Pathophysiology and Treatment of Essential Hypertension

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Natural History of Essential Hypertension

Premature Death
- Generalized arteriosclerosis and atherosclerosis
- Heart disease
- Stroke
- Kidney Failure
- Malignant Hypertension (fibrinoid necrosis)

Hypertension Is a Component of a Chronic Cardiovascular Syndrome

Persons with hypertension have more cardiovascular disease
Life Expectancy: reduced by ~ 5 yrs
(Franco et al. Hypertension, 2005)

Implications for treatment:
Treatment should focus on lowering CV risk as well as lowering BP

Classification of BP for Adults*

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mm Hg</th>
<th>or</th>
<th>DBP mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>or</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>or</td>
<td>80–89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140–159</td>
<td>or</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥160</td>
<td>or</td>
<td>≥100</td>
</tr>
</tbody>
</table>

SBP=systolic BP, DBP=diastolic BP.
Hypertension is common and is strongly related to CV disease.

- Lowering blood pressure reduces CV disease in everyone: The ‘sicker’ (and older) you are, the greater benefit from lowering BP.

- If you are ‘older’ (>60, >65, >70); Systolic BP predicts outcomes.

- Prehypertension: you can’t be too normotensive.

Hypertension is Common:
Persons who are normotensive at age 55 have a 90% lifetime risk for developing HTN. (Framingham Data)
Global Burden of Hypertension:
1 billion 2000, 1.5 billion 2025

• 2001: 7.6 million deaths (13.5% global total)
• 54% stroke, 47% IHD
• 1/3 deaths in Europe and Asia

Most of the disease burden is in low and middle income economies

Hypertension is Strongly Related to CVD

• The relationship of BP to risk of CVD is continuous, consistent, and independent of other risk factors.

• Hypertension acts synergistically with other CV risk factors

• 24 hour BP, nighttime BP, BP variability – 24 hour, and visit to visit are associated with increased CV risk
  (Rothwell et al; ASCOT trial, 2010)

Other Hemodynamic Measurements and CV Risk: Pulse Wave Velocity

• Aortic Pulse Wave Velocity: indirect measurement of arterial stiffness measured non invasively
  - PWV depends on BP and characteristics of aortic wall and increases with age

• Aortic Stiffness may persist with good BP control

• Meta analysis (n=15,877) of longitudinal data
  (Vlachopoulos et al, 2010)

PWV is an independent predictor of CV outcomes

CV Mortality Risk Doubles with Each 20/10 mm Hg BP Increment*

*Individuals aged 40-70 years, starting at BP 115/75 mm Hg.
CV, cardiovascular; SBP, systolic blood pressure; DBP, diastolic blood pressure

CV mortality risk
SBP/DBP (mm Hg)
115/75 135/85 155/95 175/105
0 1 2 3 4 5 6 7 8

* 2001 Twijnemaar EJ.
Central Pressure Measurement

- Noninvasive measurement of impact of the reflected arterial pulse wave on the central circulation
- Central pressures are affected by arterial stiffness, heart rate, and possibly dietary Na
- Central BP may be a better predictor of CV outcomes than brachial BP. *Roman et al*

Should ‘Prehypertension’ be Treated?

- No data from RCT’s supporting drug Rx
- Benefits of drug treatment in patients with prehypertension would be small:
  - Systolic of 130-139 c/w <120 mm Hg would result in .7 deaths/100 patients over 25 years)
  - Lifestyle modification is appropriate for all adults

Hypertension is the most easily treatable risk factor for cardiovascular disease (‘low hanging fruit’)

Unequivocal Benefits of Lowering BP:

- Relative Risk Reduction Constant
- Absolute Risk Reduction Varies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Average Percent Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke incidence</td>
<td>35–40%</td>
</tr>
<tr>
<td>Myocardial infarct</td>
<td>20–25%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>50%</td>
</tr>
</tbody>
</table>
Persons with highest overall CV risk benefit most from lowering BP

- Relative risk: likelihood of developing CV disease in hypertensives relative to normotensives (CVD Incidence HT/CVD Incidence NT) and is similar in both high and low risk patients.
- Absolute risk: incidence of CV disease in a population (normotensive or hypertensive) determined by synergistic effect of all CV risk factors e.g. age, gender, symptomatic CVD, LVH, GFR, smoking, lipids, diabetes.
- Relative risk reduction is the reduction in risk relative to baseline risk and is similar in high and low risk groups (CVDi Placebo – CVDi Rx/CVDi Placebo).
- Reductions in absolute risk are greater, number needed to treat is smaller with higher blood pressure and multiple cardiovascular risk factors.

Hypertension Epidemiology
Summary

- Hypertension is common and is strongly related to CV disease.
- Lowering blood pressure reduces CV disease in everyone: The ‘sicker’ (and older) you are, the greater benefit from lowering BP.
- If you are ‘older’ (? > 60, ? > 65); It’s the Systolic.
- Prehypertension: you can’t be too normotensive, but benefits of pharmacologic treatment remain unproven.

Ambulatory BP Monitoring

- ABPM is indicated for evaluation of ‘suspected’ white-coat HTN (newly diagnosed stage 1, no target organ injury, females, non-smokers).
- Risk stratification: Non-Dipping (failure of nocturnal decrease in by 10 to 20% is associated with increased risk for cardiovascular events; Higher nighttime BP – increased CV risk.
- Hypotensive episodes.
- National Institute for Health and Clinical Excellence (NICE) recommends ABPM to confirm diagnosis of HTN.

Diagnostic Thresholds for Ambulatory Blood Pressure

**Kikuye et al 2007**

<table>
<thead>
<tr>
<th>Category</th>
<th>24 hour systolic/diastolic (mm Hg)</th>
<th>Daytime (mm Hg)</th>
<th>Nighttime (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>115/75</td>
<td>120/80</td>
<td>100/65</td>
</tr>
<tr>
<td>Normal</td>
<td>125/75</td>
<td>130/85</td>
<td>110/70</td>
</tr>
<tr>
<td>Hypertension</td>
<td>130/80</td>
<td>140/85</td>
<td>120/70</td>
</tr>
</tbody>
</table>
Home BP Monitoring

• Provides out of office readings, BP variability, identification of WCH and MH

• Lower cost, high availability, easy application, useful over long periods of time

• Improved BP, Fewer medications, better results when used with a program for adjustment of medications (McManus 2010; Agarwal 2011)

Home Blood Pressure Monitoring

• NICE guidelines for confirmation of HTN
- Take 2 consecutive readings 1 min apart
- Seated position
- Record BP twice daily AM and PM
- 4 to 7 days of recording

BP Measurement: Summary

• Although office BP is the most widely used method, ambulatory BP is a better predictor of CV risk

• ABP is the gold standard test for diagnosing white coat hypertension

• Hypertension on ABP is defined as a mean 24 hour BP of > 130/80 mm Hg

Pathophysiology:
Hypertension is a Heterogeneous Disorder, But.....
Pathophysiology of Hypertension: Decreased Na Excretion

- Essential Hypertension
- Dysregulation of hormones (Ang II, RAS)
- Decreased nephron number
- Genetic variations in sodium-regulatory proteins

Pathophysiology of Hypertension: Research Directions

- RAS system: AT2 Receptor effects, ACE-2: Ang 1-7
- Genetics: GWAS – limited by heterogeneity of phenotype, polygenic nature of 'essential hypertension'
- Single gene defects: WNK kinases – familial hyperkalemic hypertension
- Interrelationships between SNS, obesity, RAS
- Newly discovered potential mediators of blood pressure: renalase (metabolizes catecholamines), incretins (GLP-1), DPP 4 inhibitors, adipokines (leptin, adiponectin), TGF-β.

Treatment of Hypertension

Goals of Rx

- To reduce morbidity and mortality by the least intrusive means possible. This may be accomplished by achieving and maintaining
  - SBP <140 mm Hg
  - DBP <90 mm Hg

- (?) Different targets for Elderly, Diabetics, proteinuric renal disease, CHD

- Controlling other cardiovascular risk factors

Major Risk Factors That Increase Mortality in Hypertension

- Smoking
  - 5-year risk of Major CV Event for 50 year old man with BP 160/110 mmHg
    - + high cholesterol: 2.5-5%
    - + high cholesterol and smoking: 15-30%

- Gender: men, postmenopausal women
- Family history
- Albuminuria
Lifestyle Modification: Do they work?

<table>
<thead>
<tr>
<th>Modification</th>
<th>Approximate SBP reduction (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>5–20 mmHg/10 kg weight loss</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>8–14 mmHg</td>
</tr>
<tr>
<td>Dietary sodium reduction (2.4 Na g/d or 6 NaCl g/d)</td>
<td>2–8 mmHg</td>
</tr>
<tr>
<td>Physical activity (30-45 min most days of the week)</td>
<td>4–9 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>2–4 mmHg</td>
</tr>
</tbody>
</table>

Treatment of Hypertension

- When Should treatment be initiated?
- What are the treatment targets? (how low should you go?)
- What drugs should you use?

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults – JNC 8

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD; Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH; Michael L. LeFevre, MD, MPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS; Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD; Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH

Although this guideline provides evidence-based recommendations for the management of high BP and should meet the clinical needs of most patients, these recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient.

JAMA Published online December 18, 2013.

Recommendation 1

- In the general population aged ≥60 years
  - Initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP) 150 mmHg or diastolic blood pressure (DBP) 90 mmHg
  - Treatment goal SBP < 150 mm Hg and goal DBP < 90 mmHg
    - (Strong Recommendation – Grade A)
Recommendation 1 Corollary Recommendation

- In the general population aged ≥60 years
  - Treatment does not need to be adjusted
    - if pharmacologic treatment for high BP results in lower achieved SBP (eg, <140 mmHg) and treatment is well tolerated and without adverse effects on health or quality of life.
      - (Expert Opinion – Grade E)

Treatment of Hypertension in the Very Elderly (Beckett et al, 2008)

- 4,000 subjects: Indapamide vs Placebo
- Average age 83 years
- Baseline blood pressure ~ 173/90 mm Hg
- 6% diabetes, 60% female, BMI 24

Kaplan-Meier Estimates of the Rate of End Points, According to Study Group

Treatment of Hypertension in Elderly

- Effects on mortality of aggressive treatment remain unproven (HYVET)
- Metaanalysis suggests benefit for stroke and CHF (Rx vs placebo)
- Treatment to lower targets (<140) unproven (may contribute to cognitive decline)
- Avoid overtreatment!
### Treatment of Hypertension in Elderly

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Population</th>
<th>Targets</th>
<th>Outcomes</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYVET (2008)</td>
<td>83 (n=3845)</td>
<td>Caucasian</td>
<td>&lt;160</td>
<td>Mortality, Stroke (2 yrs)</td>
</tr>
<tr>
<td>JATOS (2008)</td>
<td>74 (n=2212)</td>
<td>Japanese</td>
<td>&lt;140 vs &lt;160</td>
<td>Composite CV, Renal (2 yrs)</td>
</tr>
<tr>
<td>CARDIO-Sis (2009)</td>
<td>67 (n=1111)</td>
<td>European</td>
<td>&lt;140 vs &lt;130</td>
<td>LVH (ECG), Composite CV (2 yrs)</td>
</tr>
<tr>
<td>VALISH (2010)</td>
<td>76 (n=3260)</td>
<td>Japanese</td>
<td>&lt;140 vs 140-150</td>
<td>Composite CV, Renal (3 yrs)</td>
</tr>
</tbody>
</table>

### Recommendation 2

- In the general population <60 years
  - Initiate pharmacologic treatment to lower DBP 90mmHg
  - **Treatment goal** DBP<90mmHg.
- For ages 30-59 years
  - Strong Recommendation – Grade A
- For ages 18-29 years
  - Expert Opinion – Grade E

### Recommendation 3

- In the general population <60 years
- Initiate pharmacologic treatment to lower BP at SBP ≥ 140mmHg
- **Treatment goal** SBP <140mmHg.
  - (Expert Opinion – Grade E)

### How Low Should You Go?

- < 90 mm DBP: HDFP, Hypertension-Stroke Cooperative, MRC, ANBP, VA Cooperative
- HOT study: 18,790 patients age of 61.5 years treated with felodipine-based therapy: no additional benefit of DBP <85 or 80 mm Hg in non diabetics
- Previous guidelines: AHA, JNC 7 – 130/80 for CKD and diabetes
Recommendation 4

- In the population aged ≥18 years with chronic kidney disease (CKD)

- Initiate pharmacologic treatment to lower BP at SBP ≥ 140mmHg or DBP ≥ 90mmHg

- Treatment goal SBP<140mmHg and goal DBP<90mmHg.
  - (Expert Opinion – Grade E)

Treatment Targets in CKD

- MDRD: low targets reduced progression to ESRD
- African American Study of Kidney Disease (AASK): no difference in cardiorenal outcomes between intensive (<120/80) and standard (135–140/85–90)
- ALLHAT, ACCORD: no difference in outcomes related to drugs or targets
- Lower treatment targets may be appropriate in proteinuric CKD (IRMA-2)
- SPRINT trial in progress

Recommendation 5

- In the population aged ≥18 years with diabetes

- Initiate pharmacologic treatment to lower BP at SBP ≥ 140mmHg or DBP ≥ 90mmHg

- Treatment goal SBP <140mmHg and DBP <90mmHg.
  - (Expert Opinion – Grade E)
Recommendation 6

- General nonblack population, including those with diabetes
- Initial antihypertensive treatment should include:
  - A thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB).
  - Moderate Recommendation – Grade B

Does Initial Drug Choice Matter?

- Monotherapy with most drugs is effective about 50% of the time (in unselected patients)
- Most patients with stage 2 or higher need more than 1 drug
- Are there class-specific attributes of drugs that are associated with benefits beyond lowering blood pressure?

Special Considerations in Selecting Drug Therapy

- Proven efficacy in preventing CVD
- Demographics
- Coexisting diseases and therapies
- Quality of life
- Physiologic and biochemical measurements
- Drug interactions
- Economic considerations

Demographics and Antihypertensive Drugs

- Younger white patients respond well to ACE inhibitors and β-blockers. Older black patients respond well to diuretics and calcium channel blockers (VA Cooperative Study)
- There is heterogeneity across all age and ethnic subgroups
Renin Profiling and Choice of Antihypertensive Drugs

- 40% low renin; 15%-20% high renin; 40% medium renin
- Small studies demonstrate efficacy of diuretics and calcium channel blockers in low-renin HTN. ACE inhibitors and β-blockers demonstrate efficacy in high-renin HTN
- Small clinical trial (Egan et al) demonstrates feasibility and efficacy of strategy
- Large studies evaluating this strategy have not been done

Do Antihypertensive Drugs offer cardiovascular protection beyond blood pressure lowering?

Is one drug better than another?

- Metaanalysis of trials involving over 464,000 hypertensive patients
- Thiazides and ACE inhibitors may prevent CHF more than CCBs
- Beta blockers prevent recurrent CHD, but not recommended by JNC 8 as first line Rx
- Calcium channel blockers prevent stroke

Recommendation 7

- General black population, including those with diabetes
- Initial antihypertensive treatment should include a thiazide-type diuretic or CCB (based on prespecified subgroup of ALLHAT).
- **For general black population**
  - Moderate Recommendation – Grade B
- **For black patients with diabetes**
  - Weak Recommendation – Grade C)
Hypertension in Blacks Consensus Statement ISHIB 2010

- Higher prevalence of HTN, increased cardiorenal complications and mortality
- Emphasize importance of socioeconomic rather than racial/genetic factors
- Lower targets: < 135/85 for low risk; < 130/80 for high risk
- Combination therapies, lifestyle modifications and attention to comorbidities
- Deemphasis on using race to select antihypertensive drug regimen although recommend starting with diuretic or CCB

Recommendation 8

- In the population aged ≥18 years with CKD
  - Initial (or add-on) antihypertensive treatment
    - Should include an ACEI or ARB to improve kidney outcomes.
  - Applies to all CKD patients with hypertension regardless of race or diabetes status.
    - Moderate Recommendation – Grade B

Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults With Hypertension

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Population</th>
<th>Goal BP, mm Hg</th>
<th>Initial Drug Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNC 8</td>
<td>General ≥60 y</td>
<td>&lt;130/80</td>
<td>Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB</td>
</tr>
<tr>
<td></td>
<td>General &lt;60 y</td>
<td>&lt;130/80</td>
<td>Black: thiazide-type diuretic or CCB</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>&lt;140/90</td>
<td>Thiazide-type diuretic, ACEI, ARB, or CCB</td>
</tr>
<tr>
<td>NICE 2011</td>
<td>General &lt;55 y</td>
<td>&lt;140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>KDIGO 2012</td>
<td>CKD no proteinuria</td>
<td>&lt;140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td>CKD + proteinuria</td>
<td>&lt;130/80</td>
<td>ACEI or ARB</td>
</tr>
</tbody>
</table>

Diabetes and Antihypertensive Rx

- ~1,000 patients treated with ‘newer drugs’ to avoid 6 iatrogenic cases of diabetes
- ~1000 patients would have to be treated for 1 year with an ARB (vs placebo) to prevent 2 cases of new onset diabetes (TRANSCEND, PROFESSION)
- Ramipril c/w placebo did not reduce incidence of diabetes
**Beta Blockers 2014**

**Cons:**
- Increased insulin resistance
- ? Inferior stroke protection (LIFE, ASCOT)
- ? Less favorable effects on arterial stiffness
- Known adverse effects and decreased efficacy in elderly

**Pros:**
- Post MI, CHD
- Migraines
- Tachyarrhythmias
- ‘Special Effects’: nebivolol nitric oxide donor, ? Metabolically neutral?

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**Diuretics 2014**

**Pros**
- Widely effective
- Enhances effects of other drugs (e.g. ACE Is)
- CHF, CKD
- Thiazide, K sparing, Loop

**Cons**
- Metabolic: Na; Ca; K; Uric acid; glucose;
- Erectile dysfunction
- Antiandrogen effects of MR antagonists

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**Chlorthalidone vs HCTZ**  
*Dorsch et al 2011*

- Retrospective cohort analysis of MRFIT study
- Despite lower potassium and higher uric acid, there was a slight increase in CV events in HCTZ group
- Chlorthalidone is more potent, lowered SPB more than HCTZ and is longer acting
- LDL and glucose levels were lower on Chlorthalidone

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**Thiazide vs. ‘Thiazide Like’**

- Network Meta-analysis: Chlorthalidone is superior to HCTZ in preventing CV events – not due to differences in BP levels. *Roush et al Hypertension 2012*
- Meta-Analysis of dose response relationships for HCTZ, chlorthalidone: Chlorthalidone is 3X more potent than HCTZ and this may explain better outcomes. *Peterzan et al Hypertension 2012*
- Unresolved whether one drug is ‘better’
Calcium Channel Blockers 2015

Pros
- Effective, well tolerated (good for Na sensitive HTN, eg. Elderly, blacks)
- May be more protective against stroke
- DHP and non-DHP can be combined

Cons
- Constipation, sympathetic nervous system stimulation, edema, headaches
- DHPs may increase intraglomerular pressure

ACE Inhibitors

Pros
- Effective, well tolerated
- Renoprotective, cardio protective
- Favorable metabolic profile
- ? Antiinflammatory

Cons
- Cough
- Angioedema
- Hyperkalemia
- ? Ang II escape

ARB's 2015

Pros
- Safe, effective, minimal side effects
- No cough (mostly)

Cons
- Some angioedema
- Hyperkalemia
- Dual RAS blockade: hyperkalemia, decreased GFR
- ??? Cancer– NO!

Other Antihypertensives

- Aldosterone blockade
- Centrally acting alpha agonists (clonidine, methyldopa)
- Alpha blockade (e.g. doxazocin)
- Direct vasodilators (hydralazine, minoxidil)
**Aldosterone**

- Fibrotic effects: CHF, progression of renal disease
- Treatment of resistant hypertension with aldosterone blockade
- Role in essential hypertension
- ‘Epidemic’ of primary aldosteronism

**Combination Therapy**

- Guidelines recommend initiating combination therapy for stage 2 hypertension, and for those with BP > 15/10 mm Hg above goal
- Recommended by ISHIB for African Americans
- *Egan et al. 2012*: Initial therapy with single pill combination therapy (HR 1.53) provided better hypertension control in the first year than free combinations (HR 1.34) or monotherapy.

**Resistant Hypertension**

- Failure to achieve targets on 3 drugs (including diuretic)
- Older age, BMI, African American, excess sodium, alcohol
- Secondary causes: Aldo, Sleep Apnea, RVH
- Excess sympathetic tone, increased aldo
- Lifestyle, diuretics, aldosterone blockade
- Renal Nerve ablation: ?????
Sleep Apnea

- 1 in 4 Americans at risk
- Linked to obesity
- High prevalence in resistant hypertension
- Pathogenesis: SNS, sodium, aldosterone, insulin resistant
- CPAP, lifestyle, aldo blockade

JNC 8: 2014

- Evidence Based Guidelines Addressing:
  - Health benefits of treating specific BP thresholds with antihypertensive therapy
  - Health benefits of achieving specific BP targets
  - Comparative benefits of various antihypertensive drugs/classes

JNC 8

- Hypertensives > 60 years should be treated to BP < 150/80 mm Hg
- Hypertensives < 60 years should be treated to a diastolic goal < 90 mm Hg
- Lack of evidence for persons < 30 years; Recommend BP < 140/90 mm Hg

Conclusions

- Hypertension is the most treatable CVD risk factor
- Hypertension is responsible for tremendous global burden of disease
- Assess and treat concomitant risk factors; Lifestyle modification for all patients
- Lowering blood pressure is more important than how you lower BP; most patients require 2 or more agents
- Combination therapy is reasonable for stage 2 hypertensives
### Some Recent Antihypertensive Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Age</th>
<th>Drugs</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOP HTN-2</td>
<td>6614</td>
<td>76</td>
<td>Conventional Drugs vs ACE and Ca blockers</td>
<td>CV mortality</td>
<td>No differences observed</td>
</tr>
<tr>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIFE 2000</td>
<td>9193</td>
<td>67</td>
<td>ARB vs β Blockers</td>
<td>CV events</td>
<td>ARB better, Mostly stroke</td>
</tr>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ALLHAT 2002</td>
<td>33,330</td>
<td>67</td>
<td>Diuretic/ACE/ Ca blocker</td>
<td>Major CAD events</td>
<td>No difference 36% Blacks</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ANBP 2003</td>
<td>6083</td>
<td>72</td>
<td>ACE vs Diuretic</td>
<td>CV events, death</td>
<td>ACE better: white men</td>
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</tr>
<tr>
<td>ASCOT 2005</td>
<td>19,257</td>
<td>40-79</td>
<td>BB/diuretic vs Ca blocker/ACE</td>
<td>Non fatal/fatal MI, total CVD</td>
<td>'Newer' drugs: fewer endpts, less diabetes</td>
</tr>
</tbody>
</table>