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ВЛИЯНИЕ ИНГИБИТОРОВ НАТРИЙ-ГЛЮКОЗНОГО КОТРАНСПОРТЕРА 2 ТИПА НА РАЗВИТИЕ И ТЕЧЕНИЕ ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ

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Effect of Sodium-Glucose Cotransporter Type 2 Inhibitors on The Development and Course of Atrial Fibrillation

Резюме

Фибрилляция предсердий — одно из самых распространенных нарушений сердечного ритма, связанное с повышенным риском инсульта, смертности от сердечно-сосудистых заболеваний и госпитализаций. На развитие аритмии влияет ряд факторов риска, включая артериальную гипертензию, хроническую сердечную недостаточность, ишемическую болезнь сердца и эндокринные расстройства. Новые рекомендации Европейского общества кардиологов (2024) подчеркивают важность управления факторами риска для повышения эффективности лечения и улучшения прогноза у пациентов с фибрилляцией предсердий. Ингибиторы натрий-глюкозного котранспортера 2 типа (глифлозины), изначально применявшиеся как гипогликемические препараты, сегодня широко используются и для снижения риска неблагоприятных сердечно-сосудистых событий. Однако вопрос о применении этих препаратов с целью снижения риска возникновения и улучшения течения фибрилляции предсердий остается открытым. С целью поиска ответа на него был проведен обзор литературы, который показал, что ингибиторы натрий-глюкозного котранспортера 2 типа теоретически могут обладать антиаритмическим эффектом, реализующимся за счет нескольких механизмов. Анализ научных данных говорит о том, что в большинстве случаев использование ингибиторов натрий-глюкозного котранспортера 2 типа уменьшает риск развития впервые возникшей фибрилляции предсердий, положительно влияет на течение аритмии и снижает риск ее рецидива после аблации. При этом до конца не ясно, являются ли обсуждаемые вопросы класс-эффектом или препараты, входящие в группу глифлозинов, имеют разную эффективность. Обозначенные вопросы обуславливают необходимость проведения дальнейших проспективных исследований для подтверждения антиаритмического эффекта у ингибиторов натрий-глюкозного котранспортера 2 типа.

Ключевые слова: *фибрилляция предсердий, ингибиторы НГЛТ2, глифлозины, сахарный диабет*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Atrial fibrillation is one of the most common heart rhythm disorders associated with an increased risk of stroke, cardiovascular mortality and hospitalizations. The development of arrhythmias is influenced by a number of risk factors, including arterial hypertension, chronic heart failure, coronary heart disease and endocrine disorders. New guidelines from the European Society of Cardiology (2024) emphasize the importance of managing risk factors to improve treatment efficacy and prognosis in patients with atrial fibrillation. Sodium-glucose cotransporter type 2 inhibitors (gliflozins), originally used as hypoglycemic drugs, are now also widely used to reduce the risk of adverse cardiovascular events. However, the use of these drugs to reduce the risk of atrial fibrillation and improve the course of atrial fibrillation remains an open question. In order to find an answer to this question, a literature review was conducted, which showed that inhibitors of sodium-glucose cotransporter type 2 can theoretically have an antiarrhythmic effect realized through several mechanisms. Analysis of scientific data suggests that in most cases, the use of sodium-glucose cotransporter type 2 inhibitors reduces the risk of first-time atrial fibrillation, has a positive effect on the course of arrhythmia and reduces the risk of its recurrence after ablation. At the same time, it is not clear to the end whether the discussed issues are class-effect or the drugs belonging to the gliflozin group have different efficacy. The mentioned issues necessitate further prospective studies to confirm the antiarrhythmic effect in sodium-glucose cotransporter type 2 inhibitors.

Key words: *atrial fibrillation, SGLT2 Inhibitors, gliflozins, diabetes mellitus*

Conflict of interests

The authors declare no conflict of interests

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AF — atrial fibrillation, CHF — chronic heart failure, DM — diabetes mellitus, SGLT2i — sodium-glucose linked transporter-2 inhibitors, RCS — randomised controlled studies, NHE1 — type 1 Na+/H+ exchanger, ACVD — atherosclerotic cardiovascular diseases, DPP4i — dipeptidyl peptidase-4 inhibitors

Introduction

Atrial fibrillation (AF) is the most common type of rhythm disturbance, which is associated with a higher risk of cardioembolic stroke, cardiovascular deaths, and hospitalisations [1]. The incidence of AF is 2 %. In Russia, the rates are similar [2, 3]. In some cohorts, this value can be even higher. For example, during the first month after the infection, the incidence of atrial arrhythmias among post-COVID patients is 12 times higher than in the general population [4]. Given the longer life expectancy of the population, the incidence of AF is likely to be even higher: over the next 50 years, the incidence of arrhythmias can double [5].

In a majority of cases, the exact aetiology of AF is unknown; however, some clinical conditions are associated with a higher rate of arrhythmia. They include a number of cardiovascular diseases: arterial hypertension, chronic heart failure (CHF), ischaemic heart disease, acquired and congenital heart disorders [6, 7]. In the Framingham Heart Study, CHF increases the risk of AF by 8.5 times in men and by 14 times in women [8]. Common causes are also endocrine disorders, including diabetes mellitus (DM), which increases the risk of AF by 28 % [9]. DM-related factors, not the cardiovascular comorbidity, contribute to the development of arrhythmia: unstable blood glucose level, oxidative stress, and inflammation [10].

The new European Society of Cardiology Guidelines for the Management of AF (ESC, 2024) focus on comorbidities. CARE approach (C — Correction of comorbidities and risk factors; A – Avoidance of stroke and thromboembolism; R — Reducing symptoms by effective use of heart rate and rhythm control; E — Evaluation and follow-up) in comorbid patients involves control of risk factors in order to prevent AF recurrences and progression. It allows boosting treatment efficiency, improving prognosis, and preventing unfavourable outcomes [11].

Recently, sodium-glucose linked transporter-2 inhibitors (SGLT2i, gliflozins) have been widely used in clinical settings. Initially claimed as hypoglycaemic agents, these medications demonstrated the ability to reduce the number of adverse cardiovascular events and lower the risk of hospitalisations for CHF, as well as showed effects on the reduction of the risk of chronic kidney disease progression [12, 13]. Currently, dapa- and empagliflozins are recommended to all patients with CHF irrespective of their ejection fraction, including those with AF [11, 14]. Although SGLT2 inhibitors have proven to be efficient, it is still unclear whether they can be used to reduce the risk of AF and impact the existing arrhythmia.

The objective of this review is to study the ability of SGLT2i to reduce the risk of development and improved course of AF.

Methods of search

A literature search was conducted, which included relevant articles in PubMED, eLIBRARY databases and also at ClinicalTrials, both in Russian and English, over a period from 2016 to 2024. The following keywords and phrases containing such keywords were used in the literature search: SGLT2 inhibitors, gliflozins, atrial fibrillation, diabetes mellitus, antiarrhythmic effect. The search included systemic reviews, meta-analyses, both published and unpublished randomised controlled studies (RCS), and observational studies. The final analysis of publications did not include theses, poster reports, thesis papers, and conference materials. All in all, 130 publications were analysed; the final analysis comprised 18 publications, including five publications discussing possible antiarrhythmic mechanism of action of SGLT2i [19-23], and 13 publications discussing the efficacy of gliflozins in the reduction of risk of AF and impact for existing arrhythmias [24-36].

Mechanisms of antiarrhythmic effects of SGLT2i

To date, a number of pleiotropic effects of gliflozins have been described, which include reduction of albuminuria, blood pressure, body mass, and uric acid levels [15-18]. However, their antiarrhythmic effects are still unclear. At the same time, oxidative stress and energy deficit of cardiac cells, which underlie the AF arrhythmogenesis, are associated with mitochondria dysfunction and impaired sodium and calcium exchange, which can be a point of intervention with gliflozins.

The possible mechanism of antiarrhythmic effects of gliflozins is additional inhibition of type 1 Na+/H+ exchanger (NHE1) [19]. The main cause of excessive NHE1 activation is intracellular acidosis induced by myocardial ischemia [20]. In addition, the experimental model demonstrated that NHE1 is activated also during atrial tachycardia [21]. Later, Chinese authors (2008) reported that NHE1 activity is clearly higher both in ageing atria and in fibrillating atria [22]. Irrespective of the cause of excessive NHE1 activation, it results in cytomatrix overloading with Na+ ions, which alters inversely the function of Na+/Ca2+ exchanger and contributes to cytomatrix overloading with Ca2+ ions. This is associated with the development of cardiac dysfunction, abnormal conductivity and triggered activity, which can add to AF arrhythmogenesis [20, 23]. Simultaneously, Na+/Ca2+ exchanger is activated on the mitochondria membrane, causing higher Ca2+ outflow from the organelle. Reduced intramitochondrial concentration of Ca2+ leads to impairment of a number of essential functions, including ATP synthase dysfunction and excessive synthesis of reactive oxygen intermediates, which results in more significant atrial remodelling, also in patients with existing AF [19]. However, it does not eliminate the contribution of other possible mechanisms in the creation of antiarrhythmic effects of SGLT2i (Fig. 1), given there is no clear answer to the question about the key mechanism.

Role of SGLT2i in the reduction of the risk of AF de novo

A majority of large RCS study the effects of SGLT2i on the incidence of atherosclerotic cardiovascular (ACVD) complications and CHF. One of them, DECLARE-TIMI 58, studied the effects of dapagliflozin on DM patients

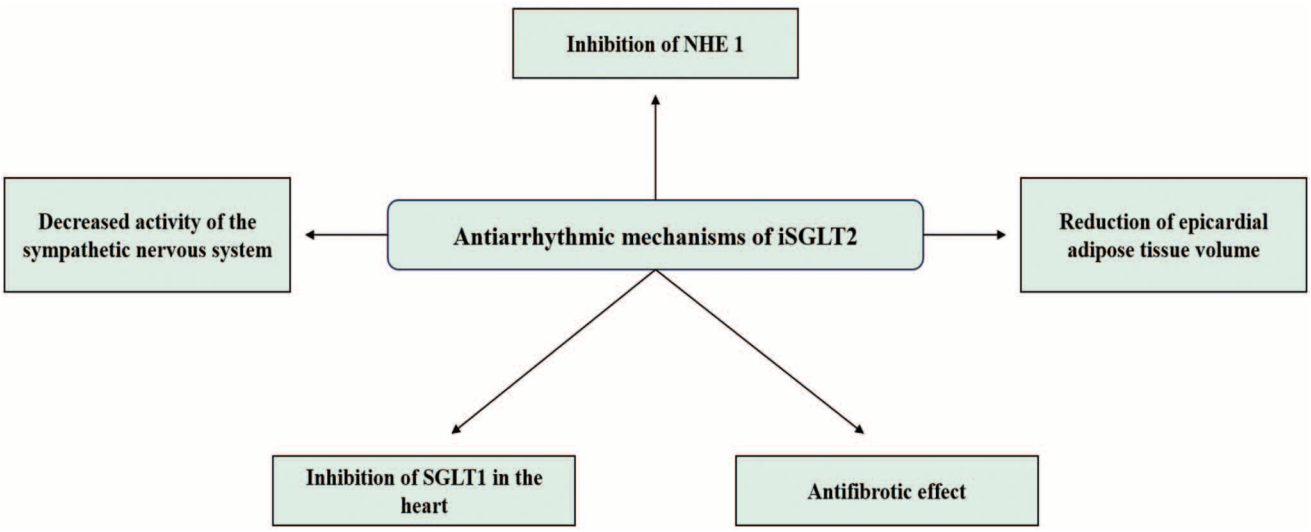

Figure 1. *Mechanisms putatively underlying the antiarrhythmic effect of iSGLT2*
Note. iSGLT2 — sodium-glucose cotransporter type 2 inhibitors, SGLT1 — sodium-glucose cotransporter type 1, NHE1 — Na+/H+ exchanger type 1

with ACVD (n=6,974) or with a high risk of such diseases (n=10,186). Since the authors of the original study did not aim at identifying the ability of SGLT2i to delay the onset of AF, an additional retrospective analysis was conducted in a separate arm (n=1,116), which showed 19 % reduction in the risk of arrhythmia vs. placebo (OR 0.81; 95 % CI: 0.68–0.95; p=0.009). The results did not depend on a history of a specific diagnosis of ACVD or CHF [24].

Alternative results were reported in the DAPA-HF study. Butt J.H. et al. (2022) demonstrated that the use of dapagliflozin did not reduce the risk of AF de novo in patients (n=2,834) with CHF and decreased ejection fraction (OR 0.81; 95 % CI: 0.60–1.22). This can be a result of the study characteristics, which was probably conducted for a shorter period of time than needed to see the antiarrhythmic effects of SGLT2i: the median observation time was 18 months, while in DECLARE-TIMI 58, the observation lasted for 48 months; and the effects for AF were usually seen 24 months after dapagliflozin initiation, however in a completely different patient population. Also, AF monitoring in DAPA-HF was not active enough, which could result in missed episodes of arrhythmia and a low number of patients with AF de novo (n=123; 4.3 %) [25].

It appears that the problem of AF underdiagnosing is present in other large RCS of SGLT2i, because AF recording was not an endpoint and the condition was treated as an adverse event; the disease was often diagnosed only on the basis of the medical history and ECG recording during control visits. For example, in the EMPA-REG OUTCOME study, the incidence of AF de novo was also low and did not differ between placebo (n=106; 1.6 %) and empagliflozin (n=153; 2.3 %) [26].

The favourable effects of SGLT2i in the prevention of AF de novo are supported by the fact that analysis results of DECLARE-TIMI 58 were similar to those of meta-analyses. For example, a meta-analysis of 34 studies (n=63,166, 63 % of males, mean age: 60 years) demonstrated that the use of SGLT2i reduced the risk of any atrial arrhythmias in patients with DM (OR 0.81; 95 % CI: 0.69–0.95; p=0.008) [27]. However, in a larger sample (46 studies, n=101,100) in another meta-analysis, the results differed again: according to the authors, SGLT2i did not reduce the risk of AF irrespective of the follow-up duration, drug type or dose, and patient population [28].

It is likely that the contradictory conclusions can be a result of characteristics of the studies included in the meta-analysis. All studies had significantly differing designs and follow-up duration; none of them had AF as an endpoint, and the history of AF was not taken into account during patient enrolment [29].

SGLT2i and AF progression

Up to date, there are just a few literature reports on the studies, aiming at establishing the relationship between SGLT2i and AF progression in patients with DM and pre-existing AF. In one study, the authors compared the efficacy of SGLT2i and dipeptidyl peptidase-4 inhibitors (DPP4i) during the period from 2014 to 2019 (cohort study). The primary endpoint was AF-associated events: hospitalisation, A&E visits, electrical cardioversion or catheter ablation. Secondary parameters included all-cause mortality, hospitalisation for decompensated CHF, ischaemic stroke or transient ischaemic attack. Among 2,242 patients with DM and AF, who were followed up for an average period of three years, the primary endpoint was recorded in 8.7 % (n=97) of patients in SGLT2i group vs. 10.0 % (n=112) of patients in DPP4i group (OR 0.73; 95 % CI: 0.55–0.96; p=0.03). SGLT2i were associated with significantly reduced all-cause mortality rates and hospitalisations for CHF, but did not show any difference in the risk of ischaemic stroke/transient ischaemic attack [30].

Similar results were obtained in a study by Korean authors (2024), who conducted a retrospective analysis of a database of patients (n=11,012) with DM and AF: the use of SGLT2i resulted in significantly lower all-cause mortality (OR 0.43; 95 % CI: 0.29–0.67) and marked kidney protection, which is also very important: higher blood creatinine levels of over 50 % or dialysis initiation were less common in SGLT2i group (OR 0.50; 95 % CI: 0.38–0.66; p<0.001) [31].

Undoubtedly, a major fault of these studies is their retrospective nature, which has practical limitations for the use of these studies due to the low level of evidence. This problem is being resolved: the EMPA-AF (NCT04583813) and BEYOND (NCT05029115) studies are being currently planned.

SGLT2i and reduction in post-ablation rates of AF

There are a number of articles describing that SGLT2i can reduce the risk of AF recurrences after ablation. One of the major studies in this domain is a study by Abu-Qaoud M.R. et al. (2023) [32]. The study included DM patients, who underwent AF ablation in 2014 to 2021. The patients were divided into two equal arms (n=2,225) depending on SGLT2i status. The primary endpoint was an episode of AF recurrence during the 12-month follow-up. The secondary endpoints were: decompensated CHF, ischaemic stroke, all-cause hospitalisations and death during the same period. The use of SGLT2i was associated with a significantly lower risk of AF recurrence (OR 0.68; 95 % CI: 0.602–

0.776; p<0.0001). Elements of the secondary endpoint were also less common (OR 0.85; 95 % CI: 0.77–0.95; p=0.003); however, the incidence of strokes had only minor differences.

Similar results were reported also by Japanese colleagues (2022), who conducted a prospective randomised study to compare the efficacy of SGLT2i and DPP4i in AF recurrence after ablation. Seventy patients with AF and DM were randomised to tofogliflozin group (n=38) or anagliptin group (n=32); also, patients were stratified depending on the left atrial diameter and AF pattern. The primary endpoint was AF recurrence during 12 months after ablation. In anagliptin group, AF recurrences were more common than in tofogliflozin group (47 % vs. 24 %, p=0.0417) [33].

The limitation of these studies can be inclusion only of DM patients, therefore, the results cannot be extrapolated to all AF patients, and another RCS is required to assess the effects of SGLT2i on AF recurrences after ablation, irrespective of DM status of patients.

Efficacy of specific SGLT2 inhibitors

Are the above issues class effects, or do various gliflozins have various efficacy? The mentioned meta-analysis of 34 studies showed that only dapagliflozin was associated with a significantly reduced risk of atrial arrhythmias in DM patients (OR 0.74; 95 % CI: 0.60–0.91; p=0.005), while canagliflozin showed statistically insignificant results (OR 0.81; 95 % CI: 0.60–1.08; p=0.15), empagliflozin did not affect the risk of AF (OR 1.17; 95 % CI: 0.75–1.82; p=0.49) [27].

Similar results were obtained by investigators in South Korea (2024). In an observational study, conducted in 2016–2018, DM patients (n=137,928, mean age: 55 years old, males: 58 %) were treated with dapa- or empagliflozin. In dapagliflozin group, events of AF were less common (OR 0.89; 95 % CI: 0.79–0.99). It is worth noting that the results were similar both in groups of low and high cardiovascular risk. Age, gender, body mass index, diabetes duration, and renal function did not affect the final result [34].

The fly in the ointment is a retrospective cohort study conducted by Japanese authors (2022), where the national database analysis was used to compare specific SGLT2i and their role in primary prevention of CHF, ischaemic heart disease, stroke and AF in DM patients (n=25,315, mean age: 52 years, 82.5 % of males). The risks of the mentioned cardiovascular events were similar with the use of specific SGLT2 inhibitors. However, the database had a number of significant limitations: there was no preliminary information on DM duration; patients over 75 years old were excluded; there were no data on the socio-economic status of patients [35].

It is important to note that if the antiarrhythmic effect is indeed a result of NHE1 inhibition, then there cannot be a significant difference in the efficacy of various SGLT2 inhibitors, as demonstrated by Uthman L. et al. (2018) in their study in laboratory mice [36].

Conclusion

Thus, there is no clear answer to whether SGLT2i are efficient in reduction of the risk and improvement of existing AF; however, there are abundant facts about the effects of these medications on the reduction of arrhythmia burden, especially in DM patients. This situation necessitates further prospective studies.

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Ишмаев Д.А.: сбор и обработка материала, написание рукописи

Васильева М.С.: анализ и интерпретация данных, редактирование рукописи

Дупляков Д.В.: разработка концепции и дизайна, научное консультирование, редактирование рукописи, утверждение окончательного варианта статьи

Author contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Ishmaev D.A.: collecting and processing material, manuscript writing

Vasileva M.S.: data interpretation and analysis, editing the article

Duplyakov D.V.: concept and design development, scientific advice, editing the article, approval of the final version of the manuscript

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