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 (>140/90)
• Risk for poor control: Latinos, Blacks, age 18-44 and ≥80, <300% poverty, < college degree more uncontrolled BP control
• 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</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
- Findings persisted at visit, clinician and patient levels
- Quality of care measures need to consider co-morbid conditions

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## 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

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*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%

Ovbiagele B, JAMA 2011; 306: 2137-44

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
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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 ≥135/85

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


Number of BP Measurements to Influence Decisions

- Compare Home, Clinic and research BP measurements in VAMC setting
- 444 patients, 92% men, inadequate control
- Only 33% consistently categorized as being out of 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 ≥160 or ≥100

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

When to Treat Hypertension

- Lifestyle advice for all
- Initial lifestyle for stage 1 HTN
- Drug treatment for all with SBP > 160
- Drug treatment for all with CV co-morbidity and SBP > 140 or DBP > 90
- Drug treatment for all with DBP > 100
- If lifestyle fails, drugs for DBP > 90
- If lifestyle fails, drugs for SBP >140
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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.
**CURRENT STRATEGIES IN HYPERTENSION**

**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

**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

**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
CURRENT STRATEGIES IN HYPERTENSION

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

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
CURRENT STRATEGIES IN HYPERTENSION

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

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 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>
CURRENT STRATEGIES IN HYPERTENSION

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

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

Valsartan for Prevention of DM and CV Events in Patients with Pre-Diabetes

- 9306 patients, 50% women, with pre-DM and CV risk factors or disease
- Valsartan 160 mg or placebo plus lifestyle
- Follow for 5 years, outcomes are new diabetes and CV events
- Diabetes: 33.1% vs. 36.8% (HR = 0.86; 0.80-0.92)
- No benefit on CV outcomes: 14.5% vs. 14.8%
- DREAM Trial showed no benefit (ramipril)

The Navigator Study Group. NEJM 2010; 362: 1477-1490
**CURRENT STRATEGIES IN HYPERTENSION**

**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

**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>
## CURRENT STRATEGIES IN HYPERTENSION

### 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

### 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