New Drugs

Direct Renin Inhibitors

Endothelin Antagonists
DRI Works at the Point of Activation of the RAAS

Inhibits renin at the point of activation

**ARB Feedback Loop**
Results in increased PRC, PRA, Ang I, and Ang II

**ACEI Feedback Loop**
- Results in increased PRC, PRA, and Ang I
- Decreases Ang II

**Direct renin inhibitor**
- Binds directly to renin
- Inhibits the conversion of angiotensinogen to Ang I
- Increases PRC
- Reduces production of Ang I, Ang II, and PRA

The clinical implications of the changes in PRA are not known, were not dose-related, and did not correlate with reductions in blood pressure. Whether aliskiren affects other RAAS components, eg, ACE or non-ACE pathways, is not known. PRC = plasma renin concentration.

Aliskiren Reduced PRA Alone and in Combination With Ramipril*

The primary endpoint was reduction in msDBP.

*The clinical implications of the different effects of aliskiren, ramipril, or the combination of both on PRA were not known, were not dose related, and did not correlate with blood pressure reduction.

†Data are shown as percentage change in geometric mean PRA (95% confidence interval) for the intent-to-treat population.

**Aliskiren Maintained 80% SBP Reduction 4 Days After Last Dose**

**SBP (at 8 weeks)**
- Placebo: n=163
- Aliskiren 300 mg QD: n=166

Mean baseline BP: 152/99 mm Hg
Aliskiren is dosed once daily.

In this double-blind trial, 672 hypertensive patients with msDBP $\geq$95 mm Hg and <110 mm Hg were randomized to aliskiren 300 mg QD or placebo. The primary end point of this study was msDBP at 8 weeks. After 8 weeks, all study medications were discontinued. BP was measured 4 days later. Two weeks after last dose, msSBP/msDBP reductions were 5/5 mm Hg with placebo, 8/7 mm Hg with aliskiren 150 mg QD, and 7/7 mm Hg with aliskiren 300 mg QD. Results rounded to the nearest whole numbers. Data are from a clinical trial that measured rebound hypertension.

Why Use a DRI? Aliskiren and Aliskiren + HCTZ Have an Established Safety and Tolerability Profile

Discontinuation Rates Due to Adverse Events

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent of Patients</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>3.5%</td>
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<tr>
<td>Aliskiren</td>
<td>2.2%</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.6%</td>
</tr>
<tr>
<td>Aliskiren/HCTZ</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

Important Considerations: Adverse events observed in patients taking Tekturna at an incidence greater than placebo included: diarrhea, cough, rash, elevated uric acid, gout, and renal stones. Adverse events observed more often in patients taking Tekturna HCT than placebo included: dizziness, influenza, diarrhea, cough, vertigo, asthenia, and arthralgia.

Endothelin Antagonists

• Endothelin (ET) antagonists such as bosentan have been used successfully to treat pulmonary hypertension.
• Trials with multiple ET antagonists are under way in hypertension and CHF.
• The selective ET A antagonist, darusentan, may be approved by the FDA in 2009.
New Goals

- Uncomplicated Hypertension
- Diabetes
- Renal Disease
- Diabetes + Renal Disease
- Coronary Disease
### How Low Should Blood Pressure Be Lowered?

#### JNC 7\(^1\): Blood Pressure Goals

<table>
<thead>
<tr>
<th>Condition</th>
<th>BP Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated HTN</td>
<td>&lt;140/90 mm Hg</td>
</tr>
<tr>
<td>HTN + Diabetes</td>
<td>&lt;130/80 mm Hg</td>
</tr>
<tr>
<td>HTN + Chronic Renal Disease</td>
<td>&lt;130/80 mm Hg</td>
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</table>

#### AHA\(^2\): Blood Pressure Goals

<table>
<thead>
<tr>
<th>Condition</th>
<th>Target</th>
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</thead>
<tbody>
<tr>
<td>Uncomplicated HTN</td>
<td>&lt;140/90 mm Hg</td>
</tr>
<tr>
<td>HTN + high risk of CAD(^*)</td>
<td>&lt;130/80 mm Hg</td>
</tr>
<tr>
<td>HTN + angina</td>
<td>&lt;130/80 mm Hg</td>
</tr>
</tbody>
</table>

*Diabetes mellitus, chronic kidney disease, known CAD or CAD equivalent, or 10-year Framingham risk score ≥10%.

JNC = Joint National Committee; HTN = hypertension; AHA = American Heart Association; CAD = coronary artery disease.

New Approaches

• Emphasis on Cost:Benefit
• Emphasis on Systolic Blood Pressure
• Combination Therapy
• Emphasis on Endpoints
Emphasis on Cost:Benefit

- Many generic antihypertensive agents are now available for as little as $10/90 days.
- A 4 drug antihypertensive regimen utilizing diuretics, Beta blockers, ACE-Is and CCBs can be used at a cost of $162.22/year or $0.44/day
Prevalence of Hypertension Increases With Age

Prevalence of Hypertension Among U.S. Adults, 1999–2000 (NHANES*)

*National Health and Nutrition Examination Survey.
Isolated Systolic Hypertension Accounts for Most Uncontrolled HTN in the Elderly

Americans With Uncontrolled Hypertension, by Age and Hypertension Subtype

- ISH (SBP ≥140/DBP <90 mmHg)
- SDH (SBP ≥140/DBP ≥90 mmHg)
- IDH (SBP <140/DBP ≥90 mmHg)

HTN=hypertension; ISH=isolated systolic hypertension; SDH=combined systolic/diastolic hypertension; IDH=isolated diastolic hypertension; SBP=systolic blood pressure; DBP=diastolic blood pressure.

Relative Importance of DBP and SBP as Predictors of CHD as a Function of Age

*Difference in proportional hazards regression coefficients as indicator of CHD risk
DBP = diastolic blood pressure; SBP = systolic blood pressure; CHD = coronary heart disease

Adapted from Franklin SS et al. *Circulation.* 2001;103:1245-1249.
## Systolic vs Diastolic BP as Predictors of Outcomes in ASCOT-BPLA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR/1 SD</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td><strong>MI + CHD Death + Revascularization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• SBP</td>
<td>1.16</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>• DBP</td>
<td>0.94</td>
<td>.03</td>
</tr>
<tr>
<td>• PP</td>
<td>1.23</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Fatal + Nonfatal Stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• SBP</td>
<td>1.38</td>
<td>&lt;.0001</td>
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<tr>
<td>• DBP</td>
<td>0.99</td>
<td>.75</td>
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<tr>
<td>• PP</td>
<td>1.45</td>
<td>&lt;.0001</td>
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</table>
Combination Antihypertensive Therapy
Evolution and Rationale
Historical Evolution of Fixed-Dose Combination Agents

1960s
- Reserpine-hydralazine-hydrochlorothiazide (Ser-Ap-EsR)
- Methyldopa/thiazide diuretic

1970s
- Thiazide/potassium-sparing diuretic
- Thiazide/spironolactone
- β-Blocker/thiazide diuretic
- Clonidine/thiazide diuretic

1980s
- Angiotensin-converting enzyme inhibitor/thiazide diuretic

1990s
- Low-dose β-blocker/low-dose thiazide diuretic
- Angiotensin-converting enzyme inhibitor/calcium antagonist
- Angiotensin II receptor blocker/thiazide diuretic

BP Control Usually Requires Combination Therapy

Most patients require on average ≥2 antihypertensives to reach BP goal

BP=blood pressure; SBP=systolic blood pressure.

JNC VII

- “The initiation of therapy with more than one drug increases the likelihood of achieving BP goal in a more timely fashion.”
- “The use of fixed-dose combinations may be more convenient and simplify the treatment regimen, and may cost less than the individual components prescribed separately.”
“The use of multidrug combinations often produces greater BP reduction at lower doses of the component agents, resulting in fewer side effects.”

“However, caution is advised in initiating therapy with multiple agents, particularly in some older persons and in those at risk for orthostatic hypotension, such as diabetics with autonomic dysfunction.”
Combination Antihypertensive Therapy: Potential Reductions in Dose-Related Side Effects

- **Thiazide diuretics with potassium-sparing diuretics**
  - May reduce K+ loss and decrease the risk of hypokalemia

- **Thiazide diuretics with ARBs or ACE inhibitors**
  - May reduce risk of hypokalemia

- **ACE inhibitors and dihydropyridine CCBs**
  - Combinations may have less edema than seen with dihydropyridines alone

- **Beta-adrenoreceptor-blockers and direct vasodilators or dihydropyridine CCBs**
  - Beta-blockers reduce tachycardia seen with these agents

## Guideline Recommendations Regarding Initial Use of Combination Therapy

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td><strong>JNC 7</strong></td>
<td>&gt;20/10 mm Hg</td>
</tr>
<tr>
<td><strong>ISHIB</strong></td>
<td>&gt;15/10 mm Hg</td>
</tr>
<tr>
<td><strong>ESH</strong></td>
<td>&gt;20/10 mm Hg OR high cardiovascular risk</td>
</tr>
<tr>
<td><strong>AHA</strong></td>
<td>SBP &gt;=160 mm Hg or DBP &gt;=100 mm Hg irrespective of the BP goals</td>
</tr>
<tr>
<td><strong>NKF K/DOQI</strong></td>
<td>SBP &gt;20 mm Hg above goal according to the stage of CKD and CVD risk</td>
</tr>
</tbody>
</table>

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**Links**

- JNC 7=Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
- ISHIB=International Society on Hypertension in Blacks
- ESH=European Society of Hypertension
- AHA=American Heart Association
- NKF K/DOQI=National Kidney Foundation Kidney Disease Outcomes Quality Initiative

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Patients switched to separate pill therapy had lesser persistence compared with patients who remained on SPC regimens over 12 month follow-up period. 

*Persistency was measured by the percent of patients remaining on therapy without a lapse of >30 days from the date of end of supply of the prior medication during the 12 months after the index date.

†Single-pill combination: Referred to as fixed-dose combination in data on file.

‡Separate pill therapy: Referred to as free combination in data on file.

As a retrospective analysis of administrative claims data, patients were not randomly assigned and could not be matched by any empirical methods. Although we know that prescriptions were filled based on these claims data, it is unknown if patients specifically took the medication as prescribed. Levels of disease severity as defined by clinical measurements were not available within the design of the study. There may exist other factors that might have influenced selection or use of antihypertensive agents that could not be captured or assessed in the study.

Single Pill Combination Therapy Demonstrates Improved Compliance in Hypertensive Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor et al</td>
<td>0.74 (0.67, 0.81)</td>
<td>27.1</td>
</tr>
<tr>
<td>Dezii</td>
<td>0.74 (0.65, 0.84)</td>
<td>13.9</td>
</tr>
<tr>
<td>NDC dataset</td>
<td>0.81 (0.77, 0.86)</td>
<td>46.4</td>
</tr>
<tr>
<td>Dezii</td>
<td>0.71 (0.62, 0.80)</td>
<td>12.6</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>0.77 (0.73, 0.80)</td>
<td>P&lt;.0001</td>
</tr>
</tbody>
</table>

Favors FDC Agent
Favors Individual Agents Given Separately

Retrospective Study
FDC – fixed dose combination
Potential Benefits of Single-Pill Combinations

✓ GREATER CONVENIENCE
Less pill burden for patients vs taking two pills separately

✓ GREATER COMPLIANCE & PERSISTENCY
May allow for greater persistency as compared with separate pill therapy

✓ FEWER STEPS
In appropriate patients, beginning treatment with SPCs* can help reduce added steps of titrations, add-ons, switches that delay achievement of BP goal

✓ ONE CO-PAY

*SPC=Single-pill combination


Please see accompanying full Prescribing Information.
Emphasis on Endpoints

• New Lessons from Clinical Trials
• Does which drugs we use matter?
  – In moderate risk patients?
  – In high risk patients?
  – In very high risk patients?
ALLHAT

• Does the First Drug Matter?
  – Moderate Risk
  – Diuretic vs ACE-I vs CCB
ALLHAT

• Design: Double-blind, randomized, prospective
• Patients: 42,418, mean age 67, with HTN +1 other risk factor, controlled on no more than 2 drugs, partially treated BP 156/89
• Intervention: Chlorthalidone 12.5-25 mg vs amlodipine 2.5-5 mg vs lisinopril 10-40 mg vs doxazosin 1-8 mg
• Primary Endpoint: MI or CHD death
ALLHAT Mean Systolic and Diastolic Blood Pressure During Follow-up

Compared to chlorthalidone:
- SBP significantly higher in amlodipine (~1 mmHg) and lisinopril (~2 mmHg) groups.
- DBP significantly lower in amlodipine group (~1 mmHg).

SBP = systolic blood pressure
DBP = diastolic blood pressure

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ALLHAT Primary Outcome by Treatment Group

Cumulative Fatal CHD and Nonfatal MI event rate (%)

- Chlorthalidone
- Amlodipine
- Lisinopril

Time to event, yrs

No. at Risk
Chlorthalidone  15255  14477  13820  13102  11362  6340  2956  209
Amlodipine  9048  8576  8218  7843  6824  3870  1878  215
Lisinopril  9054  8535  8123  7711  6662  3832  1770  195

Copyright ©2002, American Medical Association.
ALLHAT Conclusions

- The doxazosin arm was stopped early for higher CHF rates.
- The Primary Combined Endpoint of MI + CHD Death was not different with chlorthalidone, amlodipine or lisinopril.
- BP was lower in the chlorthalidone group as were CVA, angina and revascularization.
- The long term significance of more new onset diabetes in the chlorthalidone group is unclear.
OnTarget

- **Design:** Double-blind, randomized, prospective
- **Patients:** 25,620 with vascular disease or DM with TOD, treated BP at baseline 142/82
- **Intervention:** ramipril 10 mg vs telmisartan 80 mg vs the combination
- **Primary Endpoint:** MI, CVA, CV death or CHF hospitalization
Kaplan-Meier Curves for the Primary Outcome in the Three Study Groups

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Telmisartan</th>
<th>Ramipril</th>
<th>Telmisartan plus ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Years of Follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telmisartan</td>
<td>8542</td>
<td>8177</td>
<td>7778</td>
</tr>
<tr>
<td>Ramipril</td>
<td>8576</td>
<td>8214</td>
<td>7832</td>
</tr>
<tr>
<td>Telmisartan plus ramipril</td>
<td>8502</td>
<td>8133</td>
<td>7738</td>
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</tbody>
</table>
## Relative Risks in Prespecified Subgroups

### Table A

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Incidence of Primary Outcome in Ramipril Group (%)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite</td>
<td>17,118</td>
<td>16.5</td>
<td></td>
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<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>15,627</td>
<td>16.8</td>
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<tr>
<td>No</td>
<td>1,486</td>
<td>13.1</td>
<td></td>
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<tr>
<td>Systolic blood pressure</td>
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<tr>
<td>≤134 mm Hg</td>
<td>5,704</td>
<td>16.2</td>
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<tr>
<td>&gt;134 to ≤150 mm Hg</td>
<td>6,042</td>
<td>14.9</td>
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<tr>
<td>&gt;150 mm Hg</td>
<td>5,352</td>
<td>18.4</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Yes</td>
<td>6,391</td>
<td>20.7</td>
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<td>No</td>
<td>10,722</td>
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<td>≤3.677</td>
<td>5,751</td>
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<tr>
<td>&gt;3.677 to ≤4.090</td>
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<td>&gt;4.090</td>
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<td>Age</td>
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<td>&lt;65 yr</td>
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<td>≥65 to &lt;75 yr</td>
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<td>≥75 yr</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
<td>12,337</td>
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<tr>
<td>Female</td>
<td>4,581</td>
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</table>

### Table B

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Incidence of Primary Outcome in Ramipril Group (%)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite</td>
<td>17,078</td>
<td>16.5</td>
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<tr>
<td>Cardiovascular disease</td>
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<td>Yes</td>
<td>15,589</td>
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<td>&gt;150 mm Hg</td>
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<td>Sex</td>
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<tr>
<td>Male</td>
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<td>Female</td>
<td>4,581</td>
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## Discontinuation of Study Medications and Selected Reasons for Permanent Discontinuation

### Table 2. Discontinuation of Study Medications and Selected Reasons for Permanent Discontinuation.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ramipril (N=8576)</th>
<th>Telmisartan (N=8542)</th>
<th>Combination Therapy (N=8502)</th>
<th>Telmisartan vs. Ramipril</th>
<th>Combination Therapy vs. Ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td></td>
<td></td>
<td>Relative Risk</td>
<td>P Value</td>
</tr>
<tr>
<td>Total no. of discontinuations†</td>
<td>2099 (24.5)</td>
<td>1962 (23.0)</td>
<td>2495 (29.3)</td>
<td>0.94</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypotensive symptoms</td>
<td>149 (1.7)</td>
<td>229 (2.7)</td>
<td>406 (4.8)</td>
<td>1.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Syncope</td>
<td>15 (0.2)</td>
<td>19 (0.2)</td>
<td>29 (0.3)</td>
<td>1.27</td>
<td>0.49</td>
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<tr>
<td>Cough</td>
<td>360 (4.2)</td>
<td>93 (1.1)</td>
<td>392 (4.6)</td>
<td>0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (0.1)</td>
<td>19 (0.2)</td>
<td>39 (0.5)</td>
<td>1.59</td>
<td>0.20</td>
</tr>
<tr>
<td>Angioedema</td>
<td>25 (0.3)</td>
<td>10 (0.1)</td>
<td>18 (0.2)</td>
<td>0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>60 (0.7)</td>
<td>68 (0.8)</td>
<td>94 (1.1)</td>
<td>1.14</td>
<td>0.46</td>
</tr>
</tbody>
</table>

* There were no predefined criteria for each of the adverse events listed. Reasons listed are those provided by the investigator for the discontinuation of study drug.

† A patient could have multiple discontinuations, since patients were encouraged to restart study medications whenever possible after discontinuation.
OnTarget Conclusions

• The Primary Composite Endpoint of MI, CVA, CV Death or CHF hospitalization did not differ between ramipril, telmisartan or the combination.

• Telmisartan was better tolerated than ramipril and both were better tolerated than the combination.

• For cardioprotection in patients with vascular disease or diabetes, telmisartan is equal to ramipril and the combination of ACEI and ARB has no advantage and is less well tolerated.
LIFE

- Design: Double-blind, randomized, prospective
- Patients: 9,193 with HTN and LVH, mean age 67, untreated BP at baseline 174/98
- Intervention: losartan 50-100 mg vs atenolol 50-100 mg
- Primary Endpoint: MI, CVA or death

www.hypertensiononline.org
**LIFE Study Primary Composite Endpoint**

**Intention-to-treat**

Adjusted risk reduction 13·0%, P=0·021
Unadjusted risk reduction 14·6%, P=0·009

**Study Month**

<table>
<thead>
<tr>
<th>Study Month</th>
<th>Losartan (n)</th>
<th>Atenolol (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4605</td>
<td>4588</td>
</tr>
<tr>
<td>6</td>
<td>4524</td>
<td>4494</td>
</tr>
<tr>
<td>12</td>
<td>4460</td>
<td>4414</td>
</tr>
<tr>
<td>18</td>
<td>4392</td>
<td>4349</td>
</tr>
<tr>
<td>24</td>
<td>4312</td>
<td>4289</td>
</tr>
<tr>
<td>30</td>
<td>4247</td>
<td>4205</td>
</tr>
<tr>
<td>36</td>
<td>4189</td>
<td>4135</td>
</tr>
<tr>
<td>42</td>
<td>4112</td>
<td>4066</td>
</tr>
<tr>
<td>48</td>
<td>4047</td>
<td>3992</td>
</tr>
<tr>
<td>54</td>
<td>3897</td>
<td>3821</td>
</tr>
<tr>
<td>60</td>
<td>1889</td>
<td>1854</td>
</tr>
<tr>
<td>66</td>
<td>901</td>
<td>876</td>
</tr>
</tbody>
</table>

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www.hypertensiononline.org
**LIFE Study Fatal and Non-Fatal Stroke**

Intention-to-treat

Adjusted risk reduction 24.9%, \( P=0.001 \)

Unadjusted risk reduction 25.8%, \( P=0.0006 \)


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www.hypertensiononline.org
LIFE Diabetes and ISH

- Does the First Drug Matter?
  - Very High Risk
  - ARB vs Beta Blocker
LIFE Study Diabetes Subgroup
Total Mortality

Adjusted risk reduction 38.7%,
P = 0.002
Unadjusted risk reduction 40.1%,
P = 0.001

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LIFE: Total Mortality
Diabetes Subgroup

Study Month

Proportion of patients (%)

0 6 12 18 24 30 36 42 48 54 60 66


Adjusted Risk Reduction 38.7%, p=0.002
Unadjusted Risk Reduction 40.1%, p=0.001

Atenolol

Losartan
LIFE Study ISH Subgroup
Total Mortality

Unadjusted relative risk reduction = 30%;
P = 0.03

Adjusted relative risk reduction = 28%;
P = 0.046

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LIFE Conclusions

• The Primary Combined Endpoint of MI, CVA or Death, but particularly CVA, were lower with losartan than with atenolol.

• In the Very High Risk, Diabetes and ISH subgroups, even Total Mortality was lower with losartan.

• In High Risk patients with hypertension, initial therapy with ARB is superior to Beta Blocker.
ASCOT-BPLA

• Do the First and Second Drug Matter?
  – High Risk
  – CCB + ACEI vs Beta Blocker + diuretic
ASCOT-BPLA

- Design: Double-blind, randomized, prospective
- Patients: 19,257, mean age 63, with HTN + 3 other risk factors, untreated BP 165/95
- Intervention: amlodipine 5-10 mg + perindopril 4-8 mg vs atenolol 50-100 mg + bendroflumethiazide 1.25-2.5 mg
- Primary Endpoint: MI (clinical or silent) or CHD death
ASCOT – BPLA

Primary Endpoint — Risk Reduction

Non-fatal MI, fatal CHD

Atenolol ± thiazide
(474 events)

Amlodipine ± perindopril
(429 events)

HR=0.90 (95% CI, 0.79–1.02)
P=0.1052

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

**ASCOT – BPLA**

*Secondary Endpoints*

---

**Unadjusted Hazard Ratio**

(95% CI)

---

**Endpoint (n – amlo vs aten)**

- Non-fatal MI* + fatal CHD (390 vs 444)
- Total coronary endpoint (753 vs 852)
- Total CV event and procedures (1362 vs 1602)
- All-cause mortality (738 vs 820)
- Cardiovascular mortality (263 vs 342)
- Fatal and non-fatal stroke (327 vs 422)
- Fatal and non-fatal heart failure (124 vs 159)

---

**P Value**

- $P = 0.0003$
- $P = 0.0070$
- $P < 0.0001$
- $P = 0.0247$
- $P = 0.0010$
- $P = 0.0003$
- $P = 0.1257$

---

The area of each square is proportional to the amount of statistical information.

*Excludes silent non-fatal MI.

ASCOT-BPLA Conclusions

- The Primary Combined Endpoint of MI or CHD Death and most secondary endpoints, including total mortality, were lower in the amlodipine-perindopril (CCB-ACEI) than in the atenolol-thiazide group.
- BP was lower in the CCB-ACEI group, but the Hazard Ratios for the Primary Endpoint and CVA were still significant when adjusted for BP.
- The CCB-ACEI regimen was superior to the Beta Blocker-Thiazide regimen.
ACCOMPLISH

• Does the Second Drug Matter?
  – High Risk
  – ACEI + CCB vs diuretic
ACCOMPLISH

- Design: Double-blind, randomized, prospective
- Patients: 11,506, mean age 68, with HTN and vascular disease or DM or LVH or CKD,
- Treated BP with a mean of 2 drugs 145/80
- Intervention: benazepril 20-40 mg + amlodipine 5-10 mg vs hydrochlorothiazide 12.5-25 mg
- Primary Endpoint: MI, CVA, CHF, coronary intervention, resuscitated SCD or CVD death
The mean SBP/DBP following titration was 131.6/73.3 mm Hg in the benazepril/amlodipine group and 132.5/74.4 mm Hg in the benazepril/HCTZ group. The mean difference in SBP/DBP between the 2 groups was 0.9/1.1 mmHg (p<0.001).

ACCOMPLISH

Primary Endpoint

- Time to first CV mortality/morbidity (days)

- Cumulative event rate

- HR 0.80 (95%CI 0.72–0.90); p<0.001

- Benazepril/amlodipine (552 patients with events: 9.6%)
- Benazepril/HCTZ (679 patients with events: 11.8%)

- Months 0 6 12 18 24 30 36 42
- Patients at risk (N)
- Benazepril/amlodipine 5,512 5,317 5,141 4,959 4,739 2,826 1,447
- Benazepril/HCTZ 5,483 5,274 5,082 4,892 4,655 2,749 1,390

**ACCOMPLISH**

*Components of the Primary Endpoint*

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite CV mortality/morbidity</td>
<td>0.80 (0.72–0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0.80 (0.62–1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>MI (fatal/non-fatal)</td>
<td>0.78 (0.62–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke (fatal/non-fatal)</td>
<td>0.84 (0.65–1.08)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hospitalisation for unstable angina</td>
<td>0.75 (0.50–1.10)</td>
<td>0.14</td>
</tr>
<tr>
<td>Coronary revascularisation procedure</td>
<td>0.86 (0.74–1.00)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Only the first event in an individual patient was counted in the analysis of the primary end point

## Subgroup analyses for the primary endpoint

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Benazepril/amlodipine N=5744</th>
<th>Benazepril/HCTZ N=5762</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>365 (10.6)</td>
<td>461 (13.1)</td>
<td>0.80 (0.69–0.91)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>187 (8.1)</td>
<td>218 (9.7)</td>
<td>0.83 (0.68–1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>386 (10.1)</td>
<td>474 (12.4)</td>
<td>0.81 (0.71–0.92)</td>
<td>0.002</td>
</tr>
<tr>
<td>≥70 years</td>
<td>260 (11.0)</td>
<td>323 (13.8)</td>
<td>0.79 (0.67–0.93)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>307 (8.8)</td>
<td>383 (11.0)</td>
<td>0.79 (0.68–0.92)</td>
<td>0.003</td>
</tr>
<tr>
<td>No</td>
<td>245 (10.8)</td>
<td>296 (12.9)</td>
<td>0.82 (0.69–0.97)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
ACCOMPLISH Conclusions

- In the total cohort, as well as the 6,946 patients with diabetes, the Primary Combined Endpoint (-20%), as well as MI (-20%) and coronary revascularization (-14%), were lower in the benazepril-amlodipine than in the benazepril-hydrochlorothiazide group.

- When added to initial therapy with ACEI, CCB is superior to thiazide diuretic.
Summary: New Drugs

- The first Direct Renin Inhibitor, aliskiren, is effective and very well tolerated.
- The place of Direct Renin Inhibition in the anti-hypertensive armamentarium is as yet undetermined.
- The first selective antagonist of the endothelin A receptor, darusentan, may be approved this year for treatment of hypertension.
- The place of Selective Endothelin Receptor Antagonism in the antihypertensive armamentarium is as yet undetermined.
Summary: New Goals

• The goal BP for patients with low risk, uncomplicated hypertension remains unchanged at <140/90.
• The goal BP for patients with Diabetes, CKD, Angina or high risk of CAD is <130/80.
• The goal BP for patients with Diabetes + CKD is <120/70.
• In 2010, JNC VIII may revise these goals.
Nearly all patients with hypertension can be treated for less than $0.45 per day.

“Thiazide-type diuretics are superior in preventing 1 or more major forms of CVD and are less expensive. They should be preferred for first-step antihypertensive therapy.” The ALLHAT authors. Adopted in JNC VII.

Based upon current costs and subsequent clinical trials, this conclusion is no longer valid.
• After age 55, Systolic BP is a strong predictor of CV events and Diastolic BP becomes a negative predictor.
• Initial treatment with combination therapy is reasonable and appropriate for patients with BP >20/10 mmHg above goal BP.
• Single Pill combination therapy has several advantages over Separate Pill therapy, especially better compliance.
Summary: Emphasis on Endpoints

• While BP reduction is of primary importance in treating hypertension, choice of agent is important in High Risk Patients.

• With different agents, at the same reduction in BP, there may be differences in MI, CVA, other CV endpoints, Total Mortality and new onset Diabetes.

• Multiple clinical trials support the superiority of ACE-Is, ARBs and CCBs over Beta Blockers and thiazide diuretics.