IMPACT OF SGLT2 INHIBITOR ON CARDIAC REMODELLING IN PATIENTS WITH CHRONIC HEART FAILURE

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Abstract: SGLT2 inhibitor reduces the risk of heart failure (HF) in diabetics, and it has shown to improve the prognosis of patients with HF across all ranges of left ventricular ejection fraction (LVEF), by preventing HF decompensations and cardiovascular death[1]. This raises the question of what other mechanisms underlie these effects beyond sodium–glucose cotransporter 2 (SGLT2) inhibition. The effect of SGLT2 inhibitors on cardiac remodelling evaluated by imaging and related biomarkers remains uncertain, with scarcity of studies in HF patients and contradictory results mainly focused on patients with diabetes and reduced LVEF[2,3] Indeed, no data exist supporting a direct effect of SGLT2 inhibitor on cardiac geometry, function and biomarkers in presence of HF, irrespective of LVEF. Adverse myocardial remodelling affecting the left ventricle is a key factor in the progression of HF and current well-established HF phenotypes are based on LVEF. However, other relevant players have received less attention, such as the left atrium. Indeed, the left atrium plays a critical role in cardiac function, particularly in left ventricular (LV) filling during diastole. Additionally, atrial dysfunction can directly lead to pulmonary congestion. Left atrial (LA) remodelling occurs in HF irrespective of the degree of LV systolic dysfunction, and can be observed in the presence of preserved or reduced LVEF[4,5] The geometry of the left atrium is a predictor for the development of HF in high-risk patients,[5] and has been consistently linked to higher rates of hospitalization and death in patients with HF[6,7]. As a result, atrial disease has become an important concept that has been highlighted in the most recent guidelines for HF from the European Society of Cardiology (ESC)[8]. The aim of this study was to investigate the impact of SGLT2 inhibitor on cardiac remodelling parameters, specifically LA remodelling, in patients with HF regardless of their LVEF.

Keywords: SGLT2 inhibitor , heart failure, cardiac remodeling, atrial dysfunction

ВЛИЯНИЕ ИНГИБИТОРА SGLT2 НА РЕМОДЕЛИРОВАНИЕ СЕРДЦА У ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

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Аннотация: Ингибиторы SGLT2 снижает риск развития сердечной недостаточности (СН) у больных сахарным диабетом, и было показано, что он улучшает прогноз пациентов с СН во всех диапазонах фракции выброса левого желудочка (ФВЛЖ), предотвращая декомпенсацию СН и сердечно-сосудистую смерть.[1] В связи с этим возникает вопрос о том, какие еще механизмы лежат в основе этих эффектов, помимо ингибирования натрий-глюкозного котранспортера 2 (SGLT2). Влияние ингибиторов SGLT2 на ремоделирование сердца, оцениваемое с помощью визуализации и связанных биомаркеров, остается неясным, при этом количество исследований с участием пациентов с СН и противоречивые результаты в основном сосредоточены на пациентах с сахарным диабетом и сниженной ФВЛЖ.[2,3] Действительно, нет данных, подтверждающих прямое влияние ингибиторов SGLT2 на геометрию сердца, функцию и биомаркеры в присутствии СН, независимо от ФВЛЖ. Неблагоприятное ремоделирование миокарда, поражающее левый желудочек, является ключевым фактором в прогрессировании СН, и современные хорошо

установленные фенотипы СН основаны на ФВЛЖ. Тем не менее, другие соответствующие игроки получили меньше внимания, такие как левое предсердие. Действительно, левое предсердие играет решающую роль в сердечной функции, особенно в наполнении левого желудочка (ЛЖ) во время диастолы. Кроме того, дисфункция предсердий может напрямую привести к застою в легких. Ремоделирование левого предсердия (ЛП) происходит при СН независимо от степени систолической дисфункции ЛЖ и может наблюдаться при наличии сохраненной или сниженной ЛЖ.[4,5] Геометрия левого предсердия является предиктором развития СН у пациентов с высоким риском,[4] и неизменно связана с более высокими показателями госпитализации и смертности у пациентов с СН[.6,7] В результате, Заболевание предсердий стало важным понятием, которое было освещено в последних рекомендациях по СН от Европейского общества кардиологов (ESC).[20] Целью данного исследования было изучение влияния ингибиторов SGLT2 на параметры ремоделирования сердца, в частности ремоделирования ЛП, у пациентов с СН независимо от их ФВЛЖ.

Ключевые слова: ингибитор SGLT2, сердечная недостаточность, ремоделирование сердца, систолической дисфункции.

INTRODUCTION

Chronic heart failure (CHF) remains a leading cause of morbidity and mortality worldwide, affecting millions of individuals and placing a significant burden on healthcare systems. The condition is characterized by structural and functional impairments of the heart, leading to insufficient blood supply to meet the metabolic demands of the body. Cardiac remodeling, a pivotal process in the progression of CHF, encompasses changes in the size, shape, and function of the heart in response to injury or stress. Understanding and mitigating the mechanisms driving cardiac remodeling are central to improving outcomes in CHF patients.

Sodium-glucose co-transporter-2 (SGLT2) inhibitors, initially developed as antidiabetic agents, have emerged as a promising therapeutic class for cardiovascular diseases. Beyond their glucose-lowering effects, SGLT2 inhibitors exhibit profound benefits on cardiac function, as evidenced by recent large-scale clinical trials. These drugs have been shown to reduce hospitalization rates, improve left ventricular function, and attenuate the progression of cardiac remodeling in CHF patients.

Despite the growing body of evidence, the precise mechanisms underlying the cardioprotective effects of SGLT2 inhibitors remain an area of active investigation. Hypothesized mechanisms include hemodynamic improvements, metabolic shifts, anti-inflammatory effects, and direct myocardial benefits. This study aims to explore the impact of SGLT2 inhibitors on cardiac remodeling in patients with CHF, providing insights into their therapeutic potential and underlying mechanisms.

This investigation not only holds promise for advancing the understanding of CHF management but also addresses a critical need for novel strategies to improve the quality of life and survival rates of patients. By elucidating the role of SGLT2 inhibitors in modulating cardiac remodeling, this study seeks to contribute to the growing body of literature that bridges the gap between clinical efficacy and mechanistic understanding.

METHODS

The study design is a multicentre, single-arm, open-label, prospective and interventional study, specifically designed to assess the effect of SGLT2 inhibitor on cardiac remodelling parameters over a period of 6 months, in stable patients with chronic HF irrespective of LVEF

The study population included stable out-setting patients with established diagnosis of chronic HF and receiving an optimized guideline-directed therapy, for at least 1 month, except that they were not on SGLT2 inhibitor or any other SGLT2 inhibitor at the time of screening. Subjects eligible for inclusion in this study have to fulfill all of the following criteria: age >18 years; prior diagnosis of HF, with at least one hospitalization for HF at any time; New York Heart Association (NYHA) class I–IV; LVEF available (echocardiogram or cardiac magnetic resonance imaging) within the last 12 months prior to enrolment; treatment according to contemporary guideline recommendations and with stable doses of oral loop diuretics for at least 4 weeks; N-terminal pro-B-type natriuretic peptide (NT-proBNP) >600 pg/ml at screening (≥400 pg/ml if hospitalized for HF within the previous 12 months; ≥900 pg/ml if concomitant atrial fibrillation at screening irrespective of time to last HF hospitalization). Among exclusion criteria, there were: prescription of SGLT2 inhibitor at any time within the previous 6 months; diagnosis of type 1 diabetes mellitus; any worsening HF episode, with or without hospitalization, within 4 weeks prior to enrolment; presence at screening of an estimated glomerular filtration rate <30 ml/min/1.73 m^2 or symptomatic hypotension, or systolic blood pressure <95 mmHg .

RESULTS

A total of 162 patients (64.2% men) were enrolled with a mean age of 70.5 ± 10.6 years (40% >75 years). The study flow chart is presented in online supplementary. Among clinical characteristics, 43% had permanent atrial fibrillation, 36% had coronary artery disease, 22% were diabetics and most patients were in NYHA class II (80%) at baseline. As a pre-specified inclusion criteria, all patients had a previous HF hospitalization, with a median time from last admission of 1.2 years. The patient characteristics differed between the HF with reduced ejection fraction (HFrEF) and LVEF >40% groups, as expected. Patients in the HFrEF group had higher rates of male sex and ischaemic disease, while patients in the LVEF >40% group were older and had higher rates of hypertension, atrial fibrillation and valvular disease. The patients included in the study were receiving optimized therapy, with a high adherence to guideline-directed treatments for HFrEF. Specifically, 94% of patients were on beta-blockers and renin–angiotensin system inhibitors (or angiotensin receptor–neprilysin inhibitor), and 87% were on mineralocorticoid receptor antagonists. No differences were found in terms of analytical parameters. A with an earlier response seen in terms of volumes at 30 days. At 180 days, a significant reduction in LV mass index was observed (−13.9% [95% CI −18.7, −8.7], $p < 0.001$). The reduction in LV end-diastolic volume (−8.0% [95% CI −11.6, −4.2], $p < 0.001$) and LV end-systolic volume (−11.9% [95% CI −16.7, −6.8], $p < 0.001$) at 180 days was associated with an improvement in LVEF (5.0% [95% CI 0.2–9.9], $p = 0.040$) and global longitudinal strain (8.9% [95% CI 0.6–17.9], $p = 0.036$). Although no change was observed in Doppler filling pressures, NT-proBNP concentrations showed a trend toward early reduction at 30 days (−8.3% [95% CI −16.6, 0.7], $p = 0.070$), which reached significance at 180 days (−18.2% [95% CI −27.1, −8.2], $p < 0.001$). Hs-TnT concentrations were steady across the study visits (baseline vs. 180 days: 1.2% [95% CI −4.2, 6.9], $p = 0.667$).

DISCUSSION

The study's key finding was that SGLT2 inhibitor had similar positive effects on LA geometry and function in patients with chronic HF, regardless of LVEF-based phenotypes. Even after accounting for higher rates of permanent atrial fibrillation in patients with LVEF >40%, this finding remained consistent. However, it is worth noting that the studied population had long-standing chronic HF and well-optimized treatment, yet a significant proportion of patients (42%) had severely dilated left atria and all evaluated LA parameters were affected, indicating an

established LA disease. The relationship between left atrium and HF progression is unclear. LA disease could contribute to HF irrespective of LVEF, or it may simply reflect a passive role in HF, representing the chronicity of elevated LV pressures across the LVEF spectrum.

CONCLUSION

SGLT2 inhibitor administration in stable out-setting patients with chronic HF and optimized therapy results in global reverse remodelling of cardiac structure, including reductions in LA volumes and improvement in left ventricular geometry and NT-proBNP concentrations.

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