CURRENT STRATEGIES IN HYPERTENSION

Current Strategies in Hypertension: Getting Ready for JNC 8

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Declaration of full disclosure: No conflict of interest

Summary of Presentation

• Update on recent studies
• JNC 7 Review
• Role of Lifestyle Change
• Medication Choice
• Recommendations

Current Status of Hypertension

• Prevalence 29%; Blacks 33.5%
• About 72.5% treated; 53.5% uncontrolled

• Risk for poor control: Latinos, Blacks, age 18-44 and ≥80, <300% poverty, < college degree

• Better control: Any insurance, ≥2 visits, and a usual source of care

Hypertension Control by Cardiovascular Disease and Risk: NHANES, 2003-04

<table>
<thead>
<tr>
<th>Condition</th>
<th>%HTN</th>
<th>%Rx</th>
<th>% Not Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Risk</td>
<td>34</td>
<td>66</td>
<td>35</td>
</tr>
<tr>
<td>Diabetes</td>
<td>85</td>
<td>96</td>
<td>54</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>83</td>
<td>95</td>
<td>53</td>
</tr>
<tr>
<td>CHF</td>
<td>86</td>
<td>98</td>
<td>50</td>
</tr>
<tr>
<td>Cardiovascular Dis</td>
<td>85</td>
<td>95</td>
<td>51</td>
</tr>
<tr>
<td>Framingham Score ≥10</td>
<td>77</td>
<td>68</td>
<td>59</td>
</tr>
</tbody>
</table>

MMWR 2012;61: 703-709
Bertoia ML, Hypertension 2011
CURRENT STRATEGIES IN HYPERTENSION

Co-morbid Conditions and Hypertension Management
- Clinicians are being “graded” for level of BP control
- 140/90 held as standard
- In primary care visit, other factors intervene with “control”
- Retrospective cohort of 15,459 patients with uncontrolled HTN with 200 clinicians
- 6 sites through EMR
- Effect of 28 conditions on intensification

Co-morbid Conditions and Hypertension Control
- Average of 2.2 unrelated conditions
- Intensification of treatment decreased with number of conditions from OR = 0.85 for one to OR = 0.59 for 7 or more
- Quality of care measures need to consider co-morbid conditions

Ann Internal Medicine 2008; 148: 578-586

Hypertension Treatment after 80 y
- No clinical trial showing clear benefit
- Meta-analysis of 7 RCT, 1670 patients, 75% women showed a 3.3% absolute reduction in stroke (NNT = 30) and 2.1% reduction in CHF (NNT = 48)
- Borderline trend to increase deaths from any cause in treated group
- Observational data showed risk of death inversely related to BP level

Hypertension in the Very Elderly Trial (HYVET)
- 3845 patients ≥ 80 y
- >160 mm Hg – goal of 150/80 mm Hg
- Indapamide SR 1.5 mg vs. placebo
- Added perindopril if needed
- Follow up of 2 years
- 60% women, age 83.6 y, BP = 173/91
- 12% with CV disease, 7% diabetes, 64% already treated for hypertension

Beckett NS, NEJM 2008; 358: 1887-1898
CURRENT STRATEGIES IN HYPERTENSION

HYVET Study Results
Beckett NS, NEJM 2008; 358: 1887-1898

<table>
<thead>
<tr>
<th>End Point</th>
<th>Meds</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>12.4</td>
<td>17.7</td>
<td>0.64 (0.46 - 0.95)</td>
</tr>
<tr>
<td>CVA Death</td>
<td>6.5</td>
<td>10.7</td>
<td>0.55 (0.33 - 0.93)</td>
</tr>
<tr>
<td>CHF</td>
<td>5.3</td>
<td>14.8</td>
<td>0.28 (0.17 - 0.48)</td>
</tr>
<tr>
<td>CV Death</td>
<td>23.9</td>
<td>30.7</td>
<td>0.73 (0.55 - 0.97)</td>
</tr>
<tr>
<td>Any Death</td>
<td>47.2</td>
<td>59.6</td>
<td>0.72 (0.59 - 0.88)</td>
</tr>
</tbody>
</table>

Conclusions and Implications: Always Offer Treatment

- Benefits appear at 1 year of Rx
- NNT = 20 to prevent one stroke
- NNT = 10 to prevent one CHF
- Not a specific drug effect
- Never too old to treat SBP > 160
- Goal does not have to be < 140

SBP and Risk of Recurrent Stroke

- 20,330 patients ≥50 y with CVA < 120 day followed for 2.5 years, 695 centers
- Outcome: recurrent stroke any type
- Predictors: SBP in mm Hg
  - <120 8.0%
  - 120-<130 7.2%
  - 130 -<140 6.8% **Optimal SBP**
  - 140 - <150 8.7%
  - ≥150 14.1%

Treatment Based on What Blood Pressure Measurement?

- Home BP measurement leads to less intensive drug Rx & BP control
- Identifies “white-coat” HTN
- Ambulatory monitor measures – higher correlation with CVD
- Office clinician measures are standard, used in trials, one point
- Automated Office BP monitors may lead to more standard measures

Ovbiagele B, JAMA 2011; 306: 2137-44
**CURRENT STRATEGIES IN HYPERTENSION**

**Clinic, Home and Ambulatory BP in Diagnosis of Hypertension**

- Systematic review comparing measures in initial diagnosis
- 20 studies with 5683 patients, compared to ambulatory monitor daytime mean \( \geq 135/85 \)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Definition</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home</td>
<td>135/85 mean</td>
<td>85.7%</td>
<td>62.4%</td>
</tr>
<tr>
<td></td>
<td>+LR = 2.28</td>
<td>-LR= 0.23</td>
<td></td>
</tr>
<tr>
<td>Clinic</td>
<td>140/90 mean</td>
<td>74.6%</td>
<td>74.6%</td>
</tr>
<tr>
<td></td>
<td>+LR = 2.94</td>
<td>+LR = 0.34</td>
<td></td>
</tr>
</tbody>
</table>


**Number of BP Measurements to Influence Decisions**

- Compare Home, Clinic and research BP measurements in VA setting
- 444 patients, 92% men, inadequate control
- Clinic > Home > Research measures
- Within patient variance reduced by doing more — plateau at 5-6 measures
- Rarely should a decision to initiate or change treatment be based on one reading


**JNC 7 Classification of Blood Pressure**

- Normal: \(<120 \) and \(<80\)
- Pre-hypertension: 120-139 or 80-89
- Hypertension
  - Stage 1: 140-159 or 90-99
  - Stage 2: \( \geq 160 \) or \( \geq 100 \)

Risk of CVD doubles with each increment of 20/10 mm Hg – SBP more important risk factor

**When to Treat Hypertension**

- Initial lifestyle for stage 1 HTN
- If lifestyle fails, drugs for DBP > 90
- If lifestyle fails, drugs for SBP >140

- Drug treatment for all with CV co-morbidity and SBP > 140 or DBP > 90
- Drug treatment for all with SBP > 160
- Drug treatment for all with DBP > 100
**Individual Lifestyle Modifications for Hypertension Control**

- **Weight loss if overweight:** 5-20 mm Hg/10-kg weight loss
- **Limit alcohol to ≤1 oz/day:** 2-4 mm Hg
- **Reduce sodium intake to ≤100 meq/d (2.4 g Na):** 2-8 mm Hg in SBP
- **DASH Diet:** 6 mm alone; 14 mm plus Na
- **Physical activity 30 min/day:** 4-9 mm Hg
- **Habitual caffeine consumption not associated with risk of HTN**

**Salt and Public Policy**

- **Coronary Heart Disease Policy Model to quantify benefits of 3 g salt/day reduction in US—average is 8-10 g/d**
  - **Benefit through a reduction in SBP from 1-9 mm Hg in selected populations**
  - **New cases of CHD decrease by 4.7 - 8.3 and stroke by 2.4 to 3.9 /10,000**
  - **Regulatory change leads to wide benefit and is cost-effective**

Bibbins-Domingo K, et al. NEJM 2010

**Where is the salt?**

- **80% in processed or pre-prepared foods**

Sources: Mattes et al.

**Sources of salt in our grocery bags**

- **35% from cereal and cereal products**
  - breads, cereals, pastries
- **26% from meat & meat products**
- **8% from milk & milk products**
  - milk, cheese
CURRENT STRATEGIES IN HYPERTENSION

60 Year Old Man, BP=160/96; Which treatment first?

1. Thiazide diuretic 12.5 or 25 mg
2. Beta blocker of choice
3. Ace Inhibitor or ARB
4. Calcium Channel Blocker
5. Alpha-blocker
6. Intensify lifestyle

60 Year Old woman, BP=160/96, with diabetes?

1. Thiazide diuretic 12.5 or 25 mg
2. Beta blocker of choice
3. Ace Inhibitor or ARB
4. Calcium Channel Blocker
5. ACE/ARB plus Diuretic
6. ACE/ARB plus CCB

Initial Drug Treatment of Hypertension

Initial Drug Choices

Stage 1: Thiazides for most
Stage 2: 2-drug combination for most – thiazides plus β-blockers, ACE-I, ARB, CCB

Based on randomized controlled trials

Possible JNC 8 Recommendations

• Medication choice menu: Thiazides, Ace Inhibitor or Ace Receptor Blocker, Calcium Channel Blocker
• Beta blockers restricted to <60 years
• Use urinary albumin to identify patients with diabetes and CKD for ACE/ARB Rx
• Combination of ACE + CCB preferred over ACE + HCTZ in persons at highest risk
• Coordinate with pharmacists to enhance adherence
CURRENT STRATEGIES IN HYPERTENSION

Compelling Indications for Drug Selection in Hypertension

- Low EF Heart Failure: Beta B, ACE-I or ARB, and aldosterone antagonist
- Post ant MI: Beta Blocker, ACE-I
- CAD Risk: BB or just lower SBP
- Diabetes with proteinuria: ACE-I, ARB
- Renal Disease: ACE-I, ARB
- Recurrent stroke prevention: thiazide, ACE-I

NICE Guidance: Management of Hypertension

- Guideline development in the UK
- If BP 140/90, use amb monitor to confirm
- Estimate CV risk, evaluate for target organ effects such as LVH, CKD, retinopathy
- Treat stage 1 with meds only if target organ damage, known CVD, diabetes, 10-year CV risk ≥ 20%
- Offer meds to all at any age with stage 2 (>155/95) independent of other effects

Krause T, et al, BMJ 2011; 343:d4891

Summary of antihypertensive drug treatment

Thiazide Diuretics

- Very effective for systolic BP
- Do not increase sudden death
- Most effective in LVH regression
- Lipid effects are short lasting (1 y)
- Hyperglycemia only in high doses
- Still effective in early chronic kidney disease (to GFR 40-45)
- Erectile dysfunction in 20%
- More effective in Blacks and older
CURRENT STRATEGIES IN HYPERTENSION

Chlorthalidone vs. HCTZ
Return of MRFIT

- 6441 men treated with either drug, 35-57 yrs, 88% White, primary prev
- Both drugs reduced CV events: CTD hazard ratio = 0.51 and for HCTZ, HR = 0.65 with overlapping CI
- CTD had fewer events in comparison to HCTZ; HR = 0.79 (0.68-0.92)
- Higher doses CTD and more potent drug at equivalent mg

Dorsch MP et al, Hypertension 2011; 57: 689-694

Chlorthalidone Treatment in Systolic Hypertension

- 2365 treated with CTD and 2371 with placebo in 4.5 y RCT
- Outcomes determined at 22 years with national death index
- CV Death reduced by 11%, but no difference in all-cause mortality
- One month of treatment = 1 day life extension


Efficacy of HCTZ by Ambulatory Monitoring

Messerli FH, et al, JACC 2011; 57: 590-600

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Decrease in mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCTZ 12.5 -25 mg</td>
<td>6.5/4.5</td>
</tr>
<tr>
<td>HCTZ 50 mg</td>
<td>12.0/5.4</td>
</tr>
<tr>
<td>ACE-I</td>
<td>12.9/7.7</td>
</tr>
<tr>
<td>ARB</td>
<td>13.3/7.8</td>
</tr>
<tr>
<td>CCB</td>
<td>11.0/8.1</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>11.2/8.5</td>
</tr>
</tbody>
</table>

Beta Blockers

- More effective as mono-therapy in younger persons and Whites
- Adverse effects limited: Do not cause depression or sexual dysfunction
- Glucose elevation with A1C increase by 0.2% — less with carvedilol
- No lasting effect on lipids
- Compelling evidence to use in CAD and systolic HF to decrease mortality
- Less efficacy in stroke prevention among those older than 60 years
CURRENT STRATEGIES IN HYPERTENSION

**Atenolol in hypertension: is it a wise choice?**

Bo Carlberg, LANCET 2004, Vol 364

- No benefit to prevent MI or All-cause mortality

**ACE–I or ARB**

- 30% reduction of ESRD (dialysis) and of doubling of serum creatinine; optimal with GFR 30-60, proteinuria
- Not better tolerated than other drugs
- Regression of LVH not more than other drugs–SBP reduction
- Elevates K+
- Do not use in women < 50 y
- Works less well in Blacks as 1 drug
- Best choice in diabetes?
- Infrequent need to combine

**Benazepril for CKD: Is it Ever Too Late to Try?**

- 442 patients randomized to benazepril or placebo and followed for 3.4 years
- Creatinine 1.5 to 3: benazepril 20 mg (1)
- Creatinine 3.1 to 5: benazepril vs. placebo
- Outcomes: ESRD, 2X creatinine or death
- 22% in group 1; 41% in group 2 on ACE vs. 60% on placebo
- Similar AE; not mediated by SBP

NEJM 2006; 131-140

**Calcium Channel Blockers**

- Effective in Blacks and elderly
- Effective in preventing CV events
- Do not reverse atherosclerosis
- No increase risk of cancer
- Short acting CCB may be harmful
- Effective in systolic hypertension
- Better outcomes in latest trials
CURRENT STRATEGIES IN HYPERTENSION

ACCOMPLISH
Calcium Blockers combined with ACE
- Comparison of combinations: ACE-I + hctz vs. ACE-I + amlodipine for htn
- RCT, 11,506 patients, ≥ 65 y, 60% men, 83% White, 60% diabetes, BMI = 31
- Outcomes: CV death, MI, stroke, hospitalization for angina, resuscitation after cardiac arrest, CABG or PCI
- Follow-up 36 months
- Funded by Novartis: USA and 4 N. Europe

Jamerson K, NEJM 2008; 359:2417-28

ACCOMPLISH Results

<table>
<thead>
<tr>
<th>Primary Outcomes</th>
<th>Benazepril + Amlodipine N=5744</th>
<th>Benazepril + HCTZ N=5762</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Events</td>
<td>552 (9.6%)</td>
<td>679 (11.8%)</td>
<td>0.80 (0.72-0.90)</td>
</tr>
<tr>
<td>CV Death</td>
<td>107 (1.9%)</td>
<td>134 (2.3%)</td>
<td>0.80 (0.62-1.03)</td>
</tr>
<tr>
<td>All MI</td>
<td>125 (2.2%)</td>
<td>159 (2.8%)</td>
<td>0.78 (0.62-0.99)</td>
</tr>
<tr>
<td>All Strokes</td>
<td>112 (1.9%)</td>
<td>133 (2.3%)</td>
<td>0.84 (0.65-1.08)</td>
</tr>
<tr>
<td>Revasc procedure</td>
<td>334 (5.8%)</td>
<td>386 (6.7%)</td>
<td>0.86 (0.74-1.00)</td>
</tr>
</tbody>
</table>

ACCOMPLISH Conclusions
- Combination of CCB and ACE was superior to ACE/HCTZ
- BP differences of 1 mm only
- Different populations may matter
- Chlorthalidone vs. HCTZ?
- Recommendation to change practice in highest risk patients – ACE and CCB may have special benefits

What About Other Drugs?
- Spironolactone
- CNS sympatholytics: Clonidine
- No reason to use methyldopa
- Alpha-1 blockers: OK but inferior as single drug and tachyphylaxis
- Labetalol good 5th or 6th choice
- Direct vasodilators - hydralazine or minoxidil - need more diuretics
- Peripheral adrenergic antagonists
CURRENT STRATEGIES IN HYPERTENSION

Take Home Points 1

- Risk of CVD is linear to SBP level
- 120-139/80-89 is “pre-hypertension” and merits lifestyle modifications in all and may need drug treatment with co-morbidity of DM, CAD, CKD
- Set goal SBP and treat with drugs at any age for SBP >160
- Goal SBP level is relative, not fixed

Take Home Points 2

- Most patients will need two or more drugs to achieve goal SBP
- Thiazides, ACE-I, ARB, and CCB are similar—combinations in almost all
- Co-morbid condition and age considerations in selecting meds
- Control only occurs with motivated patients who trust their clinician