Optimizing Outcomes for In-Hospital and Post-Discharge ACS Patients with Oral Antiplatelet Therapies

9:15 – 10:45 am

Cardiology Updates
Philadelphia, Pennsylvania
May 6, 2015
Session 2: Optimizing Outcomes for In-Hospital and Post-Discharge ACS Patients with Oral Antiplatelet Therapies

Learning Objectives

1. Evaluate in-hospital utilization of aspirin and clopidogrel including prudent timing and location of use of therapy.
2. Review in-hospital use of prasugrel and ticagrelor including efficacy and safety data and the new ACS guideline recommendations.
3. Summarize current recommended use of oral antiplatelet therapy after ACS hospital discharge for ACS patients and interpret clinical data from studies investigating the duration of dual antiplatelet therapy after ACS and PCI.

Faculty

**Jeffrey L. Anderson, MD**
Professor of Internal Medicine
University of Utah
School of Medicine
Salt Lake City, Utah

Dr Jeffrey Anderson is professor of medicine at the University of Utah School of Medicine and associate chief of cardiology, director of cardiovascular research at the Intermountain Heart Institute, and vice chair of research, department of internal medicine, at the Intermountain Medical Center. He graduated from Harvard Medical School with honors and completed a post doctoral fellowship in cardiology at Stanford University. He is board certified in internal medicine, cardiovascular disease, and clinical electrophysiology. He is a master of the American College of Physicians and past governor for the Utah Chapter. Dr Anderson was awarded the 2013 AHA physician volunteer of the year. He is immediate past chair, American Heart Association, western states affiliate. He is chair of the ACCF/AHA task force on practice guidelines. Dr Anderson has contributed to cardiovascular research over a broad area, including thrombolytic and antithrombotic therapy of acute myocardial infarction and unstable angina, antiarrhythmic therapy, trials in congestive heart failure and, currently, research on genetic polymorphisms and other new risk factors for cardiovascular disease and pharmacogenetic interactions. He has served on and chaired FDA’s advisory committee on cardiorenal drugs and on several other guidelines committees. He is an author or coauthor on over 600 original or invited publications and over 400 abstracts.

**Tyler J. Gluckman, MD**
Medical Director, Clinical Transformation
Providence St. Vincent
Medical Center
Portland, Oregon

Dr Tyler Gluckman is medical director, clinical transformation at the Providence St. Vincent Medical Center, Portland, Oregon, and adjunct faculty at The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, Maryland. Dr Gluckman received his medical degree from Northwestern University Medical School and did his internal medicine training at McGaw Medical Center of Northwestern University, remaining as chief resident and instructor in medicine. He completed his cardiology fellowship training at Johns Hopkins. His principal clinical and research interests include the management of acute coronary syndromes, the evaluation of premature graft failure after coronary artery bypass graft surgery, and variability in responsiveness to antiplatelet agents. Dr Gluckman serves as associate editor for practice guidelines and clinical documents for CardioSource and is an editorial consultant for CardioSource WorldNews. He is published in Archives of Internal Medicine, JAMA, and the Journal of the American College of Cardiology. He is an active councilor and director of quality for the state of Oregon chapter of the American College of Cardiology and a board member of the Portland Metro and SW Washington chapter of the American Heart Association/American Stroke Association.
Faculty Financial Disclosure Statements

The presenting faculty reports the following:

Dr Anderson has no financial relationships to disclose.

Dr Gluckman reports receiving consulting fees from Takeda Pharmaceuticals.

Education Partner Financial Disclosure Statements

The content collaborator at Voxmedia has no financial relationships to disclose.

Suggested Reading List


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SPEAKERS
Tyler Gluckman, MD
Jeffrey Anderson, MD

Presenter Disclosure Information
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Off-Label/Investigational Discussion
► In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Drug List

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
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</thead>
<tbody>
<tr>
<td>Vorapaxar</td>
<td>Zontivity</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Plavix</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Effient</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Brilinta</td>
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<td>Ticlopidine</td>
<td>Ticlid</td>
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<tr>
<td>Edoxaban</td>
<td>Savaysa</td>
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<tr>
<td>Rivaroxaban</td>
<td>Xarelto</td>
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<tr>
<td>Apixaban</td>
<td>Eliquis</td>
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<tr>
<td>Dabigatran</td>
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<td>Bivalirudin</td>
<td>Angiomax</td>
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<td>Fondaparinux</td>
<td>Arixtra</td>
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<tr>
<td>Abciximab</td>
<td>ReoPro</td>
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<tr>
<td>Tirofiban</td>
<td>Aggrastat</td>
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<tr>
<td>Eptifibatide</td>
<td>Integril</td>
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Learning Objectives

• Evaluate in-hospital utilization of aspirin and clopidogrel including prudent timing and location of use of therapy.

• Review in-hospital use of prasugrel and ticagrelor including efficacy and safety data and the new ACS guideline recommendations.

• Summarize current recommended use of oral antiplatelet therapy after ACS hospital discharge for ACS patients and interpret clinical data from studies investigating the duration of dual antiplatelet therapy after ACS and PCI.

In-Hospital Oral Antiplatelet Therapy in Acute Coronary Syndrome

Ty J. Gluckman MD, FACC, FAHA
Medical Director, Clinical Transformation
Providence Heart and Vascular Institute

Antithrombotic Treatment Options in Coronary Artery Disease
Use of Aspirin in Patients with ACS Treated With or Without PCI

Efficacy of Aspirin on Efficacy in Secondary Prevention

<table>
<thead>
<tr>
<th>Category</th>
<th>% Odds Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td>-</td>
</tr>
<tr>
<td>Acute CVA</td>
<td>-</td>
</tr>
<tr>
<td>Prior MI</td>
<td>-</td>
</tr>
<tr>
<td>Prior CVA/TIA</td>
<td>-</td>
</tr>
<tr>
<td>Prior CVA/MI</td>
<td>-</td>
</tr>
<tr>
<td>Prior MI/MI</td>
<td>-</td>
</tr>
<tr>
<td>Other high risk CVOD</td>
<td>-</td>
</tr>
<tr>
<td>(e.g. unstable angina, heart failure)</td>
<td>-</td>
</tr>
<tr>
<td>PAD</td>
<td>-</td>
</tr>
<tr>
<td>(e.g. intermittent claudication)</td>
<td>-</td>
</tr>
<tr>
<td>High-risk embolism (e.g. AMI)</td>
<td>-</td>
</tr>
<tr>
<td>Other (e.g. DM)</td>
<td>-</td>
</tr>
<tr>
<td>All trials</td>
<td>-</td>
</tr>
</tbody>
</table>

Aspirin provides consistent ischemic benefit in at-risk patients

Choosing the Right Aspirin Dose After PCI in ACS

<table>
<thead>
<tr>
<th>Event</th>
<th>Low dose (75mg)</th>
<th>High dose (150mg)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>3.1%</td>
<td>3.3%</td>
<td>0.61</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.3%</td>
<td>2.9%</td>
<td>0.22</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>4.8%</td>
<td>4.6%</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Higher dose aspirin does not improve efficacy and increases the risk of minor bleeding

Initial Aspirin Therapy: Guideline Recommendations

Non-enteric coated aspirin (162-325 mg) should be given promptly after presentation to all 1) STEMI patients undergoing fibrinolysis (Class I, Level A), 2) STEMI patients undergoing primary PCI (Class I, Level B), and 3) NSTE-ACS patients (Class I, Level A)

Choosing Your P2Y₁₂ Inhibitor in Patients with ACS Treated With or Without PCI
**Basic P2Y₁₂ Inhibitor Pharmacology**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Class</th>
<th>Activation</th>
<th>Onset of Effect*</th>
<th>Half-life</th>
<th>Duration of Effect</th>
<th>Withdrawal before major surgery</th>
<th>Special instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>Thienopyridine</td>
<td>Prodrug, limited by metabolism</td>
<td>2-4 hours</td>
<td>6 hours</td>
<td>3-10 days</td>
<td>5 days</td>
<td>Reduced platelet inhibition with some CYP450 polymorphisms</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Thienopyridine</td>
<td>Prodrug, not limited by metabolism</td>
<td>30 minutes</td>
<td>7 hours</td>
<td>5-10 days</td>
<td>7 days</td>
<td>Should only be used in conjunction with low dose aspirin (75 mg/day)</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Triazokynidine</td>
<td>Active drug</td>
<td>30 minutes</td>
<td>7 hours</td>
<td>3-4 days</td>
<td>5 days</td>
<td></td>
</tr>
</tbody>
</table>

*Time delay of platelet aggregation

**P2Y₁₂ Inhibitor Metabolic Pathways**

**P2Y₁₂ Inhibition in Medically Managed STEMI**

COMMIT/CC2 Trial

45,852 patients presenting within 24 hours of a STEMI treated medically (50% with fibrinolysis) and randomized to clopidogrel (75 mg daily) vs. placebo

- Dual antplatelet therapy provides superior efficacy in medically managed STEMI

**P2Y₁₂ Inhibition in ACS Treated with PCI**

Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38)

13,608 patients with ACS and planned PCI randomized to clopidogrel (300 mg LD and 75 mg MD) or prasugrel (60 mg LD and 10 mg MD) for up to 12 months

- Prasugrel provides superior efficacy in patients with ACS undergoing PCI

**P2Y₁₂ Inhibition in STEMI Treated with Fibrinolytic Therapy**

Clopidogrel as Adjuvant Reperfusion Therapy in Thrombolysis in Myocardial Infarction (CLARITY) Trial

3,491 patients (<75 years of age) presenting within 12 hours of a STEMI treated with fibrinolytic, aspirin, and heparin and randomized to clopidogrel (300 mg load followed by 75 mg daily) vs. placebo

- Clopidogrel benefits STEMI patients treated with fibrinolytics

**TRITON-TIMI 38 Major Efficacy End Points**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Prasugrel (n=6413)</th>
<th>Clopidogrel (n=6793)</th>
<th>Hazard Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke*</td>
<td>9.0%</td>
<td>12.1%</td>
<td>0.75</td>
<td>0.03</td>
</tr>
<tr>
<td>CV death</td>
<td>2.3%</td>
<td>2.4%</td>
<td>0.89</td>
<td>0.33</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>7.3%</td>
<td>9.5%</td>
<td>0.75</td>
<td>0.05</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>1.0%</td>
<td>1.0%</td>
<td>1.02</td>
<td>0.23</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>3.0%</td>
<td>3.2%</td>
<td>0.95</td>
<td>0.64</td>
</tr>
<tr>
<td>CV death, nonfatal MI, or urgent TVR</td>
<td>10.0%</td>
<td>12.3%</td>
<td>0.81</td>
<td>0.05</td>
</tr>
<tr>
<td>Death from any cause, nonfatal MI, or nonfatal stroke</td>
<td>10.7%</td>
<td>12.7%</td>
<td>0.83</td>
<td>0.05</td>
</tr>
<tr>
<td>Urgent TVR</td>
<td>2.3%</td>
<td>3.7%</td>
<td>0.66</td>
<td>0.06</td>
</tr>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke, or rehospitalisation for ischemia</td>
<td>12.3%</td>
<td>14.6%</td>
<td>0.84</td>
<td>0.05</td>
</tr>
<tr>
<td>Definite or probable stent thrombosis</td>
<td>1.1%</td>
<td>2.4%</td>
<td>0.48</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Primary end point

**Compared to cardiac death, expedited revascularisation, and need for urgent revascularisation

** COMMIT/CC2 randomized arm 2005;366:1607

** CLARITY-TIMI 7 randomized arm 2007;357:2001

** TRITON-TIMI 38 randomized arm 2011;32:2999
**P2Y₁₂ Inhibition in STEMI Treated with Primary PCI**

**PLATO Major Efficacy End Points**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Ticagrelor (n=9333)</th>
<th>Clopidogrel (n=5293)</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke*</td>
<td>9.8%</td>
<td>11.7%</td>
<td>0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>4.0%</td>
<td>5.1%</td>
<td>0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>5.8%</td>
<td>6.9%</td>
<td>0.84</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>1.5%</td>
<td>1.3%</td>
<td>1.17</td>
<td>0.22</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>4.5%</td>
<td>5.5%</td>
<td>0.78</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Death from any cause, nonfatal MI, or nonfatal stroke</td>
<td>10.2%</td>
<td>12.3%</td>
<td>0.84</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke, recurrent ischemia, TIA, or other arterial thrombotic events</td>
<td>14.6%</td>
<td>16.7%</td>
<td>0.88</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Definite or probable stent thrombosis</td>
<td>2.2%</td>
<td>2.9%</td>
<td>0.75</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Primary PCI: Wallentin L, O’Gara MT, Montalescot G. CV=Cardiovascular, PT=Percutaneous coronary intervention, TIMI=Thrombolysis in Myocardial Infarction, STEMI=ST-Elevation myocardial infarction, TIA=Transient ischemic attack, TIMI=Thrombolysis in Myocardial Infarction, STEMI=ST-Elevation myocardial infarction, TIA=Transient ischemic attack.

**P2Y₁₂ Inhibition in STEMI: Guideline Recommendations**

**Fibrinolytic Therapy**

Load with clopidogrel using:

- 300 mg for those ≤75 years
- 75 mg for those >75 years

Continue clopidogrel (75 mg daily) for:

- At least 14 days (Class I, Level A)
- Up to 1 year (Class I, Level C)

**PCI after Fibrinolytic Therapy**

Load with clopidogrel (300 mg) if PCI ≥24 hours after lysis and (600 mg) if PCI ≥24 hours after lysis

Continue clopidogrel (75 mg daily) for at least 1 year after PCI with a DES and at least 30 days and up to 1 year after a BMS

Load with prasugrel (60 mg) if PCI >24 hours after lysis with a fibrin-specific agent or >48 hours with a non-fibrin specific agent

Continue prasugrel (10 mg daily) for at least 1 year after PCI with a DES and at least 30 days and up to 1 year after a BMS
P2Y₁₂ Inhibition in STEMI: Guideline Recommendations

Primary PCI

- Load as early as possible or at the time of PCI with:
  - Clopidogrel 600 mg
  - Prasugrel 60 mg
  - Ticagrelor 180 mg

Continue for 1 year after PCI with a DES/BMS with:

- Clopidogrel 75 mg daily
- Prasugrel 10 mg daily
- Ticagrelor 90 mg twice daily*

Use beyond 1 year may be considered with a DES

*The benefit of clopidogrel is limited to patients taking 75 mg of aspirin per day

Aspirin

The CABG=Coronary

CV=Cardiovascular,

BMS=Bare

Frequency

point (%)

Clopidogrel (300 mg)

I IIa IIb III

I IIa IIb III

I IIa IIb III

benefit

P₂Y₁₂ Inhibition

Ticagrelor provides improved efficacy with no increased risk of bleeding in medically managed NSTE-ACS

PLATO NSTE-ACS Without Revascularization Substudy

5,366 patients with a NSTE-ACS managed without revascularization randomized to clopidogrel (300-600 mg LD and 75 mg MD) or ticagrelor (180 mg LD and 90 mg twice daily MD) for 12 months

• Clotagrel (300 mg or 600 mg loading dose followed by 75 mg daily) should be given for up to 12 months.
• Ticagrelor (380 mg loading dose followed by 90 mg twice daily) should be given for up to 12 months.*

It is reasonable to use ticagrelor in preference to clopidogrel

P2Y₁₂ Inhibition in Medically Managed NSTE-ACS

P2Y₁₂ Inhibition in Medically Managed NSTE-ACS

Clopigrel in Unstable Angina to Prevent Recurrent Events (CURE) Trial

12,562 patients with a NSTE-ACS randomized to daily aspirin (75-325 mg) or clopidogrel (300 mg load, 75 mg thereafter) plus aspirin (75-325 mg) for a mean of 9 months

Dual antiplatelet therapy with clopidogrel is more efficacious than aspirin monotherapy in NSTE-ACS

P2Y₁₂ Inhibition in Medically Managed NSTE-ACS

Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS)

7,243 patients with a medically managed NSTE-ACS randomized to prasugrel (10 mg) or clopidogrel for up to 30 months

Prazugrel does not provide improved efficacy in medically managed NSTE-ACS

P2Y₁₂ Inhibition in NSTE-ACS: Guideline Recommendations

Ischemia-Guided Strategy

- Clopidogrel (300 mg or 600 mg loading dose followed by 75 mg daily) should be given for up to 12 months.
- Ticagrelor (380 mg loading dose followed by 90 mg twice daily) should be given for up to 12 months.*

*The benefit of clopidogrel is limited to patients taking 75 mg of aspirin per day

ETCER=Event Thrombolytic in Acute Coronary Syndromes

JACC 2001;345:494-499
Optimal Oral Antiplatelet Therapy in NSTE-ACS Treated with PCI

**P2Y₁₂ Inhibition in PCI for NSTE-ACS**

Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events—Optimal Antiplatelet Strategy for Interventions (CURRENT-OASIS 7) Trial

25,087 patients with an ACS (of which 17,263 underwent PCI) randomized in a 2 x 2 factorial trial to a low dose clopidogrel (600 mg LD, 150 mg MD x 7 days), then 75 mg MD thereafter vs. standard dose clopidogrel (300 mg LD and 75 mg MD) and high dose aspirin (300-325 mg) vs. low dose aspirin (75-100 mg).

Double dose clopidogrel provides superior efficacy of NSTE-ACS treated with PCI

**P2Y₁₂ Inhibition in PCI for NSTE-ACS**

PLATO NSTE-ACS With Revascularization Substudy

5,714 patients with a NSTE-ACS managed with revascularization* randomized to clopidogrel (300-600 mg LD and 75 mg MD) or ticagrelor (180 mg LD and 90 mg twice daily MD) for 12 months

Ticagrelor provides improved efficacy with increased risk of bleeding in NSTE-ACS treated with PCI

**P2Y₁₂ Inhibition in NSTE-ACS: Guideline Recommendations**

Early Invasive Strategy

Prior to coronary angiography:

- Clopidogrel (300 mg or 600 mg loading dose followed by 75 mg daily)
- Ticagrelor (180 mg loading dose followed by 90 mg twice daily)*
- It is reasonable to use ticagrelor in preference to clopidogrel

*The benefit of ticagrelor is limited to patients taking ≥200 mg of aspirin per day

*Mehta R et al. JACC 2014;64:e139
P2Y$_{12}$ Inhibition in NSTE-ACS: Guideline Recommendations

**Early Invasive Strategy**

- With PCI using a bare metal or drug eluting stent:
  - Clopidogrel (300 mg or 600 mg loading dose followed by 75 mg daily for at least 12 months)
  - Prasugrel (60 mg loading dose followed by 10 mg daily for at least 12 months)
  - Ticagrelor (180 mg loading dose followed by 90 mg twice daily for at least 12 months)*
  - It is reasonable to use prasugrel over clopidogrel in those who undergo PCI who are not at high risk of bleeding complications
  - It is reasonable to use ticagrelor in preference to clopidogrel in patients treated with an early invasive strategy and/or coronary stenting

---

**Summary Effects of P2Y$_{12}$ inhibitors**

**Efficacy of Dual Antiplatelet Therapy in ACS**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary End Point</th>
<th>A + C</th>
<th>A + P (T)</th>
<th>P-value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE</td>
<td>CVD, MI, CVA</td>
<td>9.3%</td>
<td>11.4%</td>
<td>&lt;0.001</td>
<td>48</td>
</tr>
<tr>
<td>CLARITY</td>
<td>CVD, MI, UR*</td>
<td>11.6%</td>
<td>14.1%</td>
<td>0.03</td>
<td>40</td>
</tr>
<tr>
<td>COMMIT</td>
<td>CVD, MI, CVA</td>
<td>9.2%</td>
<td>10.1%</td>
<td>0.002</td>
<td>111</td>
</tr>
<tr>
<td>TRITON-TIMI 38</td>
<td>CVD, MI, CVA</td>
<td>12.1%</td>
<td>9.9%*</td>
<td>0.0004</td>
<td>46</td>
</tr>
<tr>
<td>PLATO</td>
<td>CVD, MI, CVA</td>
<td>11.7%</td>
<td>9.8%*</td>
<td>&lt;0.001</td>
<td>54</td>
</tr>
</tbody>
</table>

**Safety of Dual Antiplatelet Therapy in ACS**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Aspirin Dose</th>
<th>A + C</th>
<th>A + P (T)</th>
<th>P-value</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE</td>
<td>75-325 mg</td>
<td>3.7%</td>
<td>2.7%</td>
<td>&lt;0.001</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>&lt;100 mg</td>
<td>2.6%</td>
<td>2.0%</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100-200 mg</td>
<td>3.5%</td>
<td>2.3%</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;200 mg</td>
<td>4.9%</td>
<td>4.0%</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>CLARITY</td>
<td>75-162 mg</td>
<td>1.9%</td>
<td>1.7%</td>
<td>.002</td>
<td>167</td>
</tr>
<tr>
<td>COMMIT</td>
<td>162 mg</td>
<td>0.6%</td>
<td>0.5%</td>
<td>.59</td>
<td></td>
</tr>
<tr>
<td>TRITON-TIMI 38</td>
<td>75-162 mg</td>
<td>1.8%</td>
<td>2.4%*</td>
<td>.03</td>
<td>167</td>
</tr>
<tr>
<td>PLATO</td>
<td>75-325 mg</td>
<td>2.2%</td>
<td>2.8%*</td>
<td>.03</td>
<td>167</td>
</tr>
</tbody>
</table>

**Efficacy/Safety of Dual Antiplatelet Therapy in ACS with PCI**

**Rates of ischemic events in ACS patients undergoing PCI**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary End Point</th>
<th>A + C</th>
<th>A + P (T)</th>
<th>P-value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRITON-TIMI 38</td>
<td>CVD, MI, CVA</td>
<td>12.1%</td>
<td>9.9%*</td>
<td>.0004</td>
<td>46</td>
</tr>
<tr>
<td>PLATO**</td>
<td>CVD, MI, CVA</td>
<td>10.7%</td>
<td>9.0%*</td>
<td>.0025</td>
<td>59</td>
</tr>
</tbody>
</table>

**Rates of major bleeding in ACS patients undergoing PCI**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Aspirin Dose</th>
<th>A + C</th>
<th>A + P (T)</th>
<th>P-value</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRITON-TIMI 38</td>
<td>75-162 mg</td>
<td>1.8%</td>
<td>2.4%*</td>
<td>.03</td>
<td>167</td>
</tr>
<tr>
<td>PLATO†</td>
<td>75-162 mg</td>
<td>2.2%</td>
<td>2.8%</td>
<td>.08</td>
<td>---</td>
</tr>
</tbody>
</table>

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**Post-Discharge Management of ACS with Antiplatelet Therapies**

Jeffrey L Anderson, MD, FACC, FAHA, MACP
Intermountain Heart Institute
Intermountain Medical Center
University of Utah School of Medicine
Salt Lake City, Utah
Non-enteric-coated aspirin (162-325 mg/d) should be given to all NSTE-ACS patients promptly after presentation, and a maintenance dose (81-325 mg/d) should be continued indefinitely.

In NSTE-ACS patients unable to take aspirin because of hypersensitivity or GI intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered.

It is reasonable to use an aspirin maintenance dose of 81 mg per day in preference to higher maintenance doses in patients with NSTE-ACS treated either invasively or with coronary stent implantation.

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**CURE: Long-term benefit of clopidogrel**

12,562 Patients with NSTEACS (mostly conservatively managed)

---

**CHARISMA Trial Design**

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**Primary Efficacy Results (MI/Stroke/CV Death) by Pre-Specified Entry Category**

Population RR (95% CI) p value

**Qualifying CAD, CVD or PAD** *(n=12,153)*

0.88 (0.77, 0.998) 0.046

**Multiple Risk Factors** *(n=3,284)*

1.20 (0.91, 1.59) 0.20

**Overall Population** *(n=15,603)*

0.93 (0.83, 1.05) 0.22
**Timing of Benefit (Landmark Analysis)**

- **Clopidogrel**
  - HR 0.82
  - P=0.01
  - Loading Dose
  - Days
  - Maintenance Dose

- **Prasugrel**
  - HR 0.80
  - P=0.003

**Efficacy of ticagrelor vs clopidogrel over time**

18,624 Patients w/in 24 hrs of onset of ACS (64% underwent PCI)

**Co-Primary Effectiveness End Point**

- **MACCE (composite of death, MI, or stroke)**

**Stent & Drug Types**

- Drug Eluting Stent Type
- Thienopyridine Type

**Co-Primary Effectiveness End Point**

- **MACCE (composite of death, MI, or stroke)**

**Dual Antiplatelet Therapy (DAPT) Study: Design**

- Randomization
- Study Drug Treatment Ends

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

- Time in months after index stent procedure
- # At Risk

**Co-Primary Effectiveness End Point**

- **Stent Thrombosis**
Co-Primary Effectiveness End Points & Components: 12-30 Months

Treatment Effect According to ACS Status
Myocardial Infarction Type, 12-30 M follow-up
All Randomized Subjects (N=11648)

Treatment Effect According to ACS Status
Secondary Endpoints at 12-30 Months
All Randomized Subjects (N=11648)

Primary Safety End Point (Moderate or Severe Bleeding): 12-30 Months

Limitations

- Post-hoc subgroup analyses
  - Interaction testing not powered
  - Multiple hypotheses tested
- 1st generation DES included
  - Largest RCT of antiplatelet duration of 2nd generation DES (> 4500 everolimus-eluting stent patients randomized).
- Did not assess overall benefit vs. risk of continued thienopyridine accounting for both ischemia and bleeding.
  - Ischemia outcomes may exceed bleeding in terms of impact on patient quality-adjusted life years.*

Conclusions

• Although they are younger with fewer comorbidities, ACS patients are at higher risk for late ischemic events than non-ACS patients.

• Compared to treatment with aspirin alone, continuation of thienopyridine plus aspirin beyond one year reduces the risk of ischemic events among both ACS and non-ACS patients.

• Driven by reductions in both stent thrombosis and myocardial infarction not related to stent thrombosis.

• Absolute risk reductions in ischemic events were greater in ACS patients, but present in both groups.


Conclusions

• The benefit of extended thienopyridine treatment was tempered by an increase in bleeding events in both ACS and non-ACS patients

• Among non-ACS patients, death occurred more commonly in the continued thienopyridine group.

• Difference in death mainly not related to bleeding (Mauri NEJM 2014) and not present in meta-analysis of prior randomized studies of thienopyridine duration (Elmariah Lancet 2015)

Continuation of dual antiplatelet therapy for 30 months should be strongly considered in both ACS and non-ACS patients who have tolerated 1 year of treatment.

**Summary**

- Adding ticagrelor to low-dose aspirin in stable patients with a history of MI reduced the risk of CV death, MI or stroke.
- The benefit of ticagrelor was consistent:
  - For both fatal & non-fatal components of primary endpoint
  - Over the duration of treatment
  - Among major clinical subgroups
- Ticagrelor increased the risk of TIMI major bleeding, but not fatal bleeding or ICH.
- The two doses of ticagrelor had similar overall efficacy, but bleeding and other side effects tended to be less frequent with 60 mg bid dose.

**Conclusion**

Long-term dual antiplatelet therapy with low-dose aspirin and ticagrelor should be considered in appropriate patients with a myocardial infarction.

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**Vorapaxar – Protease-Activated Receptor (PAR)-1**

- Vorapaxar is an oral, potent, and selective antagonist of PAR-1.
- Metabolism by CYP3A4 enzymes.
- No meaningful renal clearance.
- Long half-life (T1/2 >100 hours).

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**Central Role of Platelets and Interaction with Coagulation in the Genesis of Thrombosis**

- COX = cyclooxygenase. PAR = protease-activated receptor. TP = thromboxane receptor.

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**Efficacy by Time from Qual MI**

**Prior MI Cohort**

**Time from qualifying MI to Randomizations**

- **< 3 months**
  - HR 0.82
  - p = 0.011
  - Placebo 10.4% vs Vorapaxar 8.9%

- **3 to 6 months**
  - HR 0.79
  - p = 0.023
  - Placebo 9.4% vs Vorapaxar 7.5%

- **> 6 months**
  - HR 0.78
  - p = 0.026
  - Placebo 8.8% vs Vorapaxar 7.1%

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**Efficacy Early and Late**

**Prior MI Cohort**

**Days 0 to 360**

- HR 0.79
- p = 0.003
- Placebo 3.2% vs Vorapaxar 3.2%

---

**Days 360 to 1080**

- HR 0.82
- p = 0.004
- Placebo 5.5% vs Vorapaxar 5.5%

---

*Adapted from Vu TH et al. Cell 1991;64:1057-1066.*
**DAPT Duration: Conclusions**

1. "One size shoe" approach for DAPT duration is unlikely to fit all patients: i.e., ACS vs non-ACS, diabetes, CABG-SVG / ISR.
2. Stent platforms differ in their risk for early, late, and very late stent thrombosis events ("All DES are not created equal").
3. After the minimum necessary duration of DAPT to treat the specific stent and stent-related lesion, longer term therapy is directed more to non-stent and non-target lesion burden and vulnerability.
4. Conclusions regarding "optimal" DAPT duration should be based on individual assessment of ischemic event prevention vs. bleeding risk and on adequately powered RCCT.
5. Better scoring tools are needed for determining individual ischemic risk, bleeding risk, and the balance of ischemic to bleeding risk with extended DAPT to assist in more personalized therapeutic decision-making.

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**Case Study**
**Case Study**

**HPI:** RM is a 72 year old man who presents to his local ED with stuttering “aching” in his chest. He states that it began about 24 hours earlier. Initially he thought this was related to a large meal, but became worried with continued symptoms that did not respond to over the counter antacids.

**PMH:** Hypertension, hypercholesterolemia, stage 3 CKD, and a prior TIA that manifested as clumsiness in his left hand.

**Allergies:** He reports prior intolerance to lisinopril (cough).

**Medications:** Aspirin (81 mg QD), losartan (25 mg QD), hydrochlorothiazide (25 mg QD), and simvastatin (10 mg QHS).

**ED Course:** Upon arrival, he is administered non-enteric-coated, chewable aspirin (81 mg x 4), sublingual nitroglycerin (0.4 mg x 2), and metoprolol tartrate (25 mg PO x 1) which renders him free of “chest discomfort”. His TIMI risk score is calculated to be 6.

After consultation with the cardiologist on call, he is administered IV unfractionated heparin (60 U/kg IV bolus [maximum of 4000 U] and 12 U/kg/hr IV gtt [maximum of 1000 U/hr] with a plan to take him to the cardiac catheterization laboratory that afternoon.

**Labs:**
- Serum Cr=1.5 mg/dl (estimated CrCl=61.2 ml/min), Glucose=184 mg/dl, HbA2c=8.2%, cTnI=2.6 (ULN 0.1)
- Wt=216 lbs, BMI=31.9 kg/m2
- CrCl=61.2 ml/min
- ULN 0.1

**ECG:**
- Sinus rhythm with a rate of 88 bpm and 1.5 mm of downsloping ST segment depression in the inferior and lateral leads.

**Ext:**
- No edema, 2+ distal pulses

**BP=146/94, HR=69**, Wt=216 lbs, BMI=31.9 kg/m²

**Interventions:***
- **PCI** 30-80% of patients
- **CABG** 10%
- **STEMI**
- **Medical Management** 25-40%
- **PCI 90%**
- **CABG 6-8%**
- **Medical Management 2-4%**

Adapted from Cohil DP et al. Circulation 2016;133:3993-3998

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**When to start a P2Y12 Inhibitor in NSTE-ACS Treated with an Early Invasive Strategy**

**SH:** He quit smoking in 2007 (38 year pack history). No ETOH.

**FH:** His father died of a heart attack at age 49.

**PE:**
- **BP=146/94, HR=69**, Wt=216 lbs, BMI=31.9 kg/m²
- **CV:** JVP 6 cm H2O, regular rhythm, no S3, no murmurs
- **Lungs:** Clear to auscultation, no rales
- **Ext:** No edema, 2+ distal pulses

**Labs:**
- Serum Cr=1.5 mg/dl (estimated CrCl=61.2 ml/min), Glucose=184 mg/dl, HbA2c=8.2%, cTnI=2.6 (ULN 0.1)

---

**Management of Patients with Coronary Ischemia**

**NSTE-ACS**

- **Medical Management** 35%
- **PCI** 35%
- **CABG** 10%
- Angiography without revascularization 20%

**NSTEMI**

- **PCI 30-80%**
- **Medical Management 25-40%**
- **CABG 10%**

**STEMI**

- **PCI 90%**
- **CABG 6-8%**
- **Medical Management 2-4%**

---

**Should There be P2Y12 Inhibitor Pretreatment in NSTE-ACS?**

**Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) Trial**

4,033 patients with NSTE-MI scheduled to undergo coronary angiography within 2 to 48 hours randomized to pretreatment (30 mg prasugrel) before angiography and 30 mg at the time of PCI or placebo (60 mg of prasugrel at the time of PCI)

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3%</td>
<td>2.5%</td>
</tr>
<tr>
<td>10.8%</td>
<td>10.8%</td>
</tr>
<tr>
<td>9.8%</td>
<td>9.8%</td>
</tr>
<tr>
<td>0.9%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

**Primary end point at 7 days**

**Primary end point at 30 days**

**CV death, MI, stroke at 30 days**

**Non-CABG TIMI major bleeding at 7 days**

**Conclusion:**

*Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) Trial*
Should There be P2Y₁₂ Inhibitor Pretreatment in NSTE-ACS?

<table>
<thead>
<tr>
<th>Moderate-to-high risk NSTE-ACS</th>
<th>Scheduled angiography within 24-48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>High bleeding risk</td>
<td>PCI not indicated</td>
</tr>
<tr>
<td>No</td>
<td>No CAD</td>
</tr>
<tr>
<td>CAD not in need of or amenable to PCI</td>
<td>Load with clopidogrel or ticagrelor</td>
</tr>
<tr>
<td>No P2Y₁₂ inhibitor</td>
<td>Load with clopidogrel or ticagrelor</td>
</tr>
<tr>
<td>Load with clopidogrel or ticagrelor</td>
<td>Load with clopidogrel, prasugrel, or ticagrelor on the table</td>
</tr>
</tbody>
</table>


Case Study

Hospital Course: He undergoes PCI of a bifurcation lesion involving the proximal left circumflex and ostial first obtuse marginal arteries with two drug eluting stents.

He remains free of any ischemic symptoms post PCI. He undergoes a transthoracic echocardiogram that demonstrates mild hypokinesis of the lateral wall with a LV EF of 45%. He is discharged hospital day #2 with follow up in 1 week.

Discharge medications include: aspirin (81 mg QD), ticagrelor (90 mg BID), metoprolol succinate (25 mg QD), losartan (100 mg QD), atorvastatin (80 mg QD) and, metformin 850 mg BID (after checking Cr in 48 hours).

In Hospital Take Aways

- Aspirin (162-325 mg) should be administered as soon as possible in ACS
- Low dose aspirin (75-81 mg) is preferred after PCI in ACS
- Dual antiplatelet therapy should be continued for 12 months in:
  - Fibrinolysis for STEMI using clopidogrel
  - PCI after successful fibrinolysis for STEMI using clopidogrel or prasugrel
  - Primary PCI for STEMI using clopidogrel, prasugrel, or ticagrelor
  - Medical management of NSTE-ACS using clopidogrel or ticagrelor
  - PCI for NSTE-ACS using clopidogrel, prasugrel, or ticagrelor
- In invasively managed ACS, compared to clopidogrel, both prasugrel and ticagrelor are associated with superior efficacy (mortality reduction with ticagrelor) and a small increased risk of major bleeding.

Take Home Points

Post Discharge Take Aways

- "One size fits all" approach for duration of DAPT is unlikely to fit all patients.
- After the minimum necessary duration of DAPT to treat the specific stent and stent-related lesion, longer term therapy is directed more to non-stent and non-target lesion burden and vulnerability.
- Conclusions regarding “optimal” DAPT duration should be based on evaluating the trade-off between ischemic and bleeding risk according to the patient’s clinical profile and on adequately powered randomized controlled clinical trials.