Cilostazol Response Was High in Diabetes Patients

BY MITCHEL L. ZOLER

FROM THE EUROPEAN SOCIETY OF CARDIOLOGY CONGRESS 2010

STOCKHOLM – Adding cilostazol to a standard, dual-antiplatelet therapy regimen significantly decreased platelet reactivity in patients, especially in those with diabetes, in a controlled study with 80 patients.

"Despite marked platelet inhibition, cilostazol does not change thrombin-mediated hemostasis, which may help explain its ischemic benefit without an increased risk of bleeding," Dr. José Luis Ferreiro said at the congress.

Based on the new findings, cilostazol can have a role for "patients in whom you'd like more potent platelet inhibition who have a high risk for bleeding," he said.

In addition, cilostazol treatment seems particularly appropriate for patients with diabetes, in whom it "works much better," compared with patients without diabetes. It's also well suited as a third antiplatelet agent in patients on dual-antiplatelet therapy with aspirin and clopidogrel who have peripheral artery disease, an approved indication for cilostazol treatment, said Dr. Ferreiro, a cardiologist at the University Hospital of Bellvitge in Barcelona.

Cilostazol also has Food and Drug Administration approval to prevent thromboembolism in patients with coronary stents.

Despite data like these that show incremental value from adding cilostazol to a dual-antiplatelet regimen, the drug remains largely unused in Western countries, probably because most of the evidence supporting its efficacy comes from Asian studies, especially from Korean researchers, Dr. Ferreiro said. In addition, about a quarter of patients do not tolerate cilostazol treatment because of adverse effects, which commonly include headache and diarrhea.

VITALS

Major Finding: Adding cilostazol, 100 mg twice daily, to a standard regimen of dual-antiplatelet therapy with aspirin and clopidogrel cut platelet reactivity by an average of 23% in patients with diabetes, and by an average of 15% in patients without diabetes, statistically significant differences.

Data Source: A single-center, crossover study of 40 patients with diabetes and 39 without diabetes, all with stable coronary artery disease.

Disclosures: Dr. Ferreiro said that he had no disclosures.

Despite these drawbacks, cilostazol may be an attractive addition for antiplatelet therapy, compared with the new antiplatelet drugs prasugrel and ticagrelor, when drug cost is a consideration or for patients at high risk for bleeding complications, he said in an interview.

Dr. Ferreiro and his associates ran the new study to assess cilostazol's ability to reduce platelet reactivity in 40 patients with diabetes (including some with type 1 and some with type 2 disease), compared with 39 patients without diabetes. The patients all had stable coronary artery disease and averaged 61 years old; about two-thirds were men.

All enrolled patients had received 81-mg aspirin and 75-mg clopidogrel daily for a month, and remained on dual-antiplatelet therapy during the study. The researchers randomized the patients to either 100-mg cilostazol twice daily or placebo daily for 2 weeks, followed by a 1 week washout and then a crossover to another 2 weeks of treatment with the alternative agent. The study's primary end point was the difference in the reactivity of the platelet $P2Y_{12}$ receptor, measured in a vasodilator-stimulated phosphoprotein (VASP) flow-cytometry assay, at the end of 2 weeks of treatment with either cilostazol or placebo.

Patients with diabetes averaged 53% on the $P2Y_{12}$ reactivity index (PRI) while on placebo and 30% while on cilostazol, a 23% absolute, average drop in PRI attributable to cilostazol, a statistically significant effect. Patients without diabetes averaged 48% on placebo and 33% on cilostazol, a 15% absolute, average drop in their PRI attributable to cilostazol, also statistically significant. The difference in the average impact that cilostazol had on PRI between the patients with diabetes and those without diabetes (a 23% reduction vs. a 15% drop), also reached statistical significance, said Dr. Ferreiro.

Cilostazol may be an attractive addition for antiplatelet therapy when drug cost is a consideration.

DR. FERREIRO

Other assays of platelet reactivity used as secondary end points showed similar results. The study did not include enough patients to determine whether cilostazol had different effects in patients with type 1 and type 2 diabetes. ■

Cystatin C May Be a Biomarker for Diabetic Nephropathy

BY BRUCE JANCIN

FROM A CONFERENCE ON MANAGEMENT OF DIABETES IN YOUTH

KEYSTONE, COLO. – Serum cystatin C isn't ready for primetime use in clinical practice as an alternative to urinary albumin excretion and serum creatinine in screening for diabetic nephropathy, but the unfolding research on this novel biomarker is definitely worth keeping an eye on.

"From a pediatric diabetes perspective, were we to have more data on cystatin C, it would sure be appealing to be able to collect it from a blood sample and not have to try to get overnight urines or even spot urines. This is a biomarker that may pan out as something useful in the future," Dr. David M. Maahs said at the conference, sponsored by the Children's Diabetes Foundation at Denver.

Growing evidence suggests serum cystatin C provides a more accurate estimate of glomerular filtration rate (GFR) than do predictive equations based upon serum creatinine, such as the widely used Cockroft-Gault or Modification of Diet in Renal Disease equations.

"Cystatin C has been described as like an HbA_{1c} for renal function," observed Dr. Maahs of the Barbara Davis Center for Childhood Diabetes and the University of Colorado, Denver.

Cystatin C also appears to be superior to serum creatinine as a predictor of the risk of death and cardiovascular events in the elderly in general (N. Engl. J. Med. 2005;352:2049-60). Furthermore, in an analysis restricted to 691 elderly diabetics in the Cardiovascular Health Study, cystatin C–based estimated GFR predicted mortality more strongly than did serum creatinine–based estimated GFR (Diabetes Care 2009; 32:1833-8).

Moreover, in a study of 509 adults with type 1 diabetes followed for 2.5 years, Dr. Maahs and coworkers showed that serum cystatin C predicted progression of subclinical coronary atherosclerosis as reflected by coronary artery calcification better than serum creatinine, estimated glomerular filtration rate, or albumin excretion rate (Diabetes 2007;56:2774-9).

That being said, data on cystatin C's performance in pediatric populations with diabetes remain lacking, he noted.

Serum cystatin C goes up as the GFR goes down. Cystatin C is thought to better reflect GFR than does serum creatinine because it is independent of age, sex, and muscle mass. Cystatin C is a stable protein produced by nucleated cells at a constant rate. It is freely filtered at the glomerulus because of its small molecular mass, it is not reabsorbed, and it is eliminated by the kidneys.

Putting aside for the future the question of cystatin C as a potential tool for following GFR in diabetic patients, Dr. Maahs stressed the importance of following guidelines for screening for diabetic nephropathy in young patients. About 20%-40% of patients with diabetes develop nephropathy. Indeed, diabetic nephropathy has become the number-one cause of end-stage renal disease in the United States, accounting for 40% of all new cases, he said.

The earliest clinical evidence of nephropathy is persistent microalbuminuria. Among 3,259 participants in the SEARCH for Diabetes in Youth study, Dr. Maahs and coworkers found that the prevalence of an elevated albumin-to-creatinine ratio indicative of microalbuminuria was 9.2% among type 1 and 22.2% in type 2 diabetic individuals under age 20 (Diabetes Care 2007;30:2593-8).

Because persistent microalbuminuria is the reversible stage of diabetic nephropathy if treated with an ACE inhibitor or angiotensin receptor blocker along with intensified glycemic control, smoking cessation, and treatment of hypertension if present, the American Diabetes Association recommends performing an annual test to assess urine albumin excretion in all patients who've had type 1 diabetes for at least 5 years and in all type 2 diabetes patients starting at the time of diagnosis.

The screening for microalbuminuria can be performed by one of three methods: measurement of the albumin to creatinine ratio in a random spot urine; a 24-hour urine collection; or a timed urine collection, often done overnight. A diagnosis of persistent microalbuminuria requires a positive result on two of three tests conducted within a 3-6 month period.

The American Diabetes Association guidelines also call for measurement of serum creatinine at least annually in all adults with diabetes regardless of their degree of urine albumin excretion. The serum creatinine is to be used to estimate GFR.

Because it's important to identify progression to microalbuminuria in a timely way in patients with type 1 diabetes, Dr. Maahs and his coworkers have developed and validated a prediction rule that identifies a subset of patients at high risk. The idea is that a few relatively easily obtainable patient characteristics can be used to help physicians identify a patient subgroup likely to benefit from screening for microalbuminuria more frequently than once yearly.

The prediction rule was developed using data from 1,115 patients in the European Diabetes Prospective Complications Study, then validated in the Finnish Diabetic Nephropathy Study, the Coronary Artery Calcification in Type 1 Diabetes Study, and the Pittsburgh Epidemiology of Diabetes Complication Study. The key variables used in the prediction rule are the albumin excretion rate, body mass index, waist:hip ratio, and a history of ever having smoked.

Thirteen percent of patients progressed to microalbuminuria during 7 years of follow-up. A high-risk subgroup consisting of 8% of the patient population was identified as having a risk of progression of 32% (Diabetologia 2010;53:254-62).

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