Overcoming Challenges in Acute Coronary Syndrome: Case Studies in ACS Management

Presented as a Midday Symposium and Live Webinar at the 49th ASHP Midyear Clinical Meeting and Exhibition

Monday, December 8, 2014
Anaheim, California

Action Reminder

Planned and conducted by ASHP Advantage and supported by an educational grant from The Medicines Company
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Overcoming Challenges in Acute Coronary Syndrome:
Case Studies in ACS Management

Agenda

11:30 a.m. – 11:45 a.m. Welcome and Introduction
Paul P. Dobesh, Pharm.D., FCCP, BCPS (AQ Cardiology)

11:45 a.m. – 12:00 p.m. Perioperative Management
Douglas Jennings, Pharm.D., AACC, BCPS (AQ Cardiology)

12:00 p.m. – 12:10 p.m. Clopidogrel Nonresponsiveness: What Does It Mean to You?
Paul P. Dobesh, Pharm.D., FCCP, BCPS (AQ Cardiology)

12:10 p.m. – 12:20 p.m. Management of Bleeding from Antiplatelet Therapy
Douglas Jennings, Pharm.D., AACC, BCPS (AQ Cardiology)

12:20 p.m. – 12:45 p.m. What’s Next?
Toby C. Trujillo, Pharm.D., FCCP, FAHA, BCPS (AQ Cardiology)

12:45 p.m. – 1:00 p.m. Faculty Discussion and Audience Questions
All Faculty

Food and beverage are no longer provided at Midday Symposia. This ASHP policy considers the varied internal policies of commercial supporters related to the Physician Payments Sunshine Act.

Faculty

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

Douglas Jennings, Pharm.D., AACC, BCPS (AQ Cardiology)
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Clinical Pharmacist-Advanced Heart Failure and Cardiac Surgery
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Aurora, Colorado
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- Paul P. Dobesh, Pharm.D., FCCP, BCPS (AQ Cardiology), declares that he served as a consultant for Astra Zeneca; Bristol-Myers Squibb/Pfizer; Daiichi Sankyo, Inc.; Gilead Sciences, Inc.; and Janssen Pharmaceuticals, Inc.; and also received research grants from AstraZeneca and Daiichi Sankyo, Inc. and Eli Lilly and Company alliance.

- All other faculty and planners report no financial relationships relevant to this activity.
Activity Overview

Acute coronary syndrome (ACS) is a term used to describe the condition in which patients present with either unstable angina, non–ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction. With mortality from ACS in the United States ranging from 9-19% in the first six months after diagnosis, appropriate management of ACS is essential to optimize patient outcomes. During this activity, the faculty will use patient case scenarios to address common clinical challenges in the management of patients with ACS, including perioperative management, clopidogrel nonresponsiveness, and bleeding. Evidence related to the use of new and emerging agents will also be discussed.

Learning Objectives

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

- Describe the pathophysiology and management of acute coronary syndrome (ACS) with a focus on the role of oral antiplatelet therapy.
- Develop management plans for perioperative management and bleeding by incorporating clinical data with pharmacokinetic and pharmacodynamic data.
- Implement evidence regarding management of clopidogrel nonresponsiveness and evolving data in the care of patients with ACS.
- Using patient case scenarios, develop comprehensive treatment strategies for patients with ACS and complex clinical issues.

List of Abbreviations

For a list of abbreviations used in this activity, please see page 52.

Other Educational Opportunities

Visit the initiative website for another educational activity related to this topic (1 hour CPE)

Check back in March 2015 for an on-demand activity based on today’s live symposium (1.5 hours CPE)

Please note that individuals who claim CPE credit for the live symposium or webinar are ineligible to claim credit for the on-demand activity

www.ashpadvantage.com/acs
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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 1.5 hours (0.15 CEUs – no partial credit) of continuing pharmacy education credit (ACPE activity #0204-0000-14-705-L01-P for the live activity and ACPE activity #0204-0000-14-705-H01-P for the on-demand activity).

Complete instructions for receiving your statement of continuing pharmacy education credit online are on the next page.

Webinar Information

Visit www.ashpadvantage.com/go/acs/challenges/webinar to find
• Webinar registration link
• Group viewing information and technical requirements

ACTION REMINDER EMAIL

Have ideas about what YOU want to remember to do as a result of what you are learning in this educational session? Use the Action Reminder tool via your smart device, and you will be sent an email reminder from YOURSELF next month.

If you do not have a smart device, access the Action Reminder for this activity at www.ashpadvantage.com/go/acs/challenges/remindme
CPE Instructions for Pharmacists and Technicians

Per ACPE, CPE credit must be claimed no later than 60 days from the date of the live activity or completion of a home study activity. All ACPE-accredited activities processed on the eLearning site will be reported directly to CPE Monitor. To claim pharmacy credit, you must have your NABP e-Profile ID, birth month, and birth day. If you do not have an NABP e-Profile ID, go to www.MyCPEMonitor.net for information and application. Follow these instructions to process your CPE credit for this activity.

1. Access the e-Learning site at http://elearning.ashp.org/my-activities

2. If you already have an ASHP account, log in using your username and password.

   If you do not have an ASHP account, click on the Register link and follow the registration instructions. You do not have to be a member to create an account.

For Midyear Attendees in Anaheim

- Once logged in, select “Conferences” and click on the conference name under Your Conferences.

- Under Add Sessions enter your attendance code announced during the activity, and click Submit.

   Helpful Tip: If your code is not redeeming successfully, verify that you have clicked on the title of your conference to access the Attendance Code field, not the Enrollment Code field.

- Each session will be listed under Your Sessions. Click Claim Credit for a particular session.

- Complete any requirements for each session by clicking on the name of the activity and following the instructions.

- Click Claim Credit. See steps 3-5 below.

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- Once logged in, enter the enrollment code (announced during the webinar) into the “ENROLLMENT CODE” box for the activity and click Redeem.
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- The title of this activity will appear in a pop-up box on your screen. Click on the Go button or the activity title.

- Complete all required elements. A green check should appear as each required element is completed. You can now claim your credit.

3. Available credit(s) will appear beneath the completed required activities. Look for your profession in the list of available credits and click the appropriate Claim button. You might have to click to see more credit options if you do not see your profession listed.

4. Review the information for the credit you are claiming. If all information appears to be correct, check the box at the bottom and click Claim. You will see a message if there are any problems claiming your credit.

5. After successfully claiming credit, you may print your statement of credit by clicking on Print. If you require a reprint of a statement of credit, you can return at any time to print a duplicate. For CPE credit for pharmacists and technicians, printed statements may not be necessary because your credit is reported directly to CPE Monitor.

NEED HELP? Contact eLearning@ashp.org

<table>
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<th>Date of Activity:</th>
<th>Monday December 8, 2014</th>
<th>Code:</th>
<th>CPE Hours:</th>
<th>1.5</th>
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Overcoming Challenges in Acute Coronary Syndrome:  
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Paul P. Dobesh, Pharm.D., FCCP, BCPS (AQ Cardiology), Activity Chair  
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 Distinguished Educator of the Year Award for 2012, an award he has received three times within the last seven years. In 2013, he received the UNMC campus wide Outstanding Educator Award.

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.
Douglas Jennings, Pharm.D., AACC, BCPS (AQ Cardiology)
Assistant Professor
Nova Southeastern University
Ft. Lauderdale, Florida
Clinical Pharmacist-Advanced Heart Failure and Cardiac Surgery
University of Miami Jackson Memorial Hospital
Miami, Florida

Douglas Jennings, Pharm.D., AACC, BCPS (AQ Cardiology), is Assistant Professor of Pharmacy at Nova Southeastern University in Ft. Lauderdale, Florida. He also has a practice in advanced heart failure and cardiac surgery at Jackson Memorial Hospital in Miami.

Dr. Jennings earned his Doctor of Pharmacy degree from Wayne State University in Detroit, Michigan. After a pharmacy practice residency at the Medical University of South Carolina in Charleston, he completed a cardiovascular specialty residency at Henry Ford Hospital in Detroit. Dr. Jennings then stayed at Henry Ford Hospital, practicing as a clinical pharmacy specialist in the cardiovascular intensive care unit. He also established and served as Program Director for Henry Ford Hospital’s 24-month pharmacotherapy residency, a program that successfully received ASHP accreditation. He is board-certified as a pharmacotherapy specialist with added qualifications in cardiology.

In his current position at Nova Southeastern University, Dr. Jennings is actively involved in research with his primary interest being the pharmacotherapy of patients with mechanical circulatory support. He has published nearly 50 peer-reviewed abstracts and manuscripts in journals, including *Annals of Pharmacotherapy, ASAIO Journal, The International Journal of Artificial Organs*, and *Pharmacotherapy*.

Dr. Jennings is active in professional organizations. He currently serves as Chair-elect for the Cardiology PRN within the American College of Clinical Pharmacy.
Toby C. Trujillo, Pharm.D., FCCP, FAHA, BCPS (AQ Cardiology)
Associate Professor
Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado Anschutz Medical Campus
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Aurora, Colorado

Toby C. Trujillo, Pharm.D., FCCP, FAHA, BCPS (AQ Cardiology), is Associate Professor of Clinical Pharmacy at Skaggs School of Pharmacy and Pharmaceutical Sciences on the University of Colorado Anschutz Medical Campus in Aurora. 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.

Dr. Trujillo has served in several capacities within the American Heart Association and the Society of Critical Care Medicine. 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.
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Disclosures

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• Implement evidence regarding management of clopidogrel nonresponsiveness and evolving data in the care of patients with ACS

• Using patient case scenarios, develop comprehensive treatment strategies for patients with ACS and complex clinical issues
Introduction and Background

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

Platelet Cascade in ACS

1. Adhesion
   - Platelet
   - Collagen
   - GP IIb/IIIa Bind
   - von Willebrand Factor/GP Ib Bind

2. Activation
   - Thrombin
   - ADP
   - 5 HT
   - TXA2

3. Aggregation
   - Activated GP IIb/IIIa
   - Fibrinogen

4. Platelet Plug

Aspirin Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>ACC/AHA</th>
<th>AHA/MAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-enteric-coated chewable aspirin (162 mg to 325 mg) should be given to ALL patients with NSTE ACS without contraindications as soon as possible.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Aspirin indefinitely for NSTE ACS patients treated with or without stenting</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Aspirin allergic patients with NSTE ACS treated medically (without stenting) use clopidogrel or ticagrelor for up to 12 months</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>After PCI, it is reasonable to use aspirin 81 mg daily in preference to higher doses</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

Amsterdam EA et al. J Am Coll Cardiol. 2014 Sep 18. [Epub ahead of print]

Antiplatelet Trialists’ Collaboration: Meta-analysis

<table>
<thead>
<tr>
<th>Aspirin Dose</th>
<th># Trials</th>
<th>OR (%)</th>
<th>Odds Ratio</th>
</tr>
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<tbody>
<tr>
<td>500-1500 mg</td>
<td>34</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>160-325 mg</td>
<td>19</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>75-150 mg</td>
<td>12</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>&lt;75 mg</td>
<td>3</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Any aspirin</td>
<td>65</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

Treatment effect p<0.0001

Relationship Between Major Bleeding and ASA Dose in ACS Patients

(Post-hoc analysis from CURE)

ASA dose (range 75-325 mg)


P2Y₁₂ Inhibitor Recommendations

<table>
<thead>
<tr>
<th>ACC/AHA</th>
<th>ACC/AHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOE</td>
<td>LOE</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

A P2Y₁₂ inhibitor (clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE ACS without contraindications who are treated with an ischemia-guided strategy.

It is reasonable to use ticagrelor in preference to clopidogrel for P2Y₁₂ treatment in patients with NSTE ACS who undergo an ischemia-guided strategy.

In patients receiving a stent (BMS or DES) during PCI for NSTE ACS, P2Y₁₂ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months.

It is reasonable to use prasugrel or ticagrelor over clopidogrel for P2Y₁₂ treatment in patients with NSTE ACS treated with an early invasive strategy.

Prasugrel should not be administered in patients with a prior history of stroke or TIA.


**Biotransformation and Mode of Action**

*Clopidogrel, Prasugrel, and Ticagrelor*

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**CURE Study Design**

- Clopidogrel 300-mg loading dose
- Clopidogrel 75 mg qd + ASA 75-325 mg qd (6259 patients)
- Placebo + ASA 75-325 mg qd (6303 patients)

- Patients with Acute Coronary Syndrome
  - Unstable angina
  - Non–ST-segment elevation MI

- 3 months ≤ double-blind treatment ≤ 12 months

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**Primary Endpoint: MI/Stroke/CV Death**

- Cumulative Hazard Rate
  - Placebo + ASA
  - Clopidogrel + ASA

- RRR: 20%
  - p = 0.00009
  - n = 12,562
Clopidogrel in ACS

• NSTE ACS
  - CURE (n=12,562)
    - 300/75 vs. placebo within 24 hours of symptom onset
      - Significant reductions in death, MI and stroke
  - PCI-CURE (n=2,658)
    - 75 mg vs placebo after 28 days
      - 27% RRRI with death & stroke 1 year
      - 18.5% RRRI in Death, MI, UTVR
    - Benefit only seen if load > 6 hours prior to PCI
  - CREDO (n=1,116)
    - 300/75 vs placebo 3-24 h before PCI
      - 75 mg vs placebo after 28 days
      - 27% RRRI with death & stroke 1 year
      - 18.5% RRRI in Death, MI, UTVR
    - Benefit only seen if load > 6 hours prior to PCI
  - ACUITY (n=13,819)
    - Benefit with bivalirudin mono-treatment contingent on clopidogrel loading pre-PCI

• STEMI
  - CLARITY (n=3,491)
    - Patients age 18-75 within 12 hours
      - Clopidogrel 300/75
      - Placebo
      - Significant reductions in occluded vessel, death, MI by angiography and up to 30 days
  - COMMIT (n=45,852)
    - Patients within 24 hours of suspected MI
      - Clopidogrel 75 mg
      - Placebo
      - 9% reduction in death/MI/stroke over treatment period

Clinical Issues with Clopidogrel

• Variability of platelet inhibition
  - Drug – Drug interactions (PPIs)
  - Up to 40% of patients are “nonresponsive”
  - Role of platelet function testing?
  - What to do with the results?

• Genetic polymorphisms in metabolism
  - Prodrug that must undergo two CYP450 enzymes conversion steps
  - CYP 2C19 loss-of-function alleles
    - Heterozygous vs. homozygous
    - Connection of clinical outcomes debated

Biotransformation and Mode of Action

Clopidogrel, Prasugrel, and Ticagrelor

TRITON TIMI-38
ACS (STEMI or UA/NSTEMI) & planned PCI

CLOPIDOGREL
300 mg LD/75 mg MD

PRASUGREL
60 mg LD/10 mg MD

n = 13,608

Median duration of therapy - 12 months

1º endpoint: CV death, MI, stroke
2º endpoints: CV death, MI, stroke, rehosp-recurr. ischemia
CV death, MI, UTVR
Stent thrombosis (ARC definite/probable)
Safety endpoints: TIMI major bleeds, life-threatening bleeds


TRITON TIMI-38 Trial - Results


TRITON TIMI-38 Trial
Timing of Benefit

Biotransformation and Mode of Action
Clopidogrel, Prasugrel, and Ticagrelor

PLATO Study Design

- NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
- Clopidogrel-treated or naïve; randomized within 24 hours of index event
- n=18,624

Clopidogrel
- If pre-treated, no additional loading dose.
- If naïve, standard 300 mg loading dose; then 75 mg qd 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

- Cumulative incidence (%)
- Days after randomization

PLATO Trial
Timing of Benefit

*Composite of CV death, MI, or stroke


PLATO Results – Major Bleeding
Non-CABG and CABG Related

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

Perioperative Management of Antiplatelet Therapy

Douglas Jennings, Pharm.D., AACC, BCPS (AQ-Cardiology)

Patient Case: PD

- PD is 67-year-old female patient who presents with acute 10/10 CP lasting 3 hours
- PMH: HTN, DM, gout, OA
- MPTA: lisinopril, allopurinol, metformin, APAP
- ECG: ST elevation in V1-V4
- Labs: within normal limits
- CXR: clear
- Initial therapy: ASA 325 mg, ticagrelor 180 mg, heparin 4000 units IV

Patient Case: PD

- PD undergoes successful PCI to her LAD with a DES
- Meds: ASA 81 mg daily, ticagrelor 90 mg bid, atorvastatin 80 mg daily
- HPI: 3 days after PCI, she develops acute HF, and is found to have papillary muscle rupture and severe mitral regurgitation. She is stabilized with an IABP, and a plan is made for emergent valve replacement surgery.
Which of the following strategies would you recommend for PD?

a. Continue ASA + ticagrelor pre/postop
b. Stop ticagrelor 5 days preop, resume postop
c. Stop ticagrelor 5 days preop, initiate GP IIb/IIIa inhibitor periop, resume ticagrelor postop
d. Stop ticagrelor 5 days preop, initiate i.v. heparin periop, resume ticagrelor postop

Perioperative Management of Antiplatelet Therapy


Overall Approach to Perioperative Management

- Bleeding
  - Type of surgery
  - Consequences
- Ischemic Event
  - Disease specific
  - Type and location of stent
Balancing Risks

Thrombosis
Bleeding

ACU/STEMI
DES (high-risk vessel)
Neurological
Orthopedic, general


Guideline Recommendations
Continue ASA

- Minor surgery (Dental)
- Mod-high risk of CV events
- Undergoing CABG surgery

Stop ASA-DAPT

- Low risk of CV events (ASA)
- Stop DAPT* at least 5 days before CABG surgery

**DAPT = clopidogrel or prasugrel


Guideline Recommendations
Recent Coronary Artery Stenting

Delay possible
- Postpone surgery at least
  - 6 weeks for BMS (1C)
  - 6 months for DES (1C)

Emergent
- Continue DAPT instead of stopping 7-10 days prior to surgery (2C)

Douketis JD. Chest. 2012; 141(Suppl 2):e326S–e350S.
Bridging Therapy

Stop P2Y₁₂ antagonist 5-7 days prior to surgery (Continue ASA)

Start GP IIb/IIIa inhibitor 3 days prior and then stop 4-6 hr preop

Resume ASA, P2Y₁₂ antagonist +/- GP IIb/IIIa inhibitor postop


Bridging: Future Options

- Cangrelor: Intravenous P2Y₁₂ receptor antagonist
  - Rapid acting: quick onset (within minutes)
  - Plasma half-life of 3 – 6 minutes
  - Continuous infusion
  - 60 minutes for return to normal platelet function


BRIDGE Trial Design

Objectives
- Demonstrate that cangrelor infusion maintains PRU<240
- Assess rates of major surgical bleeding and ischemic complications

**BRIDGE Trial: Efficacy**

Percent of patients with all on-treatment samples <240 PRUs

- **Cangrelor**: 98.8%
- **Placebo**: 19%

\[ p=0.001 \]
\[ OR (95\% CI) \]
\[ 353 (45.6-2728) \]

Ischemic Events
- Cangrelor: 2.8% (3 of 106)
- Placebo: 4.0% (4 of 101)

**Ischemic Events**

**OR (95% CI)**

**p<0.001**

**Angiolillo DJ et al. JAMA. 2012; 307:265-74.**

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**BRIDGE Trial: Bleeding**

<table>
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<tr>
<th>Event Type</th>
<th>Cangrelor</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>CABG-related*</td>
<td>11.8</td>
<td>10.4</td>
</tr>
<tr>
<td>ACUITY Major</td>
<td>2.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Gusto Severe</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>TIMI Major</td>
<td>0.9</td>
<td>0.0</td>
</tr>
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</table>

*Excessive CABG-related bleeding defined as at least 1 of the following: Surgical re-exploration, 24-hour chest tube output > 1.5 liters, incidence of PRBC transfusion > 4 units

\[ p=0.76 \]
\[ p=0.35 \]

**Angiolillo DJ et al. JAMA. 2012; 307:265-74.**

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**BRIDGE Trial: Interpretation**

- **Cangrelor effective antiplatelet agent**
- **Strength**: included some ACS patients → CABG
- **Small sample size**
- **Unable to evaluate clinical outcomes**
- **Heterogeneous population**
- **<50% had ACS/MI, data regarding stenting not reported**
Potential Bridging Therapy

Stop P2Y12 antagonist 5-7 days prior to surgery (Continue ASA)
Start cangrelor within 72 hr and then stop 1-6 hr preop
Resume ASA, P2Y12 antagonist +/- cangrelor postop


Which of the following strategies would you recommend for PD?

a. Continue ASA + ticagrelor pre/postop
b. Stop ticagrelor 5 days preop, resume postop
c. Stop ticagrelor 5 days preop, initiate GP IIb/IIIa inhibitor periop, resume ticagrelor postop
d. Stop ticagrelor 5 days preop, initiate i.v. heparin periop, resume ticagrelor postop

Key Takeaways

- Perioperative management requires careful assessment of risk versus benefit of antiplatelet therapy
- Aspirin is safe to continue in most cases
- Limited data to guide clinicians regarding antiplatelet bridging in the perioperative setting
Clopidogrel Nonresponsiveness: What Does It Mean to You?

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

Patient Case: RQ

RQ is a 67-year-old male patient who presented with NSTE ACS. He has diffuse disease and has received a total of 4 DES. His cardiologist is concerned that if RQ has another thrombosis, he may not survive.

The cardiologist asks for information about appropriate antiplatelet therapy and platelet function testing.

Which of the following statement(s) is/are true regarding the cardiologist’s question? Select all that apply.

a. Patients with high on-treatment platelet reactivity have higher risk of adverse CV outcomes
b. Changing antiplatelet therapy based on testing results is easy way to reduce adverse CV outcomes
c. Initial therapy with more potent antiplatelet therapy is best way to prevent adverse CV outcomes
d. None of the above is correct
Variability in Clopidogrel Response in 544 Volunteers


Clinical Implications of Clopidogrel Nonresponsiveness

• First trial to correlate a lower antiplatelet effect 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 5d
    • LTA with ADP 5 μmol/L and epinephrine 10 μmol/L
    • Cone and platelet analyzer
  – Patients separated into quartiles based on ADP-induced platelet aggregation
  – Major adverse cardiac events evaluated at 6 months

Clinical Implications of Clopidogrel Nonresponsiveness

6-Month Recurrent CV Events (%)


<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matetzky S et al.</td>
<td>CV events</td>
<td>40% in 1st quartile vs. 6.7% in 2nd and 0% in 3rd &amp; 4th (p=0.007)</td>
</tr>
<tr>
<td>PREPARE POST-STENTING</td>
<td>CV events</td>
<td>32% in 1st quartile vs. 10% in 4th (p=0.02)</td>
</tr>
<tr>
<td>Sibbing D et al.</td>
<td>Stent thrombosis</td>
<td>2.2% NR vs. 0.2% R (p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>1.2% NR vs. 0.4% R (p=0.07)</td>
</tr>
<tr>
<td>ARMYDA-PRO</td>
<td>Death, MI, TVR</td>
<td>20% NR vs. 3% R (p=0.034)</td>
</tr>
<tr>
<td>Geisler T et al.</td>
<td>CV death, MI, stroke</td>
<td>22.7% NR vs. 5.6% R (p=0.004)</td>
</tr>
<tr>
<td>Buonamici P et al.</td>
<td>Stent thrombosis</td>
<td>8.6% NR vs. 2.3% R (p&lt;0.001)</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 μM-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 dose (LD) - ASA 250mg
- Clopidogrel 600mg

VASP ≥ 50%

Randomization (n=429)

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

Maintenance dose - ASA 160 mg
- Clopidogrel 75 mg daily

Up to 3 additional LD of 600 mg 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%†

17 patients (8%)
† p <0.01


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=215)</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>

**GRAVITAS Trial**

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

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

- **Nonresponder**
  - PRU ≥ 230
  - A: n=1109

- **Responder**
  - PRU < 230
  - B: n=1105

- **Random selection**
  - C: n=586

"Tailored therapy" clopidogrel 150 mg/day

"Standard therapy" clopidogrel 75 mg + placebo/day

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

Primary endpoint: 6 month CV death, nonfatal MI, ARC def/prob stent thrombosis


---

**GRAVITAS Trial Results**

<table>
<thead>
<tr>
<th>PR = platelet reactivity</th>
<th>% of Patients</th>
<th>CV Death/MI/ST</th>
<th>GUSTO Severe/Mod Bleeding</th>
<th>Any GUSTO Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>High PR - High Dose</td>
<td>12%</td>
<td>2.3%</td>
<td>0.4%</td>
<td>2.3%</td>
</tr>
<tr>
<td>High PR - Standard Dose</td>
<td>12%</td>
<td>2.3%</td>
<td>0.4%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Normal PR - Standard Dose</td>
<td>12%</td>
<td>2.3%</td>
<td>0.4%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

p = 0.18


---

**GRAVITAS Results**

CV Events and Post-PCI PRU

- **PRU 12 - 24 hr post-PCI**
  - n=1105
  - n=586

- **High Residual Reactivity**
- **No High Residual Reactivity**

Red dots: patients with CV death, MI, or ST

**GRAVITAS Results**

CV Events and Post-PCI PRU

<table>
<thead>
<tr>
<th>PRU 12 - 24 hr post-PCI</th>
<th>Red dots: patients with CV death, MI, or ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Residual Reactivity</td>
<td>Not High Residual Reactivity</td>
</tr>
<tr>
<td>n=1105</td>
<td>n=586</td>
</tr>
</tbody>
</table>


**ARCTIC Trial Design**

Patients scheduled for coronary stenting without STEMI or planned use of GP Ib/IIa inhibitor therapy

Randomization after coronary angiography and before the intervention procedure was begun

Treatment with oral antiplatelet therapy was left to the physician’s discretion, but a loading dose of P2Y12 inhibitors had to be administered at least 6 hours before stenting was recommended

Conventional Strategy
- Clopidogrel (94% → 86%)
- Prasugrel (6%)

Monitoring Strategy


**ARCTIC Trial Design**

Assessment for high platelet reactivity by the VerifyNow Assay
- Aspirin ≥ 550 aspirin reaction units (ARU)
- P2Y12 inhibitors ≥ 235 platelet reaction units (PRU) or 15% less inhibition

High Platelet Reactivity before stenting (34.5%)
- GP Ib/IIa inhibitor and additional clopidogrel LD of ≥ 600 mg, then 150 mg daily or prasugrel LD of 60 mg, then 10 mg daily

Adequate Response (65.5%)
- No changes made

Reassessment of platelet reactivity in 2 to 4 weeks

High Platelet Reactivity before stenting (15.6%)
- Switch to prasugrel 10 mg daily or increase dose of clopidogrel by 75 mg daily

Adequate Response (65.5%)
- No changes made

ARCTIC Trial Results

<table>
<thead>
<tr>
<th>% of Patients</th>
<th>Primary Endpoint</th>
<th>Death or MI</th>
<th>Stent thrombosis</th>
<th>Major Bleeding</th>
<th>Major or Minor Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Patients</td>
<td>Conventional Strategy</td>
<td>Monitoring Strategy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>31.1%</td>
<td>34.6%</td>
<td>23.6%</td>
<td>8.7%</td>
<td>1.3%</td>
</tr>
<tr>
<td>10%</td>
<td>31.7%</td>
<td>31.7%</td>
<td>8.7%</td>
<td>3.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>20%</td>
<td>34.6%</td>
<td>34.6%</td>
<td>3.3%</td>
<td>4.5%</td>
<td>1.1%</td>
</tr>
<tr>
<td>30%</td>
<td>31.7%</td>
<td>31.7%</td>
<td>8.7%</td>
<td>3.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>40%</td>
<td>34.6%</td>
<td>34.6%</td>
<td>3.3%</td>
<td>4.5%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Primary Endpoint: Death from any cause, MI, stent thrombosis, stroke or TIA, or urgent revascularization


ARCTIC Trial Discussion

- Higher risk patients – still only 27% ACS
- Myocardial infarction rate of ~ 30%
  - Rate of CV death, MI, or stroke typically ~ 10%
  - Even after changing MI definition, composite endpoint still > 20%
- Monitoring group heterogeneous
  - 2/3 of patients did not receive any changes
    - Dilutes impact of dose adjustments in other 1/3
    - Is this what we want to know?
    - Does a change 2 to 4 weeks later matter?

Clopidogrel Nonresponsiveness and On-Treatment Platelet Reactivity

Where are we now?

- Clopidogrel variability as measured by platelet function tests correlates with clinical outcomes in PCI patients
  - Good negative predictive value
  - Poor positive predictive value
- Utilizing platelet tests for individualized dosing is advancing
  - Studies have not evaluated high-risk patients
  - VerifyNow is most convenient assay
- The platelet function test that best predicts clinical outcomes is not known
Patient Case: RQ

RQ is a 67-year-old male patient who presented with NSTE ACS. He has diffuse disease and has received a total of 4 DES. His cardiologist is concerned that if RQ has another thrombosis, he may not survive.

The cardiologist asks for information about appropriate antiplatelet therapy and platelet function testing.

Which of the following statement(s) is/are true regarding the cardiologist's question?
Select all that apply.

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b. Changing antiplatelet therapy based on testing results is easy way to reduce adverse CV outcomes
c. Initial therapy with more potent antiplatelet therapy is best way to prevent adverse CV outcomes
d. None of the above is correct
Management of Bleeding from Antiplatelet Therapy

Douglas Jennings, Pharm.D., AACC, BCPS (AQ-Cardiology)

Patient Case: CC

- CC: 68-year-old female patient who presents with 3 days of melena and dizziness
- PMH: HTN, DM, NSTEMI (6 weeks prior) with placement of DES to LAD (currently taking aspirin + ticagrelor)
- Objective: Hgb = 6.8 mg/dL, BP = 85/55, HR = 115
- Patient receives crystalloids and pRBC transfusion, and EGD is scheduled for next day.
- Would you transfuse platelets in this patient?

Would you transfuse platelets in this patient?

a. Yes
b. No
Platelet Transfusion: Ex-vivo Clopidogrel

Normalization of platelet reactivity in clopidogrel-treated subjects

Results
- Preoperative transfusion of 10 platelet concentrate units (the equivalent of 40% V-PRP) after a 300-mg clopidogrel loading or 12.5 units (50% V-PRP) after a 600-mg loading may adequately reverse clopidogrel-induced platelet disaggregation to facilitate postoperative hemostasis.
- An additional 2.5 units fully normalized platelet function.


Platelet Transfusion: Ex-vivo Prasugrel

Acute Coronary Syndromes

RESTORING PLATELET FUNCTION EX VIVO BY ADDING FRESH PLATELETS WITHIN 24 HOURS OF A PRASUGREL 60 mg LOADING DOSE

Results
- Concentrated platelets from untreated donors were added ex vivo to subject's blood after 2h, 6h, 12h and 24h, aimed at raising the blood platelet counts by 40%, 60% and 80%.
- Reactivity in all samples increased, sharpest increase from 2h to 6h.
- Full restoration of platelet function is not feasible within 24h even with substantial platelet infusions.


Platelet Transfusion: Ex-vivo Ticagrelor

Acute Coronary Syndromes

REVERSAL OF TICAGRELOR-INDUCED INHIBITION OF ADP-INDUCED PLATELET AGGREGATION BY THE ADDITION OF UNINHIBITED PLATELETS IN VITRO

Results
- When ADP-induced aggregation (control level 73%) was inhibited to different levels by ticagrelor, an “in vitro transfusion” of 40% reversed aggregation – 60% → 71% (p<0.01), 34% → 60% (p<0.05) and 6% → 16% (p<0.05).
- In vitro the platelet inhibition achieved by ticagrelor can be partly reversed by un-inhibited platelets.

Platelet Transfusion: *In-vivo Data*

**Predictors of Mortality in Trauma Patients With Intracranial Hemorrhage on Preinjury Aspirin or Clopidogrel**

**Results**
- Sixty-one patients = aspirin, 17 patients = clopidogrel, and 31 patients = both
- No platelets (69) versus platelets transfused in 1st 24 hr (40)
- Mortality ↑ if platelets given (28% vs 13% p = 0.064)


Platelet Transfusion: *In-vivo Data*

Platelet transfusion for reversal of dual antiplatelet therapy in patients requiring urgent surgery: a pilot study

**Results**
- 2 platelet pools transfused 1-2 hr preop
- 12/14 patients = uneventful course
- No postop transfusions required
- 1 patient had postop MI (supply/demand)


**Desmopressin**

- Stimulates vWF factor release
  - Ultralarge multimers → enhance platelet function
- Dose: 0.3-0.4 mcg/kg intravenously
  - Every 12 hours up to 6 doses, rapid onset
- Data limited, mostly with aspirin
  - Very small human and animal studies

Patient Case: CC

- CC: 68-year-old female patient who presents with 3 days of melena and dizziness
- PMH: HTN, DM, NSTEMI (6 weeks prior) with placement of DES to LAD (currently taking aspirin + ticagrelor)
- Objective: Hgb = 6.8 mg/dL, BP = 85/55, HR = 115
- Patient receives crystalloids and pRBC transfusion, and EGD is scheduled for next day.
- Would you transfuse platelets in this patient?

Would you transfuse platelets in this patient?

a. Yes
b. No
Key Takeaways

- Data regarding reversal of antiplatelet agents during acute bleeding are limited
- *Ex vivo* data suggests partial reversal may be possible
- No data *in vivo* to define clinical risk/benefit ratio

What’s Next?
Evolving Evidence and Applications for Antithrombotic Therapy in Cardiovascular Disease

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

Case Study: BJ

- BJ is a 66 year-old female with a PMH of HLD, DM, HF, CAD (s/p MI, PCI x 2 with DES placement 1 year ago) presenting to the hospital ED with a 2 hour history of chest squeezing and tightness
- **PE**
  - BP 115/72 mm Hg, HR 98 bpm; Ht 62 in, Wt 70 kg, afebrile
  - 5 cm JVD, lungs rales; regular S1, S2, +S3, -S4, no murmur
  - Abdomen obese, soft, with mild epigastric tenderness
  - Extremities 1+ pitting edema, pulses 1-2+ throughout
Case Study: BJ

- ECG: 2 mm ST depression, Leads V3-V6 with symmetrical T wave inversion
- CXR: heart failure
- Labs:
  - Hct 38, WBC 8.7, Plts 168K
  - Na 132, K 4.8
  - BUN 41, Scr 1.82 mg/dL
  - Glucose 162 mg/dL
  - Est CrCl 34 mL/min (CG)
  - CK-MB 6 (ULN <6)
  - TnT 6.70 (ULN <0.10)
  - LDL-C 90 mg/dL, HDL-C 38 mg/dL, TGs 157 mg/dL

Case Study: BJ

- Medications taken prior to admission
  - Aspirin 81 mg daily
  - Clopidogrel 75 mg daily
  - Glipizide XL 10 mg daily
  - Lisinopril 20 mg daily
  - Metoprolol 100 mg daily
  - Spironolactone 25 mg daily
  - Atorvastatin 20 mg daily
  - SL NTG 0.4 mg prn chest pain

Case Study: BJ

BJ is managed with an invasive strategy for her recurrent MI, recovers quickly, and is discharged home. She returns for follow-up with her cardiologist 1 week later. As the clinical pharmacist in the cardiology clinic, you are asked if there are any improvements that can be made in the antithrombotic regimen.
You recommend which of the following for BJ?

a. Aspirin 81 mg daily + prasugrel 10 mg daily
b. Aspirin 81 mg daily + clopidogrel 75 mg daily + vorapaxar 2.5 mg daily
c. Aspirin 81 mg daily + clopidogrel 75 mg daily + rivaroxaban 2.5 mg twice daily
d. Aspirin 81 mg daily + ticagrelor 90 mg twice daily

Vorapaxar

- Protease-activated receptor-1 (PAR-1) antagonist
- Indicated for reduction of CV events in patients with previous MI or PAD
- 1 tablet daily (2.08 mg)
- Boxed warning – do NOT use in history of stroke, TIA, ICH, or active bleeding
- CYP 3A4 metabolism – avoid strong inhibitors, inducers
- No adjustment for renal impairment
- Terminal elimination half-life (t½) = 8 days

TRACER – Trial Design

ACS Patients – received standard of care (DAPT)

Key inclusion criteria
- Within 24 hr of symptoms
- 1 biomarker or ECG changes
- 1 other high-risk feature

Follow-up: 1, 4, 8, 12 months, then every 6 months

Efficacy Endpoints
- Primary: CV death, MI, stroke, hospitalization for ischemia, urgent revascularization
- Key Secondary: CV death, MI, stroke
- Bleeding Endpoints: GUSTO moderate or severe and clinically significant TIMI bleeding

TRACER - Selected Efficacy Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=6471)</th>
<th>Vorapaxar (N=6473)</th>
<th>2-yr KM rate (%)</th>
<th>2-yr KM rate (%)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>19.9</td>
<td>18.5</td>
<td>0.92 (0.85–1.01)</td>
<td>0.072</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>3.8</td>
<td>3.8</td>
<td>1.00 (0.83–1.22)</td>
<td>0.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>12.5</td>
<td>11.1</td>
<td>0.88 (0.79–0.98)</td>
<td>0.021</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>2.1</td>
<td>1.9</td>
<td>0.93 (0.70–1.23)</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for ischemia</td>
<td>1.5</td>
<td>1.6</td>
<td>1.14 (0.83–1.58)</td>
<td>0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent revascularization</td>
<td>3.5</td>
<td>3.8</td>
<td>1.07 (0.88–1.31)</td>
<td>0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent thrombosis*</td>
<td>1.5</td>
<td>1.7</td>
<td>1.12 (0.78–1.62)</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6.1</td>
<td>6.8</td>
<td>1.95 (1.80–2.13)</td>
<td>0.52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ARC definite or probable; data are proportions of patients


TRACER - Bleeding Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=6441)</th>
<th>Vorapaxar (N=6446)</th>
<th>2-yr KM rate (%)</th>
<th>2-yr KM rate (%)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO moderate or severe</td>
<td>3.2</td>
<td>5.2</td>
<td>1.35 (1.16–1.58)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically significant TIMI</td>
<td>14.6</td>
<td>28.2</td>
<td>1.43 (1.31–1.57)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GUSTO severe</td>
<td>1.8</td>
<td>2.6</td>
<td>1.66 (1.27–2.16)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI major</td>
<td>2.5</td>
<td>4.0</td>
<td>1.53 (1.24–1.90)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>0.15</td>
<td>0.35</td>
<td>1.89 (0.80–4.45)</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.24</td>
<td>1.07</td>
<td>3.39 (1.78–6.45)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG-related TIMI major*</td>
<td>7.3</td>
<td>9.7</td>
<td>1.34 (0.92–1.96)</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are proportions of patients


TRACER

• January 8, 2011 DSMB recommend to stop trial prior to June 4 end date
  – No differences in efficacy
  – Increased risk of bleeding

• Recommended to terminate study drug in patients with history of stroke in TRA-2P trial

TRA 2P – TIMI 50: Trial Design

Stable atherosclerosis: History of MI, stroke, or PAD
Receiving standard of care

Placebo
Vorapaxar 2.5 mg daily

n=26,449

Primary Efficacy Endpoint: CV death, MI, stroke, recurrent ischemia leading to revascularization
Primary Bleeding Endpoint: GUSTO moderate or severe bleeding

Median treatment duration of 30 months
At 2 years, study halted in the ischemic stroke group due to increase in risk of ICH

Key exclusion criteria: planned revascularization, history of bleeding diathesis, recent abnormal bleeding, warfarin, hepatobiliary disease


TRA 2P – TIMI 50: Efficacy Results

All Patients

Event Rate (%)
CV Death, MI, Stroke, or Recurrent Ischemia Leading to Urgent Coronary Revascularization (UCR)

CV Death, MI, or Stroke
HV 0.87
(95% CI, 0.80 – 0.95)
p=0.001

CV death (%) 2.4 2.0 0.86 (0.73 – 0.93)
MI (%) 5.6 4.7 0.82 (0.73 – 0.93)
Stroke (%) 1.4 1.0 0.67 (0.52 – 0.87)
UCR (%) 2.8 2.5 0.88 (0.74 – 1.04)


Endpoints Placebo (n=10,090) Vorapaxar (n=10,080) Hazard Ratio (95% CI) p-value

1st Endpoint: CV death, MI, stroke, UCR (%)
10.6 8.9 0.83 (0.76 – 0.90) <0.001

CV death, MI, Stroke (%) 5.4 6.8 0.80 (0.73 – 0.89) <0.001
CV death (%) 2.4 2.0 0.86 (0.71 – 0.93)
MI (%) 5.6 4.7 0.82 (0.73 – 0.93)
Stroke (%) 1.4 1.0 0.67 (0.52 – 0.87)
UCR (%) 2.8 2.5 0.88 (0.74 – 1.04)

Zontivity (vorapaxar) prescribing information. May 2014.
TRA 2P – TIMI 50: Safety Results
Patients Without a History of Stroke or TIA

<table>
<thead>
<tr>
<th>GUSTO Bleeding (%)</th>
<th>Placebo</th>
<th>Vorapaxar</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>0.3</td>
<td>1.0</td>
<td>1.24 (0.92 – 1.66)</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>2.0</td>
<td>3.0</td>
<td>1.55 (1.30 – 1.86)</td>
</tr>
<tr>
<td>Any (severe/mod/nil)</td>
<td>17.6</td>
<td>25.0</td>
<td>1.52 (1.43 – 1.61)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0.1</td>
<td>0.2</td>
<td>1.15 (0.56 – 2.36)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.3</td>
<td>0.4</td>
<td>1.46 (0.92 – 2.31)</td>
</tr>
<tr>
<td>Clinically significant bleeding (TIMI)</td>
<td>9.5</td>
<td>13.4</td>
<td>1.47 (1.35 – 1.60)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>3.0</td>
<td>4.0</td>
<td>1.37 (1.18 – 1.59)</td>
</tr>
</tbody>
</table>

Zontivity (vorapaxar) prescribing information. May 2014.

ATLAS ACS 2 – TIMI 51
Background: Thrombin in ACS

- There is excess thrombin generation that persists for 6 months following an index ACS event.1
- Thrombin is the most potent stimulant of platelet aggregation.2
- Reduction of thrombin generation by warfarin reduces recurrent MI by 44% in a meta-analysis of 10 ACS trials.3
- Rivaroxaban is a direct factor Xa inhibitor which blocks initiation of the final common pathway leading to thrombin generation.
- Based upon safety and efficacy in Phase II, 5.0 mg bid and 2.5 mg bid doses of rivaroxaban were chosen for Phase III evaluation in ATLAS ACS 2 – TIMI 51.4


Design

Recent ACS: STEMI, NSTEMI, UA
Stabilized 1-7 Days Post-Index Event
Exclusions: increased bleeding risk, warfarin use, ICH, prior stroke if on ASA + thienopyridine

ASA 75 to 100 mg/day
Stratified by Thienopyridine Use at MD Discretion

Placebo
n=5178
Rivaroxaban
2.5 mg BID
n=5174
Rivaroxaban
5.0 mg BID
n=5176

PRIMARY ENDPOINTS
EFFICACY: CV Death, MI, Stroke (Ischemic, Hemorrhagic, or Uncertain Origin)
SAFETY: TIMI major bleeding not associated with CABG

Event-driven trial with 1002 primary efficacy events
Months After Randomization

ATLAS ACS 2 – TIMI 51 PRIMARY
Efficacy Endpoint: CV Death / MI / Stroke

Rivaroxaban (both doses)

HR 0.84
(0.74-0.96)

mITT p = 0.008
ITT p = 0.002

ARR 1.8%
NNT = 56

Estimated Cumulative Incidence (%)

Placebo

Rivaroxaban

ATLAS ACS 2 – TIMI 51 Stent Thrombosis:
ARC Definite / Probable / Possible

Rivaroxaban (both doses)

HR 0.69
(0.51-0.93)

mITT p = 0.016
ITT p = 0.008

ARC Definite/probable: HR=0.65, mITT p=0.017, ITT p=0.012

Estimated Cumulative Incidence (%)

Placebo

Rivaroxaban

ATLAS ACS 2 – TIMI 51 Efficacy Endpoints:
Low Dose Rivaroxaban 5.0 mg BID

CV Death / MI / Stroke

Rivaroxaban

5 mg BID

NNT=53

Cardiovascular Death

Rivaroxaban

5 mg BID

ATLAS ACS 2 – TIMI 51 Primary Efficacy Endpoint: Rivaroxaban 2.5 mg PO BID

CV Death / MI / Stroke

Cardiovascular Death

All Cause Death

Estimated Cumulative Incidence (%)

HR 0.84

mITT p<0.001

ITT p<0.001

ATLAS ACS 2 – TIMI 51 Efficacy Endpoints:

Very Low Dose Rivaroxaban 2.5 mg BID

 Patients Treated with ASA + Thienopyridine

CV Death / MI / Stroke

Cardiovascular Death

All Cause Death

Estimated Cumulative Incidence (%)

HR 0.85

mITT p=0.039

ITT p=0.011

HR 0.62

mITT p<0.001

ITT p<0.001

ATLAS ACS 2 – TIMI 51 Safety Endpoints

Treatment-Emergent Non-CABG TIMI Major Bleeding

Liver Function Test (ALT > 3xULN)

ALT > 3X ULN 1.6% 1.3% 1.4%

p=NS

p=NS

p=NS

There was no excess of either combined ALT > 3x ULN and Total Bilirubin > 2x ULN cases among patients treated with rivaroxaban, or SAEs.

Post-Treatment CVD / MI / Stroke

1-10 Days After Last Dose

1.8% 1.4% 2.2%

p=NS

p=NS
Triple Antithrombotic Therapy
Potential Options
Caution with Making These Types of Comparisons!! Not Scientifically Valid

- **Efficacy – CV Death, MI Stroke**
  - ASA/Clop/Vorapaxar: 10.5% vs 9.3% (HR 0.87 - 95% CI = 0.80 – 0.94) p<0.001
  - ASA/Clop/Rivaroxaban: 10.7% vs 9.1% (HR 0.84 - 95% CI = 0.72 – 0.97) p=0.02
  - ASA/Ticagrelor: 11.7% vs 9.8% (HR 0.84 - 95% CI = 0.77 – 0.92) p<0.001

- **Safety – Non CABG TIMI Major**
  - ASA/Clop/Vorapaxar: 1.8% vs 2.8% (HR 1.46 - 95% CI = 1.22 – 1.75) p<0.001
  - ASA/Clop/Rivaroxaban: 0.6% vs 2.1% (HR 3.96 - 95% CI = 2.46 – 6.38) p<0.001
  - ASA/Ticagrelor: 2.2% vs 2.8% (HR 1.25 - 95% CI = 1.03 – 1.53) p<0.025

Case Study: BJ

BJ is managed with an invasive strategy for her recurrent MI, recovers quickly, and is discharged home. She returns for follow-up with her cardiologist 1 week later. As the clinical pharmacist in the cardiology clinic, you are asked if there are any improvements that can be made in the antithrombotic regimen.
You recommend which of the following for BJ?

a. Aspirin 81 mg daily + prasugrel 10 mg daily
b. Aspirin 81 mg daily + clopidogrel 75 mg daily + vorapaxar 2.5 mg daily
c. Aspirin 81 mg daily + clopidogrel 75 mg daily + rivaroxaban 2.5 mg twice daily
d. Aspirin 81 mg daily + ticagrelor 90 mg twice daily
Biotransformation and Mode of Action

Clopidogrel, Prasugrel, and Ticagrelor

ATLAS ACS 2 – TIMI 51 PRIMARY
EFFICACY ENDPOINT: CV Death / MI / Stroke

Placebo
Rivaroxaban (both doses)

HR 0.84 (0.74-0.96)
mITT p = 0.008
ITT p = 0.002
ARR 1.8%
NNT = 56

No. at Risk
Placebo 5113 4307 3470 2664 1831 1079 421
Rivaroxaban 10229 8502 6753 5137 3554 2084 831

HR and 95% CI estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches. Mega JL et al. N Engl J Med. 2012; 366:9-19.
Self-assessment Questions

1. As shown in the TRITON TIMI-38 Trial, which of the following statements best describes the benefit of prasugrel compared with clopidogrel?
   a. Prasugrel produced significantly less cardiovascular death, MI, and stroke.
   b. Prasugrel produced significantly less major bleeding.
   c. The primary benefit of prasugrel was demonstrated in the first few days.
   d. The primary benefit of prasugrel was demonstrated after 60 days.

2. Which of the following characteristics is a potential advantage of using cangrelor instead of other antiplatelet therapies as bridging therapy in patients with acute coronary syndrome undergoing surgery?
   a. Availability of an oral dosage form.
   b. Rapid onset of action.
   c. Long duration of action.
   d. Irreversible binding to P2Y₁₂ receptors.

3. Using definitions from the 2010 consensus document by Bonello et al., determine which of the following laboratory test results would indicate high on-treatment platelet reactivity or clopidogrel nonresponsiveness.
   a. PRI 45% (platelet reactivity index) by vasodilator-stimulated phosphoprotein (VASP) phosphorylation.
   b. 348 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. 28% maximal ADP 5 μM-induced aggregation by light transmission aggregometry.

4. WP is a 69-year-old man with a past medical history of hyperlipidemia, diabetes mellitus, heart failure, and coronary artery disease who had an MI and percutaneous intervention with DES placement one year ago. He presents to the hospital emergency department with a 2-hour history of chest squeezing and tightness. Electrocardiogram shows 2 mm ST depression in leads V3-V6 with symmetrical T wave inversion. WP is managed with an invasive strategy for his recurrent MI, recovers quickly, and is discharged home. He returns for follow up with the cardiologist one week later. As the clinical pharmacist in the cardiology clinic, you and the cardiologist discuss options for improving WP’s antithrombotic regimen. All of the following antithrombotic regimens would be acceptable indicated options for WP EXCEPT
   a. Aspirin 81 mg daily plus prasugrel 10 mg daily.
   b. Aspirin 81 mg daily plus clopidogrel 75 mg daily plus vorapaxar 2.5 mg daily.
   c. Aspirin 81 mg daily plus clopidogrel 75 mg daily plus rivaroxaban 2.5 mg twice daily.
   d. Aspirin 81 mg daily plus ticagrelor 90 mg twice daily.

Answers

1. a  2. b  3. b  4. c
List of Abbreviations Used in Presentations

ACS acute coronary syndrome
ACUITY Acute Catheterization and Urgent Intervention Triage Strategy
ADP adenosine diphosphates
ALT alanine aminotransferase
APAP acetaminophen
ARC Academic Research Consortium
ARR absolute risk reduction
ARU aspirin reaction units
ASA aspirin
BID twice daily
BMS bare-metal stent
BP blood pressure
BUN blood urea nitrogen
CABG coronary artery bypass grafting
CAD coronary artery disease
CG Cockcroft-Gault
CI confidence interval
CK-MB creatine kinase MB
CP chest pain
CrCl creatinine clearance
CV cardiovascular
CVD cardiovascular disease
CXR chest xray
CYP cytochrome P
DAPT dual antiplatelet therapy
DES drug-eluting stent
DM diabetes mellitus
DSMB Data and Safety Monitoring Board
DST definite stent thrombosis
ECG electrocardiogram
GP glycoprotein
GUSTO Global Use of Strategies to Open Occluded Coronary Arteries
HDL-C high-density lipoprotein cholesterol
Hct hematocrit
HF heart failure
Hgb hemoglobin
HLD hyperlipidemia
HPI history of present illness
HR hazard ratio
HR heart rate
Overcoming Challenges in Acute Coronary Syndrome: Case Studies in ACS Management

HTN hypertension
5-HT 5-hydroxytryptophan
IABP intra-aortic balloon pump
ICH intracranial hemorrhage
ITT intent-to-treat
IV intravenous
JVD jugular venous distention
KM Kaplan-Meier
LAD left anterior descending
LD loading dose
LDL-C low-density lipoprotein cholesterol
LTA light transmission aggregometry
MACE major adverse coronary event
MD maintenance dose
MI myocardial infarction
mITT modified intent-to-treat
MPTA medications prior to admission
NNH number needed to harm
NNT number needed to treat
NR nonresponsive
NSTE non-ST-segment elevation
NSTEMI non-ST-segment elevation myocardial infarction
NTG nitroglycerin
OA osteoarthritis
OR odds ratio
PAD peripheral arterial disease
PAR protease-activated receptor
PCI percutaneous coronary intervention
Plts platelets
PMH past medical history
PPI proton pump inhibitor
PR platelet reactivity
PRBC packed red blood cell
PRI platelet reactivity index
PRU P2Y12 reaction units
qd daily
R responsive
RRR relative risk reduction
SL sublingual
ST stent thrombosis
STEMI ST-segment elevation myocardial infarction
TEG thromboelastogram
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>TG</td>
<td>triglyceride</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>TIMI</td>
<td>Thrombolysis in Myocardial Infarction</td>
</tr>
<tr>
<td>TnT</td>
<td>troponin T</td>
</tr>
<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>UCR</td>
<td>urgent coronary revascularization</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>UTVR</td>
<td>urgent target vessel revascularization</td>
</tr>
<tr>
<td>VASP</td>
<td>vasodilator-stimulated phosphoprotein</td>
</tr>
<tr>
<td>V-PRP</td>
<td>volunteers-platelet rich plasma</td>
</tr>
<tr>
<td>vWF</td>
<td>von Willebrand factor</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
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