Major Cardiovascular Events in Hypertensive Patients Randomized to Doxazosin vs Chlorthalidone

Preliminary Results from ALLHAT

The ALLHAT Collaborative Research Group
Study Leadership - 1

- **Steering Committee chairs:**
  - Curt Furberg, MD (chair); Jackson Wright, Jr., MD, PhD (vice-chair)

- **NHLBI:**
  - Jeffrey Cutler, MD, MPH; Gerald Payne, MD; David Gordon, MD, PhD; Chuke Nwachuku, MA, MPH

- **Clinical Trials Center (Houston):**
  - Barry Davis, MD, PhD; C. Morton Hawkins, ScD; Charles Ford, PhD; Sara Pressel, MS
• **Region 1 (VA):** William Cushman, MD; H. Mitchell Perry, Jr., MD; Sandra Walsh, MA; Therese Geraci, MSN, RN, CS

• **Region 2 (Cleveland):** Jackson Wright, Jr., MD, PhD; Mahboob Rahman, MD; Robert Pospisil, RN; Anne Juratovac, RN

• **Region 3 (New York):** Michael Alderman, MD; Lillian Carroll, RN, MA; Sheila Sullivan, BA; Kim Brennan, BS
Study Leadership - 3

- **Region 4 (Chicago):** Henry Black, MD; Tracy Lucente, MPH; Gail Barone, RN; Rudell Christian, MPH; Sharon Feldman, MPH

- **Region 5 (Birmingham):** Suzanne Oparil, MD; C. E. Lewis, MD, MSPH; Kim Jenkins, MPH; Peggy McDowell, RN

- **Region 6 (Seattle):** Jeffrey Probstfield, MD; Becky Letterer, RN, BSN; Connie Kingry, RN, BSN; Janice Johnson, BS
Study Leadership - 4

- **Region 7 (Minneapolis):** Richard Grimm, MD, PhD; Karen Margolis, MD; Leslie Ann Holland, BA; Brenda Jaeger-Fox, BA

- **Region 8 (New Orleans):** Paul Whelton, MD, MSC; Jeff Williamson, MD, MHS; Gail Louis, RN; Angela Williard, RN, BSN; Pamela Ragusa, RN, BSN; Laurie Quint Adler

- **Region 9 (Canada):** Frans Leenen, MD; Joanna Tanner; Sue Ferguson, RN
Study Leadership - 5

- **Other Steering Committee members:** Julian Haywood, MD; Charles Francis, MD; John LaRosa, MD
- **Central Laboratory (Minneapolis):** John Eckfeldt, MD, PhD; Bernadette Gloeb
- **ECG Coding Center (Minneapolis):** Richard Crow, MD; Maren Nowicki, MT; Jean Bucksa, MT
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Curt Furberg, MD (chair)
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Barry Davis, MD, PhD (CTC)
Jeffrey Cutler, MD, MPH (NHLBI)
William Cushman, MD (1)
H. Mitchell Perry, Jr., MD (1)
Michael Alderman, MD (3)
Henry Black, MD (4)
Suzanne Oparil, MD (5)
Jeffrey Probstfield, MD (6)
Richard Grimm, MD, PhD (7)
Paul Whelton, MD, MSC (8)
Frans Leenen, MD (9)
Julian Haywood, MD
Charles Francis, MD
John LaRosa, MD
Participating Investigators

• 625 clinical sites
• United States, Canada, Puerto Rico, US Virgin Islands
• VA, private & group general medicine practices, community health centers, HMOs, specialty practices
• Variety of research experience
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.
Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

- Practice-based, randomized, multi-center trial
- Antihypertensive component
  - 42,448 high-risk hypertensives ≥ 55 years
  - whether newer agents reduce incidence of CHD compared to a diuretic
  - blinded
  - no placebo
ALLHAT

Plus:

- Lipid-lowering component - subset of participants
  - 1/4 of antihypertensive trial cohort (10,357)
  - moderately hypercholesterolemic patients
  - does reduction of LDL cholesterol reduce all-cause mortality?
  - unblinded (pravastatin vs “usual care”)

ALLHAT
Secondary Objectives

• Secondary outcomes
  – All-cause mortality
  – Stroke
  – Combined CHD – nonfatal MI, CHD death, coronary revascularization, hospitalized angina
  – Combined CVD – combined CHD, stroke, lower extremity revascularization, treated angina, fatal / hospitalized / treated CHF, hospitalized or outpatient PAD
Major Subgroups

• Age 65+
• Women
• African-Americans
• Diabetics
Inclusion Criteria for Antihypertensive Trial - 1

• Age/sex: men and women aged ≥ 55 years

• History of hypertension:
  — Previously documented or on treatment.
  — May be newly diagnosed prior to or at visits 1-2 by JNC V criteria.

• Seated blood pressure (2 categories):
  1) Treated for @ least 2 months.
  2) Not on drugs or on drugs < 2 months.
Diagnosis of Hypertension

- Should not be diagnosed on the basis of a single measurement
- Initial elevations confirmed on at least two more visits over 1 to several weeks (unless BP very high)
- Avg DBP $\geq 90$ mmHg and/or SBP $\geq 140$ mmHg
- BP representative of patient’s usual levels
<table>
<thead>
<tr>
<th>Status at Visit 1 and Visit 2</th>
<th>Visit 1 &amp; Visit 2</th>
<th>Lower Limit (mm Hg)</th>
<th>Upper Limit (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On 1-2 drugs used for hypertension &gt;= 2 months</td>
<td>Visit 1</td>
<td>---</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>Visit 2</td>
<td>---</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>110</td>
</tr>
<tr>
<td>On drugs for &lt; 2 months or currently untreated</td>
<td>Visit 1 &amp; Visit 2</td>
<td>140</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90</td>
<td>110</td>
</tr>
</tbody>
</table>

SBP or DBP lower limit must be met at Visit 1 and Visit 2
SBP and DBP upper limit must be met at Visit 1 and Visit 2
Inclusion Criteria: HTN Trial - 2

At least one of the following:

• Myocardial infarction or stroke: age-indeterminate or at least 6 months old
• History of revascularization procedure
• Other documented ASCVD
• Major ST segment depression or T-wave inversion
Inclusion Criteria: HTN Trial - 3

At least one of the following (cont.)

• Type II diabetes mellitus

• HDL cholesterol < 35 mg/dl on any 2 or more determinations in past 5 years

• Left ventricular hypertrophy (past 2 years)
  — ECG or echo - combined wall thickness (septum + posterior wall) >= 25 mm

• Current cigarette smoking
Exclusion Criteria - 1

- Symptomatic MI or stroke within 6 months
- Symptomatic CHF and/or EF < 35%, if known, within past 6 months.
- Symptomatic angina pectoris within past 6 months (OK if asymptomatic on treatment)
- Known renal insufficiency - creatinine >= 2 mg/dl
Exclusion Criteria - 2

- Requiring diuretics, CaCB, ACEI or alpha blockers for reasons other than hypertension
  - May switch from CCB to beta blocker or nitrates for angina
  - May switch from alpha blocker to Proscar for BPH

- Sensitivity/contraindication to any first-line medication (not just prior side effects)
Exclusion Criteria - 3

- Low likelihood of compliance - dementia, drug or alcohol abuse, clear unreliability
- Diseases likely to cause death within 6 years
- SBP > 180 mmHg or DBP > 110 mmHg more than once during step-down or screening
- Participation in another clinical trial
Eligibility Criteria for Lipid-Lowering Trial

• Eligible and enrolled in antihypertensive trial

• Moderate hypercholesterolemia
  — LDL 120-189 mg/dl without CHD
  — LDL 100-129 mg/dl with known CHD

• Triglyceride level <350 mg/dl
Exclusion Criteria for Lipid-Lowering Trial

• Continuing use of prescribed lipid-lowering agents or large doses of niacin

• Contraindications to HMG CoA (hepatic or renal disease, organ transplant, known allergy or intolerance)

• Known secondary cause of elevated serum cholesterol

• ALT > 2 times ULN
Randomized Design of ALLHAT

High-risk hypertensive patients → Consent / Randomize

Amlodipine
Chlorthalidone
Doxazosin
Lisinopril

Eligible for lipid-lowering → Consent / Randomize

Pravastatin
Usual care

Not eligible for lipid-lowering

Follow until death or end of study (4-8 yr, ave 6 yr).
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Chlorthalidone (15,268)</th>
<th>Doxazosin (9,067)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BL SBP/DBP</td>
<td>146 / 84</td>
<td>146 / 84</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>Black non-Hisp, %</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>Women, %</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>Current smoking %</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>ASCVD, %</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Type II diabetes, %</td>
<td>36</td>
<td>35</td>
</tr>
</tbody>
</table>
Full Crossovers by Antihypertensive Treatment Group

Chlorthalidone: not on assigned medicine or open-label diuretic, but on open-label alpha-blocker
Doxazosin: not on assigned medicine or open-label alpha-blocker, but on open-label diuretic

<table>
<thead>
<tr>
<th></th>
<th>12M</th>
<th>24M</th>
<th>36M</th>
<th>48M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlor</td>
<td>0.4</td>
<td>0.6</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Dox</td>
<td>4.8</td>
<td>6.6</td>
<td>9.2</td>
<td>9.7</td>
</tr>
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</table>
SBP Results by Treatment Group

ALLHAT

Chlorthalidone
Doxazosin

<table>
<thead>
<tr>
<th>BL</th>
<th>6M</th>
<th>1Y</th>
<th>3Y</th>
<th>5Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>146.2</td>
<td>138.3</td>
<td>136.7</td>
<td>135.5</td>
</tr>
<tr>
<td>D</td>
<td>146.3</td>
<td>141.2</td>
<td>139.8</td>
<td>137.7</td>
</tr>
</tbody>
</table>

SBP: Systolic Blood Pressure

BL = Baseline
6M = 6 months
1Y = 1 year
3Y = 3 years
5Y = 5 years
DBP Results by Treatment Group

Chlorthalidone

Doxazosin

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>6M</th>
<th>1Y</th>
<th>3Y</th>
<th>5Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>84.0</td>
<td>80.2</td>
<td>79.2</td>
<td>77.0</td>
<td>75.4</td>
</tr>
<tr>
<td>D</td>
<td>83.9</td>
<td>80.0</td>
<td>79.3</td>
<td>76.6</td>
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</table>

mm Hg BP vs. Months
Losses to Follow-up by Antihypertensive Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>12M</th>
<th>24M</th>
<th>36M</th>
<th>48M</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlor</td>
<td>2.1</td>
<td>3.3</td>
<td>3.9</td>
<td>4.0</td>
<td>3.3</td>
</tr>
<tr>
<td>Dox</td>
<td>2.5</td>
<td>3.6</td>
<td>4.0</td>
<td>3.8</td>
<td>3.7</td>
</tr>
</tbody>
</table>
Decision to Drop an ALLHAT Arm

• January 24, 2000 – NHLBI Director accepts recommendation of independent review to terminate doxazosin arm
  – Futility of finding a significant difference for primary outcome
  – Statistically significant 25 percent higher rate of major secondary endpoint, combined CVD outcomes
Cardiovascular Disease

Rel Risk  95% CL
1.25  1.17-1.33

z = 6.77,  p < 0.0001

C: 15,268
D:  9,067

C: 12,990
D:  7,382

C: 9,443
D:  5,285

C: 4,827
D:  2,654

C: 2,010
D:  1,083

Cumulative Event Rate

0  1  2  3  4
Years of Follow-up

0.00  0.05  0.10  0.15  0.20  0.25  0.30

ALLHAT
Relative Risks and 95% CI Combined CVD Doxazosin/Chlorthalidone

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Age &lt;65</th>
<th>Age 65+</th>
<th>BNH Men</th>
<th>WNH Men</th>
<th>HISp Men</th>
<th>BNH W</th>
<th>WNH W</th>
<th>HISp W</th>
<th>Diab</th>
<th>Nondia</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>1.33</td>
<td>1.31</td>
<td>1.40</td>
<td>1.66</td>
<td>1.29</td>
<td>2.17</td>
<td>1.59</td>
<td>1.42</td>
<td>1.50</td>
<td>1.38</td>
<td>1.37</td>
</tr>
<tr>
<td>Low</td>
<td>1.17</td>
<td>1.04</td>
<td>1.20</td>
<td>1.20</td>
<td>1.06</td>
<td>1.21</td>
<td>1.12</td>
<td>1.05</td>
<td>0.71</td>
<td>1.12</td>
<td>1.16</td>
</tr>
<tr>
<td>RR</td>
<td>1.25</td>
<td>1.17</td>
<td>1.29</td>
<td>1.41</td>
<td>1.17</td>
<td>1.62</td>
<td>1.33</td>
<td>1.22</td>
<td>1.03</td>
<td>1.25</td>
<td>1.26</td>
</tr>
</tbody>
</table>
Congestive Heart Failure

Rel Risk | 95% CL
---------|-------
2.04     | 1.79-2.32

z = 10.95, p < 0.0001

ALLHAT

Cumulative Event Rate

doxazosin

chlorthalidone

C: 15,268
D: 9,067

Years of Follow-up

0.10
0.08
0.06
0.04
0.02
0.00

0 1 2 3 4
7,845 9,541 5,457 5,531 2,427
13,644 3,089 1,351

0,000 0,020 0,040 0,060 0,080 0,100

0.00 0.02 0.04 0.06 0.08 0.10

C: 15,268
D: 9,067
Relative Risks and 95% CI Congestive Heart Failure Doxazosin/Chlorthalidone
Relative Risks and 95% CI
Congestive Heart Failure
Doxazosin/Chlorthalidone

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Age &lt;65</th>
<th>Age 65+</th>
<th>BNH Men</th>
<th>WNH Men</th>
<th>Hisp Men</th>
<th>BNH W</th>
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<th>Hisp W</th>
<th>Diab</th>
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<tbody>
<tr>
<td>High</td>
<td>2.32</td>
<td>2.53</td>
<td>2.41</td>
<td>2.81</td>
<td>2.40</td>
<td>4.14</td>
<td>3.21</td>
<td>2.62</td>
<td>3.97</td>
<td>2.59</td>
<td>2.37</td>
</tr>
<tr>
<td>Low</td>
<td>1.79</td>
<td>1.51</td>
<td>1.78</td>
<td>1.47</td>
<td>1.58</td>
<td>1.11</td>
<td>1.67</td>
<td>1.49</td>
<td>0.85</td>
<td>1.76</td>
<td>1.67</td>
</tr>
<tr>
<td>RR</td>
<td>2.04</td>
<td>1.96</td>
<td>2.07</td>
<td>2.04</td>
<td>1.94</td>
<td>2.15</td>
<td>2.32</td>
<td>1.98</td>
<td>1.84</td>
<td>2.14</td>
<td>1.98</td>
</tr>
</tbody>
</table>
Non-CHF Cardiovascular Disease

Rel Risk 95% CL
1.13 1.06-1.21

z = 3.53, p < 0.001

Doxazosin
Chlorthalidone

C: 15,268
D: 9,067

Years of Follow-up

Cumulative Event Rate

0.00 0.05 0.10 0.15 0.20 0.25

2,058 1,156
4,917 2,773
9,541 5,457
13,053 7,535

ALLHAT
Cumulative Event Rate

Stroke

Rel Risk  95% CL
1.19  1.01-1.40

$z = 2.05$, $p = 0.04$

C: 15,268
D: 9,067

ALLHAT

0.06

0.04

0.02

0.00

Years of Follow-up

0 1 2 3 4

13,646 7,984 10,373 5,588 2,455

10,373 6,028 5,588 3,214 1,431

C: 15,268
D: 9,067

Rel Risk

Chlorthalidone

Doxazosin
Coronary Heart Disease

Rel Risk 95% CL
1.03 0.90-1.17

$z = 0.38, \ p = 0.71$

Doxazosin

chlorthalidone

Cumulative Event Rate

Years of Follow-up

C: 15,268
D: 9,067

ALLHAT
Conclusions

Chlorthalidone is superior to doxazosin for:

♥ Hypertension control
♥ Drug compliance
♥ Reduction of cardiovascular complications

In addition, chlorthalidone is much less expensive
Lessons Learned - 1

• For some drugs, BP lowering is an inadequate marker (surrogate) of health benefits in hypertension

• Antihypertensive drugs can have important non-BP actions that may alter the benefit of BP lowering
Lessons Learned - 2

• Comparative outcome trials, like ALLHAT, are essential for documenting optimal drug benefit / risk balance and for guiding the practice of medicine

• All major health outcomes of a treatment should be evaluated
Recommendations

- Chlorthalidone (diuretic) is the recommended drug of choice for initial antihypertensive treatment in high risk hypertensive patients.

- Doxazosin is not recommended as first-line therapy in hypertension.
ALLHAT does not allow an assessment of the effect of doxazosin compared with placebo on the incidence of CVD.

The use of doxazosin as a step-up drug for treating hypertension was not tested in this trial.

These findings are likely to apply to all alpha-blockers.
All-Cause Mortality

Rel Risk  95% CL
1.03     0.90-1.15

z = 0.58, p = 0.56

Cumulative Event Rate

C: 15,268  D: 9,067

Years of Follow-up

0.00  0.02  0.04  0.06  0.08  0.10

0  1  2  3  4

13,739  10,513  5,702  2,530
8,054   6,118   3,287  1,481