MINIREVIEW

CHRONIC HEART FAILURE AND DIABETES MELLITUS: TWO UNSUITABLY MATCHED PARTNERS

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ABSTRACT

Diabetes mellitus (DM) and heart failure (HF) are often associated and each disease independently increases the risk for the other. It is well recognized that diabetes is a risk factor for mortality among individuals with heart failure. The risk of incident HF among patients with DM increases with older age, obesity, retinopathy, hypertension, coronary artery disease, peripheral arterial disease, nephropathy, longer duration of DM and higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) value. The treatment of each pathology in the presence of the other raise difficulties in the clinical practice. First-line treatment of DM in patients with HF should include metformin and SGLT2 inhibitors; conversely, saxagliptin, pioglitazone and rosiglitazone are not recommended in patients with DM and HF.

Keywords: diabetes mellitus, heart failure, HbA1c, glucose-lowering agents.

RéSUMÉ

Insuffisance cardiaque chronique et diabète sucré: deux partenaires mal assortis

Le diabète sucré (DS) et l’insuffisance cardiaque (IC) sont souvent associés et chaque maladie augmente indépendamment le risque pour l’autre. Il est bien reconnu que le diabète est un facteur de risque de mortalité chez les personnes souffrant d’insuffisance cardiaque. Le risque d’incidence de l’IC chez les patients atteints de DS augmente avec l’âge, l’obésité, la rétinopathie, l’hypertension, la maladie coronarienne, la maladie artérielle périphérique, la néphropathie, la durée plus longue de la DS et le peptide natriurétique de type N-terminal pro-B supérieur (NT-proBNP). Le traitement de chaque pathologie en présence de l’autre pose des difficultés dans la pratique clinique. Le traitement de première intention de la DS chez les patients atteints d’IC devrait inclure la metformine et les inhibiteurs de SGLT2; à l’inverse, la saxagliptine, la pioglitazone et la rosiglitazone ne sont pas recommandées chez les patients atteints de DS et d’HF.

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INTRODUCTION

Diabetes mellitus (DM) is a progressive chronic disease and its prevalence worldwide continues to increase. DM and heart failure (HF) are often associated and each disease independently increases the risk for the other. Also, epidemiological evidence indicates a strong association between DM and HF. It is well recognized that diabetes is a risk factor for mortality among individuals with heart failure. Framingham Heart Study documented a 2.4-fold increased incidence of HF in diabetic men and a 5-fold increase of HF in diabetic women.

The prevalence of type 2 DM has increased by 30% globally in the past 10 years, with the number of patients affected increasing from 333 million in 2005 to 435 million in 2015.

The Emerging Risk Factor Collaboration, a meta-analysis of 102 prospective studies, showed that DM confers a two-fold excess risk of vascular outcomes (coronary heart disease, ischemic stroke, and vascular deaths), independent of other risk factors. Also, poor glycemic control is associated with a greater risk for the development of symptomatic HF in patients with asymptomatic left ventricular (LV) systolic dysfunction. The risk of incident HF among patients with DM increases with older age, obesity, retinopathy, hypertension, coronary artery disease (CAD), peripheral arterial disease, nephropathy, longer duration of DM and higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) value. These data demonstrate the high incidence, prevalence and mortality of HF in individuals with diabetes.

Antidiabetic medications increase the risk of mortality and hospitalization for HF in patients with and without pre-existing heart failure. DM can contribute to the development of structural heart disease and HF via systemic, myocardial, and cellular mechanisms. The altered systemic and cardiac glucose metabolism of patients throughout the evolution of the disease goes from impaired glucose control to DM and contributes to the structural and functional abnormalities of the heart, that culminate into cardiac dysfunction. In diabetic patients, HF develops not only because of the underlying CAD, but also because of the multiple metabolic and pathophysiological abnormalities induced by altered glucose metabolism.

The European Society of Cardiology Guidelines on Diabetes, Pre-Diabetes and Cardiovascular Disease recommend a HbA1c target of <7% (<53 mmol/mol) in order to reduce microvascular complications, while evidence for an HbA1c target to reduce macrovascular risk is less compelling. HbA1c targets should be individualized, with more-stringent goals [6.0–6.5% (42–48 mmol/mol)] in younger patients with a short duration of DM and no evidence of cardiovascular disease (CVD), if achieved without significant hypo-glycemia. Less-stringent HbA1c goals [e.g. <8% (64 mmol/mol) or ≤9% (75 mmol/mol)] may be adequate for elderly patients with long-standing DM and limited life expectancy, and frailty with multiple comorbidities, including hypo-glycemic episodes.

The American Heart Association Guidelines recommend precise glycemic targets or ranges, but most agree on HbA1c thresholds ≤7.0% for most of the adults with DM and no significant comorbidities or DM complications, who do not experience severe hypoglycemia. Older patients (particularly those with established microvascular or macrovascular complications or extensive comorbid conditions) are advised to target higher HbA1c levels, up to 8% to 8.5%, depending on the guideline. Patients with short life expectancy, advanced microvascular or macrovascular complications, or any end-stage comorbidity should be treated to minimize symptomatic hyperglycemia and hypoglycemia, corresponding to HbA1c 8% to 9%.

First-line treatment of DM in HF should include Metformin and SGLT2 inhibitors. Treatment of HF encompasses pharmacological and device therapies with confirmed benefits in randomized control trials (RCTs), in which 30–40% of patients had DM. Treatment effects are consistent, with and without DM, with the exception of Aliskiren, which is not recommended in patients with DM because of the risk of serious adverse events. Lifestyle management should be part of the care of patients with DM and HF, because DM is linked to obesity, inactivity and poor dietary choices. Also, exercise is safe and beneficial in patients with HF and DM. Future research should address the risks of polypharmacy, in terms of adherence, adverse reactions and interactions, especially among vulnerable patients with HF and DM, such as elderly patients.

GLUCOSE-LOWERING AGENTS: NEW EVIDENCE FROM CARDIOVASCULAR OUTCOME TRIALS

The classes of antidiabetic drugs are synthesized in Table 1. Metformin is safe in all stages of HF with...
preserved or stable moderately reduced renal function (i.e. eGFR >30 mL/min), and results in a lower risk of death and HF hospitalization compared with insulin and sulfonylureas. Also, metformin reduced the rate of myocardial infarction (MI) and increased survival when the study was extended for another 8–10 years of intensified therapy, including the use of other drugs.

Data on the effects of sulfonylureas on HF are inconsistent. Addition of a sulfonylurea to metformin was associated with a higher risk of adverse events and death, compared with the combination of metformin and a DPP4 inhibitor. Since the 1960s, there has been an ongoing debate on the cardiovascular (CV) safety of sulfonylureas. Also, sulfonylureas carry the risk of hypoglycemia.

Acarbose didn’t alter major adverse cardiovascular events (MACE) in patients with impaired glucose tolerance (IGT) and cardiovascular disease (CVD) during the large 5-year prospective ACE trial. Thiazolidinediones or Sulfonylureas and Cardiovascular Accidents Intervention Trial (TOSCA.IT)—a large, randomized, but unblinded comparison of pioglitazone vs. sulfonylurea as add-on to metformin—was stopped prematurely because of futility. The composite endpoint and the individual components of the composite endpoint were similar in the two groups. The results of this trial showed over a median observation period of almost 5 years that both sulfonylureas (mostly glimepiride and glitazide) or pioglitazone have a similar effect as add-on to metformin on the incidence of total cardiovascular events. This finding suggests that in patients with type 2DM without CVD and with reasonable glucose control, the choice of the treatment strategy when metformin monotherapy fails might not have a major effect on CV complications. The two treatment strategies effectively controlled blood glucose in the long-term, with few clinically relevant side-effects.

In the ORIGIN trial, 12,537 people (mean age 63.5 years) at high CVD risk, with impaired fasting glucose (IFG), IGT, or DM, were randomized to long-acting insulin glargine or standard care. After a median follow-up of 6.2 years, the rates of CV outcomes were similar in the two groups. Seven CVOTs have examined the effects of GLP1-RAs on CV events in patients with DM and high CV risk. In the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) study of a DM population, in whom 73% had experienced a previous CV event, Exenatide 2 mg once weekly showed non-inferiority vs. placebo and a numerical, but non-significant, 14% reduction of the primary three-point MACE. In the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) study of a DM population, in whom 73% had experienced a previous CV event, Exenatide 2 mg once weekly showed non-inferiority vs. placebo and a numerical, but non-significant, 14% reduction of the primary three-point MACE. In the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) study of a DM population, in whom 73% had experienced a previous CV event, Exenatide 2 mg once weekly showed non-inferiority vs. placebo and a numerical, but non-significant, 14% reduction of the primary three-point MACE. In the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) study of a DM population, in whom 73% had experienced a previous CV event, Exenatide 2 mg once weekly showed non-inferiority vs. placebo and a numerical, but non-significant, 14% reduction of the primary three-point MACE.
vitreous hemorrhage, blindness, or requirement for intravitreal agent or photocoagulation, the implications of which require further study33.

Saxagliptin is a selective dipeptidyl peptidase-4 (DPP-4) inhibitor. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVORTIMI 53) trial was designed to evaluate the long-term cardiovascular efficacy and safety of Saxagliptin in patients with DM at risk of cardiovascular events34. Over a median of 2.1 years follow-up, Saxagliptin neither increased nor decreased the risk of the primary or secondary composite endpoints. This report explores further on the observation surrounding hospitalizations for HF by examining baseline risk factors associated with an increased risk of hospitalizations, the timing of them and the risk of recurrent events. Also, it reveals the association between baseline levels of natriuretic peptides and future hospitalizations for HF events34.

The CV benefits of SGLT2 inhibitors are mostly unrelated to the extent of glucose lowering and occur too early to be the result of weight reduction. The rapid separation of placebo and active arms in the four studies in terms of reduction in HF hospitalizations indicates that the beneficial effects achieved in these trials are more likely the result of a reduction in HF-associated events35-38.

For the first time in the history of DM, there are data from several CVOTs that indicate CV benefits from the use of glucose-lowering drugs in patients with CVD or at very high/high CV risk. The results obtained from these trials, using both GLP1-RAs (LEADER, SUSTAIN-6, Harmony Outcomes, REWIND, and PIONEER 6) and SGLT2 inhibitors (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and CREDENCE), strongly suggest that these drugs should be recommended in patients with T2DM with prevalent CVD or very high/high CV risk, such as those with target-organ damage or several cardiovascular risk factors (CVRFs), whether they are treatment-naïve or already on metformin. In addition, based on the mortality benefits seen in LEADER and EMPA-REG OUTCOME, liraglutide is recommended in patients with prevalent CVD or very high/high CV risk, and empagliflozin is recommended in patients with prevalent CVD, to reduce the risk of death. The recommendation for empagliflozin is supported by a recent meta-analysis which found high heterogeneity between CVOTs in mortality reduction39.

**Specific Cardiovascular Therapies**

Patients with DM treated with long-term beta-blocker have recently been evaluated by a prospective observational study, as well as a post hoc analysis from the ACCORD study, suggesting increased all-cause death in DM patients treated with beta-blockers40,41. Carvedilol and nebivolol may be preferred because of their ability to improve insulin sensitivity, with no negative effects on glycemic control42,43.

Treatment with angiotensin-converting enzyme inhibitors (ACEIs) is recommended to prevent major CV events and HF in all patients with chronic coronary syndrome (CCS) or ACS and systolic LV dysfunction, based on a systematic review of randomized controlled trials (RCTs)44.

Nitrates, preferably short-acting, and calcium channel blockers are indicated for relief of angina symptoms, are frequently used when beta-blockers are contraindicated or not tolerated, or in addition to beta-blockers if patients remain symptomatic, but offer no prognostic benefit45.

Statins are safe and generally well tolerated by patients with DM. Consistent data have demonstrated the efficacy of statins in preventing CV events and reducing CV mortality in patients with DM, with no evidence for sex differences46.

Ranolazine is a selective inhibitor of the late sodium current, effective in the treatment of chronic angina45. Ranolazine also has metabolic effects and may lower HbA1c levels in patients with DM47.

Trimetazidine is an anti-ischemic metabolic modulator that improves glucose control and cardiac function in patients with DM48,49. These drugs should be considered as second line treatment44.

There is no evidence to support different anti-platelet strategies in patients with ACS or CCS with vs without DM11,50.

In the SHIFT trial (Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial), Ivabradine significantly reduced the primary endpoint of CVD or HF hospitalization in patients with and without DM. There was also a significant reduction in HF hospitalization in both groups51.

**Conclusions**

HF has a high prevalence in populations with diabetes, due to a high incidence rate. This underlines the need to focus on the prevention of HF in individuals with diabetes. Also, the coexistence of DM and HF leads to a higher risk of hospitalization for HF and all-cause death52,53. Prevention of HF should be a priority. First-line treatment of DM in patients with
HF should include metformin and SGLT2 inhibitors; conversely, saxagliptin, pioglitazone and rosiglitazone are not recommended in patients with DM and HF11.

Author contributions
M.A.M. and C.C.D. conceived the original draft preparation. G.G., A.M.A.S., and O.G.B. were responsible for conception and design of the review. M.A.M. and T.P.N. were responsible for the data acquisition. M.A.M., G.G. and C.C.D. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed to the published version of the manuscript.

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