International Journal of Arrhythmia

REVIEW

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# SGLT2 inhibitors and the cardiac rhythm: unraveling the connections

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**Abstract**

Sodium-glucose co-transporter 2 inhibitors (SGLT2is), primarily used for managing type 2 diabetes mellitus, have recently gained attention for their potential cardiovascular benefits. This review explores the emerging evidence surrounding the association between SGLT2is and arrhythmias. Initial studies and large cardiovascular outcome trials have indicated that SGLT2is may reduce major adverse cardiovascular events, including HFHs, which inherently suggests a potential anti-arrhythmic role. Mechanistic insights propose that SGLT2is may exert their anti-arrhythmic effects by modulating cardiac ion channels, thereby impacting cardiac action potentials. Direct clinical evidence linking SGLT2 is to reduced arrhythmias remains limited but evolving. Potential implications of these findings could revolutionize treatment approaches, expanding the indications for SGLT2is prescriptions beyond the diabetic population and possibly providing a novel therapeutic avenue for patients at risk of arrhythmias. However, the exact mechanism, efficacy, and safety profile need further investigation. While various post-hoc and meta-analyses shed light on the topic, prospective, randomized controlled trials are warranted to explicate the potential of SGLT2is in arrhythmia management, their place in clinical guidelines, and their overall impact on patient outcomes.

## Background

Sodium-glucose co-transporter-2 inhibitors (SGLT2is), commonly referred to as the "flozin" group of drugs, were initially approved by the U.S. Food and Drug Administration (FDA) for managing hyperglycemia in patients with type 2 diabetes mellitus (T2DM). They work by blocking SGLT2 transporters in the proximal tubules of the kidneys. This inhibition decreases glucose reabsorption, increasing glucose excretion in the urine and consequently lowering blood glucose levels. The first SGLT2i to gain FDA approval was canagliflozin in March 2013 [1]. This followed the approval of dapagliflozin in January 2014 [2] and empagliflozin in August 2014 [3]. These medications are indicated as pharmacological adjuncts to exercise and diet to improve blood sugar management in adults with T2DM.

Since their initial approval for T2DM, some SGLT2is have garnered additional indications related to heart failure and kidney disease. The FDA has approved dapagliflozin and empagliflozin for adults with heart failure with reduced ejection fraction (HFrEF), irrespective of the presence of T2DM to be added to standard pharmacological therapy. This approval was based on the outcomes of the DAPA-HF [4] and EMPEROR-reduced [5] trials which demonstrated that these drugs could considerably lower the risks of cardiovascular death and heart failure hospitalizations (HFH) in these patients. In 2020, canagliflozin received approval for treating diabetic kidney disease, stemming from the CREDENCE trial's results [6]. The CANVAS trial [7] also revealed that it could reduce the incidence of major adverse cardiovascular events (MACE), such as heart attacks, strokes, or deaths due to cardiovascular causes in T2DM adults with known cardiovascular disease. Following the EMPEROR-preserved trial results in 2022 [8], empagliflozin was

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approved for the adjunctive treatment of heart failure with preserved ejection fraction (HFpEF). Additionally, based on the DELIVER trial outcomes [9], the European Union approved dapagliflozin for treating HFpEF.

These extended indications underscore the multi-system advantages of SGLT2is, which extend beyond their initially studied antihyperglycemic effects. Other notable outcomes, like a decrease in sudden cardiac death (SCD), emerged from these trials [10], which prompted more in-depth investigations into the SGLT2is effects on ventricular arrhythmias (VAs), a primary cause of SCD in HF patients [11]. Subsequent post-hoc analyses of datasets from these prospective trials have indicated a statistically significant association with arrhythmia incidence when using SGLT2is. This review begins by examining the independent arrhythmia risks in HF and T2DM, laying a foundation to help understand SGLT2is' therapeutic implications for arrhythmias. Finally, we conclude by compiling evidence drawn from contemporary scientific literature on this topic.

## Understanding the increased risk of arrhythmias with T2DM

Numerous research studies have found a robust association between T2DM and atrial tachyarrhythmias. A meta-analysis conducted by Huxley et al. in 2011, which incorporated various cohort studies, deduced that T2DM correlated with a 40% increased risk of atrial fibrillation (AF) [12]. Similarly, the Rotterdam study found that diabetes correlated with a 1.4-fold surge in the risk of AF, despite accounting for other risk determinants like age, hypertension, and heart failure [13]. The prospective Danish Diet, Cancer, and Health study also recorded a 34% escalated risk of AF among diabetes patients, even after adjustments for other recognized risk contributors [14].

Various studies also discuss the association of T2DM with VAs. One such study by Weidner et al. investigated the relationship between T2DM patients and mortality secondary to ventricular tachyarrhythmias [15] and found that T2DM was independently correlated with a heightened risk of all-cause mortality in patients with ventricular tachyarrhythmias, unexplained by other risk factors such as age, sex, or other comorbidities. Predominant mechanisms deal with cardiac fibrosis, which is a known contributor to the arrhythmogenic substrate in both atrial and VAs. Studies have shown that diabetes can induce miR-29a transcription, leading to enhanced cardiac fibrosis and specifically increased vulnerability to VAs [16], along with QT interval changes [17], and alteration in levels and activities of calcium and potassium channels, increasing the susceptibility to VAs [18] (Fig. 1).

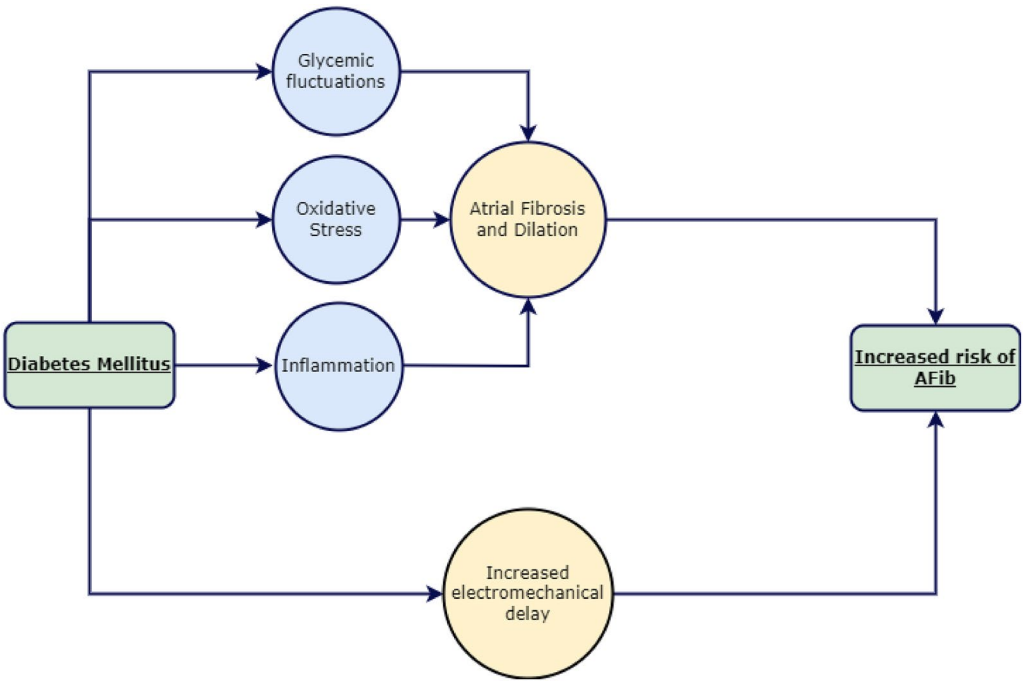


**Fig. 1** Association between T2DM and elevated risk of atrial fibrillation

## Understanding the increased risk of arrhythmias with HF

Patients with heart failure suffer from concomitant development of arrhythmias [19]. HFH are rising, and a significant number of these cases might be connected to supraventricular arrhythmias (SVAs), including AF or other SVAs [20]. An association between these disease processes has been suspected since results from the Framingham Heart Study, where 26% of patients who were diagnosed with either new onset HF or AF, developed concomitant AF and HF [21]. AF alone raises the risk of death and stroke; and HF patients often experience thromboembolism complications and undetected AF [22], which often are the first manifestation of AF in these patients [23]. Additionally, bradyarrhythmia conditions such as sinus bradycardia, tachy-brady syndrome, and atrioventricular blocks are also frequent in HF patients [11, 24].

In HF patients, SCD is a predominant cause of fatality and is commonly related to heart rhythm disturbances, mainly VAs [11]. A study by Stevenson et al. (1983) found that patients with advanced HF had a high incidence of VAs, and these were linked to an increased risk of SCD [25] (Fig. 2).

Electrical remodeling, myocardial fibrosis, ischemic arrhythmogenic foci, dysregulation of intracardiac calcium, and neurohormonal activation through elevated levels of renin, angiotensin, and aldosterone are the primarily proposed mechanisms behind the increased risk of arrhythmias in HF patients [26] (Fig. 3).

## SGLT2 inhibitors: What are they, and how do they work?

The SGLT2 transporters belong to a broad group of membrane proteins in charge of the transport of various solutes, driven by a sodium gradient. Two primary SGLTs exist within the human body: SGLT1 and SGLT2. The SGLT2 symporter predominantly resides in kidney tissues, while SGLT1 has a broader distribution, appearing in the kidneys, small bowel, heart, and skeletal muscles.

In the kidney, both SGLT1 and SGLT2 play pivotal roles in sodium and glucose reabsorption within the proximal convoluted tubules. Their fundamental functional role is the complete reabsorption of filtered glucose, which prevents energy wastage through glycosuria. SGLT2is work by blocking these channels, resulting in glucose excretion via urine and consequently reduced serum glucose levels. This action enhances HbA1c levels, mitigating both the macrovascular and microvascular complications linked to T2DM [27].

Alongside glycosuria, SGLT2 inhibition instigates natriuresis, leading to a negative salt and water balance.

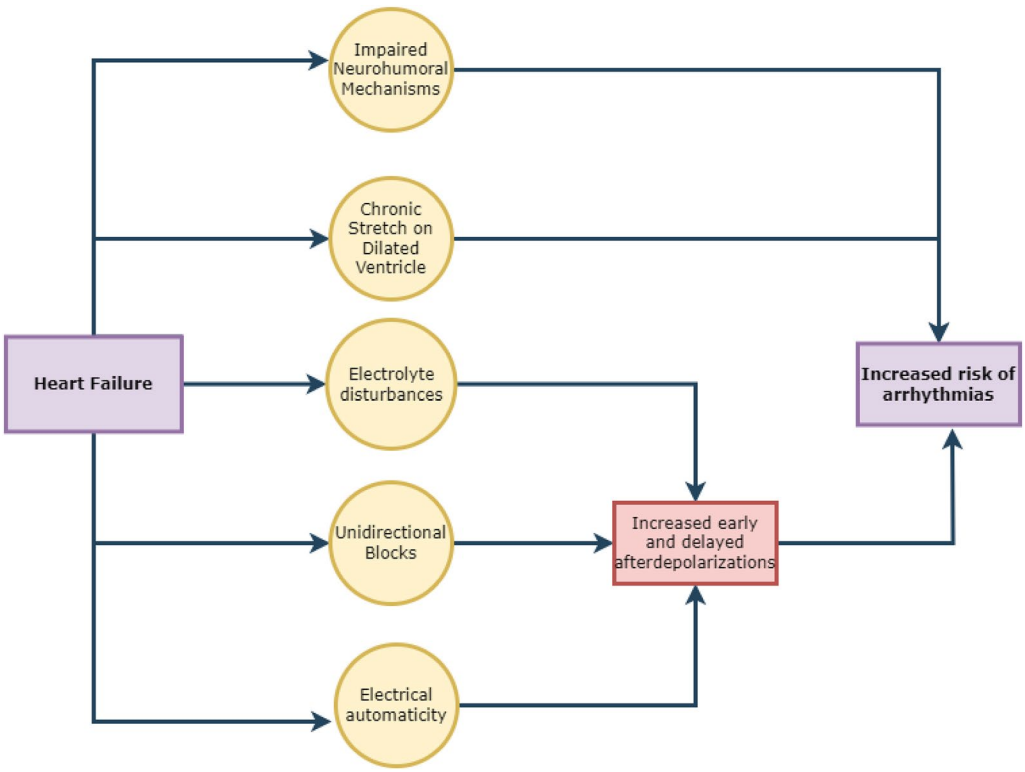


**Fig. 2** Association between HF and elevated risk of arrhythmias

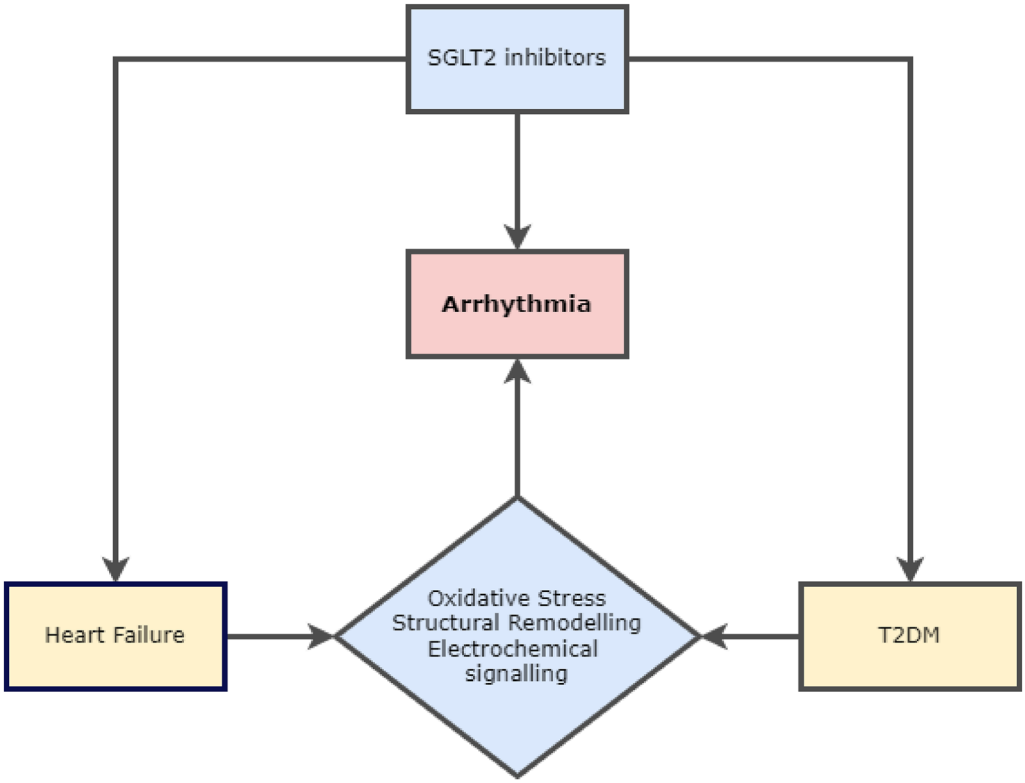


**Fig. 3** Relationship between T2DM, HF and arrhythmias

This process contributes to improved blood pressure and counteracts the tubuloglomerular feedback stimulation [28]. Clinical studies involving patients, both with, and without diabetes have also noted substantial reductions in albuminuria levels [29]. SGLT2is are recommended for diabetic individuals aiming for weight loss, given their role in promoting caloric loss associated with diabetes [30]. Additionally, these inhibitors enhance the release of hypoxia-inducible factors (HIF 1 and 2) from the juxtaglomerular apparatus and alleviate anemia through EPO release [31].

Natriuresis/diuresis, inducing ketone bodies and fatty acids utilization, reducing hyperinsulinemia, anti-inflammatory and anti-fibrotic effects, and reduction in epicardial fat appear to be the primary mechanisms that mediate the cardiovascular protective effects demonstrated in the recent studies on both HFrEF and HFpEF patients [32] (Fig. 4). However, a more detailed scrutiny is needed to understand the proposed anti-arrhythmic properties of these drugs.

## Proposed mechanisms for reduction of arrhythmias by SGLT2is

There are two main theories regarding the mechanisms of anti-arrhythmic properties of SGTL2is; the first being amelioration of mechanical factors, through a reduction in blood pressure (that reduces myocardial strain through reduced afterload) and reduced venous return, preventing excess dilation and stretch of the myocardium; both of which collectively reduce myocardial remodeling [33]. The second theory pertains to changes in the ionic balance within the myocardial cellular environment. Studies indicate that SGLT2is might indirectly influence arrhythmias by enhancing cardiac function and mitigating inflammation and oxidative stress, both of which are potential precursors to arrhythmias. Diminished activation of the cardiac NLRP3 (nucleotide-binding domain-like receptor protein 3) inflammasome [34, 35] appears to be a well-studied mechanism, that improves myocardial functioning by reducing inflammation otherwise associated with T2DM, thus preventing inflammation and

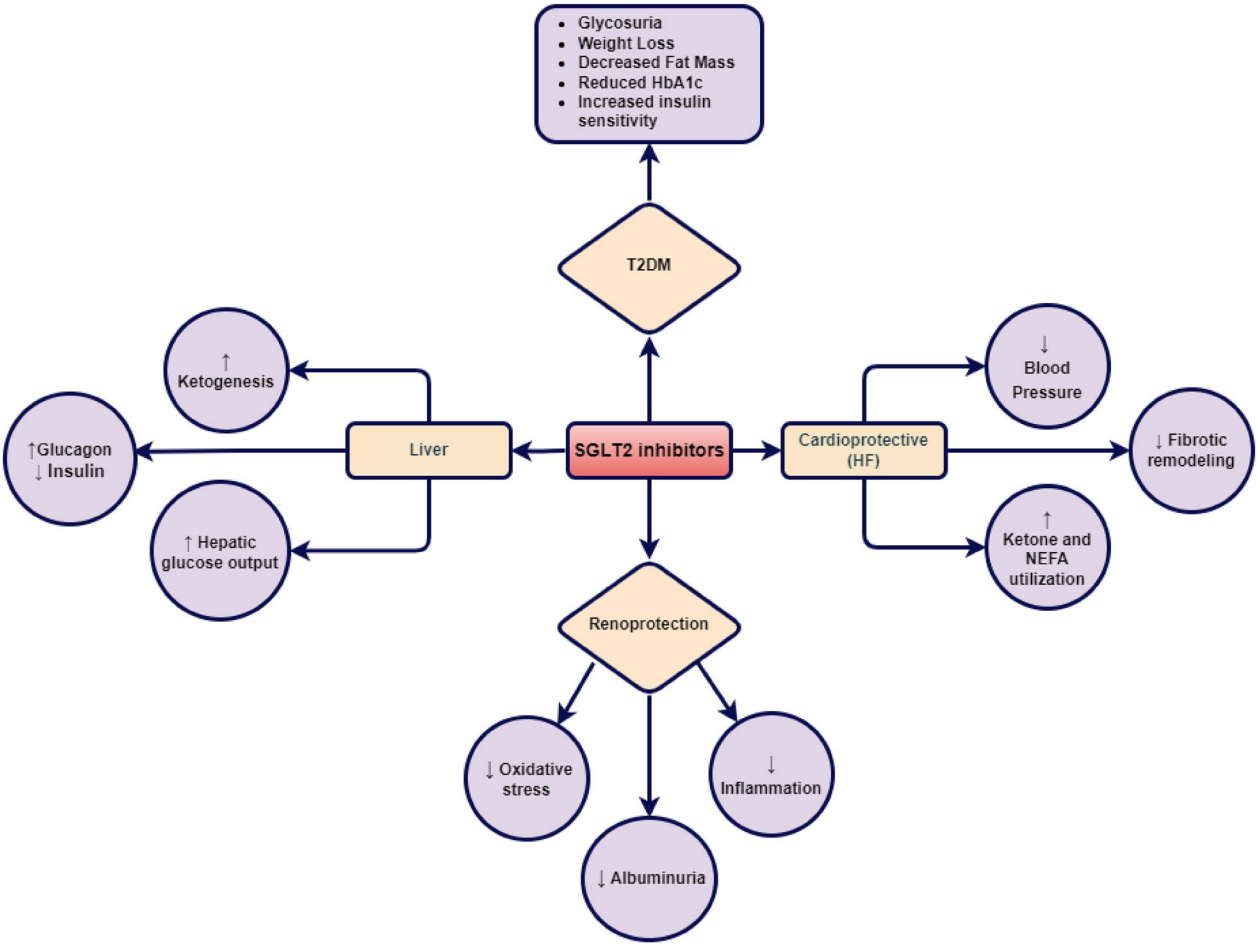


**Fig. 4** Multisystemic benefits of SGLT2 inhibitors: beyond glycemic control

fibrosis. Moreover, calcium ionophores seemed to blunt this effect, which hints at a dependence on intracardiac calcium levels. A study employing artificial intelligence determined that empagliflozin could potentially reverse 59% of protein alterations associated with HFpEF [36]. The main mechanism was via inhibition of the NHE1 ($Na^+/H^+$ exchanger 1), rather than SGLT2 itself. Jiang et al. also found similar findings in myocardial infarction (MI) mice models where empagliflozin was found to decrease cardiac fibrosis, and improve heart function and survival [37]. This action primarily affects cardiomyocyte oxidative stress and influences factors like cardiomyocyte stiffness and systemic inflammation, through concomitant changes in cytoplasmic and mitochondrial calcium levels that appeared to be the trigger for myocyte death. Alterations in the sympathetic nervous system through reduction of TNF-α and elevation of IL-1β levels by dapagliflozin have also been demonstrated in mice studies, which could be attributed to both cardio and renal protective effects of the class of drugs [38]; which has also been concluded subsequently by Shimizu et al. [39] from the EMBODY trial data. Another animal study with mice on empagliflozin concluded that the drug prevented left atrial changes in the presence of diabetes mellitus; most possibly through the peroxisome proliferator-activated receptor-c coactivator 1α (PGC-1α)/nuclear respiratory factor-1 (NRF-1)/mitochondrial transcription factor A (Tfam) signaling pathway [40]. This could be a potential mechanism specifically in the prevention of atrial arrhythmias. Lahnwong et al. [41] found that dapagliflozin exerts significant cardio-protection against ischemic reperfusion injury in rats pretreated with dapagliflozin for 4 weeks before induced MI; however, no changes in PGC-1α were noted. They instead observed an increase in Bcl2 gene expression resulting in an anti-apoptotic mechanism. Other notable molecular mechanisms that have been found to play a role in post-MI cardiac remodeling benefits of SGLT2is are the upregulation of STAT3 phosphorylation [42, 43]; increased ERK1/2 phosphorylation [44]; and regulation of cGH1 gene resulting in

increased nitric oxide and decreased free radicals like superoxide and nitro tyrosine through tetrahydrobiopterin [45].

Certain electrochemical mechanisms have also been suggested in the literature. SGLT2is have demonstrated positive effects on electrolyte balance, further reducing arrhythmia susceptibility [46]. Inhibition of the cardiac sodium current's late component [35], and suppression of the sodium–hydrogen exchanger [47] appear to be significant among the studied ionic mechanisms. Modulation of electrical currents through the effects of secretome from epicardial fat has also been shown to be a prospective mechanism [48]. Sotagliflozin, which is an inhibitor of both SGLT1 and SGLT2, has also been shown to reduce arrhythmias in in-vitro cardiomyocytes through a reduction in spontaneous calcium release events; which have been associated with increased arrhythmias in HFpEF [49]. Another proposed mechanism is a modest increase in serum magnesium levels in patients on SGLT2is, observed from analysis of datasets from the SGLT2 HF trials [50], since a decreased magnesium level has been shown to increase sinus node automaticity and affect myocardial excitability, being an essential cofactor in the functioning of the $Na^+/K^+$ ATPase pump [51].

Another mechanism that has gained interest is the SGLT1 distribution in cardiac myocytes, which have been shown to reduce oxidative stress by decreasing ROS through NADPH oxidase expression. SGLT1 has shown high affinity for empagliflozin [52]; while other animal studies have demonstrated that dapagliflozin and canagliflozin exert anti-oxidative properties through an SGLT1 mediated mechanism [53, 54]. This is especially of interest since SGLT1 has been shown to mediate ischemic injury through the upregulation of extracellular signal-regulated kinases (ERKs) causing oxidative stress in mice [55].

The crux of whether the observed benefits are rooted in structural modifications or ionic shifts remains unresolved; or whether mediated through SGLT1 or SGLT2. The effect is likely to be a sequela of the intricate interplay between both the mechanical and electrochemical processes coupled with a collection of multiple subtle effects.

## SGLT2 inhibitors and atrial tachyarrhythmias-evidence from clinical studies

The major cardiovascular trials involving SGLT2is did not primarily focus on AF/AFL events. However, post-hoc analyses of these trials suggest potential anti-arrhythmic effects. Notably, the DECLARE-TIMI 58 trial, as reported by Zelniker et al. [56], highlighted significant anti-arrhythmic effects of dapagliflozin. In contrast, trials like DAPA-HF [57], EMPA-REG [58], and CREDENCE [59] did not report substantial anti-arrhythmic outcomes. Despite this, various meta-analyses using SGLT2is trial data have indicated a statistical association between the use of SGLT2is and a reduction in atrial tachyarrhythmias. It is important to recognize, however, that this evidence is derived from post-hoc observations rather than from prospective studies specifically targeting AF burden as a primary outcome [56, 60–71]. These reveal a reduction in AF or AF/atrial flutter (AFL) composite outcome disease burden. A more detailed tabular representation of these articles, including relevant results, inclusion criteria, and sample sizes, can be found in Table 1.

Interestingly, multiple studies found the most statistical significance with dapagliflozin [60, 62–64, 66, 67, 70]. This is likely attributed to the highest sample size and number of arrhythmic events reported in dapagliflozin trials. Certain studies performed an analysis after excluding the DECLARE TIMI-58 trial data, substantiating that the statistical significance was indeed due to the larger sample size, as the relationship vanished once this study data was removed [60, 62]. In Zheng et al.'s analysis [66], canagliflozin was a close second in terms of significance, but it didn't reach statistical levels. Ong et al. found a significant association only in patients on Dapagliflozin who had T2DM and CKD and were followed up for over a year [64]. Contrastingly, Sfairopoulous et al. demonstrated statistical significance in empagliflozin, suggesting that the effect is not solely due to sample size disparity, even though their meta-analysis included more patients in the dapagliflozin group [70]. Chen et al. [69] focused on the link between SGLT2is and new-onset arrhythmias; where analysis revealed a benefit that was most pronounced in all-cause mortality but also significant in reducing the events of AF, SVAs, and VAs.

Li et al. [63] compared the anti-arrhythmic effects of SGLT2is and GLP-1 (Glucagon-like peptide-1) agonists. They concluded a significant relationship with dapagliflozin, while dulaglutide was a close second but without statistical significance. Nevertheless, when comparing all SGLT2is and GLP-1 agonists holistically, no significant difference between the two groups was found; even though Bonora et al. [72] concluded reduced AF-related adverse event reporting with SGLT2is compared to other anti-diabetic drugs.

Extrapolating the DECLARE TIMI-58 trial data, Zelniker et al. [56] found that similar statistical significance was achieved on removing the patients who reported a 19% decrease in AF/AFL events within 2 weeks of HFH, and a 23% decrease in total AF/AFL events. This was also the case in patients who did not have any history of HFH or MI, which led them to conclude that the anti-arrhythmic effect of dapagliflozin as observed in their analyses, was independent of the cardiovascular mortality

**Table 1** Summary of study results on the association between SGLT2 inhibitors (SGLT2i) and atrial arrhythmias

| Study name | SGLT2i | Year | Number of patients | Inclusion criteria | Findings |
|---|---|---|---|---|---|
| Fatima et al. [60] | Multiple (Meta analysis) | 2023 | 111,773 | All RCTs that evaluated SGLT2is against placebo or another medication | Decrease in AF episodes when SGLT2is are administered as a standalone treatment, with a more pronounced effect in T2DM patients |
| Li HL et al. [61] | Multiple (Meta analysis) | 2021 | 52,115 | RCTs involving patients with T2DM, chronic kidney disease (CKD), or HF comparing SGLT2i to a placebo | SGLT2is were linked to a reduced risk of AF, AF/AFL and embolic stroke |
| Li Daobo et al. [62] | Multiple (Meta analysis) | 2021 | 66,685 | RCTs that compare SGLT2i against a corresponding placebo and report on AF/AFL results | Only dapagliflozin showed a significant decrease in AF/AFL, while other SGLT2is did not |
| Li Wen Jie et al. [63] | Multiple (Meta analysis) | 2022 | 85,701 | RCTs that assesses SGLT2is against GLP-1 receptor agonists (GLP-1RAs), or compare either to placebo in patients with T2DM | Relative to a placebo, both SGLT2is and GLP-1RAs decreased the likelihood of AF/AFL. Among the SGLT2is, only dapagliflozin showed a significant reduction in AF/AFL |
| Ong et al. [64] | Multiple (Meta analysis) | 2022 | 35,702 | RCTs with a placebo control that examine the results of stroke and/or AF in patients receiving SGLT2is | Patients taking SGLT2is showed a reduced likelihood of AF relative to those on placebo. This significant association persisted in studies that had a follow-up period exceeding 1 year, particularly in those that used dapagliflozin |
| Pandey et al. [65] | Multiple (Meta analysis) | 2021 | 75,279 | RCTs assessing SGLT2is or dual SGLT1/2 inhibitors | Reduction in total AF events with SGLT inhibitors |
| Zheng et al. [66] | Multiple (Meta analysis) | 2022 | 63,604 | Patients who were exposed to SGLT2is and had their AF risks documented were included | Treatment with SGLT2is was linked to a significant decrease (18%) in the likelihood of new-onset AF compared to the control; the effect was most pronounced with dapagliflozin |
| Fernandes et al. [67] | Multiple (Meta analysis) | 2021 | 63,166 | Randomized and double-blind design; SGLT2i and presence of a control group with diagnosed T2DM, HF, or both; and mandated follow-up of 24 weeks | Therapy using SGLT2i was linked to a notable decrease in the likelihood of developing atrial arrhythmias |
| Liao et al. [68] | Multiple (Meta analysis) | 2022 | 33,124 SGLT2is and 26,568 controls | RCTs that contrast any of the SGLT2is, GLP1RAs, or DPP4is against a placebo | Compared to placebos, SGLT2is were linked to reduced incidences of AF and bradycardia events |
| Chen et al. [69] | Empagliflozin and dapagliflozin | 2020 | 79,150 SGLT2is and 79,150 controls | Patients above 20 years of age taking SGLT2is and diagnosed with T2DM | The group treated with SGLT2is had a reduced likelihood of all-cause death and the development of new arrhythmias |
| Zelniker et al. [56] | Dapagliflozin (DECLARE-TIMI 58) | 2020 | 17,160 | Patients taking SGLT2is with T2DM and ASCVD risk factors or known ASCVD | Dapagliflozin decreased the likelihood of AF/AFL occurrences by 19% |
| Sfairopoulous et al. [70] | Multiple (Meta analysis) | 2023 | 9467 | Adult patients with HFrEF which compared SGLT2i with placebo arm | Reduction in AF risk; AF/AFL reduction. Empagliflozin was found to have a significant association |

**Table 1** (continued)

| Study name | SGLT2i | Year | Number of patients | Inclusion criteria | Findings |
|---|---|---|---|---|---|
| Yin et al. [71] | Multiple (Meta analysis) | 2022 | 10,344 | RCTs with HF with SGLT2i vs. placebo arm. AF, AF/AFL outcomes of interest | SGLT2i reduced the incidence of AF by 37% and AF/AFL by 34 |

benefits of the drug. One noteworthy prospective study conducted by Kishima et al. [73] distributed patients into tofogliflozin vs. anagliptin groups. The main outcome was an AF recurrence up to 1-year post-catheter ablation, and a significant reduction in AF recurrence was observed in patients taking tofogliflozin, irrespective of blood glucose levels. While the study had a sample size of 70 patients, it is the only prospective study we came across involving SGLT2is, that looks at the occurrence of AF as a primary outcome. There is no evidence that suggests that the anti-arrhythmic benefit of SGLT2is is dependent on the T2DM disease severity, especially since the anti-arrhythmic benefit observed was irrespective of the blood glucose levels.

Despite the encouraging evidence suggesting the anti-arrhythmic benefits of SGLT2is, several analyses present contradicting evidence [59, 74–76]. For instance, Ouyang et al. [75] did not find a statistically significant association between AF and SGLT2is, despite a large sample size in their analysis. Surprisingly, while analyzing the EMPA-REG outcome trial data, Böhm et al. [58] found an increased incidence of new-onset AF in patients on empagliflozin, although their sample contained less than 10% of patients with HF and lacked baseline data on patients' arrhythmic status.

The observed quantitative reduction in arrhythmia burden is likely a class effect of SGLT2 inhibitors, as demonstrated in the meta-analysis by Fernandes et al. This analysis, encompassing canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, reported a 19% reduction in atrial arrhythmia incidence [67]. The comparable sample sizes across each drug group further support the likelihood of a class-wide effect rather than an effect specific to any single agent. Recurrent AF after catheter ablation, and decreased rates of cardioversion or redo ablation [77] was also found to be class-specific, however the only prospective study that measures this outcome was performed with tofogliflozin [73, 78]. The observed reduction in AF/AFL-related complications with canagliflozin might be attributed to a drug-specific effect [76]. Nevertheless, further studies are warranted, particularly with other SGLT2is, where such outcomes are the primary endpoint.

## SGLT2 inhibitors and ventricular tachyarrhythmias and SCD-evidence from clinical studies

While multiple studies have found a significant association between atrial arrhythmias and SGLT2is, there seem to be fewer studies on VAs. It would be logical to think that SGLT2is, being proven to prevent ventricular remodeling, would significantly decrease the disease burden of VAs; however, the evidence appears to be inconsistent.

As with the atrial arrhythmias section, a concise tabular format of the relevant information of the studies can be found in Table 2. Hang Long Li conducted a robust meta-analysis that looked at outcomes including both atrial and VAs [61]. Along with a significant reduction in AF disease burden (as discussed in the previous section), the authors also found a 27% risk reduction in ventricular tachycardia in patients on SGLT2is, compared to placebo: including patients with T2DM, CKD, and HF.

Curtain et al.'s research, drawing data from the DAPA-HF trial, showed that the addition of dapagliflozin to conventional HF medications resulted in a 1.5% decrease in the combined event of VAs, resuscitated cardiac arrest, or SCD compared to those receiving a placebo [10]. This effect was even more pronounced in patients with NT pro-BNP levels below the median, suggesting potential enhanced benefits in the early stages of HFrEF. Fernandes et al. found decreased SCD rates in patients on SGLT2is, but no association with VA events. Notably, there were very few reported VA events in the study population, which significantly reduced the power of the analysis. This, however, is backed by an analysis by Oates et al. who considered SCD as a primary outcome and found similar findings [74]. Interestingly, when the patients were stratified on Left Ventricular Ejection Fraction (LVEF) < 40%, the significance disappeared. The authors opine that this could be due to the low duration of follow-up. One important point to consider is that very few patients in these studies had a Cardiovascular Implantable Electronic Device, which may have led to substantial underreporting of arrhythmic events. Yin et al. also reported no significant association between ventricular fibrillation or ventricular tachycardia (VT) and SGLT2is, even though they identified a significant association with AF [71]. Hence, reduction in incident VAs and SCD events appear to be common class effects as evidenced by meta-analysis including multiple SGLT2is [61, 67].

The evidence, while dearth, much like with AF, appears to be conflicting. The relationship between AF and SGLT2is appears to be better studied with more studies elucidating on the mechanisms. However, von Lewinski et al. [79] are currently conducting a noteworthy prospective study (ERASe trial) on patients with reduced or mid-level EF. These patients have received Implantable Cardioverter Defibrillator + Cardiac Resynchronization Therapy (ICD ± CRT) therapy for over 3 months and have a history of VT. They are being subjected to ertugliflozin and a matching placebo. This trial stands out as the pioneering study examining the effect of ertugliflozin in HF patients with a non-preserved EF who are simultaneously on ICD ± CRT therapy, irrespective of their diabetes condition. Consequently, the ERASe trial might potentially broaden the understanding of the role of SGLT2is

**Table 2** Summary of study results on the association between SGLT2 inhibitors (SGLT2i) and ventricular arrhythmias

| Study name | SGLT2i | Year | Number of patients | Inclusion criteria | Findings |
|---|---|---|---|---|---|
| Li et al. [61] | Multiple (Meta Analysis) | 2021 | 52,115 | RCTs that assigned patients with T2DM, CKD, or HF to either SGLT2is or a placebo | SGLT2i were associated with a 27% risk reduction in VT compared to placebo with highest reduction found for Canagliflozin |
| Curtain et al. [10] | Dapagliflozin (DAPA-HF trial) | 2021 | 4744 | Adults with HF at NYHA functional class II–IV, an LVEF of ≤ 40%, raised NT-proBNP levels and were managed with both drug and device treatments for HFrEF | Patients on Dapagliflozin had reduced risk of VT, Cardiac Arrest or SCD compared to the control group |
| Fernandes et al. [67] | Multiple (Meta Analysis) | 2021 | 63,166 | Randomized and double-blind design; SGLT2i and presence of a control group with diagnosed T2DM, HF, or both; and mandated follow-up of 24 weeks | Treatment with SGLT2is was linked to a significant decrease in the SCD outcome when contrasted with the control |
| Oates et al. [74] | Multiple (Meta Analysis) | 2023 | 10,796 SGLT2is and 10,796 controls | Patients with HF on SGLT2is and placebo | The use of SGLT2i therapy significantly reduced the likelihood of SCD |
| von Lewinski et al. [79] | Ertugliflozin | 2022 | 402 | Patients with either reduced or mid-level EF, who had undergone ICD ± CRT treatment for over 3 months and had a history of VT were randomized in a 1:1 manner to either ertugliflozin or its corresponding placebo | This will be the inaugural trial evaluating ertugliflozin in HFrEF patients undergoing ICD ± CRT treatment, irrespective of their diabetes condition |

in enhancing cardiac remodeling, encompassing the decrease in VA load.

A salient question that emerges from this line of inquiry pertains to the differential outcomes among T2DM patients as compared to non-diabetic patients who are diagnosed with arrhythmias. Can we delineate a distinct therapeutic response based on the diabetic status of the patient? Furthermore, the distinction between atrial and VAs remains to be clarified: Do SGLT2is exhibit a preference in terms of their therapeutic efficacy toward one over the other?

## Clinical implications

Should a significant association be confirmed between SGLT2is and decreased incidence of arrhythmias, it could lead to improved clinical outcomes for a broad spectrum of patients. Arrhythmias, particularly VAs, have been definitively linked to increased morbidity and mortality, including SCD. Reduction in these arrhythmic events could lead to prolonged life expectancy and improved quality of life. SGLT2is might be combined with other anti-arrhythmic medications, enhancing their efficacy or even allowing dose reductions of other drugs, potentially minimizing side effects. It would also be beneficial in HF patients since there is already a clear association between HF and arrhythmias, especially due to its role in preventing cardiac remodeling. Such approval would also necessitate rigorous post-marketing surveillance to monitor for unanticipated adverse effects, especially when used in a broader population. Patients could have more options in their treatment arsenal, potentially leading to better disease management and improved outcomes. The potential association between SGLT2is and reduced arrhythmia risk offers a promising avenue in cardiovascular medicine. However, as with all medical interventions, the benefits must be weighed against potential risks, and a comprehensive, patient-centered approach should be maintained.

Additionally, certain preliminary studies have alluded to the potential of these inhibitors being particularly efficacious in the early stages of HF. Given this proposition, it becomes imperative to investigate whether their potency is indeed emphasized in the early phases of cardiac dysfunction. Given that SGLT2is have already been integrated into the Guideline-Directed Medical Therapy (GDMT) for HF management [80], it becomes intriguing to extrapolate their efficacy concerning arrhythmic events, particularly when we consider the intricate interplay between T2DM, HF and arrhythmias. If a mortality benefit is established in this overlap, it would further emphasize the potential of SGLT2is in comprehensive cardiac care.

To solidify these potential benefits, well-designed, multi-centric prospective trials are crucial. These should ideally adopt a multi-centric framework, ensuring a wide patient demographic and encompassing varied clinical settings, thereby improving the generalizability and applicability of the findings. Such endeavors would not only explain the pharmacological landscape of arrhythmia management but also guide future therapeutic strategies in cardiovascular care.

## Conclusion

The current literature underscores that SGLT2is mitigate arrhythmic burden and arrhythmia-related adverse events in T2DM and HF patients. Consistent atrial and ventricular arrhythmia incidence reduction has been observed, and mostly appears to be an effect common to the class of drug. Numerous ongoing research endeavors are currently delving into the potential role of SGLT2is in the context of arrhythmia management [81–85]. These investigations aim to ascertain not only if SGLT2is indeed play a pivotal role but also to demarcate the precise extent of their influence. The anti-arrhythmic properties of these drugs are believed to stem from enhanced cardiac function, decreased myocardial scarring and improved electrolyte balance. Future investigations should focus on identifying the precise mechanisms through which SGLT2is confer these advantages and examining how diabetes severity influences the reduction of arrhythmias.

**Acknowledgements**
Not applicable.

**Author contributions**
OW conceptualized the study. AP performed the literature review and contributed to writing the first draft of the manuscript. CT contributed to making amendments and creating diagrams and tables. OW and CT helped in reviewing the manuscript and making necessary changes. All authors read and approved the final manuscript.

**Funding**
No funding was received for this study.

**Availability of data and materials**
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

Received: 16 November 2023 Accepted: 8 January 2024
Published online: 23 January 2024

**References**


1. U.S. FDA Approves INVOKANA™ (Canagliflozin) for the Treatment of Adults with Type 2 Diabetes| Johnson & Johnson. Content Lab U.S. https://www.jnj.com/media-center/press-releases/us-fda-approves-invokana-canagliflozin-for-the-treatment-of-adults-with-type-2-diabetes. Accessed 7 Aug 2023.
2. US FDA approves FARXIGA™ tablets for the treatment of adult patients—AstraZeneca. Published January 13, 2014. https://www.astrazeneca.com/media-centre/press-releases/2014/us-fda-approved-farxiga-treatment-type-2-diabetes-patients-13012014.html. Accessed 7 Aug 2023.
3. Commissioner O of the. FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes. FDA. Published March 24, 2020. https://www.fda.gov/news-events/press-announcements/fda-approves-jardiance-reduce-cardiovascular-death-adults-type-2-diabetes. Accessed 7 Aug 2023.
4. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008. https://doi.org/10.1056/NEJMoa1911303.
5. Packer M, Anker SD, Butler J, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction. Circulation. 2021;143(4):326–36. https://doi.org/10.1161/CIRCULATIONAHA.120.051783.
6. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295–306. https://doi.org/10.1056/NEJMoa1811744.
7. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57. https://doi.org/10.1056/NEJMoa1611925.
8. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385(16):1451–61. https://doi.org/10.1056/NEJMoa2107038.
9. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387(12):1089–98. https://doi.org/10.1056/NEJMoa2206286.
10. Curtain JP, Docherty KF, Jhund PS, et al. Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. Eur Heart J. 2021;42(36):3727–38. https://doi.org/10.1093/eurheartj/ehab560.
11. Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. Circulation. 1989;80(6):1675–80. https://doi.org/10.1161/01.cir.80.6.1675.
12. Huxley RR, Filion KB, Konety S, Alonso A. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. Am J Cardiol. 2011;108(1):56–62. https://doi.org/10.1016/j.amjcard.2011.03.004.
13. Heeringa J, van der Kuip DAM, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. 2006;27(8):949–53. https://doi.org/10.1093/eurheartj/ehi825.
14. Lacoppidan SA, Kyrø C, Loft S, et al. Adherence to a healthy nordic food index is associated with a lower risk of type-2 diabetes—the Danish diet. Cancer Health Cohort Study Nutr. 2015;7(10):8633–44. https://doi.org/10.3390/nu7105418.
15. Weidner K, Behnes M, Schupp T, et al. Type 2 diabetes is independently associated with all-cause mortality secondary to ventricular tachyarrhythmias. Cardiovasc Diabetol. 2018;17(1):125. https://doi.org/10.1186/s12933-018-0768-y.
16. Sassi Y, Avramopoulos P, Ramanujam D, et al. Cardiac myocyte miR-29 promotes pathological remodeling of the heart by activating Wnt signaling. Nat Commun. 2017;8:1614. https://doi.org/10.1038/s41467-017-01737-4.
17. Chen-Scarabelli C, Scarabelli TM. Suboptimal glycemic control, independently of QT interval duration, is associated with increased risk of ventricular arrhythmias in a high-risk population. Pac Clin Electrophysiol. 2006;29(1):9–14. https://doi.org/10.1111/j.1540-8159.2006.00298.x.
18. Ozturk N, Uslu S, Ozdemir S. Diabetes-induced changes in cardiac voltage-gated ion channels. World J Diabetes. 2021;12(1):1–18. https://doi.org/10.4239/wjd.v12.i1.1.
19. Aistrup GL, Balke CW, Wasserstrom JA. Arrhythmia triggers in heart failure: the smoking gun of [Ca2+]i dysregulation. Heart Rhythm. 2011;8(11):1804–8. https://doi.org/10.1016/j.hrthm.2011.06.012.
20. Ehrlich JR, Nattel S, Hohnloser SH. Atrial fibrillation and congestive heart failure: specific considerations at the intersection of two common and important cardiac disease sets. J Cardiovasc Electrophysiol. 2002;13(4):399–405. https://doi.org/10.1046/j.1540-8167.2002.00399.x.
21. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation. 2003;107(23):2920–5. https://doi.org/10.1161/01.CIR.0000072767.89944.6E.
22. Olsson LG, Swedberg K, Ducharme A, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. J Am Coll Cardiol. 2006;47(10):1997–2004. https://doi.org/10.1016/j.jacc.2006.01.060.
23. Pozzoli M, Cioffi G, Traversi E, Pinna GD, Cobelli F, Tavazzi L. Predictors of primary atrial fibrillation and concomitant clinical and hemodynamic changes in patients with chronic heart failure: a prospective study in 344 patients with baseline sinus rhythm. J Am Coll Cardiol. 1998;32(1):197–204. https://doi.org/10.1016/s0735-1097(98)00221-6.
24. Cleland JG, Swedberg K, Cohen-Solal A, et al. The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. Eur J Heart Fail. 2000;2(2):123–32. https://doi.org/10.1016/s1388-9842(00)00081-7.
25. Stevenson WG, Stevenson LW, Middlekauff HR, Saxon LA. Sudden death prevention in patients with advanced ventricular dysfunction. Circulation. 1993;88(6):2953–61. https://doi.org/10.1161/01.cir.88.6.2953.
26. Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure. Circulation. 2009;119(18):2516–25. https://doi.org/10.1161/CIRCULATIONAHA.108.821306.
27. Fonseca-Correa JI, Correa-Rotter R. Sodium-glucose cotransporter 2 inhibitors mechanisms of action: a review. Front Med. 2021;8: 777861. https://doi.org/10.3389/fmed.2021.777861.
28. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes Metab. 2013;15(9):853–62. https://doi.org/10.1111/dom.12127.
29. Adachi T, Yasuda K, Okamoto Y, et al. T-1095, a renal Na+-glucose transporter inhibitor, improves hyperglycemia in streptozotocin-induced diabetic rats. Metabolism. 2000;49(8):990–5. https://doi.org/10.1053/meta.2000.7729.
30. Del Prato S, Nauck M, Durán-Garcia S, et al. Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. Diabetes Obes Metab. 2015;17(6):581–90. https://doi.org/10.1111/dom.12459.
31. Vallon V, Rose M, Gerasimova M, et al. Knockout of Na-glucose transporter SGLT2 attenuates hyperglycemia and glomerular hyperfiltration but not kidney growth or injury in diabetes mellitus. Am J Physiol Renal Physiol. 2013;304(2):F156-167. https://doi.org/10.1152/ajprenal.00409.2012.
32. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nat Rev Cardiol. 2020;17(12):761–72. https://doi.org/10.1038/s41569-020-0406-8.
33. Ni L, Yuan C, Chen G, Zhang C, Wu X. SGLT2i: beyond the glucose-lowering effect. Cardiovasc Diabetol. 2020;19:98. https://doi.org/10.1186/s12933-020-01071-y.
34. Byrne NJ, Matsumura N, Maayah ZH, et al. Empagliflozin blunts worsening cardiac dysfunction associated with reduced NLRP3 (nucleotide-binding domain-like receptor protein 3) inflammasome activation in heart failure. Circ Heart Fail. 2020;13(1): e006277. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006277.
35. Philippaert K, Kalyaanamoorthy S, Fatehi M, et al. Cardiac late sodium channel current is a molecular target for the sodium/glucose

cotransporter 2 inhibitor empagliflozin. Circulation. 2021;143(22):2188–204. https://doi.org/10.1161/CIRCULATIONAHA.121.053350.
36. Bayes-Genis A, Iborra-Egea O, Spitaleri G, et al. Decoding empagliflozin's molecular mechanism of action in heart failure with preserved ejection fraction using artificial intelligence. Sci Rep. 2021;11(1):12025. https://doi.org/10.1038/s41598-021-91546-z.
37. Jiang K, Xu Y, Wang D, et al. Cardioprotective mechanism of SGLT2 inhibitor against myocardial infarction is through reduction of autosis. Protein Cell. 2022;13(5):336–59. https://doi.org/10.1007/s13238-020-00809-4.
38. Matthews VB, Elliot RH, Rudnicka C, Hricova J, Herat L, Schlaich MP. Role of the sympathetic nervous system in regulation of the sodium glucose cotransporter 2. J Hypertens. 2017;35(10):2059. https://doi.org/10.1097/HJH.0000000000001434.
39. Shimizu W, Kubota Y, Hoshika Y, et al. Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: the EMBODY trial. Cardiovasc Diabetol. 2020;19(1):148. https://doi.org/10.1186/s12933-020-01127-z.
40. Shao Q, Meng L, Lee S, et al. Empagliflozin, a sodium glucose co-transporter-2 inhibitor, alleviates atrial remodeling and improves mitochondrial function in high-fat diet/streptozotocin-induced diabetic rats. Cardiovasc Diabetol. 2019;18(1):165. https://doi.org/10.1186/s12933-019-0964-4.
41. Lahnwong S, Palee S, Apaijai N, et al. Acute dapagliflozin administration exerts cardioprotective effects in rats with cardiac ischemia/reperfusion injury. Cardiovasc Diabetol. 2020;19(1):91. https://doi.org/10.1186/s12933-020-01066-9.
42. Lee TM, Chang NC, Lin SZ. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. Free Radic Biol Med. 2017;104:298–310. https://doi.org/10.1016/j.freeradbiomed.2017.01.035.
43. Andreadou I, Efentakis P, Balafas E, et al. Empagliflozin limits myocardial infarction in vivo and cell death in vitro: role of STAT3, Mitochondria, and Redox aspects. Front Physiol. 2017;8:1077. https://doi.org/10.3389/fphys.2017.01077.
44. Hu Z, Ju F, Du L, Abbott GW. Empagliflozin protects the heart against ischemia/reperfusion-induced sudden cardiac death. Cardiovasc Diabetol. 2021;20(1):199. https://doi.org/10.1186/s12933-021-01392-6.
45. Asensio Lopez MDC, Lax A, Hernandez Vicente A, et al. Empagliflozin improves post-infarction cardiac remodeling through GTP enzyme cyclohydrolase 1 and irrespective of diabetes status. Sci Rep. 2020;10(1):13553. https://doi.org/10.1038/s41598-020-70454-8.
46. Kolesnik E, Scherr D, Rohrer U, et al. SGLT2 inhibitors and their antiarrhythmic properties. Int J Mol Sci. 2022;23(3):1678. https://doi.org/10.3390/ijms23031678.
47. Uthman L, Baartscheer A, Bleijlevens B, et al. Class effects of SGLT2 inhibitors in mouse cardiomyocytes and hearts: inhibition of $Na^+/H^+$ exchanger, lowering of cytosolic $Na^+$ and vasodilation. Diabetologia. 2018;61(3):722–6. https://doi.org/10.1007/s00125-017-4509-7.
48. Jhuo SJ, Liu IH, Tsai WC, et al. Effects of secretome from fat tissues on ion currents of cardiomyocyte modulated by sodium-glucose transporter 2 inhibitor. Mol Basel Switz. 2020;25(16):3606. https://doi.org/10.3390/molecules25163606.
49. Bode D, Semmler L, Wakula P, et al. Dual SGLT-1 and SGLT-2 inhibition improves left atrial dysfunction in HFpEF. Cardiovasc Diabetol. 2021;20(1):7. https://doi.org/10.1186/s12933-020-01208-z.
50. Tang H, Zhang X, Zhang J, et al. Elevated serum magnesium associated with SGLT2 inhibitor use in type 2 diabetes patients: a meta-analysis of randomised controlled trials. Diabetologia. 2016;59(12):2546–51. https://doi.org/10.1007/s00125-016-4101-6.
51. Khan AM, Lubitz SA, Sullivan LM, et al. Low serum magnesium and the development of atrial fibrillation in the community: the Framingham Heart Study. Circulation. 2013;127(1):33–8. https://doi.org/10.1161/CIRCULATIONAHA.111.082511.
52. Li X, Lu Q, Qiu Y, et al. Direct cardiac actions of the sodium glucose co-transporter 2 inhibitor empagliflozin improve myocardial oxidative phosphorylation and attenuate pressure-overload heart failure. J Am Heart Assoc. 2021;10(6): e018298. https://doi.org/10.1161/JAHA.120.018298.
53. Lee CC, Chen WT, Chen S, Lee TM. Dapagliflozin attenuates arrhythmic vulnerabilities by regulating connexin43 expression via the AMPK pathway in post-infarcted rat hearts. Biochem Pharmacol. 2021;192:114674. https://doi.org/10.1016/j.bcp.2021.114674
54. Kondo H, Akoumianakis I, Badi I, et al. Effects of canagliflozin on human myocardial redox signalling: clinical implications. Eur Heart J. 2021;42(48):4947–60. https://doi.org/10.1093/eurheartj/ehab420.
55. Li Z, Agrawal V, Ramratnam M, et al. Cardiac sodium-dependent glucose cotransporter 1 is a novel mediator of ischaemia/reperfusion injury. Cardiovasc Res. 2019;115(11):1646–58. https://doi.org/10.1093/cvr/cvz037.
56. Zelniker TA, Bonaca MP, Furtado RHM, et al. Effect of dapagliflozin on atrial fibrillation in patients with type 2 diabetes mellitus. Circulation. 2020;141(15):1227–34. https://doi.org/10.1161/CIRCULATIONAHA.119.044183.
57. Butt JH, Docherty KF, Jhund PS, et al. Dapagliflozin and atrial fibrillation in heart failure with reduced ejection fraction: insights from DAPA-HF. Eur J Heart Fail. 2022;24(3):513–25. https://doi.org/10.1002/ejhf.2381.
58. Böhm M, Slawik J, Brueckmann M, et al. Efficacy of empagliflozin on heart failure and renal outcomes in patients with atrial fibrillation: data from the EMPA-REG OUTCOME trial. Eur J Heart Fail. 2020;22(1):126–35. https://doi.org/10.1002/ejhf.1663.
59. Zhou Z, Jardine MJ, Li Q, et al. Effect of SGLT2 inhibitors on stroke and atrial fibrillation in diabetic kidney disease: results from the CREDENCE trial and meta-analysis. Stroke. 2021;52(5):1545–56. https://doi.org/10.1161/STROKEAHA.120.031623.
60. Fatima K, Suri A, Rija A, et al. The effect of sodium-glucose co-transporter 2 inhibitors on stroke and atrial fibrillation: a systematic review and meta-analysis. Curr Probl Cardiol. 2023;48(4): 101582. https://doi.org/10.1016/j.cpcardiol.2022.101582.
61. Li HL, Lip GYH, Feng Q, et al. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and cardiac arrhythmias: a systematic review and meta-analysis. Cardiovasc Diabetol. 2021;20(1):100. https://doi.org/10.1186/s12933-021-01293-8.
62. Li D, Liu Y, Hidru TH, et al. Protective effects of sodium-glucose transporter 2 inhibitors on atrial fibrillation and atrial flutter: a systematic review and meta-analysis of randomized placebo-controlled trials. Front Endocrinol. 2021. https://doi.org/10.3389/fendo.2021.619586.
63. Li W, Chen X, Xie X, et al. Comparison of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide receptor agonists for atrial fibrillation in type 2 diabetes mellitus: systematic review with network meta-analysis of randomized controlled trials. J Cardiovasc Pharmacol. 2022;79(3):281–8. https://doi.org/10.1097/FJC.0000000000001197.
64. Ong HT, Teo YH, Teo YN, et al. Effects of sodium/glucose cotransporter inhibitors on atrial fibrillation and stroke: a meta-analysis. J Stroke Cerebrovasc Dis. 2022;31(1): 106159. https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.106159.
65. Pandey AK, Okaj I, Kaur H, et al. Sodium-glucose co-transporter inhibitors and atrial fibrillation: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc Cardiovasc Cerebrovasc Dis. 2021;10(17): e022222. https://doi.org/10.1161/JAHA.121.022222.
66. Zheng RJ, Wang Y, Tang JN, Duan JY, Yuan MY, Zhang JY. Association of SGLT2 inhibitors with risk of atrial fibrillation and stroke in patients with and without type 2 diabetes: a systemic review and meta-analysis of randomized controlled trials. J Cardiovasc Pharmacol. 2022;79(2):e145–52. https://doi.org/10.1097/FJC.0000000000001183.
67. Fernandes GC, Fernandes A, Cardoso R, et al. Association of SGLT2 inhibitors with arrhythmias and sudden cardiac death in patients with type 2 diabetes or heart failure: a meta-analysis of 34 randomized controlled trials. Heart Rhythm. 2021;18(7):1098–105. https://doi.org/10.1016/j.hrthm.2021.03.028.
68. Liao XX, Li WQ, Peng ZK, Yu HB, Tan J. Three new categories of hypoglycaemic agents and various cardiovascular diseases: a meta-analysis. J Clin Pharm Ther. 2022;47(5):636–42. https://doi.org/10.1111/jcpt.13588.
69. Chen HY, Huang JY, Siao WZ, Jong GP. The association between SGLT2 inhibitors and new-onset arrhythmias: a nationwide population-based longitudinal cohort study. Cardiovasc Diabetol. 2020;19(1):73. https://doi.org/10.1186/s12933-020-01048-x.
70. Sfairopoulos D, Liu T, Zhang N, et al. Association between sodium-glucose cotransporter-2 inhibitors and incident atrial fibrillation/atrial flutter in heart failure patients with reduced ejection fraction: a meta-analysis of randomized controlled trials. Heart Fail Rev. 2023;28(4):925–36. https://doi.org/10.1007/s10741-022-10281-3.
71. Yin Z, Zheng H, Guo Z. Effect of sodium-glucose co-transporter protein 2 inhibitors on arrhythmia in heart failure patients with or without type 2 diabetes: a meta-analysis of randomized controlled trials. Front

Cardiovasc Med. 2022;9: 902923. https://doi.org/10.3389/fcvm.2022.902923.
72. Bonora BM, Raschi E, Avogaro A, Fadini GP. SGLT-2 inhibitors and atrial fibrillation in the Food and Drug Administration adverse event reporting system. Cardiovasc Diabetol. 2021;20(1):39. https://doi.org/10.1186/s12933-021-01243-4.
73. Kishima H, Mine T, Fukuhara E, Kitagaki R, Asakura M, Ishihara M. Efficacy of sodium-glucose cotransporter 2 inhibitors on outcomes after catheter ablation for atrial fibrillation. JACC Clin Electrophysiol. 2022;8(11):1393–404. https://doi.org/10.1016/j.jacep.2022.08.004.
74. Oates CP, Santos-Gallego CG, Smith A, et al. SGLT2 inhibitors reduce sudden cardiac death risk in heart failure: meta-analysis of randomized clinical trials. J Cardiovasc Electrophysiol. 2023;34(5):1277–85. https://doi.org/10.1111/jce.15894.
75. Ouyang X, Wang J, Chen Q, Peng L, Li S, Tang X. Sodium-glucose cotransporter 2 inhibitor may not prevent atrial fibrillation in patients with heart failure: a systematic review. Cardiovasc Diabetol. 2023. https://doi.org/10.1186/s12933-023-01860-1.
76. Li C, Yu J, Hockham C, et al. Canagliflozin and atrial fibrillation in type 2 diabetes mellitus: a secondary analysis from the CANVAS program and CREDENCE trial and meta-analysis. Diabet Obes Metab. 2022;24(10):1927–38. https://doi.org/10.1111/dom.14772.
77. Abu-Qaoud MR, Kumar A, Tarun T, et al. Impact of SGLT2 inhibitors on AF recurrence after catheter ablation in patients with type 2 diabetes. JACC Clin Electrophysiol. 2023;9(10):2109–18. https://doi.org/10.1016/j.jacep.2023.06.008.
78. Zhao Z, Jiang C, He L, et al. Impact of sodium-glucose cotransporter 2 inhibitor on recurrence after catheter ablation for atrial fibrillation in patients with diabetes: a propensity-score matching study and meta-analysis. J Am Heart Assoc. 2023;12(24): e031269. https://doi.org/10.1161/JAHA.123.031269.
79. von Lewinski D, Tripolt NJ, Sourij H, et al. Ertugliflozin to reduce arrhythmic burden in ICD/CRT patients (ERASe-trial)—a phase III study. Am Heart J. 2022;246:152–60. https://doi.org/10.1016/j.ahj.2022.01.008.
80. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895–1032. https://doi.org/10.1161/CIR.0000000000001063.
81. Ewha Womans University Mokdong Hospital. The effect of SGLT-2 inhibitor in patient with atrial fibrillation and diabetes mellitus. clinicaltrials.gov; 2023. https://clinicaltrials.gov/study/NCT05029115. Accessed 31 Dec 2022.
82. Soliman A. Effect of sodium glucose co-transporter 2 inhibitors on left atrium remodeling in non-valvular paroxysmal atrial fibrillation patients. clinicaltrials.gov; 2023. https://clinicaltrials.gov/study/NCT05993897. Accessed 31 Dec 2022.
83. University of Oklahoma. Dapagliflozin in patients with atrial fibrillation. clinicaltrials.gov; 2022. https://clinicaltrials.gov/study/NCT05174052. Accessed 31 Dec 2022.
84. Anagnostopoulos I. Dapagliflozin to prevent atrial fibrillation recurrence after transcatheter pulmonary venous isolation. clinicaltrials.gov; 2021. https://clinicaltrials.gov/study/NCT04780438. Accessed 31 Dec 2022.
85. Rambam Health Care Campus. The effect of empagliflozin versus placebo on the rate of arrhythmic events in heart failure patients. clinicaltrials.gov; 2018. https://clinicaltrials.gov/study/NCT03271879. Accessed 31 Dec 2022.

## Publisher's Note