doi:10.1002/ejhf.3262
Online publish-ahead-of-print 28 April 2024

Association of sodium–glucose cotransporter 2 inhibitors with changes in comprehensive geriatric assessment in elderly diabetic patients with heart failure: Data from MAGIC-HF

Heart failure (HF) represents the primary cause of hospitalization, disability, mortality, and healthcare costs in elderly patients.[1] The comprehensive geriatric assessment (CGA) is a multidimensional tool for assessing cognitive function, mood symptoms, and functional abilities that can predict short- and long-term mortality in patients with HF, despite some limitations in different clinical domains of elderly HF patients.[2,3]

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have been shown to improve clinical prognosis in HF. Additionally, a study in murine models with type 2 diabetes mellitus (T2DM) and Alzheimer's disease demonstrated that SGLT2i can reduce vascular damage and cognitive impairment (CoI).[4] Furthermore, an observational real-life study showed a significant beneficial effect of empagliflozin on cognitive and physical impairment in frail older adults with diabetes and HF with preserved ejection fraction.[5] However, the potential role of SGLT2i on CGA scales in elderly patients with HF with reduced ejection fraction (HFrEF) has not been investigated.

Therefore, the aim of this study was to evaluate the possible association of SGLT2i with CGA variations in a cohort of HFrEF elderly with T2DM; sex differences in these associations and determination of oxidative stress and platelet activation biomarkers were also assessed.

The 'MAgna Graecia evaluation of Comorbidities in patients with Heart Failure' (MAGIC-HF) study is an observational registry that includes adult patients with HF referred to the HF Centre of the Geriatric Division at the 'Magna Graecia' University of Catanzaro. From an initial cohort of 432 patients, 134 consecutive elderly outpatients with HFrEF and T2DM were considered for the present study (online supplementary *Figure S1*) after applying the following selection criteria: elderly outpatients with HFrEF and T2DM as inclusion criteria; and severe chronic kidney disease, clinically manifest dementia or severe psychiatric disorders, Child–Pugh C liver cirrhosis, and waiting list for heart transplantation as exclusion criteria.

All patients underwent a comprehensive medical history with CGA and physical, laboratory and instrumental examination, before the introduction of SGLT2i, and after 6 months of treatment. Quality of life assessment was performed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ).[6]

The protocol was approved by the University Ethics Committee (2022.384) and informed consent was obtained from all participants to the MAGIC-HF study (ClinicalTrials.gov Identifier: NCT05915364). All investigations were made in accordance with the principles of the Declaration of Helsinki.

Changes in key study variables between baseline and follow-up were compared between men and women using the Mann–Whitney test. In the entire population, a simple linear regression analysis was performed to assess the correlation between the change in Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Geriatric Depression Scale (GDS), and Short Physical Performance Battery (SPPB) values, expressed as (Δ) between baseline and follow-up (ΔT0–6), and the change in several covariates, also expressed as ΔT0–6. Variables that reached statistical significance were entered into a stepwise multivariate linear regression model to assess their adjusted associations with Δ MMSE, MoCA, GDS, and SPPB. Differences were considered significant at $p < 0.05$. Statistical analysis was performed using SPSS V20.0 program for Windows (SPSS Inc., Chicago, IL, USA).

The study population included 82 men (61.2%) and 52 women (38.8%), with an average age of 72.6 ± 6.6 years; all patients were >65 years old. Clinical characteristics were comparable between sexes, except for ischaemic heart disease and chronic obstructive pulmonary disease that were more prevalent in males (50 [60.9%] and 31 [37.8%], respectively), and chronic kidney disease and dyslipidaemia that were more prevalent in females (27 [51.9%] and 50 [96.2%], respectively) (online supplementary *Table S1*). At baseline, 38.8% of patients started therapy with dapagliflozin and 61.2% with empagliflozin. Women were more symptomatic than men and had higher circulating levels of NADPH oxidase 2 (Nox-2) and lower estimated glomerular filtration rate (eGFR) values (online supplementary *Table S1-S2*).

After 6 months on SGLT2i, a significant improvement in clinical symptoms was detected by changes in MLHFQ score from 83.6 ± 5.0 to 79.4 ± 4.6 ($p < 0.0001$); no episodes of symptomatic hypotension were reported. A slight reduction in eGFR values (68.4 ± 24.9 vs. 64.1 ± 10.0 ml/min/1.73 m^2; $p = 0.003$) was noted alongside a significant decrease in uric acid (6.7 ± 0.6 vs. 5.6 ± 0.8 mg/dl, $p < 0.0001$). At 6-month follow-up, a significant improvement in oxidative stress and platelet activation biomarkers was observed: Nox-2 (1.2 ± 0.2 vs. 0.8 ± 0.1 nmol/L; $p < 0.0001$), 8-isoprostane (70.5 ± 11.9 vs. 64.5 ± 10.0 pg/ml, $p < 0.0001$), and sP-selectin (129.9 ± 10.2 vs. 103.5 ± 12.9 ng/ml; $p < 0.0001$) (online supplementary *Table S3*).

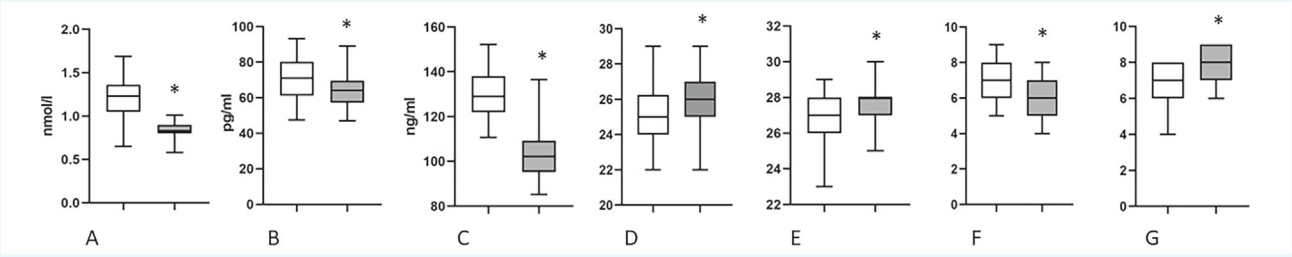

Figure 1 (*A*) Serum levels of the oxidative stress biomarker Nox-2, at baseline and 6-month follow-up. (*B*) Serum levels of the oxidative stress biomarker 8-isoprostane, at baseline and 6-month follow-up. (*C*) Serum levels of the platelet activity biomarker sP-selectin, at baseline and 6-month follow-up. (*D*) Mini-Mental State Examination score, at baseline and 6-month follow-up. (*E*) Montreal Cognitive Assessment score, at baseline and 6-month follow-up. (*F*) Geriatric Depression Scale score, at baseline and 6-month follow-up. (*G*) Short Physical Performance Battery score, at baseline and 6-month follow-up. *$p < 0.0001$ versus baseline.

Table 1 Changes in major parameters between baseline and follow-up according to gender

	All population ($n = 134$)	Males ($n = 82$)	Females ($n = 52$)	p-value*
Δ MMSE, pt	1.0 (0, 1.0)	1.0 (0, 1.0)	0 (0, 1.0)	**0.048**
Δ MoCA, pt	0 (0, 1.0)	1.0 (0.0, 2.0)	0 (0, 1.0)	**<0.0001**
Δ GDS, pt	−1.1 (−1, −1)	−1.0 (−1.0, −1.0)	−1.0 (−2.0, −1.0)	**0.003**
Δ SPPB, pt	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	1.0 (0.8, 1.0)	**<0.0001**
Δ BMI, kg/m^2	−0.7 (−1.0, −0.4)	−0.6 (−0.8, −0.4)	−0.7 (−1.0, −0.5)	0.052
Δ MLHFQ, pt	−4.0 (−4.8, −3.0)	−4.0 (−4.0, −3.0)	−4.0 (−5.0, −3.0)	0.115
Δ 8-isoprostane, pg/ml	−4.4 (−8.0, −2.0)	−3.9 (−7.2, −1.7)	−4.9 (−8.5, −2.2)	0.236
Δ Nox-2, nmol/L	−0.3 (−0.5, −0.2)	−0.3 (−0.5, −0.2)	−0.4 (−0.6, −0.3)	**0.007**
Δ sP-selectin, ng/ml	−28.7 (−37.8, −15.7)	−30.2 (−38.1, −17.5)	−23.1 (−32.4, −10.4)	0.756
Δ HOMA	−2.7 (−3.8, −1.1)	−3.1 (−3.9, −1.1)	−2.1 (−3.3, −1.1)	0.171
Δ HbA1c, %	−1.2 (−2.0, −0.8)	−1.2 (−1.7, −0.8)	−1.4 (−2.2, −0.7)	0.304
Δ Uric acid, mg/dl	−1.1 (−1.6, −0.6)	−1.0 (−1.6, −0.6)	−1.1 (−1.6, −0.7)	0.604
Δ hs-CRP, mg/L	−0.7 (−0.8, −0.6)	−0.7 (−0.8, −0.6)	−0.7 (−0.9, −0.6)	0.184
Δ NT-proBNP, pg/ml	−352.5 (−851.5, −181.5)	−275.0 (−738.8, −177.0)	−629.5 (−1192.2, −231.7)	**0.011**
Δ Cardiac index, ml/min/1.73 m^2	113.6 (81.5, 140.8)	129.8 (113.6, 153.0)	69.8 (44.6, 88.7)	**<0.0001**
Δ GLS, %	−1.3 (−2.3, −1.2)	−1.3 (−2.3, −0.9)	−1.3 (−2.1, −1.2)	0.565

BMI, body mass index; GDS, Geriatric Depression Scale; GLS, global longitudinal strain; HbA1c, glycated haemoglobin; HOMA, homeostasis model assessment; hs-CRP, high-sensitivity C-reactive protein; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; Nox-2, NADPH oxidase 2; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pt, point; SPPB, Short Performance Physical Battery.
*Performed by Mann–Whitney test.
[Correction added on 27 May 2024, after first online publication: In column 1, 'Δ eGFR' has been corrected to 'Δ Cardiac index' in this version.]

A significant improvement in MMSE (25.4 ± 1.6 vs. 26.1 ± 1.5; $p < 0.0001$) and MoCA (26.7 ± 1.3 vs. 27.5 ± 1.5; $p < 0.0001$) score, with a statistically significant reduction in GDS score (7.1 ± 0.9 vs. 6.0 ± 0.9; $p < 0.0001$), and increase in SPPB (6.7 ± 1.0 vs. 7.8 ± 0.9; $p < 0.0001$) (*Figure 1*), were observed. Of interest, a cognitive improvement was also observed in patients with CoI. The number of patients with CoI detected by MMSE decreased from 39 (29.1%) at baseline to 19 (14.2%) at follow-up ($p = 0.001$), while those with MoCA score decreased from 55 (41.0%) at baseline to 28 (20.9%) at follow-up ($p = 0.0003$).

The magnitude of changes between baseline and follow-up in the study population variables was similar between men and women, except for cognitive function, cardiac index (CI), and functional abilities. Interestingly, ΔMMSE, ΔMoCA, ΔCI, and ΔSPPB were greater in men than in women. On the contrary, GDS and Nox-2 improved more in women than in men (*Table 1*).

Considering MMSE variation as the dependent variable, ΔCI, ΔNox-2, Δ homeostasis model assessment (HOMA), ΔsP-selectin, and Δ N-terminal pro-B-type natriuretic peptide (NT-proBNP) were associated with 53.8% of MMSE variation. When ΔMoCA was considered as the dependent variable, ΔCI was associated with 20.5% of MoCA variation; the addition of ΔNox-2, Δ sP-selectin, and Δ glycated haemoglobin correlated for 33% of ΔMoCA. Considering ΔGDS as the dependent variable, ΔHOMA was associated with 22% GDS variation, and ΔCI and ΔsP-selectin also entered into the model and correlated for a total of 29.5% of GDS variations. Finally, for ΔSPPB, ΔHOMA correlated for 34.1% of ΔSPPB, and ΔCI, ΔsP-selectin, Δ global longitudinal strain, and ΔNT-proBNP were associated with the dependent variables for a total of 49.7% (online supplementary *Tables S4-S5*, *Figure S2*).

In conclusion, this study was conducted in an elderly population suffering from chronic HFrEF and T2DM with several comorbidities, in which the addition of SGLT2i to optimal medical therapy for 6 months was associated with important improvements in clinical,

metabolic, and haemodynamic outcomes. These changes were associated with an improvement in cognitive, mood, and functional status, as well as markers of oxidative stress and platelet activation in the whole population. Of particular interest, improvement in cognitive function was observed in those patients with an already known diagnosis of CoI. The potential mechanisms explaining these effects could be found in the anti-oxidant and vascular damage-reducing action by SGLT2i. In addition, they could have a direct neuroprotective effect with inhibition of acetylcholinesterase and increased brain levels of brain-derived neurotrophic factor.[5] However, the improvements in cognitive and functional scores were greater in men, while the improvement in depressive symptoms and oxidative stress markers was greater in women, thus highlighting the importance of sex difference in the management of HF, particularly in the response to treatment, a highly topical knowledge gap. The present study also has several limitations; firstly, it is not a randomized clinical trial, and a matched control group is not available. Another important limitation is represented by the relatively small sample size. The imbalance of patient numbers according to gender, with a higher prevalence of males, may also represent an intrinsic limitation of our study.

Conflict of interest: none declared.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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