OBJECTIVES

• Review recent evidence affecting the diagnosis and management of patients with elevated blood pressure.

• Discuss the therapeutics of various antihypertensive agents used in managing patients with hypertension.

• Compare and contrast BP targets and first-line therapy options from various clinical practice hypertension guidelines (e.g., JNC 8, ADA).
RESOURCES

• The 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, & Treatment of High BP (JNC 7). 2003

• 2014 Evidence-based guideline for management of high BP in adults: report from the panel members appointed to the 8th JNC (JNC-8)
  – JAMA 14;311:507-20
RESOURCES

• Treatment of Hypertension in Patients With Coronary Artery Disease: AHA/ACC/ASH
  – Circulation. 2015; 131: e435-e470
  – http://circ.ahajournals.org/content/131/19/e435

• 2015 Canadian HTN Education Program
CASE

• 55 y/o male routine f/u visit
• PMH: HTN, type 2 DM, hyperlipidemia,
• SHx: 1 ppd, etoh 1/d
• FHx: Father MI 54 y/o; brother MI 55 y/o
• Meds
  – HCTZ 25 mg/d
  – Metformin 850 mg bid
  – Simvastatin 40 mg/d
EXAM/LAB

• BP 156/86, P 76, RRR
• 5’7”, 128 kg, BMI 44.2
• SCr 0.9, BUN 18, K 3.8, CO2 28.7, FPG 175
• Lipids
  – TC 180; TG 96; HDL 35; LDL 115
• A1C 8%
• AHA/ACC CV risk >30%
• What next?
HYPERTENSION

• Most common modifiable CVD risk factor
  – Contributes to >50% of adverse CVD outcomes
    JAMAD 16;17:571-3. edit.
  – Morbidity/mortality correlates with BP > 115/75

• BP control
  – Reduces HF 50%; CVA 40%; MI 25%

• Presence of other CV risk factors
  – “multiplicative increase in risk for CV events”
    Circulation 15;131:e435-e70
HYPERTENSION

• 33% of adults
  – 60% increase by 2025
• Worldwide responsible for 1 out of 8 deaths
• Average 5 y loss of life
• Risk factor for CAD, HF, chronic kidney disease, CVA, and retinopathy
  – Reducing BP reduces the incidence
  – The big question is what goal BP is optimum

Med Clin N Am 16;100:665-93
HTN IN US – AHA 2014 UPDATE

• ~78 million adults (33% of population)
  – By 2030 ~41.4%

• NHANES 2010
  – 81.5% aware
  – 74.9% current treatment
  – 52.5% controlled
  – 47.5% not controlled

• ~75% have visits at least 2x/y

Screening for High BP in Adults

• Office BP monitoring (OBPM)
• Ambulatory BP monitoring (ABPM)
  – Record regular intervals (eg, 20-30 min) over 24-48h
• Home BP measurement (HBPM)
  – Record BP by automated oscillometric devices

BP MEASUREMENT

• “use of HTN guidelines is inappropriate without accurate and reliable BP readings.”

• “… accurate BP readings & recognizing white-coat and masked hypertension is imperative”

• HBPM and ABPM correlate better with HTN outcomes than OBPM


• 5-65% elevated OBPM screen are normotensive on ABPM confirmatory testing

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Adults aged 18 years or older</td>
<td>The USPSTF recommends screening for high blood pressure in adults aged 18 years or older. The USPSTF recommends obtaining measurements outside of the clinical setting for diagnostic confirmation before starting treatment (see the</td>
</tr>
</tbody>
</table>

Screening for High BP in Adults: A Systematic Review for the USPSTF

- OBPM elevated BP best confirmed by ABPM
  - Decreases overdiagnosis of isolated clinical HTN & overtreatment
- “convincing evidence” that ABPM best for confirming elevated OBPM
- “Good-quality evidence” that confirmation of HTN by HBPM may be acceptable
- “USPSTF considers ABPM to be the reference standard for confirming the diagnosis of HTN”
CHOICE OF ANTIHYPERTENSIVE

• Primary prevention of CV complication
  – Lowering BP more important than the choice of drug

• Secondary CV protection with underlying comorbid illnesses (compelling indications)
  – Not all antihypertensives provide the same benefit
  – Assumption is that for the most part there are class effects for thiazides, ACEIs, ARBs
  – Class effects may not occur for βBs & CCBs

Circulation 15;131:e435-e70
## Thiazide (-Like) Diuretics

<table>
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<tr>
<th></th>
<th>Relative potency</th>
<th>Oral bioavailability</th>
<th>T1/2</th>
<th>Ineffective GFR &lt; 30-40</th>
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<tr>
<td>HCTZ</td>
<td>1</td>
<td>~70%</td>
<td>~ 2.5 h</td>
<td>Yes</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>2*</td>
<td>~65%</td>
<td>~ 47 h</td>
<td>Yes</td>
</tr>
<tr>
<td>Indapamide</td>
<td>20</td>
<td>~93%</td>
<td>~14 h</td>
<td>No</td>
</tr>
<tr>
<td>Metolazone</td>
<td>10</td>
<td>~65%</td>
<td>?</td>
<td>No</td>
</tr>
</tbody>
</table>

*Twice as potent in lowering BP on mg-per-mg basis as HCTZ.*

Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e. 2011
Pharmacotherapy: A Pathophysiologic Approach, 9e. 2014
Guidelines for Use of Diuretics: A View From a Member of JNC 7

• Benefit either as 1st- or 2nd-line therapy

• CTD twice as potent as HCTZ
  – CTD longer duration of action

• HCTZ 25-50 mg/d vs. CTD 12.5-25 mg/d
  – Lower doses may have less CV benefit

• HCTZ may have less than 24 h activity
  – BP at end of dosing interval (eg, before next dose)
  – If 24-h control not optimal & HCTZ is continued consider 2xd

HCTZ VS. CHLORTHALIDONE (CTD)

• Thiazide RCTs consistently show:
  – Decreased mortality, CVA, coronary events, CHF, renal failure, and malignant HTN
  – Major studies used CTD

• No randomized head-to-head outcome studies
CTD vs. HCTZ
  – Meta-analyses: no difference OR better outcomes with CTD

• USE CTD OR HCTZ?
HCTZ VS. CHLORTHALIDONE

• AHA and ASH recommends Chlorthalidone
  – More potent and longer acting vs. HCTZ
  Circulation 08;117:e510-e26 J Clin Hypertens 14;16:14-26

• “superior potency, longer half-life, & evidence
  … improved CV outcomes, … diuretic agent of choice” if eGFR is >30 mL/min

• Chlorthalidone is preferred
  Circulation 15;131: e435-e70
Head-to-Head Comparisons of HCTZ With Indapamide & Chlorthalidone

- Meta-analysis
- INDAP & CTD > lowering SBP
  - -5 to -3.6 vs. HCTZ; P=0.004 & P=0.052
- No differences in metabolic effects
- HCTZ < 24 h duration & < nighttime BP control
- “these results support the view that CTD and INDAP are preferable to HCTZ for managing hypertension in general”

Hypertension 15;65:1041-6. editorial 15;65:983-4
RECENT CASE

• 78 y/o female admitted with feeling “icky” (nausea) for several days. Vomited twice
• PMH: HTN dx 3 wks PTA 163-173/82-85 at 3 office visits; DM; LDL
• Meds
  – Enalapril 10 mg 2xd
  – Metfomin 1000 mg 2xd
  – Simvastatin 20 mg/d
  – Oxybutynin 5 mg 2xd
  – ASA 81 mg/d
  – Chlorthalidone 12.5 mg/d for 3 wks
• ROS neg except for nausea
• 158/88; HR 90; RR 18; 36.4C; 69kg; 5’; BMI 30
  – Alert/oriented; Exam normal
• Na 115; K 3.8; Cl 84; CO2 23; BUN 11; SCr 0.6
  – 2 months prior Na 134, K 4.6, BUN 23, SCr 0.9
• On discharge Na 131
• WHAT CAUSED THIS ADMISSION?
• HYPONATREMIA??
  – CHLORTALIDONE
MAJOR HTN DRUG TRIALS

• STOP-2: Diuretic + βB vs ACEI + CCB  NO DIFFERENCE
• ALLHAT: Diuretic vs. ACEI vs. CCB  NO DIFFERENCE
• INVEST: Diuretic + βB vs CCB + ACEI  NO DIFFERENCE
• ASCOT: Diuretic + βB vs CCB + ACEI  NO DIFFERENCE
• LIFE: ARB vs βB  NO DIFFERENCE
• ANBP2: Diuretic vs ACEI  ACEI superior in men
• ACCOMPLISH: ACEI + Diuretic vs ACEI + CCB ACEI/CCB superior

NEJM 09;361:878-87
βBs AS INITIAL THERAPY IN HTN

- βBs less suitable for routine initial therapy, especially elderly
  - < effective at preventing major CV events, especially CVA than CCBs and ACEIs
  - > new onset diabetes
  - Unfavorable effect on the metabolic profile, especially in combination with diuretics

- May not be true for vasodilating βBs (eg. Carvedilol, Nebivolol, Labetalol)

Cochrane Database Syst Rev. 2012;11:CD002003
ESH/ESC HTN Guidelines J Hypertens 13;31:1281-135 Wiysonge & Opie JAMA 13;310:1851-2
<table>
<thead>
<tr>
<th>JNC</th>
<th>Year</th>
<th>Initial Antihypertensive</th>
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<tbody>
<tr>
<td>1</td>
<td>1977</td>
<td>Thiazide</td>
</tr>
<tr>
<td>2</td>
<td>1980</td>
<td>Diuretic</td>
</tr>
<tr>
<td>3</td>
<td>1984</td>
<td>Thiazide or βB</td>
</tr>
<tr>
<td>4</td>
<td>1988</td>
<td>Diuretic or βB or CCB or ACEI</td>
</tr>
<tr>
<td>5</td>
<td>1993</td>
<td>Diuretic or βB</td>
</tr>
<tr>
<td>6</td>
<td>1997</td>
<td>Diuretic or βB</td>
</tr>
<tr>
<td>7</td>
<td>2003</td>
<td>Thiazide for most without compel indication; Compel indication use thiazide, ACEI, ARB, βB or CCB</td>
</tr>
<tr>
<td>8</td>
<td>12/13</td>
<td>ACEI or ARB, CCB or diuretic; specific med for race, CKD or DM</td>
</tr>
</tbody>
</table>
**JNC 7 – TREATING BP TO GOAL**

<table>
<thead>
<tr>
<th>Patient type</th>
<th>JNC 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated*</td>
<td>&lt; 140/90</td>
</tr>
<tr>
<td>DM**, CKD</td>
<td>&lt; 130/80</td>
</tr>
</tbody>
</table>

* “there is little evidence to support this recommendation for elderly patients”
Clin Interventions Aging 13;8:1505-17

** Recommendation not based on evidence from randomized, controlled trials.
NEJM 10;362:1628-30. editorial
TREATING BP TO GOAL STUDIES

• African American Study of Kidney Disease and Hypertension (AASK) trial – SBP <140 vs <130
  – No decrease in progression of CKD or mortality
  NEJM 10;363:918-29

• Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial – SBP <140 vs <120
  – No decrease in composite of CV events
  – CVA reduced 0.32% vs. 0.53% (HR 0.59, p=0.01)
  – Serious ADEs 3.3% vs 1.3% (p<0.001)
  NEJM 10;362:1575-85
<table>
<thead>
<tr>
<th>Age</th>
<th>Initiate BP</th>
<th>Goal BP</th>
<th>Initial meds</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60 y</td>
<td>≥ 150/90</td>
<td>&lt; 150/90</td>
<td><strong>Nonblack:</strong> thiazide-type, ACEI, ARB or CCB alone or in comb.</td>
</tr>
<tr>
<td>&lt; 60 y</td>
<td>≥ 140/90</td>
<td>&lt; 140/90</td>
<td><strong>Black:</strong> thiazide-type or CCB alone or in comb.</td>
</tr>
<tr>
<td>DM, no CKD</td>
<td>≥ 140/90</td>
<td>&lt; 140/90</td>
<td><strong>All races:</strong> ACEI or ARB alone or in comb. with other class</td>
</tr>
<tr>
<td>CKD, ± DM</td>
<td>≥ 140/90</td>
<td>&lt; 140/90</td>
<td></td>
</tr>
</tbody>
</table>
Meds in Presence of Certain Medical Conditions

- CAD/Post MI: BB, ACEI
- Systolic HF: ACEI or ARB, BB, aldosterone blocker, thiazide
- Diastolic HF: ACEI or ARB, BB, thiazide
- DM: ACEI or ARB, thiazide, BB, CCB
- Kidney disease: ACEI or ARB
- Stroke or TIA: Thiazide, ACEI

An effective approach to high blood pressure control: science advisory from AHA/ACC/CDC. Hypertension 2014;63:878-85
ANTIHYPERTENSIVES DOSING
JNC 8 – STRATEGIES

• Doses to achieve outcomes seen in the RCTs
• Strategy A
  – One drug titrate to max and then add 2nd drug
• Strategy B
  – One drug started and then add 2nd drug before max dose of the initial drug
• Strategy C
  – Start 2 drugs especially for higher BP, eg > 20/10 above goal BP
<table>
<thead>
<tr>
<th></th>
<th>Initial daily dose (mg)</th>
<th>Target dose (mg)</th>
<th>Doses/d</th>
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<tr>
<td>Captopril</td>
<td>50</td>
<td>150-200</td>
<td>2</td>
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<tr>
<td>Enalapril</td>
<td>5</td>
<td>20</td>
<td>1-2</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>Losartan</td>
<td>50</td>
<td>100</td>
<td>1-2</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40-80</td>
<td>160-320</td>
<td>1</td>
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<tr>
<td>Atenolol</td>
<td>25-50</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>50</td>
<td>100-200</td>
<td>1-2</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>2.5</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Diltiazem XR</td>
<td>120-180</td>
<td>360</td>
<td>1</td>
</tr>
<tr>
<td>HCTZ</td>
<td>12.5-25</td>
<td>25-100</td>
<td>1-2</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>12.5</td>
<td>12.5-25</td>
<td>1</td>
</tr>
</tbody>
</table>
Proportion of US Adults Potentially Affected by 2014 HTN Guideline

• Data from NHANES 2005-2010

• Treatment-eligible HTN JNC 7 vs JNC 8
  – 18-59 y – 20.3% vs. 19.2%
  – > 60 y – 68.9% vs. 61.2%

• Met BP goals JNC 7 vs JNC 8
  – 18-59 y – 41.2% vs. 47.5%
  – ≥ 60 y – 40% vs. 65.8%

DM and HTN Goals
ADA Guidelines 2017

• Most SBP target of < 140/90 (A)
  – Lower targets (eg, < 130/80) may be appropriate in some patients (C)
    • High CV risk if can be achieved without undue treatment burden
  – SPRINT did not include DM

• BP > 120/80
  – Should be advised on lifestyle changes (B)

Diabetes Care 17;40(suppl 1)
http://professional.diabetes.org/content/clinical-practice-recommendations
DM and HTN Goals
ADA Guidelines 2017

• Confirmed office-based BP
  – > 140/90
    • Prompt drug initiation & titration to achieve BP goals (A)
  – >160/100
    • Start 2 drugs demonstrated to reduce CV events in DM (A)

• Therapy
  – ACEI, ARBs, thiazide, DHP CCBs
  – Albuminuria – ACEI or ARB

Diabetes Care 17;40(suppl 1)
http://professional.diabetes.org/contentclinical-practice-recommendations
<table>
<thead>
<tr>
<th></th>
<th>YR</th>
<th>Goal BP</th>
<th>GOAL BP ↑ AGE</th>
<th>GOAL BP DM, CKD</th>
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<td>&lt;140/90</td>
<td>&lt; 140/90</td>
<td>&lt;130/80</td>
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<tr>
<td>JNC 8</td>
<td>2014</td>
<td>&lt;140/90</td>
<td>≥60y &lt;150/90</td>
<td>&lt;140/90</td>
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<td>ACC/AHA</td>
<td>2015</td>
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<td>CAD ≤ 80y</td>
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<td>&lt;140/90; &gt;80y &lt;150/90</td>
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<td>ASH/ISH</td>
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<td>&lt;140/90</td>
<td>&lt; 80y SBP &lt;140; ≥ 80y SBP &lt;150</td>
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<tr>
<td>ADA</td>
<td>2017</td>
<td></td>
<td></td>
<td>&lt;140/90</td>
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<tr>
<td></td>
<td>Year</td>
<td>Goal BP</td>
<td>Goal BP ↑ Age</td>
<td>Goal BP DM, CKD</td>
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<td>&lt;80 y SBP</td>
<td>DM &lt;140/85</td>
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<td>&lt;140; &gt;80 y SBP</td>
<td>CKD SBP &lt;140</td>
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<td>SBP &lt;130</td>
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<tr>
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<td>2015</td>
<td>&lt;140/90</td>
<td>≥80 y</td>
<td>DM &lt;130/80</td>
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<td>CKD &lt;140/90</td>
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<td>2012</td>
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<td>No protein</td>
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<td>Improving</td>
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<td>Protein &lt;130/80</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
SBP Intervention Trial (SPRINT)

- Effect of more intensive BP treatment in non DM with much increased risk of CV events
  - SBP < 120 vs. < 140

- Primary outcome CVD composite of 1\textsuperscript{st} occurrence
  - MI, non-MI ACS, CVA, ADHF, or CVD death

- Sponsored by NHLBI; National Institutes of: DM & Digestive & Kidney Diseases, Neurological Disorders & Stroke, and Aging

NEJM 15;373:2103-16
INCLUSION/EXCLUSION CRITERIA

INCLUSION

• ≥ 50 y
• SBP 130-180 (treated or untreated)
• ≥ 1 additional CVD risk
  – Clinical or subclinical CVD (excluding CVA)
  – CKD (eGFR 20- <60)
  – Framingham Score 10-y CVD risk ≥ 15%
  – ≥ 75 y

EXCLUSION

• CVA
• DM
• Polycystic kidney disease
• HF (s/s or EF < 35%)
• Proteinuria >1 g/d
• CKD with eGFR < 20
• Adherence concerns
SPRINT ANTIHYPERTENSIVES

- Used regimens that have been shown to confer strong CV benefits from previous RCTs
- Preferred regimens
  - A thiazide-type diuretic, CCB, ACEI and ARB
    - > 50% of intensive group on these agents
  - The preference for the order of use left to investigators
RECOMMENDATIONS FOR DRUG SELECTION

• CTD 12.5-25 mg/d was diuretic of choice
  – More potent and longer-acting than HCTZ
• Amlodipine CCB of choice
• ACEI (& other RAAS inhibitors
  – < effective lowering BP & preventing CVD in African Americans unless combined with thiazide-type diuretic or CCB
RECOMMENDATIONS FOR DRUG SELECTION

• Loop diuretic may be needed in CKD with eGFR <30

• Combination of ACEI, ARB, and renin inhibitor is discouraged.

• ßBs
  – Now considered to be < effective in preventing CVD events as primary treatment of hypertension
  – May be indicated for HTN in some patients
    • eg, Post MI, HF, AF
Summary and Conclusions

• BP response in study – baseline 139.7/78
  – Intensive 121.4/68.7 vs. standard 136.2/76.3
  – Intensive 2.8 meds vs standard 1.8 meds

• Trial stopped early (9/11/15) after median of 3.26 y
  – Composite of CVD events  RRR 25%
    • ≥ 75y RRR 33%
    • 50-75y RRR 20%
  – All-cause mortality RRR 27% (p=0.005)
    • CV mortality RRR 43% (p=0.002)

NEJM 15;373:2103-16
Summary and Conclusions

• No difference in serious adverse events
• More common (0.6-1% more) in Intensive Group
  – Hypotension, syncope, electrolyte abnormalities, and hospital discharge reports of AKI
• CKD
  – At baseline, no differences in renal outcomes
  – Without at baseline eGFR reduction ≥ 30% more common
• Benefits exceeded potential for harm

NEJM 15;373:2103-16
Generalizability of SPRINT Results to the U.S. Adult Population

- Population-based study from NHANES 2007-12 using SPRINT study inclusion/exclusion criteria
- Meeting eligibility criteria
  - All US adults 219.4 M
  - 7.6% (16.8 M) US adults
  - 16.7% (8.2 M) treated for HTN (1 in 6 patients)
  - 25.5 M at increased CV risk

JACC 16;67:463-72
Generalizability of SPRINT Results to the U.S. Adult Population

- Usually SBP > 140 used to guide when to start antihypertensives or intensify therapy
- SPRINT trial showed benefit for SBP < 120 in those without DM or CVA
- ~16.8 M may be eligible for starting or notifying antihypertensive therapy
- Additional data needed to quantify the medical & economic implications of this goal across the population

JACC 16;67:463-72
SPRINT
To Whom Do the Results Apply?

• Key question is with SBP 130-139
  – Should therapy be intensified to further ↓ BP?
  – Most studies show that within this range there are the lowest CV events (except CVA) vs. above or below
  – Also show a J-shaped curve in those with CAD

• SPRINT used a unique study population excluding those with DM, CVA & drug-resistant HTN

Gradman AH. Edit. JACC 16;67:473-5
SPRINT
To Whom Do the Results Apply?

• Cannot be applied to every eligible patient
  – May belong to subgroup with a small contribution to the overall results
  – A study just with subgroup may see different results

• “residual uncertainty regarding optimal BP targets … not prudent to radically alter treatment [if] achieved SBP levels considered optimal on the basis of prior evidence.”

• “I favor the addition of 1 (only) additional agent … without further pursuit of SBP<120”
SPRINT
To Whom Do the Results Apply?

• Some untreated SBP 130-139 could be treated
  – CKD, CAD, LVH, and/or HF
  – Some of these conditions should be treated with drugs such as ACEI, βBs, etc regardless of BP
    – compelling indications

Gradman AH. Edit. JACC 16;67:473-5
SPRINT
To Whom Do the Results Apply?

• Small number of untreated patients the SPRINT results “are also insufficient to mandate drug treatment … SBP 130-139 and a high Framingham risk score”

• Many treat BP to 130-139 in high-risk patients on the basis of epidemiologic evidence of increased risk

Gradman AH. Edit. JACC 16;67:473-5
SPRINT
To Whom Do the Results Apply?

• “The SPRINT findings are consistent with this practice, and treatment is a reasonable option.

• “There is presently no justification for extending the findings of SPRINT to encompass the >25 million Americans >50 years of age with SBP >120 mm Hg and increased CV risk”

Gradman AH. Edit. JACC 16;67:473-5
SPRINT RAMIFICATIONS

• High CV risk patients will have greatest benefit
  – SBP target < 120 is appropriate if > 50 y & at high risk for CV events if there are low side effects

• What about the low CV risk patients?

• “The results of SPRINT should be carefully weighed in the context of current guidelines”

Med Clin N Am 16;100:665-93
BP Lowering in Intermediate-Risk Persons without CVD. HOPE-3

• RCT 12,705 men > 55 and women > 65
  – ~ 38% had HTN
  – > 1 CV risk factor: increased waist-to-hip ratio; low HDL; current or recent tobacco, dysglycemia, FHx premature coronary disease; mild renal dysfunction
  • Women ≥ 60 y who had ≥ 2 risk factors
    – Exclusion: known CVD; indications or contraindications to trial drugs; > moderate CKD; symptomatic hypotension

Sponsored by AstraZeneca & Canadian Institutes of Health Research
Published on April 2, 2016, at NEJM.org. DOI: 10.1056/NEJMoa1600175
BP Lowering in Intermediate-Risk Persons without CVD. HOPE-3

• Candesartan 16 mg/d + HCTZ 12.5 mg/d vs placebo for a median of 5.6 y
  – Also evaluated rosuvastatin 10 mg/d alone & candesartan/HCTZ + rosuvastatin

• Co primary outcomes
  – Composite of death from CV, nonfatal MI or CVA
  – Additionally included resuscitated cardiac arrest, HF and revascularization
BP Lowering in Intermediate-Risk Persons without CVD. HOPE-3

• About ~ 38% had HTN at enrollment
  – ~22% taking BP agents other than ACEIs, ARBs or thiazides

• BP response
  – Baseline 138.1/81.9
  – Active decreased 5.7 vs. placebo 2.7
    • ACCORD and SPRINT > decrease in BP

• No difference in coprimary outcomes
HOPE-3 SBP SUBGROUPS

• The greater the baseline SBP may see reduced CV risk with small decreases in BP

• SBP > 143.5 subgroup
  – ~25% decrease in primary outcomes

• SBP 131.6-143.5
  – No benefit in either outcomes (HR ~1.05)

• SBP ≤ 131.5
  – Trend to harm (HR 1.16 1st coprimary to 1.25 2nd coprimary)
BP Lowering in Intermediate-Risk Persons without CVD. HOPE-3

• Evaluated fixed-dose combination of an ARB and a thiazide
  – Relatively low doses
  – Persons at intermediate risk who did not have CVD
  – Very few had DM or CKD & ~20% had been on antihypertensives

• No significant benefit of BP-lowering
  – The higher SBP subgroups therapy reduced the risk of CV events

Published on April 2, 2016, at NEJM.org. DOI: 10.1056/NEJMoa1600175
Effects of intensive BP lowering on CV & renal outcomes

• Updated systematic review and meta-analysis
  – 19 trials with 44,989 participants

• Intensive lowering 133/76 vs less intense 140/81

• Benefits
  – Major CV events RRR 14% (p=0.005)
  – MI RRR 13% (p=0.042)
  – CVA RRR 22% (p=0.001)
  – Albuminuria RRR 10%
  – Retinopathy progression RRR 19%

Lancet 16;387:435-43
Effects of intensive BP lowering on CV & renal outcomes

• No clear benefits
  – HF, CV death, total mortality, ESRD, CV death
• Additional lowering of BP had benefit even in SBPs < 140
• Most benefits in trials in patients with vascular disease, CKD ir DM
• Severe hypotension more frequent RR 2.68 (0.3% vs 0.1%) p=0.015

Lancet 16;387:435-43
Effects of intensive BP lowering on CV & renal outcomes

• “clear evidence of the benefits of more intensive blood pressure lowering, including in high-risk patients whose systolic blood pressure is lower than 140 mm Hg.”

• “Existing clinical guidelines should be revised accordingly, to recommend more intensive blood pressure-lowering treatment in high-risk patient groups”

Lancet 16;387:435-43
Redefining BP Targets – SPRINT Starts the Marathon

• Currently difficult to determine who benefits from BP lowering or from specific target
• SPRINT supports drug decisions based on absolute risk levels
  – Similar to current the lipid lowering guideline
• Those at high CV risk
  – SPB < 120 is appropriate

Perkovic V & Rodgers A. Edit. NEJM 15;372:2175-8
BP Lowering for Prevention of CVD and Death: Review & Meta-analysis

• 123 studies with 613,815
• Every SBP decrease by 10 reduced
  – Major CV events by 20%
  – CHD 17%
  – CVA 27%
  – HF 28%
  – All-cause mortality 13%
• Benefit was not reduced if SBP <130

Lancet 16;387:957-67
BP Lowering for Prevention of CVD and Death: Review & Meta-analysis

• Benefit not reduced even if baseline SBP < 130 in CV high risk – no J curve??
• Larger benefit in those at high absolute CV risk
• Lack of benefit for renal failure
• Drug classes were mostly similar
  – ßB inferior: CV events, CVA, renal failure, trend for all-cause mortality
  – CCBs: superior for CVA; inferior for HF
  – Diuretics: superior for HF

Lancet 16;387:957-67
IMPLICATIONS

• Demonstrates that BP lowering results in proportional reductions in risk of CVD and death to a mean baseline SBP < 130

• BP lowering to < JNC 8 target (<140) decreases CVD risk

• No evidence a BP lowering threshold for reducing CVD risk
  – Individualize BP decrease for potential net benefit
  – Do not reduce BP as a treatment of a risk factor to a specific target

Lancet 16;387:957-67
IMPLICATIONS

• Findings are consistent with or without prior CVD
  – May simplify guidelines for use of BP drugs

• Differences between classes of agents
  – Use targeted drugs for individuals at high risk of specific outcomes – eg, specific indications
    • eg, CCBs is high risk of CVA

Lancet 16;387:957-67
IS THERE EVIDENCE TO:

“suggest that revision is urgently needed to recent BP lowering guidelines that have relaxed the BP lowering thresholds.”

“shift …focus from rigid BP targets to risk-based targets, even when starting SBP is lower than 130 mm Hg”

Lancet 16;387:957-67
Redefining BP Targets – SPRINT Starts the Marathon

- “Current guidelines and guideline processes require revision.”
- “SPRINT redefines BP target goals & challenges us to improve BP management. Success will require a marathon effort.”

Perkovic V & Rodgers A. Edit. NEJM 15;372:2175-8
GOAL BP IN $\geq$ 60 YEARS

JNC 8

- Goal < 150/90 reduces CVA, HF, CHD
  - Good evidence from RCTs
- SBP < 140
  - No additional benefit vs. SBP 140-160 or 140-149 in this age
- Panel did not all agree
  - Some wanted to continue SBP < 140 as goal based on expert opinion
SPRINT
To Whom Do the Results Apply?

• “little evidence, however, to support routine antihypertensive therapy in adults > 75 w SBP >130”
  – “SPRINT results are consistent with the possibility of significant benefit, they must be considered preliminary and insufficient to mandate universal drug therapy”
  – Treatment is an acceptable option
  – Need more clinical trials in elderly

Gradman AH. Edit. JACC 16;67:473-5
GOAL BP IN ≥ 60 y/o

• “Older persons are currently being undertreated for hypertension.”

• JNC 8 ramifications
  – 6 million no longer eligible for therapy
  – Treatment intensity reduced for 13.5 million
    • Increased CV events?

Aronwo WS. Edit. JAMAD 16;17:571-3
Optimal SBP Goal Be in Treating Older Persons with HTN?

• “… SPRINT data, which included frail older persons, I recommend reducing the SBP in the elderly at increased CV risk to < 120 or to < 130 depending on clinical judgment for each individual person.”

• Intensive monitoring if < 120:
  – Hypotension, syncope, electrolytes, AKI
  – Increases cost of care

Aronwo WS. Edit. JAMAD 16;17:571-3.
ANTIHYPERTENSIVE ADHERENCE

- Newly diagnosed HTN
  - >40% d/c 1st-line antihypertensives within 1 y
  - ~ 20% continue
  - ~ 22% combine
  - ~ 18% switch

H Hypertens 05;23:2093-100

- “What hope is there for us to convince patients with mild hypertension to take 3 … drugs for the duration of their lifetime to achieve lower SBP targets?”

Lobo MD. Editorial JACC 16;67:1372-4
SUMMARY

BENEFITS OF TREATING HYPERTENSION

“Reducing chronically increased blood pressure using medications clearly reduces the incidence of coronary artery disease, stroke, congestive heart failure, and chronic kidney disease”

Med Clin N Am 16;100:665-93
GUIDELINES

• Provide a population-based minimum standard
  – Useful in treating most patients

• Should not be substitute for good clinical judgment

• Being linked to performance measures and clinicians may become less likely to deviate from guidelines

• Individual patients and unique circumstances may mean guideline exceptions