

Pharmacy Benefit Spending Poised to Increase for Antithrombotic Drug Therapy—Prasugrel Versus Clopidogrel

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Clopidogrel is now commonly ranked among the top 5 drugs by expenditure in most pharmacy benefit plans. If price was a proxy for value (efficacy and safety), clopidogrel would be high-value because its average wholesale price is \$5.60 per 75 mg tablet or about \$152 per 30-day supply at discount price from www.drugstore.com.¹ This high per-unit price propels high expenditures; for every patient on clopidogrel, the annual drug cost is approximately \$1,825, before member cost-share.¹ Clopidogrel (Plavix) had sales of \$3.80 billion in U.S. community pharmacies in 2008,² up 23% from \$3.08 billion in 2007.³ This change pushed Plavix from its 2007 rank of #5 in total community pharmacy brand drug sales to its 2008 rank of #3.³ In just 6 years, Plavix annual sales increased 3-fold, from \$1.26 billion in 2002 when it ranked 25th by total community pharmacy sales.⁴

New Drug Entities Will Propel Spending on Antithrombotic Drugs

Drug benefit spending on antithrombotic drugs is poised to escalate. On February 3, 2009, the U.S. Food and Drug Administration's (FDA) Cardiovascular and Renal Drugs Advisory Committee recommended approval of prasugrel for its proposed indication, treatment of acute coronary syndrome (ACS) in patients who present with either (a) unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) managed with percutaneous coronary intervention (PCI) or (b) ST segment elevation myocardial infarction (STEMI) managed with primary or delayed PCI.^{5,6} As with almost all new drugs, all of the clinical evidence about prasugrel that we have today stems from drug trials sponsored by its manufacturers (Daiichi Sankyo and Eli Lilly), and only 1 clinical study of end point outcomes served as the basis for the FDA's consideration of prasugrel for marketing in the United States.⁷ The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 was a comparative effectiveness clinical trial, comparing prasugrel+aspirin with the alternative regimen, clopidogrel+aspirin.⁸ TRITON-TIMI 38 has been criticized for using a low (300 mg) loading dose of clopidogrel, potentially handicapping the efficacy of clopidogrel.⁹ In patients with NSTEMI, who constituted 74% of the TRITON-TIMI 38 sample, the recommended loading dose of clopidogrel for PCI is 600 mg.¹⁰

Potentially more important than the potential handicap for clopidogrel in a lower loading dose than recommended for nearly three-quarters of the TRITON-TIMI 38 study patients is the concern expressed by a platelet researcher, Victor Serebruany, MD, PhD, of Johns Hopkins University Medical School, in the public hearing segment of the FDA advisory committee meeting—that the definition of myocardial infarction (MI), a key component of the study's primary endpoint, had been changed to include “transient increases in biomarkers.”⁶ Serebruany asserted that the clinical benefit of prasugrel would have disappeared in the overall TRITON-TIMI 38 sample and in both the UA/STEMI and NSTEMI cohorts if the analysis had considered only MIs reported by clinicians during PCI. Serebruany also hypothesized that the more powerful antiplatelet effects of prasugrel might explain a potentially higher rate of cancer with prasugrel than with clopidogrel that developed at 4 months after randomization in the TRITON-TIMI 38 study.⁶

In the May 2009 issue of *JMCP*, Schafer et al. summarized the key findings from the primary analysis of the TRITON-TIMI 38 study, including the conclusion that 24 cardiovascular end points (composite of nonfatal MI, nonfatal stroke, and death from cardiovascular causes) would be prevented for every 1,000 patients treated for a median duration of 14.5 (range 6 to 15) months with prasugrel+aspirin instead of clopidogrel+aspirin.¹¹ However, this relatively small reduction in the absolute rate of the composite end point (Kaplan-Meier estimates of the end point rates at 15 months: 9.9% [643 events among 6,813 patients] for prasugrel+aspirin vs. 12.1% [781 events among 6,795 patients] for clopidogrel+aspirin) was offset by increased risk of bleeding.^{8,11} Although rates of death from cardiovascular causes were not significantly different for prasugrel+aspirin (2.1% [n=133]) than for clopidogrel+aspirin (2.4% [n=150]; hazard ratio [HR]=0.89, 95% CI=0.70-1.12, P=0.31), death from thrombolysis in myocardial infarction (TIMI) bleeding not related to coronary artery bypass grafting (CABG) was significantly more frequent with prasugrel+aspirin than with clopidogrel+aspirin (0.4% [n=21] vs. 0.1% [n=5], respectively; HR=4.19, 95% CI=1.58-11.11, P=0.002).^{8,12} Rates of life-threatening TIMI bleeding were elevated with prasugrel as well (1.4% [n=85] vs. 0.9% [n=56]; HR=1.52, 95% CI=1.08-2.13, P=0.01).⁸

The increased risk of bleeding with prasugrel was particularly pronounced for patients who had received at least 1 dose of prasugrel (n=179) or clopidogrel (n=189) prior to undergoing

CABG (13.4% vs. 3.2%, respectively; HR=4.73, 95% CI=1.90-11.82, $P<0.001$).⁸ On February 3, 2009, the FDA advisory committee concluded that the benefit-risk profile of prasugrel plus aspirin was acceptable but that “preference should be given to the use of prasugrel only following coronary angiography, as it was in the [TRITON-TIMI 38] study, so that coronary anatomy is known to allow assessment of the likelihood of requiring [CABG] surgery.”⁵

In this issue of *JMCP*, Spinler and Rees review the background information on prasugrel that was known at the time that the FDA advisory committee met, with a focus on the subgroup analyses that followed the principal report from TRITON-TIMI 38.¹³ The analysis by Montalescot et al. for the subgroup of patients with STEMI ($n=3,534$), found a small difference between prasugrel+aspirin and clopidogrel+aspirin for the primary cardiovascular end point at 15 months (10.0% vs. 12.4%, respectively; HR=0.79, 95% CI=0.65-0.97, $P=0.022$), without elevated risk of TIMI bleeding unrelated to CABG ($P=0.645$). The difference was driven by more favorable outcomes for secondary PCI (defined as PCI from 12 hours up to days after onset of MI symptoms; 9.6% for prasugrel+aspirin vs. 14.1% for clopidogrel+aspirin, $P=0.015$); however, no significant advantage was observed for prasugrel+aspirin in primary PCI (occurring less than 12 hours after onset of MI symptoms).¹⁴

Other subgroup analyses suggested that prasugrel+aspirin was superior to clopidogrel+aspirin in the rates of the composite cardiovascular end point in patients with or without diabetes, but the rate of major bleeding was higher for prasugrel+aspirin in patients without diabetes (2.4% for prasugrel+aspirin vs. 1.6% for clopidogrel+aspirin, $P=0.02$).¹⁵ For the subgroup analysis by type of stent, both the composite cardiovascular end point and stent thrombosis were less frequent in the prasugrel+aspirin patients regardless of whether they received bare-metal stents or drug-eluting stents.¹⁶

Status of Drug Therapy for Antithrombosis

Currently, about 4 months after the FDA advisory committee recommended approval of prasugrel+aspirin for restricted indications for patients expected to undergo PCI, the FDA has not yet formally approved prasugrel for marketing in the United States. The delay is not surprising for a couple of reasons. First, the increased risk of bleeding with prasugrel compared with clopidogrel has been suspected for almost 2 years; this suspicion was highlighted just prior to release of the TRITON-TIMI 38 results, when 2 smaller clinical trials of prasugrel were suspended in October 2007 by the prasugrel manufacturers without explanation.¹⁷ Second, there was controversy surrounding the conduct of the FDA advisory committee meeting in February 2009 when the FDA “disinvited” Sajay Kaul, MD, a cardiologist at Cedars-Sinai Heart Institute in Los Angeles. The FDA later

admitted that it had made a “mistake” in excluding Dr. Kaul from the advisory committee meeting based on questions from the prasugrel manufacturer associated with Kaul writing “several papers that had been critical of prasugrel.”¹⁸

At the present time, clopidogrel is approved by the FDA for secondary prevention in patients with (a) recent MI, stroke, or established peripheral arterial disease, (b) NSTEMI including patients who are to be managed medically and those who are to be managed with PCI (with or without stent) or CABG, and (c) STEMI.¹⁹ Based on the summary notes from the FDA advisory committee meeting on February 3, 2009, the approved indications for prasugrel are likely to be more narrow, including restrictions against its use in patients with a history of stroke or transient ischemic attack (TIA), patients with body weight less than 60 kg, and patients aged 75 years or older.^{5,8}

Clopidogrel had worldwide manufacturer sales of \$7.2 billion in 2007 and \$8.2 billion in 2008,^{20,21} making it second only to atorvastatin (Lipitor). In addition to the anticipated FDA approval of prasugrel, a second new molecular entity is in the middle of safety testing in Phase 2 clinical trials for patients who receive balloon angioplasty and stents. In February 2009, Novartis agreed to pay Portola Pharmaceuticals (San Francisco) \$75 million to license elinogrel plus as much as \$500 million more if the company meets certain regulatory and commercial milestones.²² Elinogrel may have an advantage over clopidogrel and prasugrel in faster onset and reversal of antiplatelet effects.

Patients with ACS undergoing PCI, the target group for prasugrel based on the TRITON-TIMI 38 results, are estimated to account for only about 20% of the current market for prasugrel.²³ The other 80% of the prasugrel market is expected to be medical management of ACS patients. As noted by Schafer et al., it will take additional trials, such as the TRILOGY study, a comparison of prasugrel+aspirin with clopidogrel+aspirin in medically managed patients with UA/NSTEMI ACS,²⁴ for the manufacturer of prasugrel to seek regulatory approval for additional indications. The TRILOGY results are not expected until 2012, and clopidogrel will be available by generic name in the United States before 2012.²³ Nevertheless, it is reasonable and prudent to expect that prasugrel will be used outside of the FDA-approved label indications. Choudhry et al. (2008) found that only 39% of clopidogrel users enrolled in the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) program met FDA-approved indications for use of clopidogrel.²⁵ Prior authorization (PA) interventions can be used by managed care plans to prevent inappropriate use of prasugrel and clopidogrel for primary prevention and to protect patients who will not benefit from prasugrel (e.g., aged 75 years or older, body weight lower than 60 kg) or who are at risk of harm from prasugrel (e.g., history of stroke/TIA).²⁶

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DISCLOSURES

The authors report no conflicts of interest related to the subjects or products discussed in this article.

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