Initial CHARISMA Results Create Antiplatelet Anxiety

BY BRUCE JANCIN
Denver Bureau

ATLANTA — The world's major cardiology organizations have had to scramble to issue public health alerts warning patients who take clopidogrel not to stop taking it on their own in response to confusing media reports on the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance trial.

CHARISMA was an ambitious 15,063-patient randomized trial aimed at expanding the indications for dual antiplatelet therapy with clopidogrel (Plavix) and low-dose aspirin. It was, overall, a negative study—and therein lay the misunderstanding, as many lay media reports failed to note that the existing applications for such therapy remain fully intact.

In patients with atherothrombotic disease, a 12.5% relative risk reduction favored dual antiplatelet therapy.

DR. BHATT

Situations in which clopidogrel plus aspirin is of proven benefit over aspirin alone include those in patients with ST-elevation MI, in whom it reduced mortality in clinical trials; in patients with acute coronary syndromes, in whom it decreased the composite of death, MI, or stroke; and in recently stented patients.

In the days following initial presentation of CHARISMA at the annual meeting of the American College of Cardiology in Atlanta, the ACC, the American Heart Association, and the European Society of Cardiology each issued public alerts. The impetus was feedback from member physicians who reported fielding queries from panicky patients, although prominent cardiologists contacted by this news organization indicated they were receiving few such calls.

In presenting the CHARISMA results at the ACC meeting, principal investigator Dr. Deepak L. Bhatt characterized the study as "a complex trial with somewhat unanticipated findings."

The study comprised two distinct groups: roughly 12,000 enrollees with documented baseline stable coronary, cerebrovascular, and/or symptomatic peripheral arterial disease; and the remainder (the primary prevention cohort) who had multiple cardiovascular risk factors.

The primary efficacy end point—MI, stroke, or cardiovascular death—occurred in 7.3% of the dual antiplatelet therapy group and in 6.8% on aspirin alone during 28 months of follow-up, a nonsignificant difference.

The primary safety end point—the rate of severe bleeding—was also similar at 1.7% with dual therapy and 1.3% with aspirin, noted Dr. Bhatt of the Cleveland Clinic Foundation.

The prespecified subgroup analysis showed dichotomous results in the primary and secondary prevention subgroups. Among the 12,000 patients with documented atherothrombotic disease at baseline, the primary efficacy end point occurred in 6.9% on dual therapy and in 7.9% on aspirin, resulting in what Dr. Bhatt termed a "modest" but statistically significant 12.5% relative risk reduction favoring dual antiplatelet therapy, with no increase in serious bleeding.

In sharp contrast, there was a suggestion of harm with dual therapy in the primary prevention group. They had significant increases in both cardiovascular mortality (3.9% versus 2.2%) and bleeding.

One biologically plausible hypothesis for the disparate results is that patients in the secondary prevention category have hyperactive platelets, which mitigate the bleeding risk; the addition of clopidogrel to aspirin in such patients restores their platelets to a steady state, affording partial protection against atherothrombotic events.

In contrast, further reduction of platelet activity in asymptomatic patients without baseline platelet activation would expose them to increased risk of bleeding complications, the cardiologist speculated.

Discussant Dr. Matthew R. Wolff, chief of cardiovascular medicine at the University of Wisconsin, Madison, said, "I think the investigators and sponsors went for a home run and maybe got a broken-bat single."

Dr. Bhatt said, "We like to think of it as a solid double," adding that there will be much clinically useful data to come from planned future CHARISMA subanalyses.

In his own clinical practice, the cardiologist continued, he'll use the initial CHARISMA findings to better individualize secondary preventive therapy.

"If I had a patient in front of me who'd had multiple heart attacks in the past while taking aspirin but was tolerating aspirin well in terms of not having any bleeding problems, I would now consider adding clopidogrel. On the other hand, if I had a patient with an MI in the past but who has been rock-stable since, and last month while on aspirin had a bleeding ulcer, I don't think I'd add clopidogrel," he explained.

Dr. Prakash Deedwania said in an interview that he won't change anything about how he uses clopidogrel, based on CHARISMA.

"I wasn't at all surprised at the results. There was no rationale to think that patients with no prior CAD events should benefit, as there is no evidence that clopidogrel should work when plaque is not disrupted," said Dr. Deedwania of the University of California, San Francisco, and chief of cardiology at the Veterans Affairs Central California Health Care System, Fresno.

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Late Thrombosis Rate Tripled With Drug-Eluting Stents

BY MITCHEL L. ZOLER
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ATLANTA — Patients with a drug-eluting coronary stent had a 4.9% rate of cardiac death or myocardial infarction during the first year after they stopped daily treatment with clopidogrel, more than three times the rate in patients with bare-metal stents in a study with 743 patients.

The incidence of clinical events related to late stent thrombosis was 2.4% in patients with drug-eluting stents (DES), compared with 0.8% in those with bare-metal stents (BMS), Dr. Matthias E. Pfisterer said at the annual meeting of the American College of Cardiology.

On the basis of these findings, he calculated that for every 100 patients who receive a DES instead of a BMS in a coronary artery, the consequence is an extra 3.3 late deaths and myocardial infarctions. This was balanced against a DES benefit of 5 fewer patients who needed target-vessel revascularization for every 100 treated, compared with BMS, said Dr. Pfisterer, head of the division of cardiology at University Hospital Basel (Switzerland).

"You're trading late restenosis for deaths and MI. It's a very important and worrisome trade-off," commented Dr. William W. O'Neill, corporate chief of cardiology at William Beaumont Hospital in Royal Oak, Mich.

The finding "may be practice changing," commented Dr. Robert Harrington, of the department of medicine at Duke University in Durham, N.C.

The risk of late thrombosis lasted throughout a yearlong follow-up period after discontinuation of clopidogrel treatment. Events did not cluster early after the drug was stopped, but were scattered; some thromboses did not occur until the end of the follow-up period.

For the time being, the best way to treat late stent thrombosis in patients who have received a DES is to continue dual antiplatelet therapy with clopidogrel and aspirin indefinitely, Dr. Pfisterer said in an interview.

Another way is to use the DES judiciously. In patients with focal lesions, the advantage of a DES over a BMS is small. In the future, new types of stents that are bioabsorbable or that contain different drug coatings and formulations may provide the solution.

The rate of thrombosis-related events linked with DESs was higher in this study than in past reports, most likely because the study enrolled all patients who needed a coronary stent at University Hospital Basel during May 2003 to May 2004, regardless of their indication for stenting. The only exclusion was in patients with a target vessel diameter of 4.0 mm or greater, because the largest DES available at the time had a diameter of 3.5 mm.

As a result, the cohort included a large fraction of patients with unstable coronary disease, Dr. Pfisterer said. More than two-thirds of patients had multivessel disease, and 60% had acute coronary syndrome at the time of enrollment. The patients received an average of 1.9 stents each.

The Basel Stent Kosten Effektivitäts Trial (BASKET) was initially designed to compare the cost effectiveness of sirolimus-eluting stents (Cypher), paclitaxel-eluting stents (Taxus), and BMS. The study did not have any industry funding.

The primary results of the study, which followed patients for 6 months after stent implantation, showed that the incremental cost-effectiveness ratio of DES to BMS was about 20,000 euros to avoid one major adverse cardiac event, and more than 50,000 euros per quality life year gained (Lancet 2005;366:921-9).

Dr. Pfisterer and his associates suggested limiting the use of DES to certain high-risk subgroups, such as elderly patients with triple-vessel disease, or patients with long lesions or lesions in small vessels.

All of the patients in the trial were taken off clopidogrel treatment after 6 months and continued to take aspirin daily, which provided an opportunity to assess the risk of late stent thrombosis after dual antiplatelet therapy was stopped.

For this analysis, the 502 patients who had been initially randomized to receive either a sirolimus- or paclitaxel-eluting stent were combined into a single DES group and were compared with the 244 patients initially randomized to receive a BMS. Three patients from the DES group did not have follow-up, which reduced the group to 499 patients.

During the year off dual therapy, 4.9% of the DES patients had cardiac death or a nonfatal MI, compared with 1.3% of patients in the BMS group. The incidence of restenosis that required target-vessel revascularization was 6.7% in the BMS group and 4.5% in the DES group. When late thrombosis occurred in either group, it was usually clinically significant, with 88% of thrombotic events leading to death or MI.

In a multivariate analysis of risk factors for late stent thrombosis, three items emerged as significant predictors of risk. The use of a DES was the most potent risk, raising the incidence of thrombosis 3.9-fold, compared with patients who got a BMS. The other factors were the use of a glycoprotein IIb/IIIa inhibitor during stent placement (a marker for acute coronary syndrome at the time of stenting), which raised the risk 3.4-fold, and a history of MI, which raised the risk 3.0-fold, Dr. Pfisterer said.