sciendo Acta Marisiensis - Seria Medica / Ahead of Print DOI: 10.2478/amma-2025-0042

REVIEW

Sodium-glucose transporter 2 inhibitors and their antiarrhythmic role: New insights and future perspective

Diana-Ioana Praţia-Aron[1], Dan-Alexandru Cozac[1,2,3*], Alina Scridon[2,4]

1. Emergency Institute for Cardiovascular Diseases and Transplantation of Targu Mures, Targu Mures, Romania
2. Physiology Department, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Targu Mures, Romania
3. Doctoral School of Medicine and Pharmacy, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Targu Mures, Romania
4. Center for Advanced Medical and Pharmaceutical Research, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Targu Mures, Romania

Sodium-glucose transporter 2 inhibitors have been identified as pleiotropic pharmacological agents with demonstrated efficacy in a wide range of pathologies. Given the strong association between arrhythmias and significant comorbidities, exploring the potential antiarrhythmic effects of sodium-glucose transporter 2 inhibitors represents a critical therapeutic opportunity, particularly considering the limited efficacy and adverse profile of current antiarrhythmic drugs. The antiarrhythmic mechanisms of sodium-glucose transporter 2 inhibitors operate through direct cardiac ion channel modulation. Along with the ion channel effects, sodium-glucose transporter 2 inhibitors improve gap junction coupling by modulating connexin-43, lower sympathetic tone, maximize mitochondrial function, and induce metabolic reprogramming through adenosine monophosphate-activated protein kinase/sirtuin 1 activation and autophagy enhancement. Translating these encouraging mechanisms into focused antiarrhythmic strategies still requires establishing clear cause-and-effect links between sodium-glucose transporter 2 inhibitor therapy and arrhythmia prevention. Nevertheless, the current evidence regarding these effects remains inconsistent, underscoring the necessity for further research to elucidate the underlying mechanisms and resolve existing controversies.

Keywords: anti-arrhythmia agents, ion channels, sodium-glucose transporter 2 inhibitors

Received 27 July 2025 / Accepted 27 August 2025

Introduction

Contemporary antiarrhythmic drugs (AADs) are characterized by narrow therapeutic windows, significant proarrhythmic potential, and complex multi-organ toxicity profiles that frequently limit their clinical utility [1]. Moreover, efficacy limitations represent a fundamental challenge in current arrhythmias management [2]. The limited efficacy of existing agents, combined with their adverse effect profiles and the growing prevalence of arrhythmias in an aging population with increasing comorbidity burden, underscores the urgent need for novel therapeutic approaches [3].

Sodium-glucose transporter 2 (SGLT2) inhibitors have emerged as a versatile therapeutic option with a broad spectrum of proven clinical benefits [4]. This trajectory of serendipitous discovery appears to be extending into the realm of cardiac electrophysiology [5]. SGLT2 inhibitors seem to exert antiarrhythmic effects through several off-target mechanisms [6]. Recent evidence reveals that SGLT2 inhibitors demonstrate consistent antiarrhythmic effects with an up to 25% reduction in atrial fibrillation (AF) serious events and a 14% decrease in AF occurrence [7,8], representing a paradigm shift in cardiovascular pharmacology. However, data regarding ventricular arrhythmias remain conflicting, highlighting the need for further comprehensive studies [9,10].

Therefore, this review will critically evaluate the clinical and mechanistic evidence supporting the potential of SGLT2 inhibitors as antiarrhythmic agents, highlighting their strengths and limitations.

The antiarrhythmic effects of SGLT2 inhibitors in clinical trials

The potential antiarrhythmic properties of SGLT2 inhibitors first emerged as secondary observations within large-scale cardiovascular outcome trials primarily designed to evaluate HF and cardiovascular mortality endpoints. These landmark studies, including EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, and CANVAS, have provided unprecedented opportunities to assess arrhythmic outcomes in well-characterized patient populations through robust methodology and extended follow-up periods [11–14].

The EMPA-REG study [15] demonstrated a significant reduction in all-cause and cardiovascular mortality in patients receiving empagliflozin compared to placebo, along with a tendency towards a reduced risk of sudden cardiac death (SCD). In EMPEROR-Preserved trial [13] along with its subsequent pre-defined secondary analysis [16], empagliflozin demonstrated a reduction in the risk of hospitalization for HF or cardiovascular death, with similar outcomes observed in both patients with and without AF (HR 0.78 [95% CI 0.66-0.93] *vs.* 0.78 [95% CI 0.64-0.95]). The study demonstrated a potential trend toward

* Correspondence to: Dan Alexandru Cozac
E-mail: dan-alexandru.cozac@umfst.ro

reduction in SCD incidence, with 7.3% of events occurring in the empagliflozin group compared to 8.2% in the placebo group.

The most compelling evidence comes from the EMPA-ICD trial, the first prospective study that investigated the antiarrhythmic properties of empagliflozin [17]. In 150 patients with diabetes and implantable cardioverter-defibrillators (ICD), empagliflozin reduced ventricular arrhythmias by 1.69 events compared to no change with placebo (coefficient -1.07, 95% CI -1.29 to -0.86, p<0.001). This objective, device-based evidence definitively establishes direct antiarrhythmic properties independent of secondary cardiovascular benefits.

A post-hoc analysis of the DECLARE-TIMI 58 trial revealed potential antiarrhythmic benefits by showing a significant (19%) reduction in the risk of developing AF in individuals with T2D who were taking dapagliflozin (HR 0.81, 95% CI 0.68-0.95) [18]. Furthermore, this observation presents consistent benefits regardless of previous AF history or baseline cardiovascular status [18]. Another post-hoc analysis emerged from the DAPA-HF trial [10] demonstrated that dapagliflozin treatment was associated with a reduction in the incidence of the composite endpoint that included serious ventricular arrhythmias, cardiac arrest, and SCD in patients with HFrEF. Although the literature documented suppression of both supraventricular and ventricular arrhythmias, the underutilization of Holter ECG monitoring limited the accurate quantification of arrhythmic burden.

Recently, a comprehensive meta-analysis, including 38 randomized controlled trials with 88,704 patients, demonstrated that SGLT2 inhibitors were associated with a significant reduction in the incidence of AF (OR 0.87, 95% CI 0.76-0.98, p=0.03) compared with the control group [9]. Nevertheless, the authors did not find any significant association between SGLT2 inhibitors and the incidence of ventricular arrhythmias (OR 1.03, 95% CI 0.84-1.26, p=0.77), but probably these results depict a lack of statistical power, rather than a lack of effect [9]. Nonetheless, Lin *et al*. [19] reported contrasting findings, showing that in patients with non-advanced HF, treatment with SGLT2 inhibitors was linked to a significantly lower risk of ventricular arrhythmias and SCD.

To synthesize the most significant findings on the antiarrhythmic effects of SGLT2 inhibitors, we conducted a comparative analysis of the most relevant primary studies identified in our literature search, including those previously discussed as well as several additional key publications [10, 16-18, 20–31] (Table I).

Collectively, current evidence suggests that SGLT2 inhibitors exert clinically meaningful antiarrhythmic effects, particularly in reducing AF and SCD risk, thereby positioning them as promising candidates for future recognition within antiarrhythmic therapy paradigms.

Potential physiopathological mechanisms involved in the anti-arrhythmic effects of SGLT2 inhibitors

The complex interplay between cardiac fibrosis, inflammation, oxidative stress, and autonomic nervous system dysregulation creates a heterogeneous environment that can promote arrhythmogenesis [5]. Understanding and quantifying the contribution of each of these elements is crucial for developing effective strategies to prevent and manage arrhythmias, while SGLT2 inhibitors appear as promising agents to target these mechanisms (Figure 1).

Cardiac remodeling – fibrosis, inflammation and oxidative stress

SGLT2 inhibitors have shown to modulate structural cardiac remodeling, thereby contributing significantly to the management of arrhythmogenesis. A study published by Quagliariello *et al.* [32] identified that administration of empagliflozin significantly reduced cardiac fibrosis and apoptosis induced by doxorubicin by reducing collagen 1a1, Matrix metalloproteinase-9 (MMP-9), and caspase-3 expression, pro-inflammatory markers (IL-8, IL-6, IL-1β, leukotrienes B4), Nuclear Factor Kappa B (NF-kB) activation, Myeloid Differentiation Primary Response 88 (MyD88) and Nucleotide-binding Oligomerization Domain – NOD -, Leucine-Rich Repeats - LRR - and Pyrin domain-containing protein 3 (NLRP3) expression. Consistent with the aforementioned findings, an experimental preclinical study identified the upregulation of Sirtuin 6 (SIRT6) expression that leads to a reduction of oxidative stress as an additional mechanism by which empagliflozin and dapagliflozin counteract cardiac fibrosis [33]. Moreover, Transforming Growth Factor Beta (TGF-β) plays a major role in arrhythmogenesis, and SGLT2 inhibitors have been shown to reduce its expression [34]. Thus, SGLT2 inhibitors mitigate key profibrotic and proinflammatory pathways, thereby attenuating structural remodeling and limiting the anatomical substrate for arrhythmogenesis.

Atrial remodeling and wall stress

Atrial remodeling serves as a well-established substrate for atrial arrhythmias, particularly AF [35]. Empagliflozin showed a significant protective effect against the development of left atrial (LA) enlargement, interstitial fibrosis, and AF inducibility in T2D rats [36]. These preclinical findings are supported by clinical results from a second analysis of the EMPATROPISM trial [37] which revealed a significant reduction of LA volume in patients treated with empagliflozin versus placebo [38], thereby reflecting the alleviation of diastolic dysfunction. Moreover, the EMPA Hemodynamics subanalysis indicated that empagliflozin determined a significant improvement of LA function, quantified by the increase of LA strain reservoir and contraction phase values when compared with placebo [39]. These findings underscore the association between

Table I. Primary research evidence regarding the impact of sodium-glucose transporter 2 inhibitors on atrial fibrillation and ventricular arrhythmias

Study	SGLT2 inhibitor	Control	Population	Arrhythmia	SGLT2 inhibitor effect	Follow-up duration
Zelniker et al. (2020) (18)	dapagliflozin	placebo	T2D who had or were at risk for atherosclerotic cardiovascular disease	AF/AFl	HR = 0.81 (95% CI 0.68-0.95, p = 0.009) - reduction in first-event AF/AFl and IRR = 0.77 (95% CI 0.64-0.92, p = 0.005)	Median follow-up = 4.2 years
Butt et al. (2022) (20)	dapagliflozin	placebo	HFrEF	AF	HR = 0.86 (95% CI 0.6-1.22, not statistically significant)	Median follow-up = 18.2 months
Filippatos et al. (2023) (16)	empagliflozin	placebo	HFmrEF and HFpEF	AF	Incidence of new onset AF - HR = 1.00 (95% CI 0.77-1.29, p = 0.98)	Median follow-up = 26 months
Cesaro et al. (2022) (21)	canagliflozin, dapagliflozin, empagliflozin	Other oral anti-diabetic agents	T2D with acute myocardial infarction	AF	No independent effect (p = 0.03, unadjusted)	In-hospital (median 5 days)
Abu-Qaoud et.al (2023) (29)	canagliflozin, dapagliflozin, empagliflozin, tofogliflozin	Non-SGLT2 therapies	>18 year old, T2D patients who have undergone ablation	AF	AF reccurence (cardioversion, new AAD use or redo ablation) - OR = 0.68 (95% CI 0.602-0.776) and event free survival at 12 months – HR = 0.85 (95% CI 0.77-0.95, p = 0.003)	3 and 12 months
Ling et al. (2020) (22)	canagliflozin, empagliflozin	DPP4 inhibitors	T2D	AF	Incidence of new-onset AF – HR = 0.61 (95% CI 0.5-0.73, p < 0.001)	31 months
Engstrom et al. (Scandinavian Cohort Study) (2023) (23)	canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	GLP-1 receptor agonists	New users of SGLT2 inhibitors	AF	New onset AF - aHR = 0.89 (95% CI 0.81-0.96) and as-treated HR = 0.87 (95% CI 0.76-0.99)	5 years
Kishima et al. (2022) (30)	tofogliflozin	anagliptin	AF patients with T2D	AF reccurence post ablation	AF reccurence at 12 months after catheter ablation – absolute reduction – 23% (p = 0.0417)	12-month follow-up
Chan et al. (2022) (24)	dapagliflozin	DPP4 inhibitors, GLP-1RA	T2D without preexisting AF	AF	New onset AF - compared to DPP4i – HR = 0.90 (95% CI 0.84-0.96, p = 0.0028) and compared to GLP-1RA - HR = 0.74 (95% CI 0.63-0.88, p = 0.0007)	44 months
Noh et al. (2024) (25)	dapagliflozin	placebo	T2D with AF refractory to AADs	AF	AF recurrence – aHR = 0.15 (95% CI 0.07-0.35, p < 0.001) and after propensity score-matching – HR = 0.17 (95% CI 0.06-0.51, p = 0.002)	After 3-month blanking period
Zhao et al. (2023) (26)	canagliflozin, dapagliflozin, empagliflozin	Non-SGLT2	T2D patients after catheter ablation	AF	AF reccurence – HR, 0.63 (95% CI 0.44-0.90, p = 0.007 and aHR = 0.58 (95% CI 0.42–0.84, p < 0.001)	18 months
Curtain et al. (2021) (10)	dapagliflozin	placebo	HFrEF	VA/cardiac arrest/sudden death	HR = 0.79 (95% CI 0.63-0.99, p = 0.037) For VA alone - HR = 0.76 (95% CI 0.53-1.10, not statistically significant)	Median follow-up = 18.2 months
Fujiki et al. (2024) (17)	empagliflozin	placebo	T2D with ICD or CRT-D devices	VA (VT/VF/NSVT)	Mean difference = -1.07 (95% CI -1.29 - 0.86, p < 0.001)	24 weeks
Bendekit et al. (2024) (31)	ertugliflozin	placebo	HFrEF or HFmrEF with ICD or CRT-D	VT/VF episodes	Terminated early – no reliable statistical results	52 weeks
Cesaro et al. (2022) (21)	SGLT2 inhibitors	Other oral anti-diabetic agents	T2D with acute myocardial infarction	VT/VF	A lower rate of VT/VF (univariate p-value = 0.032) and OR - 0.20 (95% CI 0.04-0.97, p = 0.046)	5 days
Minguito Carazo et al. (2024) (27)	SGLT2 inhibitors	Without SGLT2 inhibitor	HF with ICD, with or without CRT	VA (SVT,VF, appropriate therapy – result in relevant VA; adding NSVT – result in all VA)	Following SGLT2 inhibitor initiation: - all VA - OR = 0.35 (0.24-0.50, p < 0.001) - relevant VA - OR = 0.30 (0.17-0.52, p < 0.001)	One year following and one year before SGLT2 inhibitor initiation
Hu et al. (2021) (28)	empagliflozin	control	Male Sprague Dawley rats	VT	VT – 40% vs. 100% (p=0.008)	7 days of empagliflozin administration

AAD – antiarrhythmic drug; AF – atrial fibrillation; Afl – atrial flutter; aHR – adjusted Hazard Ratio; CI – confidence interval; CKD – chronic kidney disease; CRT-D - cardiac resynchronization therapy with defibrillator; DPP4 – dipeptidyl peptidase-4; GLP1 – glucagon-like peptide-1; HF – heart failure; HfmEF – heart failure with mildly reduced ejection fraction; HFpEF – heart failure with preserved ejection fraction; HfrEF – heart failure with reduced ejection fraction; HR – hazard ratio; ICD –implantable cardioverter-defibrillator; IRR – incidence rate ratio; NSVT – non-sustained ventricular tachycardia; OR – odds ratio; RR – relative risk; SGLT 2 – sodium-glucose transporter 2; SVT – sustained ventricular tachycardia; T2D – type 2 diabetes; VA – ventricular arrhythmias; VF - ventricular fibrillation; VT – ventricular tachycardia.

SGLT2 inhibitors and the prevention of cardiac remodeling, a well-known contributor to arrhythmogenesis.

Autonomic system modulation

SGLT2 inhibitors have been shown to interact with autonomic nervous system (ANS), thereby modulating another pathway involved in arrhythmogenesis. A preclinical study by Basalay *et al.* [40] demonstrated that prolonged administration of the SGLT2 inhibitor ertugliflozin in rats with myocardial infarction led to a significant reduction in infarct size compared to controls and a threefold increase in the activity of vagal neurons, indicating enhanced parasympathetic activity. The EMBODY trial showed that empagliflozin produced an enhancement of the autonomic balance in T2D patients with acute myocardial infarction, but the results were significant only in the empagliflozin

Fig. 1. Multifaceted antiarrhythmic pathways mediated by sodium-glucose transporter 2 (SGLT2) inhibitors – an integrative approach - There are at least five main mechanisms by which SGLT2 inhibitors may exert their potential antiarrhythmic effects: 1. Antifibrotic and anti-inflammatory effects: decreasing Transforming Growth Factor Beta (TGF-β), collagen 1a1, Matrix metalloproteinase-9 (MMP-9), caspase-3, IL-8, IL-6, IL-1β, leukotrienes B4, Nucleotide-binding Oligomerization Domain – NOD -, Leucine-Rich Repeats - LRR - and Pyrin domain-containing protein 3 (NLRP3), Nuclear Factor Kappa B (NF-κB), Myeloid Differentiation Primary Response 88 (MyD88), reactive oxygen species (iROS), malondialdehyde (MDA), 4- Hydroxynonenal - 4-HNE, Hypoxia-Inducible Factor 2 Alpha (HIF-2α) and increasing Sirtuin 6 (SIRT 6) pathway and M2 (anti-inflammatory) over M1 (pro-inflammatory) macrophage phenotype; 2. Prevention of atrial remodelling (reducing left atrium – LA - volume and increasing left atrium strain); 3. Modulation of autonomic nervous system through reduction of heart rate variability (HRV); 4. Targeted effects on ionic channel activity: decreasing action potential duration (APD), QT, refractoriness, late sodium current (INaL), peak sodium current, Na+- H+ exchanger, Ca2+/calmodulin-dependent protein kinase II (CaMKII), increasing Sarcoplasmic/endoplasmic reticulum Ca2+- ATP - ase (SERCA2a) activity and having different effects on potassium channels` currents; 5. Optimization of metabolic processes through increased ketone body utilization, leading to elevated ATP production in cardiomyocytes.

group, with no significant differences between treatment and placebo arms [41]. There were also 2 clinical trials (EMPACT-MI and DAPA-MI) [42,43] that did not prove important reductions in mortality or primary composite outcomes regarding initiation of SGLT2 inhibitors in early post-myocardial infarction patients. Nevertheless, neither DAPA-MI nor EMPACT-MI directly evaluated arrhythmic endpoints, so maybe further targeted studies will clarify the potential antiarrhythmic effects of SGLT2 inhibitors in this setting. Thus, SGLT2 inhibitors may modulate autonomic activity and hold potential antiarrhythmic effects, but targeted clinical studies are still needed to confirm this.

SGLT2 inhibitors and the "sodium-interactome" pathway: mechanistics insights into atrial fibrillation progression

Preclinical research indicates that cardiac sodium (Na^+) channels play a crucial role in arrhythmogenesis and are key targets of SGLT2 inhibitors in the prevention or modulation of atrial arrhythmias, including AF [44]. Direct cardiac ion channel effects represent the most immediate antiarrhythmic mechanism, and SGLT2 inhibitors potently inhibit the late Na^+ current (INaL) with impressive selectivity. By reducing INaL, these agents decrease action potential (AP) duration, prevent early afterdepolarizations, and reduce arrhythmia susceptibility specifically in diseased hearts while sparing healthy myocardium [45]. For instance, empagliflozin was shown to reduce INaL in cardiomyocytes isolated from rodent models of HF [45]. Another subsequent study [46] demonstrated that INaL is increased in a HFpEF murine model, and that empagliflozin reverses the INaL upregulation and associated arrhythmogenic AP changes.

Homeostasis of intracellular calcium (Ca^{2+}) plays a crucial role in the pathophysiology of AF, as dysregulation of Ca^{2+} handling proteins directly contributes to arrhythmogenesis [47]. SGLT2 inhibitors increase sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA2a) expression, improve phospholamban activity, and reduce Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) hyperactivation [47]. The net effect is more stable intracellular Ca^{2+} cycling with reduced spontaneous Ca^{2+} release events that trigger arrhythmias [47]. Empagliflozin has been shown to reduce cytosolic Ca^{2+} levels while increasing mitochondrial Ca^{2+}, as well as inhibiting CaMKII phosphorylation of the ryanodine receptor (RyR) [48]. Improved SERCA2a and RyR2 function, along with reduced CaMKII hyperphosphorylation, facilitate the suppression of abnormal Ca^{2+}

release and promote electrical stability [49].

In addition to the involvement of Na^+ and Ca^{2+} channels in the antiarrhythmic effects of SGLT2 inhibitors, potassium (K^+) channels may also play a significant role. A recent study demonstrated that acute administration of dapagliflozin (100 μM) in *Xenopus laevis* oocytes expressing human cardiac K^+ channels led to a significant stimulating effect on two-pore-domain potassium channels ($K_{2P}2.1$ and $K_{2P}17.1$) [50]. AF has been associated with downregulation of $K_{2P}2.1$ and $K_{2P}17.1$ channels, suggesting that SGLT2 inhibitors may help reduce the incidence of AF by shortening atrial APs through modulation of K^+ channels [50].

By exerting multichannel cardiac effects-modulating Na^+, Ca^{2+}, and K^+ currents-SGLT2 inhibitors contribute to the stabilization of electrical activity and may reduce susceptibility to arrhythmias.

Current limitations and future directions regarding SGLT2 inhibitors and their potential antiarrhythmic properties

It is important to emphasize the need for future randomized controlled trials that should specifically assess the antiarrhythmic efficacy of these agents as primary endpoints. Moreover, further experimental research, especially *in vitro* studies, is essential to precisely elucidate the off-target mechanisms by which SGLT2 inhibitors act on the heart and to explore their potential interactions with current AADs. Contradictory findings concerning the effects of gliflozins on ion channel modulation, along with variations in dosage, duration of exposure, differential responses between atrial and ventricular cardiomyocytes, and potential interactions with standard AADs and other antidiabetic agents, represent critical areas that indicate the need for further systematic research.

However, while multiple research directions are emerging, there remains a critical need to move beyond observational associations and establish definitive cause-and-effect relationships - an objective that, although essential, is frequently challenging to achieve.

Conclusions

SGLT2 inhibitors are versatile compounds with a revolutionary advance in cardiac arrhythmia prevention, with a possible adjuvant antiarrhythmic role, particularly in the management of atrial arrhythmias, with AF being the most common.

The antiarrhythmic effects of SGLT2 inhibitors, like their cardiovascular benefits, were initially serendipitous discoveries, suggesting that these molecules may soon warrant formal recognition within a revised classification system of antiarrhythmic drugs. Their unique ability to simultaneously target the arrhythmogenic triad, substrate, trigger, and autonomic modulation, through integrated metabolic and electrophysiological mechanisms, emphasizes the possible advent of a new AAD class.

Authors contribution

PADI - conceptualization; methodology; writing original draft; writing - review&editing;
CDA - conceptualisation; methodology; supervision; writing- review&editing;
AS - conceptualisation; validation; methodology; writing - review&editing.

Conflict of interest

None to declare.

Funding

No external funding was received.

References

1. Zimetbaum P. Antiarrhythmic Drug Therapy for Atrial Fibrillation. Circulation. 2012;125(2):381–9.
2. Bray JJH, Warraich M, Whitfield MG, et al. Oral Class I and III antiarrhythmic drugs for maintaining sinus rhythm after catheter ablation of atrial fibrillation. Cochrane Database of Systematic Reviews. 2023;(3).
3. Saljic A, Heijman J, Dobrev D. Recent Advances in Antiarrhythmic Drug Therapy. Drugs. 2023;83(13):1147–60.
4. Fatima A, Rasool S, Devi S, et al. Exploring the Cardiovascular Benefits of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors: Expanding Horizons Beyond Diabetes Management. Cureus. 2023;15(9).
5. Duan HY, Barajas-Martinez H, Antzelevitch C, Hu D. The potential anti-arrhythmic effect of SGLT2 inhibitors. Cardiovascular Diabetology. 2024;23(1):1–17.
6. Chen S, Coronel R, Hollmann MW, Weber NC, Zuurbier CJ. Direct cardiac effects of SGLT2 inhibitors. Cardiovasc Diabetol. 2022;21(1):1–13.
7. Fedele D, Casuso Alvarez M, Maida A, et al. Prevention of atrial fibrillation with SGLT2 inhibitors across the spectrum of cardiovascular disorders: a meta-analysis of randomized controlled trials. Eur Heart J Cardiovasc Pharmacother. 2025;00:1–10.
8. 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. 2021;10(17):22222.
9. Jaiswal V, Ang SP, Kumar D et al. Sodium-Glucose Cotransporter-2 Inhibitors and Arrhythmias: A Meta-Analysis of 38 Randomized Controlled Trials. JACC: Advances. 2025;4(3).
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.
11. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413–24.
12. 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.
13. 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.
14. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017;377(7):644–57.
15. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117-2128.
16. Filippatos G, Farmakis D, Butler J, et al. Empagliflozin in heart failure with preserved ejection fraction with and without atrial fibrillation. Eur J Heart Fail. 2023;25(7):970–7.
17. Fujiki S, Iijima K, Nakagawa Y, et al. Effect of empagliflozin on ventricular arrhythmias in patients with type 2 diabetes treated with an implantable cardioverter-defibrillator: the EMPA-ICD trial. Cardiovasc Diabetol. 2024;23(1).
18. Zelniker TA, Bonaca MP, Furtado RHM, et al. Effect of Dapagliflozin on Atrial Fibrillation in Patients with Type 2 Diabetes Mellitus: Insights from the DECLARE-TIMI 58 Trial. Circulation. 2020;141(15):1227–34.
19. Lin M, Zhang S, Zhang L, et al. Redefining outcomes of ventricular arrhythmia for SGLT2 inhibitor medication in heart failure patients: a meta-analysis of randomized controlled trials. Syst Rev. 2025;14(1).
20. 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.
21. Cesaro A, Gragnano F, Paolisso P, et al. In-hospital arrhythmic burden reduction in diabetic patients with acute myocardial infarction treated with SGLT2-inhibitors: Insights from the SGLT2-I AMI PROTECT study. Front Cardiovasc Med. 2022;9.
22. Ling AWC, Chan CC, Chen SW, et al. The risk of new-onset atrial fibrillation in patients with type 2 diabetes mellitus treated with sodium glucose cotransporter 2 inhibitors versus dipeptidyl peptidase-4 inhibitors. Cardiovasc Diabetol. 2020 ;19(1):188.
23. Engstrom A, Wintzell V, Melbye M, et al. Sodium–Glucose Cotransporter 2 Inhibitor Treatment and Risk of Atrial Fibrillation: Scandinavian Cohort Study. Diabetes Care. 2023;46(2):351–60.
24. Chan YH, Chao TF, Chen SW, et al. The risk of incident atrial fibrillation in patients with type 2 diabetes treated with sodium glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and dipeptidyl peptidase-4 inhibitors: a nationwide cohort study. Cardiovasc Diabetol. 2022;21(1).
25. Noh HJ, Cha SJ, Kim CH, Choi SW, Lee CH, Hwang JK. Efficacy of dapagliflozin in improving arrhythmia-related outcomes after ablation for atrial fibrillation: a retrospective single-center study. Clinical Research in Cardiology. 2024;113(6):924–32.
26. 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):31269.
27. Minguito Carazo C, Rodriguez Manero M, Garcia Seara J, et al. Impact of SLGT2 inhibitors treatment initiation on the reduction of atrial and ventricular arrhythmias in patients with implanted cardiac defibrillator. Eur Heart J. 2024;45(Supplement_1).
28. Hu Z, Ju F, Du L, Abbott GW. Empagliflozin protects the heart against ischemia/reperfusion-induced sudden cardiac death. Cardiovasc Diabetol. 2021;20(1).
29. 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. Clinical Electrophysiology. 2023;9(10):2109–18.
30. 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.
31. Benedikt M, Oulhaj A, Rohrer U, et al. Ertugliflozin to Reduce Arrhythmic Burden in Patients with ICDs/CRT-Ds. NEJM evidence. 2024;3(10).
32. Quagliariello V, De Laurentiis M, Rea D, et al. The SGLT-2 inhibitor empagliflozin improves myocardial strain, reduces cardiac fibrosis and pro-inflammatory cytokines in non-diabetic mice treated with doxorubicin. Cardiovasc Diabetol. 2021;20(1).
33. Ma HX, Wu K, Dong FH, Cai BK, Wu D, Lu HY. Effects of Empagliflozin and Dapagliflozin in alleviating cardiac fibrosis through SIRT6-mediated oxidative stress reduction. Sci Rep. 2024;14(1).
34. Chen X, Yang Q, Bai W, et al. Dapagliflozin Attenuates Myocardial Fibrosis by Inhibiting the TGF- β1/Smad Signaling Pathway in a Normoglycemic Rabbit Model of Chronic Heart Failure. Front Pharmacol. 2022;13.
35. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. Circ Arrhythm Electrophysiol. 2008;1(1):62–73.
36. 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):1–14.
37. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, et al. Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction. J Am Coll Cardiol. 2021;77(3):243–55.
38. Santosgallego CG, Requena-Ibanez JA, Vargas A, et al. The SGLT2 Inhibitor Empagliflozin Ameliorates Left Atrial Dilatation in Non-Diabetic Patients With Heart Failure With Reduced Ejection Fraction: A Secondary Analysis of the EMPATROPISM Trial. Circulation. 2020;142(Suppl_3).
39. Thiele K, Rau M, Grebe J, et al. Empagliflozin Improves Left Atrial Strain in Patients with Type 2 Diabetes: Data from a Randomized, Placebo-Controlled Study. Circ Cardiovasc Imaging. 2023;16(4):E015176.
40. Basalay M V., Korsak A, He Z, Gourine A V., Davidson SM, Yellon DM. SGLT2 Inhibition Induces Cardioprotection by Increasing Parasympathetic Activity. Circ Res. 2024;136:229–31.
41. 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 Sep 25; 19(1):1–12.
42. Butler J, Jones WS, Udell JA, et al. Empagliflozin after Acute Myocardial Infarction. New England Journal of Medicine. 2024;390(16):1455–66.
43. James S, Erlinge D, Storey RF, et al. Dapagliflozin in Myocardial Infarction without Diabetes or Heart Failure. NEJM Evidence. 2023;3(2).
44. Valdivia CR, Chu WW, Pu J, et al. Increased late sodium current in myocytes from a canine heart failure model and from failing human heart. J Mol Cell Cardiol. 2005;38(3):475–83.
45. 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.
46. Hegyi B, Mira Hernandez J, Shen EY, Habibi NR, Bossuyt J, Bers DM. Empagliflozin Reverses Late Na+Current Enhancement and Cardiomyocyte Proarrhythmia in a Translational Murine Model of Heart Failure with Preserved Ejection Fraction. Circulation. 2022;145(13):1029–31.
47. Mustroph J, Wagemann O, Lücht CM, et al. Empagliflozin reduces ca/calmodulin-dependent kinase ii activity in isolated ventricular cardiomyocytes. ESC Heart Fail. 2018;5(4):642–8.
48. Gager GM, von Lewinski D, Sourij H, Jilma B, et al. Effects of SGLT2 Inhibitors on Ion Homeostasis and Oxidative Stress associated Mechanisms in Heart Failure. Biomedicine & Pharmacotherapy. 2021;143:112169.
49. Mustroph J, Baier MJ, Pabel S, et al. Empagliflozin Inhibits Cardiac Late Sodium Current by Ca/Calmodulin-Dependent Kinase II. Circulation. 2022;146(16):1259–61.
50. Müller ME, Petersenn F, Hackbarth J, et al. Electrophysiological Effects of the Sodium-Glucose Co-Transporter-2 (SGLT2) Inhibitor Dapagliflozin on Human Cardiac Potassium Channels. Int J Mol Sci. 2024;25(11):5701.