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Review

Dissecting the reduction in cardiovascular death with SGLT2 inhibitors: Potential contribution of effects on ventricular arrhythmias and sudden cardiac death?

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ABSTRACT

Type 2 diabetes is associated with a higher risk of cardiac arrhythmias, especially in presence of cardiovascular disease and/or heart failure. Ventricular arrhythmias (VA: tachycardia/fibrillation) may lead to sudden cardiac arrest/death (SCA/SCD). Sodium-glucose cotransporter type 2 inhibitors (SGLT2is) exert a remarkable protection against cardiovascular disease, especially hospitalisation for heart failure, yet their effects on malignant cardiac arrhythmias are poorly known. Nevertheless, findings derived from experimental animal and clinical studies suggested that SGLT2is could reduce the risk of not only supraventricular but also ventricular cardiac arrhythmias. A trend for less VA and SCA/SCD events was reported in post hoc analyses of randomised controlled trials/cardiovascular outcome trials versus placebo, yet statistical significance was not reached presumably because of too few events in both treatment groups. Retrospective observational cohort studies that reported malignant cardiac arrhythmias in patients treated with SGLT2is versus other glucose-lowering agents are scare, compared to the numerous ones that focused on atrial fibrillation/flutter. Further studies specifically devoted to the effects of SGLT2is on malignant cardiac arrhythmias are needed to confirm positive effects in patients with diabetes and/or heart failure and if possible to carefully dissect the underlying anti-arrhythmic protective mechanisms.

Introduction

Type 2 diabetes (T2D) is associated with a higher risk of cardiovascular disease (CVD, including coronary artery disease and heart failure (HF). Besides vascular and mechanical abnormalities, altered electrical function is another major feature of the diabetic myocardium, which can lead to severe cardiac arrhythmias [1,2]. Long-lasting T2D may be complicated by both diabetic cardiomyopathy and cardiac autonomic neuropathy. In patients with T2D, around 50% of deaths due to cardiovascular (CV) causes are so-called sudden cardiac deaths (SCD) [3,4]. In 10 patient-based prospective studies, the summary risk of SCD for diabetes patients vs. patients without diabetes was increased by 75% for all patients combined, 63% for coronary heart disease patients, and 85% for HF patients [5]. HF is an increasingly common complication in patients with T2D [6,7] and also increases the risk of severe cardiac arrhythmias [8–10].

Sodium-glucose cotransporter type 2 inhibitors (SGLT2is) reduce the risk of hospitalisation for heart failure (hHF), CV mortality and major CV adverse events (MACE-3 points: CV mortality, non-fatal myocardial infarction, non-fatal stroke) compared with placebo both in patients with T2D and in non-diabetic patients with HF [11–13]. The contribution of a potential reduction in malignant cardiac arrhythmias and SDC on CV death rate remains poorly documented in available publications that assessed the overall CV protective effect of SGLT2is in patients with T2D and/or HF [14,15].

The aim of the present short narrative review is to analyse the effects of SGLT2is on the risk of ventricular arrhythmias (VA: tachycardia and fibrillation), sudden cardiac arrest (SCA) and SCD in patients with T2D and in those with HF (with or without T2D) (Fig. 1). Preliminary experiments in animals and human studies suggested potential anti-arrhythmic effects of SGLT2is. Confirmatory clinical findings were mainly collected in randomised controlled trials (RCTs)/cardiovascular outcome trials (CVOTs) versus placebo (mostly in post hoc analyses and not collected as prespecified endpoints) [16] while real-life retrospective observational studies versus other glucose-lowering agents are scarce in comparison with those that focused on supraventricular arrhythmias [17].

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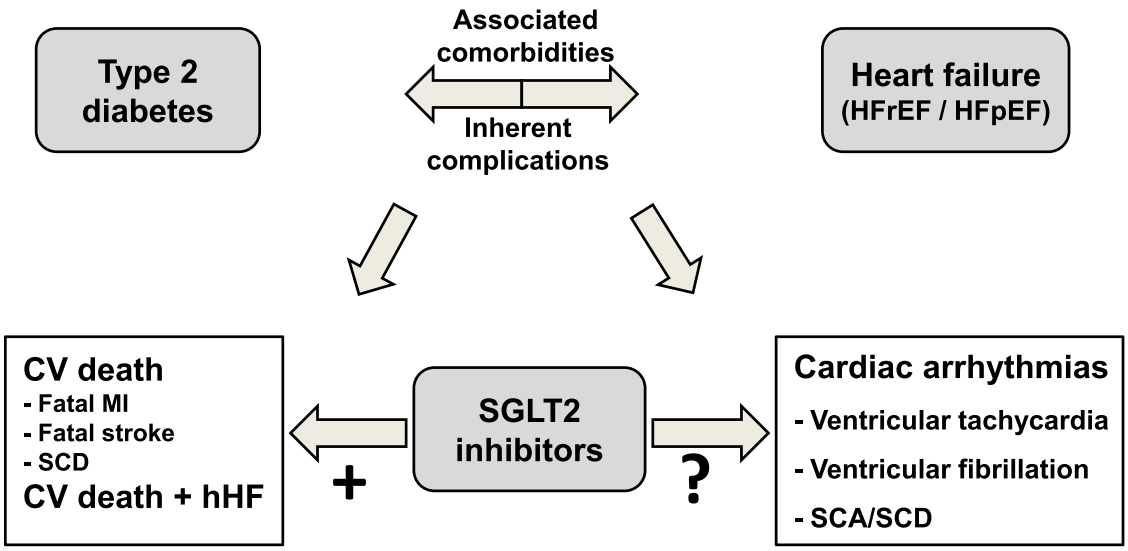

Fig. 1. Type 2 diabetes and heart failure associated with severe ventricular arrhythmias and sudden cardiac arrest/death: potential effects of SGLT2 inhibitors.
CV: cardiovascular. hHF: hospitalisation for heart failure. MACEs: major cardiovascular events. MI: myocardial infarction. HFpEF: heart failure with preserved ejection fraction. HFrEF: heart failure with reduced ejection fraction. SCA: sudden cardiac arrest. SCD: sudden cardiac death. SGLT2is: sodium-glucose cotransporter 2 inhibitors.

Animal data

Experimental findings in a rat model showed that pretreatment with empagliflozin protects the heart from subsequent severe lethal VA induced by myocardial ischaemia and reperfusion injury [18]. In an ex-vivo model of heart global ischaemia-reperfusion in rabbits, empagliflozin treatment reduced VA vulnerability and mitigated contractile dysfunction [19]. Empagliflozin significantly attenuates QTc prolongation in rats due to sotalol, a beta-blocker belonging to a class 3 antiarrhythmic drug known to prolong QT interval and increase the risk of torsade de pointe, a malignant arrhythmia. This finding suggests that the SGLT2i could interfere with potassium channels [20].

There is strong evidence that the induction of late-I_{Na} is involved in the aetiology of HF and arrhythmias [21]. Experimental results provided evidence that late-I_{Na} may be an important molecular target in the heart for SGLT2is (as shown for empagliflozin). These findings suggested a plausible molecular mechanism by which SGLT2is are associated with a robust protection against HF and also have antiarrhythmic effects leading to a reduction in SCD [22].

Animal studies suggested that SGLT2is could ameliorate the deleterious effects of myocardial injury, through various mechanisms including a reduction in sympathetic activity, improved oxidative stress, reduced low-grade inflammation, enhanced tissue oxygenation, autophagy, improved heart energy metabolism, and cardiac remodelling (review in [23–25]).

Human findings

A lengthening of the QT interval duration correlates strongly with the risk of developing torsade de pointes, a form of ventricular tachycardia that can degenerate into ventricular fibrillation and SCD [1]. Dapagliflozin [26] and empagliflozin [27], even at supratherapeutic doses, do not prolong QT interval in thorough QT/QTc studies in healthy subjects.

Clinical studies suggested that SGLT2is can modulate the CV autonomic nervous system, and thereby reduce the risk of cardiac arrhythmias [28–31]. In the EMBODY trial that recruited Japanese patients with T2D and acute myocardial infarction, empagliflozin compared with placebo was associated with greater improvements in indicators of cardiac sympathetic/parasympathetic nerve activity, which are related to the risk of VA [32]. A reduction in sympathetic nervous system activity by SGLT2is may potentially translate into a reduction in arrhythmic risk and SCD [33]. Clinical studies suggested that SGLT2is can modulate the CV autonomic nervous system [28,29,30], and thereby reduce the risk of malignant VA and SCD [15]. Of note however, in a recent meta-analysis of 4 RCTs in a total of 247 subjects with T2D, SGLT2i treatment does not seem to provide any significant beneficial effect on cardiac autonomic neuropathy indices [34].

In a double-blind, crossover, placebo-controlled trial in 19 T2D patients with HF and reduced ejection fraction (HFrEF), a 2-week treatment with dapagliflozin resulted in a significant reduction in ventricular ectopy burden, a finding that suggests an early antiarrhythmic benefit induced by the drug [35].

In a recent case-control study amongst patients with cancer and T2D who were treated with anthracyclines, anti-cancer drugs whose potential cardiotoxicity is well known, SGLT2is were associated with lower rate of cardiac events (HF incidence, HF admissions, new cardiomyopathy, and clinically significant arrhythmias) [36].

Secondary analyses of CVOTs

In EMPA-REG OUTCOME, empagliflozin compared with placebo was associated with a reduction in SCD (38 vs 53 events, 1.1% vs 1.6%) whose majority was most probably arrhythmic in nature [37]. All categories of CV death contributed to the risk reduction with empagliflozin, with the most frequent modes being SCD (29.4%) and presumed CV death (40.1%). In a sensitivity analysis, when presumed CV death was excluded, the reduction in CV death with empagliflozin versus placebo remained statistically significant ($P < 0.001$) [38]. In a post-hoc analysis of DAPA-HF, dapagliflozin compared with placebo reduced the risk of any serious VA, SCA, or SCD event when added to conventional therapy in patients with HFrEF. Of participants assigned to dapagliflozin, 140/2373 patients (5.9%) experienced the composite outcome (time-to-first occurrence of any serious VA, resuscitated SCA, or SCD) compared with 175/2371 patients (7.4%) in the placebo group (HR 0.79, 0.63–0.99, $P = 0.037$), and the effect was consistent across each of the components of the composite outcome [39]. In DECLARE-TIMI 58, SCD vas the primary driver of CV death, accounting for 58% of total events. In a post-hoc analysis, dapagliflozin compared with placebo reduced SCD in T2D patients with HFrEF (5% vs 7.1%), but not in those without HFrEF (1.5 vs 1.4%) [40]. In a pre-

Table 1
Meta-analyses of RCTs that compared the incidence of ventricular arrhythmias in patients treated with a SGLT2i versus controls (mainly treated with a placebo).

References	Arrhythmias	N RCT	N events/ N patients SGLT2i	N events/ N patients Control	Risk ratio	95% CI	P value
Li et al. 2021 [44]	VT	8	76/23,884	87/20,079	0.73	0.53–0.99	NA
Fernandes et al. 2021 [45]	VA	14	109/27,351	111/22,612	0.85	0.66–1.11	0.23
Sfairopoulos et al. 2022 [46]	VA	17	126/29,462	134/25,105	0.84	0.66–1.06	0.14
Yin et al. 2022 [47]	VF	4	22/4523	16/4520	1.40	0.73–2.67	0.31
	VT	5	90/4794	94/4793	0.90	0.44–1.82	0.77
	VF/VT	6	112/4834	110/4833	0.95	0.54–1.68	0.86

CI: confidence interval. NA: not available. RCT: randomised controlled trial.
SGLT2i: sodium-glucose cotransporter 2 inhibitor. VA: ventricular arrhythmia.
VF: ventricular fibrillation. VT: ventricular tachycardia.

specified analysis from the DAPA-CKD devoted to mortality in patients with chronic kidney disease (2152 patients in each treatment group), the number of SCD was quite low: 24 with dapagliflozin versus 27 with placebo), without difference between the two groups (HR 0.89, 0.52–1.55) [41]. No specific data on cardiac arrhythmias and SCD were reported in EMPEROR-Reduced in patients with HFrEF [42]. In EMPEROR-Preserved, a CVOT in patients with HF and preserved ejection fraction (HFpEF), a SCD rate of 3.3% (99 patients) was reported in the empagliflozin group versus 3.8% (114 patients) in the placebo group [43].

Thus, these post-hoc analyses of CVOTs do not allow to draw any definite conclusion because a rather low rate of reported events. However, a trend for less malignant cardiac arrhythmias was generally recorded in SGLT2i-treated patients compared with placebo-treated patients.

Meta-analyses

Several meta-analyses of RCTs provided valuable data on incident VA (Table 1) and SCA/SCD events (Table 2) in patients treated with SGLT2i compared to controls [44–47]. All gave consistent results with a trend for a reduction in VA (ventricular fibrillation or ventricular tachycardia) and SCA/SCD in patients treated with SGLT2is compared to controls (mostly placebo-treated). In most meta-analyses, however, statistical significance was not reached, presumably because the number of VA events was too low. This contrasts with a significant SGLT2i-associated reduction in new-onset atrial fibrillation/flutter episodes, more frequently encountered in patients with T2D, as recently discussed in a recent review [17]. Available meta-analyses mixed RCTs in patients with T2D and in patients with HF, without separating the two types of population. In the meta-analysis by Li et al. [44], subgroup analyses stratifying studies according to baseline condition, presence of atherosclerotic CVD, type of SGLT2i agent, and follow-up duration did not identify a significant between-subgroup heterogeneity for both VA and SCA/SCD events. In the meta-analysis by Fernandes et al. [45], all eligible studies were performed in patients with T2D and only one was dedicated to patients with HF (both with and without diabetes). In the meta-analysis by Sfairopoulos et al. [46], no differences were found in subgroups analyses according to baseline condition (patients with HF or chronic kidney disease), type of comparator (placebo vs active), treatment duration and type of SGLT2 compound. When VA events were split into ventricular tachycardia and ventricular fibrillation, no significant protective effect by SGLT2is was observed in neither arrhythmia. Finally, the meta-analysis by Yin et al. [47] was the only one that clearly distinct the different types of VA events (tachycardia versus fibrillation) (Table 1); however, in contrast to the other three meta-analyses, it did not investigate the effect of SGLT2is on SCA/SCD (Table 2), but demonstrated a clear-cut reduction in supraventricular arrhythmias with SGLT2is.

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Observational studies

In contrast to studies that investigated atrial fibrillation/flutter [17], few observational studies were interested in the risk of VA or SCD with SGLT2 therapy. In a large retrospective study that included patients diagnosed with T2D and controlled hypertension from Taiwan, patients on SGLT2i therapy presented a significant reduction in the incidence of total cardiac arrhythmias compared to SGLT2i non-users (after matched-pairs analysis: HR 0.58, 0.38–0.89, P = 0.013). Unfortunately, this report did not discriminate VA from other arrhythmias such as atrial fibrillation [48].

With a mean follow-up period of about 2 years after stabilized acute myocardial infarction in people with T2D, 3 (4.5%) patients in SGLT2i users (n = 66) versus 22 (16.7%) patients in SGLT2i non-users (n = 132) experienced rehospitalization for acute coronary syndrome, while 1 (1.5%) patient with SGLT2i and 7 (5.3%) patients without SGLT2i suffered SCD. According to the multivariate analysis, the use of SGLT2is (P = 0.039, 95% CI: 0.116–0.947) was an independent predictor of adverse cardiovascular outcomes [49].

Ongoing dedicated studies

The question whether SGLT2is may reduce severe cardiac arrhythmias will be clarified in ongoing prospective studies in patients treated with an implantable cardioverter-defibrillator or cardiac resynchronization therapy system, devices that can monitor these VA episodes [14]. The Japanese EMPA-ICD trial will investigate the

Table 2
Meta-analyses of RCTs that compared the incidence of sudden cardiac arrest and sudden cardiac death in patients treated with a SGLT2i versus controls (mainly treated with a placebo).

References	Arrhythmias	N RCT	N events/ N patients SGLT2i	N events/N patients Control	Risk ratio	95% CI	P value
Li et al. 2021 [44]	SCA	7	78/24,463	79/20,288	0.83	0.61–1.14	NA
Fernandes et al. 2021 [45]	SCD	19	97/24,918	90/20,565	0.72	0.54–0.97	0.03
Sfairopoulos et al. 2022 [46]	SCD	9	48/26,318	57/22,411	0.74	0.50–1.08	0.12

CI: confidence interval. NA: not available. RCT: randomised controlled trial.
SCA: sudden cardiac arrest. SCD: sudden cardiac death.
SGLT2i: sodium-glucose cotransporter 2 inhibitor.

impact of empagliflozin on the burden of VA in such patients with T2D [50]. The ERASe trial, an Austrian multicentre study, will investigate the effect of ertugliflozin on the risk of VA in HF patients treated with such protective devices irrespective of the diabetes status [51].

Discussion

Data regarding the potential effects of glucose-lowering agents, including SGLT2is, on malignant cardiac arrhythmias in patients with T2D are disparate and generally of poor quality [16]. Overall, they are less numerous compared to those devoted to atrial fibrillation/flutter [17]. Of note, cardiac arrhythmias were not pre-specified endpoints in all RCTs and CVOTs. They were only registered as adverse events by the investigators and generally not adjudicated by an independent expert committee. Furthermore, in CVOTs, CV death was included in a composite CV enpoint, MACE-3-points that combined CV death with nonfatal myocardial infarction and nonfatal stroke. Of note, CV death is a composite endpoint it and of itself as it may include acute myocardial infarction, fatal stroke, HF and SCD [52]. Fortunately aggregates of the composite CV death may be specified as secondary endpoints in CVOTs, at least as supplementary material. However, their individual elements were not similarly reported in all studies and details about cardiac death, especially severe cardiac arrhythmias (VA) and SCD were generally not reported in original publications. Obviously, this lack of clarity and reporting heterogeneity render interpretation of data more difficult. Thus, a call for more complete reporting of CV death in CVOTs has been addressed [52]. In observational studies, the quality of collected data raises even more concern because of the retrospective nature of these studies and possible recruitment biases [53]. Overall, data regarding the impact of SGLT2is on VA or SCD are less numerous than those focusing on atrial fibrillation/flutter [17], not only in RCTs but mainly in observational studies, presumably because of difficulties to collect valid data in real-life conditions of less common adverse events.

With all these limitations in mind, overall most results issued from CVOTs, meta-analyses of RCTs and observational studies showed at least a trend for a reduction in incident VA and/or SCA/SCD events in patients treated with SGLT2is compared with those treated with placebo or other glucose-lowering agents. Statistical significance was not reached in most reports, presumably because of a too low rate of these severe events. SGLT2is may exert numerous effects that could contribute to improve CV prognosis in general and reduce the risk of severe cardiac arrhythmias in particular [14,15,25]. However, in recent years, the focus was mainly put on protection against HF rather than on antiarrhythmic properties [54]. Given the effects of SGLT2is on cardiac remodelling [55] and the remarkable protective effect of SGLT2is against HF [56], on the one hand, and the closed relationship between HF and an increased risk of severe cardiac arrhythmias, including SCD [8–10], on the other hand, one may hypothesize that this pharmacological class would exert a stronger antiarrhythmic effect among T2D subpopulations with rather than without HF [24,57]. In a post-hoc analysis of DECLARE-TIMI 58, dapagliflozin compared with placebo reduced SCD in T2D patients with HFrEF, but not in those without HFrEF [40]. However, available data from CVOTs that specifically recruited patients with HF (both HFrEF and HFpEF) are insufficient to draw any conclusion yet [39,42,43].

A detailed analysis about the underlying mechanisms that may explain anti-arrhythmic properties of SGLT2is is beyond the scope of this review but has been extensively discussed in other papers [14,15,25,57,58]. SGLT2is have been shown to exert numerous pleiotropic effects [13], some of them being capable to reduce the risk of arrhythmias in the heart of patients with diabetes, CVD and HF, for instance reductions in sympathetic activity, oxidative stress, low-grade inflammation; improved intracellular ionic homoeostasis, cardiac remodelling, . . . [14,15,25,58].

Conclusion

Patients with T2D as well as patients with HF are exposed to a higher risk of malignant cardiac arrhythmias, which may contribute to increase cardiac death. Data on the effects of SGLT2is on VA/SCD are rather scarce in the international literature and somewhat heterogeneous. Discrepancies may be due to the insufficient number of these VA/SCD events in the different studies, including in meta-analyses, which is likely to bias conclusions. Caution is required before drawing any definite conclusion because none of these randomised controlled trials or observational studies were specifically conducted to test the hypothesis that glucose-lowering agents such as SGLT2is could reduce the risk of malignant cardiac arrhythmias. Thus, further dedicated studies are needed to conclude about the potential impact of SGLT2is agents on VA and SCD. Nevertheless, overall, available evidence suggests that SGLT2is could reduce the risk of malignant cardiac arrhythmias. However, the contribution of these cardiac events, including SCD, on the composite endpoint “cardiovascular death” remains largely unknown and should be better investigated in further studies or post-hoc analyses of already published CVOTs. Finally, no consistent pathway or mechanism has been clearly identified to explain the antiarrhythmic properties of SGLT2is, which most probably result from a variety of intra-cardiac changes secondary to the use of this unique pharmacological class.

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Significance of acronyms used for randomised controlled trials

- DAPA-CKD: A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease
- DAPA-HF**:** Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure
- DECLARE-TIMI 58: Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events
- EMPA-REG OUTCOME **:** EMPAgliflozin cardiovascular OUTCOME events in type 2 diabetes mellitus patients
- EMPEROR-Preserved: EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction
- EMPEROR-Reduced : EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction
- ERASe: Ertugliflozin to Reduce Arrhythmic Burden in ICD/CRT patientS

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