Heart Failure: The Most Important, Preventable, and Treatable Cardiovascular Complication of Type 2 Diabetes

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Concerns about cardiovascular disease in type 2 diabetes have traditionally focused on atherosclerotic vasculo-occlusive events, such as myocardial infarction, stroke, and limb ischemia. However, one of the earliest, most common, and most serious cardiovascular disorders in patients with diabetes is heart failure (1). Following its onset, patients experience a striking deterioration in their clinical course, which is marked by frequent hospitalizations and eventually death. Many sudden deaths in diabetes are related to underlying ventricular dysfunction rather than a new ischemic event. As effective treatments for heart failure have emerged, the risk of sudden death has declined, even in the absence of an implantable cardioverter-defibrillator (2).

Heart failure and diabetes are linked pathophysiologically. Type 2 diabetes and heart failure are each characterized by insulin resistance and are accompanied by the activation of neurohormonal systems (norepinephrine, angiotensin II, aldosterone, and neprilysin) (3). The two disorders overlap; diabetes is present in 35–45% of patients with chronic heart failure, whether they have a reduced or preserved ejection fraction. A similar prevalence of diabetes in acute heart failure is reported in this issue of *Diabetes Care* by van den Berge et al. (4). The interplay between diabetes and heart failure is particularly striking among those with heart failure and preserved ejection fraction, who typically have features of metabolic syndrome. As noted by Sandesara et al. (5) in this issue, the presence of diabetes markedly increases the risk of morbidity and mortality of patients with heart failure and preserved ejection fraction, particularly if the microvascular complications of diabetes are also present.

There exists a relationship between the severity of type 2 diabetes and the risk of heart failure, but this association may be explained by the adverse effects of hyperinsulinemia rather than hyperglycemia. Treatments that lower blood glucose do not exert any consistently favorable effect on the risk of heart failure in patients with diabetes (6). In contrast, treatments that increase insulin signaling are accompanied by an increased risk of heart failure. Insulin use is independently associated with an enhanced likelihood of heart failure (7). Thiazolidinediones promote insulin signaling and have increased the risk of heart failure in controlled clinical trials (6). With respect to incretin-based secretagogues, liraglutide increases the clinical instability of patients with existing heart failure (8,9), and the dipeptidyl peptidase 4 inhibitors saxagliptin and alogliptin are associated with an increased risk of heart failure in diabetes (10). The likelihood of heart failure with the use of sulfonylureas may be comparable to that with thiazolidinediones (11). Interestingly, the only two classes of drugs that ameliorate hyperinsulinemia (metformin and sodium–glucose cotransporter 2 inhibitors) are also the only two classes of antidiabetes drugs that appear to reduce the risk of heart failure and its adverse consequences (12,13). These findings are consistent with experimental evidence that insulin exerts adverse effects on the heart and kidneys that can contribute to heart failure (14). Therefore, physicians can prevent many cases of heart failure in type 2 diabetes by careful consideration of the choice of agents used to achieve glycemic control. Importantly, these decisions have an immediate effect; changes in risk are seen within the first few months of changes in treatment. This immediacy stands in contrast to the years of therapy required to see a benefit of antidiabetes drugs on microvascular risk.

As reported by van den Berge et al. (4), the prognosis of patients with heart failure has improved over the past two decades; heart failure with a reduced ejection fraction is a treatable disease. Inhibitors of the renin-angiotensin system are a cornerstone of the management of both disorders; they prevent the onset of heart failure and the progression of nephropathy in patients with diabetes, and they reduce the risk of cardiovascular death and hospitalization in those with established heart failure (3,15). Diabetes does not influence the magnitude of the relative benefit of ACE inhibitors in patients with heart failure, but patients with diabetes experience a greater absolute benefit

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from treatment (16). Uptitration to high doses has not enhanced the mortality benefit of ACE inhibitors in heart failure in large-scale trials, even in patients with diabetes (16,17). In this issue, Witte et al. (18) suggest that the dose of ACE inhibitor matters with respect to survival (18), but their finding is based on an observational analysis that could not account for all potential confounders.

Because the mortality effects of ACE inhibitors are not sensitive to dose, additional treatments are used to enhance their survival benefits. In patients with heart failure, spironolactone/eplerenone and sacubitril/valsartan each reduce mortality by an additional 20–30% when prescribed with an inhibitor of the renin-angiotensin system (19,20). Importantly, in a trial of eplerenone in mild heart failure, patients with glucose intolerance (as evidenced by obesity or diabetes) were particularly likely to show a reduction in morbidity and mortality with treatment (19). By contrast, diabetes appeared to maintain the benefits of sacubitril/valsartan on heart failure hospitalization while attenuating the risks of treatment. Specifically, when prescribed sacubitril/valsartan instead of enalapril, patients with diabetes were less likely than those without diabetes to experience hypotension, and they were more likely to experience advantages of neprilysin inhibition with respect to renal function (20). Notably, both aldosterone and neprilysin have been implicated in insulin resistance as well as the microvascular complications of diabetes (4).

The most effective drugs for heart failure are the β-adrenergic blockers. In the past, this class of drugs was avoided in patients with diabetes because of concerns that they increase the risk and mask the symptoms of hypoglycemia (21). With the advent of newer antidiabetes drugs, the risk of hypoglycemia has diminished. More importantly, trials have shown that patients with diabetes with heart failure experience a reduction in morbidity and mortality with the use of β-blockers that is as great as, if not greater than, their counterparts without diabetes (22). In randomized controlled clinical trials, even low doses of carvedilol were effective in decreasing the early risk of serious cardiovascular events (23). Witte et al. (18) suggest that the dose of the β-blocker matters, particularly in patients with diabetes. Again, this finding is based on an observational analysis that could not adjust for all possible confounders. Patients taking higher doses may have a lower mortality because patients with a better prognosis can generally tolerate (and thus, receive) higher doses of β-blockers. In patients with heart failure with preserved ejection fraction, the only drug with evidence supporting efficacy is spironolactone. Since many of these patients are obese, it is noteworthy that, in the trial used for the analyses reported by Sandesara et al. (5), patients who were obese were particularly likely to experience a reduction in morbidity and mortality with spironolactone (24). Ongoing studies are evaluating the effects of sacubitril/valsartan (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction [PARAGON-HF]) and empagliflozin (EMPEROR-Preserved [EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction]) in patients with heart failure and preserved ejection fraction, with and without diabetes. Because obesity may potentiate the effects of neprilysin inhibition and because patients with obesity-related heart failure appear to have a relative deficiency of natriuretic peptides (25), the results of the PARAGON-HF trial will be of particular interest.

The totality of evidence from randomized trials, which is supported by the observational analyses published in this issue of *Diabetes Care* (4,5,18), demonstrates that in patients with diabetes, heart failure is not only common and clinically important, but it can also be prevented and treated. This conclusion is particularly significant because physicians have long ignored heart failure in their focus on glycemic control and their concerns about the ischemic macrovascular complications of diabetes (1).

Duality of Interest. M.P. has recently consulted for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Celyad, Daiichi Sankyo, Relypsa, Sanofi, Gilead, and Novo Nordisk.

None of these relationships have any bearing on the topic of this article.

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