Korean Study Questions Dual-Antiplatelet Tx

BY MITCHEL L. ZOLER

ATLANTA—Results from a study branded by its principal investigator as underpowered to produce a meaningful result still sparked attention at a major cardiology meeting by fanning the controversy swirling around clopidogrel's role following percutaneous coronary interventions with drug-eluting stents.

The Korean study that tried to test the long-term role of clopidogrel for preventing adverse cardiovascular events following placement of drug-eluting stents (DES) in roughly 2,700 patients "had insufficient statistical power to allow a firm conclusion," Dr. Seung-Jung Park said at the annual meeting of the American College of Cardiology. That fact mitigated what would have otherwise been a highly surprising and troubling finding: More than a year out from coronary stenting, patients treated with aspirin alone fared no worse than and even trended toward better outcomes compared with patients maintained on dual-antiplatelet therapy with aspirin and clopidogrel.

The underpowered study size might, in other circumstances, have caused the report to be dismissed and quickly forgotten. But two extenuating circumstances instead thrust the study into the spotlight: First, despite its problems, the study simultaneously ran in the New England Journal of Medicine (2010 March 15 [doi:10.1056/NEJMoa1001266]). Second, the report came just days after the Food and Drug Administration on March 12 roiled concerns about clopidogrel's efficacy in patients who recently received a coronary stent by adding a boxed warning to the label of clopidogrel (Plavix) alerting prescribers that certain patients do not metabolize clopidogrel effectively, thereby blunting the drug's efficacy in these people (see article below). Such "poor metabolizers," the FDA said, comprise an estimated 2%-14% of the American public and perhaps as high as 50% of some Asian populations.

"We see tremendous variability of responsiveness to clopidogrel and aspirin" in patients attributable to genetic differences in features such as the metabolic activation of clopidogrel, said Dr. George D. Dangas, a cardiologist at the Center for Interventional Vascular Therapy at Columbia University in New York. "How can we have a question of [clopidogrel treatment] duration in patients who are not responding? I'm not sure that makes much sense. Perhaps patients in Dr. Park's study were hyporesponders [to clopidogrel] and that's behind what he sees."

The Korean study enrolled 2,701 patients who had received at least one DES and had been event free while on combined antiplatelet therapy with aspirin and clopidogrel for at least 12 months. Their average age was 62, and 70% were men. A median of 13 months after stent placement, the researchers randomized the patients to continue on 75 mg clopidogrel and 100-200 mg aspirin daily or just aspirin alone. Follow-up continued for a median of 19 months, but the total number of end point events remained low, about a quarter of the expected number, probably because the study involved low-risk patients, said Dr. Park, professor of medicine in the Heart Institute at Asan Medical Center in Seoul, South Korea.

The primary end point, the combined rate of MI or cardiac death, occurred in 1.8% of patients treated with clopidogrel and aspirin and in 1.2% of those on aspirin only, a nonsignificant, 65% relative increased risk of events among patients on the dual-antiplatelet regimen compared with aspirin alone.

In two other outcome measures the worse performance by the combined regimen just missed statistical significance. The combined rate of MI, stroke, or death from any caused occurred in 3.2% of the combined-treatment patients and in 1.8% of the aspirin-alone controls, and the rate of MI, stroke, or cardiac death tallied in 2.7% of the aspirin plus clopidogrel patients compared with 1.3% of patients on aspirin only. Rates of all-cause death and stent thrombosis were nearly identical in both treatment groups.

Many experts who heard these potentially troubling findings that seemingly cast doubt on clopidogrel's efficacy and safety as well as on prolonged dual-antiplatelet therapy following coronary stenting uniformly dismissed the findings as unreliable.

"The answers are not definitive. The lack of power is the primary concern," said Dr. Laura Mauri, chief scientific officer of the Harvard Clinical Research Institute in Boston.

"We won't know [how long to treat these patients with clopidogrel] until we have an adequately powered study," said Dr. Dean J. Kereiakes, chief executive officer of the Ohio Heart Health Center in Cincinnati.

While Dr. Dangas agreed that the results were inconclusive, he suggested that they may offer some guidance "until definitive studies come out." The results were "reassuring that perhaps in patients who did well over the first year [following placement of DES] it might be okay to consider taking them off clopidogrel," he said.

The study received no industry support. Dr. Park said that he and his associates had no disclosures.

Dr. Dangas reported financial relationships with several pharmaceutical and device companies, including Daiichi-Sankyo, Sanofi-Aventis, Boston Scientific, AstraZeneca, and Cordis. Dr. Mauri reported receiving consulting fees or honoraria from Cordis and Medtronic Vascular. Dr. Kereiakes reported financial relationships with Reva Medical, Eli Lilly, Boston Scientific, Cordis, Devax, and Abbott Vascular, Amylin, and Daiichi Sankyo, among other drug and device makers. ■

MY TAKE

Results Won't Change My Practice

Despite the study's limited power, it generates some interesting hypotheses. Perhaps we need to consider the level of risk that patients face from major adverse events following coronary stenting with DES when evaluating dual antiplatelet therapy. The new results suggest that in low-risk patients this balance tips in favor of stopping dual antiplatelet drug therapy a year after stenting. It's not clear what mechanism might produce the apparent risk from clopidogrel treatment beyond 1 year in this study.

Asian populations have a high prevalence of cytochrome P2C19 genes that produce little or no active enzyme needed to metabolize clopidogrel to its active form. This may mean that many patients in the study were genetically unable to benefit from clopidogrel treatment.

The new results suggesting that low-risk patients exist who may not benefit from continued clopidogrel treatment, are not convincing. I have sufficient uncertainty that I'm not willing to change my practice, even in low-risk patients. My approach has been to have a low threshold for continuing dual-antiplatelet therapy in DES patients. Until now, all of the data supporting this approach came from observational studies. This is no substitute for prospective, controlled studies, so the Korean study is a laudable first step. What's needed are larger studies with longer follow-up, such as study the Dual Antiplatelet Therapy (DAPT) study, with an expected enrollment of more than 20,000 patients.

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Clopidogrel Gets Boxed Warning on Poor Metabolizers

BY ALICIA AULT

The Food and Drug Administration updated the labeling for clopidogrel to emphasize that new data definitively shows that the drug is less effective—and may not work at all—in patients defined as "poor metabolizers."

The agency is notifying physicians that testing is available for the genotypes that are associated with poor metabolism, but it stopped short of recommending that all patients receive such testing before starting a course of clopidogrel (Plavix).

About 2%-14% of the population probably have those alleles and are poor metabolizers, with the rate varying by racial background, according to the FDA.

The issue of reduced metabolism was first highlighted in the clopidogrel label in May 2009. But the agency decided to add a stronger, boxed warning to clopidogrel because of the mounting evidence about poor metabolizers, including a required post-marketing study conducted by the drug's manufacturer, Sanofi-Aventis, that was submitted to the FDA, said Mary Ross Southworth, Pharm.D., a clinical analyst in the Division of Cardiovascular and Renal Products in the FDA's Center for Drug Evaluation and Research, in a briefing with reporters.

That 40-patient study confirmed that patients with the *2 and *3 alleles of the CYP2C19 liver enzyme were likely to be poor metabolizers. The *4, *5, *6, *7 and *8 alleles are associated with little to no metabolism of clopidogrel but occur less commonly than *2 and *3 alleles.

In acute situations, such as during a MI or coronary angioplasty, waiting for test results won't be reasonable, said Dr. Robert Temple, deputy director for clinical science in FDA's Center for Drug Evaluation and Research, in the briefing.

For chronic use of clopidogrel in poor metabolizers, the FDA is urging physicians to consider use of other antiplatelets, such as ticlopidine (Ticlid) or prasugrel (Effient), or potentially increasing the clopidogrel dose.

Ms. Southworth and Dr. Temple acknowledged that physicians would likely have to test patients to determine first if they were poor metabolizers, but said that there are not enough data to say that testing should be required.

Only one diagnostic for liver enzyme metabolism—the Amplichip, made by Roche—has been approved, and it is not specifically approved for CYP2C19, said Dr. Courtney Harper, director of the division of chemistry and toxicology devices at the FDA's Center for Devices and Radiologic Health. Roche cannot promote the test, since it would be an off-label use. ■