Prasugrel's Benefit for ACS Enhanced in Diabetics

BY MITCHEL L. ZOLER
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MUNICH — The investigational antiplatelet drug prasugrel was particularly effective for cutting ischemic events in patients with diabetes and relatively less effective in patients without diabetes in a prespecified analysis of the more than 13,000 patients in the drug's pivotal trial.

Initial results reported in November 2007 from the Trial to Assess Improvements in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI-38) showed that in moderate- to high-risk patients with acute coronary syndrome who were scheduled to undergo percutaneous coronary intervention treatment with prasugrel led to a 19% relative risk reduction in the rate of cardiovascular death, myocardial infarction, or stroke, compared with patients treated with the standard drug, clopidogrel (N. Engl. J. Med. 2007;357:2001-15). But because prasugrel treatment was also linked with a 32% relative increase in major bleeding events, compared with clopidogrel, some physicians wondered whether the benefits of prasugrel were worth its increased risk.

"Prasugrel is not a drug for all patients," Dr. Stephen D. Wiviott said while presenting a poster on the diabetes analysis at the European Society of Cardiology. "Physicians need to weigh things like a patient's age, their bleeding risk, and their risk for ischemic events."

An increased risk for ischemic events in diabetics is one reason why prasugrel was especially effective for those patients. The combination of higher clinical event rates and a greater relative treatment effect in diabetic patients led to markedly greater absolute event reductions in these patients, compared with those without diabetes, Dr. Wiviott and his associates reported.

Outcomes With Prasugrel Compared With Clopidogrel by Diabetic Status

	Diabetic patients (n = 3,146)	Nondiabetic patients (n = 10,462)
Primary end point		
Prasugrel	12.2%	9.2%
Clopidogrel	17.0%	10.6%
Relative risk reduction with prasugrel	30.0%*	14.0%*
Major bleeds		
Prasugrel	2.5%	2.4%
Clopidogrel	2.6%	1.6%
Relative risk change with prasugrel	+6.0%	+43.0%*

Notes: Primary end point is the combined rate of death, MI, and stroke; *statistically significant difference in relative risk change.
Source: Dr. Wiviott

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The study enrolled 3,146 patients with diabetes and 10,462 patients without diabetes. Among the diabetic patients, 776 (25%) required insulin treatment. The incidence of cardiovascular death, nonfatal MI, or nonfatal stroke (the combined primary end point for the study) was 32% higher among the diabetic patients not taking insulin, compared with the nondiabetics. The event rate was 84% higher in the patients on insulin, compared with the nondiabetic patients.

Patients with unstable angina or ST-elevation myocardial infarction were randomized to treatment with either prasugrel or clopidogrel prior to undergoing percutaneous coronary intervention, and continued on the study medication for a median of 14.5 months, which was also the median time for tallying the incidence of clinical end points. The average age of the patients was 61 years.

In all patients with diabetes, the incidence of the combined primary end point was 12.2% among the patients treated with prasugrel and 17% among those treated with clopidogrel, a 30% relative risk reduction by prasugrel that was statistically significant. (See box.) In contrast, among patients without diabetes, the event rate was 9.2% in patients treated with prasugrel and 10.6% in those treated with clopidogrel, a relative risk reduction by prasugrel of 14% that was still large enough to be statistically significant, reported Dr. Wiviott, a cardiologist at Brigham and Women's Hospital and Harvard University in Boston.

The added benefit from prasugrel, compared with clopidogrel, was even more dramatic in the insulin-requiring diabetics. Within this subgroup of 776 patients, the combined event rate on prasugrel was 14%, compared with 22% in the clopidogrel group, a 37% relative risk reduction. Among the 2,370 patients with diabetes who did not require insulin, prasugrel treatment produced an 11.5% combined event rate and clopidogrel had a 15.3% rate, for a relative risk reduction of 26%.

The extra benefit from prasugrel in patients with diabetes was not associated with an increased risk in major bleeds. In all of the diabetic patients the major bleeding rate was 2.5% with prasugrel and 2.6% with clopidogrel. The excess of major bleeds linked with prasugrel seen in the entire study was entirely driven by the excess in patients without diabetes. In that subgroup, patients on prasugrel had a 2.4% major bleed rate, compared with a 1.6% rate in patients treated with clopidogrel, a relative increased risk of 43% with prasugrel that was statistically significant.

Another prespecified analysis of the study was to evaluate the net clinical benefit of treatment, which was calculated by adding the rate of the composite primary end point and the incidence of major bleeds. In the patients with diabetes, this quadruple tally of adverse events occurred in 15% of the prasugrel-treated patients and 19% of those on clopidogrel, a 26% relative reduction with prasugrel that was statistically significant. In nondiabetic patients, the quadruple composite rate was about 12% in both groups. Prasugrel reduced the risk by a relative 8%, but this difference was not statistically significant.

On the basis of other analyses from the study, prasugrel treatment did not have an advantage over clopidogrel in patients with a history of stroke or a history of bleeding, and in patients aged 75 or older, and so these parameters define patients who are not good candidates for treatment with prasugrel, Dr. Wiviott said in an interview. The results also suggested that the prasugrel dosage used in the study, a 60-mg loading dose followed by a daily 10-mg maintenance dose, probably should be reduced in patients who weigh less than 60 kg.

Prasugrel has been under review by the Food and Drug Administration since early this year At press time, no decision had been announced.

The study was sponsored by Daiichi Sankyo Co. and by Eli Lilly & Co. Dr. Wiviott said that he has received research grants and lecture fees from both companies, as well as from other drug companies. ■

Greater Coffee Consumption Linked to Lower MI Mortality

BY BRUCE JANCIN
Denver Bureau

MUNICH — Prognosis following an acute MI may be better for people who drink more coffee on a regular basis.

The mechanism for the observed inverse relationship between usual coffee intake and mortality after MI remains unknown. It doesn't appear to involve lipid levels or inflammatory biomarkers, according to Dr. Imre Janszky of the Karolinska Institute, Stockholm.

She reported on 1,369 participants in the Swedish Heart Epidemiology Program (SHEEP) study, all of whom had a confirmed first acute MI during 1992-1994. They reported their customary coffee consumption during the preceding 12 months using a standardized questionnaire that they completed during their hospitalization.

During a mean follow-up of 8 years, 21% of patients died. In a multivariate analysis adjusted for numerous potential confounders, coffee consumption showed a strong inverse relationship to mortality, Dr. Janszky reported at the annual congress of the European Society of Cardiology.

Patients who reported a usual coffee consumption of at least 1 and less than 3 cups daily had an adjusted 32% lower risk of mortality than did those who quaffed less than 1 cup per day. Those who drank at least 3 and less than 5 cups daily had a 48% risk reduction. And those who reported consuming 7 or more cups of coffee had a 42% reduction in mortality, compared with patients who drank less than a cup a day.

Coffee consumption bore no relationship to rates of hospitalization for stroke or heart failure.

The SHEEP study was supported by the Swedish Council for Social Research and the Swedish Council for Working Life and Social Research. ■

Smoking's Cardiac Effects Appear 14.5 Years Earlier in Women

BY BRUCE JANCIN
Denver Bureau

MUNICH — Women who smoke tend to have their first acute MI considerably earlier in life than do male smokers.

This observation in a Norwegian case-control study suggests that smoking increases the risk of cardiovascular disease to a relatively greater degree in women than in men, Dr. Morten Grundtvig said at the annual congress of the European Society of Cardiology.

Indeed, the Norwegian data indicate women smokers lose more than twice as many years of good health, compared with men who smoke, added Dr. Grundtvig of Innlandet Hospital, Lillehammer, Norway.

He reported on 1,784 consecutive patients, of whom 38% were women, who presented to the hospital with a first MI during 1998-2005. Overall, 39% of the men and 23% of the women were current smokers.

Among the men, the average age at which the first MI occurred was 63.9 years in current smokers, 74.7 years in ex-smokers, and 72.2 years in nonsmokers. The age differential was far greater among the women; the first MI occurred at age 66.2 years in current smokers, 74.4 years in ex-smokers, and 80.7 years in nonsmokers.

In other words, smoking women experienced their first MI 14.5 years prematurely, while men who smoked had their first MI 8.3 years prematurely.

After adjustment for differences in hypertension, diabetes, and other cardiovascular risk factors, 13.7 years of the age difference between women with an MI who smoked and those who never smoked were attributed to smoking. In men, the adjusted difference was 6.2 years, according to Dr. Grundtvig. ■