Experience of First in Human Study in Japan

Teikyo University Hospital
Cardiocore Japan
Ken Kozuma
History of Cardiocore Japan

- **2003/05** Cardiocore Japan Started operation
- **2006** Introduced QCU Analysis Software
- **2009** Expand Analysis Center (Present location)
  - Introduced Image Server (Toshiba MS)
  - Increased Analysis Machine (CAAS, QCA-CMS each 2 units)
  - Introduced OCT Analysis Software
- **2010** Started Operation at Yokohama QCU Center
- **2011** Unify Database (Toshiba MS)
  - Increase Analysis Machine (QCA-CMS 3 units)
  - Introduced QVA Analysis Software
- **2012** Approved ISO9001
- **2014** Started CTA analysis
- **2015** Started UCG (TTE) analysis
## Evolution of PCI

<table>
<thead>
<tr>
<th></th>
<th>POBA</th>
<th>BMS</th>
<th>1\textsuperscript{st} gen. DES</th>
<th>2\textsuperscript{nd} gen. DES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decade</td>
<td>1980s</td>
<td>1990s</td>
<td>2000s</td>
<td>2010s</td>
</tr>
<tr>
<td>Acute Success rate</td>
<td>70-85%</td>
<td>&gt;95%</td>
<td>&gt;95%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Restenosis</td>
<td>40-45%</td>
<td>20-30%</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Early Thrombosis</td>
<td>3-5%</td>
<td>1-2%</td>
<td>0.3-2%</td>
<td>0.3-1%</td>
</tr>
<tr>
<td>&lt;30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late Thrombosis</td>
<td>NA</td>
<td>&lt;0.5%</td>
<td>0.3-2%</td>
<td>0.1-0.3%</td>
</tr>
<tr>
<td>&gt;30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Late</td>
<td>NA</td>
<td>≈0%</td>
<td>0.3-2%</td>
<td>0-0.2%</td>
</tr>
<tr>
<td>Thrombosis (&gt;1y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Unresolved issues related to 2nd generation DES

- **Efficacy issues**
  - Late catch-up
  - Stent overlap (long stent)
  - Bifurcation (2 stent)
  - Hemodialysis, Diabetes

- **Safety issues**
  - Improved endothelialization and vasomotion
  - Prevent inflammation/ hypersensitivity reaction
  - Eliminate risk of very late stent thrombosis
  - DAPT duration

- **Technical issues (CTO)**
Components of DES

Drug

Eluting Stent

Carrier Matrix

Platform
Coating integrity

Effects of stent expansion

Effects of sterilization
Marked Inflammatory Sequelae to Implantation of Biodegradable and Nonbiodegradable Polymers in Porcine Coronary Arteries

- **Biodegradable polymers**
  - PGLA (polyglycolic acid/polyactic acid)
  - PCL (polycaprolactone)
  - PHBV (polyhydroxybutyrate)
  - POE (polyorthoester)
  - PEO/PBTP (polyethylenoxide)

- **Nonbiodegradable polymers**
  - PUR (polyurethane)
  - SIL (silicone)
  - PETP (polyethylene terephthalate)

## Japan Stent Technology
### JF-03 (BMS) n=102

<table>
<thead>
<tr>
<th></th>
<th>In-segment</th>
<th>Proximal</th>
<th>In-stent</th>
<th>Distal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late loss (mm)</td>
<td>0.47 ± 0.58</td>
<td>0.25 ± 0.48</td>
<td>0.69 ± 0.47</td>
<td>0.05 ± 0.42</td>
</tr>
<tr>
<td>Late loss index</td>
<td>0.42 ± 0.28</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Restenosis (%)</td>
<td>10.2</td>
<td>2.0</td>
<td>10.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Target of Restenosis Inhibition by Drug eluting stent

Arterial Injury
- Thrombus (platelets)
- Inflammation (macrophage)

Growth Factors & Cytokines

Receptor activation
- Signal Transduction
  - Cell Cycle
  - Cell proliferation
- Extracellular matrix
  - Migration
  - Main target

SMC
DRUGS WORK!...

- Trapidil: P < .01
- Fish oil: P = .03
- Probucol: P = .003
- Verapamil: P = .005
- Tranilast: P = .05
- Cilostazol: P < .001

Restenosis reduction (%)
Anti-restenosis trials using drugs (Meta-analysis)

Aspirin (5)
Ticlopidine (3)
TXA2 inhibit (5)
Prostacyclin (3)
Anticoagulants (10)
Calcium antagonists (5)
Steroids (3)
ACE inhibitors (3)
Trapidil (3)
Fishoil (11)
Statins (5)
Antioxydants (5)
Colchicine (1)
Serotonin antagonists (3)
Angiopeptin (3)

66 randomized trials
20,914 patients
Drug for anti-restenosis

**Anti-Inflammatory Immunomodulators**
- Dexamethasone
- M-prednisolone
- Interferon \( \gamma \)-1b
- **Sirolimus**
- Tacrolimus
- **Everolimus**
- **Biolimus**
- Mycophenolic acid
- Mizoribine
- Cyclosporine
- Tranilast

**Anti-Proliferative**
- QP-2, *Taxol*
- Actinomycin
- Methotrexate
- Angiopeptin
- Vincristine
- Mitomycin
- Statins
- C MYC antisense
- RestenASE
- 2-chloro-deoxyadenosine
- PCNA Ribozyme
- Cilostazol

**Migration Inhibitors ECM-Modulators**
- Batimastat
- Prolyl hydroxylase inhibitors
- Halofuginone
- C-proteinase inhibitors
- Probucol

**Promote Healing & Re-Endothelialization**
- BCP671
- VEGF
- Estradiols
- NO donors
- EPC antibodies
- Biorest
- Advanced coatings
Biodegradable polymer-based, argatroban-eluting, cobalt-chromium stent (JF-O4) for treatment of native coronary lesions: final results of the first-in-man study and lessons learned

Yoshihiro Morino¹*, MD; Tetsuya Tobaru², MD; Satoshi Yasuda³, MD; Kazuaki Kataoka⁴, MD; Kengo Tanabe⁵, MD; Atsushi Hirohata⁶, MD; Ken Kozuma⁷, MD; Takeshi Kimura⁸, MD

<table>
<thead>
<tr>
<th></th>
<th>JF-O4</th>
<th>MOMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platform</td>
<td>L605 cobalt-chromium, identical design</td>
<td></td>
</tr>
<tr>
<td>Coating</td>
<td>biodegradable</td>
<td>durable</td>
</tr>
<tr>
<td>Drug</td>
<td>argatroban</td>
<td>none</td>
</tr>
<tr>
<td>Clinical study</td>
<td>first-in-man</td>
<td>first-in-man</td>
</tr>
<tr>
<td>Countries</td>
<td>Japan</td>
<td>UK, Germany</td>
</tr>
<tr>
<td>Number of patients</td>
<td>31</td>
<td>40</td>
</tr>
<tr>
<td>In-stent late loss, mm</td>
<td>1.01±0.48</td>
<td>NA</td>
</tr>
<tr>
<td>In-segment late loss, mm</td>
<td>0.74±0.51</td>
<td>0.54±0.3</td>
</tr>
<tr>
<td>Restenosis rate, %</td>
<td>29.0</td>
<td>12.5</td>
</tr>
<tr>
<td>Ischaemia-driven TVR, %</td>
<td>12.9</td>
<td>7.5</td>
</tr>
</tbody>
</table>

TVR: target vessel revascularisation
## Cilostazol: Mechanism of Action

<table>
<thead>
<tr>
<th>Target Cell</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet</td>
<td>Anti-platelet effect</td>
</tr>
<tr>
<td>Smooth muscle cell</td>
<td>Vasodilating effect Inhibition of proliferation</td>
</tr>
<tr>
<td>Endothelial cell</td>
<td>Improvement of function Promote re-endothelialization</td>
</tr>
</tbody>
</table>
Effects of Cilostazol (PDE-III inhibitor)

- **Platelets**
  - Anti-thrombotic
  - eNOS
  - NO
  - Microcirculation ↑

- **Cilostazol**
  - Adhesion molecules
  - VCAM-1
  - Anti-inflammatory

- **WBC**
  - Cytokines
    - TNF-α
    - PDGF

- **Endothelial protection**
Effect of cilostazol for Endothelial cell

Re-endothelialization after balloon injury in rat carotid artery

<table>
<thead>
<tr>
<th>Time after Injury (week)</th>
<th>Control</th>
<th>Cilostazol</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>49.6 ± 4.9%</td>
<td>80.4 ± 5.8%</td>
</tr>
<tr>
<td>4 weeks</td>
<td>91.6 ± 3.4%</td>
<td>91.4 ± 3.7%</td>
</tr>
</tbody>
</table>

NO production in vitro (HAEC)

<table>
<thead>
<tr>
<th>Cilostazol (μmol/L)</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>10</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂⁻ (nmol/well)</td>
<td></td>
<td></td>
<td></td>
<td>**</td>
<td>**</td>
</tr>
</tbody>
</table>

cilostazol
Cilostazol

- Cilostazol or Aspirin
- Anti-platelet drug
- Balloon angioplasty
- Randomized
- n=252

Tsuchikane et al.,
Circulation 1999
Cilostazol

- Cilostazol or Ticlopidine
- Anti-platelet drug
- Stenting
- randomized
- n=130

Kozuma et al.,
AHJ 2001

p = .04
C R E S T
Cilostazol for RESTenosis Trial

John S. Douglas, Jr, David Holmes, Dean Kereiakes, Cindy L. Grines, Elizabeth Block, Karen Parker, Claudine Jurkowitz, Nancy Murrah, Jovonne Foster, Paul Kolm, John Mancini, William S. Weintraub

Emory University, Mayo Clinic, William Beaumont Hospital, Lindner Research Center, University of British Columbia

Douglas, John S. Jr. Cilostazol for Restenosis Trial (CREST): Late Breaking Clinical Trials from Plenary Session I and Interventional Cardiology, AHA, November 9, 2003
Design

- Multicenter, randomized double blind clinical trial
- 705 patients at 19 sites

Douglas, John S. Jr. Cilostazol for Restenosis Trial (CREST); Late Breaking Clinical Trials from Plenary Session I and Interventional Cardiology, AHA, November 9, 2003
Restenosis Rate

Cilostazol
Restenosis Trial

Cilostazol vs Placebo

Restenosis Rate in Segment

- Cilostazol: 20.88% (n=249)
- Placebo: 34.50% (n=258)

Relative Risk Reduction (RRR): 39.5%, 95% CI 34.9-44.2%

P-value: 0.0006

Restenosis Rate in Stent

- Cilostazol: 20.08% (n=249)
- Placebo: 31.37% (n=255)

RRR: 36.0%, 95% CI 31.6-40.6%

P-value: 0.0038

Douglas, John S. Jr. Cilostazol for Restenosis Trial (CREST); Late Breaking Clinical Trials from Plenary Session I and Interventional Cardiology, AHA, November 9, 2003

Circulation 2005
Efficacy of Cilostazol in reducing restenosis in patients undergoing contemporary stent based PCI: a meta-analysis of randomised controlled trials

Umesh Tamhane¹, MD; Pascal Meier¹, MD; Stanley Chetcuti¹, MD, FACC; Kang-Yin Chen², MD, PhD; Seung-Woon Rha³, MD, PhD, FACC, FAHA; Michael P. Grossman¹, MD, FACC; Hitinder Gurm¹*, MD, FACC

Figure 3. The Forest plot of odds ratios of binary angiographic restenosis. Sizes of data markers are proportional to the weight of each study in the meta-analysis. Horizontal bars=95% CI.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Stent type</th>
<th>Year</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
<th>Restenosis / Total</th>
<th>Odds ratio and 95% CI</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREST</td>
<td>BMS</td>
<td>2005</td>
<td>0.537</td>
<td>0.364</td>
<td>0.791</td>
<td>0.002</td>
<td>57 / 259</td>
<td>92 / 267</td>
<td>39.86</td>
</tr>
<tr>
<td>CHEN YD et al</td>
<td>BMS</td>
<td>2006</td>
<td>0.339</td>
<td>0.127</td>
<td>0.904</td>
<td>0.031</td>
<td>7 / 52</td>
<td>17 / 54</td>
<td>6.21</td>
</tr>
<tr>
<td>Min PK et al</td>
<td>BMS</td>
<td>2007</td>
<td>0.355</td>
<td>0.095</td>
<td>1.327</td>
<td>0.124</td>
<td>4 / 35</td>
<td>8 / 30</td>
<td>3.44</td>
</tr>
<tr>
<td>DECLARE-DIABETES</td>
<td>DES</td>
<td>2008</td>
<td>0.470</td>
<td>0.232</td>
<td>0.951</td>
<td>0.036</td>
<td>13 / 163</td>
<td>26 / 167</td>
<td>12.06</td>
</tr>
<tr>
<td>DECLARE-Long</td>
<td>DES</td>
<td>2007</td>
<td>0.565</td>
<td>0.282</td>
<td>1.132</td>
<td>0.107</td>
<td>14 / 210</td>
<td>23 / 205</td>
<td>12.41</td>
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<tr>
<td>Kim DH et al</td>
<td>DES</td>
<td>2008</td>
<td>1.333</td>
<td>0.284</td>
<td>6.260</td>
<td>0.715</td>
<td>4 / 55</td>
<td>3 / 54</td>
<td>2.50</td>
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<tr>
<td>CIDES</td>
<td>DES</td>
<td>2008</td>
<td>0.450</td>
<td>0.196</td>
<td>1.034</td>
<td>0.060</td>
<td>9 / 113</td>
<td>20 / 124</td>
<td>8.64</td>
</tr>
<tr>
<td>Loo-DES II</td>
<td>DES</td>
<td>2008</td>
<td>0.463</td>
<td>0.192</td>
<td>1.112</td>
<td>0.085</td>
<td>8 / 168</td>
<td>16 / 164</td>
<td>7.77</td>
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<tr>
<td>Hong SJ et al</td>
<td>DES</td>
<td>2008</td>
<td>0.600</td>
<td>0.133</td>
<td>2.700</td>
<td>0.506</td>
<td>3 / 39</td>
<td>5 / 41</td>
<td>2.65</td>
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<tr>
<td>Jeong JW et al</td>
<td>DES</td>
<td>2008</td>
<td>0.756</td>
<td>0.237</td>
<td>2.405</td>
<td>0.635</td>
<td>7 / 23</td>
<td>11 / 30</td>
<td>4.46</td>
</tr>
</tbody>
</table>

Combined OR 0.517 0.405 0.660 0.000

Favours Cilostazol  Favours Placebo
Components of CES-1

- シロスタゾール溶出ステント (CES-1)

【CES-1】

<table>
<thead>
<tr>
<th>Parts</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent</td>
<td>Platform Cobalt Chromium L605 (ASTM90)</td>
</tr>
<tr>
<td>Coating</td>
<td>Drug Cilostazol: 766 μg/cm² 651 μg/unit (3.0 x 18 mm)</td>
</tr>
<tr>
<td></td>
<td>Polymer PDLGA: 766 μg/cm²</td>
</tr>
<tr>
<td>Balloon</td>
<td>R X タイプ PEBAX</td>
</tr>
</tbody>
</table>

Stent size: 3.0 mm × 18 mm
Objective: Exploratory investigation of CES-1 for the treatment of de novo coronary lesions (Feasibility study)

De novo native coronary artery lesion
Reference diameter: 2.75mm~3.25mm  lesion length < 15mm
Stent size: 3.0mmx18mm  DAPT 6 months
Open label single arm registry

30 patients in 6 sites

Clinical Follow up

Primary Endpoint:  In-segment late loss at 9 months
Secondary Endpoint: TLF, TVF, stent thrombosis, POCE

%DS (in-stent/in-segment) & Binary restenosis rates (in-stent/in-segment)
Neointimal volume, %Volume obstruction
ISA%, %Strut coverage
Igaki-Tamai Stent (2000)

Hideo Tamai, MD
Died 14 Feb, 2009
Summary

- Although technologies of drug-eluting stents has matured, there still remain unresolved issues.
- For the innovation and further improvement of PCI, there is a chance to utilize Japanese original materials and technologies.