HEART FAILURE OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: FINDINGS FROM THE CARDIOVASCULAR OUTCOME TRIALS OF ANTIDIABETES AGENTS

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Type 2 diabetes mellitus (T2DM) is a recognised risk factor for several cardiovascular (CV) conditions including heart failure (HF). Findings that reflect CV risk associated with T2DM medications have led to regulatory requirement of conducting CV outcome trials (CVOTs) for new antidiabetes drugs. Over the years, several CVOTs using different glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter-2 inhibitors have reported neutral or improved CV risks or hospitalisation for HF. However, these studies included only a small proportion of the patients with baseline HF thus limiting the available evidence. Ongoing trials such as EMPEROR programme and DAPA-HF in large patient populations with chronic HF could potentially broaden the use of these drugs beyond their conventional therapeutic indication.

KEYWORDS: cardiovascular outcome trials; DPP-4 inhibitors; GLP-1 receptor agonists; heart failure; SGLT-2 inhibitors; type 2 diabetes mellitus

ИСХОДЫ ПО СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2-ГО ТИПА: ДАННЫЕ ИССЛЕДОВАНИЙ СЕРДЕЧНО-СОСУДИСТЫХ ИСХОДОВ ПРОТИВОДИАБЕТИЧЕСКИХ ПРЕПАРАТОВ

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Сахарный диабет 2 типа (СД2) — общепризнанный фактор риска сердечно-сосудистых заболеваний (ССЗ), включая сердечную недостаточность (СН). Данные о сердечно-сосудистом риске, ассоциированном с СД2, обусловили появление нормативного требования по проведению исследований сердечно-сосудистых исходов (ИССИ) для новых противодиабетических препаратов. За прошедшие годы несколько ИССИ различных агонистов рецепторов глюкагоноподобного пептида-1 (ГПП-1), ингибиторов дипептидилпептидазы-4 и ингибиторов натрий-глюкозного ко-транспортера-2 опубликовали данные о нейтральном или положительном влиянии на сердечно-сосудистые риски или частоту госпитализации по поводу СН. Однако эти исследования включали лишь небольшую долю пациентов с исходной СН, ограничивая тем самым имеющиеся доказательства. Продолжающиеся исследования, такие как программа EMPEROR и DAPA-HF, на больших популяциях пациентов с хронической СН могли бы расширить область применения этих препаратов за пределы их стандартных терапевтических показаний.

КЛЮЧЕВЫЕ СЛОВА: исследования сердечно-сосудистых исходов; ингибиторы ДПП-4; агонисты рецепторов ГПП-1; сердечная недостаточность; ингибиторы НГЛТ-2; сахарный диабет 2-го типа

Cardiovascular disease (CVD) is a major cause of mortality and morbidity in patients with type 2 diabetes mellitus (T2DM) and targeting the CV risk factors is of critical importance for optimal management of the disease. This review will discuss the effect of the antidiabetes drugs on the CV risk, limitations pertaining to CV outcome trials (CVOTs) and the future directions in evaluating the heart failure (HF) outcomes of antidiabetes drugs.

OVERVIEW OF CARDIOVASCULAR RISK IN TYPE 2 DIABETES MELLITUS

Cardiovascular diseases such as atherosclerotic CVD (ASCVD), HF and chronic kidney disease (CKD) together effects approximately 15%–25% of people with T2DM [1]. Life expectancy of patients with T2DM is reduced by 11.2 years in men and 14.3 years in women with history of CVD [2]. Moreover, T2DM is associated with increased risk for developing CVD where each percentage increase in glycated haemoglobin (HbA1c), increases the relative risk of CVD by 18% [3]. In addition, the Framingham Heart Study conducted in large populations has reported 2-fold increase in risk of HF in men and 5-fold increase in women with T2DM [4].

Prior to the 2008 US Food and drug administration (FDA) guidance, patient population included in the studies were relatively younger with a shorter duration of disease and low CV risk, which led to inconsistency in reporting CV outcomes due to lack of well-defined endpoints. Furthermore, the adverse CV outcomes from University Group Diabetes Programme (UGDP) and Action to Control Cardiovascular

Received: 10.09.2019. Accepted: 15.10.2019

Risk in Diabetes (ACCORD) studies have also emphasised the necessity of evaluating CV risks during development of antidiabetes drugs and to design studies that are adequately powered to evaluate the CV outcomes [5,6,7].

Over the years, several CVOTs were completed and many are ongoing on different glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors and sodium-glucose co-transporter-2 (SGLT-2) inhibitors [8,9]. Although the results of the CVOTs have translated in the updated diabetes guidelines focussing on the strategies to manage CVD in patients with T2DM, there is still a need to include higher proportion of patients with HF and specifically evaluate the HF outcomes to tailor the glucose-lowering therapy in patients with T2DM and HF risk [10].

This review describes the effects of antidiabetes drugs on HF outcomes in patients with T2DM and status of completed and ongoing CVOTs in terms of risk for HF and other CV outcomes.

EFFECT OF ANTIDIABETES DRUGS ON CARDIOVASCULAR OUTCOMES

Despite potential glycaemic control, the effect of different antidiabetes drugs on CV outcomes varies and a class effect could not be determined [11,12]. Glycaemic control with thiazolidinediones and insulin was associated with an increased risk of HF, whereas, metformin (biguanide) and SGLT-2 inhibitors have resulted in reduction of HF risk [13,14].

The results of large CVOTs with GLP-1 agonists such as LEADER (liraglutide) and SUSTAIN-6 (semaglutide) have demonstrated reductions in rates of major adverse cardiovascular events (MACE) (hazard ratio [HR] [95% confidence interval [CI]]: 0.87 [0.78–0.97; P<0.001 for noninferiority and P=0.01 for superiority] and 0.74 [0.58–0.95; P<0.001 for noninferiority], respectively) [15,16]. On the other hand, the primary composite outcome with lixisenatide (ELIXA) and exenatide (EXSCEL) was noninferior (P<0.001) to placebo (HR [95% CI]: 1.02 [0.89–1.17] and 0.91 [0.83–1.00], respectively) [17,18].

Various studies conducted with DPP-4 inhibitors have reported neutral cardiac function and no HF risk. The composite of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalisation for unstable angina with sitagliptin (TECOS) was noninferior to placebo (HR [95% CI]: 0.98 [0.88–1.09]; P<0.001) and rates of hospitalisation for heart failure (hHF) was similar (HR [95% CI]: 1.00 [0.83–1.20]; P=0.98) [19]. However in SAVOR-TIMI-53, the proportion of patients with hHF were more with saxagliptin than placebo (3.5% vs 2.8%, HR [95% CI]: 1.27 [1.07–1.51]; P=0.007) [20]. In patients treated with alogliptin (EXAMINE) hHF was higher but insignificant (3.9% vs. 3.3%, HR [95% CI]: 1.19 [0.90–1.58]; P=0.220) when compared to placebo [21]. A meta-analysis of CV safety of vildagliptin use in ~17000 patients has shown neutral effect on MACE (0.86% vs. 1.20%, risk ratio [RR] [95% CI]: 0.82 [0.61–1.11]) and the rate of HF events was insignificant (RR [95% CI]: 1.08 [0.68–1.70]) when compared with other antidiabetes drugs [22]. In the VIVIDD study, the only prespecified trial to evaluate the effects of DPP-4 inhibitors till date , the trend of increase in left ventricular ejection fraction (LVEF) was shown in favour of vildagliptin compared to placebo (4.95% vs. 4.33%, 95% CI: −2.21–3.44; P=0.667) [23].

Additionally, inhibitors of the renin-angiotensin system, which are primarily antihypertensive agents, are also known to prevent the onset of HF and progression of diabetic nephropathy while reducing CV risks and hHF [24]. Valsartan in combination with sacubitril (PARADIGM-HF) has shown significantly low rate of hHF (12.8% vs. 15.6%, HR [95% CI]: 0.79 [0.71–0.89]; P<0.001) and similar rate of decline in renal function (2.2% vs. 2.6%, HR [95% CI]: 0.86 [0.65–1.13]; P=0.28) when compared to enalapril [25].

MECHANISMS OF ACTION OF ANTIDIABETES DRUGS ON CARDIOVASCULAR RISK REDUCTION

Although several studies have proposed the underlying mechanisms for the cardio-protective activity of various antidiabetes drug classes, there still exists few lacunae [4]. Improved CV outcomes with metformin were reported in patients with T2DM, which could be due to the improved endothelium-independent blood flow and enhancement of nitric oxide dependent or independent vasodilation [26]. The cardiac protective effects of the GLP-1 agonists is due to their renal protection, reduction in ischaemic injury, chronic inflammation and ectopic fat deposition [27,28].

Inhibition of SGLT-2 in the proximal renal tubule reduces the total body and cellular glucose toxicity that has metabolic and haemodynamic consequences resulting in improved cardiac outcomes [29]. Additionally, SGLT-2 inhibition has shown short-term diuretic effect in patients with T2DM, along with the long-term decrease in the systolic blood pressure and improved renal function, sustained reduction in body weight and plasma volume. However, the reduction in HF with SGLT-2 inhibitors could be due to the interference with the renal sodium-hydrogen exchanger 3 (NHE3) causing natriuresis. Inhibition of cardiac NHE leads to a decrease in the intracellular sodium and consequent calcium concentrations, leading to prevention of cardiomyopathy and thus HF [14]. Affinity of various SGLT-2 inhibitors is highly variable to SGLT-1 and SGLT-2 receptors [30]. Similar to the cardiac protective action of SGLT-2 inhibitors, the CV effects of a few DPP-4 inhibitors could also be due to the suppression of NHE3 activity [31].

CARDIOVASCULAR OUTCOMES WITH SGLT-2 INHIBITORS

According to the FDA 2008 guidance, clinical outcomes of antidiabetic drugs were to be evaluated by conducting long-term CVOTs or by performing meta-analysis. Over the years, seven CVOTS have been completed for GLP-1 receptor agonists, four for DPP-4 inhibitors and three for SGLT-2 inhibitors and many more are yet to be reported (Figure 1) [5,6]. Among the reported CVOTs, those conducted on SGLT-2 inhibitors and a few on GLP-1 receptor agonists have reported cardiac protection.

Results from CVD-REAL and CVD-REAL-2 studies conducted in patients with T2DM in real-world scenario, suggest lower risk of CV outcomes with SGLT-2 inhibitors. Risk of hHF is suggested to be 39% lower with SGLT-2 inhibitors (pooled HR 0.61 [95% CI: 0.51–0.73; P<0.001] in the CVD-REAL population) and 36% lower (pooled

HR 0.64 [95% CI: 0.50–0.82; P=0.001] in CVD-REAL-2 population) when compared to other antidiabetes drugs. Lack of heterogeneity in results across countries in CVD-REAL study is taken in to consideration which suggests a class effect for SGLT-2 inhibitors [32,33]. However, the favourable CV outcomes of SGLT-2 inhibitors reported from the CVD-REAL and EASEL studies are very inconsistent with data from large randomised trials. This may be due to the inherent observational nature of the study, differences in the drugs that are not fully understood yet, along with technical issues of the analyses such as immortal time bias which have not been taken care off. Hence, it remains uncertain whether the significant outcomes with empagliflozin (particularly for CV and all-cause mortality) also fully apply to all other SGLT-2 inhibitors [34].

Results from the integrated dataset of CANVAS and CANVAS-R (CANVAS Program using canagliflozin) studies demonstrated significant lower risk of MACE (death due to CV causes, nonfatal MI/stroke) in patients with T2DM and high CV risk (HR [95% CI]: 0.86 [0.75–0.97]; P<0.001 for noninferiority and P=0.02 for superiority) but a 2-fold increased risk of amputation. In addition, the all-cause mortality and CV death were similar and statistically insignificant between treatment groups based on the integrated databases and with removal of all study time and mortality events prior to last unblinding [35]. Dapagliflozin (DECLARE-TIMI 58 study) has shown a significantly lower rate of combined event of CV death or hHF when compared to placebo (4.9% vs. 5.8%; HR [95% CI]: 0.83 [0.73–0.95]; P=0.005), mostly driven by lower HF incidence and in subgroup of patients with established ASCVDs. However, in patients with T2DM and ASCVD, the rate of MACE was not significantly lower (8.8% vs. 9.4%; HR [95% CI]: 0.93 [0.84–1.03]; P=0.17) [36]. In patients with T2DM and high risk for CV events, empagliflozin (EMPA-REG) demonstrated a low rate of death from CV causes, nonfatal MI, or nonfatal stroke (10.5% vs. 12.1%; HR [95% CI]: 0.86 [0.74–0.99]; P=0.04 for superiority]) than patients receiving placebo [37]. A recent meta-analysis that included data from CANVAS programme, DECLARE TIMI 58 and EMPA-REG trials, has shown moderate benefits on atherosclerotic MACE (myocardial infarction, stroke, and cardiovascular death) in patients with established ASCVD. A significant reduction in CVD or hHF (24%, HR [95% CI]: 0.76 [0.69–0.84]; P<0.0001) was observed in patients with ASCVD and irrespective of baseline HF status [38].

The results from these studies provided robust data for the influence of the agents on the incidence and worsening of HF among the high-risk T2DM population [39], which is further recognised in recent consensus documents [40].

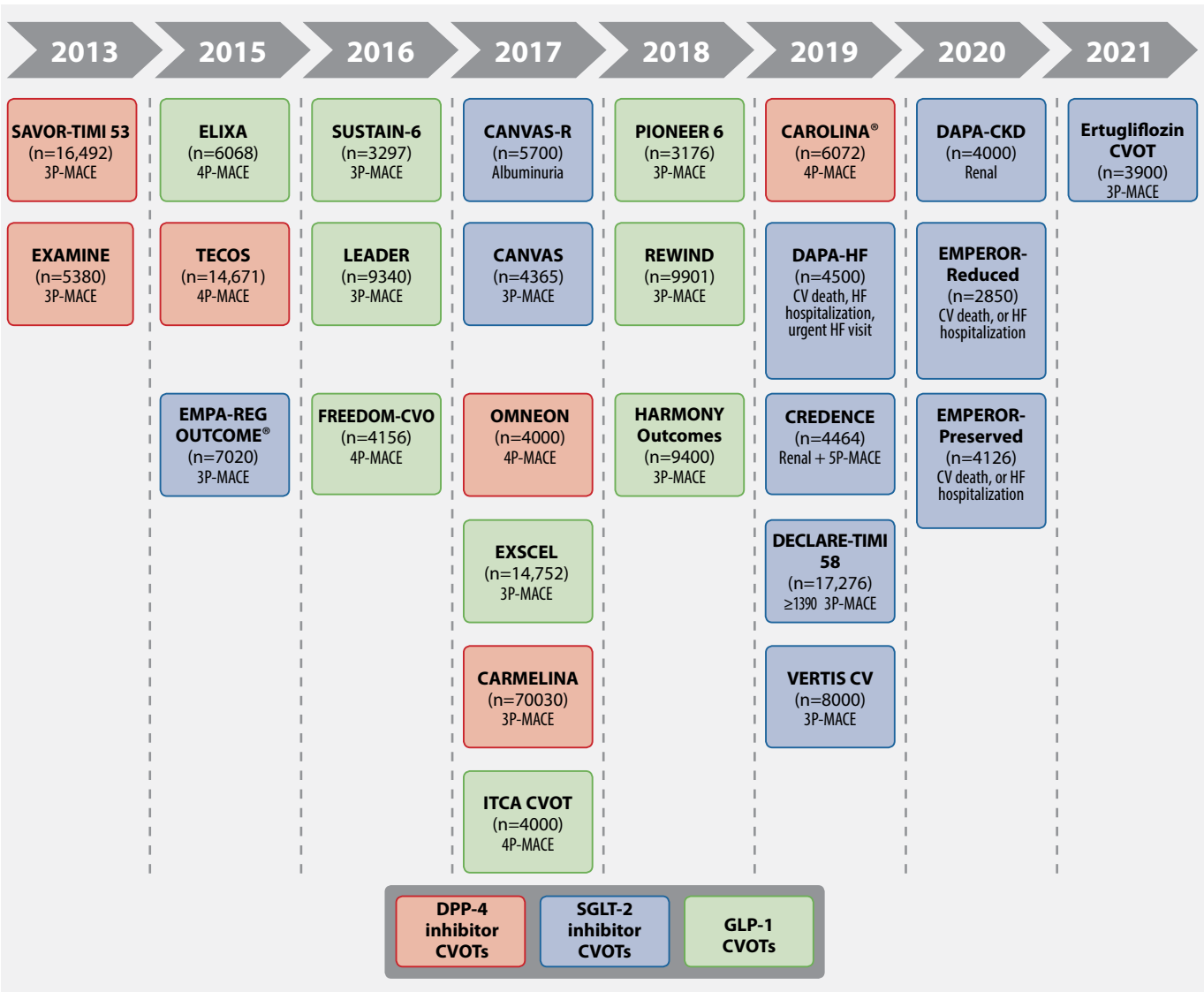

Figure 1. Overview of completed and ongoing CVOTs

However, in all the studies, only a small proportion of patients were recorded to have HF at baseline (~10%), but in none of these studies were these patients well described in terms of HF aetiology, NYHA functional class, LVEF or plasma levels of natriuretic peptides. As the patient population in these studies are at high-risk of CVD, it is unclear whether results could be generalised to patients with a shorter duration of T2DM or without established CV complications [5].

Recent ongoing CVOTs such as EMPEROR programme (using empagliflozin) and DAPA-HF (using dapagliflozin) are being conducted on a large patient population having chronic HF (NYHA class II–IV) with reduced or preserved ejection fraction to evaluate the risk for CV death or hHF [41,42]. In DAPA-HF study, 32% of patients are with NYHA functional class III/IV and the proportion of patients is similar to those in other contemporary registries such as ESC Long-Term Registry (31%), ASIAN-HF (33%) and CAMP-HF (32%) [43]. These studies could provide better understanding of the effect of the antidiabetes drugs on HF in patients with or without T2DM, and could potentiate to broaden the use of these drugs beyond their conventional therapeutic use. Moreover, many co-morbidities other than T2DM and prediabetes such as cachexia and muscle wasting, anaemia and iron deficiency, chronic obstructive pulmonary disease and sleep apnoea are also important in managing HF patients [44–50].

CONCLUSIONS

Based on the FDA guidance, several CVOTs were completed and many more are to be reported. Few antidiabetes drugs have shown CV risk (thiazolidinediones), several do not increase CV risk (DPP-4 inhibitors), but few drugs in SGLT-2 and GLP-1 class have demonstrated CV benefit. Although the findings have revealed the pleiotropic effects of the antidiabetes agents, few limitations of the CVOTs exist. These trials need to be specifically designed by including a higher proportion of patients with baseline HF along with well-characterised data and should be adequately powered to evaluate endpoints for HF outcomes. Nevertheless, results from ongoing trials such as EMPEROR programme and DAPA-HF in patients with HF with reduced or preserved ejection fraction may reveal findings that hold a promising future for better management of patients with T2DM and HF.

ADDITIONAL INFORMATION

Source of funding. The publication of this article was supported by Novartis Pharma AG, Basel, Switzerland.

Conflict of interests. Anker SD has received research support from DZHK Germany, European Union, Vifor International & Abbott Vascular, and fees for consultancy and speaking from Astra-Zeneca, Bayer, Boehringer Ingelheim, Respicardia, Impulse Dynamics, Janssen, Novartis, Servier and Vifor International. The article is based on the presentation by the author at Diabetes Scientific School "T2D patients' journey: holistic approach and quality of life" held at Moscow (11–12 April 2019).

Authors involvement. The author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and has given final approval to the version to be published.

Acknowledgements. The author acknowledges Deepak Reddy Gade, PhD and Ishita Guha Thakurta, PhD, CMPP of Novartis Healthcare Private Limited, India for medical writing support in accordance with good publication practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

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TO CITE THIS ARTICLE:

Anker SD. Heart failure outcomes in patients with type 2 diabetes mellitus: findings from the cardiovascular outcome trials of antidiabetes agents. *Diabetes Mellitus*. 2019;22(5):467-472. doi: 10.14341/DM10374

ЦИТИРОВАТЬ:

Anker SD. Исходы по сердечной недостаточности у пациентов с сахарным диабетом 2-го типа: данные исследований сердечно-сосудистых исходов противодиабетических препаратов // *Сахарный диабет*. — 2019. — Т. 22. — №5. — С. 467-472. doi: 10.14341/DM10374