Addition of Cilostazol to Conventional Dual Antiplatelet Therapy Reduces the Risk of Cardiac Events and Restenosis after Drug-Eluting Stent Implantation

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Conflict of interest : None
Restenosis is one of major limitations of BMS;
DES significantly reduce the risk of restenosis;
However, restenosis has not been eliminated (occur in 3%-20% patients).
One report estimated 200,000 repeat revascularizations are performed every year in the United States for DES failure.

Introductions (2)

- **Risk factors for restenosis:**
  2. Lesion-associated: small or longer lesions, diffuse lesion, bifurcation, calcification, et al.
  3. Stent-associated: Zotarolimus- or Everolimus- stents is superior to Paclitaxel-stents
  4. Stenting technique: associated with PCI experience
     - (stent-underexpansion; residual uncovered plaques)
Options for DES restenosis:

1. Simple balloon dilation,
2. Cutting balloon,
3. Restenting with the same DES,
4. Restenting with a new-generation DES,
5. Redilation with a drug-eluting balloon
6. Vascular brachytherapy
7. Bypass surgery
8. Oral therapy (?)
Mechanism of Cilostazol

Cilostazol → Phosphodiesterase-3

\[ \text{cAMP} \uparrow \] → ADP \[ \downarrow \]

Platelet activation

Mechanism of Cilostazol

Cilostazol → cAMP

- Antioncogenes (p53, p21) ↑
- HGF ↑
- P-selectin, Mac-1 ↑

VSMC apoptosis ↑

VSMC growth ↓

Neointimal hyperplasia and restenosis ↓

Objectives

- **Efficacy evaluation**: compared the risk of cardiac events and restenosis between **triple antiplatelet therapy** (TAT, addition of cilostazol to aspirin and clopidogrel) and conventional **dual antiplatelet therapy** (DAT, aspirin and clopidogrel) in **drug-eluting stents** (DES) implantation patients.

  1. **Cardiac events**: MACE, TVR, TLR, MI and cardiac-/all-cause death;
     (MACE: death, fatal or nonfatal MI and ischemic-driven TLR)
  2. **Restenosis**: angiographic restenosis and late loss

- **Safety evaluation**: compared the risk of stent thrombosis, bleeding and gastrointestinal trouble between TAT and DAT group.
Methods

- Two independent reviewers systematically searched PUBMED, MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials
- From January 2001 to June 2011
- For all randomized controlled trials (RCT) and reporting clinical outcomes.
Methods

- **key words:**

  1. “cilostazol” and “aspirin” and “clopidogrel”,
  2. “triple antiplatelet” and “dual antiplatelet”,
  3. “drug-eluting stent” or “coronary intervention”
     or “stent implantation”
# Included and excluded criteria

- **Included:**
  
  (a) Direct comparison between the effect of TAT and DAT  
  (b) DES implantation  
  (c) outcomes were published in the last 10 years  
  (d) at least one of following outcomes was reported: MACE/TVR/TLR/angiographic restenosis/late loss;  
  (e) more than 6-month follow-up

- **Excluded:**
  
  (a) duplicate reports  
  (b) lack of detailed data of stent type (BMS or DES)  
  (c) studies in which end-points were not evaluated  
  (d) uncontrolled studies
(1) Five studies were included.
(2) 3,526 patients were included (1,761 patients in TAT group and 1,765 patients in DAT group)
(3) Clinical follow-up period was 9 to 12 months.
Excluded important studies

  ---- The period of follow up only 1-6 month;
- **Douglas 2005** and **Chen 2006:**
  ---- BMS implantation;
- **Chen KY:**
  ---- a nonrandom trial;
# Results—Baseline clinical characteristics

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Sample size</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>Diabetes (%)</th>
<th>Primary end point</th>
<th>Follow-up(m)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAT</td>
<td>DAT</td>
<td>TAT</td>
<td>DAT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee SW 2007</td>
<td>250</td>
<td>250</td>
<td>60.9</td>
<td>61.2</td>
<td>321(64.2%)</td>
<td>166(33.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>in-stent late loss</td>
<td></td>
</tr>
<tr>
<td>Lee SW 2008</td>
<td>200</td>
<td>200</td>
<td>61.0</td>
<td>60.7</td>
<td>232(58.0%)</td>
<td>400(100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>in-stent late loss</td>
<td></td>
</tr>
<tr>
<td>Han Y 2009</td>
<td>604</td>
<td>608</td>
<td>59.6</td>
<td>60.2</td>
<td>889(73.3%)</td>
<td>263(21.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MACE</td>
<td></td>
</tr>
<tr>
<td>Lee SW 2011</td>
<td>250</td>
<td>249</td>
<td>60.9</td>
<td>62.1</td>
<td>353(70.7%)</td>
<td>176(35.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>in-stent late loss</td>
<td></td>
</tr>
<tr>
<td>Suh JW 2011</td>
<td>457</td>
<td>458</td>
<td>64.8</td>
<td>64.0</td>
<td>647(70.7%)</td>
<td>307(33.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MACE,TLR,MI, cardiac death</td>
<td></td>
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</table>
## Results -- Angiographic characteristics and follow-up data

<table>
<thead>
<tr>
<th>variables</th>
<th>Lee SW 2007</th>
<th>Lee SW 2008</th>
<th>Han Y 2009</th>
<th>Lee SW 2011</th>
<th>Suh JW 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAT</td>
<td>DAT</td>
<td>TAT</td>
<td>DAT</td>
<td>TAT</td>
</tr>
<tr>
<td>Sample size</td>
<td>250</td>
<td>250</td>
<td>200</td>
<td>200</td>
<td>604</td>
</tr>
<tr>
<td>Cilostazol dosage (mg/d)</td>
<td>200</td>
<td>--</td>
<td>200</td>
<td>--</td>
<td>200</td>
</tr>
<tr>
<td>Cilostazol duration (m)</td>
<td>6</td>
<td>--</td>
<td>6</td>
<td>--</td>
<td>6</td>
</tr>
<tr>
<td>DES usage</td>
<td>250</td>
<td>250</td>
<td>200</td>
<td>200</td>
<td>328</td>
</tr>
<tr>
<td>--SES</td>
<td>125</td>
<td>125</td>
<td>100</td>
<td>100</td>
<td>--</td>
</tr>
<tr>
<td>--PES</td>
<td>125</td>
<td>125</td>
<td>100</td>
<td>100</td>
<td>--</td>
</tr>
<tr>
<td>--ZES</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>2.84</td>
<td>2.82</td>
<td>2.81</td>
<td>2.78</td>
<td>--</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>34.3</td>
<td>34.0</td>
<td>26.7</td>
<td>26.3</td>
<td>--</td>
</tr>
<tr>
<td>Total stent length (mm)</td>
<td>41.4</td>
<td>40.3</td>
<td>33.5</td>
<td>32.1</td>
<td>37.9</td>
</tr>
<tr>
<td>Late loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--in segment (mm)</td>
<td>0.34</td>
<td>0.51</td>
<td>0.42</td>
<td>0.53</td>
<td>--</td>
</tr>
<tr>
<td>--in stent (mm)</td>
<td>0.22</td>
<td>0.32</td>
<td>0.25</td>
<td>0.38</td>
<td>--</td>
</tr>
</tbody>
</table>
Results—Risk of MACE

- A total of 132 events (7.50%) occurred in TAT group, and 197 events (11.16%) occurred in DAT.
- TAT was associated with a 36% reduction in major adverse cardiac events (MACE) (OR=0.64; 95% CI=0.51-0.81, P<0.01)
Results—Risk of MACE (subgroup analysis)

6-9 month follow-up

<table>
<thead>
<tr>
<th>Group</th>
<th>TAT</th>
<th>DAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>2.89</td>
<td>7.33</td>
</tr>
</tbody>
</table>

P = 0.003

Intergroup difference P = 0.09

12 month follow-up

<table>
<thead>
<tr>
<th>Group</th>
<th>TAT</th>
<th>DAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>9.08</td>
<td>12.47</td>
</tr>
</tbody>
</table>

P = 0.005

△ 30%

△ 62%
Results—Risk of MI, cardiac/all-cause death

Myocardial infarction: Odds Ratio 0.92 (0.42--2.03), P=0.84

Cardiac death: Odds Ratio 0.62 (0.33--1.15), P=0.13

All-cause death: Odds Ratio 0.75 (0.46--1.24), P=0.27
Results—Risk of TVR

- A total of 199 patients received TVR after DES implantation, with 76 patients (5.83%) in TAT group and 123 patients (9.41%) in DAT group.
- TAT was associated with a 40% reduction in the incidence of TVR ($P<0.01$).
Results—Risk of TVR (subgroup analysis)

- 6-9 month follow-up:
  - TAT: 3.56% (P=0.01)
  - DAT: 7.56%

- 12 month follow-up:
  - TAT: 7.03% (P=0.01)
  - DAT: 10.39%

Intergroup difference P=0.31
**Results—Risk of TLR**

- TLR was needed in a total of 55 patients assigned to TAT group and 88 patients assigned to DAT group.
- The incidence of TLR in TAT group was significantly lower than that in DAT group (4.51% vs. 7.61%, P=0.02)
Results—Risk of TLR (subgroup analysis)

6-9 month follow-up

- TAT: 2.67%
- DAT: 6.89%
- Inter-group difference: P = 0.004

12 month follow-up

- TAT: 6.08%
- DAT: 8.06%
- Inter-group difference: P = 0.28

Overall trend: 63%
Results—Risk of restenosis

In-segment restenosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee SW 2007</td>
<td>0.57</td>
<td>[0.28, 1.13]</td>
</tr>
<tr>
<td>Lee SW 2008</td>
<td>0.47</td>
<td>[0.23, 0.95]</td>
</tr>
<tr>
<td>Lee SW 2011</td>
<td>0.56</td>
<td>[0.33, 0.94]</td>
</tr>
</tbody>
</table>

P<0.01

In-stent restenosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee SW 2007</td>
<td>0.53</td>
<td>[0.37, 0.77]</td>
</tr>
<tr>
<td>Lee SW 2008</td>
<td>0.56</td>
<td>[0.39, 0.83]</td>
</tr>
<tr>
<td>Lee SW 2011</td>
<td>0.56</td>
<td>[0.39, 0.83]</td>
</tr>
</tbody>
</table>

P<0.01
Results—Change of late loss

In-segment late loss

- Lee SW 2007: -0.35 [-0.54, -0.15]
- Lee SW 2008: -0.22 [-0.44, -0.01]
- Lee SW 2011: -0.28 [-0.47, -0.09]

In-stent late loss

- Lee SW 2007: -0.20 [-0.39, -0.01]
- Lee SW 2008: -0.24 [-0.46, -0.03]
- Lee SW 2011: -0.21 [-0.40, -0.02]

P<0.01

P<0.01
Results—risk of stent thrombosis
Results—Risk of bleeding

![Graph showing odds ratios with confidence intervals for different studies.](image)
Results—Risk of gastrointestinal trouble
Conclusions

- Addition of cilostazol to DAT reduced the incidence of MACE, which was most benefit from the reduction of TLR risk.
- TAT could also reduce the risk of restenosis and late loss in patients after DES implantation.
- TAT do not increase the bleeding risk after DES implantation.
Limitations

- The number of eligible trials was relatively small
- There were still 48% of patients underwent BMS implantation in Han Y’s study, which could influence the clinical application of our findings. However, after eliminating this trial, the risk of MACE, TVR and TLR between TAT and DAT group was still similar to our meta-analysis
- The longest period of follow-up was 12months in the enrolled trials; therefore, long-term follow-up will be needed to assess the long-term outcomes.
Thank you for your attention!