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Lower risk of death and cardiovascular events in patients with diabetes initiating glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 inhibitors: A real-world study in two Italian cohorts

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Abstract

Aim: To examine the efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors compared with other antihyperglycaemic agents (AHAs) in large and unselected populations of the Lombardy and Apulia regions in Italy.

Materials and Methods: An observational cohort study of first-time users of GLP-1RAs, SGLT2 inhibitors or other AHAs was conducted from 2010 to 2018. Death and cardiovascular (CV) events were evaluated using conditional Cox models in propensity-score-matched populations. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for each region and in a meta-analysis for pooled risks.

Results: After propensity-score matching, the Lombardy cohort included 18 716 and 11 683 patients and the Apulia cohort 9772 and 6046 patients for the GLP-1RA and SGLT2 inhibitor groups, respectively. Use of GLP-1RAs was associated with lower rates of death (HR 0.61, CI 0.56-0.65, Lombardy; HR 0.63, CI 0.55-0.71, Apulia), cerebrovascular disease and ischaemic stroke (HR 0.70, CI 0.63-0.79; HR 0.72, CI 0.60-0.87, Lombardy), peripheral vascular disease (HR 0.72, CI 0.64-0.82, Lombardy; HR 0.80, CI 0.67-0.98, Apulia), and lower limb complications (HR 0.67, CI 0.56-0.81, Lombardy; HR 0.69, CI 0.51-0.93, Apulia). Compared with other AHAs, SGLT2 inhibitor use decreased the risk of death (HR 0.47, CI 0.40-0.54, Lombardy; HR 0.43, CI 0.32-0.57, Apulia), cerebrovascular disease (HR 0.75, CI 0.61-0.91, Lombardy; HR 0.72, CI 0.54-0.96, Apulia), and heart failure (HR 0.56, CI 0.46-0.70, Lombardy; HR 0.57, CI 0.42-0.77, Apulia). In the pooled cohorts, a reduction in heart failure was also observed with GLP-1RAs (HR 0.89, 95% CI 0.82-0.97). Serious adverse events were quite low in frequency.

Conclusion: Our findings from real-world practice confirm the favourable effect of GLP-1RAs and SGLT2 inhibitors on death and CV outcomes across both regions

consistently. Thus, these drug classes should be preferentially considered in a broad type 2 diabetes population beyond those with CV disease.

KEYWORDS
antihyperglycaemic drugs, cardiovascular outcomes, death, glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors

1 | INTRODUCTION

Patients with diabetes are at high risk of adverse outcomes from atherosclerotic cardiovascular (CV) disease[1–4], heart failure (HF), and renal disease. Intensive and early control of hyperglycaemia in patients with type 2 diabetes (T2D) may reduce the incidence of nonfatal myocardial infarction and coronary artery disease, while it does not affect the incidence of stroke and mortality[5–8]. Until recently, however, antihyperglycaemic therapy was not conclusively shown to reduce overall macrovascular events in T2D, and there was even concern that some medications could cause CV harms and increase mortality[9,10]. However, a series of large CV outcomes trials (CVOTs) in T2D patients, principally designed to meet regulatory requirements for CV safety, recently assessed the effects of new antihyperglycaemic agents (AHAs), such as glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors, in addition to standard of care. In most cases, the results of these trials showed a significant reduction of major CV outcomes with the investigational drug compared with placebo (ie, standard of care).[11,12] Specifically, GLP-1RAs showed a CV benefit in terms of reduced incidence of atherosclerotic events, such as nonfatal myocardial infarction and stroke, while SGLT2 inhibitors consistently reduced the risk of hospitalization for HF. The use of both drug classes was also associated with reductions in the risk of renal endpoints, with SGLT2 inhibitors acting both on the decline of glomerular filtration rate and albuminuria, and GLP-1RAs mainly on the latter[13–20]. Based on these results, in patients with established CV disease or at high CV risk, established kidney disease or HF, treatment with GLP-1RAs or SGLT2 inhibitors is currently recommended as part of the glucose-lowering regimen.[21–22]

The clinical trials showed that treatment with GLP-1RAs and SGLT2 inhibitors is also associated with specific adverse events, such as increased risk of gastrointestinal side effects, genitourinary tract infections, and fractures.[19,23,24] This may limit the inclusion of these drugs in the therapeutic regimen, as well as patients' adherence to and persistence with these therapies in the long term.

Some real-world studies have also investigated the efficacy and mortality outcomes of these new drugs, showing that initiation of SGLT2 inhibitors versus other AHAs was associated with a pertinent lower incidence of hospitalization for HF and death; however, the safety outcomes were not investigated or were investigated only in a limited sample size in this setting.[25–29] In addition, these observational studies have largely focused on the comparison between SGLT2 inhibitors and other AHAs, while information on population-based cohort studies comparing the efficacy and safety of GLP-1RAs versus other AHAs is more limited.[30,31]

To assess whether the results of randomized clinical trials with the new AHAs are generalizable to the whole diabetes population it is important to analyse cohorts of patients treated in daily practice. The current availability of large administrative databases allows the expected clinical benefits and risks in routine clinical settings to be verified. In this study, we used administrative data from two highly populated Italian regions, Lombardy and Apulia, to analyse large and unselected populations with diabetes. We report the clinical characteristics and risks of death and major CV events, as well as the safety profiles, in first-time users of GLP-1RAs and SGLT2 inhibitors in comparison with other AHAs.

2 | METHODS

2.1 | Data source

Our study used linkable administrative health databases from the Lombardy and Apulia regions in Italy, which include population registries with demographic data on all residents and detailed information on drug prescriptions and hospital records. Data are available for approximately 10 and four million inhabitants of Lombardy and Apulia, respectively, from 2000 to 2018. Access to data is allowed within agreements between the *Istituto di Ricerche Farmacologiche Mario Negri* (IRFMN) and Regional Health Ministry of Lombardy and between the IRFMN and Regional Healthcare Agency of Apulia.

Healthcare in Italy is publicly funded for all residents, irrespective of social class or employment, and every resident is assigned a personal identification number kept in the National Civil Registration System. All residents are assisted by general practitioners under the National Health System (NHS). The pharmacy prescription database contains the medication name and anatomical therapeutic chemical (ATC) classification code, quantity, and date of dispensation of drugs reimbursed by the NHS. No information is available on drugs dispensed in hospital. The hospital databases contain information on the date of admission, discharge, death, primary diagnosis, and up to five coexisting clinical conditions and procedures received.

The diagnoses, uniformly coded according to the 9th International Classification of Diseases Clinical Modification (ICD-9-CM) system and standardized in all Italian hospitals, are compiled by the hospital specialists directly in charge of the patients and are validated by hospitals against detailed clinical instrumental data, as they determine

reimbursement from the NHS. A unique identification code allows linkage of all databases. To ensure privacy, each identification code was automatically converted into an anonymous code before we received the dataset. In Italy, studies using retrospective aggregated anonymous data from administrative databases do not require ethics committee/institutional review board approval or notification.

2.2 | Study cohorts and follow-up

We conducted a cohort study using the two administrative health databases from Lombardy and Apulia, respectively. Patients aged 50 years and older with chronic exposure to AHAs (at least two packages in the year [ATC code A10*]) from January 1, 2010 to December 31, 2018, were included in the analysis. Patients were split into three groups according to first exposure (first-time users) to one of the following drug classes: GLP-1RAs, SGLT2 inhibitors or other AHAs including metformin, sulphonylureas, glinides, thiazolidinediones, acarbose, and dipeptidyl-peptidase-4 (DPP-4) inhibitors. To avoid potential bias and in order to compare relatively similar populations, patients who were first-time users for insulin treatment were not included in the other AHAs group. Indeed, insulin therapy may be a marker of more severe and/or advanced disease, and we could not adjust for disease severity due to the lack of availability of full clinical data for these cohorts. However, a proportion of patients within the other AHAs group may have had previous insulin exposure before entering the cohort, but not as a chronic treatment. First-time users were defined as patients whose first exposure (index date) to one of the AHA classes occurred in the index year, with no prior exposure to any medications belonging to the same class in the previous 5 years. These groups, therefore, included patients who added an oral AHA to the therapeutic regimen, changed (switched) from one to another oral AHA or, in a negligible percentage, started taking an oral AHA without having taken any in the previous years. Therefore "first-time users" should be considered as "patients starting to take a new AHA". Moreover, once assigned to a given group, the patient remained in that group until outcome occurrence or censoring (intention-to-treat approach). Patients initiating GLP-1RAs or other AHAs were included in the study cohort from 2010, while patients initiating SGLT2 inhibitors were included in the study cohort from 2015, reflecting the availability of these drugs in the Italian market.

Propensity-score matching (PSM) was used to reduce confounding due to imbalance in study covariates. A systematic approach to selection of variables was used to create balanced cohorts, attempting to exclude as few patients as possible. A group PSM matching was used to match GLP-1RA and SGLT2 inhibitor cohorts with other AHAs in a 1:1 ratio using the following variables: age group (5-year intervals); sex; index year; prior exposure to insulin; duration of diabetes; and Drug Derived Complexity Index (DDCI) as a proxy of comorbidities. The DDCI is a predictive score derived from drug prescriptions that stratifies the general population according to the risk of 1-year and long-term mortality, as well as the risk of unplanned hospitalization and hospital readmission.[32] Date of entry into the study cohorts is the date on which the patient adds, changes or starts an AHA. Therefore, patients with diabetes who never change their AHA class from their inception do not enter our cohorts, unless they start as naïve during the observation period. Patients were followed up from drug initiation until the first occurrence of (a) outcomes of interest, or (b) migration, admission to a nursing home, or the end of follow-up (December 31, 2018). A sensitivity analysis with first-time users of DPP-4 inhibitors as a comparator cohort was also carried out. This comparison allowed assessment of the effects of GLP-1RAs and SGLT2 inhibitors versus a drug class—DPP-4 inhibitors—known to exhibit neutral effects on major CV outcomes in T2D patients[33–36]; moreover, GLP-1RAs, SGLT2 inhibitors and DPP-4 inhibitors are prescribed only by diabetes specialists in Italy.

2.3 | Comorbidities and pharmacological treatments

Prevalence of comorbidities was assessed for the 5 years before the index date using hospital records according to ICD 9-CM codes as primary diagnosis and up to five coexisting conditions. Previous exposure to any class of AHAs, hospital admissions and DDCI were collected for the previous 5 years, while information on the other medications of interest was retrieved for the previous 12 months. Information on duration of diabetes was collected for the period from 2000 to 2018 (Appendix S1).

2.4 | Study outcomes

Outcomes included the following events: death from any cause, hospital admission for cerebrovascular disease, CV disease, ischaemic stroke, acute coronary syndrome, HF, peripheral vascular disease, and lower limb complications as primary diagnosis. Serious adverse events included hospital admission for hypoglycaemia, ketoacidosis, diabetes with coma, amputation, acute renal failure, syncope, and fracture as primary diagnosis. All clinical events were collected using hospital admission according to the ICD 9-CM codes (Appendix S1). Renal outcomes were not analysed because the initiation of SGLT2 inhibitor therapy during the time frame of the study was indicated only in individuals with estimated glomerular filtration rate (eGFR) >60 mL/min/1.73m^2; this will probably select patients with better renal health compared to those treated with other AHAs, representing a potential bias for analysing renal outcomes.

2.5 | Statistical analysis

Baseline characteristics of patients in each group of treatment were evaluated using descriptive statistics. Categorical variables were described by frequencies and percentages and compared using the chi-squared test; continuous variables were described using mean ± standard deviation (SD) and compared using Student's *t*-test. DDCI,

previous hospital admission, history of diabetes, and follow-up times were expressed as median and interquartile range (IQR).

Patients were matched on the logit of the propensity score using calipers of width equal to 0.1 of the SD of the logit of the estimated propensity score.[37] Specifically, based on PSM, patients receiving GLP-1RAs or SGLT2 inhibitors were matched 1:1 with those receiving other AHAs. The adequacy (congruency) of PSM was assessed by standardized differences of postmatching patient characteristics. To evaluate the balance between groups after matching, we calculated the standardized mean difference; good balance is conventionally set at a standardized mean difference of less than 0.10 [38].

Longitudinal analyses were performed in matched populations. Outcomes were calculated as crude incidence rates, that is, the number of incident events divided by the total number of person-years at risk, and expressed per 100 person-years with 95% confidence intervals (CIs). The percentage of events in each group was calculated as the number of incident events divided by the total number of persons at risk. A Cox proportional hazard regression model based on time to first event was used to estimate hazard ratios (HRs) and 95% CIs for each outcome, comparing the treatment effect of GLP-1RAs and SGLT2 inhibitors versus other AHAs (reference group). HRs were adjusted for all comorbidities (cerebrovascular and CV disease, HF, peripheral vascular disease, lower limb complications, renal disease, neuropathy, retinopathy, chronic obstructive pulmonary disease, and cancer) reported at baseline. Outcomes were analysed using an intention-to-treat approach. All patients included in the analysis were followed up according to treatment status (starting from the first exposure index date), regardless of whether they received the treatment throughout the study period. The frequency of serious adverse events was calculated as the number of events divided by the total population in each treatment group.

Results are presented for each region separately because the Italian Privacy Policy on data protection does not allow pooled data to be exported from multiple health administrative databases from distinct Italian regions. Pooled risks from the two regions are presented as a meta-analysis for an overall summary. The I-squared statistic was used to calculate heterogeneity among the studies. A probability value of $I^2 \geq 50\%$ indicated the presence of significant heterogeneity. A fixed-effects model was used in the presence of no significant interstudy heterogeneity; otherwise, a random-effects model was used. The log-rank test, stratified by region, was used for comparisons, and the HRs with 95% CIs of events were calculated. A P value <0.05 was considered statistically significant. A sensitivity analysis was computed comparing GLP-1RA and SGLT2 inhibitor use with DPP-4 inhibitor use. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

3 | RESULTS

A flowchart of the study for all databases combined from the Lombardy and Apulia regions is provided in Appendix S1. Overall, during the study period, 29 634 first-time users of GLP-1RAs, 25 141 new users of SGLT2 inhibitors and 280 375 new users of other AHAs were identified (baseline patient characteristics before matching are reported in Table S1 and S2). After PSM, the Lombardy study cohort included 18 716 and 11 683 patients in the GLP-1RA and SGLT2 inhibitor groups, respectively, while the Apulia study cohort comprised 9772 and 6046 patients in the GLP-1RA and SGLT2 inhibitor groups, respectively (Tables 1 and 2). After matching, the variables included in the PSM were well balanced (all standardized differences were <0.1). In general, in both regions, patients newly prescribed a GLP-1RA or an SGLT2 inhibitor had similar comorbidities to patients in the other AHAs group, although patients initiating SGLT2 inhibitors were more likely to have CV disease in comparison with first-time users of other AHAs. In the GLP-1RA and SGLT2 inhibitor groups, 4.0% to 7.0% and 12% to 16% of patients had established cerebrovascular and CV diseases, respectively, in the two regions (Tables 1 and 2). The median (IQR) follow-up time for GLP-1RAs and the matched other AHAs group was 3.9 (1.7-6.8) and 3.7 (1.5-6.7) years in Lombardy, and 2.8 (1.1-6.2) and 2.9 (1.3-6.1) years in Apulia, respectively. The median follow-up time for SGLT2 inhibitors and the matched other AHAs group was 1.8 (1.0-2.7) and 1.6 (0.7-2.5) years in Lombardy and 1.6 (0.7-2.2) and 1.5 (0.7-2.3) years in Apulia. Patients belonging to the GLP-1RA or SGLT2 inhibitor groups presented with higher rates of background antihyperglycaemic treatment and received slightly more antihypertensive and lipid-lowering medications as compared to the other AHAs cohort (Tables 1 and 2). Differences between the GLP-1RA and SGLT2 inhibitor groups in both regions were observed in mean age (67-68 vs 64-65 years for the GLP-1RA and SGLT2 groups, respectively), history of diabetes (a higher percentage of patients in the SGLT2 inhibitor group had a duration of T2DM ≥10 years compared to the GLP-1RA group), and previous prescription of insulin (29% and 34% in the GLP-1RA and SGLT2 inhibitors groups, respectively).

The risks of death and clinical outcomes in propensity-score-adjusted populations by treatment status for Lombardy and Apulia regions are reported in Figures 1A,B and 2A,B.

In the Lombardy cohort, initiation of a GLP-1RA was associated with a lower risk of death (HR 0.61, 95% CI 0.56-0.65), cerebrovascular disease (HR 0.70, 95% CI 0.63-0.79), ischaemic stroke (HR 0.72, 95% CI 0.60-0.87), peripheral vascular disease (HR 0.72, 95% CI 0.64-0.82), and lower limb complications (HR 0.67, 95% CI 0.56-0.81) in comparison with the other AHAs group. In the Apulia cohort, patients who received GLP-1RAs also exhibited a lower risk of death (HR 0.63, 95% CI 0.55-0.71), peripheral vascular disease (HR 0.80, 95% CI 0.67-0.98), and lower limb complications (HR 0.69, 95% CI 0.51-0.93) with respect to those treated with other AHAs.

In the Lombardy cohort, initiation of SGLT2 inhibitors was associated with a lower risk of death (HR 0.47, 95% CI 0.40-0.54), cerebrovascular disease (HR 0.75, 95% CI 0.61-0.91), and HF (HR 0.56, 95% CI 0.46-0.70) in comparison with other AHAs. Similar results were obtained with SGLT2 inhibitors in the Apulia cohort with risk reductions for death (HR 0.43, 95% CI 0.32-0.57), cerebrovascular disease (HR 0.72, 95% CI 0.54-0.96), and HF (HR 0.57, 95% CI 0.42-0.77) compared with other AHAs. The effect on death and CV outcomes of the GLP-1RAs and SGLT2 inhibitors in comparison with other AHAs was similar in men and women (Tables S15 and S16). When results from the two cohorts were

TABLE 1 Baseline characteristics of matched populations according to treatment status in Lombardy

Variables	Matched population			Matched population		
	GLP-1RA[a] (N = 18 716)	Other AHAs (N = 18 716)	Standardized differences	SGLT2 inhibitors[b] (N = 11 683)	Other AHAs (N = 11 683)	Standardized differences
Mean (±SD) age, years	65.4 ± 8.0	65.5 ± 8.0	−0.01	68.2 ± 7.2	68.8 ± 8.3	−0.07
Women, n (%)	8355 (44.6)	8248 (44.1)	0.01	4433 (37.9)	4501 (38.5)	−0.01
Comorbidities of interest, n (%)						
Cerebrovascular disease	695 (3.7)	935 (5.0)	−0.06	512 (4.4)	647 (5.5)	−0.05
CV disease	2201 (11.8)	2273 (12.1)	−0.01	1784 (15.3)	1456 (12.4)	0.08
HF	670 (3.6)	816 (4.4)	−0.03	428 (3.6)	641 (5.5)	−0.08
Peripheral vascular disease	627 (3.4)	757 (4.0)	−0.03	454 (3.9)	488 (4.2)	−0.01
Lower limb complication	154 (0.8)	260 (1.4)	−0.05	111 (0.9)	184 (1.5)	−0.05
Renal disease	318 (1.7)	613 (3.3)	−0.10	131 (1.1)	460 (3.9)	−0.18
Neuropathy	415 (2.2)	383 (2.0)	0.01	158 (1.3)	133 (1.1)	0.01
Diabetic retinopathy	19 (0.1)	29 (0.2)	−0.01	15 (0.1)	19 (0.1)	−0.00
Chronic obstructive pulmonary disease	661 (3.5)	808 (4.3)	−0.04	406 (3.5)	566 (4.8)	−0.06
Cancer	1244 (6.6)	1558 (8.3)	−0.06	675 (5.8)	929 (7.9)	−0.08
Previous antihyperglycaemic drugs, n (%)						
GLP-1RAs	0 (0.0)	134 (0.7)	0.11	183 (1.6)	45 (0.4)	0.12
SGLT2 inhibitors	0 (0.0)	4 (0.0)	−0.00	0 (0.0)	0 (0.0)	0.00
Insulin	4858 (26.0)	4644 (24.8)	0.02	4081 (34.9)	3495 (29.9)	0.10
Other AHAs	18 675 (99.8)	17 938 (95.8)	0.25	11 610 (99.4)	11 152 (95.0)	0.24
Metformin	17 879 (95.5)	14 429 (77.1)	0.55	10 908 (93.4)	8907 (76.2)	0.49
Sulphonylureas	12 769 (68.2)	10 092 (53.9)	0.29	6652 (56.9)	5544 (47.4)	0.19
Glinides	3002 (16.0)	1491 (8.0)	0.25	1433 (12.3)	745 (6.4)	0.20
Glitazones	6340 (33.9)	1619 (8.7)	0.64	2619 (22.4)	721 (6.2)	0.47
Acarbose	1656 (8.8)	13 (0.1)	0.43	1139 (9.7)	10 (0.1)	0.45
DDP-4 inhibitors	6430 (34.4)	184 (1.0)	0.97	3755 (32.1)	70 (0.6)	0.94
Number of antihyperglycaemic drugs, n (IQR)	3 (2,4)	1 (1,2)	1.02	3 (2,4)	1 (1,2)	0.91
Patients with no previous antihyperglycaemic drug treatment, n (%)	87 (0.5)	823 (4.4)	0.25	73 (0.6)	531 (4.5)	0.24
Other medications of interest, n (%)						
Antihypertensive drugs	15 460 (82.6)	14 438 (77.1)	0.13	9669 (82.7)	9192 (78.7)	0.10
ACE inhibitors/ARBs	13 771 (73.6)	12 331 (65.9)	0.16	8358 (71.5)	7737 (66.2)	0.11
Lipid-lowering drugs	12 408 (66.3)	10 665 (57.0)	0.19	8113 (69.4)	7058 (60.4)	0.19
Antiplatelet drugs	7460 (39.9)	7002 (37.4)	0.05	4412 (37.7)	3920 (33.5)	0.08
Oral anticoagulant drugs	968 (5.2)	1059 (5.7)	−0.02	723 (6.2)	956 (8.2)	−0.07
DDCI index, median (IQR)	4 (2.7)	4 (2.7)	−0.00	4 (2.7)	4 (2.7)	0.00
Hospital admission, median (IQR)	1 (0.2)	1 (0.2)	−0.07	0 (0.2)	1 (0.2)	−0.09
Duration of diabetes, n (%)						
0-4	1900 (10.2)	1843 (9.8)	0.02	74 (0.6)	186 (1.6)	0.08
5-9	6009 (32.1)	5754 (30.7)		3097 (26.5)	3002 (25.7)	
10+	10 853 (58.0)	11.165 (59.7)		8512 (72.8)	9495 (72.7)	

Abbreviations: ACE, angiotensin-converting enzyme; AHA, antihyperglycaemic agent; ARB, angiotensin II receptor agonist blocker; CV, cardiovascular; DDCI, Drug Derived Complexity Index; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; IQR, interquartile range; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2.

[a]From 2010 to 2018 for GLP-1RAs and other AHAs.

[b]From 2015 to 2018 for SGLT2 inhibitors.

TABLE 2 Baseline characteristics of matched populations according treatment status in Apulia

Variables	Matched population			Matched population		
	GLP-1RA[a] (N = 9772)	Other AHAs (N = 9772)	Standardized differences	SGLT2 inhibitors[b] (N = 6046)	Other AHAs (N = 6046)	Standardized differences
Mean (±SD) age, years	64.6 ± 7.7	64.3 ± 7.9	0.03	67.2 ± 7.6	67.33 ± 7.9	−0.01
Women, n (%)	4892 (50.1)	4876 (49.9)	0.00	2714 (44.9)	2857 (47.2)	−0.04
Comorbidities of interest, n (%)						
Cerebrovascular disease	523 (5.3)	679 (6.9)	−0.06	409 (6.8)	430 (7.1)	−0.01
CV disease	1167 (11.9)	1257 (12.9)	−0.02	979 (16.2)	768 (12.7)	0.09
HF	408 (4.2)	541 (5.5)	−0.06	290 (4.8)	371 (6.1)	−0.05
Peripheral vascular disease	594 (6.1)	548 (5.6)	0.02	320 (5.3)	323 (5.3)	−0.00
Lower limb complication	73 (0.7)	106 (1.1)	−0.03	47 (0.8)	72 (1.2)	−0.04
Renal disease	315 (3.2)	418 (4.3)	−0.05	154 (2.5)	328 (5.4)	0.14
Neuropathy	279 (2.9)	298 (3.0)	−0.01	141 (2.3)	129 (2.1)	0.01
Diabetic retinopathy	24 (0.2)	20 (0.2)	0.00	9 (0.1)	12 (0.2)	−0.01
Chronic obstructive pulmonary disease	553 (5.7)	611 (6.2)	−0.02	323 (5.3)	402 (6.6)	−0.05
Cancer	817 (8.4)	972 (9.9)	−0.05	494 (8.2)	578 (9.6)	−0.04
Previous antihyperglycaemic drugs, n (%)						
GLP-1RAs	0 (0.0)	77 (0.8)	−0.12	63 (1.0)	24 (0.4)	0.07
SGLT2 inhibitors	0 (0.0)	0 (0.0)	0.00	0 (0.0)	0 (0.0)	0.00
Insulin	2890 (29.6)	2628 (26.9)	0.05	1984 (32.8)	1876 (31.0)	0.03
Other AHAs	9748 (99.7)	9338 (95.6)	0.28	6031 (99.8)	5817 (96.2)	0.25
Metformin	9539 (97.6)	7942 (81.3)	0.55	5813 (96.1)	4917 (81.3)	0.48
Sulphonylureas	5365 (54.9)	4289 (43.9)	0.22	2974 (49.2)	2259 (37.4)	0.24
Glinides	3314 (33.9)	1228 (12.6)	0.52	1821 (30.1)	721 (11.9)	0.45
Glitazones	3028 (31.0)	1027 (10.5)	0.52	1237 (20.5)	448 (7.4)	0.38
Acarbose	811 (8.3)	17 (0.2)	0.41	570 (9.4)	6 (0.1)	0.44
DDP-4 inhibitors	3640 (37.2)	94 (1.0)	1.04	2132 (35.3)	48 (0.8)	1.00
Number of antihyperglycaemic drugs, n (IQR)	3 (2.4)	2 (1.2)	0.94	3 (2.3)	2 (1.2)	0.92
Patients with no previous antihyperglycaemic drug therapy, n (%)	24 (0.2)	434 (4.4)	0.28	15 (0.2)	229 (3.8)	0.25
Other medications of interest, n (%)						
Antihypertensive drugs	8433 (86.3)	7869 (80.5)	0.15	5102 (84.4)	4847 (80.2)	0.11
ACE inhibitors/ARBs	7426 (76.0)	6772 (69.3)	0.15	4335 (71.7)	4079 (67.5)	0.09
Lipid-lowering drugs	6992 (71.5)	5789 (59.2)	0.26	4490 (74.3)	3752 (62.0)	0.26
Antiplatelet drugs	5760 (58.9)	5058 (51.8)	0.14	3787 (62.6)	3269 (54.1)	0.17
Oral anticoagulant drugs	467 (4.8)	596 (5.2)	−0.01	328 (5.4)	407 (6.7)	−0.05
DDCI index, median (IQR)	5 (3.7)	5 (3.7)	0.03	5 (3.7)	5 (3.7)	−0.00
Hospital admission, median (IQR)	1 (0.2)	1 (0.2)	−0.02	1 (0.2)	1 (0.2)	−0.01
Duration of diabetes, n (%)						
0-4	876 (9.0)	913 (9.3)	0.02	75 (1.2)	108 (1.8)	0.04
5-9	3974 (40.7)	3885 (39.8)		1489 (24.6)	1448 (23.9)	
10+	4922 (50.4)	4974 (50.9)		4482 (74.1)	4490 (74.3)	

Abbreviations: ACE, angiotensin-converting enzyme; AHA, antihyperglycaemic agent; ARB, angiotensin II receptor agonist blockers; CV, cardiovascular; DDCI, Drug Derived Complexity Index; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; IQR, interquartile range; SD, standard deviation; SGLT2, sodium glucose cotransporter-2.

[a]From 2010 to 2018 for GLP-1RAs and other AHAs.

[b]From 2015 to 2018 for SGLT2 inhibitors.

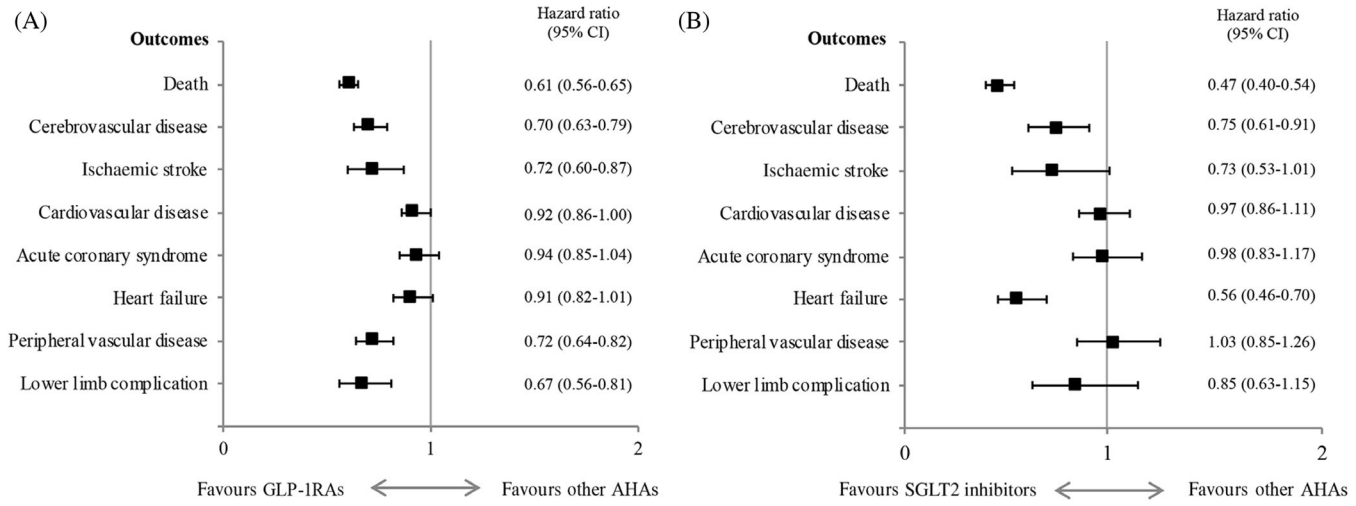

FIGURE 1 A, B, Hazard ratios (95% confidence interval [CI]) for death and clinical events in matched populations according to treatment status in Lombardy. GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2; AHA, antihyperglycaemic agent

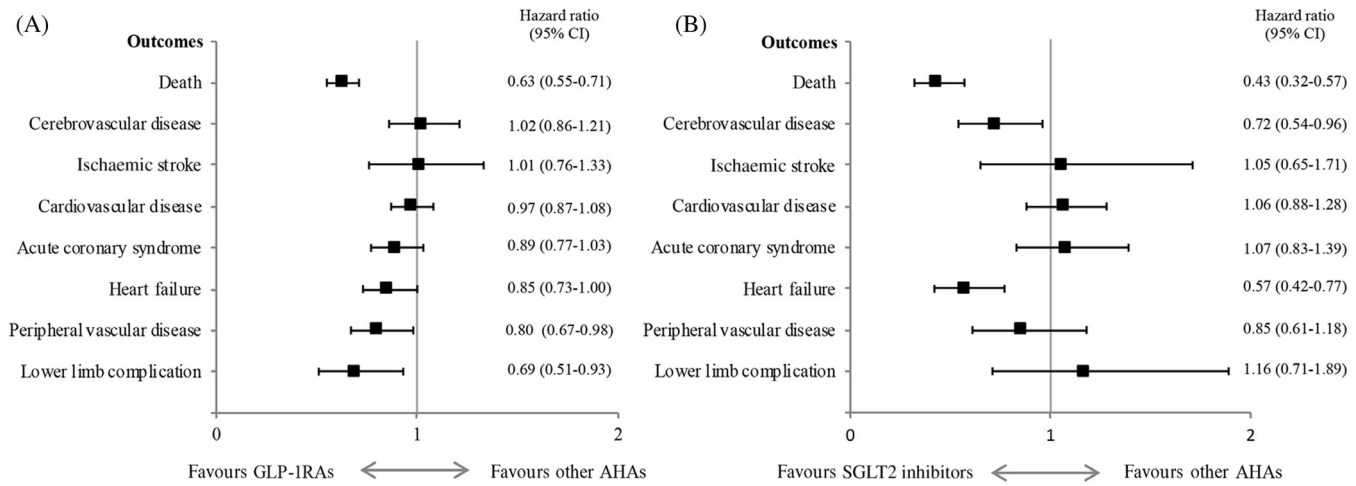

FIGURE 2 A, B, Hazard ratios (95% confidence interval [CI]) for death and clinical events in matched populations according to treatment status in Apulia. GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2; AHA, antihyperglycaemic agent

pooled, a small but significant reduction in the risk of hospitalization for HF (HR 0.89, 95% CI 0.82-0.97) with GLP-1RAs compared with other AHAs was also apparent (Figure S1, Appendix S1).

During follow-up, the rate of serious adverse events was quite low in each region. In general, fractures were documented more frequently; however, the rate of this event was slightly lower in the SGLT2 inhibitor group (∼1%) than in the GLP-1RA and other AHAs groups (2.5%; Table 3).

Results of the preplanned sensitivity analysis comparing GLP-1RAs and SGLT2 inhibitors with DPP-4 inhibitors for each region are reported in Appendix S1, showing baseline characteristics of matched and unmatched populations as well as risks for all considered outcomes. After PSM, the populations of the two cohorts were well matched for multiple clinical variables (all standardized differences were <0.1, except for renal disease and HF in some of the comparisons; Appendix S1). In comparison with patients who received DPP-4 inhibitors, those initiating GLP-1RAs showed statistically significant risk reductions for death, cerebrovascular disease, peripheral vascular disease, lower limb complications (Lombardy cohort; Table S9), and death and lower limb complications (Apulia cohort; Table S11); those initiating SGLT2 inhibitors had risk reductions for death, cerebrovascular disease and HF (Lombardy cohort; Table S10), and death and HF (Apulia cohort; Table S12). These results were therefore similar to those observed in comparison with other AHAs.

4 | DISCUSSION

In the present analysis, we examined large cohorts of patients with T2D initiating treatment with GLP-1RAs or SGLT2 inhibitors

TABLE 3 Frequency of serious adverse events in matched populations by treatment in Lombardy and Apulia

Events	Lombardy, n (%)				Apulia, n (%)			
	GLP-1RA[a] (N = 18 716)	Other AHAs (N = 18 716)	SGLT2 inhibitor[b] (N = 11 683)	Other AHAs (N = 11 683)	GLP-1RA[a] (N = 9772)	Other AHAs (N = 9772)	SGLT2 inhibitor[b] (N = 6046)	Other AHAs (N = 6046)
Hypoglycaemia	22 (0.12)	20 (0.11)	2 (0.02)	11 (0.09)	8 (0.08)	10 (0.10)	1 (0.02)	4 (0.07)
Ketoacidosis	8 (0.04)	12 (0.06)	5 (0.04)	3 (0.03)	14 (0.14)	14 (0.14)	1 (0.02)	1 (0.02)
Diabetic coma	6 (0.03)	11 (0.06)	2 (0.02)	3 (0.03)	2 (0.02)	6 (0.06)	0	0
Amputations	121 (0.65)	208 (1.11)	54 (0.46)	63 (0.54)	44 (0.45)	69 (0.71)	15 (0.25)	24 (0.40)
Acute renal failure	17 (0.09)	10 (0.05)	2 (0.02)	2 (0.02)	14 (0.14)	16 (0.16)	4 (0.07)	6 (0.10)
Syncope	91 (0.49)	99 (0.53)	27 (0.23)	29 (0.25)	28 (0.29)	57 (0.58)	6 (0.10)	17 (0.28)
Fractures	462 (2.47)	517 (2.76)	150 (1.28)	176 (1.51)	224 (2.29)	249 (2.55)	44 (0.73)	78 (1.29)

Abbreviations: AHA, antihyperglycaemic agent; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2.
[a]From 2010 to 2018 for GLP-1RAs and other AHAs.
[b]From 2015 to 2018 for SGLT2 inhibitors.

compared with other antihyperglycaemic therapies, including DPP-4 inhibitors, in routine clinical settings. The available information refers to data from two distinct Italian regions, Lombardy and Apulia, and allows an epidemiological assessment unbiased by patient selection. In Italy, all patients are covered by the NHS, according to distinct reimbursement policies, with a high level of completeness regarding drug prescriptions, diagnosis, and length of observation. Administrative databases have been increasingly recognized as a reliable tool to prospectively describe the pharmaco-epidemiology and outcomes of large patient cohorts representing real clinical care because they collect data over time in a standardized way and at low cost.[39,40] We found that initiation of GLP-1RA therapy was associated with consistent risk reductions in all-cause death and hospitalization for peripheral vascular disease and lower limb complications, with additional risk reductions for cerebrovascular disease and ischaemic stroke that were evident in the Lombardy cohort. Initiation of SGLT2 inhibitors was associated with risk reductions of all-cause death, hospitalization for cerebrovascular disease, and HF. These risk reductions were apparent in comparison with the initiation of other AHAs (except insulin), irrespective of gender; most differences were also observed after comparing the first-time users of GLP-1RAs or SGLT2 inhibitors with patients initiating DPP-4 inhibitors.

As of today, results from seven CVOTs with GLP-1RAs have been disclosed. The definition of secondary prevention cohorts according to previous CV disease of the enrolled population varied among these trials, and so did the proportion of such patients.[11] Nevertheless, the ELIXA and HARMONY Outcome studies involved only patients with recent acute coronary syndrome or with any CV disease, respectively; by contrast, REWIND assessed a population with 70% of individuals without prior CV disease and with the lowest proportion (only 8%) with congestive HF. Large observational studies assessing CV outcomes with GLP-1RAs are not available at present. The CVOTs with SGLT2 inhibitors enrolled patients at high CV risk (with percentages of participants with atherosclerotic CV disease ranging from 41% in DECLARE-TIMI 58 to 65% in CANVAS and 100% in EMPA-REG). In these trials, at baseline, participants with HF ranged from 10% to 14% of the population, while between 6.5% and 23.3% had experienced a stroke.[12] In the real-world observational studies assessing CV outcomes with SGLT2 inhibitors, the CV risk level of the examined populations was very different. CVD-REAL and CVD-REAL-2 included 13% and 26% of patients with T2D and established CV disease, respectively, [25,29] while in CVD-REAL Nordic, this proportion was 25%.[41] In the CVD-REAL programme, the proportion of patients with HF at baseline ranged from 3% to 6.8%. By contrast, EASEL involved only patients with T2D and established CV disease.[26] In the present study, the proportion of individuals with CV disease was between 12% and 16% and that with HF was between 3% and 6% (Table 1). Moreover, these proportions did not appear to differ between the Lombardy and Apulia cohorts. Therefore, the population examined had a level of CV risk largely lower than those in the CVOTs with GLP-1RAs or SGLT2 inhibitors, and was somewhat similar to that in the CVD-REAL observational study with SGLT2 inhibitors.

In the present analysis, first use of GLP-1RAs was associated with 37% to 39% reduced risk of all-cause death and with reductions of peripheral vascular disease and lower limb complications. Meta-analysis of the CVOTs with GLP-1RAs also showed an overall 12% reduction in the risk of all-cause mortality,[14] while the effects on peripheral vascular disease and lower limb complications were not considered as primary or secondary endpoints in those trials. The risk reductions for cerebrovascular disease and ischaemic stroke observed in the Lombardy cohort are of interest, given that in some GLP-1RA CVOTs, such as REWIND [16] and SUSTAIN-6,[42] the risk of stroke was also reduced with the investigational GLP-1RA. In a recent study in a relatively small cohort from North-East Italy, including approximately 2800 propensity-score-matched patients initiating GLP-1RAs or DPP-4 inhibitors, 15% of whom had preexisting CV disease, reduced rates of a composite of all-cause death, myocardial infarction, or stroke (HR 0.67, 95% CI 0.53-0.86) were found with GLP-1RAs compared to DPP-4 inhibitors.[31] Why risk reductions for cerebrovascular disease and ischaemic stroke were not found to be reduced in the Apulia cohort in the present analysis is unclear, but potential factors

include differences in population size, baseline cerebrovascular risk (higher in the Apulia cohort; Tables 1 and 2), and level of glucose control during follow-up.

In the present analysis, first use of SGLT2 inhibitors was associated with important risk reductions for all-cause death (by 53%-57%) and HF (by 43%-44%), as well as for cerebrovascular disease (by 25%-28%). The risk reduction in HF hospitalization has been consistently observed in all CVOTs and observational studies with SGLT2 inhibitors, while all-cause death was reduced in EMPA-REG and in the observational studies. Of note, the effect size of those reductions resembles that observed in the present analysis. Results from Lombardy and Apulia also consistently show a reduction in the risk of cerebrovascular disease with SGLT2 inhibitors. While the risk of fatal or nonfatal stroke was not changed in the three major CVOTs with SGLT2 inhibitors, the observational study CVD-REAL 2 (conducted in Australia, Canada, Israel, Japan, Singapore and South Korea in 235 064 patients with T2DM) also showed an association of SGLT2 inhibitor use with a significantly reduced risk of stroke (HR 0.68; 95% CI 0.55-0.84),[29] in line with the present analysis.

Some, but not all, of the results in the present analysis show a greater effect size associated with the use of GLP-1RAs and SGLT2 inhibitors when compared with those seen in the CVOTs. This difference could be potentially attributable to differences in patient characteristics and clinical setting. However, our data are in line with those of other observational studies (focused mainly on SGLT2 inhibitors), such as CVD-REAL and EASEL, in which a stronger effect associated with the use of these drugs was observed.[25,26,29]

The results of the meta-analysis on both the Lombardy and Apulia cohorts largely confirmed the results obtained from the main analysis of the individual regions and provided further information. Pooling of data showed that initiation of GLP-1RAs was not associated with a lower risk of cerebrovascular disease and ischaemic stroke, as observed in the Lombardy region. However, GLP-1RA initiation was associated with a small but significantly lower risk of HF. This observation is in line with a recent meta-analysis of the GLP-1RA CVOTs[14] and deserves further investigation with dedicated studies.

Similar risk reductions were found for all-cause death and other CV outcomes comparing initiation of GLP-1RAs with that of DPP-4 inhibitors, while patients initiating SGLT2 inhibitors had consistent risk reductions for death and HF in both regional cohorts. These data are of interest because initiation of GLP-1RAs and SGLT2 inhibitors is being compared with a drug class, DPP-4 inhibitors, that also does not cause hypoglycaemia or weight gain. Moreover, these treatment strategies are equally positioned in the Italian treatment algorithm and can be prescribed only by diabetes specialists in patients exposed to a similar clinical setting. Such direct comparisons have not been addressed in the CVOTs, while a single additional analysis from CVD-REAL Nordic showed that the SGLT2 inhibitor dapagliflozin was also associated with significantly lower incidence of hospitalization for HF, all-cause mortality and major adverse CV events in comparison with DPP-4 inhibitors[43]; moreover, an interim analysis from the ongoing EMPRISE observational study, including 224 528 patients with T2D with and without established CV disease, reported that initiation of SGLT2 inhibitors was associated with a 48% lower rate of hospitalization for HF in comparison with DPP-4 inhibitors.[27]

In general, the present analysis shows a low occurrence of adverse effects that could be captured using the administrative databases, including ketoacidosis, amputations, renal failure, syncope and fractures, which represent the most worrisome adverse events associated with SGLT2 inhibitor use emerging from randomized controlled trials.[44]

To our knowledge, this is the first study of real-world evidence to evaluate the effect of GLP-1RAs on mortality and major adverse CV events in comparison with other AHAs. The analysis was conducted in a large number of patients after PSM (30 399 in Lombardy and 15 818 in Apulia), initiating either GLP-1RA or SGLT2 inhibitors. Results found with GLP-1RAs and SGLT2 inhibitors in comparison with other AHAs were largely confirmed when DPP-4 inhibitors were used as a comparator. The length of observation was approximately 4 years for GLP-1RAs and 2 years for SGLT2 inhibitors. Finally, Lombardy and Apulia are two representative regions of Northern and Southern Italy, respectively; the results of this analysis, therefore, could be potentially generalized to the whole Italian population.

The present analysis also has several limitations that are typical of all investigations using administrative databases. First, on the basis of the available information, we were unable to distinguish between type 1 diabetes and T2D, so both are considered in this study, although more than 95% of the cohort were estimated to have T2D.[45] Moreover, some specific information on clinical variables (eg, body mass index), laboratory tests (eg, glycated haemoglobin [HbA1c], eGFR), or socioeconomic status that deserves attention when referring to glycaemic status, lifestyle habits, CV risk factors, or NYHA class was not available. Thus, we could not correct for these confounding factors, or distinguish between primary versus secondary CV prevention. Although such analyses could potentially generate novel information not available from the CVOTs, we could not consider all the patients that were not hospitalized for CV reasons or HF in the 5 years before entering the study cohort as primary prevention patients. Our results must be interpreted with caution because the study was not randomized, and some clinically important characteristics might not have been considered. Finally, length of follow-ups differed between the GLP-1RA and SGLT2 inhibitor groups, and somewhat greater use of antihypertensive and lipid-lowering medications was found in the GLP-1RA and SGLT2 inhibitor groups compared with the other AHAs group.

A potential issue with large pharmaco-epidemiological studies, such as CVD-REAL, EASEL, EMPRISE and the present analysis, is the possibility of bias such as "immortal time bias" and "time lag", which could exaggerate the observed benefits regarding rates of all-cause death.[46,47] Unlike the design used in other observational studies, patients were included in our analysis from the date of the first (change of) prescription of the drug of interest. Moreover, while PSM of patients treated with SGLT2 inhibitors, GLP-1RAs or other AHAs minimizes the risk of biases, residual confounding could still influence

results even after PSM because we had no access to clinical data such as HbA1c or eGFR or data on lifestyle, socioeconomic status and effective treatment options.

In conclusion, reduction of all-cause death, vascular outcomes and HF was consistently observed with use of GLP-1RAs and SGLT2 inhibitors in two Italian regions, resembling the pattern of protection for each class seen in the CVOTs and, when available, in observational studies from the real world (eg, hospitalization for HF with SGLT2 inhibitors, effects on CV disease and stroke with GLP-1RAs). The different mechanisms of action of these two drug classes may explain the differences in the outcomes, with GLP-1RAs acting largely through anti-inflammatory and antiatherosclerotic effects and SGLT2 inhibitors exerting haemodynamic and diuretic effects in addition to inducing potential changes in myocardial metabolism. The favourable effects of both GLP-1RAs and SGLT2 inhibitors on all-cause death and several CV endpoints observed in the present cohorts, together with the reassuring safety profile of these drugs, suggests that they should be preferentially considered over other glucose-lowering therapies in a broader population of T2D patients and not only in high CV risk patients.

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AUTHOR CONTRIBUTIONS

M.B., S.G., V.L., A.N., M.C.R. and F.G. contributed to the development of the study concept and design, interpretation of data, and writing of the article. P.C., F.R., M.T., A.D.'E. and I.F. contributed to data collection, analysis, interpretation of data, and critical review of the article. F.A. contributed to data report finalization, critical review and revision of the article.

CONFLICTS OF INTEREST

S.G.: received research funding from Novartis and has been a consultant for, or received honoraria from Abbott Diabetes Care, AstraZeneca, Boehringer Ingelheim, Bruno Farmaceutici, Eli Lilly, Hikma Pharmaceuticals, Janssen, Johnson &Johnson, Menarini, Merck Sharp & Dohme, Molteni Farmaceutici, Mundipharma, Novartis, Novo Nordisk, Sanofi and Takeda. A.N.: received research grants form AlfaSigma, Astra Zeneca, Eli Lilly, Medtronic, Novo Nordisk, Pikdare, Theras, Sanofi, Shionogi, and SOBI. F.G.: received research support from Eli Lilly, Lifescan and Takeda, is a consultant for Boehringer Ingelheim, Lifescan, Merck Sharp & Dohme, Sanofi, AstraZeneca, Medimmune and Roche Diabetes Care, and has served on advisory boards for AstraZeneca, Eli Lilly, Novo Nordisk, Roche Diabetes Care and Sanofi. M.B., V.L., P.C., F.R, M.T., A. D.'E., F.A., I.F. and MC.R.: declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14361.

DATA AVAILABILITY STATEMENT

Access to row data is allowed only to the investigators within the Agreement between the Lombardy Region and the Istituto di Ricerche Farmacologiche Mario Negri. Row data cannot be shared out of that Agreement according to the Regional Low Privacy. Programme code can be shared following the permission granted from the Lombardy Region Health Ministry.

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SUPPORTING INFORMATION

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

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