OUTSIDE START Cilostazol Bridge Study:
8 year experience with Outpatient Cilostazol Bridging in High Stent Thrombosis Risk Paclitaxel Drug Eluting Stents in Patients having Surgery during the Proven at risk Period

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OUTSIDE START Cilostazol Bridge Study:

(OUTpatient peri-Surgical Interruption of Drug Eluting STent Antiplatelet Regimen Testing a Cilostazol) Bridge Study

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Background:

Dual antiplatelet therapy (DAPT) with a P2Y12 inhibitor + aspirin (ASA) ↓ drug-eluting stent (DES) thrombosis.

Annually 5%-10% of DES patients (pts) advised DAPT interruption to reduce peri-operative (peri-op) bleeding.

Premature DAPT stoppage esp. early during first 1 year after (post) early generation DES has high stent thrombosis (ST) rates of 10-20%, 25% in first 1 month. (Serruys, 2009 and others)

Paclitaxel eluting DES (PES) = highest ST rates off DAPT prematurely with ↑ major adverse cardiac event (MACE) rates (= 7% >1yr post implant) persisting to 30 mths post PES placed. (DAPT & TL-PAS studies, 2014)

There is no consensus as to the best bridging in DES patients taken prematurely off DAPT preoperatively.
Background:

DES bridging in pts. taken off DAPT pre-op has been tried with:

- ASA alone, heparin, GP-2B3A inhibitors, low molecular weight heparins, IV Cangelor:

- all either have limited/variable success, high cost and/or require prolonged pre, peri and post-op inpt. IV therapy.

Cilostazol as an antiplatelet agent:

- DES studies show cilostazol benefit as a supportive/added third antiplatelet agent in high risk pts → =/↓MACE &/or restenosis. (eg. DECLARE-DM, DECLARE-LONG, RCT meta-analyses of others/Korean studies).

- 1 RCT study (CIDES) substituted cilostazol for clopidigrel + asa begin. 1 month after DES placed with = low MACE and 50%↓ (=8 vs16%) restenosis versus traditional DAPT by 7 month F/U.

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Background:

Cilostazol as an antiplatelet agent:

- Cilostazol is a phosphodiesterase inhibitor-type 3 approved for use in claudication with warnings of potential to worsen CHF: C/I’d in moderate-severe heart failure; ↑effect = severe renal failure, azoles, diltiazem, omeprazole

- Works by ↑C-AMP method to reversibly inhibit platelet activation and aggregation.

- Half life= 10-12 hours, thus effect can be greatly ↓ by 1/2 to 3/4 by 48-60 hrs, 90% by 72hrs post stopping.

- Prior studies suggests a shorter and less aggressive effect on bleeding times/pero-op than thienopyridines.

- DES studies extensively studied in Korea as populations has as much as 50-60% prevalence of lost function CYP219 allele with relatively high on treatment platelet reactivity on clopidigrel associated with ↑ MACE risk.
Background:

- Initial idea to use cilostazol was out of clinical necessity and not intended as research:

- based on anecdotal literature of cilostazol as an antiplatelet agent and on 2003 CRT conference suggesting cilostazol as possible bridging:

- we used as “last resort” in 6 inpts. for urgent/unavoidable surgeries in 2005: bridging ranged from 3-6 mths post sirolimus or pacilitaxel eluting DES placed: good success with minimal nuisance bleeds/no MACE.

- received repeated calls from surgeons (up to 4-5/week) in high-volume practice of over 800 DES pts >90% paclitaxel DES from 2005-2007 to advise urgent approach to interrupting DAPT peri-op. Pts offered choice of delaying vs bridging with inpt IV Rx’s and outpt LMWHeparin: majority chose cilostazol.

- local surgeons were very bleeding adverse, anti-LMWH and GP2B3A: insisted on stopping both asa & clopidigrel and thus, inadvertent experience gained with this (in retrospect) ↑risk peri-op ST risk population.
**Methods:** - 2005-2012: cilostazol peri-op DES bridging used in consecutive agreeable pts advised to stop both DAPT.

- Initially DAPT only ACC advised for 6 mths post PES 2003-2006, later extended to 1 yr (2007), and favored indefinitely by 2008, given late ST reports out to several yrs.

- Respecting the concurrent ACC DAPT advice in effect at surgery’s time, early bridging experience was done in urgent unavoidable surgeries during the high risk first 6 and later 12 mths post DES.

- by 2008, after ↑confidence/early success in some 28 urgent pts < 1 yr post DES, cilostazol DES surgical bridging of pts off DAPT offered to higher bleeding risk, semi-urgents and to all DES pt’s including >1-5 yrs post DES placement (given the very late ST reports/MACE seen). Subsequently, opted to evaluate and report our 8 year experience.

- MACE (death, MI or urgent revasc.) felt relevant if occurred off DAPT peri-op or within 30 days post-op.

- We hereby report retrospective results for **peri-op cilostazol bridging off DAPT in a consecutive PES pt sub-series of all those DES pts.** bridged between 2 wks to 60 mths post latest PES in the 8 yr period from 2005-2012.
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**Methods:**

2 cilostazol dosing regimens were tailored to reduce risk and degree of expected peri-op bleeding.

- Both DAPT stopped for all after last doses on 8th day pre-op and cilostazol 100mg po bid started on the 7th pre-op day

- **For low risk-moderate bleeding surgeries:**
  - cilostazol stopped 24-30 hrs pre-op after 1300 mg goal and **DAPT resumption advised at 12-24 hrs post-op.**

- **For high bleeding risk surgeries (eg. epidurals; back, urologic, plastic):**
  - cilostazol stopped 54-60 hrs pre-op after 1000 mg goal and **DAPT resumption advised 24-36 hrs post-op.**

- for those who didn’t tolerate cilostazol 100mg, dose was reduced to 50mg po bid.

- pts deemed adequately bridged if they took >600 mg of cilostazol pre-op and resumed DAPT within 48 hrs post-op.

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Results:

- 108 pts (with at least 1 PES) with 183 consecutive surgeries advised DAPT stoppage were bridged by a cilostazol and DAPT resumption protocol. 9% pts had side effects (headache, gi upset, palpitations, dizzy) → ↓ dose or under-bridged.

- 104 (57%) surgeries bridged with full 1300 mg protocol; 60 (32%) surg’s bridged with 1000 mg for high bleeding risk or pt intolerance issues; 10 (5.5%) bridged with 650-900 mg due to intolerance or shortened pre-op timeline;

- other 8 pts had “inadequate” pre-op dose of 0-600 mg cilostazol; 8 patients didn’t resume DAPT within 72 hrs post-op.

- Bridging of following surgeries occurred:
  - low bleeding risk: (dental/oral surgery) (n=10); dermatologic surgery (n=3);
  - moderate bleeding risk: (GI endoscopy w biopsy (n=54); cardiovascular/thoracic (n=13); orthopedic (n=13);
  - abdominal/gyne (n=10); head and neck (n=7); plastic/reconstructive (n=3);
  - high bleeding risk: (back surgeries/epidurals (n=55); urologic (n=12); high risk ophthalmologic (n=3).
**Results:**

- 183 pts = 1.7 +/- 1 PES/pt; 70% male, 64 +/- 9 yrs; aver. PES diam 3.1 +/- 0.3 mm; Total at risk DES= 42 +/- 20 mm.

- 132/132 surgeries successfully bridged by “adequate” cilostazol dosing/DAPT resumed by 48 hrs post-op protocols without bleeding within the literature confirmed 30 Month paclitaxel DES extended risk period off DAPT.

- 171/183 surgeries = adequately bridged @optimal dose of 100mg bid (or 50mg if intolerant) and DAPT resumed by 48 hrs.

- 100% success (=0% MACE) seen in 171 full bridged and surprisingly in 8/12 pts who were incompletely bridged.

- Overall, a very low MACE rate of 1.8 % (= 1/55 cilostazol bridged surgeries) off DAPT in highest risk first 12 mths post PES: ie. vs historical MACE rates of 10-25% with paclitaxel DES in the first yr post DES if DAPT stopped prematurely.
## Results:

<table>
<thead>
<tr>
<th>Timing Surgical Bridging by # Months Post-PES Placed &amp; # bridged</th>
<th>Adequate Cilostazol Bridge/DAPT Resumption Dosing</th>
<th>Suboptimal (or No) Cilostazol Bridge/DAPT Resumption “Controls”</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 mths: = 26 pts</td>
<td>No MACE = n (%) 23 (88%)</td>
<td>No MACE = n (%) 3 (12%)</td>
</tr>
<tr>
<td>&gt;6-12 mths: n = 29 pts</td>
<td></td>
<td>Actual MACE = n (%) 1 (3.4%) by Event type &amp; timing post PES placed</td>
</tr>
<tr>
<td>&gt;12-24 mths: n = 49 pts</td>
<td></td>
<td>(Events occurred only in those without any bridging)</td>
</tr>
<tr>
<td>&gt;24-36 mths: n = 48 pts</td>
<td>48 (98%)</td>
<td>1 (3.4%) = urgent repeat PCI @ 7.5 mths (2005)</td>
</tr>
<tr>
<td>&gt;36-60 mths: n = 31 pts</td>
<td>45 (94%)</td>
<td>1 (2.1%) = urgent repeat PCI @ 28 mths</td>
</tr>
<tr>
<td>N = 183 total N=171 (93%) N=8 (4.4%) N=4 (2.2%)</td>
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MACE Results in comparative unbridged “controls”:

- 12 “un/underbridged” pts took < 600 mg of cilostazol and/or failed to resume DAPT by 72 hrs post-op due to surgeon aborting protocol with little if any cilostazol started and/or no DAPT resumed by 3-7 days post-op.

- 4/12 essentially “un-bridged” pts (= 33%) had MACE or 4/183 (= 2.1% MACE by overall bridge intention to treat)

- Majority: = 3 of 4/12 PES pts with MACE off peri-op DAPT without bridging occurred > 1-4 yrs post PES placed.

- In 4 pts with MACE: 2/4 took only “inadequate” cilostazol dosing pre-op (200 and 300 mg), missing more than 5.5 days and failed any DAPT resumption, each having urgent PCI on post-op day 7. (13-14 days post any cilostazol taken)

- 2 pts. quit DAPT, refused/advised by surgeon not to take any cilostazol pre-op nor alternative bridging and didn’t resume DAPT post-op: each had MACE off DAPT on pre-op day # 2 (MI) and post-op day # 2 (death).
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Limitations:

- Most contemporary surgeries don’t stop ASA when taken off DAPT, thus this series may theoretically be higher ST risk pts than other studies assessing PES risk off DAPT?

- retrospective, non-randomized, thus subject to usual methodological biases and protocol violations were difficult to control compared to an actual trial.

- Less extensive experience with similar success in our larger series with current generation of DES and bare metal stents, but beyond scope of this focused report.

- This study is thus hypothesis generating: all these concepts ideally should be further verified preferably in controlled trials involving current generation of DES and bare metal stents with all current anti-platelets agent in current use and respecting current DAPT duration guidelines.

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SUMMARY:

- Cilostazol peri-op DES bridging off DAPT is feasible with low bleeding and low MACE in highest risk Paclitaxel DES pts. bridged during high ST rates period both <1yr and >several yrs post PES implanted.

- When PES pts are off DAPT, bridging success requires strict/aggressive patient and surgeon counselling in adhering to the tested cilostazol regimen and DAPT resumption schedules: Peri-op bridging non-compliance with PES’s during documented ST risk period appears a considerable MACE risk as seen in our “un-bridged” pts:

- close patient and surgeon involvement/regular discussion and post-op follow-up appears essential to bridging success: alternative strategies may be in-order in those in which protocol non-compliance occurs: These may include: inpatient monitoring, alternative bridging, consider cancelling procedure, insistence on urgent DAPT resumption.

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