

A new door opens, but it is essential to accumulate further clinical evidence to control heart failure in diabetes with preserved ejection fraction

HEART FAILURE IN DIABETES

The current American College of Cardiology/American Heart Association guideline defines heart failure as a complex clinical syndrome that can result from any structural or functional cardiac disorders that impair the ability of the ventricle to fill with or eject blood. Heart failure (HF) is one of the major clinical problems to determine the prognosis of patients with diabetes mellitus. It is generally accepted that the prevalence of HF in diabetes patients is twofold higher in male and fivefold higher in female patients compared with age-matched non-diabetic individuals. Furthermore, approximately 12% of patients with type 2 diabetes mellitus are suffering from HF. Approximately 3.3% of type 2 diabetes patients develop HF each year; elderly patients with type 2 diabetes have a 1.3-fold greater risk of developing HF than age-matched non-diabetic individuals. The prevalence of HF in aged diabetes patients is 39%, and a 1% rise in HbA1c is associated with a 15% increased risk of HF in elderly diabetes¹. However, there is no definite evidence to show a significant improvement of HF as a result of strict glycaemic control. As a background of increased chronic HF in diabetes, Rubler *et al.*² reported on patients with chronic HF associated with diabetic glomerulosclerosis without coronary artery disease, cardiac hypertrophy and valvular diseases as a new type of cardiomyopathy.

HEART FAILURE WITH PRESERVED EJECTION FRACTION

Recently, HF is classified into two types: (i) HF with reduced ejection fraction (HFrEF, ejection fraction [EF] <40%); and (ii) HF with preserved ejection fraction (HFpEF, EF ≥50%). The values between EF 40 and 49% are defined as mid-range. The HFpEF is clinically characterized as HF with preserved EF showing reduced diastolic function. Left ventricular stiffness that impairs left ventricular filling in diastole at rest or during exercise appears to be essential. In most cases, HFpEF occurs in older individuals and is more common in women than in men. This type of HF is reported to be clinically associated with hypertensive heart, diabetes and obesity with cardiac hypertrophy and/or myocardial fibrosis, and is less responsive to any drug treatment. It is also accepted that multiple left

ventricular diastolic dysfunction parameters are negatively correlated with glycated hemoglobin and fasting plasma glucose levels, without evidence of abnormal wall movement and systolic ejection fraction.

The Candesartan in Heart failure: Assessment of Resolution in Mortality and morbidity (CHARM) trial³ studied a population with both HFrEF and HFpEF among patients with or without diabetes. The results showed that both men and women with diabetes exhibited a higher risk of cardiovascular death or hospitalization of HF (HHF) compared with patients without diabetes. Furthermore, differential analyses in patients with or without diabetes and HFrEF or HFpEF showed that the highest mortality or hospitalization as a cause of HF was found in diabetes patients with HFrEF, followed by diabetes with HFpEF. In addition, the risk of first admission for HF was 116.6 per 1,000 patient-years in diabetes patients with HFpEF, and 155.4 per 1,000 patient-years in diabetes patients with HFrEF. Thus, compared with individuals without diabetes, the incidence of HHF was reported to be almost doubled in patients with diabetes independent of HFpEF or HFrEF (CHARM). The prognostic significance of diabetes with at least one microangiopathy ($n = 352$) or without ($n = 739$) microangiopathy was compared with non-diabetic patients ($n = 2,294$) who had HFpEF in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOP-CAT)⁴. Cumulative incidences of HF, HHF and cardiovascular death were significantly greater in diabetes patients with any types of microvascular complications, as compared with non-diabetes and diabetes patients without microangiopathy, respectively. These results suggest that the existence of microvascular complications in diabetes patients with HFpEF might be inherent in the risk of cardiovascular death and heart failure.

PREVENTION OF HEART FAILURE IN THE TREATMENT OF SODIUM–GLUCOSE COTRANSPORTER 2 INHIBITORS

Recently, a sodium–glucose cotransporter 2 inhibitor has shown unexpected cardiorenal benefits in large-scale clinical trials among type 2 diabetes patients with either established cardiovascular diseases or multiple cardiovascular risk factors in the Empagliflozin Cardiovascular Outcome Event Trial in type 2

Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) study. Although a significant improvement of three-point major adverse cardiac events was shown (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke), it is particularly noteworthy that cardiovascular death and hospitalization for HF were significantly reduced by 38 and 35%, respectively. This most favorable effect of sodium–glucose cotransporter 2 inhibitors was also confirmed in the Canagliflozin Cardiovascular Assessment Study (CANVAS) program. Canagliflozin produces an almost identical reduction of HHF (HR 0.67 in the CANVAS program). Consistent with this, the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial was the largest cardiovascular outcome trial including 17,160 patients with type 2 diabetes mellitus who were followed for 4.2 years. In that trial, 59% of the patients did not have a history of atherosclerotic cardiovascular diseases and estimated glomerular filtration rate >60 mL/min/1.73 m². In that megatrial, the incidences of cardiovascular death or HHF were significantly lower in patients with dapagliflozin treatment compared with placebo (hazard ratio 0.83, *P* < 0.005). This beneficial drug effect was mostly explained by an improvement of HHF (hazard ratio 0.73, *P* < 0.001).

In subanalysis of the CANVAS program⁵, retrospective secondary assessment data of ejection fraction, which was measured by echocardiography and left ventriculography, was

examined in the written medical records, although the values were not necessarily at baseline value. The incidence of HF is evaluated in the difference between EFpHF (≥50%) and EFrHF (EF <50%). However, the results do not show a clear difference in protective canagliflozin effects on progression of HFpEF and HFrEF events, respectively. This might provide some hope for treatment of type 2 diabetes patients with HFpEF. Further intervention studies await the improved prognosis of HFpEF in patients with type 2 diabetes mellitus in response to the treatment of sodium–glucose cotransporter 2 inhibitors.

As shown in Figure 1, hypothetically, type 2 diabetes patients are characterized in roughly two types. One group is patients with type 2 diabetes mellitus with visceral obesity with insulin resistance and hyperinsulinemia with or without lipid abnormalities and hypertension, even though not necessarily co-existing obesity. In contrast, the second group is type 2 diabetes patients with microangiopathy, such as diabetic nephropathy and severe retinopathy, because of long-term poor glycemic control, even though not necessarily co-existing obesity and insulin treatment. Type 1 diabetes with long-term poor glycemic control is generally included in this second group. The former type 2 diabetes patients are in a higher risk group for acute coronary syndrome that then might result in acute and chronic left ventricular systolic dysfunction leading to HFrEF. In contrast, the second group is shown to be not only prone to major cardiovascular events, but also shows diffuse narrowing

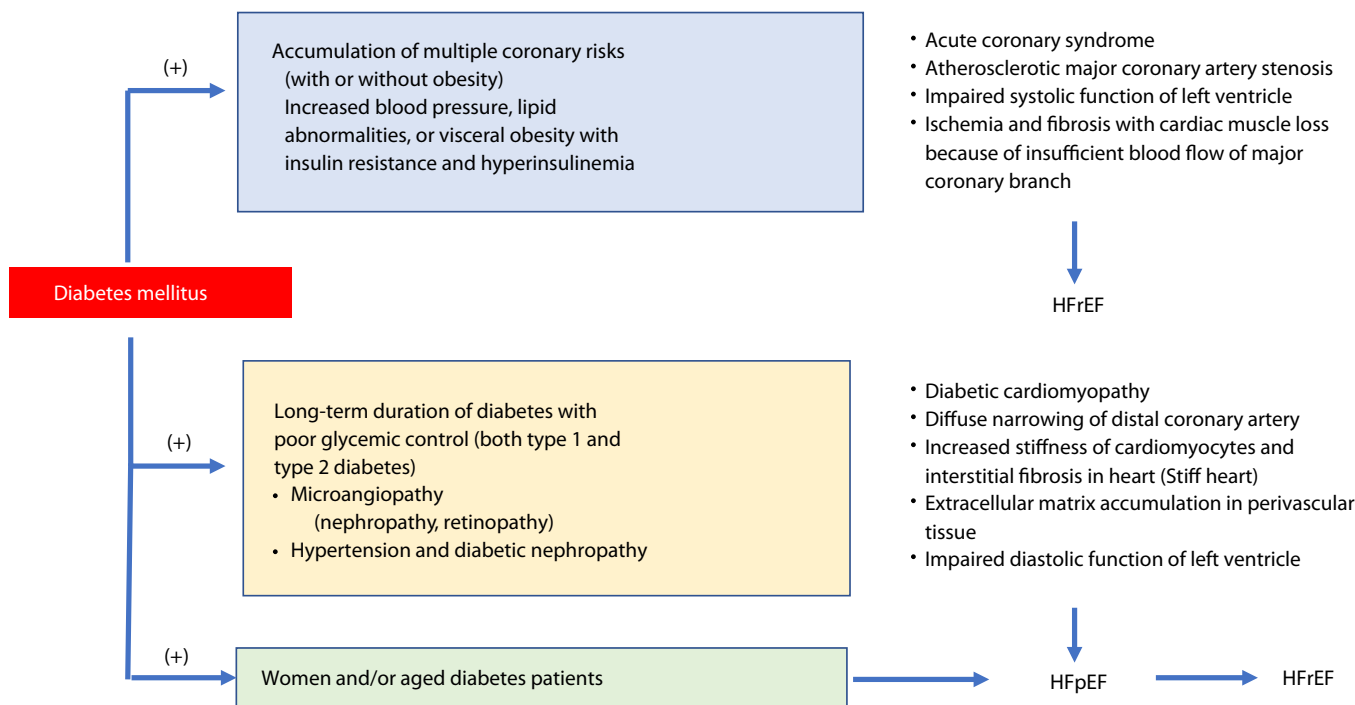


Figure 1 | Hypothetical views for progression of heart failure in diabetes. There are two types of heart failure. One is heart failure with reduced ejection fraction (HFrEF) and the other is heart failure with preserved ejection fraction (HFpEF). Long term-duration of diabetes has a risk for HFpEF. This type of heart failure is generally accepted to be less responsive to any drug treatment. Sodium–glucose cotransporter 2 (SGLT2) inhibitors have some hope to improve HFpEF in diabetes.

of distal coronary artery and microvascular dysfunction. Myocardial ischemia with oxidative stress leads to myocyte stiffening and then, ultimately, diastolic dysfunction⁶. Furthermore, progression of hypertension with diabetic nephropathy might be a strong inducer of progression of HFpEF and then progression to HFrEF. In addition, both women and/or older patients with diabetes have a higher risk for HFpEF. Thus, a new approach to the diagnosis and treatment of HFpEF in diabetes will be an important area in clinical diabetes.

DISCLOSURE

The author declares no conflict of interest.

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