Diabetes Updates

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Empagliflozin in paroxysmal or persistent atrial fibrillation: a possible antiarrhythmic effect

Fazio G* and Schirò P

Casa di Cure Triolo Zancla – Piazza Fonderia 23 – 90100 – Palermo, Italy

Abstract

Background: Many studies have highlighted an increased risk of developing atrial fibrillation (AF) in diabetic patients. The SGLT2 inhibitors, in addition to glycaemic control, have shown pleiotropic effects on the cardiovascular system, proving to be particularly advantageous in patients with heart failure. In this study we evaluated a group of patients with paroxysmal AF (PAF) or persistent AF (PeAF) affected by type 2 diabetes and treated with empagliflozin.

Methods: This is a case-crossover study obtained from our database of patients affected by PAF or PeAF. We extracted 23 consecutive subjects ICD wearers and affected by diabetes that started treatment with empagliflozin during the follow-up.

Results: All enrolled patients were ICD wearers because at high risk of sudden cardiac death and received amiodarone; empagliflozin was added during follow-up for the treatment of diabetes. We evaluated the recurrence of PAF and the days free from AF one year before and one year after starting treatment with empagliflozin. The recurrence of AF was significantly lower after starting empagliflozin than before the treatment (p: 0.001).

Conclusion: Our data suggest that empagliflozin is able to reduce the recurrences of AF in diabetic patients with PAF or PeAF. Further studies might demonstrate an antiarrhythmic effect of empagliflozin and change the therapeutic approach in subjects at high risk of AF.

Abbreviations: CHD: Chronic heart failure; HF: Herat failure; PAF: paroximal atriale fibrillation; AF: Atrial fibrillation; SGLT: Sodium/glucose co-trasporter 2.

Introduction

Traditionally, diabetes mellitus has been associated with coronary heart disease (CHD), but the possible correlation with arrhythmic diseases is a more recent concern. Over the last decade many studies have highlighted the association between diabetes mellitus and increased risk of developing atrial fibrillation (AF) relative to patients without diabetes [1-7]. The SGLT2 inhibitors, in addition to the hypoglycaemic effect, have shown pleiotropic effects on the cardiovascular system, proving to be particularly advantageous in patients with heart failure. The post-hoc analysis of the DECLARE-TIMI 58 study conducted by Zelniker and colleagues, recently published in Circulation, for the first time demonstrated a favourable effect of treatment with the SGLT2 inhibitor dapagliflozin on the incidence of FA and FLA in patients with type 2 diabetes, independently of previous history of FA / FLA, atherosclerotic disease or heart failure [8]. The mechanisms underlying this effect are not yet well known and are probably multiple: from the natriuretic, diuretic and hemodynamic effect of these drugs that could prevent atrial dilation and cardiac remodelling, to the effects on blood pressure, body weight, oxidative stress and reduction of epicardial fat.

In this study we analysed retrospectively our experience in a cohort of diabetic patients with paroxysmal AF (PAF) or persistent AF (PeAF) in treatment with empagliflozin for diabetes.

Methods

Data of the present case-crossover study were retrospectively obtained from our database of patients affected by PAF or PeAF: from 2540 patients followed for AF by our cardiology unit, we extracted 23 consecutive subjects ICD wearers and affected by diabetes that started treatmentwith empagliflozin during the follow-up. The mean age of this study group was 72,6 ± 6 years. PAF were diagnosedin 88,5% subjects whereas PeAF in the remaining 12,5%. All enrolled patients were ICD wearers and received amiodarone. The ICD was implanted due to high cardiovascular risk when the FE was ≤ 35% and/or the QT was elongated; empagliflozin was added during follow-up for the treatment of diabetes (Table 1).

All patients are monitored at least twice per year, through a clinical examination, an electrocardiogram and blood routine examinations. Given the need for renewal of the therapeutic plan, all patients treated with empaglifozin must return at least once six months to the prescriber centre and therefore none of the patients who continued the treatment was lost at the follow-up. No patient discontinued the treatment.

Patient notes were reviewed, and the following data recorded: age, sex, indication for empaglifozin, duration of treatment, concomitant therapy, creatinine and haemoglobin level before and after treatment.

The present project is an observational retrospective study and so it is not subject to the directive 2001/20/CE of the European Parliament regulating the application of a good clinical practice during clinical

Correspondence to: Giovanni Fazio, MD, PhD, FESC, FEACVI, Casa di Cure Triolo Zancla – Piazza Fonderia 23 – 90100 – Palermo, Italy, E-mail: Faziogiova@gmail.com

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experimentation (Art. 1 comma 1; Art 2/c) and so it was not necessary to require an Ethics Committee ruling.

Results

We evaluated the recurrence of PAF and the days free from AF one year before and one year after starting treatment with empagliflozin. The recurrence of AF was lower after starting empagliflozin than before the treatment. We reported statistical differences both in the number of episodes of recurrence and on days without arrhythmia (p: 0.001 and p: 0.04) (Table 2).

Discussion

Atrial fibrillation is the most frequent sustained cardiac arrhythmia, associated with a significant increase in the risk of thromboembolic events and mortality. From 50 years onwards, the prevalence of AF doubles every 10 years, reaching 10% after 80 years [9]. Treatment of AF has as first aim the restoration and maintenance of the sinus rhythm. However, drugs used to date have limitations in terms of side and pro-arrhythmic effects, compared to a limited antiarrhythmic effect. Due to contraindications and possible risks, rhythm control in elderly patients with AF is an actionable goal only in selected patients, while in most subjects the only achievable objective remains control of frequency. The post-hoc analysis of the DECLARE-TIMI 58 study conducted by Zelniker and colleagues, published last January in Circulation, suggests first a possible role of a SGLT2 inhibitor in the prevention of AF [8]. In addition, many new antidiabetic agents have been recently demonstrating possible therapeutic benefits even in patients without diabetes. This is what emerges from the phase III trials DAPA-HF and EMPEROR-Reduced where the effect of dapagliflozin and empagliflozin, respectively, on HF, in addition to the standard of care, has been investigated in adult patients with reduced ejection fraction with and without type 2 diabetes [10,11]. Our clinical experience with empagliflozin suggests that this molecule may also exertan antiarrhythmic effect on the heart, in a similar way to that observed with dapagliflozin in DECLARE-TIMI 58. Empagliflozin is an oral antidiabetic drug that acts by inhibiting the action of the sodium-glucose cotransporter 2 at the level of the renal tubule with a greater selectivity than dapagliflozin. Recent studies on the cardiovascular safety profile of the drug have shown that empagliflozin reduces mortality and hospitalization for heart failure (HF) compared to placebo, but to date it is not clear which mechanisms are responsible for these effects [12-15]. Data obtained from our small-scale study indicate that, in addition to already known effects, empagliflozin might exert an antiarrhythmic effect. The mechanisms underlying the possible protective effect of empagliflozin on FA are still unknown. We therefore hypothesize that SGLT2 inhibitors modulate various risk factors for FA such as myocardial remodelling, blood pressure, body weight, inflammation, oxidative stress and adrenergic hyperactivity [16-19]. Further studies should investigate the role of SGLT inhibitors in the prevention and treatment of FA thus unveiling potential new treatment of AF, especially in people with HF.

Table 1. Characteristics of patients

No. of patients [*n* (%)]	23
Age (years) [mean ± SDI]	72,7 ± 6
Male/female [*n* (%)]	48%/52%
Creatinine (mg/dL) [mean ± SD]	1.2 ± 1
Months of anticoagulation therapy [mean ± SD]	24 ± 2
Paroximal AF [*n* (%)]	88,50%
persistent AF [*n* (%)]	12,50%
Hypertension [*n* (%)]	83%
Hypertensive Cardiomyopathy	23%
Diabetes mellitus [*n* (%)]	100%
Heart failure [*n* (%)]	13000%
Previous Stroke/TIA [*n* (%)]	8,30%
Ischemic cardiomyopathy [*n* (%)]	60,00%
β-Blockwera [*n* (%)]	36,25%
Amiodaron [*n* (%)]	100,00%
empaglifozin	100,00%
insulin	23,00%
metformin	93,00%
CHA2DS2-VASc (mean ± SD)	4.02 ± 1.5
HAS-BLED score (mean ± SD)	2.50 ± 0.7

Table 2. Results of the analysis

	Before empaglifozin	After empaglifozin	P
Recurrences of paroxysmal at rial fibrillation/patients year	6,5	2,3	0,001
Days free from AF/patient year	244	303	0,04
Cardiovascular death	3%	3100%	NS
TIA	6,25%	1,2%	0,0046
Stroke	0%	0,02%	NS
Systemic embolism	0%	0,001%	NS
Pulmonary embolism	0%	0,001%	NS

Conclusion

Our data might suggest that empagliflozin is able to reduce the recurrences of AF in diabetic patients with PAF or PeAF. This small-scale case-crossover study aims to encourage research of clinical evidence, through specially designed studies, in order to optimize the use of available antidiabetic drugs for the prevention and treatment of cardiovascular diseases in patients at high cardio-metabolic risk.

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