Impact of Adjunctive Cilostazol Therapy on Platelet Function Profiles in Patients With and Without Diabetes Mellitus on Aspirin and Clopidogrel Therapy


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Cilostazol Effect on P2Y_{12} Receptor Signaling

Adapted from Angiolillo DJ et al JACC 2007

Cilostazol

P2X_1

ATP

Ca^{2+} flux

Shape change

G_q

G_{12}

“Rho”

Shape change

IP3

DAG

PKC

Ca^{2+} mobilization

GP IIb/IIIa receptor activation

Initiation of Platelet Aggregation

PIP2

PLCB

P2Y_{12}

ADP

PKB/Akt

Rap1b

GP IIb/IIIa receptor activation

Stabilization of Platelet Aggregation

MLCK-P

Granule secretion

Pi3K

AC

cAMP

VASP

VASP-P

GP IIb/IIIa receptor activation

Cilostazol

PDE

HOOC

N

Cl

HOOC

PGE_1

β

γ

α

i

PDE-III

PDE-III
In patients undergoing PCI, cilostazol therapy in addition to DAPT (AAS and a thienopyridine) reduces the risk of ischemic outcomes, including ST, compared with DAPT. Despite higher platelet inhibition, cilostazol does not increase bleeding outcomes. Cilostazol benefit is higher in high-risk settings, such as DM. Cilostazol impacts intraplatelet cAMP levels, abnormal in DM patients, which may contribute to explain its particular benefit in this population.
OPTIMUS-2: Cilostazol Antiplatelet Effect in Diabetic Patients on DAPT

$\Delta = 23.6$

The different degree of clinical benefit observed with cilostazol in DM patients compared with non-DM patients may be due to a more effective inhibition of platelet function in DM patients.

**Aim:** To compare cilostazol-induced effects on platelet P2Y$_{12}$ signaling in patients with and without DM on treatment with standard DAPT.
Patients with and without DM with stable coronary artery disease on aspirin (81 mg) + clopidogrel (75 mg) therapy for $\geq 1$ month

Cilostazol 100 mg b.i.d. for 2 weeks

Placebo b.i.d. for 2 weeks

Randomization

Baseline
Visit 1

2 weeks
Visit 2

4 weeks
Visit 3

Cilostazol 100 mg b.i.d. for 2 weeks

Placebo b.i.d. for 2 weeks

Study Design

Prospective, randomized, double-blind, placebo-controlled, cross-over design

Primary endpoint: comparison of the mean differences in P2Y$_{12}$ reactivity index (PRI) following cilostazol versus placebo achieved in patients with and without diabetes
Study Population

Patients assessed for eligibility (n=736)

- Not meeting inclusion criteria (n=486)
- Eligible patients (n=250)
- Refused (n=139)

Randomized (n=111): 58 DM and 53 non-DM

- Platelet Function (V1 - baseline)

  Allocated to cilostazol 100 mg b.i.d. for 2 weeks
  - DM (n=31) and non-DM (n=28)
  - Discontinued due to side effects: DM (n=8) and non-DM (n=3)
  - Decided to withdraw consent: DM (n=1) and non-DM (n=1)
  - Invalidated samples: DM (n=0) and non-DM (n=0)

  Allocated to placebo b.i.d. for 2 weeks
  - DM (n=27) and non-DM (n=25)
  - Discontinued due to side effects: DM (n=1) and non-DM (n=2)
  - Decided to withdraw consent: DM (n=0) and non-DM (n=2)
  - Invalidated samples: DM (n=0) and non-DM (n=2)

- Platelet Function (V2 - 2 weeks)
  - Patients analyzed: 48 DM and 43 non-DM

  Crossover to placebo b.i.d. for 2 weeks
  - DM (n=22) and non-DM (n=24)
  - Discontinued due to side effects: DM (n=2) and non-DM (n=1)

  Crossover to cilostazol 100 mg b.i.d. for 2 weeks
  - DM (n=26) and non-DM (n=19)
  - Discontinued due to side effects: DM (n=6) and non-DM (n=3)

- Platelet Function (V3 - 4 weeks)
  - Patients analyzed: 40 DM and 39 non-DM
Platelet Function Analysis

- **Primary endpoint:**
  - VASP flow cytometric analysis: P2Y\textsubscript{12} reactivity index (PRI)

- **Secondary endpoints:**
  - Light transmittance aggregometry (LTA): AggLate
    - ADP 5 and 20 µmol/L + PGE1
  - VerifyNow® (VN) P2Y12 assay: PRU and %IPA
  - Thromboelastography®: R and TMRTG
## Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DM (n = 40)</th>
<th>No-DM (n = 39)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>60.5 ± 8.5</td>
<td>61.2 ± 8.5</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Gender (male), n (%)</strong></td>
<td>25 (63)</td>
<td>28 (72)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>30 (77)</td>
<td>30 (75)</td>
<td>1.00</td>
</tr>
<tr>
<td>African-American</td>
<td>9 (23)</td>
<td>7 (18)</td>
<td>0.82</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Risk factors/past medical history, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Smoking</td>
<td>11 (28)</td>
<td>19 (49)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>40 (100)</td>
<td>37 (95)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38 (95)</td>
<td>34 (87)</td>
<td>0.26</td>
</tr>
<tr>
<td>Body mass index</td>
<td>31.7 ± 5.4</td>
<td>29.0 ± 6.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>24 (60)</td>
<td>25 (64)</td>
<td>0.89</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>13 (33)</td>
<td>8 (21)</td>
<td>0.34</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>21 (53)</td>
<td>24 (62)</td>
<td>0.56</td>
</tr>
</tbody>
</table>
Concomitant Medical Treatments

<table>
<thead>
<tr>
<th>Treatments, n (%)</th>
<th>DM (n = 40)</th>
<th>No-DM (n = 39)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>30 (75)</td>
<td>34 (87)</td>
<td>0.27</td>
</tr>
<tr>
<td>Nitrates</td>
<td>8 (20)</td>
<td>15 (38)</td>
<td>0.12</td>
</tr>
<tr>
<td>ACE inhibitors/ARB</td>
<td>32 (80)</td>
<td>28 (72)</td>
<td>0.55</td>
</tr>
<tr>
<td>PPI-2C19 specific</td>
<td>13 (33)</td>
<td>9 (23)</td>
<td>0.50</td>
</tr>
<tr>
<td>PPI-Non 2C19 specific</td>
<td>4 (10)</td>
<td>0</td>
<td>0.12</td>
</tr>
<tr>
<td>CYP3A4 metabolizing statin</td>
<td>26 (65)</td>
<td>30 (77)</td>
<td>0.36</td>
</tr>
<tr>
<td>Non-CYP3A4 metabolizing statin</td>
<td>9 (23)</td>
<td>7 (18)</td>
<td>0.82</td>
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</tbody>
</table>
**P2Y\textsubscript{12} Reactivity Index (PRI)**

\[ \Delta = 23.1^* \]

\[ \Delta = 15.0^* \]

\[ p < 0.0001 \]

\[ p < 0.0001 \]

* \( p \) between \( \Delta = 0.039 \)

*Diabetics*  

*Non Diabetics*
## VN-P2Y$_{12}$ and LTA Data

<table>
<thead>
<tr>
<th></th>
<th>DM between-treatment difference (95% CI)</th>
<th>Non-DM between-treatment difference (95% CI)</th>
<th>p value</th>
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<tbody>
<tr>
<td><strong>VN-P2Y$_{12}$ assay</strong></td>
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<tr>
<td>%IPA</td>
<td>17.9 (12.7-23.1)</td>
<td>10.7 (6.4-15.0)</td>
<td>0.035</td>
</tr>
<tr>
<td>PRU</td>
<td>58.2 (41.5-74.8)</td>
<td>35.0 (17.8-52.1)</td>
<td>0.031</td>
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<td><strong>LTA</strong></td>
<td></td>
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<tr>
<td>ADP 20µmol/L+PGE$_1$</td>
<td>16.7 (11.5-21.8)</td>
<td>10.5 (5.9-15.1)</td>
<td>0.039</td>
</tr>
<tr>
<td>ADP 5µmol/L+PGE$_1$</td>
<td>9.8 (5.5-14.0)</td>
<td>4.9 (1.7-8.0)</td>
<td>0.026</td>
</tr>
</tbody>
</table>
Cilostazol and Thombin Generation: TEG Data

- R Diabetics: p = 0.78
- TMRTG Diabetics: p = 0.20
- R Non-Diabetics: p = 0.20
- TMRTG Non-Diabetics: p = 0.27
Conclusions

- Cilostazol reduces platelet reactivity both in patients with and without DM

- Platelet inhibition achieved with cilostazol is enhanced in DM patients

- Despite the marked platelet inhibition, cilostazol does not alter thrombin-mediated hemostatic processes
  - This may contribute to explain its ischemic benefit without increased risk of bleeding