Diabetes Linked to Low-Dose Aspirin Resistance

BY BRUCE JANCIN
Denver Bureau

New Orleans — Diabetic patients exhibit a higher prevalence of aspirin resistance at a dosage of 81 mg/day than do nondiabetics with coronary artery disease, Dr. Paul A. Gurbel said at the annual meeting of the American College of Cardiology.

"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.

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DR. GURBEL

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 myocardial infarction rates, compared with nondiabetics with CAD.

The idea that diabetic patients have a 'hotter' arterial wall may help explain their higher MI rates.

DR. ROSENSON

Dr. Gurbel noted that aspirin did not exhibit a dose-dependent inhibition of ADP-induced platelet aggregation in the diabetic patients. This suggests a potential benefit for combining ADP-receptor blockers, such as clopidogrel, with higher-dose aspirin in diabetic patients, a possibility that deserves testing in a large-scale clinical trial, he said.

He predicted that funding will eventually be obtained for a large prospective study that establishes the link between platelet function and subsequent cardiovascular events. Once those data are available, he added, platelet-function testing will become routine in all patients with vascular disease. ■

New Strategy Sought

LDL *from page 1*

guideline revision creating an optional more aggressive LDL target of less than 70 mg/dL, he added.

Of patients admitted for CAD, 79% had an acute coronary syndrome (ACS). Only 21% of the total patient population were on lipid-lowering therapy prior to admission. The mean age of the patients was 65 years; 80% were white, 32% had diabetes, 63% were men, 33% were smokers, 20% had had a prior myocardial infarction, and nearly 7% had a history of stroke.

Mean lipid values recorded within the first 24 hours of hospitalization for CAD were 105 mg/dL for LDL, 40 mg/dL for HDL, and 161 mg/dL for triglycerides, although lipid levels during an ACS are probably lower than baseline chronic levels, said Dr. Fonarow, professor of medicine at the University of California, Los Angeles, and director of the Ahmanson–UCLA Cardiomyopathy Center.

Mean LDL, HDL, and triglycerides at admission declined over the study period.

Discussant Dr. James H. Stein called the Get With the Guidelines report an invaluable snapshot of how patients with ACS are presenting at a wide range of U.S. hospitals. It's a picture that contains surprises.

"We often hear messages that we're not getting LDLs to target, but this shows we actually are," observed Dr. Stein, associate professor of medicine and director of the vascular health screening program at the University of Wisconsin Hospital and Clinics, Madison.

The trouble is, getting LDL down to a target of 100 mg/dL isn't enough to guarantee cardiovascular protection, because one-half of patients with an ACS had an LDL below that value, he added.

Many patients with an LDL below 100 mg/dL also had low HDL, suggesting the importance of combining LDL-lowering with HDL-raising as a preventive strategy.

"I've always found it interesting that the small studies that have combined niacin with statins or resins have the greatest relative risk reduction," Dr. Stein said.

He added that he's eagerly awaiting the results of the 20,000-patient sequel to the landmark Heart Protection Study, called HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events).

Now getting underway, this randomized trial is studying whether an investigational Merck tablet combining niacin with a novel drug that minimizes niacin's side effects will further reduce major cardiovascular events in a population already getting LDL-lowering therapy.

"When I look at these [Get With the Guidelines] data I'm worried to see the decline in HDL levels over time. I suspect we're seeing the epidemic of obesity and overweight at work here," Dr. Stein said.

The key lesson provided by the Get With the Guidelines database is that it takes more factors than an LDL of less than 100 mg/dL to prevent coronary events.

"People still have ACS at that level, so we need to do more. We can lower it further. We can raise HDL. We can work on the predictors of these abnormalities by helping people lose weight and avoid diabetes and treat dyslipidemia more aggressively," the cardiologist concluded. ■

Owning a Dog Can Help Patients Keep Physically Fit

Glasgow, Scotland — Want your diabetes patients to get more exercise? Tell them to go get dogs, Dr. Steve Cleland said at the Diabetes U.K. Annual Professional Conference.

Not only do animals require their owners to increase their physical activity, but they also provide companionship, which reduces depression and can aid in diet management, said Dr. Cleland, who is a consultant in diabetes and endocrinology at Stobhill Hospital, Glasgow. One other benefit of dogs is that they also eat leftovers, he added.

Dr. Cleland's theory arose after observing that in his career only five of his patients had managed to improve their metabolism through exercise, and all of them have dogs. He explained that for many patients with diabetes, formal exercise can seem daunting. "For someone who is 50, carrying excess weight, and not used to it, exercise can be difficult," he said. However, simply increasing activity levels—as opposed to embarking on a specific training regime—can burn calories. Dr. Cleland accused diabetologists of having "failed in being evangelists for exercise" in their efforts to encourage their diabetic patients to give up their sedentary lifestyles.

There is a precarious balance between taking in enough calories to replace those burned by moving around, and taking in too many calories, according to Dr. Cleland. "When humans become overweight, obese, and inactive, energy supply exceeds demand," he said. "Fat cells spewing out fatty acids that are not being used in muscle contraction [cause problems]."

Among these problems are reduced mitochondrial capacity, as well as abnormal changes in the sympathetic nerve system and in the neuroendocrine and adipocyte feedback systems—in addition to the obvious accumulation of fat in places where it does not belong. The results, said Dr. Cleland, are accelerated aging of cells, heart problems, and perhaps cancer and dementia.

Exercise involves a balance between two states: catabolic and metabolic, both of which involve hormones. And the body has developed many biologic backup mechanisms to respond to exercise, he said.

—Hannah Brown