EDITORIALS

Cardiac and Renovascular Complications in Type 2 Diabetes — Is There Hope?

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According to the current posting on the website of the World Health Organization, the worldwide prevalence of diabetes mellitus among persons 18 years of age or older is 8.5% and increasing. Most of those affected have type 2 diabetes, which has been epidemic for several decades and is associated with many complications, including premature macrovascular and microvascular diseases affecting the eyes, heart, kidneys, and the circulation. We know that diabetes is associated with major morbidity and mortality, with an estimated 1.5 million deaths in 2012 being directly due to diabetes.[1]

Various approaches in the treatment of type 2 diabetes have been introduced recently, but whether these therapies alter cardiovascular and renal risk remains uncertain. Despite weight control (by diet and recently, in some patients, by gastric bypass) and the use of recently developed oral hypoglycemic agents and insulin, premature cardiovascular disease, kidney failure, retinal disease, and peripheral vascular disease develop in patients with type 2 diabetes. Three novel pharmacologic approaches have been approved in the past decade: first, glucagon-like peptide 1 (GLP-1) agonists, which stimulate insulin release; second, dipeptidyl peptidase 4 (DPP-4) inhibitors, which act along the same pathway and prevent the breakdown of GLP-1, also stimulating insulin release; and third, sodium–glucose cotransporter (SGLT) inhibitors (mainly inhibitors of type 2 [SGLT2]), which prevent the resorption of glucose by the proximal tubule. This action decreases the plasma glucose level and also depletes sodium and decreases the single-nephron glomerular filtration rate by means of tubuloglomerular feedback, by which glomerular filtration and resorption of electrolytes are coordinated, as well as altering the activity of the renin–angiotensin system mediated through the macula densa. SGLT2 inhibitors also tend to be associated with weight loss, and they frequently lower lipid and uric acid levels and decrease oxidative stress.

In the United States, three SGLT inhibitors — canagliflozin, dapagliflozin, and empagliflozin — have been approved by the Food and Drug Administration (FDA) for the treatment of type 2 diabetes. Approved GLP-1 agonists include liraglutide, exenatide, dulaglutide, and albiglutide, and approved DPP-4 inhibitors include sitagliptin, saxagliptin, alogliptin, and linagliptin. Additional agents in these classes are in various stages of trial and approval applications.

Notwithstanding government approval and current widespread use, the effectiveness and safety of these new agents are cause for reflection. Among the DPP-4 inhibitors studied recently, alogliptin (in the EXAMINE [Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care] trial),[2] saxagliptin (in the SAVOR-TIMI 53 [Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53] trial),[3] and sitagliptin (in TECOS [Trial Evaluating Cardiovascular Outcomes with Sitagliptin]),[4] were not associated with a lower rate of cardiovascular events than occurred with the control of diabetes with the use of other methods. Similar results were found with the GLP-1 agonist lixisenatide, which is now under review by the FDA, in the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial.[5]

Those trials were at least as large as the Lira-

glutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial of liraglutide, the results of which are now reported in the *Journal*.[6] Among the SGLT2 inhibitors that have been studied to date, only empagliflozin reached its end point of a lower rate of cardiovascular events, when added to standard therapy, as shown in the EMPA-REG OUTCOME trial in 2015.[7] A trial of pioglitazone, a thiazolidinedione, previously showed a lower rate of macrovascular events than were observed with matched placebo.[8] A number of other trials are in progress.[9]

In the EMPA-REG OUTCOME trial, patients with established cardiovascular disease and an estimated glomerular filtration rate (eGFR) of at least 30 ml per minute per 1.73 m^2 of body-surface area were randomly assigned to receive empagliflozin at a dose of 10 mg, empagliflozin at a dose of 25 mg, or placebo once daily in addition to standard-of-care therapy.[7] In the primary outcome of that trial, the rate of death due to cardiovascular causes was significantly lower in the pooled empagliflozin group than in the placebo group; there was no significant between-group difference in the risk of myocardial infarction or stroke. Furthermore, the pooled empagliflozin group and the placebo group had similar rates of hospitalization for unstable angina.[7]

The report from the EMPA-REG OUTCOME trial on the composite microvascular end point, now published in the *Journal*,[10] focuses on the renal microvascular outcomes — incident or worsening nephropathy, defined as progression to macroalbuminuria (urinary albumin-to-creatinine ratio, >300 mg of albumin per gram of creatinine), a doubling of the serum creatinine level (accompanied by an eGFR of ≤45 ml per minute per 1.73 m^2 [as calculated by the Modification of Diet in Renal Disease formula]), the initiation of renal-replacement therapy, or death from renal disease. This new report indicates that empagliflozin was associated with a slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care in patients at high cardiovascular risk.

In the randomized LEADER trial, 1.8 mg of daily liraglutide or placebo delivered subcutaneously was added to standard care in more than 9000 patients who were followed from 42 to 60 months, with a primary outcome of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The rate of death from any cause was lower in the liraglutide group than in the placebo group, whereas the rates of myocardial infarction, stroke, and hospitalization for heart failure were not significantly lower with liraglutide than with placebo. In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo.

Why do the EMPA-REG OUTCOME and LEADER trials show cardiovascular and microvascular benefit, whereas other trials have come close yet have not shown similar results? Are the differences due to the inclusion and exclusion criteria in the specific trials? Patients in the liraglutide trial had higher glycated hemoglobin levels (mean, 8.7%) than did those in most other studies. Patients were eligible if they either had not taken a hypoglycemic agent previously or had been treated with an oral hypoglycemic agent or insulin; in addition, eligible patients were 50 years of age or older and had at least one coexisting cardiovascular condition or were 60 years or older and had at least one cardiovascular risk factor, as determined by the investigator. Concomitant conditions in the participants in the two groups of the LEADER trial were similar. Participants in the LEADER trial had a lower prevalence of cardiovascular disease (72.4%) than did those in the EXAMINE trial (alogliptin), the SAVOR-TIMI 53 trial (saxagliptin), or TECOS (sitagliptin), all of which recruited patients with established cardiovascular disease, not just a risk factor for it.

Yet, although there may have been differences among the participants that account for the positive results in the EMPA-REG OUTCOME and LEADER trials, such differences alone do not fully explain the results. We are left with differences that appear encouraging, yet are not a "home run" with regard to the management of diabetes. In the coming years, controlled and comparative effectiveness trials that uniformly combine newer agents with older agents may help to delineate an even more effective treatment plan for the millions of people whose lives are affected by type 2 diabetes.

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Von Willebrand Factor — A Rapid Sensor of Paravalvular Regurgitation during TAVR?

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Von Willebrand factor is unique among coagulation factors by virtue of its highly multimeric structure, which allows it to function as an endogenous sensor of hemodynamic forces.[1] Under conditions of low shear stress (below the usual physiologic range), von Willebrand factor self-associates into compacted, high-molecular-weight (HMW) multimers that are unable to promote platelet adhesion. During physiologic shear stress (shear rate of 100 to 5000 sec^{-1}), von Willebrand factor undergoes partial unfolding and elongation, exposing binding sites for platelets and collagen and allowing the metalloprotease ADAMTS13 to regulate the size distribution of the HMW multimers by cleaving von Willebrand factor monomers within the A2 domain[1] (see Animation, available with the full text of the article by Van Belle et al.[2] in this issue of the *Journal* at NEJM.org).

Pathological conditions associated with supraphysiologic shear stress (shear rate >10,000 sec^{-1}) can cause excessive degradation of von Willebrand factor multimers by ADAMTS13, leading to acquired von Willebrand factor deficiency and major bleeding. This form of acquired von Willebrand factor deficiency occurs with congenital and valvular heart disease (e.g., Heyde's syndrome),[3] hypertrophic cardiomyopathy, circulatory-assist devices, and extracorporeal membrane-oxygenation systems. Alteration of the distribution of von Willebrand factor multimers in response to changes in shear stress is highly dynamic; loss of HMW multimers occurs rapidly after the onset of supraphysiologic shear stress, and the multimer distribution normalizes within minutes after restoration of normal blood flow.[4]

Van Belle et al. provide evidence that changes in von Willebrand factor function can be monitored during transcatheter aortic-valve replacement (TAVR) to predict the presence of paravalvular regurgitation.[2] TAVR has become an established therapy for patients with severe aortic stenosis who are at high risk for complications after surgical aortic-valve replacement, and it is undergoing evaluation for patients at intermediate or low surgical risk. Despite improvements in valve design, paravalvular regurgitation remains a procedural complication that is associated with high mortality at 1 year.[5] The incidence of moderate or severe paravalvular regurgitation on day 30 after TAVR was approximately 12% with the first-generation SAPIEN valve (Edwards