Dual Antiplatelet duration in ACS: too long or too short?

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Paradigm Shift

the ideal duration of DAPT: a moving target

- Early (stent-related) thrombotic events prevention
  *(Treating the stent)*

- Secondary CV Prevention
  *(Treating the patient)*

*Which way? Drug therapy for Shorter or Longer Time?*
The need for dual antiplatelet therapy

"mandatory"

< 12 months

"possibly beneficial"

> 12 months

* Premature discontinuation of DAPT would lead to an unacceptably high rate of ST

* Mitigating the risk of recurrent ischemic events unrelated to previous PCI

EXCELLENT
RESET
SECURITY
ISAR SAFE
OPTIMIZE

ARCTIC INTERRUPTION
DES-LATE
REAL/ZEST
DAPT
PEGASUS
TRA 2° P-TIMI 50

PRODIGY
ITALIC
NIPPON
Prasugrel and ticagrelor
Increasing benefit during the first year

Cardiovascular death / myocardial infarction / stroke

Clopidogrel
9.9
Prasugrel
12.1

TRITON

Clopidogrel
11.7
Ticagrelor
9.8

PLATO

Endpoints in studies evaluating abbreviated duration of DAPT (6 months or less) after stenting in populations having a majority of ACS patients.

<table>
<thead>
<tr>
<th></th>
<th>Stent thrombosis</th>
<th>MACE</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S-DAPT</td>
<td>L-DAPT</td>
<td>S-DAPT</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>15 (1.5)</td>
<td>13 (1.3)</td>
<td>98 (10.0)</td>
</tr>
<tr>
<td>RESET</td>
<td>2 (0.2)</td>
<td>3 (0.3)</td>
<td>8 (0.8)</td>
</tr>
<tr>
<td>EXCELLENT</td>
<td>6 (0.9)</td>
<td>1 (0.1)</td>
<td>56 (8.0)</td>
</tr>
<tr>
<td>Total n/N (%)</td>
<td>23/2532 (0.9)</td>
<td>17/2529 (0.7)</td>
<td>162/2532 (6.4)</td>
</tr>
</tbody>
</table>
Design

Randomization*

47% ACS

Study Drug Treatment Ends

12-Month Observational Period: Open-Label Thienopyridine + Aspirin Required

3-Month Observational Period: Off Thienopyridine, On Aspirin

Thienopyridine + Aspirin

Placebo + Aspirin

Time in months after index stent procedure (not to scale)

0 12 30 33

Enrolled: Subjects treated with FDA-approved DES or BMS. Subjects on oral anticoagulant therapy or with life expectancy < 3 years excluded.

Randomized: Free from MI, stroke, repeat revascularization, and moderate or severe bleeding, and adherent with thienopyridine (80% to 120% of doses taken and no interruption > 14 days).

Mauri, Kereiakes et al AHJ 2010; 160(6): 1035-1041

ClinicalTrials.gov number NCT00977938
Bleeding End Point during Month 12 to Month 30

Trial Design

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

RANDOMIZED DOUBLE BLIND

- Ticagrelor 90 mg bid
- Ticagrelor 60 mg bid
- Placebo

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

Minimum 1 year follow-up
Event-driven trial

Bonaca MP et al. *Am Heart J* 2014;167:437-44

Primary Endpoint

CV death, MI or stroke

N = 21,162
Median follow-up 33 months

Placebo (9.0%)
Ticagrelor 90 (7.8%)
Ticagrelor 60 (7.8%)

Ticagrelor 90 mg
HR 0.85 (95% CI 0.75 – 0.96)
P=0.008

Ticagrelor 60 mg
HR 0.84 (95% CI 0.74 – 0.95)
P=0.004

Bleeding

Ticag 90: HR 2.69 (1.96-3.70)
Ticag 60: HR 2.32 (1.68-3.21)

P < 0.001

3-Year KMI Event Rate (%)

TIMI Major
TIMI Minor
Fatal bleeding or ICH
ICH
Fatal Bleeding

P = NS
P = NS
P = NS

Ticagrelor 90 mg
Ticagrelor 60 mg
Placebo

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Results of the 5 studies which tested stronger antiplatelet Rx beyond 1 year vs. standard of care, in pts with proven CAD.
Risk of All-Cause Mortality With More Intensive Antiplatelet Therapy for Long-term Secondary Prevention in Patients With Prior Myocardial Infarction

Bonaca MP, Sabatine MS JAMA Cardiology 2016
Outcomes over 1 Year for 10,000 Patients with Prior MI Initiated on Ticagrelor

P values based on Cox regression

Events extrapolated from 3-yr KM rates from ITT population

P value | Ticagrelor 90 mg bid | Ticagrelor 60 mg bid
--- | --- | ---
CV Death, MI, or Stroke | 0.008 | 0.004
CV Death | 0.15 | 0.07
MI | 0.01 | 0.03
Stroke | 0.14 | 0.03
Fatal bleed or ICH | 0.43 | 0.47
TIMI major bleed | <0.001 | <0.001

Irreversible Damage

Number of Events Prevented or Caused over 1 Year per 10,000 Patients Initiated on Treatment (SEM)
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>Dyspnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor 90</td>
<td>19.0%</td>
<td>7.8%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Ticagrelor 60</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>

Number of Patients

- Placebo: 388
  - Other: 243
  - Arrhythmia: 96
  - Dyspnea: 51
  - Bleeding: 86

- Ticagrelor 90 mg BID: 365
  - Other: 287
  - Arrhythmia: 78
  - Dyspnea: 430
  - Bleeding: 103

- Ticagrelor 60 mg BID: 385
  - Other: 311
  - Arrhythmia: 103
  - Dyspnea: 297
  - Bleeding: 354

P=NS each for D/C for arrhythmia or other
2017 ESC Focused Update on DAPT

Algorithm for DAPT in pts treated with PCI

**Recommendations**

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
</tr>
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<tbody>
<tr>
<td>IIb</td>
<td>A</td>
</tr>
<tr>
<td>IIb</td>
<td>B</td>
</tr>
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</table>

In patients with ACS who have tolerated DAPT without a bleeding complication, continuation of DAPT for longer than 12 months may be considered.

In patients with MI and high ischaemic risk who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg b.i.d. for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel.

- **A** = Aspirin
- **C** = Clopidogrel
- **P** = Prasugrel
- **T** = Ticagrelor
Which patients with ACS will likely derive the greatest benefit-risk profile from long-term intensive antiplatelet therapy?

Much of the literature that currently shapes cardiovascular practice fails to offer meaningful information to help clinicians identify or act on heterogeneity
Average treatment effect assessed in a heterogeneous population

- = expected to derive benefit from treatment
- = expected to have an equivocal response
- = expected to be harmed by treatment
- = response in the “average”

Estimation of average treatment effect
Identification of heterogeneous responses to treatment

Segregation of patient population based on treatment response

- expected to derive benefit from treatment
- expected to have an equivocal response
- expected to be harmed by treatment
Means to Improve Personalized Care in Cardiovascular Disease

- Subgroup Analyses of RCTs
- Risk Models (Scores)
- Decision Tools
Important Shortcomings in Subgroup Analyses of RCTs

- Heterogeneity in treatment response may be best identified by stratification based on multiple factors rather than single variables.
- RCTs are rarely powered to detect statistical interactions between subgroups.
- The identification of treatment effect heterogeneity has generally examined interactions on the relative rather than absolute scale.
Important Shortcomings in Risk Models

- The events studied are frequently a mix of entities without a common causal pathway.
- There may be no evidence that any intervention exists to mitigate the risk being predicted.
- Risk scores too often use predicted risk as a surrogate for the expected treatment effect.
Identifying Heterogeneous Treatment Responses

Rationale of Decision Tools

1. Differences in risk between pts must be identifiable by the tool more reliably than by clinical judgment alone (*identifiable heterogeneity*).

2. The identified risks should be modifiable by clinical decisions (*actionability*).

3. The tool should be able to be adopted into practice (*implementability*).
## The DAPT Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Characteristic</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>≥ 75</td>
<td>-2</td>
</tr>
<tr>
<td>65 - &lt;75</td>
<td>-1</td>
</tr>
<tr>
<td>&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>
<tr>
<td><strong>Index Procedure Characteristic</strong></td>
<td></td>
</tr>
<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; 3mm</td>
<td>1</td>
</tr>
</tbody>
</table>

### Distribution of DAPT Scores among all randomized subjects in the DAPT Study

![Distribution of DAPT Scores](chart.png)
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 ischemia = 153
  - NNH to cause bleeding = 64

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

DAPT Score may help clinicians decide *who should*, *and who should not* be treated with extended DAPT.
DAPT Score External Validation (PROTECT)

DAPT ability to predict events was modest (c statistic: ischemic model, 0.64; bleeding model, 0.64).

Yeh RW et al JAMA 2016; 315:1735-1749
### The PRECISE-DAPT Score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (for each increase of 10 years)</td>
<td>1.34 (1.11–1.48)</td>
<td>0.005</td>
</tr>
<tr>
<td>Previous bleeding</td>
<td>4.14 (1.22–14.02)</td>
<td>0.023</td>
</tr>
<tr>
<td>White-blood-cell count (for each increase of $10^3$ cells per μL)</td>
<td>1.06 (0.99–1.13)</td>
<td>0.078</td>
</tr>
<tr>
<td>Haemoglobin at baseline (for each increase of 1 g/dL)</td>
<td>0.67 (0.53–0.84)</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine clearance (for each increase of 10 mL/min)</td>
<td>0.90 (0.82–0.99)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Costa F et al. Lancet 2017; 389: 1025–34*
Personalized stratification of DAPT duration - PRECISE-DAPT -

Absolute risk difference long DAPT vs. short DAPT

-1.2  -0.2  0.4  0.3  1.4  2.6
very low  low  moderate  high (≥25)

Ischaemic events
Bleeding events

* p < 0.05

PRECISE-DAPT score

ACS Secondary Prevention: Unmet Needs

Tailoring therapy to risk

The challenge:
Develop a model that will account for variation of risk over time in a specific patient.

Clinicians must remain aware and vigilant that current risk scores, although useful to improve the accuracy of the prognostic assumptions affecting clinical decisions, cannot be considered a clear-cut decision rule or a substitute for case-by-case critical judgment.
None of these risk prediction models has been prospectively tested in the setting of prospective randomized controlled studies. Therefore, their value in improving patient outcomes remains unclear.
Which patients with an MI will likely derive the greatest benefit-risk profile from long-term intensive antiplatelet therapy?

**Diabetes**


**Renal dysfunction**


**MVD**


**MVD**

Annualized discontinuation rates in PEGASUS-TIMI 54 Trial

Ischaemic risk and efficacy of ticagrelor in relation to time from P2Y12 inhibitor withdrawal in pts with prior MI

Withdrawn < 30 days

Withdrawn >30 days < 1 year

Withdrawn >1 year

Is prolonged intensive antiplatelet therapy the new gold standard after ACS?

“Not for all patients.”

- Only patients who have tolerated and adhered to therapy during the previous 12 months should be considered for long-term intensive antiplatelet therapy.

- Prolonged therapy should be avoided in high risk patients for bleeding.

- Although prolonged intensive antiplatelet Rx is effective at reducing MACE across the MI population, such therapy may be particularly attractive in pts with characteristics associated with heightened ischemic risk (diabetes, MVD, renal dysfunction, or PAD) in whom there are greater absolute risk reductions in MACE and/or notable reductions in CV mortality.