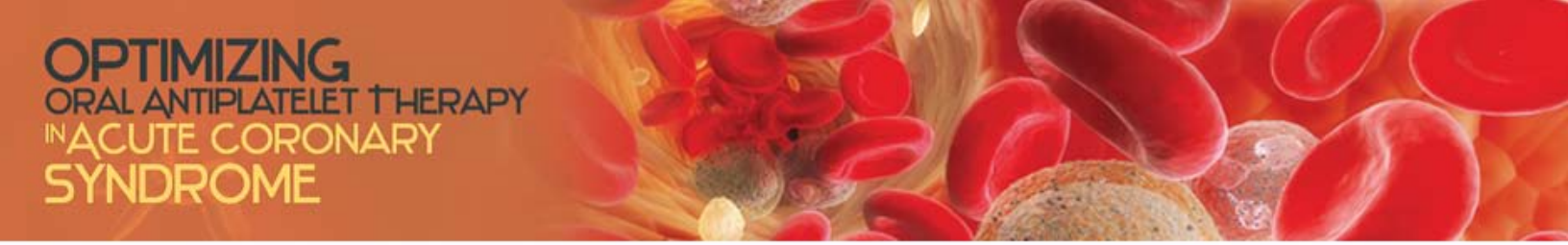

Why Focus on Antiplatelet Therapy?

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Oral antiplatelet therapy plays an important role in treating patients with acute coronary syndrome (ACS), including patients with non-ST segment elevation ACS and patients with ST-segment elevation myocardial infarction (STEMI). Roughly a decade ago, a paradigm shift in ACS took place, moving from the use of aspirin monotherapy to dual antiplatelet therapy with aspirin and the thienopyridine clopidogrel. This paradigm shift was supported by clinical trials demonstrating that dual therapy was associated with a reduced risk for ischemic events (myocardial infraction [MI], stroke, urgent target vessel revascularization) and death in patients with ACS compared with aspirin monotherapy.[1-4] This improved efficacy, however, was associated with an increased risk for bleeding. Despite the gains in morbidity and mortality with dual antiplatelet therapy, patients with ACS continued to experience residual ischemic events.[5] Within this context, it was discovered that the antiplatelet effects of clopidogrel are variable from patient to patient. Sources of variable response to clopidogrel may include genetic polymorphisms in metabolism, variability in formation of the active metabolite and platelet inhibition (i.e., response to the drug), and interactions with proton pump inhibitors (PPIs). Questions about the usefulness of laboratory testing of platelet function and genotypes in patients receiving clopidogrel have arisen and remain unresolved. Several *ex vivo* assays of platelet function are available, but none is ideal for predicting cardiovascular events.

Several strategies have been put forward to address the variable response to clopidogrel, including altering the dose of established antiplatelet agents or using new agents that might have a more consistent dose response. Each of these strategies has the potential to improve outcomes in patients with ACS. This information plus the frequent release of new information related to emerging antiplatelet agents (e.g., ticagrelor, vorapaxar) and treatment strategies (e.g., the use of cilostazol as part of triple antiplatelet therapy) makes it important for pharmacists to stay abreast of current thinking on the optimal approach to using oral antiplatelet agents in patients with ACS.

New Educational Initiative

ASHP Advantage recently embarked on a new multi-format educational initiative focusing on issues related to optimizing the use of oral antiplatelet therapy in patients with acute coronary syndrome. The initiative is supported by an educational grant from Astra Zeneca. A Midday Symposium, *Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome*, was presented at the 45th ASHP Midyear Clinical Meeting and Exhibition in Anaheim, California, on December 7, 2010. The symposium was simultaneously webcast, enabling a total of more than 600 individuals to participate. Attendees

submitted questions about unresolved issues and controversies, and these were later addressed by Initiative Chair Paul P. Dobesh, Pharm.D., in a live webinar on March 2, 2011, and are the basis of the frequently asked questions in this e-newsletter.

If you missed the Midyear symposium, it is now available as a web-based activity and is approved for two hours of continuing pharmacy education credit. Its "on-demand" format is convenient since it may be completed at any time. For more information and to access the web-based activity, go to the web portal at www.ashpadvantage.com/optimize.

Faculty Podcast Interviews

Visit the Optimize ACS web portal or click here to listen to podcast interviews with the initiative faculty. Three interviews, each lasting 6 to 8 minutes, are available:

- Current Options for Managing Antiplatelet Therapy in Acute Coronary Syndrome – Toby Trujillo, Pharm.D.
- Potential Use of Platelet Function and Genetic Testing in Guiding Oral Antiplatelet Therapy in Acute Coronary Syndrome – Julie H. Oestreich, Pharm.D., Ph.D.
- Alternative Approaches to Oral Antiplatelet Management in Acute Coronary Syndrome – Paul P. Dobesh, Pharm.D.

Frequently Asked Questions

This e-newsletter features frequently asked questions (FAQs) addressed by the faculty pertaining to current information about interactions between clopidogrel and PPIs and the role of prasugrel (a newer thienopyridine) in treating patients with ACS. FAQs pertaining to laboratory testing of platelet function and genotype in patients receiving clopidogrel and emerging oral antiplatelet therapies will be discussed in the next e-newsletter.

Question: Should clopidogrel be avoided in all patients receiving PPIs or only those receiving omeprazole?

Clopidogrel is a prodrug that undergoes a two-step activation process, and both steps take place within the liver.[6] Although multiple enzymes may take part in clopidogrel activation, cytochrome P450 (CYP) 2C19 is a key enzyme in both steps.[6] Omeprazole and other PPIs are CYP2C19 inhibitors that can reduce the antiplatelet activity of clopidogrel. There is pharmacokinetic and pharmacodynamic evidence of an interaction between clopidogrel and PPIs,[7] but the evidence of clinical relevance of the interaction is conflicting and inconclusive.[8-14]

In a population-based nested case-control study of more than 13,000 patients with acute MI who received clopidogrel, the use of PPIs was associated with an increased risk of reinfarction within 90 days after hospital discharge.[8] However, a stratified analysis revealed that pantoprazole, which is a weak inhibitor of CYP2C19, was not associated with an increased risk of reinfarction. A retrospective cohort study of more than 8000 patients with ACS receiving clopidogrel after hospital discharge showed that the use of clopidogrel plus a PPI was associated with an increased risk of death or rehospitalization for ACS compared with the use of clopidogrel without a PPI.[9]

The labeling for clopidogrel was modified by the Food and Drug Administration (FDA) in March 2010 to reflect information available at the time about the interaction with PPIs, but more recent data from prospective studies and registries do not support a clinically meaningful interaction between the drugs.

In the Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) trial (a randomized, double-blind, double-dummy, placebo-controlled, parallel-group, phase 3 efficacy and safety study), a fixed-dose combination of clopidogrel (75 mg) and omeprazole (20 mg) known as CGT-2168 was compared with clopidogrel alone in 3761 patients with ACS.[10] The COGENT trial was terminated early because the sponsor declared bankruptcy. The rates of survival and cardiovascular events over a 1-year period were similar in the two treatment groups.

A recently published analysis of data from 2353 patients with MI treated with clopidogrel in the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (known as FAST-MI) revealed no significant differences between users and non-users of PPIs in the rates of in-hospital death or a composite of death, MI, or stroke.[11] No significant differences in the in-hospital or 1-year rates of death, MI, or stroke were observed when the type of PPI or CYP 2C19 genotype was taken into account [Figures 1 and 2].

Figure 1: FAST-MI Registry: In-hospital Death, MI, or Stroke[11]

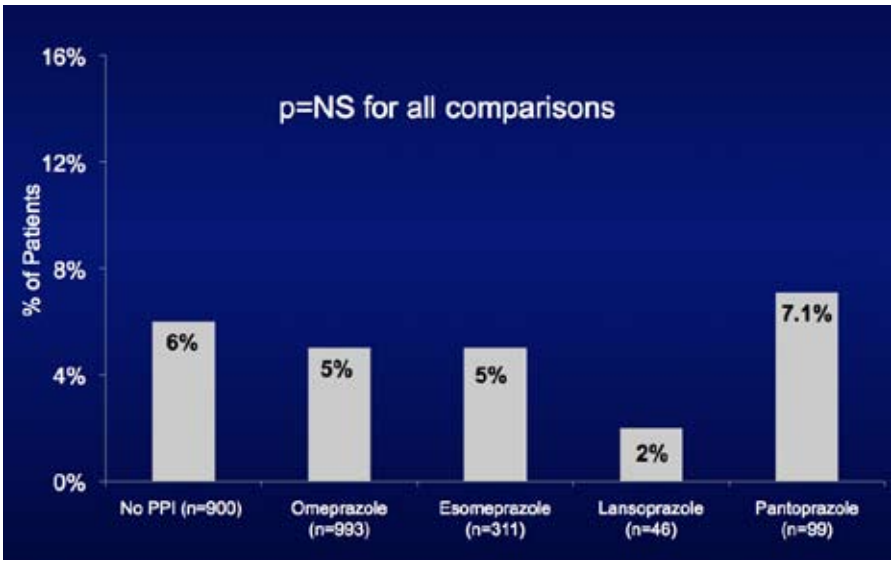
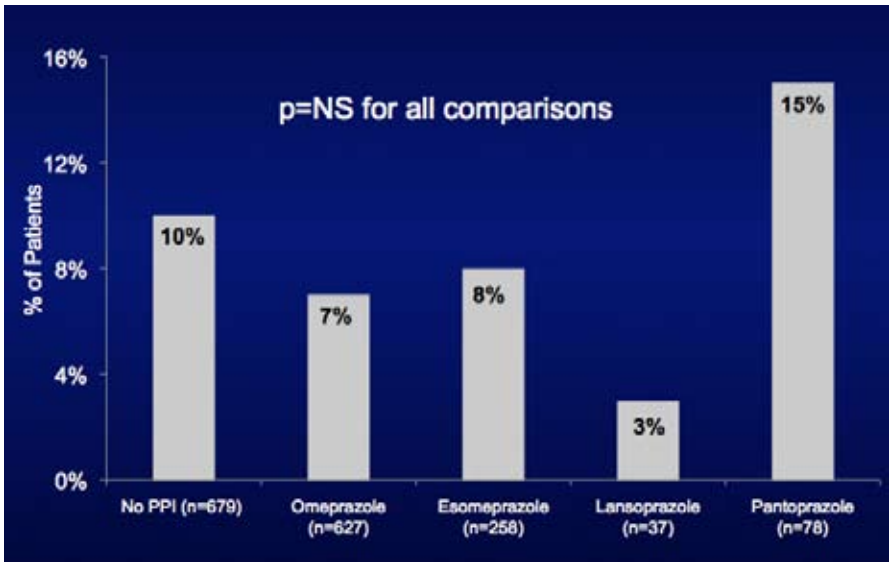


Figure 2. FAST-MI Registry: One-Year Death, MI, or Stroke[11]



In the TRITON-TIMI 38 study comparing clopidogrel and prasugrel in patients with planned percutaneous coronary intervention (PCI), roughly one third of participants received PPIs.[12,13] There was no association between PPI use or the type of PPI used (omeprazole, esomeprazole, lansoprazole, pantoprazole) and patient outcomes (ischemic events and cardiovascular death).[13]

In a Danish cohort study of more than 56,000 adults discharged from the hospital after a first MI, including 24,702 patients who received clopidogrel and 6753 who received concomitant PPIs, there was no significant difference between patients receiving a PPI without clopidogrel and patients receiving a PPI plus clopidogrel in the risk of cardiovascular death, MI, or stroke.[14] Thus, PPIs appear to be associated with cardiovascular risk independent of clopidogrel use.

The FDA-approved clopidogrel labeling leaves little room for interpretation despite the available scientific evidence. In patients receiving clopidogrel, the use of omeprazole should be avoided, the adequacy of platelet inhibition during concomitant clopidogrel and omeprazole therapy should be verified using platelet function testing, or the clopidogrel dosage should be increased (perhaps to 150 mg daily, although an appropriate dosage has not been established).[15] Using pantoprazole or another acid-suppressant agent with less CYP2C19 inhibitory activity instead of other PPIs or using prasugrel instead of clopidogrel is an alternative in patients who require concurrent PPI and antiplatelet therapies. Prasugrel is a prodrug that is rapidly hydrolyzed in the intestine by esterases and then undergoes a one-step activation process involving multiple CYP enzymes (primarily CYP3A4 and CYP2B6 and to a lesser extent CYP2C9 and CYP2C19).[16] Inhibition of CYP2C19 is not a concern with the use of prasugrel. If the investigational thienopyridine ticagrelor is approved, it may be another option since ticagrelor does not undergo biotransformation.[17]

Question: What is the role of prasugrel in treating patients with ACS?

Prasugrel, which received FDA approval in 2009, is a thienopyridine with more efficient generation of its active metabolite, more rapid onset of antiplatelet effect, and less variability compared with clopidogrel. Platelet inhibition with both drugs is irreversible, which is a concern for patients who may undergo coronary artery bypass graft (CABG) surgery because of the risk of bleeding. In the TRITON-TIMI 38 trial, dual therapy with prasugrel plus aspirin was significantly more effective for reducing the risk of death from cardiovascular causes, nonfatal MI, or nonfatal stroke (the primary end point) than clopidogrel plus aspirin in patients with planned PCI.[12] The relative reduction in risk of the primary end point was 19%, primarily because of a reduction in nonfatal MI. However, this benefit was accompanied by a significantly increased risk for major bleeding (hazard ratio 1.32 for non-CABG-related TIMI major bleeding and 4.73 for CABG-related TIMI major bleeding). There was no significant difference between treatment groups in mortality.

The increased risk of bleeding associated with prasugrel use was primarily observed in patients 75 years of age or older, those weighing less than 60 kg, or those with a history of stroke or transient ischemic attack (TIA).[12] As such, there was no difference in net clinical benefit (defined as the rate of death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding) between the agents in patients 75 years of age or older and patients weighing less than 60 kg. Furthermore, a net harm was associated with the use of prasugrel in patients with a history of stroke or TIA, resulting in the current FDA-approved labeling stating that prasugrel use in this population is contraindicated. Despite the elevated risk in these patient groups, a subgroup analysis demonstrated they comprised only 20% of the overall study population, and a significant reduction in the primary end point without increased risk of bleeding occurred in four out of five TRITON-TIMI 38 participants.[12]

Certain pre-specified subgroups in TRITON-TIMI 38 received a larger clinical benefit than the general population. The reduction in incidence of the primary end point associated with prasugrel use was larger in patients with STEMI than in other patients and in patients with diabetes than in patients without diabetes.[18] Thus, prasugrel might be a suitable alternative to clopidogrel in patients with diabetes or STEMI and patients less than 75 years of age, weighing 60 kg or more, and without a history of stroke or TIA.

Surprising results of an observational study of a subgroup of 346 TRITON-TIMI 38 patients who underwent CABG at some point during the 15-month trial recently were reported.[19] The all-cause mortality rate during the study period was significantly lower with prasugrel (2.3%) than with clopidogrel (8.7%), representing a 74% reduction in risk from the use of prasugrel instead of clopidogrel in this subgroup. These findings suggest that concerns about CABG-related bleeding with prasugrel may not have an impact on mortality, however, this subgroup analysis was performed with a small number of patients.

Redesigned ASHP Advantage Website Launched

Visit the redesigned ASHP Advantage website to browse listings of convenient on-demand educational activities, as well as publications, podcasts, and live webinars. The redesign has made it easier to find continuing-education activities and register for upcoming live webinars and other events. Visit www.ashpadvantage.com for a full listing of topics and activities.

Share Your Ideas

After participating in this educational initiative, have you come up with a unique approach to optimizing oral antiplatelet therapy at your institution that might be helpful to your colleagues? Share your ideas for how to incorporate into practice the concepts learned through this initiative. Send your ideas by e-mail to support@ashpadvantage.com (put "Optimize ACS" in the subject line).

To share this e-newsletter with a colleague, go to www.ashpadvantage.com/optimize and click on Refer a Colleague.

Continuing Pharmacy Education

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

For complete information about educational activities that are part of this initiative, visit www.ashpadvantage.com/optimize. There is no charge for the activities, and ASHP membership is not required.

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