive either 10 mg/5 mg CR oxycodone/CR naloxone or placebo every 12 h, titrated weekly according to efficacy and tolerability to 20 mg/10 mg, 30 mg/15 mg or 40 mg/20 mg every 12 h. After four weeks, patients crossed over to the alternative treatment for an additional four weeks. Acetaminophen/Codeine (300 mg/30 mg every 4 h to 6 h as needed) was provided as rescue medication.

RESULTS: Of the 83 randomized patients, 54 (65%) comprised the per-protocol population. According to per-protocol analysis, CR oxycodone/CR naloxone resulted in significantly lower mean (± SD) pain scores measured on a visual analogue scale (48.6 ± 23.1 mm versus 55.9 ± 25.4 mm; P=0.0296) and five-point ordinal pain intensity scores (2.1 ± 0.8 versus 2.4 ± 0.9; P=0.0415) compared with placebo. After the double-blinded phase, patients and investigators both preferred CR oxycodone/CR naloxone over placebo. These outcomes continued in the 79% of patients who chose to continue receiving CR oxycodone/CR naloxone in a six-month, open-label evaluation.

CONCLUSIONS: In patients complying with treatment as per protocol, CR oxycodone/CR naloxone was effective for the management of chronic low back pain of moderate or severe intensity.


5. Results of a double-blind, placebo-controlled, fixed-dose assessment of once-daily OROS® hydromorphone ER in patients with moderate to severe pain associated with chronic osteoarthritis.

OBJECTIVE: Opioids are recommended for patients with moderate to severe pain due to osteoarthritis (OA), who do not receive adequate analgesia from nonopioid treatment. The objective of this study was to evaluate the efficacy and safety of OROS hydromorphone extended-release (ER) compared with placebo in patients with moderate to severe pain associated with OA.

METHODS: This was a randomized, placebo-controlled, double-blind, fixed-dose study. Patients received placebo or fixed-dose OROS hydromorphone ER (8 or 16 mg). The primary efficacy measure was pain intensity score (11-point Numeric Rating Scale) at Maintenance Week 12, analyzed with baseline observation carried forward (BOCF) imputation for missing data.

RESULTS: This study did not meet the primary efficacy measure using the BOCF imputation. Study discontinuation was high (52%). When analyzed using last observation carried forward (LOCF) imputation, the prespecified alternate method, OROS hydromorphone ER 16 mg provided significantly better analgesia than placebo (P = 0.0009). Treatment was associated with significant improvements in patient global assessment (P = 0.01), the overall Western Ontario and McMaster Osteoarthritis Index (WOMAC) (P = 0.0003), and its subscales: pain (P = 0.0001), stiffness (P = 0.0023), and physical function (P = 0.0006). Gastrointestinal adverse events, such as constipation and nausea, were common among patients receiving OROS hydromorphone ER.

CONCLUSIONS: OROS hydromorphone ER failed to achieve statistical significance for the primary endpoint using the prespecified imputation method (BOCF), likely due to the high discontinuation rate associated with the fixed-dose design. When data were analyzed
6. Hydromorphone extended release for neuropathic and non-neuropathic/nociceptive chronic low back pain: a post hoc analysis of data from a randomized, multicenter, double-blind, placebo-controlled clinical trial

**OBJECTIVE:** The aim of this study was to determine the efficacy and tolerability of hydromorphone extended release (ER) in patients with chronic low back pain (LBP) with or without a neuropathic component.

**DESIGN:** This was a post hoc analysis of data from a multicenter, double-blind, placebo-controlled clinical trial using a randomized withdrawal design, performed in patients with moderate to severe chronic LBP. Patients achieving stable doses of hydromorphone ER during a 2- to 4-week conversion and titration phase were randomized to continue treatment with hydromorphone ER or taper-down to placebo during a 12-week double-blind phase. The primary efficacy outcome was the mean change in 11-point Numeric Rating Scale (NRS) pain intensity score from randomization to the final visit of the double-blind phase. Tolerability was assessed by recording adverse events (AEs). Data were analyzed separately for patients with non-neuropathic and neuropathic LBP.

**RESULTS:** A total of 173 patients with non-neuropathic/nociceptive LBP and 94 with neuropathic LBP were randomized into the double-blind phase. During the conversion and titration phase, mean (SD) NRS scores decreased significantly from 6.5 (1.87) and 6.4 (1.99) at screening to 3.3 (0.98) and 3.2 (1.05), respectively. For both LBP subgroups, patients randomized to hydromorphone ER maintained this improvement over the double-blind treatment period, whereas those randomized to placebo reported significant increase in NRS scores. Across subgroups, the incidence of 1 or more AE was 54 percent to 57 percent in the conversion and titration phase and 47 percent to 55 percent in the double-blind phase.

**CONCLUSIONS:** The results of this study indicate that hydromorphone ER is efficacious and generally well tolerated in the management of patients with non-neuropathic and neuropathic chronic LBP.

**TRIAL REGISTRATION:** ClinicalTrials.gov NCT00549042.


7. A randomized, double-blind, double-dummy comparison of short- and long-acting dihydrocodeine in chronic non-malignant pain

Guidelines for opioid treatment of chronic non-malignant pain recommend long-acting over short-acting opioid formulations. The evidence for this recommendation is weak. This study is a randomized, double-blind, double-dummy, 8-week comparison of long-acting dihydrocodeine tablets (DHC-Continus) with short-acting dihydrocodeine tablets in 60 patients with chronic non-malignant pain who were referred to a multidisciplinary pain clinic. All patients used codeine-paracetamol tablets before the trial, and paracetamol was added in both groups during the trial. The primary outcome was stability in pain intensity, measured as the difference between the highest and least pain intensity reported on an 11-point numerical rating scale in a 7-day diary. The secondary outcomes were differences in quality of life, quality of sleep, depression, and episodes of breakthrough pain between the 2 formulations. Spontaneously reported adverse events were recorded. In all, 38 patients completed the trial, and 22 withdrew before the end. The reasons for withdrawal were adverse events, lack of efficacy, or both, and were similar between the groups. There were no significant differences in stability of pain intensity between groups. There were no significant differences between groups in quality of sleep, depression, health-related quality of life, or adverse events. Breakthrough pain was experienced in both groups during the trial. Long-acting dihydrocodeine was not observed to be superior for any of the outcomes in this trial. The results of this study do not support current guidelines recommending long-acting opioids.


What is the evidence that opioids may not be very effective for chronic pain?

8. Buprenorphine for neuropathic pain in adults: meta-analysis

**BACKGROUND:** Opioid drugs, including buprenorphine, are commonly used to treat neuropathic pain, and are considered effective by some professionals. Most reviews have examined all opioids together. This review sought evidence specifically for buprenorphine, at any dose, and by any route of administration. Other opioids are considered in separate reviews.

**OBJECTIVES:** To assess the analgesic efficacy of buprenorphine for chronic neuropathic pain in adults, and the adverse events associated with its use in clinical trials.

**SEARCH METHODS:** We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE from inception to 11 June 2015, together with reference lists of retrieved papers and reviews, and two online study registries.

**SELECTION CRITERIA:** We included randomised, double-blind studies of two weeks' duration or longer, comparing any oral dose or formulation of buprenorphine with placebo or another active treatment in chronic neuropathic pain.

9. Fentanyl for neuropathic pain in adults

BACKGROUND: Opioid drugs, including fentanyl, are commonly used to treat neuropathic pain, and are considered effective by some professionals. Most reviews have examined all opioids together. This review sought evidence specifically for fentanyl, at any dose, and by any route of administration. Other opioids are considered in separate reviews.

OBJECTIVES: To assess the analgesic efficacy of fentanyl for chronic neuropathic pain in adults, and the adverse events associated with its use in clinical trials.

SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase from inception to June 2016, together with the reference lists of retrieved articles, and two online study registries.

SELECTION CRITERIA: We included randomised, double-blind studies of two weeks' duration or longer, comparing fentanyl (in any dose, administered by any route, and in any formulation) with placebo or another active treatment in chronic neuropathic pain.

DATA COLLECTION AND ANALYSIS: Two review authors independently searched for studies, extracted efficacy and adverse event data, and examined issues of study quality. We did not carry out any pooled analyses. We assessed the quality of the evidence using GRADE.

MAIN RESULTS: Only one study met our inclusion criteria. Participants were men and women (mean age 67 years), with postherpetic neuralgia, complex regional pain syndrome, or chronic postoperative pain. They were experiencing inadequate relief from non-opioid analgesics, and had not previously taken opioids for their neuropathic pain. The study used an enriched enrolment randomised withdrawal design. It was adequately blinded, but we judged it at unclear risk of bias for other criteria. Transdermal fentanyl (one-day fentanyl patch) was titrated over 10 to 29 days to establish the maximum tolerated and effective dose (12.5 to 50 µg/h). Participants who achieved a prespecified good level of pain relief with a stable dose of fentanyl, without excessive use of rescue medication or intolerable adverse events ('responders'), were randomised to continue with fentanyl or switch to placebo for 12 weeks, under double-blind conditions. Our prespecified primary outcomes were not appropriate for this study design, but the measures reported do give an indication of the efficacy of fentanyl in this condition. In the titration phase, 1 in 3 participants withdrew because of adverse events or inadequate pain relief, and almost 90% experienced adverse events. Of 258 participants who underwent open-label titration, 163 were 'responders' and entered the randomised withdrawal phase. The number of participants completing the study (and therefore continuing on treatment) without an increase of pain by more than 15/100 was 47/84 (56%) with fentanyl and 28/79 (35%) with placebo. Because only 63% responded sufficiently to enter the randomised withdrawal phase, this implies that only a maximum of 35% of participants entering the study would have had useful pain relief and tolerability with transdermal fentanyl, compared with 22% with placebo. Almost 60% of participants taking fentanyl were 'satisfied' and 'very satisfied' with their treatment at the end of the study, compared with about 40% with placebo. This outcome approximates to our primary outcome of moderate benefit using the Patient Global Impression of Change scale, but the group was enriched for responders and the method of analysis was not clear. The most common adverse events were constipation, nausea, somnolence, and dizziness. There was no information about other types of neuropathic pain, other routes of administration, or comparisons with other treatments. We downgraded the quality of the evidence to very low because there was only one study, with few participants and events, and there was no information about how data from people who withdrew were analysed.

AUTHORS' CONCLUSIONS: There is insufficient evidence to support or refute the suggestion that fentanyl works in any neuropathic pain condition.


10. Oxycodone for neuropathic pain in adults

BACKGROUND: This is an update of an earlier review that considered both neuropathic pain and fibromyalgia (Issue 6, 2014), which has now been split into separate reviews for the two conditions. This review considers neuropathic pain only. Opioid drugs, including oxycodone, are commonly used to treat neuropathic pain, and are considered effective by some professionals. Most reviews have examined all opioids together. This review sought evidence specifically for oxycodone, at any dose, and by any route of administration. Separate reviews consider other opioids.

OBJECTIVES: To assess the analgesic efficacy and adverse events of oxycodone for chronic neuropathic pain in adults.

SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE from inception to 6 November 2013 for the original review and from January 2013 to 21 December 2015 for this update. We also searched the reference lists of retrieved studies and reviews, and two online clinical trial registries. This update differs from the earlier review in that we have included studies using oxycodone in combination with naloxone, and oxycodone used as add-on treatment to stable, but inadequate, treatment with another class of drug.

SELECTION CRITERIA: We included randomised, double-blind studies of two weeks' duration or longer, comparing any dose or formulation of oxycodone with placebo or another active treatment in chronic neuropathic pain.
AUTHORS’ CONCLUSIONS: There was only very low quality evidence that oxycodone (as oxycodone MR) is of value in the treatment of painful diabetic neuropathy or postherpetic neuralgia. There was no evidence for other neuropathic pain conditions. Adverse events typical of opioids appeared to be common.


11. Hydromorphone for neuropathic pain in adults

BACKGROUND: Opioid drugs, including hydromorphone, are commonly used to treat neuropathic pain, and are considered effective by some professionals. Most reviews have examined all opioids together. This review sought evidence specifically for hydromorphone, at any dose, and by any route of administration. Other opioids are considered in separate reviews. This review is part of an update of a previous review, Hydromorphone for acute and chronic pain that was withdrawn in 2013 because it needed updating and splitting to be more specific for different pain conditions. This review focuses only on neuropathic pain.

OBJECTIVES: To assess the analgesic efficacy of hydromorphone for chronic neuropathic pain in adults, and the adverse events associated with its use in clinical trials.

AUTHORS’ CONCLUSIONS: There was insufficient evidence to support or refute the suggestion that hydromorphone has any efficacy in any neuropathic pain condition.


12. Efficacy, Tolerance, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain: A Systematic Review and Meta-analysis

IMPORTANCE: Opioid analgesics are commonly used for low back pain, however, to our knowledge there has been no systematic evaluation of the effect of opioid dose and use of enrichment study design on estimates of treatment effect.

OBJECTIVE: To evaluate efficacy and tolerability of opioids in the management of back pain; and investigate the effect of opioid dose and use of an enrichment study design on treatment effect.

DATA SOURCES: Medline, EMBASE, CENTRAL, CINAHL, and PsycINFO (inception to September 2015) with citation tracking from eligible randomized clinical trials (RCTs).

STUDY SELECTION: Placebo-controlled RCTs in any language.

DATA EXTRACTION AND SYNTHESIS: Two authors independently extracted data and assessed risk of bias. Data were pooled using a random effects model with strength of evidence assessed using the grading of recommendations assessment, development, and evaluation (GRADE).

MAIN OUTCOMES AND MEASURES: The primary outcome measure was pain. Pain and disability outcomes were converted to a common 0 to 100 scale, with effects greater than 20 points considered clinically important.

RESULTS: Of 20 included RCTs of opioid analgesics (with a total of 7925 participants), 13 trials (3419 participants) evaluated short-term effects on chronic low back pain, and no placebo-controlled trials enrolled patients with acute low back pain. In half of these 13 trials, at least 50% of participants withdrew owing to adverse events or lack of efficacy. There was moderate-quality evidence that opioid analgesics reduce pain in the short term; mean difference (MD), -10.1 (95% CI, -12.8 to -7.4). Meta-regression revealed a 12.0 point greater pain relief for every 1 log unit increase in morphine equivalent dose (P = .046). Clinically important pain relief was not observed within the dose range evaluated (40.0-240.0-mg morphine equivalents per day). There was no significant effect of enrichment.
13. Long-term opioid management for chronic non-cancer pain

BACKGROUND: Opioid therapy for chronic non-cancer pain (CNCP) is controversial due to concerns regarding long-term effectiveness and safety, particularly the risk of tolerance, dependence, or abuse.

OBJECTIVES: To assess safety, efficacy, and effectiveness of opioids taken long-term for CNCP.

SEARCH STRATEGY: We searched 10 bibliographic databases up to May 2009.

SELECTION CRITERIA: We searched for studies: 1. collected efficacy data on participants after at least 6 months of treatment; were full-text articles; did not include redundant data; were prospective; enrolled at least 10 participants; reported data of participants who had CNCP. Randomized controlled trials (RCTs) and pre-post case-series studies were included.

DATA COLLECTION AND ANALYSIS: Two review authors independently extracted safety and effectiveness data and settled discrepancies by consensus. We used random-effects meta-analysis to summarize data where appropriate, used the I(2) statistic to quantify heterogeneity, and, where appropriate, explored heterogeneity using meta-regression. Several sensitivity analyses were performed to test the robustness of the results.

MAIN RESULTS: We reviewed 26 studies with 27 treatment groups that enrolled a total of 4893 participants. Twenty five of the studies were case series or uncontrolled long-term trial continuations. The other was an RCT comparing two opioids. Opioids were administered orally (number of study treatments groups [abbreviated as "k"] = 12, n = 3040), transdermally (k = 5, n = 1628), or intrathecally (k = 10, n = 231). Many participants discontinued due to adverse effects (oral: 22.9% [95% confidence interval (CI): 15.3% to 32.8%]; transdermal: 12.1% [95% CI: 4.9% to 27.0%]; intrathecal: 8.9% [95% CI: 4.0% to 26.1%]); or insufficient pain relief (oral: 10.3% [95% CI: 7.6% to 13.9%]; intrathecal: 7.6% [95% CI: 3.7% to 14.8%]; transdermal: 5.8% [95% CI: 4.2% to 7.9%]). Signs of opioid addiction were reported in 0.27% of participants in the studies that reported that outcome. All three modes of administration were associated with clinically significant reductions in pain, but the amount of pain relief varied among studies. Findings regarding quality of life and functional status were inconclusive due to an insufficient quantity of evidence for oral administration studies and inconclusive statistical findings for transdermal and intrathecal administration studies.

AUTHORS' CONCLUSIONS: Many patients discontinue long-term opioid therapy (especially oral opioids) due to adverse events or insufficient pain relief; however, weak evidence suggests that patients who are able to continue opioids long-term experience clinically significant pain relief. Whether quality of life or functioning improves is inconclusive. Many minor adverse events (like nausea and headache) occurred, but serious adverse events, including iatrogenic opioid addiction, were rare.


Clinical question: Are opioids effective in the treatment of chronic low-back pain?

Study design: Meta-analysis (randomized controlled trials)

Setting: Various (meta-analysis)

Synopsis: This is an update to a Cochrane Review published in 2007. The authors systematically searched several databases to identify randomized trials comparing opioids with placebo or other drugs. The studies had to have masked outcome assessments and evaluated at least one of the following: pain, function, global improvement, or the proportion of patients reporting 30% or 50% pain relief. Two authors independently assessed studies for inclusion, reconciling disagreements by discussion. Additionally, 3 authors independently extracted data from included studies. Finally, they used an explicit approach to assess the quality of each study and to assess the role of publication bias. Eventually, these authors included 15 trials with 5540 participants. For the most part, the reviewed trials had low to moderate quality, high drop-out rates, short duration, and limited interpretability of functional improvement. Six studies evaluated tramadol alone or in combination with acetaminophen (5 compared with placebo, 1 as an active comparator against a centrally acting non-opioid); 2 studies compared buprenorphine with placebo; and 7 studies assessed strong opioids (morphine, oxymorphone, hydromorphone, oxycodone). Of the 7 trials of strong opioids, 3 were not really designed to assess opioid efficacy. Twelve of the 15 total studies were at low risk of bias. The 5 studies comparing tramadol with placebo generally had more methodologic bias and showed greater overall pain relief than placebo and greater improvement in functional outcomes than placebo. In the 2 studies of buprenorphine, the authors found very-low-quality evidence that this agent reduces pain more than placebo and that it does anything for function. The studies of strong opioids found small reductions in pain and small improvements in function.

Bottom line: Overall, in patients with chronic low-back pain, opioids are moderately more effective than placebo in the short term for pain relief and slightly more effective in the short term for improving function. However, data for long-term use are pretty much nonexistent. The long-term use of opioids for patients with chronic low-back pain is controversial. Physicians are asked to provide comfort to patients, yet the regulatory and safety concerns of long-term use are a sobering counterpoint.

What can primary care clinicians do to improve management of their patients with chronic pain?

15. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016

**IMPORTANCE:** Primary care clinicians find managing chronic pain challenging. Evidence of long-term efficacy of opioids for chronic pain is limited. Opioid use is associated with serious risks, including opioid use disorder and overdose.

**OBJECTIVE:** To provide recommendations about opioid prescribing for primary care clinicians treating adult patients with chronic pain outside of active cancer treatment, palliative care, and end-of-life care.

**PROCESS:** The Centers for Disease Control and Prevention (CDC) updated a 2014 systematic review on effectiveness and risks of opioids and conducted a supplemental review on benefits and harms, values and preferences, and costs. CDC used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework to assess evidence type and determine the recommendation category.

**EVIDENCE SYNTHESIS:** Evidence consisted of observational studies or randomized clinical trials with notable limitations, characterized as low quality using GRADE methodology. Meta-analysis was not attempted due to the limited number of studies, variability in study designs and clinical heterogeneity, and methodological shortcomings of studies. No study evaluated long-term (≥1 year) benefit of opioids for chronic pain. Opioids were associated with increased risks, including opioid use disorder, overdose, and death, with dose-dependent effects.

**RECOMMENDATIONS:** There are 12 recommendations. Of primary importance, non-opioid therapy is preferred for treatment of chronic pain. Opioids should be used only when benefits for pain and function are expected to outweigh risks. Before starting opioids, clinicians should establish treatment goals with patients and consider how opioids will be discontinued if benefits do not outweigh risks.

When opioids are used, clinicians should prescribe the lowest effective dosage, carefully reassess benefits and risks when considering increasing dosage to 50 morphine milligram equivalents or more per day, and avoid concurrent opioids and benzodiazepines whenever possible. Clinicians should evaluate benefits and harms of continued opioid therapy with patients every 3 months or more frequently and review prescription drug monitoring program data, when available, for high-risk combinations or dosages. For patients with opioid use disorder, clinicians should offer or arrange evidence-based treatment, such as medication-assisted treatment with buprenorphine or methadone.

**CONCLUSIONS AND RELEVANCE:** The guideline is intended to improve communication about benefits and risks of opioids for chronic pain, improve safety and effectiveness of pain treatment, and reduce risks associated with long-term opioid therapy.


16. Empowering Patients with Persistent Pain Using an Internet-based Self-Management Program

New strategies are needed to improve access to cognitive and behavioral therapies for patients with persistent pain. The purpose of this randomized, controlled trial was to determine the effectiveness of the Chronic Pain Management Program, an 8-week online intervention targeting cognitive, emotional, behavioral, and social pain determinants. Program efficacy and engagement was evaluated for 92 individuals with a diagnosis of chronic non-cancer pain who had a current opioid prescription. Participants were recruited from primary care practices and Internet sites, then randomly assigned to receive access to the intervention either immediately (treatment group) or after an 8-week delay (wait-list comparison). Biweekly self-report measurements were collected using online surveys on pain, depressive symptoms, pain self-management behaviors, and health care utilization during the 8-week trial. Additional measurements of opioid misuse behaviors, pain self-efficacy, and medicine regimens were completed at baseline and week 8. Engagement was evaluated by examining completion of program learning modules. The results from analysis of variance showed that at week 8, the treatment group had significantly greater improvements on pain self-efficacy and opioid misuse measures than the wait-list comparison group. Engagement level was positively associated with improvements in pain intensity, pain interference, and pain self-efficacy. In conclusion, patients on opioids were able to engage and demonstrate positive outcomes using an Internet-based self-management program. Future efforts toward heightening engagement could further maximize impacts.


17. Telecare collaborative management of chronic pain in primary care: a randomized clinical trial

**IMPORTANCE:** Chronic musculoskeletal pain is among the most prevalent, costly, and disabling medical disorders. However, few clinical trials have examined interventions to improve chronic pain in primary care.

**OBJECTIVE:** To determine the effectiveness of a telecare intervention for chronic pain.

**DESIGN, SETTING, AND PARTICIPANTS:** The Stepped Care to Optimize Pain Care Effectiveness (SCOPE) study was a randomized trial comparing a telephone-delivered collaborative care management intervention vs usual care in 250 patients with chronic (≥3 months) musculoskeletal pain of at least moderate intensity (Brief Pain Inventory [BPI] score ≥5). Patients were enrolled from 5 primary care clinics in a single Veterans Affairs medical center from June 2010 through May 2012, with 12-month follow-up completed by June 2013.

**INTERVENTIONS:** Patients were randomized either to an intervention group (n = 124) or to a usual care group whose members...
received all pain care as usual from their primary care physicians (n = 126). The intervention group received 12 months of telecare management that coupled automated symptom monitoring with an algorithm-guided stepped care approach to optimizing analgesics.

**MAIN OUTCOMES AND MEASURES:** Primary outcome was the BPI total score, which ranges from 0 ("no pain") to 10 ("pain as bad as you can imagine") and for which a 1-point change is considered clinically important. Secondary pain outcomes included BPI interference and severity, global pain improvement, treatment satisfaction, and use of opioids and other analgesics.

**RESULTS:** Overall, mean (SD) baseline BPI scores in the intervention and control groups were 5.31 (1.81) and 5.12 (1.80), respectively. Compared with usual care, the intervention group had a 1.02-point lower (95% CI, -1.58 to -0.47) BPI score at 12 months (3.57 vs 4.59). Patients in the intervention group were nearly twice as likely to report at least a 30% improvement in their pain score by 12 months (51.7% vs 27.1%; relative risk, 1.9 [95% CI, 1.4 to 2.7]), with a number needed to treat of 4.1 (95% CI, 3.0 to 6.4) for a 30% improvement. Secondary pain outcomes also improved. Few patients in either group required opioid initiation or dose escalation.

**CONCLUSIONS AND RELEVANCE:** Telecare collaborative management increased the proportion of primary care patients with improved chronic musculoskeletal pain. This was accomplished by optimizing non-opioid analgesic medications using a stepped care algorithm and monitoring.

**TRIAL REGISTRATION:** clinicaltrials.gov Identifier: NCT00926588.


18. Opioid users did as well as non-users in a telephone intervention to reduce chronic pain

**OBJECTIVE:** To examine effects of pre-enrollment opioid use on outcomes of a 12-month collaborative pain care management trial. We hypothesized that participants with opioid use would have worse pain at baseline; use more health care services and analgesics; and have worse pain outcomes during the trial.

**DESIGN:** Secondary analysis of randomized controlled trial data.

**SETTING:** Veterans Affairs (VA) primary care.

**SUBJECTS:** Patients age 18-65 years with chronic pain of at least moderate severity who were enrolled in a 12-month pragmatic trial of a telephone-based collaborative care intervention for chronic musculoskeletal pain.

**METHODS:** Participants were categorized as opioid users (n = 84) or non-users (n = 166) at baseline and trial randomization was stratified by opioid use. We used logistic regression to examine cross-sectional associations with baseline opioid use and mixed-effect models for repeated measures to examine baseline opioid use as a predictor of Brief Pain Inventory (BPI) scores over 12 months.

**RESULTS:** At baseline, 33.6% reported use of prescribed opioids. Baseline opioid users had higher baseline BPI scores and higher health-related disability than non-users. Baseline opioid users also had more outpatient visits (15.0 vs. 10.1; p = 0.001) and received more analgesics (p < 0.001) during the trial. In the final multivariable model examining effects of baseline opioid use on BPI over 12 months, opioid users and nonusers had a non-significant difference of 0.25 points (p = 0.098). In conclusion, although baseline opioid users had worse pain at baseline and used more health care during the study, response to the intervention was not significantly modified by pre-existing opioid therapy.


19. Therapeutic Interactive Voice Response (TIVR) to reduce analgesic medication use for chronic pain management

This paper examines whether a telephone-based, automated maintenance enhancement program can help to reduce opioid and nonsteroidal anti-inflammatory drugs (NSAID) analgesic use in patients with chronic pain. Following 11 weeks of group cognitive-behavioral therapy (CBT), 51 subjects with chronic musculoskeletal pain were randomized to 1 of 2 study groups. Twenty-six subjects participated in 4 months of a Therapeutic Interactive Voice Response (TIVR) program in addition to standard follow-up care, while a control group of 25 subjects received standard follow-up care only. TIVR is an automated, telephone-based tool developed for the maintenance and enhancement of CBT skills. Opioid analgesic use decreased in the experimental group in both follow-ups: 4 and 8 months post CBT. In addition, at 8-month follow-up, 21% of the TIVR subjects had discontinued the use of opioid analgesics, 23% had discontinued NSAIDs, and 10% had discontinued antidepressant medications. In contrast, the control group showed increases in opioid and NSAIDs use. Analysis of covariance (ANCOVA) revealed significant between-group differences in opioid analgesic use at 8-month follow up (P = .004). We have previously demonstrated the efficacy of TIVR to decrease pain and improve coping; this analysis demonstrates that the use of TIVR may also result in concurrent reductions in opioid analgesic and NSAID medications use.

**AUTHORS CONCLUSIONS:** This article demonstrates that the Therapeutic Interactive Voice Response maintenance enhancement program can help to reduce opioid analgesic use in patients with chronic pain. This automated maintenance enhancement program could potentially assist patients not only to decrease pain and improve coping, but also to diminish the likelihood of opioid dependence.


20. RCT: Treatment outcome of chronic non-malignant pain patients managed in a Danish multidisciplinary pain center compared to general practice
This randomised controlled study investigated the effect of outpatient multidisciplinary pain centre treatment (MPT) compared with treatment by a general practitioner after initial supervision by a pain specialist (GP-group) and with a group of patients waiting for 6 months before treatment was initiated (WL-group). One-hundred-and-eighty-nine chronic non-malignant pain patients were studied. At referral, and after 3 and 6 months patients filled in questionnaires evaluating pain intensity, health related quality of life (HRQL) and use of analgesics. HRQL was evaluated using the Medical Outcome Study-Short Form (SF-36), the Hospital Anxiety and Depression scale (HAD) and the Psychological General Well-being Scale (PGWB). After 6 months patients allocated to MPT (n=63) reported statistically significant reduction in pain intensity (VAS-score, P<0.001), improvement in psychological well-being (PGWB, P<0.001), quality of sleep (P<0.05) and physical functioning (SF-36-Physical Functioning, P<0.05). No improvements were seen in the GP-group (n=63). In the WL-group (n=63) a statistically significant deterioration was observed in PGWB-scores, HAD-scores and in 6 of 8 SF-36-subscores (P <= 0.05). A reduction in use of opioids administered on demand was obtained in the group receiving MPT (P<0.001). In the MPT- and GP-groups a decrease in the use of short acting opioids was observed (P<0.01). No change in use of analgesics was seen in the WL-group. The study showed that (i) in the MPT-group there was a significant reduction in pain intensity and improvement of HRQL compared to the WL-group, and (ii) the mere establishment of a pain diagnosis and a pain management plan by a pain specialist was not sufficient to enable the referring GP to manage severely chronic pain patients.

21. Prescription Opioids and Risk of Dementia or Cognitive Decline: A Prospective Cohort Study

OBJECTIVES: To determine whether prescription opioid use is associated with higher dementia risk or greater cognitive decline.

DESIGN: Prospective cohort study.

SETTING: Group Health, an integrated healthcare delivery system.

PARTICIPANTS: Community-dwelling individuals aged 65 and older without dementia with at least 10 years of Group Health enrollment at baseline (N = 3,434; median age 74).

MEASUREMENTS: The Cognitive Abilities Screening Instrument (CASI) was administered every 2 years. Low scores triggered detailed evaluation, and a multidisciplinary committee assigned dementia diagnoses. From computerized pharmacy data, cumulative opioid exposure was defined as total standardized doses (TSDs) dispensed over 10 years (excluding the most recent year because of possible prodromal symptoms). For comparison, use of nonsteroidal anti-inflammatory drugs (NSAIDs), characterized similarly, was examined. Dementia risk was analyzed using Cox proportional hazards models and CASI trajectory using linear regression models and generalized estimating equations.

RESULTS: Seven hundred ninety-seven participants (23%) developed dementia over a mean follow-up of 7.3 years; 637 (19%) had possible or probable Alzheimer's disease. For cumulative opioid use, the hazard ratios (HRs) for dementia were 1.06 (95% confidence interval (CI) = 0.88-1.26) for 11 to 30 TSDs, 0.88 (95% CI = 0.70-1.09) for 31 to 90 TSDs, and 1.29 (95% CI = 1.02-1.62) for 91 or more TSDs, versus 0 to 10 TSDs. A similar pattern was seen for NSAID use. Heavier opioid use was not associated with more-rapid cognitive decline.

CONCLUSION: People with the heaviest opioid or NSAID use had slightly higher dementia risk than people with little or no use. These results may reflect an effect of chronic pain on cognition or residual confounding. Although opioids have other risks, little evidence of long-term cognitive harm specific to opioids was found.


Bottom Lines

1. Opioids are somewhat effective for chronic non-cancer pain of up to 6 months duration. However, the comparisons have been with placebo rather than other active pain medications and treatments.

2. There are no randomized trials of long term use of opioids for chronic pain.

3. Opioids are generally ineffective for neuropathic pain.

4. For acute low back pain, use naproxen.

5. Start an opioid treatment policy and protocol for your practice that is informed by the CDC guidelines.
5. Use an interdisciplinary approach to treating patients with chronic pain; consider innovative interventions and don’t go it alone.

6. There is little evidence that opioid use leads to long term cognitive impairment.
Editor’s Choice 2017

These POEMs were selected because they don’t fit in other categories, but are worth knowing about.

1. Antipsychotics worsen symptoms in patients with delirium who receive palliative care

**Clinical question:** Do antipsychotic drugs improve symptoms of distress associated with delirium in patients receiving palliative care?

**Study design:** Randomized controlled trial (double-blinded)

**Allocation:** Concealed

**Setting:** Inpatient (ward only)

**Synopsis:** These authors searched multiple databases (PubMed, EMBASE, Cochrane, and others) to identify observational studies and randomized trials of patients who had minor outpatient cutaneous surgical procedures in which the physician used either sterile or nonsterile gloves. The procedures included excisions, Mohs surgery, laceration repairs, and tooth extractions. They identified both observational studies and randomized controlled trials. They included pretty much any comparative study, including nonrandomized trials and before/after studies, as long as the original authors used validated instruments to assess burnout, emotional exhaustion, or depersonalization. Two reviewers independently assessed articles for potential inclusion and methodologic quality.

**Characterized by emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment, burnout has been associated with medical errors, diminished engagement, adverse personal health, and departure from practice. These authors systematically reviewed multiple databases and registries, and references of relevant studies and past reviews, to identify studies reporting the outcomes of interventions to prevent and reduce physician burnout. They included pretty much any comparative study, including nonrandomized trials and before/after studies, as long as the original authors used validated instruments to assess burnout, emotional exhaustion, or depersonalization. Two reviewers independently assessed articles for potential inclusion and methodologic quality. They resolved discrepancies by consensus. They anticipated significant heterogeneity so the authors used conservative (inappropriate behavior, inappropriate communication, and illusions/hallucinations) Each item was scored from 0 to 2, based on the presence and intensity of the symptom, for a total score of 0 to 6. The primary outcome was the average of the last 2 delirium symptom scores on day 3 of treatment. The 3 study groups had similar delirium symptom scores at baseline. The mean age in each group was 75 years and almost 90% of patients had cancer. Analysis was by intention to treat. Overall, patients who received haloperidol and patients who received risperidone had significantly higher delirium symptom scores at day 3 as compared with those who received placebo by an average of 0.48 and 0.24, respectively. Both intervention groups also required more rescue midazolam than did the placebo group. Finally, the haloperidol group was noted to have decreased overall survival compared with the placebo group (hazard ratio 1.73; 95% CI 1.20 - 2.50; P = .003). The authors suggest that this may be due to prolonged delirium or longer exposure to antipsychotics. Survival was also decreased in the risperidone group, though this did not reach statistical significance.

**Bottom line:** For hospitalized patients with acute delirium and symptoms of distress who are receiving palliative care, the use of risperidone or haloperidol at conservative oral doses worsens symptoms and may shorten overall survival. (LOE = 1b)


2. Use of nonsterile gloves does not increase risk of infection for outpatient skin procedures

**Clinical question:** Does the use of sterile gloves when performing minor outpatient cutaneous surgeries reduce the risk of infection?

**Study design:** Meta-analysis (randomized controlled trials)

**Setting:** Various (guideline)

**Synopsis:** These researchers enrolled 247 hospitalized patients who were receiving palliative care and had delirium-related symptoms of distress. Patients were randomized, using concealed allocation, to receive either oral risperidone, haloperidol, or placebo for 72 hours for the management of these symptoms. There were slightly more than 80 patients in each of the 3 arms. The initial dose for both risperidone and haloperidol was 1 mg, with maintenance doses of 0.5 mg every 12 hours titrated to a maximum dose of 4 mg per day. Patients older than 65 years received half this dose. All patients also received nonpharmacologic measures for delirium treatment, such as vision and/or hearing aids and frequent reorientation, as well as treatment for reversible precipitants of delirium. Subcutaneous midazolam was given as needed for patients who required immediate intervention for safety or distress. Delirium symptoms scores were obtained every 8 hours using the 3 items on the Nursing Delirium Screening Scale that are considered measures of distress (inappropriate behavior, inappropriate communication, and illusions/hallucinations). Each item was scored from 0 to 2, based on the presence and intensity of the symptom, for a total score of 0 to 6. The primary outcome was the average of the last 2 delirium symptom scores on day 3 of treatment. The 3 study groups had similar delirium symptom scores at baseline. The mean age in each group was 75 years and almost 90% of patients had cancer. Analysis was by intention to treat. Overall, patients who received haloperidol and patients who received risperidone had significantly higher delirium symptom scores at day 3 as compared with those who received placebo by an average of 0.48 and 0.24, respectively. Both intervention groups also required more rescue midazolam than did the placebo group. Finally, the haloperidol group was noted to have decreased overall survival compared with the placebo group (hazard ratio 1.73; 95% CI 1.20 - 2.50; P = .003). The authors suggest that this may be due to prolonged delirium or longer exposure to antipsychotics. Survival was also decreased in the risperidone group, though this did not reach statistical significance.

**Bottom line:** It is fine to use nonsterile gloves for common outpatient skin procedures, such as laceration repair and lesion excisions.


3. Individual and organizational approaches can ease physician burnout

**Clinical question:** What strategies are effective in easing physician burnout?

**Study design:** Meta-analysis (other)

**Setting:** Various (meta-analysis)

**Synopsis:** Nearly half of all physicians experience at least one symptom of burnout, though rates vary greatly among specialties. Characterized by emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment, burnout has been associated with medical errors, diminished engagement, adverse personal health, and departure from practice. These authors search multiple databases and registries, and references of relevant studies and past reviews, to identify studies reporting the outcomes of interventions to prevent and reduce physician burnout. They included pretty much any comparative study, including nonrandomized trials and before/after studies, as long as the original authors used validated instruments to assess burnout, emotional exhaustion, or depersonalization. Two reviewers independently assessed articles for potential inclusion and methodologic quality. They resolved discrepancies by consensus. They anticipated significant heterogeneity so the authors used conservative approaches to estimating the effects of the interventions. Ultimately, they included 15 randomized trials with 716 physicians, and 37 observational studies with 2914 physicians. Among the randomized trials, 3 addressed organizational changes (eg, work intensity,
changes in work processes) and 12 addressed individual approaches (eg, self-care, stress management, mindfulness). Among the 37 observational studies, 17 involved structural interventions and 20 focused on the individual. In the randomized trials, the interventions had no effect on overall burnout or depersonalization scores, but slightly reduced emotional exhaustion scores. Among the observational studies, the overall burnout and emotional exhaustion scores improved, but the depersonalization scores did not. When the authors pooled all studies, overall burnout, emotional exhaustion, and depersonalization scores improved. The authors note that a 1-point change in burnout scores is associated with a meaningful difference in self-perceived major medical errors and suicidal ideation. Finally, among the randomized trials, the authors report the absolute rate of burnout was 54% in control groups compared with 44% in the intervention groups (number needed to treat [NNT] = 10; 95% CI 8 - 20). High emotional exhaustion decreased from 38% to 24% (NNT = 7; 6 - 9) and high depersonalization minimally decreased from 38% to 34% (NNT = 25).

**Bottom line:** In this systematic review, individual and organizational approaches can prevent and reduce physician burnout, improve emotional exhaustion, and slightly decrease depersonalization. (LOE = 2a⁻)


### 4. Guideline for the management of primary aldosteronism

**Clinical question:** What is the best evidence regarding the diagnosis and treatment of primary aldosteronism?

**Study design:** Practice guideline

**Funding source:** Foundation

**Setting:** Various (guideline)

**Synopsis:** Previous studies report PA in 5% to 10% of patients with hypertension. Patients with PA have higher cardiovascular morbidity and mortality than age- and sex-matched patients with the same degree of blood pressure (BP) elevation. This is a guideline developed by the Endocrine Society, with input from the European Society of Endocrinology, the American Heart Association, the American Association of Endocrine Surgeons, and several other relevant groups. There was no input from primary care organizations, though.

The group was not supported by any industry funding, and a majority of guideline panelists did not have a relevant conflict of interest. Rather than do their own systematic reviews, they relied on 4 previously published systematic reviews. Recommendations were graded as very low–quality, low-quality, moderate-quality, or high-quality evidence; most of the recommendations in this guideline were in the very low or low categories, and were accordingly based on expert opinion. The authors recommend looking for PA in patients with any of the following: BP higher than 140/90 despite 3 antihypertensives, or BP lower than 140/90 while taking 4 antihypertensives; hypertension plus hypokalemia; hypertension and adrenal incidentaloma; hypertension and sleep apnea; hypertension and a family history of early-onset hypertension; and any first-degree relatives with confirmed PA who are also hypertensive. Basically, patients with high-risk, hard-to-control hypertension and those with concomitant adrenal lesion or hypokalemia. The prevalence of PA ranges from 2% to 34% in these groups. The initial test should be a plasma aldosterone-renin ratio, obtained at least 2 hours after awakening, and after the patient has been seated comfortably for approximately 10 minutes. Withdraw any agents that markedly affect the plasma aldosterone-renin ratio (such as spironolactone, eplerenone, amiloride, and triamterene, potassium-wasting diuretics, and products derived from licorice root) for at least 4 weeks before test. There is no need for confirmatory testing in patients with hypokalemia, an undetectable plasma renin level, and a plasma aldosterone concentration greater than 20 ng/dL (550 pmol/L). For other patients, a confirmatory test—such as an oral sodium loading test, a captopril challenge test, or a saline infusion test—should be performed, and all patients should have an adrenal computed tomography to evaluate for adrenocortical carcinoma or large adenoma. Recommended treatment for unilateral PA is a laparoscopic adrenalectomy (hypertension is improved in all patients and cured in 30% to 60%), and medical therapy with spironolactone or eplerenone for patients who refuse surgery or have bilateral disease.

**Bottom line:** Consider primary aldosteronism (PA) in patients with hard-to-control hypertension, and those with hypertension and concomitant hypokalemia or sleep apnea. The initial test is the plasma aldosterone-renin ratio, and the treatment may be surgical or medical. (LOE = 1a⁻)


### 5. Guideline for the management of primary adrenal insufficiency

**Clinical question:** What is the latest evidence regarding the management of primary adrenal insufficiency?

**Study design:** Practice guideline

**Funding source:** Foundation

**Setting:** Various (guideline)

**Synopsis:** This guideline was developed by the Endocrine Society, the European Society of Endocrinology, and the American Association for Clinical Chemistry. The guideline committee included 9 endocrinologists, a methodologist, and a medical writer. The authors had a number of financial conflicts of interest, but according to the description of methods, most did not have interests related to the question at hand. The guideline was not funded by industry in any way. The committee commissioned 2 systematic reviews, one on the accuracy of high-dose versus low-dose adrenocorticotropic hormone stimulation tests, and the second on the comparative efficacy of various glucocorticoid regimens. Evaluation for PAI should be undertaken in acutely ill patients with otherwise unexplained symptoms such as hypotension, hyponatremia, hyperkalemia, volume depletion, hyperpigmentation, or hypoglycemia. The authors include unexplained abdominal pain and fever in that list, but PAI seems pretty far down the list of causes, so these symptoms probably shouldn't be included in the first wave. The recommended tests are an intravenous corticotropin stimulation test with a dose of 250 micrograms for adults and children 2 years and older, 125 micrograms for children younger than 2 years, and 15 micrograms per kg for infants. A peak cortisol level of less than 500 nmol/L (18 micrograms/dL) at 30 or 60 minutes is diagnostic for adrenal insufficiency. The recommended treatment regimen is hydrocortisone in a dose of 20 mg to 35 mg per day, given in 2 or 3 divided doses. The largest
dose should be given in the morning, and the second dose given 2 hours after lunch. For a 3-dose regimen, the third dose would be
given later in the afternoon. Patients should also receive fludrocortisone, beginning at a dose of 50 to 100 micrograms; patients should
not restrict their salt intake. Dexamethasone should be avoided. DHEA replacement can be considered in women with PAI who have
depression, fatigue, or low libido. If adrenal crisis is suspected, a 100-mg dose of hydrocortisone should be given immediately.
**Bottom line:** This guideline provides recommendations regarding the diagnosis and treatment for patients with primary adrenal
insufficiency (PAI). (LOE = 1a)

6. 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)
**Funding source:** Government
**Allocation:** Uncertain
**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. (LOE = 1b)
Hamdy FC, Donovan JL, Lane JA, et al, for the ProtecT Study Group. 10-Year outcomes after monitoring, surgery, or radiotherapy for

7. Least adverse treatment outcomes with active surveillance of clinically localized prostate CA
(ProtecT)

**Clinical question:** How do the different treatment options for localized prostate cancer affect quality of life, treatment complications,
and other patient-reported outcomes?
**Study design:** Randomized controlled trial (single-blinded)
**Funding source:** Government
**Allocation:** Uncertain
**Setting:** Outpatient (specialty)
**Synopsis:** This large, well-designed clinical trial randomized men aged 50 to 69 years with localized, screen-detected prostate cancer
(stage T1c or 2) to receive 1 of 3 management strategies: (1) active surveillance (AS) with frequent prostate-specific antigen tests and
biopsy and/or treatment of significant elevations, (2) radiotherapy, or (3) radical prostatectomy. Mortality results are reported in another
study (N Engl J Med 2016;375(15):1415-1424). Patients filled out questionnaires at baseline, at 6 months and 12 months after
enrollment, and annually after that. A variety of validated measures of urinary function, sexual function, bowel function, and overall
quality of life were used. In general, urinary outcomes were worst for surgery and similar for AS or radiotherapy (approximately 50% of
the men who underwent surgery used at least one pad per day at 6 months, declining to approximately 20% at 4 years; no more than
approximately 12% used at least one pad per day in the other groups). Nocturia was initially worse in patients who underwent
radiotherapy, but recovered within 1 year. Erectile function declined in all groups but remained worse in the prostatectomy group at all
evaluation points. Additionally, patients in the radiotherapy group had worse outcomes than those in the AS group for some of the
measures (eg, erection firmness), especially in the first year after randomization. Bowel function was slightly worse for patients who
underwent radiotherapy, but was generally similar between groups. Finally, overall health-related quality of life was similar between
groups. However, this is a fairly blunt instrument that focuses on things like activities of daily living and functional status, and does not
do a good job of assessing the impact of the specific complications of prostate cancer treatment
**Bottom line:** In general, patients with clinically localized prostate cancer who were randomized to receive active surveillance had better
patient-reported outcomes related to incontinence, erectile function, and bowel function than those who received radiotherapy, and
especially better than those who received radical prostatectomy. (LOE = 1b)
8. Men with localized prostate cancer have inaccurate perceptions of their prognosis

Clinical question: What do men with localized prostate cancer believe about their likely outcomes with treatment and without treatment?

Study design: Cross-sectional

Setting: Population-based

Synopsis: This team of researchers used the Metropolitan Detroit Cancer Surveillance System to identify 118 black men and 119 white men younger than 75 years with localized prostate cancer. They surveyed the men about their cancer treatment choice, reasons for that choice, and what options were offered and recommended. They also asked the men 2 additional questions: "How long do you expect you would live without any treatment for your prostate cancer?" and "How long do you expect you would live with your treatment of choice for your prostate cancer?" Approximately 33% of the men reported they would live less than 5 years without treatment, about 40% said they would live 5 to 10 years, and about 26% thought they would live more than a decade. However, nearly 90% of the men thought they would live more than a decade with the treatment they chose. The authors found no substantive differences in these responses by race or actual tumor risk. There were some minor differences based on actual treatment choice, overall health perception, and the perception of the seriousness of cancer in general.

Bottom line: Men younger than 75 years with localized prostate cancer grossly underestimate their survival chances without treatment and significantly overestimate the survival associated with treatment. This is probably a reflection of the messages men get from the media and from various medical groups. (LOE = 2c)


9. ACP chronic insomnia guideline: CBT before drugs

Clinical question: How should chronic insomnia be managed?

Study design: Practice guideline

Setting: Various (guideline)

Synopsis: This guideline addresses the treatment of chronic insomnia, defined as a sleep disorder that causes significant functional distress or impairment at least 3 nights a week for 3 months. The recommendations are based on a systematic review of treatment options. Based on moderate-quality evidence, cognitive behavioral therapy aimed at insomnia improved remission, treatment response, time to sleep, waking after sleep onset, and sleep quality. Treatment can be delivered as individual or group therapy, by telephone, web-based, or via self-help books. Harm with therapy may occur but has not been reported in studies. Cognitive behavioral therapy for insomnia consists of: (1) Cognitive therapy aimed at dysfunctional beliefs and attitudes toward sleep and insomnia; (2) stimulus control: avoiding nonsleep activities in the bedroom; (3) sleep restriction: limiting time in bed to match perceived sleep duration to assure that more than 85% of time spent in bed was spent sleeping; (4) sleep hygiene: typical measures of alcohol, caffeine, and nicotine intake and sleep scheduling; and (5) relaxation techniques: meditation, mindfulness, and so forth. Drug therapy using newer hypnotics—eszopiclone (Lunesta), zolpidem (Ambien), and suvorexant (Belsomra)—improves some aspects of sleep, though most studies of these drugs were of low quality. Benzodiazepine hypnotics have not been studied for long-term use. Doxepin, in a low-quality study, was shown to improve total sleep time and waking after sleep onset, but other older medicines, such as diphenhydramine and trazodone, have not been studied. Drug treatment was judged to be second-line therapy because of its cost and harms. This group suggests using medicine for no longer than 4 to 5 weeks, if possible.

Bottom line: Based on a systematic review of randomized trials, the American College of Physicians recommends cognitive behavioral therapy as initial treatment for insomnia, reserving pharmacologic therapy as second-line treatment after a discussion of benefits and risks with the patient. Unfortunately, the guideline does not present the data in a way that would facilitate this discussion. (LOE = 5)


10. Over-reading of breast biopsy samples is common

Clinical question: How accurate are breast biopsy interpretations and can they be improved?

Study design: Diagnostic test evaluation

Setting: Other

Synopsis: There is no consensus on when second opinions should be solicited with regard to interpretation of breast biopsy specimens. To test different approaches, these U.S. investigators selected 240 breast biopsy specimens and sent them to 115 pathologists, each pathologist receiving 60 slides. The 240 cases included benign without atypia (30%), atypia (30%), ductal carcinoma in situ (30%), and invasive cancer (10%), as determined by an expert panel. Using the results of the readings by the sample of pathologists, the authors were able to compare 12 different strategies for acquiring independent second opinions; that is, find the best approach for when to request a second opinion. The overall misclassification rate was 24.7%. On average, 3.9% of invasive breast cancers were missed with a single read. Overinterpretation was common. Of benign samples, 12.9% were overinterpreted when read
by just one pathologist; 17.4% of atypia and 2.6% of ductal carcinoma in situ were also over-interpreted. The misclassification rate decreased to 14.3% (95% CI 10.9% - 18.0%) when all specimens were interpreted by 2 pathologists with a high-volume (at least 10 breast biopsy specimens per week) practice. The lowest rate of improvement occurred with dual reading of only initial interpretations of invasive breast cancer, which is a common guideline in the United States. The reference standard used in this study -- consensus among 3 experts -- simply amounts to a triple reading, but is probably the best we can do.

**Bottom line:** Approximately 1 in 4 breast biopsies (24.7%) will be misclassified. Only 1 in 25 (3.9%) of invasive breast cancers will be missed, but overinterpretation -- assigning a higher-than-actual level of pathology -- is common with a single reading. Dual reading of initial interpretations of invasive cancers only is the least effective means of decreasing misclassification; the best method, in this study, was dual reading of all specimens by high-volume pathologists. Educate patients to ask for a second opinion of a positive biopsy result, especially in communities in which pathologists do not interpret breast biopsies routinely. (LOE = 1c)


### 11. Evidence limited for hidradenitis suppurativa treatment; ATNF inhibitors may be helpful

**Clinical question:** What are effective treatments for hidradenitis suppurativa?

**Study design:** Systematic review

**Funding source:** Self-funded or unfunded

**Setting:** Various (meta-analysis)

**Synopsis:** HS is a chronic, painful condition that causes nodules, sinus tracts, and inflammation, most often in the axilla and inguinal region. This systematic review summarized the limited body of evidence and identified some new, potentially effective treatments. The authors wrote this review for the Cochrane Database and used their usual thorough search strategy and methods. They identified 26 articles that summarized 12 randomized controlled trials; only 2 were suitable for meta-analysis. The primary outcomes were dermatologic-specific quality-of-life scale scores and adverse effects. The overall risk of bias of the included studies was high, due primarily to failure to mask, selective reporting, failure to conceal allocation, and uncertain randomization. The studies were also small, with only 615 adults in the 12 studies. A single study of topical clindamycin with 30 patients found that it improved a disease-specific measure of symptoms. Another small study compared oral tetracycline with topical clindamycin, and found that the oral therapy was superior. Both studies were at high risk of bias. More promising were therapies using anti-tumor necrosis factor drugs. Although etanercept 50 mg twice weekly and adalimumab 40 mg every other week were not effective, adalimumab 40 mg weekly was minimally effective, and infliximab 5 mg per kg at weeks 0, 2, and 6 was also effective. A variety of other therapies, such as intense pulsed light, laser therapy, photodynamic therapy, and surgical insertion of gentamicin sponges were examined in small studies at high risk of bias, and no conclusions can be drawn regarding their efficacy.

**Bottom line:** The literature base for the treatment of hidradenitis suppurativa (HS) is quite poor. There is limited evidence of effectiveness for some newer biologic agents (adalimumab and infliximab). (LOE = 1a-)


### 12. Providing patients with the costs of care does not reduce health care spending

**Clinical question:** Does offering a price transparency tool to employees with a choice of where to obtain medical treatment decrease health care spending?

**Study design:** Case-control

**Funding source:** Foundation

**Setting:** Population-based

**Synopsis:** Increasing health care value by improving quality and/or reducing costs is a high priority. Various efforts have been made, including giving patients price information on their health care costs and allowing them to choose less-expensive interventions. These investigators identified 2 populations of employees from 2 different organizations located in separate places in the United States. All employees received instructions on using the Truven Treatment Cost Calculator (TTCC), which provides users with estimated total and out-of-pocket spending for various imaging and outpatient procedures, as well as for office visits. Individual deductibles ranged from $500 to $2500 per year. The intervention populations were restricted to enrollees in a single health care plan in the 12 months before and the 12 months after the introduction of the tool. A control population that did not receiving the TTCC included employees enrolled in a different health plan over the same study period matched to each case using variables such as plan type, deductible, age, sex, and comorbidities. The primary outcome was total annual spending per individual for outpatient care. In the cohort exposed to the TTCC, mean total outpatient spending increased from $2021 to $2233 yearly per person, while the control cohort's spending increased from $1985 to $2138, with an adjusted difference associated with a significantly higher mean spending in the TTCC exposure group ($59; 95% CI $25-$93). Similarly, mean annual out-of-pocket spending in the TTCC exposure group was also significantly higher than in the control group ($18; $12-$25). A subgroup analysis found no difference in annual spending among employees with a higher annual deductible (> $1250) or with more chronic health conditions. Only 10% of patients with the opportunity to consult the TTCC actually did so at least once.

**Bottom line:** Employees in the current United States health care system who have the opportunity to price shop for their medical care rarely do so. In addition, having access to specific price information does not reduce annual outpatient health care spending, including individual out-of-pocket deductible expenses. In this study, employees who were provided with specific information on the cost of their health care and the opportunity to price shop for less expensive care actually significantly did the opposite and purchased the more expensive care. (LOE = 3b)
13. Genetic test results that identify increased risk do not change behavior

Clinical question: Does genetic testing for disease risk motivate people to change their behavior?
Study design: Meta-analysis (randomized controlled trials)
Funding source: Government
Setting: Various (meta-analysis)
Synopsis: These researchers identified 18 studies by searching 5 databases, including the Cochrane Register, as well as by performing citation searches. The studies were randomized or quasi-randomized controlled trials of adults receiving personalized DNA-based risk estimates for which a behavior change might reduce risk. In other words, people at increased risk of disease—for example, smokers or patients with a family history of melanoma—underwent DNA analysis and were told they had an increased risk based on a personalized risk estimate. Most of the studies were of low quality (which typically favors treatment) and may have been too small to find small differences. Two authors selected studies for inclusion and abstracted the data. The studies were homogeneous. Overall, communicating specific risk did not change behavior. Telling smokers that they are at increased risk of lung cancer, based on their genetic makeup, did not induce them to quit smoking. Similarly, people told they are at risk of melanoma did not use more sunscreen; patients at risk for developing diabetes, obesity, cardiovascular disease, hypertension, or Alzheimer disease did not change their diet or physical activity; and patients at particular risk of alcohol use disorder did not change their drinking.
Bottom line: If you forgot for a moment that humans are irrational beings, here’s yet another reminder. Patients informed, via genetic test results, that they were at increased risk for disease did not subsequently alter their behaviors: for example, people at increased risk of diabetes or hypertension were no more likely to change their diet or increase their physical activity. So, you can forget the fancy tests as motivators of behavior change. (LOE = 1a−)

14. Colorectal cancer screening modalities: variable uptake, variable yield (SAVE)

Clinical question: How acceptable are various colorectal cancer screening modalities and what is the yield in population-based screening programs?
Study design: Randomized controlled trial (nonblinded)
Funding source: Government
Allocation: Unconcealed
Setting: Population-based
Synopsis: These researchers assigned 16,087 patients to 1 of 4 screening approaches: three cycles of FIT every 2 years (n = 9739), a single reduced-preparation computed tomographic colonography (n = 2617), a single full-preparation computed tomographic colonography (n = 2625), or a single colonoscopy (n = 1106). The participants were all residents of a single region in Italy, were between the ages of 55 and 64 years, and had not had recent colorectal cancer screening. If a FIT result or any of the colonography results were abnormal, the patients were invited to have colonoscopy. One of two experienced pathologists evaluated all the colorectal lesions; the paper does not report if they were aware of allocation. The researchers classified lesions as follows: hyperplastic polyp; or serrated, tubular, tubulovillous, or villous adenoma or adenocarcinoma. Additionally, they defined advanced adenoma as being greater than 9 mm or with more than 20% villous histological component or with severe dysplasia (or any combination of these). They also defined advanced neoplasia as cancer or advanced adenoma. Finally, to avoid differential participation in the program, spouses were clustered to the same screening modality. This paper presents data from the first screening round. Slightly more than half of the patients were women and slightly less than half were of low socioeconomic status; the average age was 59 years. Among the invitees, half completed the first round of FIT, approximately 25% completed each of the 2 colonography modalities, and approximately 12% completed the colonoscopy. Keep in mind that the FIT group still has 2 more cycles to complete, so the participation rate for the whole megillah is likely to be much lower. So, what did they find? Depends on the denominator. First, regardless of denominator, they only found 20 cancers. If you look at everyone who was invited, approximately 1% of the time the modalities detected advanced adenomas and advanced neoplasms. Among the 6116 participants who were actually screened, however, the numbers look different. FIT identified advanced adenomas and advanced neoplasms slightly less than 2% of the time, while the various colonographies found them approximately 5% of the time and colonoscopy came in at 7%. A downside to colonography is the age-old bane of clinicians: 5% of the time radiologists found stuff outside the area of interest that were of uncertain importance and were likely to boost the cost without improving outcomes.
Bottom line: Based on the initial round of screening in this randomized trial, it appears that more patients complete fecal immunochemical testing (FIT) than colonoscopy or colonography. Using the most conservative estimate, the yield of advanced adenomas and advanced neoplasms are similar. If only considering those participants who were actually screened (not the total number invited to participate), colonoscopy found more of these lesions but also had the lowest participation rate. (LOE = 2b)

15. New definition of sepsis, new bedside screen to identify patients at high-mortality risk
Clinical question: What are the best criteria to identify sepsis and septic shock?

Study design: Other

Funding source: Foundation

Allocation: Uncertain

Setting: Inpatient (ward only)

Synopsis: Systemic inflammatory response syndrome (SIRS) criteria are present in many hospitalized patients, even those without infections or life-threatening illnesses. The use of these criteria to identify sepsis may lead to misdiagnosis. Funded by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine, an international task force consisting of 19 critical care, infectious disease, surgical, and pulmonary specialists convened to update the definitions of sepsis and septic shock and identify clinical criteria that can be used to recognize patients at high risk for mortality. Researchers conducted a systematic review and meta-analysis of observational studies followed by a Delphi consensus process to determine appropriate criteria for identifying septic shock. Furthermore, they validated and confirmed the ability of different clinical criteria, including the SIRS criteria and the SOFA score, to predict poor outcomes in patients with suspected infection. Per the task force’s recommendations, sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis in which there is an increased risk of mortality due to profound circulatory and cellular metabolism abnormalities. Sepsis can be identified by an increase in the SOFA score of 2 points or more. This is associated with an in-hospital mortality exceeding 10%. Septic shock can be identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and a serum lactate level greater than 18 mg/dL (> 2 mmol/L) after adequate fluid resuscitation. This combination of clinical criteria is associated with a hospital mortality rate of 40%. Using a derivation and validation cohort of approximately 75,000 patients, the group also developed a new bedside clinical measure termed quickSOFA, or qSOFA, which consists of a respiratory rate of 22 per minute or greater, altered mental status, and systolic blood pressure of 100 mm Hg or less. Patients with suspected infection who are not in the intensive care unit and have at least 2 of these 3 criteria are at higher risk of poor outcomes from sepsis (area under receiver operating characteristics curve = 0.81).

Bottom line: An international task force of experts has updated the definitions of sepsis and septic shock and created a new bedside scoring tool to identify patients with suspected infection who may be at high risk for poor outcomes. Based on the Sequential Organ Failure Assessment (SOFA) score, the new quickSOFA states that meeting 2 of 3 clinical criteria (respiratory rate of 22 per minute or greater, systolic blood pressure of 100 mm Hg or less, and altered mental status) identifies patients at high risk of poor outcomes from sepsis. This score will need to be validated further in multiple health care settings before it can be widely accepted in clinical practice. (LOE = 5)


16. Adhesive strips do not improve outcomes when added to dermal suturing alone for wound closure

Clinical question: Is the combination of adhesive strips and dermal suturing more effective than dermal suturing alone?

Study design: Randomized controlled trial (single-blinded)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (specialty)

Synopsis: Belt, or belt and suspenders? These authors identified adults with at least a 3-cm wound from undergoing a surgical procedure (mostly Mohs) in the dermatology clinic. A surgeon closed the wound using concealed vertical mattress sutures, and left the room. The nurse then opened the opaque envelope to determine which side of the wound received adhesive strips and which did not. Of 57 patients screened for inclusion, 48 were enrolled, and 45 showed up 3 months later for follow-up. The mean age of patients was 63 years, 69% were men, and all but 2 were white. At 3 months, there was no difference in the surgeon’s assessment of the wound healing using a validated assessment tool. Complications occurred in 9 patients without an adhesive strip (including 6 suture abscesses and 2 wound dehiscences) compared with 4 patients in the adhesive strip group (3 suture abscesses and 1 wound dehiscence), a difference that was not statistically significant. The authors do not report sample size calculations, although they do say the study was underpowered for complications. Assessments of scar healing were very similar between groups (overall opinion 2.6 vs 2.8 for physicians, 3.4 vs 3.4 for patients).

Bottom line: When closing a wound with dermal suturing, adhesive strips are unlikely to improve long-term appearance, but may decrease the likelihood of short-term complications. (LOE = 1b–)

Custis T, Armstrong AW, King TH, Sharon VR, Eisen DB. Effect of adhesive strips and dermal sutures vs dermal sutures only on wound closure: a randomized controlled trial. JAMA Dermatol 2015;151(8):862-867.

17. For hospitalized patients: repeat hemoglobin testing within a 24-hour period is of little value

Clinical question: Is it useful to repeat a hemoglobin test within a single calendar day for a hospitalized patient?

Study design: Cross-sectional

Funding source: Government

Allocation: Uncertain

Setting: Inpatient (any location)

Synopsis: These investigators obtained electronic health record data on all adult medical and surgical patients hospitalized at a single hospital during a 1-year period to find patients who had exactly 2 hemoglobin values checked on the same calendar day without any red blood cell transfusions given. Overall, the investigators identified 88,722 hemoglobin test results obtained from 12,877 patients over a total of 86,859 hospital days. The primary analysis consisted of 6969 hospital days during which 2 hemoglobin tests were ordered without a transfusion being given. The mean value of the first and second hemoglobin tests were 10.5 g/dL and 10.4 g/dL, respectively.
with the second test .07 g/dL lower on average than the first test. Of the 6969 repeated hemoglobin tests, only 13.5% were greater than 1 g/dL lower than the initial value from that day. Additionally, only a small percentage of the repeat hemoglobin values reached transfusion thresholds (6.9% were < 8 g/dL, 0.9% were < 7 g/dL). Hemoglobin values were more likely to drop if they were obtained on admission day or if the initial hemoglobin was greater than 10 g/dL. Other factors associated with a significant hemoglobin drop included a discharge diagnosis of bleeding and blood testing in the intensive care unit. Of note, the analysis was unable to exclude repeat hemoglobin testing that occurred because of other purposes, such as testing done as part of a panel to monitor platelets or leukocytes.

**Bottom line:** In this study, repeat hemoglobin testing within a 24-hour period for hospitalized patients showed a greater than 1 g/dL drop only 13.5% of the time. In other words, almost 90% of the time, there is no clinically significant change in hemoglobin values over the course of a calendar day. This result should be taken into account when considering repeat testing, especially in patients without any suspicion of bleeding. Although the percentage of hospital days during which 2 hemoglobin values were obtained and no transfusions were given was small (8%) in this analysis, the potential impact of unnecessary repeat testing—including false positive readings, higher costs, and the potential for hospital-acquired anemia—is not negligible. (LOE = 2c)


### 18. Timing of RRT in critically ill patients with acute kidney injury: verdict still out

**Clinical question:** When is the best time to initiate renal replacement therapy in critically ill patients with acute kidney injury?

**Study design:** Randomized controlled trial (nonblinded)

**Allocation:** Concealed

**Setting:** Inpatient (ICU only)

**Synopsis:** These investigators enrolled patients who were admitted to the intensive care unit (ICU) with stage 3 AKI in the setting of acute tubular necrosis due to toxins or ischemia who were also receiving either mechanical ventilation and/or vasopressors. (Stage 3 AKI is defined as anuria for > 12 hours, serum creatinine > 4 mg/dL, urine output < 0.3 mL/kg/hour for more than 24 hours, or a 3-fold increase in serum creatinine from baseline.) The patients in this study were randomized, using concealed allocation, into an early-strategy group or a delayed-strategy group. In the early-strategy group (n = 311), RRT was initiated within 6 hours of documentation of stage 3 AKI; in the delayed-strategy group (n = 308) RRT was initiated only if patients developed an absolute indication, including oliguria/anuria for longer than 72 hours, severe uremia or acidosis, or refractory hyperkalemia or overload. The method of RRT, either intermittent or continuous, was at the discretion of the study site, but more than 50% of the patients received intermittent dialysis. The 2 groups had similar Sepsis-related Organ Failure Assessment scores at baseline. Overall, 98% of patients in the early group received RRT as compared with only 51% of the delayed group. For the primary outcome of 60-day all-cause mortality, there was no significant difference detected between the 2 groups, with approximately 50% deaths in both groups. Additionally, the 2 groups did not differ in number of ventilator-free and vasopressor-free days or in hospital or ICU length of stay. Although the patients in the early-strategy group had more catheter-related bloodstream infections (10% vs 5%; P = .03; number needed to treat to harm [NNTH] = 20) and hypophosphatemia (22% vs 15%; P = .03; NNTH = 14), there were no other differences in complications due to AKI or RRT between the 2 groups.

**Bottom line:** A recent single-center trial suggested that early initiation of renal replacement therapy (RRT) in critically ill patients with acute kidney injury (AKI) improves mortality as compared with a delayed strategy (*JAMA* 2016;315(20):2190-2199). In that trial, nearly all patients in both groups started RRT, though the early group had decreased overall duration of RRT. The current multicenter study detected no mortality difference between the 2 strategies and also found that half the patients in the delayed group could avoid RRT altogether. As compared with the previous study, this study was larger (619 vs 231 patients), performed at more sites, and enrolled patients with more advanced AKI (stage 3 vs stage 2). The results suggest that it is probably safe to delay RRT in patients who have AKI but no life-threatening complications. (LOE = 1b)


### 19. CA125 relatively specific for diagnosing endometriosis

**Clinical question:** Is serum cancer antigen 125 an accurate noninvasive test for diagnosing endometriosis in symptomatic women?

**Study design:** Meta-analysis (other)

**Setting:** Various (meta-analysis)

**Synopsis:** This is a well-designed meta-analysis of 22 observational studies (16 cohort and 6 case-control; N = 3626 women) to assess the accuracy of CA125 as a noninvasive diagnostic test for endometriosis. The gold standard for diagnosis of endometriosis is histological, requiring an invasive procedure. The authors calculated pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio. They considered different cut-off values for CA125 results and performed multiple other subgroup analyses, including disease stage (1-2 vs 3-4). Quantitative meta-analysis included 14 studies (n = 2920 women) using a cut-off of at least 30 units/mL as a positive result. The pooled sensitivity was 52% (95% CI 38% - 66%) and pooled specificity was 93% (89% -95%). Although CA125 showed higher sensitivity 63% (42% - 77%) when disease severity was limited to advanced disease, it was still not enough to recommend using the test to rule out disease.

**Bottom line:** For women with symptoms suggestive of endometriosis, serum cancer antigen 125 (CA125) is a relatively specific (93%) and noninvasive test. It can be used to make a presumptive diagnosis in cases for which a medical management approach is being considered without having to perform a (gold-standard) laparoscopic procedure to confirm. At minimum, a pelvic ultrasound to assess
for other conditions (ovarian cancer or uterine fibroids) that can raise CA125 levels is needed. CA125 is not a sensitive test for endometriosis (52%), and therefore not helpful in ruling out the disease. Approximately half the women with histologically proven endometriosis have normal CA125 levels. (LOE = 1a−)


20. Meta-analysis: Antibiotics for appendicitis results in fewer surgeries but more recurrence

**Clinical question:** What are the trade-offs when patients with acute appendicitis are treated with antibiotics?

**Study design:** Meta-analysis (randomized controlled trials)  
**Funding source:** Foundation

**Setting:** Inpatient (any location) with outpatient follow-up

**Synopsis:** These authors searched 2 databases and 2 clinical trials registries to identify randomized trials comparing antibiotics with appendectomy in patients with acute appendicitis. Two of the authors independently evaluated each study for inclusion and resolved any disagreements with a third member of the research team. The authors assessed each study’s risk of bias, but the paper doesn’t say whether this was done in a paired, independent manner. Ultimately the authors included 5 randomized trials with approximately 1100 patients in the main analysis and one quasi-experimental study in a sensitivity analysis. The meta-analysis included patients from 5 to 75 years of age, but 4 of the studies recruited only adults and the other 2 studies recruited only children. Computed tomography or ultrasound were not consistently used across the studies. After 1 year, the drop-out rate ranged from 7% to 22%. Virtually 100% of the 562 patients allocated to surgery underwent surgery, 75% of which were open laparotomies. Of the 550 patients allocated to receive antibiotics, approximately 8% underwent surgery within 1 month. Approximately 5% of patients treated with antibiotics experienced major complications (compared with 8% of those undergoing surgery). Similarly, the rate of minor complications was 3% and 12%, respectively. Finally, nearly 20% of patients treated with antibiotics had a confirmed recurrence of appendicitis within the following year; another 14 patients had recurrent pain and underwent surgery only to remove normal appendices. Among the studies reporting these outcomes, surgically treated patients had nearly 12-hour shorter hospital lengths of stay, but there was no difference in the duration of sick leave. The authors reported significant heterogeneity for minor complications and hospital lengths of stay and modest heterogeneity for major complications.

**Bottom line:** In this meta-analysis, most patients with appendicitis who are treated with antibiotics do quite well, but 1 in 5 will have a recurrence in the following year. (LOE = 1a−)
