Improving Effect of ARB to Asian Hypertension Patients

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Hypertension is the most powerful risk factor for cardiovascular morbidity and mortality.
### How about hypertension in Asia

<table>
<thead>
<tr>
<th>Region</th>
<th>Death</th>
<th>Disability*</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Asia &amp; Pacific</td>
<td>13.6%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Europe &amp; Central Asia</td>
<td>35.0%</td>
<td>19.6%</td>
</tr>
<tr>
<td>Latin America &amp; The Caribbean</td>
<td>13.0%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Middle East &amp; North Africa</td>
<td>16.5%</td>
<td>6.1%</td>
</tr>
<tr>
<td>South Asia</td>
<td>9.6%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>4.0%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Low-/ middle-income economies</td>
<td>12.9%</td>
<td>5.6%</td>
</tr>
<tr>
<td>High-income economies</td>
<td>17.6%</td>
<td>9.3%</td>
</tr>
<tr>
<td>World</td>
<td>13.5%</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

* Disability-adjusted life years

BP reduction reduces CV risk

Relative risk of CV death vs SBP reduction (mmHg)

- Actively controlled trials
- Placebo-controlled studies or trials with an untreated control group

Interaction between Risk and Therapy

RAS-Inhibition – CV Global Protection?
The ACEi ramipril reduces CV mortality and morbidity in CV high-risk patients

**HOPE:** CV high-risk patients; mean baseline SBP/DBP 139/79 mmHg

<table>
<thead>
<tr>
<th>Event</th>
<th>Treatment vs Placebo</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite CV endpoint†</td>
<td>-22%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>-26%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>MI</td>
<td>-20%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>-32%</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

Ramipril, n = 4,645
Placebo, n = 4,652

† Composite CV endpoint = death from CV causes + MI + stroke
HOPE = Heart Outcomes Prevention Evaluation

Concerns about Angiotensin receptor blockers (ARB)

- ARBs ‘may increase myocardial infarction’: ARB-MI Paradox
  Verma and Strauss. BMJ 2004;329:1248

- There were similar BP-dependent effects of ACE inhibitors and ARBs for the risk of stroke, coronary artery disease, & heart failure. And only for ACE inhibitors but not for ARBs, was there evidence of a BP-independent effect on the risk of major coronary disease events.
  BP lowering treatment trialists collaboration, J Hypertens 2007;25:951
The ARB telmisartan is similarly effective to ACE inhibitor ramipril in preventing CV events in CV high-risk patients.

Reduction in composite CV risk
(Primary endpoint: CV mortality, non-fatal MI, hospitalisation for CHF, non-fatal stroke)

Valsartan in a Japanese population with HT and other CVD (Jikei Heart Study):
a randomised, open-label, blinded endpoint morbidity-mortality study

Seibu Mochizuki, Bjorn Dahlof, Mitsuyuki Shimizu, Katsunori Ikewaki, Makoto Yoshikawa, Ikuo Taniguchi, Makoto Ohta, Taku Yamada, Kazuhiko Ogawa, Kiyoshi Kanae, Makoto Kawai, Shingo Seki, Fumiko Okazaki, Masayuki Taniguchi, Satoru Yoshida, Naoko Tajima, for the Jikei Heart Study group*

Lancet 2007;369:1431-1439
Blood Pressure Results

Valsartan arm (n=1,541) vs. Non-ARB arm (n=1,540)

- Mean SBP: 131 vs. 132 mmHg
  - Valsartan vs. Non-ARB: 8.2/4.7
  - Reductions from baseline: Valsartan 8.2 mmHg, Non-ARB 4.7 mmHg

- Mean DBP: 77 vs. 78 mmHg
  - Valsartan vs. Non-ARB: 7.2/3.7
  - Reductions from baseline: Valsartan 7.2 mmHg, Non-ARB 3.7 mmHg

Mean SBP 131 vs. 132 mmHg
Valsartan vs. non-ARB Δn.s.

Mean DBP 77 vs. 78 mmHg
Valsartan vs. non-ARB Δn.s.
Primary endpoint
Fatal & non-fatal cardiovascular events

Hazard ratio
0.55 (95% CI: 0.42-0.72)
p = 0.00001

Valsartan  83 pts (5.4%)
Non-ARB  155 pts (10.2%)

45%
**ARB Effects on Asian Hypertension**

*JIKEI Heart study*

- **CV mortality and morbidity†**: 39* with valsartan-based therapy compared with non-ARB therapy
  - p=0.0002
- **Stroke/TIA**: 40* with valsartan-based therapy compared with non-ARB therapy
  - p=0.0280
- **Hospitalization for HF**: 47* with valsartan-based therapy compared with non-ARB therapy
  - p=0.0293
- **Hospitalization for angina**: 65* with valsartan-based therapy compared with non-ARB therapy
  - p=0.0001

*TIA = transient ischemic attack

†Primary endpoint

Effect of valsartan in Japanese hypertensive patients with coronary artery disease: Results from the Jikei Heart Study

Mitsuyuki Shimizu 1, Hiroshi Yoshida 2, Katsunori Ikewaki 3, Ikuo Taniguchi 1, Michihiro Yoshimura 1, Björn Dahlöf 4, Seibu Mochizuki 1, for the Jikei Heart Study group

1 Division of Cardiology
2 Department of Laboratory Medicine, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan.
3 Division of Anti-Aging, Department of Internal Medicine, National Defense Medical College, Saitama, Japan.
4 Institute of Medicine, Department of Emergency and Cardiovascular Medicine, Sahlgrenska University Hospital Östra, Göteborg, Sweden
AIM

The risk of cardiac events in hypertensive patients with coronary artery disease (CAD) was higher than in those without CAD. We here report the result of a sub-analysis of a large-scale trial [JIKEI HEART Study (JHS)] which demonstrated that the addition of the angiotensin II receptor blocker (ARB) valsartan to standard cardiovascular treatments significantly reduced the primary composite endpoint of cardiovascular complications as compared with conventional treatments without ARB in Japanese patients.
Effect of valsartan in Japanese hypertensive with coronary artery disease

**JIKEI HEART Study**
3081 Patients

**Trial profile**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CAD+</th>
<th>CAD-</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1,036</td>
<td>34%</td>
<td>66%</td>
</tr>
<tr>
<td>N=2,045</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Primary endpoint**

- CAD+ 75 (7.2%)
- CAD- 163 (7.3%)

**Hazard ratio**

- 1.76 (95% CI 1.34-2.32) \( P<0.001 \)

**Valsartan**

- N=514
  - CAD+ HF- N=486
  - CAD+ HF+ N=28

**Non-ARB**

- N=522
  - CAD+HF- N=486
  - CAD+HF+ N=36

**Endpoint**

- MI
- Angina
- CHF

- CAD- HF+ N=286
- CAD- HF- N=1759
Effect of valsartan in Japanese hypertensive with coronary artery disease

Kaplan-Meier curve of cumulative frequency of the composite primary endpoint: patients with or without CAD

Presence of CAD (1,036 patients)

Hazard ratio 2.72 (95% CI 1.93-3.85) p<0.0001

Absence of CAD (2,045 patients)
Kaplan-Meier curve of cumulative frequency of the fatal and non-fatal coronary events: patients with CAD

- Non-ARB, n=522
- Valsartan, n=514

Hazard ratio: 0.44 (95% CI: 0.27-0.71) p = 0.0007
Kaplan-Meier curve of cumulative frequency of the cardiac events: patients with or without CAD

- **Presence of CAD**
  - Hazard ratio: 0.49 (95% CI: 0.33–0.71)  
  - p < 0.0001

- **Absence of CAD**
  - Hazard ratio: 0.67 (95% CI: 0.34–1.32)
JIKEI HEART Study

Effect of treatment on endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite endpoint</td>
<td></td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>0.125-0.25</td>
<td>0.0280</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.5</td>
<td>0.7545</td>
</tr>
<tr>
<td>Hospitalisation for angina pectoris</td>
<td>1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hospitalisation for heart failure</td>
<td>0.25-0.5</td>
<td>0.0293</td>
</tr>
<tr>
<td>Dissecting aortic aneurysm</td>
<td>0.5-1</td>
<td>0.0340</td>
</tr>
<tr>
<td>Transition to dialysis, doubling of serum Cr levels</td>
<td>1-2</td>
<td>0.8966</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2-4</td>
<td>0.7537</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>2-4</td>
<td>0.9545</td>
</tr>
</tbody>
</table>

Incidence of endpoint reduced  Incidence increased

Mochizuki S et al, for the Jikei heart study group: Lancet 2007; 369 1431-9
Effect of valsartan in Japanese hypertensive patients with coronary artery disease

Percent changes in LVMI: patients with CAD

Regression model analysis
p<0.0001
KYOTO HEART Study: Effect of Valsartan on cardiovascular outcomes in patients with high-risk hypertension: updated ancillary analyses

Kyoto Prefectural University of Medicine, Kyoto, Japan
**Study background and hypothesis**

- Although many reports show that ACEi and ARB are superior for prevention of CV events, data are not enough for the patients with high risk hypertension.
- In Japan, there were only a few large-scale trials for CVD prevention, and it has not been clarified whether the evident in Western countries could be unqualifiedly applied to Japanese patients.
- *Valsartan will improve the CV morbidity and mortality when added to the conventional anti-hypertensive treatment in high-risk Japanese patients with uncontrolled hypertension.*
Study purpose

As the ancillary analysis of the KYOTO HEART study, we investigated:

1) Effects of valsartan on primary and secondary prevention
2) Combination therapy with calcium channel blockers (CCB)
3) Additional analysis of angina & stroke events
Changes of Blood pressure

- **SBP**:
  - 1st prevention: Baseline 157±14, Treatment period (mean) 134±11
  - 1st prevention Non-ARB: Baseline 157±14, Treatment period (mean) 134±11
  - 2nd prevention Valsartan: Baseline 157±15, Treatment period (mean) 134±11
  - 2nd prevention Non-ARB: Baseline 155±14, Treatment period (mean) 134±11

- **DBP**:
  - 1st prevention: Baseline 90±11, Treatment period (mean) 77±8
  - 1st prevention Non-ARB: Baseline 89±11, Treatment period (mean) 77±8
  - 2nd prevention Valsartan: Baseline 86±11, Treatment period (mean) 75±8
  - 2nd prevention Non-ARB: Baseline 86±11, Treatment period (mean) 75±8

Not Significant
Repeated measure ANOVA
KYOTO HEART Study
n=3031

- Coronary heart disease (n=707)
- Cerebrovascular disease (n=123)
- Heart failure (n=193)

**Primary endpoint**
Hazard ratio 2.65 (95%CI 2.01-3.50)
p<0.0001

**Absence of CV disease**
n=2116
- Valsartan n=1065
- Non-ARB n=1051

**Presence of CV disease**
n=915
- Valsartan n=452
- Non-ARB n=463
Comparison between primary and secondary prevention

Probability of events (%)

Month

Primary prevention (n=2116) 4.8%
Secondary prevention (n=915) 14.4%

HR 2.67
95% CI: 2.52-3.02
p<0.0001
Effect of valsartan for primary and secondary prevention

Secondary non-ARB
HR 0.63
95%CI: 0.44-0.89
p=0.0088

Secondary + Valsartan

Primary non-ARB
HR 0.44
95%CI: 0.294-0.68
p=0.0002

Primary + Valsartan

Proximity of events (%) vs. Month

Secondary
Non-ARB: 18.1%
Valsartan: 11.5%

Primary
Non-ARB: 6.7%
Valsartan: 3.0%
Combination therapy with CCB

KYOTO HEART Study n=3031

With CCB n=1807
- Valsartan+CCB N=773
- Non-ARB+CCB n=1034

Without CCB n=1224
- Valsartan+Others n=744
- Non-ARB+Others n=480

‘With CCB’ is defined as the usage of CCBs more than 12 months.
Comparison between With CCB and Without CCB

With CCB: n=1807, event: 7.7%
Without CCB: n=1224, event: 8%

HR 0.975 (95% CI 0.96-0.99)  p=0.037
Combination therapy
With valsartan and CCB

- Other: 11.0%
- CCB+Other: 9.8%
- Valsartan+Other: 6.0%
- Valsartan+CCB: 5.0%

- Non-ARB no CCB
- Non-ARB + CCB
- Valsartan no CCB
- Valsartan + CCB

HR 0.55, 95% CI: 0.37-0.80, p=0.002
HR 0.50, 95% CI: 0.35-0.73, p=0.0003
analysis of stroke events

<table>
<thead>
<tr>
<th></th>
<th>TIA</th>
<th>SAH</th>
<th>Bleeding</th>
<th>Infarction*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsartan</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Non-ARB</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>36</td>
<td>46</td>
</tr>
</tbody>
</table>

(SAH, sub-arachnoid hemorrhage; *<0.05)

HR: 0.55 (95% CI: 0.3 - 0.9) p=0.01488

at risk (n)

<table>
<thead>
<tr>
<th></th>
<th>Valsartan</th>
<th>Non-ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1517</td>
<td>1514</td>
</tr>
<tr>
<td>12</td>
<td>1335</td>
<td>1347</td>
</tr>
<tr>
<td>18</td>
<td>1289</td>
<td>1262</td>
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<tr>
<td>24</td>
<td>1210</td>
<td>1182</td>
</tr>
<tr>
<td>36</td>
<td>1084</td>
<td>1048</td>
</tr>
<tr>
<td>42</td>
<td>900</td>
<td>868</td>
</tr>
<tr>
<td>48</td>
<td>759</td>
<td>749</td>
</tr>
<tr>
<td></td>
<td>680</td>
<td>631</td>
</tr>
<tr>
<td></td>
<td>380</td>
<td>351</td>
</tr>
<tr>
<td></td>
<td>220</td>
<td>178</td>
</tr>
</tbody>
</table>
## Hazard ratio and 95% confidence intervals

<table>
<thead>
<tr>
<th>Event</th>
<th>Valsartan</th>
<th>Non-ARB</th>
<th>0.25</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>HR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>22</td>
<td>44</td>
<td>1.45%</td>
<td>2.91%</td>
<td></td>
<td></td>
<td>0.51</td>
<td>0.30 - 0.90</td>
<td>0.0106</td>
</tr>
<tr>
<td>Effort</td>
<td>16</td>
<td>34</td>
<td>1.05%</td>
<td>2.25%</td>
<td></td>
<td></td>
<td>0.47</td>
<td>0.26 - 0.86</td>
<td>0.0134</td>
</tr>
<tr>
<td>Unstable</td>
<td>3</td>
<td>9</td>
<td>0.20%</td>
<td>0.59%</td>
<td></td>
<td></td>
<td>0.33</td>
<td>0.09 - 1.22</td>
<td>0.0974</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>1</td>
<td>0.20%</td>
<td>0.06%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td>7</td>
<td>11</td>
<td>0.46%</td>
<td>0.73%</td>
<td></td>
<td></td>
<td>0.65</td>
<td>0.20 - 1.80</td>
<td>0.6500</td>
</tr>
<tr>
<td>ACS</td>
<td>10</td>
<td>20</td>
<td>0.66%</td>
<td>1.32%</td>
<td></td>
<td></td>
<td>0.53</td>
<td>0.24 - 1.14</td>
<td>0.1019</td>
</tr>
<tr>
<td>Coronary</td>
<td>29</td>
<td>55</td>
<td>1.91%</td>
<td>3.63%</td>
<td></td>
<td></td>
<td>0.54</td>
<td>0.35 - 0.85</td>
<td>0.0082</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; ACS, acute coronary syndrome, AMI+unstable angina; Coronary, all events
Summary

- In JIKEY HEART Sub-Study done in 3081 Japanese patients with hypertension, coronary heart disease, and/or heart failure, valsartan adding to conventional therapy resulted in significant 51% reduction in the risk of CV events in CAD patients.

- In the KYOTO HEART subanalysis stratified among primary- and secondary-prevention patients,
  - the benefit of treatment was largest among primary-prevention patients, 56%, and 37% among secondary-prevention patients, which, while smaller, was still statistically significant.
  - patients treated with the valsartan-CCB combination had lower event rates compared with patients in the non-ARB/CCB arm (5.0% vs 9.8%).
Conclusion:
ARB in Japanese Hypertensives

• ARB is, at least, as effective in Japanese hypertensives as shown in Western patients. This is probably true in other eastern Asians.

• “ARBs might not be inferior to ACEIs with respect to prevention of MI and CV death”. Therefore, there exits BP-independent effect of ARB in hypertension with high CV risk.
Summary

- Valsartan was more effective for both primary prevention (3.0% vs 6.7%) and secondary prevention (11.5% vs 18.1%), in which primary stroke and secondary AP events are significantly inhibited, respectively.

- Combination with Valsartan+CCB showed lower primary events than non-ARB+CCB (5.0% vs 9.8%)

- Stroke prevention by Valsartan was mainly due to inhibition of cerebral infarction (18 vs 36) but not bleeding.

- Valsartan was significantly effective for prevention of effort angina (1.1% vs 2.3%), but not for unstable angina (0.20% vs 0.59%, p=0.10).