Diagnosis and treatment of hypertension

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Epidemiology of Hypertension

- Affects over 65 million US adults
  - 1/3 of US adults over age 18
- Less than 1/3 of those being treated have achieved goals of <140/90
- Leading risk factor for CHD, CHF, CVA, renal disease
- Amount of BP reduction is the major determinant of risk reduction, NOT the choice of medication
Diagnosis of hypertension

- 2+ or more readings at 3+ visits (if no end organ damage)
- Proper technique for BP

**Sit for 5 minutes**
- Support arm
- Correct cuff size

Okay to take BP over clothes

<table>
<thead>
<tr>
<th>BP Stages</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-HTN</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Stage 1 HTN</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 HTN</td>
<td>≥160</td>
<td>≥100</td>
</tr>
</tbody>
</table>
Evaluation of Hypertension

- End Organ Damage
- Major CV Risk Factors
- r/o secondary causes
- Hypertensive urgency/emergency: BP > 180/120
  - Acute target organ damage [encephalopathy, unstable angina, MI, Pulmonary edema, stroke, aortic dissection] → Hospitalization
  - Usual first line therapy: sodium nitroprusside
  - If no acute target organ damage, usually require combination therapy, close follow-up, evaluation of secondary causes of hypertension
History

- Patient age
- Family history of premature CVD (men <55 years or women <65 years)
- Diabetes
- Smoking, alcohol, illicit drug use
- weight/ diet/ physical inactivity
- End organ damage
  - LVH, CAD, angina, prior MI/ PCI, CHF
  - Stroke or transient ischemic attack
  - Chronic kidney disease
  - Peripheral arterial disease
  - Retinopathy
Physical exam

- BMI
- Repeat blood pressure with correct cuff size (cuff encircling at least 80% of the arm)
- Fundoscopic exam (retinal changes)
- Thyroid exam
- CV exam – PMI, murmurs, peripheral pulses, bruits
- Neurologic exam
Consider secondary hypertension

- Age < 30 or > 55 at onset (negative family hx).
- Abrupt or severe hypertension
- Resistant to therapy
- Target organ damage
- Unprovoked hypokalemia (aldosteronism)
- Diffuse arterial disease
- Ace inhibitor induced renal dysfunction (RAS)
- Labile BP with sweats/tremor/headache (pheo)

Calhoun, Circulation, 2008
Common causes of secondary hypertension

- Sleep apnea (witnessed apneas, fatigue, snoring)
- Chronic kidney disease
- Renovascular disease
  - Arterial 90%, muscular dysplasia 10% (younger women)
- Primary aldosteronism (HTN, ↓K, metabolic alkalosis)
  - Aldosterone renin ratio
    - High negative predictive value
    - Low specificity: low renin states are common in uncontrolled HTN

Calhoun, Circulation, 2008
Uncommon Secondary Causes

- **Cushing syndrome** (central obesity, ecchymosis, muscle weakness) → 24 hour urine
- **Pheochromocytoma** → 24 hour urine
- **Coarctation of the aorta** (↓ or lag in peripheral pulse)
- **Parathyroid disease**
Lab tests and diagnostic studies

- CBC, chem. 7, Calcium, fasting lipids, UA, TSH
- EKG
- Secondary causes
  - aldo/renin ratio
  - 24 hour urine for cortisol & metanephrines, creatinine clearance
  - Ca/Phos/PTH
Causes of resistant hypertension

- Non adherence to medications
- Improper measurement
- Volume overload
  - Excess sodium intake
  - Volume retention from kidney disease
  - Inadequate diuretic therapy
- Excess alcohol intake (>2 drinks/day men, >1 for women)
- White Coat hypertension -
  - Home monitoring (24 hour or BP cuff)
  - Up to 20% of patients in some series
Drug-induced hypertension

- NSAIDs
- Cocaine, amphetamines, other illicit drugs
- Sympathomimetics (decongestants, anorectics)
- Oral contraceptives
- Corticosteroids
- Less common: Cyclosporine, tacrolimus, EPO, licorice
- OTC supplements: (eg, ephedra, ma haung, bitter orange)
Medication adherence

- Patients will not tell you they are non-adherent:
  - Medicare survey: 27% who stopped medication due to side effects, perceived non-efficacy did NOT tell their physician (Wilson, JGIM, 2007)

- High rate of non-adherence for BP medications: ranges from 25-50% (Ho, Circulation, 2009)

- Need to assess in clinic: “Most people forget to take their medications occasionally. How often does this happen to you?” (Choo, 1999, Medical care)
Interventions to improve adherence

- Give once a day medications!
- Meta-analysis of interventions for chronic disease
  - Reduced dosing demands
  - Monitoring and feedback to patients
  - Most informational only interventions did not improve clinical outcomes
  
- Frequent visits, use of pharmacists and home monitoring

Kripalani, Archives, 2007
# Treatment of Hypertension

<table>
<thead>
<tr>
<th>BP Stages</th>
<th>SBP</th>
<th>DBP</th>
<th>Drug Therapy</th>
<th>Promote Lifestyle modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-HTN</td>
<td>&lt; 120</td>
<td>&lt; 80</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Stage 1 HTN</td>
<td>120-139</td>
<td>80-89</td>
<td>Consider for those with DM</td>
<td>Consider thiazide unless contraindicated</td>
</tr>
<tr>
<td>Stage 2 HTN</td>
<td>140-159</td>
<td>90-99</td>
<td>Drug therapy with 2+ drugs</td>
<td></td>
</tr>
</tbody>
</table>

SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure.
Treatment goals

- <140/90 mmHg for uncomplicated HTN
- <130/80 mmHg
  - Diabetes
  - Proteinuric CKD
  - Vascular disease
- Elderly: DBP >65 mmHg
- Largest decrease in BP usually noted with ½ standard dose for most medications
Key Messages - Lifestyle modifications

- Loose weight (5-10% of body weight), or maintain normal BMI < 25
  - 2/3 of obese vets have hypertension (Nelson, JGIM, 2006)
- Stay active
- Eat right (Low sodium, DASH diet)
- Don’t smoke
- Moderate alcohol consumption
Clinical benefits from modest weight loss

<table>
<thead>
<tr>
<th>Weight loss</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5 kg</td>
<td>30% ↓ in need for medications for blood pressure</td>
</tr>
<tr>
<td>10 kg</td>
<td>5 - 20 mmHg ↓ in SBP</td>
</tr>
<tr>
<td>10%</td>
<td>↓ systolic BP by 6.1 mm Hg</td>
</tr>
</tbody>
</table>

Whelton, JAMA, 1998
Poobalan, Obesity Reviews: 5, 43 - 50
Addressing weight loss during a clinic visit

Introducing the topic of weight:
- What would you say your ideal weight is?
- How much would you like to weigh?
- Has your weight changed in the last year?

Brief counseling: “As your primary doctor, I’m concerned about your weight. Your weight is contributing to your high blood pressure”
## Physical activity

<table>
<thead>
<tr>
<th>Goal</th>
<th>Duration and intensity</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health benefits</td>
<td>30 min moderate</td>
<td>5+ days/wk</td>
</tr>
<tr>
<td></td>
<td>20 minutes vigorous</td>
<td>3+ days/wk</td>
</tr>
<tr>
<td>Weight loss</td>
<td>90 min moderate</td>
<td>5-7 days/wk</td>
</tr>
<tr>
<td></td>
<td>60 min vigorous</td>
<td></td>
</tr>
<tr>
<td>Weight loss maintenance</td>
<td>60 min moderate</td>
<td>5-7 days/wk</td>
</tr>
<tr>
<td></td>
<td>30 min vigorous</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical benefit of regular physical activity**

- ↓ SBP by 4mm Hg
- ↓ DBP by 3 mm Hg
## Low sodium and DASH diet

<table>
<thead>
<tr>
<th>Diet composition</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium 100 meq/ day (2.4 g sodium)</td>
<td>2 - 8 mmHg ↓ in SBP</td>
</tr>
<tr>
<td>DASH diet: rich in fruits, vegetables and low fat dairy products, reduced saturated and total fat</td>
<td>8 - 14 mmHg ↓ in SBP</td>
</tr>
</tbody>
</table>
Treatment Guidelines
Key messages of JNC VII

- Risk of CVD doubles with each ↑ of 20/10 mmHg over 115/75 mmHg
- Pre-hypertensive 120-139/80-89
- Thiazides should be used for most patients
- Most patients will require > 1 medication especially if >20/10 mmHg over goal
- Treatment ↓ CVA 35-40%, ↓ MI by 20-25%, ↓ CHF by 50%
Not at goal with Lifestyle modifications (<140/90, or <130/80 with DM, CKD)

No compelling indication

Stage I
SBP 140-150, DBP 80-90

Thiazide

Stage II
SBP >150, DBP >90

2+ medications, dual therapy

Compelling indications
## Compelling indications

<table>
<thead>
<tr>
<th></th>
<th>Preferred Agents</th>
<th>Additional/Alternatives</th>
<th>Other Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>ACEi, Thiazides</td>
<td>ARB, CCB, β blocker</td>
<td></td>
</tr>
<tr>
<td>Systolic HF</td>
<td>ACEi, β blocker</td>
<td>ARB, Hydralazine/ Nitrate, K+ sparing diuretic</td>
<td>Diuretic CCB</td>
</tr>
<tr>
<td>CKD</td>
<td>ACEi, ARB, Diuretic</td>
<td>β blocker, CCB</td>
<td></td>
</tr>
<tr>
<td>Post stroke</td>
<td>Thiazides, ACEi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post - MI</td>
<td>β blocker, ACEi</td>
<td>CCB, Thiazides</td>
<td></td>
</tr>
</tbody>
</table>
## Pros and Cons of commonly used medications

<table>
<thead>
<tr>
<th>Agents</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>+ outcome data, all endpoints; Effective in African Americans (AA); Inexpensive</td>
<td>Gout at higher doses, (Metabolic effects), K</td>
</tr>
<tr>
<td>β Blockers</td>
<td>+ outcome data for CHF, stroke, post-MI Inexpensive</td>
<td>Impotence, Fatigue, Impaired exercise tolerance; May not work as well in elderly or AA</td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>Outcomes as good as diuretic/ BB</td>
<td>Cough with ACE; Angioedema (esp in AA); C/ I pregnancy</td>
</tr>
<tr>
<td>CCB</td>
<td>Salt-sensitive &amp;/ or African American, Useful in pts with stable angina</td>
<td>Ankle swelling, headaches</td>
</tr>
</tbody>
</table>
Hypertension studies – Key Messages

- Use a diuretic
  - HCTZ 25 = Chlorthalidone 12.5
  - Check K within 2 weeks

- Treat the elderly

- ACE + ARB are not additive

- Combo therapy >20/10 mmHg above goal

- Most comparison trials do not show any differences in primary outcomes as long as equivalent decreases in BP were achieved (Chobanian, NEJM 2008)
Case studies

See handout
Current studies

- Meta-analysis
- Monotherapy
- Dual therapy
Meta-analysis of hypertension trials, n=464,000

- Literature search 1966 – 2007
- Categories of participants
  - No history of cardiovascular disease
  - History of CHD
  - History of stroke
- Combined studies using random effects model (most conservative approach)
- Included 147 trials

Law, M R et al. BMJ 2009;338:b1665
Relative risk estimates of coronary heart disease events in single drug blood pressure difference trials according to drug (beta blockers or other), presence of CHD, and for beta blockers according to acute MI on entry

<table>
<thead>
<tr>
<th>Trials of β blockers</th>
<th>No of trials</th>
<th>No of events</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with history of coronary heart disease</td>
<td>37</td>
<td>2524</td>
<td>0.71 (0.66 to 0.78)</td>
</tr>
<tr>
<td>Entry after acute myocardial infarction</td>
<td>27</td>
<td>2155</td>
<td>0.69 (0.62 to 0.76)</td>
</tr>
<tr>
<td>Entry after long term coronary heart disease</td>
<td>11</td>
<td>369</td>
<td>0.87 (0.71 to 1.06)</td>
</tr>
<tr>
<td>People with no history of coronary heart disease</td>
<td>6</td>
<td>851</td>
<td>0.89 (0.78 to 1.02)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trials of drugs other than β blockers</th>
<th>No of trials</th>
<th>No of events</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with history of coronary heart disease</td>
<td>37</td>
<td>5834</td>
<td>0.85 (0.79 to 0.91)</td>
</tr>
<tr>
<td>People with no history of coronary heart disease</td>
<td>24</td>
<td>3217</td>
<td>0.84 (0.79 to 0.90)</td>
</tr>
<tr>
<td>All trials except ones of β blockers in people with history of coronary heart disease</td>
<td>64</td>
<td>9417</td>
<td>0.85 (0.81 to 0.89)</td>
</tr>
</tbody>
</table>

Law, M R et al. BMJ 2009;338:b1665
Relative risk estimates of coronary heart disease events and stroke in single drug blood pressure difference trials according to class of drug, n=464,000

* excluding CHD events in trials of {beta} blockers in people with history of CHD

<table>
<thead>
<tr>
<th></th>
<th>No of trials</th>
<th>No of events</th>
<th>Relative risk (95% CI)</th>
<th>No of trials</th>
<th>No of events</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazides</td>
<td>11</td>
<td>1710</td>
<td>0.86 (0.75 to 0.98)</td>
<td>10</td>
<td>1370</td>
<td>0.62 (0.53 to 0.72)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>6</td>
<td>851</td>
<td>0.89 (0.78 to 1.02)</td>
<td>7</td>
<td>690</td>
<td>0.83 (0.70 to 0.99)</td>
</tr>
<tr>
<td>Angiotensin</td>
<td>21</td>
<td>4083</td>
<td>0.83 (0.78 to 0.89)</td>
<td>13</td>
<td>1220</td>
<td>0.78 (0.66 to 0.92)</td>
</tr>
<tr>
<td>Angiotensin receptor</td>
<td>4</td>
<td>378</td>
<td>0.86 (0.53 to 1.40)</td>
<td>0</td>
<td>0</td>
<td>0.66 (0.58 to 0.75)</td>
</tr>
<tr>
<td>Calcium channel</td>
<td>22</td>
<td>2009</td>
<td>0.85 (0.78 to 0.92)</td>
<td>9</td>
<td>976</td>
<td>0.66 (0.58 to 0.75)</td>
</tr>
<tr>
<td>Drug choice open</td>
<td>5</td>
<td>871</td>
<td>0.89 (0.78 to 1.01)</td>
<td>4</td>
<td>763</td>
<td>0.96 (0.75 to 1.23)</td>
</tr>
<tr>
<td>All classes of drug</td>
<td>64</td>
<td>9417</td>
<td>0.85 (0.81 to 0.89)</td>
<td>38</td>
<td>4712</td>
<td>0.73 (0.66 to 0.80)</td>
</tr>
</tbody>
</table>

[Graph showing specified drug better and placebo better with relative risk estimates for different classes of drugs]
Relative risk of CHD and stroke in 46 drug comparison trials comparing each of the five classes of blood pressure lowering drug with any other class of drug

<table>
<thead>
<tr>
<th>Blood pressure difference (mm Hg)</th>
<th>Coronary heart disease events</th>
<th>Strokes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>Diastolic</td>
<td>No of trials</td>
</tr>
<tr>
<td>Thiazides vs any other</td>
<td>-1.4</td>
<td>0.2</td>
</tr>
<tr>
<td>β blockers vs any other</td>
<td>1.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors vs any other</td>
<td>0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Angiotensin receptor blockers vs any other</td>
<td>-0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Calcium channel blockers vs any other</td>
<td>-0.4</td>
<td>-0.9</td>
</tr>
</tbody>
</table>
Meta-analysis conclusions

- All classes of blood pressure lowering drugs have a similar effect in reducing CHD and stroke except:
  - Beta blockers have extra protective effect post-MI
  - CCB have additional benefit in preventing stroke

- Reduction in CHD was similar regardless of baseline BP or presence of pre-existing CHD
Monotherapy

ALLHAT

HYVET
ALLHAT study population

- n = 33,357 ages 55 years or older with hypertension
- High risk population
  - mean age 67 years
  - 47% women
  - 35% African American, 19% Hispanic
  - 36% with diabetes
  - 22% smokers
  - 51% with atherosclerotic CVD
- No significant differences in patient characteristics between treatment arms
ALLHAT Study Design

- 4 arms in Randomized Controlled Trial
  - Thiazide diuretic [chlorthalidone 12.5 - 25 mg]
  - CCB [amlodipine 2.5 - 10 mg]
  - ACE inhibitor [lisinopril 10 - 40 mg]
  - Alpha blocker [doxazosin] stopped due to 25% ↑ risk for CV/CHF

- 5 year follow up period
- Funded by NHLBI

ALLHAT Outcomes

- **Intermediate endpoints**
  - metabolic effects
  - blood pressure control

- **Primary outcomes**
  - combined fatal CHD or non-fatal MI

- **Secondary outcomes**
  - all cause mortality
  - stroke
  - combined CHD and CVD outcomes
**ALLHAT Metabolic effects**

Mean fasting glucose levels \{mg/ dL\}  
[ n=24,673 ]

<table>
<thead>
<tr>
<th></th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>123.5</td>
<td>123.1</td>
<td>122.9</td>
</tr>
<tr>
<td>4 Year</td>
<td>126.3</td>
<td>123.7</td>
<td>121.5</td>
</tr>
<tr>
<td>p value</td>
<td>0.11</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
ALLHAT Blood pressure control

2 mm Hg

0.8 mm Hg
No difference in combined fatal CHD or non-fatal MI
No difference in 6 year CHD event rate

<table>
<thead>
<tr>
<th></th>
<th>per 100 persons (SE)</th>
<th>p value vs Chlorthalidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>11.5 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>11.3 (0.4)</td>
<td>0.65</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>11.4 (0.4)</td>
<td>0.81</td>
</tr>
</tbody>
</table>
Lisinopril had higher 6-yr event rates for stroke, combined CVD and HF than chlorthalidone

<table>
<thead>
<tr>
<th>Condition</th>
<th>Chlorthalidone</th>
<th>Lisinopril</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>17.3</td>
<td>17.2</td>
<td>1.00 (0.94-1.08)</td>
</tr>
<tr>
<td>Stroke</td>
<td>5.6</td>
<td>6.3</td>
<td>1.15 (1.02-1.30)</td>
</tr>
<tr>
<td>African Am.</td>
<td></td>
<td></td>
<td>1.40 (1.17-1.68)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>30.9</td>
<td>33.3</td>
<td>1.10 (1.05-1.16)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7.7</td>
<td>8.7</td>
<td>1.19 (1.07-1.31)</td>
</tr>
</tbody>
</table>
Amlodipine had higher 6 year event rate for heart failure than chlorthalidone

<table>
<thead>
<tr>
<th></th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause mortality</td>
<td>17.3</td>
<td>16.8</td>
<td>0.96 (0.89-1.02)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7.7</td>
<td>10.2</td>
<td>1.38 (1.25-1.52)</td>
</tr>
</tbody>
</table>
ALLHAT Study Limitations

- Didn’t include beta-blockers or newer agents [ARBs]
- Equivalent blood pressure reduction was not achieved within all groups
  - Lisinopril group could not use other agents tested in the ALLHAT trial for step-up therapy
- Only tested one agent within each class of medications
ALLHAT conclusions

- No difference in fatal CHD or non-fatal MI between the treatment arms
- No difference in all-cause mortality
  - Metabolic effects did not change mortality
- Lisinopril higher 6 yr stroke, heart failure and combined CVD event rate than chlorthalidone
- Amlodipine higher 6 yr heart failure rate than chlorthalidone
HYVET
Hypertension in the Very Elderly Trial

- N = 3845 patients 80 years or older (Europe, China, Australia and Tunisia)
- SBP 160-199 mm Hg; treatment goal 150/80
- Placebo vs. diuretic (indapimide 1.5 mg qd) with the addition of ACE inhibitor (perindopril 4-8 mm Hg) as needed
- Stopped early due to large benefit
- 30% ↓ CVA, 21% ↓ all cause-mortality
HYVET Results

![Graph showing blood pressure changes over years for placebo and active-treatment groups.](image)

- **Systolic blood pressure**
  - Placebo group
  - Active-treatment group

- **Diastolic blood pressure**
  - Placebo group
  - Active-treatment group

<table>
<thead>
<tr>
<th>Year</th>
<th>Placebo Group</th>
<th>Active-treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1912</td>
<td>1933</td>
</tr>
<tr>
<td>1</td>
<td>1468</td>
<td>1540</td>
</tr>
<tr>
<td>2</td>
<td>701</td>
<td>754</td>
</tr>
<tr>
<td>3</td>
<td>330</td>
<td>373</td>
</tr>
<tr>
<td>4</td>
<td>191</td>
<td>207</td>
</tr>
<tr>
<td>5</td>
<td>116</td>
<td>118</td>
</tr>
</tbody>
</table>
HYVET results

A Fatal or Nonfatal Stroke

B Death from Any Cause

C Death from Cardiovascular Causes

D Death from Stroke

E Heart Failure
Dual Therapy Trials

ACCOMPLISH

ONTARGET
ACCOMPLISH Study Population

- $N=11,506$ with hypertension, at high risk for CV events
  - Previous vascular events, DM, renal disease, CABG
- Randomized controlled trial
  - Benazepril + HCTZ (12.5 – 25mg) or
  - Benazepril + Amlodipine
- Followed for 36 months
- Industry sponsored

Jamerson, NEJM, 2008
Primary endpoint: composite death from CV causes, non-fatal MI, non-fatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revasc.
ACCOMPLISH results

Jamerson, NEJM, 2008
ACCOMPLISH Results

![Graph showing patients with primary events over months for Benazepril plus hydrochlorothiazide and Benazepril plus amlodipine.](image)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril plus amlodipine</td>
<td>5512</td>
</tr>
<tr>
<td></td>
<td>5317</td>
</tr>
<tr>
<td></td>
<td>5141</td>
</tr>
<tr>
<td></td>
<td>4959</td>
</tr>
<tr>
<td></td>
<td>4739</td>
</tr>
<tr>
<td></td>
<td>2826</td>
</tr>
<tr>
<td></td>
<td>1447</td>
</tr>
<tr>
<td>Benazepril plus hydrochlorothiazide</td>
<td>5483</td>
</tr>
<tr>
<td></td>
<td>5274</td>
</tr>
<tr>
<td></td>
<td>5082</td>
</tr>
<tr>
<td></td>
<td>4892</td>
</tr>
<tr>
<td></td>
<td>4655</td>
</tr>
<tr>
<td></td>
<td>2749</td>
</tr>
<tr>
<td></td>
<td>1390</td>
</tr>
</tbody>
</table>
## ACCOMPLISH results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of death from cardiovascular causes and cardiovascular events</td>
<td>0.80 (0.72–0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Component</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>0.80 (0.62–1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>Myocardial infarction (fatal or nonfatal)</td>
<td>0.78 (0.62–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke (fatal or nonfatal)</td>
<td>0.84 (0.65–1.08)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>0.75 (0.50–1.10)</td>
<td>0.14</td>
</tr>
<tr>
<td>Coronary revascularization procedure</td>
<td>0.86 (0.74–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Resuscitation after sudden cardiac arrest</td>
<td>1.75 (0.73–4.17)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Benazepril plus Amlodipine Better*  
*Benazepril plus Hydrochlorothiazide Better*
Criticism: Chlorthalidone has double the potency of HCTZ and much longer duration of action

- ALLHAT Chlorthalidone 50 mg
- ACCOMPLISH HCTZ 12.5 – 25 mg (less potent)

“Doses of thiazide diuretics equivalent to 25mg/day or less of HCTZ may be less effective in preventing CVD... than full doses of amlodipine” Wright, Archives, 2009
ONTARGET study

N = 25,620 patients with vascular disease or DM with no renal insufficiency

Intervention: telmisartan 80 mg/d + ramipril 10 mg/day vs. telmisartan 80 mg/d vs. ramipril 10 mg/day

Primary outcome: death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

Other endpoints: dialysis, doubling of creatinine

Yusef, NEJM, 2008
ONTARGET results

Yusef, NEJM, 2008
## ONTARGET results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ramipril (N=8576)</th>
<th>Telmisartan (N=8542)</th>
<th>Combination Therapy (N=8502)</th>
<th>Telmisartan vs. Ramipril</th>
<th>Combination Therapy vs. Ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td></td>
<td></td>
<td>relative risk (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Renal impairment‡</td>
<td>871 (10.2)</td>
<td>906 (10.6)</td>
<td>1148 (13.5)</td>
<td>1.04 (0.96–1.14)</td>
<td>1.33 (1.22–1.44)§</td>
</tr>
<tr>
<td>Renal failure requiring dialysis</td>
<td>48 (0.6)</td>
<td>52 (0.6)</td>
<td>65 (0.8)</td>
<td>1.09 (0.74–1.61)</td>
<td>1.37 (0.94–1.98)</td>
</tr>
</tbody>
</table>

**RR 1.33**
Hypertension studies – Key Messages

- Use a diuretic
  - HCTZ 25 = Chlorthalidone 12.5
  - Check K within 2 weeks
- Treat the elderly
- ACE + ARB are not additive
- Combo therapy >20/10 mmHg above goal (ACE + CCB)
- Most comparison trials do not show any differences in primary outcomes as long as equivalent decreases in BP were achieved (Chobanian, NEJM 2008)
ASCOT trial

- N = 19,000 adults with hypertension and 3+ risk factors
- Beta-blocker + thiazide (if needed) vs. CCB Amlodipine + ACE (if needed)
- Followed by 5.5 years
- Trial stopped early, lower CV events and total mortality in group receiving CCB
Follow up intervals

- Follow up intervals
  - < 1 month for SBP > 160, DBP > 100
  - 2 months SBP 140-159, DMP 90-99
  - Well controlled BP q 6 months