Editorial

HEART FAILURE IN TYPE 2 DIABETES – THE "FORGOTTEN" COMPLICATION

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Diabetes, particularly type 2 diabetes (T2DM), was recognized as the new "worldwide pandemic" of the 21st century, with an estimated 8.8% of the adult population (~425 million subjects) afflicted by this condition in 2017 [1]. In the same time, diabetes represents a massive public health issue, being one of the major causes of morbidity and mortality in the modern societies, with high social and economic costs. It is estimated that chronic diseases (including diabetes) have surpassed infectious diseases as the first cause of premature mortality worldwide [2]. In addition, healthcare expenditure related to diabetes in USA reached a staggering 322-377 billion USD [1,2], with a worldwide estimate of 727 billion USD in 2017 according to the latest IDF data [1].

It was long time established that cardiovascular disease (CVD) represents the first cause of death and probably the main cause of disability in subjects with T2DM, with some estimates indicating an 80% excess mortality due to CVD in T2DM [3]. Progresses in the treatment of T2DM and associated CVD risk factors (especially hypertension and dyslipidemia) have led to a continuous decline in the CVD associated morbidity and mortality in diabetes subjects [4,5]. Still, a recent analysis of data from the Swedish National Diabetes Register have shown that T2DM subjects continue to have a 2-4 fold increased risk of death from any cause, death from CVD and death from coronary heart disease (CHD) compared with non-diabetic subjects [4]. This could be explained by the fact that frequently T2DM subjects have asymptomatic / unrecognized CVD, including silent myocardial ischemia and heart failure (HF).

Heart failure and diabetes - Epidemiological data

It was long time recognized that T2DM subjects have an increased risk of developing HF. Thus, results from the Framingham Study published in 1974 showed that diabetic subjects had 2-5 times increased risk of congestive heart failure compared to non-diabetics [6]. Already at that time authors remarked that "... *excessive risk appears to be caused by factors other than accelerated atherogenesis and coronary heart disease*", most probable cause being the recently described "diabetic cardiomyopathy" [7]. More than 4 decades passed by and situation is similar; with current estimates indicating a 2-to-4 fold increased risk of HF in T2DM subjects [8-10], both for the form with reduced ejection fraction (HFrEF) and that with preserved ejection fraction (HFpEF). The morbid association

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between the two conditions is bidirectional, with diabetes being highly prevalent in cohorts of patients diagnosed with HF. Thus, it was shown that approximately 30-40% of subjects included in studies of patients with HFpEF [11], patients with HFrEF [12] or registries of HF patients [13] have diabetes.

Frequently, HF is unrecognized in diabetes subjects due to lack of classical symptoms such as exercise breathlessness / reduced exercise tolerance which are wrongly attributed to obesity associated reduced mobility or chronic obstructive pulmonary disease. Thus, the reported prevalence of HF in different cohorts of diabetes subjects (based on diabetes patients charts) ranged from 9.5 to 22.3% [14]. However, if using echocardiography for diagnosis, a recent study analyzing a Dutch cohort of T2DM subjects aged >60 years indicated a prevalence of undiagnosed HF of 28%: 5% for HFrED and 23% for HFpEF [14]. The prevalence of HF in different T2DM trials (including the recent CV outcome trails - CVOTs) varied between 10 and 30% [15].

Diabetes patients have not only a higher prevalence of HF but also a poor prognosis, higher rates of hospitalization and an increased risk of death due to HF compared to non-diabetic HF patients [15]. Thus, a meta-analysis of studies including patients with HF followed-up for a median of 3 years indicated that T2DM increases significantly the risk of all-cause death (HR 1.28), cardiovascular death (HR 1.34), and hospitalization for HF/all-cause death (HR 1.41), the association being significant after adjustment for multiple covariates [16]. In addition, recent data show an extremely high 5-year mortality rate of T2DM subjects with HF at around 75% [17]. Last, but not least, T2DM subjects with HF have a poorer quality of life compared with non-diabetic HF subjects.

Mechanisms of heart failure in diabetes

HF in diabetes subjects can be generally divided in a "primary" form, generally designated as diabetic (metabolic) cardiomiopathy, and a "secondary" form, most often related to coronary artery disease and its consequences (including myocardial infarction) [18]. The first is most often associated with left ventricle diastolic dysfunction, leading to HFpEF. It is estimated that diastolic dysfunction may be found in approximately 3/4 of T2DM patients [15], being correlated with the degree of metabolic control. The second is more often associated with left ventricle systolic dysfunction, leading to HFrEF, usually accompanied by more severe diabetes complications [15,18].

There are multiple pathways by which diabetes, insulin resistance and chronic hyperglycemia contribute to the pathogenesis of myocardial dysfunction and HF, a detailed review of these being beyond the scope of this material. However, in brief, they include accumulation/deposition of advanced glycation end-products, increased uptake of free fatty acids and lipotoxicity, increased activation of the rennin angiotensin aldosterone system, increased oxidative stress, increased activation of the sympathetic nervous system and autonomic dysfunction, endothelial dysfunction and so on [18,19]. Multiple inter-relations between these pathways lead to a potentiation of the detrimental effects on cardiomyocytes, finally leading to their reduced contractility (systolic dysfunction) or myocardial hypertrophy (diastolic dysfunction).

It should be also remembered that other "classical" HF risk factors, including hypertension, CHD, dyslipidemia, chronic kidney disease, etc. are more frequently encountered in diabetes subjects and my contribute to the high prevalence and poor

prognosis of this condition in T2DM. Consequently, it could be inferred that a multi-factorial approach in T2DM patients, targeting blood glucose, hypertension, plasma lipids, etc. may have beneficial effects in reducing the risk of HF. This was recently proved in patients from the STENO-2 study, indicating a 70% reduction of the HF risk in the intensive compared to the conventional therapy groups (HR 0.3, p=0.002) [20].

Impact of diabetes medications on HF risk

With increased recognition of the importance of HF in the prognosis of T2DM subjects came renewed interest in the effect of various diabetes medications on the evolution of these patients. For "older" drugs, available information is derived mainly from observational studies / retrospective registry analyses with all the limitations of these approaches. For the modern "innovative" classes, more robust information was provided by the recently published CVOT trials analysing the CV safety of these drugs.

Insulin was reported to be associated with fluid retention, hence a potential detrimental effect on HF, a hypothesis apparently supported by data from older observational studies [21]. However, results of the ORIGIN study showed that treatment with basal insulin glargine in patients with IFG/IGT or recently diagnosed T2DM is safe and does not increase CV risk [22]. Specifically, occurrence of the composite endpoint including hospitalization for HF was similar for insulin glargine subjects compared to standard of care patients.

Metformin was classically contraindicated in HF patients due to a putative increased risk of lactic acidosis. However, numerous observational studies and meta-analyses have shown that metformin treatment in T2DM subjects with HF is associated with a decreased risk of death or hospitalizations [23,24], prompting the FDA to remove HF as a contraindication for metformin treatment.

Sulphonylureas lead to increased insulin levels and are associated with a high risk of hypoglycaemia. Recent observational data and registry analyses have shown that, when compared to metformin, sulphonylureas lead a higher risk of CV events, including hospitalizations for HF or CV death [25]. No direct causal effect can be established at this point between the two; however caution is granted when using this class of drugs in HF subjects.

Thiazolidindiones, despite their positive impact on insulin resistance and low risk of hypoglycaemia, are associated with marked fluid retention, oedema and weight increase, limiting their use in HF subjects. In fact, both the PROACTIVE study with pioglitazone [26] and RECORD study with rosiglitazone [27] reported an increased risk of hospitalization for HF (both pioglitazone and rosiglitazone) and death due to HF (rosiglitazone). Consequently, thiazolidin-diones are contraindicated in patients with HF in NYHA III and IV stages.

Dipeptidyl Peptidase 4 Inhibitors (DPP4i) were the first class of drugs to publish the results of "modern" CVOT trials in diabetes subjects, proving their CV safety. However, in the SAVOR-TIMI 53 Trial [28], treatment with saxagliptin led to a statistically significant increase in the risk of hospitalization for HF (HR=1.27) compared to placebo. Events were more frequent in patients with known HF at baseline. Though no definite biologic mechanism can explain this finding, the FDA mandated a black-box label for saxaglitpin in patients with HF. Subsequently, data of the EXAMINE trial indicated a 19% increased risk of hospitalization for HF in patients treated with aloglitpin compared to placebo (HR=1.19),

though not statistically significant (p=0.22) [29]. Finally, contrasting with the previous two studies, sitagliptin was proven to be safe in patients with HF, results of the TECOS study showing no increased risk of hospitalization for HF (HR=1) [30]. Overall, results of these 3 trials are somehow discrepant, raising questions if the increased risk of HF is a class effect or limited to specific molecules. Te results of the CVOTs with linagliptin (CAROLINA and CARMELINA) will bring new information in this respect.

Glucagon Like Peptide 1 Receptor Agonists (GLP-1RAs) have several effects (improved glycemic control, increased insulin sensitivity, weight loss, reduced blood pressure) that should theoretically improve the prognosis of HF subjects. Despite the reduced risk for the occurrence of the primary CV outcome (CV death, non-fatal myocardial infarction and non-fatal stroke) for liraglutide in the LEADER trial [31] and semaglutide in the SUSTAIN-6 trial [32], GLP-1RAs showed no impact on the risk for HF hospitalization in the 4 CVOTs published to date. Thus, HR for HF hospitalization were 0.96 (p=0.75) for lixisenatide in the ELIXA trial [33], 0.87 (p=0.14) for liraglutide in the LEADER trial [31], 1.11 (p=0.57) for semaglutide in the SUSTAIN-6 trial [32] and 0.94 for exanatide QW in the EXSCEL trial [34].

Sodium Glucose Co-Transporter 2 Inhibitors (SGLT2i) inhibit reabsorbtion of glucose and sodium in the renal convoluted tubules, leading to increased diuresis and natriuresis. They are also associated with weight loss and reduced blood pressure, with potentially positive effect on HF. In addition, SGLT2i treatment is associated with an increase in hematocrit and red blood cell mass (Hb), that may lead to an increase in oxygen delivery to the heart [35]. Finally, SGLT2i are associated with a moderate rise in plasma ketones, including beta-hydroxybutyrate, hypothesized to be a sort of "super-fuel" that can be taken up by the heart and used very efficiently [36]. A detailed description of their specific effects in various randomized and observational studies is given below.

Sodium Glucose Co-Transporter 2 Inhibitors effect in T2DM subjects with HF

Results of randomized CVOTs

The first CVOT of a SGLT2i to publish its results was the EMPA-REG OUTCOME trial in September 2015 [37]. The study evaluated the CV safety of empagliflozin compared to placebo on a total of 7020 T2DM subjects with established CV disease. After a median of 3.1 years of exposure, empagliflozin treated patients had a significant (HR=0.86, p=0.04) reduction of the primary endpoint - time to first MACE (CV death, non-fatal myocardial infarction or non-fatal stroke) occurrence. Analysis of the secondary endpoints revealed a 38% reduction of CV death (p<0.0001), a 32% reduction of all-cause death and a 35% reduction of HF hospitalizations [37]. The reduction in HF hospitalization was constant in subgroup analyses, both in subjects with or without HF at baseline, regardless of medication at baseline [38].

Canagliflozin was the second SGLT2i to complete a large scale CVOT in T2DM subjects with high CV risk [39]. In fact the program included 2 parallel trials with a merged analysis of the results: CANVAS (Canagliflozin Cardiovascular Assessment) and CANVAS-R (Renal). These studies tested the CV safety of canagliflozin versus placebo in 10142 T2DM subjects (4330 in CANVAS and 5812 in CANVAS-R) at high CV risk (66% with established CV disease, 14% with HF at baseline), with a median follow-up of 2.4 years

[39]. The results showed that canagliflozin treated patients had a significant (HR=0.86, p=0.02) reduction of the primary endpoint – time to classical three point MACE. In respect to HF, canagliflozin treated patients exhibited a 33% reduction of the risk for HF hospitalization (HR=0.67, 95%CI 0.52-0.87), a result almost identical with that reported for empagliflozin in the EMPA-REG study.

The benefits of these two SGLT2i in reducing the risk of HF were acknowledged by the European Society of Cardiology (ES) in the "*2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure*" [40], respectively a recent position statement on T2DM and HF [15].

Results of observational "Real World Evidence" studies

The results of the EMPA-REG OUTCOME and CANVAS studies led to a huge interest in the study of the SGLT2i effects on CVD in diabetes subjects, particularly their effect on HF. In order to evaluate if the reported benefits may represent a class effect (and are not limited to empagliflozin and canagliflozin) and if they can be expanded to T2DM subjects from the general population with various degrees of CV risk (and are not limited to subjects with established CVD / high CV risk as those included in the CVOT trials), large scale "real world practice" studies were initiated. The first such study to publish its results was the CVD-REAL study in 2017 [41]. This was a retrospective, registry-based analysis of more than 300.000 T2DM subjects from the USA, UK, Germany, Sweden, Norway and Denmark that analysed the hospitalization for HF and all-cause death in patients that initiated treatment with a SGLT2i (154.528 subjects) compared with those who initiated treatment with other diabetes medications (154.528 subjects). Approximately 87% of these patients did not have established CVD. The study showed that SGLT2i (canagliflozin mainly used in the USA cohort, dapagliflozin mainly used in the European countries) use was associated with a 39% decrease of hospitalizations for HF and a 51% decreased risk of all-cause death [41].

More recently, in a "second" CVD-REAL study, the initial results were reproduced with a similar methodology in a cohort of >400.000 T2DM subjects from Australia, Canada, Israel, Japan, Singapore and South Korea [42]. SGLT2i used included (apart empagliflozin, dapagliflozin and canagliflozin) some specific for these geographic areas: ipragliflozin, tofogliflozin and luseogliflozin. In the CVD-REAL 2.0 trial, patients newly initiated with a SGLT2i exhibited a 36% reduction of hospitalizations for HF and 49% reduction of all-cause death compared to those who initiated another glucose lowering medication.

Very similar results were reported by another large-scale "real world evidence" cohort study performed in the USA – the EASEL Population Based Cohort Study [43]. In this cohort of T2DM patients, initiation of a SGLT2i was associated with a 43% reduction of hospitalization for HF and all-cause death.

Upcoming trials with SGLT2i in HF subjects

The CV safety of dapagliflozin in T2DM subjects is currently tested in a large scale CVOT: DECLARE-TIMI 58 (NCT01730534). The study randomized 17160 T2DM subjects to dapagliflozin 10 mg QD or matching placebo, both add-on to standard of care [44]. In this respect, DECLARE is to date the largest CVOT in T2DM subjects. In contrast with the EMPA-REG OUTCOME and CANVAS trials, the DECLARE study enrolled a higher percentage of subjects with only risk factors for CVD (59.4%) and only 40.6% subjects with established atherosclerotic CVD. Thus, the study is expected to offer an image of dapagliflozin safety in a

broader patient population compared to previously published CVOTs. Finally, after the initiation of the study and following the publication of the EMPA-REG OUTCOME trial results, the steering committee decided to add a second co-primary composite end-point including hospitalization for HF and CV death. Consequently, DECLARE will be the first large scale CVOT to test the effect of a SGLT2i on HF as a primary endpoint [44]. The final results of the study are expected to be announced before the end of 2018.

Other currently ongoing CVOTs with SGLT2i in T2DM subjects are the VERTIS CVO (NCT01986881) analysing the CV safety of ertugliflozin (planned enrolment of 8000 subjects) and SCORED (NCT03315143) analysing the CV safety of sotagliflozin (planned enrolment of 10500 participants) [45].

Finally, it should be noted that three large scale randomized controlled trials (RCTs) with SGLT2i were started in patients with HF irrespective of their glycemic status (both patients without or with T2DM). These are EMPEROR-Reduced (NCT03057977) testing the effect of empagliflozin in subjects with HFrEF (planned enrolment of 2850 subjects), EMPEROR-Preserved (NCT03057951) testing the effect of empagliflozin in subjects with HFpEF (planned enrolment of 4126 subjects) and Dapa-HF (NCT03036124) testing the effect of dapagliflozin in subjects with HFrEF (planned enrolment of 4500 subjects). Several other smaller RCTs with different SGLT2i are planned to test various aspects of HF [15,23,45].

Conclusions

T2DM is a major risk factor for heart failure, and the prevalence of both is continuously increasing. Prognosis of subjects with T2DM and HF is blink, with 75% mortality at 5-years. Thus, there is a critical need for novel management strategies to improve outcomes in this high-risk group. SGLT2i have been shown to improve CV outcomes in patients with T2DM, particularly hospitalizations for HF and mortality in both RCTs and real world evidence studies.

Mechanisms of cardiovascular protection with SGLT2i include increased natriuresis/diuresis, increased hematocrit/red blood count, and a possible shift in heart fuel metabolism.

Large CVOTs with SGLT2i, as well as specific RCTs in patients with HF are ongoing. These trials will provide further insight into the cardiovascular and HF protective signals seen with this class of diabetes drugs.

Duality of interest

Cristian Guja participated in scientific advisory boards and received consulting fees from AstraZeneca, Bayer AG, Boheringer Ingelheim, Berlin-Chemie Mennarini, Eli Lilly, Merck KGaA, Merck Sharp & Dohme, Novo Nordisk, and Sanofi.

Rucsandra Dănciulescu Miulescu reports no dualities related to the subject of this editorial.

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