From Evidence to Practice: A Clinical Update in Hypertension

- Current State of Hypertension Management
- ALLHAT Trial: Background and Results
- Relevance of ALLHAT to Clinical Practice
- Clinical Trials that support compelling Indications IDNT RENAL and LIFE
- Summary and Conclusions
From Evidence to Practice
Update in Hypertension: ALLHAT

- Current State of Hypertension Management
  - Epidemiology
  - Systolic vs Diastolic BP as Risk Factors
  - Treatment Gap Between Systolic and Diastolic BP Control

- ALLHAT Trial: Background and Results

- Summary and Conclusions
CVD and Hypertension: Worldwide Morbidity and Mortality

- Cardiovascular disease accounted for 16.6 million deaths in 2000
  - 7.3 million ischemic heart disease deaths
  - 5.4 million stroke deaths

- High blood pressure is associated with an estimated 7.1 million deaths
  - 13% of total deaths worldwide
  - 50% of CVD burden associated with suboptimal blood pressure
  - 61% of CVD burden associated with the combination of suboptimal blood pressure and suboptimal cholesterol levels

- Estimated 690 million persons have hypertension; most remain untreated or uncontrolled

Effect of Systolic BP and Diastolic BP on CHD Mortality: MRFIT Screenees (N=316,099)*

*Men aged 35-57 years followed for a mean of 12 years.

Stroke and IHD Mortality vs Usual Systolic BP by Age

IHD = ischemic heart disease
Stroke Mortality vs Usual BP by Age

Systolic Blood Pressure

Ischemic Heart Disease Mortality vs Usual BP by Age

**Systolic Blood Pressure**

- Age at risk:
  - 80-89 years
  - 70-79 years
  - 60-69 years
  - 50-59 years
  - 40-49 years

**Diastolic Blood Pressure**

- Age at risk:
  - 80-89 years
  - 70-79 years
  - 60-69 years
  - 50-59 years
  - 40-49 years

MRC Trial: Design

- **N**: 17,354; 52% men
- **Age**: 35-64 years
- **BP**: diastolic BP 90 to 109 mm Hg
- **Design**: 3 treatment groups
- **Treatment**: bendrofluazide vs propranolol vs placebo
- **Diastolic BP difference**: 6 mm Hg
- **Duration**: 5.5 years

MRC Trial: Endpoints

Active Therapy vs Placebo

Relative Risk (95% CI)

Stroke CHD CVD Death

-45% -6% -19% -2%

SHEP Trial: Design

- N: 4736; 43% male
- Age: ≥60 years
- BP: systolic BP 160-219 mm Hg and diastolic BP <90 mm Hg
- Design: placebo-controlled, double-blind
- Active treatment: chlorthalidone (atenolol as step 2)
- Systolic BP difference: 12 mm Hg
- Duration: 4.5 years

SHEP Trial: Endpoints

Active Therapy vs Placebo

Stroke
CHD
CHF
CVD
Death

Relative Risk (95% CI)

-37%
-25%
-54%
-32%
-13%

From Evidence to Practice
Update in Hypertension: ALLHAT

- **Current State of Hypertension Management**
  - Epidemiology
  - Systolic vs Diastolic BP as Risk Factors
  - Treatment Gap Between Systolic and Diastolic BP Control

- **ALLHAT Trial: Background and Results**

- **Summary and Conclusions**
Competing Paradigms
1982 – 2002

BP Lowering

Type of Drug
Clinical Questions in Hypertension Management

◆ Are there differences in the effects from BP lowering with various antihypertensive agents?

◆ What is the optimal antihypertensive regimen to achieve systolic BP goals?

◆ What is the optimal approach to hypertension management in different types of patients: blacks, the elderly, patients with diabetes?
Rational for ALLHAT

Many trials have evaluated the effects of different antihypertensive regimens in specific populations, eg, patients with vascular disease, diabetes, renal disease, the elderly – MRFIT and diuretics

Meta-analyses have compared active treatments with placebo and with other active treatments – increased MI, Cancer and Bleeding with CCBs

ALLHAT is the largest randomized clinical trial undertaken to answer the question whether there are differences among classes of antihypertensive agents—diuretic (chlorthalidone), alpha blocker (doxazosin), ACEI (lisinopril), and CCB (amlodipine)
Event Reduction in SHEP, Syst-Eur, and HOPE

SHEP: Systolic Hypertension in the Elderly, n=4,736; chlorthalidone
Syst-Eur: Systolic Hypertension in Europe, n=4,695; nitrendipine
HOPE: Heart Outcomes Prevention Evaluation Study, n=9,297; ramipril
ALLHAT: Design

- Practice-based randomized clinical trial in high-risk patients with hypertension
- Patients 55 years and older; intention to recruit broad-based population including women, blacks, patients with diabetes
- Double-blinded assignment to initial antihypertensive therapy with amlodipine, chlorthalidone, lisinopril, or doxazosin
- Substudy: open-label pravastatin vs usual care in planned 20,000 moderately hypercholesterolemic patients
- Planned follow-up: 6 years

ALLHAT: Hypothesis

- The combined incidence of fatal CHD and nonfatal MI will be lower in hypertensive patients randomized to
  1. an ACEI, or
  2. a CCB, or
  3. an alpha-adrenergic blocker

as first-line therapy than in those randomized to a thiazide-like diuretic

ALLHAT: Primary Endpoint

- Combined CHD deaths\textsuperscript{1} and nonfatal MI\textsuperscript{2}

\textsuperscript{1} Excluded stroke deaths.

\textsuperscript{2} By discharge summary, face sheet, including suspect MI with thrombolysis, or biennial ECG.

ALLHAT: Prespecified Secondary Endpoints

- All-cause mortality
- Combined CHD (CHD or revascularization procedures or hospitalized angina)
- Stroke
- Combined CVD (combined CHD, stroke, CHF, or PAD)
- Renal disease (ESRD/slope and reciprocal of serum creatinine)

- Hospitalized gastrointestinal bleeding
- Cancer
- LVH
- Health-related quality of life
- Major costs of medical care

ALLHAT: Criteria for HF Evaluation

Must have 1 from each category:

Category “A”
- Paroxysmal nocturnal dyspnea
- Dyspnea at rest
- NYHA Classification III
- Orthopnea

Category “B”
- Rales
- Ankle edema
- Tachycardia
- Cardiomegaly by CXR
- CXR characteristic of CHF
- S₃ gallop
- Jugular venous distention

ALLHAT Manual of Operations, 5.3.4.
ALLHAT: Entry Criteria

- Untreated systolic and/or diastolic hypertension (≥140/90 mm Hg but <180/110 mm Hg at 2 visits), OR
- Treated hypertension (≤160/100 mm Hg on 1-2 antihypertensive drugs at visit 1; ≤180/110 mm Hg at visit 2, when medication may have been partially withdrawn)
- Age ≥55 years old
- At least 1 additional risk factor for CV morbidity, including:
  - Old MI or stroke
  - History of revascularization
  - Other documented ASCVD
  - Type 2 diabetes mellitus
  - Cigarette smoking
  - Low HDL cholesterol
  - LVH

ALLHAT: Exclusion Criteria

- Recent MI or stroke (≤ 6 months)
- Symptomatic CHF
- Known LVEF < 35%
- Known renal insufficiency (creatinine ≥ 2.0 mg/dL)
- Requirement for more than 2 drugs to achieve BP control

ALLHAT: Study Design

High-Risk Hypertensive Patients → Randomize

Eligible for Lipid Lowering

Randomize

Pravastatin

Usual Care

Follow for Occurrence of CHD Until Death or End of Study

Not Eligible for Lipid Lowering

Amlodipine

Chlorthalidone

Doxazosin*

Lisinopril

*On January 24, 2000, the National Heart, Lung, and Blood Institute decided to discontinue the doxazosin arm of the antihypertensive trial and report results.

ALLHAT: Recruitment and Randomization

- 623 centers in US, Canada, Puerto Rico, and the US Virgin Islands
- Randomization schedule 1.7:1:1 (chlorthalidone, amlodipine, lisinopril); stratified by center and blocked
- Study closeout: October 1, 2001, through March 31, 2002
The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

Geographic distribution of ALLHAT Clinical Sites that enrolled participants in the trial, February 14, 1994 - January 31, 1998

ALLHAT is sponsored by the National Heart, Lung, and Blood Institute. National Institutes of Health, in collaboration with the Department of Veterans Affairs

Region 1 (Memphis, TN)
Region 2 (Cleveland, OH)
Region 3 (Bronx, NY)
Region 4 (Chicago, IL)
Region 5 (Birmingham, AL)
Region 6 (Seattle, WA)
Region 7 (Minneapolis, MN)
Region 8 (New Orleans, LA)
Region 9 (Ottawa, ON)

Colors indicate the respective Clinical Sites supported by the nine corresponding Regional Coordinating Centers.
ALLHAT: BP Treatment

- BP goal <140/90 mm Hg
- Visit BP was the average of 2 seated measurements
- Unless original drug regimen required tapering for safety reasons, subjects continued prior meds until randomization and receipt of study drug
- Nonpharmacologic treatments in accordance with national guidelines
- Dose titration of randomized drug approximately monthly until at goal (chlorthalidone 12.5, 12.5, 25 mg/day; amlodipine 2.5, 5, 10 mg/day; lisinopril 10, 20, 40 mg/day)

ALLHAT: Study Medications

**S**tep 1: Monthly dose titration to achieve BP <140/90 mm Hg
- Amlodipine (2.5, 5, 10 mg/d)
- Lisinopril (10, 20, 40 mg/d)
- Chlorthalidone (12.5, 12.5, 25 mg/d)

**S**tep 2: Medication if not at goal
- Reserpine (0.05-0.2 mg/d)
- Clonidine (0.1-0.3 mg bid)
- Atenolol (25-100 mg/d)

**S**tep 3: Medication if not at goal
- Hydralazine 25-100 mg bid

Screening and Randomization

Decision to Drop the Doxazosin Arm of ALLHAT

- January 24, 2000—NHLBI Director accepts recommendation of independent review to terminate doxazosin arm for the following reasons:
  1. Unlikely to find a significant difference in the primary outcome between doxazosin and chlorthalidone arms
  2. Statistically significant 25% higher rate of major secondary endpoint—combined CVD outcomes, principally CHF

- Doxazosin arm was not discontinued for safety reasons

ALLHAT: Primary and Secondary Endpoints (Doxazosin vs Chlorthalidone)

1° Fatal CHD and Nonfatal MI

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>1.03</td>
<td>0.90-1.17</td>
<td>0.38</td>
<td>0.71</td>
</tr>
<tr>
<td>Doxazosin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2° Combined CV Disease

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>1.25</td>
<td>1.17-1.33</td>
<td>6.77</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Doxazosin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALLHAT: Statistics

- Intention-to-treat analysis
- 83% power to detect a 16% reduction in the risk of the primary outcome between chlorthalidone and each other arm at a 2-sided alpha = .0178 (to account for the original 3 comparisons)

## ALLHAT: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Chlorthalidone (15,255)</th>
<th>Amlodipine (9048)</th>
<th>Lisinopril (9054)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. Randomized</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Women, %</strong></td>
<td>47.0</td>
<td>47.3</td>
<td>46.2</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td>66.9</td>
<td>66.9</td>
<td>66.9</td>
</tr>
<tr>
<td><strong>White, non-Hispanic, %</strong></td>
<td>47.2</td>
<td>47.6</td>
<td>47.1</td>
</tr>
<tr>
<td><strong>Black, non-Hispanic, %</strong></td>
<td>31.9</td>
<td>32.2</td>
<td>32.3</td>
</tr>
<tr>
<td><strong>White Hispanic, %</strong></td>
<td>12.5</td>
<td>12.2</td>
<td>12.5</td>
</tr>
<tr>
<td><strong>Black Hispanic, %</strong></td>
<td>3.3</td>
<td>3.3</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Other, %</strong></td>
<td>5.1</td>
<td>4.7</td>
<td>4.9</td>
</tr>
<tr>
<td><strong>Baseline BP (mm Hg) (overall)</strong></td>
<td>146/84</td>
<td>146/84</td>
<td>146/84</td>
</tr>
<tr>
<td><strong>Cig. smoker, %</strong></td>
<td>21.9</td>
<td>21.9</td>
<td>21.9</td>
</tr>
<tr>
<td><strong>ASCVD, %</strong></td>
<td>51.8</td>
<td>51.0</td>
<td>51.7</td>
</tr>
<tr>
<td><strong>Type 2 diabetes, %</strong></td>
<td>36.2</td>
<td>36.7</td>
<td>35.5</td>
</tr>
<tr>
<td><strong>LVH by ECG, %</strong></td>
<td>16.2</td>
<td>16.9</td>
<td>16.3</td>
</tr>
<tr>
<td><strong>LVH by echocardiogram, %</strong></td>
<td>4.6</td>
<td>4.6</td>
<td>4.5</td>
</tr>
</tbody>
</table>

### ALLHAT: Baseline Characteristics

#### Laboratory/Renal

<table>
<thead>
<tr>
<th>No. Randomized</th>
<th>Chlorthalidone 15,255</th>
<th>Amlodipine 9048</th>
<th>Lisinopril 9054</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K⁺, mmol/L</td>
<td>4.3</td>
<td>4.3</td>
<td>4.4</td>
</tr>
<tr>
<td>Fasting serum glucose, mg/dL (mmol/L)</td>
<td>123.5 (6.9)</td>
<td>123.1 (6.8)</td>
<td>122.9 (6.8)</td>
</tr>
<tr>
<td>Cholesterol, mg/dL (mmol/L)</td>
<td>216.1 (5.6)</td>
<td>216.5 (5.6)</td>
<td>215.6 (5.6)</td>
</tr>
<tr>
<td>LDL-C, mg/dL (mmol/L)</td>
<td>135.9 (3.5)</td>
<td>135.7 (3.5)</td>
<td>135.9 (3.5)</td>
</tr>
<tr>
<td>HDL-C, mg/dL (mmol/L)</td>
<td>46.8 (1.2)</td>
<td>47.2 (1.2)</td>
<td>46.7 (1.2)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL (mmol/L)</td>
<td>172.8 (2.0)</td>
<td>173.1 (2.0)</td>
<td>173.0 (2.0)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Estimated GFR, mL/min/1.73 m²</td>
<td>77.6</td>
<td>78.0</td>
<td>77.7</td>
</tr>
</tbody>
</table>

GFR=glomerular filtration rate.

ALLHAT: Patients on Step 1 or Equivalent Treatment by Antihypertensive Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>1 Year</th>
<th>2 Years</th>
<th>3 Years</th>
<th>4 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chlorthalidone</strong></td>
<td>87.1</td>
<td>84.7</td>
<td>82.7</td>
<td>80.8</td>
<td>80.5</td>
</tr>
<tr>
<td><strong>Amlodipine</strong></td>
<td>87.6</td>
<td>85.2</td>
<td>83.2</td>
<td>80.5</td>
<td>80.4</td>
</tr>
<tr>
<td><strong>Lisinopril</strong></td>
<td>82.4</td>
<td>78.4</td>
<td>77.1</td>
<td>74.8</td>
<td>72.6</td>
</tr>
</tbody>
</table>

ALLHAT Follow-up Status

- Mean length of follow-up: 4.9 years

- At closeout, unknown vital status in 2.7% chlorthalidone, 2.8% amlodipine, 3.0% lisinopril patients
  - Distributions of most baseline factors similar among 3 groups
  - Unknown vital status participants assigned to lisinopril less likely to be black, more likely to be women, have untreated hypertension, evidence of CHD or ASCVD, and lower mean serum glucose

### ALLHAT: Most Common Reasons for Not Taking Step 1 Medication (at 5 Years)*

<table>
<thead>
<tr>
<th>Reason</th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unspecified refusals, %</td>
<td>41.4</td>
<td>40.5</td>
<td>37.9</td>
</tr>
<tr>
<td>Symptomatic adverse effects (AEs), %</td>
<td>15</td>
<td>16.4</td>
<td>18.1</td>
</tr>
<tr>
<td>Elevated BP, %</td>
<td>4.5</td>
<td>3.5</td>
<td>9</td>
</tr>
<tr>
<td>Other AE, including abnormal lab values, %</td>
<td>3.8</td>
<td>1.6</td>
<td>2.3</td>
</tr>
</tbody>
</table>

*Reported values do not equal 100.

ALLHAT: Average Systolic BP

**BP △ vs Chlorthalidone at 5 Years**

- **Lisinopril**: +2 mm Hg, *P*<.001
- **Amlodipine**: +0.8 mm Hg, *P*=.03
- **Chlorthalidone**

ALLHAT: Average Diastolic BP

Blood Pressure, mm Hg

Follow-up, Years

BP $\Delta$ vs Chlorthalidone at 5 Years

- Lisinopril: 0 mm Hg
- Amlodipine: -0.8 mm Hg, $P<.001$
- Chlorthalidone

ALLHAT: Distribution of Diastolic BP

Baseline diastolic BP

36-month diastolic BP

BP Control in ALLHAT Participants: % Meeting Goal by Year of Follow-up

Mean BP

<table>
<thead>
<tr>
<th>Year</th>
<th>Baseline</th>
<th>6 mo</th>
<th>1 y</th>
<th>2 y</th>
<th>3 y</th>
<th>4 y</th>
<th>5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>145/83</td>
<td>140/81</td>
<td>138/79</td>
<td>137/78</td>
<td>136/77</td>
<td>135/76</td>
<td>135/75</td>
</tr>
<tr>
<td>DBP</td>
<td>–</td>
<td>1.3</td>
<td>1.4</td>
<td>1.6</td>
<td>1.7</td>
<td>1.8</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Medication Use and BP Control in ALLHAT

ALLHAT BP Control Implications

- Systolic BP was more difficult to control than was diastolic BP
  - Diastolic BP <90 mm Hg in 92% of participants
  - Systolic BP <140 mm Hg in 67% of participants

- Average of 2 drugs required for BP control in 2/3 of participants, primarily to control systolic BP

- Clinical practice data suggest that the majority of patients will require at least 2 antihypertensive medications to achieve the goal of <140/90 mm Hg

- Achieving lower goals, as is recommended for patients with diabetes, will likely require even more drugs

ALLHAT Primary Endpoint: CHD Death and Nonfatal MI

Relative Risk (95% CI)

Amlodipine 0.98 (0.90-1.07)

Lisinopril 0.99 (0.91-1.08)

ALLHAT: Amlodipine vs Chlorthalidone
Primary Endpoint (Nonfatal MI + CHD Death) Subgroups

Relative Risk (95% CI)

- Total: 0.98 (0.90-1.07)
- Age <65: 0.99 (0.85-1.16)
- Age ≥65: 0.97 (0.88-1.08)
- Men: 0.98 (0.87-1.09)
- Women: 0.99 (0.85-1.15)
- Black: 1.01 (0.86-1.18)
- Nonblack: 0.97 (0.87-1.08)
- Diabetic: 0.99 (0.87-1.13)
- Nondiabetic: 0.97 (0.86-1.09)

ALLHAT: Lisinopril vs Chlorthalidone
Primary Endpoint (Nonfatal MI + CHD Death) Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Relative Risk (95% CI)</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>0.99 (0.91-1.08)</td>
<td>Lisinopril</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>0.95 (0.81-1.12)</td>
<td>Lisinopril</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>1.01 (0.91-1.12)</td>
<td>Chlorthalidone</td>
</tr>
<tr>
<td>Men</td>
<td>0.94 (0.85-1.05)</td>
<td>Chlorthalidone</td>
</tr>
<tr>
<td>Women</td>
<td>1.06 (0.92-1.23)</td>
<td>Chlorthalidone</td>
</tr>
<tr>
<td>Black</td>
<td>1.10 (0.94-1.28)</td>
<td>Chlorthalidone</td>
</tr>
<tr>
<td>Nonblack</td>
<td>0.94 (0.85-1.05)</td>
<td>Lisinopril</td>
</tr>
<tr>
<td>Diabetic</td>
<td>1.00 (0.87-1.14)</td>
<td>Chlorthalidone</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>0.99 (0.88-1.11)</td>
<td>Lisinopril</td>
</tr>
</tbody>
</table>

ALLHAT: Secondary Endpoints: Total Mortality

Relative Risk (95% CI)

Amlodipine 0.96 (0.89-1.02)
Lisinopril 1.00 (0.94-1.08)

ALLHAT: Total Mortality (Amlodipine vs Chlorthalidone)

Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>0.96 (0.89-1.02)</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>0.96 (0.83-1.10)</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>0.96 (0.88-1.03)</td>
</tr>
<tr>
<td>Men</td>
<td>0.95 (0.87-1.04)</td>
</tr>
<tr>
<td>Women</td>
<td>0.96 (0.86-1.07)</td>
</tr>
<tr>
<td>Black</td>
<td>0.97 (0.87-1.09)</td>
</tr>
<tr>
<td>Nonblack</td>
<td>0.94 (0.87-1.03)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>0.96 (0.87-1.07)</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>0.95 (0.87-1.04)</td>
</tr>
</tbody>
</table>

ALLHAT: Total Mortality
(Lisinopril vs Chlorthalidone) Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1.00 (0.94-1.08)</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>0.93 (0.81-1.08)</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>1.03 (0.95-1.12)</td>
</tr>
<tr>
<td>Men</td>
<td>0.99 (0.91-1.08)</td>
</tr>
<tr>
<td>Women</td>
<td>1.02 (0.91-1.13)</td>
</tr>
<tr>
<td>Black</td>
<td>1.06 (0.95-1.18)</td>
</tr>
<tr>
<td>Nonblack</td>
<td>0.97 (0.89-1.06)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>1.02 (0.91-1.13)</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>1.00 (0.91-1.09)</td>
</tr>
</tbody>
</table>

ALLHAT: Secondary Endpoints: Stroke

Relative Risk (95% CI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>0.93 (0.82-1.06)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.15 (1.02-1.30)</td>
</tr>
</tbody>
</table>

ALLHAT: Stroke (Amlodipine vs Chlorthalidone) Subgroups

Relative Risk (95% CI)

Total: 0.93 (0.82-1.06)
Age <65: 0.93 (0.73-1.19)
Age ≥65: 0.93 (0.81-1.08)
Men: 1.00 (0.85-1.18)
Women: 0.84 (0.69-1.03)
Black: 0.93 (0.76-1.14)
Nonblack: 0.93 (0.79-1.10)
Diabetic: 0.90 (0.75-1.08)
Nondiabetic: 0.96 (0.81-1.14)

ALLHAT: Stroke (Lisinopril vs Chlorthalidone) Subgroups

Relative Risk (95% CI)

Total: 1.15 (1.02-1.30)
Age <65: 1.21 (0.97-1.52)
Age ≥65: 1.13 (0.98-1.30)
Men: 1.10 (0.94-1.29)
Women: 1.22 (1.01-1.46)
Black: 1.40 (1.17-1.68)
Nonblack: 1.00 (0.85-1.17)
Diabetic: 1.07 (0.90-1.28)
Nondiabetic: 1.23 (1.05-1.44)

ALLHAT: Secondary Endpoints: Combined CHD

Relative Risk (95% CI)

Amlodipine  1.00 (0.94-1.07)

Lisinopril  1.05 (0.98-1.11)

Favors Amlodipine  Favors Lisinopril  Favors Chlorthalidone

ALLHAT: Combined CHD (Amlodipine vs Chlorthalidone) Subgroups

Relative Risk (95% CI)

- Total: 1.00 (0.94-1.07)
- Age <65: 0.94 (0.84-1.05)
- Age ≥65: 1.04 (0.96-1.12)
- Men: 0.99 (0.92-1.08)
- Women: 1.02 (0.91-1.13)
- Black: 1.03 (0.91-1.17)
- Nonblack: 0.99 (0.92-1.07)
- Diabetic: 1.04 (0.94-1.14)
- Nondiabetic: 0.97 (0.89-1.06)

ALLHAT: Combined CHD (Lisinopril vs Chlorthalidone) Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1.05 (0.98-1.11)</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>0.94 (0.84-1.05)</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>1.11 (1.03-1.20)</td>
</tr>
<tr>
<td>Men</td>
<td>1.03 (0.95-1.12)</td>
</tr>
<tr>
<td>Women</td>
<td>1.05 (0.95-1.17)</td>
</tr>
<tr>
<td>Black</td>
<td>1.15 (1.02-1.30)</td>
</tr>
<tr>
<td>Nonblack</td>
<td>1.01 (0.93-1.09)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>1.03 (0.93-1.14)</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>1.06 (0.97-1.15)</td>
</tr>
</tbody>
</table>

ALLHAT: Secondary Endpoints: Combined CVD

Relative Risk (95% CI)

Amlodipine  1.04 (0.99-1.09)

Lisinopril  1.10 (1.05-1.16)

Favors Amlodipine
Favors Lisinopril
Favors Chlorthalidone

ALLHAT: Combined CVD (Amlodipine vs Chlorthalidone) Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1.04 (0.99-1.09)</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>1.03 (0.94-1.12)</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>1.05 (0.99-1.12)</td>
</tr>
<tr>
<td>Men</td>
<td>1.04 (0.98-1.11)</td>
</tr>
<tr>
<td>Women</td>
<td>1.04 (0.96-1.13)</td>
</tr>
<tr>
<td>Black</td>
<td>1.06 (0.96-1.16)</td>
</tr>
<tr>
<td>Nonblack</td>
<td>1.04 (0.97-1.10)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>1.06 (0.98-1.15)</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>1.02 (0.96-1.09)</td>
</tr>
</tbody>
</table>

ALLHAT: Combined CVD (Lisinopril vs Chlorthalidone)

Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1.10 (1.05-1.16)</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>1.05 (0.97-1.15)</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>1.13 (1.06-1.20)</td>
</tr>
<tr>
<td>Men</td>
<td>1.08 (1.02-1.15)</td>
</tr>
<tr>
<td>Women</td>
<td>1.12 (1.03-1.21)</td>
</tr>
<tr>
<td>Black</td>
<td>1.19 (1.09-1.30)</td>
</tr>
<tr>
<td>Nonblack</td>
<td>1.06 (1.00-1.13)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>1.08 (1.00-1.17)</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>1.12 (1.05-1.19)</td>
</tr>
</tbody>
</table>

ALLHAT: Secondary Safety Endpoints: Cancer and Hospitalized GI Bleeding

**Cancer**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>1.01 (0.92-1.11)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.02 (0.93-1.12)</td>
</tr>
</tbody>
</table>

**GI bleed (hospitalized)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>0.92 (0.82-1.03)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.11 (0.99-1.24)</td>
</tr>
</tbody>
</table>

Favors Amlodipine

Favors Lisinopril

Favors Chlorthalidone

ALLHAT: Secondary Endpoints: ESRD

Relative Risk (95% CI)

Amlodipine 1.12 (0.89-1.40)

Lisinopril 1.11 (0.88-1.38)

Favors Amlodipine
Favors Lisinopril
Favors Chlorthalidone

ALLHAT: Components of Secondary Endpoints*: Components of Secondary Endpoints*:

Heart Failure (Not Prespecified)

- **Heart failure** is a component of combined CVD.

- **ALLHAT Collaborative Research Group. JAMA. 2002;288:2981-2997.**

### Relative Risk (95% CI)

<table>
<thead>
<tr>
<th>Heart Failure (fatal, nonfatal, hospitalized or treated)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>1.38 (1.25-1.52)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.19 (1.07-1.31)</td>
</tr>
</tbody>
</table>

### Hospitalized/Fatal HF

- **Favors Amlodipine**
  - Amlodipine: 1.35 (1.21-1.50)
  - Lisinopril: 1.10 (0.98-1.23)

*Heart failure is a component of combined CVD.

**ALLHAT: Heart Failure**

*Heart failure was not a prespecified endpoint.*

**ALLHAT: Heart Failure* (Amlodipine vs Chlorthalidone)**

### Subgroups

<table>
<thead>
<tr>
<th>Group</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>1.38 (1.25-1.52)</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>1.51 (1.25-1.82)</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>1.33 (1.18-1.49)</td>
</tr>
<tr>
<td>Men</td>
<td>1.41 (1.24-1.61)</td>
</tr>
<tr>
<td>Women</td>
<td>1.33 (1.14-1.55)</td>
</tr>
<tr>
<td>Black</td>
<td>1.47 (1.24-1.74)</td>
</tr>
<tr>
<td>Nonblack</td>
<td>1.33 (1.18-1.51)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>1.42 (1.23-1.64)</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>1.33 (1.16-1.52)</td>
</tr>
</tbody>
</table>

*Heart failure was not a prespecified endpoint.

**ALLHAT: Heart Failure* (Lisinopril vs Chlorthalidone)**

**Subgroups**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1.20 (1.09-1.34)</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>1.23 (1.01-1.50)</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>1.20 (1.06-1.35)</td>
</tr>
<tr>
<td>Men</td>
<td>1.19 (1.03-1.36)</td>
</tr>
<tr>
<td>Women</td>
<td>1.23 (1.05-1.43)</td>
</tr>
<tr>
<td>Black</td>
<td>1.32 (1.11-1.58)</td>
</tr>
<tr>
<td>Nonblack</td>
<td>1.15 (1.01-1.30)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>1.22 (1.05-1.42)</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>1.20 (1.04-1.38)</td>
</tr>
</tbody>
</table>

*Lisinopril Better* vs *Chlorthalidone Better*

*Heart failure was not a prespecified endpoint.*

ALLHAT: Components of Secondary Endpoints: Angina

Relative Risk (95% CI)

Angina, hospitalized or treated

- Amlodipine: 1.02 (0.94-1.10)
- Lisinopril: 1.11 (1.03-1.20)

Angina, hospitalized

- Amlodipine: 0.98 (0.89-1.08)
- Lisinopril: 1.09 (0.99-1.20)

Favors Amlodipine
Favors Lisinoprul
Favors Chlorthalidone

ALLHAT: Components of Secondary Endpoints: Coronary Revascularizations and Peripheral Arterial Disease*

*Hospitalized or outpatient revascularization.

<table>
<thead>
<tr>
<th>Component</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary revascularizations</strong></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>1.09 (1.00-1.20)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.10 (1.00-1.21)</td>
</tr>
<tr>
<td><strong>Peripheral arterial disease</strong></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>0.87 (0.75-1.01)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.04 (0.90-1.19)</td>
</tr>
</tbody>
</table>

# ALLHAT: Intermediate Outcomes

## Biochemical Changes at 4 Years: Potassium

<table>
<thead>
<tr>
<th></th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
<th>Amlodipine vs Chlorthalidone</th>
<th>Lisinopril vs Chlorthalidone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>14,487</td>
<td>8586</td>
<td>8573</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K, mmol/L</td>
<td>4.3</td>
<td>4.3</td>
<td>4.4</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>% K &lt;3.5 mmol/L</td>
<td>3.4</td>
<td>3.4</td>
<td>2.6</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td><strong>4 Years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>8315</td>
<td>4919</td>
<td>4618</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K, mmol/L</td>
<td>4.1</td>
<td>4.4</td>
<td>4.5</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% K &lt;3.5 mmol/L</td>
<td>8.5</td>
<td>1.9</td>
<td>0.8</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

# ALLHAT: Intermediate Outcomes Biochemical Changes at 4 Years: Fasting Glucose

<table>
<thead>
<tr>
<th></th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
<th>Amlodipine vs Chlorthalidone</th>
<th>Lisinopril vs Chlorthalidone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>11,273</td>
<td>6648</td>
<td>6752</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSG, mg/dL (mmol/L)</td>
<td>123.5 (6.9)</td>
<td>123.1 (6.8)</td>
<td>122.9 (6.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% ≥126 mg/dL (≥7 mmol/L)</td>
<td>28.9</td>
<td>29.2</td>
<td>29.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4 Years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>4972</td>
<td>2954</td>
<td>2731</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSG, mg/dL (mmol/L)</td>
<td>126.3 (7.0)</td>
<td>123.7 (6.9)</td>
<td>121.5 (6.7)</td>
<td>.2</td>
<td>.002</td>
</tr>
<tr>
<td>% ≥126 mg/dL (≥7 mmol/L)</td>
<td>32.7</td>
<td>30.5</td>
<td>28.7</td>
<td>.11</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

FSG=fasting serum glucose.

### ALLHAT Fasting Glucose Among Nondiabetics With Baseline Fasting Glucose <126 mg/dL (<7 mmol/L)

<table>
<thead>
<tr>
<th></th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of participants</strong></td>
<td>6766</td>
<td>3954</td>
<td>4096</td>
<td></td>
</tr>
<tr>
<td><strong>Mean FSG, mg/dL (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>93 (5.2)</td>
<td>93 (5.2)</td>
<td>93 (5.2)</td>
<td></td>
</tr>
<tr>
<td>2 Years</td>
<td>102 (5.7)</td>
<td>99 (5.5)</td>
<td>97 (5.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>4 Years</td>
<td>104 (5.8)</td>
<td>103 (5.7)</td>
<td>101 (5.6)</td>
<td>.11</td>
</tr>
<tr>
<td><strong>% ≥126 mg/dL (≥7 mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Years</td>
<td>9.6</td>
<td>7.4</td>
<td>5.8</td>
<td>.006</td>
</tr>
<tr>
<td>4 Years</td>
<td>11.6</td>
<td>9.8</td>
<td>8.1</td>
<td>.04</td>
</tr>
</tbody>
</table>

### ALLHAT: Intermediate Outcomes

#### Biochemical Changes at 4 Years: Cholesterol

<table>
<thead>
<tr>
<th></th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
<th>Amlodipine vs Chlorthalidone</th>
<th>Lisinopril vs Chlorthalidone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>14,483</td>
<td>8586</td>
<td>8573</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mg/dL (mmol/L)</td>
<td>216.1 (5.6)</td>
<td>216.5 (5.6)</td>
<td>215.6 (5.6)</td>
<td>.005</td>
<td>.13</td>
</tr>
<tr>
<td>% ≥240 mg/dL (≥6.2 mmol/L)</td>
<td>26.5</td>
<td>26.6</td>
<td>25.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4 Years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>8495</td>
<td>5025</td>
<td>4711</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mg/dL (mmol/L)</td>
<td>197.2 (5.1)</td>
<td>195.6 (5.1)</td>
<td>195.0 (5.0)</td>
<td>.009</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% ≥240 mg/dL (≥6.2 mmol/L)</td>
<td>14.4</td>
<td>13.4</td>
<td>12.8</td>
<td>.13</td>
<td>.005</td>
</tr>
</tbody>
</table>

### ALLHAT: Intermediate Outcomes

#### Estimated GFR at 4 Years*

<table>
<thead>
<tr>
<th></th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>14,492</td>
<td>8589</td>
<td>8577</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>77.6</td>
<td>78.0</td>
<td>77.7</td>
</tr>
<tr>
<td><strong>4 Years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>8316</td>
<td>4924</td>
<td>4621</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>70.0</td>
<td>75.1</td>
<td>70.7</td>
</tr>
</tbody>
</table>

*Baseline mean estimated GFR was 78 mL/min/1.73 m².

From Evidence to Practice
Update in Hypertension: ALLHAT

- **Current State of Hypertension Management**
  - Epidemiology
  - Systolic vs Diastolic BP as Risk Factors
  - Treatment Gap Between Systolic and Diastolic BP Control

- **ALLHAT Trial: Background and Results**

- **Summary and Conclusions**
ALLHAT is the largest hypertension trial with great clinical relevance

ALLHAT emphasizes the importance of controlling systolic BP

ALLHAT demonstrates that aggressive treatment is necessary to achieve systolic BP goals

ALLHAT shows that multiple medications often are required to get to BP goal

In ALLHAT, patients taking amlodipine had results comparable to the diuretic for the primary endpoint of CHD death and nonfatal MI, and the secondary endpoints of total mortality, stroke, combined CHD, combined CVD, and renal disease.

In ALLHAT, amlodipine was efficacious and safe for lowering BP in a broad range of hypertensive patients (older and younger patients, African Americans, patients with diabetes).

ALLHAT demonstrated that the lisinopril-based treatment was not as effective as the diuretic for reducing systolic BP.

Contrary to expectations, ALLHAT showed that results for the group taking lisinopril were not superior to the diuretic group with regard to CHD and CVD morbidity and mortality in the overall hypertensive population and in diabetics.

Hypertension Awareness, Treatment, and Control: US 1976 to 2000

NHANES III (Phase 2) 1991-1994
NHANES III (Phase 1) 1988-1991
NHANES II 1976-1980
NHANES 1999-2000


Hypertension Awareness, Treatment, and Control: Worldwide

Comparison of Hypertension Surveys in 5 Countries

- **Prevalence**
- **Awareness**
- **Treatment**
- **Control**

For each country:
- United States
- Canada
- Egypt
- China
- England

Source:
Many Patients in the US Are Not at JNC VI—Recommended BP Goals

NHANES (1999-2000)

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Goal BP (mm Hg)</th>
<th>% Not at Goal*</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hypertensives</td>
<td>&lt;140/90</td>
<td>57%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>&lt;140/90</td>
<td>60%</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Mexican American/Hispanic</td>
<td>&lt;140/90</td>
<td>63%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Older patients (≥60 years)</td>
<td>&lt;140/90</td>
<td>71%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Symptomatic CHD</td>
<td>&lt;140/90</td>
<td>47%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Patients with diabetes†</td>
<td>&lt;130/85</td>
<td>81%</td>
<td>24%</td>
<td></td>
</tr>
</tbody>
</table>

Barriers to Hypertension Control
Survey of PCPs of Patients With Uncontrolled HTN in Large US Health System*

- Self-reported adherence with JNC VI guidelines—14% always, 62% usually
- PCPs satisfied with BP values, despite 93% of systolic BP values being at or above 140 mm Hg
- Physicians reported 150 mm Hg was lowest systolic BP and 91 mm Hg lowest diastolic BP for recommending pharmacotherapy
- 48% of surveyed physicians believed risk of MI and stroke greater with BP of 135/95 vs 150/80 mm Hg

Barriers to Hypertension Control: New England VA Study

- 800 hypertensive veterans followed for 2 years
- 40% of patients had BP $\geq 160/90$ mm Hg despite average of $>6$ visits for hypertension per year
- Clinicians more likely to increase BP medication for diastolic BP elevation than for systolic BP elevation:
  - Rx increased 22% of time if systolic BP $\geq 165$ mm Hg and diastolic BP $<90$ mm Hg
  - Rx increased 35% of time if diastolic BP $\geq 90$ mm Hg and medications changed at previous visit

Hypertension in High-Risk Patients: Number of Agents Used to Treat BP

- **UKPDS** (<85 mm Hg, diastolic)
- **MDRD** (92 mm Hg, MAP)
- **HOT** (<80 mm Hg, diastolic)
- **AASK** (<92 mm Hg, MAP)
- **RENAAL** (<140/90 mm Hg)
- **IDNT** (≤135/85 mm Hg)

UKPDS=United Kingdom Prospective Diabetes Study; MDRD=Modification of Diet in Renal Disease; HOT=Hypertension Optimal Treatment; AASK=African American Study of Kidney Disease; RENAAL=Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; IDNT=Irbesartan Diabetic Nephropathy Trial; MAP=mean arterial pressure.

Critical Clinical Trials Supporting: Compelling Indications for Antihypertensive therapy

IDNT
RENAAL
LIFE
Overview

- Introduction
- IDNT
- IRMA2
- RENAAAL
- Comparison of Trials
- Conclusions/Implications
Introduction / Background

- ACEI renoprotective in type I DM and are standard of care for hypertensive and non-hypertensive type I DM with any level of proteinuria.

- Role of ACEI/blockade of the RAS in type II DM remains undefined despite higher prevalence of type II DM.
Introduction
Purpose of this presentation

◆ To gain an overview of most recent clinical trials of ARBs for treatment of hypertensive Type II diabetics

◆ To further assess the role of CCBs in the treatment of nephropathy and CV disease in these patients.
This study was initiated by the Collaborative Study Group to address the following issues:

1) Will treatment of hypertension in type II diabetes confer the same benefit as for type I?

2) Will the same benefits be seen for ARBs as for ACEI?

3) What are the effects of the CCB Amlodipine on renal and cardiovascular outcomes

4) What is the impact of treatment with an ARB or CCB on mortality in this high risk population?
IDNT
Study Design

- International, prospective, randomized, double-blind, placebo controlled trial in hypertensive patients with nephropathy due to type II DM

- 1715 type II DM Hypertensives (BP > 135/85) age 30 – 70

- Proteinuria ≥ 900mg/day

- Increased SCr (1.2 – 3.0mg/dl in men and 1.0 – 3.0mg/dl in women)
Randomized:
- Irbesartan 75 – 300mg
  forced up-titration if tolerated
- Amlodipine 2.5 – 10mg
  forced up-titration if tolerated
- Placebo (mainly beta-blockers + diuretics)
- BP goal <130/85, or >10mmHg decrease if baseline SBP > 145

Other BP agents added (except ARB, ACEi or CCBs)

Follow-up: minimum 2 years, average 2.6 yrs
IDNT - Endpoints

Primary:
Time to Composite:
- Doubling baseline Scr
- ESRD
- Death

Secondary:
Time to Composite:
- CV death
- Non-fatal MI
- Hospitalization for CHF
- Stroke
- Above ankle amputation
- Revascularization (data not presented)
IDNT - Baseline Demographics

- Sex (% male) 66.8
- Age at entry, years 58.9 ± 7.7
- Duration of diabetes, years 14.9 ± 8.5
- Retinopathy (%) 66.3
- Neuropathy (%) 47.9
- BMI (Kg/m²) 31 ± 6.9
- Current smokers (%) 17.1
- Previous smokers (%) 44.5
- BP, mm Hg 155.8 ±18.4/85.4 ± 10.7
Baseline Demographics continued

- **Scr mg/dl (μmol/l)** 1.7 ± 0.6 (150.3 ± 53.0)
- **ClCr ml/min** 66.1 ± 33.8
- **Proteinuria, g/24 hours** 4.02 ± 3.50
- **Total chol. mg/dl** 229 ± 58
- **Hb A1c (%)** 8.1 ± 1.7
### IDNT

**RESULTS - BP**

<table>
<thead>
<tr>
<th></th>
<th>Irbesartan</th>
<th>Amlodipine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP, mm Hg</td>
<td>140/77</td>
<td>141/77</td>
<td>144/80</td>
</tr>
</tbody>
</table>

- Average number of BP lowering agents: > 3.0
- Same proportion of drugs used in all 3 groups, but higher doses required in Placebo
- On average, patients did **not** meet target BP goals
RESULTS - Primary Endpoint

Overall, 37% of patients reached primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>Irbesartan</th>
<th>Amlodipine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients</td>
<td>32</td>
<td>41</td>
<td>39</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>I vs P: 0.80</td>
<td>I vs A: 0.77</td>
<td>A vs P: 1.04</td>
</tr>
<tr>
<td></td>
<td>P=0.024</td>
<td>P=0.006</td>
<td>P = NS</td>
</tr>
</tbody>
</table>
### IDNT

**RESULTS- Components of Primary End-point**

<table>
<thead>
<tr>
<th>RR</th>
<th>Irbesartan</th>
<th>Amlodipine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doubling Scr</strong></td>
<td>I vs P: 0.67</td>
<td>I vs A: 0.63</td>
<td>A vs P: 1.06</td>
</tr>
<tr>
<td>(22% patients)</td>
<td>P=0.003</td>
<td>P= 0.001</td>
<td>P= NS</td>
</tr>
<tr>
<td><strong>ESRD</strong></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>(data not shown)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All Cause mortality</strong></td>
<td>I vs P: 0.92</td>
<td>I vs A: 0.88</td>
<td>A vs P: 1.04</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

- Rate of loss of renal function was 25% better on I vs A,P
- Time to doubling of Scr not related to BP control
- Time from dbl SCr to ESRD was 23% better on I vs A,P (av12mo)
There were no significant differences in the percentage of patients reaching secondary endpoints.

<table>
<thead>
<tr>
<th></th>
<th>Irbesartan</th>
<th>Amlodipine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Pts</td>
<td>24</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>RR</td>
<td>I vs P: 0.91</td>
<td>I vs A: 1.03</td>
<td>A vs P: 0.88</td>
</tr>
<tr>
<td></td>
<td>P= NS</td>
<td>P=NS</td>
<td>P=NS</td>
</tr>
</tbody>
</table>
IDNT RESULTS
Secondary End-points - Components

- Non-fatal MI: NSS difference in favor of amlodipine
- Hosp for CHF: fewer for Irbesartan (I vs A, p= 0.001)
- Stroke: NSS difference in favor of amlodipine
- Amputations: no hard data – but fewer on amlodipine
IDNT RESULTS

Adverse events were similar among groups

<table>
<thead>
<tr>
<th></th>
<th>Irbesartan</th>
<th>Amlodipine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>% D/C Treatment</td>
<td>23</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>&gt; 1 SAE (%)</td>
<td>60</td>
<td>61</td>
<td>62 (p=NS)</td>
</tr>
</tbody>
</table>
IDNT
Interpretations

- Irbesartan’s effect on primary EP driven by the doubling of SCr component
- No benefit of Irbesartan on hard EP of death, ESRD and Total CV events
- Benefit of Irbesartan on CHF is expected.
- Placebo group treated with diuretics and beta-blockers which are proven therapies for CHF
IDNT Interpretations

- No differences in total CV events and death strongly supports amlodipine safety in DM
  - Unlike ABCD, FACET

- Strengthens role of ARB for hypertensive DM (JNC VI already recommends ACEi, ARB as alternative)

- Combination therapy still critical to control BP

- Study does not address ACEi vs ARB
RENAAL

- Reduction of Endpoints in NIDDM with the Ang II Antagonist Losartan
- Primary hypothesis is that long term use of Losartan vs Placebo (alone or with other non-ACEI therapy) in type II diabetics with nephropathy will increase the time to ESRD or death.
RENAAL

- 1513 hypertensive DM, age 31-70
- Nephropathy: urine alb /Cr ratio > 300mg/g (500 mg/d), SCr 1.5 – 3.0 in men and 1.3 – 3.0 in women
- Randomized to losartan 50 –100mg vs Placebo on top of non ACEi therapy
- BP goal: < 140 /90
- Mean follow-up 3.4 years
- Stopped prematurely following HOPE results
RENAAL

- **Primary End-point:**
  - Doubling of SCr
  - ESRD
  - Death

- **Secondary End-point:**
  - Time to CV M & M events
  - Reduction in proteinuria
  - Slowing progression of renal impairment
  - Others ??
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age</strong></td>
<td>60 years</td>
</tr>
<tr>
<td><strong>% males</strong></td>
<td>62-65</td>
</tr>
<tr>
<td><strong>BP</strong></td>
<td>152/82 mm Hg</td>
</tr>
<tr>
<td><strong>% neuropathy</strong></td>
<td>50</td>
</tr>
<tr>
<td><strong>% retinopathy</strong></td>
<td>62</td>
</tr>
<tr>
<td><strong>Total cholesterol</strong></td>
<td>227-229 mg/dl</td>
</tr>
<tr>
<td><strong>SCr</strong></td>
<td>1.9 mg/dl</td>
</tr>
</tbody>
</table>
RENAAL RESULTS

- 4/2 difference in BP at 1 year
- Final BP 140/74 losartan, 142/74 placebo (NSS)
- Losartan group: 27% on 50mg, 71% on 100mg
- Additional drugs:

<table>
<thead>
<tr>
<th></th>
<th>Losartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CCB (%)</td>
<td>87</td>
<td>90</td>
</tr>
<tr>
<td>DHP (%)</td>
<td>61</td>
<td>64</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>Alpha-blocker (%)</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>34</td>
<td>36</td>
</tr>
</tbody>
</table>
RENAAL RESULTS

- Primary EP was 16% lower with losartan than placebo, \( p=0.024 \)
  - 2X SCr 25% lower than placebo, \( p=0.006 \)
  - ESRD 28% lower than placebo, \( p=0.002 \)
  - Death 2% higher than placebo, \( p=NS \)
  - ESRD+death 20% lower than placebo, \( p=0.01 \)
  - Time to reach ESRD from doubling time: 30% lower, \( p=0.013 \)
RENAAL
RESULTS

- **Secondary EP**
  - Total CV M/M 10% ↓ L vs P, p=NS
    - CHF 32% ↓ L vs P, p=0.005
    - CV death 12% ↑ L vs P, p=NS
    - MI 28% ↓ L vs P, p=0.08
    - Other CV events minimal differences
  - Proteinuria 35% ↓ L vs P, p=0.0001

- NNT = 16 to prevent 1 ESRD
RENAAL Interpretations

- Losartan decreased the primary EP by delaying the doubling of SCr and ESRD
- BP was not equally controlled for first year yet authors claim benefit beyond BP control
- No benefit on CV events or death
- Supports combination therapy with RAS blocker
LIFE: Cumulative Event Rates

Primary Composite Endpoint

- ARR 13.0%, \( P=0.021 \)
- URR 14.6%, \( P=0.009 \)

Fatal/nonfatal Stroke

- ARR 24.9%, \( P=0.001 \)
- URR 25.8%, \( P=0.0006 \)

Fatal/nonfatal MI

- ARR -7.3%, \( P=NS \)
- URR -5.0%, \( P=NS \)

CV Mortality

- ARR 11.4%, \( P=NS \)
- URR 13.3%, \( P=NS \)

Odds Ratio for CV Events and Systolic BP Difference: Recent and Older Trials

Recent and Older Trials

<table>
<thead>
<tr>
<th>Recent trials</th>
<th>Older trials placebo</th>
<th>Older trials active</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.50</td>
<td>1.25</td>
<td>1.00</td>
</tr>
<tr>
<td>0.75</td>
<td>0.50</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Difference (reference minus experimental) in systolic pressure (mm Hg)

Recent trials:
- AASK L vs H
- ABCD/NT L vs H
- ALLHAT/Aml
- ALLHAT/Lis
- ALLHAT/Lis ≥65
- ALLHAT/Lis Blacks
- ANBP2
- CONVINCE
- DIABHYCAR
- ELSA
- IDNT2
- LIFE/ALL
- LIFE/DM
- NICOLE
- PREVENT
- SCOPE

Older trials:
- ALLHAT/Dox
- ATMH
- EWPHE
- HEP
- HOPE
- HOT
- HOT M vs H
- INSIGHT
- MIDAS/NICS/VHAS
- L vs H
- MRC
- MRC2
- PART2/SCAT
- PATS
- PROGRESS/Per
- PROGRESSION/Com
- RCT70-80
- RENAAL
- SHEP
- STONE
- STOP 1
- STOP2/CCBs
- STOP2/ACEIs
- Syst-China
- Syst-Eur
- UKPDS C vs A
- UKPDS L vs H

BP-Lowering Treatment Trialists

Stroke

Relative Risk of Stroke

Systolic Blood Pressure Difference Between Randomised Groups (mm Hg)

CHD

Relative Risk of CHD

Systolic Blood Pressure Difference Between Randomised Groups (mm Hg)

*Lancet.* In press.
BP-Lowering Treatment Trialists

Heart Failure

Relative Risk of Heart Failure


Systolic Blood Pressure Difference
Between Randomised Groups (mm Hg)
Implications for Clinical Practice

- Elevated SBP is a strong predictor of cardiovascular events
- Patients should be advised on lifestyle modification as primary prevention of hypertension
- When pursuing goal BP, polypharmacy is the dominating strategy; clinical picture should dictate the order in which drugs are added
- Treatment with >2 agents is particularly important to control BP to recommended goals in high-risk patients (eg, patients with diabetes or prior cardiovascular events, renal patients)
- Preponderance of evidence suggests the importance of BP control over drug selection in patients with hypertension; however, need for renoprotection may warrant specific agents (eg, ARBs)
- Diuretics are important for BP control in complex (>2) antihypertensive regimens
- In clinical studies, CCBs, ACEIs, and ARBs have proved beneficial and are relatively safe agents to include in intensive, targeted polypharmacy regimens