Prevention of Stroke in the 21st Century

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DISCLOSURES

• HONORARIA FROM PFIZER, MERCK FOR OCCASIONAL CME LECTURES
TRADITIONAL RISK FACTORS FOR STROKE: POTENTIALLY MODIFIABLE

- HYPERTENSION
- DYSLIPIDEMIA
- CIGARETTE SMOKING
- ATRIAL FIBRILLATION
- DIABETES
- CAROTID STENOSIS
- OBESITY
- PHYSICAL INACTIVITY
- OTHERS (e.g., HEAVY ETOH USE, COCAINE, ETC)
TRADITIONAL RISK FACTORS FOR STROKE: NOT MODIFIABLE

- ADVANCING AGE
- MALE GENDER
- RACE/ETHNICITY: AFRICAN AMERICANS
- FAMILY HISTORY OF STROKE
ADDITIONAL SELECTED RISK FACTORS FOR CV DISEASE

• LVH
• ALBUMINURIA
• REDUCED eGFR
• ELEVATED PULSE PRESSURE
Hypertension is the most important stroke risk factor—aggressive treatment can lead to the prevention of thousands of strokes.

Derived by multiplying the population attributed risk (%) times the estimated number of annual strokes (500,000), provided by the American Heart Association. The estimates do not take into account adjustment for other factors or possible interactions.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)
For persons over age 50, SBP is more important than DBP as a CVD risk factor.

Starting at 115/75 mmHg, CVD risk doubles with each increment of 20/10 mmHg throughout the BP range.

Persons who are normotensive at age 55 have a 90% lifetime risk for developing HTN.

Those with SBP 120–139 mmHg or DBP 80–89 mmHg should be considered prehypertensive who require health-promoting lifestyle modifications to prevent CVD.
New Features and Key Messages (Continued)

- Thiazide-type diuretics should be initial drug therapy for most, either alone or combined with other drug classes (based on ALLHAT).

- Certain high-risk conditions are compelling indications for other drug classes.

- Most patients will require two or more antihypertensive drugs to achieve goal BP.

- If BP is >20/10 mmHg above goal, initiate therapy with two agents, one usually should be a thiazide-type diuretic.
## Blood Pressure Classification

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>80–89</td>
</tr>
<tr>
<td>Stage 1 HBP</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 HBP</td>
<td>≥160</td>
<td>≥100</td>
</tr>
</tbody>
</table>
## Benefits of Lowering BP

<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 infarction</td>
<td>20–25%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>50%</td>
</tr>
</tbody>
</table>
Major Outcomes in High Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

The ALLHAT Collaborative Research Group

Sponsored by the National Heart, Lung, and Blood Institute (NHLBI)

JAMA. 2002;288:2981-2997
Randomized Design of ALLHAT

High-risk hypertensive patients → Consent / Randomize (42,418)

Amlodipine
Chlorthalidone
Doxazosin
Lisinopril

Eligible for lipid-lowering → Consent / Randomize (10,355)

Pravastatin → Usual care

Follow for CHD and other outcomes until death or end of study (up to 8 yr).

Not eligible for lipid-lowering
# Step 1 Treatment Protocol

<table>
<thead>
<tr>
<th>Step 1 Agent</th>
<th>Initial Dose*</th>
<th>Dose 1*</th>
<th>Dose 2*</th>
<th>Dose 3*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>25</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>2.5</td>
<td>2.5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10</td>
<td>10</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

* mg/day
Decision to Drop an ALLHAT Arm

- January 24, 2000 – NHLBI Director accepts the recommendation of an independent review group 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
Compared to chlorthalidone:

SBP significantly higher in the amlodipine group (~1 mm Hg) and the lisinopril group (~2 mm Hg).

Compared to chlorthalidone:

DBP significantly lower in the amlodipine group (~1 mm Hg).
# ALLHAT

## Step Up Treatment Protocol

<table>
<thead>
<tr>
<th>Step 2 Agents:</th>
<th>Dose 1*</th>
<th>Dose 2*</th>
<th>Dose 3*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reserpine</td>
<td>0.05 qd</td>
<td>0.1 qd</td>
<td>0.2 qd</td>
</tr>
<tr>
<td></td>
<td>or 0.1 qod</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine (oral)</td>
<td>0.1 bid</td>
<td>0.2 bid</td>
<td>0.3 bid</td>
</tr>
<tr>
<td>Atenolol</td>
<td>25 qd</td>
<td>50 qd</td>
<td>100 qd</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 3 Agent:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td>25 bid</td>
<td>50 bid</td>
<td>100 bid</td>
</tr>
</tbody>
</table>

*All doses in mg
### Cumulative Event Rates for the Primary Outcome (Fatal CHD or Nonfatal MI) by ALLHAT Treatment Group

<table>
<thead>
<tr>
<th>Years to CHD Event</th>
<th>Cumulative CHD Event Rate</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Number at Risk:</th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>15,255</td>
<td>14,477</td>
<td>13,820</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>9,048</td>
<td>8,576</td>
<td>8,218</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>9,054</td>
<td>8,535</td>
<td>8,123</td>
</tr>
</tbody>
</table>

### RR (95% CI) p value

- **A/C**: 0.98 (0.90-1.07) 0.65
- **L/C**: 0.99 (0.91-1.08) 0.81
Cumulative Event Rates for Stroke by ALLHAT Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/C</td>
<td>0.93 (0.81-1.06)</td>
<td>0.28</td>
</tr>
<tr>
<td>L/C</td>
<td>1.15 (1.02-1.30)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Number at risk:

<table>
<thead>
<tr>
<th></th>
<th>Chlor</th>
<th>Amlo</th>
<th>Lisin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15,255</td>
<td>9,048</td>
<td>9,054</td>
</tr>
<tr>
<td>1</td>
<td>14,515</td>
<td>8,617</td>
<td>8,543</td>
</tr>
<tr>
<td>2</td>
<td>13,934</td>
<td>8,271</td>
<td>8,172</td>
</tr>
<tr>
<td>3</td>
<td>13,309</td>
<td>7,949</td>
<td>7,784</td>
</tr>
<tr>
<td>4</td>
<td>11,570</td>
<td>6,937</td>
<td>6,765</td>
</tr>
<tr>
<td>5</td>
<td>6,385</td>
<td>3,845</td>
<td>3,891</td>
</tr>
<tr>
<td>6</td>
<td>3,217</td>
<td>1,813</td>
<td>1,828</td>
</tr>
<tr>
<td>7</td>
<td>567</td>
<td>506</td>
<td>949</td>
</tr>
</tbody>
</table>
## Stroke – Subgroup Comparisons – RR (95% CI)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Amlodipine</th>
<th>Chlorthalidone</th>
<th>Total</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Diabetic</td>
<td>0.96</td>
<td>0.93</td>
<td>0.96</td>
<td>1.15</td>
</tr>
<tr>
<td>Diabetic</td>
<td>0.90</td>
<td>0.90</td>
<td>0.90</td>
<td>1.13</td>
</tr>
<tr>
<td>Non-Black</td>
<td>0.93</td>
<td>0.93</td>
<td>0.93</td>
<td>1.10</td>
</tr>
<tr>
<td>Black</td>
<td>0.93</td>
<td>0.93</td>
<td>0.93</td>
<td>1.21</td>
</tr>
<tr>
<td>Men</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.07</td>
</tr>
<tr>
<td>Women</td>
<td>0.84</td>
<td>0.84</td>
<td>0.84</td>
<td>1.00</td>
</tr>
<tr>
<td>Age &lt; 65</td>
<td>0.93</td>
<td>0.93</td>
<td>0.93</td>
<td>1.13</td>
</tr>
<tr>
<td>Age &gt;= 65</td>
<td>0.93</td>
<td>0.93</td>
<td>0.93</td>
<td>1.13</td>
</tr>
<tr>
<td>Age &lt; 65</td>
<td>0.93</td>
<td>0.93</td>
<td>0.93</td>
<td>1.13</td>
</tr>
<tr>
<td>Age &gt;= 65</td>
<td>0.93</td>
<td>0.93</td>
<td>0.93</td>
<td>1.13</td>
</tr>
<tr>
<td>Women</td>
<td>0.84</td>
<td>0.84</td>
<td>0.84</td>
<td>1.22</td>
</tr>
<tr>
<td>Men</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.10</td>
</tr>
<tr>
<td>Non-Black</td>
<td>0.93</td>
<td>0.93</td>
<td>0.93</td>
<td>1.10</td>
</tr>
<tr>
<td>Black</td>
<td>0.93</td>
<td>0.93</td>
<td>0.93</td>
<td>1.10</td>
</tr>
<tr>
<td>Diabetic</td>
<td>0.90</td>
<td>0.90</td>
<td>0.90</td>
<td>1.07</td>
</tr>
<tr>
<td>Non-Diabetic</td>
<td>0.96</td>
<td>0.96</td>
<td>0.96</td>
<td>1.23</td>
</tr>
</tbody>
</table>

**ALLHAT**
P = .01 for interaction
ALLHAT CONCLUSIONS

• ALLHAT… THE LARGEST TRIAL EVER DONE IN PATIENTS WITH HBP
• PRIMARY ENDPOINT (CHD DEATH AND NONFATAL MI) IDENTICAL FOR AMLODIPINE, DIURETIC AND ACEI
• ALPHA BLOCKER NOT APPROPRIATE FIRST LINE THERAPY FOR HBP
• OVER 40% OF PTS REQUIRE STEP 2 OR 3 RX FOR HBP
SHORTCOMINGS OF THE ALLHAT STUDY

• NO BETA BLOCKER ARM
• NO ANGIOTENSIN RECEPTOR ANTAGONIST ARM
• UNEQUAL BP CONTROL IN THE DIFFERENT TREATMENT ARMS
The **Losartan Intervention For Endpoint Reduction in Hypertension Study**

An investigator initiated community-based study in 945 sites in 7 countries enrolling 9,193 patients

- **Steering Committee Chair/Vice-Chair**: B. Dahlof, D. Devereux
- **European/US Coordinators**: S.E. Kjeldsen, S. Julius
- **Data and Safety Monitoring Committee Chair**: J. Kjekshus
- **Clinical Endpoint Classification Committee**: D. Levy, K. Thygesen

*B Dahlof et al. Lancet 2002;359:995-1003*
LIFE: Background/Rationale

- LVH strong and independent risk factor
- Selective AT₁-receptor blockade potentially more effective than a beta-blocker in reversing LVH
Cerebrovascular Events in Hypertensive Patients With and Without LVH

LIFE: Design Dosing

Titration to target blood pressure: <140 / <90 mmHg

*Other antihypertensives excluding ACEIs, All antagonists, beta-blockers.
LIFE: Blood Pressure Results; Follow-up

**Systolic**
- Atenolol 145.4 mmHg
- Losartan 144.1 mmHg

**Diastolic**
- Atenolol 80.9 mmHg
- Losartan 81.3 mmHg

**Mean Arterial**
- Losartan 81.3 mmHg
- Atenolol 80.9 mmHg

LIFE: ECG-LVH Regression from Baseline

-18 -16 -14 -12 -10 -8 -6 -4 -2 0

Cornell Product

Sokolow-Lyon

Change from baseline, %

Losartan

Atenolol

LIFE: Distribution of Therapy for the Two Treatment Groups *

Losartan
Mean dosage mg 82

- 50% 50 mg only
- 18% 50 mg plus additional therapy including HCTZ
- 9% 100 mg with or without additional therapy including HCTZ
- 23% Off study therapy

Atenolol
Mean dosage mg 79

- 43% 50 mg only
- 27% 50 mg plus additional therapy including HCTZ
- 10% 100 mg with or without additional therapy including HCTZ
- 20% Off study therapy

* At endpoint or end of follow-up

LIFE: TRIAL END POINTS

• PRIMARY COMPOSITE END POINT:
  – FATAL OR NON-FATAL MI
  – FATAL OR NON-FATAL STROKE
LIFE: Primary Composite Endpoint

Intention-to-Treat

Adjusted Risk Reduction 13.0%, p=0.021
Unadjusted Risk Reduction 14.6%, p=0.009

LIFE: Fatal/Nonfatal Myocardial Infarction

Intention-to-Treat

Adjusted Risk Reduction -7.3%, p=0.49
Unadjusted Risk Reduction -5.0%, p=0.63

LIFE: Fatal/Nonfatal Stroke

Adjusted Risk Reduction 24.9%, p=0.001
Unadjusted Risk Reduction 25.8%, p=0.0006

LIFE: Primary Composite End Point in Patients With ISH

Primary Composite End Point

- **Atenolol**
- **Losartan**

Relative Risk = 0.75
(95% CI, 0.56–1.01)

*P* = 0.06

ISH = isolated systolic hypertension; CI = confidence interval.

LIFE: Stroke Risk Reduction in Patients With ISH

Stroke

- Atenolol
- Losartan

Patients, %

Study Month

Relative Risk = 0.60
(95% CI, 0.38–0.92)
P = 0.02

LIFE: Conclusions

• A losartan-based regimen reduced the risk of stroke, compared to an atenolol-based regimen, despite equal blood pressure lowering.

• Losartan reduced LVH much more than atenolol, despite equal blood pressure lowering.

AT-2 Receptor Blockade Reduces New-onset AF and Subsequent Stroke Compared to Atenolol.

- LIFE study, 9193 pts with HBP and LVH, 8851 without AF at entry.
- At 4.8 yrs, new-onset AF occurred in 150 pts in Losartan arm vs 221 in Atenolol arm, p<0.001
- New-onset AF was associated with a 3x increase in stroke incidence.

Wachtell et al; JACC, March 2005
Amiodarone, Losartan, and Perindopril in Atrial Fibrillation

Trial Design: The study was a randomized trial of amiodarone alone (n=59), amiodarone plus losartan (n=59) or amiodarone plus perindopril (n=59) for 2 years in patients with lone paroxysmal AF. Primary endpoint was incidence of AF from >14 days to 2 years.

![Atrial fibrillation incidence graph](image)

<table>
<thead>
<tr>
<th>Atrial fibrillation</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone alone</td>
<td>41</td>
</tr>
<tr>
<td>Amiodarone + Losartan</td>
<td>19</td>
</tr>
<tr>
<td>Amiodarone + Perindopril</td>
<td>24</td>
</tr>
</tbody>
</table>

Results
- Compared with amiodarone alone, primary endpoint of AF by 24 months ↓ in amiodarone+losartan group and amiodarone+perindopril group, with no difference between losartan and perindopril groups (Figure)
- Left atrial diameter at 24 months ↓ in amiodarone+losartan group and amiodarone+perindopril group vs amiodarone alone group (36 mm and 35 mm vs 38 mm, respectively; p=0.001 for each)
- Frequency of adverse events similar between groups (8.5% for amiodarone alone and amiodarone + losartan groups, 14% for amiodarone + perindopril group)

Conclusions
- Among patients with lone paroxysmal AF, treatment with amiodarone + losartan or amiodarone + perindopril was associated with reduction in recurrent AF through 2 years compared with amiodarone alone
- Prior studies complicated by inclusion of patients with LV dysfunction and hypertension so difficult to attribute reason for reduction in AF with addition of ACE-I or ARB

Eur Heart J 2006; 27: 1841-1846
MANY STUDIES HAVE SHOWN REDUCTION IN STROKE WITH STATINS

- CARE
- 4S
- HEART PROTECTION STUDY
- ASCOT
- CARDS
COLLABORATIVE ATORVASTATIN DIABETES STUDY

- ATORVASTATIN 10 MG VS. PLACEBO IN PATIENTS WITH DIABETES
- NO HISTORY OF MI OR STROKE
- AT LEAST ONE OTHER RISK FACTOR (AGE, HYPERTENSION, ALBUMINURIA, SMOKER, ETC)
# CARDS: Patient Baseline Lipids

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=1410) Mean (SD)</th>
<th>Atorvastatin (n=1428) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dL)</td>
<td>207 (32)</td>
<td>207 (32)</td>
</tr>
<tr>
<td></td>
<td>(mmol/L) 5.4 (0.8)</td>
<td>(mmol/L) 5.4 (0.8)</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>117 (27)</td>
<td>118 (28)</td>
</tr>
<tr>
<td></td>
<td>(mmol/L) 3.02 (0.7)</td>
<td>(mmol/L) 3.04 (0.7)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>55 (13)</td>
<td>54 (12)</td>
</tr>
<tr>
<td></td>
<td>(mmol/L) 1.42 (0.3)</td>
<td>(mmol/L) 1.39 (0.3)</td>
</tr>
<tr>
<td>TGs (mg/dL)</td>
<td>148 (104-212)*</td>
<td>150 (106-212)*</td>
</tr>
<tr>
<td></td>
<td>(mmol/L) 1.67 (1.2-2.4)*</td>
<td>(mmol/L) 1.70 (1.2-2.4)*</td>
</tr>
</tbody>
</table>

*IQR=interquartile range.
CARDS: Lipid Levels by Treatment

TC (mg/dL)
Average difference 26%
54 mg/dL (1.4 mmol/L) P < .0001

LDL-C (mg/dL)
Average difference 40%
46 mg/dL (1.2 mmol/L) P < .0001

CARDS: Effect of Atorvastatin on the Primary End Point of Major CV Events Including Stroke

Relative Risk Reduction 37% (95% CI, 17-52)

\[ P = .001 \]

Placebo
127 events

Atorvastatin
83 events

Cumulative Hazard (%)

Years

<table>
<thead>
<tr>
<th>Years</th>
<th>Placebo</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1410</td>
<td>1428</td>
</tr>
<tr>
<td>1</td>
<td>1351</td>
<td>1392</td>
</tr>
<tr>
<td>2</td>
<td>1306</td>
<td>1361</td>
</tr>
<tr>
<td>3</td>
<td>1022</td>
<td>1074</td>
</tr>
<tr>
<td>4</td>
<td>651</td>
<td>694</td>
</tr>
<tr>
<td>4.75</td>
<td>305</td>
<td>328</td>
</tr>
</tbody>
</table>

# CARDS: Treatment Effect on the Primary End Point

## Number of Patients With an Event (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=1410)</th>
<th>Atorvastatin (n=1428)</th>
<th>Hazard Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>127 (9.0%)</td>
<td>83 (5.8%)</td>
<td>0.63 (0.48-0.83)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>P</em>= .001</td>
</tr>
<tr>
<td>Acute coronary events</td>
<td>77 (5.5%)</td>
<td>51 (3.6%)</td>
<td>0.64 (0.45-0.91)</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>34 (2.4%)</td>
<td>24 (1.7%)</td>
<td>0.69 (0.41-1.16)</td>
</tr>
<tr>
<td>Stroke</td>
<td>39 (2.8%)</td>
<td>21 (1.5%)</td>
<td>0.52 (0.31-0.89)</td>
</tr>
</tbody>
</table>

Heart Protection Study (HPS)
Life-Table Plot of Effects of Simvastatin on Stroke

Logrank $P<0.0001$

Placebo-allocated

Simvastatin-allocated

Benefit (SE)/1,000 allocated simvastatin

2 (1) 7 (2) 10 (2) 13 (3) 14 (4) 15 (10)

TRADITIONAL RISK FACTORS FOR HEART ATTACK AND STROKE: NOT MODIFIABLE

• ADVANCING AGE
• MALE GENDER
• RACE/ETHNICITY; AFRICAN AMERICANS
• FAMILY HISTORY
TRADITIONAL RISK FACTORS FOR HEART ATTACK AND STROKE: MODIFIABLE

- HYPERTENSION
- DYSLIPIDEMIA
- CIGARETTE SMOKING
- ATRIAL Fibrillation
- DIABETES
- CAROTID ARTERY STENOSSES
- OBESITY
- PHYSICAL INACTIVITY
- OTHERS (e.g., HEAVY ETOH USE, COCAINE,)
ADDITIONAL SELECTED RISK FACTORS FOR CV DISEASE

• LVH: MODIFIABLE
• ALBUMINURIA: MODIFIABLE
• REDUCED eGFR: ?? MODIFIABLE
• INCREASED PULSE PRESSURE: ?? MODIFIABLE