



Resistance to Daily Aspirin Therapy Seen in Diabetics

Diabetic patients exhibit a higher prevalence of aspirin resistance at a dosage of 81 mg/day than do nondiabetics with coronary artery disease.

“In selected diabetic patients, an 81-mg dose of aspirin may not be sufficient protection against the formation of platelet aggregations, the pivotal event that causes heart attacks,” said Dr. Gurbel, director of the center for thrombosis research at Sinai Hospital and a cardiologist at Johns Hopkins University, both in Baltimore.

A second key finding of his study of aspirin resistance in 120 patients with stable CAD, including 30 with diabetes, was that not all of aspirin's antiplatelet effects in diabetic patients were mediated by inhibition of cyclooxygenase-1, the pathway previously believed to be solely responsible for the drug's antithrombotic efficacy.

“Our findings suggest that in diabetic patients there may be another pathway or pathways by which aspirin affects platelet inhibition beyond the way we conventionally think of how aspirin works,” he said.

Participants in the double-blind, crossover trial got aspirin at a daily dosage of 81, 162, and 325 mg for 4 weeks each in a randomized sequence. At the end of each 4-week treatment period, platelet aggregation was measured in a host of ways, including arachidonic acid-induced light transmittance aggregation, thromboelastography, urinary thromboxane levels, the VerifyNow aspirin resistance assay, and adenosine phosphate- and collagen-induced aggregation.

The prevalence of aspirin resistance at 81 mg/day was less than 5% in nondiabetic patients, but markedly higher in the diabetics. In most instances, however, boosting the dose in the diabetic patients reduced the prevalence of aspirin resistance to nearly the same low level that was seen in nondiabetics.

For now, in the absence of clinical outcomes data from large trials, Dr. Gurbel considers 162 mg/day better than 81 mg/day for cardioprotection in diabetic patients, while recognizing that as the dose goes up, so does the bleeding risk.

An intriguing novel finding was that a dose-dependent increase in inhibition of platelet stickiness was seen in the diabetic patients even though their cyclooxygenase-1 activity was maximally inhibited at 81 mg/day.

“There's a disconnect between inhibition of the pathway that we thought was the sole pathway that conferred antiplatelet and antithrombotic effects, [and] the dose-dependent effect we see on other

pathways,” he explained.

The two additional pathways that appeared to be important in diabetic but not the nondiabetic patients involved collagen- and ADP-induced platelet aggregation.

Blood gets exposed to collagen in sections of the arterial wall that are denuded or damaged by chronic inflammation. No aspirin dose effect was observed with respect to how collagen activates platelets in nondiabetic patients, whereas collagen's ability to stimulate platelet aggregation in diabetics went down markedly and in dose-dependent fashion at higher aspirin doses.

Session chair Dr. Robert S. Rosenson, of the department of medicine and director of the preventive cardiology center at Northwestern University, Chicago, commented that he found fascinating the suggestion that diabetic patients not only have more reactive blood components than do nondiabetic patients, but also a “hotter,” more reactive arterial wall. These observations could help explain their higher acute MI rates, compared with nondiabetics with CAD.

“I think a one-size-fits-all concept for dosing antiplatelet therapy is flawed,” Dr. Gurbel said. “I think the day is coming when we will measure the aggregability of platelets as a cardiovascular risk factor. It's the fundamental event that drives the lethality of heart disease, so why are we not measuring it?”

Presented by Dr. Paul A. Gurbel said at the annual meeting of the American College of Cardiology, May 2007.

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