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ORIGINAL ARTICLE

# Trend 2010–2018 in the clinical use of GLP-1 receptor agonists for the treatment of type 2 diabetes in routine clinical practice: an observational study from Northeast Italy

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## Abstract

**Aims** Several GLP-1 receptor agonists (GLP-1RA) have become available for the treatment of type 2 diabetes (T2D), and evidence on their beneficial effects has evolved. We evaluated how the clinical phenotype of patients initiating GLP-1RA changed from 2010 to 2018.

**Methods** This was a retrospective study conducted at six diabetes outpatient clinics in Northeast Italy. We collected data of T2D patients who initiated new GLP-1RA between 2010 and 2018. We recorded baseline characteristics, including demographics, anthropometrics, cardiovascular risk factors, glucose control, lipid profile, liver enzymes, renal function and concomitant medications. We recorded updated HbA1c and body weight at follow-up.

**Results** There were 83,116 T2D patients from a general population of ~ 1,380,000 inhabitants. Among 6167 cases of GLP-1RA initiation, 5408 were analyzed after excluding intra-class switchers. Prescription of GLP-1RA increased exponentially, and the change in the type of GLP-1RA reflected waves of their entering the market. From 2010 to 2018, there were significant increases in baseline age, diabetes duration and prevalence of male sex, of cardiovascular disease and of insulin users. Blood pressure and cholesterol levels decreased concomitantly with increasing use of medications for the control of cardiovascular risk. Baseline average HbA1c (8.3% [67 mmol/mol]) and BMI (34 kg/m$^2$) and their improvement after GLP-1RA initiation did not change over time.

**Conclusions** Despite the early positioning of GLP-1RA in T2D treatment algorithms, GLP-1RA have been prescribed in patients with progressively more advanced disease stage and especially in the presence of cardiovascular disease. Optimization of GLP-1RA use in routine clinical practice is still needed.

**Keywords** Pharmacoepidemiology · Real-world · Observational study · Effectiveness

## Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RA) are routinely used for the management of type 2 diabetes (T2D). GLP-1RA lower blood glucose by potentiating meal-induced insulin release. In addition, they have a variety of additional functions, such as slowing gastric emptying, inducing satiety and improving glucagon release. Furthermore, GLP-1RA mildly reduce blood pressure, thanks to the action of GLP-1 on vascular nitric oxide production, and may improve cardiac function [1]. Such effects contribute to the broad efficacy profile of GLP-1RA, spanning a wide-range glycemic and extra-glycemic benefits [2, 3].

The first GLP-1RA, exenatide *bis in die* (BID), received marketing authorization approval for the European Union in

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November 2006. Since then, several other GLP-1RA have reached the market, including liraglutide, exenatide once weekly (OW, or long-acting release), lixisenatide, albiglutide (withdrawn in 2018), dulaglutide and semaglutide. They differ in molecular structure (exendin-based or human GLP-1-based), half-life (from hours to several days) and administration frequency (from twice daily to once weekly) [4].

Cardiovascular outcome trials (CVOTs) have shown that therapy with either liraglutide [5], albiglutide [6], dulaglutide [7] or semaglutide [8] can reduce the rate of major adverse cardiovascular events (MACE) when added to standard care in patients with T2D, mostly with established cardiovascular disease (CVD). The CVOT for exenatide OW showed a reduced trend for MACE rate ($P = 0.05$) [9], and there is general agreement that GLP-1RA as a class improve cardiovascular outcomes [10, 11]. In addition, there is evidence that GLP-1RA can improve renal outcomes by reducing new-onset macroalbuminuria [12].

According to the most recent consensus statements on the management of T2D, GLP-1RA should be prioritized over other glucose-lowering medications (GLM), especially for patients with CVD and/or renal disease [13]. However, it is well known that treatment recommendations and guidelines may not be readily incorporated into clinical practice [14].

Owing to the fact that different GLP-1RA became available over the years and based on the accumulating evidence from CVOTs, it is expected that the clinical phenotype of patients at the time they receive first prescription of GLP-1RA is changing over time.

The present study was designed to evaluate the time trend of baseline clinical characteristics and effectiveness parameters of patients who initiated GLP-1RA from 2010 to 2018. To this end, we used a retrospective study on routinely accumulated clinical data.

## Methods

### Study design and participants

The GLP-1REWIN (GLP-1 REal World evIdeNce) was a retrospective study performed at six diabetes outpatient clinics in the Veneto Region, Northeast Italy. The study has been approved by the local Ethical Committees and each participating center and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. In agreement with national regulations on retrospective studies and on data protection and privacy, no informed consent was collected because the database was anonymous.

The study design has been published before [15]. In brief, we retrospectively collected data of all consecutive patients who initiated a new prescription of GLP-1RA from January 1, 2010, to December 31, 2018. The types and order of GLP-1RA that entered the pharmaceutical market in Italy were exenatide BID, liraglutide, lixisenatide, exenatide OW and dulaglutide. In late 2017, two fixed-dose associations of basal insulin and GLP-1RA were commercialized: lixisenatide/insulin glagine (LixiLan) and liraglutide/insulin degludec (iDegLira). Albiglutide was never commercialized in Italy, and semaglutide became available in 2019, outside the study data collection period.

In this analysis, we considered only patients with a diagnosis of T2D (as recorded in the chart) who were prescribed for the first time a given GLP-1RA without being previously treated with the same or another GLP-1RA. The purpose of this study was to evaluate how clinical characteristics of patients initiating a GLP-1RA changed from 2010 to 2018.

### Data collection

Patients' data were extracted from the same electronic chart system at all centers (MyStarConnect/SmartDigitalClinic), using a dedicated automatic software. The data extraction software automatically interrogated the electronic chart and recorded relevant patients' data without manual intervention. The baseline was set as the date patients received prescription of GLP-1RA. The following information was collected from each patient at the time they received first prescription of the GLP-1RA (baseline data): age, sex, diabetes duration (defined as time since the first diagnosis of T2D), current smoking habit (defined as the habitual smoking of one or more cigarettes per day), body weight and height for the calculation of body mass index (BMI), waist circumference, systolic and diastolic blood pressure, heart rate, fasting plasma glucose, HbA1c, total cholesterol, HDL cholesterol, triglycerides (LDL cholesterol was calculated using Friedwald's equation), liver enzymes, serum creatinine for the calculation of estimated glomerular filtration rate (eGFR) according to the CKD-EPI equation and urinary albumin excretion rate, reported as urinary albumin/creatinine ratio (UACR).

We also recorded detailed information on diabetic complications. Chronic kidney disease was defined as an eGFR < 60 ml/min/1.73 $m^2$. Micro- and macroalbuminuria were defined according to the standard UACR cutoffs of 30 and 300 mg/g, respectively. Retinopathy (any grade) and macular edema were defined based on ophthalmologic examination. Peripheral neuropathy was defined based on signs and symptoms, eventually confirmed by evaluation of nerve conduction velocity of vibratory perception threshold. Autonomic neuropathy was defined in the presence of at least two pathologic cardiovascular autonomic tests out of four (deep breathing, Valsalva maneuver, lying-to-standing and orthostatic hypotension). Peripheral arterial disease (PAD) was defined as claudication or rest pain with

or without ulcers in the presence of ultrasound or angiography evidence of significant stenosis of leg arteries, or as a history of peripheral arterial revascularization. Foot disease was defined as a history active ulcer, minor/major amputation or deformities (e.g., Charcot foot). Stroke and transient ischemic attacks (TIA) were defined based on a history of focal neurologic symptoms suggestive of cerebral ischemia, eventually confirmed (for stroke) by coherent cerebral imaging (computed tomography or magnetic resonance scans). Carotid atherosclerosis was defined as evidence of plaques narrowing the carotid lumen (any degree) at ultrasound, either symptomatic or not, or a history of carotid revascularization. Ischemic heart disease was defined as a history of myocardial infarction or unstable angina, evidence of myocardial ischemia at a stress test or evidence of hemodynamically significant stenosis of coronary arteries, or a history of coronary revascularization. We constructed a variable called "hard cardiovascular disease (hCVD)" defined as a history of myocardial infarction or stroke/TIA or any site revascularization. Left ventricular hypertrophy was defined, as reported in the electronic chart, based on the results of echocardiography, when available. Not all information was available for all patients, and some diagnosis may have been underreported.

Finally, we collected information on ongoing medications for the treatment of diabetes (GLM that the patients were prescribed concomitantly with GLP-1RA) and for the treatment of cardiovascular risk factors. We had no information on drug refill rates and on whether the patients actually took the prescribed medications.

During the study, we also collected updated information on HbA1c and body weight at the first available follow-up visit 3–12 months after first prescription of GLP-1RA. These updated data were used to evaluate the trend in effectiveness of GLP-1RA over time.

Patients were divided according to the calendar year of first GLP-1RA prescription from 2010 to 2018. A few prescription preceding 2010 were aggregated in the calendar year 2010. Patients undergoing GLP-1RA intra-class switch were excluded.

### Statistical analysis

Data are presented as mean and standard deviation for continuous variable or as percentage for categorical variables. Before analysis, non-normal variables were log-transformed. Normality was checked using the Kolmogorov–Smirnov test. The time trend was analyzed by dividing patients according to the calendar year of first GLP-1RA prescription. Spearman's rho was used to evaluate trends in clinical characteristics from 2010 to 2018. Statistical significance was accepted at $P < 0.05$.

## Results

### Patient characteristics and disposition

The total background population was composed of 83,116 T2D patients from the six outpatient clinics, referred to a general population of ~ 1,380,000 inhabitants of the Veneto Region, Northeast Italy. Among them, 6167 patients (7.4%) received a new prescription of GLP-1RA during the study period. After excluding patients undergoing intra-class switch, 5408 were finally included in the analysis. Average clinical characteristics of study patients are summarized in Table 1. The number of patients who were prescribed GLP-1RA accrued over time in an exponential way and about 50% initiated treatment from 2016 to 2018 (Fig. 1a). The types of GLP-1RA that alternated over time reflected commercialization dates in the Italian pharmaceutical market (Fig. 1b). Exenatide BID was the prevailing GLP-1RA in 2010, was rapidly offset by liraglutide already in 2011 and virtually disappeared by 2015. The proportion of patients initiating liraglutide increased steadily until 2013 and then reduced when weekly GLP-1RA entered the market. The proportion of patients initiating exenatide OW reached almost 40% of new GLP-1RA users in 2015 and then reduced after dulaglutide became available. Since 2016, > 50% of new GLP-1RA prescriptions was for dulaglutide. The basal insulin/GLP-1RA fixed-dose combinations reached 25% of new GLP-1RA prescriptions in 2018.

### Trend in baseline clinical characteristics

The trend over time in each clinical variable is reported in the two right columns of Table 1. Among clinical characteristics recorded at baseline, there was a significant increase in average age (from 60.2 to 63.7 years), diabetes duration (with a J-shaped curve from 10.1 to 11.3 years) and proportion of male patients (from 55.5 to 63.2%), with no substantial difference among the various GLP-1RA (Fig. 2a–c). There was also a progressive reduction in diastolic blood pressure, heart rate and cholesterol levels, which may reflect the improved care of cardiovascular risk factors from 2010 to 2018. There was no change in the baseline values of BMI and HbA1c, irrespectively of GLP-1RA type (Fig. 2d, e). eGFR did not show a linear trend over time but, since 2015, eGFR at time of GLP-1RA prescription tended to be lower for liraglutide than for exenatide OW (up to 10 ml/min/1.73 $m^2$) and dulaglutide (up to 5 ml/min/1.73 $m^2$) (Fig. 2f). Among complications, there was a striking increase in the baseline prevalence of macroangiopathies (Table 1) and of a composite of hCVD

**Table 1** Clinical characteristics of study patients

| | *n* (%) | Value | Trend | *P* |
|---|---|---|---|---|
| Age (years) | 5408 (100.0) | 61.5 ± 10.0 | ↗ | < 0.001 |
| Sex male (%) | 5408 (100.0) | 60.9 | ↗ | 0.005 |
| Current smoking (%) | 1303 (24.1) | 18.0 | | 0.250 |
| Diabetes duration (years) | 5408 (100.0) | 10.2 ± 7.1 | ↗ | 0.026 |
| Body weight (kg) | 5072 (93.8) | 97.7 ± 19.4 | | 0.282 |
| Body mass index (kg/m$^2$) | 5035 (93.1) | 34.3 ± 6.4 | | 0.107 |
| Waist circumference (cm) | 2479 (45.8) | 114.8 ± 13.5 | | 0.829 |
| Systolic blood pressure (mmHg) | 4618 (85.4) | 141.9 ± 19.9 | | 0.430 |
| Diastolic blood pressure (mmHg) | 4609 (85.2) | 82.1 ± 10.6 | ↘ | 0.001 |
| Heart rate (bpm) | 1702 (31.5) | 78.7 ± 12.6 | ↘ | < 0.001 |
| Fasting blood glucose (mg/dl) | 4724 (87.4) | 174.3 ± 52.2 | | 0.054 |
| HbA1c (%) (mmol/mol) | 5085 (94.0) | 8.3 ± 1.3 (67 ± 10) | | 0.068 |
| Total cholesterol (mg/dl) | 4000 (74.0) | 177.1 ± 41.8 | ↘ | 0.005 |
| HDL cholesterol (mg/dl) | 3830 (70.8) | 46.4 ± 12.2 | | 0.055 |
| Triglycerides (mg/dl) | 3942 (72.9) | 167.1 ± 115.2 | | 0.245 |
| LDL cholesterol (mg/dl) | 3736 (69.1) | 97.6 ± 35.1 | ↘ | 0.007 |
| AST (U/l) | 2714 (50.2) | 24.5 ± 14.2 | | 0.435 |
| ALT (U/l) | 2764 (51.1) | 30.2 ± 19.9 | ↘ | < 0.001 |
| eGFR (ml/min/1.73 m$^2$) | 3745 (69.2) | 83.4 ± 19.9 | | 0.633 |
| UACR (mg/g) | 2358 (43.6) | 90.9 ± 324.5 | | 0.906 |
| *Complications* | | | | |
| CKD (%) | 3745 (69.2) | 13.7 | | 0.399 |
| Microalbuminuria (%) | 2358 (43.6) | 25.4 | | 0.807 |
| Macroalbuminuria (%) | 2358 (43.6) | 5.7 | | 0.853 |
| Retinopathy (%) | 3907 (72.2) | 15.6 | | 0.447 |
| Macular edema (%) | 3907 (72.2) | 3.1 | ↗ | 0.012 |
| Peripheral neuropathy (%) | 1519 (28.1) | 18.0 | | 0.945 |
| Autonomic neuropathy (%) | 1519 (28.1) | 3.1 | | 0.152 |
| Peripheral arterial disease (%) | 1306 (24.1) | 16.2 | ↗ | 0.001 |
| Peripheral revascularization (%) | 1306 (24.1) | 2.6 | ↗ | < 0.001 |
| Foot disease (%) | 1421 (26.3) | 17.2 | | 0.219 |
| Stroke/TIA (%) | 3113 (57.6) | 3.3 | ↗ | 0.018 |
| Cerebral revascularization (%) | 1306 (24.1) | 2.6 | | 0.114 |
| Carotid atherosclerosis (%) | 3113 (57.6) | 47.7 | ↗ | 0.002 |
| Ischemic heart disease (%) | 4036 (74.6) | 12.1 | ↗ | < 0.001 |
| Coronary revascularization (%) | 1306 (24.1) | 2.6 | ↗ | < 0.001 |
| Left ventricular hypertrophy (%) | 4036 (74.6) | 3.2 | ↗ | 0.010 |
| Microangiopathy (%) | 5408 (100.0) | 32.0 | | 0.073 |
| Macroangiopathy (%) | 5408 (100.0) | 34.0 | ↗ | < 0.001 |
| *GLP-1RA type* | | | | |
| Exenatide BID (%) | 5408 (100.0) | 12.9 | ↘ | < 0.001 |
| Exenatide OW (%) | 5408 (100.0) | 5.4 | | 0.327 |
| Liraglutide (%) | 5408 (100.0) | 37.8 | | 0.422 |
| Lixisenatide (%) | 5408 (100.0) | 2.6 | | 0.637 |
| Dulaglutide (%) | 5408 (100.0) | 32.6 | ↗ | < 0.001 |
| IdegLira (%) | 5408 (100.0) | 7.5 | | 0.064 |
| LixiLan (%) | 5408 (100.0) | 1.1 | | 0.058 |
| *Other glucose-lowering medications* | | | | |
| Metformin (%) | 5408 (100.0) | 88.1 | ↘ | 0.025 |
| SU/Rep (%) | 5408 (100.0) | 25.7 | ↘ | < 0.001 |
| Pioglitazone (%) | 5408 (100.0) | 9.9 | | 0.590 |

**Table 1** (continued)

| | *n* (%) | Value | Trend | *P* |
|---|---|---|---|---|
| Acarbose (%) | 5408 (100.0) | 0.8 | | 0.077 |
| Insulin (%) | 5408 (100.0) | 26.3 | ↗ | < 0.001 |
| *Other therapies* | | | | |
| ACEi/ARB (%) | 4739 (87.6) | 71.5 | | 0.178 |
| Calcium channel blockers (%) | 4739 (87.6) | 25.8 | | 0.541 |
| Beta-blockers (%) | 4739 (87.6) | 33.0 | ↗ | < 0.001 |
| Diuretics (%) | 4739 (87.6) | 44.7 | | 0.625 |
| Anti-platelet agents (%) | 4739 (87.6) | 42.5 | | 0.113 |
| Statin (%) | 4739 (87.6) | 64.7 | | 0.325 |
| Ezetimibe (%) | 4739 (87.6) | 9.1 | ↗ | < 0.001 |
| Warfarin (%) | 4739 (87.6) | 3.7 | ↗ | 0.043 |

For each variable, the number and percentage of patients with available data are reported in addition to the summary statistics. When a statistically significant time trend over time was noted, an arrow trend was indicated (↗ increase; ↘ decrease) along with the respective *P* value

*HDL* high-density cholesterol, *LDL* low-density cholesterol, *AST* aspartic aminotransferase, *ALT* alanine aminotransferase, *eGFR* estimated glomerular filtration rate, *UACR* urinary albumin creatinine ratio, *CKD* chronic kidney disease, *TIA* transient ischemic attack, *BID* bis in die, *OW* once weekly, *SU/rep* sulphonylurea or repaglinide, *ACEi* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin receptor blockers

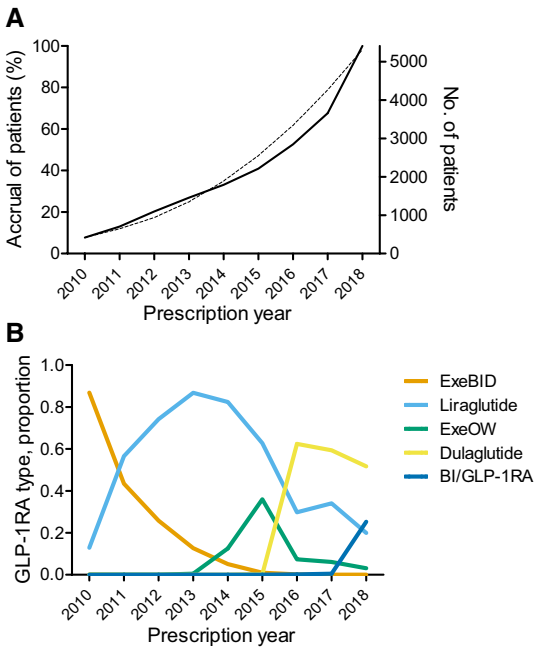


**Fig. 1** Patient accrual and disposition. **a** Accrual of patients over time: the left *Y*-axis indicates the percentage of patients, where 100% is the total number of patients who initiated a GLP-1RA from 2010 to 2018. The right *Y*-axis indicates patients number. The dashed thin line represents base 2 exponential growth. **b** Proportion of patients receiving first prescription of each GLP-1RA by year. For each year, the sum of proportions is equal to 100%

(from 7.7 to 16%), which was particularly evident for liraglutide (from 10.2 to 23.5%) (Fig. 2g). Vice versa, with the exception of a minor increase in macular edema, there was no overall change in baseline prevalence of microangiopathy (Fig. 2h).

As for concomitant glucose-lowering medications, there was a clear increase in the prevalence of patients concomitantly treated with insulin (from 4.4 to 43.4%), which was particularly evident for liraglutide and, in 2018, partly driven by the fixed-dose combinations (Fig. 3a). The notch of the time trend in insulin users, observed in 2014, reflects that reimbursement of GLP-1RA in association with insulin was transiently withdrawn in Italy. The number of oral GLM showed a small but significant decreasing trend over time, irrespectively of the GLP-1RA type (Fig. 3b).

## Trend in effectiveness

We then evaluated the change in HbA1c and body weight, the two main targets of GLP-1RA therapy, from baseline to the first available visit 3–12 months after baseline, when available. There were 3204 patients with updated HbA1c valued and 3435 patients with updated values of body weight. After an average follow-up of 5.8 months, HbA1c declined by 0.74% (5.6 mmol/mol) and body weight declined by 2.8 kg. The change in body weight and HbA1c displayed no significant trend over time (Fig. 4a, b).

## Discussion

In this study, we examined the trend in clinical use of GLP-1RA from 2010 to 2018 in Italy and the change over time in the baseline clinical characteristics of patients who received a new prescription of GLP-1RA. Data indicate that

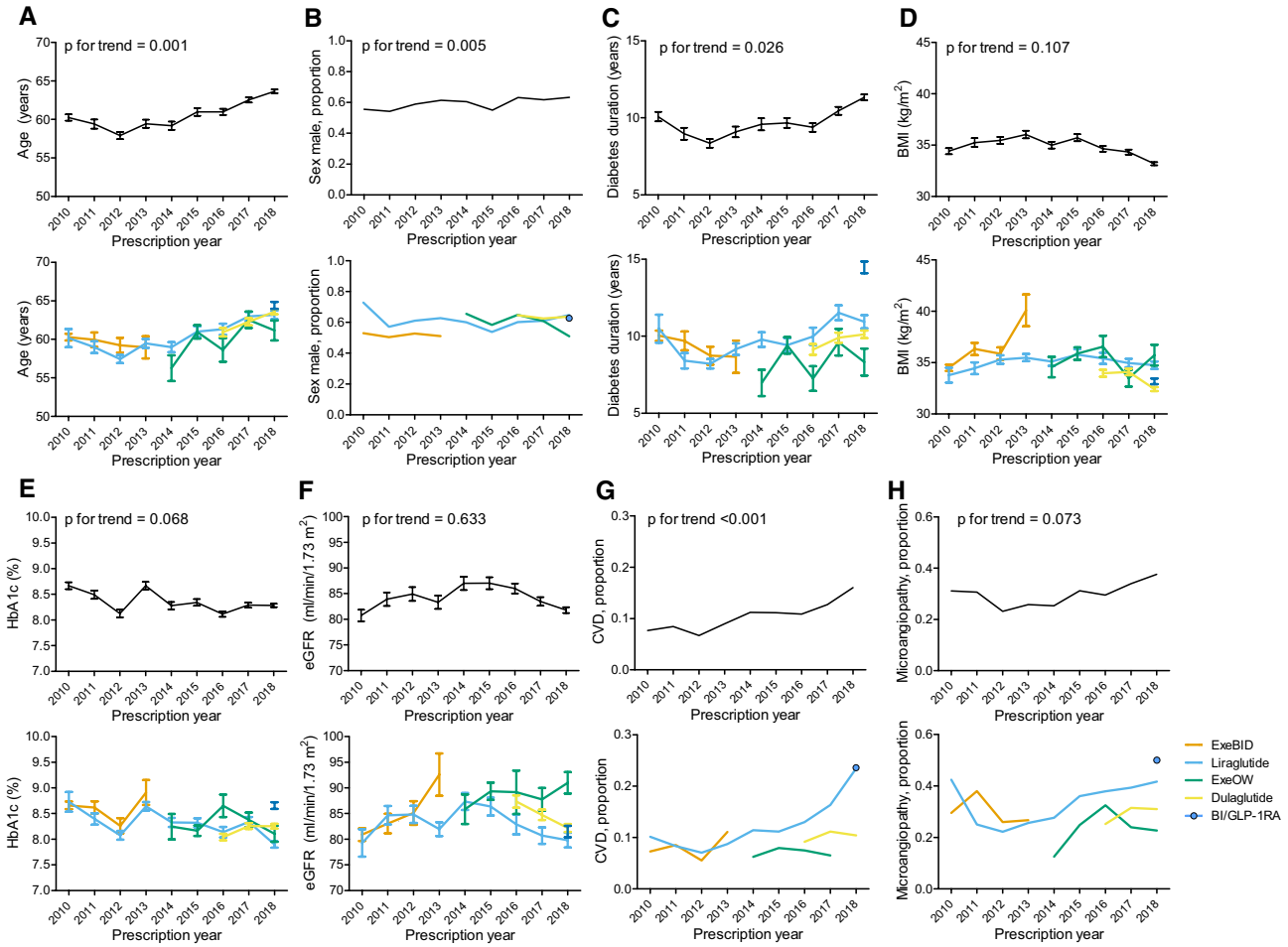


**Fig. 2** Time trend in baseline clinical characteristics. From **a** to **h**, for each baseline clinical variable, the black line in the upper panel shows the average trend observed for pooled GLP-1RA, while individual colored lines in the bottom panel show the time trend for individual GLP-1RA. These curves start and end when the number of patients was at least > 10. *P* for trend is related to Spearman's rho correlation coefficient relating prescription year with summary statistics (mean for continuous variables and proportion for categorical variables). Error bars for continuous variables indicate standard error

GLP-1RA have been used in progressively older patients with longer diabetes duration and who were more often males. Most importantly, the prevalence of hCVD (myocardial infarction, stroke or any site arterial revascularization) at the time patients initiated a GLP-1RA increased significantly and more than doubled from 2010 to 2018. The increasing concomitant use of insulin, beta-blockers, combined lipid-lowering therapies, and anti-coagulants likely reflected such an increasing prevalence of hCVD.

Since publication of results of the LEADER trial, showing that liraglutide reduced MACE incidence in patients with T2D and CVD [5], the interest around the cardiovascular effects of GLP-1RA has raised substantially. Similar results have been obtained with semaglutide [8], dulaglutide [7] and albiglutide [6]. Although albiglutide has never been commercialized in Italy and data on semaglutide were not yet available, it seems that the cardiovascular benefits observed in these trials have promoted the use of GLP-1RA more often in diabetic patients with established CVD and a more advanced disease stage. However, treatment algorithms have repositioned GLP-1RA in the earlier disease stages, and most recently, GLP-1RA have been recommended as the first injectable therapy, before insulin [13]. In addition, the European Society of Cardiology guidelines prioritize GLP-1RA even for drug-naïve T2D patients with CVD [16].

To limit the burden of hyperglycemia and its adverse legacy on the risk of complications [17], treatment intensification should be performed timely using drugs with the best safety and efficacy profiles. We detected no obvious reduction in average HbA1c levels at the time of GLP-1RA initiation from 2010 to 2018. It should be noted that, in Italy, reimbursement criteria for GLP-1RA have changed during this long period. In 2014, reimbursement in association with insulin was transiently withdrawn generating a notch

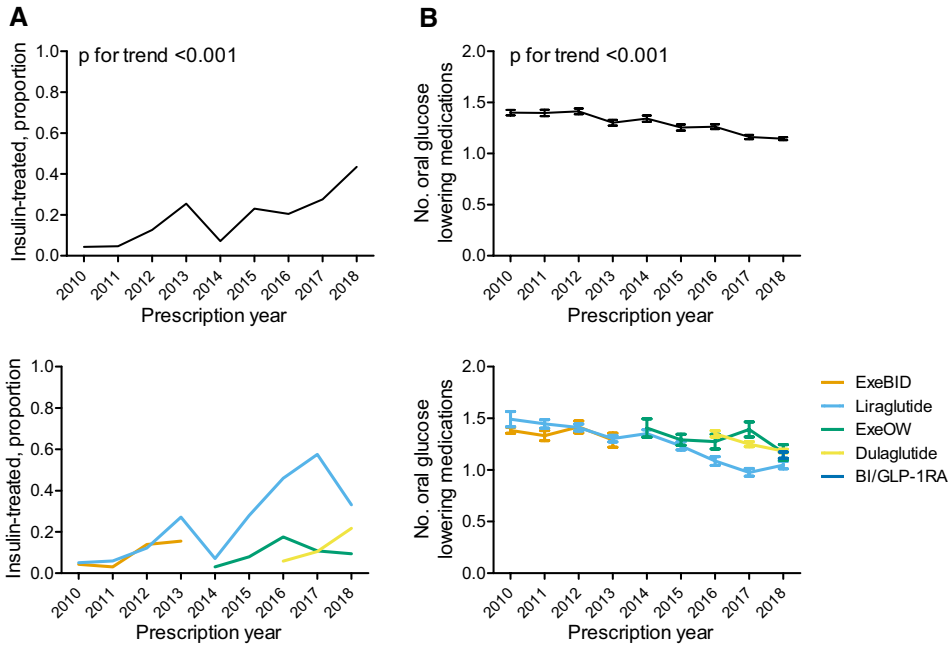


**Fig. 3** Time trend in concomitant glucose-lowering medications. In **a**, **b**, the black line in the upper panel shows the average trend observed for pooled GLP-1RA, while individual colored lines in the bottom panel show the time trend for individual GLP-1RA. These curves start and end when the number of patients was at least > 10. *P* for trend is related to Spearman's rho correlation coefficient relating prescription year with summary statistics (proportion in **a** and mean in **b**). Error bars in **b** indicate standard error

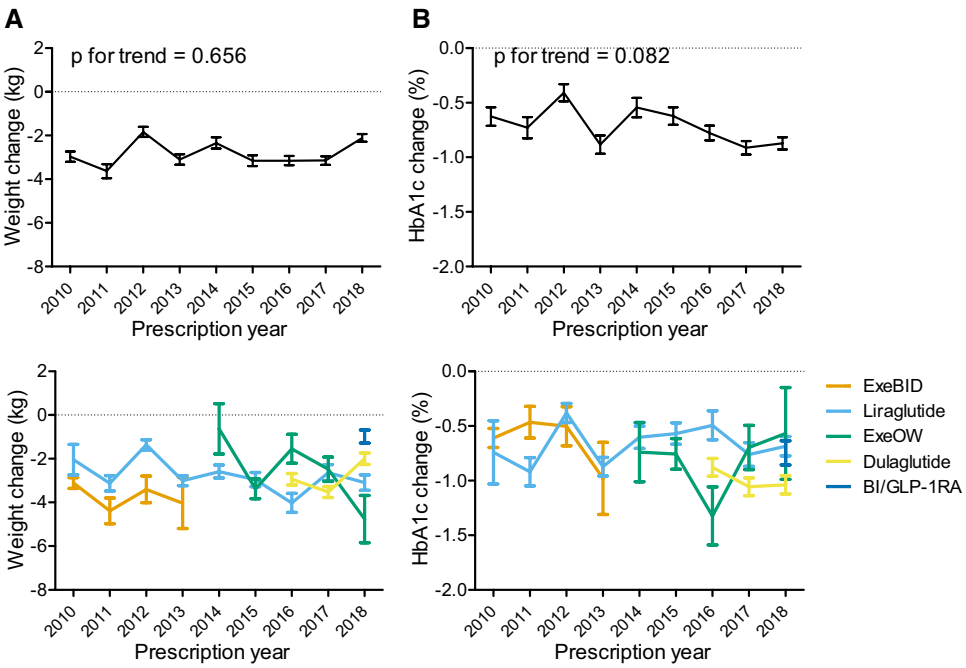


**Fig. 4** Time trend in GLP-1RA effectiveness on HbA1c and body weight. In **a**, **b**, the black line in the upper panel shows the average trend observed for pooled GLP-1RA, while individual colored lines in the bottom panel show the time trend for individual GLP-1RA. These curves start and end when the number of patients was at least > 10. *P* for trend is related to Spearman's rho correlation coefficient relating prescription year with mean response variable. Error bars indicate standard error

visible in Fig. 3a. In addition, reimbursement was limited to patients with a baseline HbA1c of 7.5% (58 mmol/mol) to 9.0% (73 mmol/mol) and such limitation was waived in 2018. It should be noted that local guidelines also changed from 2010 to 2018. The two major Italian diabetes societies tended to adopt international guidelines, especially those issued by the European Association for the Study of Diabetes and the American Diabetes Association, but GLP-1RA have been repositioned earlier in the treatment algorithm only recently. Nonetheless, our data suggest that GLP-1RA are still being initiated relatively late, despite new GLP-1RA provided with easier administration schedules and wide cardio-renal benefits have become available. To what extent our findings can be translated to other European countries or worldwide needs to be ascertained by dedicated studies.

Although the effects of GLP-1RA on body weight reduction make this therapy particularly attractive for obese patients, the benefits of GLP-1RA on glucose control, blood pressure and cardio-renal outcomes should be extended to non-obese diabetic patients. Yet, from 2010 to 2018, we

observed no reduction in average baseline BMI at the time of GLP-1RA initiation, suggesting that this therapy is still mainly used in obese diabetic patients.

Therefore, data collected in the first decade of GLP-1RA use in Italy indicate no anticipation of GLP-1RA prescription in the natural history of T2D, but suggest that the evidence generated by CVOTs in patients with established CVD has been incorporated into clinical practice, with GLP-1RA being prescribed in a progressively higher proportion of patients with hCVD.

Despite the phenotype of patients receiving first prescription of GLP-1RA evolved, there was no change in the drug effectiveness on HbA1c and body weight reduction. The present analysis was not designed to perform a comparative assessment of effectiveness among the various GLP-1RA, but this finding is reassuring on the consistent clinical effects obtained with GLP-1RA as a class across the years and in different patient phenotypes.

In summary, our study shows that, in Italy, GLP-1RA are still being prescribed mainly for obese diabetic patients with high HbA1c and/or in the presence of established CVD. Evidence accumulated from CVOTs suggests that the benefits of GLP-1RA extend to patients without a prior cardiovascular event and are consistent irrespectively of baseline HbA1c and BMI. Contrary to what initially believed [18], recent data suggest that GLP-1RA can exert cardio-renal protection independently from the baseline cardiovascular risk, as observed for dulaglutide in the REWIND trial, wherein less than one third of patients had established CVD [7].

Therefore, our data highlight the unmet clinical need of promoting an earlier use of GLP-1RA in the natural history of T2D. Improving therapeutic appropriateness of T2D would result in more patients being treated with GLM able to reduce the risk of adverse hard outcomes, which is the ultimate goal of T2D therapy.

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**Author contributions** GPF contributed to study design, analysis and manuscript writing. VF, MR, NS, AL, AP and AA helped in study design, data collection and manuscript revision. FT and MDA contributed to data collection and manuscript revision. All authors read and approved the final version of the manuscript.

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## Compliance with ethical standards

**Conflict of interest** GPF received grant support, lecture or advisory board fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Mundipharma, NovoNordisk, Sanofi, Genzyme, Abbott, Novartis, Merck Sharp and Dohme. VF served as consultant for NovoNordisk. MR received lecture and advisory board fees from AstraZeneca, Boehringer Ingelheim, Novonordisk and Sanofi-Aventis. NS received lecture or consultancy fees from AstraZeneca, Boehringer–Lilly, Novartis, NovoNordisk, Sanofi-Aventis, Takeda, Merck Sharp and Dohme, Abbott and research support from NovoNordisk. AL received grant support, lectures or advisory board fees from Novo Nordisk, Sanofi, Abbott and Eli Lilly. AA received research grants, lecture or advisory board fees from Merck Sharp and Dome, AstraZeneca, Novartis, Boehringer Ingelheim, Sanofi, Mediolanum, Janssen, Novo Nordisk. FT, AP and MDA declare no conflict of interest.

**Ethical standard statement** The study protocol was approved by the local ethical committee of each participating center.

**Informed consent** In agreement with National regulations retrospective studies and on data protection and privacy, no informed consent was collected because the database was anonymous.

## References

1. Drucker DJ (2016) The Cardiovascular Biology of Glucagon-like Peptide-1. Cell Metab 24:15–30
2. Campbell JE, Drucker DJ (2013) Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab 17:819–837
3. Drucker DJ (2001) Development of glucagon-like peptide-1-based pharmaceuticals as therapeutic agents for the treatment of diabetes. Curr Pharm Des 7:1399–1412
4. Sfairopoulos D, Liatis S, Tigas S, Liberopoulos E (2018) Clinical pharmacology of glucagon-like peptide-1 receptor agonists. Hormones (Athens) 17:333–350
5. Marso SP, Daniels GH, Brown-Frandsen K et al (2016) Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 375:311–322
6. Hernandez AF, Green JB, Janmohamed S et al (2018) Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (harmony outcomes): a double-blind, randomised placebo-controlled trial. Lancet 392:1519–1529
7. Gerstein HC, Colhoun HM, Dagenais GR et al (2019) Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 394:121–130
8. Marso SP, Bain SC, Consoli A et al (2016) Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 375:1834–1844
9. Imprialos KP, Stavropoulos K, Doumas M (2017) Once-weekly exenatide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 377:2502
10. Kristensen SL, Rorth R, Jhund PS et al (2019) Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol 7:776–785
11. Caruso I, Cignarelli A, Giorgino F (2019) Heterogeneity and similarities in GLP-1 receptor agonist cardiovascular outcomes trials. Trends Endocrinol Metab 30:578–589
12. Giugliano D, Maiorino MI, Bellastella G et al (2019) GLP-1 receptor agonists for prevention of cardiorenal outcomes in type 2 diabetes: an updated meta-analysis including the REWIND and PIONEER 6 trials. Diabetes Obes Metab 21:2576–2580
13. Davies MJ, D'Alessio DA, Fradkin J et al (2018) Management of hyperglycemia in type 2 diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018(41):2669–2701
14. Fadini GP, Frison V, Simioni N et al (2019) Changes in the prescription of glucose-lowering medications in patients with type 2

diabetes mellitus after a cardiovascular event: a call to action from the DATAFILE study. J Am Heart Assoc 8:e012244
15. Morieri ML, Rigato M, Frison V et al (2019) Fixed versus flexible combination of GLP-1 receptor agonists with basal insulin in type 2 diabetes: a retrospective multicentre comparative effectiveness study. Diabetes Obes Metab 21:2542–2552
16. Cosentino F, Grant PJ, Aboyans V et al (2019) ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 34:3035–3087
17. Paul SK, Klein K, Thorsted BL, Wolden ML, Khunti K (2015) Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. Cardiovasc Diabetol 14:100
18. Zelniker TA, Wiviott SD, Raz I et al (2019) Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. Circulation 139:2022–2031