Disclosures

Steering Committee Disclosures

The steering committee reported the following relevant financial relationships that they or their spouse/partner have with commercial interests:

Tracy Y. Wang, MD, MHS, MSc, FACC, FAHA: Research: AstraZeneca, Bristol-Myers Squibb, Cryolife, Portola, Regeneron; Consultant/Advisory Board: AstraZeneca, Sanofi

Marlene S. Williams, MD, FACC: Advisory Board: Haemonetics

Non-faculty Content Contributors

Non-faculty content contributors and/or reviewers reported the following relevant financial relationships that they or their spouse/partner have with commercial interests:

Terry Ann Glauser, MD, MPH; Blair St. Amand; INCEDO: Nothing to disclose

Educational Objectives

At the conclusion of this activity, participants should be able to:

- Apply the 2016 ACC/AHA guideline focused update on DAPT recommendations when developing individualized management plans for patients with CAD
- Consider the results of recent clinical trials investigating the optimal management of DAPT when creating management plans for patients with CAD
- Identify validated tools that can be used to individualize DAPT therapy
Dual Antiplatelet Therapy (DAPT)

DAPT has been used to specifically refer to combination antiplatelet therapy with aspirin (ASA) and a P2Y$_{12}$ receptor inhibitor (clopidogrel, prasugrel, or ticagrelor)

P2Y$_{12}$ Inhibitors
**Oral P2Y\textsubscript{12} Inhibitors**

**Mechanism of Action**

**Dosing**

- **Clopidogrel**
  - Loading dose 300 mg or 600 mg
  - Maintenance dose 75 mg

- **Prasugrel**
  - Loading dose 60 mg
  - Maintenance dose 10 mg daily (consider 5 mg daily if weight <60 kg)

- **Ticagrelor**
  - Loading dose 180 mg
  - Maintenance dose 90 mg twice daily for 1 year post ACS then 60 mg twice daily

**CURE: Long-term Benefit of Clopidogrel**

*12,562 Patients with NSTE-ACS, Mostly Conservatively Managed, Followed for 12 months*

**CV Death, MI, or Stroke, First 30 Days**

<table>
<thead>
<tr>
<th>Week</th>
<th>Proportion Event-Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>0.99</td>
</tr>
<tr>
<td>2</td>
<td>0.98</td>
</tr>
<tr>
<td>3</td>
<td>0.98</td>
</tr>
<tr>
<td>4</td>
<td>0.97</td>
</tr>
</tbody>
</table>

**RRR: 21% 95% CI, 0.67–0.92**

*P* = 0.003

**CV Death, MI, or Stroke, >30 Days–1 Year**

<table>
<thead>
<tr>
<th>Month</th>
<th>Proportion Event-Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.99</td>
</tr>
<tr>
<td>4</td>
<td>0.98</td>
</tr>
<tr>
<td>6</td>
<td>0.98</td>
</tr>
<tr>
<td>8</td>
<td>0.97</td>
</tr>
<tr>
<td>10</td>
<td>0.97</td>
</tr>
<tr>
<td>12</td>
<td>0.96</td>
</tr>
</tbody>
</table>

**RRR: 18% 95% CI, 0.70–0.95**

*P* = 0.009

### Clopidogrel: Genetic Variations and Clinical Outcomes

#### 1° Efficacy Outcome

- **Carrier of 2C19 reduced-function allele**
  - CV death, MI, or stroke (%)
  - Days Since Randomization:
    - 0: 12.1
    - 30: 8.0
  - *P* = 0.01

- **Non-carrier of 2C19 reduced-function allele**
  - CV death, MI, or stroke (%)
  - Days Since Randomization:
    - 0: 3.0
    - 30: 5.0

#### Stent Thrombosis

- **Carrier of 2C19 reduced-function allele**
  - Definite or Probable Stent Thrombosis (%)
  - Days Since Randomization:
    - 0: 2.6
    - 30: 0.8
  - *P* = 0.02

- **Non-carrier of 2C19 reduced-function allele**
  - Definite or Probable Stent Thrombosis (%)
  - Days Since Randomization:
    - 0: 8.0
    - 30: 12.1
  - *P* = 0.01

---

### TRITON-TIMI 38: Prasugrel Efficacy and Safety

- **CV Death/MI/Stroke**
  - Clopidogrel: 12.1%
  - Prasugrel: 9.9%
  - *HR* = 0.81 (0.73-0.90)
  - *P* < 0.001
  - NNT = 46

- **TIMI Major Non-CABG Bleeds**
  - Clopidogrel: 2.4%
  - Prasugrel: 1.8%
  - *HR* = 1.32 (1.03-1.68)
  - *P* = 0.03
  - NNH = 167

---

*NNT = number needed to treat; NNH = number needed to harm
TRITON TIMI 38: Net Clinical Benefit
Prasugrel vs Clopidogrel Subgroups; Post-hoc Analysis

Prior Stroke / TIA
- Yes
- No

Risk (%)
- 54
- 16

Prior Stroke / TIA
- Yes
- No

Risk (%)
- 54
- 16

Age, yr
- ≥75
- <75

Risk (%)
- 1
- 16

Weight
- <60 kg
- ≥60 kg

Risk (%)
- 3
- 14

OVERALL

Risk (%)
- 13

Prasugrel Better
Clopidogrel Better

HR


PLATO: Ticagrelor Efficacy
Kaplan-Meier Estimate of Time to First Primary Efficacy Event*

Cumulative incidence (%)

0 1 2 3 4 5 6 7 8 9 10 11 12 13

Days after randomisation

Clopidogrel

HR 0.84 (95% CI 0.77–0.92), P=0.0003

Ticagrelor

HR 0.84 (95% CI 0.77–0.92), P=0.0003

* Composite of CV Death, MI, or Stroke

© 2020 Rockpointe
**PLATO: Ticagrelor Safety**

*Time to Non-procedure-related Major Bleeding*

![Graph showing time to non-procedure-related major bleeding between Ticagrelor and Clopidogrel](image)


Completeness of follow-up: 99.97% = 5 patients lost to follow-up

---

**2016 ACC/AHA Guideline**

*Selecting a Maintenance P2Y₁₂ Inhibitor in ACS Patients*

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is reasonable to <strong>choose ticagrelor over clopidogrel</strong> for maintenance P2Y₁₂ treatment in ACS patients treated with an early invasive strategy and/or PCI.</td>
<td>IIA</td>
<td>B-R</td>
</tr>
<tr>
<td>It is reasonable to <strong>choose prasugrel over clopidogrel</strong> for maintenance P2Y₁₂ treatment in ACS patients who undergo PCI who are not at high risk for bleeding complications.</td>
<td>IIA</td>
<td>B-R</td>
</tr>
<tr>
<td><strong>Prasugrel should not</strong> be administered to patients with a prior history of stroke or TIA.</td>
<td>III: Harm</td>
<td>B-R</td>
</tr>
</tbody>
</table>

## Duration of P2Y$_{12}$ Inhibitor Therapy

### Recommendations COR LOE

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>After ACS treated with either BMS or DES, P2Y$_{12}$ inhibitor therapy should be given for at least 12 months</td>
<td>I</td>
<td>B-R</td>
</tr>
<tr>
<td>In patients with ACS treated with coronary stent implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk, continuation of DAPT for longer than 12 months may be reasonable</td>
<td>IIb</td>
<td>A</td>
</tr>
<tr>
<td>In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding or develop significant overt bleeding, discontinuation of P2Y$_{12}$ inhibitor therapy after 6 months may be reasonable</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

2016 ACC/AHA Guideline
DAPT in Stable Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with SIHD treated with DAPT after BMS implantation, P2Y₁₂ inhibitor therapy (clopidogrel) should be given for a minimum of 1 month</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>In patients with SIHD treated with DAPT after DES implantation, P2Y₁₂ inhibitor therapy (clopidogrel) should be given for at least 6 months</td>
<td>1</td>
<td>B-R SR</td>
</tr>
<tr>
<td>In patients with SIHD treated with DAPT after BMS or DES, without a bleeding complication, and who are not at high bleeding risk (e.g. prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT with clopidogrel for longer than 1 month in patients treated with BMS or longer than 6 months in patients treated with DES may be reasonable</td>
<td>IIb</td>
<td>A SR</td>
</tr>
<tr>
<td>In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (e.g. treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g. major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y₁₂ inhibitor therapy after 3 months may be reasonable</td>
<td>IIb</td>
<td>C-LD</td>
</tr>
<tr>
<td>In patients with SIHD, treatment with DAPT (with clopidogrel initiated early postoperatively) for 12 months after CABG may be reasonable to improve vein graft patency</td>
<td>IIb</td>
<td>B-NR</td>
</tr>
</tbody>
</table>


CHARISMA: Clopidogrel Plus ASA vs ASA Alone
Primary Composite Endpoint for Patients Followed for a Median of 28 Months

*All patients received ASA 75-162 mg/day
CHARISMA: Subgroup of Patients with Prior MI
Post-hoc Exploratory Analysis


PEGASUS TIMI-54
Ticagrelor in Patients 1-3 Years Post MI

**Meta-analysis: Extended DAPT in Prior ACS or MI**

### Risk of CV Death/MI/Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Extended DAPT</th>
<th>Aspirin Alone</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>125/1903</td>
<td>122/1943</td>
<td>0.77 (0.61-0.98)</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>63/732</td>
<td>67/733</td>
<td>0.91 (0.65-1.28)</td>
</tr>
<tr>
<td>ARCTIC-Int’n</td>
<td>3/156</td>
<td>4/167</td>
<td>0.79 (0.18-3.51)</td>
</tr>
<tr>
<td>DAPT</td>
<td>59/1805</td>
<td>108/1771</td>
<td>0.52 (0.38-0.72)</td>
</tr>
<tr>
<td>DES-LATE</td>
<td>56/1512</td>
<td>66/1551</td>
<td>0.85 (0.60-1.21)</td>
</tr>
<tr>
<td>PEGASUS</td>
<td>980/14095</td>
<td>578/7067</td>
<td>0.84 (0.76-0.94)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1286/20203</td>
<td>987/13232</td>
<td>0.78 (0.67-0.90)</td>
</tr>
</tbody>
</table>

P = 0.001

1.1% absolute risk reduction for DAPT compared with ASA (mean 31 months)

---

### Major Bleeding

<table>
<thead>
<tr>
<th>Study</th>
<th>Extended DAPT</th>
<th>Aspirin Alone</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>45/1903</td>
<td>39/1943</td>
<td>1.17 (0.76-1.79)</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>9/732</td>
<td>6/733</td>
<td>1.50 (0.53-4.20)</td>
</tr>
<tr>
<td>ARCTIC-Int’n</td>
<td>2/156</td>
<td>0/167</td>
<td>5.35 (0.26-110.6)</td>
</tr>
<tr>
<td>DAPT</td>
<td>34/1805</td>
<td>14/1771</td>
<td>2.38 (1.27-4.43)</td>
</tr>
<tr>
<td>DES-LATE</td>
<td>39/1512</td>
<td>31/1551</td>
<td>1.27 (0.79-2.03)</td>
</tr>
<tr>
<td>PEGASUS</td>
<td>242/13946</td>
<td>54/6996</td>
<td>2.50 (1.86-3.36)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>371/20054</td>
<td>144/13161</td>
<td>1.73 (1.19-2.50)</td>
</tr>
</tbody>
</table>

P = 0.004

0.8% absolute increase in major bleeding for DAPT compared with ASA (mean 31 months)
2016 ACC/AHA Guideline
Updated Recommendations for DAPT and Duration

• Class IIb recommendation for use beyond 12 months
• Consider ischemic risk and bleeding risk
  – Shorter duration for those with low ischemic risk and high bleeding risk
  – Longer duration for high ischemic risk and lower bleeding risk
• NSTE-ACS and STEMI – same recommendations
• Aspirin 81 mg should be continued indefinitely


Tools to Inform Duration of DAPT
DAPT Score and Duration of Therapy

DAPT Score
- ≥2 Benefit prolong DAPT
- <2 Shorter duration of DAPT

Net Adverse Events

Clinical Prediction Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</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>Cigarette smoking</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>MI at presentation</td>
<td>1</td>
</tr>
<tr>
<td>Prior PCI or prior MI</td>
<td>1</td>
</tr>
<tr>
<td>Paclitaxel-eluding stent</td>
<td>1</td>
</tr>
<tr>
<td>Stent diameter &lt;3mm</td>
<td>1</td>
</tr>
<tr>
<td>CHF or LVEF &lt;30%</td>
<td>2</td>
</tr>
<tr>
<td>Vein graft stent</td>
<td>2</td>
</tr>
</tbody>
</table>

Total score range: -2 to 10

PARIS Registry Risk Score

Predicting Bleeding and Stent Thrombosis Post-DES for DAPT Duration

Risk Score for Major Bleeding

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0</td>
</tr>
<tr>
<td>&lt;50</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>+1</td>
</tr>
<tr>
<td>60-69</td>
<td>+2</td>
</tr>
<tr>
<td>70-79</td>
<td>+3</td>
</tr>
<tr>
<td>≥80</td>
<td>+4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>+2</td>
</tr>
<tr>
<td>25-34.9</td>
<td>0</td>
</tr>
<tr>
<td>≥35</td>
<td>+2</td>
</tr>
<tr>
<td>Current Smoking</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>+2</td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>+3</td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>CrCl &lt; 60 mL/min</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>+2</td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Prior PCI</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>+2</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Prior CABG</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>+2</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>

Risk Score for Coronary Thrombosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Non-insulin dependent</td>
<td>+1</td>
</tr>
<tr>
<td>Insulin dependent</td>
<td>+3</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes, Tn-negative</td>
<td>+1</td>
</tr>
<tr>
<td>Yes, Tn-positive</td>
<td>+2</td>
</tr>
<tr>
<td>Current Smoking</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>+1</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>CrCl &lt; 60 mL/min</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>+2</td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Prior PCI</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>+2</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Prior CABG</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>+2</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>
Real-World Use of P2Y$_{12}$ Inhibitors in Patient Types

**SWEDENHEART Registry**

- Prospective cohort study
- 45,073 ACS patients discharged on ticagrelor ($n = 11954$) or clopidogrel ($n = 33119$)
  - Mean age 70 years, 70% male
  - 22.5% DM, 54.4% HTN, 24.5% current smokers, 0.5% on dialysis

**US National Cardiovascular Data Registry**

*Ticagrelor Uptake Over Time*

- Mean age: PLATO Trial 62, NCDR Ticagrelor 62, NCDR Clopidogrel 65
- Male: PLATO Trial 71.7, NCDR Ticagrelor 69.7, NCDR Clopidogrel 65.6
- BMI: PLATO Trial 27, NCDR Ticagrelor 29.7, NCDR Clopidogrel 29.5
- Diabetes: PLATO Trial 24.9, NCDR Ticagrelor 29.2, NCDR Clopidogrel 35.7
- Prior MI: PLATO Trial 20.4, NCDR Ticagrelor 20.4, NCDR Clopidogrel 27.5
- STEMI: PLATO Trial 37.5, NCDR Ticagrelor 56.0, NCDR Clopidogrel 36.7
- Prior CABG: PLATO Trial 5.7, NCDR Ticagrelor 9.4, NCDR Clopidogrel 16.0
- Discharge ASA >81 mg: PLATO Trial 0, NCDR Ticagrelor 2.5, NCDR Clopidogrel 28.2

_Basra SS et al. J Am Heart Assoc, 2018;7:e008125._

---

**2016 ACC/AHA Recommendation**

*Managing Patients Treated with Triple Therapy*

- Assess ischemic and bleeding risks using validated risk predictors (e.g. CHA2DS2-VASc, HAS-BLED)
- Keep triple-therapy duration as short as possible; dual therapy only (oral anticoagulant and clopidogrel) may be considered in select patients
- Consider a target INR of 2.0-2.5 when warfarin is used
- Clopidogrel is the P2Y12 inhibitor of choice
- Use low-dose (≤100 mg daily) aspirin
- PPIs should be used in patients with a history of gastrointestinal bleeding and are reasonable to use in patients with increased risk of gastrointestinal bleeding

2016 ACC/AHA Recommendations

**DAPT and PPIs**

- PPI should be used if prior GI bleeding – Class I
- If risk of GI bleeding/Age/Warfarin/Steroids/NSAIDS, use of PPI reasonable – Class IIa
- NOT recommended in patients at low risk of GI bleeding – Class III


---

**2016 ACC/AHA Recommendations**

*For Perioperative Management*

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective non-cardiac surgery should be delayed 30 days after BMS implantation and optimally 6 months after DES implantation</td>
<td>I</td>
<td>BR</td>
</tr>
<tr>
<td>In patients treated with DAPT after coronary stent implantation who must undergo surgical procedures that mandate the discontinuation of P2Y₁₂ inhibitor therapy, it is recommended that aspirin be continued if possible and the P2Y₁₂ platelet receptor inhibitor be restarted as soon as possible after surgery</td>
<td>I</td>
<td>C-E0</td>
</tr>
<tr>
<td>When non-cardiac surgery is required in patients currently taking a P2Y₁₂ inhibitor, a consensus decision among treating clinicians as to the relative risks of surgery and discontinuation or continuation of antiplatelet therapy can be useful</td>
<td>IIa</td>
<td>C-E0</td>
</tr>
<tr>
<td>Elective non-cardiac surgery after DES implantation in patients for whom P2Y₁₂ inhibitor therapy will need to be discontinued may be considered after 3 months if the risk of further delay of surgery is greater than the expected risks of stent thrombosis</td>
<td>IIb</td>
<td>C-E0</td>
</tr>
<tr>
<td>Elective non-cardiac surgery should not be performed within 30 days after BMS implantation or within 3 months after DES implantation in patients in whom DAPT will need to be discontinued perioperatively</td>
<td>III: Harm</td>
<td>B-NR</td>
</tr>
</tbody>
</table>

What’s New Since The Guidelines?

PEGASUS TIMI 54 Subanalysis
Long-term Secondary Prevention

• Post-MI patients who did not receive a stent are at elevated risk for recurrent spontaneous atherothrombosis

• Benefits of long-term DAPT are driven by decrease in events related to patient risk and not to the presence of a stent

### PEGASUS TIMI 54

**Reduction in Subtype and Size of Recurrent MI**

**Reduction in MI by Type**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Ticagrelor Better (%)</th>
<th>Placebo Better (%)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any MI</td>
<td>4.60</td>
<td>4.53</td>
<td>0.87 (0.69 - 0.95)</td>
<td>0.0066</td>
</tr>
<tr>
<td>Type 1 MI</td>
<td>3.55</td>
<td>3.47</td>
<td>0.94 (0.71 - 1.01)</td>
<td>0.019</td>
</tr>
<tr>
<td>Type 2 MI</td>
<td>0.69</td>
<td>0.70</td>
<td>0.87 (0.50 - 1.19)</td>
<td>0.58</td>
</tr>
<tr>
<td>Type 4 MI</td>
<td>0.44</td>
<td>0.49</td>
<td>0.66 (0.40 - 1.10)</td>
<td>0.33</td>
</tr>
<tr>
<td>PCI related</td>
<td>0.59</td>
<td>0.71</td>
<td>0.80 (0.50 - 1.32)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

**Reduction in MI by Size**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Ticagrelor Better (%)</th>
<th>Placebo Better (%)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any MI</td>
<td>4.40</td>
<td>4.53</td>
<td>0.84 (0.66 - 0.88)</td>
<td>0.0055</td>
</tr>
<tr>
<td>MI with Tn</td>
<td>1.74</td>
<td>1.66</td>
<td>0.77 (0.65 - 0.91)</td>
<td>0.0062</td>
</tr>
<tr>
<td>MI with Tn</td>
<td>1.20</td>
<td>1.14</td>
<td>0.71 (0.53 - 0.91)</td>
<td>0.0044</td>
</tr>
<tr>
<td>MI with Tn</td>
<td>1.19</td>
<td>1.05</td>
<td>0.70 (0.52 - 0.94)</td>
<td>0.0096</td>
</tr>
<tr>
<td>MI with Tn</td>
<td>0.94</td>
<td>0.91</td>
<td>0.79 (0.54 - 1.08)</td>
<td>0.0012</td>
</tr>
<tr>
<td>MI with Tn</td>
<td>0.92</td>
<td>0.80</td>
<td>0.71 (0.47 - 1.07)</td>
<td>0.031</td>
</tr>
</tbody>
</table>


### COMPASS Trial

**Stable CAD or PAD**

- CAD defined as prior MI, multivessel CAD s/p PCI or CABG
- Enriched with >65 years or multiple risk factors
- Excludes patients on DAPT

The AUGUSTUS Trial

**Inclusion**
- AF
- ACS and/or PCI with planned P2Y<sub>12</sub> inhibitor for ≥6 months

**Randomize**
- n = 4,600 Patients

**Exclusion**
- Other reason for warfarin (prosthetic valve, mod/sev MS)

---

**Apixaban**
- P2Y<sub>12</sub> inhibitor for all patients × 6 months
- Aspirin for all on the day of ACS or PCI
- Aspirin vs placebo after randomization

**Warfarin**
- ASA placebo

---

**Primary outcome:** Major/clinically relevant bleeding (through 6 months)

**Secondary objective:** Death, MI, stroke, stent thrombosis

---

Bleeding Outcomes

**Aspirin vs Placebo**


Ischemic Outcomes
Aspirin vs Placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Aspirin (N=2307)</th>
<th>Placebo (N=2307)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death / Ischemic Events (%)</td>
<td>6.5</td>
<td>7.3</td>
<td>0.89 (0.71–1.11)</td>
</tr>
<tr>
<td>Death (%)</td>
<td>3.1</td>
<td>3.4</td>
<td>0.91 (0.66–1.26)</td>
</tr>
<tr>
<td>CV Death (%)</td>
<td>2.3</td>
<td>2.5</td>
<td>0.92 (0.63–1.33)</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>0.9</td>
<td>0.8</td>
<td>1.06 (0.56–1.98)</td>
</tr>
<tr>
<td>Myocardial Infarction (%)</td>
<td>2.9</td>
<td>3.6</td>
<td>0.81 (0.59–1.12)</td>
</tr>
<tr>
<td>Definite or Probable Stent Thrombosis (%)</td>
<td>0.5</td>
<td>0.9</td>
<td>0.52 (0.25–1.08)</td>
</tr>
<tr>
<td>Urgent Revascularization (%)</td>
<td>1.6</td>
<td>2.0</td>
<td>0.79 (0.51–1.21)</td>
</tr>
</tbody>
</table>


TWILIGHT: Ticagrelor Plus ASA vs Ticagrelor Alone

- Objective: To compare antiplatelet monotherapy with ticagrelor alone vs ticagrelor plus ASA in patients with NSTE-ACS undergoing PCI with DES who had completed 3 months of ticagrelor plus ASA
- Endpoints
  - Primary: Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding between 0-12 months after randomization
  - Secondary: Non-fatal MI, stroke, or all-cause death between 0-12 months after randomization
- Randomization
  - 3,555 to ticagrelor alone
  - 3,564 to ticagrelor plus ASA

**TWILIGHT: Ticagrelor plus ASA vs Ticagrelor alone**

Primary endpoint: BARC 2, 3, 5

Secondary endpoint: Any cause death, nonfatal MI, nonfatal stroke

Ticagrelor monotherapy may be a suitable antiplatelet strategy to lower bleeding risk while preserving ischemic benefit in patients who have undergone PCI. Effects appear consistent in both stable angina and ACS.


**ISAR-REACT 5: Ticagrelor vs Prasugrel in ASC Patients Undergoing PCI**

- Open label
- 2,012 randomized to ticagrelor
  - Received drug immediately after randomization
  - 32% not on assigned drug at discharge or at one year
- 2,006 randomized to prasugrel
  - STEMI patients given drug ASAP after randomization
  - In ACS not STEMI, drug not given until time of PCI (~1 hour)
  - 30% not on assigned drug at discharge or 1 year

ISAR-REACT 5: Ticagrelor vs Prasugrel in ASC Patients Undergoing PCI

Primary endpoint: Death, MI, or stroke
- Hazard ratio, 1.36 (95% CI, 1.09–1.70)
- P = 0.006

Secondary endpoint: BARC 3, 4, or 5
- Hazard ratio, 1.12 (95% CI, 0.83–1.51)
- P = 0.46

Lower incidence of death, MI, or stroke in ACS patients receiving prasugrel compared with ticagrelor.

No difference in bleeding between prasugrel and ticagrelor.


Switching P2Y12 Inhibitors
**P2Y<sub>12</sub> Inhibitor Switching**

7.6% of 8,672 MI Patients Switched within 1-year Post Discharge

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-discharge switch</td>
<td>3.6%</td>
<td>28.3%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Days to switch</td>
<td>21</td>
<td>62</td>
<td>80</td>
</tr>
</tbody>
</table>

**Patient-reported reason for switch**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding*</td>
<td>6.9%</td>
<td>10.9%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Other side effect</td>
<td>31.9%</td>
<td>18.8%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Cost</td>
<td>7.9%</td>
<td>43.6%</td>
<td>39.1%</td>
</tr>
</tbody>
</table>

**Event triggering switch**

<table>
<thead>
<tr>
<th>Event</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI/stroke/unplanned revasc</td>
<td>18.5%</td>
<td>1.8%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Bleeding*</td>
<td>0.9%</td>
<td>1.6%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>


---

**P2Y<sub>12</sub> Inhibitor Escalation**

### Acute Phase

- Loading dose anytime after last clopidogrel dose
  - Prasugrel 60 mg
  - Ticagrelor 180 mg
- Maintenance dose prasugrel 10 mg OR ticagrelor 90 mg twice daily

### Non-Acute Phase

- No loading dose either agent
- Maintenance dose 24 hours after last clopidogrel dose
- Timing similar for elderly or low-body-weight patients using prasugrel 5 mg
### P2Y$_{12}$ Inhibitor De-escalation

**Prasugrel to Clopidogrel**

**Acute Phase**
- 600 mg loading dose 24 hours after last prasugrel dose then maintenance
- No loading if bleeding

**Non-Acute Phase**
- No loading dose
- Clopidogrel 75 mg (maintenance dose) 24 hours after last prasugrel dose

**Ticagrelor to Clopidogrel**

**Acute Phase**
- 600 mg loading dose of clopidogrel 24 hours after last ticagrelor dose

**Non-Acute Phase**
- No loading if bleeding; use maintenance dose only
### Change Between Higher Potency P2Y₁₂ Inhibitors

**Acute and Non-Acute Phases**

- Ticagrelor → Prasugrel

**60 mg loading dose prasugrel 24 hours after last ticagrelor dose**

- **Non-Acute Phase**
  - No ticagrelor loading dose needed
  - Start 90 mg ticagrelor 24 hours after last prasugrel dose then maintenance 90 mg ticagrelor twice daily

- **Acute Phase**
  - Can consider loading dose 24 hours after last prasugrel dose

### SWAP-4 Results

**Switching from Ticagrelor to Clopidogrel**

- De-escalation from ticagrelor to clopidogrel therapy is associated with increased platelet reactivity
- The use of a loading dose before a maintenance dose mitigates this increased platelet reactivity

PRU = P2Y₁₂ reaction units

Communicating with Patients for Optimal Results

Being a Part of the Team
The Patient Perspective

Patients want:

1. All of their options explained in language they can understand
2. To be a part of the team
3. To be listened to and understood
4. To be given time to absorb the information before making a critical decision
5. To have a trustworthy place to find information
How You Can Help

1. Don’t use acronyms or medical jargon. Explain the diagnosis and/or options in simple terms.
2. Talk with the patient in a back-and-forth dialogue. Ask questions to determine their level of understanding.
3. Remember that this may be routine to you, but this can be a life-changing moment for the patient.
4. For a critical diagnosis or major decision, consider giving the patient time and follow-up (either in person or via telephone) to assure they understand what is happening.
5. Provide your patients with websites (they are going to Google anyway) that are filled with good information.
6. Consider their emotional needs: Connect them with support services or support groups in your hospital.

Educational Resources

Mended Hearts
www.mendedhearts.org
1-888-HEART-99

Go-To Guides
Heart Guides
Discussion Guides
Summary DAPT Recommendations

• DAPT should be continued for one month in SIHD with BMS and six months with DES
• DAPT should be continued for twelve months in ACS (sp PCI/CABG/medical management)
• ASA dosing should be 81 mg (75-100 mg) with DAPT
• Elective non-cardiac surgery should not be performed within 30 days after BMS or 3 months after DES (Class III)

Summary DAPT Recommendations (2)

• Real-world studies show the benefit of ticagrelor over clopidogrel in reduction of ischemic events; however, bleeding events are increased
• De-escalation from ticagrelor to clopidogrel requires a loading dose of clopidogrel
• Extended duration DAPT should be considered based on ischemic and bleeding risks, risk scores (e.g. DAPT score) help in decision-making
Thank you for joining us today!

Please remember to complete the POSTTEST and EVALUATION.

Your participation will help shape future CME activities.