Heart Failure Increases New-Onset Diabetes Risk

BY MITCHEL L. ZOLER

ORLANDO — Patients with heart failure had a greater than twofold increased risk of developing diabetes compared with people without heart failure in a review of more than 4,600 individuals in the Framingham Offspring Study.

The analysis showed a strong association between severity of heart failure (HF) symptoms and risk for new-onset diabetes: Patients with higher New York Association Class HF faced a greater risk for developing diabetes than did patients with less severe HF symptoms, Dr. Ankit Rathod said at the annual scientific sessions of the American Heart Association.

Patients who first developed HF had a statistically significant 2.5-fold increased risk for future diabetes.

DR. RATHOD

The implications are that patients with HF should undergo more intensive surveillance for development of insulin resistance and diabetes. The findings also present a new reason for optimized HF treatment to minimize symptom severity because this may cut the patient's risk for developing diabetes, Dr. Rathod said in an interview.

The hypothesized causal link between HF and diabetes is the neurohormonal, sympathetic activation that characterizes HF. This leads to norepinephrine release, which can trigger insulin resistance and hence increased susceptibility to developing diabetes, said Dr. Rathod, an internal medicine physician at Wayne State University, Detroit. In addition, patients with more severe HF symptoms have reduced activity, which might exacerbate insulin resistance and the risk for developing diabetes.

"I believe the connections between insulin resistance and neurohormonal activation are a real phenomenon," said Dr. Clyde W. Yancy, medical director of the Baylor Heart and Vascular Institute at Baylor University Medical Center in Dallas. He cited study results showing that treatment with drugs that block neurohormonal activation also cut development of diabetes, such as with ramipril in the HOPE study (N. Engl. J. Med 2000;342:145-53) and treatment with carvedilol in the CAPRICORN study (Lancet 2001;357:1385-90).

Dr. Rathod's study used data collected from the more than 4,900 people enrolled into the Framingham Offspring Study in 1971. He and his associates excluded people with a history of diabetes or HF at the time of enrollment, as well as those who had missing data on their subsequent rate of new-onset diabetes. The 4,614 people included in the study had an average age of 35, and about half were women.

During an average follow-up of 24 years, 123 developed HF, and 468 developed new-onset diabetes. Forty-one of the 123 patients (33%) who developed HF later developed diabetes, compared with 427 new cases of diabetes among the other 4,491 people (10%).

In a multivariate analysis that adjusted for baseline demographic and clinical differences, including drug treatments and baseline blood glucose levels, patients who first developed HF had a statistically significant 2.5-fold increased risk for later developing diabetes compared with those who did not have HF.

The link between HF and diabetes should be examined in other databases, Dr. Rathod said. He and Dr. Yancy disclosed having no financial conflicts of interest. ■

ADVANCE Yields More Data On Heart Risk in Diabetes

BY MIRIAM E. TUCKER

MONTREAL — The largest-ever clinical trial in patients with type 2 diabetes continues to yield data that are expected to lead to improved prediction of cardiovascular risk as well as a better understanding of the relationship between intensive metabolic control and cardiovascular outcomes.

In a symposium lecture at the World Diabetes Congress, Dr. John P. Chalmers summarized data from published and unpublished substudies of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study, a randomized, placebo-controlled trial that examined the effect of both intensive blood glucose and blood pressure control on micro- and macrovascular complications. The trial involved a multiethnic cohort of 11,140 patients with type 2 diabetes from 215 centers in 20 countries.

The glucose-lowering arm of ADVANCE, funded by grants from the French pharmaceutical company Servier and the National Health and Medical Research Council of Australia, used modified-release gliclazide along with other glucose-lowering drugs to target a hemoglobin A_{1c} of 6.5%.

The intensive-treatment group achieved a mean HbA_{1c} of 6.5%, vs. 7.3% in the standard-treatment group. At a median of 5 years, the intensive group had a 10% relative reduction in the combined outcome of major macro- and microvascular events vs. standard care, primarily as a consequence of a 21% relative reduction in nephropathy. There was a positive trend toward reduction of major cardiovascular (CV) events (N. Engl. J. Med. 2008;358:2560-72). There was no excess mortality, weight gain, or severe hypoglycemic episodes in the intensive group, said Dr. Chalmers, coprincipal investigator for ADVANCE.

In the blood pressure control arm, routine administration of a fixed combination of perindopril and indapamide was associated with a 9% reduction in the relative risk of a major macro- or microvascular event (Lancet 2007;370:829-40).

In a new, not-yet published subgroup analysis of the glucose-lowering arm, the results held true regardless of age, duration of diabetes, sex, body mass index, HbA_{1c} at study entry, urinary albumin excretion, glomerular filtration rate, or initial glucose-lowering treatment, said Dr. Chalmers, senior director of the George Institute for International Health, Sydney.

Cognitive function, however, was an independent predictor of cardiovascular risk. Mild and severe cognitive dysfunction increased the risk for major CV events. with hazard ratios of 1.27 and 1.42, respectively. Cardiovascular death was increased by hazard ratios of 1.41 and 1.56 for mild and severe cognitive dysfunction, respectively, and all-cause death by 1.33 and 1.50 (Diabetologia 2009;52:2328-36).

Another new and unpublished analysis showed that the risk for microvascular complications had a strong linear relationship with HbA_{1c} values down to 6.0%. Each percentage point reduction reduced the risk by 22%. For macrovascular events, CV death, and all-cause death, the risk reduction was linear down to an HbA_{1c} of 7.0%, then leveled off between 7% and 6%.

A substudy of 647 participants showed no significant associations between CV risk and body mass index, but there was a relationship with waist-hip ratio, a better index of visceral fat. Urinary albumin excretion also predicted risk: For every tenfold increase, there was a twofold increase in macrovascular events. Similarly, a halving of glomerular filtration rate was associated with a twofold increased risk for CV events, Dr. Chalmers said.

With ADVANCE data on CV risk predictors, the investigators are developing a risk engine specific for people with diabetes. Data from two other studies presented at the congress showed that neither Framingham score nor the risk engine derived from the 1998 United Kingdom Prospective Diabetes Study (UKPDS) is an accurate risk predictor for patients receiving modern treatments for glucose, blood pressure, and lipid levels.

Dr. Andre Pascal Kengne, also of the George Institute, presented one of these studies, which found that major cardiovascular risk among 7,502 ADVANCE participants was overestimated by 170% and 202% with use of two different Framingham equations. ■

Disclosures: *Dr. Chalmers is on the advisory board for Servier. Dr. Kengne stated that he had no conflicts of interest.*

Noninvasive CIMT Scan Predicts Poor Myocardial Perfusion

BY DENISE NAPOLI

Increased carotid intima-media thickness as seen on ultrasound independently predicted abnormal myocardial perfusion in diabetes patients who were otherwise asymptomatic for heart disease.

The finding suggests that "the truly noninvasive, inexpensive, and radiation-free nature of CIMT may represent an important advantage over other suggested screening techniques" for heart disease in diabetes patients.

Led by Dr. Roxana Djaberi of the department of cardiology at Leiden (the Netherlands) University Medical Center, the researchers looked at 98 patients with type 2 diabetes recruited from an outpatient diabetes clinic. All were asymptomatic for heart disease according to the Rose questionnaire (Diabetes Care 2009 Nov. 16 [doi:10.2337/dc09-1301]).

The patients' mean age was 54 years; 51% were male. Overall, the mean summed stress score (SSS) was 3.1, with 34 patients (35%) showing abnormal perfusion on single-photon emission computed tomography imaging (SSS greater than or equal to 3), and 14 patients (14%) showing severely abnormal perfusion (SSS of at least 8). According to Dr. Djaberi, "Abnormal perfusion was present in 9% of patients with normal CIMT versus 75% of patients with increased CIMT [defined as thickness at or above the 75th percentile of reference values]."

Moreover, "severely abnormal perfusion increased from 3% in patients with normal CIMT to 28% in those with increased CIMT," she added.

The authors cited the lack of a nondiabetic control group as a study limitation.

Nevertheless, "Considering the high global prevalence of type 2 diabetes, a broad screening strategy of all asymptomatic patients using [single-photon emission computed tomography] perfusion imaging does not appear feasible or cost-effective," concluded the authors.

"Initial risk-stratification using CIMT may allow selective referral of asymptomatic patients with type 2 diabetes requiring further imaging and intensification of therapy," they added.

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