Global Regulatory and Academic Partnerships
- How Can The CSRC Increase Its Impact?

Japanese Regulatory Perspective

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• The number of approved drugs based on global clinical trials (GCTs) has increased.
• 65 applications were approved based on GCT as of April 1, 2014.
Because of globalization of new drug development, number of global clinical trials (GCTs) is increasing.

GCTs include patients from many different countries and areas in the world, often with a limited number of patients from each country.

Consideration of regional differences is particularly important not only for planning and conducting GCTs appropriately, but also for evaluating efficacy and safety (including CV safety) of the drug.

The need for sharing information from each country is increasing.
Regional Differences Related to Drug Development

Regional differences exist in:

- Incidence/prevalence of cardiac diseases
- Impact of cardiac disease on morbidity and mortality
- Standard of care, including available therapeutic options
- Clinical and regulatory environment for benefit/risk assessment of drug therapy
Heart failure in Japan

- **Incidence and underlying causes of heart failure (HF)**
  - Incidence of myocardial infarction ~1/6 of US
  - Hypertension more common both in general and as underlying cause of HF in Japan
  - Dilated cardiomyopathy more often observed

- **Mortality**
  - Mortality rate of chronic HF is relatively low in Japan

- **Differences in clinical practice**
  - Japanese guidelines are similar, but not identical, to AHA and ESC
  - Average stay for acute HF is 21 days and out-patient visits are more frequent as compared to EU and US
Differences in clinical practice (cont.)

- Drugs approved for treatment of heart failure in Japan, not widely used in EU/US, include:
  - carperitide (alpha-human atrial natriuretic peptide)
  - tolvaptan (vasopressin V2-receptor antagonist)
  - nicorandil (ATP-sensitive potassium channel opener)
  - pimobendan (Ca2+ sensitizer, PDE III inhibitor)

Differences in dosage of drugs

- Dosage of drugs for HF are lower in Japan:
  - β blocker
  - Angiotensin II Receptor Blocker (ARB)

- There is a concerns regarding potential ethnicity-based differences in drug pharmacokinetics
Clinical and regulatory environment for benefit/risk assessment of drug therapy

- Regional differences exist in the perception of acceptable risk
- In Japan, there is a great emphasis on safety, sometimes even at the cost of efficacy

Japan has a large target patient population, with wide access to new drugs, once approved
Conclusions

- CSRC can provide excellent opportunities to share information about regional differences that are essential to clarify characteristics of new drugs, including CV safety.
- A Japanese regulatory perspective on CV safety is also needed.

*In my view, CSRC can increase its’ impact by also taking this perspective into account*
Regional Difference in Cardiovascular Event Rates in Patients with Atherothrombosis

REACH registry

Table 5. Geographic Variation of 1-Year CV End Points in the REACH Registry, Adjusted for Sex and Age*

<table>
<thead>
<tr>
<th>Event</th>
<th>Global Population (n = 64,977)</th>
<th>North America (n = 25,999)</th>
<th>Latin America (n = 18,35)</th>
<th>Western Europe (n = 17,142)</th>
<th>Eastern Europe (n = 56,22)</th>
<th>Middle East (n = 840)</th>
<th>Asia (n = 56,71)</th>
<th>Australia (n = 2,847)</th>
<th>Japan (n = 5,021)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>2.58 (2.37-2.79)</td>
<td>2.51 (2.26-2.77)</td>
<td>3.30 (2.41-4.19)</td>
<td>2.68 (2.37-3.00)</td>
<td>3.63 (2.96-4.30)</td>
<td>3.07 (1.66-4.44)</td>
<td>2.95 (2.38-3.52)</td>
<td>2.40 (1.64-3.16)</td>
<td>1.48 (1.07-1.88)</td>
</tr>
<tr>
<td>CV death</td>
<td>1.65 (1.48-1.82)</td>
<td>1.50 (1.30-1.70)</td>
<td>2.23 (1.48-2.98)</td>
<td>1.75 (1.49-2.01)</td>
<td>2.90 (2.28-3.52)</td>
<td>2.71 (1.39-4.00)</td>
<td>2.04 (1.56-2.52)</td>
<td>1.41 (0.84-1.97)</td>
<td>0.74 (0.44-1.04)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>1.14 (1.00-1.28)</td>
<td>1.29 (1.09-1.49)</td>
<td>0.96 (0.47-1.45)</td>
<td>1.07 (0.87-1.27)</td>
<td>1.25 (0.91-1.60)</td>
<td>2.66 (1.44-3.87)</td>
<td>0.82 (0.53-1.11)</td>
<td>0.91 (0.56-1.27)</td>
<td>0.80 (0.43-1.17)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>1.66 (1.49-1.84)</td>
<td>1.18 (1.01-1.35)</td>
<td>2.74 (1.89-3.58)</td>
<td>1.53 (1.28-1.77)</td>
<td>3.78 (3.10-4.45)</td>
<td>2.21 (1.01-3.39)</td>
<td>2.60 (2.06-3.13)</td>
<td>0.94 (0.59-1.29)</td>
<td>1.80 (1.36-2.25)</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>4.24 (3.97-4.51)</td>
<td>3.70 (3.40-4.01)</td>
<td>5.76 (4.57-6.93)</td>
<td>4.14 (3.74-4.53)</td>
<td>7.62 (6.70-8.53)</td>
<td>6.99 (5.01-8.92)</td>
<td>5.27 (4.53-6.01)</td>
<td>3.13 (2.39-3.86)</td>
<td>3.22 (2.59-3.84)</td>
</tr>
<tr>
<td>hospitalization for atherothrombotic event(s)†‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: CV, cardiovascular; MI, myocardial infarction.
*Calculated on the basis of the sample of patients with nonmissing outcomes and nonmissing covariates.
†Covariates missing precluding adjustment: 228 were missing from the global population; 126, North America; 9, Latin America; 75, Western Europe; 2, Eastern Europe; 6, the Middle East; 9, Asia; 1, Australia; and 0, Japan.
‡Transient ischemic attack, unstable angina, or worsening of peripheral arterial disease.

Ethnic Difference in the Risk of Intracranial Hemorrhage among Patients with Atrial Fibrillation

White
Hispanic
Black
Asian


Ethnic Difference in the Optimal Intensity of Oral Anticoagulation with VKA

Europe and US  INR 2.0 - 3.0
Japan        INR 1.6 - 2.6 for 70 years or more
China        INR 1.8 - 2.4
Ethnic differences may exist in this area

- The Japanese are more concerned about bleeding events than is the case in the Western world
- The perception of the benefit/risk balance of NOACs may therefore be different

- **Domestic Ph3 study or Global Ph3 study including Japanese pts**
  - The recommended clinical dose can be different between Japanese and non-Japanese patients when their pharmacokinetic profiles are markedly different.
  - Different doses in Japan – domestic Ph 3 study in Japan
    - **Rivaroxaban**
      - Same doses in Japan – a global Ph 3 study
    - **Dabigatran, Apixaban, Edoxaban**
Dose selection for Rivaroxaban in Japanese patients

Predicted value from PK/PD modeling

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>Caucasian</th>
<th>Japanese</th>
</tr>
</thead>
<tbody>
<tr>
<td>20mg</td>
<td>15mg</td>
<td>20mg</td>
</tr>
</tbody>
</table>

Simulation value

- Cmax
  - Caucasian: 20mg
  - Japanese: 15mg, 20mg

- AUC₀-24
  - Caucasian: 20mg
  - Japanese: 15mg, 20mg
Major bleeding + non-major clinically relevant bleeding events

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Riviroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET AF</td>
<td>13,962</td>
<td>6,958</td>
<td>7,004</td>
</tr>
<tr>
<td>J-ROCKET AF (Japanese)</td>
<td>1,274</td>
<td>637</td>
<td>637</td>
</tr>
</tbody>
</table>

Stroke or non-CNS systemic embolism

HR(95% CI): 0.49(0.24, 1.00)  
P = 0.050

Cumulative event rate

Days from first dose

No. at risk:
Rivoxaban 639 593 553 542 443 313 217 156 48 0
Warfarin 639 581 547 517 406 285 212 154 48 0