CURRENT STATUS OF HYPERTENSION

- Prevalence is 28.7%, Blacks 33.5%
- About 60% are treated and 31% controlled
- Predictors of less control: Mexican-Americans, men, age >65, and lack of visits
- Predictors of control: Insurance and continuity of care (place and clinician)

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>Lipidemia</td>
<td>52</td>
<td>68</td>
<td>49</td>
</tr>
<tr>
<td>CVD</td>
<td>77</td>
<td>83</td>
<td>52/39</td>
</tr>
</tbody>
</table>

MANAGEMENT OF HYPERTENSION: TREATMENT THRESHOLDS AND MEDICATION SELECTION

Co-morbid Conditions and Hypertension Control
- 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

Comorbid 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 compared to none
- Findings persisted at visit, clinician and patient levels
- Quality of care measures need to consider co-morbid conditions

Hypertension Treatment after 80
- 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
- Also: observational data showed risk of death inversely related to BP level

Hypertension in the Very Elderly Trial
- 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% treated for hypertension

Ann Internal Medicine 2008; 148: 578-586
MANAGEMENT OF HYPERTENSION: TREATMENT THRESHOLDS AND MEDICATION SELECTION

**HYVET Study Results**

<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**

- Benefits appear within 1 year of starting treatment
- NNT = 20 to prevent one stroke
- NNT = 10 to prevent one case of CHF
- Never too old to treat SBP > 160
- Goal does not have to be < 140
- Diuretics are an effective medication

**How Intensively Should We Treat SBP in Older Adults?**

- Goal SBP may be < 140, but are we doing harm if DBP is lowered too much?
- Syst-Eur Trial
- RCT, 60 year and up (mean 70.2 yrs), 4695 patients
- Mortality and event outcomes

**Fagard et al., Arch Intern Med 2007; 167: 1884**

**How Intensively Should We Treat SBP in Older Adults?**

- 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 if patient had CHD at baseline
- Limit intensity of SBP treatment to DBP 70 mm Hg; if CHD present or 55 mm Hg if not

**Fagard et al., Arch Intern Med 2007; 167: 1884**
**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

Arch Intern Med 2005; 165: 923-8

**Treatment of hypertension with any drug prevents development of CKD**

Use estimated GFR to risk stratify and intensify intervention at GFR of <50

BP control in 10,813 patients with CKD was only 13.2%; worse in early CKD

Arch Med 2008; 121: 332-40

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**Personalized Medicine: The Time has Come?**

- 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


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**Treatment Based on Home Blood Pressure?**

- RCT in Belgium
- Less intensive drug treatment and less control of BP
- No difference in well being
- Identify the “white-coat” patients
- Home and ambulatory measures should be complementary
45 year old woman, non-smoker with normal lipids. What is the lowest BP for which you would start a medication?

1. At or over 140/80
2. At or over 140/90
3. At or over 140/100
4. At or over 160/90
5. At or over 160/100

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
• Consider drugs for SBP 140-159

JNC VII 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>&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>

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 alone: 6 mm Hg
• Physical activity 30 min/day: 4-9 mm Hg
• Habitual caffeine consumption not associated with risk of HTN
Drugs consistently better than lifestyle in head-to-head comparisons

Lifestyle Modification: Premier Trial

- 18 Month Trial Comparing:
  - Established lifestyle
  - Lifestyle plus DASH
  - Advice only

- 810 pts, 60% women SBP = 120 to 159
- SBP at 6 m decreased 10.5, 11.1, 6.6
- Prevalence of stage 2 HTN was 17%, 12%, 26% at 6 m; OR = 0.77 (0.62 to 0.97)
- No significant effects at 18 m

Empowering Patients Works!

- RCT of 182 clinicians with 1341 patients with BP >140/90 twice - VA
- 3 conditions: Clinician education ± email alerts, patient education only
- 6 months follow up:
  - Patient education: 138/75
  - Clinician education: 145/78
  - Plus email alerts: 146/76

45 year old woman, non-smoker with normal lipids. BP 162/102, despite non-drug therapy. Which medication(s) would you start first?

1. Thiazide
2. Beta blocker
3. Ace inhibitor
4. Angiotension receptor blocker
5. Calcium channel blocker
6. A combination of two of the above
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

Compelling Indications for Drug Classes in JNC VII
- Heart Failure: Thiazide, BB, ACE-I, ARB, and aldosterone antagonist
- Post MI: BB, ACE-I, AA
- CAD Risk: thiazide, BB, ACE-I, CCB
- Diabetes: thiazide, BB, ACE-I, ARB
- Renal Disease: ACE-I, ARB
- Recurrent stroke prevention: thiazide, ACE-I

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

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?
**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
- Benefit for CKD and CHD
- Recommended as first drug in patients with elevated creatinine, proteinuria and probably DM
- Not better tolerated than other drugs
- Regression of LVH not more than other drugs–SBP reduction
- No effect on lipids, elevates K+
- Works less well in Blacks as 1 drug

**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%
- NNT = 50

**Do ACE and ARB Prevent Diabetes?**

- DREAM Trial: 5269 patients 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

**References**

LANCET 2005;366:1545-53


Do ACE and ARB Prevent Diabetes? (Dream Trial; NEJM 2006; 355:1551-62)
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

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

- 442 patients, benazepril or placebo, 3.4 years
- Creatinine 1.5 to 3: benazepril 20 mg (1)
- Creatinine 3.1 to 5: benazepril vs. placebo (2)
- Outcomes: ESRD, 2X creatinine or death
- 22% in group 1; 41% in group 2 on ACE vs. 60% on placebo
- Similar adverse events
- Results not mediated by BP control

ACE Inhibitors and Pregnancy

- Contraindicated in pregnancy or women at risk for pregnancy
- Known teratogen in 2nd and 3rd trimester
- Study from Tennessee Medicaid showed congenital malformations in women exposed to ACE in first trimester
- 29,096 infants born between 1985-2000; 209 exposed to ACE, 202 to other BP meds
- Risk ratio = 2.71 (1.72 to 4.27)
- CV and CNS malformations most common

Do We Want to Treat Prehypertension?

- 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?
**Calcium Channel Blockers**

- Effective therapy in Blacks and elderly
- As effective as other drug classes in preventing CV events
- Do not reverse atherosclerosis
- No evidence of increase risk of cancer
- In CAD, short acting dihydropyridines lead to dose dependent increase in risk of MI
- I use as fifth choice or in combination
- Worsen proteinuria in CKD
- Effective in systolic hypertension

**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

**What About Other Drugs?**

- CNS sympatholytics: Clonidine, methyldopa
- Alpha-1 blockers: OK but inferior as single drug and tachyphylaxis
- Labetalol good 6th choice
- Direct vasodilators - more diuretics
- Peripheral adrenergic antagonists?
- What about statins: 2-3 mm Hg drop

**Take Home Points 1**

- SBP is greater risk factor than DBP
- Risk of CVD doubles with each increment of 20/10 mm Hg
- 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
MANAGEMENT OF HYPERTENSION: TREATMENT THRESHOLDS AND MEDICATION SELECTION

Take Home Points 2

- Set goal SBP and treat with drugs at any age—Control level is relative
- Thiazides, ACE-I, ARB, beta blockers and CCB are similar—combinations
- Co-morbid condition and age considerations in selecting meds

Take Home Points 3

- Thiazides for most patients, alone or combined—always in top 3 choices
- Most patients will need two or more drugs to achieve or be close to goal SBP
- Control only occurs with motivated patients who trust their clinician