The Road to Renin System Optimization: Renin Inhibitor
A New Perspective on the Renin-Angiotensin System (RAS)

Yong-Jin Kim, MD
Seoul National University Hospital
Human and Economic Costs of Hypertension (HT)

- Single-most common cause of physician visits
- 1/3 of American adults have HT
- Major multiplicative factor for cardiovascular disease
- Total costs of HT: $64 billion annually

Hypertension: A Risk Factor for CV Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary disease</td>
<td>2.0</td>
<td>2.2</td>
<td>3.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>2.0</td>
<td>3.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>4.0</td>
<td>3.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk ratio: Biennial Age-Adjusted Rate per 1000 Patients

CV Mortality Risk Doubles With Each 20 and/or 10 mm Hg BP Increment*

*Individuals aged 40 to 69 years, starting at blood pressure 115/75 mm Hg
A Small Difference in BP Produces a Difference in Risk of CV Events

- Meta-analysis of 61 observational studies
- 1 million adults

For every 2 mm Hg decrease in mean SBP:
- 7% reduction in risk of CHD mortality
- 10% reduction in risk of stroke mortality

RAS Activation/ A II Formation in Regulating BP

Cascade Model of the RAS

- Angiotensinogen
- Renin
- ACE
- Non-ACE pathways (Chymase)
- A I
- A II
- AT$_1$
- AT$_2$

- Vasoconstriction
- Heart contractility

A I = angiotensin I; A II = angiotensin II; ACE = angiotensin-converting enzyme.
RAS Activation/ Angiotensin II Formation in Target Organ Damage

Angiotensin II

Heart | Brain | Kidney | Blood Vessel
Current Pharmacologic Interventions of the RAS

Angiotensinogen

\[ \text{Angiotensinogen} \rightarrow \text{A I} \rightarrow \text{A II} \rightarrow \text{ACE} \rightarrow \text{A II} \]

\[ \text{A II} \rightarrow \text{AT}_1 \rightarrow \text{AT}_2 \]

\[ \text{A II} \rightarrow \rightarrow \text{Renin} \]

\[ \text{ACE} \rightarrow \rightarrow \text{ACEIs} \]

\[ \text{A II} \rightarrow \rightarrow \text{ARBs} \]

\[ \text{A II} \rightarrow \rightarrow \text{Aldosterone blockers} \]

\[ \text{A II} \rightarrow \rightarrow \text{Aldosterone} \]
PROs: RAS Blockade
Via ACEIs or ARBs

ACEI and ARBs

- Highly effective
- Well tolerated
- Benefits in addition to lowering BP
  - Chronic kidney disease
  - Diabetes
  - Heart failure
  - Recurrent stroke prevention*
  - Post-MI

*Only ACEIs have an indication for recurrent stroke prevention.
Current RAS-Blocking Agents Interrupt the RAS Negative-Feedback Loop

Angiotensinogen → Renin → Ang I → Ang II

Plasma Renin Activity (PRA) decreases

Feedback Loop

ACEIs & ARBs increase PRA through compensatory feedback mechanisms
Angiotensin II Escape With Long-Term ACEI Therapy

Plasma A II levels increase with time despite suppressed plasma ACE activity

$*P < 0.001$ vs placebo.

CONs: RAS Blockade Via ACEIs or ARBs

ACEI and ARBs

- ACEIs & ARBs:
  - Renin, Ang I and Ang II elevations
  - May prevent full BP-lowering potential
- ACEIs: incomplete RAS suppression d/t “A II escape phenomenon”
- ACEIs: cough, rash and angioedema

ALLHAT: Primary Composite Endpoints

Number at Risk:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>15,255</td>
<td>14,477</td>
<td>13,820</td>
<td>13,102</td>
<td>11,362</td>
<td>6,340</td>
<td>2,956</td>
<td>209</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>9,048</td>
<td>8,576</td>
<td>8,218</td>
<td>7,843</td>
<td>6,824</td>
<td>3,870</td>
<td>1,878</td>
<td>215</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>9,054</td>
<td>8,535</td>
<td>8,123</td>
<td>7,711</td>
<td>6,662</td>
<td>3,832</td>
<td>1,770</td>
<td>195</td>
</tr>
</tbody>
</table>
**VALUE: Composite Cardiac Endpoints**

![Graph showing the proportion of patients with first event over time for Valsartan-based and Amlodipine-based regimens.]

- **Valsartan-based regimen**
  - HR = 1.03; 95% CI = 0.94–1.14; $P = 0.49$

- **Amlodipine-based regimen**

PEACE trial

CV death, nonfatal MI, coronary revascularization

P = 0.43

21.9 22.5

Trandolapril  Placebo
CAMELOT: CV events Enalapril vs Placebo

- Event rate for Enalapril: 23.1%
- Event rate for Placebo: 20.2%
- 15.3% reduction in event rate
- p = 0.16

How Do We Improve RAS Inhibition?

• Optimal Dosing of RAS blockers:
  – Ongoing clinical trials with Valsartan 640mg, Candesartan 128mg, and Irbesartan 900mg

• Combining RAS (ACEI + ARB) blockers:
  – May reduce the Ang II escape seen with ACEIs
  – Benefits in heart failure (CHARM-Added)
  – May reduce proteinuria (COOPERATE)
How Do We Improve RAS Inhibition?

• Target renin:
  – Renin’s high specificity for its only known substrate, angiotensinogen:
    • specific RAS inhibition without other metabolic effects
  – Potential to block the RAS at its initial point of activation

How Do We Improve RAS Inhibition?

• Target Renin:
  – Counteract feedback by ACEI/ARB
  – Proximal blockade prevents both A I and A II
    • may be more efficacious than distal RAS inhibition via ACEIs and ARBs
    • a possible therapeutic profile distinct from those of both ACEIs and ARBs

# How Do We Improve RAS Inhibition?

<table>
<thead>
<tr>
<th>Ang I</th>
<th>Ang II</th>
<th>Renin</th>
<th>PRA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACEI</strong></td>
<td>🔺</td>
<td>🔻</td>
<td>🔺</td>
</tr>
<tr>
<td><strong>ARB</strong></td>
<td>🔺</td>
<td>🔺</td>
<td>🔺</td>
</tr>
<tr>
<td><strong>Renin Inhibitor</strong></td>
<td>🔻</td>
<td>🔻</td>
<td>🔺</td>
</tr>
</tbody>
</table>

Azizi M et al. 2006
Plasma Renin Activity Predicts the Incidence of Myocardial Infarction

<table>
<thead>
<tr>
<th>Risk Status†</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Renin Activity</td>
<td>Normal</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>MI rate/1000 person-years</td>
<td>0</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>

†Risk status: high, ≥2 risk factors (smoking, cholesterol, LVH); moderate, 1 risk factor; low, no risk factors.
PRA, plasma renin activity.
**PRA Is the Strongest Predictor of Mortality in Chronic Heart Failure**

<table>
<thead>
<tr>
<th>Variables</th>
<th>$P$ value</th>
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</thead>
<tbody>
<tr>
<td>Renin activity</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV stroke work index</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum Cr concentration</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Other vasodilators</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Functional class</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other vasodilators</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

History of Renin Inhibitor Development

• A wide variety have been developed over past 20 years, but none have been clinically useful as a result of:
  - Low potency
  - Lack of orally active synthetic compounds
  - Short duration of action/rapid elimination
  - Poor bioavailability
Renin Inhibitor: Aliskiren

Angiotensinogen binds to a pocket in the renin molecule, blocking cleavage of angiotensinogen to angiotensin I

Adapted from Wood JM, et al. 2003
Clinical Data of Aliskiren
Reductions in PRA: Aliskiren vs Losartan


<table>
<thead>
<tr>
<th>Drug</th>
<th>110</th>
<th>-55</th>
<th>-60</th>
<th>-77</th>
<th>-83</th>
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<tbody>
<tr>
<td>Losartan</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Aliskiren 37.5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliskiren 75 mg</td>
<td></td>
<td></td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Aliskiren 150 mg</td>
<td></td>
<td></td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Aliskiren 300 mg</td>
<td></td>
<td></td>
<td></td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>
Plasma A II Suppression in Humans: Aliskiren vs Enalapril

Mean
n = 6 - 12

Ambulatory BP Reductions: Aliskiren vs Losartan

Diastolic & Systolic BP Reductions: Aliskiren vs Irbesartan


*P<0.05 vs irbesartan 150 mg.
24-hour BP Profiles: Aliskiren vs Losartan

Safety and Tolerability: Aliskiren vs Irbesartan

All Adverse Events

Patients (%)

- Placebo: 32.1%
- Aliskiren 150 mg: 26.8%
- Aliskiren 300 mg: 36.2%
- Aliskiren 600 mg: 33.1%
- Irbesartan 150 mg: 36.6%
Aliskiren as a Combination Therapy in Hypertension
Clinical Trials Illustrate a Need for Multiple Antihypertensive Agents

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target BP (mm Hg)</th>
<th>Average Number of Antihypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>UKPDS*</td>
<td>DBP &lt; 85</td>
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</tr>
<tr>
<td>ABCD*</td>
<td>DBP &lt; 75</td>
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<tr>
<td>MDRD*</td>
<td>MAP &lt; 92</td>
<td></td>
</tr>
<tr>
<td>HOT*</td>
<td>DBP &lt; 80</td>
<td></td>
</tr>
<tr>
<td>AASK*</td>
<td>MAP &lt; 92</td>
<td></td>
</tr>
<tr>
<td>IDNT†</td>
<td>SBP/DBP ≤ 135/85</td>
<td></td>
</tr>
<tr>
<td>ALLHAT‡</td>
<td>SBP/DBP ≤ 140/90</td>
<td></td>
</tr>
</tbody>
</table>

Best Combinations Offer……

• Long durations of action
• Complementary mechanisms of action
• Components with the potential to provide benefits beyond BP reduction
• Reductions in drug-related adverse events
Rationale for ARB/ACEI + Renin Inhibitor Combinations

Peripheral vasoconstriction & hypertension

Further lowering of BP and potential end-organ protection

Compensatory response mechanism blocked with RI

Complementary Mechanism

Stimulation of RAS & SNS

Ang II production

PRA

ARBs/ACEIs

BP

Renin inhibitor
Peripheral vasoconstriction & hypertension

Renin inhibitor

Diuretics

Further lowering of BP and potential end-organ protection

Compensatory response mechanism blocked with RI

Stimulation of RAS & SNS

Volume reduction & lower BP

Rationale for Diuretic + Renin Inhibitor Combinations

Ang II production

PRA

Peripheral vasoconstriction & hypertension

Complementary Mechanism

Stimulation of RAS & SNS

Renin inhibitor

Further lowering of BP and potential end-organ protection

Compensatory response mechanism blocked with RI

Volume reduction & lower BP
Effects of Aliskiren + Valsartan on Plasma Renin Activity

Effects of Aliskiren + Valsartan on Angiotensin II Levels


The diagram illustrates the changes in plasma angiotensin II (pg/mL) over time (h) for different treatments: Aliskiren 300 mg, Valsartan 160 mg, Aliskiren 150 mg + Valsartan 80 mg, and placebo. Data are geometric means.
Changes in **Daytime ABP:**
With Aliskiren Plus Irbesartan

<table>
<thead>
<tr>
<th></th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irbesartan 150 mg</td>
<td>-11.7</td>
<td>-6.7*</td>
</tr>
<tr>
<td>Irbesartan 150 mg + aliskiren 75 mg</td>
<td>-15.1</td>
<td>-8.3*</td>
</tr>
<tr>
<td>Irbesartan 150 mg + aliskiren 150 mg</td>
<td>-13.4</td>
<td>-6.8</td>
</tr>
</tbody>
</table>

*P<0.05 compared with irbesartan 150 mg

Changes in **Nighttime ABP:**
With Aliskiren Plus Irbesartan

% Change in BP from baseline (mm Hg)

<table>
<thead>
<tr>
<th></th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irbesartan 150 mg</td>
<td>-8.2</td>
<td>-3.9</td>
</tr>
<tr>
<td>Irbesartan 150 mg + aliskiren 75 mg</td>
<td>-16.8</td>
<td>-8.3*</td>
</tr>
<tr>
<td>Irbesartan 150 mg + aliskiren 150 mg</td>
<td>-13.4</td>
<td>-6.9*</td>
</tr>
</tbody>
</table>

*P<0.05 compared with irbesartan 150 mg
Benefits of Aliskiren
Incremental to BP lowering
Reduction of New-Onset Diabetes With RAS Blockade

Regression of Left Ventricular Hypertrophy

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
- ACEIs: -10
- ARBs: -13

*P<0.05 vs beta-blockers.

### JNC 7: Compelling Indications for Specific Antihypertensive Agents

Based on Favorable Outcome Data From Clinical Trials

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diuretic</th>
<th>BB</th>
<th>ACEI</th>
<th>ARB</th>
<th>CCB</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Post-MI</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD risk</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Renal disease</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


ASPIRE HIGHER: a morbidity and mortality trial programme for aliskiren
m1 Phil: please can you provide updated version (AVIATOR should be deleted)
marmont_n, 2007-03-12
Summary

- Direct renin inhibition with aliskiren suppresses the entire renin-angiotensin system, providing effective BP lowering and the potential for organ protection.
Multiple Factors for the Choice of Pharmacotherapy

- Efficacy
- Adverse Effects
- Adherence
- CV Protection

Multiple Factors for the Choice of Pharmacotherapy
Antihypertensive Therapies Have Evolved Over the Past 50 Years

Moser M. Am J Hypertens. 1997;10:2S-8S.
Aliskiren profiling programme
Ongoing intermediate clinical endpoint studies

• Diabetic Nephropathy
  • Aliskiren vs Placebo in addition to Losartan 100mg
  • UACR Endpoint
  • FIR May 2007
  • Publication planned in ACC / AHA / EASD

• Heart Failure
  • Aliskiren vs Placebo on top of standard HF therapy
  • Safety and Tolerability Endpoint
  • FIR May 2007
  • Publication planned in ACC / AHA

• LVH
  • Aliskiren vs Losartan vs Combination
  • LVH Regression Endpoint
  • FIR December 2007
  • Publication planned in ESC
Reduction of New-Onset Diabetes With RAS Blockade

Patients with LV Dysfunction ± CHF Have Increased PRA Levels

Regression of Left Ventricular Hypertrophy

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

% Reduction in Left Ventricular Mass Index

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- Diuretics: -8
- CCBs: -11
- ACEIs: -10
- ARBs: -13

*P<0.05 vs beta-blockers.

Recent Study Shows High PRA Predicts MI in Both Controlled and Uncontrolled Hypertensive Patients

- An increase of 2 ng/mL/h in plasma renin levels was associated with a 23% increase in MI and revascularization procedures after controlling for other variables.
- Men with high plasma renin levels had twice the risk of MI or a revascularization procedure versus those with lower renin rates, even though BP was treated successfully.

Can RIs Be More Effective Than Other RAS Inhibitors in Reducing End-organ Damage?

- Early studies indicate RIs are very effective for reducing blood pressure
- Reducing target end-organ damage
  - The organ-protective benefits of ACEIs and ARBs might be synergistically enhanced by addressing the incomplete RAS suppression/compensatory feedback loop associated with these agents
- More proximal blockade may prove to be important in limiting changes in structure and function of vascular beds and target organs and limit long-term injury
Conclusions

- Getting BP to below 140/90 mm Hg as quickly as possible is a priority for maintaining excellent CV health
  - Using a RAS blocker may provide additional protective benefits
- Proximal RAS blockade with renin inhibitors may provide more opportunistic chances in controlling BP and reducing CV events
- Combining a renin inhibitor with other RAS modulators may provide incremental BP-lowering effects
Despite Increasing Treatment, 2/3 of Patients are Still Uncontrolled

NHANES = National Health and Nutrition Examination Survey.
Summary

- Optimal Renin System suppression
  - aliskiren inhibits all key Renin System components alone and in combination
- Highly effective as monotherapy
  - aliskiren monotherapy has demonstrated robust BP reductions
- Strength in combination therapy
  - adding aliskiren provides an additional 30–50% reduction in BP
- Smooth, sustained BP control **beyond** 24 hours
  - due to 40-hour half-life
  - BP reductions return gradually to baseline after stopping aliskiren treatment
- Safety and tolerability
  - placebo-like, low potential for DDIs, no dosage adjustments required
- Organ protection potential
  - proven in preclinical data; clinical studies underway