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Comparing medication persistence among patients with type 2 diabetes using sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide-1 receptor agonists in real-world setting

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ABSTRACT

Aim: To assess and compare the persistence with drug therapy between patients treated with glucagon-like peptide-1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2-I) therapy.

Methods: The 126,493 residents of the Lombardy Region (Italy) aged ≥ 40 years newly treated with metformin during 2007–2015 were followed until 2017 to identify those who started therapy with GLP1-RA or SGLT2-I. To make GLP1-RA and SGLT2-I users more comparable, a 1:1 matched cohort design was adopted. Matching variables were sex, age, and adherence to the first-line therapy with metformin. Log-binomial regression models were fitted to estimate the propensity to 1-year treatment persistence in relation to the therapeutic strategy.

Results: The final matched cohort was composed by 1,276 GLP1-RA—SGLT2-I pairs. About 24% and 29% of cohort members respectively on GLP1-RA and SGLT2-I discontinued the drug treatment. Compared with patients starting SGLT2-I, those on GLP1-RA had 15% (95% confidence interval, 3–25%) lower risk of discontinuation of the treatments of interest and 45% (28–57%) lower risk of discontinuing any antidiabetic drug therapy. Persistence was better among GLP1-RA users who received a once-weekly administration.

Conclusions: In a real-life setting, patients who were prescribed a GLP1-RA exhibited more frequently better persistence to treatment than those prescribed a SGLT2-I therapy.

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1. Introduction

Because of its high and growing prevalence [1], and the associated macro- and micro-vascular complications and mortality, diabetes is a major public health issue worldwide [2]. Clinical guidelines recommend managing patients with diabetes through several strategies, including diet and exercise, and drug therapy for patients who cannot achieve glycaemic control by lifestyle changes [3–5].

Although metformin was the recommended first-line drug treatment, patients often require multiple antidiabetic agents to achieve and maintain glycaemic control [6]. Recently, randomized controlled trials showed that some classes of antidiabetic drugs, i.e., glucagon-like peptide-1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2-I), are able to reduce the incidence of cardiovascular events among patients with type 2 diabetes [7–9]. As such, recent guidelines recommend them as the preferential add-on therapy to metformin in patients with or at high risk for cardiovascular events [10] or the first-choice treatment in patients naïve to the treatment with metformin [4]. However, the use of these drugs was linked with the occurrence of some side effects, i.e., nausea and vomiting are the most common adverse effects reported with GLP1-RA, especially in the initial phase of the treatment [11], whereas an increase in urogenital infections with mild/moderate symptoms has been observed among SGLT-I users [12]. Because the side effects, as well as other factors (including demographic characteristics, clinical factors, administration route of the therapy, costs, etc.), affect drug adherence, the protective action of these drugs in routine clinical practice might be downgraded, with significant clinical and public health implications.

To address the gap in knowledge, a very large investigation in the real-world setting of the Italian Lombardy Region was carried out. The aim was to assess and compare the discontinuation rates of patients newly treated with GLP1-RA and SGLT2-I.

2. Materials and methods

2.1. Setting

The data used for the current study were retrieved from the Healthcare Utilization databases of Lombardy, a region of Italy that accounts for about 16% (almost 10 million) of the entire Italian population. Italian citizens have equal access to essential healthcare services provided by the National Health Service (NHS). In Lombardy, management of healthcare services is allowed by an automated system of databases that provides information on administrative data, drug prescriptions (according to the ATC system) and hospital admissions (including inpatient diagnoses and procedures coded according to the ICD-9-CM system). Because patients are recorded in all the above-mentioned databases via a single identification code, these databases can be interconnected to search out the complete care pathway supplied to NHS beneficiaries. In order to preserve privacy, each identification code was automatically anonymized, the inverse process being only allowed to the Regional Authority upon request of judicial Authorities. Further details on healthcare utilization databases of the Lombardy region in the field of diabetes have been reported in previous studies [13–15].

2.2. Cohort selection and follow up

The target population included Lombardy residents aged 40 years or older who were beneficiaries of the NHS. Of these, those who received at least one prescription of metformin between 2007 and 2015 were identified and the date of the first prescription was defined as *entry date*. Patients were excluded if they (i) were not beneficiaries of the NHS for at least 3 years before the entry date, (ii) received at least one antidiabetic drug prescription within 3 years before the entry date, and (iii) did not received at least two prescriptions of metformin within 6 months following the entry date. The remaining patients were included into the *first cohort* whose members accumulated person-years of follow-up from the entry date until the earliest date among those of GLP1-RA or SGLT2-I dispensing, death, emigration or June 30th, 2017. GLP1-RA and SGLT2-I included all agents available in the Italian market during the study follow-up, i.e., exenatide, liraglutide, lixisenatide and dulaglutide (GLP1-RA), and dapagliflozin, canagliflozin and empagliflozin, including the corresponding fixed-dose combinations with metformin (SGLT2-I).

Patients who started drug therapy with GLP1-RA or SGLT2-I were identified and the date of the first prescription of these drugs was defined *index date*. Exclusion regarded patients who (1) did not renew the initial prescription of GLP1-RA/SGLT2-I and (2) did not reach at least 1 year of follow-up. The remaining patients were included into the *final cohort* whose members were followed for 1 year after the index date.

2.3. Antidiabetic drug exposure and outcome onset

For each member of the final cohort, antidiabetic drugs dispensed during the follow-up were identified. The period covered by GLP1-RA prescriptions was calculated by dividing the total amount of the prescribed drug for the defined daily dose. Because the defined daily dose leads to underestimating drug availability for all other oral antidiabetic agents [16], the period covered by other agents (including SGLT2-I) was calculated from the number of tablets in the dispensed canister, assuming a treatment schedule of one tablet per day (except for the fixed-dose combination metformin/SGLT2-I which is prescribed twice a day). For overlapping prescriptions, the patient was assumed to have used the entire drug included in the former prescription before starting the latter.

Starting from the index prescription, consecutively refilled prescriptions were considered to be uninterrupted (persistent) if the time-span between the end of one prescription and the beginning of the following one was less than 60 days [17]. Discontinuation of the initial therapy was assumed otherwise, that is the corresponding patient was considered to experiencing the outcome.

Two outcome measures were considered. First, discontinuation from initial antidiabetic drug was separately calculated for each of the two antidiabetic agents of interest. In this case, a patient who started with GLP1-RA (or with SGLT2-I) discontinued if he/she did not renew the prescription of GLP1-RA (or SGLT2-I). A patient who switched from GLP1-RA to another antidiabetic agent, including SGLT2-I (as well as a patient who switched from SGLT2-I to another antidiabetic agent, including GLP1-RA) was considered as experiencing this first category of outcome. Second, discontinuation from any antidiabetic drug was taken into account. In this case, a patient who switched from an antidiabetic agent to another was considered persistent, while this second category of outcome was considered experienced by patients who interrupted any antidiabetic drug therapy.

2.4. *Covariates*

Baseline characteristics measured at index date included sex, age, comorbidities (previous hospitalization for cardiovascular disease, cancer, depression, respiratory and kidney diseases) and co-treatments (antihypertensive, antithrombotic, lipid-lowering, antidepressants drugs, NSAIDs, digitalis, nitrates, and drugs for pulmonary diseases). In addition, duration of, and adherence with the first-line therapy with metformin was assessed. Adherence to drug therapy was evaluated according to the Proportion of Days Covered (PDC) measure, i.e., the ratio between the number of days in which the drug was available and the days of follow-up [18]. Finally, the clinical status of the patients was further assessed by the Multisource Comorbidity Score (MCS), a prognostic score that has been shown to predict all-cause mortality and hospitalization of Italian people better than other widely used score systems [19,20]. Three categories of clinical status were considered: good ($0 \leq$ score ≤ 4), intermediate ($5 \leq$ score ≤ 14) and poor (score ≥ 15).

2.5. *Data analysis*

Standardized mean differences for binary covariates were used when appropriate to test between-group differences. Equipoise was considered to be reached when the between-group comparison of covariates had a mean standardized difference of <0.1 [21].

With the aim of making patients starting on GLP1-RA and SGLT2-I as far as possible comparable, a 1:1 matched cohort design was adopted, i.e. for each individual initiating GLP1-RA therapy, a patient starting SGLT2-I was randomly identified. Matching variables were sex, age (±3 years), entry and index dates (±30 days), and adherence to the first-line therapy with metformin (PDC ± 5%).

Log-binomial regression models were fitted to estimate the risk ratio (RR), and its 95% confidence interval (CI), of both the outcomes separately associated with exposure to GLP1-RA against SGLT2-I (reference). Adjustments were made for the aforementioned baseline covariates. The association of interest was also assessed after patient stratification for sex, age, and cardiovascular disease. In addition, GLP1-RA users were stratified according to the treatment regimen, i.e., once-weekly vs. once-daily regimens.

2.6. *Sensitivity analyses*

Two sensitivity analyses were performed. First, to avoid the arbitrary nature of the threshold used to assess treatment persistence (i.e., 60 days), in a secondary analysis we used more permissive (90 days) and more restrictive (30 days) thresholds to define drug discontinuation.

Second, to account for the possible difference in the clinical status and other characteristics between patients on GLP1-RA and SGLT2-I, data were also analysed according to the high-dimensional propensity score matching approach [22]. The propensity of being treated with SGLT2-I was obtained through a logistic regression model that included as covariates the above-mentioned baseline data, plus the 200 most predictive covariates retrieved from the healthcare utilization databases. Briefly, this algorithm (i) identifies candidate covariates as all possible causes of hospitalization (three-digit ICD-9 codes) experienced by the patients, and all drugs prescribed (ATC codes, third level) to cohort members over the 2-year period prior to the index date, and (ii) selects those most imbalance between groups (i.e., SGLT2-I and GLP1-RA users) and independently associated with the study outcome (i.e., drug discontinuation). Groups were matched 1:1 based on their propensity score, using a nearest neighbour matching algorithm without replacement [23].

The Statistical Analysis System Software (version 9.4; SAS Institute, Cary, North Carolina, USA) was used for the analyses. For all hypotheses tested, two-tailed P values less than 0.05 were considered to be significant.

3. Results

3.1. *Patients*

The distribution of the exclusion criteria is shown in Fig. 1. Among the 473,121 patients on treatment with metformin between 2007 and 2015, 126,493 were incident users. Among this latter, 3,965 and 3,012 patients who respectively started GLP1-RA and SGLT2-I were included into the study cohort. Compared to patients included in the final cohort, those excluded because did not renew the initial prescription and/or did not reach at least 1 year of follow-up were older, less adherent to the first-line therapy with metformin and more treated with lipid-lowering drugs (**Supplementary Table S1**). Among patients under initial GLP1-RA, 1,044 (26%) were prescribed a once-weekly administration (**Supplementary Table S2**).

The characteristics of the cohort members according to the employed drug therapy are shown in Table 1. Compared to patients starting on SGLT2-I, those on GLP1-RA were younger and more often females. The first-line therapy with metformin was employed from less time, and with higher adherence by patients on GLP1-RA than those on SGLT2-I. No between-group differences in comorbidities and co-treatments were noticed, except for NSAIDs, which were more used among GLP1-RA patients. Patients on GLP1-RA had worse clinical complexity than those on SGLT2-I.

During the period between entry (i.e., first metformin prescription) and index date (i.e., first prescription of GLP1-RA or

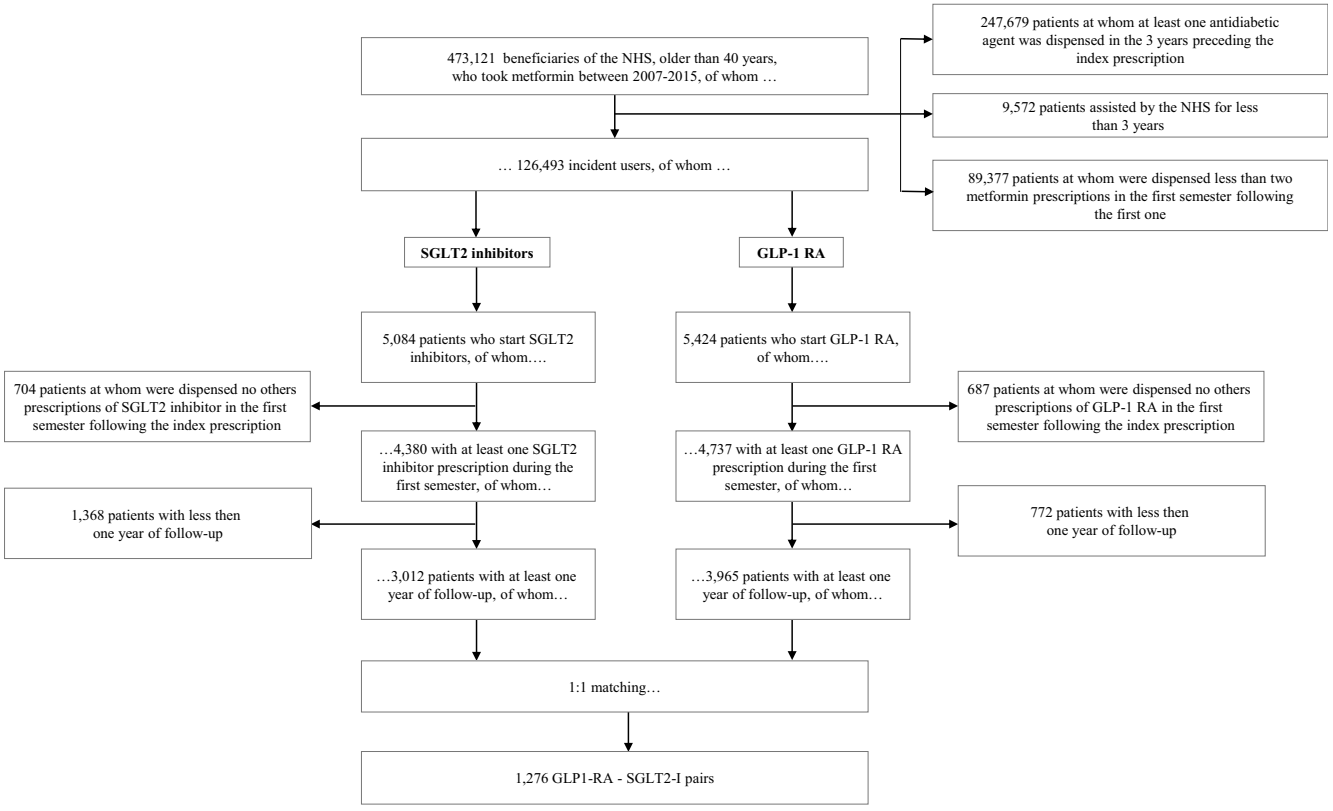

Fig. 1 – Flow-chart of inclusion and exclusion criteria that were used to select the final cohort.

Table 1 – Baseline characteristics of cohort members according to drug treatment.

	SGLT2-I (N = 3,012)	GLP1-RA (N = 3,965)	Standardize difference
Male sex	1,903 (63.2%)	2,171 (54.8%)	0.171
Age (years)			
40–64	1,997 (66.3%)	2,976 (75.1%)	0.198
≥ 65	1,015 (33.7%)	989 (24.9%)	
First-line therapy based on metformin			
Duration (years)	4.6 (2.7)	3.5 (2.6)	0.415
Adherence (PDC†)	0.55 (0.2)	0.58 (0.3)	0.118
Comorbidities			
Cardiovascular disease	412 (13.7%)	562 (14.2%)	0.014
Kidney disease	28 (0.9%)	32 (0.8%)	0.011
Cancer	117 (3.9%)	155 (3.9%)	0.000
Respiratory disease	748 (24.8%)	1,154 (29.1%)	0.097
Depression	53 (1.8%)	77 (1.9%)	0.007
Co-treatments			
Antihypertensive agents	2,322 (77.1%)	3,135 (79.1%)	0.048
Antithrombotic drugs	1,084 (36.0%)	1,368 (34.5%)	0.031
Lipid-lowering drugs	2,028 (67.3%)	2,486 (62.7%)	0.097
Digitalis	35 (1.2%)	51 (1.3%)	0.009
Nitrates	136 (4.5%)	170 (4.3%)	0.010
NSAIDs	1,127 (37.4%)	1,779 (44.9%)	0.153
Respiratory drugs	698 (23.2%)	1,090 (27.5%)	0.099
Antidepressant drugs	380 (12.6%)	597 (15.1%)	0.072
Clinical status‡			
Good	2,020 (67.1%)	2,477 (62.5%)	0.109
Intermediate	895 (29.7%)	1,344 (33.9%)	
Poor	97 (3.2%)	144 (3.6%)	

Data are N (%); or mean (SD); † PDC: proportion of days covered; ‡The clinical status was assessed by the Multisource Comorbidity Score (MCS). Patients were categorized as having good (0–4), intermediate (5–14) or poor (≥15) clinical status.

SGLT2-I), about 50% of patients used other antidiabetic drugs other than metformin (**Supplementary Table S3**). About 30% of them were treated with sulfonylureas, while 12% and 21% of cohort members respectively on GLP1-RA and SGLT2-I used insulin.

3.2. *Discontinuation of SGLT2-I or GLP1-RA*

After the matching procedure, the final cohort was composed by 1,276 pairs who started with GLP1-RA or SGLT2-I. No between-group differences in comorbidities and co-treatments were noticed, except for NSAIDs, which were more used among GLP1-RA patients (Table 2).

About 24% (307 patients) and 29% (368 patients) of cohort members respectively on GLP1-RA and SGLT2-I discontinued initial antidiabetic drug during the first year after the index date. As shown in Fig. 2, compared with patients starting on SGLT2-I, those on GLP1-RA had 15% (95% CI, 3% to 25%) lower risk of discontinuation of the treatment. This was also the case in female patients, for patients younger than 65 years, and irrespectively of the presence of cardiovascular disease. Stratified analyses for the treatment regimen showed that, compared with patients starting on SGLT2-I, the risk of discontinuation was lower among GLP1-RA users who received a once-weekly administration (RR: 0.72, 95% CI: 0.54–0.96) but not among those on a daily administration (0.90, 0.76–1.06).

At the time of discontinuation, almost 70% of patients on either GLP1-RA or SGLT2-I was on combined therapy involving metformin and another antidiabetic agent, whereas only 15% of them were on monotherapy with metformin (**Supplementary Table S4**).

3.3. *Discontinuation of any antidiabetic drug therapy*

About 6.2% (79 patients) and 12.5% (160 patients) of cohort members respectively on GLP1-RA and SGLT2-I interrupted any antidiabetic drug therapy during the first year after the index date. As shown in Fig. 3, compared with patients starting on SGLT2-I, those on GLP1-RA had 45% (95% CI, 28% to 57%) lower risk of discontinuing antidiabetic drug therapy. Persistence was better in patients on GLP1-RA in each stratum of age, sex, and cardiovascular disease. Finally, there was evidence that the risk of discontinuation was lower among GLP1-RA users who received a once-weekly administration (RR: 0.31, 0.22–0.47), whereas there was no difference between those on a GLP1-RA daily administration and patients on SGLT-2I (0.80, 0.55–1.14).

3.4. *Sensitivity analyses*

The main findings did not change substantially by modifying the threshold used to define treatment discontinuation and

Table 2 – Baseline characteristics of cohort members according to drug treatment after matching for sex, age, first-line therapy based on metformin (duration and adherence) and index date.

	SGLT2-I (N = 1,276)	GLP1-RA (N = 1,276)	Standardize difference
Male sex	795 (62.3%)	795 (62.3%)	MV†
Age (years)			
40–64	887 (69.5%)	887 (69.5%)	MV†
≥ 65	389 (30.5%)	389 (30.5%)	
First-line therapy based on metformin			
Duration (years)	4.7 (2.7)	4.7 (2.7)	MV†
Adherence (PDC‡)	0.55 (0.2)	0.55 (0.2)	MV†
Comorbidities			
Cardiovascular disease	136 (10.7%)	123 (9.6%)	0.040
Kidney disease	12 (0.9%)	8 (0.6%)	0.035
Cancer	28 (2.2%)	20 (1.6%)	0.044
Respiratory disease	309 (24.2%)	317 (24.8%)	0.014
Depression	19 (1.5%)	11 (0.9%)	0.055
Co-treatments			
Antihypertensive agents	963 (75.5%)	997 (78.1%)	0.062
Antithrombotic drugs	402 (31.5%)	381 (29.9%)	0.035
Lipid-lowering drugs	835 (65.4%)	852 (66.8%)	0.030
Digitalis	10 (0.8%)	11 (0.9%)	0.010
Nitrates	46 (3.6%)	35 (2.7%)	0.052
NSAIDs	464 (36.4%)	540 (42.3%)	0.121
Respiratory drugs	291 (22.8%)	297 (23.3%)	0.012
Antidepressant drugs	137 (10.7%)	141 (11.1%)	0.013
Clinical status§			
Good	1,006 (78.8%)	964 (75.6%)	0.072
Intermediate	266 (20.9%)	305 (23.9%)	
Poor	4 (0.3%)	7 (0.6%)	

Data are N (%); or mean (SD); †MV: matching variable; ‡ PDC: proportion of days covered; § The clinical status was assessed by the Multisource Comorbidity Score (MCS). Patients were categorized as having good (0–4), intermediate (5–14) or poor (≥15) clinical status.

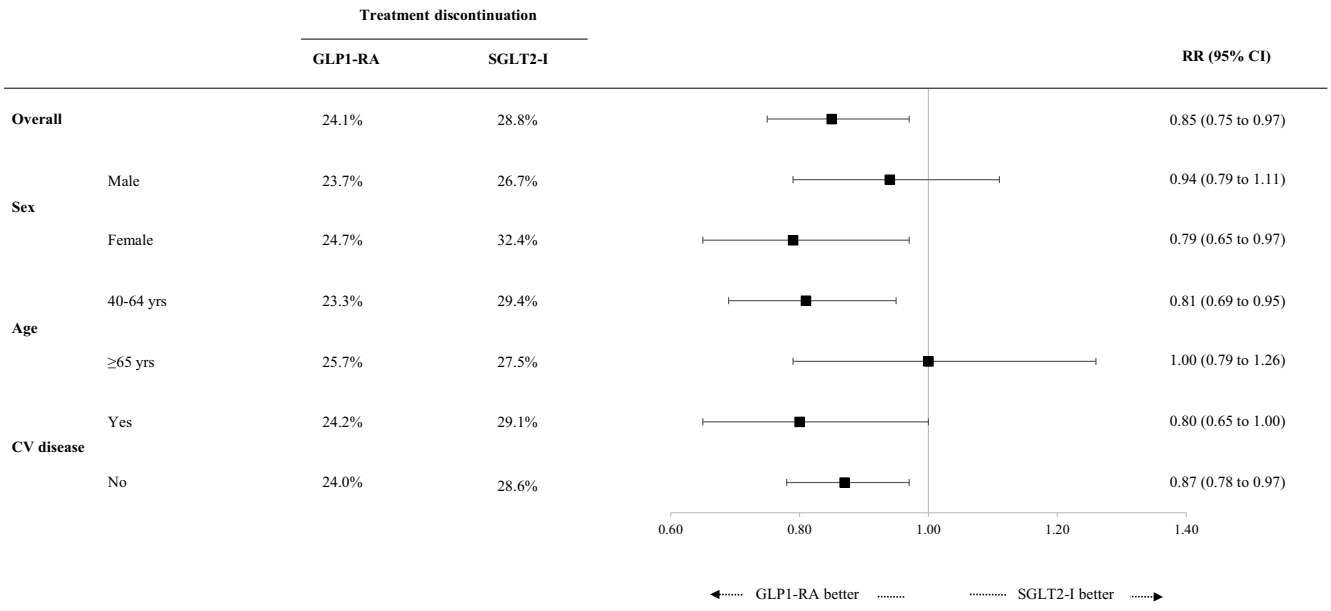

Fig. 2 – Adjusted risk ratio (RR), and 95% confidence intervals (CI), of treatment discontinuation with the drug started at the index date (i.e., GLP1-RA or SGLT2-I) in the whole cohort and according to sex, age and cardiovascular (CV) disease.

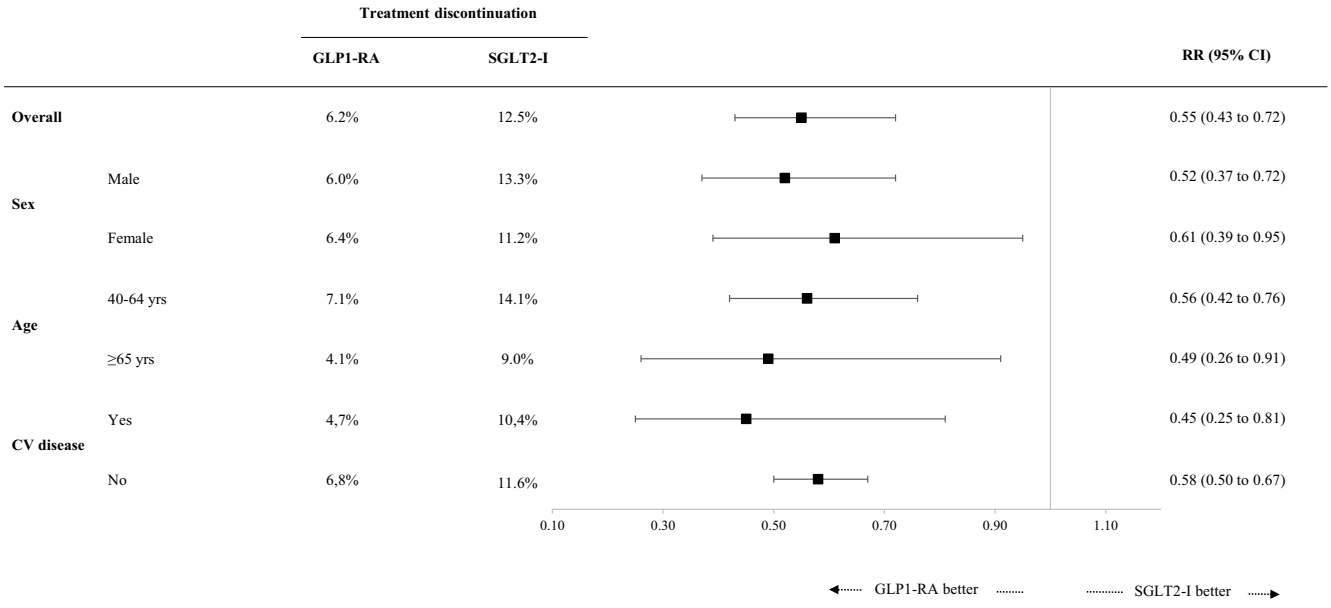

Fig. 3 – Adjusted risk ratio (RR), and 95% confidence intervals (CI), of discontinuation antidiabetic drug therapy in the whole cohort and according to sex, age and cardiovascular (CV) disease.

adopting the high-dimensional propensity score algorithm (**Supplementary Table S5**).

4. Discussion

The present study, based on almost 7,000 patients newly treated with GLP1-RA and SGLT2-I, confirms previous observations that the discontinuation rate of antidiabetic drug treatment is high in 'real-life' practice [24–26]. In addition, evidence that a substantial number of patients discontinued therapy initially employed [27] was confirmed from our study, being 13% those who did not renew the initial prescription within one year after treatment starting.

However, our study further provides three new findings. First, discontinuation occurred more often among patients whom SGLT2-I therapy was initially employed compared to those on GLP1-RA. The between-drug differences were not trivial because, compared to the initial GLP1-RA, the discontinuation rate observed in patients in whom SGLT2-I was initially prescribed was 15% greater. Second, just a few patients completely interrupted the antidiabetic drug therapy after the discontinuation. Indeed, 70% of patients who interrupted

GLP1-RA or SGLT2-I continued therapy with a combination of metformin and other agents, and almost 15% with metformin only. Third, a worrying fraction of patients discontinued any antidiabetic treatment during the first year from starting, this fraction being particularly high for patients in SGLT2-I (12%) but not even irrelevant to those on GLP1-RA (6%). This is of particularly concern because the literature consistently reports larger improvements in glycaemic control among patients who adhere and persist with treatment [28,29].

Our findings are in contrast with the results reported by some authors in which SGLT2-I have been associated with better adherence and persistence than GLP1-RA [30–32]. Two main reasons could explained this discrepancy. First, to limit the inclusion of patients with type 1 diabetes, we excluded patients younger than 40 years, and Jermendy et al. showed that the between-group difference in treatment discontinuation in favour to SGLT2-I was greater among patients $\leq$ 40 years [32]. Second, dulaglutide was not included in previous investigations because it was approved by the FDA after the end of the studies selection window [30,31] and evidence exist that dulaglutide users were more persistent compared with initiators of other GLP1-RA (exenatide or liraglutide) [33].

The main weakness of our study is that we cannot explain the reasons of drug discontinuation. Indeed, because the reasons for discontinuation are not recorded in our database, and the common adverse effects usually do not require hospitalization, we cannot assess these events. However, other studies have addressed this question and identified factors affecting persistence with drug therapy. These factors include those related to the patient (e.g., age, education level, income), the therapy (e.g., complexity, administration route, posology and cost) and the healthcare system (e.g., integrated care, clinical inertia) [34]. As in Italy outpatient dispensing medicaments for chronic conditions, including diabetes, is free of charge, and because it has been shown that discontinuation of chronic drug treatments is independent by patient's income [35], socioeconomic factors unlikely affected our findings. Rather, the most common reasons for discontinuing SGLT2-I are genitourinary tract infections and, less frequently, dehydration or other rarer side effects [36–38], whereas gastrointestinal issues are reported as the main reason for GLP1-RA discontinuation [39].

According with previous observations suggesting higher adherence for once-weekly regimens rather than once-daily ones [40], our findings clearly showed higher persistence among patients who took weekly formulation of GLP1-RA.

The present study has several elements of strength. First, the investigation was based on a very large unselected population, which was made possible because in Italy a cost-free healthcare system involves virtually all citizens. Second, the drug prescription database provided highly accurate data because pharmacists are required to report prescriptions in detail in order to obtain reimbursement, and incorrect reports about the dispensed drugs have legal consequences [41]. Third, because no antidiabetic drug was prescribed in the previous 3 years before the entry date, cohort members could be legitimately identified at the beginning of the drug treatment, thus the complete sequence of subsequent healthcare services supplied by the NHS was identified. Finally, a number of sensitivity analyses confirmed the robustness of our findings.

The study also has some limitations that need to be taken into account. Exposure misclassification may affect our results in several ways. First, treatment persistence was derived from drug prescriptions, which requires the assumption that drug prescriptions correspond to drug consumption, which may not invariably be the case [42]. Second, because the prescribed daily doses are not recorded in our database, we approximated the period covered by each prescription from the defined daily doses and the number of tablets in the dispensed canister, so likely introducing misclassified categorical exposures [16]. However, as the main findings were confirmed by modifying thresholds for defining discontinuation, we are confident that this source of misclassification, although plausible, marginally affected our main findings. Third, our database did not record drugs prescribed outside the NHS (i.e., over-the-counter drugs), though free-of-charge drug availability makes unlikely this possibility.

Finally, because in our study allocation of antidiabetic therapy was not randomized, the results may be affected by confounding factors. That is, the observed treatment → persistence association might rather have been generated by patients' characteristics, such as severity of diabetes, glycated haemoglobin level, body mass index, in general by features which healthcare utilization data source as the ours does not report. Although robustness of our findings were confirmed by applying a high-dimensional propensity score 1:1 matching design, residual confounding cannot be excluded. Therefore, future researches on this topic are needed. Notwithstanding the reasons, the findings of our study point out that patients starting a drug therapy based on SGLT2-I should be monitored more carefully than patients on GLP1-RA because at higher risk to interrupt the treatment.

In conclusion, our observational investigation confirms that persistence to GLP1-RA and even more to SGLT2-I is suboptimal in clinical practice. Understanding the reasons underlying this issue will likely help to develop interventions aimed to improve the management of the disease. These efforts would most likely substantially reduce long-term outcomes, healthcare resource utilization and costs.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Giovanni Corrao received research support from the European Community (EC), the Italian Agency of Drug (AIFA), and the Italian Ministry of Education, University and Research (MIUR). He took part to a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN and BMS). He also received honoraria as member of Advisory Board from Roche. Other authors declare that they have no conflict of interest to disclose.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2021.109035.

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