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Metabolic effectiveness of gliflozins and gliptins in the routine clinical practice of patients with type 2 diabetes: preliminary results from GIOIA, a prospective multicentre study

Katherine Esposito [a,1], *Miriam Longo* [b,1], *Maria Ida Maiorino* [a,1], *Michela Petrizzo* [a], *Maurizio Gicchino* [a], *Giuseppe Bellastella* [b], *Dario Giugliano* [b,*]

[a] *Diabetes Division, Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy*
[b] *Division of Endocrinology and Metabolic Diseases, Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy*

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ABSTRACT

Aims: GIOIA is an ongoing prospective multicentre study aiming to assess the vascular and metabolic effects of SGLT-2 inhibitors (gliflozins) and DPP-4 inhibitors (gliptins) in the routine clinical practice of patients with type 2 diabetes (T2D). Herein we describe the preliminary effectiveness data at 6 months.

Methods: SGLT-2i and DPP-4i-naïve adult patients with T2D (N = 301 and 260, respectively), with glycated haemoglobin A1c (A1C) >7%, an estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 m^2, on background therapy with metformin, insulin or both, are being followed to evaluate markers of vascular (carotid intima-media thickness), myocardial (myocardial diastolic function) and renal (urinary albumin/creatinine ratio) damage during treatment with SGLT-2i or DPP-4i for a period of 24 months.

Result: At baseline, patients initiated on SGLT-2i are younger (about 6 years) and more heavy (about 7.5 kg), have higher A1C level (0.5% more), a longer diabetes duration and more CV events (20% more) than patients initiated on DPP-4i. At 6 months, patients on SGLT-2i (N = 298) and DPP-4i (N = 258) exhibit significant ameliorations in A1C (−1.% and −0.7%, respectively), which were greater (−1.2% and −0.81%) in those on a background metformin treatment only. The composite endpoint (A1C ≤ 7.0% + weight loss ≥ 3 kg) was achieved by 24% and 16% of patients receiving SGLT-2i or DPP-4i, respectively. No unexpected adverse events were reported.

Conclusions: Both SGLT-2i and DPP-4i provide substantial improvements in metabolic parameters in the usual clinical practice of T2D, especially when used as second-line treatment.

* Corresponding author at: Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", 80138 Naples, Italy.
E-mail address: dario.giugliano@unicampania.it (D. Giugliano).
[1] Share first authorship.
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1. Introduction

Type 2 diabetes mellitus (T2D) is one of the major chronic disease of this century and is considered one of the major health burden on a global scale [1]. Atherosclerotic cardiovascular disease (ASCVD) is still the principal cause of death, hospitalization, disability and reduced life-expectancy among patients with diabetes mellitus [2,3]. Treatment of T2D is rapidly evolving, especially after the introduction of innovative drugs, such as dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide 1 receptor agonists (GLP1-RAs), and sodium-glucose cotransporter 2 inhibitors (SGLT-2i). DPP-4i are characterized by intermediate glucose-lowering efficacy, good tolerability, low risk of hypoglycemia and neutral effects on weight [4]. GLP1-RAs are more effective in lowering glucose levels, and have a positive effects on an array of cardiovascular (CV) risk factors [5]. SGLT-2i block sodium-glucose tubular co-transporter 2, thereby promoting urinary glucose excretion, which in turn lowers blood glucose concentrations, and also reduces body weight [6].

In 2008, the US Food and Drug Administration issued guidance to pharmaceutical sponsors to ensure cardiovascular safety as a prerequisite for the approval of new glucose-lowering drugs, which led to dedicated cardiovascular outcome trials (CVOTs) [7]. A significant reduction in the incidence of major cardiovascular events (MACE) has been observed from the analysis of the 12 CVOTs so far published [8,9]; in particular, use of both GLP-1RAs and SGLT-2i is associated with significant reductions of MACE (12% and 11%, respectively), while DPP-4i show a neutral effect (1% reduction). Due to inherent limitations of CVOTs (mainly lack of generalisability to a wider diabetic population), observational studies from large retrospective data have assessed a broad population of T2D patients and yielded results consistent with those obtained in CVOTs [10]. However, and despite the use of sophisticated statistical techniques, these retrospective data have important limitations and may overestimate the effectiveness of these medications [11].

Both SGLT-2i and DPP-4i are oral drugs being used to treat hyperglycaemia in T2D patients, have a comparable efficacy in controlled trials at lowering haemoglobin A1c (A1C) values (between 0.5% and 0.7%) [12,13], have an acceptable safety and tolerability profile, and can be used as add-on to metformin or insulin therapy; moreover, DPP-4i are among the most commonly used second-line treatment in Italy [14]. However, there is limited information concerning prospective outcomes in patients receiving these drugs in the current clinical practice.

The aim of the present study is to evaluate prospectively effectiveness and safety of SGLT-2i and DPP-4i in the treatment of T2D within the context of usual clinical practice in the Campania County, South Italy. This report describes the baseline data of the enrolled patients and effectiveness results after 6 months of treatment.

2. Subjects, materials and methods

2.1. Study design

GIOIA (effects of **glifl**ozins and gliptins on markers of cardiovascular damage in type 2 **dia**betes) is an ongoing prospective multicentre study carried out in the setting of usual clinical practice in the Campania County. To be eligible for the study, patients must have been SGLT-2i or DPP-4i naïve and at least 18 years of age, with inadequate glycaemic control (A1C > 7%) at baseline. Patients can be enrolled if they initiate treatment with any SGLT-2i (canagliflozin, dapagliflozin, empagliflozin) and any DPP-4i (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) as add-on to metformin or basal insulin as part of an optimal treatment approach in each single center, are stable under previous antidiabetic drug regimen for at least 30 days, have an estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m^2, and give informed consent. These criteria allow to: a) limit the possible combinations of SGLT-2i or DPP-4i to metformin (the most used association) and insulin (association reimbursed by the Italian Health System) only; b) avoid the use of any sulfonylurea; and c) have a similar background glucose-lowering treatment (metformin and/or insulin). Exclusion criteria are history of use of SGLT-2i or DPP-4i, history of diabetic ketoacidosis, autoimmune diabetes (eg, type 1 diabetes mellitus or latent autoimmune diabetes in adults), history of diabetes secondary to pancreatitis or pancreatectomy, receipt of an investigational drug within the 3 months prior to initiation (Supplementary Table 1). The study protocol has been approved by the Medical Ethics Committee of University of Campania "Luigi Vanvitelli" and is registered on ClinicalTrials.gov (**NCT03918148**). The protocol complies with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All participating patients have to provide signed informed consent, confirming that they understand the procedures.

2.2. Study follow-up

Recruitment for the study has begun in March 2018. Subjects undergo a screening visit for a preliminary eligibility assessment; all eligible patients are followed-up for up to 24 months. Follow-up visits are scheduled every 3 months (Supplementary Table 2). All participants are followed by their usual-care physicians at each visit to receive individualized appropriate treatment. During the observation period, any needed adjustment of anti-hyperglycaemic treatment is performed by varying the titration of the existing therapy (metformin and/or insulin). In the case of A1C value still higher than the patient's individualized target, physician can add insulin or metformin (when not used yet), but not the opposite drug (SGLT-2i in those given DPP-4i, and vice versa) because the Italian Health System does not reimburse the combination of the two drugs. Treatment adherence is evaluated at scheduled visits, being based on the percentage of

prescribed pills missed in the last 14 days as reported by patients. All sexually active participants have to practice a highly effective method of birth control.

2.3. Study outcomes

GIOIA is a prospective study with pre-specified analyses for primary and secondary outcomes (Supplementary Table 3). The primary outcomes of the study are the changes of markers of organ damage, such as carotid intima-media thickness (CIMT), myocardial diastolic function, and urinary albumin/creatinine ratio (UACR), from baseline to 12 and 24 months, and also changes of A1C levels (each three month).

Change of durability of glycaemic control, percentage of patients reaching the A1C targets ≤7% or ≤7.5%, fasting glucose, glucose variability indices, body weight and BMI, waist circumference, lipid profile, systolic (SBP) and diastolic (DBP) blood pressure, estimated glomerular filtration rate (eGFR), and combined endpoints (A1C ≤7% + weight loss ≥3 kg; A1C ≤7.5% + weight loss ≥2 kg) are secondary outcomes.

Primary outcomes

- Progression of vascular damage is defined as any increase in mean CIMT from baseline to the end of follow-up; regression of vascular damage is defined as a reduction ≥0.020 mm on mean CIMT [15,16] (Supplementary data).
- Progression of cardiac damage is defined according to American Society of Echocardiography and the European Association of Cardiovascular Imaging [17] and is detailed in Supplementary data.
- Progression of renal damage is defined as change from either normo-albuminuria to micro-albuminuria or macro-albuminuria or from microalbuminuria to macro-albuminuria; regression of renal damage is defined as change from either micro- or macro-albuminuria to normo-albuminuria.

2.4. Methods

All patients are instructed on study design and outcomes through a specific information sheet; at the screening visit they are provided with informed consent, consent to the processing of personal data and informative letter to their physician.

Physical examination- Height and weight are recorded using a Seca 200 scale (Seca, Hamburg, Germany) with attached stadiometer. Body mass index (BMI) are calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Waist circumference is measured in every patient in orthostatic position on the horizontal plane at the superior border of iliac crest, using an appropriate graduated tape. Arterial blood pressure is measured thrice, at the end of the physical examination with the patients in sitting position, after a rest of 15 min.

Glucose variability - Glycaemic readings from a flash glucose monitoring device are evaluated with the EasyGV[a] software (www.phc.ox.ac.uk/research/diabetes/software/easygv/) to calculate different glucose variability indices, particularly the mean amplitude of glycaemic excursions (MAGE) and the glucose coefficient of variation (CV).

Hypoglycaemia - Level 1 hypoglycaemia is defined as glucose level <70 mg/dl associated with symptoms or signs (sweating, tremor, tachycardia); level 2 hypoglycaemia is defined as a blood glucose concentration <54 mg/dL; and level 3 (severe) hypoglycaemia is defined as glucose level <50 mg/dl or needing the assistance of a third party [18].

Laboratory analysis- A1C, fasting plasma glucose, total and high-density lipoprotein cholesterol, triglycerides, and creatinine levels are measured according to each center facilities. The Friedwald equation is used to calculate low-density lipoprotein (LDL) cholesterol. Estimated glomerular filtration rate (eGFR) is calculated using the MDRD formula. Screening for micro- and macro-albuminuria is performed on 24 h urine sampling. Microalbuminuria and macroalbuminuria are defined as UACR 30–299 mg/24 h and ≥300 mg/24 h values, respectively.

Medication adherence: medication taking is calculated as the ratio between the number of pills taken by a patient in a given time divided by the number of pills prescribed by the physician in the same time. A ratio >80% indicate good adherence to treatment [19].

2.5. Statistical analyses

Sample size calculation was made on assumption of any CIMT changes from baseline to 24 months. There is evidence that patients with T2D have a mean increase in CIMT of 0.0364 ± 0.054 mm/year and that improvement in A1C is associated with a 0.02-mm/year improvement in CIMT [15,16]. Based on these assumptions, and in a conservative way, a sample size of 500 patients is required to achieve a difference of 0.04 mm in CIMT as compared with baseline after 2 years of follow-up, assuming a standard deviation of 0.108, with an α power of 90%, a drop-out rate of 5%, and a level of significance of 0.05 (PASS, version 11).

Categorical variables are expressed as frequencies and proportions, continuous variables as mean ± standard deviation (variables normally distributed) or median and interquartile range (variables not normally distributed). Differences between baseline parameters are assessed by t test for comparisons between groups. Changes in organ damage markers, as well as metabolic or CV variables from baseline to 24 months are assessed by two-sample t test for comparisons within groups. Time spent between the first assumption of prescribed treatment and the first change in primary outcomes are analysed through Cox proportional hazards model. Cumulative progression rate for each outcome are expressed graphically by Kaplan-Meier analysis to better evaluate progression time and durability of treatment effects. Propensity score matching can generate a quasi-experimental condition that makes a prospective study very close to a randomized controlled trial [20]: an outcome, post-hoc analysis after propensity score matching will be performed at the end of observation (24 months) to compare the two groups, if the conditions for comparing are not precarious. All the analyses relative to the primary outcome of the study will be applied at the term of the observation period.

3. Results

3.1. Baseline characteristics

Table 1 shows the baseline characteristics of the patients enrolled in the study. In the SGLT-2i group, empagliflozin was used by 50% of patients, dapagliflozin by 35% and cangliflozin by 15%; in the DPP-4i group, sitagliptin was used by 32% of patients, vildagliptin by 30%, linagliptin by 28%, alogliptin by 9%, and saxagliptin by 1%. There was no difference between the baseline characteristics of patients according to any single drug of the two classes (data not shown); therefore, the patients are presented all together within each group.

Significant differences between groups were detected for most variables: patients initiated on SGLT-2i are younger (about 6 years) and more heavy (about 7.5 kg), have higher A1C level (0.5% more), a longer diabetes duration and more CV events (20% more) than patients initiated on DPP-4 inhibitors. Metformin use is common in both groups, accounting for about three/fourth of the patients; basal insulin use is almost double and significantly higher in the SGLT-2i as compared with DPP-4i group (27% vs 14%); hence, the combined insulin+metformin treatment was more frequent in the SGLT-2i group. The baseline lipid profile is slightly but significantly worse (higher levels of total cholesterol and triglycerides) in the SGLT-2i group. The frequency of renal damage (micro and macroalbuminuria) is low-to-moderate (20%) at baseline and not significantly different between the two groups. Mean eGFR values are within the normal range for age in both groups, although they are significantly higher in the SGLT-2i group. Indices of CV damage, including CIMT and LVEF, as well as blood pressure and heart rate values are also similar. Only two patients in the SGLT-2i group had a LVEF <40% and none in the DPP-4i group. The analysis of baseline characteristics excluding patients with a previous CV event in both groups does not change the significance of the findings (Table 4, supplementary data).

Table 1 – Baseline characteristics of patients.

	SGLT2-i (N = 301)	DPP4-i (N = 260)	P
Age (years)	61.1 ± 8.93	66.9 ± 10.6	<0.001
Males (%)	55	56.2	0.915
Smoking (%)	20	18	0.652
Diabetes duration (years)	8.5 ± 6.5	6.9 ± 6.4	0.004
Weight (Kg)	86.6 ± 16.8	79.2 ± 14.0	<0.001
BMI (Kg/m^2)	32.3 ± 6.7	29.7 ± 4.7	0.001
Waist circumference (cm)	107.9 ± 12.4	105.3 ± 8.6	0.221
A1C (%)	8.4 ± 1.5	7.9 ± 0.9	<0.001
Fasting glucose (mg/dl)	162 ± 54	158 ± 40	0.295
SBP (mmHg)	136.7 ± 11.4	134.2 ± 12.7	0.542
DBP (mmHg)	80.9 ± 9.5	81.9 ± 9.4	0.316
Heart rate (b/pm)	75.8 ± 9.8	72.7 ± 7.3	0.059
Total cholesterol (mg/dl)	179.6 ± 38.4	169.9 ± 33.4	0.028
LDL-cholesterol (mg/dl)	103.5 ± 33.1	96.4 ± 31.6	0.116
HDL-cholesterol (mg/dl)	44.9 ± 12.5	45.6 ± 13.2	0.622
Triglycerides (mg/dl)	170.5 ± 96.7	140.6 ± 59.0	0.004
Creatinine (mg/dl)	0.8 ± 0.2	0.9 ± 0.3	<0.001
eGFR ($ml/min/1.73\ m^2$)	89.1 ± 21.5	82.7 ± 18.7	0.046
UACR (mg/g)	14.5 (7.6–26.0)	12.0 (6.5–29.3)	0.118
Microalbuminuria (%)	19	17	0.856
Macroalbuminuria (%)	3	1	0.753
Diabetic retinopathy (%)	19	16	0.410
SWd (cm)	1.1 ± 0.2	1.1 ± 0.2	0.413
LVEF (%)	61.9 ± 13.2	61.5 ± 4.6	0.310
CIMT (mm)	1.0 ± 0.2	1.0 ± 0.2	0.838
History of heart failure (%)	0	0	
LVDD (%)	22	18	0.252
Prior cardiovascular event (%)	32.9	13.1	<0.001
Statins users (%)	55	46	0.124
Antihypertensive users (%)	55	52	0.648
ACE-i users (%)	20	22	0.643
ARBs users (%)	29	28	0.966
Metformin use (%)	81	74	0.218
Insulin use (%)	27	14	0.011
Insulin + metformin (%)	16.5	8.6	0.006

Data are expressed as mean ± SD, or median (interquartile range), or percent.

ACE-I, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers, BMI, body mass index; CIMT, carotid intima-media thickness; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVEF, Left ventricular ejection fraction; LVDD, left ventricular diastolic dysfunction; SBP, systolic blood pressure; SWd, septal wall thickness during diastole; UACR, urinary albumin creatinine ratio.

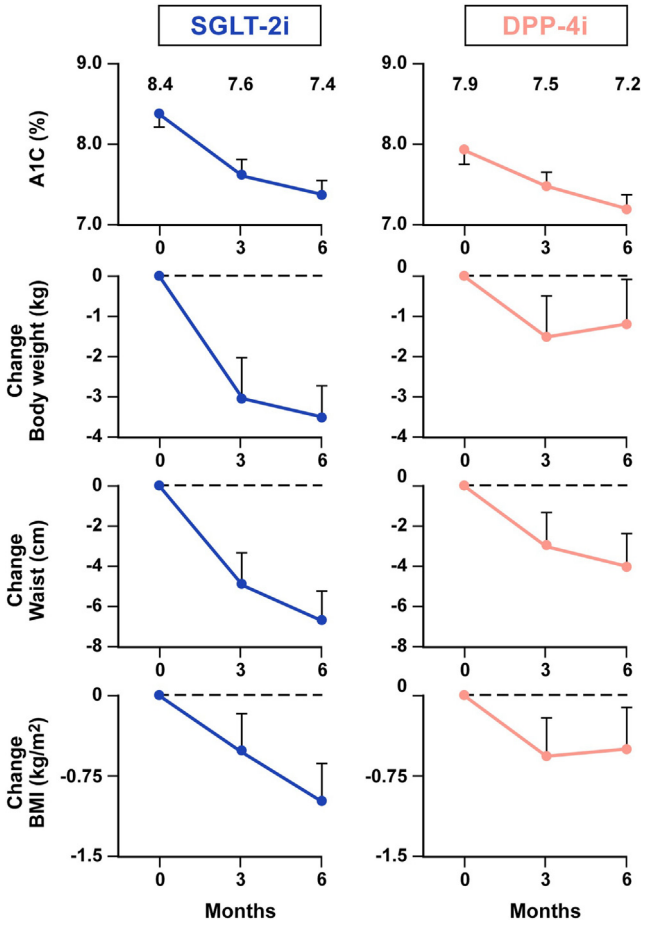

Fig. 1 – Change from baseline in A1C, body weight, waist circumference and BMI over 6 months. Data are mean (Standard Error).

3.2. *Preliminary results of effectiveness*

At six months, patients of the SGLT-2i group (n = 298) exhibit significant ameliorations in A1C (−1.0%), fasting plasma glucose (−28 mg/dl), body weight (−3.4 kg), waist (−7 cm), and BMI (−0.9 kg/m^2), without any significant changes of both systolic (−1.4 mm Hg) and diastolic (−1.4 mm Hg) blood pressure (Fig. 1 and Table 2); in the patients on a background metformin treatment only (64%), the decrease of A1C was greater (-1.2 ± 1.3, P <0.001) than that observed in patients on insulin (−0.65% ± 1.0, P <0.008). Patients of the DPP-4i group (n = 258) also show significant improvements in A1C (−0.70%), fasting plasma glucose (−30 mg/dl), body weight (−1.3 kg), waist (−3.7 cm), BMI (−0.67 kg/m^2), with no significant changes of both systolic (−1.7 mm Hg) and diastolic (−1.6 mm Hg) blood pressure (Fig. 1 and Table 2); even in this group, the decrease of A1C was greater (−0.81% ± 0.8, P <0.001) in those on background metformin (80%) as compared with those on insulin (−0.62% ± 0.8, P = 0.002).

The proportion of patients achieving the A1C level ≤7% increased steadily over time, reaching 44% in the SGLT-2i group and 51% in the DPP-4i group at 6 months (Fig. 2). The same percentage of patients (66% and 65%, respectively) achieved the A1C level of ≤7.5%. The composite endpoint (A1C ≤7.0% and weight loss ≥3 kg) was achieved by 24% and 16% of patients receiving SGLT-2i or DPP-4i, respectively. Over 60% of patients experienced weight loss, with approximately 25% experiencing weight loss ≥3 kg after 6 months of treatment in the SGLT-2i group, and 15% in the DPP-4i group (Fig. 3).

Significant ameliorations in the lipid profile are seen in both groups, with a significant reductions of total cholesterol, LDL-cholesterol and triglycerides in SGLT-2i users and of total and LDL-cholesterol in DPP-4i users (Table 2). No significant changes in both eGFR and UACR have occurred at 6 months in both groups.

The incidence of adverse events (AEs) is low (Supplementary Table 5). In total, 56 of 561 patients (10%) report 66 AEs within the first 6 months of treatment. No amputation, death, fractures are being reported during the observation. The proportion of patients presenting level 1 hypoglycaemia was 4% and 2% in the SGLT-2i and DPP-4i groups, respectively, while less than 1% of patients in both groups experienced levels2 or 3 hypoglycaemia. There were five drop-outs, 3 in the

Table 2 – Effectiveness results at 6 months.

	SGLT-2i			DPP-4i		
Variable	Baseline	6 months	P value	Baseline	6 months	P value
A1C (%)	8.4 ± 1.3	7.4 ± 1.1	<0.001	7.9 ± 1.0	7.2 ± 0.7	<0.001
Glucose (mg/dl)	163 ± 40	135 ± 36	<0.001	162 ± 37	132 ± 27	<0.001
Weight (kg)	88 ± 14	84.6 ± 14	0.049	76 ± 14	74.8 ± 14	0.081
BMI (kg/m^2)	32.3 ± 6.7	31.4 ± 5.3	<0.001	29.3 ± 6.7	28.6 ± 6.0	0.450
Waist (cm)	113 ± 13	106 ± 12	<0.001	105 ± 11	101 ± 11	0.012
SBP (mm Hg)	136.4 ± 13.8	135.0 ± 15	0.554	135.0 ± 13	133.3 ± 11	0.123
DBP (mm Hg)	81.4 ± 8.8	80.0 ± 9.1	0.350	82.5 ± 6.9	80.9 ± 5.7	0.680
Cholesterol (mg/dl)	183 ± 42	173 ± 35	0.039	177 ± 27	169 ± 28	0.044
HDL-C (mg/dl)	45.5 ± 12	47.5 ± 10	0.148	46.5 ± 8.9	47.9 ± 10	0.360
LDL-C (mg/dl)	105 ± 26.5	97.8 ± 24.4	0.021	104 ± 25.9	95 ± 28	0.020
Triglycerides (mg/dl)	167 ± 90	139 ± 56	0.004	134 ± 59	144 ± 68	0.249
eGFR (ml/min/1.73 m^2)	91 ± 20	90 ± 20	0.679	83 ± 19	81.4 ± 19	0.295
UACR (mg/24 h)	30.4 ± 35	25.7 ± 34	0.206	16 ± 7	15 ± 4.5	0.696

Data are mean ± SD.

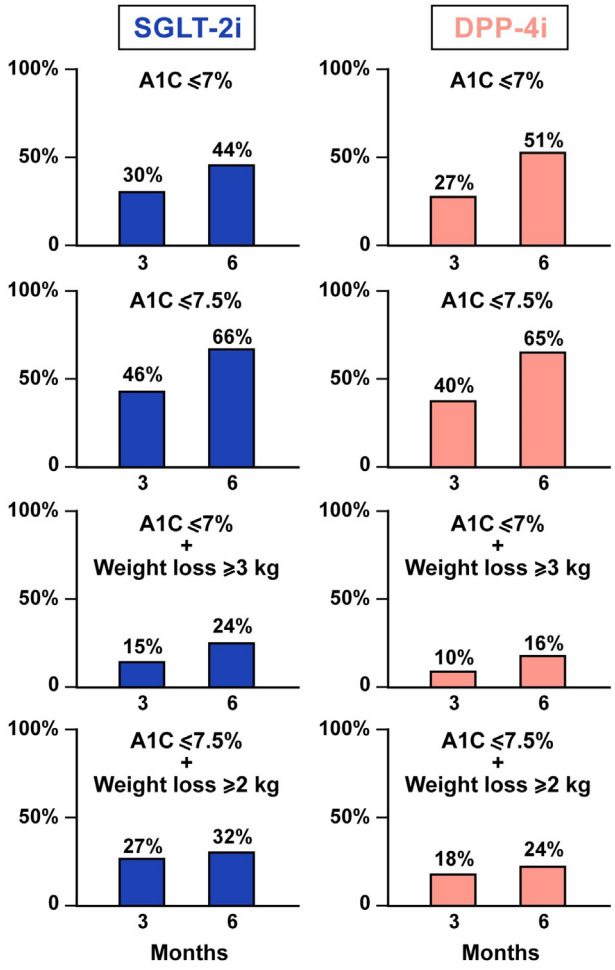

Fig. 2 – Proportion of patients achieving A1C ≤7% and ≤7.5%, and proportion of patients achieving the combined endpoints (A1C ≤7% + weight loss ≥3 kg, A1C ≤7.5% + weight loss ≥2 kg) after six months of treatment with SGLT-2i or DPP-4i.

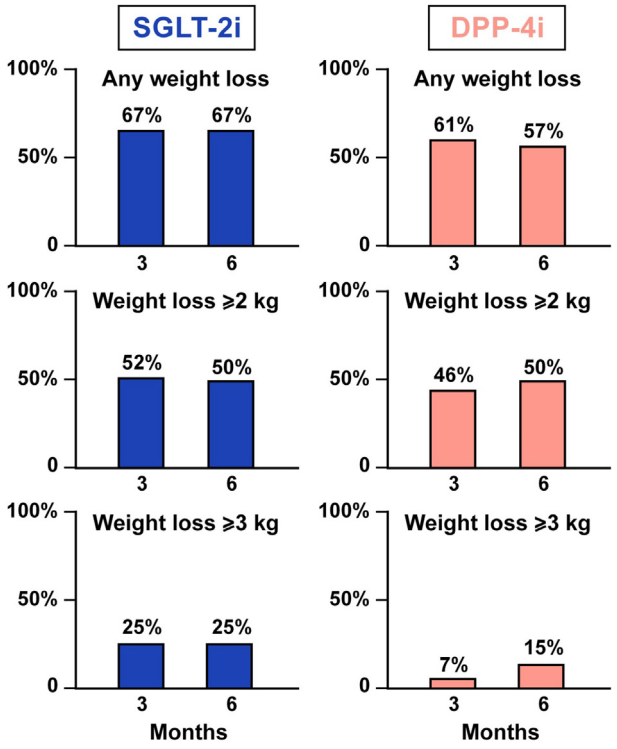

Fig. 3 – Proportion of patients achieving any weight loss, weight loss ≥2 kg and weight loss ≥3 kg after six months of treatment with SGLT-2i or DPP-4i.

SGLT-2i group and 2 in DPP-4i group: two patients in the SGLT-2i group have discontinued study treatment because of AEs, mainly genital fungal infections, while the other 3 patients changed residence or town. No patients required rescue medication during the observation period.

Medication adherence is greater than 90% with both treatments (93.7% with SGLT-2i and 96.3% with DPP-4i).

4. Discussion

GIOIA is a prospective observational study which aims to reduce the gap in knowledge about prospective outcomes in T2D patients receiving SGLT-2i and DPP-4i in routine clinical practice.

The analysis of baseline characteristics of the two groups of patients reveal a marked and significant difference (about 0.5%) in A1C value: this seems to indicate that SGLT-2i are being preferentially used in patients with moderately uncontrolled T2D, as often happens with newly marketed drugs that are initially tested in the more difficult-to-treat patients. Moreover, their preferential use in the obese T2D patients, whether or not insulin-treated, to reduce body weight or further weight gain, may also have played a role.

The phenotypic profile of the patient starting SGLT-2i seems to be the one of a middle-aged person with T2D, typically overweight or obese, with a longer diabetes duration, in poorer glycaemic control and with a previous CV event, which happened at least in about one/third (33%) of them; on the contrary, the phenotypic profile of the DPP-4i starter behaves as a more aged patient, less heavy, with a less compromised glycaemic control, for the most (87%) without a previous CV event. It seems that current prescribing patterns, at least in the Campania County, are based more on the expected metabolic effects (weight reduction and need to improve a poor glycaemic control for SGLT-2i, safety issue in the more elderly patient for DPP-4i) than on the need to prevent CV or kidney disease, as suggested by more recent guidelines. The American Diabetes Association [21] suggests use of new classes of glucose-lowering medicaments, such as SGLT-2i, with demonstrated CV disease benefits in patients with T2D and established ASCVD and/or chronic kidney disease. In general, recent prescribing patterns increasingly favour the newer more expensive treatments, leading to a rapid increase in cost of prescribing over recent years. For example, DPP-4i use has increased markedly in the U.K., and is now the most common second-line drug (43% prescriptions in 2016); the use of SGLT-2i also increased rapidly (14% new second-line in 2016) [22]. This trend is also present in other countries [23,24], whereas in Italy the global prescription of SGLT-2i is still low (about 3% of oral drugs vs 12% by DPP-4i) [14].

The analysis of effectiveness at 6 months shows significant improvements in A1C with both SGLT-2i (−1.0%) and DPP-4i (−0.7%), with a similar percentage of patients (44% and 51%) in both groups reaching the A1C level of ≤7%; the lower starting A1C level in the DPP-4i group may have compensated for the greater A1C reduction observed in the SGLT-2i group, with similar post-treatment (6 months) A1C level (7.4% vs 7.2%, respectively). Overall, this represents a good performance, given that all patients had, per protocol, a basal A1C level >7%. In general, our results seem better than the findings released from RCTs [25]. Although A1C reductions in the real-world are lower than those obtained in RCTs, at least for DPP-4i [26], the real world data suffer from the limitations of any retrospective analysis. Moreover, poor medication adherence has emerged as the key driver behind the disconnect [27]. In our study, medication adherence was good (>90% of the ratio between the prescribed and assumed pills), so we are confident that the prescribed treatment is being followed by the vast majority of patients. Finally, our patients are naïve to both SGLT-2i and DPP-4i, and their background glucose-lowering treatment is composed most by metformin (around 80%), insulin (around 20%) or both (around 12%), which avoid the possible interference by other drugs. Supporting this, the greatest A1C reduction (about 1.2% from baseline) has been obtained in patients of the SGLT-2i group taking metformin as the only background glucose-lowering treatment.

Body weight, BMI and waist circumference are reduced over time with use of SGLT-2i, and to a lesser and more vanishing extent with DPP-4i, which is consistent with published literature documenting the effects of SGLT-2i on body weight and modulation of visceral fat [27]. In addition, changes in anthropometric measures are important and relevant to patients, and they have been associated with improvements in patient adherence to medication [28]. Over the 6-month study period, about one quarter of patients in the SGLT-2i group achieve the harder composite endpoint (A1C ≤7% + weight loss ≥3 kg) and 32% of them achieve the softer composite endpoint (A1C ≤7.5% + weight loss ≥2 kg); the corresponding percentages in the DPP-4i group are 16% and 24%, respectively.

The overall incidence of AEs is low, with most being either mild or moderate in severity. Only two patients had to abandon the study because of genital mycotic infection not responsive to current treatment (either oral and topic). The vast majority of polyuria events occurred during the first 3 months after initiation of SGLT-2i treatment but declined over time in both sexes.

The present study has the limitations inherent to the lack of randomization, as evidenced by the imperfect alignment of baseline characteristics. However, this apparent drawback has given the opportunity to assess how physicians prescribe SGLT-2i and DPP-4i in routine clinical practice; moreover, randomization is useful to compare treatments or drugs, and this is an observational study. Given that large or very-large real-world studies are retrospective and hence report data of the past, a further strength of this study is that it is evaluating the current prescribing patterns of nowadays, starting from 2018 and continuing until 2020–2021.

In conclusion, the final GIOIA results will hopefully contribute to reduce the gap of knowledge existing about prospective outcomes in patients receiving SGLT-2i and DPP-4i in the current clinical practice in Italy. In the meantime, the analysis of the baseline characteristics of the enrolled patients suggest that physicians use SGLT-2i either to prevent further CV disease (in about one/third of patients) or to ameliorate glycaemic control and reduce weight gain in those without CV at baseline. DPP-4i use seems to be reserved to a more easy-to-treat and aged patients. Moreover, the preliminary results at 6 months show a good effectiveness in both groups, with more weight loss with SGLT-2i than DPP-4i, as expected, and no signal that the glucose lowering effect is waning, especially in patients that use these drugs as second-line treatment.

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Composition of the GIOIA study

Carmen Annunziata, Francesco Caiazzo, Carla Carbone, Raffaela Carotenuto, Paola Caruso, Filomena Castaldo, Laura Castellano, Angela Costantino, Rosa Di Fraia, Annalisa Sarnataro, Lorenzo Scappaticcio (Unità Operativa Complessa di Endocrinologia e Malattie del Metabolismo, Università della Campania "Luigi Vanvitelli", Napoli); Alessandro Pontillo (Unita di Programma di Diabetologia, Università della Campania "Luigi Vanvitelli", Napoli); Annalisa Capuano, Giulia Gritti, Antonio Giustino Guerrera, Concetta Rafaniello (Centro Regionale di Farmacovigilanza e Farmacoepidemiologia della Campania, Università della Campania "Luigi Vanvitelli", Napoli); Diego Carleo, Concetta Aragiusto, Nicoletta De Rosa (Distretto sanitario 43 Casoria, ASL Napoli 2 Nord); Silvio Settembrini (Distretto Sanitario 26 Soccavo, ASL Napoli 1 Centro); Stefano De Riu (Distretto Sanitario 33, Piazza Nazionale, Napoli, ASL Napoli1 Centro); Marisa Conte (Distretto sanitario 41 Sant'Antimo, ASL Napoli 2 Nord); Giuseppe Di Giovanni (Distretto sanitario 24 Loreto Crispi, ASL Napoli 1 Centro); Luigi Lucibelli (Distretto sanitario 56 - Poliambulatorio di Torre Annunziata – Diabetologia, ASL Napoli 3 Sud); Stefano Masi, Tommasina Sorrentino (Distretto sanitario 52, Unità Operativa di Diabetologia, ASL Napoli 3 Sud); Vincenzo Nuzzo, Ornella Romano (Unità Operativa Semplice Dipartimentale di Endocrinologia e Malattie del Metabolismo, Ospedale del Mare, Napoli); Chiara De Sio, Ferdinando Carlo Sasso (Medicina Interna, Università della Campania "Luigi Vanvitelli", Napoli);. Collection and management of data: Mariangela Caputo, Paolo Cirillo, Antonietta Maio, Vlenia Pernice (Dipartimento di Scienze Mediche e Chirurgiche Avanzate, Università della Campania "Luigi Vanvitelli", Napoli)

Author contributions

Design and analyses: K.E, M.I.M, M.L., M.P., M.G., G.B., D.G.; manuscript writing: K.E., M.L., M.I.M., D.G.; manuscript

revising for intellectual content: M.P., M.G., G.B. All authors approved the final version of the manuscript.

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Declaration of Competing Interest

D. G. received a consultancy fee from Eli Lilly and has given lectures for Eli Lilly, Sanofi, Novartis and Novo Nordisk. M.I. M. has given lectures for Novo Nordisk, Astrazeneca, Novartis, and Sanofi, and received a consultancy fee from MSD. K. E received a consultancy fee from Eli Lilly and has given lectures for Eli Lilly, Sanofi, Novo Nordisk, Novartis and Roche. M.P. has given lectures for Roche, Lifescan, and Medtronic. G.B. has given lectures for Novartis. M.L., and M.G. declare no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107787.

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