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Commentary Article

Insights of Cardiovascular Pharmacology Research

SGLT2 Inhibitors and Supraventricular Arrhythmias: The Antiarrhythmic Role of Gliflozins

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Abstract

Sodium-glucose cotransporter 2 inhibitors are a class of drugs used for the treatment of patients with type 2 diabetes mellitus and heart failure regardless of the coexistence of diabetes. The potential impact of this treatment in patients with heart failure is so huge that they have been named "the statins of the 21st century". In some studies they appeared to mildly reduce the risk of atrial fibrillation and atrial flutter , however, the available data so fare are scanty.

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) are a class of drugs developed for the treatment of patients with type 2 diabetes mellitus (T2DM) that were subsequently approved also for the treatment of patients with heart failure with reduced ejection fraction (HFrEF) regardless of the coexistence of diabetes. The main mechanism of action of these drugs relies on the blockade of sodium and glucose reabsorption mediated by SGLT2 in the proximal renal tubule. The consequent glycosuria and natriuresis lead to an increase in diuresis without increasing the risk of hypoglycemia [1].

Large randomized controlled trials have shown a substantial reduction in the risk of hospitalization for HF and death from cardiovascular causes in patients with both HFrEF and heart failure with preserved ejection fraction (HFpEF) treated with SGLT2i on top of optimal medical therapy (OMT) [1, 2]. Although the precise mechanisms underlying the cardiovascular beneficial effects associated with SGLT2is remain unknown, several of their effects might contribute to provide a cardioprotective impact, including diuretic activity and reduction in blood pressure, body weight, myocardial fibrosis, sympathetic nervous activity, left ventricular wall stress and hypertrophy [3].

The potential impact of this drugs on heart failure is so huge that a recent editorial has defined them "the statins of the 21st century" [4].

After the introduction of SGLT2is into clinical practice, a few other unexpected beneficial effects have emerged. Specifically, in some studies they appeared to mildly reduce the risk of atrial fibrillation (AF) and atrial flutter (AFL). Differently from the impact of SGLT2is on cardiovascular outcomes their ability to prevent at impact of SGLT2is on rial arrhythmias has been less investigated so far [5].

The DECLARE-TIMI 58 trial investigated safety and efficacy of dapagliflozin versus placebo in more than 17 000 patients with T2DM, roughly 10% of whom affected by HF. A post-hoc analysis of this trial reported that dapagliflozin was associated with a 19% reduction in the incidence of a first episode of AF/AFL and with a 23% reduction in the number of total AF/AFL [6].

A post-hoc analysis of the DAPA-HF trial investigated the efficacy and safety of dapagliflozin in HFrEF patients with and without AF. The study confirmed that dapagliflozin reduces worsening HF events and improves symptoms, when added to optimized medical therapy, regardless the presence of AF, but did not significantly reduce the incidence of new-onset AF in these patients [7].

On the other hand, a large meta-analysis including more than 34 trials and 63,000 patients evaluated the association between SGLT2is and atrial arrhythmias in patients with T2DM and/or HF. This study demonstrated a significant 19% reduction in the incidence of atrial arrhythmias in patients treated with SGLT2is. Interestingly, this meta-analysis suggested that the anti-arrhythmic effect of SGLT2is might not be a class effect: in fact, only dapagliflozin was associated with a significant reduction in the risk of atrial arrhythmias, whereas canagliflozin led to a numerically lower but statistically not significant reduction in the rate of AF/AFL. In contrast, there were no differences in the incidence of

atrial arrhythmias in patients treated with empagliflozin. Finally, the number of reported events in patients treated with ertugliflozin was too low to perform subgroup analysis [8].

A very small study (23 patients enrolled) on a specific population of ICD carriers with diabetes and AF in therapy with amiodarone, showed a reduction in AF recurrences after empaglifozin initiation9. However, these results should be considered cautiously due to the small sample size of the study.

There are several potential mechanisms by which SGLT2is might reduce the risk of atrial arrhythmias. First, an improvement in cardiac function might attenuate atrial remodeling, thereby reducing the risk of AF/AFL. Indeed, the favorable hemodynamic effects of SGLT2is, such as plasma volume contraction and blood pressure reduction, result in a decrease in both cardiac preload and afterload and, consequently, in a decrease in wall stress and NT-proBNP levels. However, there are no robust studies available directly addressing this aspect. In addition, SGLT2is might act directly on cardiac myocytes through the inhibition of myocardial sodium/hydrogen exchanger-1 (NHE-1). This exchanger is over-expressed in patients with HF and has been associated with spontaneous calcium release from sarcoplasmatic reticulum, enhanced myocardial fibrosis, hypertrophy, augmented epicardial adipose tissue and increased adverse remodeling, all factors potentially causing systolic and diastolic dysfunction. Finally, SGLT2is might contribute to improve neurohormonal balance attenuating sympathetic nervous system activity [10, 11]. Despite the evidence discussed so far, a few critical issues should be pointed out.

First, as already mentioned, the prevention of supraventricular arrhythmias has not been demonstrated to be a class effect: some drugs showed a stronger antiarrhythmic activity, such as dapaglifozin, whereas some others drugs did not show this peculiar property. Future studies on this topic are needed and they should focus on the single molecules individually [8].

Second, another important issue when interpretating the available studies is represented by the heterogeneity of patients enrolled in the trials, which encompass a broad spectrum of different conditions: from patients with T2DM and a structurally normal heart to patients with HFrEF and HFpEF. As the mechanisms of atrial arrhythmias are different in each subgroup of patients, it is very difficult to consider all them together. Future studies should focus on each specific subset of patients in order to clarify whether the reduction of atrial arrhythmias is just a consequence of an improvement in HF management or depends on antiarrhythmic properties of these drugs.

Third, another major issue is the low statistical power of the available studies, mainly due to the fact that trials were not specifically designed to detect AF. As an example, the number of episodes of AF detected in the DAPA-HF is roughly five times lower than the episodes detected in the DECLARE-TIMI58 trial. Albeit the population in the two studies is very diverse, it is likely that the lower rate of AF events detected in the DAPA-HF could contribute to the absence of a statistically significant reduction in the incidence of AF events in patients treated with SGLT2is.

In addition, atrial arrhythmias were identified with different tools in the different studies and only in one small study9 continuous rhythm monitoring devices were used. Therefore, it is likely that in the other studies the incidence of atrial arrhythmias might have been not detected
precisely.

Conclusion:

In conclusion, some encouraging data on the antiarrhythmic role of gliflozins in preventing atrial arrhythmias are emerging. Nevertheless, future studies are necessary: randomized, focusing on specific subsets of patients, with a longer follow-up period and using reliable AF detection tools.

Conflict of Interest

The author declares no conflict of interest, financial or otherwise.

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References

1. McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., et al. (2021). 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal, 42(36), 3599-3726.
2. Markenson, D., Ferguson, J. D., Chameides, L., Cassan, P., Chung, K. L., et al. (2010). Part 17: first aid: 2010 American Heart Association and American Red Cross guidelines for first aid. Circulation, 122(18_suppl_3), S934-S946.
3. Huynh, K. (2019). Dapagliflozin—a breakthrough in the search for drugs to treat HFrEF. Nature Reviews Cardiology, 16(12), 700-700.
4. Anker, S. D., Butler, J., Filippatos, G., Ferreira, J. P., Bocchi, E., et al. (2021). Empagliflozin in heart failure with a preserved ejection fraction. New England Journal of Medicine, 385(16), 1451-1461.
5. Braunwald, E. (2022). SGLT2 inhibitors: the statins of the 21st century.
6. Kolesnik, E., Scherr, D., Rohrer, U., Benedikt, M., Manninger, M., et al. (2022). SGLT2 inhibitors and their antiarrhythmic properties. International Journal of Molecular Sciences, 23(3), 1678.
7. Zelniker, T. A., Raz, I., Sabatine, M. S., & Wiviott, S. D. (2020). Response by Zelniker et al to Letter Regarding Article,"Effect

of Dapagliflozin on Atrial Fibrillation in Patients with Type 2 Diabetes Mellitus: Insights From the DECLARE-TIMI 58 Trial". Circulation, 142(10), e129-e130.
8. Butt, J. H., Docherty, K. F., Jhund, P. S., De Boer, R. A., Böhm, M., et al. (2022). Dapagliflozin and atrial fibrillation in heart failure with reduced ejection fraction: insights from DAPA-HF. European journal of heart failure, 24(3), 513-525.
9. Fernandes, G. C., Fernandes, A., Cardoso, R., Penalver, J., Knijnik, L., et al. (2021). 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, 18(7), 1098-1105.
10. Fazio G* and Schirò P. Empagliflozin in paroxysmal or persistent atrial fibrillation: a possible antiarrhythmic effect. Diabetes Updates, 2021 doi: 10.15761/DU.1000151
11. Lahnwong, S., Chattipakorn, S. C., & Chattipakorn, N. (2018). Potential mechanisms responsible for cardioprotective effects of sodium–glucose co-transporter 2 inhibitors. Cardiovascular diabetology, 17(1), 1-17.
12. Curtain, J. P., Docherty, K. F., Jhund, P. S., Petrie, M. C., Inzucchi, S. E., et al. (2021). Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. European Heart Journal, 42(36), 3727-3738.