Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

Presented as a Midday Symposium at the 45th ASHP Midyear Clinical Meeting and Exhibition

Tuesday, December 7, 2010
Anaheim, California

Planned and conducted by ASHP Advantage and supported by an educational grant from AstraZeneca
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AGENDA

11:30 a.m. – 11:35 a.m. | Introductory Remarks  
Paul P. Dobesh, Pharm.D., FCCP, BCPS (AQ-Cardiology)

11:35 a.m. – 12:00 p.m. | Update on Oral Antiplatelet Therapy in Acute Coronary Syndrome  
Toby C. Trujillo, Pharm.D., BCPS (AQ-Cardiology)

12:00 p.m. – 12:40 p.m. | Clinical Challenges in Oral Antiplatelet Therapy  
Julie H. Oestreich, Pharm.D., Ph.D.

12:40 p.m. – 1:15 p.m. | Emerging P2Y₁₂ Treatment Strategies  
Paul P. Dobesh, Pharm.D., FCCP, BCPS (AQ-Cardiology)

1:15 p.m. – 1:30 p.m. | Faculty Discussion and Audience Questions  
All Faculty

FACULTY

Paul P. Dobesh, Pharm.D., FCCP, BCPS (AQ Cardiology)
Activity Chair and Moderator  
Associate Professor of Pharmacy Practice  
College of Pharmacy  
University of Nebraska Medical Center  
Omaha, Nebraska

Julie H. Oestreich, Pharm.D., Ph.D.  
Assistant Professor of Pharmacy Practice  
College of Pharmacy  
University of Nebraska Medical Center  
Omaha, Nebraska

Toby C. Trujillo, Pharm.D., BCPS (AQ Cardiology)
Associate Professor  
University of Colorado Denver School of Pharmacy  
Clinical Specialist – Cardiology/Anticoagulation  
University of Colorado Hospital  
Aurora, Colorado
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The faculty and planners report the following relationships:

**Paul P. Dobesh, Pharm.D., FCCP, BCPS (AQ Cardiology)**

Dr. Dobesh declares that he has served as a consultant to sanofi-aventis and has received research grants from AstraZeneca and Eli Lilly and Company.

**Julie H. Oestreich, Pharm.D., Ph.D.**

Dr. Oestreich declares that she has no relationships pertinent to this activity.

**Toby C. Trujillo, Pharm.D., BCPS (AQ Cardiology)**

Dr. Trujillo declares that he has served as a speaker for sanofi-aventis.

**Carla J. Brink, M.S., B.S.Pharm.**

Ms. Brink declares that she has no relationships pertinent to this activity.
ACTIVITY OVERVIEW

Despite recent advances in the treatment of acute coronary syndrome (ACS), mortality associated with both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) remains unacceptably high. Patients who experience an acute myocardial infarction are at increased risk for future coronary episodes, and mortality increases with subsequent events.

While the need for dual antiplatelet therapy in patients with ACS is well established, pharmacists are met with many clinical dilemmas as they seek to optimize therapy. In this symposium, the faculty will tackle many of these questions, including duration of oral antiplatelet therapy, clopidogrel nonresponsiveness, drug interactions with proton pump inhibitors, and laboratory testing of platelet reactivity and patient genotypes. In addition, emerging treatment strategies, including triple antiplatelet therapy and pipeline antiplatelet agents, will be addressed.

Using patient case examples and interactive questions, the faculty will engage participants in the clinical decision-making process involved in optimizing oral antiplatelet therapy for patients with ACS.

ACTIVITY OBJECTIVES

At the conclusion of this knowledge-based educational activity, participants should be able to

- Identify patient factors to consider when selecting an appropriate oral antiplatelet therapy.
- Describe the implications of recent clinical trials evaluating the safety and efficacy of current and emerging oral antiplatelet therapies for patients with acute coronary syndrome.
- Define clopidogrel nonresponsiveness and devise a treatment strategy to manage it.
- List factors to consider when deciding whether to use laboratory testing of platelet reactivity or patient genotype to guide selection of oral antiplatelet therapy.

LIST OF ABBREVIATIONS

For a list of abbreviations used in this symposium, please see page 76.
CONTINUING EDUCATION ACCREDITATION

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 2 hours (0.2 CEUs) of continuing pharmacy education credit (ACPE activity #204-000-10-480-L01P).

Attendees must complete a Continuing Pharmacy Education Request online and may immediately print their official statements of continuing pharmacy education credit at the ASHP Learning Center at http://ce.ashp.org following the activity.

Complete instructions for receiving your statement of continuing pharmacy education online are on the next page. Be sure to record the session code beginning with “A” announced during the activity.

Your educational opportunities related to antiplatelet therapy in patients with ACS reach beyond today’s symposium…

A live webinar on March 2, 2011, where faculty will explore issues raised by participant questions in today’s symposium (1 hour CPE).

Informational podcast interviews with the faculty about their experiences managing patients with ACS.

e-Newsletters featuring tips for incorporating information related to the use of oral antiplatelet therapy in ACS into practice, as well as updates on emerging information.

Web-based activity based on today’s live symposium (2 hours CPE, but please note that individuals who claim CPE credit for the live symposium are ineligible to claim credit for the web-based activity).

For more information and to sign up to receive e-mail updates about this educational series, go to

www.ashpadvantage.com/optimize
Instructions for Processing CPE online at http://ce.ashp.org

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http://ce.ashp.org

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2. Once logged in to the site, click on “Process Meeting CE.”

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   If you are not registered to attend the ASHP Midyear Clinical Meeting, click on the start link to the right of the activity title. If this activity title does not appear in your meeting list, enter the 5-digit activity code in the box above the list and click submit. The activity code for this activity is 10480. Click register again when prompted. When you receive the “thank you for registering” message, click continue. This step will bring you back to your meeting list. Click on the start link to the right of the activity title. Do not click on “remove” or you will not be able to process CE for this activity.

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5. Enter the session code (e.g., A12345 and note that the letter is case sensitive) that was announced during the activity, and select the number of hours equal to your participation in the activity.

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7. Confirm your participation and click submit.

8. New this year, complete the overall Midyear evaluation and click the “finish” button. You will then be able to view and print your transcript.

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<th>Activity Code</th>
<th>Session Code (announced during the live activity)</th>
<th>CPE credit hours</th>
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<td>Tuesday December 7, 2010</td>
<td>10480</td>
<td>2</td>
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</tr>
</tbody>
</table>

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Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome
Toby C. Trujillo, Pharm.D., BCPS (AQ Cardiology)
Associate Professor
University of Colorado Denver School of Pharmacy
Clinical Specialist – Cardiology/Anticoagulation
University of Colorado Hospital
Aurora, Colorado

Toby C. Trujillo, Pharm.D., BCPS (AQ Cardiology), is Associate Professor of Clinical Pharmacy at the University of Colorado Denver School of Pharmacy in Aurora, Colorado. He also serves as Clinical Specialist in cardiovascular pharmacotherapy and anticoagulation at University of Colorado Hospital.

Dr. Trujillo earned his Bachelor of Science degree in biochemistry from the University of California, Davis and his Doctor of Pharmacy degree from the University of California, San Francisco, where he also completed a residency in pharmacy practice. Dr. Trujillo completed a fellowship in cardiovascular pharmacotherapy at The University of Arizona, and he is a board-certified pharmacotherapy specialist with added qualifications in cardiology.

Dr. Trujillo’s current responsibilities at University of Colorado Hospital include providing clinical pharmacy services to cardiology, as well as directing the inpatient anticoagulation program. He also serves as co-chair of the anticoagulation subcommittee of the P&T committee. Dr. Trujillo currently serves as a preceptor to both pharmacy students and residents. His lectures at the School of Pharmacy focus on ischemic heart disease, antithrombotic therapy, and other cardiology and critical care topics.

Within the American Heart Association, Dr. Trujillo is a member of the Clinical Pharmacology Committee, which resides under the Council on Clinical Cardiology. He has also served a number of committees within the American College of Clinical Pharmacy, served as a speaker on numerous occasions on a national level, and authored several articles and book chapters in the area of cardiovascular pharmacotherapy. Dr. Trujillo is a member of the American Society of Health-System Pharmacists, and he helped develop current standards for postgraduate year 2 (PGY2) cardiology residency training programs.
Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

Toby C. Trujillo, Pharm.D., BCPS (AQ Cardiology)

PRESENTATION

Update on Oral Antiplatelet Therapy in Acute Coronary Syndrome

OVERVIEW

Antiplatelet therapy has been a cornerstone in the treatment of patients with acute coronary syndrome (ACS) since the 1980s. Depending on the ACS subpopulation being studied, the implementation of aspirin (ASA) monotherapy provided significant reductions in morbidity and mortality.

Although the routine use of ASA became the standard of care, a significant number of patients continued to suffer from major ischemic events. The development of ticlopidine and clopidogrel in the 1990s represented another major advance in the treatment of cardiovascular disease. Studies quickly established that at a minimum these agents were equivalent and sometimes superior to ASA monotherapy in the prevention of ischemic events in multiple patient populations with atherosclerotic vascular disease, including ACS. Interest in monotherapy for ACS waned with the publication of the CURE trial, which provided the initial support for dual oral antiplatelet therapy. Along with the dramatic increase in the use of stents in patients undergoing percutaneous coronary intervention (PCI), clinical trials have established the combination of ASA plus clopidogrel as standard of care in patients with ACS over the last decade.

Similar to the earlier situation with ASA monotherapy, however, substantial numbers of patients continue to experience ischemic events on dual antiplatelet therapy. In addition, there has been a growing recognition that variable response to clopidogrel may contribute to the residual clinical burden seen with dual antiplatelet therapy. Prasugrel is a new antiplatelet agent with a mechanism of action similar to clopidogrel that may offer pharmacokinetic and pharmacodynamic advantages. In a head-to-head comparison in patients with ACS, prasugrel was more effective at reducing myocardial infarction than clopidogrel when both were added to ASA therapy. The impact of dual antiplatelet therapy will continue to be modified with the development of new oral antiplatelet agents, such as prasugrel.
Update on Oral Antiplatelet Therapy in Acute Coronary Syndrome

Toby C. Trujillo, Pharm.D., BCPS (AQ Cardiology)
Associate Professor
University of Colorado Denver School of Pharmacy
Aurora, Colorado

Understanding Acute Coronary Syndrome (ACS)

Non-ST Elevation (UA/NSTEMI)  ST Elevation (STEMI)

Medical Therapy  PCI +/- Stent  Fibrinolysis

UA = unstable angina, NSTEMI = non-ST-segment elevation myocardial infarction, STEMI = ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention

ACC/AHA Guidelines

• NSTE ACS
  – Early invasive for high risk
  – β-blockers
  – Nitrates
  – ACE inhibitors/ARB
  – Aldosterone antagonists
  – Statins
  – Anticoagulants
  – Antiplatelet therapy
    • Aspirin (ASA)
    • P2Y12 receptor antagonists
    • GP IIb/IIIa inhibitors

• STEMI
  – Reperfusion therapy
    • Primary PCI
    • Thrombolytics
  – β-blockers
  – Nitrates
  – ACE inhibitors/ARB
  – Aldosterone antagonists
  – Statins
  – Anticoagulants
  – Antiplatelet therapy
    • Aspirin
    • P2Y12 receptor antagonists
    • GP IIb/IIIa inhibitors

Existing and Future Antiplatelet Agents


Aspirin in Acute Coronary Syndrome

Unstable Angina

Acute Myocardial Infarction


CURE Study

Primary Endpoint: MI/Stroke/CV Death

CURE: Bleeding Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo + ASA* N = 6303</th>
<th>Clopidogrel + ASA* N = 6259</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>2.7%</td>
<td>3.7%**</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>1.8%</td>
<td>2.2% †</td>
</tr>
<tr>
<td>Non-life-threatening bleeding</td>
<td>0.9%</td>
<td>1.5% ‡</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>2.4%</td>
<td>5.1% §</td>
</tr>
</tbody>
</table>

* In combination with standard therapy
**p = 0.001; †p = NS; ‡p = 0.002; §p < 0.001


PCI-CURE: Results

Composite of MI or cardiovascular death from randomization to end of follow-up

<table>
<thead>
<tr>
<th>Days of Follow-up</th>
<th>Placebo + ASA</th>
<th>Clopidogrel + ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12.6%</td>
<td>8.8%</td>
</tr>
<tr>
<td>120</td>
<td>0.05</td>
<td>0.002</td>
</tr>
<tr>
<td>180</td>
<td>0.01</td>
<td>0.002</td>
</tr>
<tr>
<td>240</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>300</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>400</td>
<td>0.001</td>
<td>0.002</td>
</tr>
</tbody>
</table>


CREDO

Early Effects of Pre-treatment with Clopidogrel - 28-Day Results

<table>
<thead>
<tr>
<th>Days from Randomization</th>
<th>No pre-treatment - Placebo</th>
<th>Pre-treatment - Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.5%</td>
<td>3.5%</td>
</tr>
<tr>
<td>7</td>
<td>4.5%</td>
<td>4.5%</td>
</tr>
<tr>
<td>14</td>
<td>6.5%</td>
<td>6.5%</td>
</tr>
<tr>
<td>21</td>
<td>8.5%</td>
<td>8.5%</td>
</tr>
<tr>
<td>28</td>
<td>8.5%</td>
<td>8.5%</td>
</tr>
</tbody>
</table>

*Plus ASA and other standard therapies
**p < 0.001; †p = 0.23

Clopidogrel in ACS

- **NSTE ACS**
  - CURE (n=12,562)
    - 300/75 mg vs. placebo within 24 hours of symptom onset
    - Significant reductions in death, MI, and stroke
  - PCI-CURE (n=2658)
    - 31% RRR in CV death or MI
  - CREDO (n=2116)
    - 300/75 mg vs. placebo 3-24 hours before PCI, 75 mg vs. placebo after 28 days
    - 27% RRR MI/Stroke death 1 year
    - 18.5% RRR in death, MI, UTVR
    - Benefit only seen if load > 6 hours before PCI
  - ACUITY (n=13,819)
    - Benefit with bivalirudin monotherapy contingent on clopidogrel loading pre-PCI

- **STEMI**
  - CLARITY (n=3491)
    - Patients age 18-75 yr within 12 hours
      - Clopidogrel 300/75 mg
      - Placebo
    - Significant reductions in occluded vessel, death, MI by angiography and up to 30 days
  - COMMIT (n=45,852)
    - 300/75 mg vs. placebo 3-24 hours before PCI, 75 mg vs. placebo after 28 days
    - 27% RRR MI/stroke death 1 year
    - 18.5% RRR in death, MI, UTVR
    - Benefit only seen if load > 6 hours before PCI


Limitations of Dual Antiplatelet Therapy

ASA plus Clopidogrel

- Increased bleeding
- Delayed onset
- Modest level of platelet inhibition
- Variable response
  - Pharmacogenomics
  - Drug interactions
- Irreversible mechanism of action
- Delayed offset
- Residual clinical events

Which of the following statements is true?

a. No clinical benefit is derived with increasing clopidogrel to 150 mg/day
b. Prasugrel reduces risk of CV mortality compared with clopidogrel in treatment of ACS
c. Higher aspirin dose further reduces mortality compared with aspirin 81 mg daily
d. Prasugrel increases risk of bleeding compared with clopidogrel in treatment of ACS
CURRENT Trial: Study Design

ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)
- Planned early (<24 hours) invasive management with intended PCI
- Ischemic ECG Δ (80.8%) or ↑ cardiac biomarker (42%)

Planned early (<24 hours) invasive management with intended PCI

Ischemic ECG Δ (80.8%) or ↑ cardiac biomarker (42%)

Clopidogrel 600-mg load, 150 mg/day × 7 days, then 75 mg/day

Clopidogrel 300-mg load, then 75 mg/day

Aspirin 300-325 mg/day

Aspirin 75-100 mg/day

N = 25,087

Efficacy outcomes: CV death, MI, or stroke at day 30
Stent thrombosis at day 30

Safety outcomes: Bleeding

Key subgroup: PCI vs. no PCI


CURRENT Trial Results:
Clopidogrel Double vs. Standard Dose

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standard Dose</th>
<th>Double Dose</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
<th>Inter P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death/MI/stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI (N = 17,232)</td>
<td>4.5</td>
<td>3.9</td>
<td>0.85</td>
<td>0.74-0.99</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>No PCI (N = 7855)</td>
<td>4.2</td>
<td>4.9</td>
<td>1.17</td>
<td>0.99-1.44</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Overall (N = 25,087)</td>
<td>4.4</td>
<td>4.2</td>
<td>0.95</td>
<td>0.84-1.07</td>
<td>0.370</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI (N = 17,232)</td>
<td>2.6</td>
<td>2.0</td>
<td>0.78</td>
<td>0.64-0.95</td>
<td>0.012</td>
<td>0.025</td>
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<tr>
<td>No PCI (N = 7855)</td>
<td>1.4</td>
<td>1.7</td>
<td>1.25</td>
<td>0.87-1.79</td>
<td>0.23</td>
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<tr>
<td>Overall (N = 25,087)</td>
<td>2.2</td>
<td>1.9</td>
<td>0.96</td>
<td>0.73-1.23</td>
<td>0.097</td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI (N = 17,232)</td>
<td>1.9</td>
<td>1.9</td>
<td>0.96</td>
<td>0.77-1.19</td>
<td>0.68</td>
<td>1.0</td>
</tr>
<tr>
<td>No PCI (N = 7855)</td>
<td>2.8</td>
<td>2.7</td>
<td>0.96</td>
<td>0.74-1.26</td>
<td>0.77</td>
<td></td>
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<tr>
<td>Overall (N = 25,087)</td>
<td>2.2</td>
<td>2.1</td>
<td>0.96</td>
<td>0.81-1.14</td>
<td>0.628</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI (N = 17,232)</td>
<td>0.4</td>
<td>0.4</td>
<td>0.88</td>
<td>0.55-1.41</td>
<td>0.59</td>
<td>0.50</td>
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<tr>
<td>No PCI (N = 7855)</td>
<td>0.8</td>
<td>0.9</td>
<td>1.11</td>
<td>0.68-1.82</td>
<td>0.67</td>
<td></td>
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<tr>
<td>Overall (N = 25,087)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.99</td>
<td>0.70-1.39</td>
<td>0.950</td>
<td></td>
</tr>
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</table>


Enlarged slide on page 21
CURRENT Trial Results:
ASA High Dose vs. Low Dose

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Higher Dose (P = 0.0006)</th>
<th>Lower Dose (P = 0.0001)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: death from cardiovascular causes, hospitalization, or revascularization</td>
<td>5.6% (42)</td>
<td>6.4% (50)</td>
<td>0.45</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes, hospitalization, or revascularization</td>
<td>5.6% (42)</td>
<td>6.4% (50)</td>
<td>0.45</td>
</tr>
<tr>
<td>Death from cardiovascular causes, hospitalization, or revascularization</td>
<td>5.6% (42)</td>
<td>6.4% (50)</td>
<td>0.45</td>
</tr>
<tr>
<td>Death from cardiovascular causes, hospitalization, or revascularization</td>
<td>5.6% (42)</td>
<td>6.4% (50)</td>
<td>0.45</td>
</tr>
<tr>
<td>Bleeding events</td>
<td>4.0% (32)</td>
<td>4.0% (32)</td>
<td>0.92</td>
</tr>
</tbody>
</table>


P2Y₁₂ Receptor Inhibitors

- **Clopidogrel**
  - Prodrug: 2-step cytochrome P-450 conversion
  - 2C19 patient variation
  - Drug interactions (PPIs)
  - Large amount of patient variability in response
  - Onset delayed
  - Irreversible inhibition of the P2Y₁₂ receptor (life of the platelet)

- **Prasugrel**
  - Prodrug: Single-step cytochrome P-450 conversion
  - Multiple enzymes capable of conversion
  - Lacks patient variability compared to clopidogrel
  - Provides more potent platelet inhibition compared with clopidogrel
  - Onset in about 30 minutes
  - Irreversible inhibition of the P2Y₁₂ receptor (life of the platelet)

PPIs = proton pump inhibitors

Biotransformation and Mode of Action
Clopidogrel, Prasugrel, and Ticagrelor

TRITON-TIMI 38

ACS (STEMI or UA/NSTEMI) and planned PCI

CLOPIDOGREL
300-mg loading dose
75-mg maintenance dose

PRASUGREL
60-mg loading dose
10-mg maintenance dose

N = 13,608

1st endpoint: CV death, MI, stroke
2nd endpoints: CV death, MI, stroke, rehospitalization due to recurrent ischemia
Safety endpoints: TIMI major bleeds, life-threatening bleeds

ARC = Academic Research Consortium


TRITON-TIMI 38 Trial Results

CV death/MI/Stroke

Clopidogrel

12.1

HR 0.81
(0.73-0.90)
p = 0.0004
NNT = 46

Prasugrel

9.9

TIMI Major and Non-CABG Bleeds

Clopidogrel

2.4

Prasugrel

NNT = number needed to treat
NNH = number needed to harm


Enlarged slide on page 23
### TRITON-TIMI 38 Trial

#### Bleeding Outcomes

<table>
<thead>
<tr>
<th>End Point</th>
<th>Prasugrel (N=131)</th>
<th>Clopidogrel (N=123)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CABG-related TIMI major bleeding (any severity)</td>
<td>146 (24)</td>
<td>151 (23)</td>
<td>1.02 (0.85–1.23)</td>
<td>0.90</td>
</tr>
<tr>
<td>Related to instrumentation</td>
<td>48 (7)</td>
<td>50 (6)</td>
<td>1.04 (0.71–1.52)</td>
<td>0.83</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>60 (9)</td>
<td>63 (13)</td>
<td>1.55 (1.09–2.19)</td>
<td>0.02</td>
</tr>
<tr>
<td>Related to trauma</td>
<td>8 (1)</td>
<td>12 (2)</td>
<td>6.79 (0.10–43.79)</td>
<td>0.05</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>25 (4)</td>
<td>28 (5)</td>
<td>1.78 (1.12–2.83)</td>
<td>0.04</td>
</tr>
<tr>
<td>Total</td>
<td>56 (8)</td>
<td>65 (9)</td>
<td>1.52 (1.08–2.15)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**NNH**

- **167**
- **200**
- **250**
- **334**


### TRITON-TIMI 38 Trial

#### Bleeding Risk Subgroups

<table>
<thead>
<tr>
<th>Prior Stroke / TIA</th>
<th>Yes</th>
<th>No</th>
<th>Post-hoc analysis</th>
<th>Risk (%)</th>
<th>p = 0.006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 75 yr</td>
<td>6</td>
<td>0</td>
<td>37</td>
<td>-16</td>
<td>0.018</td>
</tr>
<tr>
<td>&lt; 75 yr</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>-14</td>
<td></td>
</tr>
<tr>
<td>Weight ≤ 60 kg</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>-13</td>
<td></td>
</tr>
</tbody>
</table>

**OVERALL**

- **1.03**
- **0.09**
- **0.06**

**Prasugrel Better**

- **3.8%**

**Clopidogrel Better**

- **96%**


### TRITON-TIMI 38 Trial

#### Net Clinical Benefit by Subgroup

<table>
<thead>
<tr>
<th>Prior stroke or TIA</th>
<th>Prasugrel HR (95% CI)</th>
<th>p = 0.04</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 75 Years of age</td>
<td>0.99 (0.81–1.21)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

**Weight ≤ 60 kg | 1.03 (0.68–1.53) | 0.89 |

**80% of patients in TRITON-TIMI 38 demonstrated a significant reduction in CV death, MI, or stroke without an increase in bleeding**

2009 ACCF/AHA PCI Guidelines

Duration of Thienopyridine Therapy
- In patients receiving a stent (BMS or DES) during PCI for ACS (Class I recommendation)
  - Clopidogrel 75 mg daily for at least 12 months (Class I recommendation) or up to 15 months (Class I recommendation).
  - Prasugrel 10 mg daily for at least 12 months (Class I recommendation) or at least 15 months (Class IIb recommendation).
- Continuation of clopidogrel or prasugrel beyond 15 months may be considered in patients undergoing DES placement (Class IIb recommendation).
- If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered (Class I recommendation).


2009 ACCF/AHA PCI Guidelines

Conservative strategy (medical therapy without PCI ± stent)
- Clopidogrel loading dose 300 mg, followed by 75 mg daily at least one month and ideally up to 1 year.

Evolution of Antiplatelet Therapy in ACS

![Graph showing reduction in ischemic events and increase in major bleeds with dual antiplatelet therapy]

IPA = Inhibition of platelet aggregation

Conclusion

• Dual antiplatelet therapy represents a significant advance in the treatment of patients with ACS
• Despite proven benefits, not all patients benefit equally with ASA plus clopidogrel
• Emerging evidence suggests additional benefits may be realized with new agents or altered dosing
CURRENT Trial Results:
Clopidogrel Double vs. Standard Dose

Table 2. Major Outcomes at 50 Days, According to Dose of Clopidogrel

<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>Double Dose (N = 12,570)</th>
<th>Standard Dose (N = 12,166)</th>
<th>Hazard Ratio (% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome death from cardiovascular causes, myocardial infarction, or stroke</td>
<td>79 (4.7)</td>
<td>75 (4.4)</td>
<td>1.24 (1.05–1.46)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Safety outcomes: bleeding

<table>
<thead>
<tr>
<th>Category</th>
<th>Double Dose</th>
<th>Standard Dose</th>
<th>Hazard Ratio (% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study criteria</td>
<td>313 (2.5)</td>
<td>255 (2.0)</td>
<td>1.24 (1.05–1.46)</td>
<td>0.01</td>
</tr>
<tr>
<td>Requiring red-cell transfusion ≥ 2 units</td>
<td>267 (2.2)</td>
<td>210 (1.7)</td>
<td>1.28 (1.07–1.54)</td>
<td>0.01</td>
</tr>
<tr>
<td>Lab-related</td>
<td>162 (1.3)</td>
<td>144 (1.2)</td>
<td>1.40 (1.24–1.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>236 (1.9)</td>
<td>195 (1.6)</td>
<td>1.22 (1.01–1.47)</td>
<td>0.04</td>
</tr>
<tr>
<td>Leading to decrease in hemoglobin level ≥ 5 g/dl</td>
<td>130 (1.0)</td>
<td>107 (0.9)</td>
<td>1.22 (0.95–1.58)</td>
<td>0.13</td>
</tr>
<tr>
<td>Symptomatic intracranial</td>
<td>4 (0.03)</td>
<td>6 (0.05)</td>
<td>0.67 (0.19–2.37)</td>
<td>0.53</td>
</tr>
<tr>
<td>Fatal</td>
<td>16 (0.1)</td>
<td>15 (0.1)</td>
<td>1.07 (0.53–2.10)</td>
<td>0.85</td>
</tr>
<tr>
<td>TIMI criteria</td>
<td>210 (1.7)</td>
<td>168 (1.4)</td>
<td>1.26 (1.03–1.54)</td>
<td>0.03</td>
</tr>
<tr>
<td>Minor</td>
<td>611 (5.1)</td>
<td>558 (4.3)</td>
<td>1.18 (1.05–1.33)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CURRENT Trial Results:
ASA High Dose vs. Low Dose

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Higher Dose (N=12,507)</th>
<th>Lower Dose (N=12,537)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: death from cardiovascular causes, myocardial infarction, or stroke</td>
<td>530 (4.2)</td>
<td>549 (4.4)</td>
<td>0.97 (0.86–1.09)</td>
<td>0.61</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes, myocardial infarction, stroke, or recurrent ischemia</td>
<td>563 (4.5)</td>
<td>608 (4.8)</td>
<td>0.91 (0.83–1.04)</td>
<td>0.21</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>259 (2.1)</td>
<td>289 (2.3)</td>
<td>0.90 (0.76–1.06)</td>
<td>0.22</td>
</tr>
<tr>
<td>Stroke</td>
<td>253 (2.0)</td>
<td>261 (2.1)</td>
<td>0.97 (0.82–1.16)</td>
<td>0.76</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>70 (0.6)</td>
<td>79 (0.6)</td>
<td>1.19 (0.84–1.68)</td>
<td>0.32</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>41 (0.3)</td>
<td>65 (0.5)</td>
<td>0.63 (0.41–0.94)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Biotransformation and Mode of Action
Clopidogrel, Prasugrel, and Ticagrelor

## TRITON-TIMI 38 Results

### Table 2. Major Efficacy End Points in the Overall Cohort at 15 Months

| End Point                                                                 | Prasugrel (N = 6813) | Clopidogrel (N = 6795) | Hazard Ratio for Prasugrel (95% CI) | P Value† | NNH  
|--------------------------------------------------------------------------|----------------------|------------------------|------------------------------------|----------|------
| Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary endpoint) | 643 (9.9) 781 (11.1) | 0.81 (0.73–0.89) | <0.001                             |          |       
| Death from cardiovascular causes                                         | 133 (2.1)            | 150 (2.4)              | 0.89 (0.79–1.11)                  | 0.31     |       
| Nonfatal MI                                                               | 475 (7.3)            | 620 (8.8)              | 0.76 (0.67–0.85)                  | <0.001   |       
| Nonfatal stroke                                                           | 61 (1.0)             | 60 (1.0)               | 1.02 (0.71–1.45)                  | 0.93     |       
| Death from any cause                                                      | 188 (3.4)            | 197 (2.9)              | 0.95 (0.78–1.14)                  | 0.64     |       
| Death from cardiovascular causes, nonfatal MI, or urgent target-vessel revascularization | 652 (10.0) 798 (11.2) | 0.81 (0.73–0.89) | <0.001                             |          |       
| Death from any cause, nonfatal MI, or nonfatal stroke                     | 692 (10.7)           | 822 (12.2)             | 0.83 (0.75–0.92)                  | <0.001   |       
| Urgent target-vessel revascularization                                   | 155 (2.5)            | 233 (3.4)              | 0.66 (0.54–0.81)                  | <0.001   |       
| Death from cardiovascular causes, nonfatal MI, nonfatal stroke or rehospitalization for ischemia | 797 (12.3) 938 (13.4) | 0.84 (0.76–0.93) | <0.001                             |          |       
| Stent thrombosis                                                          | 68 (1.1)             | 142 (2.1)              | 0.48 (0.36–0.64)                  | <0.001   |       


## TRITON-TIMI 38 Trial

### Bleeding Outcomes

| End Point                                      | Prasugrel (N=6761) | Clopidogrel (N=6768) | Hazard Ratio for Prasugrel (95% CI) | P Value | NNH  
|-----------------------------------------------|--------------------|----------------------|------------------------------------|---------|------
| Non–CABG-related TIMI major bleeding (key safety end point) | 146 (2.4)          | 111 (1.6)            | 1.32 (1.03–1.68)                  | 0.03    | 167  
| Related to instrumentation                     | 45 (0.7)           | 31 (0.5)             | 1.18 (0.77–1.82)                  | 0.45    | 200  
| Spontaneous                                   | 92 (1.4)           | 61 (1.1)             | 1.51 (1.09–2.08)                  | 0.01    | 200  
| Related to trauma                             | 9 (0.2)            | 12 (0.2)             | 0.75 (0.32–1.78)                  | 0.51    |       
| Life-threatening†                              | 85 (1.4)           | 56 (0.9)             | 1.52 (1.08–2.13)                  | 0.01    | 200  
| Related to instrumentation                     | 28 (0.5)           | 18 (0.3)             | 1.55 (0.86–2.81)                  | 0.14    |       
| Spontaneous                                   | 50 (0.9)           | 28 (0.5)             | 1.78 (1.12–2.83)                  | 0.01    | 250  
| Related to trauma                             | 7 (0.1)            | 10 (0.2)             | 0.70 (0.27–1.84)                  | 0.47    |       
| Fatal‡                                        | 21 (0.4)           | 9 (0.2)              | 4.19 (1.58–11.11)                 | 0.002   | 334  
| Nonfatal                                      | 64 (1.1)           | 51 (0.9)             | 1.25 (0.87–1.81)                  | 0.23    |       
| Intracranial                                  | 19 (0.3)           | 17 (0.3)             | 1.12 (0.58–2.15)                  | 0.74    |       
| Major or minor TIMI bleeding                   | 303 (5.0)          | 231 (3.4)            | 1.31 (1.13–1.56)                  | 0.002   | 84   
| Bleeding requiring transfusion‡               | 244 (4.0)          | 192 (2.8)            | 1.34 (1.13–1.63)                  | <0.001  |     
| CABG-related TIMI major bleeding‡             | 24 (3.4)           | 6 (2.2)              | 4.73 (1.90–11.82)                 | <0.001  | 10   

TRITON-TIMI 38 Trial
Subgroups

SELECTED REFERENCES


Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome


SELF-ASSESSMENT QUESTIONS

1. Which of the following statements is true regarding the use of aspirin or clopidogrel or both in the treatment of acute coronary syndrome?
   
   a. The combination of aspirin plus clopidogrel does not increase the risk of bleeding compared with aspirin alone.
   b. The combination of aspirin plus clopidogrel reduces the risk of recurrent MI compared with aspirin alone.
   c. In the CURRENT trial, a daily dose of aspirin 300-325 mg led to a reduction in the risk of myocardial infarction (MI) compared with lower daily dose of 75-100 mg.
   d. In the CURRENT trial, a daily dose of aspirin 300-325 mg led to a reduction in the risk of total mortality compared with lower daily dose of 75-100 mg.

2. All of the following are considered limitations with dual antiplatelet therapy of aspirin plus clopidogrel EXCEPT
   
   a. Increased bleeding compared with aspirin monotherapy.
   b. Variable antiplatelet response with clopidogrel.
   c. Quick offset of action with drug discontinuation.
   d. Irreversible inhibition of platelet function.

3. The Triton-TIMI 38 study comparing clopidogrel and prasugrel in patients with acute coronary syndrome and planned percutaneous coronary intervention showed that
   
   a. Patients with a previous history of stroke had an overall net benefit with prasugrel compared with clopidogrel.
   b. Patients with a previous history of diabetes had an overall net benefit with prasugrel compared with clopidogrel.
   c. Patients aged 75 and greater had an overall net benefit with prasugrel compared with clopidogrel.
   d. Patients weighing less than 60 kg had an overall net benefit with prasugrel compared with clopidogrel.

Answers
1. b
2. c
3. b
Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

**Julie H. Oestreich, Pharm.D., Ph.D.**
Assistant Professor of Pharmacy Practice
College of Pharmacy
University of Nebraska Medical Center
Omaha, Nebraska

Julie H. Oestreich, Pharm.D., Ph.D., is Assistant Professor in the Department of Pharmacy Practice in the College of Pharmacy at the University of Nebraska Medical Center (UNMC) in Omaha, Nebraska.

Dr. Oestreich earned her Doctor of Pharmacy degree from Ohio Northern University in Ada, Ohio, and her Doctor of Philosophy in Pharmaceutical Sciences degree from the University of Kentucky College of Pharmacy in Lexington, Kentucky. She was also awarded a Graduate Certificate in Clinical Research Skills. She completed a post-doctoral fellowship at the Saha Cardiovascular Research Center in the College of Medicine at the University of Kentucky. This fellowship was supported by a Ruth L. Kirschstein National Research Service Award Institutional Training Grant (T32).

At the UNMC College of Pharmacy, Dr. Oestreich assists in the cardiology therapeutics module and coordinates an elective in pharmacogenomics. Her research specialty is platelet function testing and evaluating the effectiveness of antiplatelet agents. Her dissertation entitled, “Variability in ADP-mediated Platelet Response,” focused on platelet function in healthy volunteers, and she continues to study the variability of P2Y₁₂ and other platelet receptor pathways in humans and in animal models. Dr. Oestreich has received competitive fellowship support from the American Heart Association, Pharmaceutical Research and Manufacturers of America Foundation, American Foundation for Pharmaceutical Education, and Sigma Xi Scientific Research Society.

Dr. Oestreich is an active member of the American College of Clinical Pharmacy and currently serves as chair of its Pharmacokinetics and Pharmacodynamics Practice and Research Network. She is also an active member of the American Pharmacists Association (APhA) and will serve as chair-elect of the Clinical Sciences Section of the APhA Academy of Pharmaceutical Research and Science starting in 2011. She has authored several articles and national abstracts in the area of platelet function and antiplatelet effectiveness.
Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

Julie H. Oestreich, Pharm.D., Ph.D.

Presentation
Clinical Challenges in Oral Antiplatelet Therapy

Overview
Increasing evidence supports relevant variability in clopidogrel effectiveness as measured by platelet function tests. Several clinical studies in patients treated with aspirin and clopidogrel have associated high platelet reactivity with adverse cardiovascular events. The potential usefulness of platelet function testing is further magnified by the availability of more potent P2Y$_{12}$ receptor antagonists, including prasugrel and potentially ticagrelor. Thus far, platelet tests have been more successful at identifying patients with lower risk than predicting which patients will experience adverse outcomes and, therefore, have not been widely used.

Other unique challenges of clopidogrel therapy include recent FDA labeling changes regarding the drug interaction with omeprazole and reduced effectiveness of clopidogrel in CYP2C19 loss-of-function allele carriers. The strong FDA labeling change for omeprazole and other potent CYP2C19 inhibitors is based on consistent pharmacokinetic and pharmacodynamic effects, but the clinical relevance of this interaction is still being debated. Similarly, patients who have one or two loss-of-function alleles for the CYP2C19 gene demonstrate decreased active metabolite formation and impaired platelet inhibition with clopidogrel. The impact of CYP2C19 carrier status on cardiovascular events has varied in retrospective analyses of large-scale clinical trials, although the combined evidence suggests a small, yet significant effect. At the present time, routine genetic or platelet function testing is not recommended; nonetheless, high platelet reactivity and CYP2C19 metabolizer status, if known, should be taken into consideration—along with other clinical factors known to influence clopidogrel effectiveness and bleeding risk—when assessing appropriate antiplatelet therapy.
Clinical Challenges in Oral Antiplatelet Therapy

Julie H. Oestreich, Pharm.D., Ph.D.
Assistant Professor of Pharmacy Practice
College of Pharmacy
University of Nebraska Medical Center
Omaha, Nebraska

Which of the following is TRUE regarding clopidogrel variability?

a. Platelet reactivity on clopidogrel is a dichotomous variable allowing for highly sensitive, specific cut-off values for predicting CV events
b. Platelet function tests for clopidogrel have low negative predictive values for CV events
c. Several prospective clinical trials attributed CV events on clopidogrel to PPI use
d. Patients with high platelet reactivity on clopidogrel have increased risk for CV events

Clinical Challenge #1:
CLOPIDOGREL VARIABILITY
**Terminology**

- Clopidogrel ‘resistance’
- Clopidogrel nonresponsiveness
- High on-treatment platelet reactivity

**Context**

- Pharmacokinetic formation of active metabolite
- Pharmacodynamic platelet inhibition
- Cardiovascular events on compliant aspirin and clopidogrel treatment
Which Assay Is Best?

<table>
<thead>
<tr>
<th>Assay</th>
<th>LTA</th>
<th>VASP</th>
<th>Multiplate</th>
<th>VerifyNow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Versatile</td>
<td>Small whole blood volume</td>
<td>Physiologic environment</td>
<td>Standardized</td>
</tr>
<tr>
<td></td>
<td>Long history correlated with outcomes</td>
<td>Sensitive to P2Y_{12} effect</td>
<td>Minimal sample manipulation</td>
<td>User friendly and fast</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Not standardized</td>
<td>Expensive</td>
<td>Less experience</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td>Specialized user</td>
<td>Specialized user</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Correlation of Clopidogrel Responsiveness with Clinical Outcomes

- One of first trials to correlate lower antiplatelet effects of clopidogrel to clinical outcomes
  - 60 patients with STEMI with PCI + stent
  - Clopidogrel 300 mg LD, then 75 mg daily
  - Platelet activity assessed at PCI and daily x 5 days
- Patients separated into quartiles based on ADP-induced platelet aggregation
- Major adverse cardiac events evaluated at 6 months

High On-treatment Platelet Reactivity: PREPARE POST-STENTING Trial

- Patients undergoing elective PCI + stent (n=192) receiving clopidogrel
  - 600 mg LD (n=60); 300 mg LD (n=75)
  - Already on 75 mg daily (n=57)
- Platelet tests (pretreatment and ~24 hours post-PCI)
  - LTA with ADP 20 μmol/L
  - Thrombelastograph (TEG)
- Results at 6 months
  - 20% of patients with MACE (n=38)
  - 80% of patients event free (n=154)


PREPARE POST-STENTING Trial

<table>
<thead>
<tr>
<th></th>
<th>Patients with Ischemic Events</th>
<th>Patients without Ischemic Events</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTA-ADP 20 pre-treatment (%)</td>
<td>71 ± 9</td>
<td>73 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>LTA-ADP 20 post-treatment (%)</td>
<td>63 ± 12</td>
<td>56 ± 16</td>
<td>0.02</td>
</tr>
<tr>
<td>TEG MA pre-treatment (mm)</td>
<td>72 ± 7</td>
<td>67 ± 8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TEG MA post-treatment (mm)</td>
<td>74 ± 5</td>
<td>65 ± 5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Lowest LTA post-treatment quartile (<50% platelet aggregation) – MACE 10%
Highest LTA post-treatment quartile (>67% platelet aggregation) – MACE 32%
p = 0.02

MA = maximal absorption (clot strength)

Other Studies

- At least 28 studies link on-treatment platelet reactivity and clopidogrel responsiveness to clinical endpoints in PCI patients
  - n = 46–1608 patients
  - Multiple assays

- Clinical outcomes
  - Stent thrombosis
  - Major adverse cardiac events (death, MI, TVR)
  - Cardiac death


ROC Curve Analyses of Cut-off Values

<table>
<thead>
<tr>
<th>Study</th>
<th>Cut-off</th>
<th>Endpoint</th>
<th>AUC</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price et al.</td>
<td>&gt; 235 PRU</td>
<td>6-mo post-PCI CVD/MI/ST</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Gurbel et al. (2008)</td>
<td>ADP 5 &gt; 46%</td>
<td>2-yr post-PCI MACE</td>
<td>0.77</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>ADP 20 &gt; 59%</td>
<td></td>
<td>0.78</td>
<td>3.8</td>
</tr>
<tr>
<td>Blindt et al.</td>
<td>&gt; 48% PRI</td>
<td>6-mo ST</td>
<td>0.79</td>
<td>1.16</td>
</tr>
<tr>
<td>Frere et al.</td>
<td>ADP 10 &gt; 70%</td>
<td>1-mo post-PCI MACE + stroke</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 53% PRI</td>
<td></td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Bonello et al. (2007)</td>
<td>&gt; 50% PRI</td>
<td>6-mo post-PCI MACE</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Marcucci et al.</td>
<td>≥ 240 PRU</td>
<td>1-yr CV death + MI</td>
<td>0.66</td>
<td>2.38</td>
</tr>
<tr>
<td>Sibbing et al.</td>
<td>&gt; 468 AU/min</td>
<td>30-day ST</td>
<td>0.78</td>
<td>12.0</td>
</tr>
<tr>
<td>Cuisset et al.</td>
<td>ADP 10 &gt; 67%</td>
<td>1-mo ST</td>
<td>0.69</td>
<td>5.8</td>
</tr>
<tr>
<td>Breet et al.</td>
<td>Multiple assays</td>
<td>1-yr death, MI, ST, and stroke</td>
<td>0.61-0.63</td>
<td>2.1-2.5</td>
</tr>
</tbody>
</table>

Laboratory Definitions of High On-treatment Platelet Reactivity

- PRI > 50% by VASP phosphorylation
- > 235 – 240 PRU (P2Y12 reaction units) by VerifyNow P2Y12 assay
- > 46% maximal ADP 5 μmol/L-induced aggregation by light transmission aggregometry
- > 468 arbitrary aggregation units/min in response to ADP by the Multiplate analyzer

Platelet Function Guided Therapy

Non-emergent PCI: ACS and stable angina (n = 1122)

Loading doses (LD):
ASA 250 mg, clopidogrel 600 mg

Randomization
(n=429)

CONTROL (n =215) VASP-guided LD (n =214)

Maintenance doses:
ASA 160 mg, clopidogrel 75 mg

Up to 3 additional 600-mg LD every 24 hours until VASP < 50% before PCI

1° endpoint: Definite stent thrombosis (ARC definition)
2° endpoints: MACE including CV death, MI, and UTVR
TIMI major and minor bleeding at 30 days


Platelet Function Guided Therapy

VASP after first LD 66 ± 11 67 ± 10

VASP after sensitization 37 ± 12 p < 0.01

17 patients (8%)


Early Definite Stent Thrombosis and Other MACE during 1 Month Follow-up

<table>
<thead>
<tr>
<th>Endpoint, n (%)</th>
<th>Control Group (n=214)</th>
<th>VASP-guided Group (n=214)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute stent thrombosis</td>
<td>2 (0.9)</td>
<td>0</td>
<td>0.25</td>
</tr>
<tr>
<td>Sub-acute stent thrombosis</td>
<td>8 (3.7)</td>
<td>1 (0.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Early DST</td>
<td>10 (4.7)</td>
<td>1 (0.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>4 (1.8)</td>
<td>0</td>
<td>0.06</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10 (4.8)</td>
<td>1 (0.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Urgent revascularization</td>
<td>5 (2.3)</td>
<td>0</td>
<td>0.06</td>
</tr>
<tr>
<td>All MACE</td>
<td>19 (8.9)</td>
<td>1 (0.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The Sweet Spot: Is There a Therapeutic Window for P2Y12 Inhibition?

Platelet inhibition determined by Multiplate analyzer.


Take-home Message: Clopidogrel Nonresponsiveness and On-treatment Platelet Reactivity

- Clopidogrel variability as measured by platelet function tests correlates with clinical outcomes in patients undergoing PCI
  - Good negative predictive value
  - Poor positive predictive value
- Using platelet tests for individualized dosing is advancing
  - VerifyNow is most convenient assay
- Platelet function test that best predicts clinical outcomes is not known

Clinical Challenge #2: CLOPIDOGREL-PPI DRUG INTERACTION
OCLA Study

- Patients undergoing elective PCI with stenting (n=140)
  - ASA plus clopidogrel 300 mg LD, 75 mg qd
  - Placebo x 7 days
  - Omeprazole 20 mg qd x 7 days
  - VASP at baseline
    - 83.2% vs. 83.9%, p=NS
  - VASP at day 7
    - Placebo 39.8%
    - Omeprazole 51.4%
    - p<0.0001

Clopidogrel and Proton Pump Inhibitor Interaction

- TRITON-TIMI 38 Trial (n=13,608)
  - Clopidogrel: HR 0.94 (0.80 – 1.11)
  - Prasugrel: HR 0.99 (0.83 – 1.19)

CV Death, MI, or Stroke

PPI use did not impact:
- Primary endpoint
- MI
- Stent thrombosis
**Clopidogrel-PPI Meta-analysis**

Odds ratios for MACE according to PPI use (n = 46,037)


**PPIs Associated with CV Risk Independent of Clopidogrel Use**

Danish cohort study: hazard ratios for MACE according to PPI and clopidogrel use (n = 24,704 on clopidogrel)


**COGENT Trial Methods**

- Phase 3 efficacy and safety study of CGT-2168, a fixed-dose combination of clopidogrel (75 mg) and omeprazole (20 mg) compared with clopidogrel
- Composite endpoint of CV death, non-fatal MI, CABG or PCI, or ischemic stroke
- Target sample size increased from 3200 to ~5000 patients with an accrual period of 1 year and maximum follow up of 2 years
- Study ended at 3761 patients when the sponsor declared bankruptcy

COGENT Trial Results
Event rates at 180 days were 5.7% in placebo group and 4.9% in omeprazole group, HR = 0.99 (0.68-1.44), p = 0.96


FDA Advisory and Plavix® Labeling Change Reminder: October 27, 2010
• FDA continues to warn against the concomitant use of clopidogrel and omeprazole
  – Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction
• Recommendation applies only to omeprazole and not to all PPIs
• Pantoprazole may be an alternative PPI for consideration

U.S. Food and Drug Administration. (URL in reference list).

Take-home Message: Clopidogrel Drug Interactions
• PK/PD evidence supports an interaction between clopidogrel and PPIs
  – However, significant effects with platelet function tests have not always matched clinical outcomes
• Evidence for clinical relevance is conflicting and not yet convincing
  – Retrospective studies limited by general increased cardiovascular risk
  – COGENT study used novel formulation
• Regardless of scientific evidence, FDA label leaves little room for alternative interpretations
Clinical Challenge #3:  
**CLOPIDOGREL AND CYP2C19**

CYP2C19 Alleles and Associated Phenotypes

<table>
<thead>
<tr>
<th>CYP2C19 alleles</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or two gain-of-function alleles (**1/17 or <strong>17/17</strong>)</td>
<td>Ultrarapid metabolizer (UM)</td>
</tr>
<tr>
<td>No variant alleles (∗1∗1)</td>
<td>Extensive metabolizer (EM)</td>
</tr>
<tr>
<td>One loss-of-function allele (<strong>2,∗3, others</strong>)</td>
<td>Intermediate metabolizer (IM)</td>
</tr>
<tr>
<td>Two loss-of-function alleles (<strong>2,∗3, others</strong>)</td>
<td>Poor metabolizer (PM)</td>
</tr>
</tbody>
</table>

*CYP2C19 Genotype Frequency*

<table>
<thead>
<tr>
<th></th>
<th>European Descent (n=1356)</th>
<th>African Descent (n=966)</th>
<th>Chinese of Asian Origin (n=573)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive metabolism:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19 ∗1/1</td>
<td>74%</td>
<td>66%</td>
<td>38%</td>
</tr>
<tr>
<td>Intermediate metabolism:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19 ∗1/2 or ∗1/3</td>
<td>26%</td>
<td>29%</td>
<td>50%</td>
</tr>
<tr>
<td>Poor metabolism:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19 ∗2/2, ∗2/3, or ∗3/3</td>
<td>2%</td>
<td>4%</td>
<td>14%</td>
</tr>
</tbody>
</table>


Clopidogrel and CYP2C19: Pharmacokinetic and Pharmacodynamic Effects

Healthy carriers of one or more CYP2C19 reduced-function alleles had 32% relative reduction in active metabolite exposure and a 9% absolute reduction in MPA

\[
\frac{\text{Clopidogrel active metabolite exposure}}{\text{Clopidogrel 75 mg}} \quad \text{versus} \quad \frac{\text{Clopidogrel 75 mg}}{\text{Carriers}}
\]


**Antiplatelet response by LTA**


**Odds ratios for MACE according to CYP2C19 (n = 11,959)**

Clopidogrel and CYP2C19 Clinical Outcomes: Stent Thrombosis Meta-Analysis


Clopidogrel and CYP2C19 Clinical Outcomes: PLATO

Analysis from the PLATO trial


Clopidogrel and CYP2C19 Clinical Outcomes: CURE Trial

(n = 5059)

Usefulness of Genetic Testing for Predicting Cardiac Outcomes

- CYP2C19 is a consistent predictor of clopidogrel PK/PD and is significantly associated with clinical outcomes in some trials.
- No prospective studies have evaluated genetic testing and the effectiveness of subsequent treatment changes.
- Positive predictive value is estimated at 12-20%.

Changes to the Plavix® (Clopidogrel) Product Label

WARNING: Diminished effectiveness in poor metabolizers
The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 (see Warnings and Precautions [5.1]).
Plavix recommended doses form part of this metabolism and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy (see Clinical Pharmacology [12.15]). Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers (see Dosage and Administration [2.3]).

Plavix prescribing information. 2010 Aug (URL in ref list).

ACCF/AHA: Approaches to the FDA Boxed Warning

- ‘It neither mandates, requires, nor recommends genetic testing, thereby allowing for flexibility in clinical decisions.’
- ‘The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time.’

Take-home Message:
Clopidogrel and CYP2C19

• PK/PD and clinical evidence supports a significant
effect of CYP2C19 metabolizer status on clopidogrel
effectiveness
  – However, genetic testing demonstrates low
    positive predictive value
  – GWAS attributes 12% of variability to CYP2C19
• Key cardiology groups do not recommend routine
genetic testing for clopidogrel at this time
  – If genetic information is known, it should be
    considered in context with other risk factors
• We still do not know how to best optimize
  clopidogrel therapy and improve clinical outcomes

Amish Pharmacogenomics of
AntiPlatelet Intervention (PAPI) Study

Genome-wide association study (n = 429)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>β (SE)</th>
<th>P Value*</th>
<th>Variance of Significant Predictors, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.19</td>
<td>&lt;.001</td>
<td>3.8</td>
</tr>
<tr>
<td>Sex</td>
<td>1.75</td>
<td>.10</td>
<td>9.5</td>
</tr>
<tr>
<td>Early minor lesions</td>
<td>0.15</td>
<td>.20</td>
<td>2.1</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.01</td>
<td>.91</td>
<td>27</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&gt;0.00</td>
<td>.04</td>
<td>1.0</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.50</td>
<td>.17</td>
<td>1.3</td>
</tr>
<tr>
<td>Log triglycerides</td>
<td>0.00</td>
<td>.99</td>
<td>0.6</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>0.00</td>
<td>.99</td>
<td>0.6</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0.07</td>
<td>.42</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Attributes 12% of clopidogrel variability to CYP2C19


Genome-Wide Association Study:
PAPI Study
(n = 429)

Suboptimal Clopidogrel Response

Genetic factors
- Polymorphisms of CYP
- Polymorphisms of GPIa
- Polymorphisms of P2Y12
- Polymorphisms of GP IIIa

Cellular factors
- Accelerated platelet turnover
- Reduced CYP3A metabolic activity
- Increased ADP exposure
- Up-regulation of the P2Y1 pathway
- Up-regulation of the P2Y pathway
- Up-regulation of P2Y independent pathways

Clinical factors
- Failure to prescribe
- Poor compliance
- Under dosing
- Poor absorption
- Drug/drug interactions
- Acute coronary syndrome
- Diabetes mellitus
- Elevated body mass index


What information is necessary for appropriate clopidogrel prescribing?

Name: Ima Clotter
BMI: 22 Gender: F Age: 62
Platelet reactivity: ___
CYP2C19 metabolizer status: ___
Inflammatory index: ___
Coagulation efficiency: ___
Calculated target level of P2Y12 receptor inhibition: ___
P2Y12 antagonist: ___
Predicted dose: ___

Clopidogrel: Current Recommendations

<table>
<thead>
<tr>
<th>Testing Result</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for clopidogrel</td>
<td>No routine platelet function or genetic testing is recommended</td>
</tr>
<tr>
<td>Low or normal on-treatment platelet reactivity</td>
<td>Follow population-based guidelines</td>
</tr>
<tr>
<td>High on-treatment platelet reactivity</td>
<td>Consider alternative strategy</td>
</tr>
<tr>
<td>CYP2C19*1/*1</td>
<td>Follow population-based guidelines</td>
</tr>
<tr>
<td>CYP2C19 loss-of-function polymorphism</td>
<td>Consider alternative agent</td>
</tr>
</tbody>
</table>

*Consider other factors, including age, BMI, DM, and bleeding risk
TC is a 58-year-old man recently started on clopidogrel 75 mg daily. CYP2C19 genotype is CYP2C19*1/*2. VerifyNow test is slightly elevated (PRU = 245). What is the recommended treatment strategy for TC?

a. Continue clopidogrel 75 mg daily
b. Increase clopidogrel maintenance dose to 150 mg daily
c. Start prasugrel
d. Start ticagrelor
Clopidogrel-PPI Meta-analysis

Odds ratios for MACE according to PPI use (n = 46,037)


PPIs Associated with CV Risk Independent of Clopidogrel Use

Danish cohort study: hazard ratios for MACE according to PPI and clopidogrel use (n = 24,704 on clopidogrel)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time-Dependent Cox Proportional Hazards Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients Receiving a PPI but Not Clopidogrel</td>
</tr>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Cardiovascular death, MI, or stroke</td>
<td>1.70 (1.71–1.37)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>1.58 (1.48–1.68)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1.49 (1.38–1.60)</td>
</tr>
<tr>
<td>MI</td>
<td>1.12 (1.02–1.23)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.32 (1.17–1.49)</td>
</tr>
</tbody>
</table>

Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

SELECTED REFERENCES


SELF–ASSESSMENT QUESTIONS

1. Which of the following laboratory test results would indicate high on-treatment platelet reactivity or clopidogrel nonresponsiveness?
   a. PRI 42% (platelet reactivity index) by vasodilator-stimulated phosphoprotein (VASP) phosphorylation.
   b. 185 PRU (P2Y12 reaction units) by VerifyNow P2Y12 test.
   c. 382 arbitrary aggregation units/min in response to adenosine diphosphate (ADP) by the Multiplate analyzer.
   d. 55% maximal ADP 5 μM-induced aggregation by light transmission aggregometry.

2. Which of the following statements most appropriately describes the interaction between clopidogrel and proton pump inhibitors (PPIs)?
   a. Occurs because CYP2C19 is the only enzyme capable of converting clopidogrel to its intermediate and active metabolites.
   b. Is supported by the results of the prospective COGENT trial of a fixed-dose combination of clopidogrel and omeprazole.
   c. Is relevant because clopidogrel’s prescribing information clearly states that clopidogrel and omeprazole should not be used together.
   d. Can be easily evaluated by retrospective studies because PPI use is independent of all other risk factors.

3. According to key cardiology groups, which of the following statements best describes the role of genetic testing or platelet function testing when selecting antiplatelet therapy?
   a. Routine testing is recommended, and the results should be considered together with other risk factors.
   b. Routine testing is recommended, and the results should be the only risk factor considered.
   c. Routine testing is not recommended, but, if available, the results should be considered together with other risk factors.
   d. Routine testing is not recommended, and, if available, the results should not be considered.

Answers
1. d
2. c
3. c
Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

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Activity Chair and Moderator
Associate Professor of Pharmacy Practice
College of Pharmacy
University of Nebraska Medical Center
Omaha, Nebraska

Paul P. Dobesh, Pharm.D., FCCP, BCPS (AQ Cardiology), is Associate Professor of Pharmacy Practice at the University of Nebraska Medical Center in Omaha, Nebraska. Dr. Dobesh earned both his Bachelor of Science in pharmacy and Doctor of Pharmacy degrees from South Dakota State University. He completed a specialty residency in internal medicine at the University of Texas at Austin at Brackenridge Hospital, and he is a board-certified pharmacotherapy specialist with added qualifications in cardiology.

Dr. Dobesh’s current responsibilities at the University of Nebraska Medical Center (UNMC) include clinical practice in both internal medicine and cardiology services. He is responsible for teaching pharmacy and medical students, as well as pharmacy and medical residents. His main lecture topics include ischemic heart disease, antithrombotic therapy, and other cardiology and critical care topics. Dr. Dobesh received the UNMC College of Pharmacy Educator of the Year Award for 2010, an award he has received twice within the last four years.

Dr. Dobesh has conducted research on antiplatelet and antithrombotic therapy, focusing on the real-world use of these therapies and health-care economics. He has also published book chapters and several manuscripts in this field.
Emerging P2Y₁₂ Treatment Strategies

Overview

Dual antiplatelet therapy (clopidogrel and aspirin) has been part of standard-of-care for the management of patients with acute coronary syndrome and patients undergoing percutaneous coronary intervention for about a decade. Issues, such as a large variability of antiplatelet activity, drug-drug interactions, and pharmacogenomic polymorphisms of metabolism, have raised serious questions about the role of standard dosing of clopidogrel for all patients. A number of alternative approaches have been investigated over the last several years.

Increasing the loading and maintenance doses of clopidogrel have been explored with variable success. While this may have some benefit in patients, it is unknown if this strategy will consistently overcome issues of nonresponsiveness. Adding cilostazol has also been investigated, but large phase III trials are still needed to secure this as a solid strategy. The most promise has come in selecting newer P2Y₁₂ antiplatelet agents that do not have the same limitations as clopidogrel. Prasugrel has demonstrated a significant reduction in ischemic endpoints compared with clopidogrel, but at the cost of increased bleeding. Ticagrelor is a different type of P2Y₁₂ inhibitor that does not need to be metabolized to an active metabolite, while it also provides faster reversibility compared with both clopidogrel and prasugrel. Ticagrelor has demonstrated a significant reduction in ischemic endpoints compared with clopidogrel. While there is also an increase in bleeding with ticagrelor, the severity of the bleeding is not as high as with prasugrel. Pharmacists need to understand the pros and cons of these different options as we care for patients with acute coronary syndrome.
Emerging P2Y₁₂ Treatment Strategies

Paul P. Dobesh, Pharm.D., FCCP, BCPS (AQ Cardiology)
Associate Professor of Pharmacy Practice
College of Pharmacy
University of Nebraska Medical Center
Omaha, Nebraska

Emerging Treatment Strategies

- Increasing dose of clopidogrel
- Switching to different P2Y₁₂ inhibitor
  - Ticlopidine
  - Prasugrel
  - Ticagrelor
  - Future agents
- Triple antiplatelet therapy
  - Adding cilostazol
  - PAR-1 inhibitors

Table 4: Active Metabolite Pharmacokinetics and Antiplatelet Responses* by CYP2C19 Metabolizer Status

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cmax (ng/mL)</th>
<th>IPA (%)</th>
<th>VASP-PRI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ultrarapid (n=10)</td>
<td>Extensive (n=10)</td>
<td>Intermediate (n=10)</td>
</tr>
<tr>
<td>300 mg (24 h)</td>
<td>24 (10)</td>
<td>32 (21)</td>
<td>23 (11)</td>
</tr>
<tr>
<td>600 mg (24 h)</td>
<td>36 (13)</td>
<td>44 (27)</td>
<td>39 (23)</td>
</tr>
<tr>
<td>75 mg (Day 5)</td>
<td>12 (6)</td>
<td>13 (7)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>150 mg (Day 5)</td>
<td>18 (9)</td>
<td>19 (9)</td>
<td>18 (7)</td>
</tr>
<tr>
<td>600 mg (24 h)</td>
<td>40 (21)</td>
<td>39 (28)</td>
<td>37 (21)</td>
</tr>
<tr>
<td>75 mg (Day 5)</td>
<td>56 (13)</td>
<td>58 (19)</td>
<td>60 (18)</td>
</tr>
<tr>
<td>150 mg (Day 5)</td>
<td>68 (18)</td>
<td>73 (9)</td>
<td>74 (14)</td>
</tr>
</tbody>
</table>

* Reported as mean (SD)
OPTIMUS Study

- Patients with DM type 2 on chronic dual antiplatelet therapy were screened for clopidogrel responsiveness
  - Platelet aggregation > 50% with 20 µmol/L ADP by LTA defined nonresponsiveness
  - Screened 64 patients – 40 (62.5%) nonresponsive
    - Platelet aggregation 39.9% ± 8% in responders
    - Platelet aggregation 66.2% ± 8% in nonresponders
  - Nonresponders then randomized
    - Clopidogrel 75 mg daily (n=20)
    - Clopidogrel 150 mg daily (n=20)

Accelerated Platelet Inhibition by Double Dose Clopidogrel According to Gene Polymorphism (ACCEL-DOUBLE) Study

- 126 PCI-treated patients
- All given clopidogrel 150 mg daily x 1 month
- Genotyping
  - CYP3A5
  - CYP2C19
  - ABCB1
- Platelet function testing performed at 1 month
  - LTA with 5 and 20 μmol/L
  - VerifyNow P2Y12 test


ACCEL-DOUBLE: Results

- CYP3A5 and ABCB1 did not influence platelet reactivity
- CYP2C19 predictive of high post-treatment platelet reactivity
  - OR 5.5 (1.33-23.26) p=0.018

Enlarged slide on page 69

Dosing Based on CYP2C19 Status

- Patients with high on-treatment platelet reactivity on clopidogrel 75 mg daily
  - Identified 41 patients
    - 21 with wildtype (*1/*1) CYP2C19 status
    - 20 carriers of a C219 loss-of-function allele
  - VerifyNow P2Y12 test
    - Baseline (75 mg daily): PRU=285
    - Clopidogrel 150 mg daily: PRU=220
- PRU “normalized” (<235) with 150 mg daily in 56% of patients
- No significant difference in antiplatelet response based on 2C19 status

GRAVITAS Trial

Successful PCI with DES without major complication or GP IIb/IIa use

Post-PCI VerifyNow P2Y12 assay (PRU) 12-24 hours post-PCI

n ~ 6600

Nonresponder

PRU ≥ 230

Yes

Responder

Random selection

A n=1109

B n=1109

C n=586

"Tailored therapy"
clopidogrel 150 mg/day

"Standard therapy"
clopidogrel 75 mg + placebo/day

"Standard therapy"
clopidogrel 75 mg + placebo/day

Clinical follow-up and VerifyNow assessment at 30 days, 6 months

Primary end point: 6 month CV death, nonfatal MI, ARC definite/probable stent thrombosis


GRAVITAS Trial Results

PR = platelet reactivity

% of Patients

14% 12% 10% 8% 6% 4% 2% 0%

CV Death/MI/ST GUSTO Severe/Mod Bleeding Any GUSTO Bleeding

p=0.08 p=0.20

p=0.05

p=0.10

P=0.01

p=0.18

PR = platelet reactivity


Ongoing Clinical Trials

All trials assessing platelet reactivity by VerifyNow

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Patients</th>
<th>Outcome</th>
<th>Clopidogrel Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARCTIC</td>
<td>2500</td>
<td>Elective PCI+DES</td>
<td>12 month MACE</td>
<td>MD preference</td>
</tr>
<tr>
<td>DANTE</td>
<td>442</td>
<td>NSTE ACS PCI</td>
<td>6 &amp; 12 month MACE</td>
<td>75 mg vs. 150 mg qd</td>
</tr>
<tr>
<td>TOPAS-1</td>
<td>450</td>
<td>Previous PCI ± stent</td>
<td>6 month ST</td>
<td>600 mg LD, 75 mg qd</td>
</tr>
<tr>
<td>TRIGGER-PCI</td>
<td>2150</td>
<td>PCI</td>
<td>CV death, MI</td>
<td>600 mg LD, 75 mg qd vs. prasugrel 60 mg LD, 15 mg qd</td>
</tr>
</tbody>
</table>
Emerging Treatment Strategies

- Increasing dose of clopidogrel
- Switching to different P2Y₁₂ inhibitor
  - Ticlopidine
  - Prasugrel
  - Ticagrelor
  - Future agents
- Triple antiplatelet therapy
  - Adding cilostazol
  - PAR-1 inhibitors

---

**Clopidogrel-to-Ticlopidine Crossover Study**


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**TRITON TIMI-38 Trial: Results**

Inhibition of Platelet Aggregation (IPA) at 24 Hours

Response to Clopidogrel

*Responder = ≥ 25% IPA at 4 and 24 h

PLATO Study Design

NSTE-ACS (moderate-to-high risk) or STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomized within 24 hours of index event

Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg/day maintenance

Ticagrelor
180 mg loading dose, then
90 mg bid maintenance
(additional 90 mg pre-PCI)

Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding


PLATO Trial: Results

### PLATO Trial

#### Individual Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (n=9,333)</th>
<th>Clopidogrel (n=9,291)</th>
<th>HR for (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary objective, (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death + MI + stroke</td>
<td>9.8</td>
<td>11.7</td>
<td>0.84 (0.77–0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary objectives, (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total death + MI + stroke</td>
<td>16.2</td>
<td>12.3</td>
<td>0.84 (0.77–0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death + MI + stroke + ischemia + TIA + arterial thrombotic events</td>
<td>14.6</td>
<td>16.7</td>
<td>0.88 (0.81–0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5.8</td>
<td>6.9</td>
<td>0.84 (0.75–0.95)</td>
<td>0.005</td>
</tr>
<tr>
<td>CV death</td>
<td>4.0</td>
<td>5.1</td>
<td>0.79 (0.69–0.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.9</td>
<td>1.3</td>
<td>1.17 (0.91–1.52)</td>
<td>0.22</td>
</tr>
<tr>
<td>Total death</td>
<td>4.5</td>
<td>5.9</td>
<td>0.78 (0.69–0.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


### PLATO Results – Major Bleeding

#### Non-CABG and CABG Related

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>p=NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CABG PLATO</td>
<td>4.5%</td>
<td>3.8%</td>
<td></td>
</tr>
<tr>
<td>Non-CABG TIMI</td>
<td>2.2%</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>CABG PLATO</td>
<td>7.4%</td>
<td>7.9%</td>
<td></td>
</tr>
<tr>
<td>CABG TIMI</td>
<td>5.3%</td>
<td>5.8%</td>
<td></td>
</tr>
</tbody>
</table>

Total PLATO major bleeding: 11.6% ticagrelor vs. 11.2% clopidogrel; p=0.43
Total TIMI major bleeding: 7.9% ticagrelor vs. 7.7% clopidogrel; p=0.57


### PLATO Trial

#### Other Findings

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (n=9,235)</th>
<th>Clopidogrel (n=9,186)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dyspnea, %</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Any</td>
<td>13.8</td>
<td>7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>With D/C of study treatment</td>
<td>0.9</td>
<td>0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Ventricular pauses, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 seconds</td>
<td>5.8</td>
<td>3.6</td>
<td>0.01</td>
</tr>
<tr>
<td>≥ 5 seconds</td>
<td>2.0</td>
<td>1.2</td>
<td>0.10</td>
</tr>
<tr>
<td>At 30 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 seconds</td>
<td>2.1</td>
<td>1.7</td>
<td>0.52</td>
</tr>
<tr>
<td>≥ 5 seconds</td>
<td>0.8</td>
<td>0.6</td>
<td>0.80</td>
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PLATO Trial
Other Findings - Laboratory Parameters

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>n=9,325</td>
<td>n=9,186</td>
<td></td>
</tr>
<tr>
<td>% increase in SCr from baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 month</td>
<td>10 ± 22</td>
<td>8 ± 21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At 12 months</td>
<td>11 ± 22</td>
<td>9 ± 22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follow-up visit</td>
<td>10 ± 22</td>
<td>10 ± 22</td>
<td>0.59</td>
</tr>
<tr>
<td>% increase in uric acid from baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 month</td>
<td>14 ± 46</td>
<td>7 ± 44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At 12 months</td>
<td>15 ± 52</td>
<td>7 ± 31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follow-up visit</td>
<td>7 ± 43</td>
<td>8 ± 48</td>
<td>0.56</td>
</tr>
</tbody>
</table>


The ONSET/OFFSET Study

The ONSET/OFFSET Study

RESPOND Study

- Cross-over study
- Grouped by response to 300 mg LD of Clopidogrel
  - ≤10% absolute Δ in platelet aggregation to 20 μmol/L ADP by LTA
    - Nonresponders (n=41)
    - Responders (n=57)
- Clopidogrel 600 mg LD and 75 mg daily
- Ticagrelor 180 mg LD and 90 mg bid

What is Next?

- **Elinogrel**
  - First available i.v. and oral ADP-P2Y<sub>12</sub> receptor antagonist
  - ERASE MI Trial
  - INNOVATE PCI Trial

- **Cangrelor**
  - Parenteral ADP-P2Y<sub>12</sub> receptor antagonist
  - ATP analogue
  - Plasma half-life of 5-9 minutes
  - 20 minutes for return to normal platelet function
  - CHAMPION Trials
    - Stopped - no benefit
    - PHOENIX Trial

New P2Y<sub>12</sub> Inhibitors vs. Clopidogrel

Meta-Analysis

Results in patients undergoing any PCI

<table>
<thead>
<tr>
<th>Death</th>
<th>New P2Y&lt;sub&gt;12&lt;/sub&gt; Clopidogrel</th>
<th>Any PCI</th>
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</thead>
<tbody>
<tr>
<td>Death</td>
<td>389/3024</td>
<td>371/3024</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>389/3024</td>
<td>371/3024</td>
</tr>
</tbody>
</table>


New P2Y<sub>12</sub> Inhibitors vs. Clopidogrel

Meta-Analysis

Results in patients undergoing PCI for STEMI

<table>
<thead>
<tr>
<th>PCI for STEMI</th>
<th>New P2Y&lt;sub&gt;12&lt;/sub&gt; Clopidogrel</th>
<th>Any PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>389/3024</td>
<td>371/3024</td>
</tr>
<tr>
<td>Major Bleeding*</td>
<td>389/3024</td>
<td>371/3024</td>
</tr>
</tbody>
</table>


Enlarged slide on page 70

Enlarged slide on page 71
Emerging Treatment Strategies

- Increasing dose of clopidogrel
- Switching to different P2Y$_{12}$ inhibitor
  - Ticlopidine
  - Prasugrel
  - Ticagrelor
  - Future agents
- Triple antiplatelet therapy
  - Adding cilostazol
  - PAR-1 inhibitors

Antiplatelet Impact of Cilostazol

- OPTIMUS-2
  - 25 patients with DM type 2 and CAD on DAT
    - Placebo x 14 days with cross-over
    - Cilostazol 100 mg bid x 14 days with cross-over
  - VASP assay (36.3% cilostazol vs 59.9% placebo; p=0.0002)

- DECREASE Registry
  - Nonrandomized evaluation of DES patients
    - DAT (n=1656) vs. TAT (n=1443) for 12 months
      - Death: HR 0.76 (0.40 – 1.45); p=0.41
      - MI: HR 0.23 (0.08 – 0.70); p=0.001
      - Stent thrombosis: HR 0.14 (0.04 – 0.52); p=0.004
      - Major bleeding: HR 0.97 (0.44 – 2.12); p=0.94

Enlarged slide on page 71
Cilostazol
Triple Antiplatelet Therapy
- ACCEL-AMI: 90 patients with STEMI after PCI + stenting
  - Standard group – clopidogrel 75 mg daily
  - High maintenance dose group – clopidogrel 150 mg daily
  - Triple group – clopidogrel 75 mg daily + cilostazol 100 mg twice daily
- Platelet function testing at baseline and at 1 month


Oral Antiplatelet Therapies


Thrombin Receptor Antagonism

NSSTE ACS n=10,000
Vorapaxar program (29,500 patients)
TRA*CER trial
(TRA*CER Committees 2009)

Vorapaxar Placebo
Follow-up 1 yr minimum

TRA 2* P-TIMI 50 trial
(Morrow et al. 2009)

Vorapaxar Placebo
1ª endpoint: Composite of CV death, MI, stroke, urgent revascularization and RI w/ rehospitalization
1ª endpoint: Composite of CV death, MI, stroke, urgent revascularization

ClinicalTrials.gov Identifier: NCT00527943.
ClinicalTrials.gov Identifier: NCT00526474.
Subjects with NSTE ACS
Randomization within 72 hours of symptom onset

Double-blind Randomize 1:1:1 Double-blind
Placebo daily Atopaxar 400mg LD, 50mg/day Atopaxar 400mg LD, 100mg/day Atopaxar 400mg LD, 200mg/day

12 Weeks Active Treatment, 4 Weeks Follow-up
Primary Endpoint: Major bleeding (CURE) at 12 weeks

LANCELOT-ACS Trial

Placebo n=138
Active combined atopaxar n=455
50mg daily n=153
100mg daily n=156
200mg daily n=146

Incidence of any TIMI Bleeding
P trend = 0.63

LANCELOT-ACS Trial

Placebo n=142
Active combined atopaxar n=461
50mg daily n=156
100mg daily n=157
200mg daily n=148

Incidence of CV death, MI, or stroke
P trend = 0.28

PR is a 78-year-old man (72 kg) with a history of smoking and dyslipidemia.
• Just admitted to the hospital with unstable angina
• Scheduled to go to PCI tomorrow

Which of the following would be the most appropriate option for providing the optimal reduction in CV death, MI, and stroke?

a. Clopidogrel 300 mg LD, then 75 mg daily
b. Prasugrel 60 mg LD, then 10 mg daily
c. Ticagrelor 180 mg LD, then 90 mg twice daily
d. Clopidogrel 600 mg LD, then 75 mg daily

TB is a 67-year-old man (80 kg) with history of hypertension, DM type 2, gout, and asthma.
• Currently hospitalized with STEMI and going to PCI
• Other medical history is non-contributory, except some problems with medication adherence

Which of the following would be the best option for TB?

a. Clopidogrel 300 mg LD, then 75 mg daily
b. Prasugrel 60 mg LD, then 10 mg daily
c. Ticagrelor 180 mg LD, then 90 mg twice daily
d. Clopidogrel 300 mg LD, then 75 mg daily and cilostazol 100 mg daily

TC is a 58-year-old man recently started on clopidogrel 75 mg daily. CYP2C19 genotype is CYP2C19*1/*2. VerifyNow test is slightly elevated (PRU = 245). What is the recommended treatment strategy for TC?

a. Continue clopidogrel 75 mg daily
b. Increase clopidogrel maintenance dose to 150 mg daily
c. Start prasugrel
d. Start ticagrelor
Emerging Treatment Strategies

• Increasing dose of clopidogrel
• Switching to different P2Y₁₂ inhibitor
  – Ticlopidine
  – Prasugrel
  – Ticagrelor
  – Future agents
• Triple antiplatelet therapy
  – Adding cilostazol
  – PAR-1 inhibitors
OPTIMUS Study


ACCEL-DOUBLE: Results

- CYP3A5 and ABCB1 did not influence platelet reactivity
- CYP2C19 predictive of high post-treatment platelet reactivity
  - OR 5.5 (1.33-23.26) p=0.018

**RESPOND Study**

- Cross-over study
- Grouped by response to 300 mg LD of Clopidogrel
  - ≤ 10% absolute Δ in platelet aggregation to 20 µmol/L ADP by LTA
  - Nonresponders (n=41)
  - Responders (n=57)
- Clopidogrel 600 mg LD and 75 mg daily
- Ticagrelor 180 mg LD and 90 mg bid


---

**New P2Y₁₂ Inhibitors vs. Clopidogrel Meta-Analysis**

Results in patients undergoing any PCI

<table>
<thead>
<tr>
<th>Odds ratio, random model DL (95%CI)</th>
<th>NewP2Y12 Clopidogrel</th>
<th>OR [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prasugrel JUMBO</td>
<td>3/560</td>
<td>0.2/54</td>
</tr>
<tr>
<td>Prasugrel TRITON</td>
<td>188/6813</td>
<td>197/6765</td>
</tr>
<tr>
<td>Cangrelor CHAMPION PCI</td>
<td>40/4433</td>
<td>47/4444</td>
</tr>
<tr>
<td>Cangrelor CHAMPION Platform</td>
<td>26/2654</td>
<td>47/2641</td>
</tr>
<tr>
<td>Ticagrelor PLATO invasive</td>
<td>252/6732</td>
<td>311/6676</td>
</tr>
<tr>
<td>Elinogrel ERASE MI</td>
<td>0/64</td>
<td>0/6/14</td>
</tr>
<tr>
<td></td>
<td><strong>p=0.008</strong></td>
<td><strong>0.69 [0.59; 0.96]</strong></td>
</tr>
</tbody>
</table>

| **Major Bleeding**                  |                       |            |
| Prasugrel JUMBO                     | 3/650                 | 2/254      |
| Prasugrel TRITON                    | 145/6813              | 111/6795   |
| Cangrelor CHAMPION PCI             | 13/4433               | 14/4444    |
| Cangrelor CHAMPION Platform        | 4/2654                | 9/2641     |
| Ticagrelor PLATO invasive          | 150/6732              | 130/6676   |
| Elinogrel ERASE MI                 | 0/34                  | 2/36       |
|                                      | **p=0.01**            | **1.23 [1.04; 1.48]** |

New P2Y<sub>12</sub> Inhibitors vs. Clopidogrel Meta-Analysis

Results in patients undergoing PCI for STEMI

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
<th>Elinogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRITON STEMI</strong></td>
<td>58 / 1767</td>
<td>8 / 487</td>
<td>234 / 4229</td>
</tr>
<tr>
<td><strong>CHAMPION PCI ST</strong></td>
<td>76 / 1765</td>
<td>16 / 509</td>
<td>254 / 4229</td>
</tr>
<tr>
<td><strong>PLATO STEMI</strong></td>
<td>0 / 34</td>
<td>0 / 36</td>
<td>0 / 36</td>
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</table>

**PCI for STEMI**

<table>
<thead>
<tr>
<th></th>
<th>New P2Y12</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>OR [95%CI]</td>
<td></td>
</tr>
<tr>
<td>N = 272 / 6489</td>
<td>0.75 [0.63; 1.07]</td>
<td></td>
</tr>
<tr>
<td>N = 346 / 6539</td>
<td>0.51 [0.32; 1.21]</td>
<td></td>
</tr>
<tr>
<td>Prasugrel</td>
<td>0.81 [0.67; 0.97]</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>1.06 [0.80; 1.28]</td>
<td></td>
</tr>
<tr>
<td>Elinogrel</td>
<td>0.79 [0.66; 0.92]</td>
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</table>

**Major Bleeding**

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
<th>Elinogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 413 / 5002</td>
<td>38 / 1767</td>
<td>375 / 4201</td>
<td>0 / 34</td>
</tr>
<tr>
<td>N = 425 / 6030</td>
<td>34 / 1765</td>
<td>396 / 4239</td>
<td>0 / 36</td>
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</table>

**PCI for STEMI**

<table>
<thead>
<tr>
<th></th>
<th>OR [95%CI]</th>
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</thead>
<tbody>
<tr>
<td>N = 413 / 5002</td>
<td>1.12 [0.70; 1.79]</td>
<td></td>
</tr>
<tr>
<td>N = 425 / 6030</td>
<td>0.97 [0.63; 1.47]</td>
<td></td>
</tr>
<tr>
<td>Prasugrel</td>
<td>0.13 [0.00; 8.37]</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>0.94 [0.60; 1.48]</td>
<td></td>
</tr>
</tbody>
</table>

* Not reported in CHAMPION PCI STEMI
* Includes CABG or non-CABG bleeding in PLATO-STEMI only


---

Antiplatelet Impact of Cilostazol

![Pathway diagram showing the antiplatelet impact of Cilostazol and Clopidogrel](image)

Cilostazol

Triple Antiplatelet Therapy

- **ACCEL-AMI**: 90 patients with STEMI after PCI + stenting
  - Standard group – clopidogrel 75 mg daily
  - High maintenance dose group – clopidogrel 150 mg daily
  - Triple group – clopidogrel 75 mg daily + cilostazol 100 mg twice daily
  - Platelet function testing at baseline and at 1 month

Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

SELECTED REFERENCES


SELF–ASSESSMENT QUESTIONS

1. RJ is a 64-year old man who was recently admitted to the hospital with a non-ST-segment elevation myocardial infarction. He also has a history of hypertension, diabetes mellitus, and dyslipidemia. He received a loading dose of clopidogrel 300 mg before percutaneous coronary intervention with stent placement, followed by 75 mg daily. On day three of hospitalization, the cardiologist asks for a VerifyNow test. The results demonstrate a platelet reactive units (PRU) value of 300. How would you describe the meaning of this value to the cardiologist?
   a. This patient is most likely to have a cardiovascular event.
   b. This patient has suboptimal platelet inhibition.
   c. This patient is at increased risk for major bleeding.
   d. This patient must undergo genetic testing.

2. Which of the following would be an appropriate management strategy for RJ?
   a. Give an additional 300 mg loading dose of clopidogrel.
   b. Give an additional 600 mg loading dose of clopidogrel.
   c. Give a maintenance dose of clopidogrel 150 mg daily.
   d. Give a maintenance dose of clopidogrel 300 mg daily.

3. Which of the following outcomes was demonstrated to be significantly reduced by the use of ticagrelor compared with clopidogrel in the PLATO trial?
   a. Stroke.
   b. Major bleeding.
   c. Intracranial hemorrhage.
   d. Cardiovascular death.

4. All of the following provide platelet inhibition via binding to the P2Y$_{12}$ receptor EXCEPT
   a. Vorapaxar.
   b. Prasugrel.
   c. Ticagrelor.
   d. Elinogrel.

Answers
1. b
2. c
3. d
4. a
# Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>AC</td>
<td>adenylyl cyclase</td>
</tr>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>ACCF</td>
<td>American College of Cardiology Foundation</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>ADP</td>
<td>adenosine diphosphate, endogenous activator of the P2Y&lt;sub&gt;12&lt;/sub&gt; receptor on platelets</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>ARC</td>
<td>Academic Research Consortium</td>
</tr>
<tr>
<td>ASA</td>
<td>aspirin</td>
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<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>ATTC</td>
<td>Antithrombotic Trialists’ Collaboration</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>BMS</td>
<td>bare-metal stent</td>
</tr>
<tr>
<td>Ca</td>
<td>calcium</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
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<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
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<td>CI</td>
<td>confidence interval</td>
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<td>COX</td>
<td>cyclooxegenase</td>
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<td>cytochrome P</td>
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<td>DST</td>
<td>definite stent thrombosis</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EM</td>
<td>extensive metabolizer</td>
</tr>
<tr>
<td>5-HT2A</td>
<td>5-hydroxy tryptamine 2A</td>
</tr>
<tr>
<td>GOP</td>
<td>gain of function</td>
</tr>
<tr>
<td>GP</td>
<td>glycoprotein</td>
</tr>
<tr>
<td>GUSTO</td>
<td>Global Use of Strategies to Open Occluded Coronary Arteries</td>
</tr>
<tr>
<td>GWAS</td>
<td>genome-wide association study</td>
</tr>
<tr>
<td>HDL-C</td>
<td>high-density lipoprotein cholesterol</td>
</tr>
</tbody>
</table>
## Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>IM</td>
<td>intermediate metabolizer</td>
</tr>
<tr>
<td>IPA</td>
<td>inhibition of platelet aggregation</td>
</tr>
<tr>
<td>IP3</td>
<td>inositol triphosphate</td>
</tr>
<tr>
<td>LD</td>
<td>loading dose</td>
</tr>
<tr>
<td>LDL-C</td>
<td>low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>LOF</td>
<td>loss of function</td>
</tr>
<tr>
<td>LTA</td>
<td>light transmission aggregometry</td>
</tr>
<tr>
<td>MA</td>
<td>maximal amplitude (clot strength)</td>
</tr>
<tr>
<td>MACE</td>
<td>major adverse coronary event</td>
</tr>
<tr>
<td>MD</td>
<td>physician</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>MPA</td>
<td>maximal platelet aggregation</td>
</tr>
<tr>
<td>NNH</td>
<td>number needed to harm</td>
</tr>
<tr>
<td>NNT</td>
<td>number needed to treat</td>
</tr>
<tr>
<td>NR</td>
<td>nonresponsive</td>
</tr>
<tr>
<td>NSTE</td>
<td>non-ST-segment elevation</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>non-ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PAR-1</td>
<td>protease-activated receptor 1</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
</tr>
<tr>
<td>PGE₁</td>
<td>prostaglandin E₁</td>
</tr>
<tr>
<td>PI</td>
<td>prescribing information</td>
</tr>
<tr>
<td>PKA</td>
<td>protein kinase</td>
</tr>
<tr>
<td>PK/PD</td>
<td>pharmacokinetics and pharmacodynamics</td>
</tr>
<tr>
<td>PLC</td>
<td>phospholipase C</td>
</tr>
<tr>
<td>PM</td>
<td>poor metabolizer</td>
</tr>
<tr>
<td>PPI</td>
<td>proton pump inhibitor</td>
</tr>
<tr>
<td>PRI</td>
<td>platelet reactivity index (unit of measure for VASP phosphorylation assay that measures effectiveness of P2Y₁₂ receptor antagonists)</td>
</tr>
<tr>
<td>PRU</td>
<td>P2Y12 reaction units (unit of measure for VerifyNow P2Y12 test)</td>
</tr>
<tr>
<td>RI</td>
<td>recurrent ischemia</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operating curve, a graphical plot of true positive rate (sensitivity) versus false positive rate (1- specificity)*</td>
</tr>
<tr>
<td>RRR</td>
<td>relative risk reduction</td>
</tr>
<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
</tr>
<tr>
<td>ST</td>
<td>stent thrombosis</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td>TEG</td>
<td>thrombelastograph</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>TIMI</td>
<td>Thrombolysis in Myocardial Infarction</td>
</tr>
</tbody>
</table>
Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

<table>
<thead>
<tr>
<th>Abbreviation</th>
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</thead>
<tbody>
<tr>
<td>TVR</td>
<td>target vessel revascularization</td>
</tr>
<tr>
<td>TxA₂</td>
<td>thromboxane A₂</td>
</tr>
<tr>
<td>UA</td>
<td>unstable angina</td>
</tr>
<tr>
<td>UM</td>
<td>ultrarapid metabolizer</td>
</tr>
<tr>
<td>UTVR</td>
<td>urgent target vessel revascularization</td>
</tr>
<tr>
<td>VASP</td>
<td>vasodilator-stimulated phosphoprotein, a downstream intracellular mediator of P2Y12 receptor activation in platelets</td>
</tr>
<tr>
<td>VASP-PRI</td>
<td>vasodilator-stimulated phosphoprotein platelet reactivity index</td>
</tr>
<tr>
<td>vWF</td>
<td>von Willebrand factor</td>
</tr>
</tbody>
</table>

*ROC area under the curve (AUC) of 1.0 would represent a perfectly accurate test, and an AUC of 0.5 represents the line of no discrimination (test is equal to random guess).