Can SGLT2 Inhibitors Prevent Atrial Fibrillation in HFpEF?

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Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) frequently coexist, sharing key risk factors such as aging, obesity, diabetes, and hypertension.[1,2] When present together, they contribute synergistically to increased morbidity and mortality. AF is observed in 40%-60% of HFpEF patients and is associated with worsened prognosis due to heightened symptom burden, increased hospitalizations, and elevated thromboembolic risk. Despite advancements in HFpEF management, strategies to prevent new-onset AF or reduce its recurrence remain inadequate. Recently, sodium-glucose cotransporter-2 inhibitors (SGLT2i) have become a cornerstone in HFpEF treatment, improving the outcomes regardless of the diabetes status.[3] Their pleiotropic cardiometabolic effects have generated growing interest in their potential role in AF prevention.[4]

There is a strong pathophysiological support for using SGLT2i to prevent AF in HFpEF patients.[5] HFpEF is marked by diastolic dysfunction, elevated left atrial pressures, systemic inflammation, and neurohormonal activation; these factors contribute to atrial remodeling and electrical instability.[1] SGLT2i lowers plasma volume and left atrial pressure via osmotic diuresis and natriuresis, potentially mitigating stretch-induced atrial remodeling.[3] In addition, these agents exhibit potent anti-inflammatory and anti-fibrotic properties, partially through the inhibition of the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing 3 (NLRP3) inflammasome-a key driver of atrial fibrosis and arrhythmogenesis. Castillo et al.[6] highlighted NLRP3's involvement in postoperative AF and cardiac remodeling, proposing SGLT2i as potential inhibitors of this inflammatory pathway, with corresponding antiarrhythmic benefits. Empagliflozin, particularly, has been shown to reduce proinflammatory cytokine production, attenuate oxidative stress, and enhance mitochondrial function in cardiomyocytes, suggesting direct protective effects on atrial tissues. *Ex vivo* studies further indicate that empagliflozin promotes mitochondrial biogenesis and upregulates regulatory proteins such as peroxisome proliferator-activated receptor-gamma coactivator 1-alpha and nuclear respiratory factor 1 during atrial tachypacing, supporting improved energetics and reduced oxidative stress in atrial myocardium.[7]

Another relevant mechanism involves modulation of epicardial adipose tissue (EAT), which is particularly abundant in obese and diabetic HFpEF patients. Excessive EAT surrounding the atria exerts proinflammatory and profibrotic paracrine effects, facilitating atrial remodeling. Vincenzi et al.[8] reviewed evidence showing that SGLT2i reduces EAT volume and inflammation, potentially lowering the risk of atrial arrhythmogenesis. Moreover, the prokineticin-prokineticin receptor 1-signaling pathway, which regulates EAT dynamics, has been identified as a potential therapeutic target for mitigating HFpEF-associated atrial remodeling.

Despite these promising mechanistic insights, clinical data remain limited and inconclusive. A 2025 meta-analysis of 52 randomized controlled trials, encompassing over 112,000 patients, reported a 14% relative reduction in AF incidence and occurrence with SGLT2i use compared to placebo. However, subgroup analyses revealed that this benefit was significant only in patients with heart failure and reduced ejection fraction (HFrEF), not in those with mildly reduced or preserved ejection fraction. Specifically, the reduction in AF risk was statistically significant in HFrEF (respiratory rate, 0.86; 95% confidence interval, 0.77-0.96), whereas no meaningful effect was observed in HFpEF cohorts.[9] These findings point toward phenotype-specific efficacy, potentially reflecting different pathophysiological mechanisms underlying AF in HFpEF versus HFrEF. Lenormand et al. [1] similarly noted that, while SGLT2i are now foundational in HFpEF therapy, their role in AF prevention remains uncertain, with conventional rhythm and rate-control strategies continuing to be central for symptom management.

Further supporting the potential benefit, a recent systematic review and meta-analysis focusing on diabetic patients with AF reported that SGLT2i use was associated with significant reductions in all-cause mortality (63%), cardiovascular death (43%), and heart failure hospitalizations (34%) when compared to other glucose-lowering agents. However, no significant reduction in myocardial infarction incidence was observed. Importantly, most of the included studies were observational, and AF-specific endpoints were typically secondary, limiting the strength of the conclusions.[10]

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In HFrEF patients undergoing cryoballoon ablation for AF, SGLT2i use has also been independently associated with lower AF recurrence, reduced mortality, and fewer heart failure hospitalizations over a 1-year follow-up period.[11] Although these findings pertain to HFrEF, they support the hypothesis that SGLT2i may offer antiarrhythmic benefits beyond their diuretic and hemodynamic actions-possibly via a combination of left atrial unloading, anti-inflammatory effects, reduced fibrosis, and improved cardiomyocyte energetics.

At the molecular level, Minciună et al.[5] recently reviewed how SGLT2i modulate the key pathways involved in atrial remodeling, including inflammation, oxidative stress, mitochondrial dysfunction, and autonomic imbalance. Their pleiotropic effects encompass reductions in reactive oxygen species, inhibition of fibroblast activation, and enhanced myocardial energy efficiency via increased ketone body utilization. Together, these mechanisms may help stabilize the atrial substrate, reduce arrhythmogenic triggers, and ultimately prevent AF onset and recurrence.

Nevertheless, current clinical evidence has important limitations. Most trials were not specifically designed to assess arrhythmic endpoints, and AF detection was often reliant on adverse event reporting rather than on systematic rhythm monitoring, thereby possibly underestimating the numbers of true incidence. Moreover, HFpEF represents a heterogeneous clinical syndrome, and the subgroup of patients most likely to benefit from SGLT2i-such as obese, diabetic individuals with high EAT burden and elevated left atrial pressures-has not been adequately delineated. The heterogeneity of HFpEF, along with meta-analyses based on trial-level rather than patient-level data, precludes firm conclusions.

Future research should focus on randomized trials, specifically those evaluating the impact of SGLT2i on AF incidence and burden in HFpEF populations. These studies should incorporate rigorous rhythm surveillance strategies, such as ambulatory electrocardiographys or implantable loop recorders. Stratification based on comorbid conditions, structural atrial characteristics, and metabolic phenotypes will be essential to identify the patient groups most likely to benefit. Investigating the synergistic potential of combining SGLT2i with other upstream modulators of inflammation and fibrosis may also enhance antiarrhythmic efficacy. Moreover, continued mechanistic research is required to elucidate the molecular pathways through which SGLT2i modulate atrial remodeling-particularly with respect to their effects on mitochondrial function and autonomic regulation.

In conclusion, although current evidence does not conclusively support the use of SGLT2i for AF prevention in HFpEF, the compelling mechanistic rationale and emerging clinical signals suggest a potential benefit. Dedicated, well-designed randomized trials targeting arrhythmic outcomes are therefore necessary to confirm whether SGLT2i can mitigate the growing burden of AF in this high-risk population as well as to clarify their role in the broader HFpEF treatment paradigm.

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