Antiplatelet Therapy: Focus on Clopidogrel (Plavix®) “Resistance”

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Objectives

1. Review the pharmacology of clopidogrel
2. Review the mechanism of the drug interaction between clopidogrel and proton pump inhibitors (PPI) as well as effect of CYP2C19 poor metabolizers on clopidogrel
3. Evaluate the effect of clopidogrel interaction with PPIs on clinical outcomes
4. Evaluate options for management of CYP2C19 poor metabolizers
**Clopidogrel (Plavix®)**

- **Class**: thienopyridine platelet-aggregation inhibitor
- **Mechanism of Action**: prevents adenosine diphosphate (ADP) from binding to the P2Y12 ADP platelet receptors

![Clopidogrel Metabolism](image)

**Figure 1.** Metabolism of clopidogrel. Clopidogrel undergoes a 2-step metabolism and can involve several different cytochrome P450 enzymes.


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**Clopidogrel**

- **Indicated for secondary prevention of atherothrombotic events in patients with**:
  - Recent myocardial infarction (MI) or stroke
  - Established peripheral arterial disease (PAD)
  - Unstable angina (UA)
  - Non-ST-segment elevation MI (NSTEMI)
  - ST-segment elevation MI (STEMI)
**Clopidogrel**

- Factors that can contribute to variability in clopidogrel response:
  - Compliance with therapy
  - Variable intestinal absorption
  - Differences in platelet response to ADP
  - Genetic differences in CYP metabolic activity
  - Drug interactions

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**PPIs and CYP2C19 Metabolism**

![Diagram showing the metabolism of PPIs and CYP2C19](Diagram.png)

Clopidogrel and Gastrointestinal (GI) Injury

Platelet aggregation

Release of various platelet-derived growth factors and pro-angiogenic growth factors (vascular endothelial growth factor)

Promote angiogenesis

Repair of GI mucosal disruptions

J Am Coll Cardiol 2008; 52:1502-17.

ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use

J Am Coll Cardiol 2008;52:1502-17.
Effect of Clopidogrel Interaction with PPIs on Platelet Inhibition

Platelet Function Tests

<table>
<thead>
<tr>
<th>Platelet aggregation (light transmission or multiple-electrode platelet aggregometry)</th>
<th>Vasodilator-stimulated phosphoprotein (VASP) phosphorylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determines percent of platelet aggregation in whole blood after the introduction of a platelet agonist such as ADP</td>
<td>Directly measures the function of the P2Y12 receptor</td>
</tr>
<tr>
<td>Affected by aspirin</td>
<td>Not affected by aspirin</td>
</tr>
<tr>
<td>No consensus definition for classifying clopidogrel response</td>
<td>Platelet reactivity index (PRI): selective index of platelet reactivity to clopidogrel</td>
</tr>
<tr>
<td></td>
<td>PRI &lt; 50%: good responders</td>
</tr>
<tr>
<td></td>
<td>PRI &gt; 50%: poor responders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Type of Study and Population</th>
<th>Primary Endpoint Results</th>
<th>Authors' Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Omeprazole Clopidogrel Aspirin (OCLA) Study</strong></td>
<td>Effect of omeprazole on antiplatelet activity of clopidogrel</td>
<td>RCT in patients undergoing coronary artery stent placement (n=140)</td>
<td>Omeprazole (20mg daily X 7 days) group PRI (mean ± SD): 51.4% ± 16.4% Placebo group PRI: 39.8% ± 15.4%</td>
<td>Omeprazole decreases the antiplatelet activity of clopidogrel vs placebo</td>
</tr>
<tr>
<td><strong>Siller-Matula et al.</strong></td>
<td>Effect of pantoprazole and esomeprazole on antiplatelet activity of clopidogrel</td>
<td>Prospective study in patients undergoing percutaneous coronary intervention (PCI) who had received dual antiplatelet therapy for ~90 days (n=300)</td>
<td>PPI group mean PRI (n=226): 51% (95% CI: 48-54%) No PPI group mean PRI (n=74): 49% (95% CI: 43-55%)</td>
<td>No interaction between clopidogrel and esomeprazole or pantoprazole Presumed interaction is not a PPI class effect but instead specific to omeprazole</td>
</tr>
<tr>
<td><strong>Sibbing et al.</strong></td>
<td>Effect of PPI use (pantoprazole, omeprazole, esomeprazole) on ADP-induced platelet aggregation</td>
<td>Retrospective study in patients with coronary artery disease (CAD) who had undergone PCI and had received dual antiplatelet therapy (n=1000)</td>
<td>Significant increase in platelet aggregation (measured by multiple-electrode platelet aggregometry) demonstrated in patients receiving omeprazole vs no PPI (p=0.001) No significant difference was seen between patients receiving pantoprazole (p=0.69) or esomeprazole (p=0.88) vs no PPI</td>
<td>No interaction between clopidogrel and esomeprazole or pantoprazole Presumed interaction is not a PPI class effect but instead specific to omeprazole</td>
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**Proton Pump Inhibitors and Clopidogrel Association (PACA) Trial**

**Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation (PRINCIPLE) T304 44 Trial**

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<th>Authors' Conclusions</th>
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</thead>
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<tr>
<td><strong>Proton Pump Inhibitors and Clopidogrel Association (PACA) Trial</strong></td>
<td>Compare the influence of omeprazole and pantoprazole on the antiplatelet effect of 150 mg clopidogrel</td>
<td>Prospective, randomized study in patients undergoing coronary artery stenting for NSTEMI (n=104) on dual antiplatelet therapy -Omeprazole (n=52) -Pantoprazole (n=52)</td>
<td>PRI 1 month after hospital discharge (p=0.007): Omeprazole group:48±17% Pantoprazole group: 36±20%</td>
<td>NSTEMI patients treated with pantoprazole have a better platelet response to clopidogrel than those treated with omeprazole Interaction with PPIs is not a class effect</td>
</tr>
<tr>
<td><strong>Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation (PRINCIPLE) T304 44 Trial</strong></td>
<td>Effect of PPIs on antiplatelet activity of clopidogrel and prasugrel</td>
<td>Double-blind, two-phase crossover study with patients undergoing elective PCI (n=201) randomized to prasugrel 60mg loading dose then 15mg daily or clopidogrel 600mg loading dose then 150mg daily</td>
<td>Inhibition of Platelet Aggregation</td>
<td>There is modest attenuation of in-vitro platelet effects of both clopidogrel and prasugrel when a PPI is present</td>
</tr>
</tbody>
</table>

**J Am Coll Cardiol 2009;51:256-60. **

**Lancet 2009;374:989-97. **


**Thromb Haemost 2009; 101:714-719. **
Effect of Clopidogrel Interaction with PPIs on Clinical Outcomes

Pezalla et al.

- Type: retrospective cohort study with data from medical and pharmacy databases from Aetna®
- Population: patients <65 yo who were adherent to clopidogrel therapy for 1 year
- Primary Endpoint: acute MI rates
  - Clopidogrel + no PPI (n=4800)
  - Clopidogrel + low PPI exposure (n=721)
  - Clopidogrel + high PPI exposure (n=?)

**Pezalla et al.**

- **Results:**
  
<table>
<thead>
<tr>
<th></th>
<th>No PPI</th>
<th>Low PPI</th>
<th>High PPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year Acute MI Rates</td>
<td>1.38% (66/4800)</td>
<td>3.08% (22/712)</td>
<td>5.03% (?)</td>
</tr>
</tbody>
</table>

- **Critique and Limitations:**
  - Letter to the editor without peer review
  - Low and high PPI actual exposures not defined
  - Specific PPIs included not stated
  - Significant differences in comorbid conditions (hypertension, diabetes) between groups


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**Juurlink et al.**

- **Type:** population-based, nested case-control in Canada

- **Population:**
  - >66 yo (n=2791)
  - Discharged from the hospital with a diagnosis of ACS (April 1, 2002 – December 31, 2007) and followed for 90 days or until readmission
  - Clopidogrel prescription within 3 days of discharge
  - Cases matched to controls based on age, receipt of PCI, hospital discharge date, predicted probability of mortality

Juurlink et al.

- Primary Endpoint: death or readmission for AMI within 90 days after the initial hospital discharge

- Results:
  - Cases (n=734): died or readmitted for AMI within 90 days after discharge
  - Controls (n=2057): not readmitted within 90 days
  - Use of PPI associated with increased odds of reinfarction vs no PPI (adjusted odds ratio [OR], 1.27; 95% CI: 1.03-1.57)
  - No association between pantoprazole use and reinfarction when pantoprazole analyzed separately (adjusted OR, 1.02; 95% CI: 0.7-1.47)
  - Increased odds of reinfarction in patients receiving other PPIs (adjusted OR, 1.40; 95% CI, 1.10-1.77)

Juurlink et al.

- Authors’ conclusions:
  - Pantoprazole not associated with a significant drug interaction with clopidogrel and should be used when PPI necessary

- Critique and Limitations:
  - Subgroup analysis of patients treated with pantoprazole likely underpowered (n=46 cases, n=125 controls)
  - Subgroup analyses examining each of the other PPIs individually in combination with clopidogrel not performed
Ho et al.

• Type: retrospective cohort study from pharmacy refill data

• Population:
  – Documented MI or unstable angina discharged from a Veterans Affairs facility with a prescription for clopidogrel between October 2003 -January 2006 with or without a PPI (n=8205)
    – Omeprazole (n=3132, 59.7%)
    – Rabeprazole (n=151, 2.9%)
    – Lansoprazole (n=22, 0.4%)
    – Pantoprazole (n=15, 0.2%)
    – >1 PPI (n=1924, 36.7%)

• Primary Endpoint: death or rehospitalization for ACS

JAMA 2009;301(9):937-44.

Ho et al.

• Results:
  – Increased risk of death or rehospitalization for ACS with clopidogrel in combination with a PPI after discharge (adjusted OR, 1.25; 95% CI, 1.11-1.41)
  – Rates of adverse outcomes significantly higher with omeprazole (OR, 1.24; 95% CI, 1.08-1.41) and rabeprazole (OR, 2.83; 95% CI, 1.96-4.09) vs no PPI use

JAMA 2009;301(9):937-44.
Ho et al.

• Authors’ conclusions:
  – Concomitant use of clopidogrel and PPIs after hospital discharge for ACS is associated with an increased risk of adverse outcomes than use of clopidogrel without PPIs

• Critique and Limitations:
  – Patients in the group that received PPIs had higher rates of comorbidities (diabetes, prior MI, PCI within last 6 months, heart failure, peripheral vascular disease, cerebrovascular disease, renal disease) at discharge than patients who did not receive PPIs

Post-Hoc Analysis of the Clopidogrel for the Reduction of Events During Observation (CREDO) Trial

• Type of study: Retrospective analysis of data from patients who received clopidogrel + ASA with or without a PPI

• Purpose: assess baseline PPI use effect on 28-day and 1-year composite endpoints in patients undergoing PCI – 300mg clopidogrel loading dose + 1-year 75mg clopidogrel

<table>
<thead>
<tr>
<th></th>
<th>28 Days</th>
<th>One Year</th>
<th>p-value*</th>
<th>OR (95% CI)</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Death/MI/TVR</td>
<td>Death/MI/Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel / PPI (n=176)</td>
<td>10/176 (10.3)</td>
<td>1.754 (0.997, 3.227)</td>
<td>0.251</td>
<td>23/176 (13.3)</td>
<td>1.003 (1.015, 2.627)</td>
</tr>
<tr>
<td>Clopidogrel / no PPI (n=877)</td>
<td>41/877 (4.9)</td>
<td>0.897 (0.477)</td>
<td>0.771</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo/PPI (n=190)</td>
<td>10/190 (5.3)</td>
<td>1.000 (0.614, 1.647)</td>
<td>0.921</td>
<td>20/190 (10.5)</td>
<td>1.054 (1.031, 2.141)</td>
</tr>
<tr>
<td>Placebo / no PPI (n=873)</td>
<td>85/873 (9.7)</td>
<td>0.949 (0.613, 1.488)</td>
<td>0.749</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Multivariate logistic regression model: PPI vs. no PPI within treatment stratum † Multivariate Cox proportional hazard model: PPI vs. no PPI within treatment stratum

Circulation 2008;118:S_815 abstract 3999.
Post-Hoc Analysis of the CREDO Trial

• Authors' Conclusions:
  – PPI use at baseline associated with increased CV events in patients receiving clopidogrel and in all patients in the trial
  – PPI use, independent of clopidogrel use, was associated with increased adverse cardiovascular outcomes

• Critique and Limitations:
  – The small number of patients in the groups who received PPIs and the lack of information about baseline characteristics in these patient groups limit the conclusions that can be drawn

Post-Hoc Analysis of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON) - TIMI 38 Trial

• Primary Endpoint: composite of cardiovascular death, non-fatal MI, or non-fatal stroke

• Study Design:
  – Double blind, phase 3 trial in ACS patients (n = 13608):
    – Prasugrel 60mg loading dose then 10mg daily
    – Clopidogrel 300mg loading dose then 75mg daily
    – 4529 (33%) patients were on a PPI at randomization
      – Pantoprazole: 1844
      – Omeprazole: 1675
      – Rabeprazole: 66
      – Lansoprazole: 441
      – Esomeprazole: 613

### Prasugrel and Ticagrelor

**Figure 1. Biotransformation and Mode of Action of Clopidogrel, Prasugrel, and Ticagrelor.**

Prasugrel, a cyclopropyl methyltriazole, is rapidly absorbed in the intestines. The absorbed drug does not require further biotransformation for activation. It directly and reversibly inhibits the platelet adenosine diphosphate (ADP) receptor P2Y12. The half-life of prasugrel is 7–8 hours, the metabolites prasugrel and ticagrelor are products. Their active metabolites irreversibly bind to ADP receptors for the platelet's life span. After initial absorption of ticagrelor it releases two cytochrome P450-dependent oxidation steps to generate its active compound. Most of the CYP-dependent activation occurs in the liver. Relevant CYP isoenzymes involved in the activation of clopidogrel and prasugrel are also shown. Their activity may be affected by genetic polymorphisms.

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**Post-Hoc Analysis of the TRITON-TIMI 38 Trial Primary Endpoint Incidence**

<table>
<thead>
<tr>
<th>Drug</th>
<th>PPI (%)</th>
<th>No PPI (%)</th>
<th>Unadjusted HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>11.8</td>
<td>12.2</td>
<td>0.98 (0.84–1.14)</td>
<td>0.80</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>10.2</td>
<td>9.7</td>
<td>1.05 (0.89–1.23)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>PPI (%)</th>
<th>No PPI (%)</th>
<th>Adjusted HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>11.8</td>
<td>12.2</td>
<td>0.94 (0.80–1.11)</td>
<td>0.46</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>10.2</td>
<td>9.7</td>
<td>1.00 (0.84–1.20)</td>
<td>0.97</td>
</tr>
</tbody>
</table>
Post-Hoc Analysis of the TRITON-TIMI 38 Trial

• Authors’ Conclusions:
  – Use of a PPI not associated with a higher risk of cardiovascular events for patients on either clopidogrel or prasugrel
  – First study to show that it appears to be safe to combine a PPI with prasugrel

• Critique and Limitations:
  – Use of a PPI was not randomized in the current study
  – Patients treated with a PPI were older, had a higher index diagnosis of UA/NSTEMI, history of peptic ulcer disease
**Clopidogrel and the Optimization of Gastrointestinal Events (COGENT-1) Study**

- **Purpose**: safety and efficacy of CGT-2168 (clopidogrel 75mg/omeprazole 20mg) vs clopidogrel in reducing the incidence of GI bleeding and symptomatic ulcer disease
- **Design**: randomized, double-blind, parallel group, phase 3 trial
- **Early termination** (December 2008) by study sponsor (Cogentus Pharmaceuticals) due to bankruptcy

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**COGENT-1 Study**

- **Primary Outcome**:
  - Composite of upper gastrointestinal clinical events (symptomatic gastroduodenal ulcer, persistent pain with multiple gastric erosions, obstruction or perforation)
- **Secondary Outcomes**:
  - Composite of gastroduodenal bleeding, symptomatic gastroduodenal ulcer, obstruction or perforation
  - Composite of gastroduodenal bleeding, obstruction or perforation
  - Discontinuation of study medication attributed to gastrointestinal signs or symptoms
  - Gastroesophageal reflux disease, as evidenced by symptomatic endoscopically-confirmed erosive esophagitis
  - Dyspepsia, defined as an increase of at least ten points on the "pain intensity" component of the SODA instrument from baseline
  - Occurrence of a cardiovascular event (cardiovascular death, nonfatal myocardial infarction, CABG or PCI, or confirmed ischemic stroke)
**COGENT-1 Study**

- Number needed to treat: $3200 \rightarrow 4200 \rightarrow 5000$
  
  $- N = 3627/5000$

- Mean follow-up scheduled: $48 - 96$ weeks
  
  $- $Mean follow-up: 133 days ($\sim 19$ weeks)
  
  $- $Maximum follow-up: 362 days ($\sim 51$ weeks)

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COGENT-1 Study

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo, n</th>
<th>PPI, n</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI Events (Primary)</td>
<td>67</td>
<td>38</td>
<td>0.007</td>
</tr>
<tr>
<td>All CV Events</td>
<td>67</td>
<td>69</td>
<td>NS</td>
</tr>
<tr>
<td>MI</td>
<td>37</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>Revascularization</td>
<td>67</td>
<td>69</td>
<td>NS</td>
</tr>
</tbody>
</table>


**COGENT-1 Study**

- Authors’ Conclusions:
  - Data suggests that there is no clinically significant interaction between clopidogrel and PPIs
  - Assume that prasugrel and ticagrelor also have no interaction with PPIs
  - Consider administering clopidogrel in the morning and the PPI at night if concerned about the release kinetics of currently available formulations of either agent

- Critique and Limitations:
  - Early termination and limited ability of investigators to follow patients appropriately
  - Did not meet primary endpoint target enrollment
  - Not powered to evaluate cardiac outcomes


**Food and Drug Administration (FDA) and European Medicines Agency (EMEA) Alerts on Clopidogrel-PPI Interaction**
FDA Early Communication about an Ongoing Safety Review of Clopidogrel January 26, 2009

• FDA is continuing to study the effectiveness of clopidogrel in patients taking other medications, particularly PPIs, and in those with genetic variants linked with clopidogrel resistance and a subsequent increased risk of cardiovascular outcomes

• Published reports suggest that PPIs might interfere with the effectiveness of clopidogrel by inhibiting the enzyme that converts clopidogrel into its biologically active form but not all studies have suggested this effect

EMEA Alert on Clopidogrel-PPI Interaction May 29, 2009

• Clopidogrel may be less effective in patients receiving proton pump inhibitors (PPIs). This could result in patients being at an increased risk of thrombotic events, including acute MI

• Taking all the data into account, the Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended that the product information for all clopidogrel-containing medicines should be amended to discourage concomitant use of PPIs and clopidogrel-containing medicines unless absolutely necessary
FDA Alert on Clopidogrel-PPI Interaction
November 17, 2009

- When clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced
- Avoid using omeprazole and clopidogrel together
- Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction
- Not enough information about interaction with other PPIs other than omeprazole and esomeprazole
- The following drugs should also be avoided in combination with clopidogrel: esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine

Comparison Clopidogrel Active Metabolite Exposure and Platelet Inhibition with and without Omeprazole and Pantoprazole

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>AUC&lt;sup&gt;+&lt;/sup&gt;</th>
<th>Platelet Inhibition* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 5</td>
<td>Day 1</td>
</tr>
<tr>
<td>Clopidogrel plus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole**80 mg</td>
<td>↓46%</td>
<td>↓45%</td>
<td>↓42%</td>
</tr>
<tr>
<td>Pantoprazole 80 mg</td>
<td>↓24%</td>
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*Inhibition of platelet aggregation with 5 microM ADP
**Similar results seen when clopidogrel and omeprazole were administered 12 hours apart
*AUC at Day 5 is AUC<sub>0-24</sub>

Clopidogrel Active Metabolite Exposure and Platelet Inhibition with and without Omeprazole and Pantoprazole

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*Inhibition of platelet aggregation with 5 microM ADP
**Similar results seen when clopidogrel and omeprazole were administered 12 hours apart
*AUC at Day 5 is AUC<sub>0-24</sub>

Conclusion and Recommendation

• Evaluate the necessity of PPI therapy
  – Consider histamine H2 antagonists as an alternative to PPIs

• If PPIs necessary
  – Avoid omeprazole
  – Consider use of pantoprazole

• May consider platelet reactivity studies to determine % of platelet inhibition in select patients

Understanding the Effect of Genetic Polymorphisms on Clopidogrel
Genetic Polymorphisms related to clopidogrel

• Differing degrees of CYP2C19 function
  – Poor, intermediate, extensive and ultrarapid

• 3 major CYP2C19 polymorphisms
  – CYP2C19*1
    – Normal function
  – CYP2C19*2 & CYP2C19*3
    – Loss of function alleles
    – Account for 85% & 99% of nonfunctional alleles in whites

• Poor metabolizers have 2 loss-of-function alleles

FDA Boxed Warning

“To include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need to have been proved. Special problems, particularly those that may lead to death or serious injury, may be required by the [FDA] to be placed in a prominently displayed box.”
ACCF/AHA Clopidogrel Clinical Alert: Approaches to the FDA “Boxed Warning”

1. Adherence to ACCF/AHA guidelines for antiplatelet therapy should remain.
2. Genetic variability in CYP enzymes alter clopidogrel metabolism
   - Can affect inhibition on platelet function
3. Specific impact on individual genetic polymorphisms on clinical outcomes remains to be determined
4. Information on predictive value of pharmacogenomic testing is very limited
5. Current evidence is insufficient to recommend either routine genetic testing or platelet function testing
6. Several possible therapeutic options for patients who experience an adverse event while taking clopidogrel
7. Higher loading doses and higher maintenance doses have been found to improve platelet inhibition and may be considered alternatives

Acknowledgement

- Thank you to Mihaela Popescu, PharmD, Pharmacotherapy Resident at the Cleveland Clinic
Cleveland Clinic

Every life deserves world class care.