Ask the Expert:
Practice Pearls for Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

Presented as a Live Webinar
Wednesday, March 2, 2011

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

How do I register?
Go to http://www.ashpadvantagmedia.com/optimize/webinar/ and click on the “Register” button. You will be e-mailed computer and audio information.

What is a live webinar?
A live webinar brings the presentation to you – at your desk, in your home, through a staff inservice program. You listen to the presentation in “real time” as you watch the slides on the screen. You will have the opportunity to ask the speaker questions at the end of the program. Please join the conference at least 5 minutes before the scheduled start time for important program announcements.

How do I process my continuing education credit?
After completion of the live webinar, you will process your CE online and print your statement of credit at the ASHP Learning Center found at http://ce.ashp.org. To process your CE, you will need the Activity and Session Codes that will be announced at the end of the webinar. Complete CE processing instructions are available on the last page of this handout.

If you have questions about processing your CE online, please contact ASHP Advantage at support@ashpadvantage.com.

What do I need in order to participate in the webinar?
1. Computer with internet access and basic system requirements. When you register, the webinar system will assess your system to ensure compatibility.
2. Telephone to dial the toll-free number and listen to the presentation (if you choose not to use Voice Over IP [VoIP] via your computer).

Webinar System Requirements
PC-based attendees
Required: Windows® 7, Vista, XP, 2003 Server or 2000

Macintosh®-based attendees
Required: Mac OS® X 10.4.11 (Tiger®) or newer

What if I would like to arrange for my colleagues to participate in this webinar as a group?
One person serving as the group coordinator should register for the webinar. That group coordinator will receive an e-mail confirmation with instructions for joining the webinar. A few minutes before the webinar begins, the group coordinator should launch the webinar link. Once the webinar has been activated, the coordinator will have the option to open the audio via VoIP (Voice Over IP) on the webinar toolbar or use a touch tone phone with the provided dial-in information. At the conclusion of the activity, the group coordinator will complete a brief online evaluation and report the number of participants at that site. Each participant will process his or her individual continuing education statement online at the ASHP Learning Center.

How do I ask a question of the presenter?
Follow the instructions provided at the beginning of the activity for submitting text questions using the webinar tool. The speaker will answer as many questions as possible at the conclusion of the activity.
Ask the Expert: Practice Pearls for Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

Faculty

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

In accordance with the Accreditation Council for Continuing Medical Education’s Standards for Commercial Support and the Accreditation Council for Pharmacy Education’s Guidelines for Standards for Commercial Support, ASHP Advantage requires that all individuals who have control in planning or presenting educational content disclose all relevant financial relationships with any commercial interest. This includes faculty, teachers, authors, activity directors, and members of planning committees. An individual has a relevant financial relationship if the individual or his or her spouse/partner has a financial relationship in any amount occurring in the last 12 months with a commercial interest whose products or services are discussed in the educational activity content over which the individual has control. Relevant financial relationships will be disclosed to the activity audience.

All faculty and planners for ASHP Advantage education activities are qualified and selected by ASHP Advantage and required to disclose any relevant financial relationships with commercial interests. ASHP Advantage identifies and resolves conflicts of interest prior to an individual’s participation in development of content for an educational activity.

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.

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

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

**Susan R. Dombrowski, M.S., B.S.Pharm.**

Ms. Dombrowski declares that she has no relationships pertinent to this activity.
Ask the Expert: Practice Pearls for Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

Continuing Education Accreditation

Accreditation for Pharmacists

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. The activity provides 1 hour (0.1 CEU) of continuing pharmacy education credit (ACPE activity # 204-000-11-571-L01P).

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

Complete instructions for processing CPE can be found on the last page of this handout.

Methods and Format

This is a live online activity consisting of audio, online presentation slides, and an activity evaluation tool. Participants must participate in the entire presentation and complete the course evaluation to receive continuing pharmacy education credit. Participants may print their official statements of continuing pharmacy education credit immediately. This activity is provided free of charge.

Target Audience

This continuing pharmacy education activity was planned to meet the needs of pharmacists in a variety of practice settings, including large and small health systems, outpatient clinics, managed-care organizations, long-term care facilities, and academia. This activity would be especially beneficial for pharmacists, clinical specialists, managers, leaders, and educators who are interested in cardiology, new drug therapies, and improving the care of patients with acute coronary syndrome.
Ask the Expert: Practice Pearls for Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

Activity Overview

This activity will focus on current questions and controversies related to optimizing oral antiplatelet therapy in patients with acute coronary syndrome (ACS). During this live webinar, the faculty will address these questions and provide practice pearls for pharmacists.

Time for questions and answers will be provided at the end of the presentation.

Activity Learning Objectives

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

- Identify at least one current therapeutic issue related to the use of clopidogrel compared with other new or emerging oral antiplatelet therapies in acute coronary syndrome.
- Describe a therapeutic strategy for patients taking clopidogrel and a proton pump inhibitor.
- Outline factors to consider when evaluating the use of platelet testing or genetic testing in patients with acute coronary syndrome receiving oral antiplatelet therapy.

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- On-demand activity: Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome (2 hr CPE)
- Interviews with faculty
- e-Newsletters
- Opportunity to sign up for email updates and refer a colleague to the educational initiative
Ask the Expert:
Practice Pearls for Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome

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Acute Coronary Syndrome

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

Medical Therapy  PCI +/- Stent  Fibrinolysis

Clopidogrel in ACS
- NSTE ACS
  - CURE (n=12,562)
    - 300/75 mg vs. placebo within 24 hr of symptom onset
    - Significant reductions in death, MI, and stroke
  - PCI-CURE (n=2658)
    - 31% Relative risk reduction (RRR) in CV death or MI
  - CREDO (n=2116)
    - 300/75 mg vs. placebo 3-24 hr before PCI, 75 mg vs. placebo after 2 days
    - 27% RRR in MI/stroke/death at 1 year
    - 18.5% RRR in MI, death, UTVR
  - COMMIT (n=45,852)
    - 300/75 mg vs. placebo 3-24 hr before PCI, 75 mg vs. placebo after 28 days
    - 27% RRR in MI/stroke/death at 1 year
    - 18.5% RRR in MI, death, UTVR
  - 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 hr
      - Clopidogrel 300/75 mg
      - Placebo
    - Significant reductions in occluded vessel, death, MI by angiography and up to 30 days
  - COMMIT (n=45,852)
    - Patients within 24 hr of suspected MI
      - Clopidogrel 75 mg
      - Placebo
      - 9% Reduction in death/MI/stroke over treatment period

Clinical Issues with Clopidogrel
- Variability of platelet inhibition
  - 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 enzyme conversion steps
  - CYP2C19 loss-of-function alleles
    - Heterozygous vs. homozygous
    - Connection of clinical outcomes debated
- Drug interactions with PPIs

Current and Future Antiplatelet Agents

Enlarged slide on page 15

Biotransformation and Mode of Action
Clopidogrel, Prasugrel, and Ticagrelor


Distribution of Responsiveness to Clopidogrel in 544 Individuals
A Normal Distribution: Consistent with a Poly-Genetic and Poly-Environmental Influence


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


Clopidogrel Nonresponsiveness and On-Treatment Platelet Reactivity

Where are we now?
- 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

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

PRU ≥ 230?
Nonresponder
Responder

n=1109
n=586
n=1105

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

GRAVITAS Trial Results

- **High PR - High Dose**
  - 12%
- **High PR - Standard Dose**
  - 10%
- **Normal PR - Standard Dose**
  - 8%

*p = 0.18

CV Death/MI/ST | GUSTO Severe/Mod Bleeding | Any GUSTO Bleeding
---|---|---
PR = platelet reactivity


GRAVITAS Results

CV Events and Post-PCI PRU

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


**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/day</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/day</td>
</tr>
<tr>
<td>TRIGGER-PCI</td>
<td>2150</td>
<td>PCI</td>
<td>CV death, MI</td>
<td>600 mg LD, 75 mg/day vs. prasugrel 60 mg LD, 10 mg/day</td>
</tr>
</tbody>
</table>

**Changes to the Clopidogrel (Plavix®) Product Label**

*August 2010 Update*

**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]). Patients as recommended doses forms less of the metabolite and has a smaller effect on platelet function. Patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndromes 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 [12.5]). Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers (see Dosage and Administration [2.3]).

**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.”


**Amish Pharmacogenomics of AntiPlatelet Intervention (PAPI) Study**

- Genome-wide association study (n=429)
  - Clopidogrel 300 mg LD, then 75 mg x 7 days, healthy participants
  - Several relative pairs for estimating heritabilities
  - LTA with ADP 20 μmol/L and AA 1.6 mmol/L
  - Genotyping for diminished clopidogrel response
- Sinai Hospital of Baltimore study (n=227)
  - Patients with elective PCI receiving clopidogrel
  - Platelet reactivity and genotyping
  - Outcomes at 12 months
- Results with CYP2C19*
  - Diminished platelet response to clopidogrel
  - More CV events (20.9% vs. 10%)
  - CYP2C19 status accounts for only 12% of variation

Shuldiner AR et al. JAMA. 2009; 302:849-57
TRITON TIMI-38
ACS (STEMI or UA/NSTEMI) and planned PCI

CLOPIDOGREL
300 mg LD, 75 mg MD
n = 13,608

Median duration of therapy – 14.7 months

PRASUGREL
60 mg LD, 10 mg MD

1st endpoint: CV death, MI, stroke
2nd 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
Net Clinical Benefit by Subgroup
Prasugrel vs. Clopidogrel by Subgroup

Prior stroke or TIA
HR 1.54 (1.02 – 2.32); p=0.04 3.8%
≥ 75 Years of age
HR 0.99 (0.81 – 1.21); p=0.92 16%
Weight ≤ 60 kg
HR 1.03 (0.69 – 1.53); p=0.89 8%

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


PLATO Study Design

PLATO Trial: Results
CV Death + MI + Stroke


PLATO Results – Major Bleeding
Non-CABG and CABG Related

### PLATO Efficacy Endpoints

**U.S. vs. Non-U.S.**

<table>
<thead>
<tr>
<th>Clinical Endpoint</th>
<th>Region</th>
<th>Ticagrelor (n=9333)</th>
<th>Clopidogrel (n=9291)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, stroke</td>
<td>U.S.</td>
<td>11.9%</td>
<td>9.5%</td>
<td>1.27 (0.92-1.75)</td>
</tr>
<tr>
<td></td>
<td>Non-U.S.</td>
<td>9.0%</td>
<td>11.0%</td>
<td>0.81 (0.74-0.89)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>U.S.</td>
<td>4.0%</td>
<td>3.4%</td>
<td>1.17 (0.68-2.01)</td>
</tr>
<tr>
<td></td>
<td>Non-U.S.</td>
<td>4.3%</td>
<td>5.6%</td>
<td>0.77 (0.67-0.89)</td>
</tr>
<tr>
<td>CV death</td>
<td>U.S.</td>
<td>3.4%</td>
<td>2.7%</td>
<td>1.26 (0.69-2.31)</td>
</tr>
<tr>
<td></td>
<td>Non-U.S.</td>
<td>3.8%</td>
<td>4.9%</td>
<td>0.77 (0.70-0.90)</td>
</tr>
<tr>
<td>MI</td>
<td>U.S.</td>
<td>9.1%</td>
<td>6.7%</td>
<td>1.38 (0.95-2.01)</td>
</tr>
<tr>
<td></td>
<td>Non-U.S.</td>
<td>5.1%</td>
<td>6.4%</td>
<td>0.80 (0.70-0.90)</td>
</tr>
<tr>
<td>Stroke</td>
<td>U.S.</td>
<td>1.0%</td>
<td>0.6%</td>
<td>1.75 (0.51-5.97)</td>
</tr>
<tr>
<td></td>
<td>Non-U.S.</td>
<td>1.4%</td>
<td>1.2%</td>
<td>1.15 (0.88-1.50)</td>
</tr>
</tbody>
</table>

AstraZeneca. Presented at FDA Cardiovascular and Renal Drugs Advisory Committee meeting, July 28, 2010 (URL in ref list).

### PLATO Patients by Geography

<table>
<thead>
<tr>
<th>Factor</th>
<th>U.S.</th>
<th>Non-U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (median)</td>
<td>87 kg</td>
<td>80 kg</td>
</tr>
<tr>
<td>Diabetes</td>
<td>33%</td>
<td>24%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>27%</td>
<td>20%</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>29%</td>
<td>12%</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>17%</td>
<td>5%</td>
</tr>
<tr>
<td>STEMI</td>
<td>16%</td>
<td>40%</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>67%</td>
<td>41%</td>
</tr>
<tr>
<td>UA</td>
<td>10%</td>
<td>17%</td>
</tr>
<tr>
<td>≥ 12 index event to study drug</td>
<td>63%</td>
<td>46%</td>
</tr>
<tr>
<td>Planned invasive management</td>
<td>94%</td>
<td>70%</td>
</tr>
<tr>
<td>PCI &lt; 24 hr after randomization</td>
<td>62%</td>
<td>50%</td>
</tr>
<tr>
<td>PCI with drug eluting stent</td>
<td>46%</td>
<td>19%</td>
</tr>
<tr>
<td>PCI with bare metal stent</td>
<td>23%</td>
<td>46%</td>
</tr>
<tr>
<td>Aspirin dose (mg)</td>
<td>Median 325</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Mean   217</td>
<td>99</td>
</tr>
<tr>
<td>Compliance</td>
<td>88%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Fiorentino RP. NDA 22-433 Brilinta® (ticagrelor) efficacy review. Presented at FDA Cardio-Renal Advisory Committee meeting, July 28, 2010 (URL in ref list).

### Ticagrelor PLATO Trial

**The “U.S. Paradox”**

- “Play of chance”
- Different patients
- Aspirin interaction

### Biotransformation of Clopidogrel

OCLA Study

- Patients undergoing elective PCI with stenting (n=140)
  - ASA plus clopidogrel 300 mg LD, 75 mg/day
  - Randomized
    - Placebo x 7 days
    - Omeprazole 20 mg/day 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

- Population-based case-control study (n=13,636)
  - AMI patients on clopidogrel for re-admission of AMI
    - Current use of PPI: OR 1.27 (1.03 – 1.57)
    - Pantoprazole: OR 1.02 (0.70 – 1.47)
    - Other PPIs: OR 1.40 (1.10 – 1.77)
- Retrospective cohort study (n=8205)
  - ACS patients on clopidogrel evaluating for all-cause mortality and ACS rehospitalization
    - 64% of patients on a PPI with clopidogrel (59.7% omeprazole)
    - Primary outcome: OR 1.25 (1.11 – 1.41)
    - ACS hospitalization: OR 1.86 (1.57 – 2.20)
    - Death: OR 0.91 (0.80 – 1.05)

Ho PM et al. JAMA. 2009; 301:937-44.

Clopidogrel (Plavix®) PI
March 2010 Update

2.4 Use with Proton Pump Inhibitors (PPI)
Omeprazole, a moderate CYP2C19 inhibitor, reduces the pharmacological activity of Plavix. Avoid using omeprazole concomitantly or 12 hours apart with Plavix. Consider using another acid-reducing agent with less CYP2C19 activity. A higher dose regimen of clopidogrel concomitantly administered with omeprazole increases antplatelet response; an appropriate dose regimen has not been established

5.1 Diminished Antiplatelet Activity Due to Impaired CYP2C19 Function
Omeprazole, a moderate CYP2C19 inhibitor, has been shown to reduce the pharmacological activity of Plavix if given concomitantly or if given 12 hours apart. Consider using another acid-reducing agent with less CYP2C19 inhibitory activity. Pantoprazole, a weak CYP2C19 inhibitor, had less effect on the pharmacological activity of Plavix than omeprazole

Plavix prescribing information. 2011 Feb (URL in ref list).

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


Survival Curves for PPI Treated vs. Placebo Composite Cardiovascular Events

Total enrollment: n=3627

- Placebo: 67 events, 1821 at risk
- Treated: 69 events, 1806 at risk

HR = 1.02
95% CI 0.70 to 1.51


Clopidogrel and Proton Pump Inhibitor Interaction

- TRITON-TIMI 38 Trial (n=13,608)
  - Primary endpoint: CV Death, MI, or Stroke
  - 33% on PPI
  - Prasugrel: HR 0.99 (0.83 – 1.19)
  - PPI use did not impact
    - Primary endpoint
    - MI
    - Stent thrombosis

Clopidogrel and Proton Pump Inhibitor Interaction

TRITON-TIMI 38 Trial

<table>
<thead>
<tr>
<th>Clopidogrel</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI or stroke</td>
<td>CV death, MI or stroke</td>
</tr>
<tr>
<td>On-demand (n=505)</td>
<td>0.95 (0.75-1.20)</td>
</tr>
<tr>
<td>Prandial (n=1538)</td>
<td>0.97 (0.75-1.26)</td>
</tr>
<tr>
<td>Enteric (n=1530)</td>
<td>1.14 (0.82-1.61)</td>
</tr>
<tr>
<td>Lansoprazole (n=488)</td>
<td>1.06 (0.75-1.49)</td>
</tr>
</tbody>
</table>


PPIs Associated with CV Risk Independent of Clopidogrel Use

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time-Dependent Cox Proportional Hazards Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Receiving a PPI but Not Clopidogrel</td>
<td>Patients Receiving a PPI and Clopidogrel</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Cardiovascular death, MI, or stroke</td>
<td>1.29 (0.97-1.73)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>1.58 (1.48-1.69)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1.49 (1.38-1.61)</td>
</tr>
<tr>
<td>MI</td>
<td>1.11 (1.03-1.20)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.33 (1.17-1.50)</td>
</tr>
</tbody>
</table>


FAST-MI Registry

In-hospital Events

<table>
<thead>
<tr>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
</tr>
<tr>
<td>No PPI (n=900)</td>
</tr>
<tr>
<td>PPI (n=1453)</td>
</tr>
</tbody>
</table>

p=0.43


FAST-MI Registry

In-hospital Death, MI, or Stroke

<table>
<thead>
<tr>
<th>% of Patients</th>
</tr>
</thead>
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<td>No PPI (n=900)</td>
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<tr>
<td>Omeprazole (n=982)</td>
</tr>
<tr>
<td>Esomeprazole (n=311)</td>
</tr>
<tr>
<td>Lansoprazole (n=185)</td>
</tr>
<tr>
<td>Pantoprazole (n=99)</td>
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</table>

p=NS for all comparisons

p=NS for all comparisons


FAST-MI Registry

One Year Death, MI, or Stroke

<table>
<thead>
<tr>
<th>% of Patients</th>
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<tbody>
<tr>
<td>No PPI (n=679)</td>
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<tr>
<td>Omeprazole (n=627)</td>
</tr>
<tr>
<td>Esomeprazole (n=258)</td>
</tr>
<tr>
<td>Lansoprazole (n=37)</td>
</tr>
<tr>
<td>Pantoprazole (n=78)</td>
</tr>
</tbody>
</table>

p=NS for all comparisons

p=NS for all comparisons


Clopidogrel / PPI Drug Interaction

What do we know?

- PK/PD evidence supports an interaction between clopidogrel and PPIs
- However, significant effects with platelet function tests have not always correlated with clinical outcomes
- Evidence for clinical relevance is conflicting and not yet convincing
- Retrospective studies limited by general increased CV risk
- More recent prospective studies and registries do not support a clinically meaningful interaction
Clopidogrel / PPI Drug Interaction

What do we do?
• Regardless of scientific evidence, FDA label leaves little room for alternative interpretations
  – Avoid omeprazole specifically, or
  – Increase clopidogrel to 150 mg daily (?), or
  – Validate platelet inhibition with platelet function testing, or
  – Use prasugrel or ticagrelor

Role of Platelet Function Testing and Genetic Testing with Clopidogrel

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

Role of Platelet Function Testing and Genetic Testing with Clopidogrel

Scenario #1
  – Everyone gets standard-dose clopidogrel

Scenario #2
  – Everyone gets double-dose clopidogrel unless high-risk of bleeding
  – Those get standard-dose clopidogrel

Scenario #3
  – High-risk patients get prasugrel (or ticagrelor if approved)
    • Diabetes mellitus
    • STEMI
  – All other patients get clopidogrel

Scenario #4
  – High-risk patients get double-dose clopidogrel
  – All other patients get standard-dose clopidogrel

Scenario #5
  – Everyone gets prasugrel (or ticagrelor if approved)
    except for those with contraindications or at high-risk of bleeding
    • History of TIA or stroke
    • Age ≥ 75 years of age
    • Weight ≤ 60 kg
    • Non-ticagrelor patients? (asthma, gout, bradycardia, based on aspirin dose)
  – Those patients get standard-dose clopidogrel

Scenario #6 – Use of testing
  – Patients found to have high on-treatment platelet reactivity or a CYP2C19 polymorphism
    • These patients receive an alternative management strategy
    • Need to know BEFORE testing what that will be
  – Everyone with “normal” results receives standard-dose clopidogrel

What will it take for Scenario #6 to become the dominant strategy?
  – Clopidogrel goes generic in May 2012
  – Multiple generics available in December 2012
  – Definitive study on effective treatment plan in patients with high on-treatment platelet reactivity or in patients with a CYP2C19 polymorphism
  – Clinicians get tired of witnessing events in patients on clopidogrel
Learning Objectives

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

• Identify at least one current therapeutic issue related to the use of clopidogrel compared with other new or emerging oral antiplatelet therapies in acute coronary syndrome (ACS).

• Describe a therapeutic strategy for patients taking clopidogrel and a proton pump inhibitor.

• Outline factors to consider when evaluating the use of platelet testing or genetic testing in patients with ACS receiving oral antiplatelet therapy.
Current and Future Antiplatelet Agents


Biotransformation and Mode of Action
Clopidogrel, Prasugrel, and Ticagrelor

**Biotransformation of Clopidogrel**


**Clopidogrel and Proton Pump Inhibitor Interaction**  
**TRITON-TIMI 38 Trial**

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel CV death, MI, or stroke</th>
<th>Prasugrel CV death, MI, or stroke</th>
<th>MI</th>
<th>MI</th>
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<tbody>
<tr>
<td>Omeprazole (n=1675)</td>
<td>0.91 (0.72-1.15)</td>
<td>0.95 (0.73-1.23)</td>
<td>1.04 (0.81-1.34)</td>
<td>1.02 (0.76-1.36)</td>
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<tr>
<td>Pantoprazole (n=1844)</td>
<td>0.94 (0.74-1.18)</td>
<td>0.97 (0.75-1.24)</td>
<td>1.09 (0.86-1.39)</td>
<td>1.09 (0.83-1.43)</td>
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<tr>
<td>Esomeprazole (n=613)</td>
<td>1.07 (0.75-1.52)</td>
<td>1.18 (0.81-1.73)</td>
<td>0.86 (0.55-1.33)</td>
<td>0.92 (0.57-1.48)</td>
</tr>
<tr>
<td>Lansoprazole (n=441)</td>
<td>1.00 (0.63-1.59)</td>
<td>0.86 (0.51-1.46)</td>
<td>0.98 (0.61-1.57)</td>
<td>1.08 (0.66-1.79)</td>
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</tbody>
</table>

CV = cardiovascular, MI = myocardial infarction. Rabeprazole is not included in the table because only 66 patients were taking it at randomisation.

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>
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<tr>
<th>Outcome</th>
<th>Time-Dependent Cox Proportional Hazards Model</th>
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<tr>
<td></td>
<td>Patients Receiving a PPI but Not Clopidogrel</td>
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<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
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<tr>
<td>Cardiovascular death, MI, or stroke</td>
<td>1.29 (1.21–1.37)</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>
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<tr>
<td>MI</td>
<td>1.13 (1.02–1.26)</td>
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<tr>
<td>Stroke</td>
<td>1.32 (1.17–1.49)</td>
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</table>

Selected References


Self-Assessment Questions

1. All of the following statements characterize a current clinical issue with clopidogrel EXCEPT
   a. Inconsistent antiplatelet response with clopidogrel.
   b. Drug interaction with proton pump inhibitors.
   c. Variability in oral absorption.
   d. Genetic polymorphisms in metabolism.

2. WT is a 62-year-old man (90 kg, 5’9”) being discharged from the hospital after receiving a stent for a myocardial infarction. He also has a history of hypertension, diabetes mellitus type 2, and gastroesophageal reflux disease. You notice that he is being discharged on clopidogrel 75 mg daily and omeprazole 40 mg daily. Which of the following best represents the appropriate action(s) to take?
   a. Reduce the dose of omeprazole to 20 mg daily.
   b. Discontinue omeprazole and start pantoprazole.
   c. Discontinue clopidogrel and start prasugrel.
   d. Either discontinue omeprazole and start pantoprazole, or discontinue clopidogrel and start prasugrel.
   e. Either reduce the dose of omeprazole to 20 mg daily, or discontinue omeprazole and start pantoprazole.

3. Platelet function testing for patients on clopidogrel will give you which of the following information?
   a. Which patients have a loss-of-function CYP2C19 allele.
   b. Which patients are going to have another ischemic event.
   c. Which patients are going to have a bleeding event.
   d. Which patients would not have ischemic events on prasugrel.
   e. Which patients have a reduced antiplatelet response.

Answers

1. c
2. d
3. e
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AA</td>
<td>arachidonic acid</td>
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<tr>
<td>ACCF</td>
<td>American College of Cardiology Foundation</td>
</tr>
<tr>
<td>ACG</td>
<td>American College of Gastroenterology</td>
</tr>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>ADP</td>
<td>adenosine diphosphate, endogenous activator of the P2Y$_{12}$ receptor on platelets</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<tr>
<td>AMI</td>
<td>acute myocardial infarction</td>
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<td>ARC</td>
<td>Academic Research Consortium</td>
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<td>ASA</td>
<td>aspirin</td>
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<tr>
<td>Ca</td>
<td>calcium</td>
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<td>CABG</td>
<td>coronary artery bypass grafting</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<td>COX</td>
<td>cyclooxygenase</td>
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<td>CV</td>
<td>cardiovascular</td>
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<td>CYP</td>
<td>cytochrome P</td>
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<tr>
<td>DES</td>
<td>drug-eluting stent</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>5-HT2A</td>
<td>5-hydroxy tryptamine 2A</td>
</tr>
<tr>
<td>GERD</td>
<td>gastroesophageal reflux disease</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
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<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>HR</td>
<td>hazard ratio</td>
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<tr>
<td>LD</td>
<td>loading dose</td>
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<tr>
<td>LTA</td>
<td>light transmission aggregometry</td>
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<tr>
<td>MACE</td>
<td>major adverse coronary event</td>
</tr>
<tr>
<td>MD</td>
<td>physician</td>
</tr>
<tr>
<td>MD</td>
<td>maintenance dose</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</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>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>NSTE</td>
<td>non-ST-segment elevation</td>
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<tr>
<td>NSTEMI</td>
<td>non-ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>PAR-1</td>
<td>protease-activated receptor 1</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
</tr>
<tr>
<td>PI</td>
<td>prescribing information</td>
</tr>
<tr>
<td>PK/PD</td>
<td>pharmacokinetics and pharmacodynamics</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 P2Y&lt;sub&gt;12&lt;/sub&gt; receptor antagonists)</td>
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<tr>
<td>PRU</td>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; reaction units (unit of measure for VerifyNow P2Y&lt;sub&gt;12&lt;/sub&gt; test)</td>
</tr>
<tr>
<td>RRR</td>
<td>relative risk reduction</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>
<tr>
<td>TxA&lt;sub&gt;2&lt;/sub&gt;</td>
<td>thromboxane A&lt;sub&gt;2&lt;/sub&gt;</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 P2Y&lt;sub&gt;12&lt;/sub&gt; receptor activation in platelets</td>
</tr>
<tr>
<td>VASP-PRI</td>
<td>vasodilator-stimulated phosphoprotein platelet reactivity index</td>
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<tr>
<td>vWF</td>
<td>von Willebrand factor</td>
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Instructions for Processing Continuing Education (CE)

To obtain CE statements for live symposia, webinars, or webcasts, please visit the ASHP Learning Center at [http://ce.ashp.org](http://ce.ashp.org).

1. Select **Process Meeting CE** from bottom left. Log in to the ASHP Learning Center using your e-mail address and password.

2. **If you have not logged in to the new ASHP Learning Center (launched August 2008) and are not a member of ASHP**, you will need to create a free account by clicking on **Register** at the bottom of the **Register as a New User** panel.

3. Once logged in to the site, click on **Process Meeting CE**.

4. 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 and Session Codes** are announced at the end of the activity. Click **Submit** when prompted and then click on the **Start** link to the right of the activity title.

5. Enter the session code, which starts with the letter “A” and was announced during the activity, and select the number of hours equal to your participation in the activity. Participants should only claim credit for the amount of time they participate in an activity.

6. Click **Submit** to receive the attestation page.

7. Confirm your participation and click **Submit**.

8. Print and/or save your CE statement as appropriate.

9. Complete activity evaluation by selecting the **My Account** tab and continue to **My Transcript**.

10. Select the applicable year from the drop down menu and locate the activity.

11. Click **Complete Evaluation** under the **Status** column to be taken to the evaluation page.

12. Complete all evaluation questions and click **Finish**.

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<th>Session Code (announced during the live activity)</th>
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