Clinical evidence and treatment requirements related to heart failure in type 2 diabetes mellitus

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Heart failure (HF), which is a common and serious complication of diabetes, has received more attention in recent years. One reason for this focus on HF is that, with a large reduction in atherothrombotic events after acute myocardial infarction, HF is a relatively more frequently encountered cardiac outcome in patients with type 2 diabetes (T2DM). Another reason is the unexpected reduction in hospitalization for HF observed in cardiovascular outcome trials with sodium-glucose co-transporter-2 inhibitors (SGLT2is).[1-3] These findings led to speculation by clinicians and researchers on whether more effort should be made to differentiate patients with diabetes at a high risk of developing HF.

Type 2 diabetes and the incidence of HF

A cohort study with 1.9 million people showed that HF and peripheral arterial disease were the most common manifestations of cardiovascular (CV) disease initially found in patients with T2DM. HF accounted for 14.4% of events in people with T2DM.[4] Possible mechanisms for HF in patients with T2DM may include hyperglycemia, hypertension, microvascular disease as diabetic nephropathy and autonomic neuropathy, or glycosylation of myocardial proteins. In patients with T2DM, differences between relative risks of different cardiovascular diseases provide implications for risk assessment.

Patients with T2DM are susceptible to atherosclerotic cardiovascular disease (ASCVD), which might be the main reason for HF. However, HF can occur in patients with T2DM without vascular disease. The incidence of HF has progressively increased across age groups, both for those with vascular events ($P = 0.03$) and those without vascular events ($P < 0.001$).[5]

In a study over 10 years that included 3.25 million people, the incidence of hospitalization for HF (HHF) was 2.4, 5.6, and 12.4 per 1000 person-years for those without diabetes, those with type 1 diabetes, and those with T2DM, respectively.[6] This previous study also showed that the incidence of HHF was higher in people with diabetes, regardless of the type of diabetes, than in people without diabetes. According to data from Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) and the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF), the prevalence of HF was 39.5%, in which the prevalence of HF in Caucasians was 29.3% and that in Chinese was 42.3%.[7]

Blood glucose levels and HF in T2DM

A Swedish cohort study, with a median follow-up of 5.7 years and 175,345 deaths, showed that the level of glycated hemoglobin was the strongest or second strongest predictor for the risk of outcomes in five of eight models.[8] Additionally, the risk of HHF was consistently higher in patients with diabetes than in controls (hazard ratio [HR], 1.45; 95% confidence interval [CI], 1.34–1.57).

Mechanisms resulting in diastolic dysfunction in left ventricular hypertrophy are not well understood. However, these mechanisms might include changes in the extracellular matrix, dysfunction of vessels, and alterations in cardiomyocyte mechano-elastical properties. Remodeling in myocardial structure can cause heterogeneity in regional myocardial contractile function, resulting in diastolic dysfunction in heart failure with preserved ejection fraction (HFPEF).[9] Possible mechanisms that are involved in events in HFPEF are as follows: 1) a high prevalence of comorbidities, such as diabetes, obesity, hypertension, and chronic obstructive pulmonary disease, lead to a systemic proinflammatory state; 2) the systemic proinflammatory state results in inflammation of the

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coronary microvascular endothelium; 3) inflammation of the coronary microvascular endothelium decreases the bioavailability of nitric oxide, content of cyclic guanosine monophosphate, and activity of protein kinase G in adjacent cardiomyocytes; 4) low protein kinase G activity contributes to development of hypertrophy and increases resting tension; and 5) stiff cardiomyocytes and interstitial fibrosis cause development of HF.[10]

Glucose-lowering treatment and HF

Some glucose-lowering drugs or strategies adversely affect cardiovascular outcomes. A meta-analysis included 14 trials comprising 95,502 patients of whom 4% of the patients developed a HF event.[11] This meta-analysis showed that the association of glucose-lowering drugs or strategies and the risk of HF varied with the method of glucose lowering. Moreover, according to this meta-analysis, the risk of HF was highest with peroxisome proliferator-activated receptor agonists in six trials (relative risk [RR] = 1.42, 95% CI, 1.15–1.76), intermediate with dipeptidyl peptidase-4 inhibitors in two trials (RR = 1.25, 95% CI, 1.08–1.45), and neutral with insulin glargine treatment in one trial (RR = 0.90, 95% CI, 0.77–1.05). This meta-analysis also showed that target-based intensive glycemic control strategies in four trials (RR = 1.00, 95% CI, 0.88–1.13) and intensive weight loss strategies in one trial (RR = 0.80, 95% CI, 0.62–1.04) were not associated with development of HF.

SGLT2i treatment improves HHF in T2DM

Four cardiovascular outcome trials with SGLT2is (Empagliflozin Cardiovascular Outcome Event Trial in T2DM Patients Removing Excess Glucose [EMPA-REG OUTCOME], Canagliflozin Cardiovascular Assessment Study [CANVAS] Program, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis In Myocardial Infarction [DECLARE-TIMI 58], and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation [CREDENCE] trial) have been published in the most recent 4 years.

In EMPA-REG OUTCOME, empagliflozin significantly reduced the risk of three-point main adverse cardiovascular events (including CV death, non-fatal myocardial infarction, and non-fatal stroke) by 14%, with a 38% reduction in CV death compared with placebo ($P < 0.001$).[1] This trial also showed that empagliflozin led to a 35% reduction in HHF ($P < 0.002$), with immediate separation after initiation of treatment. This finding indicated an early effect on the risk of HF.

In the CANVAS program, canagliflozin significantly reduced the risk of the composite three-point major adverse cardiovascular events (MACE) by 14% compared with placebo ($P = 0.02$).[2] Similar to the findings in EMPAREG OUTCOME, canagliflozin significantly reduced the risk of HHF by 33% compared with placebo. The CREDENCE trial showed a 30% reduction in the primary renal outcome in canagliflozin treatment compared with placebo in patients with T2DM and chronic kidney disease (estimated glomerular filtration rate: 30 to < 90 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$). This trial also showed that canagliflozin treatment led to a significant reduction (39%) in hospitalization for HF compared with placebo ($P < 0.001$).[12]

The DECLARETIMI 58 trial randomized patients into the dapagliflozin and placebo groups and there were two primary endpoints.[3] This trial showed that, in one primary efficacy outcome, dapaglifozin did not significantly reduce three-point MACE. However, in another primary outcome, the rate of the combined endpoint of CV death or HHF was significantly decreased by 17% with dapagliflozin treatment compared with placebo ($P = 0.005$). This finding was mainly caused by a decreased risk of HHF by 27% in the dapagliflozin group compared with the placebo group (95% CI, 0.61–0.88), but there was no between-group difference in CV death (HR = 0.98, 95% CI, 0.82–1.17).

SGLT2 is consistently reduce the composite risk of HHF or CV death, regardless of existing ASCVD or a history of HF. Additionally, this type of CV benefit was not associated with the extent of glucose lowering and weight control because this benefit occurred too early to be the result of a reduction in weight. CV benefits gained by SGLT2is are more likely to be associated with a decrease in HF-associated events, involving effects on hemodynamic parameters, such as effects on cardiac metabolism, a decrease in plasma volume, or other effects on cardiovascular function.[13] As a result, guidelines that were drafted by European Society of Cardiology (ESC)/European Association for the Study of Diabetes (EASD) in 2019 recommended SGLT2is as the first-line therapy for patients with T2DM and ASCVD or with a high CV risk.[14]

Recently, the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial showed that, in patients with chronic HF, dapagliflozin treatment resulted in a significant reduction in HF by 26% compared with placebo (95% CI, 15%–35%), regardless of whether patients had T2DM.[15]

Future directions

A clinical need for differentiation of patients who require primary prevention for HF in T2DM is urgent. A cohort study of 271,174 patients with T2DM showed that the five strongest predictors regarding the risk of HHF among patients with T2DM without coexisting HF at baseline were a body mass index outside the target range, high glycated hemoglobin, levels, a low level of physical activity, smoking, and a long duration of diabetes.[8] However, when patients with HF and those without coexisting HF were pooled together, the five strongest predictors of HHF changed. Therefore, for clinicians, endocrinologists, and diabetologists, differentiating patients with T2DM who require primary prevention of HF is important.

With regard to benefits of SGLT2i treatment in improving HHF in patients with T2DM, whether these types of benefits can be achieved in the Asian population as found in the non-Asian population needs to be evaluated. The Asian population appeared to have more benefits of

SGLT2i treatment in MACE than did the total population in the EMPA-REG study.[1] However, there were no benefits of SGLT2i treatment in MACE compared with the total population in the CANVAS program.[2] Whether there are benefits of SGLT2i treatment in HHF between Asian and non-Asian patients is still unclear. However, the treatment response between Asian and non-Asian patients with T2DM in glucose control is similar with SGLT2i treatment.[16]

With the epidemic of T2DM, obesity, and metabolic syndrome, and the relationship between these metabolic maladies and cardiovascular disease, a new type of training in internal medicine called cardiometabolic medicine is required. To fulfill this type of practice, cardiometabolic specialists should be sufficiently trained in preventive cardiology, endocrinology, and internal medicine. Endocrinological training should be composed of a metabolism-centric model, including T2DM, type 1 diabetes, obesity, lipid disorders, hypertension, metabolic syndrome, and lifestyle, while cardiological training should focus on primary and secondary prevention of ASCVD.

Clinicians need to pay attention to patients with and those without HF in the T2DM, and to realize that some types of anti-diabetes treatments can benefit these patients. Furthermore, patients who require primary prevention for HF in T2DM need to be differentiated and practical training needs to be begun for clinicians to understand cardiometabolic medicine.

In conclusion, HF is currently a relatively frequently encountered cardiac outcome in T2DM. The mechanisms for HF might be associated with or without ASCVD. Primary and secondary prevention for HF in patients with T2DM are important. A large reduction in hospital admission for HF has been found in SGLT2i cardiovascular outcome trials. Such findings have led clinicians to detect patients with diabetes at high risk of developing HF and practical training for clinicians to understand cardiometabolic medicine is recommended. In this editorial, we focus on the clinical evidence and treatment requirements related to HF in T2DM. Clinicians should pay attention to patients with and those without heart failure in the T2DM population.

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Conflicts of interest

None.

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