Treatment of diabetes and heart failure: joint forces

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This editorial refers to ‘Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial’, by D. Fitchett et al. on page 1526.

People with type 2 diabetes mellitus (T2DM) are at increased risk of future cardiovascular disease, and chronic heart failure (CHF) is an important complication and cause of mortality. It has been estimated that the proportion of CHF patients with known T2DM is 20–35%.1 A Swedish registry report confirms that 25% of patients diagnosed with CHF in all day practice have previously known T2DM, a majority of ischaemic origin.2 The true proportion is probably considerably higher since undiagnosed T2DM is common, not least in populations with cardiovascular diseases.3 Further, in the population, a diagnosis of CHF is twice as common among patients with than among those without T2DM.3 The combination of T2DM and HF is expected to rise in the future, partly due to the increase in prevalence and longevity of patients with T2DM, but also due to improved survival after myocardial infarction and a more systematic screening for the combination.

Having T2DM in combination with CHF increases the risk for mortality. T2DM was indeed the most important risk factor for mortality in a multivariate model in the CHARM-programme.5 In a report from the Swedish Heart Failure Registry, patients with the combination of T2DM and CHF had an increased mortality and shorter survival time, especially if the CHF was of ischaemic origin.2

How can diabetes influence worsening HF? There is no clear answer to this question, but ischaemic heart disease (IHD) and myocardial hypertrophy caused by hypertension have been considered important contributors. Cases of CHF with both preserved systolic and reduced systolic function are more frequent among patients with T2DM, which in part may be caused by a deranged myocardial metabolism.6 Myocardial characteristics thought to be involved are myocardial lipid overload, altered myocardial production of energy-rich phosphates due to a decreased glucose oxidation, and a proportionately increased beta-oxidation of free fatty acids, mitochondrial dysfunction, oxidative stress, inflammation, and diffuse fibrosis.6 In the absence of other co-morbidities, signs of dysfunctional myocardium, possible to detect with new imaging methods such as cardiac magnetic resonance imaging (MRI) and tissue Doppler velocity, support this concept. Changes in the composition of the extracellular matrix (ECM) may also contribute to a more precarious situation. There seems to be an association between the expansion of the ECM with mechanical and vasomotor dysfunction, arrhythmias, and mortality.8 Pre-existing ECM expansion may also reduce tolerance to new ischaemic events.9 An extensive review has been published by Voors et al.1

Treatment of CHF is primarily directed towards antagonizing fluid retention and neurohormonal activation, and in this respect is not different in patients with and without T2DM.10 Considering the pathophysiological aspects on CHF in patients with T2DM, it has been postulated that strict glycaemic control should be prognostically beneficial, a still unverified hypothesis. Among the glucose-lowering drugs, the thiazolidinediones cause fluid retention and worsening of CHF, and they are thereby contraindicated in patients with compromised cardiac function. Metformin has for long been regarded as contraindicated in CHF due to an assumed risk for lactic acidosis, a worry not supported by a more recent report.11 The value of insulin in patients with diabetes and CHF is under debate. Beneficial effects on myocardial function have been reported, but it has also been reported that insulin may be associated with increased morbidity and mortality.12 Trials of the more modern glucose-lowering agents dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) agonists have not revealed any cardiovascular advantages compared with conventional glucose-lowering drugs.13 We may, however, have witnessed a recent paradigm shift regarding cardiovascular benefits of glucose-lowering drugs. In the EMPA-REG OUTCOME study,14 the sodium–glucose co-transporter inhibitor (SGLT2) empagliflozin decreased the number of cardiovascular events in patients with T2DM and established cardiovascular disease. This benefit was...
essentially driven by a 35% reduction of hospitalizations for HF, a benefit visible already within the first month on the drug.

In this issue of the journal, Fitchett and colleagues present an expanded analysis of the effect of empagliflozin in the EMPA-REG study\textsuperscript{15} by presenting a detailed report on the HF outcomes in the overall patient population and in subgroups, including patients with investigator-reported HF at baseline, and the effect of empagliflozin on hospitalization due to any cause. They show that empagliflozin was also effective across subgroups on CHF-related outcomes. Further information is also provided on patients with a history of CHF at baseline. Even if these patients had an approximately five times higher rate of hospitalization for worsening CHF, the overall rate was only \textasciitilde 5%/year which is low compared with other CHF studies. Data could not be presented by ejection fraction at baseline since this information was not collected. Accordingly, we do not know if empagliflozin is also a beneficial agent in HF with preserved ejection fraction, which would have been of great interest. Still the consistent effects including patients with CHF make the EMPA-REG study also very interesting from a CHF perspective in general.

The exact mechanisms behind these favourable effects remain to be elucidated in mechanistic studies. They cannot be reasonably explained by the modest glucose-, blood pressure-, and weight-lowering effects of empagliflozin. A more plausible explanation, still speculative but taking the rapidly visible effect into account, is that a decrease in volume load related to osmotic diuresis and increased sodium excretion, possibly in combination with a reduced arterial stiffness, may have had a favourable impact on the development of CHF, which as underlined is a very serious condition in patients with chronic heart failure (Figure 1).

Another lesson from the EMPA-REG trial\textsuperscript{15} is that worsening CHF is a frequent and important cardiovascular event, making it reasonable to include it as a component of the primary composite endpoint of future trials in patients with T2DM. This has previously not been done and was indeed not the case even in the EMPA-REG trial, making the encouraging observation on the impact on CHF coincidental. The rationale for such a change in study design was discussed by McMurray et al.,\textsuperscript{16} who underlined that the development or worsening of CHF during treatment with glucose-lowering drugs is a frequent and important outcome in many previous trials. We cannot agree more with their proposal, not the least in contemplating that the development of HF could be attenuated with a drug, empagliflozin, directed towards diabetes. With such effects, the double burden of CHF and T2DM can be addressed with one approach. The opposite, reversal of or delaying the onset of diabetes in patients with CHF, is still uncertain. There are observations in favour of this. As an example, the angiotensin receptor blocker valsartan reduced the incidence of diabetes by 14% in the NAVIGATOR trial, although there were no effects on cardiovascular outcomes.\textsuperscript{17} In the DREAM trial, the angiotensin-converting enzyme inhibitor ramipril increased the regression to normoglycaemia among persons with impaired fasting glucose or impaired glucose tolerance.\textsuperscript{18} For the cardiology community, the EMPA-REG study is of considerable interest, increasing our appetite for more information on the mechanisms behind the beneficial effects of empagliflozin and whether this drug may have a favourable impact on CHF even in patients without known T2DM.

**Conflict of interest:** K.S. has received honoraria as a consultant to AstraZeneca, Novartis, and MSD. L.R. has received research grants from Bayer AG and Boehringer Ingelheim, and fees for lectures and expert meetings from AstraZeneca, Bayer AG, Boehringer Ingelheim, and Sanofi Aventis.

![Figure 1](https://example.com/figure1.png)

**Figure 1** Effects of sodium–glucose co-transporter inhibitor 2 (SGLT2) inhibition with empagliflozin and the potential importance for the beneficial impact on heart failure in the EMPA-REG trial.

**References**

A 69-year-old female presented with four episodes of syncope in 2 months precipitated by bending forward while gardening. They were not associated with any prodromal symptoms, palpitations, or chest pain. On physical exam, a distinct low-frequency diastolic heart sound was heard at the left lower sternal border. Transthoracic echocardiogram illustrated a large mobile mass extending from the inferior vena cava (IVC) to the right atrium with prolapse across the tricuspid valve into the right ventricle in diastole (Panel A). For further characterization of the mass, a cardiac and abdominal magnetic resonance imaging (MRI) revealed a large tumour extending from the right renal vein to the IVC (Panel B) and finally into the right atrium and ventricular apex (Panel C). Computed tomography (CT) scan of the abdomen revealed a large right renal mass (Panel D). Pre-operative coronary angiography did not demonstrate any flow-limiting lesions. Intra-operative transoesophageal echocardiogram showed the extent of tumour mass within the IVC (Panel E). A level IV tumour thrombectomy and tricuspid valve annuloplasty were performed under cardiopulmonary bypass with subsequent right radical nephrectomy, retroperitoneal lymphadenectomy, and vena cavaotomy with closure. Macroscopic specimen was consistent with clear cell renal cell carcinoma and tumour extension (Panel F). We propose that bending forward resulted in complete IVC occlusion (due to the large tumour burden), leading to a precipitous drop in the preload, in turn decreasing the cardiac output (a leftward shift on the Starling curve) and cerebral perfusion, with resultant syncope. The worldwide annual incidence of renal cell carcinoma is 2.4% with 338 000 new cases diagnosed in 2012,1 out of which 1% extend into the right atrium with rare extension into the right ventricle. Syncope has not previously been reported as the initial presentation of renal cell carcinoma.

Reference


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