Understanding and Treating Acute Coronary Syndrome

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Accreditation:
Pharmacists: 0798-0000-10-064-L01-P
Pharmacy Technicians: 0798-0000-10-064-L01-T

Target Audience: Pharmacists & Pharmacy Technicians

Program Overview:
Pharmacists can make a difference in the management and treatment of acute coronary syndrome. This program will educate pharmacists on ACS treatment guidelines, provide an update on pharmacotherapy, and the challenges associated with ACS treatment so they can more comfortably counsel patients and providers as their role in pharmacists.

Objectives:
• Describe the epidemiology and etiology of acute coronary syndrome (ACS)
• Outline the evidence and guideline-based role of antiplatelet therapy in the prevention of coronary attack in patients with acute coronary syndromes (ACS)
• Describe current and emerging oral antiplatelet strategies for long-term prevention of coronary attacks in ACS patients, including mechanisms of action, efficacy, dose and duration of therapy.
• Review the pharmacist’s role in counseling patients on lifestyle changes, drug treatment strategies and medication adherence to improve the quality of life and long-term maintenance of ACS patients.

American Heart Association Heart Disease and Stroke Statistics — 2010 Update

Understanding and Treating Acute Coronary Syndrome

Speaker: Dr. Jean Nappi received her BS in Pharmacy from the State University of NY at Buffalo. She completed her Doctor of Pharmacy degree and residency in internal medicine from the University of Texas at Austin / UT Health Science Center at San Antonio. Dr. Nappi has been on the faculty at the Universities of Wisconsin, Utah, and Houston prior to her current position. She is now Professor of Clinical Pharmacy and Outcome Sciences in the South Carolina College of Pharmacy-MUSC Campus and Professor of Medicine (Cardiology) at the Medical University of South Carolina.

Speaker Disclosure: Dr. Nappi has no actual or potential conflicts of interest in relation to this program.

This webcast has been supported by an educational grant from AstraZeneca

Acute Coronary Syndrome

- The estimated number of hospital discharges associated with ACS in 2006 is 733,000 (includes MI 647,000 and unstable angina 86,000).
- >1.3 million inpatient percutaneous coronary intervention (PCI) procedures.
**Definitions**

- **Unstable Angina**
  - An ↑ in frequency and duration of ischemic episodes caused by an imbalance of O\(_2\) supply and demand due to a non-occlusive thrombus

- **Myocardial Infarction**
  - Irreversible tissue necrosis caused by an occlusive thrombus

**Definition**

- **Acute Coronary Syndrome (ACS)**
  - Patients present with acute chest pain and other signs or symptoms suggestive of myocardial ischemia.
  - Often not possible to determine whether the patient has or will sustain permanent damage to the myocardium (necrosis or AMI) or has reversible ischemia (Unstable Angina).
  - In retrospect, after either serial ECG changes and/or serial serum markers of myocardial injury, can this distinction between AMI and UA be made.
  - ACS is a useful concept because the triage, assessment, and initial management of UA and AMI are similar.

**Pathophysiology**

- **CAD** atherosclerotic heart disease
- **Plaque rupture**
  - Initiation of clotting cascade
  - Release of vasoactive substances (epinephrine, thromboxane A\(_2\), ADP, thrombin, etc)
- **Thrombus formation**
  - Myocardial O\(_2\) demand > Myocardial O\(_2\) supply
Consequences of ACS

- Progression to myocardial infarction
- Acute/chronic LV dysfunction (heart failure)
- Arrhythmia
- Death

Algorithm for Initial Assessment and Evaluation of the Patient with Acute Chest Pain

Chest pain consistent with coronary ischemia

- Within 10 minutes
  - 12 lead ECG. Establish continuous ECG monitoring
  - Establish IV with D5W
  - Aspirin 325 mg (chewed)
  - IV NTG
  - Blood for baseline serum cardiac markers

Therapeutic/Diagnostic tracking according to 12-lead ECG

Acute Coronary Syndrome

- No ST Elevation
  - NSTE-ACS
    - (-) markers
      - Unstable angina
      - NSTEMI
      - (-) markers
      - Myocardial Infarction
    - (+) markers
      - STEMI
      - Thrombogenicity of PCI
        - Thrombin Generation
          - Indirect thrombin inhibitors
            - Unfractionated heparin
            - LMWH
          - Direct thrombin inhibitors
            - Bivalirudin, argatroban
        - Platelet Activation
          - Aspirin
          - Thienopyridines
          - Glycoprotein IIb/IIIa inhibitor
      - Adhesion Molecules
        - Vessel Wall Injury Inflammation
        - High dose statin
  
Adapted from Braunwald, ACC/AHA Practice Guidelines
Understanding and Treating Acute Coronary Syndrome

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Sites of anti-thrombotic drug action

Complications of PCI

- Minutes to hours → Elastic recoil
- Hours to days → Platelet aggregation
- Weeks to months → In-stent thrombosis
- In-stent thrombosis
- Proliferation of vascular smooth muscle (restenosis)

Drug Eluting Stents

- DES are commonly used in ACS and CAD patients
- Add medication to locally inhibit cell proliferation
  - Prevent restenosis
- Dual antiplatelet therapy is recommended for at least 12 months following stent implantation
- Increase in late AMI and death due to “in stent thrombosis”
- In-stent thrombosis is a rare but potentially lethal complication

Lancet 2003;361:247-9
**Patient Case POLL QUESTION**
A 53 yo man presents to the ED complaining of 2 hours of chest tightness. His ECG reveals ST segment depression in the lateral leads.
PMH: GERD and dyslipidemia. Medications: omeprazole 20 mg qd, atorvastatin 40 mg qd.
PE: BP 134/82, HR 74, no signs of heart failure. He receives IV heparin, IV NTG, aspirin and clopidogrel and taken to cath lab later that day. He receives a drug eluting stent (Cypher) in his left circumflex artery.

**What medications should he receive at discharge?**

- a. aspirin 81 mg q AM, clopidogrel 75 mg q AM, omeprazole 20 mg hs, atorvastatin 40 mg hs
- b. aspirin 325 mg q AM, omeprazole 20 mg hs, atorvastatin 40 mg hs
- c. aspirin 81 mg q AM, clopidogrel 75 mg q AM, cimetidine 400 mg bid, atorvastatin 40 mg hs
- d. aspirin 325 mg q AM, clopidogrel 75 mg q AM, pantoprazole 40 mg hs, atorvastatin 40 mg hs

**STEMI and PCI 2009 Focused Update**

- **A loading dose of thienopyridine** is recommended for STEMI patients for whom PCI is planned. Regimens should be one of the following:
  - At least 300 to 600 mg of clopidogrel should be given as early as possible before or at the time of primary or nonprimary PCI. ([Level of Evidence: C](https://www.ncbi.nlm.nih.gov/pubmed/20073388))
  - Prasugrel 60 mg should be given as soon as possible for primary PCI ([Level of Evidence: B](https://www.ncbi.nlm.nih.gov/pubmed/20073388))
  - In STEMI patients with a prior history of stroke and transient ischemic attack for whom primary PCI is planned, prasugrel is not recommended as part of a dual-antiplatelet therapy regimen. ([Level of Evidence: C](https://www.ncbi.nlm.nih.gov/pubmed/20073388))

  

  J Am Coll Cardiol 2009;54:2205-2241

- **The duration of thienopyridine therapy should be as follows:**
  - In patients receiving a stent (Bare metal stent [BMS] or drug-eluting stent [DES]) during PCI for ACS, clopidogrel 75 mg daily ([Level of Evidence: B](https://www.ncbi.nlm.nih.gov/pubmed/20073388)) or prasugrel 10 mg daily ([Level of Evidence: B](https://www.ncbi.nlm.nih.gov/pubmed/20073388)) should be given for at least 12 months
  - If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered. ([Level of Evidence: C](https://www.ncbi.nlm.nih.gov/pubmed/20073388))
**Clopidogrel (Plavix)**

- Thienopyridine
  - Inhibits binding of ADP to the P2Y₁₂ receptor on the platelet
  - Irreversibly inhibits platelet activation
  - Reduction of atherothrombotic events associated with MI, stroke, PAD, ACS

**Drawbacks of Clopidogrel Therapy**

- Pro-drug: Delayed onset of action
- Genetic polymorphisms of CYP 2C19
- Interaction with PPIs ?

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**Risk of Adverse Outcomes Associated With Concomitant Use of Clopidogrel and Proton Pump Inhibitors Following Acute Coronary Syndrome**

*Ho et al. JAMA 2009;301:937-944*

- Study Design
  - Retrospective cohort of 8205 VA ACS patients prescribed clopidogrel after discharge
- Main outcome measure
  - All cause mortality or rehospitalization for ACS

**JAMA 2009;301:937-944**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clopidogrel no PPI N = 2961</th>
<th>Clopidogrel with PPI N = 5244</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary: Death or ACS</td>
<td>20.8%</td>
<td>29.8%</td>
<td>1.25</td>
<td>1.11-1.41</td>
</tr>
<tr>
<td>rehospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary: ACS rehospitalization</td>
<td>6.9%</td>
<td>14.6%</td>
<td>1.86</td>
<td>1.57-2.20</td>
</tr>
<tr>
<td>Secondary: revascularization</td>
<td>11.9%</td>
<td>15.5%</td>
<td>1.49</td>
<td>1.30-1.71</td>
</tr>
<tr>
<td>Secondary: All cause mortality</td>
<td>16.6%</td>
<td>19.9%</td>
<td>0.91</td>
<td>0.80-1.05</td>
</tr>
</tbody>
</table>

PPIs used: omeprazole, rabeprazole
Additional Data

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Results: Increased risk of CV events</th>
<th>PPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanek et al (SCAI 2009)</td>
<td>Retrospective cohort analysis, n=16718</td>
<td>Yes, HR = 1.51 (pooled) CI=1.39-1.64, p &lt; 0.0001 Individual agents had ↑ risk. PPIs alone ↑ risk by 11%</td>
</tr>
<tr>
<td>Juurlink et al (CMAJ 2009)</td>
<td>Retrospective cohort analysis, n=6828 on combination therapy with PPIs, n=6828 on combination therapy with placebo</td>
<td>Yes, OR = 1.27 with current PPIs CI=1.03-1.57 No association with pantoprazole OR = 1.02</td>
</tr>
<tr>
<td>TRITON-TIMI 38 (ESC 2009)</td>
<td>Cox proportional hazard model, n=6795 Clopidogrel, n=6813 Prasugrel</td>
<td>No, HR = 0.94 no increase with PPI combination for either drug</td>
</tr>
<tr>
<td>PACA Trial (JACC 2009)</td>
<td>Randomized 104 NSTEMI pts to 2 PPIs</td>
<td>Yes, OR = 2.6 CI =1.2-6.2 Platelet response (VASP) @ 30d to clopidogrel 150 mg/d Not specified</td>
</tr>
<tr>
<td>COGENT NEJM 2010</td>
<td>Randomized 3761 ACIS or DES patients to clopidogrel/omeprazole vs clopidogrel/placebo</td>
<td>No, HR = 0.99 CI=0.68-1.44 Actually designed to look at GI endpoint Special formulation combination product used</td>
</tr>
</tbody>
</table>

Randomized Data: Clopidogrel or Placebo

Post-hoc analysis of the CREDO trial (N = 2116)

<table>
<thead>
<tr>
<th>PCI + Clopidogrel x 4 weeks</th>
<th>Placebo</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death / MI / stroke at 1 year</td>
<td>Odds Ratio</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>7.7%</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel + PPI</td>
<td>13.4%</td>
<td>1.63</td>
</tr>
<tr>
<td>Placebo</td>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td>Placebo + PPI</td>
<td>15.0%</td>
<td>1.55</td>
</tr>
</tbody>
</table>

AHA Scientific Sessions 2008, abstract #3999

Possible reasons for the observed increased CV risk

- PPIs interfere with the production of the clopidogrel active metabolite
- PPIs cause direct harm
- Confounders in the observational data
  - e.g., older, sicker patients


Summary

- Observational data
  - Suggest an association between PPI use (particularly with omeprazole) and increased cardiovascular events in patients receiving clopidogrel
- Randomized data, post-hoc analysis
  - Suggests PPI use itself is associated with increased cardiovascular events, regardless of the presence or absence of clopidogrel
- Randomized trial, COGENT study (combination product)
  - Did not find an increase in CV events, although it may have been underpowered
November 18, 2009

FDA NEWS RELEASE
For Immediate Release: Nov. 18, 2009
Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA Announces New Warning on Plavix: Avoid Use with Prilosec/Priosec OTC

Patients should avoid using the stomach acid reducer Prilosec/Priosec OTC (omeprazole) with the anti-clotting drug Plavix (clopidogrel), the U.S. Food and Drug Administration warned on Nov. 17. New data suggest that when patients take both Prilosec and Plavix, Plavix’s ability to block platelet aggregation (anti-clotting effect) may be reduced by about half.

It is unknown how other PPIs may interfere with Plavix. Other drugs that should not be used with Plavix because they may have a similar interaction with CYPIC3A include Nexium (esomeprazole), Tagamet and Tagamet HB (cimetidine), Duflcan (flecainide), Nadral (ketonazole), WERD (voronozole), Intelec (ebavirine), Felbatol (felbamate), Prozac, Seralen, Symbax (fluvaxetine), Luvox (fluoxamine) and Tenid (ticlopidine).

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Expert Consensus Statement

- Dual antiplatelet therapy not routinely recommended for patients with prior ischemic stroke
- Patients with prior GI bleed are at highest risk
  - Consider other factors: age, concurrent use of anticoagulants or NSAIDs, and H pylori infection
- PPIs are recommended for patients with a hx of upper GI bleed and may be appropriate for patients with multiple risk factors
- PPIs and H2 antagonists are not recommended for routine use in patients at low risk

J Am Coll Cardiology, published online 11/8/10

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Patient Case POLL QUESTION

PMH: GERD and dyslipidemia. Medications: omeprazole 20 mg qd, atorvastatin 40 mg qd.

He receives a drug eluting stent and requires dual antiplatelet therapy. Aspirin and clopidogrel were added to his regimen.

What would you do?

- a. Discontinue omeprazole, add ranitidine
- b. Discontinue clopidogrel, add prasugrel
- c. Assess platelet reactivity with VerifyNow Assay
- d. Recommend genetic testing

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Prasugrel (Effient®)

- Thienopyridine approved July 2009
- Indicated in ACS managed with PCI
- Contraindicated in patients with a previous TIA or stroke
- Not used in elective PCI
- Benefit in patients > 75 years or < 60 kg has not been proven (May give a lower dose (5 mg) for patients <60 kg)

UK National Institute for Health & Clinical Excellence (NICE) ACS having PCI only in the following three circumstances:
- Immediate primary PCI for STEMI is necessary
- Stent thrombosis has occurred during clopidogrel treatment
- The patient has diabetes mellitus.
Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes (TRITON-TIMI 38)


- Compare prasugrel with standard dose clopidogrel in patients with ACS scheduled for PCI
- Prospective, international, double-blind, randomized
- Prasugrel 60 mg load; 10 mg daily vs Clopidogrel 300 mg load; 75 mg daily
- 13,608 patients in 707 sites

Study Population

- Inclusion Criteria
  - STEMI (n=3534)
    - Enrolled 12 hrs after onset of symptoms if primary PCI planned or within 14 days after receiving treatment
  - Moderate to High Risk UA or NSTEMI (n=10,074)
    - Ischemic symptoms lasting ≥ 10 min and occurring within 72 hours before randomization

- Exclusion Criteria
  - Increased risk of bleeding
  - Anemia
  - Thrombocytopenia
  - History of pathologic intracranial findings

Intervention

- Choice of vessels treated, devices used and adjunctive medications was left to the discretion of treating physician
- All patients received daily aspirin at a suggested dose of 75-161 mg
- Follow-up evaluations:
  - Hospital discharge, 30 days, 90 days and at 3 month intervals thereafter for 6-15 months

Results

<table>
<thead>
<tr>
<th>End Point</th>
<th>Prasugrel (N=6813)</th>
<th>Clopidogrel (N=6795)</th>
<th>Hazard Ratio for Prasugrel (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from CV causes, nonfatal MI, or nonfatal stroke</td>
<td>643 (9.9)</td>
<td>781 (12.1)</td>
<td>0.81 (0.73-0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>133 (2.1)</td>
<td>150 (2.4)</td>
<td>0.89 (0.70-1.12)</td>
<td>0.31</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>475 (7.3)</td>
<td>620 (9.5)</td>
<td>0.76 (0.67-0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>61 (1.0)</td>
<td>60 (1.0)</td>
<td>1.02 (0.71-1.45)</td>
<td>0.93</td>
</tr>
<tr>
<td>Urgent target vessel revascularization</td>
<td>156 (2.5)</td>
<td>233 (3.7)</td>
<td>0.66 (0.54-0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>68 (1.1)</td>
<td>142 (2.4)</td>
<td>0.48 (0.36-0.64)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
**Results**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Prasugrel (N=6741)</th>
<th>Clopidogrel (N=6716)</th>
<th>Hazard Ratio for Prasugrel (95%)</th>
<th>P value</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CABG-related TIMI major bleeding</td>
<td>146 (2.4)</td>
<td>111 (1.8)</td>
<td>1.32 (1.03-1.68)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>85 (1.4)</td>
<td>56 (0.9)</td>
<td>1.52 (1.08-2.13)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>21 (0.4)</td>
<td>5 (0.1)</td>
<td>4.19 (1.56-11.11)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Major or minor TIMI bleeding</td>
<td>303 (5.0)</td>
<td>231 (3.8)</td>
<td>1.31 (1.11-1.56)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Bleeding requiring transfusion</td>
<td>244 (4.0)</td>
<td>182 (3.0)</td>
<td>1.34 (1.11-1.63)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CABG-related TIMI major bleeding</td>
<td>24 (13.4)</td>
<td>6 (3.2)</td>
<td>4.73* (1.90-11.82)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Net Clinical Benefit**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
<th>Hazard Ratio for Prasugrel (95%)</th>
<th>P value</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%</td>
<td>727/6551</td>
<td>854/6539</td>
<td>0.84 (0.76-0.93)</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
<tr>
<td>Age &lt; 75 yrs, weight ≥ 60 kg AND no history of stroke or TIA</td>
<td>523/5421</td>
<td>641/5383</td>
<td>0.80 (0.71-0.89)</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
<tr>
<td>Hx of Stroke or TIA</td>
<td>57/262</td>
<td>39/256</td>
<td>1.54 (1.02-2.32)</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions**

- Prasugrel given as a loading dose of 60mg followed by a maintenance dose 10mg daily is more effective than standard dose clopidogrel at preventing ischemic events.
- Increase in effectiveness is coupled with an increase in the rate of major bleeding.

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**Other Options**

- Use H₂ blockers (but not cimetidine)
- Use prasugrel
- Do genetic testing

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**Total Deaths in TRITON Trial**

<table>
<thead>
<tr>
<th>Group</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA/NSTEMI</td>
<td>130</td>
<td>121</td>
<td>+9</td>
</tr>
<tr>
<td>STEMI</td>
<td>58</td>
<td>76</td>
<td>-18</td>
</tr>
<tr>
<td>Combined</td>
<td>188</td>
<td>197</td>
<td>-9</td>
</tr>
</tbody>
</table>

Serebruany VL. Am J Cardiol 2010; available at: www.AJConline.org.
Results from Genetic Testing

- Increase the clopidogrel dose?
- Switch to ticlopidine or prasugrel?
- Add cilostazol?

- We don't have definitive outcome data on any of these options in clopidogrel nonresponders yet.

Other Options

- Use H₂ blockers (but not cimetidine)
- Use prasugrel
- Do genetic testing
- Assess platelet reactivity with VerifyNow Assay

Recent/Ongoing Trials

- **GRAVITAS** (www.theheart.org)
  - Randomizing to high-dose vs usual-dose clopidogrel in patients “resistant to clopidogrel”
  - No significant difference in outcomes
- **TRIGGER PCI**
  - randomizing to normal dose clopidogrel or prasugrel
  - “resistance to clopidogrel” using VerifyNow Assay platelet reactivity units (PRU) > 235

Future antiplatelet agent

- **Ticagrelor** (Brilinta®, Astra Zeneca)
Ticagrelor (Brilinta®)

- Not a thienopyridine (different from ticlopidine, clopidogrel, prasugrel)
- Reversible, concentration dependent inhibition of the P2Y<sub>12</sub> receptor
- Not a prodrug
- Rapidly absorbed, one active metabolite
- Max Cp and platelet inhibition 1-3 hrs post dose
- Plasma half-life = 6-13 hours, given BID
- Functional recovery of circulating platelets within ~48 hours


PLATO

Study of Platelet Inhibition and Patient Outcomes

- Primary- Time to occurrence of composite of death from vascular causes, MI or stroke
- Secondary efficacy point- the primary in the subgroup undergoing an invasive strategy
- Safety:
  - Major, life-threatening bleeding
    - Fatal, intracranial, intrapericardial bleeding
    - Hypovolemic shock, requiring pressors/surgery
    - 5 g/dL drop in Hgb or transfusion of 4 units
  - Other major bleeding
    - Significant disability (intracranial bleeding)
    - 3 to <5 g/dL drop in Hgb or transfusion of 2 to 3 units
  - Minor bleeding

PLATO Methodology

- Patients randomized to:
  - Ticagrelor 180 mg load, 90 mg bid
  - Clopidogrel 300 mg load, 75 mg daily
  - Patients undergoing PCI after randomization received an additional dose of study drug
- Aspirin ± 325 mg load, then 75-100 mg daily
  - (325 mg x 6 months post stent)
- Outpatient visits at 1,3,6,9 and 12 months
- Safety visit 1 month following last visit
- Intention to treat analysis

PLATO Efficacy Results @ 12 Months

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>Hazard ratio (95 % CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary End Point: Composite (%)</td>
<td>9.8 N=9333</td>
<td>11.7 N=9291</td>
<td>0.84 (0.77-0.92)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Secondary End Point: (PCI planned) Composite (%)</td>
<td>8.9 N=6732</td>
<td>10.6 N=6676</td>
<td>0.84 (0.75-0.94)</td>
<td>0.003</td>
</tr>
<tr>
<td>Other 2° End Pt: Death from any causes, MI, stroke (%)</td>
<td>10.2 N=9333</td>
<td>12.3 N=9291</td>
<td>0.84 (0.77-0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other 2° End Pt: MI</td>
<td>5.8 N=9333</td>
<td>6.9 N=9291</td>
<td>0.84 (0.75-0.95)</td>
<td>0.005</td>
</tr>
<tr>
<td>Other 2° End Pt: Stroke (%)</td>
<td>1.5 N=9333</td>
<td>1.3 N=9291</td>
<td>1.17 (0.91-1.52)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

### PLATO Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>Hazard ratio (95 % CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding (%)</td>
<td>11.6%</td>
<td>11.2%</td>
<td>1.04 (0.95-1.13)</td>
<td>0.43</td>
</tr>
<tr>
<td>Life-threatening bleeding (%)</td>
<td>5.8%</td>
<td>5.8%</td>
<td>1.03 (0.90-1.16)</td>
<td>0.7</td>
</tr>
<tr>
<td>Dyspnea (%)</td>
<td>13.8%</td>
<td>7.8%</td>
<td>1.84 (1.68-2.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bradycardia (%)</td>
<td>4.4%</td>
<td>4.0%</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>≥3 second ventricular pause (first week) (%)</td>
<td>5.8%</td>
<td>3.6%</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

### PLATO Summary

- **Pros**
  - Significant decrease in primary endpoint in patients managed with invasive and non-invasive strategies
  - Significant benefit observed by 30 days
  - No excess bleeding
- **Cons**
  - No significant benefit was observed in patients living in North America, and those not receiving lipid lowering drugs at randomization
  - Discontinuation rates higher with ticagrelor 23.4% vs 21.5% (p = 0.002)

### Secondary Prevention

**Aspirin**

- All post PCI stent patients 162-325 mg without contraindications for at least 1 month following BMS, or 12 months following DES, then 75-162 mg indefinitely (Class I, LOE B)
- If higher risk of bleeding use 75-162 mg during initial period following stent implantation (Class IIa, LOE C)

**Clopidogrel**

- For all post PCI patients receiving a DES, 75 mg daily x 12 months.
- If BMS: 75 mg x 1 month minimum and ideally for 12 months unless patient is at increased risk of bleeding (Class I, LOE B)

**STEMI patients not undergoing stenting**, treat with clopidogrel for 14 days (Class I, LOE B)

Long term therapy (1 year) is reasonable in STEMI patients, regardless of whether or not they undergo reperfusion therapies (Class IIa, LOE C)
Secondary Prevention

Beta blockers
- Start and continue indefinitely in all patients who have had MI, ACS or LV dysfunction with or without symptoms of HF unless contraindicated (Class I, LOE A)

Inhibit the RAAS
- ACEI if LVEF < 40% and for patients with preserved EF with HTN, DM or CKD unless contraindicated (Class I, LOE A)
- Consider for all other patients who are not lower risk (Class I, LOE B)
- Among lower risk patients recovering from STEMI, use of ACEI is reasonable (Class IIa, LOE B)
- ARBS if intolerant to ACEI (Class I, LOE A)
- Aldosterone blockade in post MI patients without significant renal disease or hyperkalemia if: LVEF < 40% or have either DM or HF (Class I, LOE A)

Secondary Prevention

- Smoking Cessation
- Weight Reduction BMI 18.5 to 24.9 kg/m²
- Physical Activity 30 minutes/day (minimum 5 days/week)
- Dietary Changes
- Blood Pressure < 140/90 or < 130/80 if patient has DM or CKD
- Lipids Initiate therapy prior to discharge
  - LDL <100 mg/dL (LDL < 70 is reasonable)(Class IIa, LOE A)
  - If baseline LDL 70-100, it is reasonable to treat to <70mg/dL (Class IIa, LOE B)

Secondary Prevention

Diabetes HgbA₁c < 7%
Influenza vaccine Should be vaccinated annually
Musculoskeletal Assess at time of discharge, if needed
Pain begin with acetaminophen, small doses of narcotics or non-acetylated salicylate (Class I, LOE C)
Use non-selective NSAIDS (naproxen) as next step (Class IIa, LOE C)
Do not use relative COX-2 selective agents when other agents provide pain relief (Class III, LOE C)