Intervention with Pharmacologic Magic (STOP-IC Study)

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Disclosure Statement of Financial Interest

• I, (Hiroyoshi Yokoi) DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation
Mid-Term Clinical Outcome and Predictors of Vessel Patency after Femoropopliteal stenting with Self-Expanding Nitinol Stent (n=639)

Primary Patency and Secondary Patency Rate after Femoropopliteal Stenting

Primary patency: PSVR > 2.4 by duplex or >50% stenosis by angiogram

<table>
<thead>
<tr>
<th>Interval after EVT (years)</th>
<th>Event-free survival Curve (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary Patency</td>
</tr>
<tr>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>1</td>
<td>97.5%</td>
</tr>
<tr>
<td>2</td>
<td>89.3%</td>
</tr>
<tr>
<td>3</td>
<td>85.1%</td>
</tr>
<tr>
<td>4</td>
<td>79.8%</td>
</tr>
<tr>
<td>5</td>
<td>79.8%</td>
</tr>
</tbody>
</table>

Multivariate Analysis of predictors for Stent Restenosis in patients with SFA disease

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.82</td>
<td>1.33 – 2.49</td>
<td>0.0002</td>
</tr>
<tr>
<td>ABI&lt;0.6</td>
<td>1.71</td>
<td>1.25 – 2.31</td>
<td>0.0007</td>
</tr>
<tr>
<td>TASC-II C/D</td>
<td>1.98</td>
<td>1.38 – 2.85</td>
<td>0.0002</td>
</tr>
<tr>
<td>Stent Fracture</td>
<td>2.20</td>
<td>1.41 – 3.43</td>
<td>0.0005</td>
</tr>
<tr>
<td>Cilostazol (-)</td>
<td>1.87</td>
<td>1.37 – 2.54</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Multifaceted Effects of Cilostazol

- Antithrombotic activity
- In vitro inhibition of vascular smooth muscle cells
- Decreases triglycerides
- Increases HDL-C

Cilostazol

- Antiplatelet activity
- Mildly increases heart rate
- Produces vasodilation
- Increases blood flow

Reduction in Restenosis after implantation of coronary artery stents (Circulation, Nov 2005; 112: 2826 - 2832)

Improved symptoms and walking distance (Circulation.1998;98:678-68)
Recently, cilostazol therapy after EVT for FP lesions has been shown to improve clinical outcome. However, it is unknown whether it reduces angiographic restenosis after EVT.


Sufficient Treatment Of Peripheral Intervention by Cilostazol

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Kansai Rosai Hospital Cardiovascular Center
Osamu Iida
Osaka University Advanced Cardiovascular Therapeutics
Shinsuke Nanto
and
STOP-IC Investigators
To investigate whether cilostazol reduces the binary restenosis after EVT for *de novo* FP lesions by angiographic follow-up
Methods

Study Design: Prospective, multicenter (17 cardiovascular centers), open-label trial

Duration of patients entry
2009/1 ~ 2011/6

R: Randomization

EVT -3 ~ -7D
ASA: 100mg
TIC: 200mg
CIL: 200mg

4W
ASA: 100mg

12M
ASA: 100mg
CIL: 200mg

Primary EP

Duplex 3M

Duplex 6M

FU Angiography

Duplex 12M

ASA: aspirin
TIC: ticlopidine
CIL: cilostazol
Participants Centers of STOP-IC

- Kansai Rosai HP
- Omihachiman Com. Med. Center
- Kishiwada Tokushukai HP
- Hyogo College of Med. HP
- Kokura Memorial HP
- Shin Koga HP
- Kanazawa Med. Univ. HP
- Tokeidai Memorial HP
- Sendai Kousei HP
- Shinonoi General HP
- Shinshu Univ. HP
- Saiseikai Yokohama-city Eastern HP
- Kikuna Memorial HP

Locations and Participants Count:
- Kansai Rosai HP: 69
- Omihachiman Com. Med. Center: 6
- Kishiwada Tokushukai HP: 19
- Hyogo College of Med. HP: 8
- Kokura Memorial HP: 56
- Shin Koga HP: 5
- Kanazawa Med. Univ. HP: 1
- Tokeidai Memorial HP: 5
- Sendai Kousei HP: 21
- Shinonoi General HP: 1
- Shinshu Univ. HP: 2
- Saiseikai Yokohama-city Eastern HP: 3
- Kikuna Memorial HP: 4
Inclusion criteria

- Written informed consent.
- Symptomatic leg ischemia defined as Rutherford classification 2-4 patients with femoro-Popliteal de novo lesion presenting > 50% stenosis Available for angiographic follow-up at 12 months

Exclusion criteria

- Life expectancy of less than 2 year
- Symptom due to acute onset leg ischemia.
Methods

- **Primary endpoint**
  - 12 months angiographic restenosis rate (Defined as %DS>50%) evaluated by independent Core Labolatory

- **Secondary endpoint**
  - 12 months restenosis rate assessed by angiographic or duplex (PSVR<2.5)
  - Target lesion revascularization (TLR)
  - Incidence of death, major amputation and surgical conversion
Randomization according to inclusion/exclusion criteria
n = 200

12 months Angiography follow-up chart

Cilostazol group
Baseline  n = 100

7 patients

No indication for endovascular therapy after angiography assessment (n=10)

Cilostazol group
Baseline  n = 93

Non-Cilostazol group
Baseline  n = 100

3 patients

Non-Cilostazol group
Baseline  n = 97
## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cilostazol group N=93</th>
<th>Non-Cilostazol group N=97</th>
<th>All N=190</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-yrs (yrs)</td>
<td>72±9</td>
<td>73±8</td>
<td>72±9</td>
<td>0.5</td>
</tr>
<tr>
<td>Male gender-no. (%)</td>
<td>69% (64)</td>
<td>68.0% (66)</td>
<td>68% (130)</td>
<td>0.9</td>
</tr>
<tr>
<td>Body mass index</td>
<td>22 ± 3</td>
<td>22 ± 3</td>
<td>22 ± 3</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypertension-no. (%)</td>
<td>81% (75)</td>
<td>81% (78)</td>
<td>81% (153)</td>
<td>0.9</td>
</tr>
<tr>
<td>Dislipidemia-no. (%)</td>
<td>43% (40)</td>
<td>51% (49)</td>
<td>47% (89)</td>
<td>0.3</td>
</tr>
<tr>
<td>Statin treatment-no. (%)</td>
<td>29% (27)</td>
<td>40% (39)</td>
<td>35% (66)</td>
<td>0.1</td>
</tr>
<tr>
<td>Diabetes mellitus-no. (%)</td>
<td>57% (53)</td>
<td>55% (53)</td>
<td>56% (106)</td>
<td>0.7</td>
</tr>
<tr>
<td>Glycosylated hemoglobin at baseline-%</td>
<td>6.4 ± 1.7</td>
<td>6.2 ± 1.1</td>
<td>6.3 ± 1.4</td>
<td>0.4</td>
</tr>
<tr>
<td>History of Smoking-no. (%)</td>
<td>45% (42)</td>
<td>48% (46)</td>
<td>47% (88)</td>
<td>0.7</td>
</tr>
<tr>
<td>End stage renal disease on dialysis-no. (%)</td>
<td>16% (15)</td>
<td>16% (15)</td>
<td>16% (30)</td>
<td>0.9</td>
</tr>
<tr>
<td>Coronary artery disease-no. (%)</td>
<td>38% (35)</td>
<td>40% (38)</td>
<td>39% (73)</td>
<td>0.8</td>
</tr>
<tr>
<td>Cerebrovascular disease-no. (%)</td>
<td>24% (22)</td>
<td>20% (19)</td>
<td>22% (41)</td>
<td>0.5</td>
</tr>
<tr>
<td>Rutherford classification-no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>24% (22)</td>
<td>29% (28)</td>
<td>27% (50)</td>
<td>0.4</td>
</tr>
<tr>
<td>3</td>
<td>67% (62)</td>
<td>58% (55)</td>
<td>63% (117)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>9% (8)</td>
<td>13% (12)</td>
<td>11% (20)</td>
<td></td>
</tr>
<tr>
<td>Absolute claudication distance (ACD)</td>
<td>98 (50 - 133)</td>
<td>76 (50 - 101)</td>
<td>80 (50 - 115)</td>
<td>0.5</td>
</tr>
<tr>
<td>Baseline ankle brachial index ABPI</td>
<td>0.72 ± 0.16</td>
<td>0.66 ± 0.13</td>
<td>0.69 ± 0.15</td>
<td>0.008</td>
</tr>
</tbody>
</table>
## Baseline Lesion Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cilostazol group N=93</th>
<th>Non-Cilostazol group N=97</th>
<th>All N=190</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TASC II classification-no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>A</td>
<td>37% (34)</td>
<td>34% (32)</td>
<td>36% (66)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>21% (19)</td>
<td>22% (21)</td>
<td>21% (40)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>25% (23)</td>
<td>27% (25)</td>
<td>26% (48)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>17% (16)</td>
<td>17% (16)</td>
<td>17% (32)</td>
<td></td>
</tr>
<tr>
<td><strong>Length of target lesion-mm</strong></td>
<td>130 ± 89</td>
<td>124 ± 82</td>
<td>127 ± 86</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Reference vessel diameter (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>5.4 ± 1.4</td>
<td>5.3 ± 1.3</td>
<td>5.3 ± 1.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Distal</td>
<td>4.9 ± 1.0</td>
<td>5.0 ± 1.0</td>
<td>4.9 ± 1.0</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Degree of stenosis pre intervention(%)</strong></td>
<td>82 ± 21</td>
<td>81 ± 20</td>
<td>81 ± 20</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Occlusion-no of patients (%)</strong></td>
<td>39% (37)</td>
<td>35% (33)</td>
<td>37% (70)</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>MLD pre intervention-mm</strong></td>
<td>1.4</td>
<td>1.6</td>
<td>1.5</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>ALD pre intervention-mm</strong></td>
<td>1.4</td>
<td>1.7</td>
<td>1.6</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Plaque area before intervention-mm²</strong></td>
<td>63</td>
<td>81</td>
<td>70.3</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Lesion calcification-%</strong></td>
<td>47% (25)</td>
<td>51% (22)</td>
<td>49% (47)</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Number of below the knee run-off (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>0</td>
<td>4% (4)</td>
<td>1% (1)</td>
<td>3% (5)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>31% (28)</td>
<td>35% (32)</td>
<td>33% (60)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>40% (36)</td>
<td>35% (32)</td>
<td>37% (68)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>24% (22)</td>
<td>29% (27)</td>
<td>27% (49)</td>
<td></td>
</tr>
</tbody>
</table>

MLD: Minimum lumen diameter, ALD: Average lumen diameter
### Baseline Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cilostazol group</th>
<th>Non-Cilostazol group</th>
<th>All group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=93</td>
<td>N=97</td>
<td>N=190</td>
<td></td>
</tr>
<tr>
<td>Stent implantation-no. (%)</td>
<td>89% (82)</td>
<td>90% (85)</td>
<td>89% (167)</td>
<td>0.9</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>167 ± 94</td>
<td>154 ± 86</td>
<td>161 ± 90</td>
<td>0.8</td>
</tr>
<tr>
<td>Number of stent implantation</td>
<td></td>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>1</td>
<td>45% (37)</td>
<td>41% (35)</td>
<td>43% (72)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>24% (20)</td>
<td>37% (31)</td>
<td>31% (51)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>31% (25)</td>
<td>22% (19)</td>
<td>26% (44)</td>
<td></td>
</tr>
<tr>
<td>Diameter of post dilation balloon-mm</td>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>4</td>
<td>18% (16)</td>
<td>11% (10)</td>
<td>14% (26)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>46% (42)</td>
<td>60% (56)</td>
<td>53% (98)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>36% (33)</td>
<td>29% (27)</td>
<td>33% (60)</td>
<td></td>
</tr>
<tr>
<td>Degree of stenosis post intervention-%</td>
<td>20</td>
<td>22</td>
<td>21</td>
<td>1.0</td>
</tr>
<tr>
<td>MLD post intervention-mm</td>
<td>3.8</td>
<td>3.7</td>
<td>3.7</td>
<td>0.7</td>
</tr>
<tr>
<td>ALD post intervention-mm</td>
<td>11.4</td>
<td>11.3</td>
<td>11.4</td>
<td>0.7</td>
</tr>
<tr>
<td>SD/proximal RD ratio</td>
<td>1.4</td>
<td>1.3</td>
<td>1.3</td>
<td>0.7</td>
</tr>
<tr>
<td>SD/distal RD ratio</td>
<td>1.5</td>
<td>1.4</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Procedure related complication-no. (%)</td>
<td>2.2% (2)</td>
<td>3.1% (3)</td>
<td>2.7% (5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Distal embolization-no. (%)</td>
<td>1.6% (1)</td>
<td>1.6% (1)</td>
<td>1.6% (2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Puncture site complication-no. (%)</td>
<td>1.1% (1)</td>
<td>2.1% (2)</td>
<td>1.6% (3)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

MLD: Minimum lumen diameter, ALD: Average lumen diameter
Stent: SMART stent, SD: Stent diameter, RD: Reference diameter
12-month Angiography Follow-up

Randomization according to inclusion/exclusion criteria
n = 200

- Cilostazol group
  - Baseline n = 93
  - 7 patients: Death before 12-month follow-up (n=11)
    - Pneumonia 2
    - Sepsis 1
    - Lung cancer 1
    - Myocardial infarction 2
    - Unknown 1
  - 86 patients: Eligible 12-month FU
  - 11 patients: Lost to 12-month follow-up angiography (n=28)

- Non-cilostazol group
  - Baseline n = 97
  - 4 patients: Death before 12-month follow-up
    - Pneumonia 2
    - Myocardial infarction 1
    - Multiple organ failure 1
  - 93 patients: Eligible 12-month FU
  - 17 patients: Lost to 12-month follow-up angiography

12-month FU Angiography
n=75 / 86 (87%)

12-month FU Angiography
151/179 (84%)

12-month FU Angiography
n=76/93 (82%)
Representative case

-Follow up angiogram@12 months-

Lesion background: lesion length > 15cm, CTO, DM (+)
EVT procedure: S.M.A.R.T. stent 7.0*100mm*2

Cilostazol (+)

Cilostazol (-)
Results

Primary Endpoint (12 months angiographic restenosis)

<table>
<thead>
<tr>
<th></th>
<th>Intention to treat</th>
<th>Per protocol analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cilostazol</td>
<td>21% (16 of 76)</td>
<td>21% (15 of 71)</td>
</tr>
<tr>
<td>Non-Cilostazol</td>
<td>48% (36 of 75)</td>
<td>49% (37 of 76)</td>
</tr>
</tbody>
</table>

OR: 0.29 (95%CI: 0.14, 0.59)  
P=0.0005

OR: 0.28 (95%CI: 0.14, 0.58)  
P=0.0005
12-month Angiography Follow-up

Randomization according to inclusion/exclusion criteria
n = 200

No indication for endovascular therapy after angiography assessment

Cilostazol group
Baseline  n = 93

7 patients
- Pneumonia 2
- Sepsis 1
- Lung cancer 1
- Myocardial infarction 2
- Unknown 1

Death before 12-month follow-up (n=11)

86 patients

Eligible 12-month FU

Lost to 12-month follow-up angiography or duplex (n=10)

12-month FU Angiography or duplex
N=82/86 (95%)

Non-cilostazol group
Baseline  n = 97

4 patients

Pneumonia 2
Myocardial infarction 1
Multiple organ failure 1

93 patients

6 patients

12-month FU Angiography or duplex
N=87/93 (94%)
Results

Secondary endpoint (12 months restenosis assessed by angiography or duplex, *intention to treat analysis*)

![Graph showing restenosis rates at 3Mo, 6Mo, and 12Mo](graph.png)

- **3Mo**: 10% (9 of 93), 5% (5 of 97) (P=0.23)
- **6Mo**: 13% (12 of 93), 12% (12 of 97) (P=0.91)
- **12Mo**: 41% (40 of 97) (P=0.001)
Results

Secondary endpoint (12 months restenosis assessed by angiography or duplex, *per protocol analysis*)
## Results

12 months FU Clinical Outcome Data

<table>
<thead>
<tr>
<th></th>
<th>Cilostazol group N=93</th>
<th>Non-Cilostazol group N=97</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR</td>
<td>17%</td>
<td>37%</td>
<td>0.004</td>
</tr>
<tr>
<td>Surgical bypass conversion</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Stent fracture</td>
<td>17%</td>
<td>16%</td>
<td>0.90</td>
</tr>
<tr>
<td>Amputation</td>
<td>2.2% (2)</td>
<td>3.1% (3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Death</td>
<td>4.6%</td>
<td>4.4%</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Results

Subgroup analysis for efficacy of cilostazol on 12 months angiographic restenosis

Overall
- Dislipidemia: YES vs NO - P=0.02
- Diabetes Mellitus: YES vs NO - P=0.40
- Dialysis: YES vs NO - P=0.41
- Rutherford Classification: 2/3 vs 4 - P=0.75
- TASC II Classification: A/B vs C/D - P=0.64
- Length of Target lesion: <150 vs ≥150 - P=0.54
- Reference Vessel-Proximal: <5 vs ≥5 - P=0.06
- Reference Vessel-Distal: <5 vs ≥5 - P=0.78
- Degree of Stenosis: <100 vs ≥100 - P=0.42
- # of below the knee run-off: 1 vs 2 vs 3 - P=0.79
- # of stent implementation: 1 vs 2 vs 3 - P=0.61
There were no differences between the 2 groups in patient, lower limb and lesion characteristics, except for ABI before EVT.

The number of stents implanted was similar between the two groups. The occurrence of stent fracture, as observed at follow-up, was also similar.

12-month angiographic restenosis rates were significantly lower in the cilostazol group.

Target lesion revascularization was also significantly lower in the cilostazol group.
Conclusion

Cilostazol reduced angiographic restenosis rates after EVT for FP lesions.