Current Status of Antiplatelet Therapy in Acute Coronary Syndromes: Duration of DAPT in 2016

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Faculty Disclosure (12 months):

• **Research and Clinical Trials:** Abbott Vascular, Alere, Astra Zeneca, Bayer, BMS, Boehringer Ingelheim, CIHR, CSL Behring LLC, Edwards Lifesciences, Eli Lilly, Jansen, Johnson and Johnson, Matrizyme Pharma, Pfizer, Population Health Research Institute, University of Alberta Hospital Foundation
• **Honoraria:** Astra Zeneca, Bayer
• **Advisory Board:** Astra Zeneca, Bayer, Bristol Myers-Squibb/Pfizer
• **Other:** University of Alberta (employee), Alberta Health Services (Clinical privileges) and President, The Canadian Centre for Clinicians and Scientists
Reflections on DAPT therapy

We have to consider patients with Acute Coronary Syndromes separately from those with Elective Revascularization.

1. With available data – is it fair to discuss DAPT as a therapy versus C-DAPT, P-DAPT, T-DAPT?
2. Can we identify patients for prolonged versus short duration of therapy?
3. With upcoming trials – is DAPT going to remain the standard of care versus ticagrelor monotherapy, or dual pathway strategies?
Antiplatelet Therapy with ASA and Clopidogrel Improves Major Outcomes in NSTE ACS

Primary Endpoint: MI/Stroke/CV Death

- Placebo + ASA (n=6,303)
  - Cumulative Hazard Rate: 11.4%
  - RR: 0.80
  - 95% CI: 0.72–0.90
  - p<0.001

- Clopidogrel + ASA (n=6,259)
  - Cumulative Hazard Rate: 9.3%
  - RR: 0.80
  - 95% CI: 0.72–0.90
  - p<0.001

20% RRR

Major Bleeding

- Placebo + ASA (n=6,303)
  - Incidence: 3.7%
  - RR: 1.38
  - 95% CI: 1.13–1.67
  - p<0.001

- Clopidogrel + ASA (n=6,259)
  - Incidence: 2.7%

All patients received ASA and UFH or LMWH

CURE Yusuf S, et al. NEJM. 2001;345:494
Timing of Randomization and Treatment in Dual Oral Antiplatelet Trials

< 24 hrs

- CURE
  - Clopidogrel
- PLATO
  - Ticagrelor

Symptom Onset → Presentation

Selective Invasive → Medical Management

Early Invasive → Coronary Angiography

- CURRENT
  - Clopidogrel
- TRITON
  - Prasugrel

NSTE ACS < 72 hrs
STEMI < 12 hrs

Timing of Randomization and Treatment in Dual Oral Antiplatelet Trials

< 24 hrs

CURE
Clopidogrel

PLATO
Ticagrelor

Symptom Onset

Presentation

Selective Invasive

Early Invasive

Coronary Angiography

Medical Management

Medical

CABG

PCI

CURRENT
Clopidogrel

TRITON
Prasugrel

NSTE ACS < 72 hrs

STEMI < 12 hrs

Mortality According to Continuation vs. Interruption of DAPT After PCI

### A

<table>
<thead>
<tr>
<th>Event/size</th>
<th>Continuation/ interruption</th>
<th>Weight (%)</th>
<th>Odds ratio M-H random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARCTIC-Interruption</td>
<td>7/635</td>
<td>9/624</td>
<td>0.76 (0.28–2.06)</td>
</tr>
<tr>
<td>REAL-ZEST LATE&lt;sup&gt;16&lt;/sup&gt;</td>
<td>20/1348</td>
<td>13/1334</td>
<td>1.53 (0.76–3.09)</td>
</tr>
<tr>
<td>All 12 months in interruption group</td>
<td>27/1983</td>
<td>22/1958</td>
<td>p&lt;sub&gt;het&lt;/sub&gt;=0.26</td>
</tr>
<tr>
<td>Odds ratio 1.18 (0.61–2.29) p=0.62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXCELLENT&lt;sup&gt;9&lt;/sup&gt;</td>
<td>7/712</td>
<td>4/715</td>
<td>1.76 (0.51–6.06)</td>
</tr>
<tr>
<td>RESET&lt;sup&gt;18&lt;/sup&gt;</td>
<td>8/1042</td>
<td>5/1044</td>
<td>1.61 (0.52–4.93)</td>
</tr>
<tr>
<td>OPTIMISE&lt;sup&gt;9&lt;/sup&gt;</td>
<td>45/1563</td>
<td>43/1556</td>
<td>1.04 (0.68–1.59)</td>
</tr>
<tr>
<td>PRODIGY&lt;sup&gt;7&lt;/sup&gt;</td>
<td>65/984</td>
<td>69/979</td>
<td>0.99 (0.70–1.42)</td>
</tr>
<tr>
<td>All 6 months or less in interruption group</td>
<td>125/4301</td>
<td>117/4294</td>
<td>p&lt;sub&gt;het&lt;/sub&gt;=0.73</td>
</tr>
<tr>
<td>Odds ratio 1.07 (0.82–1.38) p=0.63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>152/6284</td>
<td>139/6252</td>
<td>p&lt;sub&gt;het&lt;/sub&gt;=0.74</td>
</tr>
<tr>
<td>Odds ratio 1.09 (0.86–1.38) p=0.48; I&lt;sup&gt;2&lt;/sup&gt;=0%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### B

- Favours continuation
- Favours interruption

**Major Adverse Cardiac Events:** 1.05 (0.87–1.25); p=0.62
- **Stent Thrombosis:** 0.86 (0.53–1.39); p=0.41
- **Stroke:** 1.43 (0.93–2.21); p=0.10
- **MI:** 1.03 (0.79–1.34); p=0.84
Major Bleeding According to Continuation vs. Interruption of DAPT After PCI

“…no apparent benefit but instead harm with extension of DAPT…after stenting. The consistency between findings from all trials of such interruption suggests the need for a reappraisal of guidelines for DAPT after coronary stenting towards shorter duration of treatment.”

Collet et al Lancet 2014;384:1577-85
Study Design and Patient Population

**Enrolled:** Subjects treated with FDA-approved DES or BMS (16% NSTEMI, 10% STEMI)

**Excluded:** Subjects on oral anticoagulant therapy or with life expectancy < 3 years

Stent and Drug Types

Co-Primary Effectiveness End Point Stent Thrombosis

Co-Primary Effectiveness End Point: Major Adverse Cardiovascular and Cerebrovascular Events

Primary Analysis Period

12-30 Months:
HR 0.71 (0.59-0.85)
4.3% vs. 5.9%
P<0.001

285 vs. 211

Non-Stent Thrombosis Myocardial Infarction

55% of the MI benefit is not related to stent thrombosis

12-30 Months:
HR 0.59 (0.45-0.78)
1.8% vs. 2.9%
P<0.001

All-Cause Mortality

Primary Safety Endpoint

**GUSTO**
Moderate or severe bleeding 12-30 Months

All cause mortality

<table>
<thead>
<tr>
<th>Study group</th>
<th>N (events)</th>
<th>Control group</th>
<th>N (events)</th>
<th>HR for all-cause mortality</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASPAR</td>
<td>425 (24)</td>
<td>426 (17)</td>
<td></td>
<td></td>
<td>1.44 (0.77-2.68)</td>
</tr>
<tr>
<td>SPS3</td>
<td>1503 (113)</td>
<td>1517 (77)</td>
<td></td>
<td></td>
<td>1.52 (1.14-2.04)</td>
</tr>
<tr>
<td>CHARISMA</td>
<td>7802 (371)</td>
<td>7801 (374)</td>
<td></td>
<td></td>
<td>0.99 (0.86-1.15)</td>
</tr>
<tr>
<td>ACTIVE</td>
<td>3772 (825)</td>
<td>3782 (841)</td>
<td></td>
<td></td>
<td>0.98 (0.89-1.08)</td>
</tr>
<tr>
<td>OPTIMIZE</td>
<td>1556 (45)</td>
<td>1563 (43)</td>
<td></td>
<td></td>
<td>1.05 (0.69-1.59)</td>
</tr>
<tr>
<td>EXCELLENT</td>
<td>721 (7)</td>
<td>722 (4)</td>
<td></td>
<td></td>
<td>1.75 (0.51-5.88)</td>
</tr>
<tr>
<td>RESET</td>
<td>1058 (8)</td>
<td>997 (5)</td>
<td></td>
<td></td>
<td>1.59 (0.54-4.71)</td>
</tr>
<tr>
<td>DES-LATE</td>
<td>2531 (46)</td>
<td>2514 (32)</td>
<td></td>
<td></td>
<td>1.41 (0.91-2.22)</td>
</tr>
<tr>
<td>CREDO</td>
<td>1053 (18)</td>
<td>1063 (24)</td>
<td></td>
<td></td>
<td>0.75 (0.41-1.38)</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>987 (65)</td>
<td>983 (65)</td>
<td></td>
<td></td>
<td>1.00 (0.72-1.40)</td>
</tr>
<tr>
<td>CURE</td>
<td>6259 (369)</td>
<td>6303 (390)</td>
<td></td>
<td></td>
<td>0.95 (0.82-1.09)</td>
</tr>
<tr>
<td>ARCTIC-Interruption</td>
<td>635 (7)</td>
<td>624 (9)</td>
<td></td>
<td></td>
<td>1.32 (0.49-3.55)</td>
</tr>
<tr>
<td>SECURITY</td>
<td>717 (8)</td>
<td>682 (8)</td>
<td></td>
<td></td>
<td>1.00 (0.38-2.66)</td>
</tr>
<tr>
<td>Overall (DAPT not included)</td>
<td>29019 (1906)</td>
<td>28977 (1889)</td>
<td></td>
<td></td>
<td>1.03 (0.94-1.16)*</td>
</tr>
</tbody>
</table>

Q=14.87, p=0.25; I²=19.3%

DAPT

| Overall (DAPT included) | 34881 (2012) | 34763 (1973) |                           | 1.05 (0.96-1.19)* |

Q=17.68, p=0.17; I²=26.5%

Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis

Sammy Elmariah, Laura Mauri et al; The Lancet, 2014
Figure 3 Bayesian meta-analysis of cardiovascular and non-cardiovascular mortality associated with extended duration DAPT versus short duration or no DAPT Hazard ratio for cardiovascular mortality, and (B) non-cardiovascular mortality. Results are present...

Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis

Sammy Elmariah, Laura Mauri et al; The Lancet, 2014
Interpretation

- “Extended” DAPT therapy
  - Decreases the risk of ischemic events - especially stent thrombosis and MI
    - Consistent with previous observational findings and randomized clinical trial evidence
  - Increases the risk of bleeding
- Clopidogrel based DAPT does not improve mortality
PLATO
Comparison of Ticagrelor and Clopidogrel in Patients with ACS

CV Death/MI/Stroke

- Clopidogrel (n=9,291)
  - Median follow-up 9.1 months
  - Cumulative Incidence (%): 11.7
- Ticagrelor (n=9,333)
  - Cumulative Incidence (%): 9.8

HR 0.84
95% CI 0.77–0.92
p<0.001

Major Bleeding *

- Ticagrelor (n=9235)
  - Incidence (%): 7.4
  - HR 0.95
  - 95% CI 0.85–1.06
  - p=0.32
- Clopidogrel (n=9186)
  - Incidence (%): 7.9
  - HR 1.19
  - 95% CI 1.02–1.38
  - p=0.03

CABG Major Bleed
- Ticagrelor (n=9235)
  - Incidence (%): 4.5
  - HR 1.19
  - 95% CI 1.02–1.38
  - p=0.03
- Clopidogrel (n=9186)
  - Incidence (%): 3.8

*Total major bleeding (study criteria) for ticagrelor vs clopidogrel 11.6% vs 11.2%, HR 1.04 (0.95–1.13), p=0.43.

PLATO: Secondary Efficacy Outcomes

Ticagrelor Reduced Mortality in ACS

Cardiovascular Death

All-Cause Mortality

Stable pts with history of MI 1-3 yrs prior + ≥1 additional atherothrombosis risk factor*

RANDOMIZE DOUBLE BLIND

Ticagrelor 90 mg bid

Ticagrelor 60 mg bid

Placebo

Follow-up Visits Q4 mos for 1st yr, then Q6 mos

* Age >65 yrs, diabetes, 2nd prior MI, multivessel CAD, or chronic non-end stage renal dysfunction

Planned treatment with ASA 75 – 150 mg & Standard background care

Event-driven trial

Bonaca MP et al., NEJM 2015
Primary Endpoint

N = 21,162
Median follow-up 33 months

Bonaca MP et al., NEJM 2015
Outcomes over 1 Year for 10,000 Patients with Prior MI Initiated on Ticagrelor

Bonaca MP et al., NEJM 2015

Events extrapolated from 3-yr KM rates from ITT population

P values based on Cox regression

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ticagrelor 90 mg</th>
<th>Ticagrelor 60 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>P value</td>
<td>0.008</td>
<td>0.004</td>
</tr>
<tr>
<td>CV Death, MI, or Stroke</td>
<td>-40</td>
<td>-42</td>
</tr>
<tr>
<td>TIMI major bleed</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
PEGASUS
Primary endpoint – landmark (ITT)

Ticagrelor pooled
HR 0.84
(95% CI 0.71 – 0.98)
P=0.029

Ticagrelor pooled
HR 0.86
(95% CI 0.72 – 1.03)
P=0.094

Ticagrelor pooled
HR 0.83
(95% CI 0.68 – 1.02)
P=0.084

Median 1.7 y from index MI
(1.2 – 2.3)

Median 2.7 y from index MI
(2.2 – 3.3)

Median 3.7 y from index MI
(3.2 – 4.3)

Bonaca MP et al. Presented at AHA Congress 2015 (Abstract 383)
### Adverse events leading to discontinuation

3 year KM rate (%) – *P* value for each dose vs. Placebo <0.001

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Any AE</th>
<th>Bleeding</th>
<th>Dyspnoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor 90 mg bid</td>
<td>19.0%</td>
<td>7.8%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Ticagrelor 60 mg bid</td>
<td>16.4%</td>
<td>6.2%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.9%</td>
<td>1.5%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

AE, adverse event; D/C, discontinuation; NS, not significant

*Bonaca MP et al. Presented at AHA Congress 2015 (Late Breaking Clinical Trial)*

*P*=NS each for D/C for arrhythmia or other
Discontinuation over time for dyspnoea by randomization group

Dashed lines represent median time (days) to discontinuation

Bonaca MP et al. Presented at AHA Congress 2015 (Late Breaking Clinical Trial)

$P<0.01$ for each dose vs placebo
Discontinuation over time for bleeding by randomization group

Dashed lines represent median time (days) to discontinuation
Bonaca MP et al. Presented at AHA Congress 2015 (Late Breaking Clinical Trial)
PEGASUS

Efficacy of ticagrelor – on treatment*

*N=20,942 patients who received at least one dose of study drug including events through 7 days from the last dose of study drug.

Results consistent after propensity score adjustment

CV, cardiovascular; CVD, CV death

Bonaca MP et al. Presented at AHA Congress 2015 (Late Breaking Clinical Trial)
METHODS: MODELS TO PREDICT ISCHEMIC AND BLEEDING EVENTS

Development of 2 Prediction Models within the randomized DAPT Study population (N=11648).

• **Ischemic Model** | Myocardial infarction or stent thrombosis between 12-30 months after index PCI. Includes fatal events.

• **Bleeding Model** | GUSTO moderate or severe bleeding between 12-30 months after index PCI. Includes fatal events.

• Cox regression, stepwise selection among 37 candidate variables, including randomization treatment arm. In addition, several interaction terms with treatment arm evaluated. P value of 0.05 for retention.

• Validated externally within the PROTECT trial population*

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## THE DAPT SCORE and Distribution within the DAPT Study

### Variable Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 75</td>
<td>-2</td>
</tr>
<tr>
<td>Age 65 - &lt; 75</td>
<td>-1</td>
</tr>
<tr>
<td>Age &lt; 65</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Current Cigarette Smoker</td>
<td>1</td>
</tr>
<tr>
<td>Prior PCI or Prior MI</td>
<td>1</td>
</tr>
<tr>
<td>CHF or LVEF &lt;30%</td>
<td>2</td>
</tr>
</tbody>
</table>

### Index Procedure Characteristic

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI at Presentation</td>
<td>1</td>
</tr>
<tr>
<td>Vein Graft PCI</td>
<td>2</td>
</tr>
<tr>
<td>Stent Diameter &lt; 3 mm</td>
<td>1</td>
</tr>
</tbody>
</table>

### DISTRIBUTION OF DAPT SCORES AMONG ALL RANDOMIZED SUBJECTS IN THE DAT STUDY

![Bar Chart showing distribution of DAPT scores among all randomized subjects in the DAT Study]
CONTINUED THIENOPYRIDINE VS. PLACEBO
DAPT SCORE <2 (LOW); N=5731

Myocardial Infarction or Stent Thrombosis

- Continued Thienopyridine: 1.7% vs. 2.3% (P=0.07)
- Placebo: 2.3%

Death, MI, or Stroke (MACCE)

- Continued Thienopyridine: 3.7% vs. 3.8% (P=0.73)
- Placebo: 3.8%

GUSTO Moderate/Severe Bleeding

- Continued Thienopyridine: 3.0% vs. 1.4% (P<0.001)
- Placebo: 1.4%

AHA 2015, November 10, 2015, Orlando, FL
INSERCONTINUED THIENOPYRIDINE VS. PLACEBO
DAPT SCORE ≥ 2 (HIGH); N=5917

Myocardial Infarction or Stent Thrombosis

Death, MI or Stroke (MACCE)

GUSTO Moderate/Severe Bleeding

AHA 2015, November 10, 2015, Orlando, FL
CONCLUSION

Among patients who have not had a major ischemic or bleeding event within the first year after PCI:

The DAPT Score identified patients for whom ischemic benefits outweighed bleeding risks, and patients for whom bleeding risks outweighed ischemic benefits.

- Low DAPT Score (< 2)
  - NNT to prevent ischemic = 153
  - NNH to cause bleeding = 64

- High DAPT Score (≥ 2)
  - NNT to prevent ischemic = 34
  - NNH to cause bleeding = 272

DAPT Score may help clinicians decide who should and who should not be treated with extended DAPT.
CONCLUSION

Among patients who have not had a major ischemic or bleeding event within the first year after PCI:

The DAPT Score identified patients for whom ischemic benefits outweighed bleeding risks, and patients for whom bleeding risks outweighed ischemic benefits.

- **Low DAPT Score (< 2)**
  - NNT to prevent ischemic = 153
  - NNH to cause bleeding = 64

- **High DAPT Score (≥ 2)**
  - NNT to prevent ischemic = 34
  - NNH to cause bleeding = 272

DAPT Score may help clinicians decide who should and who should not be treated with extended DAPT.

Applies to a selected population treated with C-DAPT or P-DAPT

ACS patients start with a score of 1

Interventional focused – all patients previous PCI

Scores – need to be developed in ACS specific patient population

AHA 2015, November 10, 2015, Orlando, FL
Novel strategies to improve secondary prevention following ACS

Diagnosis

One month

Dual pathway Rivaroxaban + ADP R antagonist

Ticagrelor monotherapy

Twelve months

Dual Pathway or OAC

Atrial Fibrillation

DAPT + OAC
GLOBAL LEADERS Trial

GLOBAL LEADERS flowchart

All-comers PCI population (ACS and Stable CAD patients) (N = 16,000)

- Bivalirudin* - supported
- BioMatrix Flex™ stent implantation
  1:1 Randomization, Open-Label Design

Experimental Treatment Strategy

- ASA
  1 month
- Ticagrelor
  24 months

Reference Treatment Strategy

- ASA
  24 months
- Ticagrelor
  12 months: not allowed in stable PTS
  OR
  only allowed in stable PTS
- Clopidogrel

Primary endpoint (Effectiveness):
Experimental treatment strategy superior to reference treatment strategy on cumulative 2 year composite of all cause mortality and new Q-wave MI

Scientific Grants to ECRI: Biosensors, AstraZeneca and The Medicines Company

* in countries where available

http://clinicaltrials.gov/show/NCT01813435
Dual Pathway Strategies
Phase 2 - Study design

**Recent ACS**
Stabilised >48 hours & ≤10 days from hospitalisation for index event

ASA

Stratify by MD decision to use either clopidogrel or ticagrelor

**Clopidogrel (n=1500)**
- Clopidogrel 75 mg od
- ASA 100 mg od

**Ticagrelor (n=1500)**
- Ticagrelor 90 mg bid
- ASA 100 mg od

**Clopidogrel 75 mg od + ASA 100 mg od**

**Clopidogrel 75 mg od + Rivaroxaban 2.5 mg bid**

**Ticagrelor 90 mg bid + ASA 100 mg od**

**Ticagrelor 90 mg bid + Rivaroxaban 2.5 mg bid**

Minimum 180; Maximum 360, Day F/U

**PRIMARY ENDPOINT:** TIMI clinically significant bleeding

**EXPLORATORY EFFICACY ENDPOINT:** Composite of CV death, MI, ischaemic stroke or stent thrombosis

ACS=acute coronary syndrome; ASA=acetylsalicylic acid; od=once daily; bid=twice daily; F/U=follow up; TIMI=Thrombolysis In Myocardial Infarction; CV=cardiovascular; MI=myocardial infarction.

ClinicalTrials.gov Identifier: NCT02293395.
Summary

Consider patients with **Acute Coronary Syndromes** separately from those with **Elective Revascularization**

1. In appropriately selected patients DAPT should be considered beyond 12 months – focus on ACS.
2. Further academic investment is required to develop scores to assist clinical decision for prolonged therapy.
3. The current trials may further adapt the ACS anti-thrombotic landscape.