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SGLT2-inhibitors are effective and safe in the elderly: The SOLD study

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ABSTRACT

Background and aims: Sodium-glucose co-transporter-2 inhibitors (SGLT2i) may have important benefits for the elderly with type 2 diabetes (T2D), however some safety concerns still limit their use in patients over 70 years of age. The SOLD study (*SGLT2i in Older Diabetic patients*) is a multicenter study, aimed to evaluate the effectiveness and safety of SGLT2i in the older diabetic patients in a real-life setting.
Materials and methods: We analyzed a population of 739 adults (mean age 75.4 ± 3.9 years, M/F 420/319) with T2D, which started a SGLT2i-based treatment after the age of 70, with at least one year of follow-up. Data were collected at baseline, at 6 and 12 months of follow-up.
Results: SGLT2i (37.5% Empagliflozin, 35.7% Dapagliflozin, 26.1% Canagliflozin, 0.7% Ertugliflozin) were an add-on therapy to Metformin in 88.6%, to basal insulin in 36.1% and to other antidiabetic drugs in 29.6% of cases. 565 subjects completed the follow up, while 174 (23.5%) discontinued treatment due to adverse events which were SGLT2i related. A statistically significant reduction of glycated hemoglobin (baseline vs 12 months: 7.8 ± 1.1 vs 7.1 ± 0.8%, $p < 0.001$) and body mass index values (baseline vs 12 months: 29.2 ± 4.7 vs 28.1 ± 4.5 kg/m^2, $p < 0.001$) were evident during follow-up. Overall, estimated glomerular filtration rate remained stable over time, with significant reduction of urinary albumin excretion. In the subgroup of patients which were ≥ 80 years, a significant improvement in glycated hemoglobin values without renal function alterations was evident. Overall discontinuation rate during the follow-up period was different across age groups, being urinary tract infections and worsening of renal function the most common cause.
Conclusion: SGLT2i are well-tolerated and safe in the elderly and appear as an effective therapeutic option, though some caution is also suggested, especially in more fragile subjects.

1. Introduction

Nearly 50% of individuals with type 2 diabetes (T2D) are 65 years old or older, aging predisposes to the development of T2D through several mechanisms (i. e. increased insulin resistance, apoptosis of beta cells, decreased mitochondrial activity, sarcopenia) [1–3] and thus with

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population aging, the overall prevalence of T2D has been steadily growing over the years [4]. Older diabetic patients are often affected by several comorbidities, including heart failure [5], and chronic kidney disease, which affects more than 40/50% of individuals over 70 years [6–8]. Therefore, diabetes treatment in elderly can be challenging, also particularly considering potential drug interactions [9], shortage of data from randomized controlled trials and the lack of specific guidelines. Sodium–glucose co-transporter-2 inhibitors (SGLT2i) are anti-diabetic agents, which lowers the blood glucose concentrations by increasing urinary glucose excretion [10]. Their hypoglycemic effects are independent of insulin secretion [10], allowing their use independently of disease duration and β-cell function. Moreover, SGLT2i cut hospitalizations for heart failure, preserve renal function and reduce body weight and blood pressure [11–14]. However, some of the side effects reported for SGLT2i, such as genitourinary tract infections, volume depletion, bone fractures and acute kidney injury, may be worrisome for elderly people and thus limited their use in patients 70 years old or more [9]. On the contrary, all the aforementioned cardiovascular and nephroprotective effects and the absence of significant interaction with other drugs, should rendered SGLT2i an effective therapeutic choice in elderly patients with T2D [15,16]. Aim of this study is to explore and validate the hypothesis that SGLT2i can be used safely and effectively even in a population of patients affected by T2D and older than 70 years.

2. Material and methods

The SOLD study (SGLT2i in Older Diabetic patients) was designed as a prospective, longitudinal, observational study, aimed to evaluate efficacy and safety of SGLT2i in elderly patients. The study was performed by six different diabetes oupatients clinic in Lombardia, Italy. The centers involved were: Sacco and Fatebenefratelli (Milan), Pio Albergo Trivulzio Hospital (Milan), IRCCS Humanitas (Milan), Multimedica Sesto San Giovanni Hospital, Spedali Civili Hospital (Brescia) and Grande Ospedale Metropolitano Niguarda (Milan). After the approval by the Ethical Committee "Milano Area 1, ASST Fatebenefratelli-Sacco, Milan", all patients who gave their Informed Consent to personal data treatment were enrolled in the study. Eligible patients were patients with T2D aged $\geq$ 70 years, who started SGLT2i treatment, accordingly to clinical examination and patients' phenotype, (Dapagliflozin 5 or 10 mg per day – Empagliflozin 10 or 25 mg per day – Canagliflozin 100 or 300 mg per day – Ertugliflozin 5 or 15 mg per day) and were either not on antihyperglycemic agent (AHA) therapy or on a stable regimen of AHA (s) as monotherapy or combination therapy. Data were collected before starting SGLT2i treatment and after 6 and 12 months of SGLT2i based therapy. The inclusion criteria were: (a) Diagnosis of Type 2 Diabetes Mellitus, (b) age $\geq$ 70 years old, (c) treatment with an SGLT2i started after the age of 70 years. All patients with at least one among (a) type-1 diabetes, (b) age $<$ 70 years, (c) corticosteroid medications, (d) recent hospitalization, (e) ongoing treatment with SGLT2i were not included. Moreover, every adverse event leading to SGLT2i suspension at any time during the follow-up (intolerance, unmanageable adverse event(s) or therapeutic failure) was recorded. At baseline, general informations were collected for each patient, including T2D time of diagnosis, other therapies concomitant with SGLT2i and smoking habits. At each follow-up visit, baseline, 6 and 12 months, both physical examination and biochemical exams were done. Body weight and height were measured with scale and stadiometer, respectively. Blood pressure was measured with a sphygmomanometer, before and after the patient had been sitting for at least 10 min. Serum levels of fasting plasma glucose (FPG), triglycerides, total and HDL cholesterol, aspartate transaminase, alanine transaminase, urea and creatinine were assessed. Glycated hemoglobin (HbA1c) was measured with a high-performance liquid chromatography, National Glycohemoglobin Standardization Program-certified and Diabetes Control and Complications Trial-standardized system. Urine proteins were also evaluated, as either spot albuminuria (mg/l) or albumin/creatinine ratio (ACR, mg/g). Microalbuminuria was defined as 30–300 mg albumin daily, while Macroalbuminuria defined as $>$ 300 mg albumin daily. Serum low-density lipoprotein (LDL) and Glomerular Filtration Rate (GFR) were calculated by means of the Friedewald formula and the Chronic Kidney Disease Epidemiology Collaboration formula, respectively. Body Mass Index (BMI) was estimated as patient's weight (kg) divided by his/her height (meters) squared. BMI classifications was defined as underweight (under 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), class 1 obesity (30–34.9 kg/m^2), class 2 obesity (35–39.4 kg/m^2) and class 3 obesity (40 or more). During each follow-up visit, eventual changes in therapy were recorded and adverse events known to be related with SGLT2i were registered as well. Evaluation of diabetes-related comorbidities was scheduled and performed according to Standards of Care in Diabetes, published by ADA in 2021. The results of cardiological examination, echocardiography, carotid Doppler-ultrasonography, ocular fundus examination and hepatic ultrasound were registered when performed during the follow-up period of the study. The diagnosis of carotid artery stenosis was done with imaging tests, like carotid ultrasound, computed tomography angiography, magnetic resonance angiography or cerebral angiography. The diagnosis of NAFLD was based on the following three criteria: non-alcoholic, detection of steatosis either by imaging or by histology, and appropriate exclusion of other liver diseases. All data collected were analyzed by the Coordinating Center. Quantitative data are described as mean $\pm$ standard deviation and range, whereas qualitative variables have been expressed as absolute number of cases and as percentage out of the cohort of evaluated patients. Normal distribution of all the collected parameters was assessed by means of the Shapiro Wilk test. Statistical differences have been appraised through the Mann–Whitney U test and the Student's t test for nonparametric and parametric continuous variables, respectively. Discrete variables were confronted by means of the $\chi 2$ Test or the Fisher's Exact Test. The p value for statistical significance was defined as $<$ 0.05. Differences between groups have been evaluated by ANOVA for normally distributed variables, and by Mann-Whitney test for those not normally distributed. Levels of significance has been considered for p values $<$ 0.05. Binary logistic regression with a stepwise selection approach was employed to examine the major contributors to SGLT2i suspension Dichotomic dependent variable was continuation/discontinuation (1/0) of SGLT2i, while independent variables taken in account were sex, age, years of disease, BMI (Kg/m^2), FPG (mg/dl) and HbA1c (%) values at baseline, CV disease history, S-creatinine (mg/dl) and eGFR (mL/min/1.73 m^2) values at baseline. All statistical analyses have been performed using statistical package SPSS for Windows version 20.0 (SPPS Inc. Chicago, IL). The trial is registered in https://clinicaltrials.gov/ (NCT05477017).

3. Results

3.1. Baseline evaluation

We analyzed the data from 739 patients which started SGLT2i treatment after the age of 70 years. Complete baseline characteristics are shown in Table 1. Study population had a mean age of 75.0 $\pm$ 3.9 years, with 120 (16.9%) over 80 years old, 319 (43.2%) females and 420 (56.8%) males and with mean duration of diabetes of 14.2 $\pm$ 8.4 years. Median HbA1c and median BMI at the start of the study were 7.9 $\pm$ 1.12% and 28.9 $\pm$ 4.5 kg/m^2, respectively. Regarding the BMI, 148 (20%) patients had class 1 obesity, 50 (6.7%) class 2 obesity, 20 (2.7%) class 3 obesity, while 394 (53.3%) were overweight. History of micro and macro-vascular complications are shown in Fig. 1. Arterial Hypertension was present in 564 (76.3%), dyslipidemia in 451 (61%) and NAFLD/NASH in 202 (27.3%) of patients. Nearly one third of subjects, 217 (29.3%), had a history of myocardial infarction, 61 of stroke (8.2%), while 64 (8.6%) patients had established heart failure. Diabetic retinopathy affected 201 (27%) of subjects, of which only 53 (7%) had proliferative retinopathy. 244 (33%) had detectable albuminuria, classified as micro-albuminuria, while only a small proportion, 5 (0.7%),

Table 1
Baseline characteristics of study population (n = 739).

Parameters	
Age (yrs)	75.0 ± 3.9
70–74 yrs (n, %)	356, 48.2%
75–79 yrs (n, %)	263, 35.6%
≥ 80 yrs (n, %)	120, 16.9%
Gender	420, 56.8
Male (n, %)	319, 43.2
Female (n, %)	
Years of T2D disease (yrs)	14.2 ± 8.4
HbA1c (%, mmol/mol)	7.9 ± 1.1, 63 ± 8.7
FPG (mg/dl)	184.6 ± 53.2
S-Creatinine (mg/dl)	0.9 ± 0.2
e-GFR (mL/min)	73.4 ± 18.8
LDL –Cholesterol (mg/dl)	106.8 ± 36.0
BMI (Kg/m^2)	28.9 ± 4.5
Obesity (n, %)	218, 29.5
(BMI≥30 Kg/m^2)	
Smoking status:	124, 16.8
Current (n, %)	50, 6.8
Former (n, %)	565, 76.4
Never (n, %)	
Ejection Fraction (%)	50.4 ± 8.3
Antihypertensive drugs	374, 50.6
ACEI/ARB (n, %)	266, 36
B-blockers (n, %)	148, 20
Calcium channel blockers (n, %)	170, 23
Diuretic drugs (n, %)	
Lipid-lowering agents	337, 45.6
Statins (n, %)	32, 4.3
Fibrates (n, %)	

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; FPG, Fasting Plasma Glucose; e-GFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers. Data are expressed as mean ± SD or n, %.

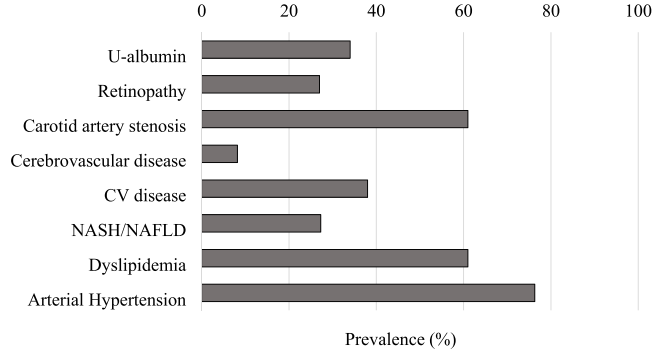


Fig. 1. Prevalence of comorbidities and complications in the study population.

had macro-albuminuria. Ejection Fraction percentage was available for 422 (57.1%) patients, and mean value at baseline was 50.45 ± 8.3%. All subjects started SGLT2 inhibitor treatment [Empagliflozin 277 (37.5%), 239 (86.3%) at dosage of 10 mg/die and 38 (13.7%) at dosage of 25 mg/die, Dapagliflozin 264 (35.7%), 255 (96.6%) at dosage of 10 mg/die and 9 (3.4%) at dosage of 5 mg/die, Canagliflozin 193 (26.1%), 78 (40.4%) at dosage of 100 mg/die and 115 (59.6%) at dosage of 300 mg/die, and Ertugliflozin 5 (0.7%), at dosage of 5 mg/die (100%)] as add-on therapy to metformin (657, 88.9%), basal insulin (267, 36.1%), rapid insulin (151, 20.4%) and others (i.e.: Dipeptidyl dipeptidas-4 inhibitors, 11.1%; Sulfonylureas/glinides, 8.7%, Pioglitazone, 4%, Acarbose, 0.7%, Glucagon Like Peptid-1 receptor agonist, 1.21%).

3.2. Follow up

Of the 739 patients starting SGLT2i, at 6 months 150 (20.3%) patients had suspended treatment due to adverse events, and at 12 months 24 additional patients interrupted treatment, bringing the prevalence of suspension of 23.5% after 1 year of treatment. 565 patients continued SGLT2i for 12 months. Table 2 shows complete glycometabolic parameters at each time point for patients which did not discontinue SGLT2i treatment. A reduction of Hb1Ac from 7.8 ± 1.1–7.1 ± 0.8% (Δ = −0.7%, p < 0.001) was observed after 12 months of therapy. Fig. 2 shows HbA1c changes from baseline accordingly to the dose of each molecule taken during the observation time. BMI decreased from 29.2 ± 4.7–28.1 ± 4.5 mg/m^2 (Δ = −1.1 kg/m^2, p < 0.001). 52.4% (296/565) of patients achieved an HbA1c value < 7.0%. Regarding the lipid profile, there was a significant reduction of total cholesterol (−8.7 mg/dl, p < 0.001), LDL cholesterol (−3.4 mg/dl, p < 0.001), without any significant changes in triglycerides and HDL cholesterol values. The main cause of the improvement in lipid profile is to be referred to the increased prescription of lipid-lowering drugs during trial period, that increased from 50.9% (288/565) at baseline to 59.6% (337/565) after 1 year. We also observed a statistically significant reduction in albuminuria (−16.5 mg/L, p = 0.008), while ACR values resulted reduced, compared to baseline, but in a non-statistically significant manner (−11.6 mg/g, p = 0.548). The albuminuria reduction was similar with all different types of SGLT2i. We than analyzed differences in albuminuria categories between baseline and 12-months evaluation: the percentage of normoalbuminuric patients remained stable (74.0% both at baseline and after 1 years), while patients with macroalbuminuria decreased from 2.6% to 1.0% with a consensual slight increase in patients with microalbuminuria (from 23.4% to 25.0%). eGFR values and serum creatinine remained stable over time. The percentage of patients receiving rapid insulin decreased from 20% to 16.4% after 12 months, basal insulin from 35% to 30.6%, sulfonylurea/glinides from 6.2% to 3.5%. Cardiovascular adverse events (MI, unstable angina or cardiac mortality) during follow-up occurred in a small proportion of patients: in the 1,4% of patients during first 6 months and 2,2% between 6 and 12 months of follow-up.

3.3. SGLT2i discontinuation

174 (23.5%) interrupted SGLT2i after 6 or 12 months. Adverse events leading to discontinuation at 6 months and 12 months are reported in Fig. 3. Genito-urinary tract infections were the main reason for discontinuation, both at 6 and 12 months, accounting for, respectively,

Table 2
Glycometabolic parameters of patients that completed follow up (n = 565).

	Baseline	6 months	12 months	P value
BMI (Kg/m^2)	29.2 ± 4.7	28.2 ± 4.5	28.1 ± 4.5	0.000
Weight (Kg)	79.3 ± 14.6	76.8 ± 14.3	76.6 ± 13.9	0.002
FPG (mg/dL)	184.6 ± 55.9	151.1 ± 35.5	144.6 ± 33.0	0.000
HbA1c (%, mmol/mol)	7.8 ± 1.1, 62.0 ± 8.7	7.3 ± 0.8, 56.2 ± 6.1	7.1 ± 0.8, 54.1 ± 6.1	0.000
S-Creatinine (mg/dL)	0.9 ± 0.2	0.94 ± 0,19	0.9 ± 0.2	0.104
eGFR (mL/min/1,73 m^2)	75.4 ± 20.2	73.7 ± 17.8	75.5 ± 16.9	0.201
ACR (mg/g)	77.3 ± 147.9	51.6 ± 99.9	65.7 ± 126.9	0.548
U-Albumin (mg/L)	46.8 ± 95.7	30.8 ± 44.9	30.3 ± 34.1	0.008
Total cholesterol (mg/dL)	174.8 ± 36.3	167.0 ± 31.0	166.1 ± 29.6	0.000
HDL (mg/dL)	45.4 ± 12.6	46.3 ± 11.9	47.0 ± 11.3	0.098
LDL (mg/dL)	103.3 ± 35.3	90.9 ± 26.9	91.2 ± 25.3	0.000
Tryglicerides (mg/dL)	141.8 ± 69.0	152.3 ± 64.0	145.2 ± 49.7	0.072
GOT (U/L)	24.4 ± 11.5	26.4 ± 11.5	25.9 ± 14.7	0.077
GPT (U/L)	24.9 ± 10.9	23.0 ± 10.9	22.7 ± 9.2	0.008

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; FPG, Fasting Plasma Glucose; HDL high density lipoprotein; LDL low density lipoprotein; eGFR Estimated Glomerular Filtration Rate; ACR albumin/creatinine ratio. ANOVA test for repeated measures. Data are expressed as mean ± SD.

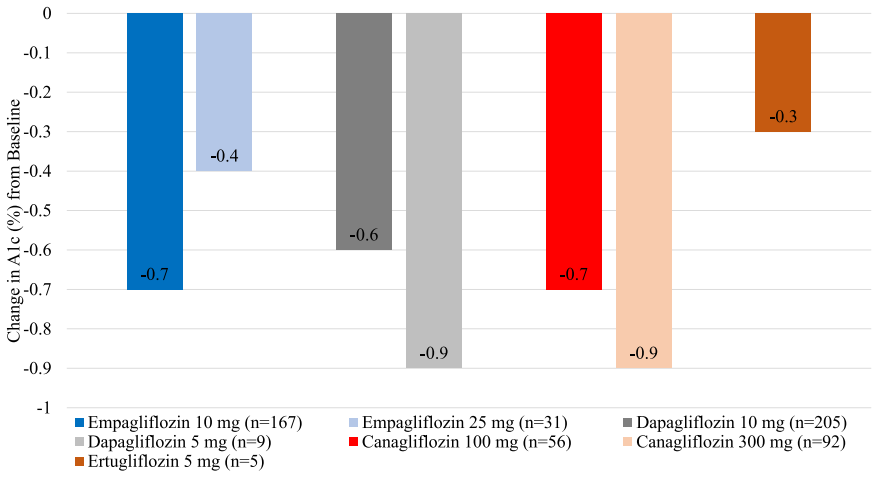


Fig. 2. Changes in A1c (%) values from baseline accordingly to different molecules.

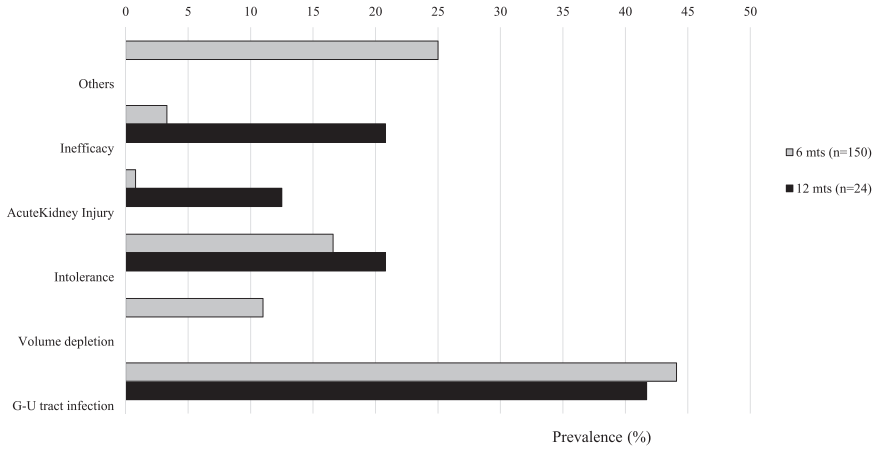


Fig. 3. Causes of treatment discontinuation at 6 and 12 months.

44.1% and 41.7%. All adverse events of urinary and genital infection were reported to be mild or moderate in intensity and responded to standard treatment. The occurrence of volume depletion (e.g.: hypotension, orthostatic hypotension, pre-syncope, syncope) was quite low, and occurred only in the first 6 months of treatment in the 11.0% of cases. Inefficacy (lack of HbA1c improvement or worsening of glycometabolic state) accounted for 3.3% at 6 months and 20.8% at 12 months, while intolerance (e.g.: excessive diuresis, nausea, lack of appetite) occurred in 16.6% at 6 months and 20.8% at 12 months. Acute kidney injury, with persistent decline in eGFR values, brought to treatment suspension in 0.8% at 6 months and 12.5% at 12 months (Fig. 3). No severe adverse events were documented in our cohort of patients (i.e. lower-extremity amputations, euglycemic-DKA, severe hypoglycemia). Table 3 compares baseline characteristics of patients that discontinued SGLT2i versus patients that did not interrupted treatment. As shown, patients that discontinued were significantly older (75.8 ± 4.2 versus 74.7 ± 3.8 years, p = 0.002), had lower BMI values (27.9 ± 3.3 versus 29.2 ± 4.7 Kg/m2, p = 0.001), higher HbA1c (8.1 ± 1.03 versus 7.8 ± 1.1%, p = 0.001) and a statistically significant worse kidney function (S-Creatinine: 0.98 ± 0.16 versus 0.91 ± 0.19 mg/dL, p < 0.001; eGFR: 67.2 ± 12.4 versus 75.4 ± 20.1 mL/min/1,73 m^2, p < 0.001). Different percentage of discontinuation accordingly to range of age are shown in Fig. 4. Discontinuations owing to adverse events were almost 2 times higher in patients aged ≥ 80 years, compared to younger patients (19.1% vs 35%, p = 0.005). A logistical binary regression was performed to determine the major contributors to SGLT2i suspension.

Table 3
Baseline characteristics of subjects that discontinued or maintained the SGLT2i treatment.

	Discontinued (n = 174)	Ongoing (n = 565)	P value
Age (yrs)	75.8 ± 4.2	74.7 ± 3.8	0.002
Sex (M/F)	101/73	319/246	0.390
BMI (Kg/m^2)	27.9 ± 3.3	29.2 ± 4.7	0.001
Weight (Kg)	78.0 ± 11.3	79.3 ± 14.6	0.067
FPG (mg/dL)	184.6 ± 55.9	184.8 ± 43.3	0.954
HbA1c (%, mmol/mol)	8.1 ± 1.03, 65.0 ± 8.2	7.8 ± 1.1, 62.0 ± 8.7	0.001
S-Creatinine (mg/dL)	0.98 ± 0.16	0.91 ± 0.19	0.000
eGFR (mL/min/1,73 m^2)	67.2 ± 12.4	75.4 ± 20.1	0.000
U-Albumin (mg/L)	32.8 ± 37.7	35.0 ± 74.0	0.722
Total cholesterol (mg/dL)	183.5 ± 35.3	174.0 ± 36.0	0.000
HDL (mg/dL)	41.4 ± 10.6	45.3 ± 12.6	0.000
LDL (mg/dL)	117.3 ± 35.3	103.3 ± 35.4	0.000
Tryglicerides (mg/dL)	130.8 ± 40.2	141.8 ± 69.0	0.055
Ejection Fraction (%)	45.9 ± 7.6	52.3 ± 7.8	0.000

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; FPG, Fasting Plasma Glucose; HDL high density lipoprotein; LDL low density lipoprotein; eGFR Estimated Glomerular Filtration Rate; ACR albumin/creatinine ratio. T- student test. Data are expressed as mean ± SD.

Results reported that insufficient glucose control (HbA1c, OR: 1927, CI: 1528–2429, p < 0.001), impaired renal function (eGFR, OR: 0969, CI: 0953–0985, p < 0.001) and lower BMI values (BMI, OR: 0920, CI:

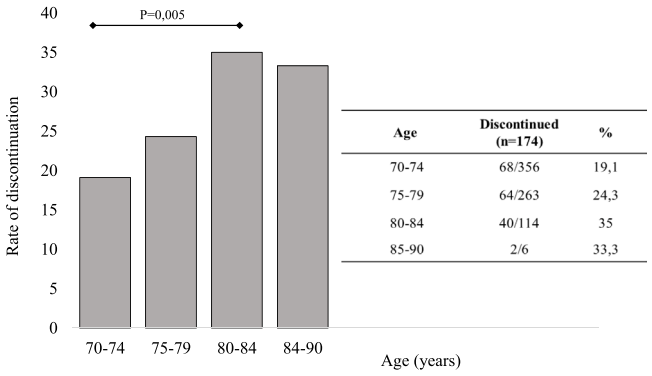


Fig. 4. Discontinuation rate for SGLT2i treatment according to age.

0875–0968, p < 0.001) at baseline were significantly related to SGLT2i suspension, while Age (OR: 1046, CI: 0997–1097, p = 0068), sex, years of disease and CV disease history were not significantly related (Fig. 5).

≥ 80 years patients.

A population of 120 subjects aged ≥ 80 years started SGLT2i, of that 78 (65%) continued treatment, 37 (30.8%) interrupted at 6 months and 5 (4.1%) at 12 months, with a whole prevalence of suspension in very old people of 35%. Patients that continued SGLT2i therapy showed benefits in glycometabolic parameters, as shown in Table 4. HbA1c reduced from 7.9 ± 0.9–6.9 ± 0.7% (Δ = −1.0%, p < 0.001), FPG reduced from 197.9 ± 57.3–145.3 ± 34.7 mg/dL after 12 months. A proportion of 64.1% (50/78) of patients achieved HbA1c values < 7.0%. BMI reduced in a non-statistically significant manner, from 28.3 ± 3.7 at baseline to 27.3 ± 3.5 mg/m^2 after 12 months (p = 0.12). Adverse events leading to discontinuation were: genito-urinary tract infections, in 33%; intolerance, in 19.4%, sympthoms of volume depletion, in 5.5%, acute kidney injury, in 2.7%.

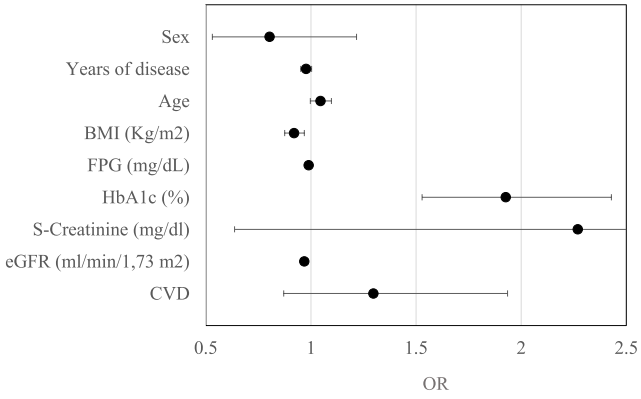
4. Discussion

Our study confirms that SGLT2i are not only broadly safe but very strongly effective in elderly patients with T2D in improving HbA1c, facilitating loss of weight and in protecting renal function. There is growing evidence that SGLT2i are disease-modifying drugs, associated with favorable cardiovascular and renal outcomes in T2D. Placebo-controlled cardiovascular and kidney clinical outcomes trials [12, 17–21], have shown clinical benefits beyond glycometabolic control, with significant reduction in major cardiovascular events, cardiovascular death, reduced progression of heart failure and kidney diseases [22,23]. These findings amplify the possibility that SGLT2i may have off-target effects, including the direct effect on the sodium-hydrogen exchanger 1 in the heart, NHE3 in the kidney, and NHE9 in inflammatory cells that could influence MACE, heart failure, and kidney outcomes [24]. Along with these aspects, SGLT2i showed a reduction of multiple cardiovascular risk factors, including glucose lowering efficacy, with mean reductions in HbA1c of 0.5–0·9%, body weight reduction, with approximately 2 kg lost and with a significant reduction for systolic and diastolic blood pressure [25]. However, there are some important considerations for the management of T2D in elderly patients. According to guidelines from the International Diabetes Federation [26] and the American Diabetes Association [27], older patients with T2D have higher rates of comorbidities, chronic kidney disease, vascular disease, heart failure, as well as geriatric syndromes such as sarcopenia, frailty and cognitive impairment/dementia. Therefore, HbA1c goals for older adults must be customized and all the comorbidities, functional status, and life expectancy of the individual considered. Most important, hypoglycemia should be avoided in older patients and deintensification (or simplification) of complex regimens is recommended to reduce the risk of hypoglycemia and polypharmacy [27]. Among our strengths we should mention that our study is based on a real-life data collection regarding patients aged ≥ 70 years treated with SGLT2i. The population is quite large and, compared to previous studies [26], is characterized by a very old age, with 263 (35.6%) and 120 (16.9%) subjects respectively

Table 4
Glycometabolic parameters of patients aged ≥ 80 at follow up (n = 78).

	Baseline	6 months	12 months	P value
BMI (Kg/m^2)	28.3 ± 3.6	27.2 ± 3.4	27.3 ± 3.5	0.123
Weight (Kg)	77.5 ± 13.9	74.3 ± 12.9	74.6 ± 13.1	0.268
FPG (mg/dL)	197.9 ± 57.3	151.5 ± 32.1	145.3 ± 34.7	0.000
HbA1c (%, mmol/mol)	7.9 ± 0.9, 63.0 ± 7.2	7.2 ± 0.6, 55.0 ± 4.6	6.9 ± 0.7, 52.0 ± 5.3	0.000
S-Creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.15	0.9 ± 0.1	0.544
eGFR (mL/min/1,73 m^2)	73.9 ± 21.4	72.4 ± 17.8	75.5 ± 16.8	0.597
U-Albumin (mg/L)	39.8 ± 56.9	28.8 ± 30.2	35.3 ± 49.9	0.515
ACR (mg/g)	122.5 ± 129.4	105.4 ± 119.7	98.4 ± 85.2	0.481
Total cholesterol (mg/dL)	181.5 ± 3.4	172.3 ± 22.6	171.4 ± 22.6	0.117
HDL (mg/dL)	43.0 ± 10.2	45.0 ± 9.9	45.1 ± 9.8	0.398
LDL (mg/dL)	115.0 ± 39.5	96.9 ± 24.9	97.2 ± 20.8	0.000
Tryglicerides (mg/dL)	126.4 ± 35.7	155.0 ± 43.9	148.3 ± 40.5	0.000

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; FPG, Fasting Plasma Glucose; HDL high density lipoprotein; LDL low density lipoprotein; eGFR Estimated Glomerular Filtration Rate. ANOVA test for repeated measures. Data are expressed as mean ± SD.



	OR	P value	95% CI
Sex	0,804	0,302	0,531- 1,217
Years of disease	0,977	0,084	0,951- 1,003
Age	1,046	0,068	0,997- 1,097
BMI (Kg/m^2)	0,920	0,001	0,875- 0,968
FPG (mg/dL)	0,990	0,000	0,985- 0,995
HbA1c (%)	1,927	0,000	1,528- 2,429
S-Creatinine (mg/dl)	2,270	0,207	0,636- 8,097
eGFR (ml/min/1,73 m^2)	0,969	0,000	0,953-0,985
CVD	1,297	0,202	0,870-1,935

Fig. 5. Factors related to a higher probability of SGLT2i suspension.

aged over 75 years and over 80 years. The main limitation of the study is the lack of a control group. In our cohort, global rate of suspension due to adverse effects related to SGLT2i was 23.5%, with percentage less than 20% in under 75 years old subjects, and 35% in over 80 years old patients. The safety profile in the current analysis was consistent with those of previous studies [28–30], but data regarding adverse events leading to SGLT2i discontinuation in patients $\geq$ 80 years, to our knowledge, are still not available. A pooled analysis of nine phase III studies investigated safety of dapagliflozin by age and reported rate of discontinuation of 14.4% in aged $\geq$ 65 years and 26.8% in 97 subjects over 75 years old [29]. Findings from another pooled analysis, reported that the incidence of overall adverse events with canagliflozin 100 and 300 mg was higher in participants aged 75 and older than in those younger than 75 [30]. As expected, the main reason for discontinuation was genito-urinary tract infections, accounting for nearly half of suspension, without distinctions in different age groups. Older patients have an increased propensity to volume depletion, which may be influenced to changes in body composition with ageing, impairments in volume regulation, diuretic treatments [31]. In our cohort, all volume reduction events were reported in the first 6 months of treatment, in more susceptible subjects, but the intensity was mild or moderate. Subjects aged over 80 years, did not showed higher incidence of volume depletion events. Interestingly, increased risk of SGLT2i discontinuation resulted related to lower BMI values, worse renal function and worse metabolic control at baseline, suggesting an advanced stage of diabetes, characterized more by relative pancreatic exhaustion than by insulin resistance. These findings are only partially consistent with previous trials, that reported that dapagliflozin discontinuation was more frequent in patients with worse glycemic state, but higher eGFR values [32]. In our cohort, patients showed an improvement in glycometabolic profile comparable to literature, with an overall reduction in HbA1c of 0.7%, that was even higher in the over 80 population, reaching 1.0% less compared to baseline values. Also, BMI values reduction was in line with literature [33], and reduction was seen also in very old patients. Renal function remained stable over time, with small transient reductions in eGFR early on in treatment. Also, in subjects aged over 80 years old, eGFR levels completely returned to baseline levels, after an initial small drop in eGFR, which is consistent with the mechanism of action of SGLT2i. The early SGLT2i related eGFR small decline, followed by long-term stability, is probably due to tubule-glomerular feedback responses and/or blood pressure reduction [34–37], and should not lead to discontinuation of SGLT2i treatment. A recent trial investigated relationship of SGLT2i initiation with the risk of AKI hospitalization in patients older than 65 years old. Results reported that the initiation of SGLT2i was associated with a nearly 30% reduction in the risk of AKI hospitalization compared with DPP-4 inhibitor initiation and a nearly 20% reduction compared with GLP-1RA initiation [38]. In our population, the relatively short timeframe of the study precludes assessment of kidney benefits over longer time horizons. Older patients might derive kidney benefits over an extended period and this hypothesis will require further analysis in future studies. Our analysis confirmed what was suggested by few recent studies, that SGLT2i may offer multiple benefits for older adults with T2D, including favorable glycemic efficacy, favorable safety profile and low risk of hypoglycemia [39–44]. Clinicians should be aware of potential safety concerns in older adults, like higher incidence of genital mycotic infections, or potential symptoms related to volume depletion, however, with monitoring and prompt treatment, these adverse events may be efficiently managed. Careful management of antihypertensive medications, especially in patients over 75 and older, may help to reduce the risk of these adverse events. Together, these findings support the use of SGLT2i as a safe and efficacious therapeutic option for individuals aged 70 and older with T2D.

Author contributions

M.E.L. and V.C. designed the study, analyzed data, and wrote the paper; A.G., L.M., I.P., M.T., N.B., G.F., M.B., L.B., C.P., G.M., C.M., P.S. M., M.M., B.P. collected data; A.G, F.F., L.L., F.B. and C.B. coordinated and designed research and edited the paper; P.F. conceived the idea, designed the study, and wrote and edited the paper.

Disclosure

The authors have nothing to disclose.

Data Availability

All requests for raw and analyzed data will be reviewed to verify if the request is subject to any intellectual property or confidentiality obligations. Any data and materials that can be shared will be released via a Material Transfer Agreement. The datasets and resources generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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