# Doubling Clopidogrel Aids Stented ACS Patients

## *In CURRENT-OASIS7, 600-mg loading dose cut ischemic and thrombotic events, increased bleeding.*

BY MITCHEL L. ZOLER

BARCELONA — Doubling the clopidogrel dosage for a week following coronary artery stenting led to significantly fewer thrombotic events and a small increase in bleeds in a major study of more than 25,000 acute coronary syndrome patients.

Clopidogrel's efficacy improved when the standard dosage doubled to loading with 600 mg followed by 150 mg/day for 7 days before falling back to the standard maintenance dosage of 75 mg/day, Dr. Shamir R. Mehta said at the annual congress of the European Society of Cardiology.

The clear superiority of this higher clopidogrel dosage in acute coronary syndrome patients undergoing a percutaneous coronary intervention led some experts to immediately declare it the new standard of care for clopidogrel (Plavix) in this setting. It also added new uncertainty about the best antiplatelet drug for these patients, an issue already roiled by the recent availability of prasugrel (Effient), and by another report at the ESC meeting on ticagrelor, a novel antiplatelet drug that surpassed standard-dose clopidogrel for treating ACS patients.

The efficacy and safety of double-dose clopidogrel compared with prasugrel and ticagrelor is a question unanswered by current data, said Dr. Frans Van de Werf, a professor of cardiovascular diseases at the University of Leuven, Belgium.

The new study was sponsored by Sanofi Aventis and Bristol-Myers Squibb, the companies that together market clopidogrel. Dr. Mehta has served as a consultant to, and has received grants and honoraria from, both companies.

The new study also examined whether aspirin, a drug always used with clopidogrel in ACS patients, worked best at a high dosage of 300-325 mg/day or at a low dosage of 75-100 mg/day. The results showed no difference between the two dosages for either efficacy or safety in the entire group of 25,087 patients, but in the subgroup of 17,232 patients who underwent PCI, the higher aspirin dosage coupled with the higher clopidogrel dosage produced the lowest event rates.

"Our center at McMaster Universtity has strongly advocated low-dose aspirin for decades," but on the basis of these new results, "our practice will now likely switch to higher-dose aspirin together with higher-dose clopidogrel because this had no downside and may produce some benefit," said Dr. Mehta, a cardiologist at McMaster University in Hamilton, Ont.

His conclusion regarding which aspirin dose is best was not uniformly shared among attendees. "There is no evidence for benefit from doses of aspirin above 100 mg/day," said Dr. Van de Werf, the official discussant for Dr. Mehta's report at the congress. Dr. Van de Werf disclosed serving on an advisory board and receiving research grants from Sanofi Aventis.

The Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Optimal Antiplatelet Strategy for Interventions (CURRENT-OASIS7) trial enrolled ACS patients with a planned early intervention with PCI at 597 sites in 39 countries. Patients were randomized in a 2x2 factorial design to receive clopidogrel at either the doubled or standard dosage (300-mg loading followed by 75 mg/day). They were also randomized to either the high or low aspirin dosage. Patients were treated and followed for 30 days. The planned PCI was actually done in 70%; common reasons why patients avoided PCI were an absence of significant coronary disease on angiography or a decision to treat with bypass surgery.

**Doubled dose would prevent six MIs and seven stent thromboses, and cause three severe bleeds, per 1,000 patients.**

DR. MEHTA

The primary outcome for the clopidogrel comparison was the combined rate of death, myocardial infarction, and stroke. For the entire group of patients, the difference between the standard and double-doses of clopidogrel was not significant.

But the study had a prespecified analysis for the PCI patients only. In this group of more than 17,000 patients, treatment with the doubled clopidogrel dose during the first week cut the combined event rate compared with standard-dose patients by an absolute 0.6%, a relative risk reduction of 15% that was statistically significant (see table).

The doubled dose cut the rate of myocardial infarctions by a relative 22%, statistically significant. The rates of cardiovascular death and stroke were each identical in the two clopidogrel arms.

The doubled clopidogrel dose also produced no significant excess in the number of fatal bleeds, bypass surgery–related bleeds, or intracranial hemorrhages, nor did it significantly increase the number of major bleeds using the criteria from the TIMI (Thrombolysis in Myocardial Infarction) study. The double dose did produce a significant excess of severe and major bleeds as defined by the criteria used in the CURRENT studies (see table), but this difference was "driven almost entirely by the need for additional red blood cell transfusions," Dr. Mehta noted. The CURRENT bleeding assessment was "more sensitive" than were other assessments, such as the TIMI major scale, he added. CURRENT took into account outcomes such as hypotension, need for inotropic support, and the need for surgery to stop bleeding.

A key secondary outcome of the clopidogrel comparison was the rate of definite stent thrombosis. The doubled clopidogrel dose cut this rate by 0.5% absolute, a 42% relative reduction compared with standard-dose clopidogrel, a statistically significant difference.

The doubled clopidogrel dosage had a consistent effect across most of the prespecified subgroups, including divisions by gender, age, diabetes, and type of ACS. Notably, the effect of the increased clopidogrel dose was not affected by concurrent use of a proton pump inhibitor, a drug class that's been implicated in blunting clopidogrel's effect. The subgroup analysis also showed that the impact of double-dose clopidogrel was enhanced in patients who smoked.

The overall results showed that, compared with standard-dose clopidogrel, the doubled dose for the first 7 days of treatment would prevent in every 1,000 treated patients an extra six myocardial infarctions and an extra seven stent thromboses, at the price of causing three excess, severe bleeds, but with no change in the rate of fatal, surgery-related, or TIMI major bleeds, Dr. Mehta said. However, ACS patients who are not undergoing PCI should continue to receive the standard clopidogrel regimen, he added.

For patients undergoing PCI, doubling the clopidogrel dose is simple and effective, requiring physicians to "go from one pill to two pills a day. The cost is negligible and the benefits are large. It will be instituted rapidly," said Dr. Mehta, adding that "this is the largest trial done so far in ACS patients."

Other experts agreed that, with these results, doubling the clopidogrel dosage for ACS patients undergoing PCI made sense. They also supported Dr. Mehta's tilt toward a higher aspirin dosage.

"I'm starting" the double clopidogrel dosage "or using prasugrel," said Dr. Christopher P. Cannon, a cardiologist at Brigham and Women's Hospital in Boston. "We've all been using a 600-mg loading dose, but not the 150 mg/day for a week."

He noted that a study now in progress is testing 6 months of clopidogrel treatment at 150 mg/day. He also agreed that high-dose aspirin periprocedurally after PCI "looks like the way to go," but stressed that after 30 days he would scale the aspirin down to a low daily dose. Dr. Cannon disclosed receiving research grants from Sanofi Aventis and Bristol-Myers Squibb and from several other drug companies.

"It's important to learn how to use clopidogrel more effectively, so this is valuable information," said Dr. Elliott M. Antman, director of the cardiac unit at Brigham and Women's Hospital in Boston. "These are the first data [on a doubled clopidogrel dosage] from a prospective, randomized trial."

But Dr. Antman cautioned that "even ramping up the clopidogrel dose may not get you there" because some patients have a genetic polymorphism that makes them less able to metabolize clopidogrel to its active form. Dr. Antman was the principal investigator for the pivotal study of prasugrel, a rival antiplatelet drug that does not require metabolic activation.

Dr. Antman has been a consultant to Sanofi Aventis, and has received research grants from Sanofi, Bristol-Myers Squibb, and other pharmaceutical companies.

A higher aspirin dosage immediately following PCI is now "routine practice," he added, although the duration varies. "I use the higher dose for 3 months, and then lower it to 81 mg/day" in patients who have received a drug-eluting stent, he said in an interview. Other physicians use high-dose aspirin in this setting for periods ranging from 1 to 6 months. ■

### Double Dose Reduces Thrombotic Events, Increases Bleeds

| Outcome | 30-Day Rate: Standard clopidogrel dosage | 30-Day Rate: Double clopidogrel dosage |
|---|---|---|
| Cardiovascular death, myocardial infarction, and stroke (primary outcome) | 4.5% | 3.9%* |
| Myocardial infarction | 2.6% | 2.0%* |
| Cardiovascular death | 1.9% | 1.9% |
| Stroke | 0.4% | 0.4% |
| Definite stent thrombosis | 1.2% | 0.7%* |
| CURRENT severe bleeds | 0.8% | 1.1%* |
| CURRENT major bleeds | 1.1% | 1.6%* |
| TIMI major bleeds | 0.5% | 0.5% |
| Fatal bleeds | 0.15% | 0.07% |
| Two or more red blood cell transfusions | 0.91% | 1.35%* |

*Statistically significant difference

Note: Based on data from 17,232 patients with ACS who underwent percutaneous coronary interventions.

Source: Dr. Mehta