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

Charles L. Laham, MD, FSCAI, Michael S Chandra, MD, Richard Kettelkamp, MD, PhD, FSCAI, Nicolas W Shammas, MD, MS, FSCAI

Holy Family Memorial Hospital, Manitowoc, WI; Unitypoint Clinic Cardiology, Cedar Rapids, IA; Midwest Cardiovascular Research Foundation, Davenport, IA

Charles Laham, MD, FSCAI, SCAI LBCT, May 2015

OUTSIDE START Cilostazol Bridge Study:

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

Charles L. Laham, MD, FSCAI, Michael S Chandra, MD, Richard Kettelkamp, MD, PhD, FSCAI, Nicolas W Shammas, MD, MS, FSCAI

No relevant Author Disclosures pertaining to this talk/study

OUTSIDE START Cilostazol Bridge Study: 8 year experience

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.

Charles Laham, MD, FSCAI, SCAI LBCT, May 2015

OUTSIDE START Cilostazol Bridge Study: 8 year experience

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.

Charles Laham, MD, FSCAI, SCAI LBCT, May 2015

OUTSIDE START Cilostazol Bridge Study: 8 year experience

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/peri-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.

OUTSIDE START Cilostazol Bridge Study: 8 year experience

Background:

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

- based on anecdoctal 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 restropsect) ↑risk peri-op ST risk population.

OUTSIDE START Cilostazol Bridge Study: 8 year experience

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.

Charles Laham, MD, FSCAI, SCAI LBCT, May 2015

OUTSIDE START Cilostazol Bridge Study: 8 year experience

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.

Charles Laham, MD, FSCAI, SCAI LBCT, May 2015

OUTSIDE START Cilostazol Bridge Study: 8 year experience

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).

-

Charles Laham, MD, FSCAI, SCAI LBCT, May 2015

OUTSIDE START Cilostazol Bridge Study: 8 year experience

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.**

- 171/183surgeries = 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.

Charles Laham, MD, FSCAI, SCAI LBCT, May 2015

OUTSIDE START Cilostazol Bridge Study: 8 year experience

Results:

Timing Surgical Bridging by # Months Post-PES Placed & # bridged	Adequate Cilostazol Bridge/DAPT Resumption Dosing	Suboptimal (or No) Cilostazol Bridge/DAPT Resumption "Controls"	
	No MACE = n (%)	No MACE = n (%)	Actual MACE = n (%) by Event type & timing post PES placed (Events occurred only in those without any bridging)
<6 mths: = 26 pts	23 (88%)	3 (12%)	----
>6-12 mths: n = 29 pts	25 (86%)	3 (10%)	1 (3.4%) = urgent repeat PCI @ 7.5 mths (2005)
>12-24 mths: n = 49 pts	48 (98%)	-----	1 (2.0%) = death at 12.5 mths
>24-36 mths: n = 48 pts	45 (94%)	2 (4.2%)	1 (2.1%) = urgent repeat PCI @ 28 mths
>36-60 mths: n = 31 pts	30 (97%)	-----	1 (2.9%) = mi at 40 mths
N = 183 total	N=171 (93%)	N=8 (4.4%)	N=4 (2.2%)

Charles Laham, MD, FSCAI, SCAI LBCT, May 2015

OUTSIDE START Cilostazol Bridge Study: 8 year experience

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).

-

OUTSIDE START Cilostazol Bridge Study: 8 year experience

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.**

Charles Laham, MD, FSCAI, SCAI LBCT, May 2015

OUTSIDE START Cilostazol Bridge Study: 8 year experience

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.

- .

Charles Laham, MD, FSCAI, SCAI LBCT, May 2015

OUTSIDE START Cilostazol Bridge Study: 8 year experience

Overview Summary Results:

- **132/132 surgeries successfully bridged by "adequate" cilostazol dosing protocol without bleeding within the literature confirmed 30 Month paclitaxel DES extended risk period off DAPT, provided DAPT resumed by 48 hrs post-op.**

- 171/183surgeries = 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.**

- **4/12 inadequately bridged pts (= 33%) had MACE or 4/183 (= 2.1% MACE by overall cilostazol bridge intention to treat)**

- 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 year post DES if DAPT stopped prematurely.

Charles Laham, MD, FSCAI, SCAI LBCT, May 2015