Antiplatelet Therapy Is First MI Advance in Years

Combining clopidogrel and aspirin has reduced coronary risk in patients with unstable angina.

BY BRUCE JANCIN
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ORLANDO, FLA. — Adding a brief course of clopidogrel to standard aspirin therapy in patients with ST-elevation MI improves arterial patency and saves lives, according to two major studies presented at the annual meeting of the American College of Cardiology.

Indeed, this dual antiplatelet therapy strategy constitutes the first advance in drug treatment shown to improve mortality in acute MI in a dozen years, since the landmark Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO I) trial showed a survival advantage for tissue plasminogen activator over streptokinase.

Marc S. Sabatine, M.D., presented the results of the Clopidogrel as Adjunctive ReperfusIon Therapy–Thrombolysis in Myocardial Infarction trial (CLARITY–TIMI 28), a double-blind study in which 3,491 patients presenting with ST-elevation MI (STEMI) within 12 hours of symptom onset received a fibrinolytic agent, aspirin, and heparin and were then randomized to oral clopidogrel or placebo. The clopidogrel regimen consisted of a 300-mg loading dose followed by 75 mg once daily. By study design, all patients underwent coronary angiography 2-8 days later. Clopidogrel was then stopped unless a stent was implanted, as occurred in nearly 60% of patients, in which case open-label clopidogrel was recommended, as is standard therapy.

The primary end point in CLARITY was a composite comprising an occluded infarct-related artery upon angiography a mean of 3.5 days after starting clopidogrel, repeat MI prior to angiography, or death. The rates were 15.0% in the clopidogrel arm and 21.7% with placebo, for a highly significant 36% reduction in the risk of the end point with clopidogrel.

The secondary end point was the 30-day combined rate of cardiovascular death, recurrent MI, or recurrent ischemia leading to urgent revascularization. The rates were 11.6% of patients in the clopidogrel arm and 14.1% on placebo, for a significant 20% risk reduction favoring clopidogrel.

There was no excess in major or minor bleeding or intracranial hemorrhage in the clopidogrel group. Surprisingly, there was no significant increase in the rate of major bleeding even among patients who underwent coronary artery bypass graft surgery less than 5 days after discontinuing clopidogrel, added Dr. Sabatine of Brigham and Women's Hospital, Boston.

A few days of clopidogrel prevented one primary event for every 16 patients treated. The number of patients needed to be treated to avoid one secondary study end point was 36.

Giving this safe, inexpensive, simple treatment to 1 million acute MI patients would save 5,000 lives.

DR. CHEN

The rationale for CLARITY was that the efficacy of fibrinolytic therapy is limited by inadequate reperfusion and/or early reocclusion in one-quarter of treated patients. An occluded infarct-related artery is linked with a twofold increase in long-term mortality.

CLARITY was designed to mimic how STEMI is managed at the 80% of U.S. hospitals lacking the capability to perform primary percutaneous intervention within a 90-minute window. Patients presenting to these hospitals receive thrombolytic therapy. Roughly three-quarters of them are referred for angiography a few days later, as a result of which two-thirds undergo a coronary revascularization procedure.

The other major clopidogrel study was the mammoth Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (COMMIT/CCS-2). Unlike CLARITY, COMMIT was powered to detect a short-term mortality benefit for the antiplatelet agent.

It involved 45,852 acute MI patients, 93% with STEMI, who presented to 1,250 Chinese hospitals within 24 hours of symptom onset. They were randomized to 75 mg/day of clopidogrel or placebo for an average of 16 days in addition to aspirin and other standard medications.

COMMIT featured a two-by-two factorial design in which patients were randomized to intravenous metoprolol or placebo, with mixed results. (See story on page 63).

In-hospital mortality occurred in 7.7% of the clopidogrel group and in 8.1% of those on placebo. This represents a highly significant 7% relative risk reduction favoring clopidogrel, reported principal investigator Zhengming Chen, M.D., of the University of Oxford (England).

The other primary outcome was the combined rate of death, repeat MI, or stroke within 28 days. The rate was 9.3% in the clopidogrel arm and 10.1% with placebo, for a significant 9% relative risk reduction. Rates of major cerebral and noncerebral in-hospital bleeding, at just over 0.5%, were not significantly increased with clopidogrel.

Clopidogrel showed a consistent benefit regardless of patient gender, age, or use of thrombolytic therapy.

The main difference in the clopidogrel regimens in CLARITY and COMMIT was the use of a loading dose in CLARITY to achieve a more rapid antiplatelet effect. Nevertheless, a significant benefit was seen with the 75 mg/day used in COMMIT even on the day of randomization.

COMMIT showed that, on average, roughly 2 weeks of clopidogrel produced an absolute benefit of 10 fewer deaths, repeat MIs, or strokes per 1,000 treated patients, with no increased risk of bleeding. Among the 12,000 participants aged 75-100 years, the absolute benefit was even greater, at 13 fewer events per 1,000 participants.

Extrapolating from COMMIT, Dr. Chen said that giving this simple, inexpensive, safe, and modestly effective treatment to 1 million acute MI patients would save 5,000 lives and prevent an additional 5,000 strokes or repeat MIs. There are an estimated 10 million acute MIs per year worldwide, a third of which are STEMI, he added.

Discussant Christopher P. Cannon, M.D., said CLARITY and COMMIT are complementary trials that collectively provide important information about how clopidogrel fits into the whole spectrum of STEMI therapy, since the management strategy was 100% noninvasive in COMMIT and entirely invasive in CLARITY.

There was a suggestion of slightly better outcomes with the 300-mg loading dose used in CLARITY. However, CLARITY included patients only up to age 75 years. So a rational, evidence-based approach drawn from the two trials would be to employ a loading dose of clopidogrel in STEMI patients up to age 75 who present within 24 hours of symptom onset, and to skip the loading dose in patients beyond that age, since there is good evidence of efficacy for the 75-mg dose in the very elderly from COMMIT but no safety data for a loading dose in that age group, said Dr. Cannon of Brigham and Women's Hospital, who together with Dr. Sabatine was co–principal investigator in CLARITY.

Dr. Cannon added that the worldwide public health implications of this new addition to the management of STEMI are profound. Two weeks of clopidogrel costs $50-$100, placing dual antiplatelet therapy within reach of many patients, even in some developing countries.

"The evidence provided by these two studies with 50,000 randomized patients is very, very strong," Dr. Cannon told this newspaper. "Obviously I can't speak for the [American College of Cardiology/American Heart Association] guideline committee, but I have heard members of the committee say these studies provide about as strong evidence as you would want to add a new treatment to the guidelines for management of STEMI."

The combination of clopidogrel and aspirin has been shown to reduce coronary risk in patients with unstable angina and in those undergoing percutaneous intervention. An ongoing study that has completed enrollment is examining whether adding long-term clopidogrel is of benefit in a broad group with high-risk vascular disease.

CLARITY was funded by Sanofi-Aventis and Bristol-Myers Squibb Co. Dr. Sabatine and Dr. Cannon have served on paid advisory boards for both companies. COMMIT was funded by those companies along with AstraZeneca, the British Heart Foundation, and the U.K. Medical Research Council. ■

CVD Rehospitalization Rate After ACS Nearly 50% at 1 Year

BY BRUCE JANCIN
Denver Bureau

ORLANDO, FLA. — Nearly half of patients hospitalized for acute coronary syndrome at one large HMO were rehospitalized for cardiovascular disease within the next 12 months, Stephen Sidney, M.D., reported at the annual meeting of the American College of Cardiology.

Within 12 months, 29% of the patients were readmitted for acute coronary syndrome (ACS). When admissions for other manifestations of coronary heart disease plus those for heart failure and stroke were added in, a total of 46% of patients were rehospitalized for cardiovascular disease (CVD) within 12 months of their index hospitalization for ACS. Nearly 10% of patients were rehospitalized for coronary revascularization via coronary artery bypass surgery, and 7.4% were admitted for percutaneous intervention.

One-year mortality following the index hospitalization for ACS was 17.2%, and nearly two-thirds of the deaths were attributed to CVD, added Dr. Sidney of Kaiser Permanente in Oakland, Calif.

Few data are available on 1-year outcomes after hospital discharge for ACS, so Dr. Sidney and his coinvestigators analyzed computerized records for 14,852 patients admitted for ACS to Kaiser Permanente of Northern California hospitals during 1999-2000. The hospitalization rate for ACS was 5.7 cases per 1,000 person-years among subscribers to the prepaid health plan, which provides coverage to 30% of the population in the San Francisco Bay Area.

At the index ACS hospitalization, 31% of patients were hypertensive, 35% were diabetic, and 28% were hyperlipidemic. The relationships between these risk factors and the risks of rehospitalization for unstable angina and acute MI differed in intriguing ways. For example, in a multivariate analysis, hyperlipidemic patients were 40% more likely to be rehospitalized for unstable angina within 12 months than were nonhyperlipidemic patients, but they were 32% less likely to experience MI.

In contrast, hypertension was associated with a 14% increased risk of rehospitalization for unstable angina but no significantly increased risk of rehospitalization for MI. Patients aged 65 or older were 16% more likely than were younger ACS patients to be rehospitalized for MI, but 12% less likely to be rehospitalized for unstable angina.

In diabetics, the likelihood of being rehospitalized for MI or unstable angina was increased by 26% and 14%, respectively, compared with nondiabetics. The Kaiser study was funded by Eli Lilly & Co. ■