NEW DEVELOPMENTS IN HYPERTENSION

Hypertension 2011: Today’s Clinical and Public Health Challenges
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Summary of Presentation
• Update on recent studies
• JNC 7 Review
• Role of Lifestyle Change
• Medication Choice
• JNC 8 Speculation

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>%HTN</th>
<th>%Rx</th>
<th>%Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CV Disease</td>
<td>23</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>Diabetes</td>
<td>77</td>
<td>84</td>
<td>61-35</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>82</td>
<td>66</td>
<td>42-23</td>
</tr>
<tr>
<td>CAD</td>
<td>73</td>
<td>89</td>
<td>50</td>
</tr>
<tr>
<td>Stroke</td>
<td>70</td>
<td>89</td>
<td>35</td>
</tr>
<tr>
<td>High Lipids</td>
<td>52</td>
<td>68</td>
<td>49</td>
</tr>
<tr>
<td>CVD ≥ 2</td>
<td>77</td>
<td>83</td>
<td>52-39</td>
</tr>
</tbody>
</table>


Co-morbid Conditions and Hypertension Management

- Clinicians are being “graded” for level of 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

Ann Internal Medicine 2008; 148: 578-586
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**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

Petersen L, Circulation 2009; 119:2978-85

**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 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
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HYVET Study Results
Beckett NS, NEJM 2006; 355: 1007-1010

<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 (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

How Intensive Should we Treat SBP in Older Adults?

- Goal SBP may be <140, but are we doing harm if DBP is lowered too much?
- Systolic Hypertension in Europe Trial examined mortality and on-treatment DBP
- Non-CV mortality increased with low DBP: HR=1.15 for 65 and 1.28 for 60 mm Hg
- CV mortality did not increase with low DBP except when patient had CHD at baseline
- Limit intensity of SBP treatment to DBP 70 mm Hg if CHD present or 55 mm Hg if not
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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
  (Ann Intern Med 2005; 143: 202-4)
• 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
• BP control in 10,813 patients with CKD was only 13.2%; worse in early CKD
  (J Am Soc Nephrol 2009; 16: 133-44)

Personalized Medicine in HTN: The Time is Not Here Yet

• NPPA gene codes for ANP precursor and may modulate effect of anti-HTN drugs
• ALLHAT: analyses 38,462 participants
• Test genotype by treatment interactions
• Event rates varied by genotype: 10% for mortality; 25% for CHD and 60% stroke
• NPPA T2238C variant modified drug effect
• C allele carriers: favorable with diuretic
• TT allele carriers: favorable with CCB

Treatment Based on Home Blood Pressure?

• Should we base treatment on what the patient measures or on what we obtain in the office? RCT in Belgium
• Less intensive drug Rx & BP control
• No difference in well being
• Identify the “white-coat” patients
• Home measures complementary
• Ambulatory measures have higher correlation with CVD outcomes
  JAMA 2004; 291: 955-964
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At What BP Level Do You Start Medication in 50 Year old woman, non-smoker with Total Cholesterol=160?

- SBP ≥ 140 and/or DBP over 90
- SBP ≥ 160 and/or DBP ≥ 100
- SBP ≥ 160 and/or DBP ≥ 90
- SBP ≥ 140 and/or DBP ≥ 100
- 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;80</td>
<td></td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120-139 or 80-89</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>140-159 or 90-99</td>
<td></td>
</tr>
<tr>
<td>Stage 1</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
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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): 2-6 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;
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Lifestyle Modification As Adjunct Therapy

• Delay onset of stage 2 HTN: 12% vs. 26%, at 6 m; OR = 0.77 (0.62 to 0.97)
• Even if effects attenuate (No significant effects at 18 m) it is good medical practice
• Regardless of drugs, Lifestyle needs to be part of the regimen
• Empower patients with education

Annals of Internal Med 2006;144:485-95

Drugs always better than lifestyle in head-to-head clinical comparisons

Better Living through chemistry

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
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60 Year Old Man, BP=160/96; lipids OK; Which drug?

• Thiazide diuretic 12.5 or 25 mg
• Beta blocker of choice
• Ace Inhibitor or ARB
• Calcium Channel Blocker
• ACE/ARB plus Diuretic
• Diuretic plus Beta-blocker

60 Year Old woman, BP=160/96, with Diabetes; which drug?

• Thiazide diuretic 12.5 or 25 mg
• Beta blocker of choice
• Ace Inhibitor or ARB
• Calcium Channel Blocker
• ACE/ARB plus Diuretic
• ACE/ARB plus CCB

Possible JNC 8 Recommendations

• Medication choice menu: Thiazides, Ace Inhibitor or Ace Receptor Blocker, Calcium Channel Blocker
• Add a second drug from above
• Third drug from a different class and now include a Beta-Blocker in options, re-assess adherence, optimize doses
• Fourth Drug as needed
• Fifth drugs: clonidine, labetalol, alpha-1 bl
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Compelling Indications for Drug Classes in JNC 7 (8)

- 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?

Treat Pre-hypertension?

- SBP 120 - 139 or DBP 85 - 89
- RCT 772 patients (40% women)
  - Canderstan vs. placebo
  - At 2 years: 13.6% vs. 40.4%
  - At 4 years: 53.2% vs. 63.0%
  - Well tolerated
  - What is the rush to treat?
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**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 201157: 689-694

**Beta Blockers**
- More effective as mono-therapy in younger persons and Whites
- Adverse effects limited: Do not cause depression or sexual dysfunction
- May be associated with glucose elevation in very high doses
- No lasting effect on lipids
- Compelling evidence to use in CAD and systolic HF to prevent mortality
- Efficacy in stroke prevention among elderly?
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Metabolic Effects of Beta Blockers on Diabetes
(JAMA, 2004; 292:2227-2235)

- Comparison of carvedilol (6.25-25 mg) and metoprolol (50-200 mg) in RCT in participants with DM and HTN
- N=1235, age 36-85, all on ACE or ARB
- Outcome: change in A1C at 5 months
- Metoprolol: 0.15%; carvedilol: 0.02%
- Insulin sensitivity improved on carvedilol
- No difference in BP control
- Intermediate outcomes better at 5 months—need clinical outcomes to change practice

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

ACE-I or ARB

- As effective as diuretics or B-blockers in reducing morbidity and mortality
- 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+; caution in women < 50 y
- Works less well in Blacks as 1 drug
- Best choice in diabetes?

LANCET 2005;366:1545-53
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Do ACE and ARB Prevent Diabetes?

- Meta-analysis of 12 RCT studies - 7 with ACE and 5 with ARB; total N = 72,333 patients showed incident diabetes at 1 to 6 yrs of 6.1% vs. 8.1% with NNT = 50
- DREAM Trial randomized 5269 with impaired fasting glucose or IGT to ramipril or placebo with 3 y FU
- Outcomes of ramipril vs. placebo:
  - Diabetes: 18.1% vs. 19.5% (HR= 0.91; 0.81-1.03)
  - Regression to normal glucose: 42.5% vs. 38.2%; HR = 1.16 (1.07-1.27)
- May need longer time; many regress on placebo
- May prefer ACE/ARB in patients with impaired fasting glucose, history of gestational diabetes, family history

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 at 14.5% vs. 14.8%

ACE Inhibitors and the Kidney

- Magnitude of proteinuria associated with increased risk of progression to ESRD
- 30% reduction of ESRD (dialysis) and of doubling of serum creatinine with ACE-I
- Greatest benefit in persons with protein in urine and creatinine clearance 30-60 ml
- Change in level of protein in urine is predictor of progression
- Dosed to maximum tolerated by BP level and serum potassium
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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

CAMELOT: Treatment of BP in Patients with CAD

- RCT in patients with documented >20% stenosis and DBP < 100 mm Hg
- 1991 patients randomized to Amlodipine 10 mg, enalapril 20 mg or placebo
- Outcome: CV Events
- Placebo: 151 (23.1%)
- Amlodipine 110 (16.6%); HR = 0.69
- Enalapril 136 (20.2%) HR = 0.85
- Amlodipine may prevent events by slowing progression of atheroma using IVUS measure
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ACCOMPLISH
Calcium Blockers Make a Big Comeback

• 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

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?
• Would not rush to change practice based on 1 trial
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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

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