# Drug Monitor

## Clopidogrel and Platelet Inhibition

Standard 75-mg clopidogrel dose regimens often yield poor antiplatelet effects, which have been linked to a greater risk of atherothrombotic events. Updated guidelines for percutaneous coronary intervention (PCI), therefore, recommend doubling the clopidogrel dose in high risk patients who demonstrate less than 50% platelet inhibition with the 75-mg dose.

But this recommendation was implemented before evidence of higher maintenance dose's impact on platelet inhibition, say researchers from the University of Florida College of Medicine and the Jacksonville Transplant Center, both at Shands Jacksonville, Jacksonville, FL. And while a few studies, since then, have investigated the functional effects of the 150-mg dose, none have done so in patients with inadequate platelet inhibition, as specified in the guidelines.

The researchers performed a subgroup analysis of the Optimizing Anti-Platelet Therapy in Diabetes Mellitus (OPTIMUS) trial, which enrolled patients aged 25 to 80 years who had type 2 diabetes, had undergone PCI for coronary artery disease, and were treated post-PCI with dual antiplatelet therapy (aspirin 81 mg/day plus clopidogrel 75 mg/day). In the OPTIMUS study, patients with greater than 50% posttreatment platelet reactivity after 20 µmol/L adenosine diphosphate (ADP) stimuli while in their steady-state phase of clopidogrel treatment were eligible for random assignment to one month of treatment with clopidogrel 150 mg/day. But, the authors of the present study point out, not all patients with elevated posttreatment platelet reactivity have inadequate platelet inhibition. In fact, only 17 of the 20 OPTIMUS patients assigned to clopidogrel 150 mg/day actually had platelet inhibition less than 50%.

Among those 17 patients, the higher clopidogrel dose increased platelet inhibition from 27% to 41% and improved other antiplatelet effects. The degree of platelet inhibition varied broadly within the group, however, and rose above 50% in only six patients (35%). Furthermore, the antiplatelet effects of high dose therapy were inferior to those experienced by a control group of diabetic patients who had greater than 50% platelet inhibition with the standard clopidogrel dose.

Given the variability of response, the researchers say their findings "may argue the implementation into clinical practice of this new recommendation, for which the safety and efficacy are yet to be proved." They also highlight the need for alternative antithrombotic strategies that result in more potent platelet inhibition.

Source: *Am J Cardiol.* 2008;101(4):440–445. doi:10.1016/j.amjcard.2007.09.087.

## Assessing the Potential for Herb-Drug Interactions

Although the potential for interactions between dietary supplements and prescription medications is high, the potential for actual harm is low, say researchers from the Mayo Clinic, Rochester MN; University of Arizona College of Medicine, Tucson; and Christian Medical College, Ludhiana, Punjab, India. Moreover, a small number of prescription medicines and dietary supplements account for most of the interactions.

The researchers administered a point-of-care survey to a cross-sectional sample of 1,818 patients in six specialty clinics at the Mayo Clinic between September 2002 and July 2003. The survey asked specifically about use of 52 dietary supplements and provided space for respondents to list other supplements used. Vitamins and minerals were excluded from the definition of dietary supplement.

A total of 1,795 patients returned the survey, for a 99% response rate. Of these, 710 (40%) said they used dietary supplements. The researchers then reviewed the electronic medical records of survey respondents to determine their use of prescription medications and the potential for interactions between these medications and dietary supplements. Of the 710 patients who reported using dietary supplements, 11 did not have information about prescription medications in their medical records and were therefore excluded from the interaction analysis.

From the medical records of the remaining 699 patients, the researchers identified 369 potential interactions among 236 patients. Only 107 of the interactions, however, were considered of potential clinical significance. Among dietary supplements, garlic, valerian, kava, ginkgo, and St. John's wort accounted for 68% of all possible interactions. Among prescription medication classes, antithrombotics, sedatives, antidepressants, and antidiabetics accounted for 94% of the possible interactions.

During the study period, no patient was hospitalized for a new or exacerbated medical problem related to an interaction. Still, until more data are available, the researchers advise counseling patients taking antithrombotics generally to avoid dietary supplements known to interact with warfarin or to have antiplatelet effects.

Continued on next page

Continued from previous page

This study found a higher prevalence of dietary supplement use compared with previous studies. The researchers attribute this to the inclusion of patients with medical conditions (such as cancer, fibromyalgia, and chronic pain) for which dietary supplement use is common. They also note that only 26% of patients who reported using dietary supplements had this use documented in their medical records.

Source: *Am J Med.* 2008;121(3):207–211. doi:10.1016/j.amjmed.2007.11.014.

## Does Early Analgesia Contribute to Delayed Appendicitis Treatment?

A number of studies over the past few decades have challenged the traditional recommendation to withhold analgesia from patients with abdominal pain until the necessity of surgery is determined. Some clinicians, however, point out limitations of these studies and question whether they have truly established the safety of analgesic use in practice.

Aiming to produce more useful results, researchers from Lehigh Valley Hospital-Muhlenberg, Bethlehem, PA; Lehigh Valley Hospital, Allentown, PA; and Danbury Hospital, Danbury, CT conducted a retrospective, matched case-control study that used delayed treatment of appendicitis as the primary outcome, attempted to control for illness severity, and considered both opiate analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs).

Of the 1,916 appendectomies performed at their three-hospital system between 1998 and 2002, 957 resulted in pathologically confirmed diagnoses of acute appendicitis, had been seen first by an emergency department (ED) provider, and had sufficient documentation. In 103 of these cases, treatment was delayed (defined as discharge after the initial ED visit or at least 20 hours between initial examination and surgery). From the remaining 854 cases (in which treatment was not delayed), the researchers randomly selected 103 control cases that were matched for Alvarado score (to control for typical or atypical appendicitis presentation), gender, age, and date of visit (within six months when possible).

When considering both types of analgesics, the researchers found no significant association with delayed treatment. Neither was there an apparent link between delayed treatment and early opiate use. By contrast, early NSAID use was twice as common in patients with delayed treatment than in controls. Comparing the 103 delayed treatment cases to all 854 unmatched controls yielded similar results. And complications occurred significantly more frequently in delayed treatment cases than in controls.

Additional analyses did implicate one possible confounder: right upper quadrant tenderness. It's possible, say the researchers, that clinicians might be predisposed to use NSAIDs when they suspect biliary colic, and those cases happen to be atypical ones that are prone to delay. But the researchers maintain that NSAIDs could be contributing to delay by mediating a decrease in peritoneal inflammation and decreasing tenderness, which could make the patient "seem better on reexamination." Thus, they advise caution with NSAID use in this setting.

Source: *Am J Emerg Med.* 2008;26(2):176–180. doi:10.1016/j.ajem.2007.04.024.

## Statins and Kidney Disease

It's been suggested that statins may help keep kidneys from deteriorating. To investigate the matter further, researchers from Central Arkansas Veterans Heathcare System and University of Arkansas for Medical Science, both in Little Rock, and New York Medical College, Valhalla analyzed data mined from the VISN 16 database, which includes approximately 15 million veterans treated in 10 hospitals in the southern United States.

Of 197,551 patients who had repeated serum creatinine measurements and no preexisting end-stage kidney disease, 58,332 (30%) had a statin prescription. Over an average of three years, 6,654 patients (3.4% of the entire cohort) developed renal dysfunction (defined as doubling of serum creatinine or an increase of 0.5 mg/dL between the first and last measurements). After adjusting for such factors as diabetes, smoking, and medications, statin use reduced the odds of developing renal dysfunction by 13%. The renal benefits appeared to be independent of the drugs' lipid lowering effects.

A meta-analysis on the same topic was conducted by researchers from University of Sydney School of Public Health, Cochrane Renal Group, and George Institute for International Health, all in Sydney, Australia; University of Queensland, Brisbane, Australia; University of Rochester, Rochester, NY; and Mario Negri Sud Consortium, Santa Maria Imbario, Italy. After analyzing data from 50 randomized and quasi-randomized, controlled trials comparing statins with placebo or other statins in 30,144 patients with chronic kidney disease, they concluded that statins safely and significantly reduce lipid concentrations and cardiovascular endpoints in these patients, irrespective of kidney disease stage. They did not find a benefit in all-cause mortality, however. They speculate that this might be due, in part, to a dearth of studies involving patients with stages 3 to 5 chronic kidney disease. They add that renoprotective effects of statins are uncertain because of relatively sparse data. ●

Sources: *Am J Cardiol.* 2008:101(7):975–979. doi:10.1016/j.amjcard.2007.11.042.

*BMJ.* 2008;336(7645):645–651. doi:10.1136/bmj.39472.580984.AE.