Balancing Ischemic and Bleeding Risk with Oral Antiplatelet Therapies in Acute Coronary Syndromes

Cardiology Updates
April 30, 2013
Anaheim, California

Faculty:
Jeffrey L. Anderson, MD
Jeffrey S. Berger, MD, MS
Session 4: Balancing Ischemic and Bleeding Risk with Oral Antiplatelet Therapies in Acute Coronary Syndromes

Learning Objectives

1. Explain the fundamental pharmacokinetics, pharmacodynamics, and pharmacogenetics of oral antiplatelet therapies.
2. Describe similarities and differences in efficacy of antiplatelet therapies in reducing ischemic events in ACS patients.
3. Discuss similarities and differences in safety profiles of antiplatelet therapies with a focus on bleeding risk.
4. Describe the roles for, and prudent use of, clopidogrel, prasugrel, and ticagrelor in management of ACS patients.

Faculty

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

Jeffrey L. Anderson, MD, graduated with honors from Harvard Medical School, after receiving his baccalaureate degree magna cum laude in chemistry at the University of Utah. He completed a postdoctoral fellowship in cardiology at Stanford University and joined the faculty at the University of Utah after two years at the University of Michigan. He currently serves as associate chief of cardiology, director of cardiovascular research, and vice-chair for medical research, department of medicine, Intermountain Medical Center, and is professor of internal medicine at the University of Utah School of Medicine. He is a fellow of the American College of Cardiology and the American Heart Association’s Clinical Council and master of the American College of Physicians. Dr Anderson has contributed to cardiovascular research over a broad area, including antithrombotic therapy of acute myocardial infarction and unstable angina, primary and secondary prevention of coronary heart disease, antiarrhythmic therapy, trials in congestive heart failure, and, currently, research on genetics, pharmacogenetics, and biomarker and imaging new risk factors for cardiovascular disease and prevention. He is an author or co-author on more than 600 original or invited publications and 460 abstracts. In addition, Dr Anderson has served as a reviewer or editorial board member of 15 peer-reviewed journals and online information resources for professionals. He also has served on and chaired the Food and Drug Administration’s Advisory Committee on Cardiorenal Drugs and on several guidelines committees (including the 2011 American College of Cardiology Foundation/American Heart Association [ACCF/AHA] Focused Update of the Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction) and volunteer leadership positions for ACCF/AHA.
Jeffrey S. Berger, MD, MS, is assistant professor of medicine and surgery in the divisions of cardiology, hematology, and vascular surgery and director of cardiovascular thrombosis at the New York University School of Medicine. Dr Berger completed a fellowship in vascular medicine and thrombosis and hemostasis at the University of Pennsylvania, and cardiology training at Duke University. He served his residencies at Beth Israel Medical Center, and completed his MS in clinical research at the Albert Einstein College of Medicine. Dr Berger was a recipient of the American Heart Association (AHA) Fellow to Faculty Award, the Doris Duke Foundation’s Clinical Scientist Development Award, and the AHA National Clinical Research Award for his studies on platelet activity in cardiovascular disease, and received a grant from the Center for AIDS Research on platelet activity and inflammation in HIV. Dr Berger has a particular interest in the field of platelet and hypercoagulable mechanisms of cardiovascular disease, with research interests that include: the role of platelet activity in patients with different high risk vascular phenotypes; platelet activity and antiplatelet therapy in the perioperative period; the clinical and platelet response to antiplatelet and antithrombotic therapeutics; the study of personalized medicine using the platelet phenotype; and sex differences in platelet activity, hypercoagulability, and response to antithrombotic strategies.

Faculty Financial Disclosure Statements
The presenting faculty reports the following:

Dr Anderson has no financial relationships to disclose. He intends to reference unlabeled/unapproved uses of drugs or products in his presentation.

Dr. Berger has received honoraria for serving on the Executive Committee of the EUCLID trial.

Education Partner Financial Disclosure Statement
The content collaborator at Voxmedia reports the following:

John F. Kocsis, PhD, has no financial relationships to disclose.

Suggested Reading List


SESSION 4
1:30 PM – 3:00 PM

Balancing Ischemic and Bleeding Risk with Oral Antiplatelet Therapies in Acute Coronary Syndromes

SPEAKERS
Jeffrey L. Anderson, MD
Jeffrey S. Berger, MD, MS

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

Drug List

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic Acid</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Pliva</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Effient</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Brilinta</td>
</tr>
<tr>
<td>Metformin</td>
<td>Glucophage, Fortamet, Glumetza, Riomet</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Diabeta, Glycetin, Glycose, Micronase</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Zestril, Prinivil</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Nitro-Par, Nitro-Tone, Nitrol, Nitrostat, Nitroglycerin E.R., Nitrolytic, Nitrogyn, Nitrovel, Nitropil</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Coumadin, Jantoven, Marfarin</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>Integrilin</td>
</tr>
</tbody>
</table>

Learning Objectives

• Explain the fundamental pharmacokinetics, pharmacodynamics, and pharmacogenetics of oral antiplatelet therapies.

• Describe similarities and differences in efficacy of antiplatelet therapies in reducing ischemic events in ACS patients.

• Discuss similarities and differences in safety profiles of antiplatelet therapies with a focus on bleeding risk.

• Describe the roles for, and prudent use of, clopidogrel, prasugrel, and ticagrelor in management of ACS patients.

Approximately how many patients do you see each week who are post-MI and are taking dual antiplatelet therapy?

1) None
2) 1 to 10
3) 11 to 20
4) 21 to 30
5) 31 to 40
6) 41 to 50
7) 51 to 60
8) >60
Outcomes Question 1
In TRITON-TIMI 38, when comparing prasugrel with clopidogrel, in terms of efficacy, prasugrel was shown to ______

1) Decrease the incidence of the composite of CV death, MI, or stroke
2) Decrease the incidence of CV death
3) Both
4) Neither

Outcomes Question 2
In PLATO, when comparing ticagrelor with clopidogrel, in terms of safety, ticagrelor was shown to ______

1) Increase the incidence of non-CABG-related TIMI major bleeding
2) Increase the incidence of CABG-related TIMI major bleeding
3) Both
4) Neither

Outcomes Question 3
Of the antiplatelet drugs clopidogrel, prasugrel, and ticagrelor, which is/are irreversible?

1) Clopidogrel only
2) Clopidogrel and prasugrel
3) Ticagrelor and prasugrel
4) All three

Traditional Antiplatelet Therapy for Acute Coronary Syndromes
Jeffrey L. Anderson, MD, FACC, FAHA, MACP
Associate Chief of Cardiology, Intermountain Medical Center, Professor of Medicine, University of Utah

Traditional Antiplatelet Therapy for Acute Coronary Syndromes

Properties of Oral Antiplatelet Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mech. / Class</th>
<th>Pro-drug?</th>
<th>T1/2</th>
<th>Reversible?</th>
<th>Metabolism</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>COX-I, salicylate</td>
<td>No</td>
<td>4 h</td>
<td>No</td>
<td>Hepatic</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>P2Y12i, thienopyridine</td>
<td>Yes</td>
<td>6 h</td>
<td>No</td>
<td>Hepatic</td>
<td>CYP2C19 inhibitors</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>P2Y13i, thienopyridine</td>
<td>Yes</td>
<td>7 h</td>
<td>No</td>
<td>Hepatic</td>
<td>---</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>P2Y12i, Non-TP</td>
<td>No</td>
<td>7 h</td>
<td>Yes</td>
<td>Hepatic</td>
<td>Strong CYP3A4 inhibitors &amp; inducers</td>
</tr>
</tbody>
</table>
Aspirin Evidence: Secondary Prevention

Effect of antiplatelet treatment* on vascular events**

<table>
<thead>
<tr>
<th>Category</th>
<th>% Odds Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td>0.5</td>
</tr>
<tr>
<td>Acute CVA</td>
<td>0</td>
</tr>
<tr>
<td>Prior MI</td>
<td>0.0</td>
</tr>
<tr>
<td>Prior CVA/TIA</td>
<td>1.5</td>
</tr>
<tr>
<td>Other high risk CVD</td>
<td>2.0</td>
</tr>
<tr>
<td>CVD (e.g. unstable angina, heart failure)</td>
<td>1.0</td>
</tr>
<tr>
<td>PAD (e.g. intermittent claudication)</td>
<td>0.5</td>
</tr>
<tr>
<td>High risk of embolism (e.g. AFib)</td>
<td>0.0</td>
</tr>
<tr>
<td>Other (e.g. DM)</td>
<td>0.0</td>
</tr>
<tr>
<td>All trials</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Aspirin was the predominant antiplatelet agent studied
**Includes MI, stroke, or death


Aspirin Evidence: Dose and Efficacy

Indirect comparisons of aspirin doses on vascular events in high-risk patients

<table>
<thead>
<tr>
<th>Aspirin Dose</th>
<th>No. of Trials (%)</th>
<th>Odds Ratio for Vascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-1500 mg</td>
<td>34</td>
<td>0.5</td>
</tr>
<tr>
<td>160-325 mg</td>
<td>19</td>
<td>0.1</td>
</tr>
<tr>
<td>75-150 mg</td>
<td>12</td>
<td>0.05</td>
</tr>
<tr>
<td>&lt;75 mg</td>
<td>3</td>
<td>0.01</td>
</tr>
<tr>
<td>Any aspirin</td>
<td>65</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Antiplatelet better 0.5 1.0 1.5 2.0 Antiplatelet worse

Aspirin Therapy: Aspirin Recommendations

- Treatment with aspirin 75 to 162 mg per day should be given and continued indefinitely in the absence of contraindications in patients with SIHD.
- Patients not on aspirin therapy should be given nonenteric aspirin 325 mg before PCI. Patients already on daily aspirin therapy should be given 81 to 325 mg prior to PCI.
- After PCI, aspirin should be continued indefinitely.
- After PCI, it is reasonable to use 81 mg per day of aspirin in preference to higher maintenance doses.

2012 ACCF/AHA SIHD Guidelines; 2011 ACCF/AHA PCI Guidelines

CURE: Clopidogrel after NSTE-ACS

MI/Stroke/CV Death

Cumulative Hazard Rate

P = 0.00009†

N = 12,562

*C in addition to other standard therapies.

P = 0.002; †P = 0.001; ‡P = 0.002; §P = 0.001


PCI-CURE: Clopidogrel after NSTE-ACS Treated with PCI

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

Cumulative Hazard Rate

P = 0.002

N = 2658

*C in addition to other standard therapies.


CURE: Bleeding Results

End Point                  | Placebo   | Clopidogrel
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASA†</td>
<td>ASA†</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.7%</td>
<td>3.7%†</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>1.8%</td>
<td>2.2%†</td>
</tr>
<tr>
<td>Non–life-threatening bleeding</td>
<td>0.9%</td>
<td>1.5%*</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>2.4%</td>
<td>5.1%†</td>
</tr>
</tbody>
</table>

*C in addition to other standard therapies.

†P = 0.001; †P = 0.01; ‡P = 0.03; §P = 0.001

CLARITY: Is Clopidogrel Useful as Adjunct to Fibrinolysis in STEMI? (1° Endpt: TIMI 0/1, D/MI)

**Graphs:**
- Odds Ratio 0.64 (95% CI 0.53-0.76) \(P=0.00000036\)
- Odds Ratio 0.64 (95% CI 0.53-0.76)

**Data:**
- Clopidogrel better
- Placebo better

**References:**

**COMMIT:** Effects of CLOPIDOGREL on Death, Re-MI or Stroke

**Graphs:**
- Event (%)
- Days since randomisation (up to 28 days)

**Data:**
- 9% (SE3)* relative risk reduction \((2P=0.003)\)
- 7% relative risk reduction, in-hospital mortality, \(P=0.03\)

**References:**

**Oral Antiplatelet Therapy Recommendations**

A loading dose of a P2Y\(_{12}\) inhibitor should be given to patients undergoing PCI with stenting. Options include (LOE B): a. clopidogrel 600 mg (ACS & non-ACS pts); b. prasugrel 60 mg (ACS patients); c. ticagrelor 180mg (ACS patients)

In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y\(_{12}\) inhibitor therapy should be given for at least 12 months. Options include:
- clopidogrel 75 mg daily, prasugrel 10 mg daily, and ticagrelor 90 mg twice daily.

In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days and prasugrel for at least 7 days to limit blood transfusions.

**References:**
2011 ACCF/AHA PCI Guidelines

**Ticagrelor Interaction with Aspirin Dose:** Hazard Ratio Compared with Clopidogrel

<table>
<thead>
<tr>
<th>Aspirin Dose (mg/day)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>= 300</td>
<td>1.45</td>
<td>1.01 - 2.09</td>
</tr>
<tr>
<td>&gt;100 – &lt;300</td>
<td>0.95</td>
<td>0.70 - 1.20</td>
</tr>
<tr>
<td>&gt;300</td>
<td>0.77</td>
<td>0.69 - 0.85</td>
</tr>
</tbody>
</table>

**Warning:** Aspirin Dose and Ticagrelor Effectiveness: Maintenance doses of aspirin above 100mg reduce the effectiveness of ticagrelor and should be avoided. After any initial dose, use with aspirin 75-100 mg per day

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022433s008lbl.pdf

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm221382.htm

Mahaffey KW et al. Circulation. 2011;124:S4-64.
Prasugrel  
- More rapid onset and greater antiplatelet effect  
- Lesser/no resistance  
- No influence of gene polymorphism and major drug-drug interactions  

Irreversible  
Reversible binding 


Variability of Antiplatelet Effect with Clopidogrel and Prasugrel 


Impact of Platelet Reactivity after PCI: Meta-Analysis of Individual Patient Data 

Brar et al., JACC 2011; 58:1945. 8 studies; 3059 patients.

CYP2C19 Genetic Polymorphisms and Outcomes With Clopidogrel 

<table>
<thead>
<tr>
<th>Major Adverse CV Events (N=9684)</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carriers vs Noncarriers</td>
<td>1.61 (1.28-2.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heterozygotes vs Wildtype</td>
<td>1.50 (1.04-2.08)</td>
<td>0.016</td>
</tr>
<tr>
<td>Homozygotes vs Wildtype</td>
<td>1.81 (1.21-2.71)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Stent Thrombosis (N=5772) 

| Carriers vs Noncarriers          | 2.78 (1.77-4.30)    | <0.001  |
| Heterozygotes vs Wildtype        | 2.51 (1.59-3.99)    | <0.001  |
| Homozygotes vs Wildtype          | 4.76 (2.01-11.39)   | <0.001  |

CYP2C19 Genetic Polymorphisms  

CYP2C19 Label Changes 

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS 
See full prescribing information for complete boxed warning. 
- Effectiveness of clopidogrel depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1) 
- Poor metabolizers treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5) 
- Tests are available to identify a patient’s CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5) 
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1) 

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020839s055lbl.pdf
Optimizing Antiplatelet Therapy: Balancing Safety and Efficacy

Inhibition of Platelet Aggregation

- High risk of ischemic events
- "Sweet spot"
- High risk of bleeding events

ACS = acute coronary syndrome; CKD = chronic kidney disease; DM = diabetes mellitus.


Optimizing Antiplatelet Therapy: Balancing Safety and Efficacy

Platelet Function Testing For Patients Undergoing PCI

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet function testing in patients at high risk for poor clinical outcomes</td>
<td>Ilb</td>
<td>C</td>
</tr>
<tr>
<td>Routine clinical use of platelet function testing to screen clopidogrel-treated patients undergoing PCI</td>
<td>III – No Benefit</td>
<td>C</td>
</tr>
<tr>
<td>Treatment with an alternate P2Y12 inhibitor (e.g., prasugrel or ticagrelor) in clopidogrel-treated patients with high platelet reactivity</td>
<td>Ilb</td>
<td>C</td>
</tr>
</tbody>
</table>

2011 ACCF/AHA PCI Guidelines

Clinical Trials Using Platelet Function Testing after PCI

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>N</th>
<th>NSTE-ACS</th>
<th>Intervention for HPR</th>
<th>CV Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARCTIC</td>
<td>NEJM 2013; 367:2100</td>
<td>1640</td>
<td>0%</td>
<td>Dose Adjustment</td>
<td>NSD</td>
</tr>
<tr>
<td>GRAVITAS</td>
<td>JAMA 2011; 305:1097</td>
<td>1691</td>
<td>34%</td>
<td>Dose Adjustment</td>
<td>1st: NSD Exploratory: CVE for PRU&lt;200</td>
</tr>
<tr>
<td>Bonello (French)</td>
<td>JACC 2008; 51:1404</td>
<td>162</td>
<td>48%</td>
<td>Serial Dose Titration</td>
<td>CV Events</td>
</tr>
</tbody>
</table>

FDA Public Health Advisory on Drug Interaction Between Clopidogrel and Omeprazole

- On 11/17/09, the FDA issued a public health advisory on concomitant use of clopidogrel and omeprazole.
- Other drugs that are potent inhibitors of CYP2C19 (e.g., cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, ticlopidine) and esomeprazole also recommended to be avoided in combination with clopidogrel.
- Clopidogrel label was updated with these new warnings.
- FDA cited no evidence that other drugs that reduce stomach acid or antacids interfere with clopidogrel’s anticoagulating activity.
- Warning was based on platelet function test data and observational studies.

COGENT Trial: Effect of PPI on Composite Cardiovascular Events

Placebo 1885 1449 945 515 250 218
Omeprazole 1876 1468 966 537 242 205

Probability of Primary CV Endpoint

HR=0.99; 95% CI, 0.68-1.44
P=0.98 by the log-rank test
66% ↓ hazard of GI events, p<0.001


ACCF/ACG/AHA Statement on Use of PPIs and Clopidogrel

- Need for clopidogrel (usually dual inhibition)
- Assess GI risk factors
- No PPI
- History of GI bleeding
- Anticoagulation or regular NSAID use
- Known H. pylori infection
- Corticosteroid use
- Advanced age
- Add PPI
- Add PPP

* H2RA = alternative, patients at low GI bleed risk
** PPIs reduce GI symptoms — may prevent antiplatelet discontinuation

Despite the appearance of newer antiplatelet agents, the advantages of low cost, broad experience, and demonstrated safety and clinical effectiveness suggest a continued major role for aspirin and clopidogrel (now generic) in cardiovascular disease prevention in 2013.

Intensifying Antiplatelet Therapy in Acute Coronary Syndromes:

Jeffrey S. Berger, MD, MS
Assistant Professor of Medicine and Surgery
Director of Cardiovascular Thrombosis

Resting Platelet → Activated Platelet

The central role of platelet activation in cardiovascular disease is the clear benefit of platelet directed therapies for prevention of cardiovascular events.

Is Increased Platelet Activity Important?

Platelet Hyper-Reactivity Following ACS Predicts 5-Year Outcomes

* Relative risk compared to group with negative aggregation.

Anti-Platelet Therapy Decreases CVD in Many Populations

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

Antithrombotic Trialists' Collaboration, BMJ 2002;324:71-96
Limitations of Clopidogrel

- Heterogenous antiplatelet response
- Genetic polymorphisms associated with poor response
- Drug-drug interaction
- Smoking interaction

Metabolism of P2Y₁₂ Receptor Blockers

Ticagrelor and Prasugrel have Rapid Consistent Greater IPA

PRINCIPLE TIMI 44: Comparison with Higher Dose Clopidogrel

IPA (%; 20 μM ADP)

N=201

P<0.0001 for each

TRITON-TIMI 38 Study Design

- ACS (STEMI or UANSTEMI) & Planned PCI
- ASA → n=13,600
- Double-blind
- CLOPIDOGREL 300 mg LD/ 75 mg MD
- PRASUGREL 60 mg LD/ 10 mg MD
- Median duration of therapy: 12 months

9o endpoint: CV death, MI, stroke
2o endpoints: CV death, MI, stroke, rehosp-rec isch
CV death, MI, UTVR

TRITON-TIMI 38: Summary of the results

- Moderate / high-risk ACS pts (n=13,608) scheduled for PCI randomized to:
  - Prasugrel (60 mg LD and 10 mg daily MD)
  - Clopidogrel (300 mg LD and 75 mg daily MD) for 6 to 15 months
- Primary end point (CV death, nonfatal MI, nonfatal stroke), 9.9% prasugrel vs 12.1% clopidogrel (HR: 0.81; p<0.001)
- Prasugrel significant ↓ MI (7.4% vs. 9.7%; p<0.001), urgent TVR (2.5% vs. 3.7%), stent thrombosis (1.1% vs. 2.4%)
- Prasugrel significantly ↓ ischemic events, including stent thrombosis, but ↑ risk major bleeding, including fatal bleeding
- Cardiovascular mortality and overall mortality did not differ significantly between groups

TRITON-TIMI 38: Bleeding Events

ICH = intracranial hemorrhage; ARD = absolute risk difference; TIA = transient ischemic attack.

TRITON-TIMI 38: Net Clinical Benefit

Bleeding Risk Subgroups

Post-hoc analysis

Risk (%) Better
Prior Stroke / TIA Yes 0.54
No 0.006

Age

>=75 1
< 75 0.18
Wgt

< 60 kg +3
>= 60 kg 0.36

OVERALL -13

Prasugrel Labeling

Prasugrel was approved for reducing thrombotic cardiovascular events, including stent thrombosis, in the following patients with acute coronary syndrome who will be managed with percutaneous coronary intervention (PCI): those with unstable angina or non-ST elevation myocardial infarction (NSTEMI) and those with ST-elevation MI (STEMI), when managed with either primary or delayed PCI.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022307s007lbl.pdf

Black Box Warning with Prasugrel

- Prasugrel can cause significant, sometimes fatal, bleeding
- Do not use prasugrel in patients with active pathological bleeding or a history of transient ischemic attack or stroke
- In patients age 75 and older, prasugrel is generally not recommended because of the increased risk of intracranial and fatal bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI). In these situations, the drug’s effect appears to be greater, and its use may be considered.
- Additional risk factors for bleeding include:
  - body weight < 60 kg
  - propensity to bleed
  - concomitant use of medications that increase the risk of bleeding

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022307s003lbl.pdf

TRILOGY ACS Study Design

Medically Managed UA/NSTEMI Patients

Randomization Stratified by:
- Age, Country, Prior Clopidogrel Treatment
  (Primary analysis cohort — Age < 75 years)
- Median Time to Enrollment = 4.5 Days

Medical Management Decision ≤ 72 hrs
- (No prior clopidogrel given) — 4% of total
- Medical Management Decision ≤ 10 days
- (Clopidogrel started ≤ 72 hrs in-hospital OR on chronic clopidogrel) — 96% of total

Minimum Rx Duration: 6 months; Maximum Rx Duration: 30 months

Primary Efficacy Endpoint: CV Death, MI, Stroke

1. All patients were on aspirin and low-dose aspirin (< 100 mg) was strongly recommended. For patients ≤ 60 kg or ≥ 75 years, 5 mg MD prasugrel was given. Adapted from Chin CT et al. Am Heart J 2010;160:16-22.e1.

TRILOGY ACS: Primary Efficacy Endpoint to 30 Months
(Age < 75 years)

HR (95% CI): 0.91 (0.79, 1.05)  P = 0.21


TRILOGY ACS: Primary Efficacy Endpoint to 30 Months
(Age < 75 years)

HR (95% CI) ≤ 1 Year: 0.60 (0.44, 0.81)  P = 0.001
HR (95% CI) > 1 Year: 0.97 (0.75, 1.25)

Interaction P = 0.07


TRILOGY ACS: TIMI Major Bleeding to 30 Months
(Age < 75 years)

HR (95% CI): 1.21 (0.91, 1.61)  P = 0.27

Ticagrelor

- Cyclopentyl-triazolopyrimidine
- Rapid oral absorption (30 minutes to onset)
- No transformation to active metabolite
- Reversibly binds to P2Y12
- Peak platelet inhibition within 1.5-3 hours
- Half life of 7-8 hours -> twice a day dosing

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022433s008lbl.pdf

clopidogrel vs. ticagrelor

ONSET/OFFSET Study

Platelet Reactivity - Ticagrelor vs. Prasugrel

44 ACS patients with High on-clopidogrel platelet reactivity post PCI

Randomized to ticagrelor 90 mg bid or prasugrel 10 mg qd
with 15 day crossover

Primary endpoint – platelet reactivity

PRU

Day 0

Day 16

Day 30

Platelet Reactivity - Ticagrelor vs. Prasugrel


PLATO study design

44 ACS patients with High on-clopidogrel platelet reactivity post PCI

Randomized to ticagrelor 90 mg LD and 90 mg bid MD
or clopidogrel 300-600 mg LD and 75 mg daily MD

Primary end point (CV death, nonfatal MI, nonfatal stroke), 9.8%
ticagrelor vs 11.7% clopidogrel (HR: 0.84; p<0.001)

Ticagrelor significant ↓ MI (7.4% vs. 9.7%; p<0.001), urgent TVR (2.5%
v 3.7%), stent thrombosis (1.1% vs. 2.4%)

Ticagrelor significantly ↓ ischemic events, including cardiovascular
death, but ↑ risk of non-CABG related major bleeding

Fatal bleeding was not significantly different between groups

Overall mortality was significantly decreased with ticagrelor (4.5% vs.
5.9%; p<0.001)


PLATO: Summary of the results

- NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI) (N=18,624)
  - Ticagrelor (180 mg LD and 90 mg bid MD) or
  - Clopidogrel (300-600 mg LD and 75 mg daily MD) for 6 to 12
    months
- Primary end point (CV death, nonfatal MI, nonfatal stroke), 9.8%
ticagrelor vs 11.7% clopidogrel (HR: 0.84; p<0.001)
- Ticagrelor significant ↓ MI (7.4% vs. 9.7%; p<0.001), urgent TVR (2.5%
v 3.7%), stent thrombosis (1.1% vs. 2.4%)
- Ticagrelor significantly ↓ ischemic events, including cardiovascular
death, but ↑ risk of non-CABG related major bleeding
- Fatal bleeding was not significantly different between groups
- Overall mortality was significantly decreased with ticagrelor (4.5% vs.
5.9%; p<0.001)

\begin{itemize}
  \item **PLATO: Primary efficacy endpoint over time**
  \begin{itemize}
    \item Composite of CV death, MI or stroke
    \item Clopidogrel vs Ticagrelor
    \item HR 0.88 (95% CI 0.77–1.00), p=0.045
    \item No. at risk:
      \begin{itemize}
        \item Clopidogrel: 9,291
        \item Ticagrelor: 9,333
      \end{itemize}
    \item Days after randomisation:
      \begin{itemize}
        \item 31
      \end{itemize}
    \item Cumulative incidence (%):
      \begin{itemize}
        \item Clopidogrel: 5.43
        \item Ticagrelor: 4.77
      \end{itemize}
    \item *Excludes patients with any primary event during the first 30 days
  \end{itemize}

  \item **PLATO – Bleeding Data**
  \begin{itemize}
    \item Ticagrelor vs Clopidogrel
    \item P-values:
      \begin{itemize}
        \item p=0.43
        \item p=0.57
        \item p=0.70
        \item p=0.88
        \item p=0.02
      \end{itemize}
    \item **PLATO non invasive: primary outcome**
    \begin{itemize}
      \item Invasive:
        \begin{itemize}
          \item HR, 0.84, 95% CI: (0.75–0.94)
        \end{itemize}
      \item Non-invasive:
        \begin{itemize}
          \item HR, 0.85, 95% CI: (0.73–1.0)
        \end{itemize}
      \item Days after randomization:
        \begin{itemize}
          \item 0
        \end{itemize}
      \item Number at risk:
        \begin{itemize}
          \item Ticagrelor: 6732 6236 6134 5972 4889 3735 3048
          \item Clopidogrel: 6676 6129 6034 5881 4815 3680 2965
        \end{itemize}
      \item Geographic Regions:
        \begin{itemize}
          \item CV Death, MI, Stroke
          \item KM at month 12
        \end{itemize}
      \item Interaction p-values:
        \begin{itemize}
          \item Asia / Australia: 0.045
          \item Central America / South America: 0.01
          \item Europe / Middle East / Africa: 0.001
          \item North America: 0.01
        \end{itemize}
      \item **Primary Efficacy Outcome**
        \begin{itemize}
          \item US and ROW by aspirin dose
          \item ASA Dose (mg): 324 352 1.62 (0.99, 2.64)
          \item Ticagrelor vs Clopidogrel
          \item HR (95% CI):
            \begin{itemize}
              \item US: 1.62 (0.99, 2.64)
              \item >100–<300: 22 16 2
              \item ≤100: 284 263 0.73 (0.40, 1.33)
              \item Non-US: 140 23 1.23 (0.71, 2.14)
              \item >100–<300: 503 63 1.00 (0.71, 1.42)
              \item ≤100: 7449 699 0.78 (0.60, 0.97)
            \end{itemize}
        \end{itemize}
  \end{itemize}


---

**PLATO Major Bleeding, TIMI Major Bleeding, Life-Threatening or Fatal Bleeding, or Fatal TIMI non-CABG Major Bleeding**
**Ticagrelor – FDA Label**

"Boxed Warning"

**WARNING: BLEEDING RISK**
- Ticagrelor, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).
- Do not use ticagrelor in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).
- Do not start ticagrelor in patients planned to undergo urgent coronary bypass graft surgery (CABG). When possible, discontinue ticagrelor at least 5 days prior to any surgery (5.1).
- Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of ticagrelor (5.1).
- If possible, manage bleeding without discontinuing ticagrelor. Stopping ticagrelor increases the risk of subsequent cardiovascular events (5.5).

**WARNING: Aspirin Dose and Ticagrelor Effectiveness**
- Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).

**http://www.pdr.net/drugpages/productlabeling.aspx?mpcode=04020155**

**How Do Different Antiplatelets Compare in the Setting of ACS?**

- **ARR – 1.9%**
  - **P<0.001**
- **ARR – 2.2%**
  - **P<0.001**
- **ARR – 2.1%**
  - **P<0.001**

**Percent (%)**

- Clopidogrel vs Placebo
- Clopidogrel vs Prasugrel
- Clopidogrel vs Ticagrelor


**Risk Associated with P2Y12 Antagonists in Patients with ACS**

<table>
<thead>
<tr>
<th>Event</th>
<th>C vs Pr</th>
<th>RR (95% Cl)</th>
<th>Pr vs C</th>
<th>RR (95% Cl)</th>
<th>Tr vs C</th>
<th>RR (95% Cl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>9.3 vs 11.4</td>
<td>0.81 (0.72-0.90)</td>
<td>9.8 vs 12.1</td>
<td>0.61 (0.73-0.50)</td>
<td>9.8 vs 11.1</td>
<td>0.84 (0.77-0.92)</td>
</tr>
<tr>
<td>MI</td>
<td>5.2 vs 6.7</td>
<td>0.77 (0.67-0.88)</td>
<td>7.3 vs 8.5</td>
<td>0.74 (0.87-0.60)</td>
<td>5.6 vs 6.8</td>
<td>0.84 (0.74-0.95)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.2 vs 1.4</td>
<td>0.86 (0.83-0.90)</td>
<td>1.0 vs 1.0</td>
<td>1.02 (0.98-1.06)</td>
<td>1.0 vs 1.2</td>
<td>1.17 (0.91-1.45)</td>
</tr>
<tr>
<td>Any Death</td>
<td>5.7 vs 6.2</td>
<td>0.92 (0.81-1.04)</td>
<td>3.0 vs 3.0</td>
<td>0.92 (0.78-1.06)</td>
<td>4.5 vs 5.0</td>
<td>0.79 (0.66-0.93)</td>
</tr>
<tr>
<td>CV Death</td>
<td>5.1 vs 5.5</td>
<td>0.93 (0.83-1.04)</td>
<td>2.1 vs 2.4</td>
<td>0.99 (0.87-1.12)</td>
<td>4.0 vs 5.1</td>
<td>0.78 (0.63-0.98)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>1.7 vs 2.7</td>
<td>1.20 (1.13-1.27)</td>
<td>2.5 vs 1.7</td>
<td>1.45 (1.15-1.85)</td>
<td>11.6 vs 11.2</td>
<td>1.64 (0.95-2.03)</td>
</tr>
</tbody>
</table>

- C = Clopidogrel
- P = Placebo
- Pr = Prasugrel
- Ti = Ticagrelor

- **C = Clopidogrel vs Placebo**
  - **Pr vs C**
  - **Tr vs C**

**UA/NSTEMI Guidelines: Key Points on Antiplatelets (Class I and III)**

- **ASA to all (clopidogrel if allergic)**
- **Medium - high risk and an invasive strategy get dual Rx**
  - Before PCI: clopidogrel, ticagrelor, GP IIb/IIIa
  - At PCI: clopidogrel, ticagrelor, prasugrel, GP IIb/IIIa
- **Conservative strategy: dual Rx w/ ASA + clopidogrel or ticagrelor**
- **Use loading doses of ADP blockers**
- **Duration for at least 12 months**
- **Class III (harm or no benefit)**
  - **low risk and on ASA/ADP blocker**
    - no benefit to GP IIb/IIIa
  - **history stroke/TIA, prasugrel potentially harmful**

- **Jneid H et al. J Am Coll Cardiol. 2012;60:645-81.**

**STEMI Guidelines: Key Points on Antiplatelets (Class I and III)**

- **ASA for all and indefinitely**
  - **Primary PCI**
    - Loading dose as early as possible or at PCI: clopidogrel, ticagrelor, prasugrel
    - ADP blockers for 1 year
  - **Class III (harm or no benefit): prasugrel potentially harmful (if his stroke/TIA)**
  - **Fibrinolysis**
    - Clopidogrel 300 mg loading dose, ≤ 75 years: 75 mg, > 75 years
    - Clopidogrel at least 14 days and up to 1 year
  - **PCI after fibrinolytic therapy**
    - Clopidogrel 300 mg if no prior loading dose + PCI within 24 hours of fibrinolytic therapy; 600 mg if PCI > 24 hours afterwards
    - Duration of clopidogrel: BMS, 30 days to 1 year; DES, at least 1 year
  - **Class III (harm or no benefit): prasugrel potentially harmful (if his stroke/TIA)**


**Case Study**

**Jeffrey L. Anderson, MD, FACC, FAHA, MACP**

**Associate Chief of Cardiology, Intermountain Medical Center, Professor of Medicine, University of Utah**
Case
75-yo Man With Chest Pain & Risk Factors

Presentation
- 75-year-old man presents to the ED with recurrent retrosternal chest pressure and dyspnea. Intermittent discomfort all day, now persistent x 2 h
- PMH
  - Positive coronary calcium scan 2y ago, but no h/o MI or prior angina
  - Hypertension
  - Mixed dyslipidemia
  - Intermediate fasting glucose
  - Central obesity (“metabolic syndrome”)  
  - GERD, past ulcer
- FH: Father had MI at age 69; sister had PCI at 64
- SH: Married, retired business executive; little regular exercise; long-time smoker, down to ½ pack/d
- Allergies: No known drug allergies

Medications/Review of Systems/Physical Examination
- Medications
  - HCTZ 12.5 mg daily
  - Lisinopril 5 mg daily
  - Omeprazole 20 mg daily
  - Omeprazole 20 mg daily
- ROS:
  - Snores; 20-lb weight gain over 2 years
- PE
  - BP 145/88 mm Hg; HR 88 bpm; Hgt 69 in; Wgt 232 lbs; BMI 34 kg/m2
  - Neck short, thick; JVP poorly assessed; lungs: bibasilar rales; heart: regular, normal S1, S2, +S4; abdomen obese, non tender; extremities with trace edema, pulses 1+ in feet

Electrocardiogram/Chest X-Ray/Laboratory Results
- ECG: 1-2 mm ST depression, T inversion in anterolateral leads
- CXR: Mild pulmonary venous congestion
- Labs
  - Hct 48%, WBC 9.6 x 109/L, platelets 325 x 109/L
  - Na 144 mEq/L, K 3.8 mEq/L, BUN 28 mg/dL, Cr 1.6 mg/dL, gluc 142 mg/dL
  - Est CrCl 43 mL/min/1.73 m2
  - CK 198 U/L (8% MB = 17 U/L)
  - Troponin-I=2.1 ng/mL (nl <0.02, diagnostic >0.4)
  - Recent lipid panel: TC 216 mg/dL, TG 246 mg/dL, HDL-C 34 mg/dL, LDL-C 134 mg/dL

LVH = left ventricular hypertrophy.

To which pathway would you triage this patient?
1) STEMI
2) Definite UA/NSTEMI
3) Possible/probable UA
4) Non-cardiac chest pain

What is the level of risk?
1) High
2) Intermediate
3) Low
TIMI Risk Score Assessment

1. Age ≥ 65 y
2. ≥ 3 CAD risk factors (high cholesterol, hypertension, diabetes, family history of CAD)
3. Prior coronary stenosis ≥ 50%
4. Aspirin in last 7 days
5. ≥ 2 anginal events ≤ 24 h
6. ST-segment deviation
7. Elevated cardiac markers (troponin or CK-MB)

Death / MI / Urgent Revasc at 14 d (%)

CAD = coronary artery disease; TIMI = thrombolysis in myocardial infarction.


• What strategy would you select?
  1) Immediately move to coronary angiography
  2) Medical stabilization followed by early (<12-24 h) coronary angiography
  3) Medical stabilization followed by delayed coronary angiography (>24 h)
  4) Medical treatment followed by non-invasive risk stratification, unless markers or ECG become more positive

TIMACS
Timing of Angiography in NSTEMI—Results by GRACE Risk Score

Design: 3531 NSTEMI patients randomized to early (<24 h) or delayed (>36 h) invasive strategy. Death, MI, CVA outcomes compared at 6 mo.

GRACE Score

Patient (%)

1-140 HR 1.12 (0.81-1.56) HR 0.65 (0.48-0.89)
>140

CVA = cerebrovascular accident; GRACE = global registry of acute coronary events; TIMACS = Timing of Intervention in Acute Coronary Syndromes.


• Which anticoagulant would you choose for an intended invasive strategy with early intervention (goal: 4-12 h)?
  1) UFH
  2) LMWH
  3) Bivalirudin
  4) Fondaparinux

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

Case
75-yr Man With Chest Pain & Risk Factors

• Which adjunctive antiplatelet therapy would you give pre-cath in addition to aspirin with an invasive strategy?
  1) Clopidogrel
  2) Prasugrel
  3) Ticagrelor
  4) GP IIb/IIIa inhibitor
  5) GP IIb/IIIa inhibitor plus 1, 2, or 3

GP = glycoprotein.
Case
75-yo Man With Chest Pain & Risk Factors

Case Management and Hospital Course
- Patient treated with O₂, nitroglycerin, aspirin, metoprolol (25 mg po q6h), heparin, ticagrelor*, metoprolol (25 mg po q6h), and atorvastatin 80 mg po—chest pain reduced from 7/10 to 2/10
- Rapid transfer arranged
- Angiography, performed in 5 h, showed 90% proximal LAD, 30% mid-LAD, 45% OMB-1 stenosis.
- DES placed in proximal LAD with relief of discomfort. Provisional eptifibatide not needed.
- Subsequent hospital course unremarkable
- Patient educated on lifestyle/smoking cessation; secondary prevention measures optimized.

*Omeprazole may interact to reduce activation of clopidogrel; *prasugrel in NSTEMI is a recommended choice after coronary anatomy is defined, with caution or avoidance for age ≥75, weight <60kg, contraindicated for prior TIA/CVA.

DES = drug-eluting stent; LAD = left anterior descending artery; OMB = obtuse marginal branch; po = per os (orally); q6h = every 6 hours; RCA = right coronary artery.

Case Commentary
75-yo Man With Chest Pain & Risk Factors
- Risk stratification (risk scores, initial and serial ECGs, and biomarker findings) is an important prerequisite to therapeutic decision-making in ACS
- Antiplatelet and anticoagulant therapy should be initiated as soon as possible after presentation; treatment should be appropriate to strategy, patient characteristics, and physician/hospital experience
- An early invasive strategy is most appropriate and effective in moderate and high-risk UA/NSTEMI patients
- Patient factors, such as age, medical history, renal function, bleeding risk, comorbidities, and drug interactions should be taken into account in selecting and dosing antithrombotic therapies
- Long-term antiplatelet and statin therapy and other measures, including rehabilitation program referral, are important parts of effective secondary prevention strategies

Mrs. Smith is a 62-year-old woman that presents to a local emergency department with 45 minutes of severe chest pain
PMH: Hypertension and diabetes
Home Meds: HCTZ 25mg daily and Metformin 1000mg bid
ECG: Sinus tachycardia at 102 bpm; Anterior ST segment elevation with reciprocal ST changes

? 

After stabilization, the most appropriate next step is:
1) If available, activate the Cath lab in preparation for PCI
2) Administer thrombolytic therapy
3) Place a intra-aortic balloon pump and then go directly to the Cath lab
4) Send to the CCU for further observation

Case Study
Jeffrey S. Berger, MD, MS
Assistant Professor of Medicine and Surgery
Director of Cardiovascular Thrombosis

Her weight is 191 lbs - BMI is 31.5
HR 105 bpm and BP is 105/60
On physical exam:
- Carotids 2+ with normal upstrokes and no bruits
- JVP was not distended
- Lungs were clear – no rales
- Cardiac exam: normal PMI, S1, S2, +S4 and a 1/6 systolic ejection murmur at the LUSB
- Abdomen is soft without masses
- 2+ pulses bilaterally
- No lower extremity edema

LUSB, left upper sternal border
Primary coronary angioplasty versus thrombolysis for AMI

23 randomized trials; 7739 Subjects

Lancet 2003;361:13–20

Primary PCI in STEMI

Primary PCI should be performed in patients with STEMI and ischemic symptoms of less than 12 hours’ duration.

Primary PCI should be performed in patients with STEMI and ischemic symptoms of less than 12 hours’ duration who have contraindications to fibrinolytic therapy, irrespective of the time delay from FMC.

Primary PCI should be performed in patients with STEMI and cardiogenic shock or acute severe HF, irrespective of time delay from MI onset.


On his cath, patient is found to have a 100% proximal LAD occlusion (IRA) that was stented with a DES

Patient is also found to have a 90% lesion in the proximal RCA.

In addition to aspirin, which additional antiplatelet drug would you use?

1. Clopidogrel 600mg
2. Prasugrel 60mg
3. Ticagrelor 180mg
4. No additional antiplatelet therapy is needed


Should PCI be performed in a non-infarct artery at the time of the primary PCI?

1. Yes
2. No

PCI should not be performed in a noninfarct artery at the time of primary PCI in patients with STEMI who are hemodynamically stable

Dual Antiplatelet Therapy in ACS

If the patient had a prior transient ischemic attack, in addition to aspirin, which additional antiplatelet drug would you use?

1) Clopidogrel 600mg
2) Prasugrel 60mg
3) Ticagrelor 180mg
4) No additional antiplatelet therapy is needed

Antiplatelet Therapy to Support Primary PCI for STEMI

Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack.

What is the appropriate dose of aspirin this patient should be continued on (after PCI)?

1) 81 mg
2) 162 mg
3) 325 mg
4) 650 mg
What is the optimal aspirin dose? OASIS-7
N=25,086; 2-by-2 factorial design; 30 day follow-up

<table>
<thead>
<tr>
<th></th>
<th>Aspirin 325mg</th>
<th>Aspirin 81mg</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>4.2</td>
<td>4.4</td>
<td>0.61</td>
</tr>
<tr>
<td>CV death</td>
<td>2.1</td>
<td>2.3</td>
<td>0.22</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>2.3</td>
<td>2.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>5.0</td>
<td>4.4</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Antiplatelet Therapy to Support Primary PCI for STEMI

It is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses after primary PCI

With a drug eluting stent, what is the appropriate minimum duration of time to treat with a P2Y12 antagonist?
1) 1 Month
2) 6 Months
3) 1 Year
4) Indefinitely

Antiplatelet Therapy to Support Primary PCI for STEMI

P2Y12 inhibitor therapy should be given for 1 year to patients with STEMI who receive a stent (BMS or DES) during primary PCI using the following maintenance doses:
- Clopidogrel 75 mg daily; or
- Prasugrel 10 mg daily; or
- Ticagrelor 90 mg twice a day

The following day the patient is feeling well and has an ejection fraction of 40% on an echocardiogram. She is discharged home 2 days later.

In addition to aspirin, P2Y12 inhibitor, statin, ace inhibitor and beta blocker, are any other medications indicated?
1) Ranolazine
2) Aldosterone antagonist
3) Amlodipine (CCB)
4) No other medications are indicated
Outcomes Question 1
In TRITON-TIMI 38, when comparing prasugrel with clopidogrel, in terms of efficacy, prasugrel was shown to ______

1) Decrease the incidence of the composite of CV death, MI, or stroke
2) Decrease the incidence of CV death
3) Both
4) Neither

Outcomes Question 2
In PLATO, when comparing ticagrelor with clopidogrel, in terms of safety, ticagrelor was shown to ______

1) Increase the incidence of non-CABG-related TIMI major bleeding
2) Increase the incidence of CABG-related TIMI major bleeding
3) Both
4) Neither

Outcomes Question 3
Of the antiplatelet drugs clopidogrel, prasugrel, and ticagrelor, which is/are irreversible?

1) Clopidogrel only
2) Clopidogrel and prasugrel
3) Ticagrelor and prasugrel
4) All three

Question & Answer