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INSTRUCTIONS FOR PARTICIPATION:

Clinical Insights® in Platelet Management readers can receive instant, free CME credit by reading this newsletter in its entirety, and completing the accompanying posttest and activity evaluation.

LEARNING OBJECTIVES:

After studying the literature presented in this issue, participants will be able to:

- Recognize the optimal dosing and duration of antiplatelet agents in a range of patient types (young vs old, women vs men, low vs high BMI) to prevent ischemic events
- Balance the efficacy of an antiplatelet therapy with the risk for bleeding
- Identify the risks and benefits of different antiplatelet and antithrombotic therapies

TARGET AUDIENCE:

Physicians and other healthcare professionals who treat patients with acute coronary syndrome

DISCLOSURE:

Some material included in this newsletter may contain off-label (*) or investigational (!) uses of products. This material will be designated as shown.

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Do Proton Pump Inhibitors Negatively Impact Clopidogrel?

Guidelines from the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents, the American College of Gastroenterologists, and the American Heart Association recommend the use of proton pump inhibitors (PPIs)* to prevent gastrointestinal (GI) bleeding in patients taking dual antiplatelet therapy with clopidogrel and aspirin.¹ However, there is much debate about whether PPIs, either individually or as a class, interfere with the metabolism of clopidogrel and thus negatively impact patient outcomes. Clopidogrel efficacy is linked largely to its P450-dependent metabolism steps, including CYP2C19 and CYP3A4. Emerging data suggest that the PPI omeprazole decreases the antiplatelet action of clopidogrel through the inhibition of the CYP2C19 enzyme. This effect may not occur with other PPIs that are metabolized by CYP2C19 to a lesser degree. Considering that PPIs are among the most widely prescribed medications worldwide, understanding the degree and specifics of clopidogrel-PPI drug interactions is critical to cardiologists administering antiplatelet therapy. In January 2009, the FDA released an early communication on clopidogrel and PPIs recommending that health providers re-evaluate the need for starting or continuing treatment with a PPI in patients taking clopidogrel and urging that side effects be reported to the FDA's MedWatch Adverse Event Reporting program.²

clopidogrel after discharge from a Veteran's hospital.³ Most patients (63.9%) were also prescribed PPIs—most commonly, omeprazole (median follow-up: 521 days). In multivariable analysis, use of clopidogrel plus PPI was associated with an increased risk of death or rehospitalization for ACS versus clopidogrel use without PPI (Odds ratio [OR], 1.25; 95% confidence interval [CI], 1.11–1.41). Rates of recurrent hospitalization for ACS (14.6% [n=764] vs 6.9% [n=205]; $P<0.001$), revascularization (15.5% [n=815] vs 11.9% [n=353]; $P<0.001$), and death (19.9% [n=1,042] vs 16.6% [n=493]; $P<0.001$) were also higher among patients taking clopidogrel and PPIs compared with those taking clopidogrel alone. Although there was no dose-response relationship between PPI dose and adverse outcomes (OR, 1.00; 95% CI, 0.99–1.01 for each 1 mg-increment), each 10% increase in the amount of time taking clopidogrel plus PPI was associated with a higher risk of death or rehospitalization (OR, 1.07; 95% CI, 1.05–1.09). The researchers advise that PPIs not be used for prevention and instead be reserved only for patients who clearly need them. This conclusion was based on adverse outcome associations with omeprazole (OR, 1.24; 95% CI, 1.08–1.41) and rabeprazole (OR, 2.83; 95% CI, 1.96–4.09). Lansoprazole and pantoprazole associations with adverse outcomes could not be explored

Recently, Ho and colleagues conducted a retrospective cohort study of 8,205 patients with acute coronary syndrome (ACS) taking

*Not FDA approved for prevention of gastrointestinal (GI) bleeding in patients taking dual antiplatelet therapy with clopidogrel and aspirin following percutaneous coronary intervention (PCI)

Continued

Disclosures:

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^b PPS Staff: Danielle Gabriel, Executive Editor; Tamara Gibb, Editor; and Steven Rifkind, VP of Program, have no relevant financial relationships to disclose. Jennifer Nisita, Senior Editor, has indicated that her spouse is a salaried employee of Merck & Co., Inc.

COMING SOON!

A CME-certified case study exploring a patient with type 2 diabetes and polyvascular disease who progresses to acute coronary syndrome, authored by **plateletNEWS.org** Expert Panel Member Christopher P. Cannon, MD.

Do Proton Pump Inhibitors Negatively Impact Clopidogrel? (Continued)

given the small numbers of patients on these medications.

Juurlink and colleagues investigated the PPI-clopidogrel interaction by evaluating 13,636 patients with myocardial infarction (MI) who were taking clopidogrel, nearly 20% of whom received a PPI within 30 days of discharge and 31% of whom received a PPI within 90 days.⁴ Overall, 734 patients were readmitted for MI, and PPIs were associated with a 27% increase in the risk of reinfarction (OR, 1.27; 95% CI, 1.03–1.57). Notably, the stratified analysis showed that there was no association with reinfarction among patients taking pantoprazole (adjusted OR 1.02, 95% CI, 0.70–1.47), which does not inhibit cytochrome P450 2C19 as do other PPIs. The PPIs omeprazole, lansoprazole, and rabeprazole, collectively conferred a 40% increased risk of recurrent MI within 90 days of hospital discharge (OR 1.40, 95% CI, 1.10–1.77). The investigators estimate that 5% to 15% of reinfarctions occur because patients on clopidogrel take a PPI that inhibits cytochrome P450 2C19. The authors concluded that concomitant treatment with clopidogrel and PPIs other than pantoprazole should be minimized.

Siller-Matula et al also examined individual PPIs—specifically pantoprazole and esomeprazole—for their interaction with clopidogrel therapy.⁵ In a study of 300 percutaneous coronary intervention (PCI) patients on clopidogrel, results indicated that both

the platelet reactivity index (PRI) and platelet aggregation did not differ between patients taking and not taking these PPIs. The PRI and the adenosine diphosphate-induced platelet aggregation values were similar between patients receiving pantoprazole (n=152; PRI=50%; aggregation=47 U), those receiving esomeprazole (n=74; PRI=54%; aggregation=42 U), and those not receiving any PPI treatment (n=74; PRI=49%; aggregation=41 U; *P*=0.382).

Results from these studies suggest that a drug-drug interaction may occur between certain PPIs (omeprazole, lansoprazole, and rabeprazole) and clopidogrel that increases the rate of adverse events in these patients. However, this is not a class effect of all PPIs since neither pantoprazole nor esomeprazole seem to impair clopidogrel metabolism.

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COMMENTARY

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Over the past few months, clinicians have been confronted with a host of data regarding a potential interaction between clopidogrel and proton-pump inhibitors (PPIs). This situation is especially concerning given that PPIs are commonly prescribed to patients treated with dual anti-platelet therapy after stent implantation. What are we to make of the current data? Should we change our current practices? To answer these questions fully, we must determine whether the current data set supports the presence of a causal link between PPI therapy and cardiac events in clopidogrel-treated patients.

Clopidogrel is a pro-drug that requires conversion to an active metabolite to exert its platelet inhibitory effect. The generation of this active metabolite is mediated by several cytochrome P450 isoenzymes, including CYP2C19. PPIs can inhibit the enzymatic activity of CYP2C19, and therefore a proposed mechanism for the clopidogrel-PPI interaction is decreased generation of the clopidogrel active metabolite in PPI-treated patients, leading to less platelet inhibition and a greater incidence of cardiovascular events. Ho and colleagues, in a large, retrospective cohort study of patients with acute coronary syndromes (ACS), observed an increased rate of death and rehospitalization for ACS in those patients treated with clopidogrel and a PPI (specifically, omeprazole or rabeprazole) compared with clopidogrel alone. Juurlink and colleagues, in a retrospective case-control study, found a higher rate of recurrent myocardial infarction in clopidogrel-treated patients who received a PPI compared with those who did not, although

CUTTING-EDGE CONTENT

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Commentary (Continued)

there was no apparent interaction with pantoprazole. These reports are difficult to interpret because, in both studies, clinical characteristics differed markedly between patients prescribed PPIs and those who were not. Patients who received PPIs were older, sicker, and more likely to have comorbid conditions associated with both increased cardiovascular risk and with clopidogrel “nonresponsiveness,” such as renal failure, diabetes, and congestive heart failure. It is unclear whether statistical adjustment can account for all potential confounders, and it certainly cannot adjust for unmeasured confounders that are likely present. In addition, there is inconsistency with the results of these retrospective studies when considering the clopidogrel-PPI interaction mechanism. For instance, rabeprazole appears to be a weaker inhibitor of CYP2C19 than omeprazole, but was noted by Ho and colleagues to be associated with an increased hazard of events. Esomeprazole is a stronger CYP2C19 inhibitor than pantoprazole, but Siller-Matula and colleagues demonstrate that the two drugs have a similar impact (not significantly different than placebo) on the anti-aggregatory effect of clopidogrel.

So where do we stand? Until the darkness is lifted with clear, prospective data and consistent elucidation of mechanism, it seems prudent to follow the clinical path of excess caution: prescribe a PPI to only those clopidogrel-treated patients who absolutely need them. And wait for the light of sound and rigorous data.

Encouraging Phase II Results for Safety and Tolerability of SCH 530348, a Novel PAR-1 Antagonist

In a phase II trial, investigators randomized 1,030 patients scheduled for nonurgent percutaneous coronary intervention (PCI) to receive either placebo or an oral loading dose of the novel platelet protease-activated receptor-1 (PAR-1) antagonist, SCH 530348* at 10 mg, 20 mg, or 40 mg.¹ This agent targets thrombin-mediated platelet activation and is designed to complement current therapy regimens administered to patients undergoing PCI. All patients undergoing PCI (primary cohort) received aspirin orally (162–325 mg) or intravenously (150–500 mg). PCI patients were administered either heparin or bivalirudin, followed by a loading dose of clopidogrel (300–600 mg[†]). Following PCI, patients continued taking an oral maintenance dose of SCH 530348 (0.5 mg, 1.0 mg, or 2.5 mg) or placebo for 60 days. A secondary cohort included 457 patients who did not undergo PCI. These patients received placebo or a loading dose of the study drug.

The primary endpoint, major or minor bleeding as defined by the thrombolysis in myocardial infarction (TIMI) study,² occurred in 2%, 3%, and 4% of patients given SCH 530348 10 mg, 20 mg, and 40 mg, respectively, versus 3% of the placebo group ($P=0.5786$). The highest dose combination of SCH 530348—40 mg loading plus 2.5 mg qd maintenance—was not associated with any TIMI major bleeding events, but was associated with TIMI minor bleeding in two (3%) of 58 patients.

Among secondary endpoints, death, major adverse cardiac event, or stroke occurred in smaller percentages of study drug patients than placebo patients (odds ratio, 0.67; 95% CI, 0.33–1.34). Myocardial infarction was also lower among patients taking SCH 530348.

SCH 530348 displayed favorable antiplatelet properties. It inhibited platelet aggregation by 80% in one-fifth of patients within 90 minutes of administration. At the highest dose, 30% of patients had $\geq 80\%$ inhibition 30 minutes after drug administration; that proportion tripled at 2 hours. Maintenance therapy of 0.5 mg qd inhibited platelet aggregation by $\geq 80\%$ in more than 90% of patients at 30 and 60 days; maintenance therapy of the higher doses (1.0 mg qd and 2.5 mg qd) inhibited platelet aggregation by 80% in all patients at 30 and 60 days.

Investigators determined that oral SCH 530348 administered concomitantly with aspirin and clopidogrel is well tolerated and does not increase TIMI bleeding.

*Investigational agent: not yet FDA approved
[†]600-mg clopidogrel loading dose not FDA approved

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US Preventive Services Task Force Releases Statement on the Use of Aspirin for Cardiovascular Disease Prevention

A new recommendation on the use of aspirin for the primary prevention of cardiovascular events stratifies risk and benefit according to sex.¹ The recommendation was generated based on results from four studies—one randomized controlled trial,² two subanalyses of randomized trials,^{3,4} and one meta-analysis.⁵ The randomized controlled trial—The Women’s Health Study—found a benefit with aspirin use for the reduction of stroke (relative risk [RR], 0.83; 95% confidence interval [CI], 0.69–0.99), especially ischemic stroke in women.² There was no statistically significant benefit in the reduction of cardiovascular events, myocardial infarction (MI), death from cardiovascular disease (CVD), or all-cause mortality. A meta-analysis involving 51,342 women and 44,114 men in six primary prevention trials showed that men taking aspirin derive benefit in the reduction of MI (odds ratio [OR], 0.68; CI, 0.54–0.86), and women taking aspirin have a reduction of ischemic strokes (OR, 0.76; CI, 0.63–0.93).⁵

As for the risks associated with aspirin use, the Women’s Health Study found that serious gastrointestinal (GI) bleeds were more common among women taking aspirin than those taking placebo (RR, 1.40; 95% CI, 1.07–1.83).² Less serious bleeding, such as peptic ulcer, bruising, and nosebleeds, was also more common in women taking aspirin. The meta-analysis found an increased risk for major bleeding in both women (OR, 1.68; 95% CI, 1.13–2.52) and men (OR, 1.72; 95% CI, 1.35–2.20) taking aspirin.⁵

Based on these findings, the task force formulated different clinical recommendations based on age and gender.⁶ For men aged 45 to 79 years, aspirin use is encouraged when the potential CVD benefit (prevention of MI) outweighs the potential harm of GI hemorrhage. For women aged 55 to 79 years, aspirin use is encouraged when the potential CVD benefit (prevention of stroke) outweighs the potential harm of GI hemorrhage. For these two populations, the recommendations are grade A. The aspirin dosages used in the supporting studies ranged from 75 mg to 500 mg qd.

Assessing adverse outcomes by aspirin dose was the objective of a recent post hoc observational analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial data (N=15,595).⁷ Steinhubl et al reported that

daily aspirin doses of ≥ 100 mg were not associated with any benefit and may cause harm in patients with heart disease or with multiple risk factors for the condition who are also taking clopidogrel. Most patients took 75 or 81 mg qd, but doses ranged up to 162 mg qd. The primary efficacy endpoint—death, MI, stroke—did not differ by aspirin dose. Among clopidogrel patients, however, increasing aspirin doses were associated with an increase in the incidence of the primary endpoint. Clopidogrel patients who received ≥ 100 mg qd of aspirin had significantly higher incidences of the composite primary efficacy endpoint (14.5% vs 7.4%; $P=0.016$), cardiovascular death (5.2% vs 3.4%; $P=0.043$), and stroke (3.6% vs 2.4%; $P=0.022$); but the incidence of MI did not differ between groups (7.4% vs 3.2%; $P=0.79$).

The incidence of the primary safety endpoint (severe or life-threatening bleeding) did not increase with greater daily doses of aspirin in the placebo group ($P=0.20$).⁷ However, in the clopidogrel group, patients receiving aspirin doses ≥ 100 mg qd were at higher risk for the primary endpoint than those treated with < 100 mg qd (2.6% versus 1.7%, respectively; $P=0.040$). The authors believe that daily aspirin doses of 75 to 81 mg may be optimal, providing the best balance between efficacy and safety in cardiac patients or those with risk factors for heart disease.

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