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Impact of sodium glucose cotransporter-2 inhibitors' therapy in Heart Failure

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Abbreviations

ACE Angiotensin-converting enzyme

ARB Angiotensin II receptor blockers

BNP B-type natriuretic peptide

CAD Coronary artery disease

CHUC Centro Hospitalar e Universitário de Coimbra (Coimbra's Hospital and University Centre)

CV Cardiovascular

DM *Diabetes mellitus*

EF Ejection fraction

HF Heart failure

HFmEF Heart failure with mid-range ejection fraction

HFpEF Heart failure with preserved ejection fraction

HFrEF Heart failure with reduced ejection fraction

IQR Interquartile range

LVEF Left ventricular ejection fraction

NT-proBNP Amino terminal cleavage fragment of the B-type natriuretic peptide

NYHA New York Heart Association

QoL Quality of life

SGLT Sodium glucose linked cotransporter

SD Standard deviation

T2DM Type 2 *Diabetes mellitus*

VAS Visual analog scale

Abstract

Sodium glucose linked cotransporter 2 (SGLT2) inhibitors are oral hypoglycemic agents, whose action mechanisms on HF have not yet been fully identified.

This study aimed at answering whether diabetic patients suffering from HF and those without formally diagnosed HF have their health related QoL and cardiac biomarkers improved when treated with the SGLT2 inhibitor sotaglifozin.

This was a retrospective observational study conducted in a population of diabetic patients originally followed in the Cardiology Service of Centro Hospitalar e Universitário de Coimbra and that were previously enrolled in the SCORED clinical trial. Data was collected retrospectively, directly from clinical files and recuring to telephone-based questionnaires to patients. The primary outcomes of this study were to evaluate changes in NT-proBNP levels and in health-related QoL, secondary outcomes were to establish the proportions of patients with improvement on NYHA functional class and of patients with improvement on self-assessed perception on health-related quality of life. Data analysis was performed using SAS software (SAS Institute, Cary NC, USA).

A decrease of the mean NT-proBNP value was observed in the sotaglifozin group and an increase in the placebo group, and no significant difference between groups was found (p=0.5445). The mean EQ-5D-3L index score decreased in both groups suggesting worsening in the perceived health status, and mean EQ-VAS increased in both groups; no beneficial effect of the intervention was found in either QoL domains (p=0.2947 and p=0.7643, respectively).

37.14% of the sotaglifozin group and 46.43% of the placebo group report self-assessed improvement (p=0.7298) in the health related QoL perception, while 20% of patients on the sotaglifozin group improved their NYHA class compared to 25% on the control group (p=0.8367).

In this study the treatment with the SGLT2 inhibitor sotaglifozin has not demonstrated to improve health related QoL in diabetic patients suffering from HF and those without formally diagnosed HF or have influence on the selected cardiac biomarker NT-proBNP, nor cause improvement in the NYHA functional class.

Keywords: Heart Failure, SGLT2 inhibitors, Quality of life, Ejection fraction

Background

Heart failure (HF), a clinical syndrome, is a major public health problem with an estimated prevalence of about 4% of the adult population in Portugal, rising above 12% in the group of 70-79 years of age and over 16% above the age of 80. With population ageing (for it is estimated that the number of Portuguese patients over 80 years of age will increase by 73% between 2011 and 2035) and established association to both high morbidity and mortality, HF negatively impacts the quality of life (QoL) of patients and implies elevated direct and indirect costs, emblazoning the enormous social and economic burden exerted by this condition. [1-4]

HF is caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress; it is characterized by the presence of typical symptoms that may or may not be accompanied by signs. [3] Multiple risk factors have been established to be associated to the condition. [1]

HF is described and defined according to the left ventricular ejection fraction (LVEF) in HF with preserved ejection fraction (HFpEF, when EF is ≥50%), HF with mid-range ejection fraction (HFmrEF, ranging from 41 to 49%) and HF with reduced ejection fraction (HFrEF, when ≤40%), associated with different demographics, etiologies, comorbidities, and therapeutic responses. [3] Natriuretic peptides, such as B-type natriuretic peptide (BNP) and its amino terminal cleavage fragment (NT-proBNP) are used as biomarker tools not only in the establishment of HF diagnosis but also as guidance for therapeutic management and optimization, as well as prognosis, due to a direct correlation between the changes in its values and the benefits of applied therapy. [5]

The treatment approach of HF is similar in both diabetic and nondiabetic patients and comprises diuretics, medication acting in the renin-angiotensin-aldosterone system such as Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin II receptor blockers (ARB), β-blockers, neprilysin inhibitor and resynchronization therapy. [3,6]

Sodium glucose linked cotransporter 2 (SGLT2) inhibitors are oral hypoglycemic agents that block the low affinity high capacity SGLT2 in the proximal convoluted tubules in the kidneys, inhibiting glucose re-absorption and resulting in its increased urinary excretion. Although the action mechanisms on HF have not yet been fully identified, it has been suggested that the cardioprotective effects of SGLT2 inhibitors rely on more than hypoglycemic action - giving rise to a shift in the treatment paradigm for all HF patients, both diabetic and nondiabetic. [6-10]

The beneficial effects of this novel class both in reducing hospitalization rates and in the prevention of cardiovascular events due to HF have been vastly reported with particular significance in patients suffering from HFrEF. Such has been evidenced by cardiovascular

outcome trials with empaglifozin, canaglifozin and dapaglifozin. [11-12] Nevertheless, data regarding the forementioned treatment approach on patients suffering from HFpEF and HFmrEF remains scarce, and other molecules such as sotaglifozin - a dual SGLT2 and 1 inhibitor - are still under various study stages. [13-14]

This study aims at answering whether diabetic patients suffering from HF and those without formally diagnosed HF have their health related QoL and cardiac biomarkers improved when treated with the SGLT2 inhibitor sotaglifozin. As such, the primary objective is to assess the impact on health related QoL and NT-proBNP domains. Secondary objectives are to describe demographics, clinical and therapeutic characteristics of patients, evaluate the functional class and patients' self-assessed QoL perception.

Materials and methods

Study design

This is a retrospective observational study conducted in a population of diabetic patients that were previously enrolled in the SCORED clinical trial - a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, in which patients were randomized (T0) in a 1:1 fashion to receive either sotaglifozin 200 mg daily or placebo (from T0 to T2), to reduce cardiovascular death or heart failure events. [15] Posterior to its conclusion (T3), clinical data was collected retrospectively, directly from patients' clinical files, and health-related QoL domains and functional class were collected recuring to telephone-based questionnaires to patients. Figure 1 illustrates the study design.

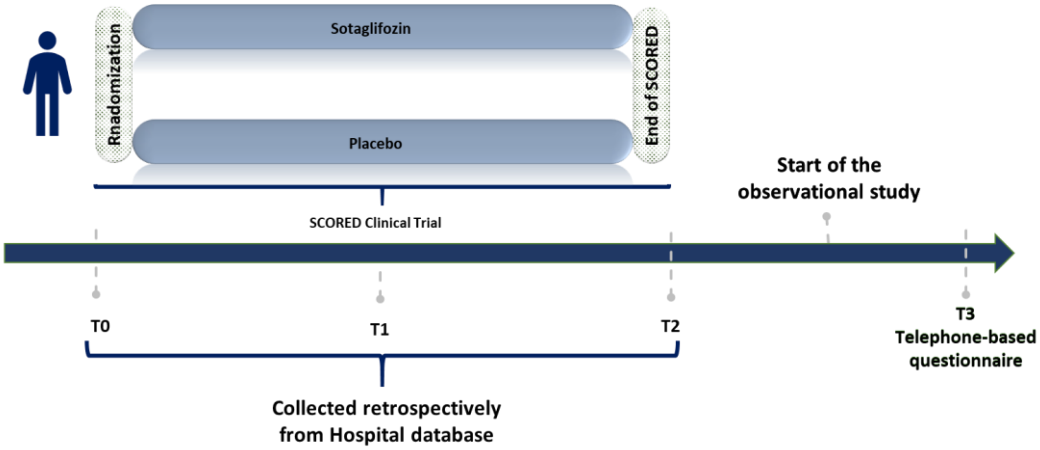

Figure 1 Study design

Subjects

The subjects of the study were selected from consultation of the database of patients followed in the Cardiology Service of Centro Hospitalar e Universitário de Coimbra (CHUC, Coimbra's Hospital and University Center) that participated in the SCORED clinical trial under informed consent, with regard to the trial's selection criteria. [15]

Data sources and variables

This study uses primary data collected through telephone-based questionnaire to patients, resorting to telephone calls from the Cardiology service of CHUC between February and March

of 2021, with regard to anonymity and voluntarist regimen, and secondary data collected directly from patients' clinical files.

The main variables measured in the study, described in detail on Table 1, were:

- NT-proBNP levels quantification in patient blood samples;
- Health related QoL, assessed through application of the Portuguese version of the EQ-5D-3L, a self-administered utility measure that consists of a 5-item health state assessment and a visual analog scale (VAS) (Annex I). [16] Lower values of EQ-5D-3L index score (0 to 1) and EQ-VAS (0 to 100) indicate worse health status;
- Functional class according to the New York Heart Association (NYHA) classification, assessed on the subgroup with formally diagnosed HF;
- Self-assessment of health related QoL perception before and after participation in the clinical trial, regarding a possible improvement, maintenance or deterioration;

The assessment of NYHA class, EQ-5D-3L index score and EQ-VAS at baseline was performed retrospectively recuring to telephone-based questionnaire to patients on T3, to capture these at the time of clinical trial enrollment.

Additionally, aiming to describe demographic, clinical and HF therapeutic characteristics of patients, the following variables were evaluated:

- Patient demographics: age, gender;
- Clinical characterization: LVEF and comorbidities;
- Therapeutic characterization: concomitant heart failure medication and other medication.

Table 1 Study variables, its operationalization and the data sources used.

Variable	Timeline	Operacionalization	Data source
Demographic characterization			
Gender	T0	Female Male	Hospital database
Age	T0	Age (number)	Hospital database
Clinical characterization			
LVEF (%)	T0	≤40% 41-49% ≥50%	Hospital database

Variable	Timeline	Operacionalization	Data source
NYHA	T0, T3	I II III IV	Telephone-based questionnaire
NT-proBNP (pg/mL)	T0, T2	NT-proBNP (pg/mL)	Hospital database
Comorbidities	T0	Heart failure Hypertension Dyslipidemia Obesity Coronary artery disease (CAD) Cardiac implant Other	Hospital database
Therapeutic history			
HF medication	T0	ACE inhibitor ARB β-blocker Neprilysin inhibitor	Hospital database
Other medication	T0	Lipid lowering drugs Antiaggregant Anticoagulant Antiarrhythmic	Hospital database
Patient reported outcomes			
Health related QoL (EQ-5D-3L)	T0, T3	Score	Telephone-based questionnaire
Self-assessed perception on health related QoL	T3	Improvement Maintenance Deterioration	Telephone-based questionnaire

Outcomes of interest

The primary outcomes of this study were to evaluate:

- changes from baseline to T2 in NT-proBNP levels;
- changes from baseline to T3 in health-related QoL;

Secondary outcomes:

- Proportion of patients with improvement on NYHA functional class;
- Proportion of patients with improvement on self-assessed perception on health-related quality of life.

Data analysis

Summary tables and/or figures are provided for the description of all variables through descriptive statistics or frequency tables. Dichotomous or categorical variables were summarized by absolute and relative frequencies, using the total number of patients for whom data was available. Continuous variables were summarized using measures of central tendency and dispersion, either as mean and standard deviation (SD), or median and interquartile range (IQR), as appropriate. Intervention (sotaglifozin) and control (placebo) groups were compared using chi-square tests or fisher exact (discrete variables) or the appropriate test for continuous data (t-test or nonparametric Wilcoxon Sign-Rank test).

Regarding the primary outcome, the intervention group was compared with the control group, performing an intention-to-treat analysis. Unadjusted mean change from baseline in the NT-proBNP and in EQ-5D-3L was calculated at T2 and at T3, respectively, using a fixed effect generalized linear regression model, including a time × group interaction term as fixed effects. This allowed to test for differences in the primary outcome between the intervention and the control groups.

A pre-specified sensitivity analysis was conducted to assess the impact of the inclusion of patients without formally diagnosed HF in NYHA functional class results.

95% confidence intervals were reported whenever relevant and applicable, and two-sided *p*-values < 0.05 were considered significant.

Data analysis was performed using SAS software (SAS Institute, Cary NC, USA).

Results

From a total of 78 patients from SCORED trial, 15 were excluded (4 died, 4 did not reply to the inquiries, 7 had either dropped out of the trial or had no measurements) resulting in a total of 63 subjects included in the study analysis, of which 35 had been assigned to receive sotaglifozin therapy and 28 had received placebo therapy, as schematized in Figure 2.

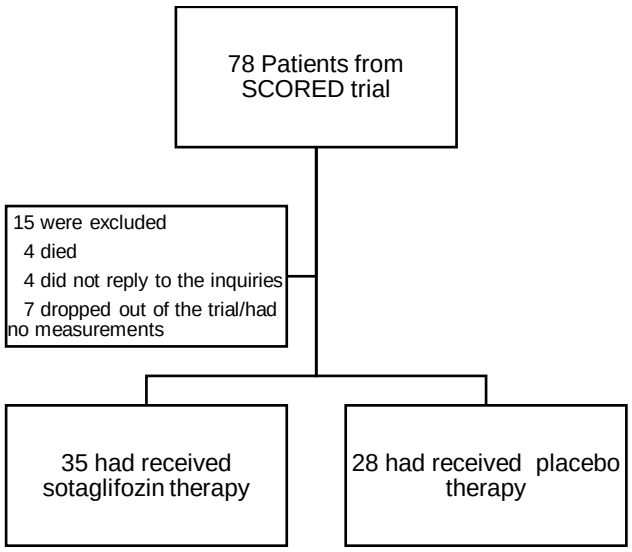

Figure 2 Study flow chart.

Descriptive statistics of characteristics at baseline are summarized in Table 2. The median age of patients was 75 years (IQR, 70-80) and sex-ratio shows a predominance of male gender on both sotaglifozin and placebo groups (62.86% and 85.71%, respectively).

Regarding NYHA functional classification, class II was the most frequently observed class on both groups (40 and 50%), followed by classes III (40%), I (25%) and IV (6.67%) on the sotaglifozin group and classes III (25%) and I (13.33%) among the placebo group.

The majority of patients had a LVEF ≥50% (71.43% on the sotaglifozin group and 67.86% on the placebo group), and 15.67% had a LVEF ≤40% (11.43% on the sotaglifozin group and 21.43% on the placebo group).

As to NT-proBNP levels, a higher mean value was observed among the placebo group (99.27 pg/mL) when comparing to the sotaglifozin group (91.93 pg/mL).

Overall, the most frequent comorbidities were hypertension (100.00%) and dyslipidemia (98.41%). HF diagnosis was formally documented in 41.27% of the subjects (45.71% of the sotaglifozin and 35.71% of the placebo group).

Generally, patients reported mean scores of 0.61 for EQ-5D-3L index score and 65.10 for EQ-VAS.

Table 2. Patient characteristics at baseline.

Characteristic at baseline	Total n=63	iSGLT2 n=35	Placebo n=28
Gender - n (%)			
Female	17 (26.98)	13 (37.14)	4 (14.29)
Male	46 (73.02)	22 (62.86)	24 (85.71)
Age, years – median (IQR)	75.00 (70.00-80.00)	75.00 (70.00-79.00)	74.50 (69.50-80.50)
NYHA functional classification n (%) (n=23)	-		
I	4 (17.39)	2 (25.00)	2 (13.33)
II	10 (43.48)	6 (40.00)	4 (50.00)
III	8 (34.78)	6 (40.00)	2 (25.00)
IV	1 (4.35)	1 (6.67)	0 (0.00)
LVEF, % - n (%)			
≤40%	10 (15.87)	4 (11.43)	6 (21.43)
41-49 %	9 (14.29)	6 (17.14)	3 (10.71)
≥50%	44 (69.84)	25 (71.43)	19 (67.86)
NT-proBNP, pg/mL - mean (SD)	94.99 (114.86)	91.93 (114.87)	99.27 (117.07)
HF medication - n (%)			
β-blocker	48 (77.42)	27 (79.41)	21 (75.00)
ACE inhibitor	22 (35.48)	13 (38.24)	9 (32.14)
ARB	34 (54.84)	18 (52.94)	16 (57.14)
Neprilysin inhibitor	7 (11.29)	2 (5.88)	5 (17.86)
Other medication - n (%)			
Lipid lowering drugs	57 (91.94)	32 (94.12)	25 (89.29)
Antiaggregant	35 (56.45)	18 (52.94)	17 (60.71)
Anticoagulant	20 (32.26)	11 (32.35)	9 (32.14)
Antiarrhythmic	5 (8.06)	3 (8.82)	2 (7.14)
Co-morbidities - n (%)			
HF	26 (41.27)	16 (45.71)	10 (35.71)
Hypertension	63 (100.00)	35 (100.00)	28 (100.00)
Dyslipidemia	62 (98.41)	28 (100.00)	34 (97.14)
Obesity	25 (39.68)	16 (45.71)	9 (32.14)
CAD	34 (53.97)	20 (57.14)	14 (50.00)
Cardiac implant	5 (7.94)	2 (5.71)	3 (10.71)
Other	39 (61.90)	22 (62.86)	17 (60.71)

Characteristic at baseline	Total	iSGLT2 n=35	Placebo n=28
Quality of life (EQ-5D-3L)			
EQ-5D-3L index score, mean (SD)	0.61 (0.29)	0.61 (0.27)	0.62 (0.31)
EQ-VAS, mean (SD)	65.10 (19.62)	62.68 (22.17)	67.92 (16.15)

Primary outcomes

After a median follow-up time of 13.64 months (IQR, 11.91-19.19), a decrease of the mean NT-proBNP value was observed in the sotaglifozin group (from 91.93 to 78.46 pg/mL) and increased in the placebo group (from 99.27 to 110.16 pg/mL). However, no significant difference between groups was found (Diff= -24.36; CI 95%, -103.13 - 54.41; *p*=0.5445).

After a median follow-up time of 25.39 months (IQR, 20.76-28.82), the mean EQ-5D-3L index score decreased in both groups between the baseline and T3 (0.61 to 0.44 among the sotaglifozin group and 0.62 to 0.56 among the placebo group), and mean EQ-VAS increased in both groups (62.68 to 65.81 and 67.92 to 68.96, on the sotaglifozin and placebo groups, respectively); no beneficial effect of the intervention was found in either QoL domains (*p*=0.2947 and *p*=0.7643, respectively). Table 3 details the primary outcomes analysis.

Table 3 Primary outcomes.

Primary Outcomes	iSGLT2	Placebo	Statistical analysis	
			Difference (95% CI)	*p*-value
NT-proBNP, pg/mL – mean (CI 95%)				
T0	91.93 (52.47-131.39)	99.27 (50.95-147.60)	-	-
T2	78.46 (52.58-104.34)	110.16 (53.16-167.16)	-	-
Change	13.47 (-36.61-63.55)	-10.89 (-71.69-49.91)	-24.36 (-103.13-54.41)	0.5445
EQ-5D-3L index score - mean (CI 95%)				
T0	0.61 (0.52-0.71)	0.62 (049-0.74)	-	-
T3	0.44 (0.32-0.56)	0.56 (0.45-0.67)	-	-
Change	0.17 (0.03-0.31)	0.06 (-0.10-0.21)	-0.12 (-0.33-0.10)	0.2947
EQ-VAS - mean (CI 95%)				
T0	62.68 (54.08-71.28)	67.92 (61.10-74.73)	-	-
T3	65.81 (59.74-71.87)	68.96 (61.73-76.19)	-	-
Change	-3.13 (-12.27-6.01)	-1.04 (-11.16-9.08)	2.09 (-11.55-15.72)	0.7643

Secondary outcomes

In what concerns the health related QoL perception on T3, 37.14% of the sotaglifozin group and 46.43% of the placebo group report self-assessed improvement (p=0.7298) after a median follow-up of 25.39 months (IQR, 20.76-28.82).

After a median follow-up of 22.24 months (IQR, 19.49-26.30), most subjects with HF diagnosis did not report HF signs and symptoms progression and maintained their NYHA class (66.67% and 50.00% on the sotaglifozin and placebo group, respectively). Moreover, about 20% of patients on the sotaglifozin group improved their NYHA class compared to 25% on the control group (p=0.8367). Sensitivity analysis showed that results obtained, including patients without formally diagnosed HF, were consistent with those from the primary analysis (Annex II). Secondary outcomes analysis is detailed on Table 4.

Table 4 Secondary outcomes analysis.

Secondary outcomes	iSGLT2	Placebo	*p*-value
QoL perception - n (%)	n=35	n=28	
Improvement	13 (37.14)	13 (46.43)	
Maintenance	21 (60.00)	14 (50.00)	0.7298
Deterioration	1 (2.86)	1 (3.57)	
Evolution of NYHA class - n (%)	n=15	n=8	
Improved NYHA (≤ 1 class)	3 (20.00)	2 (25.00)	
Maintained NYHA	10 (66.67)	4 (50.00)	0.8367
Worsening NYHA (≥ 1 class)	2 (13.33)	2 (25.00)	

Discussion

According to our results, patients' advanced median age (although slightly higher in our study when comparing to other studies with sotaglifozin and other SGLT2 inhibitors) and male gender predominance observed are consistent with previous studies and with established epidemiology for HF. [1,3,15,17]

The main comorbidities described (hypertension, dyslipidemia, CAD, obesity) have also been largely described as risk factors for the development of HF, and concomitant in T2DM patients. [1,3] T2DM has also been described as an independent predictor of poor outcome in HF. [18]

Regarding concomitant medication, the percentage of subjects described to be under β-blocker, ARB and neprilysin inhibitor therapies was higher than described by other studies. On the other hand, percentages of subjects under ACE inhibitor therapy were similar to previously described. [15]

The higher frequency of LVEF ≥50%, observed for subjects on both sotaglifozin and placebo groups has already been reported in other studies, and might be explained by both the increase in prevalence of HFpEF and the underdiagnosis of this form of HF. [3,15] Another explanation for the increased prevalence of subjects with LVEF ≥50% on our sample might be the high prevalence of diabetic cardiomyopathy. This condition has been hypothesized to be characterized by early undiagnosed diastolic dysfunction in patients suffering from T2DM, in the absence of systolic dysfunction. [13,18-19] As the SCORED trial and other studies' focus was not on diastolic dysfunction, further studies are needed to address the effect of different SGLT2 inhibitors on this type of dysfunction.

NT-proBNP levels found at baseline were lower than previously described, which might be due to a potential selection bias introduced by the SCORED clinical trial eligibility criteria. [15] Though no significant statistical difference was found between groups (p=0.5445), the decreasing tendency of mean NT-proBNP value in the sotaglifozin group is in line with previous studies that include populations under SGLT2 inhibitor therapy and may account for clinical relevance. The magnitude of this variation, however, was higher in previous studies, which may be due to the forementioned populations being composed of subjects with HFrEF, in which the SGLT2 inhibitor therapy impact has been established to be bigger. [11-12,17,19-20]

Class II, by the NYHA functional classification, was the most frequently observed among subjects with a HF diagnosis followed by class III, which aligned with previous studies. [17,20] There was no statistically significant difference between groups. Most subjects with HF diagnosis reported to have maintained their NYHA class (66.67% and 50% on the sotaglifozin and placebo

group, respectively) with about 20% patients on the sotaglifozin group reporting to have improved their NYHA class compared to 25% on the control group (p=0.8367). Sensitivity analysis showed consistency between analysis of the subgroup diagnosed with HF and results obtained, including patients without formally diagnosed HF.

No beneficial effect of the intervention was found in either QoL domains (p=0.2947 and p=0.7643, respectively). The mean baseline EQ-5D-3L index score reported by patients was lower than described in other studies (0.61 versus 0.65) and the opposite was observed for the EQ-VAS (65.1 versus 60.8), for a sample with similar approximate median age and gender ratio. [21] Our limited sample size, adding to scarce literature found on the health related QoL, disables generalization and consubstantiated result comparison.

The results found in the health related QoL domain were contradicting: while the EQ-5D-3L index score reported by patients decreased between baseline and T3, suggesting worsening in the perceived health status, the reverse was observed for the and EQ-5D-3L VAS reported (that slightly increased). The explanation for these phenomena may lie in the fact that domains of the EQ-5D-3L index score are valued differently by subjects on the considered timings.

In fact, patient reported outcomes were collected through patients or caregivers over the phone almost one year after the terminus of the SCORED trial and simultaneously almost one year into the global Coronavirus Disease (COVID) pandemic. The timing of the application of the questionnaires might have influenced the health related QoL and NYHA assessments in ways that cannot be predicted or objectively quantified. Furthermore, the assessment of QoL and NYHA domains at baseline were made retrospectively at T3, and since these were self-reported, there may be the problem of recall bias, a common established issue in retrospective studies.

Concerning the self-assessed QoL perception on T3, 37.14% of the sotaglifozin group and 46.43% of the placebo group reported an improvement, with no significant difference between groups (p=0.7298). A higher proportion of subjects reporting an improvement among the sotaglifozin group over placebo could be initially expected if the intervention had resulted in a beneficial effect, however the subjectiveness of this assessment may also have been tainted by recall bias and context, as forementioned. Also, the discordance between the self-assessed QoL perception (with the majority of the subjects reporting maintenance, 60% on the sotaglifozin group and 50% on the placebo group) whilst the EQ-5D-3L score index varied negatively would require further analysis.

Further studies with larger sample sizes are needed to enable more precise estimates of outcomes and to allow subgroup analysis by different LVEF and types of HF. Additionally, a

prospective study design, as initially desired, would allow for the bridging of gaps identified, such as the collection of baseline data at the beginning of the study, avoiding retrospective data collection and recall bias.

Conclusions

In this study the treatment with the SGLT2 inhibitor sotaglifozin has not demonstrated to improve health related QoL in diabetic patients suffering from HF and those without formally diagnosed HF or have influence on the selected cardiac biomarker NT-proBNP, nor cause improvement in the NYHA functional class.

It was possible to characterize the population regarding demographics, clinical and therapeutic characteristics of patients.

This study has also highlighted the importance of health related QoL in patients suffering from chronic conditions associated to both high morbidity and mortality. This outcome, currently undervalued in clinical trials and studies in favour of clinical outcomes, can prove to be of the utmost importance to avoid overtreatment, especially if no influence is shown in the QoL of patients.

Acknowledgements

Acknowledgement: recognition of the importance or quality of something.

Mom, without you, I dare say, I would not even be here.

To Professor Pedro Monteiro, for all the autonomy that enabled me to grow and achieve; Tânia and Sara, for the assistance, comprehension and laughter while browsing through endless drawers of files. Rodrigo, for absolutely everything – it is our work.

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It seems like I have a whole lot (of people) to be thankful to (and for); the house does not fall when the bones are good.

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Annexes

Annex I Portuguese version of the EQ-5D-3L

AVALIAÇÃO DE GANHOS EM SAÚDE
QUESTIONÁRIO EQ-5D

Assinale com uma cruz (assim X), um quadrado de cada um dos seguintes grupos, indicando qual das afirmações melhor descreve o seu estado de saúde hoje.

Mobilidade

- Não tenho problemas em andar ..... ❑1
- Tenho alguns problemas em andar ..... ❑2
- Tenho de estar na cama ..... ❑3

Cuidados Pessoais

- Não tenho problemas com os meus cuidados pessoais ..... ❑1
- Tenho alguns problemas em lavar-me ou vestir-me ..... ❑2
- Sou incapaz de me lavar ou vestir sozinho/a ..... ❑3

Actividades Habituais *(ex. trabalho, estudos, actividades domésticas, actividades em família ou de lazer)*

- Não tenho problemas em desempenhar as minhas atividades habituais ..... ❑1
- Tenho alguns problemas em desempenhar as minhas atividades habituais ..... ❑2
- Sou incapaz de desempenhar as minhas atividades habituais ..... ❑3

Dor / Mal-estar

- Não tenho dores ou mal-estar ..... ❑1
- Tenho dores ou mal-estar moderados ..... ❑2
- Tenho dores ou mal-estar extremos ..... ❑3

Ansiedade / Depressão

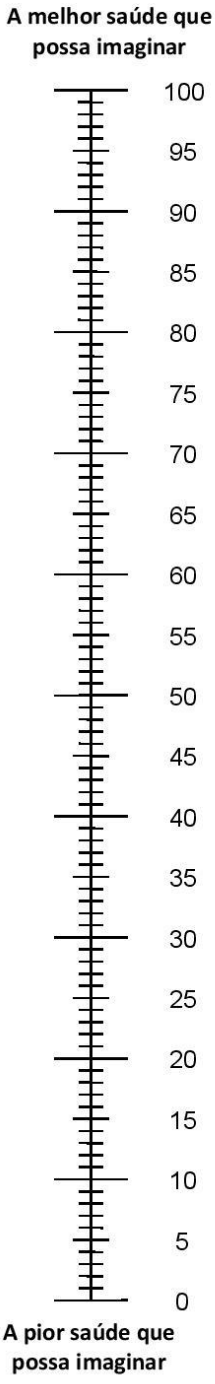
- Não estou ansioso/a ou deprimido/a ..... ❑1
- Estou moderadamente ansioso/a ou deprimido/a ..... ❑2
- Estou extremamente ansioso/a ou deprimido/a ..... ❑3

Versão Portuguesa, 1997, 2013.EQ-5D v2. Centro de Estudos e Investigação em Saúde da Universidade de Coimbra (CEISUC)

- Gostaríamos de saber o quanto a sua saúde está boa ou má HOJE

  - A escala está numerada de 0 a 100.
  - 100 significa a melhor saúde que possa imaginar.
    O significa a pior saúde que possa imaginar.
  - Coloque um X na escala de forma a demonstrar como a sua saúde se encontra HOJE.
  - Agora, por favor, escreva o número que assinalou na escala no quadrado abaixo.

A SUA SAÚDE HOJE = ☐



Muito obrigado por ter preenchido este questionário.

Annex II NYHA functional class for all subjects.

Characteristic at baseline	Total n=63	iSGLT2 n=35	Placebo n=28
NYHA functional classification - n (%)			
I	12 (19.67)	4 (11.76)	8 (29.63)
II	29 (47.54)	14 (41.18)	15 (55.56)
III	16 (26.23)	13 (38.24)	3 (11.11)
IV	4 (6.56)	3 (8.82)	1 (3.70)

Secondary outcomes	iSGLT2	Placebo	p-value
Evolution of NYHA class - n (%)			
Improved NYHA (≤ 1 class)	6 (17.65)	4 (14.81)	
Maintained NYHA	21 (61.76)	16 (59.26)	0.8711
Worsening NYHA (≥ 1 class)	7 (20.59)	7 (25.93)	