NEW DEVELOPMENTS IN HYPERTENSION

Current Issues in Hypertension

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Summary of Presentation

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

Current Population Status of Hypertension

• Prevalence is 29% with Blacks 33.5%
• About 72.5% are treated and 50.1% controlled (< 140/90)
• Whites or Blacks, women, age 40-59, and visits = better BP control
• Having insurance and continuity of care (place/clinician) = better control

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>%HTN</th>
<th>%Rx</th>
<th>%UnControlled</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>90</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 Beere ≥10</td>
<td>77</td>
<td>68</td>
<td>59</td>
</tr>
</tbody>
</table>

NEW DEVELOPMENTS IN HYPERTENSION

Co-morbid Conditions and Hypertension Management

- BP control in their patients
- Threshold of 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
- Data obtained from 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

Medically Complex Patients with Hypertension Do Receive Quality Care

- Data from the VAMC system: 141,609 patients with HTN showed odds of receiving overall good quality:
  - OR = 1.78 (1.70 - 1.87) for concordant
  - OR = 1.32 (1.23 - 1.41) for discordant
  - OR = 2.25 (2.13 - 2.38) for Both
- Unclear how this applies to non single payer systems

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

Petersen L, Circulation 2009; 119:2978-85
NEW DEVELOPMENTS IN HYPERTENSION

Hypertension in the Very Elderly Trial (HYVET)
- 3845 patients 80 y and older randomized
- >160 mm Hg to start and 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

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

<table>
<thead>
<tr>
<th>End Point</th>
<th>Drug Rx</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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.46-0.95)</td>
</tr>
<tr>
<td>CVA Death</td>
<td>6.5</td>
<td>10.7</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.33-0.93)</td>
</tr>
<tr>
<td>CHF</td>
<td>5.3</td>
<td>14.8</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.17-0.48)</td>
</tr>
<tr>
<td>CV Death</td>
<td>23.9</td>
<td>30.7</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.55-0.97)</td>
</tr>
<tr>
<td>Any Death</td>
<td>47.2</td>
<td>59.6</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(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

Chronic Kidney Disease and Hypertension
- Continuous risk significant at SBP >120 and DBP >80. The lower the better?
- BP = 140-159/90-99 leads to a relative risk of 2.59 for ESRD
- Treatment of hypertension with any drug prevents development of CKD
- Use estimated GFR to risk stratify and intervene at GFR of < 50 with ACE/ARB
- 13.2%; worse in early CKD

Treatment Based on What Blood Pressure Measurement?

• Home BP measurement by patient leads to less intensive drug Rx & BP control, Identify white-coat patients
• Ambulatory monitor measures have higher correlation with CVD outcomes
• Office clinician measures are standard but one point in time
• Automated Office BP monitors may lead to more standard measures
• Study of 4 strategies showed similar average BP
  Lamarre-Cliche, et al., Can J Cardiology 2011; 455-460

At What BP Level Do You Start Medication in 50 Year old man, non-smoker with Total Cholesterol=160?

a) SBP ≥ 140 and/or DBP over 90
b) SBP ≥ 160 and/or DBP ≥ 100
c) SBP ≥ 160 and/or DBP ≥ 90
d) SBP ≥ 140 and/or DBP ≥ 100
e) SBP 140-159 and DBP < 90 & > 80

JNC 7 Classification of Blood Pressure

<table>
<thead>
<tr>
<th>mm Hg</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>(115)&lt;120 and &lt;90</td>
<td></td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120-139 or 80-89</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>140-159 or 90-99</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥160 or ≥100</td>
<td></td>
</tr>
</tbody>
</table>
Risk of CVD doubles with each increment of 20/10 mm Hg – SBP more important risk factor

When to Treat Hypertension

• Lifestyle for all pre-hypertension: >120/80
• Initial lifestyle for all with 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 140-159
**New Developments in Hypertension**

**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
- 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 the US–average diet is 8 to 10 g/day
- Benefit through a reduction in SBP from 1 mm Hg to 9 mm Hg in selected populations
- New cases of CHD decrease by 54k to 92k or 4.7 to 8.3/10,000
  Bibbins-Domingo K, et al. NEJM 2010

**Benefits of Less Salt in Food**
- New strokes decrease by 32k to 66k or 2.4 to 3.9/10,000
- Women benefit from stroke reduction
- Regulatory intervention to reduce salt intake by 3 g/day would save 194k to 392k quality life years and $10 - $24 billion
- More cost-effective than drug treatment of hypertension
  Bibbins-Domingo K, et al. NEJM 2010

**Lifestyle Modification as Adjunct Therapy**
- 26%, at 6 m; OR = 0.77 (0.62 to 0.97)
- Even if effects attenuate — No significant effects at 18 m
- Regardless of drugs, Lifestyle needs to be part of the regimen
- Empower patients with education
  Annals of Internal Med 2006;144:485-95
NEW DEVELOPMENTS IN HYPERTENSION

Drugs always better than lifestyle in head-to-head clinical comparisons
Better Living through chemistry

Initial Drug Treatment of Hypertension

<table>
<thead>
<tr>
<th>Initial Drug Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1: Thiazides for most</td>
</tr>
<tr>
<td>Stage 2: 2-drug combination for most – thiazides plus β-blockers, ACE-I, ARB, CCB</td>
</tr>
</tbody>
</table>

Based on randomized controlled trials

### 60 Year Old Man, BP=160/96; lipids OK; Which drug?
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) Diuretic plus Beta-blocker

### 60 Year Old woman, BP=160/96, with Diabetes; which drug?
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
NEW DEVELOPMENTS IN HYPERTENSION

**Possible New 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 as needing ACE/ARB
- 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: BB, ACE-I or ARB, and aldosterone antagonist
- Post ant MI: Beta Blocker, ACE-I
- CAD Risk: BB or just lower SBP
- Diabetes: ACE-I, ARB, others
- Renal Disease: ACE-I, ARB
- Recurrent stroke prevention: thiazide, ACE-I

**Do We Change the Criteria to Start Treatment Earlier?**

- Why wait until SBP is > 140 or 160 mm Hg to treat with medications?
- Risk of SBP in the pre-hypertension range relative to values <115 mm Hg shown in observational studies
- Modeling data would support drug intervention at earlier age to lower risk on a population level
- At what point do we change normal?

**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
NEW DEVELOPMENTS 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

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 prevent mortality
- Less efficacy in stroke prevention among older than 60 years?

BETA Blockers Less Effective for Reducing Risk of Stroke

- Meta-analysis of 7 placebo control trials and 13 comparison trials
- Compared to placebo, Beta blockers reduce stroke: 2.6% vs. 3.2% (NNT = 165)
- Compared to other drugs: 3.5% vs. 3.0% (16% higher incidence)
- Atenolol was the main drug used in trials
- If patient does not have established CAD or heart failure, select alternative drug as initial therapy

LANCET 2005;366:1545-53

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
NEW DEVELOPMENTS IN HYPERTENSION

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

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 therapy in Blacks and elderly
- Effective in preventing CV events
- Do not reverse atherosclerosis
- No evidence of increase risk of cancer
- Short acting dihydropyridines may be harmful and should not be used
- 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
- 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, coronary revascular
- Follow-up 36 months
- Funded by Novartis: USA and 4 N Europe

Jamerson K. NEJM 2008; 359:2417-28
NEW DEVELOPMENTS IN HYPERTENSION

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
• Not explained by BP differences of 1 mm
• Different populations may matter
• Chlorthalidone vs. HCTZ?
• Combination of ACE and CCB may have special benefits
• One large trial — should we change practice?

What About Other Drugs?

• CNS sympatholytics: Clonidine plus
• 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—Control level is relative
NEW DEVELOPMENTS IN HYPERTENSION

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