Drug Monitor

Smoking and Clopidogrel Response

Ideally, any patient with heart disease would not still be smoking, but unfortunately, that's not always the case. Thus, it's good news that smoking status does not have an impact on platelet function in patients being treated with clopidogrel or prasugrel, according to a study by researchers from Brigham and Women's Hospital and Harvard Medical School, both in Boston, Massachusetts and Herz-Zentrum Bad Krozingen and Technische Universität München, both in Germany.

Certain characteristics have been consistently associated with altered platelet response to clopidogrel—age, sex, diabetes, and body mass index. However, only 10% to 22% of low response to clopidogrel is explained by known genetic, demographic, and clinical variables, the researchers say.

Further, previous studies have had "highly conflicting" results on whether smoking changes clopidogrel's effects. Cytochrome P4501A2 (CYP1A2) is one of the enzymes involved in the metabolism of clopidogrel. In an experimental study, smoking was associated with a dose-dependent increase in CYP1A2 function and a 1.7-fold higher enzyme activity in subjects smoking more than 20 cigarettes a day. Thus, smoking might have an impact on antiplatelet response to clopidogrel.

The researchers analyzed platelet function in 4,819 patients from several cohorts undergoing percutaneous coronary intervention (PCI). They also analyzed the potential interaction of smoking with the clinical effect of clopidogrel vs prasugrel in 13,608 patients in the TRITON-TIMI 38 study. The proportion of active smokers ranged between 10% and 20%.

The researchers found no significant differences between smokers and nonsmokers on clopidogrel therapy in platelet aggregation after loading and on maintenance therapy (75 mg and 150 mg). Only in the very small group of 16 smokers on prasugrel did they observe a significant trend for higher platelet aggregation (ie, less inhibition) with more cigarettes smoked.

To find out whether smoking alters platelet function even after someone has stopped smoking, patients were also grouped according to current and former smoking status. Mean platelet aggregation (5 µmol/L adenosine diphosphate) in the EXCELSIOR study (1,996 patients) 1 day after PCI was 8% in nonsmokers (n = 494), 8% in current smokers (n = 82), and 9% in former smokers (n = 189). The proportions of patients with a low response to clopidogrel were 28%, 24%, and 31%, respectively.

Am Heart J. 2011;162(3):518-526.e5. doi:10.1016/j.ahj.2011.06.005.

Statins Plus Antiplatelet Treatment for VTE

As evidence builds to support the theory of a possible common inflammatory mechanism for venous thromboembolism (VTE) and atherosclerotic disease, researchers from Albert Einstein Medical Center and Thomas Jefferson University Hospital, both in Philadelphia, Pennsylvania, decided to test a hypothesis that combining statins and antiplatelet therapy could help prevent VTE.

They conducted a retrospective study of 1,100 patients with an established diagnosis of atherosclerosis, including ischemic stroke and myocardial infarction. The VTE group included patients with a diagnosis of either a pulmonary embolism or a deep vein thrombosis. Patients taking oral anticoagulants were excluded.

Over the 5-year study period, VTE developed in 107 patients (9.7%). The study reinforced the "well-studied" risk factors: Metastatic cancer, immobilization, hormone use, and obesity statistically increased the risk of VTE developing. For example, rosuvastatin's efficacy was shown in healthy adults in the reduction of high-sensitive C-reactive protein levels by 37% after a 1.9-year median follow-up period. In patients with atherosclerotic disease, statins' anti-inflammatory and antithrombotic properties may have clinical implications in VTE prevention.

Similarly, the data supported statin use, both alone, with a possible dose-related response, or in combination with antiplatelet therapy. Among statin users, VTE developed in 6.3% (54 of 861) compared with 22% (53/239) in the nonuser group. After controlling for confounding factors, statin use was still associated with a lower risk of VTE developing. High-dose statin use (average 50.9 mg/day) lowered the risk of VTE compared with standard doses (average 22.2 mg/day). The statin user group had a mean follow-up period of 13.4 months (in a range of 2 to 56 months).

Antiplatelet therapy in VTE prevention is controversial, the researchers say. In this study, however, both aspirin and clopidogrel showed benefits. Moreover, dual antiplatelet therapy had a better outcome, compared with single antiplatelet therapy. The possible implication of dual antiplatelet therapy on VTE warrants further prospective studies, they conclude. The antiplatelet user group had a mean follow-up period of 13.48 months (in a range of 2 to 78 months).

The highest protective effect was seen when statins were combined with antiplatelet therapy, which further reduced the occurrence of VTE (HR 0.16). The researchers call it a "theoretically attractive possibility" that combination treatment reduces platelet thromboxane A-1 in the platelet aggregation process, "a mechanism

Continued on page 52

Continued from page 48

that may play an important role in arterial and venous thrombosis."

Am J Med. 2011;124(9):852-859.
doi:10.1016/j.amjmed.2011.04.019.

Racial Disparities in Medication Problems

Although many older adults have medication-related problems, such as undertreatment and underdosing, black patients have more than white patients: a mean of 6.3 vs 4.9, according to a study by researchers from the University of North Carolina at Chapel Hill and the Durham VAMC Center for Health Services Research, both in North Carolina.

In a prospective study involving in-home interviews and medical record reviews of 200 participants (100 blacks, 100 whites), the researchers assessed the prevalence, number, and type of medication-related problems at baseline, 6 months, and 12 months. They found medication-related problems were not only prevalent, but persistent; over that time, the number of medication-related problems increased.

The investigators looked at 7 categories: suboptimal drug; suboptimal dose, duration, frequency, or administration; adverse drug event; nonadherence; less costly drug available; undertreatment; and suboptimal medication monitoring.

Most participants in both groups were women. Whites were significantly older, had more education, and were more likely to live alone. They also used more medications, had a greater number of chronic conditions, and used more physicians. Black participants were more likely to be unable to buy their medications due to cost.

Although all the patients in the study were in primary care, receiving "standard of care," all had at least 1 medication-related problem at each time point: most commonly, undertreatment, suboptimal drug use, suboptimal dosing, nonadherence, and less costly alternative available.

The prevalence of a less costly alternative available was significantly different between blacks (49%) and whites (46%) at baseline after adjusting for fixed pharmacist effect, baseline number of medications, age, gender, and health literacy. There was also a significant difference in the prevalence of nonadherence at baseline; moreover, the rates of nonadherence increased slightly over the 12 months: from 68% to 71% for blacks and from 42% to 48% for whites.

The data also suggested that suboptimal drug use increased over time, most notably among the white participants. When nonadherence was removed from the model, the researchers say, the mean number of problems remained significantly greater for blacks than whites at baseline (4.34 vs 3.97), suggesting that other disparities in the quality of medication use exist.

Am J Geriatr Pharmacother. 2011;9(4):250-258.
doi:10.1016/j.amjopharm.2011.05.002.