US Prevalence of Hypertension

Based on NHANES III (phase 1 and 2)

Hypertension defined as blood pressure ≥140/90 mmHg or treatment

SBP in the US population increases with advancing age, while DBP tends to plateau after age 60.

Figure adapted with permission from Burt VL et al. Hypertension. 1995;25:305-313.
Lower Systolic Blood Pressure Reduces Risk of Ischemic Heart Disease and Stroke Mortality

One Million Adults, 61 Prospective Studies

Ischemic Heart Disease Mortality

<table>
<thead>
<tr>
<th>Usual Systolic BP (mm Hg)</th>
<th>120</th>
<th>140</th>
<th>160</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD Mortality (absolute risk and 95% CI)</td>
<td>256</td>
<td>128</td>
<td>64</td>
<td>32</td>
</tr>
<tr>
<td>80-89</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>70-79</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>60-69</td>
<td>16</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>50-59</td>
<td>16</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>40-49</td>
<td>16</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Stroke Mortality

<table>
<thead>
<tr>
<th>Usual Systolic BP (mm Hg)</th>
<th>120</th>
<th>140</th>
<th>160</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Mortality (absolute risk and 95% CI)</td>
<td>256</td>
<td>128</td>
<td>64</td>
<td>32</td>
</tr>
<tr>
<td>80-89</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>70-79</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>60-69</td>
<td>16</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>50-59</td>
<td>16</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

IHD = ischemic heart disease.
“High-Normal” BP Is Not Benign

Framingham Data

Cumulative Incidence of Cardiovascular (CV) Events* (%)

Time (years)

High-Normal
Normal
Optimal

Men
1.6-fold greater risk†

High-Normal = 130-139/85-89 mm Hg
Normal = 120-129/80-84 mm Hg
Optimal = < 120/< 80 mm Hg

*CV death, MI, stroke, heart failure. †Adjusted for concomitant CV risk factors.
Atherosclerosis Risk in Communities (ARIC)

- A prospective epidemiologic study of atherosclerotic diseases in 15,792 people recruited in 1987-1989 from Forsyth County, NC, Jackson, MS, Minneapolis, MN, and Washington Co. MD
- Prospective cohort analysis of 8,960 middle-aged adults
<table>
<thead>
<tr>
<th>BP</th>
<th>Overall</th>
<th>Black</th>
<th>DM</th>
<th>AGE 55-64</th>
<th>CRF</th>
<th>BMI &gt;30</th>
<th>LDL &gt;160</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120/80</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-129/80-84</td>
<td>1.81</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>130-139/85-89</td>
<td>2.33</td>
<td>3.29</td>
<td>4.1</td>
<td>2.41</td>
<td>1.9</td>
<td>3.56</td>
<td>1.85</td>
</tr>
</tbody>
</table>

AJM, Vol 119, No 2, 2006
Prehypertension - ARIC

Cumulative Incidence (%)

Follow-up Time in Years

Optimal

Normal

High normal
Feasibility of Treating Prehypertension with an Angiotensin-Receptor Blocker

TROPHY

www.nejm.org March 14, 2006
Can treatment of prehypertension prevent or postpone stage 1 hypertension?
TROPHY

Inclusion criteria: systolic pressure 130-139 mm Hg and diastolic pressure of 89 or lower, or systolic pressure of 139 mm Hg or lower and diastolic pressure of 85 to 89 mm Hg
<table>
<thead>
<tr>
<th></th>
<th>#patients</th>
<th>#HTN 2 YEARS</th>
<th>#HTN 4 YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>381</td>
<td>154</td>
<td>240</td>
</tr>
<tr>
<td>Candesartan</td>
<td>391</td>
<td>53</td>
<td>208</td>
</tr>
<tr>
<td>Risk Reduction</td>
<td></td>
<td><strong>66.3%</strong></td>
<td><strong>15.6%</strong></td>
</tr>
</tbody>
</table>
Benefits of Hypertension Treatment

• Reduction of stroke incidence by 35-40%
• 50% reduction of CHF
• Myocardial infarction lessened by 20-25%
• Prevention of dementia
• Prevention of kidney failure
• Lessens peripheral vascular disease
HOT Study

A total of 18,790 patients from 26 countries were randomized.

<table>
<thead>
<tr>
<th>Country/area</th>
<th>No. of randomized patients</th>
<th>Country/area</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>47</td>
<td>Israel</td>
<td>411</td>
</tr>
<tr>
<td>Austria</td>
<td>628</td>
<td>Italy</td>
<td>2,702</td>
</tr>
<tr>
<td>Belgium</td>
<td>755</td>
<td>Mexico</td>
<td>49</td>
</tr>
<tr>
<td>Canada</td>
<td>838</td>
<td>Norway</td>
<td>432</td>
</tr>
<tr>
<td>Denmark</td>
<td>503</td>
<td>South East Asia</td>
<td>71</td>
</tr>
<tr>
<td>East Asia</td>
<td>134</td>
<td>Spain</td>
<td>806</td>
</tr>
<tr>
<td>Finland</td>
<td>373</td>
<td>Sweden</td>
<td>492</td>
</tr>
<tr>
<td>France</td>
<td>1,574</td>
<td>Switzerland</td>
<td>797</td>
</tr>
<tr>
<td>Germany</td>
<td>4,269</td>
<td>The Netherlands</td>
<td>603</td>
</tr>
<tr>
<td>Great Britain</td>
<td>131</td>
<td>USA</td>
<td>2,646</td>
</tr>
<tr>
<td>Greece</td>
<td>335</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>194</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HOT Reduction in Cardiovascular Risk

Achieved DBP: 80 mm Hg

Optimal DBP reduction in the HOT Study: 82.6
HOT Reduction in Cardiovascular Risk

Achieved SBP

HOT Study

Optimal SBP reduction in the HOT Study

138.5

% risk reduction
HOT: Reduction of CV Events in Diabetics


### Diabetes Subgroup

<table>
<thead>
<tr>
<th>Target Diastolic BP (mmHg)</th>
<th>Number of Patients</th>
<th>Achieved† Systolic BP (mmHg)</th>
<th>Achieved† Diastolic BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 90</td>
<td>501</td>
<td>143.7</td>
<td>85.2</td>
</tr>
<tr>
<td>≤ 85</td>
<td>501</td>
<td>141.4</td>
<td>83.2</td>
</tr>
<tr>
<td>≤ 80</td>
<td>499</td>
<td>139.7</td>
<td>81.1</td>
</tr>
</tbody>
</table>

*includes all myocardial infarction, all strokes, and all other CV deaths

![Graph showing reduction of CV events in diabetics with P < .005](image)

# Published Guidelines Have Set Clear Treatment Goals

JNC 7 / ADA / NKF / ISHIB Guidelines for Hypertension and Patients at High Risk

<table>
<thead>
<tr>
<th>Condition</th>
<th>mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential hypertension</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>High-risk* hypertension</td>
<td>&lt;130/80</td>
</tr>
</tbody>
</table>

ADA=American Diabetes Association.
NKF=National Kidney Foundation.
ISHIB=International Society on Hypertension in Blacks.

*History of CVD event, stroke, transient ischemic attack, evidence of target-organ damage (e.g., left ventricular hypertrophy, microalbuminuria), CHD, or high-risk for CHD (e.g., metabolic syndrome).

ALLHAT

42,418 patients with hypertension

- SBP >140 mmHg and/or DBP >90 mmHg OR
- Took medication for hypertension and had at least one additional risk factor for CHD
- Age ≥55 years
- NHLBI funded trial

Endpoints:
- Primary – Fatal coronary heart disease and nonfatal MI
- Secondary – All-cause mortality, stroke, and major cardiovascular disease events (CHF, coronary revascularization, angina, and peripheral artery disease)
- Mean follow-up 4.9 years

Diuretic
Chlorthalidone
12-25 mg/day
(n=15,255)

Calcium Channel Blocker
Amlodipine
2.5-10 mg/day
(n=9,048)

ACE Inhibitor
Lisinopril
10-40 mg/day
(n=9,054)

Alpha Blocker
Doxazosin*
2-8 mg/day
(n=9,061)

* Discontinued prior to study completion

JAMA 2002;288:2981-2997
ALLHAT BP Controlled to <140/90 mmHg

% Patients with BP <140/90 mmHg

- **Chlorthalidone**
- **Amlodipine**
- **Lisinopril**

*P<0.001 for amlodipine vs chlorthalidone
†P<0.001 for lisinopril vs chlorthalidone

Primary Endpoint*

Chlorthalidone vs Amlodipine
Primary Endpoint
RR = 0.98
p = 0.65

Chlorthalidone vs Lisinopril
Primary Endpoint
RR = 0.99
p = 0.81

* Primary Endpoint = Fatal CHD or nonfatal MI

JAMA 2002;288:2981-2997
Secondary Endpoints
Chlorthalidone vs Amlodipine

All Cause Mortality
RR = 0.96
p = 0.20

Heart Failure
RR = 1.38
p < 0.001

JAMA 2002;288:2981-2997
Secondary Endpoints
Chlorthalidone vs Lisinopril

**All Cause Mortality**
RR = 1.00
p = 0.90

**Heart Failure**
RR = 1.19
p < 0.001

**Stroke**
RR = 1.15
p = 0.02

---

**Chlorthalidone vs Lisinopril**

- **Chlorthalidone**: 17.3%
- **Lisinopril**: 17.2%

- **Chlorthalidone**: 7.7%
- **Lisinopril**: 8.7%

- **Chlorthalidone**: 5.6%
- **Lisinopril**: 6.3%

---

*JAMA 2002;288:2981-2997*
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. Dahlöf, 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
Assessed for eligibility (n=10,780)

Ineligible (n=1,558)
  Did not meet protocol criteria (n=1,343)
  Unwilling to participate (n=215)

Randomized (n=9,222)

Excluded for irregularities (n=29)

Allocated to Losartan (n=4,605)

4605 available for ITT analyses
  - 44 withdrew consent
  - 57 vital status only
  - 4 lost to follow-up

Allocated to Atenolol (n=4,588)

4588 available for ITT analyses
  - 34 withdrew consent
  - 50 vital status only
  - 8 lost to follow-up

LIFE: Design Dosing

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

- Placebo
- Losartan 50 mg
- Atenolol 50 mg
- Losartan 50 mg + HCTZ 12.5 mg
- Atenolol 50 mg + HCTZ 12.5 mg
- Losartan 100 mg + HCTZ 12.5 mg
- Atenolol 100 mg + HCTZ 12.5 mg
- Losartan 100 mg + HCTZ 12.5-25 mg + others*
- Atenolol 100 mg + HCTZ 12.5-25 mg + others*

Day -14 Day -7 Day 1 Mth 1 Mth 2 Mth 4 Mth 6 Yr 1 Yr 1.5 Yr 2 Yr 2.5 Yr 3 Yr 3.5 Yr 4 Yr 5 Yr

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

Study Month

LIFE: Cardiovascular Mortality
Intention-to-Treat

Proportion of patients (%)

Study Month

1. Adjusted Risk Reduction 11.4%, p=0.21
2. Unadjusted Risk Reduction 13.3%, p=0.14

Atenolol
Losartan

LIFE: Fatal/Nonfatal Stroke

Intention-to-Treat

Adjusted Risk Reduction 24.9%, p=0.001

Unadjusted Risk Reduction 25.8%, p=0.0006

Proportion of patients with first event (%)

Study Month

LIFE: Fatal/Nonfatal Myocardial Infarction

Intention-to-Treat

Proportion of patients with first event (%)

Study Month

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

LIFE: New Onset Diabetes

**Intention-to-Treat**

Adjusted Risk Reduction 25%, p=0.001
Unadjusted Risk Reduction 25%, p=0.001

A randomised controlled trial of the prevention of CHD and other vascular events by BP and cholesterol lowering in a factorial study design

P. Sever (Co-chair), B. Dahlöf (Co-chair), N. Poulter (Secretary)  
H. Wedel (Statistician), G. Beevers, M. Caulfield, R. Collins  
S. Kjeldsen, A. Kristinsson, J. Mehlsen, G. McInnes, M. Nieminen  
E. O’Brien, J. Östergren, on behalf of the ASCOT Investigators

ACC – March 8, 2005
ASCOT Study Design

19,257 hypertensive patients

- atenolol ± bendroflumethiazide
- amlodipine ± perindopril

10,305 patients
TC ≤ 6.5 mmol/L (250 mg/dL)

- atorvastatin 10 mg
- placebo

Double-blind

Investigator-led, multinational randomized controlled trial

ASCOT-BPLA
ASCOT-LLA
Primary end point: Non-fatal MI, fatal CHD

Number at risk

Amlodipine ± perindopril  | 9639  | 9475  | 9337  | 9168  | 8966  | 7863
Atenolol ± thiazide      | 9618  | 9470  | 9290  | 9083  | 8858  | 7743

HR = 0.90 (0.79-1.02)  
P = 0.1052

(No. of events = 474)  
(No. of events = 429)
Fatal and non-fatal stroke

<table>
<thead>
<tr>
<th>Years</th>
<th>Amlodipine ± perindopril</th>
<th>Atenolol ± thiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>9639</td>
<td>9618</td>
</tr>
<tr>
<td>1.0</td>
<td>9483</td>
<td>9461</td>
</tr>
<tr>
<td>2.0</td>
<td>9331</td>
<td>9274</td>
</tr>
<tr>
<td>3.0</td>
<td>9156</td>
<td>9059</td>
</tr>
<tr>
<td>4.0</td>
<td>8972</td>
<td>8843</td>
</tr>
<tr>
<td>5.0</td>
<td>7863</td>
<td>7720</td>
</tr>
</tbody>
</table>

HR = 0.77 (0.66-0.89)
p = 0.0003
CV mortality

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Amlodipine ± perindopril</th>
<th>Atenolol ± thiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk (years)</td>
<td>0.0</td>
<td>9639</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>9544</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>9441</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>9322</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>9167</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>9078</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td></td>
</tr>
</tbody>
</table>

HR = 0.76 (0.65-0.90)
p = 0.0010
New-onset renal impairment

HR = 0.85 (0.75-0.97)
p = 0.0187

Number at risk
Amlodipine ± perindopril 9639 9426 9277 9093 8877 7775
Atenolol ± thiazide 9618 9431 9247 9021 8782 7640

Atenolol ± thiazide (No. of events = 469)
Amlodipine ± perindopril (No. of events = 403)
New-onset diabetes mellitus

Atenolol ± thiazide
(No. of events = 799)

Amlodipine ± perindopril
(No. of events = 567)

HR = 0.70 (0.63-0.78)
p < 0.0001

<table>
<thead>
<tr>
<th>Years</th>
<th>0.0</th>
<th>1.0</th>
<th>2.0</th>
<th>3.0</th>
<th>4.0</th>
<th>5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>0.0</td>
<td>2.0</td>
<td>4.0</td>
<td>6.0</td>
<td>8.0</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Number at risk
Amlodipine ± perindopril 9639 9383 9165 8966 8726 7618
Atenolol ± thiazide 9618 9295 9014 8735 8455 7319
New British Guidelines (National Institute for Clinical Excellence)

• First Drug $\geq 55$ years or Black CCB or thiazide
  $< 55$ years ACE-I or ARB
• Second Drug Add ACE-I/ARB, CCB/ thiazide
• Third Drug Add combo of ACE-I/ARB, CCB, and thiazide
• Fourth Drug Beta blocker, Alpha blocker, Higher dose thiazide or other
Vasodilating Beta Blockers

- Carvedilol
- Nebivolol – releases nitric oxide
International Verapamil-Trandolapril Study (INVEST)

• Prospective, Randomized, Open, Blinded End-Point Evaluation (PROBE) trial comparing verapamil- vs. atenolol-based treatment strategies

• Designed to determine if one treatment strategy was equivalent to the other in reducing all-cause mortality, nonfatal myocardial infarction, or stroke

• Men and women (n=22,576) ≥ 50 years of age with hypertension and coronary artery disease

International Verapamil-Trandolapril Study (INVEST)

- Calcium antagonist strategy (CAS) using verapamil-SR
- Non-calcium antagonist strategy (NCAS) using atenolol
- Addition of trandolapril to the regimen of patients with concomitant diabetes, renal failure, or heart failure was recommended
- Additional antihypertensive therapy was allowed to achieve and maintain goal blood pressure

INVEST: Mean Systolic and Diastolic Blood Pressure

Calcium Antagonist Strategy (CAS)  Non-Calcium Antagonist Strategy (NCAS)

## INVEST: Primary Composite Endpoint by Treatment Group

### No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>NCAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>11267</td>
<td>11309</td>
</tr>
<tr>
<td>6</td>
<td>10921</td>
<td>10991</td>
</tr>
<tr>
<td>12</td>
<td>10716</td>
<td>10512</td>
</tr>
<tr>
<td>18</td>
<td>10512</td>
<td>10785</td>
</tr>
<tr>
<td>24</td>
<td>10008</td>
<td>10048</td>
</tr>
<tr>
<td>30</td>
<td>6612</td>
<td>6604</td>
</tr>
<tr>
<td>36</td>
<td>3738</td>
<td>3706</td>
</tr>
<tr>
<td>42</td>
<td>1568</td>
<td>1563</td>
</tr>
<tr>
<td>48</td>
<td>974</td>
<td>960</td>
</tr>
<tr>
<td>54</td>
<td>393</td>
<td>390</td>
</tr>
<tr>
<td>60</td>
<td>35</td>
<td>33</td>
</tr>
</tbody>
</table>

### Time, mo

- **Calcium Antagonist Strategy (CAS)**
- **Non-Calcium Antagonist Strategy (NCAS)**

### Cumulative %

**RR = 0.98 (0.90 – 1.06)**

Log-Rank $P = .57$

---

**Pepine CJ, et al. JAMA. 2003;290:2805-2816.**

With permission from the American Medical Association.
**INVEST: Relative Risk of Primary and Secondary Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
<th>Favors CAS</th>
<th>Favors NCAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>First event*</td>
<td>0.98 (0.90 – 1.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.98 (0.90 – 1.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.99 (0.79 – 1.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.89 (0.70 – 1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1.00 (0.88 – 1.14)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CAS = Calcium Antagonist Strategy  
NCAS = Non-Calcium Antagonist Strategy  
RR (95% CI) 

* Primary Outcome = first occurrence of death, nonfatal MI, or nonfatal stroke

With permission from the American Medical Association.
INVEST: New Onset of Diabetes During Study

RR = 0.85 (0.77 – 0.95)

J Curve – DBP and MI

Ann Intern Med 2006;144:884-893
No J Curve with DBP and Stroke

Ann Intern Med 2006;144:884-893
The Dual Significance of Proteinuria

• Proteinuria (albuminuria) results from injury to glomerular circulation
  ➢ Increased proteinuria (albuminuria) is associated with progressive kidney disease

• In diabetes and hypertension, proteinuria (albuminuria) is also an indicator of injury in the systemic circulation
  ➢ Proteinuria (albuminuria) is associated with increased cardiovascular risk
Renal Disease and Hypertension
Core Concepts of Treatment

- Hypertension and proteinuria (albuminuria) are both independent variables that predict long-term decline in renal function
  - Renal disease is both a cause and consequence of hypertension
  - Reduction of blood pressure reduces cardiovascular risk and renal risk
  - Reduction of proteinuria (albuminuria) may lower both cardiovascular risk and renal risk
Meta Analysis: Lower Systolic BP Results in Slower Rates of Decline in GFR in Diabetics and Non-Diabetics

<table>
<thead>
<tr>
<th>Trial</th>
<th>Conventional care</th>
<th>Intensive care</th>
<th>Risk reduction</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>154/87</td>
<td>144/82</td>
<td>32%</td>
<td>0.019</td>
</tr>
<tr>
<td>HOT</td>
<td>144/85</td>
<td>140/81</td>
<td>66%</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Mortality endpoints are:
UK Prospective Diabetes Study (UKPDS) – “diabetes related deaths”
Hypertension Optimal Treatment (HOT) Study – “cardiovascular deaths” in diabetics

Tight Glucose vs Tight BP Control and CV Outcomes in UKPDS

- **Stroke**
  - Tight Glucose Control: 44%
  - Tight BP Control: 24%
  - *P <0.05 compared to tight glucose control

- **Any Diabetic Endpoint**
  - Tight Glucose Control: 5%
  - Tight BP Control: 12%

- **DM Deaths**
  - Tight Glucose Control: 10%
  - Tight BP Control: 32%

- **Microvascular Complications**
  - Tight Glucose Control: 32%
  - Tight BP Control: 37%

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<table>
<thead>
<tr>
<th>Quantitation</th>
<th>Total adults (in millions)</th>
<th>% of adults in US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased urine ratio albumin/creatinine (&gt;30 mg/gm)</td>
<td>20.2</td>
<td>11.7</td>
</tr>
<tr>
<td>Proteinuria (&gt;300mg/24h)</td>
<td>18.3</td>
<td>10.6</td>
</tr>
<tr>
<td>Microalbuminuria (30-300 mg/24h)</td>
<td>1.9</td>
<td>1.1</td>
</tr>
</tbody>
</table>

ACE-I Is More Renoprotective Than Conventional Therapy in Type 1 Diabetes

Baseline creatinine ≥1.5 mg/dL

% with doubling of baseline creatinine

Placebo n=202

Captopril n=207

P<.001

Years of follow-up

Impact of ACE-I on BP and GFR: Acute and Chronic Effects

*P<0.05 compared to baseline

©American Medical Association
The AASK trial enrolled 1,094 African American patients with renal disease at 21 US centers, and randomized them to receive one of 3 study drugs:

- Ramipril – ACEI or
- Amlodipine – CCB or
- Metoprolol – Beta-blocker

Results

- After adjustments for covariates, the risk reduction for ramipril vs amlodipine groups in the clinical composite outcomes (GFR, dialysis, or death) was 38% (p=0.005)

ARB (Losartan) Reduces Urinary Albumin and TGF-β1 in Type 2 Diabetes


- **24-hour Systolic BP**
  - Baseline: 160 mmHg
  - 4 Weeks: 140 mmHg
  - 8 Weeks: 130 mmHg
  - *P* < 0.01 vs baseline

- **24-hour Diastolic BP**
  - Baseline: 90 mmHg
  - 4 Weeks: 70 mmHg
  - 8 Weeks: 60 mmHg
  - *P* < 0.03 vs baseline

- **Urinary Albumin Excretion**
  - Baseline: 100 mcg/min
  - 4 Weeks: 90 mcg/min
  - 8 Weeks: 80 mcg/min
  - *P* < 0.01 vs baseline

- **TGF-β1**
  - Baseline: 5 ng/mL
  - 4 Weeks: 3 ng/mL
  - 8 Weeks: 2 ng/mL
  - *P* < 0.005 vs baseline
Reduction of Endpoints in NIDDM
With the Angiotensin II
Antagonist Losartan Study

Randomized multi-site, double-blind, placebo-controlled study to evaluate the renal protective effects of the angiotensin II receptor antagonist losartan in patients with type 2 diabetes and nephropathy

- 1,513 patients (31 to 70 years old)
  - Diagnosed type 2 diabetes and nephropathy
    - albumin/creatinine ratio ≥300 mg/g
    - serum creatinine between 1.3–3.0 mg/dL (1.5–3.0 mg/dL for men >60 kg)


www.hypertensiononline.org
RENAAL Study Design

- Open-label diuretic, calcium channel blocker, beta-blocker, alpha-blocker, or centrally acting agent
- In combination with open-label diuretic, calcium channel blocker, beta-blocker, alpha-blocker, and/or centrally acting agent

**Losartan 100 mg qd**

- Trough Blood Pressure Goal <140/<90 mmHg

**Placebo**

- n=1,513

**6 week screening phase**

Week 10

Week 14

Average follow-up 3.4 years

- Maintain antihypertensive therapy†
- (excluding ACE inhibitors & angiotensin II receptor antagonists)

†Open-label diuretic, calcium channel blocker, beta-blocker, alpha-blocker, or centrally acting agent
‡In combination with open-label diuretic, calcium channel blocker, beta-blocker, alpha-blocker, and/or centrally acting agent


www.hypertensiononline.org
## RENAAL Impact of Losartan

<table>
<thead>
<tr>
<th></th>
<th>Losartan‡ Group n=751</th>
<th>Placebo‡ Group n=762</th>
<th>P value</th>
<th>% Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n</td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td><strong>Primary composite endpoint</strong>*</td>
<td>327 43.5</td>
<td>359 47.1</td>
<td>0.02</td>
<td>16 (2 to 28)</td>
</tr>
<tr>
<td>• Doubling of creatinine</td>
<td>162 21.6</td>
<td>198 26.0</td>
<td>0.006</td>
<td>25 (8 to 39)</td>
</tr>
<tr>
<td>• <strong>ESRD</strong></td>
<td>147 19.6</td>
<td>194 25.5</td>
<td>0.002</td>
<td>28 (11 to 42)</td>
</tr>
<tr>
<td>• Death</td>
<td>158 21.0</td>
<td>155 20.3</td>
<td>0.88</td>
<td>-2 (-27 to 19)</td>
</tr>
<tr>
<td>• ESRD or Death</td>
<td>255 34.0</td>
<td>300 39.4</td>
<td>0.01</td>
<td>20 (5 to 32)</td>
</tr>
<tr>
<td>• Doubling of Creatinine/ESRD</td>
<td>226 30.1</td>
<td>263 34.5</td>
<td>0.01</td>
<td>21 (5 to 34)</td>
</tr>
</tbody>
</table>

IDNT: Primary End Point

Composite of:

• Time to occurrence of doubling of baseline serum creatinine

• End-stage renal disease (dialysis, renal transplant, or serum creatinine $\geq 6$ mg/dL)

• Death (all-cause mortality)

IDNT = Irbesartan Diabetic Nephropathy Trial.
IDNT Primary Composite End Point: Time to Doubling of Serum Creatinine, ESRD, or Death

- Irbesartan
- Amlodipine
- Control

<table>
<thead>
<tr>
<th>Follow-Up (Months)</th>
<th>Irbesartan</th>
<th>Amlodipine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>6</td>
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<tr>
<td>12</td>
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<td>18</td>
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<tr>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

No. at Risk
- Irbesartan: 579
- Amlodipine: 565
- Control: 568

20% RRR Irbesartan vs Control, \( P = .02 \)
23% RRR Irbesartan vs Amlodipine, \( P = .006 \)

Control defined as placebo plus permitted adjunctive antihypertensive therapy.

In patients with proteinuria ≥900 mg/day, monitor serum potassium.

Primary composite end point: Time to occurrence of doubling of baseline serum creatinine, end-stage renal disease (serum creatinine ≥6 mg/dL, dialysis, or renal transplantation), or all-cause death. Patients reaching primary end point: 32.6% (189/579) in the irbesartan group; 41.1% (233/567) in the amlodipine group; 39.0% (222/569) in the control group.

Reduction in Proteinuria
With ARB + ACEI Therapy
After 6 Weeks of Therapy

Mean reductions in cuff blood pressure (BP): fosinopril -9/-7 mm Hg, irbesartan -10/-7 mm Hg, irbesartan + fosinopril -15/-8 mm Hg. No significant differences between groups in ambulatory BP monitoring. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker.
Addition of ARB to Maximum Recommended Dose of ACEI

After 8 Weeks of Therapy

25% Reduction
(P<.001)

Albuminuria (mg/24 hr)

Placebo
+ Enalapril 40 mg/d

Irbesartan 300 mg/d
+ Enalapril 40 mg/d

Mean reductions in 24-hour blood pressure: irbesartan + enalapril (-8/-4 mm Hg) over placebo + enalapril, (P=.002 and P=.003, respectively, for SBP and DBP). ACEI = angiotensin-converting enzyme inhibitor. Jacobsen P et al. Kidney Int. 2003;63:1874-1880.
COOPERATE

336 patients screened

263 randomly allocated

89 losartan and placebo
89 trandolapril and placebo
88 losartan and trandolapril

86 analyzed for primary endpoint
85 analyzed for primary endpoint
85 analyzed for primary endpoint
Regression of Left Ventricular Hypertrophy

A Meta-Analysis of 80 Studies Involving 3767 Patients With Equivalent Blood Pressure Lowering

% Reduction in Left Ventricular Mass Index

- Beta-Blockers: -6
- Diuretics: -8
- CCBs: -11
- ACE-Is: -10
- ARBs: -13

CCBs = calcium-channel blockers; ACE-Is = ACE inhibitors.
*P < 0.05 vs beta-blockers.
Hospital Discharges for CHF by Gender (United States: 1970-2001)

Note: Hospital discharges include people both living and dead.
• 1668 patients with stage 2 hypertension in 384 US sites
• Randomized to valsartan or valsartan/HCTZ
• Patients treated with valsartan had significantly reduced levels of CRP as compared to those treated with the combination
Progression From Hypertension to Heart Failure

Hypertension

Risk Factors
- Obesity
- Diabetes
- Smoking
- Dyslipidemia

LVH

MI

Diastolic dysfunction

Systolic dysfunction

HF → Death

Left ventricular remodeling

Subclinical left ventricular dysfunction

Overt heart failure

Time (decades)

Time (months)

MI = myocardial infarction.
## Classification of Heart Failure: ACC/AHA Stage vs NYHA Class

<table>
<thead>
<tr>
<th>ACC/AHA Heart Failure Stage</th>
<th>NYHA Functional Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. At risk for heart failure but without structural heart disease or symptoms</td>
<td>None</td>
</tr>
<tr>
<td>B. Structural heart disease but without heart failure</td>
<td>I. Asymptomatic</td>
</tr>
<tr>
<td>C. Structural heart disease with prior or current heart failure symptoms</td>
<td>II. Symptomatic with moderate exertion</td>
</tr>
<tr>
<td></td>
<td>III. Symptomatic with minimal exertion</td>
</tr>
<tr>
<td>D. Refractory heart failure requiring specialized interventions</td>
<td>IV. Symptomatic at rest</td>
</tr>
</tbody>
</table>

ACC/AHA 2005 CHF Guidelines

- ACE-I: captopril, enalapril, fosinopril, lisinopril, quinapril, ramipril, trandolapril
- ARB: candesartan, valsartan
- Beta-blocker: bisoprolol, carvedilol, metoprolol (propranolol, timolol - MI)
- Aldosterone blocker: eplerenone (MI), spironolactone (HF)
- Digoxin
Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors

• Retrospective analysis of 29,507 infants with Tennessee Medicaid born between 1985 and 2000

• 209 infants exposed to ACE inhibitors in the first trimester were compared to 202 infants exposed to other antihypertensive medications

NEJM 2006;354:2443-51
Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors

• Infants with first trimester exposure to ACE inhibitors had an increased risk of major congenital malformations of 2.71

• The increased risk of cardiovascular malformation was 3.72 and central nervous system abnormalities was 4.39

NEJM 2006;354:2443-51
A simple view of the circulating renin-angiotensin system. (b) A more accurate view of the renin-angiotensin system based on the latest information. Ang, angiotensin; NEP, neutral endopeptidase; PEP, prolyl endopeptidase; ACE, angiotensin-converting enzyme; AT1 and AT2, angiotensin II type 1 and type 2 receptors; AP A, N, M, B, aminopeptidases A, N, M, and B; IRAP, insulin-regulated aminopeptidase. Catalytic steps are denoted by arrows and the enzyme catalysts are shown in shaded boxes. Receptors (or binding proteins) are shown in gray boxes.
Angiotensinogen
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Glu-Ser

- t-PA
- Cathepsin G
- Tomin

Renin

Angiotensin I
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu

- CAGE
- Cathepsin G
- Chymase

Angiotensin Converting Enzyme

Angiotensin II
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe

AT₁ Receptor

Renin Inhibitors
ACE Inhibitors
All Antagonists
Renin Inhibition - Aliskerin

SPP 100 (Aliskiren)
Direct Renin Inhibition Suppresses Entire Renin Angiotensin System

DRI, direct renin inhibitor; AT₁, Receptor, angiotensin I receptor; ARB, angiotensin receptor blocker; Ang, angiotensin; ACEI, angiotensin-converting enzyme inhibitor; ACE, angiotensin-converting enzyme.
Direct Renin Inhibition

- Targets the point of activation in the RAS

- Binds to renin, neutralizing its ability to convert angiotensinogen to Ang I

- Reduces plasma renin activity
  - PRA is a marker for RAS activity/stimulation
  - Elevated levels of prorenin have been shown with direct renin inhibition; potential physiological effects are being investigated in animal studies

- Decreases formation of Ang I and Ang II
  - Ang I unavailable for ACE and non-ACE conversion to Ang II
  - Ang II unavailable to stimulate AT receptors
  - Ang II unavailable for conversion to Ang subtypes [eg, Ang (2-8), also called Ang III]
**Only Direct Renin Inhibition Inhibits the Entire Renin Angiotensin System**

<table>
<thead>
<tr>
<th>Class</th>
<th>PRA</th>
<th>Ang I</th>
<th>Ang II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct Renin Inhibitor (DRI)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increased peptide levels have not been shown to overcome the blood pressure-lowering effect of these agents.

PRA, plasma renin activity; Ang, angiotensin; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Aliskerin
Reductions in Aldosterone
Aliskerin

- Binds and inactivates renin and Raises renin levels but reduces renin activity
- Reduces angiotensin I, angiotensin II, and aldosterone levels
- Long half-life of 40 hours
- Uniform BP response in entire 24 hour period without am rise in BP
- Trough/Peak ratio 0.98 for 300 mg dose
- Low side effects, no drug interactions
- Reduces ACE induced cough
- No rebound with withdrawal
Hypertension Summary

- BP goal 140/90 or less, or less than 130/80 in high risk patients
- Use initial combination of diuretic, CCB, and/or ACE-I/ARB
- Consider third generation beta blocker for selected patients