Aspirin Not Cardioprotective in Type 2 Diabetes

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Contributing Writer

New Orleans — Aspirin therapy is commonly used for primary prevention of cardiovascular events in persons with type 2 diabetes, but a Japanese study of 2,539 subjects found no statistically significant reduction in the primary end point of total atherosclerotic events, except in patients aged at least 65 years.

The study, which is the largest primary prevention trial of aspirin in type 2 diabetes, was reported at the annual scientific sessions of the American Heart Association.

In the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial, the use of daily low-dose aspirin was associated with a 20% nonsignificant reduction in the risk of the combined end point of coronary, cerebrovascular, and peripheral vascular events in the population as a whole, and a 32% statistically significant reduction in events among those aged 65 and older, reported Dr. Hisao Ogawa of the Kumamoto (Japan) University.

In the Japanese study, daily low-dose aspirin was associated with an insignificant reduction in coronary, cerebrovascular, and peripheral vascular events.

Aspirin use also significantly reduced the composite of fatal coronary and fatal cerebrovascular events.

"Although the effect of low-dose aspirin was not statistically significant for the primary end point, a significant effect was demonstrated on fatal coronary and fatal cerebrovascular events. The trial also suggests that low-dose aspirin might reduce total events in older patients," he said at a late-breaking trials session.

The results were reported online simultaneously with Dr. Ogawa's presentation (JAMA 2008;300:2134-41).

Japanese investigators from 163 institutions examined the benefit of low-dose aspirin for preventing cardiovascular events in 2,539 patients with type 2 diabetes who had no history of atherosclerotic disease. Average age of the patients was 65 years and 55% were men. Patients were randomly assigned to receive 81-100 mg aspirin per day (n = 1,262) or no aspirin (n = 1,277). The primary end point was the composite of all coronary, cerebrovascular, and peripheral vascular events.

After a median follow-up of 4.4 years, a total of 154 fatal and nonfatal atherosclerotic events had occurred: 68 in the aspirin group and 86 in the nonaspirin group. This represented a rate of 13.6 vs. 17.0 events per 1,000 person-years, for a 20% reduction in risk that was not statistically significant, Dr. Ogawa reported.

Benefit was, however, demonstrated in older patients taking aspirin. Among the 719 patients aged at least 65 in the aspirin arm, 45 events (6.3%) atherosclerotic events occurred, compared with 59 events (9.2%) in the 644 older patients in the nonaspirin group, representing a statistically significant 32% reduction in risk with aspirin use.

The combined secondary end point of fatal coronary events and fatal cerebrovascular events occurred in 1 patient (stroke) in the aspirin group and 10 patients (5 fatal myocardial infarctions and 5 fatal strokes) in the nonaspirin group, for a 90% statistically significant reduction in risk for that outcome.

Adverse effects occurred in 86 persons taking aspirin and 14 not on aspirin. Hemorrhagic events were greater with aspirin (34 vs. 10), including an increase in gastrointestinal bleeding and the need for transfusion for severe GI bleeding in four patients, but there was no increase in hemorrhagic stroke.

"JPAD supports the safety of using low-dose aspirin in diabetics for primary prevention," he said.

The investigators cautioned that the findings should be interpreted in context of the low incidence of atherosclerotic disease in Japan and the aggressive management of cardiovascular risk factors. "The event rate was lower than anticipated because the patients were so well treated," Dr. Ogawa said. "They saw their physicians every 2-4 weeks."

Dr. Marian Limacher, professor of medicine at the University of Florida, Gainesville, said JPAD was "a well-designed and well-conducted study" that aimed to address a question that "some

may have thought did not need to be answered," given the widespread recommendation for the use of aspirin in diabetic patients. "However, the evidence basis for this has been lacking until recently, and JPAD adds to this considerably," she commented at a press conference.

The findings are congruent with the recently completed Progression of Arterial Disease and Diabetes (POPADAD) study from Great Britain, she noted. POPADAD, involving 1,276 patients with asymptomatic peripheral arterial disease, found no evidence for aspirin's benefit on cardiovascular events and mortality.

As discussant of the paper, Dr. Limacher offered several possible explanations for the lack of effect on the primary end point, including the choice of population, which involved a number of percentage of women who may respond differently to aspirin than do men; the dose, which may have been too low to be protective in some patients; a too-short duration of intervention; the effect of aspirin resistance in some patients; the use of concomitant risk factor–modifying medications; and lack of power to show an effect when event rates were so low.

"We may need to rethink the guidelines," she suggested, "especially for patients younger than 65." ■