

Welcome, New House Staff

On behalf of the Department of Pharmacy Services at the University of Washington Medical Center, Harborview Medical Center, Seattle Cancer Care Alliance, and UW Medicine Neighborhood clinics, I would like to welcome you. We look forward to working with you during your residency.

You will be receiving copies of the *Drug Therapy Topics* newsletter on a quarterly basis. This newsletter is a source of current pharmacotherapy-related information as well as a major communication between the Department of Pharmacy Services, the Pharmacy and Therapeutics Committee, and the medical staff. It is intended, in part, to keep you updated on additions and deletions to the medical centers' formulary, along with changes in policies and procedures as approved by the Pharmacy and Therapeutics Committee. Your input into its content is welcome.

The medical centers' *Drug Formulary* provides key information regarding drug availability, along with procedures pertaining to medication use. You will be provided with a personal copy of the formulary. For expanded and updated clinical details on all drugs and for "alerts" regarding formulary drugs, you may also access the formulary and the UW Drug Information Center website electronically at <http://uw.pnrnrx.org>.

If you have any questions regarding pharmacy services, please ask the clinical pharmacist on the unit or in the clinic or call one of the following pharmacy phone numbers. Again, a sincere welcome from all of us.



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The Proton Pump Inhibitors and Clopidogrel Drug Interaction: What to do?

Henry Kao, Pharm.D.

Platelet activation and aggregation play an important role in the development of atherothrombotic events that can lead to acute coronary syndrome (ACS) and complications during and after percutaneous coronary intervention (PCI). Clopidogrel (*Plavix*[®]) is an antiplatelet agent commonly used to prevent these events. Its mechanism of action involves inhibiting platelet activation induced by adenosine diphosphate (ADP). Alone or in association with aspirin, clopidogrel has proven beneficial in the treatment of atherothrombotic disease.^{1,2} It also decreases the incidence of coronary artery stent thrombosis. Clopidogrel is a prodrug that must be metabolized in the liver to an active thiol metabolite, which irreversibly blocks platelet ADP P2Y₁₂ receptors (Figure 1). This conversion is performed by several different cytochrome P450 isoenzymes.³

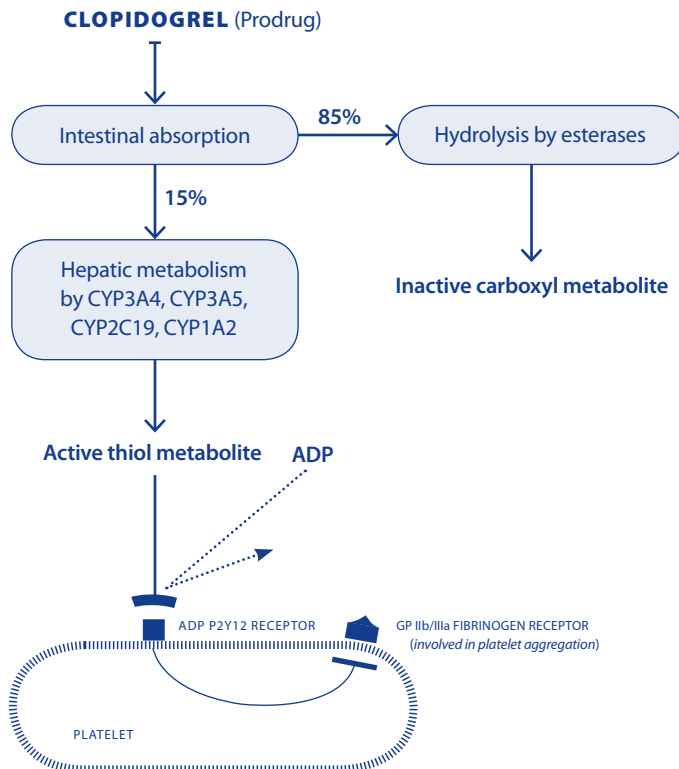


FIGURE 1: Clopidogrel Metabolism and Mechanism of Action³

Some patients who take clopidogrel are also prescribed a prophylactic proton pump inhibitor (PPI) to reduce the risk for gastrointestinal bleed while undergoing dual-antiplatelet therapy. Recent data suggest that PPIs may reduce clopidogrel's antiplatelet effect and increase the risk for cardiovascular events.⁴⁻⁶ There is significant ongoing controversy regarding the clinical outcomes of patients taking clopidogrel and PPIs. In January 2009, the FDA released an early communication about a safety review of the potential interaction between these two classes of drugs.⁷ However, there were insufficient data to make any recommendations, highlighting the need for additional studies to evaluate the effectiveness of clopidogrel when used concurrently with PPIs.

There are several studies looking at the efficacy of clopidogrel in patients also taking PPIs (Table 1). The first and only prospective randomized trial available to date looked at patients undergoing coronary artery stent placement. The primary outcome measure was day 7 platelet reactivity index (PRI), which is inversely related to clopidogrel's effectiveness at reducing platelet activation (<50% = good responder).⁴ This study, conducted by Gilard et al., found that patients who were on concomitant omeprazole and clopidogrel had statistically significant differences in day 7 PRI. Patients taking omeprazole with clopidogrel were associated with a mean PRI of 51.4% ± 16.4, which is generally considered a poor response to clopidogrel, while patients taking placebo with clopidogrel had a mean PRI of 39.8% ± 15.4, reflecting a good response to clopidogrel ($P < 0.0001$). Although this study suggested that patients have worse response while on PPIs, the clinical significance was still unknown.

Following this study, several other retrospective studies were conducted to take a closer look at clinical outcomes. The first, by Ho et al., was a retrospective cohort study of patients with ACS taking clopidogrel with PPI versus clopidogrel without PPI after discharge.⁵ The primary outcome was all-cause mortality or rehospitalization for ACS. Of patients taking clopidogrel with a PPI, 29.8% either died or were rehospitalized for ACS, versus 20.8% of patients taking clopidogrel without a

TABLE 1: Studies Detailing the Efficacy of Clopidogrel in Patients on Concurrent PPI Therapy

REFERENCE	STUDY DESIGN	RESULTS	CONCLUSION
Gilard et al., 2008 ⁴	<ul style="list-style-type: none"> Randomized, double-blind, placebo-controlled Consecutive patients undergoing coronary artery stent implantation receiving aspirin (75mg/d) and clopidogrel (300mg load, then 75mg/d) Randomized to receive omeprazole 20mg/d or placebo x7 days Clopidogrel effect tested days 1 and 7 by measuring platelet reactivity index (PRI) <ul style="list-style-type: none"> Good responders to clopidogrel: PRI < 50% Poor responders: PRI > 50% Primary endpoint: PRI at day 7 Exclusion: previous treatment with clopidogrel or PPI, history of thrombocytopenia (<150,000 platelets/mL) or bleeding disorder, liver disease, gastrointestinal ulcer, or pregnancy 	<ul style="list-style-type: none"> N = 124 Day 1: <ul style="list-style-type: none"> Placebo: mean PRI 83.2% ± 5.6 Omeprazole: mean PRI 83.9% ± 4.6 Day 7: <ul style="list-style-type: none"> Placebo: mean PRI 39.8% ± 15.4 Omeprazole: mean PRI 51.4% ± 16.4 P < 0.0001 	<ul style="list-style-type: none"> Omeprazole significantly decreased clopidogrel inhibitory effect on platelet P2Y12 Clinical impact remains uncertain but merits further investigation
Siller-Matula et al., 2009 ¹²	<ul style="list-style-type: none"> Consecutive patients with CAD undergoing PCI <ul style="list-style-type: none"> Clopidogrel 600mg loading dose at initiation of therapy Patients had been on clopidogrel 75mg/d and aspirin 100mg/d treatment for 3 months on average (at least 5 days) at time of inclusion Two PPIs used in the study: pantoprazole and esomeprazole End points: PRI and aggregometry 	<ul style="list-style-type: none"> N = 300 Mean PRI w/ PPI (n=226) = 51%; w/o PPI (n=74) = 49% (P = 0.724) No difference in ADP-induced platelet aggregation in patients with (45 U) or w/o (41 U) PPI (P = 0.619) No difference in PRI or ADP-induced platelet aggregation between patients with pantoprazole, esomeprazole, or w/o PPI (P = 0.382) 	<ul style="list-style-type: none"> Intake of pantoprazole or esomeprazole is not associated with impaired response to clopidogrel The reported omeprazole-clopidogrel drug interaction is probably not a class effect Limitations: non-randomized study design; possible residual confounding; could not compare omeprazole with pantoprazole or esomeprazole
Ho et al., 2009 ⁵	<ul style="list-style-type: none"> Retrospective cohort study Patients with ACS taking clopidogrel after discharge from 127 VA hospitals between October 1, 2003 and January 31, 2006 <ul style="list-style-type: none"> Patients given clopidogrel + PPI vs clopidogrel alone Primary outcome: all-cause mortality or rehospitalization for ACS Exclusion: patients with history of GI bleed prior to index hospitalization; patients with any bleeding events during index hospitalization or after discharge; patients who filled an H₂-receptor antagonist prescription at any time during follow-up 	<ul style="list-style-type: none"> N = 8,205; 63.9% prescribed PPI, 36.1% not prescribed PPI 59.7% (n=3,132) on omeprazole 2.9% (n=151) on rabeprazole 0.4% (n=22) on lansoprazole 0.2% (n=15) on pantoprazole 36.7% (n=1,924) on more than one type during follow-up Patients with clopidogrel + PPI at any point in time were older and had more comorbid conditions Median follow-up after discharge: 521 days Death or rehospitalization for ACS: <ul style="list-style-type: none"> 20.8% w/o PPI 29.8% w/ PPI Adjusted odds ratio 1.25; 95% CI 1.11-1.41 Patients taking clopidogrel after hospital discharge and prescribed PPI at any point during follow-up: <ul style="list-style-type: none"> Increased risk of death or rehospitalization for ACS (adjusted hazard ratio 1.27; 95% CI 1.10-1.46) Secondary outcomes: <ul style="list-style-type: none"> Clopidogrel + PPI (vs w/o PPI) had higher risk of: <ul style="list-style-type: none"> Hospitalizations for recurrent ACS: 14.6% vs 6.9%; adjusted odds ratio 1.86; 95% CI 1.57-2.20 Revascularization procedures, PCI, or CABG: 15.5% vs 11.9%; adjusted odds ratio 1.49; 95% CI 1.30-1.71 No difference for all-cause mortality following index ACS hospitalization 19.9% vs 16.6%; adjusted odds ratio 0.91; 95% CI 0.80-1.05 Patients NOT taking clopidogrel after discharge given a prescription for PPI: not associated with death or rehospitalization for ACS (adjusted odds ratio 0.98; 95% CI 0.85-1.13) 	<ul style="list-style-type: none"> Clopidogrel + PPI after hospital discharge for ACS was associated with an increased risk of adverse outcomes than use of clopidogrel w/o PPI Additional investigation needed – ideally randomized controlled trials Limitations: observational (cannot conclude causality or exclude unmeasured confounding)

TABLE 1: Studies Detailing the Efficacy of Clopidogrel in Patients on Concurrent PPI Therapy continued

REFERENCE	STUDY DESIGN	RESULTS	CONCLUSION
Juurlink et al., 2009 ⁶	<ul style="list-style-type: none"> Population-based nested case-control study Patients aged ≥ 66 years old who started clopidogrel between April 1, 2002 and December 31, 2007 following hospital discharge after treatment of acute MI Cases: patients re-admitted with acute MI within 90 days of discharge Controls: matched by age, receipt of PCI, and risk score Secondary analysis looked at events within one year 	<ul style="list-style-type: none"> 13,636 patients prescribed clopidogrel following acute MI 734 cases readmitted with MI 2,057 controls Follow-up = 90 days maximum Cases had more comorbidities, including heart failure, diabetes mellitus, and renal insufficiency PPI use within 30 days was associated with increased risk of reinfarction (adjusted odds ratio 1.27; 95% CI 1.03-1.57) No such association with previous (31-90 days) or remote (90-180 days) PPI use Stratified analysis: pantoprazole had no association with readmission for MI (adjusted odds ratio 1.02; 95% CI 0.70-1.47) Other PPIs associated with 40% increase in risk or recurrent MI No association between recurrent MI and use of H₂-receptor antagonists or patients not on clopidogrel 	<ul style="list-style-type: none"> Among patients receiving clopidogrel following acute MI, concomitant therapy with PPIs other than pantoprazole (omeprazole, lansoprazole, rabeprazole) was associated with loss of beneficial effects of clopidogrel and an increased risk of reinfarction 5-15% of early re-admissions due to MI among patients on clopidogrel could be the result of this drug interaction Limitations: no data on important cardiac risk factors such as smoking, BP, and lipids; no identification of use of other medications; imbalance of baseline characteristics of cases & controls; potential for miscoding; possible misclassification of exposure status for patients taking PPIs intermittently; lack of data on patient compliance; did not account for ethnicity
Stanek et al., 2009 ¹³	<ul style="list-style-type: none"> Retrospective cohort analysis Inclusion: <ul style="list-style-type: none"> Patients who had a coronary stent procedure between October 2005 - September 2006. Clopidogrel-naïve prior to stent New clopidogrel Rx within one month of stent Clopidogrel persisting for 12 months post-stent and high level of adherence (Medication possession ratio ≥ 0.80) Primary end point: combined hospitalization for major adverse cardiovascular event (MACE) over 12 months <ul style="list-style-type: none"> Cerebrovascular event (Stroke or TIA) ACS (MI or unstable angina) Cardiovascular death (resuscitated; resulting in hospitalization) Coronary revascularization (CABG and PCI) Secondary end points: individual components of primary end point: MI, unstable angina, CABG, PCI 	<ul style="list-style-type: none"> N = 16,718 <ul style="list-style-type: none"> N = 9,862 patients with no prescription claim for a PPI N = 6,828 on a PPI <ul style="list-style-type: none"> Esomeprazole (N = 3,257) Omeprazole (N = 2,307) Pantoprazole (N = 1,653) Lansoprazole (N = 785) Rabeprazole (N = 298) All patients on PPI were older and had significantly more comorbidities Risk of MACE was significantly higher in patients on any PPI (N = 6,828; 25.1%) vs no PPI (N = 9,862; 17.9%) (adjusted hazard ratio 1.51; 95% CI 1.39-1.64) Individual PPIs with sufficient sample size (N ≥ 674) to detect a 25% difference were: omeprazole (N = 2,307), esomeprazole (N = 3,275), pantoprazole (N = 1,653), and lansoprazole (N = 785) Each PPI was associated with increased incidence and risk of MACE vs no PPI (17.9%): <ul style="list-style-type: none"> Omeprazole (25.1%; hazard ratio 1.39; 95% CI 1.22-1.57, P < 0.0001) Esomeprazole (24.9%; hazard ratio 1.57; 95% CI 1.40-1.76, P < 0.0001) Pantoprazole (29.2%; hazard ratio 1.61; 95% CI 1.41-1.88, P < 0.0001) Lansoprazole (24.3%; hazard ratio 1.39; 95% CI 1.16-1.67, P = 0.0004) Hospitalization for upper GI bleed was 0.07% in patients not on a PPI and 1.1% for any PPI: <ul style="list-style-type: none"> Omeprazole 0.82% Esomeprazole 1.11% Pantoprazole 2.54% Lansoprazole 0.76% PPIs used in the absence of clopidogrel were not found to be associated with increased risk (N = 1,641; No PPI = 1,407; Any PPI = 234) <ul style="list-style-type: none"> Hazard ratio 1.19; 95% CI 0.84-1.70, P = 0.326 H₂-receptor antagonists had no effect on cardiovascular event incidence <ul style="list-style-type: none"> Analysis in 9,862 patients on clopidogrel but no PPI therapy over follow-up: (472 patients on H₂-receptor antagonist; 9,390 patients not on H₂-receptor antagonist) Combined CV event rate incidence: 20.3% with H₂-receptor antagonist vs 17.8% without H₂-receptor antagonist (P = 0.1579) 	<ul style="list-style-type: none"> Concomitant use of clopidogrel with PPIs as a class, and omeprazole, esomeprazole, pantoprazole, or lansoprazole individually after coronary stenting was associated with a significantly increased risk of hospitalization for MACE compared to clopidogrel alone PPI use in absence of clopidogrel was not associated with increased CV event risk More data needed to establish if newer PPIs (rabeprazole, dexlansoprazole) have similar effects Limitations: imbalance of baseline characteristics; no consideration for use of other medications; did not account for ethnicity

PPI (adjusted odds ratio 1.25; 95% CI 1.11-1.41). In secondary outcome measures, patients taking clopidogrel with a PPI had a higher risk of hospitalization for recurrent ACS (adjusted odds ratio 1.86; 95% CI 1.57-2.20) and revascularization procedures (adjusted odds ratio 1.49; 95% CI 1.30-1.71). There was no difference in all-cause mortality. The second retrospective study looking at clinical outcomes was by Juurlink et al., which was a population-based, nested case-control study of patients aged ≥ 66 years of age who started clopidogrel following hospital discharge after treatment of acute myocardial infarction (MI).⁶ Case patients were those readmitted with acute MI within 90 days of discharge, and controls were matched by age, receipt of PCI in hospital, date of hospital discharge, and predicted probability of short-term mortality using a validated cardiac risk prediction model. It was observed that patients with PPI use within 30 days of index (outcome) date had a greater risk of reinfarction (adjusted odds ratio 1.27; 95% CI 1.03-1.57).

No mechanism for the interaction between PPIs and clopidogrel has been proven.⁸ Because clopidogrel is a prodrug that must be converted to an active metabolite, a disruption in the activity of the responsible enzymes may potentially influence its efficacy. This can occur via several mechanisms—either through competitive inhibition of cytochrome P450 isoenzymes by other drugs, or through genetic polymorphisms that alter expression of cytochrome P450 isoenzymes that act on clopidogrel.⁸⁻¹¹

The prevailing theory of mechanism at this time is inhibition of CYP2C19 by certain PPIs. Pantoprazole, which along with all other PPIs except omeprazole and esomeprazole, does not inhibit CYP2C19 *in vivo*. Several studies initially found no association with pantoprazole and worse cardiovascular outcomes when used concomitantly with clopidogrel.^{6,12} However, a recent Medco outcomes study presented at the 2009 Society for Cardiovascular Angiography and Interventions (SCAI) Scientific Sessions showed otherwise.¹³ This study, which was a retrospective cohort analysis, found that the risk of major adverse cardiovascular events (MACE) was significantly higher in patients on any PPI versus no PPI (adjusted hazard ratio 1.51; 95% CI 1.39-1.64). More importantly, each PPI that was analyzed individually was associated with an increased incidence and risk of MACE versus no PPI. This included pantoprazole, which showed a 61% increased risk—the greatest risk of all analyzed PPIs. In light of these findings, the SCAI released a statement urging

health-care providers who are treating post-stenting patients on dual-antiplatelet therapy to consider prescribing an H₂-receptor antagonist or antacids instead of a PPI considering the high risk for adverse events shown in this study.

If competitive inhibition of CYP2C19 is indeed the true mechanism, one would expect other inhibitors of CYP2C19, such as fluvoxamine and fluconazole, to have a similar effect on the efficacy of clopidogrel. The interaction between these drugs and clopidogrel has not been studied. To further complicate matters, PPIs other than omeprazole and esomeprazole typically do not interact with drugs that are substrates of CYP2C19. Yet the studies discussed above found that the other PPIs affected outcomes as well, which is inconsistent with competitive inhibition of CYP2C19 as the mechanism. In addition, the half-life of omeprazole is approximately 1 hour, while the half-life of clopidogrel is approximately 2.5 hours. For competitive inhibition to occur with these drugs, the medications would need to be administered almost simultaneously. Clinicians should be able to separate the doses of PPI and clopidogrel to avoid the interaction, since the PPI will have been eliminated by the time clopidogrel is administered. However, there is no data supporting the use of this strategy.

Furthermore, polymorphisms in the hepatic enzymes involved in the metabolism of clopidogrel or within the platelet P2Y₁₂ receptor may affect platelet responses. Individual variation in enzyme activity may result in insufficient enzymatic activity for optimal conversion of clopidogrel to its active metabolite, and thus lead to altered therapeutic effect. Several studies have demonstrated that a CYP2C19 gene polymorphism is associated with greater platelet aggregation, greater clopidogrel nonresponse, and an increased risk of cardiovascular events, which is similar to the antiplatelet inhibitory effects of PPIs on clopidogrel.¹⁴⁻¹⁸ The degree of platelet inhibition following the use of clopidogrel varies from patient to patient in a normal or bell-shaped distribution. The variability in nonresponse is such that when laboratory measurements of platelet aggregation are performed, 4-30% of patients treated with clopidogrel do not have an adequate platelet response.^{9,10} This variability clouds the association seen with the previous studies looking at PPIs and clopidogrel. Because the above-mentioned studies did not account for genetic polymorphisms, the clopidogrel nonresponse that was observed in these studies may have been influenced by these polymorphisms.

Unfortunately, the data supporting the clinical impact of this drug interaction are not strong, with each study being retrospective in nature. All of these studies had potential confounding factors that were not controlled for, so the differences observed may have been related to various outside factors. In order to elucidate the true mechanism and clinical effect of this potential drug interaction, well-designed and well-controlled prospective studies are needed, including studies to examine the pharmacokinetic and pharmacodynamic effects of PPIs on clopidogrel.

Although there are no randomized controlled trials specifically looking at clinical outcomes from the use of PPIs and clopidogrel, the available data suggest that there is some risk involved. As such, clinicians should consider the following plans of action:

1. Assess whether the patient needs to be on a PPI at all, and discontinue if possible.
2. If it is assumed that competitive inhibition of CYP2C19 is the true mechanism, then doses should be separated from clopidogrel if the patient must remain on a PPI.

3. Other options for acid suppression therapy, such as H₂-receptor antagonists, are reasonable alternatives.
4. Avoid drugs known to inhibit CYP2C19, CYP1A2, or CYP3A4.
5. For high-risk patients (i.e., patients on concomitant daily PPI and clopidogrel for an extended period of time), clinicians may consider laboratory testing to assess patient response to clopidogrel. Such tests are the platelet function screen (PFA 100) or platelet aggregation panel, both used at the University of Washington Medical Center. Medicare reimbursement for these tests is approximately \$60.00 and \$120.00, respectively.

The editor and author gratefully acknowledge the assistance of John Horn, Pharm.D., FCCP in reviewing this article. Thank you also to Troy Drysdale, Pharm.D. for his help in writing the P&T Committee Brief Summary section.

REFERENCES

1. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.
2. Steinhubl SR, Berger PB, Mann JT, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411-20.
3. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009;360:363-75.
4. Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin. *J Am Coll Cardiol* 2008;51:256-60.
5. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009;301(9):937-44.
6. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009;180(7):713-8.
7. Food and Drug Administration. Early communication about an ongoing safety review of clopidogrel bisulfate (marketed as Plavix). http://www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm. Accessed May 14, 2009.
8. Hester SA. Proton pump inhibitor and Plavix interaction: Does it Exist? *Pharmacist's Letter* 2009;25:250401.
9. Hennekens CH, Cutlip D, Zehnder JL. Nonresponse and resistance to aspirin and clopidogrel. In: UpToDate, Basow, DS (ed), UpToDate, Waltham, MA, 2009.
10. Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: a review of the evidence. *J Am Coll Cardiol* 2005;45:1157-64.
11. Lau WC, Gurbel PA. The drug-drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009;180(7):699-700.
12. Siller-Matula JM, Spiel AO, Lang IM, et al. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. *Am Heart J* 2009;157:148.e1-148.e5.
13. Stanek EJ, Aubert RE, Flockhart DA, et al. A national study of the effect of individual proton pump inhibitors on cardiovascular outcomes in patients treated with clopidogrel following coronary stenting: the clopidogrel Medco outcomes study. Presented at the 2009 SCAI Scientific Sessions meeting. http://scai.org/pdf/Stanek_Clopidogrel-PPI_SCAI_2009.pdf. Accessed May 28, 2009.
14. Trenk D, Hochholzer W, Fromm MF, et al. Cytochrome P450 2C19 681G> A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. *J Am Coll Cardiol* 2008;51(20):1925-34.
15. Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet* 2009;373(9660):309-17.
16. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009;360(4):354-62.
17. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009;360(4):363-75.
18. Sibbing D, Stegherr J, Latz W, et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. *Eur Heart J* 2009;30(8):916-22.

P&T COMMITTEE BRIEF SUMMARY April 21, 2009 through June 16, 2009

FORMULARY ADDITIONS

Bendamustine (<i>Treanda</i>®) Added 04/21/09	
CLASS	Antineoplastic agent
PLACE IN THERAPY	For treatment of chronic lymphocytic leukemia and for indolent B-cell non-Hodgkin's lymphoma that has progressed after treatment with rituximab-containing regimen.
DOSAGE FORMS	10mg vial
USUAL STARTING DOSE	Per oncology
UW RESTRICTIONS	-Restricted to outpatient use -Medical Director approval required for inpatient use

Eltrombopag (<i>Promacta</i>®) Added 04/21/09	
CLASS	Thrombopoietin receptor agonist
PLACE IN THERAPY	For the treatment of chronic idiopathic thrombocytopenic purpura in patients unresponsive to corticosteroids, immunoglobulins, and/or splenectomy.
DOSAGE FORMS	25mg, 50mg tablets
USUAL STARTING DOSE	50mg PO daily
UW RESTRICTIONS	-Prescriptive authority restricted to appropriate hematologists -Prescriber responsibility to enroll themselves and patients in the PROMACTA Cares program prior to start of therapy

Fibrin sealant, human (<i>Artiss</i>®) Added 06/16/09	
CLASS	Topical sealant
PLACE IN THERAPY	<i>Artiss</i> ® is used to adhere autologous skin grafts to surgically prepared wound beds resulting from burns. Formulary fibrin sealant for hemostasis is <i>Tisseel</i> ®.
DOSAGE FORMS	4mL, 10mL pre-filled frozen syringes
USUAL STARTING DOSE	2mL-10mL, depending upon size of burn surface
UW RESTRICTIONS	Given the high cost of these agents and the controversy over when and where they are most effective, the P&T decision was to ADD <i>Artiss</i> ® to formulary and to form a multidisciplinary task force to develop guidelines and/or restrictions for use of all fibrin sealant products.

Plerixafor (<i>Mozobil</i>®) Added 06/16/09	
CLASS	Hematopoietic agent
PLACE IN THERAPY	For mobilization of hematopoietic stem cells, in combination with filgrastim (G-CSF), in autologous hematopoietic stem cell transplantation (HSCT) patients with multiple myeloma or non-Hodgkin's lymphoma who are poor mobilizers of CD34+ cells, by history or risk factors.
DOSAGE FORMS	20mg/mL (1.2mL) vial
USUAL STARTING DOSE	0.24mg/kg SQ daily
UW RESTRICTIONS	-Patient history of poor mobilization, or risk factors for it -Prescriptive authority restricted to attending physicians experienced in HSCT -Outpatient use, prior insurance authorization required -Inpatient use must be approved by Medical Director

Triamcinolone acetonide, preservative-free (<i>Triesence</i>®) Added 06/16/09	
CLASS	Corticosteroid
PLACE IN THERAPY	For intravitreal treatment of ocular inflammatory conditions; and as a visualization aid during vitrectomy. Considerably more expensive than the already available preserved product; for use in patients who have had, or at risk for inflammatory reactions after use of preserved injectable triamcinolone product.
DOSAGE FORMS	40mg/mL (1mL) vial
USUAL STARTING DOSE	4mg intraocularly
UW RESTRICTIONS	For use as above

FORMULARY DELETIONS

Rho (D) immune globulin (<i>Rhogam D Mini Dose</i>® 50mcg)	Removed due to limited indications for the low dose and to reduce the potential of under-dosing when full dose is necessary.	Removed 04/21/09
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DRUG INFORMATION CENTER

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P&T COMMITTEE BRIEF SUMMARY April 21, 2009 through June 16, 2009 *continued from inside*

RISKS ASSOCIATED WITH ATYPICAL ANTIPSYCHOTIC MEDICATION USE IN THE ELDERLY

In April 2005, FDA issued a black box warning stating that the treatment of behavioral disorders in elderly demented patients with atypical antipsychotic medications was associated with increased mortality. Out of a total of 17 placebo-controlled trials performed with various atypical antipsychotics, enrolling a total of 5106 elderly patients, 15 trials showed numerical increases in mortality in the drug-treated group compared to the placebo-treated group.¹ Multiple analyses of the data from these studies demonstrated an approximately 1.6 to 1.7-fold increase in mortality among the patients treated with atypical antipsychotics, as well as an increased risk of stroke and TIA. The specific causes of death were mostly due either to cardiac events (heart failure, sudden death) or infections (primarily pneumonia).

Atypical antipsychotics are indicated for the treatment of schizophrenia and bipolar disorder. Aripiprazole recently received FDA approved for adjunctive treatment of depression. Current indications for atypical antipsychotics do not include dementia-related psychosis or delirium. Atypical antipsychotics on the UW Medicine formulary include aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone.

A medication utilization evaluation (MUE) to quantify usage of atypical antipsychotic medications in patients over 65 years of age for non-FDA approved indications was recently performed at UWMC. A total of 96 patients (out of a total of 1760 patients receiving atypical antipsychotic

medications during a six month period) over the age of 65 years of age, filling an outpatient prescription for any atypical antipsychotic at UWMC/HMC/SCCA were identified. The medical records for all identified patients over age 65 years of age were retrospectively reviewed. The results showed that at UW Medicine, 3.25% of all ambulatory atypical antipsychotic medication use is in patients greater than 65 years of age for an off-label indication. The MUE was unable to evaluate the use of nonpharmacologic management therapies to treat neuropsychiatric symptoms in this population, but given the relatively small number of patients treated with atypical antipsychotics, it suggests that there is not large-scale misuse of these medications in the elderly population treated at UW Medicine.

There are currently no FDA approved drugs for the treatment of dementia-related psychosis. Despite limited efficacy and significant safety concerns, atypical antipsychotics remain a treatment option for severe neuropsychiatric symptoms of dementia due both to the risks associated with no treatment and a lack of better treatment alternatives. It is recommended that healthcare providers consider other management options first. However, if antipsychotics are prescribed to elderly patients with dementia-related psychosis, then the provider needs to discuss and document the risks with the patient, their family, and caregiver.

References available on request.