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Diabetes and Cardiovascular Disease in Women:

Current Challenges and New Hope

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The prevalence of type 2 diabetes mellitus continues to increase. In the United States, diabetes is diagnosed in 1 in 10 adults[1] and by 2030 will affect an estimated 54.9 million individuals.[2] The toll of diabetes on health has been well established; its diagnosis at midlife (45 years of age) can shorten lifespan by approximately 6 years.[3] The last 2 decades have witnessed a substantial reduction in diabetes-related deaths; nevertheless, mortality rates remain higher in individuals with diabetes than in those without it, and most diabetes-related deaths are attributed to cardiovascular disease.[4]

Although the prevalence of diabetes is similar in men and women, data suggest that sex differences do influence the cardiovascular consequences of diabetes and that diabetes does affect women more adversely than men.[5] In adults without diabetes, women tend to have fewer cardiovascular events than do men of similar age. In women, diabetes attenuates the protective effect of female sex on the development of cardiovascular disease.[5] A recent analysis of a Swedish national registry indicated that diabetes-associated hazard ratios for most cardiovascular disease outcomes—particularly coronary heart disease, stroke, and heart failure—are higher in diabetic women than in diabetic men.[3] Myocardial infarction generally occurs at an earlier age in women with diabetes, and the mortality rate is higher.[5] The reasons for this sex difference are likely multifactorial and may include differences in the concomitant cardiovascular risk factor burden, biologic differences attributed to sex hormones, and potential disparities in the diagnosis and treatment of diabetes and cardiovascular disease in women.[5]

A multifaceted approach to controlling risk factors is critical to prevent cardiovascular disease in both men and women with diabetes. Strategies include lifestyle modification, smoking cessation, aggressive blood pressure control, lipid control, and glycemic control.[6] Despite this knowledge, substantial gaps in achieving this goal remain. In a registry of individuals with diabetes, only 1 in 5 had achieved control of all 4 major risk factors (glucose, low-density lipoprotein cholesterol, blood pressure, and smoking status) recommended by the American Diabetes Association (ADA), and the results were much worse in women than in men.[7]

Recently, certain antihyperglycemic medications have been identified that may reduce the risk of major adverse cardiovascular events in individuals with diabetes at high risk or in individuals with established cardiovascular disease. In 2008, amid concerns of increased cardiovascular risk associated with antihyperglycemic medications, the U.S. Food and Drug Administration required that the cardiovascular safety of all new antihyperglycemic therapies be demonstrated in cardiovascular outcomes trials. Since then, multiple placebo-controlled cardiovascular outcomes trials have been performed and their results reported.[6] These trials tested dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs), and sodium-glucose cotransporter 2 (SGLT2) inhibitors against placebo.[6] In all completed trials, the tested medication proved noninferior to placebo in terms of the primary cardiovascular endpoint (namely, major adverse cardiac events, including myocardial infarction, stroke, and cardiovascular death).[6] Moreover, in 3 trials of GLP-1RAs (semaglutide, liraglutide, and albiglutide) and in 3 trials of SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin), the risk of the primary cardiovascular outcome was reduced.[6,8] In addition, hospitalization for heart failure was reduced in all of the completed SGLT2

inhibitor trials (empagliflozin, canagliflozin, and dapagliflozin).[6,8] The GLP-1RA liraglutide and the SGLT2 empagliflozin were associated with a reduction in the cardiovascular mortality rate.[6] The mechanisms behind these benefits are not fully understood, but they do not appear to be attributable to glycemic control.

As a result of these trials, the FDA has approved new indications for liraglutide and canagliflozin to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes who have established cardiovascular disease, as well as a new indication for empagliflozin to reduce the risk of death from cardiovascular causes in adults with type 2 diabetes and cardiovascular disease. Whereas women were underrepresented in these trials, making up only about one third of the study populations combined, there was no clear difference in the main cardiovascular outcome by sex. Data from these landmark trials have been incorporated into recent ADA treatment guidelines, which recommend using SGLT2 inhibitors or GLP-1RAs with demonstrated cardiovascular disease benefit in addition to metformin in patients with diabetes and established atherosclerotic disease.[6] In addition, SGLT2 inhibitors are preferred in patients with atherosclerotic cardiovascular disease who are at high risk of or already have heart failure.[6]

Data from these recent trials provide hope that we can further reduce the risk of cardiovascular disease in individuals with diabetes, but much work remains to be done. Implementing these new antihyperglycemic therapies will require multidisciplinary collaboration, including an active role of the cardiologist. Furthermore, future research and public health efforts are needed to understand mechanisms contributing to the risk of cardiovascular disease and to develop strategies for reducing potential health disparities in women with diabetes.

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