Study Report

P3-C1-008

DARWIN EU® - Drug Utilisation Study on GLP-1 receptor agonists

19/12/2024

Version 4.0

Contents

Study Title	DARWIN EU® - Drug Utilisation Study on GLP-1 Receptor Agonists
Study Report Version	V3.3
Date	19/12/2024
EU PAS number	EUPAS1000000223
Active substance	GLP-1 RA (objective 1); and other specific of medicines for diabetes and/or weight management (objective 2):

Objective	Substance name	ATC code
1	Exenatide	A10BJ01
1	Liraglutide	A10BJ02
1	Lixisenatide	A10BJ03
1	Albiglutide	A10BJ04
1	Dulaglutide	A10BJ05
1	Semaglutide	A10BJ06
1	Beinaglutide	A10BJ07
1	Tirzepatide	A10BX16
2	Orlistat	A08AB01
2	Metformin	A10BA02
2	Naltrexone/bupropion (Mysimba)	A08AA62
2	Phentermine/topiramate (Qsiva)	A08AA51
2	Phentermine	A08AA01

Medicinal product	N/A
Research question and objectives	This study aimed to provide an overview of the characteristics of patients prescribed with a GLP-1 RA medicinal product and how these have changed over the past ten years: 1) To characterise the incidence and prevalence of use (prescription/dispensation) of GLP-1 RA. Additionally, new drug users of GLP-1 RA stratified by presence or absence of diagnosis of diabetes mellitus type 2 and diagnosis of obesity were characterised by age, sex, body mass index, initial dose, cumulative dose and a list of prespecified indications/comorbidities. 2) To characterise the incidence and prevalence of use (prescription/dispensation) of other medicines used for the treatment of diabetes and weight management.
Country(-ies) of study	Belgium, Germany, Netherlands, Spain and the UK
Authors	Marta Pineda Moncusí, m.pinedamoncusi@darwin-eu.org Y. Guo, y.guo@darwin-eu.org

TITLE

DARWIN EU® - Drug Utilisation Study on GLP-1 Receptor Agonists

1. DESCRIPTION OF STUDY TEAM

Study team role	Names	Organisation
Study Project Manager/Principal Investigator	Marta Pineda Moncusí	University of Oxford
Data Scientist	Yuchen Guo Edward Burn Martí Català Sabaté	University of Oxford
Epidemiologist	Annika Jödicke Daniel Prieto Alhambra	University of Oxford University of Oxford/Erasmus MC University
Clinical Domain Expert	Annika Jödicke	University of Oxford
Data Partner*	**Names**	**Organisation**
Local Study Coordinator/Data Analyst	-	CPRD
	Talita Duarte	SIDIAP
	Fèlix Barenys	
	Irene López Sánchez	
	Katia Verhamme	IPCI
	Dina Vojinovic	IQVIA DA Germany/IQVIA LPD Belgium
	Isabella Kaczmarczyk	
	James Brash	

*Data partners' role is only to execute code at their data source, review and approve their results. These people do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for these people is not needed.

2. DATA SOURCES

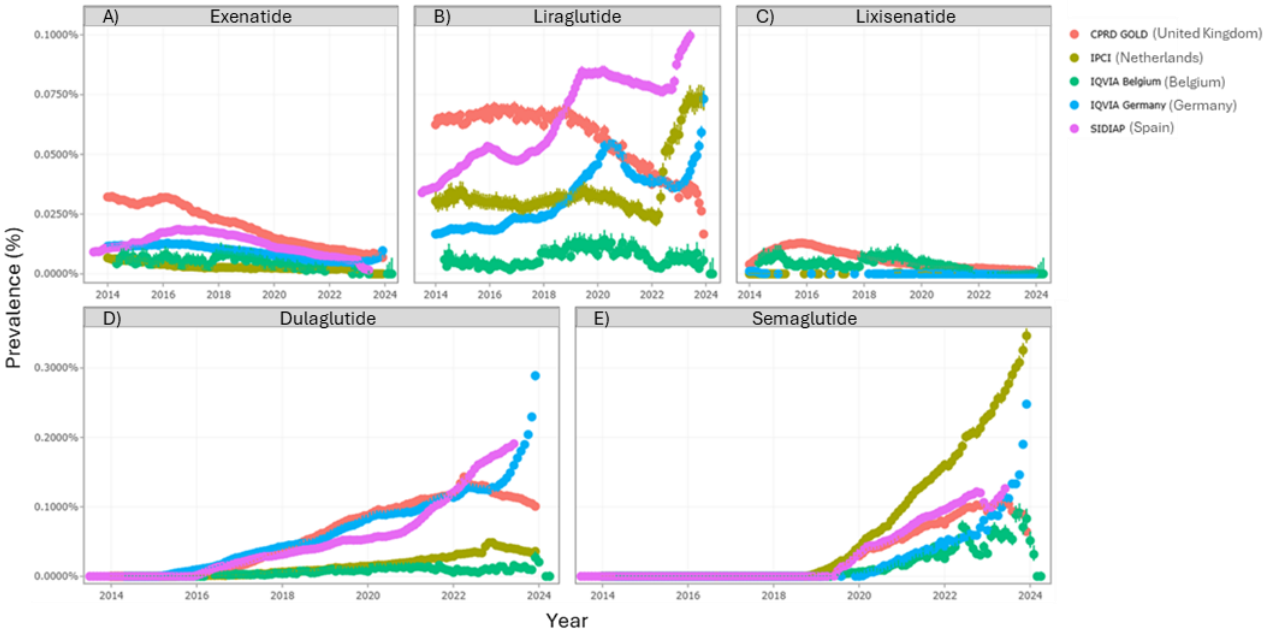
Country	Name of Database	Healthcare setting	Type of data	Number of active subjects	Calendar period covered by each data source
Spain	SIDIAP	primary care records	EHR	8.5M	01/07/2013 to 01/06/2023
Netherlands	IPCI	primary care records	EHR	2.9M	01/01/2014 to 31/12/2023
United Kingdom	CPRD	primary care records	EHR	17.4M	01/01/2014 to 15/12/2023
Germany	IQVIA DA Germany	outpatient: primary care and specialist records	EHR	43M	01/01/2014 to 31/12/2023
Belgium	IQVIA LPD Belgium	outpatient: primary care and specialist records	EHR	1.1M	01/01/2015 to 31/01/2024

3. EXECUTIVE SUMMARY

Glucagon-Like Peptide-1 receptor agonists (GLP-1 RA) are a group of medicines authorised to treat type 2 diabetes mellitus and for weight management in people with obesity. Since 2022, a shortage of some of these medicines has been ongoing in several European Union/EEA countries.

This study aimed to understand trends in GLP-1 RA prescribing over the past decade and the characteristics of persons being prescribed GLP-1 RA medications. To do so, we calculated monthly rates of use of five GLP-1 RA medicines (containing the active substances exenatide, liraglutide, lixisenatide, dulaglutide and semaglutide) over the past 10 years using healthcare data from five European countries. In addition to analysing new users of these medications (incidence), the study examined also regular users (prevalence). The use of these medicines was also examined by age, sex, and reasons for using the medications (i.e., indications of use). We analysed the characteristics of patients using GLP-1 RA medications, including their age, body mass index and starting dose. Additionally, we measured the use of five other medications for treating diabetes and help controlling weight. These analyses provide an overview of the use of GLP-1 RA medications in the selected databases, highlighting both differences and commonalities in their use.

The results show an increase in the use of dulaglutide and semaglutide in the last nine and five years, respectively, a mixed pattern for liraglutide, whilst the use of exenatide and lixisenatide decreased. ***Executive Summary Figure 1*** summarises the use of GLP-1 RA medicines in patients using these medicines regularly across the five European countries included in the study. Although the use of semaglutide started later than dulaglutide, it increased rapidly to reach similar or higher proportion of users at about 0.3% of the general population. For liraglutide, the proportion of regular users reached about one third of the maximum proportion of users seen for dulaglutide and semaglutide.



Executive Summary Figure 1. Use of GLP-1 RA medicines in regular users (i.e., prevalence of use) in 5 European populations: the United Kingdom (CPRD), Netherlands (IPCI), Germany (IQVIA Germany), Belgium (IQVIA Belgium) and Spain (SIDIAP), as indicated by different colours. *Although there may be an overestimation in the last 6 months of data for IQVIA Belgium and Germany (please see further details in*

the limitation section of the report), the following general patterns can be observed: For exenatide (A) and lixisenatide (C) a decrease of the use over the last decade can be observed in all databases, while for liraglutide (B) there are differences in the data but an increase can be observed between 2014 and 2020 in SIDAIP and IQVIA Germany, and again from 2022 onwards in SIDIAP, IPCI and IQVIA Germany. An increase in the proportion of regular users of dulaglutide was observed over the last nine years and for semaglutide since 2019, increasing up to 0.35%. The proportion of regular users was highest for dulaglutide and semaglutide, and the use was much lower for the other substances (below 0.10% for liraglutide and below 0.03% for exenatide and lixisenatide). Please note that the y-axis varies in scale to allow a detailed description.

The study also looked at the indications for which GLP-1 RA are used, and found that most people using GLP-1 medications had type 2 diabetes, with or without obesity, aligning with EU treatment guidelines.

When looking at the characteristics of the patients who started taking GLP-1 medications for the first time, the average age of people was similar across databases (between 55 and 62 years old). Additionally, very few users were under 18 years old. Obesity was documented in a large proportion of patients with available information on body mass index. Hypertension was the most common comorbidity, followed by chronic kidney disease and renal impairment

The study also collected data on five non-GLP-1 receptor agonist medicines for diabetes and weight control. We observed a low use in four of the five medicines (orlistat, naltrexone/bupropion, phentermine/topiramate, phentermine). Conversely, use of metformin seemed to remain generally stable over the past decade.

4. ABSTRACT

Title

DARWIN EU® - Drug Utilisation Study on GLP-1 receptor agonists

Rationale and Background

A shortage of medicines containing Glucagon-Like Peptide-1 receptor agonists (GLP-1 RA) has been affecting EU Member States since 2022 and has continued throughout 2024. The medicines belong to the class of GLP-1 RA are either authorised for the treatment of diabetes or authorised for weight management, with the exception of Mounjaro (tirzepatide), a glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA that is authorised for both indications.

The shortage is based on an increased demand for these medicines in addition to other causes, e.g. capacity constraints. Of concern has been the off-label use of GLP-1 RAs for weight management which has been mentioned frequently in the news and social media and is exacerbating existing shortages with serious consequences for public health.

This study aimed to provide an overview of the characteristics of patients prescribed with a GLP-1 RA medicinal product and how these have changed over the past ten years. This helps to contextualise how medical guidelines are followed and what might be driving the demand for GLP-1 RA medicines.

Research question and objectives

This study aimed to provide an overview of the characteristics of patients prescribed with a GLP-1 RA medicinal product and how these have changed over the past ten years.

The specific objectives of this study were:

1) To determine the incidence and prevalence of prescriptions of GLP-1 RA medicines at substance level (overall and stratified by age, sex, database, indications (only for incidence), and calendar time (per month), for the past 10 years. Additionally, new users of GLP-1 RA (stratified by presence or absence of diagnosis of diabetes mellitus type 2 and diagnosis of obesity indications) were characterised by age, sex, body mass index (BMI), initial dose, cumulative dose and a list of prespecified indications.

2) To determine the incidence and prevalence of prescriptions of other medicines at substance level used for the treatment of diabetes and weight management, including orlistat, naltrexone/bupropion, phentermine/topiramate, phentermine and metformin (overall and stratified by age, sex, database, and calendar time (per month), for the past 10 years.

Research Methods

Study design

- Population level cohort study (Objective 1.1, Population-level drug utilisation study on GLP-1 RA)
- Patient level cohort study (Objective 1.2, Patient-level characterisation on GLP-1 RA users stratified by presence or absence of diabetes mellitus type 2 and obesity)
- Population level cohort study (Objective 2, Population-level drug utilisation study on other medicines used for the treatment of diabetes and weight management)

Population

Population-level drug utilisation of GLP-1 RA and other medicines used for diabetes and/or weight management: All individuals present in the database in the last 10 years of available data were included in the analysis. For this population, incidence and prevalence of use of GLP-1 RA and other medicines used for the treatment of diabetes and weight management were explored.

Patient level cohort study on GLP-1 RA users stratified by presence or absence of diabetes mellitus type 2 and/or obesity: new drug users of GLP-1 RA stratified by presence or absence of diagnosis of diabetes mellitus type 2, obesity or both indications were characterised by age, sex, BMI, initial dose, cumulative dose and a list of prespecified indications/comorbidities.

Variables

Drugs of interest: list of 8 GLP-1 RA medicines (Objective 1) and 5 other medicines used for diabetes and/or weight management (Objective 2). However, no data or limited data was available for albiglutide, beinaglutide and tirzepatide, and therefore results of these three GLP-1 RA were not included in this report.

Calendar month, age, sex and indications (diabetes mellitus type 2 and obesity, and only for incidence) were used for stratification.

Age, sex, BMI, initial dose, cumulative dose and a list of prespecified indications/comorbidities were used for the characterisation.

Data sources

1) CPRD Gold (UK, Primary Care Database)
2) SIDIAP (Spain, Primary Care Database)
3) IPCI (Netherlands, Primary Care Database)
4) IQVIA DA Germany (combination of primary and secondary care (outpatient visits) database)
5) IQVIA LPD Belgium (combination of primary and secondary care (outpatient visits) database)

Sample size

No sample size was calculated. Based on a preliminary study feasibility assessment the expected number of prescriptions in the period investigated was expected to be between <1,000 and 760,000 across the five data sources considered.

Data analyses

Population-level drug utilisation study on GLP-1 RA and other medicines used for the treatment of diabetes and weight management: monthly incidence rates of use of medicines of interest per 100,000 person-years, and monthly point prevalence of medicines of interest. Incidence was stratified by age, sex and indications cohorts in each database of the study. Prevalence was stratified by age and sex in each database of the study.

Incidence and prevalence results from the last 6-months in IQVIA databases needs to be interpreted with caution since values might be overestimated due to an artefactual decrease in their denominators.

Patient-level drug utilisation study: new drug users of GLP-1 RA stratified by presence or absence of diagnosis of diabetes mellitus type 2, obesity, or both indications, were characterised by age, sex, BMI, initial dose, cumulative dose, and a list of prespecified indications/comorbidities.

Results

Objective 1

Incidence rates (IR [95%CI] per 100,000 person-years) of GLP-1 RA use showed a decline in the initiation of exenatide e.g., IR in IQVIA DA Germany decreased from 10.5 [8.0 to 13.5] in July 2014 to 3.5 [1.8 to 6.2] in July 2023) and lixisenatide (e.g., IR in CPRD decreased from 18.9 [15.2 to 23.3] in July 2014 to 1.8 [0.6 to 4.2] in October 2020). Conversely, use of dulaglutide and semaglutide increased since they started to be observed in the databases (2015-2016 for dulaglutide, and 2019-2020 for semaglutide): last IRs observed for dulaglutide ranged between 24 [18 to 31] in November 2023 in CPRD, and 177 [105 to 280] in January 2024 in IQVIA LPD Belgium; and last IRs observed for semaglutide ranged between 27 [21 to 35] in November 2023 in CPRD, and 628 [483 to 804] in January 2024 in IQVIA LPD Belgium. Moreover, liraglutide use increased after 2022 in 4 of the of the 5 DB of the study (CPRD, IPCI, SIDIAP and IQVIA LPD Belgium), but CPRD showed a marked drop in use between June and July 2023 (IR [95%CI]: 73 [63 to 86] and 27 [21 to 35] per 100,000 person-years, respectively). The most common indications to start GLP-1 RA treatment were DM2 with obesity, except for dulaglutide, exenatide and lixisenatide in IQVIA LPD Belgium where main indication was DM2 alone.

The prevalence of use of dulaglutide and semaglutide increased over time in all databases (e.g., last prevalence values observed in December 2023 were 0.03% for dulaglutide to 0.35% for semaglutide in IPCI). Prevalence of liraglutide use was lower than 0.1% in all databases, and trends in the different databases differed: while a decrease in prevalence was seen in CPRD, an increase was observed in SIDIAP, IPCI and IQVIA DA Germany. Conversely, prevalence of exenatide and lixisenatide use decreased over time, and approached 0% after June 2023.

Most new users of GLP-1 RA had a recorded history of DM2 with or without obesity (e.g., of 8,741 dulaglutide new users in CPRD, 71% had history of DM2 and obesity, 4% only DM2, 22% only obesity, and 5% no DM2 nor obesity; or of 8,680 in IPCI, 75% had history of DM2 and obesity, 16% only DM2, 7% only obesity, and 5% no DM2 nor obesity) . Additionally, the proportion of new GLP-1 RA users with a BMI ≤26 kg/m2 was <4% of those with a BMI record in all databases. Incident users in IQVIA LPD Belgium presented the lowest median BMI (ranged between 30.03 to 32.9 kg/m2 across different GLP-1 RA), compared to median BMI >33 kg/m2 in the other databases.

Objective 2

We observed stationary fluctuations in the incidence of metformin use in 3 out of 5 databases of the study (CPRD, IQVIA LPD Belgium and SIDIAP) and was stable over time except for IQVIA DA Germany and IPCI.. Incident use of naltrexone/bupropion was observed almost exclusively in IPCI and IQVIA LPD Belgium, and mostly after May 2022. Similarly, initiation of orlistat was almost exclusively seen in IQVIA Belgium and CPRD.

The prevalence of metformin use presented a moderate increase (difference between the minimum and maximum prevalence values across the entire study period was less than <0.8%) that could be considered as stable or negligible, with values between 2% and 6%, except for last 5 months of observed data in IQVIA LPD Belgium (December 2023-May 2024), which increased up to 9.2% in February 2024. Larger increases observed in IQVIA DA Germany and IQVIA LPD Belgium prevalence may be driven by an artefactual decrease in their denominators during the last 6 months of the study period. Use of orlistat was observed in CPRD and IQVIA LPD Belgium, with prevalence values between 0.02% and 0.07%, and CPRD showed a potential seasonal pattern. Prevalence of naltrexone/bupropion use gradually increased since September 2021 in IQVIA LPD Belgium and IPCI, but values remained below 0.27%.

Conclusions

Use of dulaglutide and semaglutide had increased in the last nine and five years, respectively, whilst use of exenatide and lixisenatide had decreased in the last nine. In contrast, liraglutide use exhibited variations: incidence of liraglutide was steady whilst prevalence increased in SIDIAP, IPCI, and IQVIA DA Germany, remained stable in IQVIA LPD Belgium and decreased in CPRD. Stratification by indication revealed that most GLP-1 RA users had a history of type 2 diabetes, with or without obesity, aligning with EU treatment guidelines, which require at least one of these conditions for treatment initiation.

Patient characteristics exhibited small variations among the study databases. Obesity was documented in a large proportion of patients with available information on BMI. the median BMI of patients ranged from 31.6 to 36.6 kg/m², with the lowest values in IQVIA LPD Belgium and the highest in IPCI. However, IQVIA LPD Belgium had the highest proportion of patients lacking BMI records. When recorded, individuals with a BMI ≤26 kg/m2 constituted a minority (<5%). The median age of GLP-1 RA initiation was consistent across databases. Paediatric use (initiation at ages under 18 years old) was rare.

The examination of other medications used for managing diabetes or obesity yielded limited insights in this study.

5. LIST OF ABBREVIATIONS

Acronyms/terms	Description
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CDM	Common Data Model
CI	Confidence Interval
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DUS	Drug Utilization Study
EEA	European Economic Area
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
GLP-1 RA	Glucagon-like peptide-1 receptor agonists
GP	General Practitioner
IPCI	Integrated Primary Care Information
IR	Incidence Rate/s
LPD	Longitudinal Patient Data
OMOP	Observational Medical Outcomes Partnership
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

6. AMENDMENTS AND UPDATES

None.

7. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Draft Study Protocol	29/05/2024	29/05/2024
Final Study Protocol	June 2024	29/05/2024
Creation of Analytical code	July 2024	17/07/2024
Execution of Analytical Code on the data	July-August 2024	July-August 2024
Interim Study Report (if applicable)	Not applicable	Not applicable
Draft Study Report	August 2024	30/08/2024
Final Study Report	07/10/2024	19/12/2024

8. RATIONALE AND BACKGROUND

A shortage of medicines containing glucagon-like peptide-1 (GLP-1) receptor agonists (RA) has been affecting EU Member States since 2022 and has continued throughout 2024. The shortage involves the medicinal products Ozempic (semaglutide), Victoza (liraglutide), Trulicity (dulaglutide) and Saxenda (liraglutide).[1]

The shortage is based on an increased demand for these medicines in addition to other causes, e.g. capacity constraints at some of the medicines' manufacturing sites.

Medicinal products belonging to the class of Glucagon-Like Peptide-1 receptor agonists (GLP-1 RA) are either authorised for the treatment of diabetes (Ozempic, Victoza, Trulicity, Bydureon, Rybelsus) or authorised for weight management (Saxenda, Wegovy); with the exception of Mounjaro (tirzepatide), a glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA that is authorised for both indications. Of concern has been the off-label use of GLP-1 RAs for weight management which has been mentioned frequently in the news and social media and is exacerbating existing shortages with serious consequences for public health.

This study aimed to provide an overview of the characteristics of patients prescribed with a GLP-1 RA medicines at substance level and how these have changed over the past ten years. Our study helps to contextualise what determinants might be driving the demand for GLP-1 RA vis-à-vis the observed shortage of medicines, including exploring comparative trends of prescription of other medicines used in diabetes and for weight management as well as patterns of off-label use.

9. RESEARCH QUESTION AND OBJECTIVES

Table 1. Primary and secondary research questions and objective.

A. Primary research question and objective.

Objective:	To determine the incidence and prevalence of prescriptions of the GLP-1 RA medicines at substance level during the last 10 years of available data, stratified by age, sex, indications and speciality (only for incidence), and calendar month in each of the databases. Additionally, new drug users of GLP-1 RA (stratified by presence or absence of diagnosis of diabetes mellitus type 2, obesity, or both indications) were characterised by age, sex, initial dose, cumulative dose and a list of prespecified indications/comorbidities.
Hypothesis:	Not applicable
Population ***(mention key inclusion-exclusion criteria):***	The study cohort comprised all individuals present in the database in a 10-year period from the most recent data available. Additional eligibility criteria for calculation of incidence rates was applied, where a minimum follow-up of 365 days of data availability and no prior use of the respective drug of interest were required.

Exposure:	<table><tr><th>Substance name</th><th>ATC code</th></tr><tr><td>Exenatide</td><td>A10BJ01</td></tr><tr><td>Liraglutide</td><td>A10BJ02</td></tr><tr><td>Lixisenatide</td><td>A10BJ03</td></tr><tr><td>Albiglutide</td><td>A10BJ04</td></tr><tr><td>Dulaglutide</td><td>A10BJ05</td></tr><tr><td>Semaglutide</td><td>A10BJ06</td></tr><tr><td>Beinaglutide</td><td>A10BJ07</td></tr><tr><td>Tirzepatide</td><td>A10BX16</td></tr></table>
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	The study comprised the last 10 years of available data counting backwards from the respective latest date of data lock of the respective databases (i.e., 2014 to the most recent data lock).
Setting:	Primary care and outpatient setting using data from the following data sources: 1) SIDIAP (Spain, Primary Care Database) 2) IPCI (Netherlands, Primary Care Database) 3) CPRD Gold (UK, Primary Care Database) 4) IQVIA DA Germany (Outpatient care) 5) IQVIA LPD Belgium (Primary Care Database)
Main measure of effect:	Incidence and prevalence rates of GLP-1 RA medicines

B. Secondary research question 1 and objective.

Objective:	To determine the incidence and prevalence of prescriptions of 5 medicines at substance level used for the treatment of diabetes and weight management during the last 10 years of available data, stratified by age, sex, and calendar month in each of the databases.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	The study cohort comprised all individuals present in the database in a 10-year period from the most recent data available. Additional eligibility criteria for calculation of incidence rates was applied, where a minimum follow-up of 365 days of data availability and no prior use of the respective drug of interest were required.

Exposure:	<table><tr><th>Drug name</th><th>ATC code</th></tr><tr><td>Orlistat</td><td>A08AB01</td></tr><tr><td>Metformin</td><td>A10BA02</td></tr><tr><td>Naltrexone/bupropion (Mysimba)</td><td>A08AA62</td></tr><tr><td>Phentermine/topiramate (Qsiva)</td><td>A08AA51</td></tr><tr><td>Phentermine</td><td>A08AA01</td></tr></table>
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	The study comprised the last 10 years of available data counting backwards from the respective latest date of data lock of the respective databases (i.e., 2014 to the most recent data lock).
Setting:	Primary care and outpatient setting using data from the following data sources: 1) SIDIAP (Spain, Primary Care Database) 2) IPCI (Netherlands, Primary Care Database) 3) CPRD Gold (UK, Primary Care Database) 4) IQVIA DA Germany (Outpatient care) 5) IQVIA LPD Belgium (Primary Care Database)
Main measure of effect:	Incidence and prevalence rates of prescriptions of medicines used for the treatment of diabetes and weight management

10. RESEARCH METHODS

10.1 Study type and study design

Retrospective cohort studies were conducted using routinely collected health data from five databases. The study contains two study types classified as "off-the-shelf" as described in the DARWIN EU® Complete Catalogue of Standard Data Analyses (**Table 2**):

1) A population-based cohort study was conducted to address objective 1.1 and objective 2, assessing the incidence and prevalence of use at substance level of GLP-1 RA medicines and other selected medicines used for the treatment of diabetes and weight management.
2) A patient-based cohort study was conducted to address objective 1.2, characterising first incident users of GLP-1 RA with no record of diabetes mellitus type II nor obesity.

Table 2. Description of potential study types and related study designs.

Study type	Study design	Study classification
Population Level DUS	Population Level Cohort	Off the shelf
Patient Level DUS	New drug/s user cohort	Off the shelf

10.2 Study setting and data sources

10.2.1 Data sources selected

Primary care and outpatient setting using data from the following data sources:

3) Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP, Spain)
4) Integrated Primary Care Information (IPCI, Netherlands)
5) Clinical Practice Research Datalink GOLD (CPRD, United Kingdom)
6) IQVIA Disease Analyzer Germany (IQVIA DA Germany, Germany)
7) IQVIA Longitudinal Patient Data Belgium (IQVIA LPD Belgium, Belgium)

All databases were previously mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). Information on data source(s) used in this study is described in **Table 3**.

10.2.2 Rationale for the data sources selected

This study was conducted using 5 of the 24 databases onboarded in DARWIN EU® in 2024, representing 5 European countries. The selection of databases for this study was based on data quality and relevance for the proposed research question.

GLP-1 RA medicines are commonly used/prescribed in primary care. Despite the possibility that its initiation may be given by a care specialist, GLP-1 RA medicines are often prescribed and used by primary care practitioner, and therefore appear to be prescribed often. With this in mind, we selected the following data sources, which covered the healthcare settings of interest: SIDIAP, IPCI, CPRD, IQVIA DA Germany and IQVIA LPD Belgium.

The proposed data sources captured the relevant data necessary to answer the research questions of this study, covered the healthcare settings where the drugs of interest may be used (i.e., primary care), and they had recent data covering the 10-year study period. Previous checks evaluating the reliability of the data sources performed at the time of their onboarding showed that drug records represented between the 11% and 37% of the total number of records in the selected databases. Use of medicines (prescription or dispensation) was previously captured accurately in all databases in previous DARWIN EU studies (such as EUPAS105644, EUPAS105641 or EUPAS50789).

The selected databases fulfilled the criteria required for a population-level drug utilisation study, as all these had counts for most of the GLP1-a treatments in the order of thousands of users, a consistent denominator (except for the last few months before data extraction for 4 and 5) allowing for accurate incidence estimation, and quick approvals/governance enabling rapid analyses as requested.

Table 3. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Healthcare setting	Type of Data	Number of active subjects	Feasibility count of exposure (if relevant)	Last recorded date from last data extraction
Spain	SIDIAP	Covers primary care setting where GLP-1 RA medicines are commonly used/prescribed	primary care records	EHR	8.5M	From <1000 to 347,000	2023-06-30
Netherlands	IPCI	Covers primary care setting where GLP-1 RA medicines are commonly used/prescribed	primary care records	EHR	2.9M	From <1,000 to 109,000	2024-04-30
United Kingdom	CPRD	Covers primary care setting where GLP-1 RA medicines are commonly used/prescribed	primary care records	EHR	17.4M	From 1,400 to 2.44 million	2024-01-01
Germany	IQVIA DA Germany	Covers primary care setting where GLP-1 RA medicines are commonly used/prescribed	outpatient: primary care and specialist records	EHR	43M	From 8,200 to 1.86 million	2023-12-31
Belgium	IQVIA LPD Belgium	Covers primary care setting where GLP-1 RA medicines are commonly used/prescribed	outpatient: primary care and specialist records	EHR	1.1M	From <1,000 to 188,000	2024-03-31

Feasibility count of exposure is based record counts on prescription data of the different drugs of interest. Abbreviations: GLP-1 RA = Glucagon-like peptide-1 receptor agonists, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, IPCI = Integrated Primary Care Information, CPRD = Clinical Practice Research Datalink GOLD, EHR = Electronic Heath record.

Information on data sources used is described below:

Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària [SIDIAP] (Spain, Primary Care Database)

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff.[2, 3] The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan

Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee.

Integrated Primary Care Information [IPCI] (Netherlands, Primary Care Database)

The Integrated Primary Care Information (IPCI) database is a longitudinal observational database containing routinely collected data from computer-based patient records of a selected group of GPs throughout the Netherlands (N=723). IPCI was started in 1992 by the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam with the objective to enable better post marketing surveillance of drugs. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. In 2016, IPCI was certified as Regional Data Center. Since 2019 the data is also standardised to the OMOP-CDM, enabling collaborative research in a large network of databases within the Observational Health Data Sciences and Informatics (OHDSI) community. The primary goal of IPCI is to enable medical research. In addition, reports are generated to inform GPs and their organizations about the provided care. Contributing GPs are encouraged to use this information for their internal quality evaluation.

Clinical Practice Research Datalink GOLD [CPRD] (UK, Primary Care Database)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD [4] comprises computerised records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data are available for 20 million patients, including 3.2 million currently registered patients. Access to CPRD data requires approval via the Research Data Governance Process.

IQVIA Disease Analyzer Germany [IQVIA DA Germany] (Primary and Secondary Care Database)

IQVIA DA Germany is collected from extracts of patient management software used by general practitioners (GPs) and specialists practicing in ambulatory care settings.[5] Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices.

IQVIA Longitudinal Patient Data Belgium [IQVIA LPD Belgium] (Primary Care Database)

IQVIA LPD Belgium is a computerised network of GPs who contribute to a centralised database of anonymised data of patients with ambulatory visits. Currently, around 300 GPs from 234 practices are contributing to the database covering 1.1M patients from a total of 11.5M Belgians (10.0%). The database covers time from 2005 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation studies.

10.3 Study period

The study comprised the last 10 years of available data counting backwards from the respective latest date of data lock of the respective databases (i.e., 2014 to the most recent data lock reported in **Table 3**).

10.4 Follow-up

To determine the incidence and prevalence estimates, we required the appropriate population and their contributed observation time to first be identified. The Operational Definition of follow-up is reported in **Table 4**.

Table 4. Operational definition of time 0 (index date) and other primary time anchors.

Study population name(s)	Time Anchor Description	Number of entries	Type of entry	Washout window	Care Setting [1]	Incident with respect to…
All patients with prevalent use of medicines of interest	Patient present in the database during the study period (2014 to most recent data lock)	Multiple	Prevalent	None	PC, OP	n/a
All patients with incident use of medicines of interest	Patient present in the database during the study period (2014 to most recent data lock) and with at least 365 days of valid database history.	Multiple	Incident	[-Inf, -1]	PC, OP	Specific medicine of interest

[1] PC = Primary Care, OP = outpatient, n/a = not applicable

For prevalence estimates, study participants in the denominator population began contributing to the denominator on the respective date of the latest of the following: 1) study start date 2) date at which the observation period started. Participants stopped contributing person time at the earliest date of the following: 1) end of available data in each of the data sources or 2) date at which the observation period of the specific person ended.

An example of entry and exit into the denominator population is shown in **Figure 1**. In this example, person ID 1 and 3 were included as denominators at the study start date as both had been observed in the database from a prior date. Person ID 2 entered the study at the date of starting their period of observation, which was later than the study start date. Person ID 1 and 2 were followed until the study end date (end of available data in each of the data sources) whilst Person ID 3 left when exiting the database (the end of observation period). Lastly, person ID 4 had two observation periods in the database. The first period contributed time from study start until end of observation period, the second started contributing time again on the date of their second observation period start and exited at study end date.

For incidence rates, an additional criterion was required to ensure we were capturing first incident use (i.e., new drug users). Thus, follow-up started from the date they reached at least 365 days of data availability. Thus, the denominator population began contributing person time on the respective date of the latest of the following: 1) study start date, 2) date at which the observation period starts, 3) date at which the observation period has already sufficient prior history. Participants stopped contributing person time at the earliest date of the following: 1) end of available data in each of the data sources or 2) date at which the observation period of the specific person ended.

An example of entry and exit into the denominator population is shown in **Figure 2**. In this example, person ID 1 had already sufficient prior history before the study start date and observation period ended after the study end date, so they contributed during the complete study period. Person ID 2 and 4 entered the study only when they had sufficient prior history. Person ID 3 left when exiting the database (at the end of observation period). Lastly, person ID 5 had two observation periods in the database. The first period contributed time from study start until end of observation period, the second started contributing time again once sufficient prior history was reached and exited at the study end date.

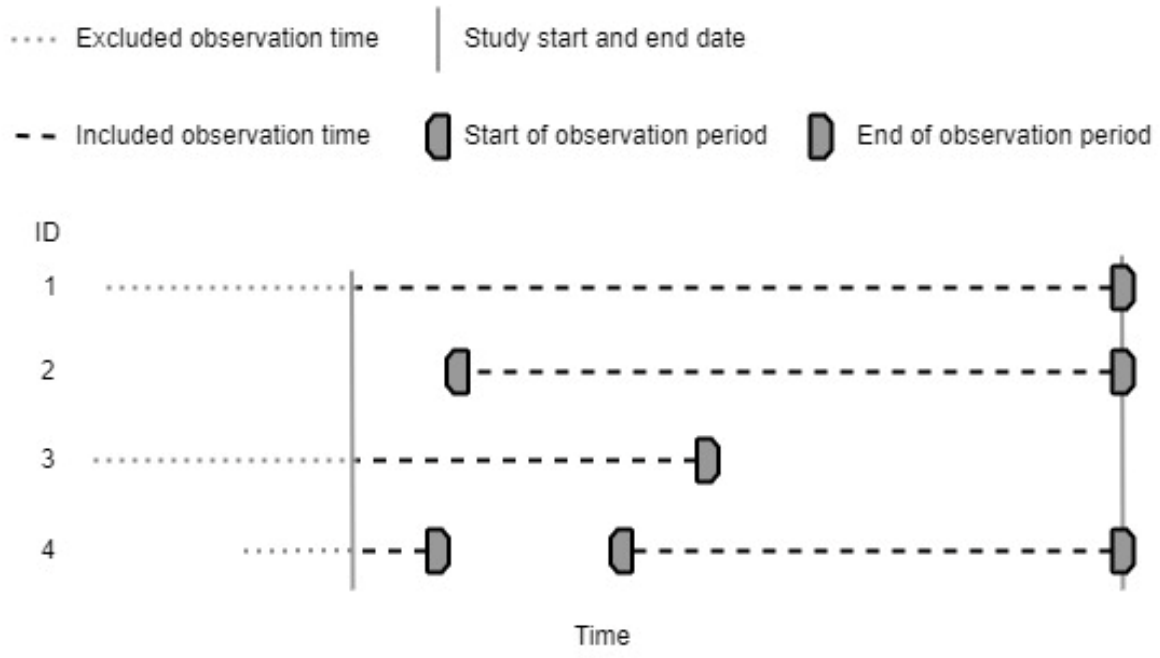


Figure 1. Included observation time for the denominator population in prevalence rates.

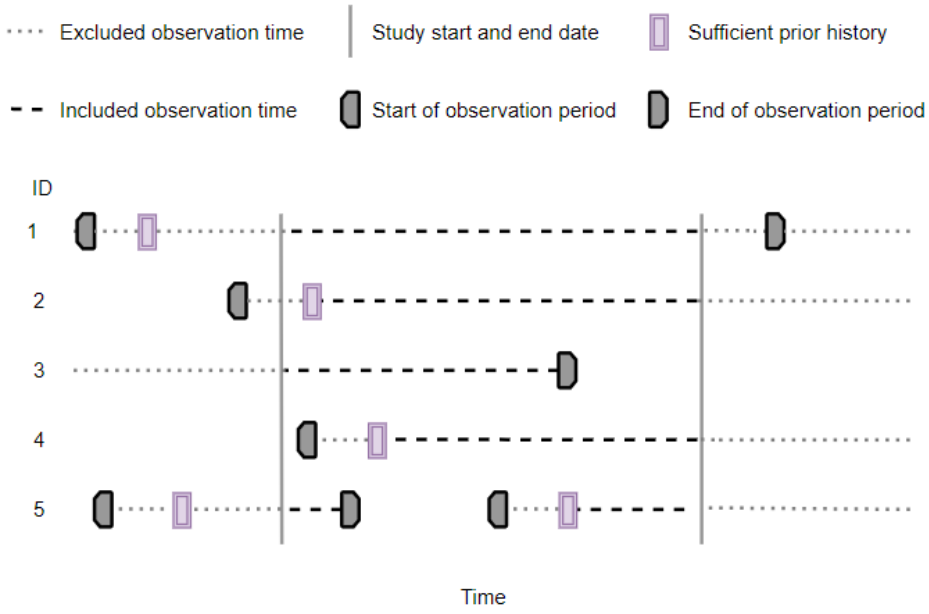


Figure 2. Included observation time for the denominator population in incidence rates.

10.5 Study population with in- and exclusion criteria

The study cohort comprised all individuals present in the database during the study period (i.e., 2014 to the most recent data lock reported).

Additional eligibility criteria for calculation of incidence rates was applied, where a minimum follow-up of 365 days of data availability was required to exclude individuals with a prior use of the respective drug of interest.

The operational definitions of the inclusion criteria are presented in **Table 5**.

Table 5. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings [1]	Applied to study populations:
Observation period in the database during the 10-year period from the latest available data	See under inclusion criterion	After	n/a	PC, OP	All individuals within the selected databases
Prior database history of 365 days for incidence rates calculation	Study participants were required to have 365 days of prior history observed before contributing observation time in incidence rate calculations.	After	[-365, -1]	PC, OP	All individuals within the selected databases
Washout period for incidence rates calculation	Study participants were required to have not used the same drug of interest before in incidence rate calculations.	After	[-Inf, -1]	PC, OP	All individuals within the selected databases

[1] PC = Primary Care, OP = outpatient, n/a = not applicable

10.6 Variables

10.6.1 Exposure/s

For this study, the exposure of interest was use (during study period) of GLP-1 RA and use of other medicines used for the treatment of diabetes and weight management at substance level. This list (with respective ATC code) is described in **Table 6**. Further details are described in the **Appendix I**.

For completion, the list contains all GLP-1 RA medicines. However, at the start of this study, albiglutide was no longer authorised, and therefore it was not included in the study. Additionally, beinaglutide use had not been approved for its use in EU yet whilst tirzepatide was recently approved for its marketing in the EU for treating not only diabetes mellitus type 2 but also for weight management.[6, 7] Thus, these two drugs presented no counts in the selected data sources and were not added in the analysis.

Details of exposure are described in **Table 7**.

Table 6. Exposure of interest.

Objective	Substance name	ATC code	Included in this study
1) GLP-1 RA	Exenatide	A10BJ01	Yes
1) GLP-1 RA	Liraglutide	A10BJ02	Yes
1) GLP-1 RA	Lixisenatide	A10BJ03	Yes
1) GLP-1 RA	Albiglutide	A10BJ04	No
1) GLP-1 RA	Dulaglutide	A10BJ05	Yes
1) GLP-1 RA	Semaglutide	A10BJ06	Yes
1) GLP-1 RA	Beinaglutide	A10BJ07	No
1) GLP-1 RA	Tirzepatide	A10BX16	No
2) Other medicines used for the treatment of diabetes and weight management	Orlistat	A08AB01	Yes
2) Other medicines used for the treatment of diabetes and weight management	Metformin	A10BA02	Yes
2) Other medicines used for the treatment of diabetes and weight management	Naltrexone/bupropion (Mysimba)	A08AA62	Yes
2) Other medicines used for the treatment of diabetes and weight management	Phentermine/topiramate (Qsiva)	A08AA51	Yes
2) Other medicines used for the treatment of diabetes and weight management	Phentermine	A08AA01	Yes

ATC = Anatomical Therapeutic Chemical, GLP-1 RA = Glucagon-like peptide-1 receptor agonists

Table 7. Operational definitions of exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Applied to study populations	Incident with respect to…
GLP-1 RA	Code lists provided in Appendix I	[-Inf, -1] for incident use only	Monthly	PC, OP	RxNorm	All individuals present in the database during the study period who have had a prescription / dispensation of the medicine of interest	Previous medicine use (of the specific drug of interest)
Other medicines for the treatment of diabetes and weight management	Code lists provided in Appendix I	[-Inf, -1] for incident use only	Monthly	PC, OP	RxNorm	All individuals present in the database during the study period who have had a prescription / dispensation of the medicine of interest	Previous medicine use (of the specific drug of interest)

[1] PC = primary care, OP = outpatient, n/a = not applicable

10.6.2 Outcome/s

None.

10.6.3 Other covariates, including confounders, effect modifiers and other variables

Covariates for stratification in population-level drug utilisation study (objective 1.1 and 2):

- Age: age was stratified in three groups (<18, 18-64, 65+).
- Sex (men/women)
- Time period: Monthly
- Prescriber speciality (when/if available, and only for incident use of GLP-1 RA)
- Indications cohorts (only for incident use of GLP-1 RA): these indications were assessed via a proxy based on pre-defined conditions recorded, and they do not constitute the specific reasons for the prescriptions of the medicinal products (*see more details in section 15.2*).

1. Users of GLP-1 RA with diagnosis of DM2[1] and obesity[2]
2. Users of GLP-1 RA with diagnosis of DM2[1] and excluding obesity[2]
3. Users of GLP-1 RA with diagnosis of obesity[2] and excluding DM2[1]
4. Users of GLP-1 RA excluding obesity[2] and DM2[1]

[1] DM2: diagnosis of diabetes mellitus type II before or on the date of first use of GLP-1 RA.

[2] Obesity: diagnosed [based on presence of clinical codes indicating obesity] or measured anytime during the observation period. Measurements that qualified as obesity were BMI values between 30 and 60 kg/m2 or, alternative, when height was not available, weights values between 120 to 200 kg or 265 and 440 pounds.

Covariates for stratification in population-level drug utilisation study (objective 1.2):

- Age: age was stratified in three groups (<18, 18-64, 65+).
- Sex (men/women)
- Body mass index (BMI): BMI [kg/m2] was stratified in groups (narrow groups: <27, 27-30, 31-35, 36-39, ≥40, and among larger groups: <27, 27-39, ≥40). The value captured in each patient was the most recent BMI value recorded during the five previous years from index date. Values below 10 and over 60 kg/m2 were truncated to diminish the risk of outliers.
- List of prespecified indications/comorbidities based on concept_ID (the unique numeric identifier representing a concept [i.e., condition, observation, drug, etc.] from the OMOP-CDM vocabulary).
  - Myocardial infarction
  - Stroke
  - Major adverse cardiac events (MACE): defined as a composite outcome of myocardial infarction and stroke
  - Heart failure
  - Hypertension
  - Chronic kidney disease
  - Chronic kidney disease and renal impairment
- Initial dose
- Cumulative dose

10.7 Study size

No sample size was calculated for this study. The expected number of prescriptions across data sources was expected to be roughly between <1,000 and 760,000.

10.8 Statistical methods

10.8.1 Federated network analyses

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources or on a simulated set of patients and quality control checks were performed. Once all the tests were passed, the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP-CDM in R Studio and reviewed and approved the by default aggregated results before returning them to the Coordination Centre. Where necessary, multiple execution iterations were performed, with additional fine tuning of the code base. A service desk was available during the study execution for support.

The study results of all data sources were checked after which they were made available to the DARWIN EU Coordination Centre team and the write-up of the study report started. All results were locked and timestamped for reproducibility and transparency.

10.8.2 Patient privacy protection

To prevent confidentiality issues, cell counts lower than 5 have been reported as “<5”.

10.8.3 Methods to derive parameters of interest

Incidence and prevalence calculations were reported overall and stratified. Characterisation of new users were only reported among new drug users of GLP-1 RA.

Calendar time

Calendar time for incidence calculations was based on monthly periods of the index prescription/dispensation in the population level analysis (e.g., 01/01/2014 – 31/01/2014, 01/02/2014 – 30/02/2014, etc.).

Calendar time for point prevalence calculations was based on the first day of each calendar month in the population level analysis (e.g., 01/01/2024, 01/02/2024, etc).

Age

Age at index date was calculated using January 1st of the year of birth as proxy for the actual date of birth. The following age groups were used for stratification: <18, 18-64, 65+.

Sex

Results were presented stratified by sex (men/women).

Speciality (when/if available, and only for incident use of GLP-1 RA)

Prescriber specialty such as general practice, gastroenterology, etc. was used to stratify incident users of each of the GLP-1 RA medicines at substance level in IQVIA DA Germany (the only database in the study containing this information).

Indications cohorts (only for incident use of GLP-1 RA)

- Diabetes mellitus type 2 (DM2): diagnosis of DM2 before first use of GLP-1 RA.

- Obesity: diagnosed [based on presence of clinical codes indicating obesity] or measured anytime during the observation period. Measurements that qualified as obesity were BMI values between 30 and 60 kg/m2 or, alternative when height was not available, weights values between 120 to 200 kg or 265 and 440 pounds.

Incidence calculations of each of the GLP-1RA were also stratified by the combination of DM2 and obesity, creating the following four cohorts:

1. Users of GLP-1 RA with diagnosis of DM2 and obesity
2. Users of GLP-1 RA with diagnosis of DM2 and excluding obesity
3. Users of GLP-1 RA with diagnosis of obesity and excluding DM2
4. Users of GLP-1 RA excluding obesity and DM2

List of prespecified indications/comorbidities

A list of prespecified indications/comorbidities was used to characterise the four indication cohorts (time window assessed was any time prior index date):

- Myocardial infarction
- Stroke

- Major adverse cardiac events (MACE): defined as a composite outcome of myocardial infarction and stroke
- Heart failure
- Hypertension
- Chronic kidney disease
- Chronic kidney disease and renal impairment

Body mass index:

Body mass index (BMI) was used to characterise the four indication cohorts. BMI was reported continuously (median [Q25 - Q75], only among those with a BMI record) and categorically (number of subjects (%) with BMI: BMI group narrow including ≤26, 27-39, ≥40 or None [i.e., not recorded]; and BMI group wide including ≤26, 27-30, 31-35, 36-39, ≥40 or None). Values below 10 and over 60 kg/m2 were truncated to diminish the risk of outliers.

Initial dose and cumulative dose:

Initial dose and cumulative dose were used to characterise the four indication cohorts.

10.8.4 Missing values

Individuals with missing or invalid age and sex were excluded.

BMI, initial dose and cumulative dose, which were only used in the characterisation of the drug users, may had contained missing values. We reported the number and percentage of missingness for each of them in each drug of interest/stratification of interest. Speciality was only available in IQVIA DA Germany, and thus only included as a stratification in this database.

No other incomplete variables were added in the study. The remaining variables used in the study were based on the recorded diagnoses and prescription codes available in the data, where the lack of a record was considered as the patient was not diagnosed/prescribed with the condition/drug of interest.

10.8.5 Population-level incidence calculations

Incidence rates are a measure of the number of new events (e.g., diagnosis of a condition, or initiation of a medicine) in a certain population and over a specific period of time. The total amount of people available in the population multiplied by the time they are observed for is the denominator in the calculation of incidence rates, known as *time-at-risk* or *person-years-at-risk*.

In this study, we estimate the incidence of initiation of different medicines of interest. Monthly incidence rates of the medicines of interest at substance level were calculated as the number of users per 100,000 person-years of the population at risk of getting exposed during the period for each calendar year. Those study participants who entered the denominator population contributed time at risk up to their first use (prescription or dispensation) during the study period. Or if they did not have a drug exposure, they contributed time at risk up as described above in section 9.4 (Follow-up). Incidence rates were given together with 95% Poisson exact confidence intervals.

An illustration of the calculation of incidence use for each of the medicines of interest is shown below in **Figure 3**.

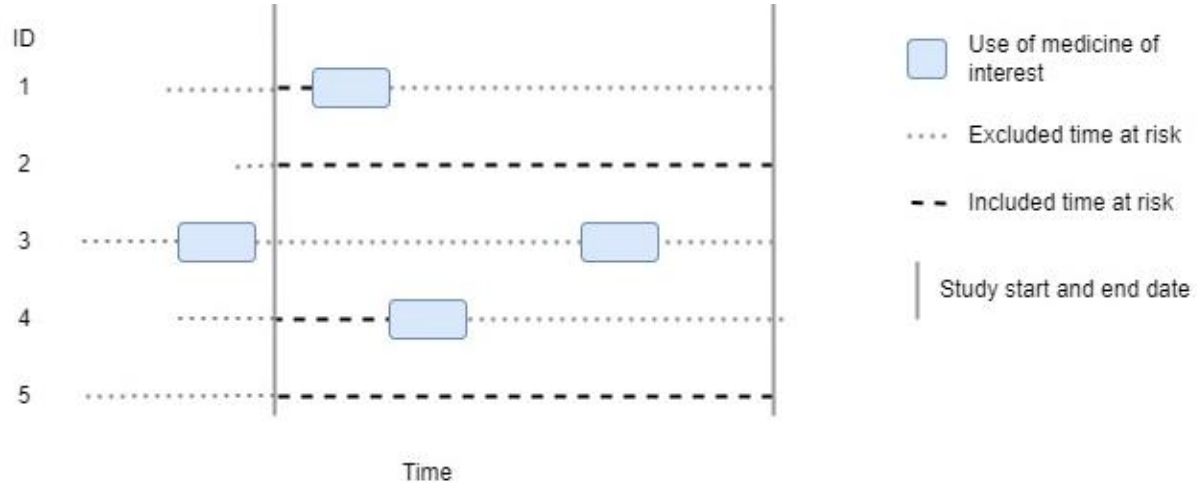


Figure 3. Example for capturing first incidence use of medicines of interest.

Patient ID 1 and 4 contributed time at risk between the study start until when they become incident users of the medicine of interest. Patient ID 2 and 5 contributed time at risk between the study start and end date as no use of medicines of interest was observed between this period nor before the study start date. Patient ID 3 was excluded from the analysis and did not contributed time at risk since a previous use of the same medicine of interest was observed before the study start date.

10.8.6 Population-level prevalence calculations

Prevalence is a measure that indicates the number of people who have a specific feature (e.g. a condition or the use of a treatment) in a specific population at a specific point in time.

In classic epidemiology textbooks, people have used the analogy of a bathtub to explain incidence rates and prevalence. In this analogy, the speed at which the water flows from the tap to the bathtub is the incidence, while the amount of water already in the bathtub at a specific time is the analogy of prevalence.

Monthly point prevalence of the medicines of interest at substance level were calculated as the total number of individuals who used the medicine of interest at the start of each calendar month (i.e., the 1st of each month), divided by the population at risk of getting exposed during that point. Therefore, point prevalence gave the proportion of individuals exposed at the first of each calendar month.

Point prevalence was given together with 95% confidence intervals. Binomial 95% confidence intervals were calculated using the Wilson Score method for binomial distribution.

An illustration of the calculation of point prevalent use for each of the medicines of interest is shown below in **Figure 4**.

Point prevalence use was captured at the different time points, represented as “t” or “t + n”. In each of the time points, the number of users of the medicine of interest contributed to the numerator. For instance, from the 5 participants, there was only one user for each time point at time “t” and at time “t + 3”, whilst “t + 1” and “t + 4” had no users, and “t + 2” had two users of the medicine of interest. Patient ID 1 and 3 only contributed one time point each: “t” and “t + 2”, respectively. Conversely, Patient ID 4 contributed to two-time points, “t + 2” and “t + 3”, as their use of the medicine of interest continued.

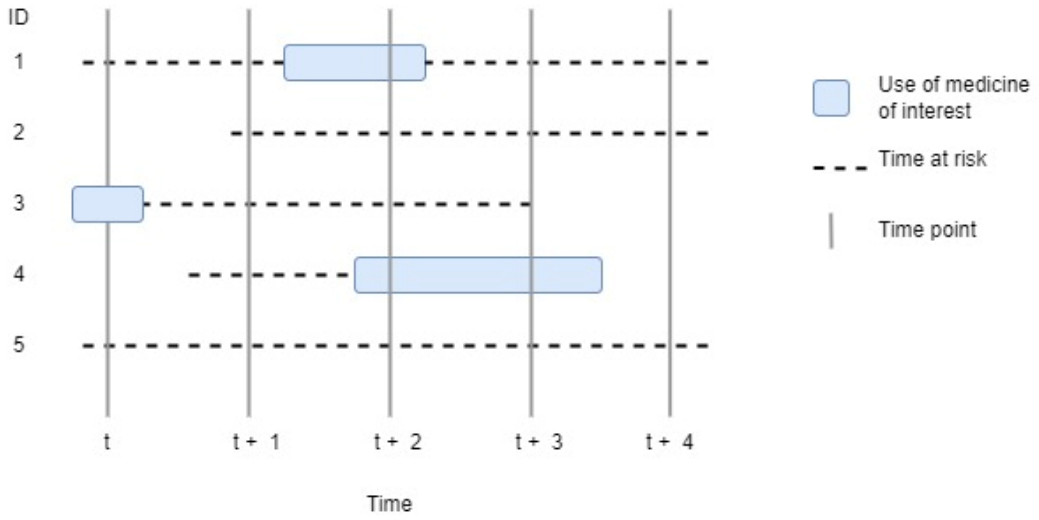


Figure 4. Example for capturing point prevalence use of medicines.

10.8.7 Patient-level characteristics on/before index date

Characteristics of the patients at the time of their first prescription of GLP-1 RA (i.e., incident users/first time use) were characterised by age, sex, body mass index, initial dose, cumulative dose, and a list of prespecified indications/comorbidities. Additionally, patient characteristics were also assessed at the beginning of each treatment episode (i.e., new episodes of drug use of GLP-1 RA), defined as continuous use of the specific GLP-1 RA drug where ≤30 days gaps in the prescription of medication are considered part of the same episode.

Both, first time use and new episodes of drug use of GLP-1 RA were also stratified by presence or absence of diagnosis of diabetes mellitus type 2, obesity, or both indications, when characterised.

Average age and number of men and women (N, %) at index date was reported. The list of prespecified indications/comorbidities was reported using the number of persons and percentage (N, %) with a record within the prespecified time windows. Body mass index was reported as average and as number of persons and percentage (N, %) among the body mass index categories described in 9.6.3.

The following time widows were included: most recent BMI value recorded during the five previous years from index date; and any time before index date for conditions.

10.8.8 Sensitivity analysis

“Concepts_id” are the unique numeric identifier representing a concept [i.e., condition, observation, drug, etc.] from the OMOP-CDM vocabulary. Overall monthly point prevalence estimates stratified for the different concepts_id (except ingredient concept_id) included in the GLP-1 RA drugs semaglutide, exenatide, liraglutide, lixisenatide and dulaglutide had been reported as sensitivity analysis to characterise the use of individual strengths.

An example of different concepts_id for semaglutide is presented in **Table 8**. Concepts with less than 30 counts were not run.

Table 8. Example of concepts_id for semaglutide that are not ingredient concept_id.

concepts_id	Ingredient name	Name
36809756	semaglutide	3 ML semaglutide 1.34 MG/ML Injectable Solution [Ozempic] by Novo Nordisk
36809755	semaglutide	3 ML semaglutide 1.34 MG/ML Injectable Solution
36809147	semaglutide	1.5 ML semaglutide 1.34 MG/ML Injectable Solution [Ozempic] by Novo Nordisk
36809148	semaglutide	1.5 ML semaglutide 1.34 MG/ML Injectable Solution

10.8.9 R packages

We used the R package "IncidencePrevalence" for the population-level estimation of drug utilisation. Additionally, we used the R package "DrugUtilization" for patient-level characterisation.

10.9 Evidence synthesis

Results from analyses described in Section 8.8 had been presented separately for each database and no meta-analysis of results were conducted.

11. DATA MANAGEMENT

All databases were mapped to the OMOP-CDM. This enabled the use of standardised analytics and tools across the network since the structure of the data and the terminology system was harmonised. The OMOP-CDM had been developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and had been described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org. The analytic code for this study was written in R. Each data partner executed the study code against their database containing patient-level data and then returned the results set which only contained aggregated data. The results from each of the contributing data sites had been combined in tables and figures for the study report.

12. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP-CDM were developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html).
In particular, it was expected that data partners had run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provided numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focused on checks that described the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality was solely focused on quantifying missingness, or the absence of data, while plausibility sought to determine the believability or truthfulness of data values. Each of these categories had one or more subcategories and were evaluated in two contexts: validation and verification. Validation related to how well data aligned with external

benchmarks with expectations derived from known true standards, while verification related to how well data conformed to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining drug cohorts, non-systemic products were excluded from the list of included codes summarised on the ingredient level. A pharmacist reviewed the codes of the antibiotics of interest. When defining cohorts for indications, a systematic search of possible codes for inclusion was conducted using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allowed the user to define a search strategy and using this could then query the vocabulary tables of the OMOP-CDM so as to find potentially relevant codes. In addition, the DrugExposureDiagnostics R package (https://github.com/darwin-eu/DrugExposureDiagnostics) was run to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error.

The study code was based on two R packages currently being developed to (1) estimate Incidence and Prevalence and (2) characterise drug utilisation using the OMOP-CDM. These packages included numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing.

The R package containing the study code is available via GitHub (https://github.com/darwin-eu-studies/P3-C1-008-GLP-1).

13. RESULTS

All results for each individual drug and database are available in the shiny app at: https://data-dev.darwin-eu.org/connect/#/apps/a6539a82-a63d-460b-ad93-c30d5200a1f7/access

The shiny contains seven tabs:

- Background: brief description of the study.
- Incidence user cohort attrition: attrition of the denominator cohorts used for the incidence rates estimates displayed as a table (Tidy table subtab) and as a flow-chart diagram (Diagram subtab).
- Prevalence user cohort attrition: attrition of the denominator cohorts used for the prevalence estimates displayed as a table (Tidy table subtab) and as a flow-chart diagram (Diagram subtab).
- Incidence: contains the population-level incidence estimates calculations displayed as a table (Raw table), plotting the incidence rates (Plot) and plotting the numerator of the incidence rates (a.k.a. number of new users of the GLP-1 RA drugs; Events Plot tab)
- Prevalence: contains the population-level prevalence estimates calculations displayed as a table (Raw table), plotting the prevalence values (Plot)
- Characteristics: contains the patient-level characteristics describing the characteristics of the individuals at the beginning of each episode of GLP-1 RA use.
- Dose: table containing the initial and cumulative dose information.
- Sensitivity Analysis - Prevalence: sensitivity analysis stratifying the point prevalence estimates by the different concepts_id to characterise the use of individual strengths.

13.1 Participants

Complete flow-charts showing the attrition of the different cohorts in each of the study databases and their respective plots were included in the study shiny app: https://data-dev.darwin-eu.org/connect/#/apps/a6539a82-a63d-460b-ad93-c30d5200a1f7/access

An example with the final overall number of individuals composing the denominator population (i.e., the column **number_subjects** in attrition tabs from the shiny app) for the incidence and prevalence analysis of semaglutide use is shown in **Table 9**.

Table 9. Number of individuals included in the denominator population for the analysis of semaglutide.

Number of individuals (n) included in the denominator cohort for:	CPRD	IQVIA LPD Belgium	IQVIA DA Germany	IPCI	SIDIAP
- Incidence analysis of semaglutide	8,313,613	701,300	15,563,713	2,173,288	7,257,323
- Prevalence analysis of semaglutide	9,201,228	1,094,027	32,818,734	2,440,366	7,513,825

13.2 Main Results

13.2.1 Population-level incidence calculations

Given that the methodology for calculating the observation period of patients in IQVIA LPD Belgium and IQVIA DA Germany was based on the last interaction of the patient with the healthcare system, these two databases presented an artefact at the end of the study period that overestimated the incidence and prevalence estimates, particularly in the last six months of observed data (*see "Database-specific limitations" in section 15.2 for further details*). Thus, we have reported the number of new users and specified whether the observed incidence trend over the last six months was corroborated by the number of new users when describing the IQVIA results.

Conversely, focusing on number of new users for CPRD results might be misleading, since the decrease of users was led by a migration of the overall CPRD population (impacting both, IR's numerators and denominators; *see "Database-specific limitations" in section 15.2 for further details*). Thus, CPRD results must be focused on the incidence estimates rather than the number of new users.

13.2.1.1 Overall incidence estimates

This section includes the incidence rates of the different GLP-1 RA medicines and of the other drugs medicines used for the treatment of diabetes and weight management with no stratification.

Use of GLP-1 RA

In the following section, the incidence (per 100,000 person-years) of all GLP-1 RA medicines have been analysed (**Figure 5**). In addition, the numerator of the incidence rates [IR], (i.e., the number of new users of all GLP-1 RA drugs) are displayed in **Figure 6**.

Overall, the incidence of dulaglutide use increased since 2016 in all databases. The increase observed in IPCI was less pronounced: IR values estimated did not exceed 40 per 100,000 person-years except for two months in 2022 (IR [95%CI] per 100,000 person-years in September: 120 [98 to 144], and October: 91 [73 to 113]) (**Figure 5**). When observing the number of new users, dulaglutide use was generally consistent after 2020 in IQVIA LPD Belgium, whilst number of new users in IQVIA Germany DA confirmed its increase in this population (**Figure 6)**.

Incidence of exenatide use declined over the study period in IQVIA DA Germany, CPRD and IQVIA LPD Belgium, and was not detected among IPCI (except for two months in 2014 with an IR [95%CI] per 100,000

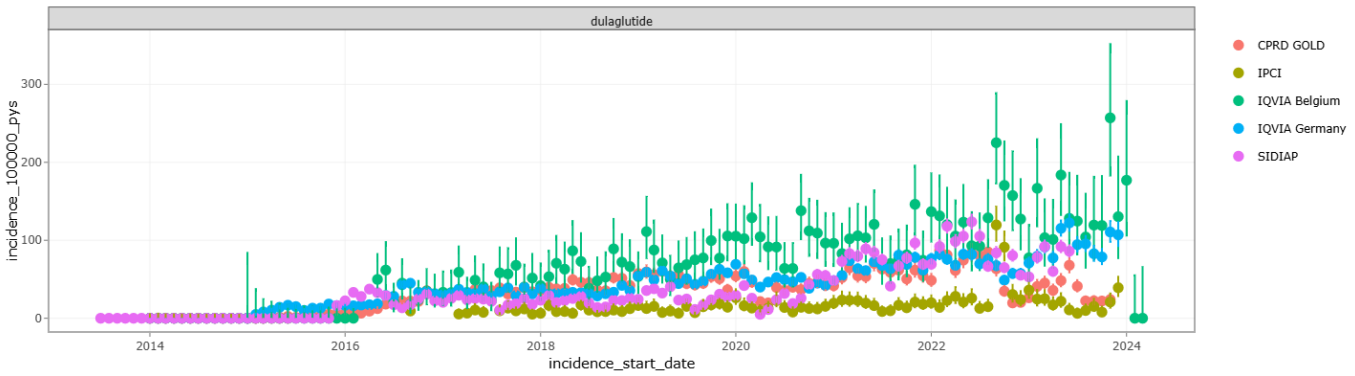
person-years of 8 [3 to 20] in March and 14 [7 to 27] in November). SIDIAP presented an initial increase in the incidence of exenatide use that peaked in October 2015 (IR [95%CI]: 20 [16 to 24] per 100,000 person-years), followed by a decrease until the last observed IR value in December 2022 of 1 [95%CI: 0.3 to 2] per 100,000 person-years. (**Figure 5**) When observing the number of new users, it presented the same trends (**Figure 6)**.

Incidence of liraglutide use in IQVIA DA Germany increased from 2014 and peaked in January 2020 (IR [95%CI]: 54[48 to 59] per 100,000 person-years) (**Figure 5**), followed by a decrease of new users (**Figure 6**). Incidence of liraglutide use in the other databases was stable, and even decreased in CPRD, until January 2022, where there was an increase in the incidence of liraglutide use in CPRD, IPCI, SIDIAP and IQVIA LPD Belgium databases. However, CPRD showed a marked drop in liraglutide use between June and July 2023 (IR [95%CI]: 73 [63 to 86] and 27 [21 to 35] per 100,000 person-years, respectively) (**Figure 5**). The number of new users showed increased IR in IQVIA LPD Belgium, albeit only in August-September 2022 (**Figure 6**).

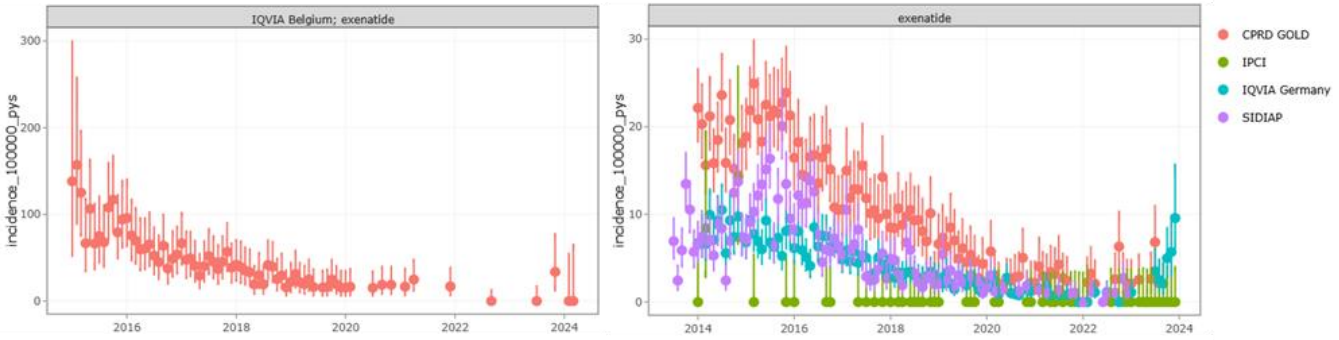
Incidence of lixisenatide use was low and observed only in CPRD (maximum IR [95%CI] per 100,000 person-years observed was 19 [15 to 23] in July 2014), IQVIA DA Germany (maximum IR: 5 [3 to 7]) and IQVIA LPD Belgium (maximum IR: 94 [43 to 179]), but decreased to <5 cases after 2020. (**Figure 5**, **Figure 6**).

Incidence (IR [95%CI] per 100,000 person-years) of semaglutide use started in 2018 in IPCI (IR: 15 [8 to 25]); in 2019 in CPRD (IR in March 2019: 22 [17 to 28]), SIDIAP (IR in May 2019: 3 [2 to 5]) and IQVIA LPD Belgium (IR in June 2019: 32 [15 to 59]); and in 2020 in IQVIA DA Germany (IR: 8 [6 to 11]). Rates of new use kept increasing in all databases, reaching a maximum IR of 330 [293 to 371] in November 2023 for IPCI, 133 [123 to 144] in June 2023 for SIDIAP, and 292 [270 to 316] in November 2023 for IQVIA DA Germany. The exceptions were IQVIA LPD Belgium and CPRD, which showed a decrease after July 2022 (IR in July was 672 [579 to 775] vs 417 [344 to 500] in August) and September 2022 (IR in September was 87 [76 to 100] vs 52 [44 to 62] in October), respectively. The number of new users in IQVIA LPD Belgium showed a second peak in semaglutide use in September 2023 (204 new users), followed by another decrease of new users later that year (e.g., 48 new users in December 2023). (**Figure 6**)

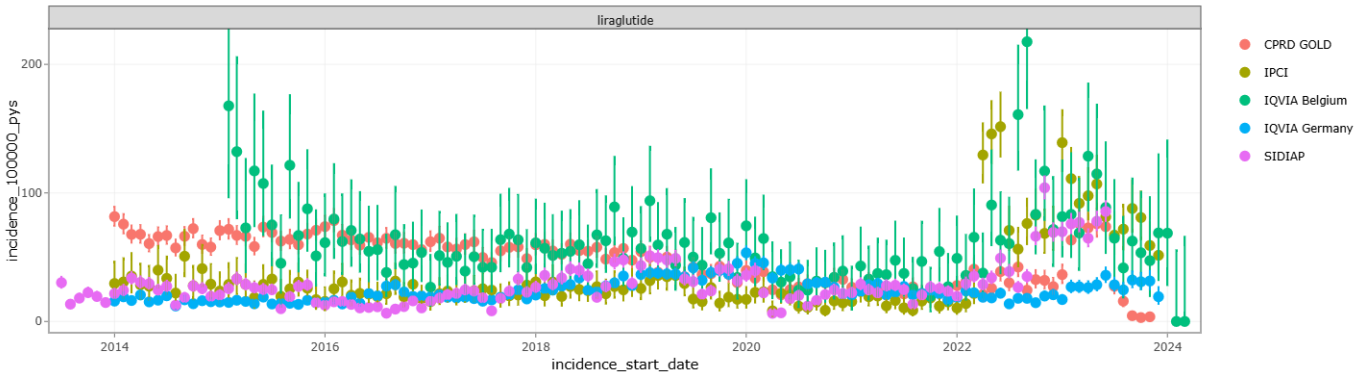
A) Dulaglutide



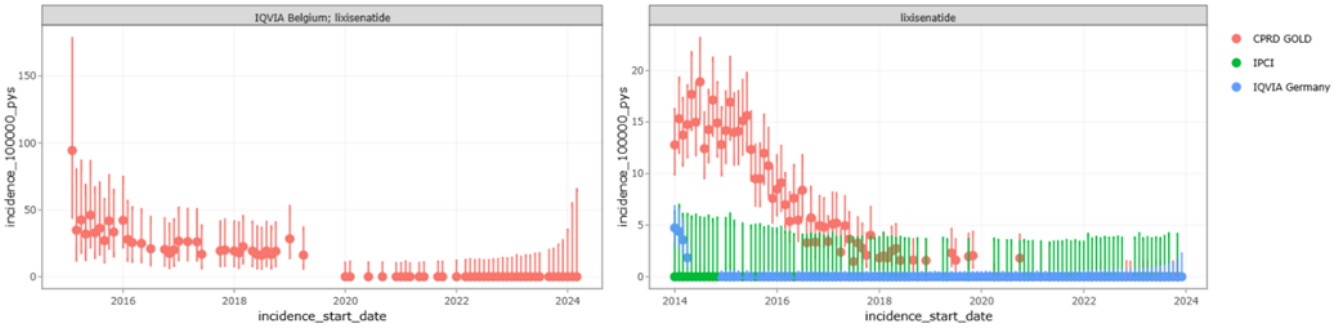
B) Exenatide (left for IQVIA LPD Belgium, right for the other databases)



C) Liraglutide



D) Lixisenatide (left for IQVIA LPD Belgium, right for the other databases)



E) Semaglutide (left for IQVIA LPD Belgium, right for the other databases)

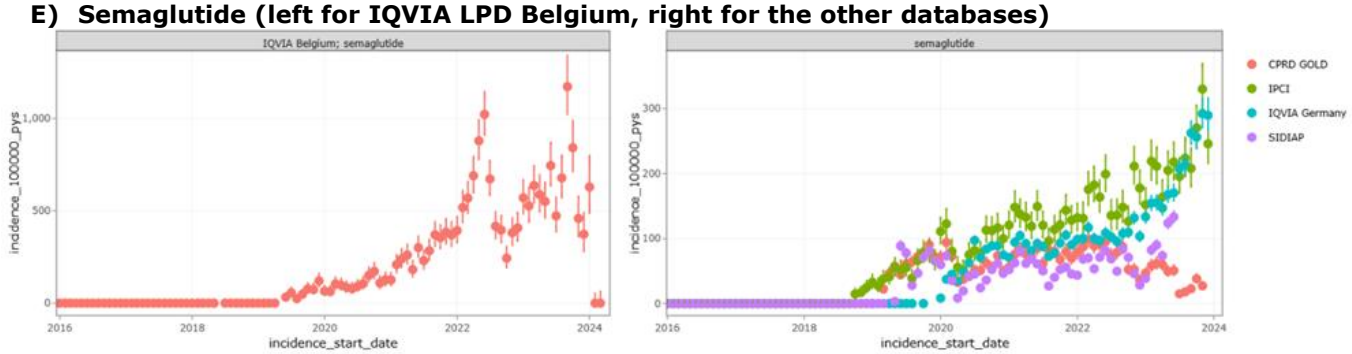
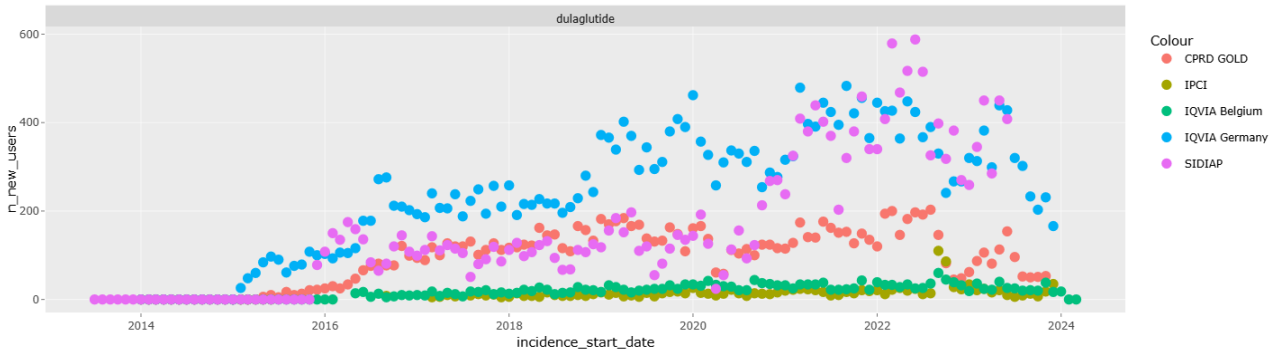
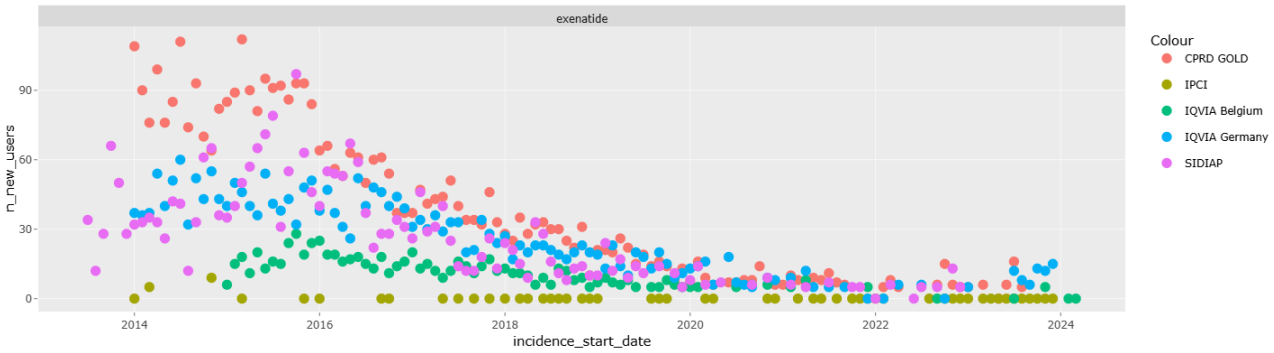


Figure 5. Incidence rates of use of the GLP-1 RA drugs [A) dulaglutide, B) exenatide, C) liraglutide, D) lixisenatide and E) semaglutide] per 100,000 person-years in the overall population (i.e., any age and sex) for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels. Last six months in IQVIA databases might contain artefacts that artificially increased their incidence rates, please see the "Number of new users" plots for evaluating the drug use in IQVIA databases during the last 6-month period.

A) Dulaglutide

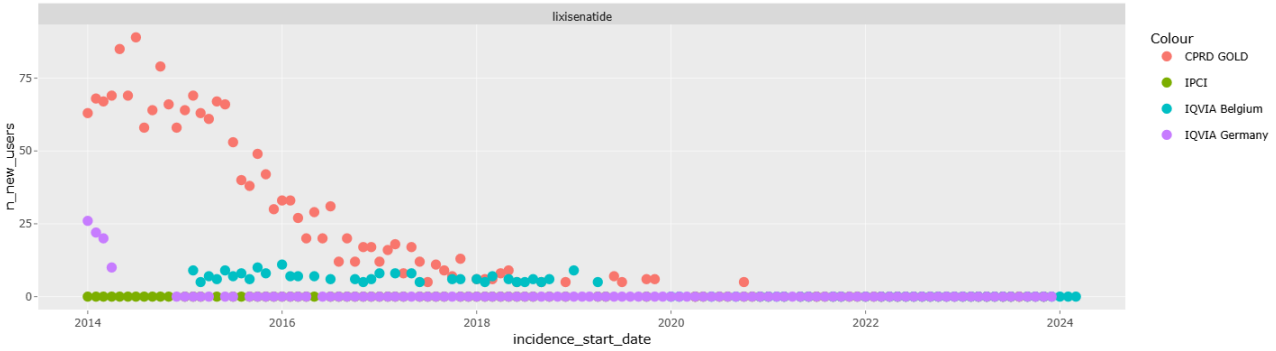


B) Exenatide



C) Liraglutide

D) Lixisenatide



E) Semaglutide

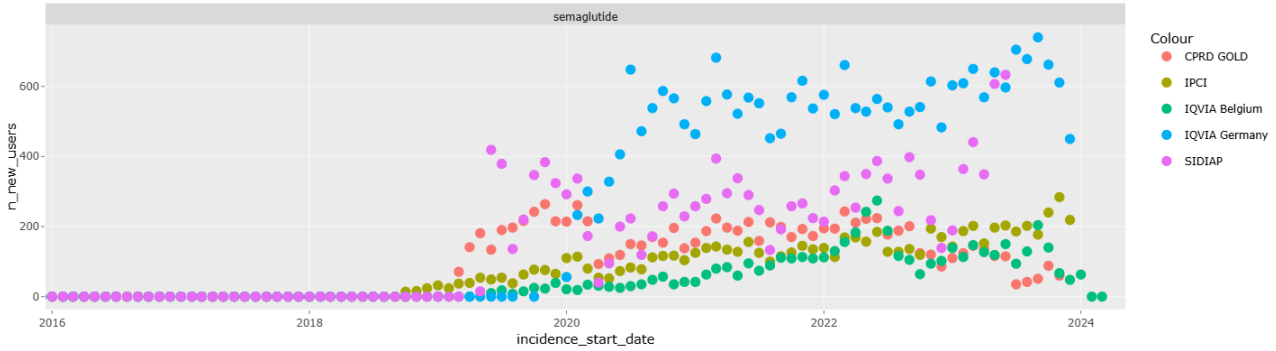


Figure 6. Number of new users (n_new_users) of the GLP-1 RA drugs [A) dulaglutide, B) exenatide, C) liraglutide, D) lixisenatide and E) semaglutide] in the overall population (i.e., any age and sex) for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels. Migration of CPRD population prevent the interpretation of number of new users in this database, please see the "Incidence rates of use of the GLP-1 RA" plots for evaluating CPRD (*see further details in section 15.2*).

Use of other drugs medicines used for the treatment of diabetes and weight management

We did not observe any incidence of phentermine use, alone or combined with topiramate, in any of the databases of the study.

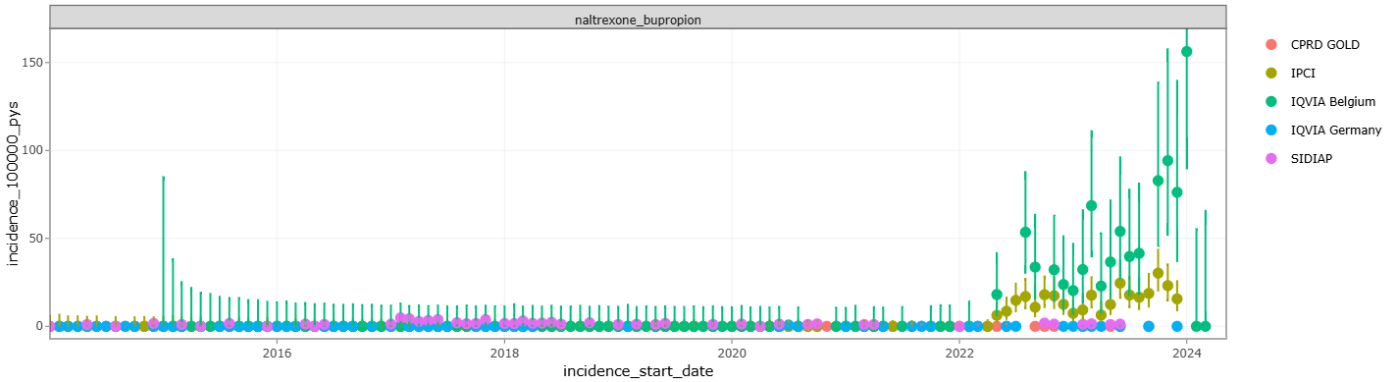
Incidence of naltrexone/bupropion use was observed only after May 2022 in IPCI and IQVIA LPD Belgium, peaking in October 2023 (IR [95%CI]: 30 [20 to 44] per 100,000 person-years) and January 2024 (IR [95%CI]: 156 [89 to 254] per 100,000 person-years), respectively; whilst SIDIAP started presenting an

incidence of 1 [95%CI: 0.3 to 2.3] in May 2014 that peaked in February 2017 (IR [95%CI]: 5 [3 to 7]), followed by a decrease (**Figure 7**).

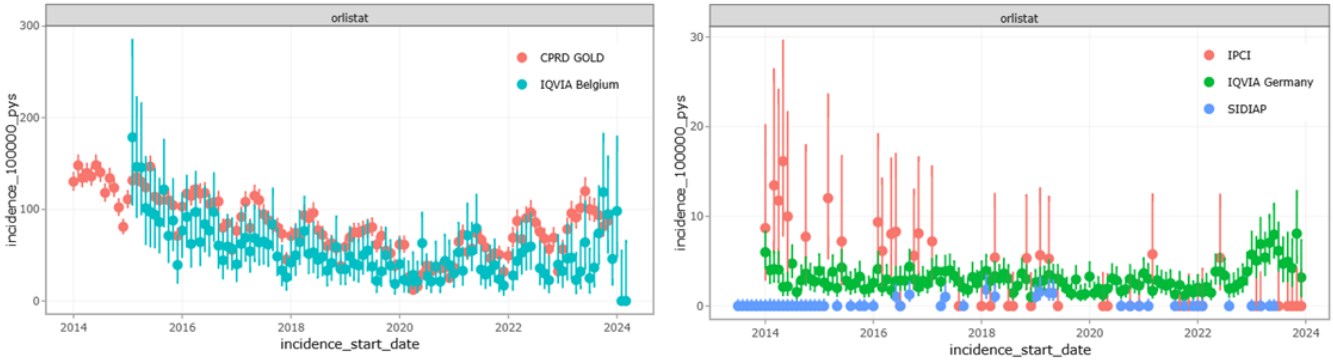
Incidence (IR [95%CI] per 100,000 person-years) of orlistat use was greater in IQVIA LPD Belgium (ranged between 17 [5 to 39] in December 2021 to 179 [104 to 286] in February 2015) and CPRD (ranged between 12 [8 to 17] in May 2020 and 148 [137 to 160] in June 2014). CPRD displayed a seasonality pattern with drops in incidence of orlistat use in December and peaks before or around summer. Conversely, this drug was not used or minimally used in SIDIAP (IR values below 1.8 [0.8 to 4]), IQVIA DA Germany (ranged between 1 [0.4 to 2] in December 2018 to 8 [5 to 13] in November 2023) and IPCI (largest value in May 2014 (16 [8 to 30] followed by a decrease with IR values remaining <6 after February 2017) (**Figure 7**).

Incidence of metformin use was stable over time, with the exceptions of IPCI, which IR[95%CI] decreased from 890 [815 to 970] to 388 [348 to 433], and IQVIA DA Germany that presented a peak in September 2016 (IR[95%CI]: 729 [708 to 751] per 100,000 person-years) and a smaller peak in January 2020 (IR[95%CI]: 590 [571 to 608] per 100,000 person-years) (**Figure 7**). Despite the fact that incidence of metformin use in both IQVIA databases seems to increase after 2022, the number of new users remained stable for Belgium and decreased for Germany (**Figure 8**).

A) Naltrexone/bupropion



B) Orlistat (left for CPRD and IQVIA LPD Belgium, right for the other databases)



C) Metformin (left for IQVIA LPD Belgium, right for the other databases)

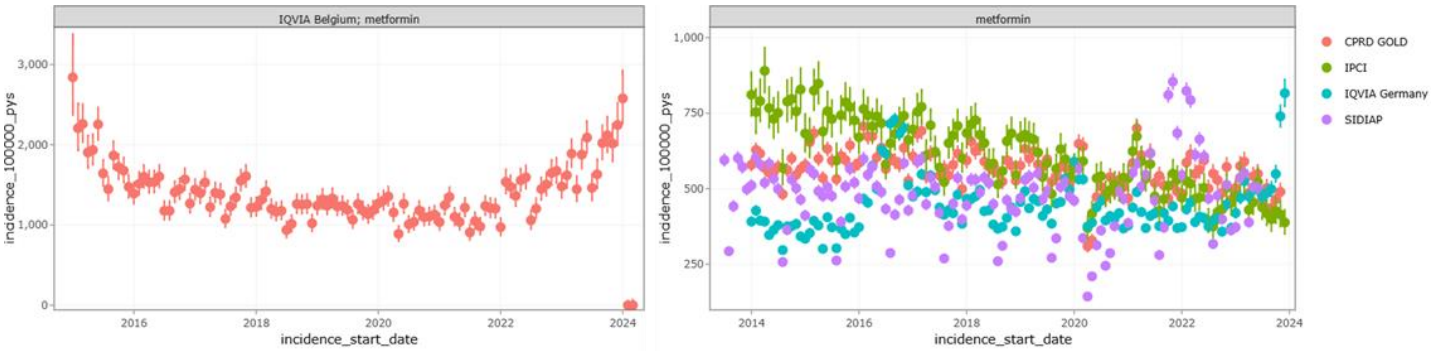
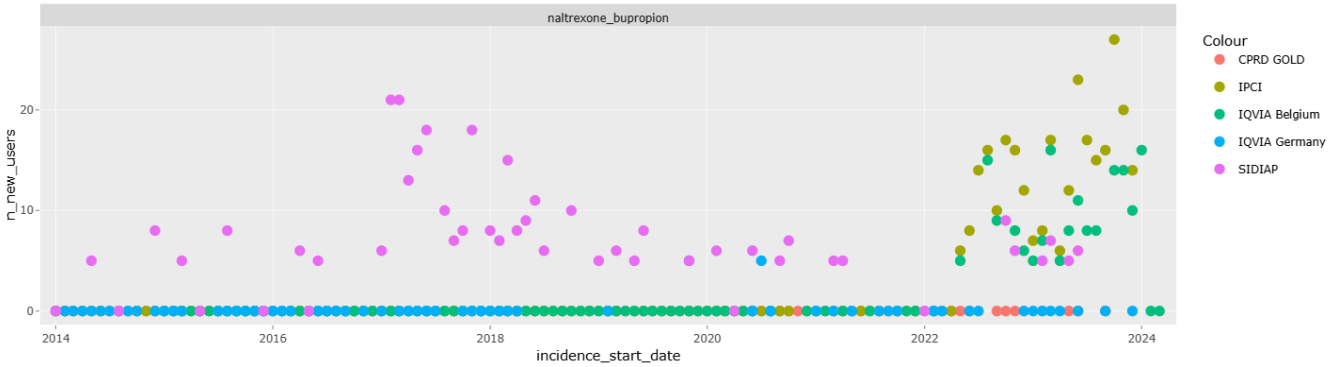
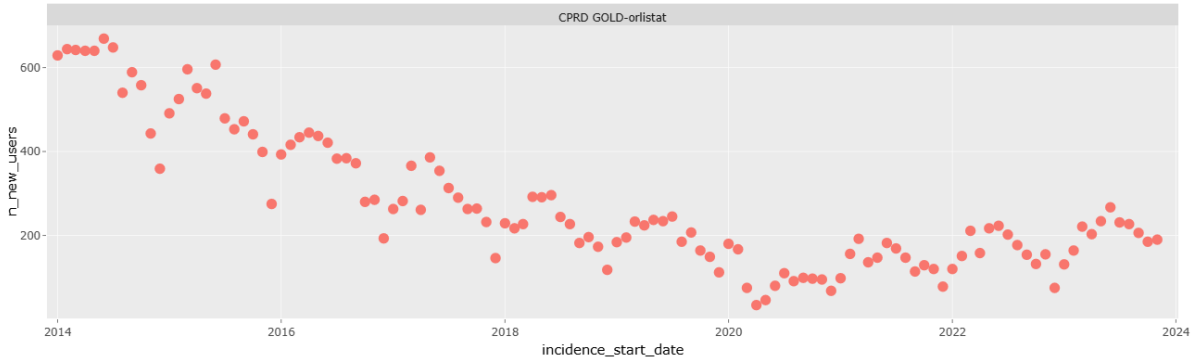


Figure 7. Incidence rates of use of other medicines used for the treatment of diabetes and weight management [A) naltrexone/bupropion and orlistat, B) orlistat and C) metformin] per 100,000 person-years in the overall population (i.e., any age and sex) for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Phentermine and phentermine/topiramate use was not observed, and therefore not included in the plots. Scale of Y axis varies across the panels. Last six months in IQVIA databases might contain artefacts that artificially increased their incidence rates, please see the "Number of new users" plots for evaluating the drug use in IQVIA databases during the last 6-month period.

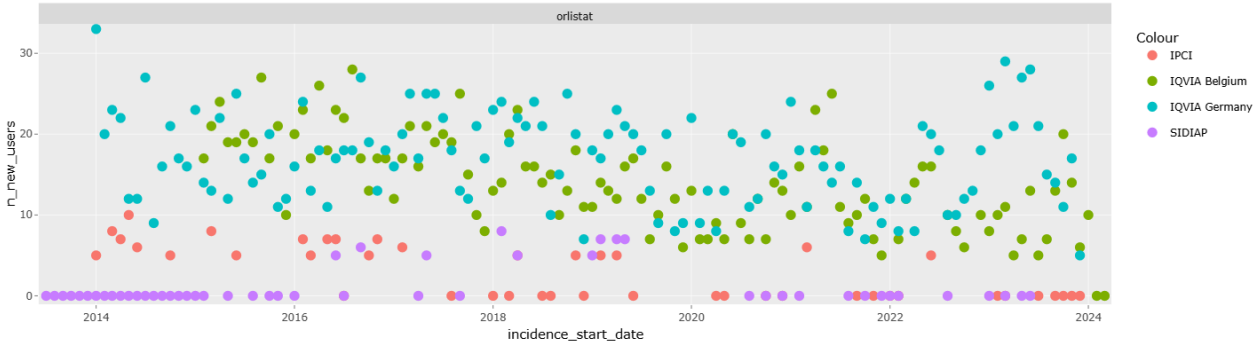
A) Naltrexone/bupropion



B) Orlistat in CPRD



C) Orlistat in ICPI, IQVIA LPD Belgium, IQVIA DA Germany, and SIDIAP



D) Metformin (left for IPCI and IQVIA LPD Belgium, right for the other databases)

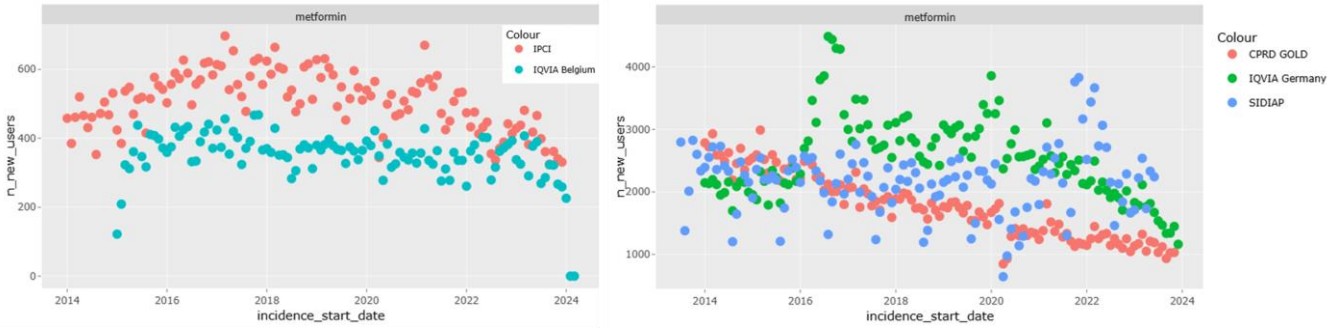


Figure 8. Number of new users (n_new_users) of the other medicines used for the treatment of diabetes and weight management [A) orlistat, naltrexone/bupropion B) in CPRD and C) in the other databases, and D) metformin] in the overall population (i.e., any age and sex) for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. New users of phentermine and phentermine/topiramate were not observed, therefore their plots were not included. Scale of Y axis varies across the panels. Migration of CPRD population prevent the interpretation of number of new users in this database, please see the "Incidence rates of use of the GLP-1 RA" plots for evaluating CPRD (*see further details in section 15.2*).

13.2.1.2 Incidence of GLP-1 RA initiation stratified by indication

All GLP-1 RA users were stratified in one of the 4 indication cohorts: DM2, obesity, DM2 with obesity, or other indications (excluding DM2 and obesity) as detailed in *section 10.6.3*. **Figure 9-Figure** 13 report the incidence of GLP-1 RA use stratified by DM2, obesity and DM2 with obesity indications, expressed as IR [95%CI] per 100,000 person-years:

Incidence (IR[95%CI per 100,000 person-years]) of dulaglutide use was higher in those individuals with an indication for DM2 with obesity in CPRD (maximum IR of 72 [62 to 84] in June 2022), IQVIA DA Germany (maximum IR of 77[68 to 87] in June 2023), IPCI (maximum IR of 99 [80 to 122] in September 2022) and SIDIAP (maximum IR of 117 [107 to 127] in June 2022); whilst it was higher in those with an indication solely for DM2 in IQVIA LPD Belgium (maximum IR of 111 [71 to 165] in February 2023).

Similarly, when used, incidence of exenatide and lixisenatide use were higher among those individuals with an indication for DM2 with obesity in CPRD, SIDIAP (for exenatide), and IQVIA DA Germany: and with an indication for DM2 in IQVIA LPD Belgium. Their correspondent maximum IR values [95%CI per 100,000 person-years] were the following:

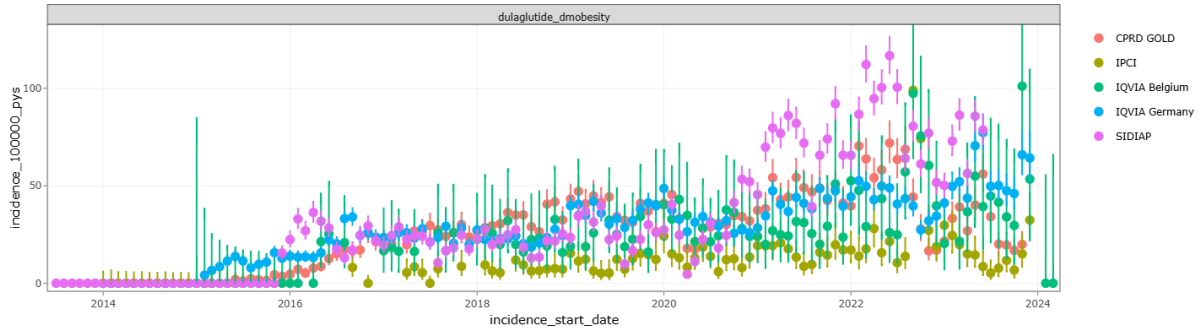
- 20 [16 to 25] in March 2015 for exenatide and 15 [12 to 19] in October 2014 lixisenatide in CPRD (indication for DM2 with obesity)

- 19 [16 to 24] in October 2015 for exenatide in SIDIAP (indication for DM2 with obesity)
- 8 [4 to 14] in December 2023 for exenatide and 4 [2 to 6] in February 2014 for lixisenatide in IQVIA DA Germany (indication for DM2 with obesity)
- 94 [43 to 179] in February 2015 for exenatide and 32 [11 to 70] in May 2015 for lixisenatide in IQVIA LPD Belgium (indication for DM2)

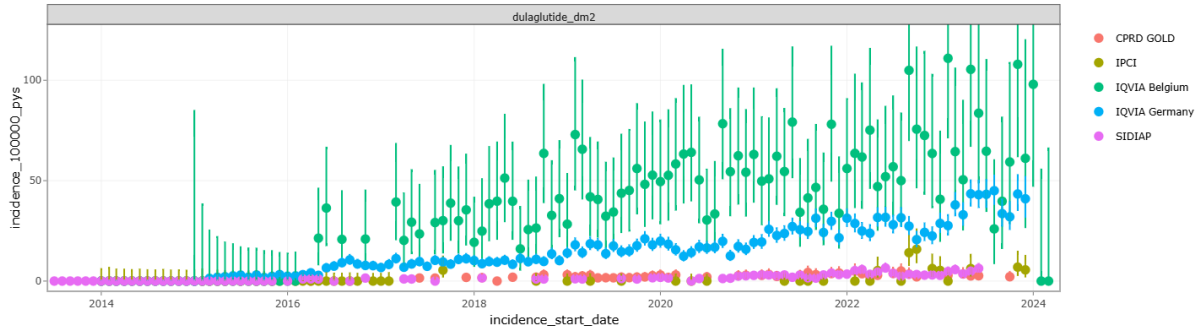
Incidence of liraglutide and semaglutide use were higher among those individuals with an indication for DM2 with obesity in all databases and the maximum values (IR [95%CI] per 100,000 person-years) ranged from 40 [36 to 45] to 154 [110 to 208] for liraglutide use (January 2020 in IQVIA DA Germany, and September 2022 in IQVIA LPD Belgium, respectively); and from 79 [68 to 91] to 720 [600 to 857] for semaglutide use (March 2022 in CPRD, and September 2023 in IQVIA LPD Belgium, respectively).

The same trends were observed when observing the number of new users (**Figure 14-Figure** 18).

A) Dulaglutide in patients with diabetes mellitus type 2 and obesity



B) Dulaglutide in patients with diabetes mellitus type 2

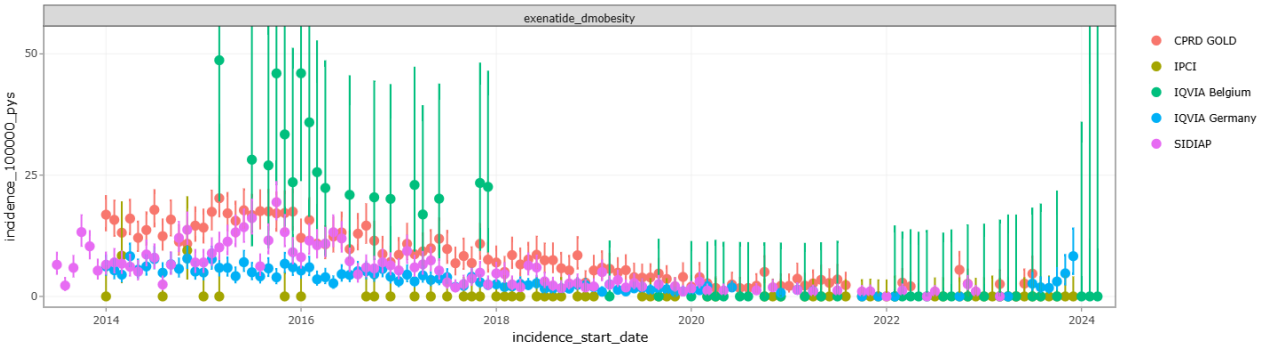


C) Dulaglutide in patients with obesity

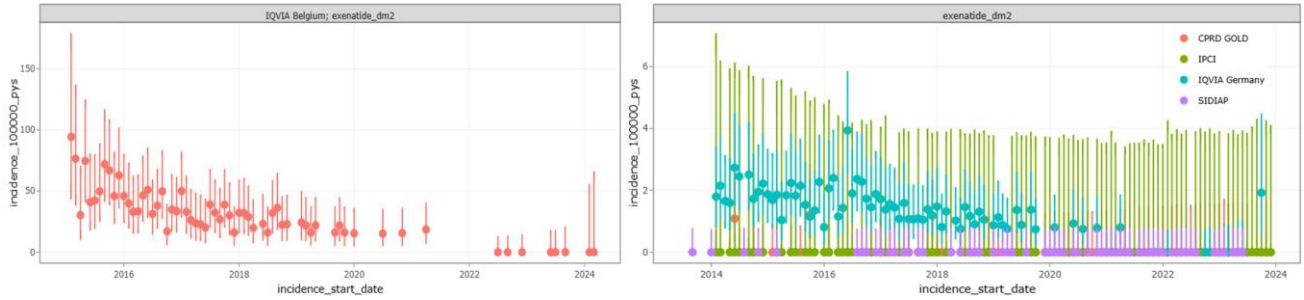
Figure 9. Incidence rates of use of the GLP-1 RA drugs [A) dulaglutide, B) exenatide, C) liraglutide, D) lixisenatide and E) semaglutide] per 100,000 person-years stratified by indications [i.e., in

patients with A) dmobesity for diabetes mellitus type 2 and obesity, B) DM2 for diabetes mellitus type 2, and C) obesity] for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels. Last six months in IQVIA databases might contain artefacts that artificially increased their incidence rates, please see the "Number of new users" plots for evaluating the drug use in IQVIA databases during the last 6-month period.

A) Exenatide in patients with diabetes mellitus type 2 and obesity



B) Exenatide in patients with diabetes mellitus type 2



C) Exenatide in patients with obesity

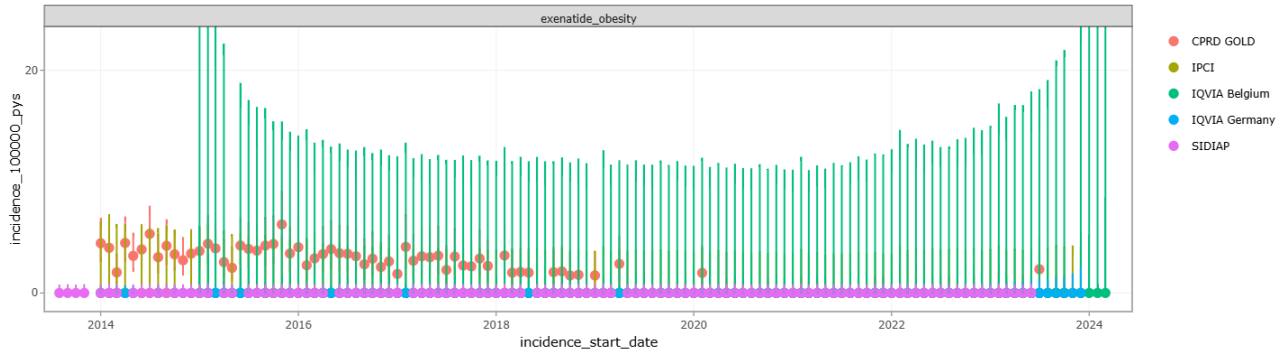
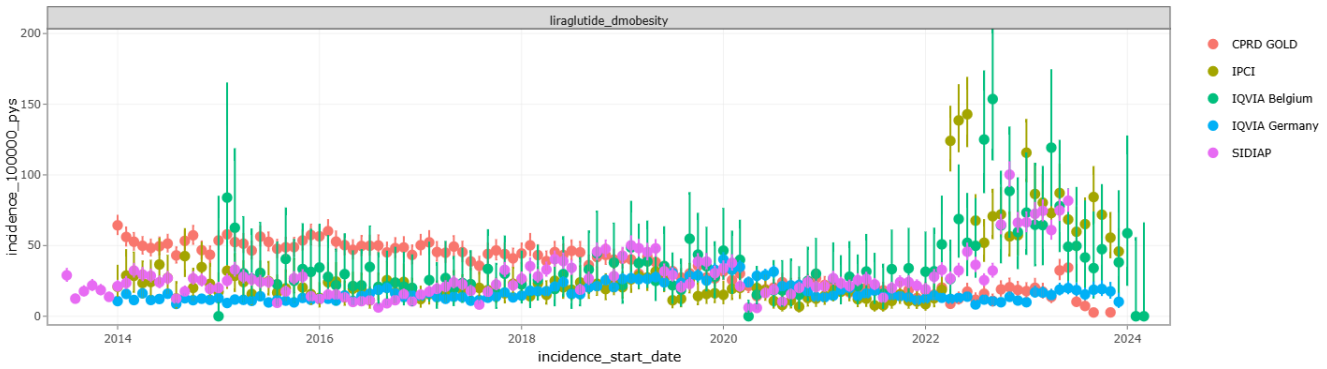
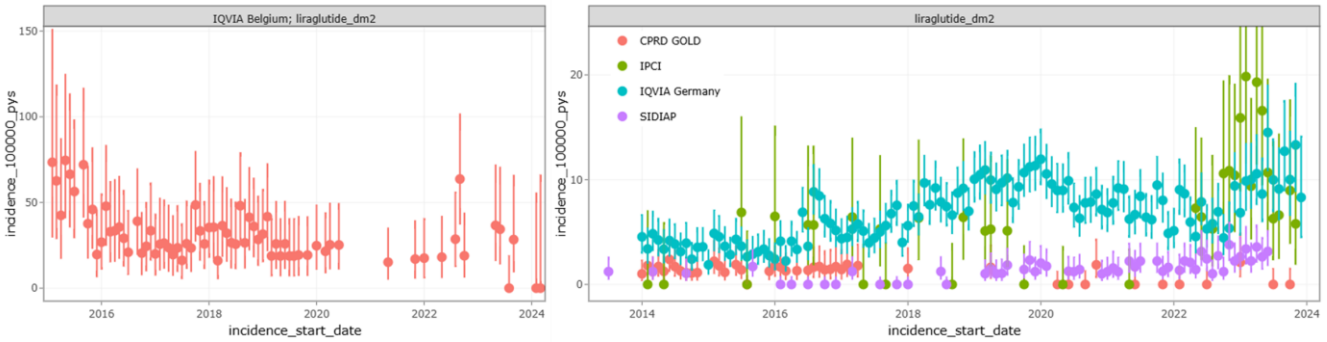


Figure 10. Incidence rates of use of exenatide per 100,000 person-years stratified by indications [i.e., in patients with A) dmobesity for diabetes mellitus type 2 and obesity, B) DM2 for diabetes mellitus type 2, and C) obesity] for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels. Last six months in IQVIA databases might contain artefacts that artificially increased their incidence rates, please see the "Number of new users" plots for evaluating the drug use in IQVIA databases during the last 6-month period.

A) Liraglutide in patients with diabetes mellitus type 2 and obesity



B) Liraglutide in patients with diabetes mellitus type 2



C) Liraglutide in patients with obesity

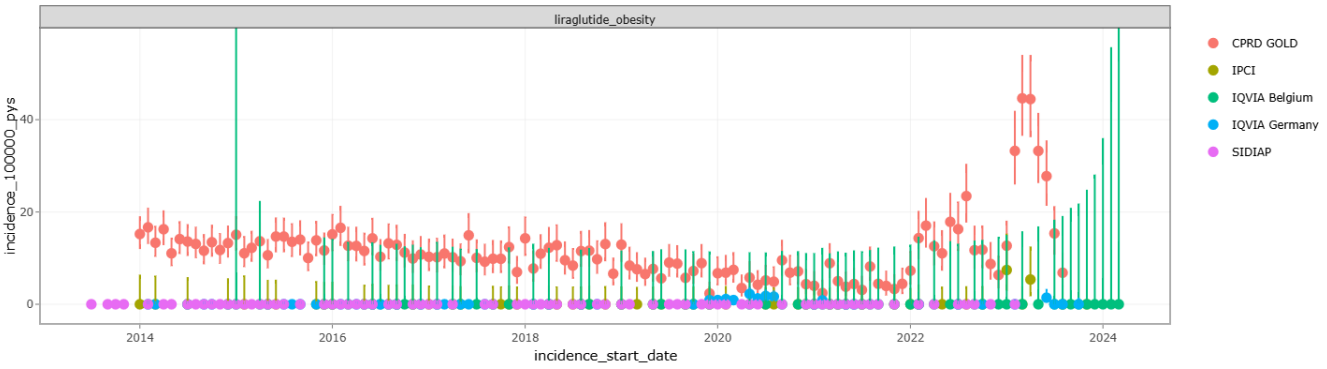


Figure 11. Incidence rates of use of liraglutide per 100,000 person-years stratified by indications [i.e., in patients with A) dmobesity for diabetes mellitus type 2 and obesity, B) DM2 for diabetes mellitus type 2, and C) obesity] for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels. Last six months in IQVIA databases might contain artefacts that artificially increased their incidence rates, please see the "Number of new users" plots for evaluating the drug use in IQVIA databases during the last 6-month period.

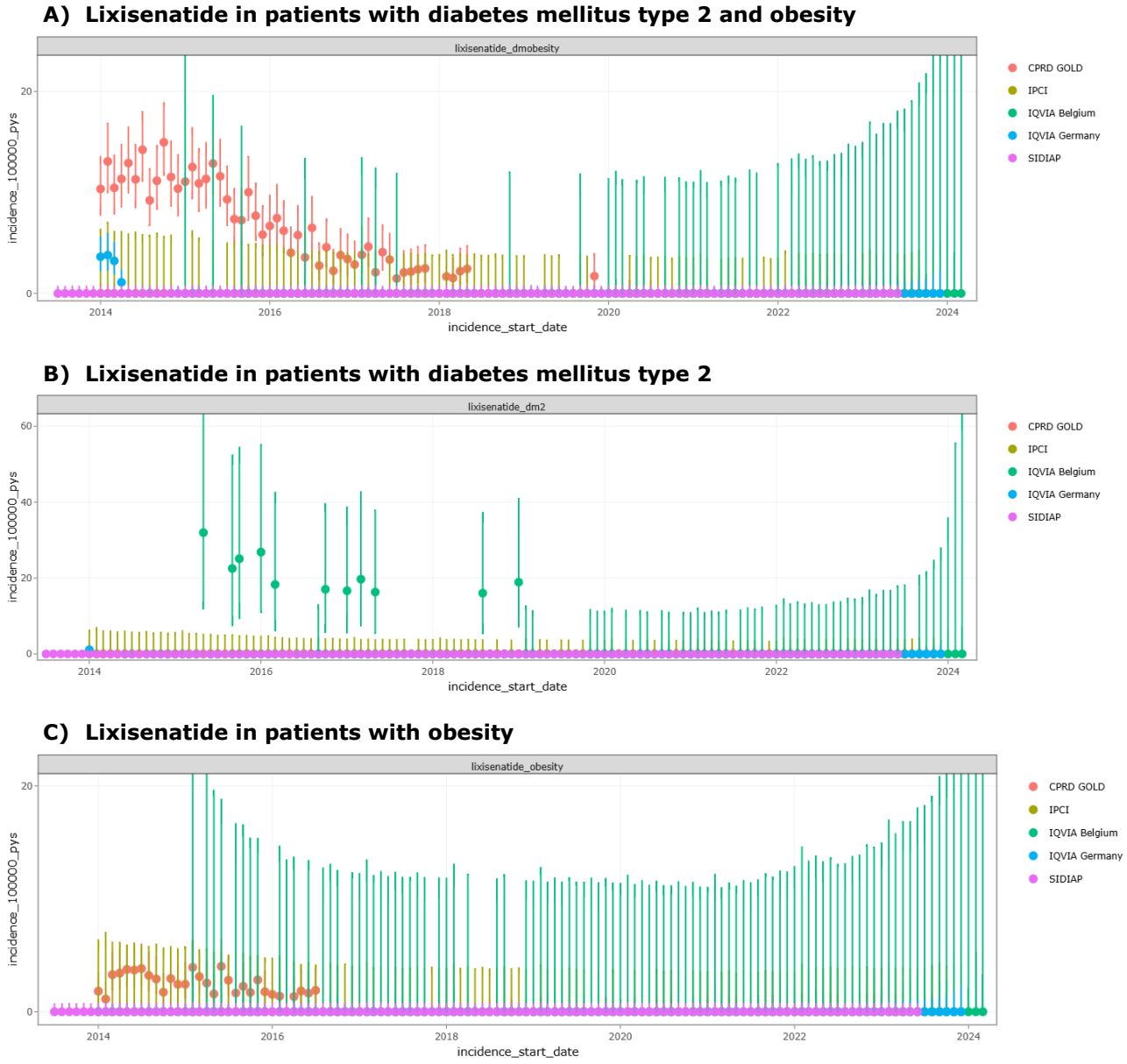
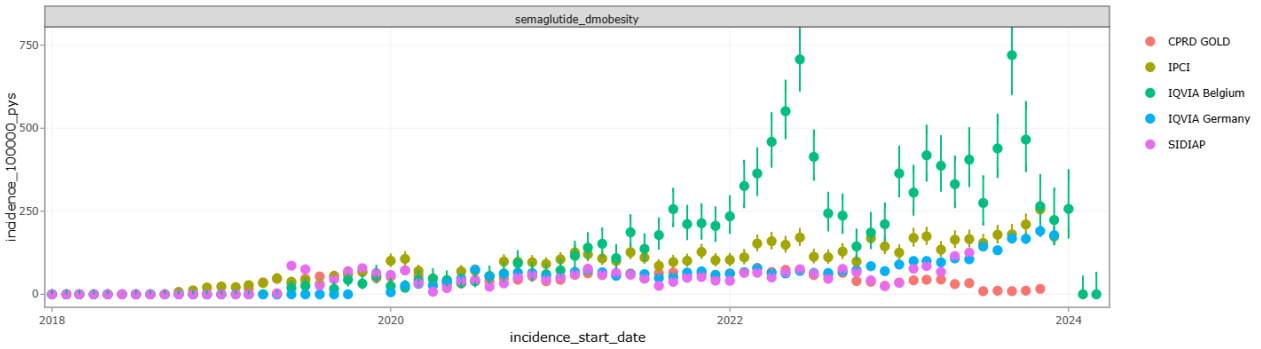
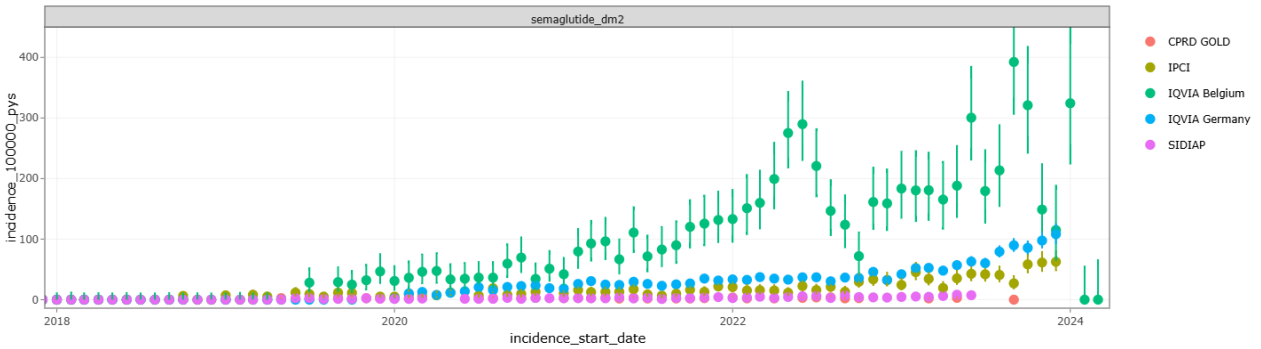


Figure 12. Incidence rates of use of lixisenatide per 100,000 person-years stratified by indications [i.e., in patients with A) dmobesity for diabetes mellitus type 2 and obesity, B) DM2 for diabetes mellitus type 2, and C) obesity] for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels. Last six months in IQVIA databases might contain artefacts that artificially increased their incidence rates, please see the "Number of new users" plots for evaluating the drug use in IQVIA databases during the last 6-month period.

A) Semaglutide in patients with diabetes mellitus type 2 and obesity



B) Semaglutide in patients with diabetes mellitus type 2



C) Semaglutide in patients with obesity

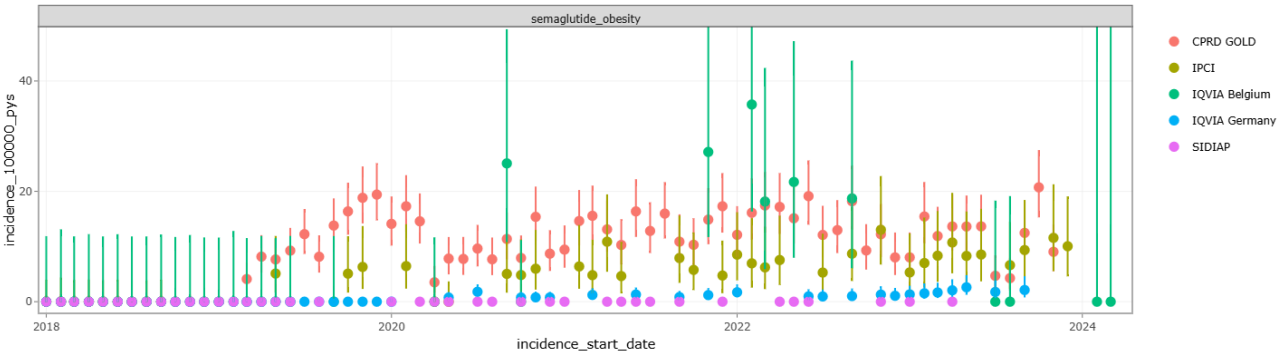
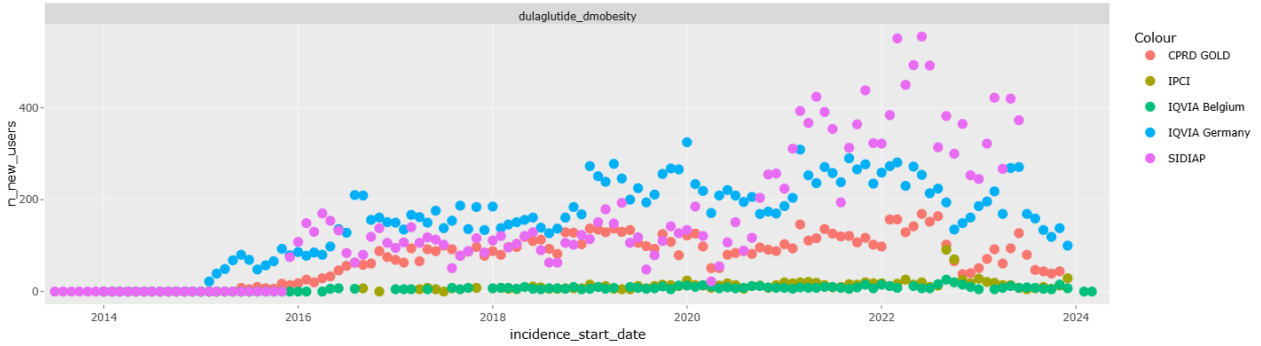
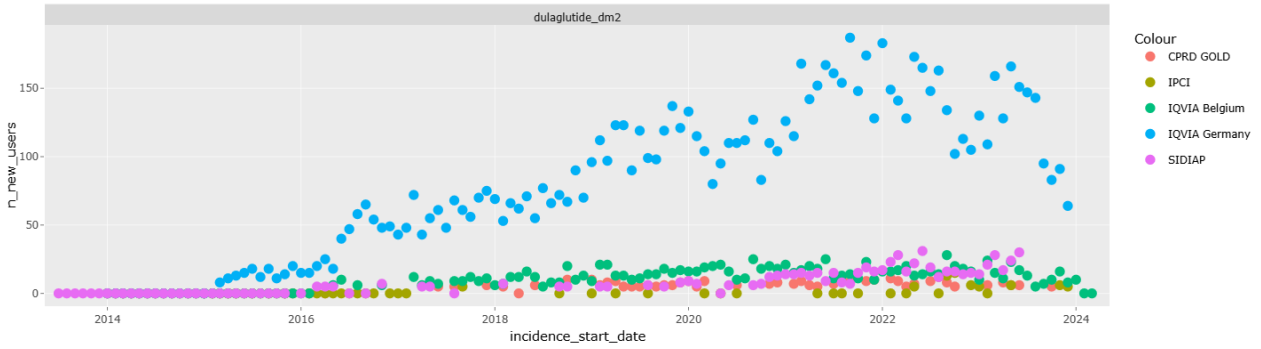


Figure 13. Incidence rates of use of semaglutide per 100,000 person-years stratified by indications [i.e., in patients with A) dmobesity for diabetes mellitus type 2 and obesity, B) DM2 for diabetes mellitus type 2, and C) obesity] for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels. Last six months in IQVIA databases might contain artefacts that artificially increased their incidence rates, please see the "Number of new users" plots for evaluating the drug use in IQVIA databases during the last 6-month period.

A) Dulaglutide in patients with diabetes mellitus type 2 and obesity



B) Dulaglutide in patients with diabetes mellitus type 2



C) Dulaglutide in patients with obesity

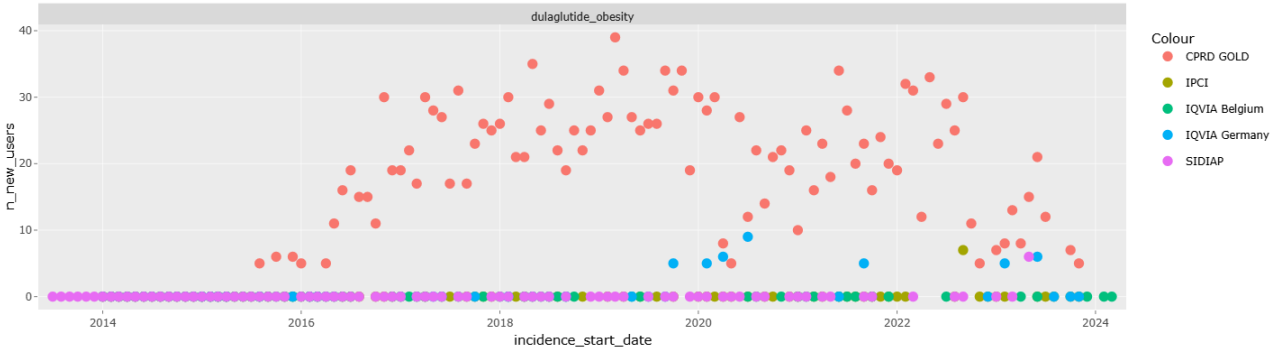
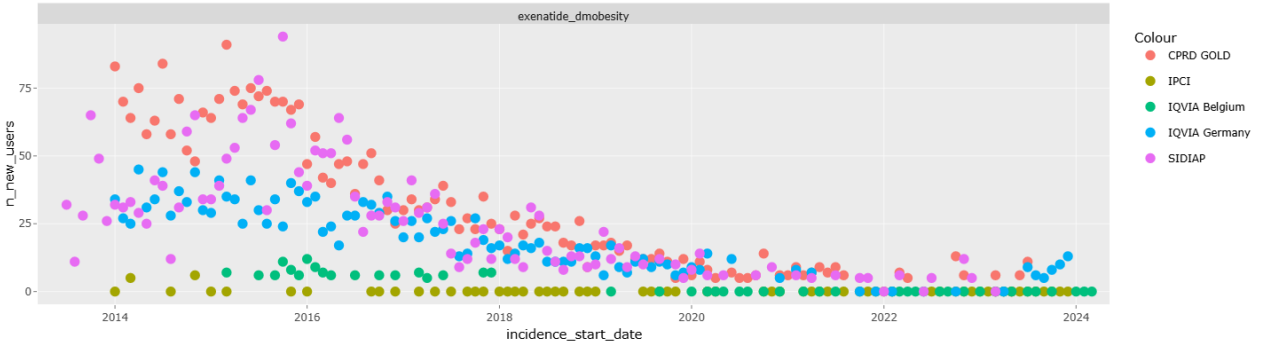
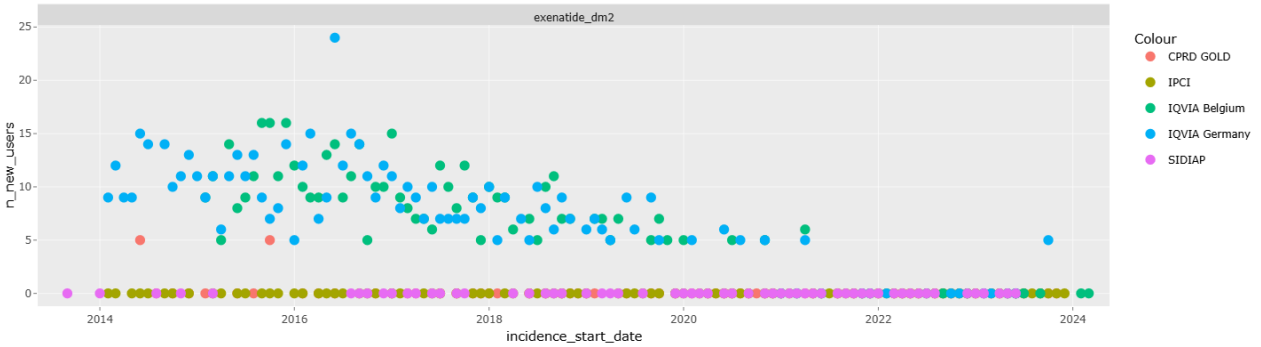


Figure 14. Number of new users (n_new_users) of dulaglutide stratified by indications [i.e., in patients with A) dmobesity for diabetes mellitus type 2 and obesity, B) DM2 for diabetes mellitus type 2, and C) obesity] for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels. Migration of CPRD population prevent the interpretation of number of new users in this database, please see the "Incidence rates of use of the GLP-1 RA" plots for evaluating CPRD (*see further details in section 15.2*).

A) Exenatide in patients with diabetes mellitus type 2 and obesity



B) Exenatide in patients with diabetes mellitus type 2



C) Exenatide in patients with obesity

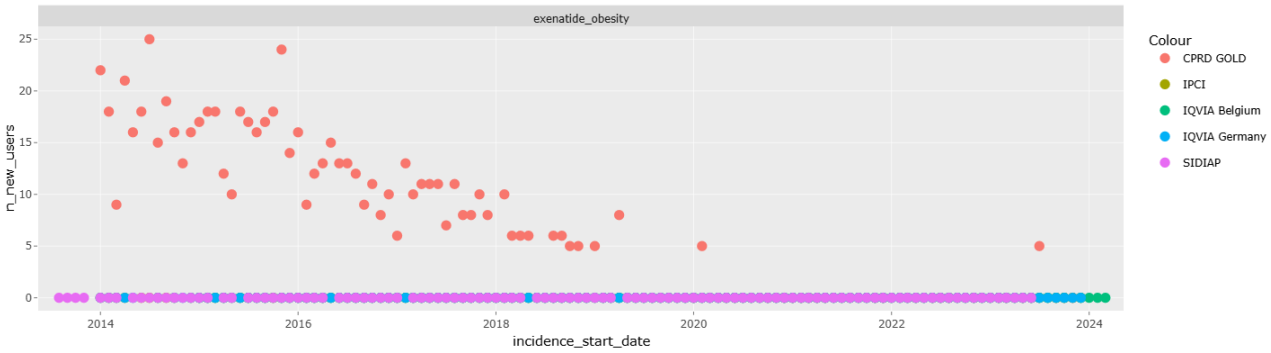
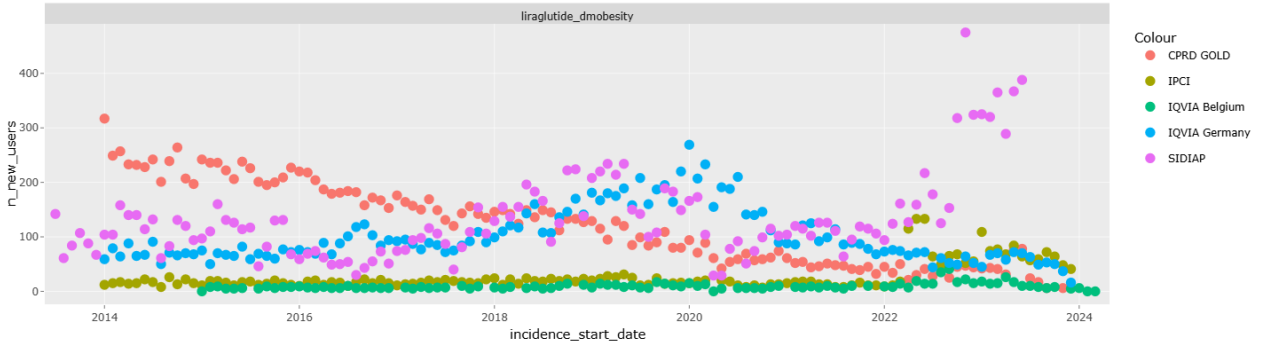
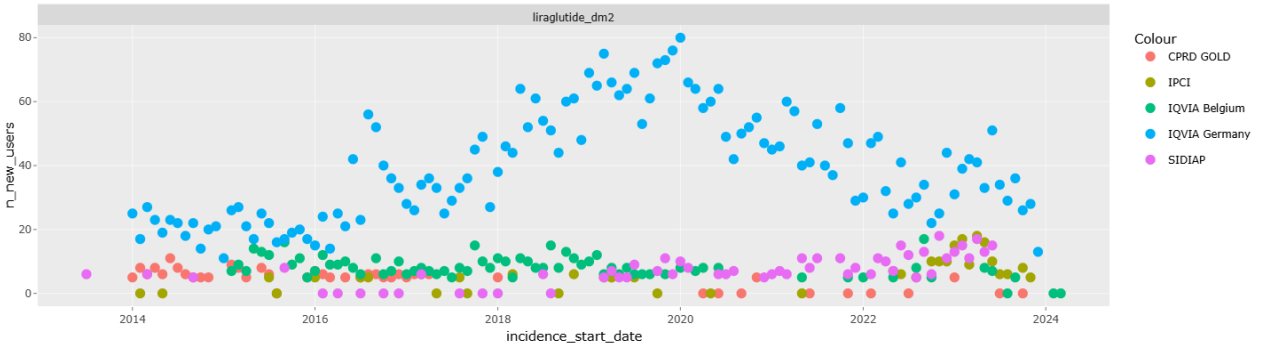


Figure 15. Number of new users (n_new_users) of exenatide stratified by indications [i.e., in patients with A) dmobesity for diabetes mellitus type 2 and obesity, B) DM2 for diabetes mellitus type 2, and C) obesity] for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels. Migration of CPRD population prevent the interpretation of number of new users in this database, please see the "Incidence rates of use of the GLP-1 RA" plots for evaluating CPRD (*see further details in section 15.2*).

A) Liraglutide in patients with diabetes mellitus type 2 and obesity



B) Liraglutide in patients with diabetes mellitus type 2



C) Liraglutide in patients with obesity

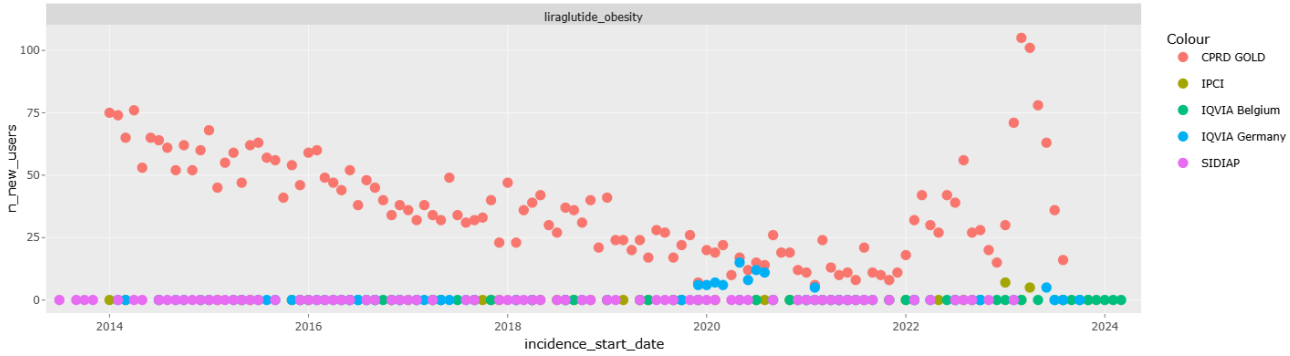


Figure 16. Number of new users (n_new_users) of liraglutide stratified by indications [i.e., in patients with A) dmobesity for diabetes mellitus type 2 and obesity, B) DM2 for diabetes mellitus type 2, and C) obesity] for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels. Migration of CPRD population prevent the interpretation of number of new users in this database, please see the "Incidence rates of use of the GLP-1 RA" plots for evaluating CPRD (*see further details in section 15.2*).

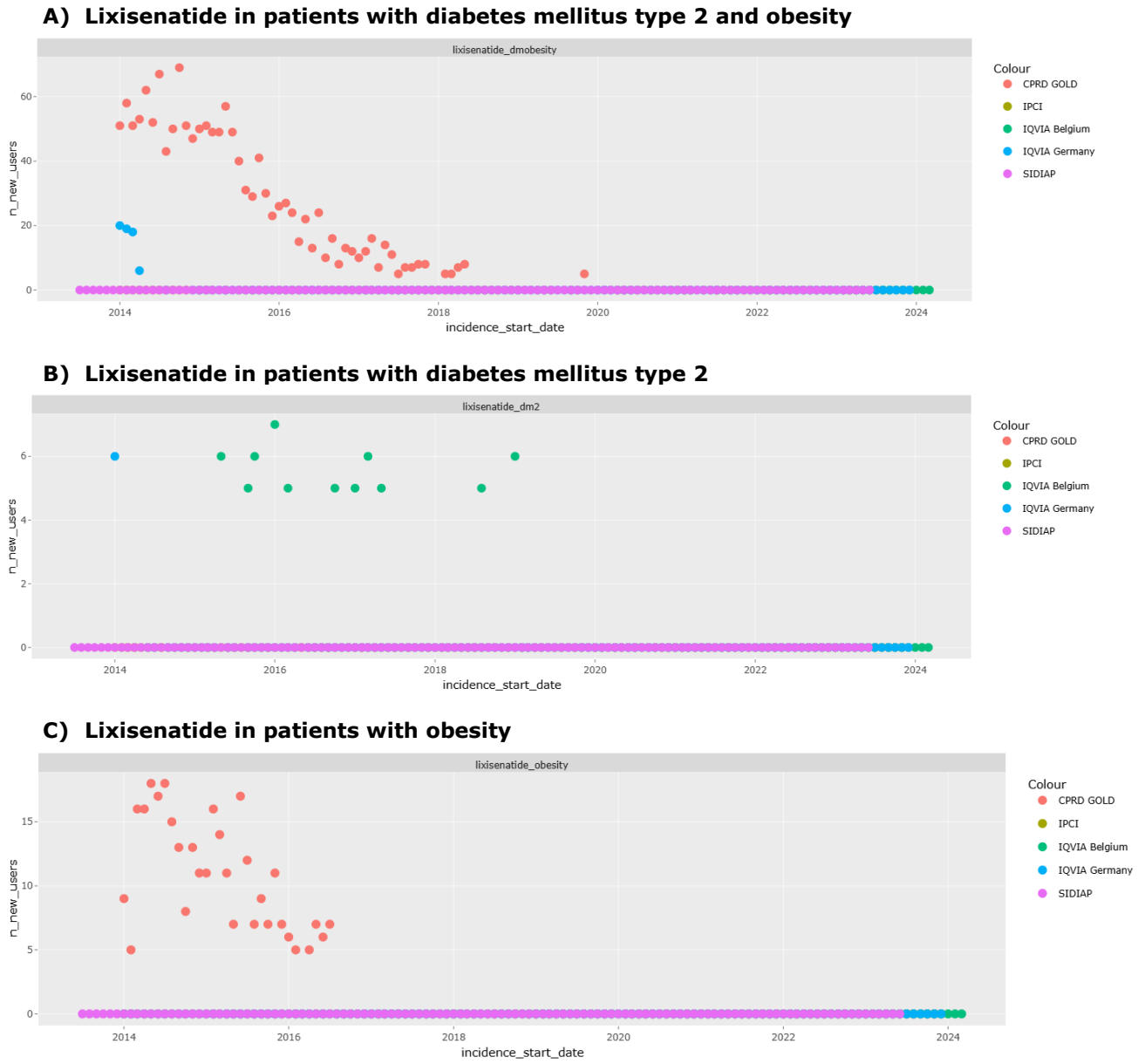
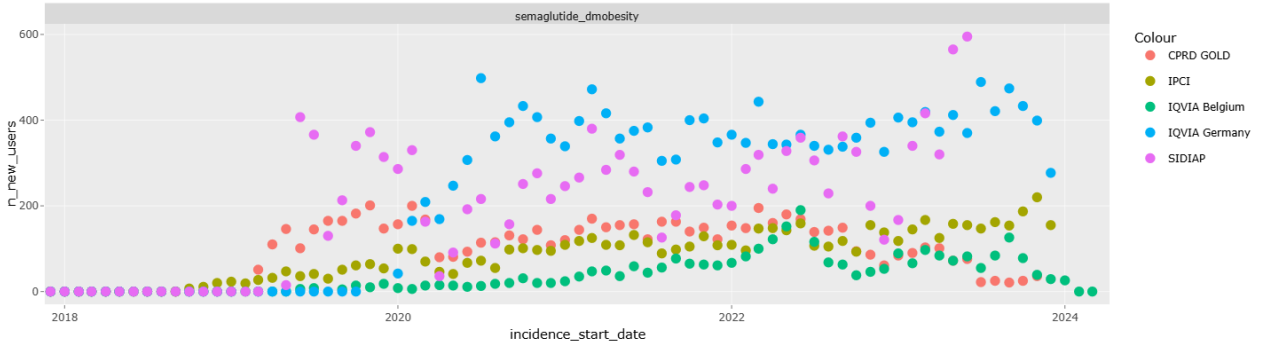
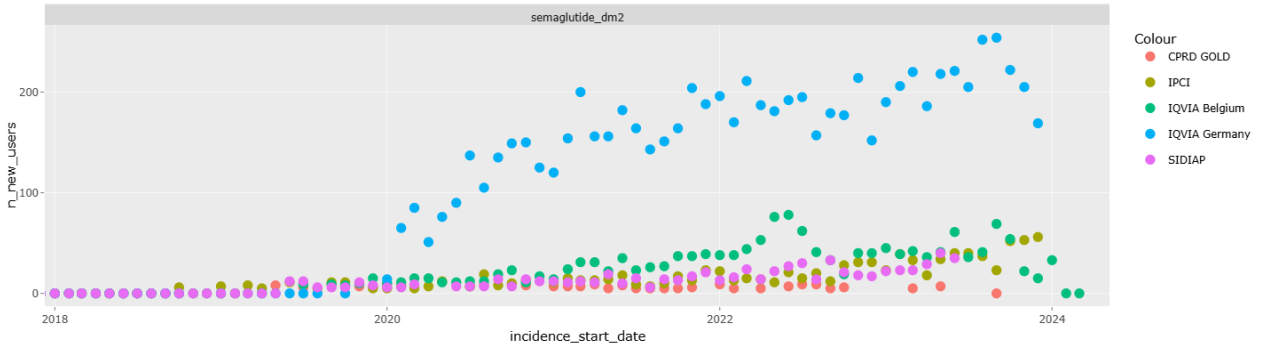


Figure 17. Number of new users (n_new_users) of lixisenatide stratified by indications [i.e., in patients with A) dmobesity for diabetes mellitus type 2 and obesity, B) DM2 for diabetes mellitus type 2, and C) obesity] for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels. Migration of CPRD population prevent the interpretation of number of new users in this database, please see the "Incidence rates of use of the GLP-1 RA" plots for evaluating CPRD (*see further details in section 15.2*).

A) Semaglutide in patients with diabetes mellitus type 2 and obesity



B) Semaglutide in patients with diabetes mellitus type 2



C) Semaglutide in patients with obesity

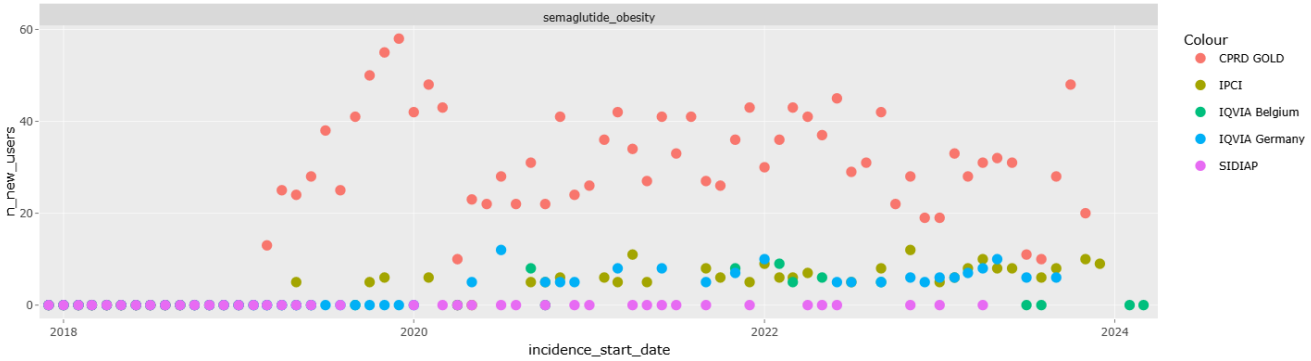
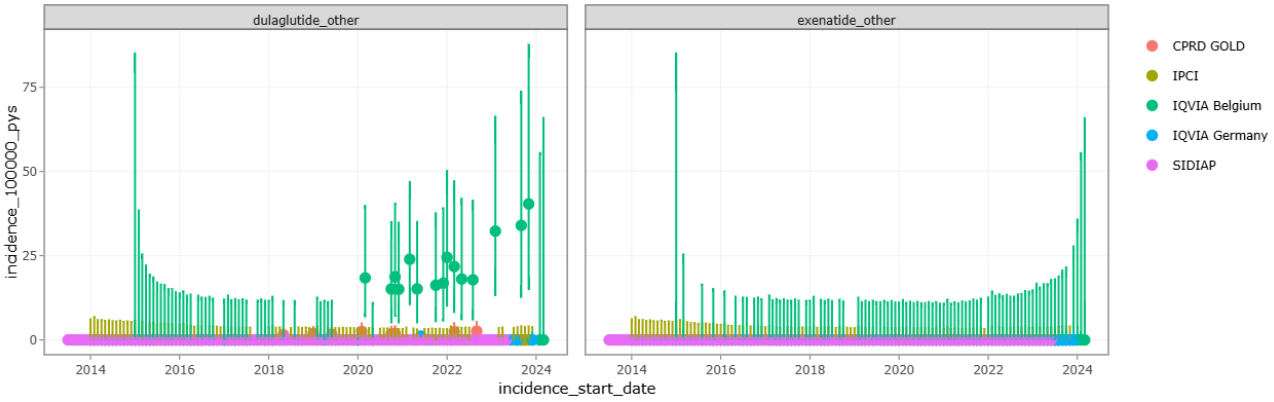


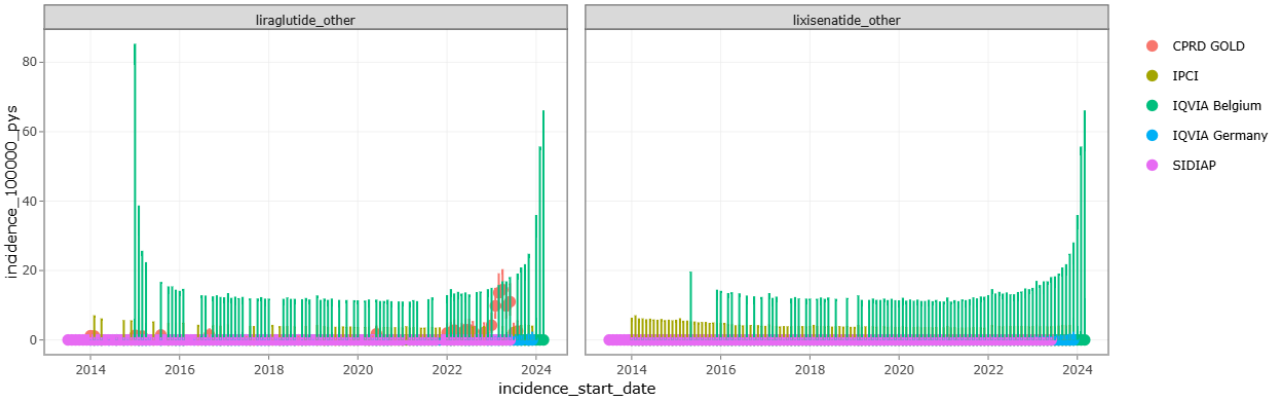
Figure 18. Number of new users (n_new_users) of semaglutide stratified by indications [e.g., in patients with A) dmobesity for diabetes mellitus type 2, B) DM2 for diabetes mellitus type 2, and C) obesity] for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels. Migration of CPRD population prevent the interpretation of number of new users in this database, please see the "Incidence rates of use of the GLP-1 RA" plots for evaluating CPRD (*see further details in section 15.2*).

Incidence of GLP-1 RA use in the other cohorts (i.e., no indication for DM2 nor for obesity) was low, with the exception of dulaglutide and semaglutide for IQVIA LPD Belgium, and liraglutide in CPRD (**Figure 19**). However, number of new users per month in IQVIA LPD Belgium were lower than 8 as shown in **Figure 20**. In CPRD, the maximum IR observed in liraglutide use was 15 [95%CI: 10 to 20] per 100,000 person-years in May 2023 (**Figure 19**).

A) Other indications in dulaglutide (left) and exenatide (right)



B) Other indications in liraglutide (left) and lixisenatide (right)



C) Other indications in semaglutide

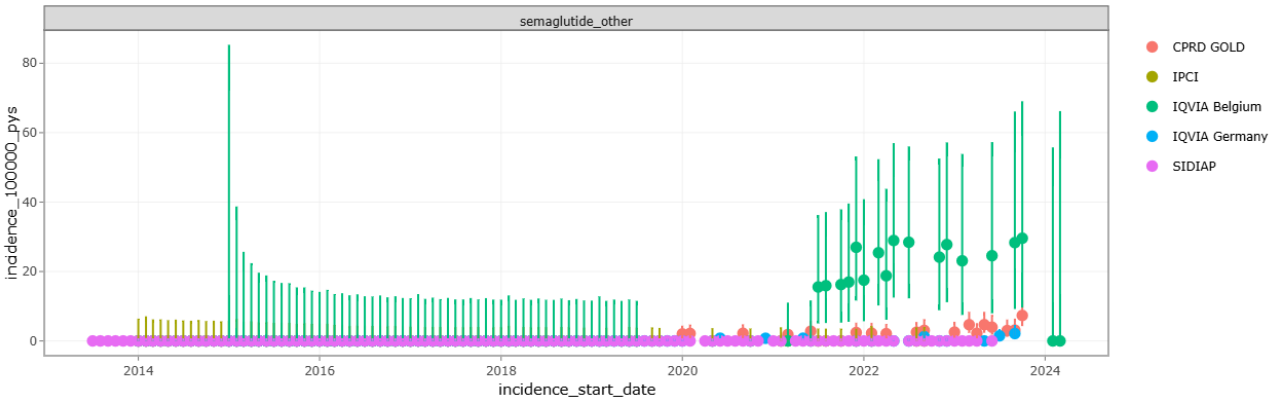


Figure 19. Incidence rates of use of the GLP-1 RA drugs [dulaglutide, exenatide, liraglutide, lixisenatide and semaglutide] per 100,000 person-years stratified by other indications [i.e., no obesity nor diabetes mellitus type 2] in each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels. Last six months in IQVIA databases might contain artefacts that artificially increased their incidence rates, please see the "Number of new users" plots for evaluating the drug use in IQVIA databases during the last 6-month period.

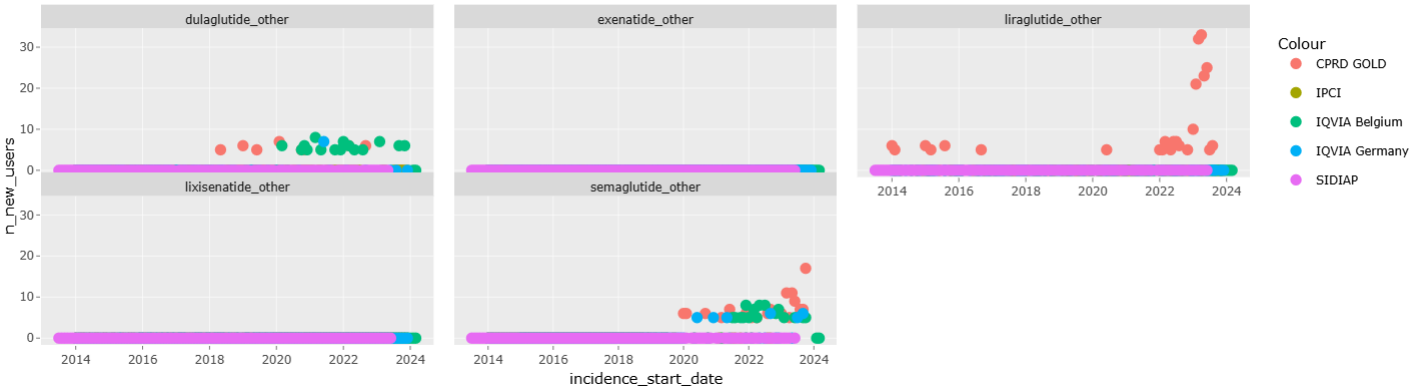


Figure 20. Number of new users (n_new_users) of the GLP-1 RA drugs [dulaglutide, exenatide, liraglutide, lixisenatide and semaglutide stratified by other indications [i.e., no obesity nor diabetes mellitus type 2] in each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Migration of CPRD population prevent the interpretation of number of new users in this database, please see the "Incidence rates of use of the GLP-1 RA" plots for evaluating CPRD (*see further details in section 15.2*).

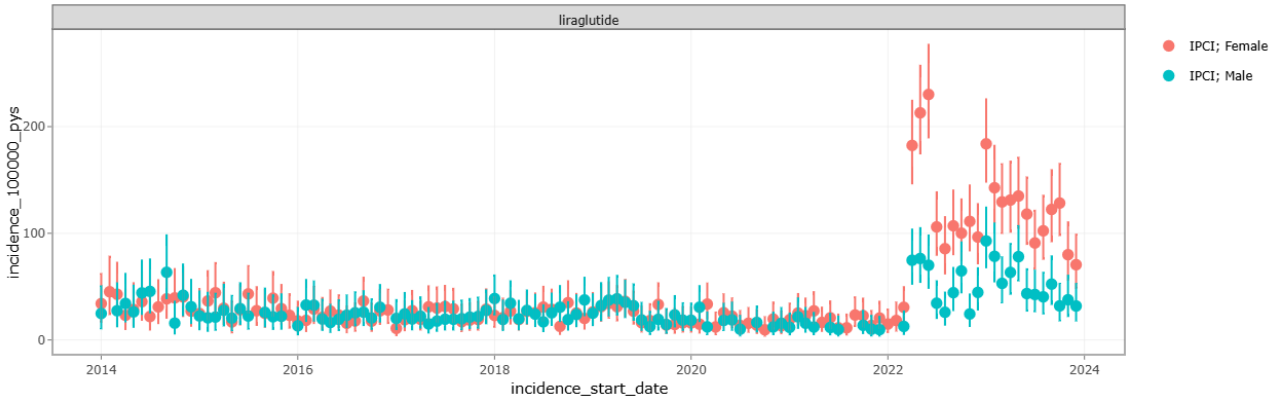
13.2.1.3 Incidence estimates stratified by age and sex

This section focuses on reporting variations in the incidence observed among different age groups and sex. When differences were not detected, they were not reported. Full results including all the age and sex stratifications are available in the shiny app [*Incidence tab – use the Denominator age group and sex sub-tabs to select them*].

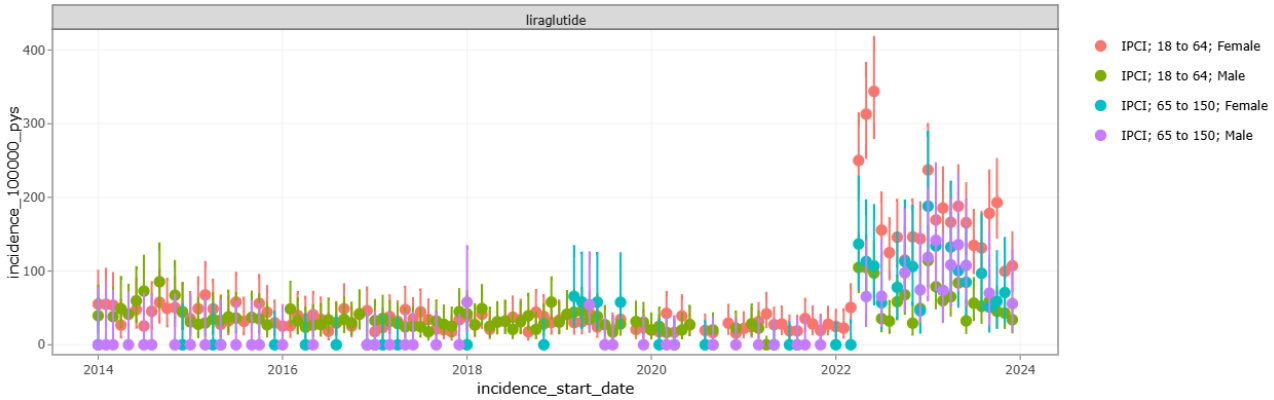
Incident use among individuals <18 years of age was only detected for metformin, liraglutide in SIDIAP after February 2023 (IR between 6.4 to 7.8 per 100,000 person-years), and orlistat in CPRD before 2016 (IR <7.9 per 100,000 person-years). [*Figures not shown, please see them in the shiny app: Incidence tab – use 0 to 17 age group in the Denominator age group sub-tab and select the cohorts of interest in the Outcome cohort name sub-tab*].

Women in ICPI had higher incidence of liraglutide use than men after 2022. Age and sex strata emphasise the three peaks from May-June 2022 are led by women aged between 18-64 years. Similar peaks regarding incidence use of liraglutide among women could be observed between August-September 2022 in IQVIA LPD Belgium (**Figure 21**). Conversely, incidence of dulaglutide and semaglutide use were higher in men than women in IQVIA DA Germany (**Figure 22**).

A) IPCI stratified by sex



B) IPCI stratified by age and sex



C) IQVIA LPD Belgium stratified by sex

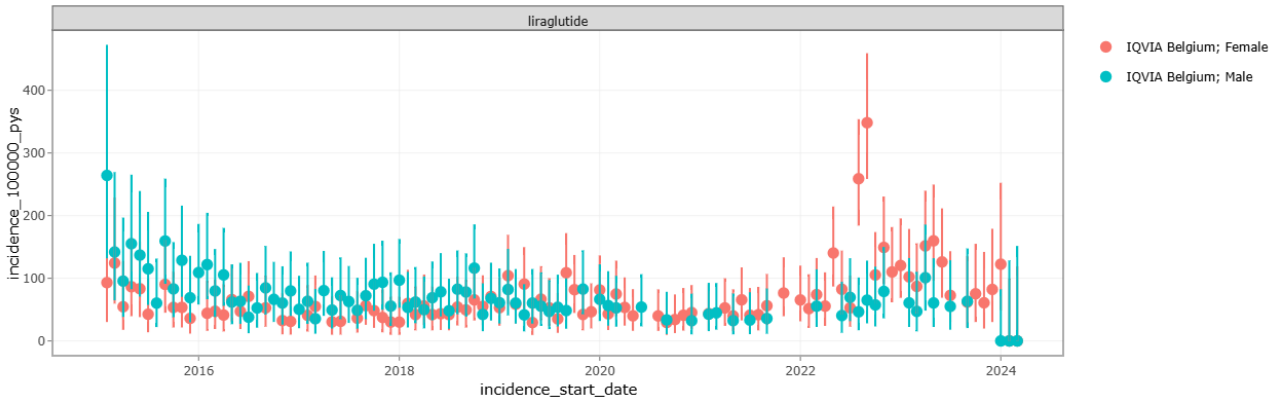


Figure 21. Incidence rates of use of liraglutide per 100,000 person-years stratified by A) age, and B) age and sex in IPCI, and by C) sex in IQVIA LPD Belgium. Scale of Y axis varies across the panels.

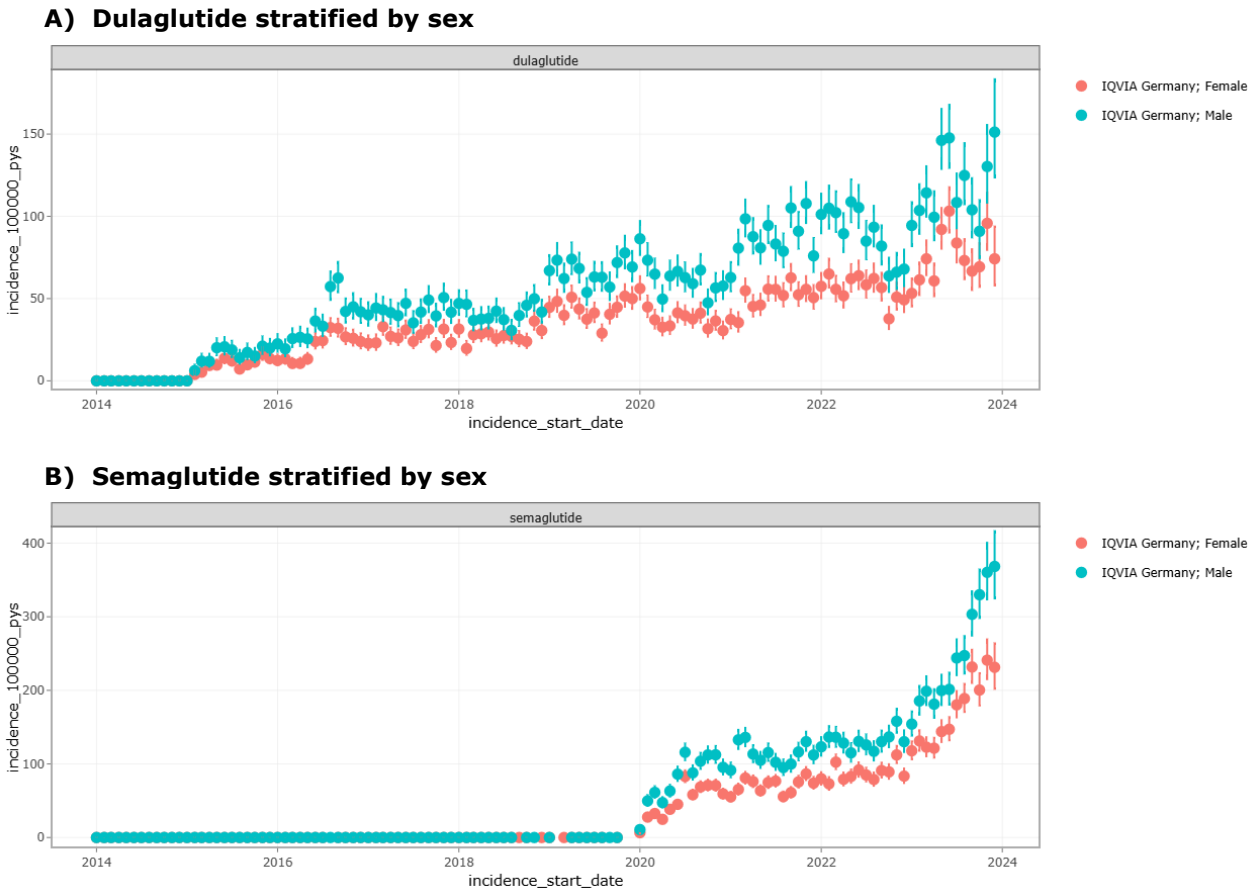


Figure 22. Incidence rates of use of dulaglutide and semaglutide per 100,000 person-years stratified by age in IQVIA DA Germany. Scale of Y axis varies across the panels.

13.2.2 Population-level prevalence calculations

13.2.2.1 Overall prevalence estimates

This section includes the prevalence of the different GLP-1 RA medicines and of the other drugs medicines used for the treatment of diabetes and weight management with no stratification.

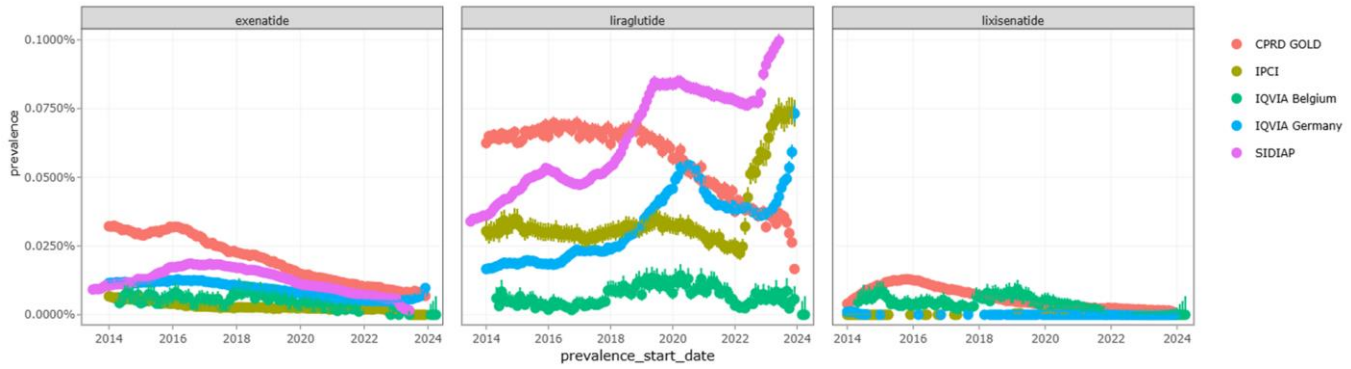
Use of GLP-1 RA

Prevalence of dulaglutide and semaglutide use increased over time in all databases. The highest prevalence increase of dulaglutide use was observed in SIDIAP, IQVIA DA Germany and CPRD, whilst for semaglutide it was IPCI that showed the largest increase (**Figure 23**).

Prevalence of liraglutide use in the general population was lower than 0.1% in all the databases. Its use in CPRD decreased since 2018, whereas its use in SIDIAP and IPCI increased after 2022, making them the two databases with the highest prevalent use of liraglutide, respectively. Its use in IQVIA DA Germany increased until 2020. In contrast, IQVIA LPD Belgium presented a small but stable trend of use (**Figure 23**).

On the other hand, prevalence of exenatide use (e.g., from 0.03% in March 2014 to 0.006% in December 2023 in CPRD; or from 0.01% in March 2016 to 0.004% in November 2022 in IQVIA DA Germany) and lixisenatide use (e.g., from 0.009% in March 2019 to <0.001 after October 2021 in IQVIA LPD Belgium) decreased over time (**Figure 23**).

A) Exenatide(left), liraglutide (centre) and lixisenatide (right)



B) Dulaglutide (left) and semaglutide (right)

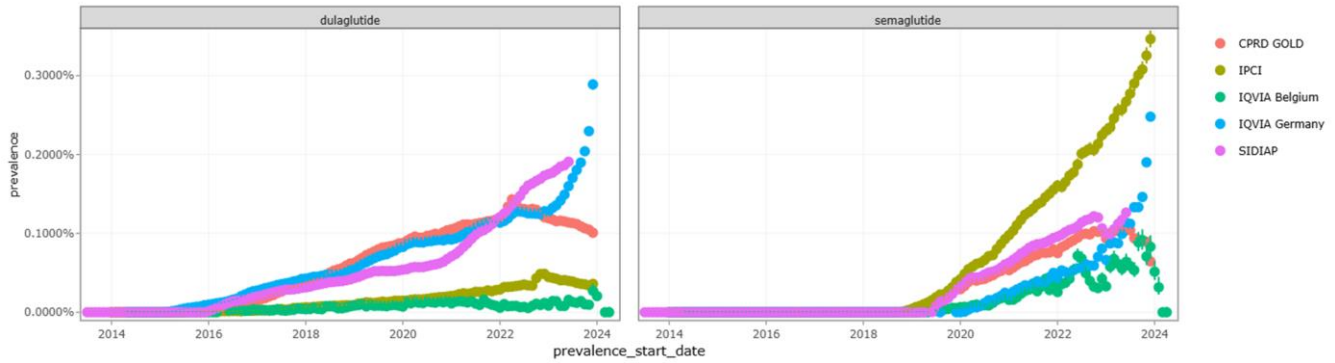


Figure 23. Prevalence of use of the GLP-1 RA drugs [A) exenatide, liraglutide and lixisenatide, B) dulaglutide and semaglutide] per 100,000 person-years in the overall population (i.e., any age and sex) for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels.

Use of other medicines used for the treatment of diabetes and weight management

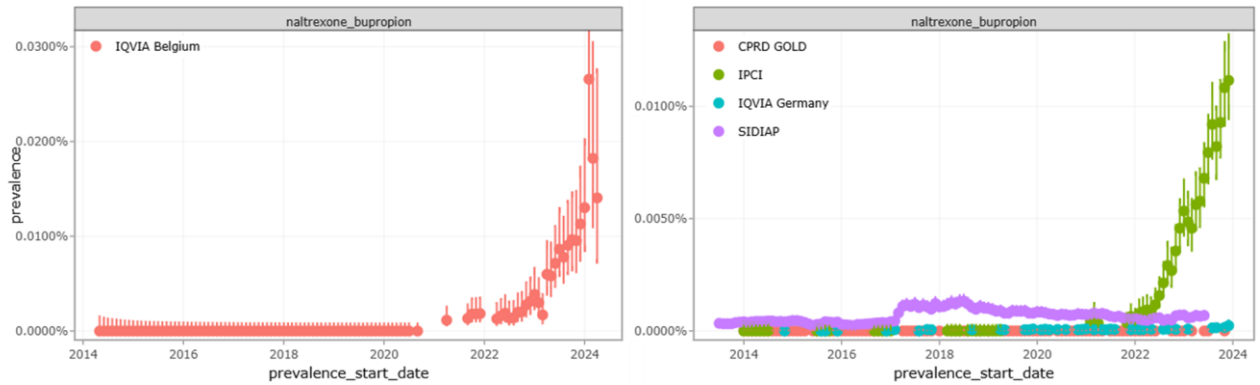
We did not observe any prevalent use of phentermine, alone or combined with topiramate, in any of the databases of the study. Use of naltrexone/bupropion started to gradually increase since September 2021 in IQVIA LPD Belgium and IPCI, but values remained below 0.27% (**Figure 24**).

Prevalence of orlistat use diminished in IPCI since May 2014 (when it was 0.005% [95%CI: 0.004 to 0.006]), whilst its prevalence in SIDIAP was lower than <0.0005%. Conversely, its use in CPRD and IQVIA LPD Belgium was higher, with prevalence values between 0.02% and 0.07%. CPRD presented a seasonality pattern, with marked drops in January and peaks generally in July (**Figure 24**).

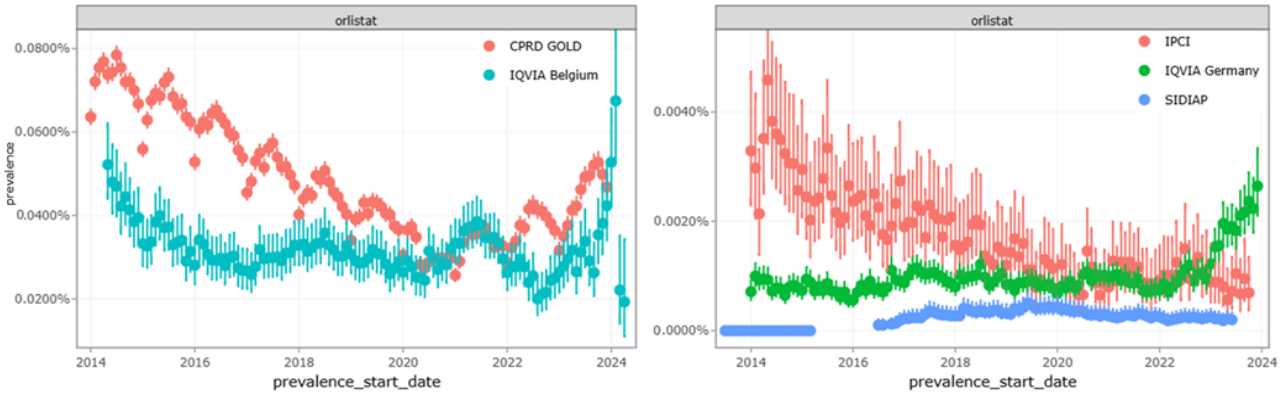
On the contrary, prevalence of metformin use presented a moderate increase in SIDIAP, IPCI and CPRD that may be perceived as stable (difference between the minimum and maximum prevalence values across the entire study period was less than <0.8%; e.g., the lowest prevalence in SIDAP was 3.6% in July 2013, while the maximum was 4.4% in July 2022) , whilst prevalence in IQVIA DA Germany increased from 0.7% in January 2014 to 3.9% in December 2023. Generally, prevalence of metformin use ranged between 1% and 5%, with the exception of the last 6 months of observed data in IQVIA LPD Belgium (December 2023-May 2024), which increased up to 9.2% [95%CI: 9.0 to 9.3] in February 2024. (**Figure 24**). The exponential increase in the last 6-months of both IQVIA databases may be driven by the artefactual decrease in the denominator. This aligns with the artefactual increase in incidence of use observed in the last 6-months of data in the IQVIA databases (*presented in section 13.2.1*), suggesting that these last six estimates are likely unreliable.

Likewise, the observed increase in the last six prevalence values of naltrexone/bupropion and metformin use in IQVIA databases may be driven by an artefact in the denominator as described in the limitations (see the limitation section for further details).

A) Naltrexone/bupropion (left for IQVIA LPD Belgium, right for the other databases)



B) Orlistat (left for CPRD and IQVIA LPD Belgium, right for the other databases)



C) Metformin (left for IQVIA LPD Belgium, right for the other databases)

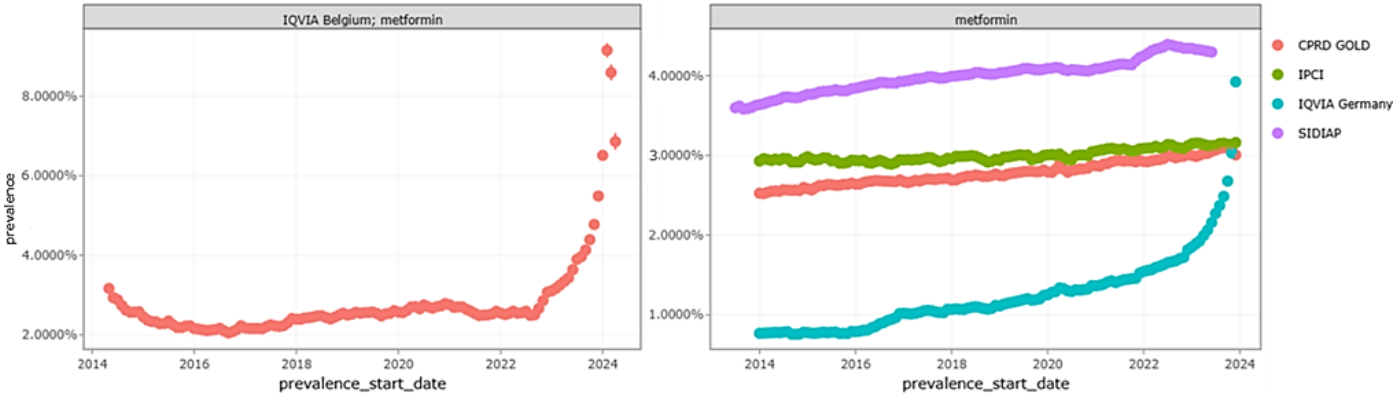


Figure 24. Prevalence of use of other medicines used for the treatment of diabetes and weight management [A) naltrexone/bupropion, B) orlistat and C) metformin] in the overall population (i.e., any age and sex) for each of the databases of the study: CPRD, IQVIA LPD Belgium, IQVIA DA Germany, IPCI and SIDIAP. Scale of Y axis varies across the panels.

13.2.2.2 Prevalence estimates stratified by age and sex

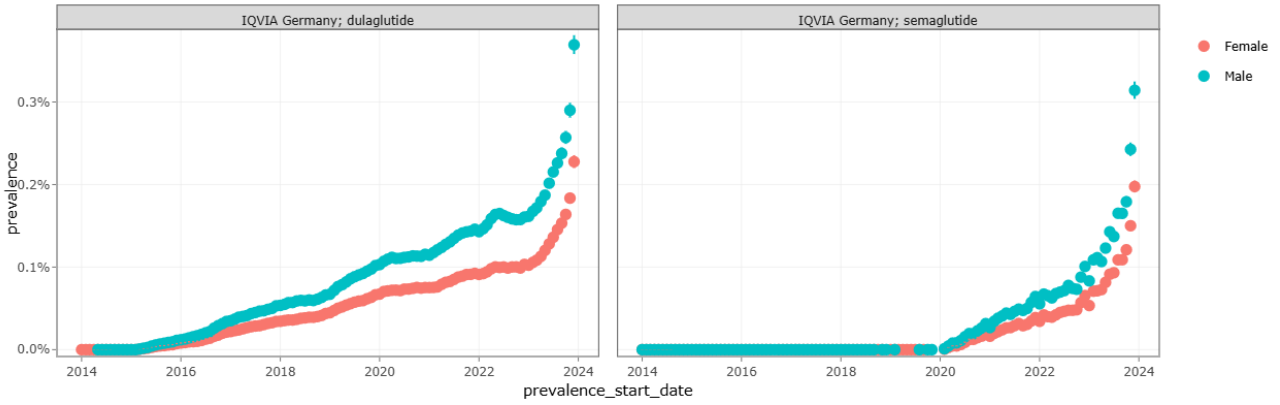
This section focuses on reporting variations in the prevalence observed among different age groups and sex. Similarly to section 12.2.1.3, we focused on reporting the observed differences. Full results including all the age and sex stratifications are available in the shiny app [*Prevalence tab – use the Denominator age group and sex sub-tabs to select them*].

Prevalent use among individuals <18 years was only detected for metformin (<0.2%), liraglutide in SIDIAP (<0.003%), and orlistat in CPRD (<0.0015%). [*Figures not shown, please see them in the shiny app: Prevalence tab – use 0 to 17 age group in the Denominator age group sub-tab and select the cohorts of interest in the Outcome cohort name sub-tab*].

Focusing on GLP-1 RA drugs, we observe a higher prevalence of use of dulaglutide and semaglutide in men from IQVIA DA Germany. Conversely, prevalence of liraglutide use was higher in women from IPCI since May 2022 (**Figure 25**).

For other medicines used for the treatment of diabetes and weight management, prevalent use of metformin was higher among those ≥65 years and men in all databases (**Figure 26**). Orlistat use was more prevalent among women ≥18 years in IQVIA LPD Belgium, whilst it was more prevalent in women between 18-64 years in CPRD (**Figure 27**).

A) Dulaglutide (left) and semaglutide (right) in IQVIA DA Germany stratified by sex



B) Liraglutide in IPCI stratified by sex

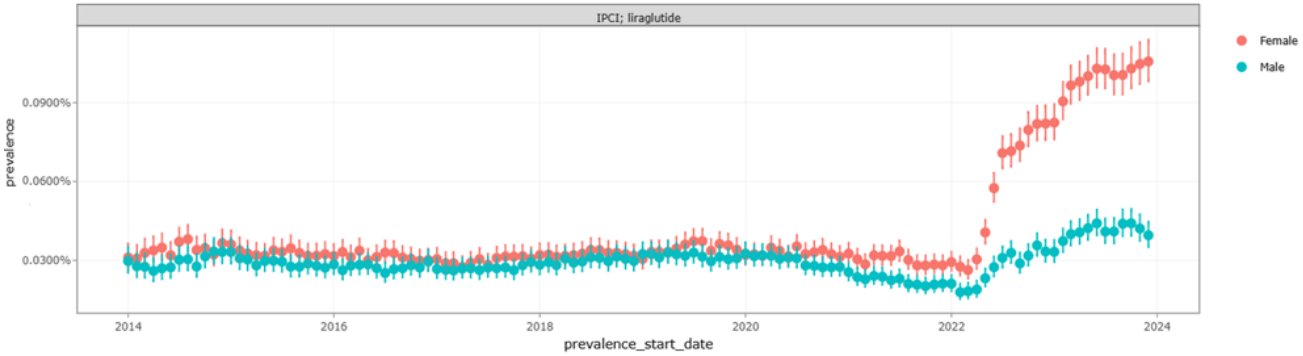


Figure 25. Prevalence of use of A) dulaglutide and semaglutide in IQVIA DA Germany, and of B) liraglutide in IPCI stratified by sex. Scale of Y axis varies across the panels.

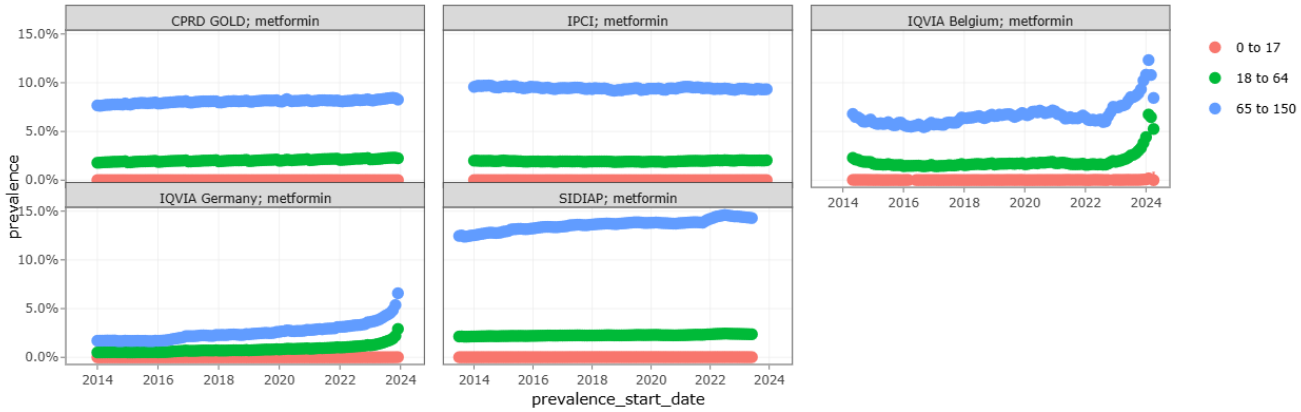


Figure 26. Prevalence of metformin use in all databases stratified by age.

A) Orlistat in CPRD stratified by age and sex

B) Orlistat in IQVIA LPD Belgium stratified by age and sex

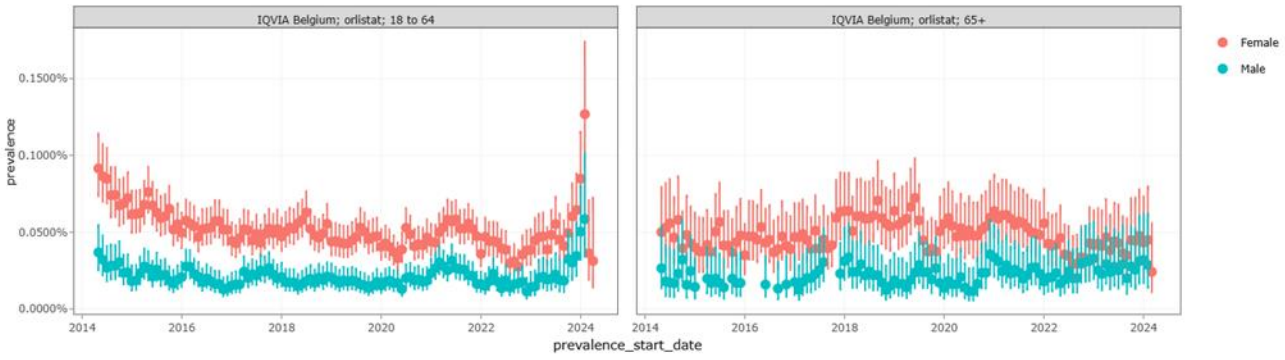


Figure 27. Prevalence of orlistat use in A) CPRD and B) IQVIA LPD Belgium), stratified by age and sex.

13.2.3 Patient-level characteristics

13.2.3.1 Characteristics of GLP-1RA patients

Overall characteristics of GLP-1RA patients

Characteristics of patients at the time of their first prescription of GLP-1 RA (i.e., incident users) are summarised in **Table 10-Table** 12 and **Figure 28-Figure** 29, and correspond to the GLP-1 RA incident cohorts from the Characteristics tab displayed in the shiny app [*select those cohorts with an "_incident" in the Denominator Cohor sub-tab*]:

The GLP-1 RA drug with highest number of incident patients in IQVIA DA Germany and SIDIAP was dulaglutide, in CPRD was liraglutide, and in IPCI and IQVIA LPD Belgium it was semaglutide. Sex distribution varied across the databases and the different GLP-1 RA, however, most of the proportion values in men were ranged between 46.9-57.6%, except for liraglutide in IPCI (35.8% were men) and IQVIA LPD Belgium (39.1% were men), and semaglutide in IQVIA LPD Belgium (37.9% were men). (**Table 10**)

Overall, there were very few users of GLP-1 RA younger than 18 years old. Median age was similar across the databases, but stratification by age groups showed certain databases preferred a specific GLP-1 RA for a specific age groups, such as larger number of users for semaglutide among 18-64 age group (proportion of semaglutide users aged 18-64 years were 69.8% and 75.8% in CPRD and IQVIA LPD Belgium, respectively) and lower number of users for individuals ≥65 years old (proportion of semaglutide users aged ≥65 years were 30.2% and 24.0% in CPRD and IQVIA LPD Belgium, respectively). (**Table 11**)

BMI values were poorly recorded in both IQVIA databases (60.8% to 85.7% of individuals did not have a BMI record in the last 5 years from starting their GLP-1 RA drug), followed by IPCI (ranged between <5% to 23.5%). Missingness in BMI records was lower than 8.4% and 8.4% in SIDIAP and CPRD, respectively. Users with a BMI ≤26 km/m2 were infrequent in all databases (≤3.9%). IQVIA LPD Belgium presented the lowest median BMI (ranged between 31.62 to 33.2 kg/m2 across different GLP-1 RA), whilst the lowest median BMI estimated in the other databases were >33 kg/m2. However, the highest percentage of missingness in the BMI records limits the interpretation of BMI in both IQVIA databases and IPCI. BMI stratification also show a marginally higher proportion of users with BMI values between 27-29kg/m2 for CPRD (proportion ranged between 6% to 9.3%) when compared to the other databases (proportion ranged between 2.5% to 7.8%). (**Figure 28**, **Table 12**)

Five comorbidities and two composite outcomes (chronic kidney disease plus renal impairment, and MACE) were analysed for patients receiving the different GLP-1 RA. Hypertension was the most common comorbidity (ranged from 24.1% up to 75.6%), followed by chronic kidney disease plus renal impairment (ranged between 1.5% to 25.6%). (**Figure 29**, **Table 12**)

Characteristics of GLP-1 RA users as assessed at the beginning of each treatment episode (i.e., new episodes of drug use of GLP-1 RA) are summarised in **Appendix II.**

Table 10. Description of new users of GLP-1 RA: number of subjects and sex distribution in each database of the study.

Variable name		Number subjects					Sex [male]				
CDM name		CPRD N (%)	IPCI N (%)	IQVIA LPD Belgium N (%)	IQVIA DA Germany N (%)	SIDIAP N (%)	CPRD N (%)	IPCI N (%)	IQVIA LPD Belgium N (%)	IQVIA DA Germany N (%)	SIDIAP N (%)
Cohort name	Dulaglutide	11,967 (29%)	1,536 (11%)	1,794 (20%)	36,340 (41%)	18,730 (36%)	6,248 (52.1%)	726 (46.9%)	999 (55.7%)	19,783 (54.4%)	9,676 (51.7%)
	Liraglutide	14,205 (34%)	3,797 (27%)	1,567 (18%)	20,064 (23%)	16,513 (32%)	6,856 (48.1%)	1,369 (35.8%)	612 (39.1%)	10,086 (50.3%)	7,100 (43.0%)
	Exenatide	4,321 (10%)	152 (1%)	551 (6%)	2,360 (3%)	2,697 (5%)	2,266 (52.3%)	75 (49.0%)	303 (55.0%)	1,256 (53.2%)	1,333 (49.4%)
	Lixisenatide	2,038 (5%)	31 (0%)	317 (4%)	176 (0%)	-	1,011 (49.5%)	19 (57.6%)	162 (51.1%)	86 (48.9%)	-
	Semaglutide	8,727 (21%)	8,626 (61%)	4,597 (52%)	29,283 (33%)	13,809 (27%)	4,336 (49.6%)	4,260 (49.1%)	1,741 (37.9%)	15,610 (53.3%)	6,631 (48.0%)

CDM, common data model.

Table 11. Description of new users of GLP-1 RA: age distribution in each database of the study.

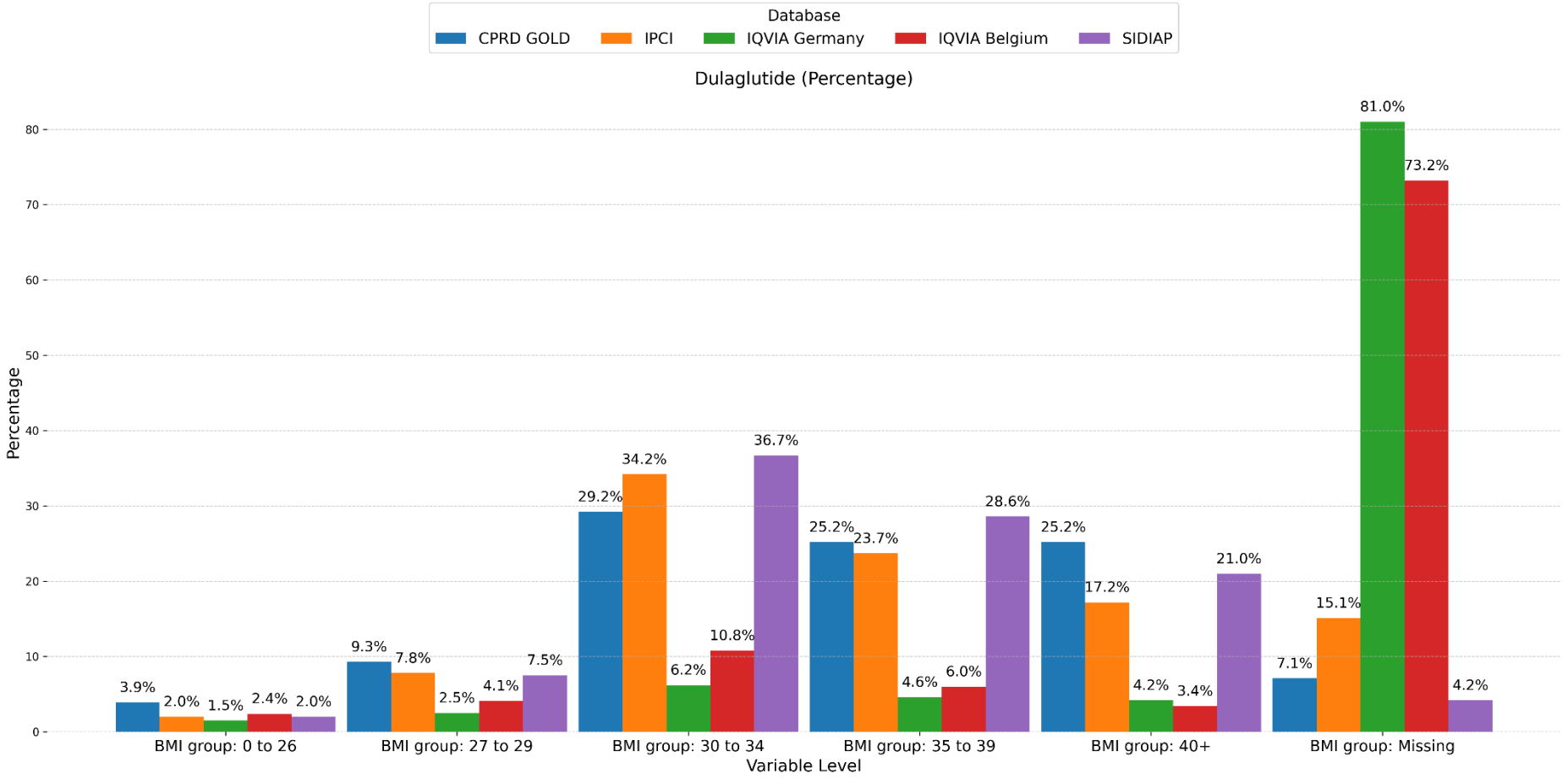
Variable name		Age (years)														
CDM name		CPRD			IPCI			IQVIA LPD Belgium			IQVIA DA Germany			SIDIAP		
Estimate name		Median [Q25 - Q75]	Mean (SD)	Range	Median [Q25 - Q75]	Mean (SD)	Range	Median [Q25 - Q75]	Mean (SD)	Range	Median [Q25 - Q75]	Mean (SD)	Range	Median [Q25 - Q75]	Mean (SD)	Range
Cohort name	Dulaglutide	60 [52 - 68]	59.57 (11.60)	16 to 94	61 [54 - 68]	60.64 (10.62)	24 to 99	63.00 [54.00 - 71.00]	62.10 (12.35)	0.00 to 95.00	62.00 [54.00 - 70.00]	61.14 (12.31)	1.00 to 98.00	62 [54 - 69]	61.13 (11.49)	17 to 93
	Liraglutide	57 [49 - 65]	56.80 (11.89)	6 to 92	56 [48 - 65]	55.72 (12.76)	7 to 87	56.00 [47.00 - 65.00]	55.25 (13.83)	13.00 to 106.00	60.00 [51.00 - 68.00]	59.11 (12.69)	0.00 to 97.00	58 [49 - 66]	56.94 (12.42)	12 to 93

Variable name		Age (years)														
CDM name		CPRD			IPCI			IQVIA LPD Belgium			IQVIA DA Germany			SIDIAP		
Estimate name		Median [Q25 - Q75]	Mean (SD)	Range	Median [Q25 - Q75]	Mean (SD)	Range	Median [Q25 - Q75]	Mean (SD)	Range	Median [Q25 - Q75]	Mean (SD)	Range	Median [Q25 - Q75]	Mean (SD)	Range
	Exenatide	59 [51 - 66]	58.33 (10.96)	16 to 90	60 [53 - 67]	59.58 (9.45)	35 to 86	62.00 [54.00 - 69.00]	61.75 (11.70)	17.00 to 91.00	61.00 [53.00 - 68.00]	60.14 (11.26)	6.00 to 94.00	59 [51 - 66]	58.45 (11.17)	15 to 95
	Lixisenatide	59 [51 - 66]	58.16 (11.16)	21 to 93	62 [56 - 68]	61.82 (8.43)	44 to 77	62.00 [52.00 - 71.00]	60.11 (13.54)	10.00 to 91.00	61.00 [52.75 - 67.00]	59.74 (11.63)	30.00 to 89.00	-	-	-
	Semaglutide	59 [51 - 66]	57.93 (11.92)	12 to 89	61 [53 - 69]	60.53 (11.22)	15 to 91	55.00 [45.00 - 64.00]	53.95 (13.66)	6.00 to 96.00	60.00 [52.00 - 68.00]	59.60 (12.52)	6.00 to 96.00	60 [51 - 67]	58.78 (12.06)	14 to 98

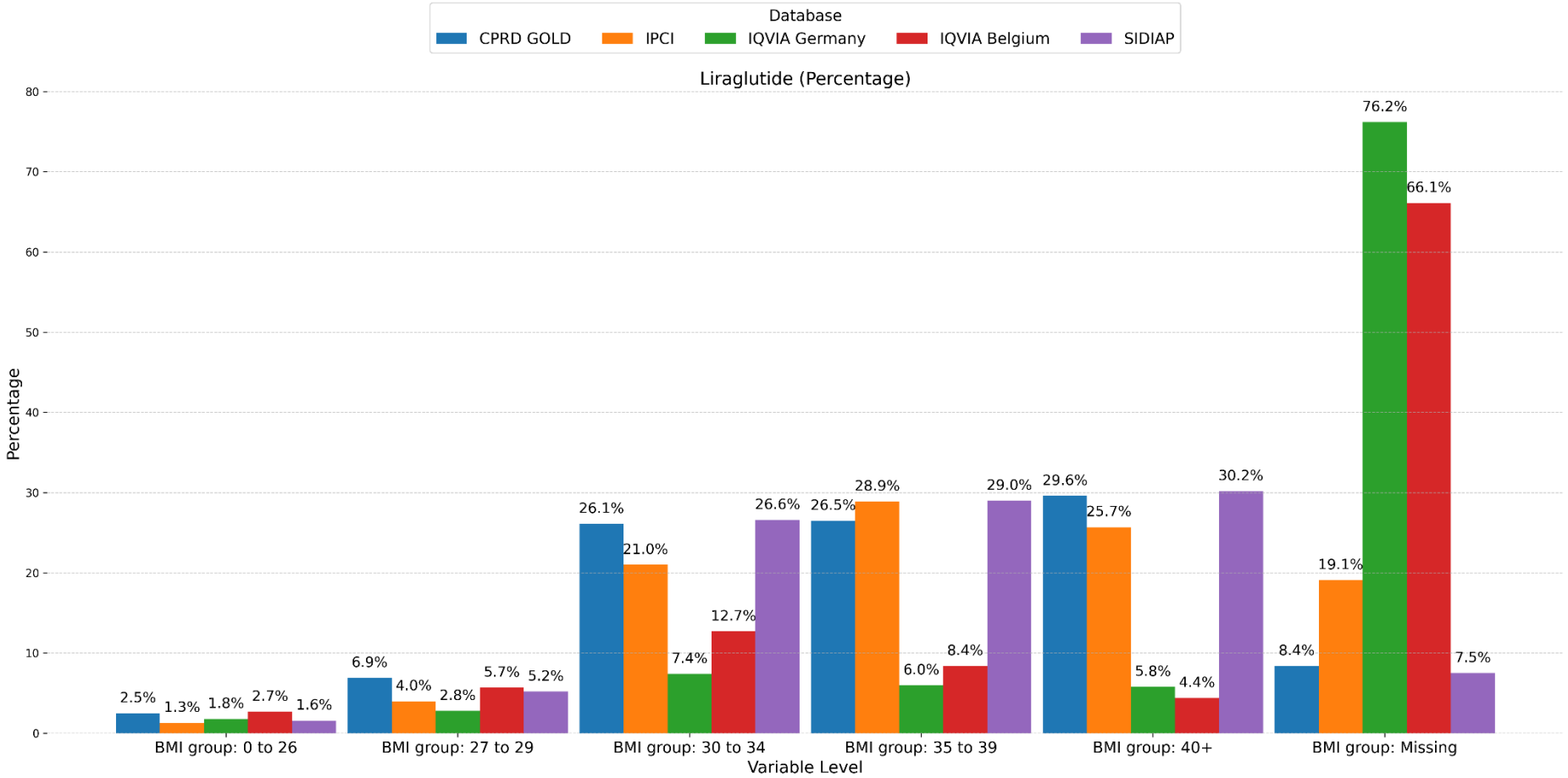
Variable name		Age group														
CDM name		CPRD	IPCI	IQVIA LPD Belgium	IQVIA DA Germany	SIDIAP	CPRD	IPCI	IQVIA LPD Belgium	IQVIA DA Germany	SIDIAP	CPRD	IPCI	IQVIA LPD Belgium	IQVIA DA Germany	SIDIAP
Variable level		0 to 17	0 to 17	0 to 17	0 to 17	0 to 17	18 to 64	18 to 64	18 to 64	18 to 64	18 to 64	65+	65+	65+	65+	65+
Estimate name		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cohort name	Dulaglutide	5 (0.0%)	-	<5 (<5%)	10 (0.0%)	<5 (<5%)	7,753 (64.7%)	954 (61.7%)	966 (53.8%)	21,669 (59.6%)	11,013 (58.8%)	4,232 (35.3%)	593 (38.3%)	824 (45.9%)	14,661 (40.3%)	7,715 (41.2%)
	Liraglutide	18 (0.1%)	8 (0.2%)	<5 (<5%)	28 (0.1%)	70 (0.4%)	10,296 (72.3%)	2,792 (73.0%)	1,134 (72.4%)	12,978 (64.7%)	11,723 (71.0%)	3,934 (27.6%)	1,023 (26.8%)	430 (27.4%)	7,058 (35.2%)	4,720 (28.6%)
	Exenatide	<5 (<5%)	-	<5 (<5%)	<5 (<5%)	<5 (<5%)	3,004 (69.4%)	106 (69.3%)	321 (58.3%)	1,524 (64.6%)	1,838 (68.1%)	1,325 (30.6%)	47 (30.7%)	229 (41.6%)	835 (35.4%)	858 (31.8%)
	Lixisenatide	-	-	<5 (<5%)	-	-	1,404 (68.8%)	19 (57.6%)	178 (56.2%)	114 (64.8%)	-	638 (31.2%)	14 (42.4%)	136 (42.9%)	62 (35.2%)	-
	Semaglutide	<5 (<5%)	<5 (<5%)	7 (0.2%)	17 (0.1%)	11 (0.1%)	6,098 (69.8%)	5,340 (61.5%)	3,486 (75.8%)	18,586 (63.5%)	9,102 (65.9%)	2,639 (30.2%)	3,338 (38.5%)	1,104 (24.0%)	10,680 (36.5%)	4,696 (34.0%)

CDM, common data model.

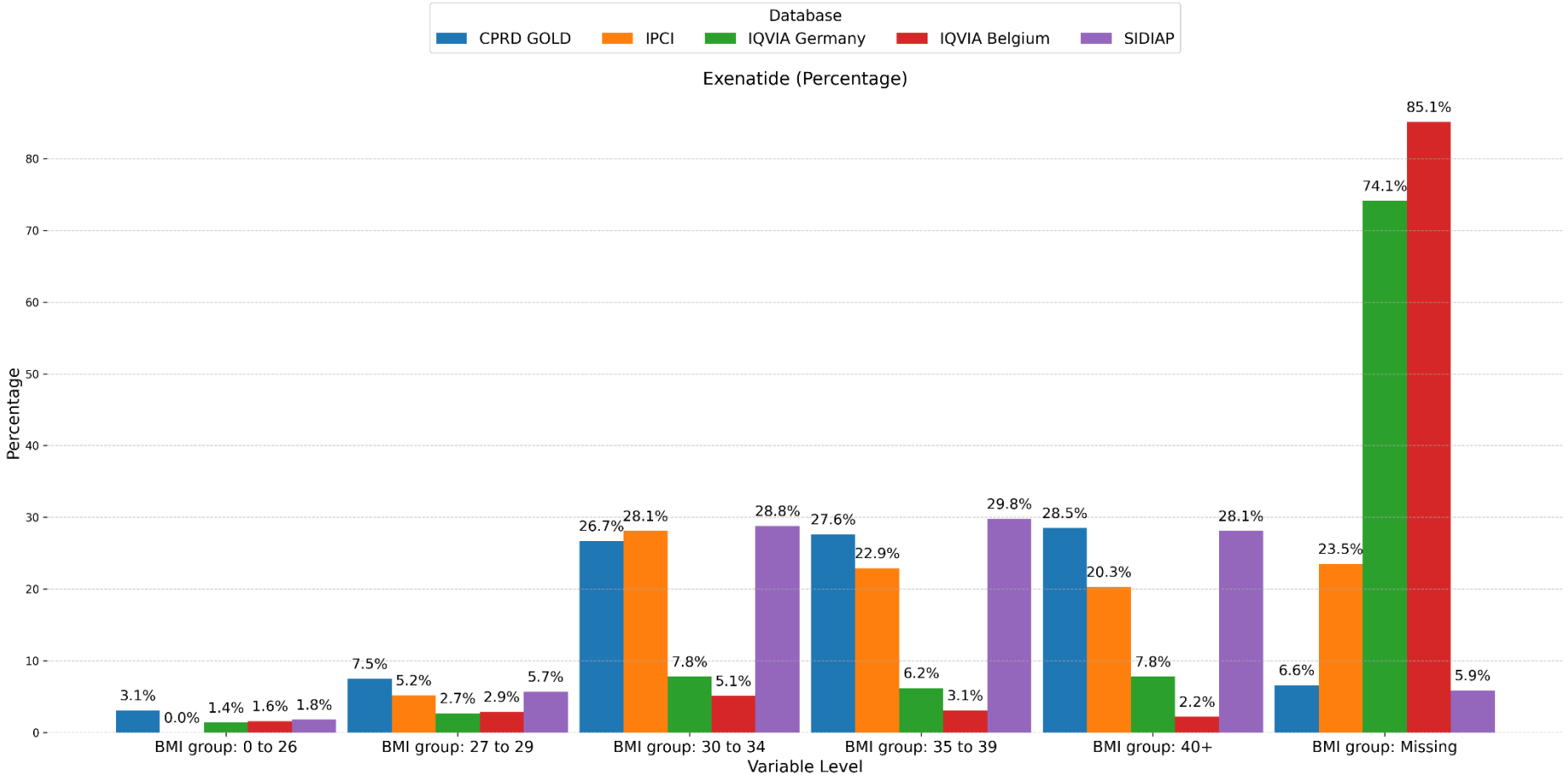
A) Dulaglutide



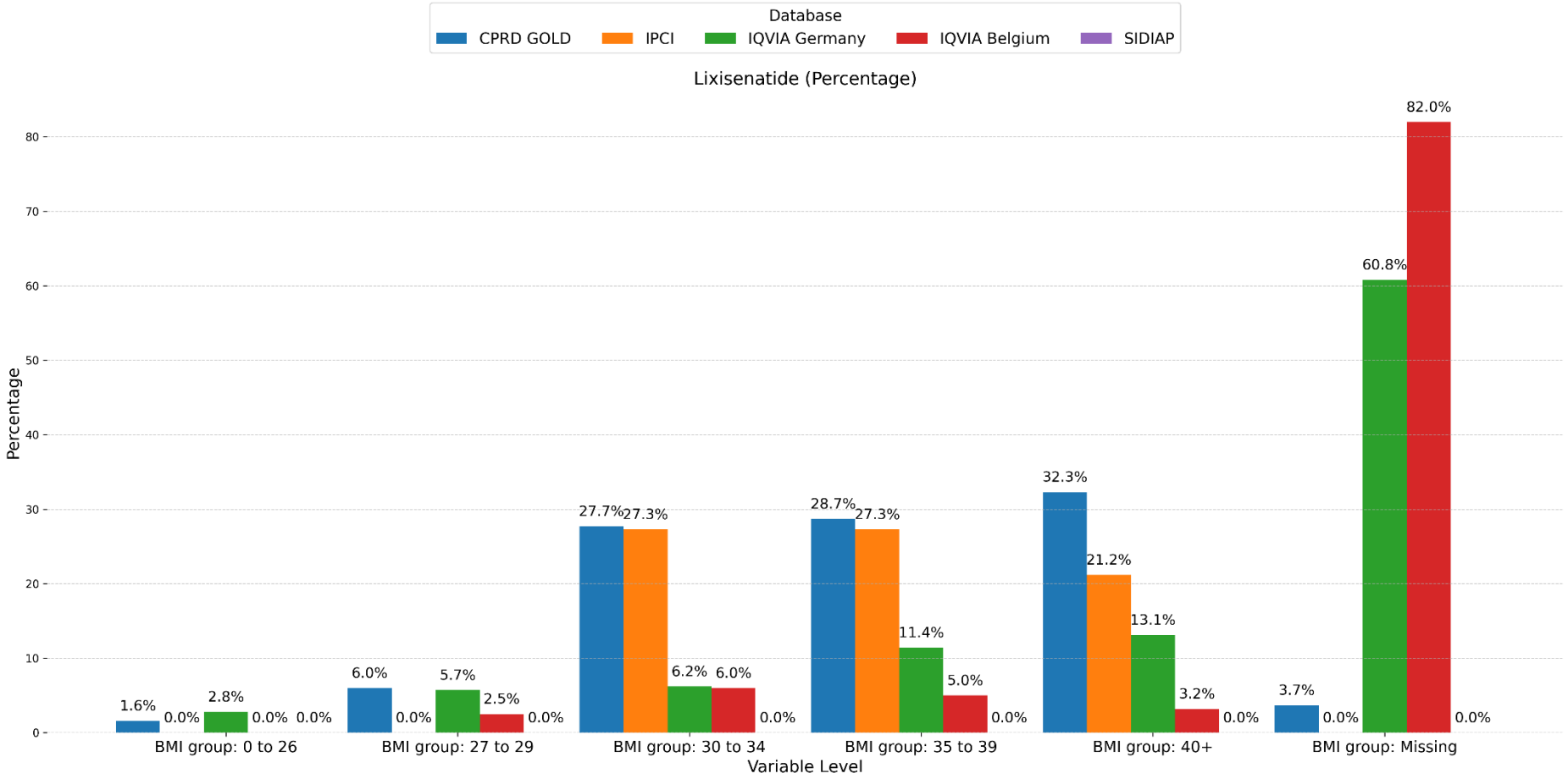
B) Liraglutide



C) Exenatide


Database
CPRD GOLD
IPCI
IQVIA Germany
IQVIA Belgium
SIDIAP
Exenatide (Percentage)
Percentage
0
10
20
30
40
50
60
70
80
3.1%
0.0%
1.4%
1.6%
1.8%
7.5%
5.2%
2.7%
2.9%
5.7%
26.7%
28.1%
7.8%
5.1%
28.8%
27.6%
22.9%
6.2%
3.1%
29.8%
28.5%
20.3%
7.8%
2.2%
28.1%
6.6%
23.5%
74.1%
85.1%
5.9%
BMI group: 0 to 26
BMI group: 27 to 29
BMI group: 30 to 34
BMI group: 35 to 39
BMI group: 40+
BMI group: Missing
Variable Level

D) Lixisenatide



E) Semaglutide

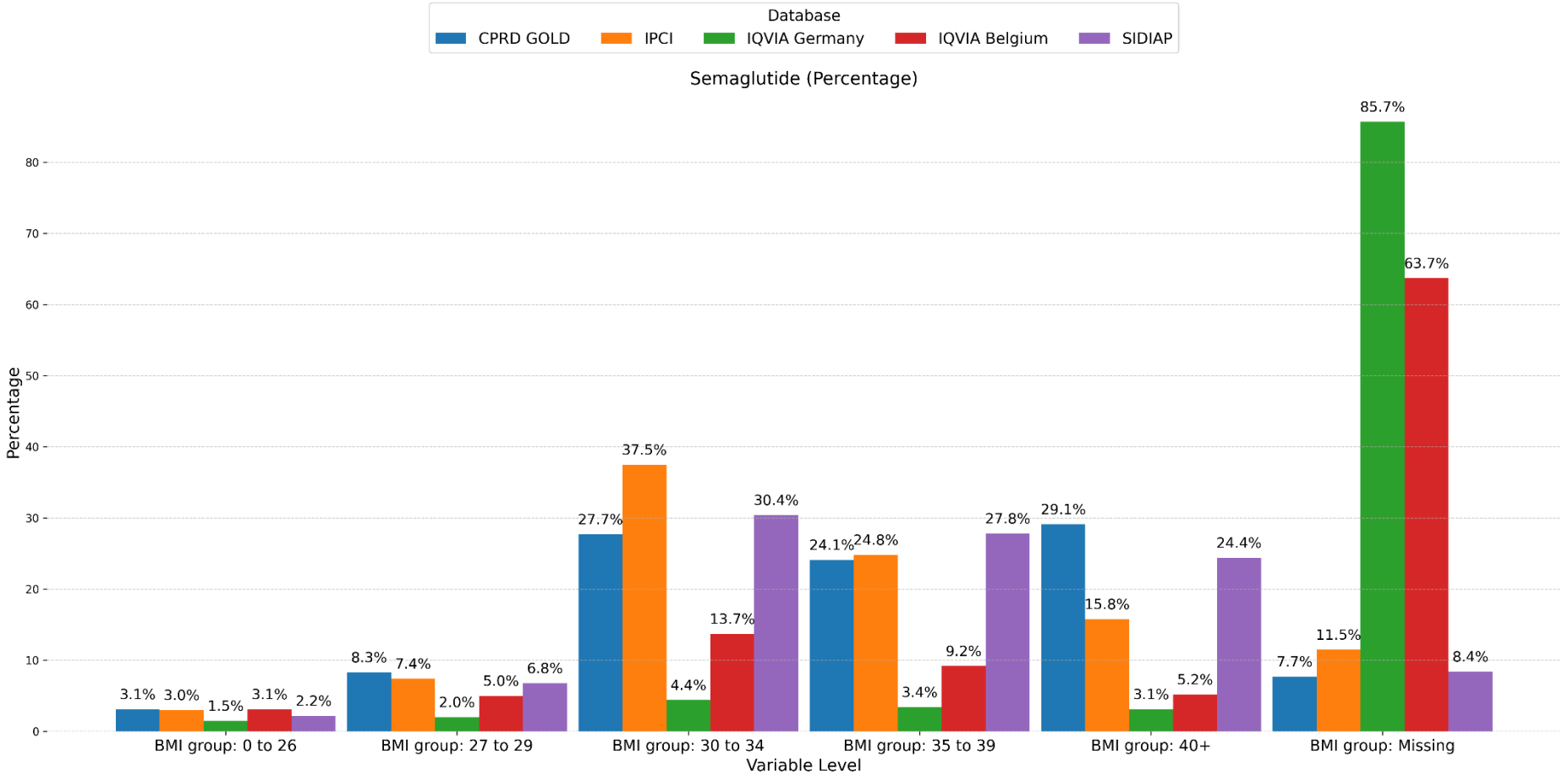
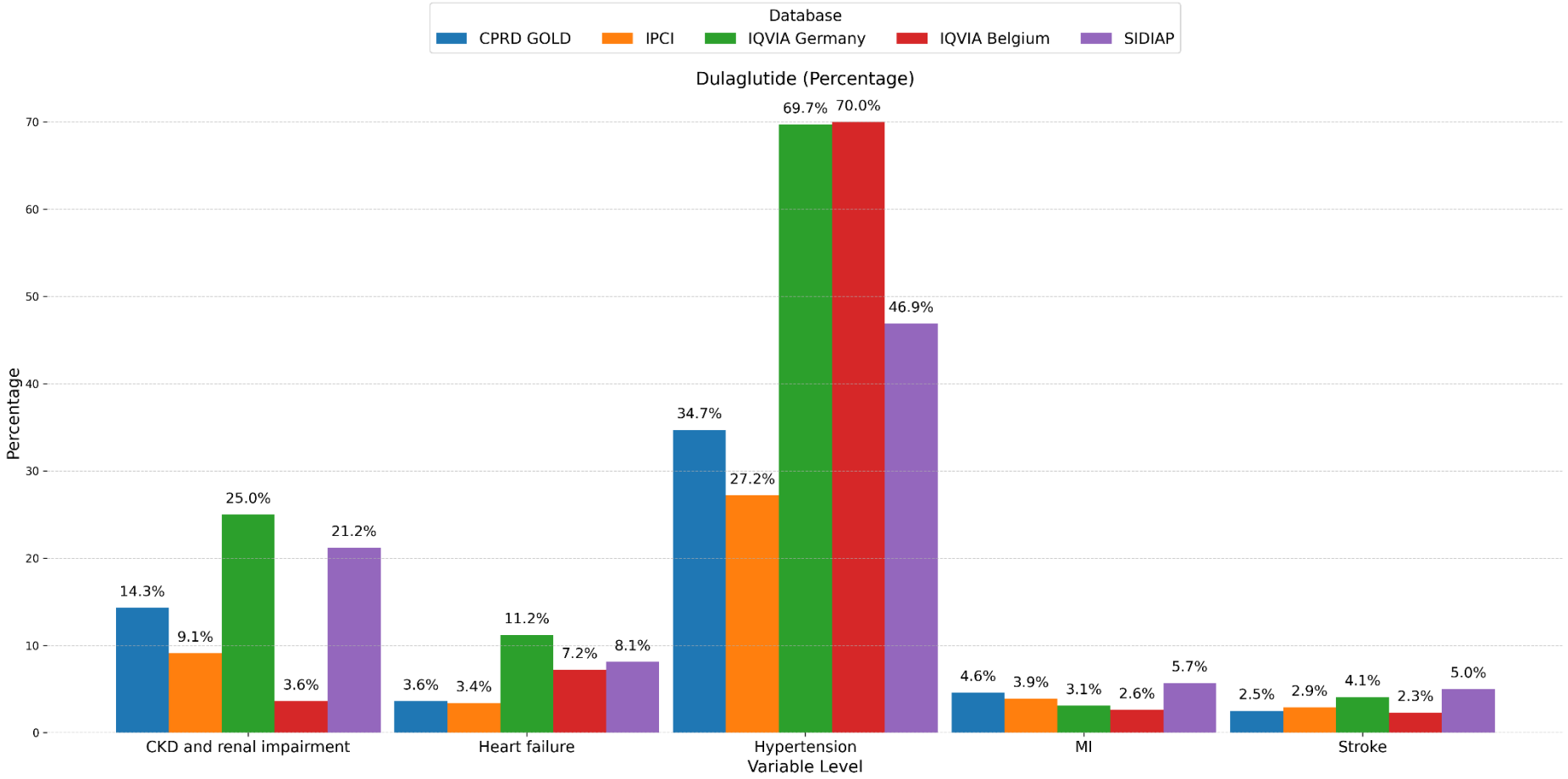
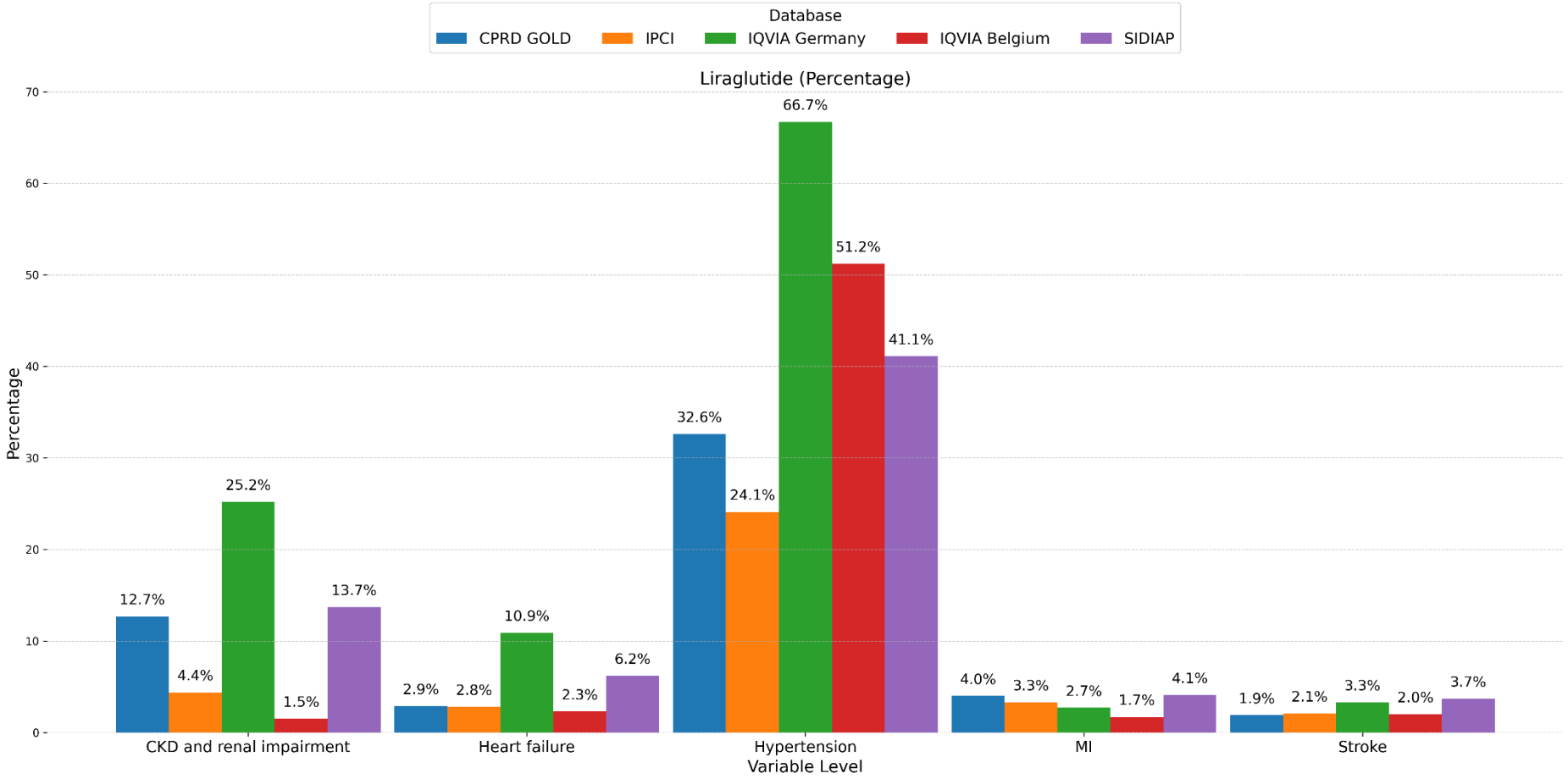


Figure 28. Characteristics of patients starting GLP-1 [A) dulaglutide, B) liraglutide, C) exenatide, D) lixisenatide and E) semaglutide] for first time: distribution of body mass index (BMI) in CPRD, IPCI, IQVIA DA Germany, IQVIA LPD Belgium and SIDIAP. Classification of BMI values: equal or below 26 kg/m2 for normal weight, between 27 to 29 kg/m2 for overweight, 30 to 34 kg/m2 for obesity class 1, 35 to 39 kg/m2 for obesity class 2 (moderate), and 40 kg/m2 or more for obesity class 3 (severe). Missing: no BMI value available.

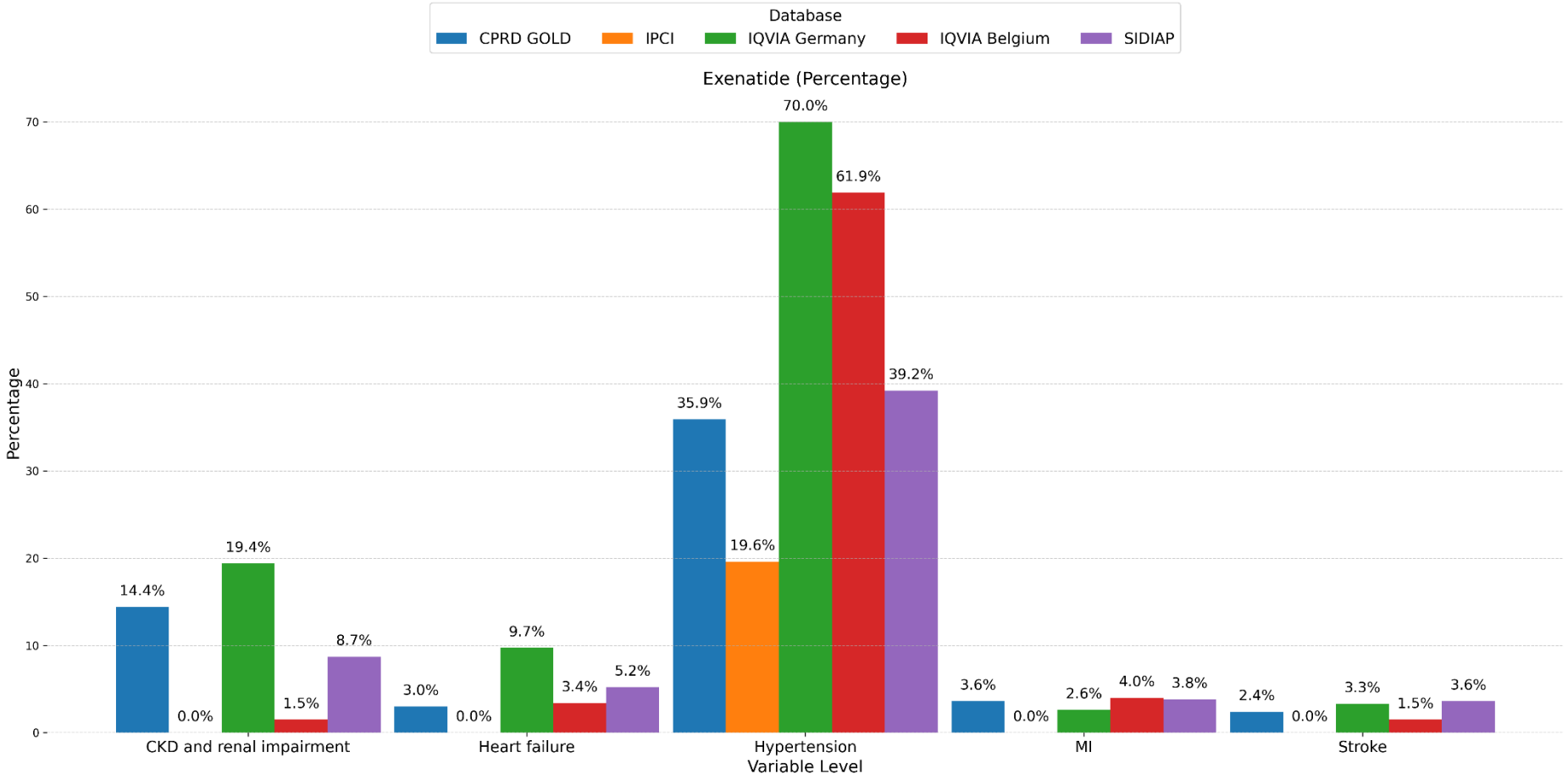
A) Dulaglutide



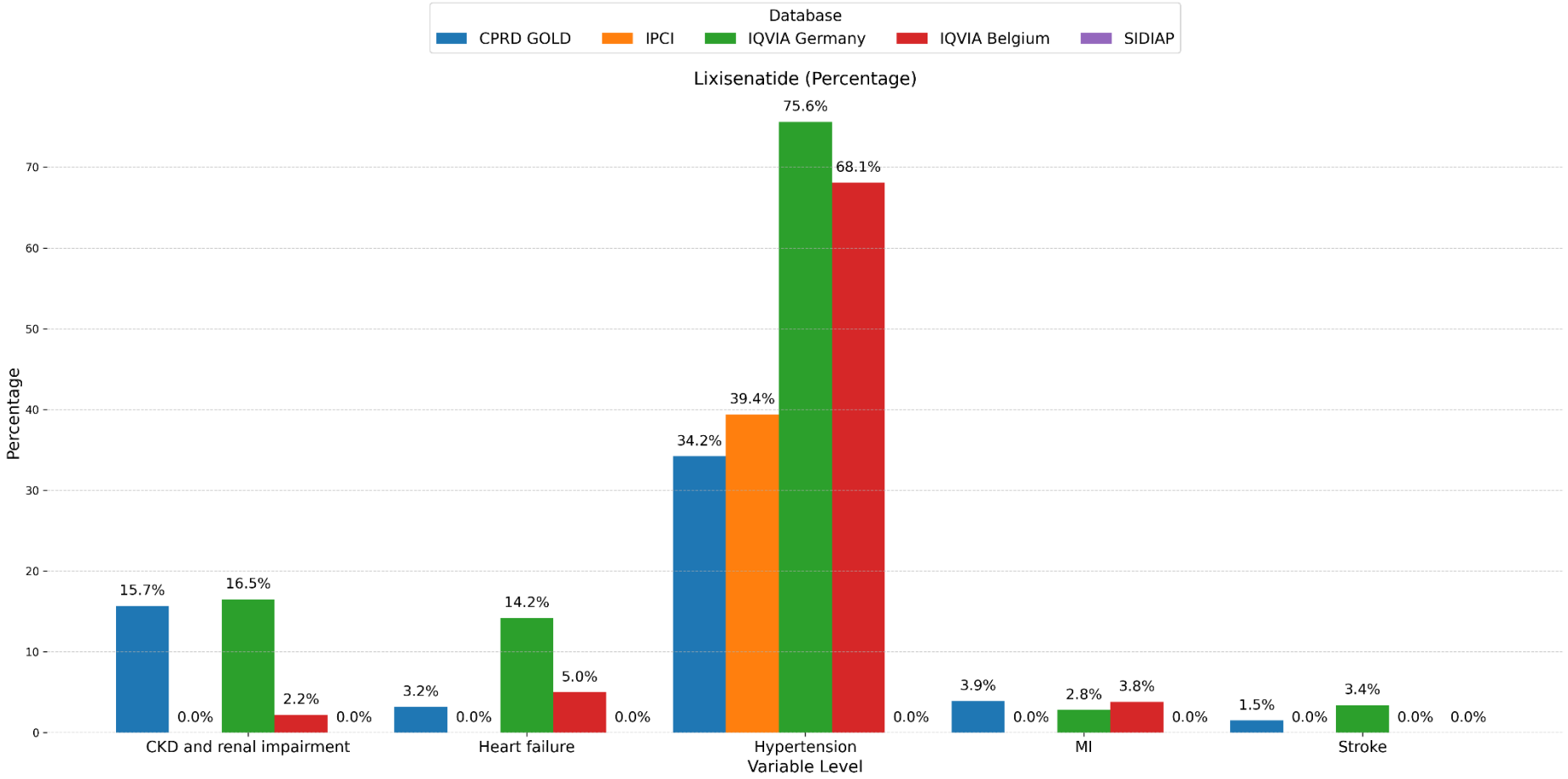
B) Liraglutide



C) Exenatide


Database
CPRD GOLD
IPCI
IQVIA Germany
IQVIA Belgium
SIDIAP
Exenatide (Percentage)
Percentage
0
10
20
30
40
50
60
70
14.4%
0.0%
19.4%
1.5%
8.7%
3.0%
0.0%
9.7%
3.4%
5.2%
35.9%
19.6%
70.0%
61.9%
39.2%
3.6%
0.0%
2.6%
4.0%
3.8%
2.4%
0.0%
3.3%
1.5%
3.6%
CKD and renal impairment
Heart failure
Hypertension
MI
Stroke
Variable Level

D) Lixisenatide



E) Semaglutide

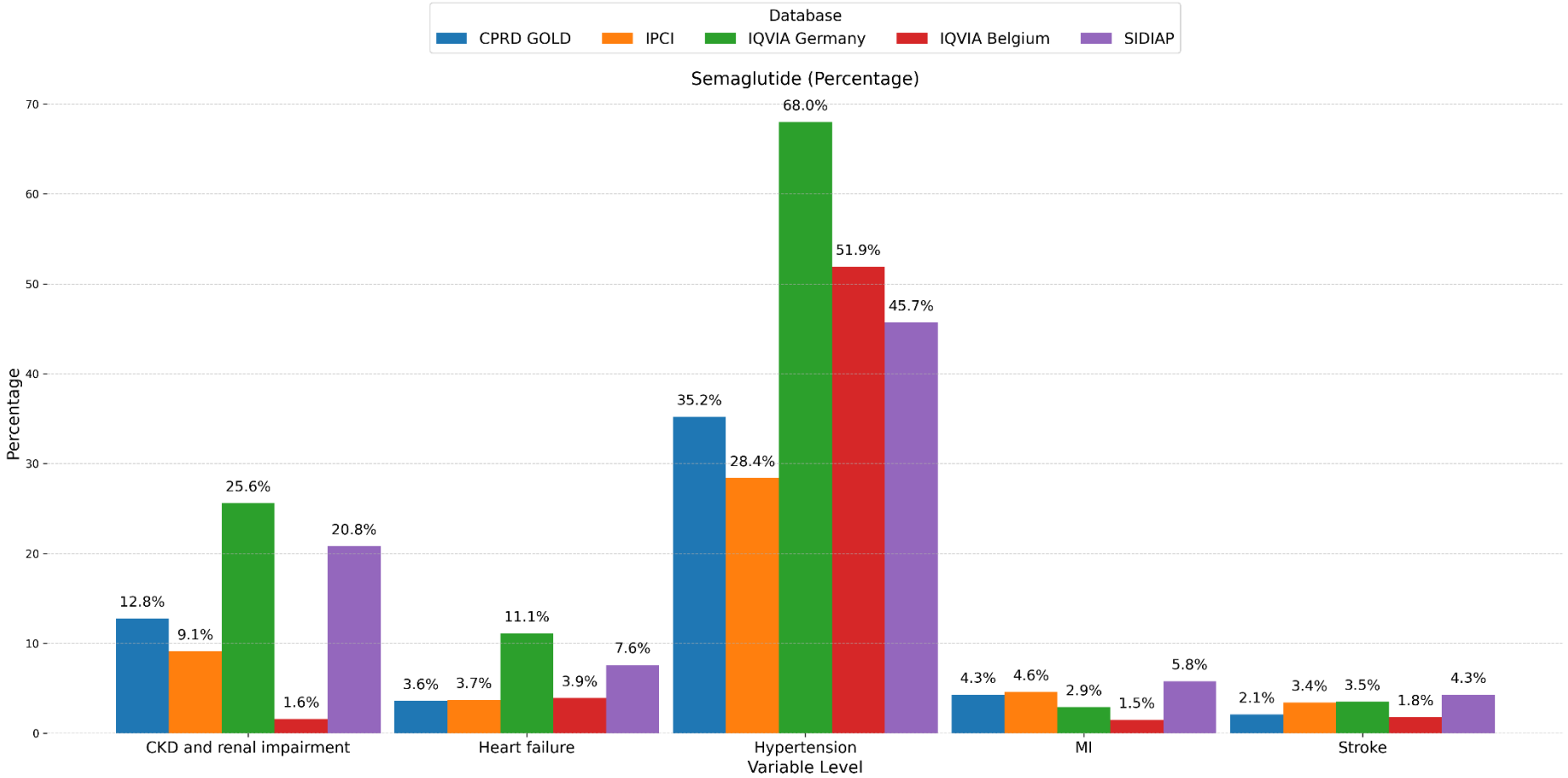


Figure 29. Characteristics of patients starting GLP-1 [A) dulaglutide, B) liraglutide, C) exenatide, D) lixisenatide and E) semaglutide] for first time: frequency of patients who had been previously diagnosed with 'chronic kidney disease (CKD) and renal impairment', heart failure, hypertension, myocardial infarction (MI) and stroke in CPRD, IPCI, IQVIA DA Germany, IQVIA LPD Belgium and SIDIAP.

Table 12. Description of new users of GLP-1 RA: body mass index and conditions in each database of the study.

Variable name	Variable level	CDM name	Estimate name	Cohort name				
				Dulaglutide	Liraglutide	Exenatide	Lixisenatide	Semaglutide
BMI Overall characteristics (kg/m2)	-	CPRD	Median [Q25 - Q75]	35.10 [31.20 - 40.00]	36.30 [32.40 - 41.10]	35.90 [32.00 - 40.90]	36.40 [32.62 - 41.48]	35.70 [31.60 - 41.00]
			Range	13.00 to 60.00	10.10 to 60.00	10.80 to 60.00	20.90 to 59.80	15.70 to 60.00
		IPCI	Median [Q25 - Q75]	34.17 [31.20 - 38.50]	36.59 [33.40 - 40.61]	35.51 [32.95 - 39.74]	36.10 [31.34 - 39.35]	33.98 [30.99 - 37.81]
			Range	20.45 to 58.70	20.31 to 60.00	26.99 to 56.90	25.40 to 47.00	17.90 to 59.57
		IQVIA LPD Belgium	Median [Q25 - Q75]	32.63 [29.70 - 36.01]	32.60 [29.59 - 36.42]	31.62 [29.08 - 37.07]	33.22 [30.39 - 38.10]	33.20 [30.02 - 37.01]
			Range	21.71 to 53.88	19.66 to 57.81	21.51 to 51.99	22.02 to 54.65	16.90 to 57.77
		IQVIA DA Germany	Median [Q25 - Q75]	33.93 [30.12 - 38.77]	34.37 [30.48 - 39.33]	35.19 [31.16 - 40.74]	36.51 [31.05 - 41.02]	33.79 [29.71 - 38.53]
			Range	15.02 to 59.88	17.84 to 59.41	22.58 to 58.34	21.44 to 48.68	17.45 to 58.82
		SIDIAP	Median [Q25 - Q75]	34.72 [31.57 - 38.77]	36.51 [32.82 - 41.14]	36.11 [32.46 - 40.58]	-	35.43 [31.99 - 39.91]

Variable name	Variable level	CDM name	Estimate name	Cohort name				
				Dulaglutide	Liraglutide	Exenatide	Lixisenatide	Semaglutide
			Range	10.38 to 59.87	12.76 to 59.99	18.29 to 59.77	-	12.48 to 59.88
BMI groups (kg/m2)	0 to 26	CPRD	N (%)	473 (3.9%)	358 (2.5%)	135 (3.1%)	32 (1.6%)	274 (3.1%)
		IPCI	N (%)	31 (2.0%)	51 (1.3%)	-	<5 (<5%)	259 (3.0%)
		IQVIA LPD Belgium	N (%)	43 (2.4%)	43 (2.7%)	9 (1.6%)	<5 (<5%)	144 (3.1%)
		IQVIA DA Germany	N (%)	559 (1.5%)	371 (1.8%)	34 (1.4%)	5 (2.8%)	428 (1.5%)
		SIDIAP	N (%)	372 (2.0%)	264 (1.6%)	49 (1.8%)	-	306 (2.2%)
	27 to 29	CPRD	N (%)	1,121 (9.3%)	985 (6.9%)	324 (7.5%)	122 (6.0%)	729 (8.3%)
		IPCI	N (%)	120 (7.8%)	152 (4.0%)	8 (5.2%)	<5 (<5%)	638 (7.4%)
		IQVIA LPD Belgium	N (%)	74 (4.1%)	89 (5.7%)	16 (2.9%)	8 (2.5%)	231 (5.0%)
		IQVIA DA Germany	N (%)	905 (2.5%)	569 (2.8%)	63 (2.7%)	10 (5.7%)	579 (2.0%)

Variable name	Variable level	CDM name	Estimate name	Cohort name				
				Dulaglutide	Liraglutide	Exenatide	Lixisenatide	Semaglutide
		SIDIAP	N (%)	1,411 (7.5%)	852 (5.2%)	154 (5.7%)	-	941 (6.8%)
	30 to 34	CPRD	N (%)	3,498 (29.2%)	3,712 (26.1%)	1,156 (26.7%)	566 (27.7%)	2,422 (27.7%)
		IPCI	N (%)	529 (34.2%)	802 (21.0%)	43 (28.1%)	9 (27.3%)	3,257 (37.5%)
		IQVIA LPD Belgium	N (%)	194 (10.8%)	199 (12.7%)	28 (5.1%)	19 (6.0%)	631 (13.7%)
		IQVIA DA Germany	N (%)	2,239 (6.2%)	1,487 (7.4%)	185 (7.8%)	11 (6.2%)	1,274 (4.4%)
		SIDIAP	N (%)	6,881 (36.7%)	4,389 (26.6%)	776 (28.8%)	-	4,202 (30.4%)
	35 to 39	CPRD	N (%)	3,023 (25.2%)	3,776 (26.5%)	1,194 (27.6%)	587 (28.7%)	2,105 (24.1%)
		IPCI	N (%)	367 (23.7%)	1,106 (28.9%)	35 (22.9%)	9 (27.3%)	2,151 (24.8%)
		IQVIA LPD Belgium	N (%)	108 (6.0%)	131 (8.4%)	17 (3.1%)	16 (5.0%)	421 (9.2%)
		IQVIA DA Germany	N (%)	1,667 (4.6%)	1,194 (6.0%)	147 (6.2%)	20 (11.4%)	1,010 (3.4%)

Variable name	Variable level	CDM name	Estimate name	Cohort name				
				Dulaglutide	Liraglutide	Exenatide	Lixisenatide	Semaglutide
		SIDIAP	N (%)	5,355 (28.6%)	4,782 (29.0%)	803 (29.8%)	-	3,833 (27.8%)
	40+	CPRD	N (%)	3,025 (25.2%)	4,218 (29.6%)	1,236 (28.5%)	659 (32.3%)	2,541 (29.1%)
		IPCI	N (%)	266 (17.2%)	982 (25.7%)	31 (20.3%)	7 (21.2%)	1,374 (15.8%)
		IQVIA LPD Belgium	N (%)	61 (3.4%)	69 (4.4%)	12 (2.2%)	10 (3.2%)	241 (5.2%)
		IQVIA DA Germany	N (%)	1,533 (4.2%)	1,161 (5.8%)	183 (7.8%)	23 (13.1%)	906 (3.1%)
		SIDIAP	N (%)	3,929 (21.0%)	4,990 (30.2%)	757 (28.1%)	-	3,363 (24.4%)
	NA (*no records in the past 5 years from index date*)	CPRD	N (%)	850 (7.1%)	1,199 (8.4%)	285 (6.6%)	76 (3.7%)	670 (7.7%)
		IPCI	N (%)	234 (15.1%)	730 (19.1%)	36 (23.5%)	<5 (<5%)	1,001 (11.5%)
		IQVIA LPD Belgium	N (%)	1,314 (73.2%)	1,036 (66.1%)	469 (85.1%)	260 (82.0%)	2,929 (63.7%)
		IQVIA DA Germany	N (%)	29,437 (81.0%)	15,282 (76.2%)	1,748 (74.1%)	107 (60.8%)	25,086 (85.7%)
		SIDIAP	N (%)	782 (4.2%)	1,236 (7.5%)	158 (5.9%)	-	1,164 (8.4%)

Variable name	Variable level	CDM name	Estimate name	Cohort name				
				Dulaglutide	Liraglutide	Exenatide	Lixisenatide	Semaglutide
Conditions	Chronic kidney disease	CPRD	N (%)	1,712 (14.3%)	1,805 (12.7%)	621 (14.3%)	315 (15.4%)	1,119 (12.8%)
		IPCI	N (%)	<5 (<5%)	7 (0.2%)	0 (0.0%)	0 (0.0%)	17 (0.2%)
		IQVIA LPD Belgium	N (%)	64 (3.6%)	24 (1.5%)	8 (1.5%)	7 (2.2%)	74 (1.6%)
		IQVIA DA Germany	N (%)	9,088 (25.0%)	5,047 (25.2%)	459 (19.4%)	29 (16.5%)	7,486 (25.6%)
		SIDIAP	N (%)	3,962 (21.2%)	2,257 (13.7%)	235 (8.7%)	-	2,879 (20.8%)
	Chronic kidney disease and renal impairment	CPRD	N (%)	1,718 (14.3%)	1,814 (12.7%)	625 (14.4%)	320 (15.7%)	1,123 (12.8%)
		IPCI	N (%)	141 (9.1%)	168 (4.4%)	<5 (<5%)	0 (0.0%)	791 (9.1%)
		IQVIA LPD Belgium	N (%)	65 (3.6%)	24 (1.5%)	8 (1.5%)	7 (2.2%)	75 (1.6%)
		IQVIA DA Germany	N (%)	9,097 (25.0%)	5,053 (25.2%)	459 (19.4%)	29 (16.5%)	7,504 (25.6%)
		SIDIAP	N (%)	3,962 (21.2%)	2,258 (13.7%)	235 (8.7%)	-	2,879 (20.8%)
	Heart failure	CPRD	N (%)	436 (3.6%)	412 (2.9%)	130 (3.0%)	66 (3.2%)	316 (3.6%)

Variable name	Variable level	CDM name	Estimate name	Cohort name				
				Dulaglutide	Liraglutide	Exenatide	Lixisenatide	Semaglutide
		IPCI	N (%)	53 (3.4%)	107 (2.8%)	<5 (<5%)	0 (0.0%)	321 (3.7%)
		IQVIA LPD Belgium	N (%)	130 (7.2%)	36 (2.3%)	19 (3.4%)	16 (5.0%)	181 (3.9%)
		IQVIA DA Germany	N (%)	4,053 (11.2%)	2,184 (10.9%)	229 (9.7%)	25 (14.2%)	3,244 (11.1%)
		SIDIAP	N (%)	1,523 (8.1%)	1,027 (6.2%)	141 (5.2%)	-	1,056 (7.6%)
	Hyper-tension	CPRD	N (%)	4,155 (34.7%)	4,639 (32.6%)	1,554 (35.9%)	699 (34.2%)	3,073 (35.2%)
		IPCI	N (%)	421 (27.2%)	921 (24.1%)	30 (19.6%)	13 (39.4%)	2,466 (28.4%)
		IQVIA LPD Belgium	N (%)	1,255 (70.0%)	803 (51.2%)	341 (61.9%)	216 (68.1%)	2,387 (51.9%)
		IQVIA DA Germany	N (%)	25,329 (69.7%)	13,381 (66.7%)	1,652 (70.0%)	133 (75.6%)	19,920 (68.0%)
		SIDIAP	N (%)	8,792 (46.9%)	6,792 (41.1%)	1,057 (39.2%)	-	6,309 (45.7%)
	Myocardial infarction	CPRD	N (%)	549 (4.6%)	563 (4.0%)	154 (3.6%)	80 (3.9%)	380 (4.3%)
		IPCI	N (%)	61 (3.9%)	125 (3.3%)	<5 (<5%)	<5 (<5%)	403 (4.6%)

Variable name	Variable level	CDM name	Estimate name	Cohort name				
				Dulaglutide	Liraglutide	Exenatide	Lixisenatide	Semaglutide
		IQVIA LPD Belgium	N (%)	46 (2.6%)	26 (1.7%)	22 (4.0%)	12 (3.8%)	69 (1.5%)
		IQVIA DA Germany	N (%)	1,143 (3.1%)	540 (2.7%)	62 (2.6%)	5 (2.8%)	837 (2.9%)
		SIDIAP	N (%)	1,059 (5.7%)	679 (4.1%)	102 (3.8%)	-	801 (5.8%)
	MACE	CPRD	N (%)	818 (6.8%)	807 (5.7%)	249 (5.8%)	108 (5.3%)	551 (6.3%)
		IPCI	N (%)	99 (6.4%)	194 (5.1%)	<5 (<5%)	<5 (<5%)	663 (7.6%)
		IQVIA LPD Belgium	N (%)	85 (4.7%)	56 (3.6%)	30 (5.4%)	14 (4.4%)	148 (3.2%)
		IQVIA DA Germany	N (%)	2,497 (6.9%)	1,147 (5.7%)	133 (5.6%)	11 (6.2%)	1,779 (6.1%)
		SIDIAP	N (%)	1,919 (10.2%)	1,240 (7.5%)	195 (7.2%)	-	1,341 (9.7%)
	Stroke	CPRD	N (%)	304 (2.5%)	273 (1.9%)	103 (2.4%)	31 (1.5%)	184 (2.1%)
		IPCI	N (%)	45 (2.9%)	79 (2.1%)	<5 (<5%)	<5 (<5%)	294 (3.4%)

Variable name	Variable level	CDM name	Estimate name	Cohort name				
				Dulaglutide	Liraglutide	Exenatide	Lixisenatide	Semaglutide
		IQVIA LPD Belgium	N (%)	41 (2.3%)	32 (2.0%)	8 (1.5%)	<5 (<5%)	84 (1.8%)
		IQVIA DA Germany	N (%)	1,483 (4.1%)	662 (3.3%)	77 (3.3%)	6 (3.4%)	1,011 (3.5%)
		SIDIAP	N (%)	943 (5.0%)	608 (3.7%)	98 (3.6%)	-	589 (4.3%)

BMI, body mass index; CDM, common data model; MACE, composite outcome including myocardial infraction and stroke; NA, not available (no BMI value recorded in the last 5 years from first use of GLP-1 RA).

Characteristics of GLP-1RA patients by indication

Full characteristics of drug users of GLP-1 at the time of their first prescription and as assessed at the beginning of each treatment episode by indication (diagnosis of obesity, diagnosis of DM2, diagnosis of DM2 and obesity, or other indications) are available in the shiny app [*see Characteristics tab – use the Denominator Cohort sub-tab to select the GLP-1 RA user cohort/s of interest (ensure those are "_incident")*]. Given the large number of results, we selected semaglutide as an example.

Table 13 presents the results for the first time users of semaglutide overall, and by the four indication cohorts. The majority of new patients treated with semaglutide had the diagnosis of DM2 with obesity indication. Individuals in the Other indication (i.e., no diagnosis of obesity nor DM2) were the smallest group and had the largest proportion of patients with missing BMI.

Characteristics of semaglutide users assessed at the beginning of each treatment episode are summarised in **Appendix II.**

Table 13. Description of new users of semaglutide use, overall and stratified by indication.

CDM name	Variable name	Variable level	Estimate name	Cohort name				
				Semaglutide (overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
CPRD GOLD	Number subjects	-	N	8,727	6,228	313	1,886	399
IPCI		-	N	8,626	6,504	1,354	628	434
IQVIA DA Germany		-	N	29,283	18,940	9,977	253	113
IQVIA LPD Belgium		-	N	4,597	2,665	1,625	121	186
SIDIAP		-	N	13,809	13,017	751	36	5
CPRD GOLD	Sex distribution (respect number of records)	Male	N (%)	4,336 (49.6%)	3,114 (49.9%)	188 (59.9%)	886 (47.0%)	203 (50.9%)
IPCI		Male	N (%)	4,260 (49.1%)	3,177 (48.5%)	729 (53.6%)	275 (43.7%)	211 (48.6%)
IQVIA DA Germany		Male	N (%)	15,610 (53.3%)	9,880 (52.2%)	5,528 (55.4%)	136 (53.8%)	66 (58.4%)
IQVIA LPD Belgium		Male	N (%)	1,741 (37.9%)	935 (35.1%)	648 (39.9%)	62 (51.2%)	96 (51.6%)
SIDIAP		Male	N (%)	6,631 (48.0%)	6,264 (48.1%)	346 (46.1%)	18 (50.0%)	<5 (<5%)

CDM name	Variable name	Variable level	Estimate name	Cohort name				
				Semaglutide (overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
CPRD GOLD	Age (years)	-	Median [Q25 - Q75]	59 [51 - 66]	59 [51 - 66]	62 [53 - 71]	59 [50 - 66]	57 [45 - 66]
			Mean (SD)	57.93 (11.92)	58.07 (11.54)	61.06 (12.01)	57.60 (12.36)	55.31 (14.53)
			Range	12 to 89	18 to 89	15 to 84	15 to 88	12 to 87
IPCI			Median [Q25 - Q75]	61 [53 - 69]	61 [53 - 68]	62 [54 - 69]	60 [52 - 68]	61 [53 - 69]
			Mean (SD)	60.53 (11.22)	60.56 (10.96)	60.98 (11.98)	59.34 (11.69)	59.93 (12.23)
			Range	15 to 91	18 to 91	16 to 90	18 to 84	15 to 83
IQVIA DA Germany			Median [Q25 - Q75]	60.00 [52.00 - 68.00]	60.00 [52.00 - 68.00]	62.00 [53.00 - 70.00]	54.00 [42.00 - 63.00]	55.00 [45.00 - 65.00]
			Mean (SD)	59.60 (12.52)	59.00 (12.30)	60.97 (12.69)	52.12 (14.52)	55.09 (14.45)
			Range	6.00 to 96.00	14.00 to 96.00	6.00 to 95.00	14.00 to 86.00	19.00 to 81.00

CDM name	Variable name	Variable level	Estimate name	Cohort name				
				Semaglutide (overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
IQVIA LPD Belgium			Median [Q25 - Q75]	55.00 [45.00 - 64.00]	53.00 [43.00 - 62.00]	57.00 [47.00 - 66.00]	61.00 [49.00 - 67.00]	63.00 [54.00 - 69.00]
			Mean (SD)	53.95 (13.66)	52.20 (13.31)	55.71 (13.84)	58.31 (13.90)	60.78 (12.16)
			Range	6.00 to 96.00	15.00 to 95.00	6.00 to 96.00	22.00 to 90.00	22.00 to 89.00
SIDIAP			Median [Q25 - Q75]	60 [51 - 67]	60 [51 - 68]	58 [48 - 65]	44 [38 - 57]	43 [30 - 43]
			Mean (SD)	58.78 (12.06)	58.96 (11.94)	56.42 (13.20)	45.31 (15.37)	41.20 (16.15)
			Range	14 to 98	14 to 93	17 to 98	18 to 78	24 to 66
CPRD GOLD	Age group [years]	0 to 17	N (%)	<5 (<5%)	-	<5 (<5%)	<5 (<5%)	<5 (<5%)
IPCI		0 to 17	N (%)	<5 (<5%)	-	<5 (<5%)	-	<5 (<5%)
IQVIA DA Germany		0 to 17	N (%)	17 (0.1%)	8 (0.0%)	8 (0.1%)	<5 (<5%)	-
IQVIA LPD Belgium		0 to 17	N (%)	7 (0.2%)	<5 (<5%)	<5 (<5%)	-	-

CDM name	Variable name	Variable level	Estimate name	Cohort name				
				Semaglutide (overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
SIDIAP		0 to 17	N (%)	11 (0.1%)	10 (0.1%)	<5 (<5%)	-	-
CPRD GOLD		18 to 64	N (%)	6,098 (69.8%)	4,381 (70.2%)	184 (58.6%)	1,310 (69.4%)	285 (71.4%)
IPCI		18 to 64	N (%)	5,340 (61.5%)	4,066 (62.1%)	800 (58.8%)	399 (63.3%)	255 (58.8%)
IQVIA DA Germany		18 to 64	N (%)	18,586 (63.5%)	12,417 (65.6%)	5,888 (59.0%)	200 (79.1%)	81 (71.7%)
IQVIA LPD Belgium		18 to 64	N (%)	3,486 (75.8%)	2,158 (81.0%)	1,154 (71.0%)	74 (61.2%)	100 (53.8%)
SIDIAP		18 to 64	N (%)	9,102 (65.9%)	8,522 (65.5%)	544 (72.4%)	32 (88.9%)	<5 (<5%)
CPRD GOLD		65+	N (%)	2,639 (30.2%)	1,859 (29.8%)	129 (41.1%)	575 (30.5%)	113 (28.3%)
IPCI		65+	N (%)	3,338 (38.5%)	2,483 (37.9%)	560 (41.1%)	231 (36.7%)	178 (41.0%)
IQVIA DA Germany		65+	N (%)	10,680 (36.5%)	6,515 (34.4%)	4,081 (40.9%)	52 (20.6%)	32 (28.3%)
IQVIA LPD Belgium		65+	N (%)	1,104 (24.0%)	503 (18.9%)	468 (28.8%)	47 (38.8%)	86 (46.2%)
SIDIAP		65+	N (%)	4,696 (34.0%)	4,485 (34.5%)	206 (27.4%)	<5 (<5%)	<5 (<5%)

CDM name	Variable name	Variable level	Estimate name	Cohort name				
				Semaglutide (overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
CPRD GOLD	BMI (kg/m2)	-	Median [Q25 - Q75]	35.70 [31.60 - 41.00]	36.30 [32.40 - 41.60]	26.55 [25.00 - 28.00]	35.50 [32.00 - 40.40]	27.60 [26.18 - 28.60]
			Range	15.70 to 60.00	22.70 to 60.00	21.00 to 29.90	15.70 to 59.80	19.80 to 29.90
IPCI	BMI (kg/m2)	-	Median [Q25 - Q75]	33.98 [30.99 - 37.81]	34.50 [31.70 - 38.20]	28.18 [26.40 - 30.48]	34.53 [31.91 - 38.10]	30.40 [28.04 - 33.88]
			Range	17.90 to 59.57	21.20 to 59.93	17.90 to 55.47	24.20 to 58.62	19.92 to 57.55
IQVIA DA Germany	BMI (kg/m2)	-	Median [Q25 - Q75]	33.79 [29.71 - 38.53]	35.15 [31.53 - 39.66]	26.87 [25.03 - 28.54]	33.16 [29.25 - 39.39]	27.16 [25.17 - 27.70]
			Range	17.45 to 58.82	17.45 to 58.82	18.61 to 29.99	20.44 to 50.75	22.77 to 28.93
IQVIA LPD Belgium	BMI (kg/m2)	-	Median [Q25 - Q75]	33.20 [30.02 - 37.01]	33.91 [31.17 - 37.56]	27.28 [25.39 - 28.67]	35.92 [32.37 - 39.21]	28.20 [26.70 - 28.34]
			Range	16.90 to 57.77	18.52 to 57.77	16.90 to 29.83	23.41 to 50.78	23.62 to 29.65
SIDIAP	BMI (kg/m2)	-	Median [Q25 - Q75]	35.43 [31.99 - 39.91]	35.70 [32.37 - 40.09]	27.21 [25.52 - 28.33]	32.56 [30.81 - 35.94]	27.68 [27.12 - 28.23]

CDM name	Variable name	Variable level	Estimate name	Cohort name				
				Semaglutide (overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
			Range	12.48 to 59.88	12.48 to 59.88	17.39 to 29.96	25.97 to 45.29	26.56 to 28.79
CPRD GOLD	BMI group [kg/m2]	0 to 26	N (%)	274 (3.1%)	105 (1.7%)	117 (37.3%)	20 (1.1%)	43 (10.8%)
IPCI		0 to 26	N (%)	259 (3.0%)	40 (0.6%)	202 (14.8%)	<5 (<5%)	33 (7.6%)
IQVIA DA Germany		0 to 26	N (%)	428 (1.5%)	138 (0.7%)	277 (2.8%)	10 (4.0%)	<5 (<5%)
IQVIA LPD Belgium		0 to 26	N (%)	144 (3.1%)	58 (2.2%)	80 (4.9%)	<5 (<5%)	<5 (<5%)
SIDIAP		0 to 26	N (%)	306 (2.2%)	154 (1.2%)	151 (20.1%)	<5 (<5%)	-
CPRD GOLD		27 to 29	N (%)	729 (8.3%)	434 (7.0%)	123 (39.2%)	95 (5.0%)	88 (22.1%)
IPCI		27 to 29	N (%)	638 (7.4%)	250 (3.8%)	333 (24.5%)	19 (3.0%)	75 (17.3%)
IQVIA DA Germany		27 to 29	N (%)	579 (2.0%)	261 (1.4%)	303 (3.0%)	10 (4.0%)	5 (4.4%)
IQVIA LPD Belgium		27 to 29	N (%)	231 (5.0%)	116 (4.4%)	107 (6.6%)	<5 (<5%)	6 (3.2%)

CDM name	Variable name	Variable level	Estimate name	Cohort name				
				Semaglutide (overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
SIDIAP		27 to 29	N (%)	941 (6.8%)	698 (5.4%)	237 (31.6%)	<5 (<5%)	<5 (<5%)
CPRD GOLD		30 to 34	N (%)	2,422 (27.7%)	1,827 (29.3%)	8 (2.5%)	603 (32.0%)	13 (3.3%)
IPCI		30 to 34	N (%)	3,257 (37.5%)	2,847 (43.5%)	145 (10.7%)	266 (42.2%)	110 (25.3%)
IQVIA DA Germany		30 to 34	N (%)	1,274 (4.4%)	1,200 (6.3%)	53 (0.5%)	21 (8.3%)	-
IQVIA LPD Belgium		30 to 34	N (%)	631 (13.7%)	587 (22.0%)	14 (0.9%)	29 (24.0%)	<5 (<5%)
SIDIAP		30 to 34	N (%)	4,202 (30.4%)	4,168 (32.0%)	20 (2.7%)	14 (38.9%)	-
CPRD GOLD		35 to 39	N (%)	2,105 (24.1%)	1,634 (26.2%)	-	485 (25.7%)	-
IPCI		35 to 39	N (%)	2,151 (24.8%)	1,916 (29.3%)	68 (5.0%)	181 (28.7%)	38 (8.8%)
IQVIA DA Germany		35 to 39	N (%)	1,010 (3.4%)	995 (5.3%)	-	15 (5.9%)	-
IQVIA LPD Belgium		35 to 39	N (%)	421 (9.2%)	398 (14.9%)	-	23 (19.0%)	-
SIDIAP		35 to 39	N (%)	3,833 (27.8%)	3,827 (29.4%)	-	6 (16.7%)	-

CDM name	Variable name	Variable level	Estimate name	Cohort name				
				Semaglutide (overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
CPRD GOLD		40+	N (%)	2,541 (29.1%)	2,082 (33.4%)	-	481 (25.5%)	-
IPCI		40+	N (%)	1,374 (15.8%)	1,233 (18.8%)	40 (2.9%)	115 (18.3%)	22 (5.1%)
IQVIA DA Germany		40+	N (%)	906 (3.1%)	888 (4.7%)	-	18 (7.1%)	-
IQVIA LPD Belgium		40+	N (%)	241 (5.2%)	223 (8.4%)	-	18 (14.9%)	-
SIDIAP		40+	N (%)	3,363 (24.4%)	3,359 (25.8%)	-	<5 (<5%)	-
CPRD GOLD		NA (*no records in the past 5 years from index date*)	N (%)	670 (7.7%)	158 (2.5%)	66 (21.0%)	203 (10.8%)	255 (63.9%)
IPCI			N (%)	1,001 (11.5%)	263 (4.0%)	573 (42.1%)	48 (7.6%)	156 (35.9%)
IQVIA DA Germany			N (%)	25,086 (85.7%)	15,458 (81.6%)	9,344 (93.7%)	179 (70.8%)	105 (92.9%)
IQVIA LPD Belgium			N (%)	2,929 (63.7%)	1,283 (48.1%)	1,424 (87.6%)	46 (38.0%)	176 (94.6%)
SIDIAP			N (%)	1,164 (8.4%)	811 (6.2%)	343 (45.7%)	7 (19.4%)	<5 (<5%)
CPRD GOLD	Conditions		N (%)	1,119 (12.8%)	889 (14.2%)	45 (14.3%)	190 (10.1%)	11 (2.8%)

CDM name	Variable name	Variable level	Estimate name	Cohort name				
				Semaglutide (overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
IPCI		Chronic kidney disease	N (%)	17 (0.2%)	12 (0.2%)	<5 (<5%)	<5 (<5%)	<5 (<5%)
IQVIA DA Germany			N (%)	7,486 (25.6%)	5,556 (29.3%)	1,816 (18.2%)	100 (39.5%)	14 (12.4%)
IQVIA LPD Belgium			N (%)	74 (1.6%)	35 (1.3%)	27 (1.7%)	5 (4.1%)	7 (3.8%)
SIDIAP			N (%)	2,879 (20.8%)	2,726 (20.9%)	146 (19.4%)	6 (16.7%)	<5 (<5%)
CPRD GOLD		Chronic kidney disease and renal impairment	N (%)	1,123 (12.8%)	891 (14.3%)	45 (14.3%)	192 (10.2%)	11 (2.8%)
IPCI			N (%)	791 (9.1%)	654 (10.0%)	102 (7.5%)	28 (4.4%)	9 (2.1%)
IQVIA DA Germany			N (%)	7,504 (25.6%)	5,565 (29.4%)	1,825 (18.3%)	100 (39.5%)	14 (12.4%)
IQVIA LPD Belgium			N (%)	75 (1.6%)	36 (1.4%)	27 (1.7%)	5 (4.1%)	7 (3.8%)
SIDIAP			N (%)	2,879 (20.8%)	2,726 (20.9%)	146 (19.4%)	6 (16.7%)	<5 (<5%)
CPRD GOLD		Heart failure	N (%)	316 (3.6%)	253 (4.1%)	6 (1.9%)	59 (3.1%)	<5 (<5%)
IPCI			N (%)	321 (3.7%)	261 (4.0%)	43 (3.2%)	16 (2.5%)	<5 (<5%)

CDM name	Variable name	Variable level	Estimate name	Cohort name				
				Semaglutide (overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
IQVIA DA Germany			N (%)	3,244 (11.1%)	2,343 (12.4%)	871 (8.7%)	26 (10.3%)	<5 (<5%)
IQVIA LPD Belgium			N (%)	181 (3.9%)	83 (3.1%)	65 (4.0%)	13 (10.7%)	20 (10.8%)
SIDIAP			N (%)	1,056 (7.6%)	1,024 (7.9%)	30 (4.0%)	<5 (<5%)	<5 (<5%)
CPRD GOLD		Hypertension	N (%)	3,073 (35.2%)	2,689 (43.1%)	85 (27.1%)	295 (15.6%)	23 (5.8%)
IPCI			N (%)	2,466 (28.4%)	2,192 (33.5%)	207 (15.2%)	70 (11.1%)	12 (2.8%)
IQVIA DA Germany			N (%)	19,920 (68.0%)	14,066 (74.3%)	5,624 (56.4%)	179 (70.8%)	51 (45.1%)
IQVIA LPD Belgium			N (%)	2,387 (51.9%)	1,314 (49.3%)	846 (52.1%)	91 (75.2%)	136 (73.1%)
SIDIAP			N (%)	6,309 (45.7%)	6,058 (46.5%)	237 (31.6%)	12 (33.3%)	<5 (<5%)
CPRD GOLD		Myocardial infarction	N (%)	380 (4.3%)	309 (5.0%)	14 (4.5%)	55 (2.9%)	<5 (<5%)
IPCI			N (%)	403 (4.6%)	316 (4.8%)	73 (5.4%)	12 (1.9%)	<5 (<5%)
IQVIA DA Germany			N (%)	837 (2.9%)	554 (2.9%)	271 (2.7%)	9 (3.6%)	<5 (<5%)
IQVIA LPD Belgium			N (%)	69 (1.5%)	20 (0.8%)	44 (2.7%)	<5 (<5%)	<5 (<5%)

CDM name	Variable name	Variable level	Estimate name	Cohort name				
				Semaglutide (overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
SIDIAP			N (%)	801 (5.8%)	758 (5.8%)	40 (5.3%)	<5 (<5%)	0 (0.0%)
CPRD GOLD		Myocardial infarction stroke	N (%)	551 (6.3%)	449 (7.2%)	17 (5.4%)	82 (4.3%)	6 (1.5%)
IPCI			N (%)	663 (7.6%)	530 (8.1%)	115 (8.4%)	20 (3.2%)	5 (1.2%)
IQVIA DA Germany			N (%)	1,779 (6.1%)	1,185 (6.3%)	572 (5.7%)	14 (5.5%)	8 (7.1%)
IQVIA LPD Belgium			N (%)	148 (3.2%)	51 (1.9%)	86 (5.3%)	<5 (<5%)	8 (4.3%)
SIDIAP			N (%)	1,341 (9.7%)	1,273 (9.8%)	63 (8.4%)	5 (13.9%)	0 (0.0%)
CPRD GOLD		Stroke	N (%)	184 (2.1%)	152 (2.4%)	<5 (<5%)	28 (1.5%)	<5 (<5%)
IPCI			N (%)	294 (3.4%)	236 (3.6%)	52 (3.8%)	10 (1.6%)	<5 (<5%)
IQVIA DA Germany			N (%)	1,011 (3.5%)	672 (3.5%)	326 (3.3%)	8 (3.2%)	5 (4.4%)
IQVIA LPD Belgium			N (%)	84 (1.8%)	34 (1.3%)	44 (2.7%)	<5 (<5%)	5 (2.7%)
SIDIAP			N (%)	589 (4.3%)	563 (4.3%)	23 (3.1%)	<5 (<5%)	0 (0.0%)

Abbreviations: BMI, body mass index; CDM, common data model; MACE, composite outcome including myocardial infraction and stroke; NA, not available (no BMI value recorded in the last 5 years from first use of GLP-1 RA).

13.2.3.2 Dose

Table 14 summarises the description of initial and cumulative dose in new users of GLP-1RA. Full dose results including new GLP-1 users stratified by indication is available in the shiny app [*see Dose tab*].

Table 14. Description of initial and cumulative dose in new users of GLP-1RA.

Data base	GLP-1 RA	Initial daily dose (milligram)					Cumulative dose (milligram)				
		Median dose	Q25	Q75	Patients with missing dose (n)	Percentage missing (%)	Median dose	Q25	Q75	Patients with missing dose (n)	Percentage missing (%)
CPRD	Exenatide	0.3	0.02	1.2	101	0.21	1.2	1.2	5.4	96	0.2
	Liraglutide	18	4.8	24	863	0.6	72	54	144	854	0.59
	Lixisenatide	0	0	0	1091	22.57	0.15	0.08	0.32	200	4.14
	Dulaglutide	0.21	0.11	0.21	34	0.17	36	12	96	33	0.16
	Semaglutide	0.29	0.29	0.57	109	0.33	8.04	4.02	18.09	89	0.27
IPCI	Exenatide	0.29	0.02	0.29	157	19.7	16.14	1.8	56	153	19.2
	Liraglutide	3	1.08	10.8	447	2.96	108	72	234.78	332	2.2
	Lixisenatide	0.02	0.02	0.12	31	46.97	1.68	1.26	2.24	23	34.85
	Dulaglutide	0.21	0.21	0.43	44	1.26	27	12	71.42	24	0.69
	Semaglutide	0.14	0.04	3	3562	21.73	42	10	300	3040	18.55
IQVIA LPD Belgium	Exenatide	6	2	16	815	21.1	16	8	24	809	20.95
	Liraglutide	36	6	72	NA	NA	90	72	108	NA	NA
	Lixisenatide	0.56	0.02	1.12	148	10.75	1.12	1.12	1.68	113	8.21

Data base	GLP-1 RA	Initial daily dose (milligram)					Cumulative dose (milligram)				
		Median dose	Q25	Q75	Patients with missing dose (n)	Percentage missing (%)	Median dose	Q25	Q75	Patients with missing dose (n)	Percentage missing (%)
	Dulaglutide	6	3	12	0	0	12	6	18	0	0
	Semaglutide	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
IQVIA DA Germany	Exenatide	0.06	0.01	0.06	0	0	1.8	1.8	1.8	0	0
	Liraglutide	1.2	1.2	10.8	0	0	180	90	270	0	0
	Lixisenatide	0.06	0.02	0.06	0	0	1.8	1.2	1.95	0	0
	Dulaglutide	0.16	0.16	0.21	0	0	18	9	54	0	0
	Semaglutide	0.03	0.03	0.05	4198	3.91	1	1	1.5	2064	1.92
SIDIAP	Exenatide	0.28	0.02	0.28	1559	25.17	25.43	5.74	134.43	681	10.99
	Liraglutide	3.60	5.96	7.18	822	3.44	395.51	1,722.00	6,120.34	522	2.18
	Lixisenatide	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Dulaglutide	0.21	0.42	0.43	33	0.15	43.71	136.47	297.35	16	0.07
	Semaglutide	0.03	0.07	0.13	36	0.21	4.66	19.43	61.66	11	0.06

NA, not available.

13.3 Sensitivity analysis

The sensitivity analysis stratifying the point prevalence estimates by the different concepts_id to characterise the use of individual strengths is available in the shiny app [*see Sensitivity Analysis – Prevalence tab*].

An example of what information is available is shown in **Figure 30**, where the use of the different exenatide products (including the specification of the strength) in CPRD is displayed.

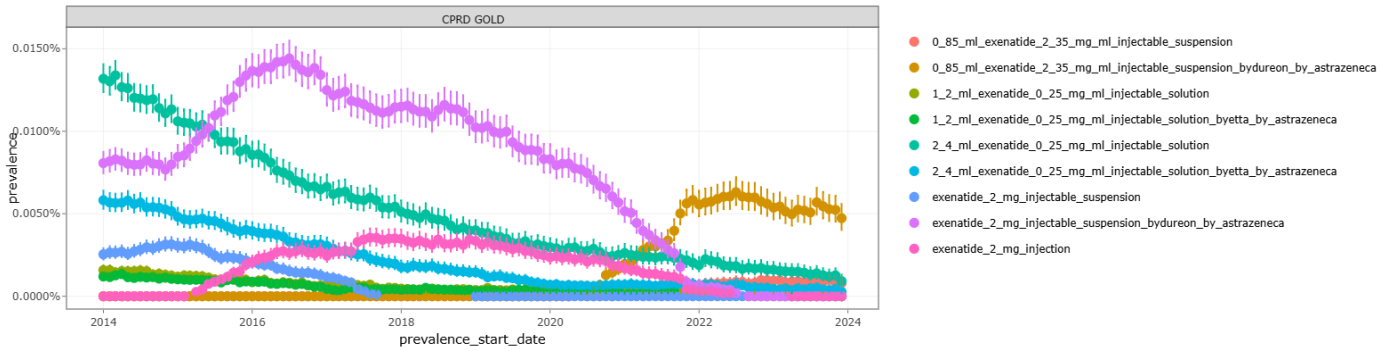


Figure 30. Point prevalence of exenatide use products in CPRD.

14. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions are not be collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

Only in case of prospective data collection, there is a need to describe the procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions.

15. DISCUSSION

15.1. Key results

The analyses of incidence of GLP-1 RA initiation showed that the use of exenatide and lixisenatide decreased, whilst the prescription of dulaglutide and semaglutide have increased over time. Over the study period, the incidence of semaglutide became higher than dulaglutide in 4 out of the 5 all databases (except SIDIAP, which it kept fluctuating which one was more used). The increase in the IR per 100,000 person-years for dulaglutide steadily rose between 2016 and 2024, not exceeding an IR of 100 cases in four of the five databases (except IQVIA LPD Belgium, which its IR exceeded the 200). In contrast, the increase in semaglutide reached equal or higher IR values in a shorter period (e.g., from its first incidence observed in CPRD in March 2019, IR increased to 94 cases per 100,000 person-years in February 2020). Moreover, incidence of liraglutide use presented an increase after 2022 in 4 of the of the 5 databases of the study (CPRD, IPCI, SIDIAP and IQVIA LPD Belgium).

Prevalence of dulaglutide and semaglutide use increased over time in all databases, with final observed values in December 2023 ranging from 0.03% for dulaglutide in IPCI to 0.35% for semaglutide in IPCI. Over the study period, prevalence of semaglutide became higher than dulaglutide in 2 out of the 5 all databases (IPCI and IQVIA LPD Belgium), and in line with incidence results, prevalence of semaglutide use increased to similar or higher values in a shorter time frame than dulaglutide. Prevalence of liraglutide use showed a mixed pattern, from an overall decrease in its prevalence in CPRD to an increase in SIDIAP, IPCI and IQVIA DA Germany. However, its prevalence did not exceed 0.1% in any of the databases. On the other hand, the prevalence of use of exenatide and lixisenatide decreased over time across all databases.

When stratified by indication, most individuals that started a GLP-1 RA treatment had a record of DM2 with obesity, except for dulaglutide, exenatide and lixisenatide in IQVIA LPD Belgium where the most common record was DM2. However, IQVIA LPD Belgium was the database where BMI data was most frequently missing.

The numbers of users who started treatment with GLP-1 RA at age <18 was so small that incidence stratified by age and sex could only be estimated for liraglutide in SIDIAP after February 2023, and for orlistat only in CPRD before 2016. Incidence of liraglutide use was higher among women in IPCI, with peaks between May-June 2022 led by women aged between 18-64 years. Similarly, peaks in incidence of liraglutide use in IQVIA LPD Belgium were observed among women between August-September 2022. Conversely, incidence of dulaglutide and semaglutide were higher in men than women in IQVIA DA Germany.

The patient-level characterisation of new GLP-1 RA users indicated that most of individuals that started GLP-1 RA had a diagnosis of DM2, with or without obesity. IQVIA DA Germany and LPD Belgium presented the highest percentage of missing BMI records (more than half patients with missing data), followed by IPCI (with up to 23.5% of patients with missing data), limiting the interpretation of BMI in these databases. Completeness of BMI records was much better and mostly >90% in primary care data from SIDIAP and CPRD. Among those with a BMI record, the characterisation of new users by BMI categories revealed that users with a BMI ≤26 kg/m2 were highly infrequent and less than 4% in all databases.

Seven comorbidities were analysed for patients at the time of their first prescription of GLP-1 RA. Hypertension was the most common comorbidity, present in 19.6% to 75.6% of the patients; followed by chronic kidney disease and renal impairment, present in up to 25.2% of the patients; and heart failure, present in up to 14.2%.

The incidence of metformin presented stationary fluctuations in 3 out of 5 databases of the study (CPRD, IQVIA LPD Belgium and SIDIAP) and was stable over time except for IQVIA DA Germany and IPCI. Incidence

of naltrexone/bupropion use was observed mostly only in IPCI and IQVIA LPD Belgium, and that occurred after May 2022. Similarly, incidence of orlistat use was mostly observed only in IQVIA LPD Belgium and CPRD, with CPRD presenting a seasonality pattern with increased incidence generally before and during summer months.

Prevalence of metformin use generally presented a moderate increase (difference between the minimum and maximum prevalence values across the entire study period was less than <0.8%) that could be considered as stable or negligible, with values between 2% and 6%, except for last 5 months of observed data in IQVIA LPD Belgium (December 2023-May 2024), which increased up to 9.2% in February 2024. Larger increases observed in IQVIA DA Germany and IQVIA LPD Belgium prevalence may be driven by an artefactual decrease in their denominators during the last 6 months of the study period. Prevalence of orlistat use was observed in CPRD and IQVIA LPD Belgium, with values ranged between 0.02% and 0.07% and with CPRD presenting a potential seasonality pattern with increased prevalence around July. Prevalence of naltrexone/bupropion use gradually increased since September 2021 in IQVIA LPD Belgium and IPCI, but values remained below 0.27%.

15.2. Limitations of the research methods

The study was conducted using routinely collected data from healthcare databases and so data quality issues must be considered. In particular, we considered patients were continuously exposed to the same drug during the 30 days after its prescription or dispensation, but a recording of a prescription or dispensation does not mean that the patient actually took the drug. In addition, assumptions around the duration of drug use were unavoidable: the methodology to calculate initial and cumulative dose in the OMOP-CDM relies on the data availability of the drug strength, which is not always captured. Additionally, the strength can be recorded differently depending on the dose form (e.g., number of tablets for pills or number of millilitres for liquids), and the record of different units for the same ingredient produces results separately for each unit. Different levels of granularity may also impact the calculation of dose and duration. However, the methodology developed to calculate dose and duration in OMOP-CDM was applicable to >85% of drugs records and its testing included CPRD, IPCI and both IQVIA databases.[8] Treatment might have been affected by shortages of individual medicines and patients could not had access to the prescribed drug for a certain time or may switch to a suitable alternative medicinal product. In this line, this study did not explore exposure to different strengths nor changes between different GLP-1 RA and could be further investigated.

The specific reason (i.e., the indication) for the prescriptions of the drugs were not recorded in any of the databases. We had assessed indication via a proxy based on pre-defined conditions recorded, being those DM2 before or on the date of first use of GLP-1 RA, and obesity diagnosed or measured anytime during the observation period. Therefore, the recording of potential indications might have been incomplete, for instance, low recording of BMI in IQVIA LPD Belgium and IQVIA DA Germany may have impacted the recording of the obesity indication. In addition, the completeness of recordings of co-morbidities used for patient characterisation might have variated across databases. For instance, records of stroke and myocardial infarction might have been incomplete at primary care records given that these two conditions are commonly treated at hospitals.

BMI is generally a stable value in adults.[9] Thus, and to reduce the missing BMI records on the date of the prescription, we captured the most recent value in the last 5 years from patient's index date. However, we cannot rule out some misclassification could had been included using this strategy (i.e., we cannot rule out that there might be some patients with a BMI value extracted e.g., 5 years before the GLP-1 RA prescription that may show a normal [≤24.9 kg/m2] or overweight [≤29.9 kg/m2] BMI, while the actual BMI value at the time the first GLP-1 RA was prescribed might have been in the overweight or obese [≥30 kg/m2] range).

Additionally, stratification of prescriber speciality was only available in IQVIA DA Germany and not standard, and could therefore not be conducted for this report.

Database-specific limitations:

In IQVIA LPD Belgium and IQVIA DA Germany, the observation period of the patients in these databases had been calculated based on the last visit, observation or interaction of the patient with the healthcare system. This methodology impacts the individuals considered "at risk" for the different medicines of interest of the study (i.e., the individuals included in the denominator populations) during the latest months of available data from the latest data lock, where healthy and/or non-frequent users of the healthcare system were not considered active. Consequently, the denominators that were used to calculate the incident and prevalent use of drugs in the population presented an artefactual decrease whilst the incident and prevalent users remained, artificially inflating the incidence and prevalence ratios towards the end of the observation period (please see incidence of metformin in **Figure 7C** vs number of metformin users shown in **Figure 8C** for IQVIA LPD Belgium, which illustrates this). The presence of these artefacts had been considered when interpreting the results in IQVIA databases, and, in order to mitigate this limitation, for the incidence estimates, we considered the trend of number of new users to confirm or deny any substantial increase at the end of the observation period.

In CPRD, GP practices from the UK using the EMIS Web® electronic patient record system software migrated from CPRD Gold to CPRD Aurum since 2018, whilst CPRD Gold maintained those GP practices using the Vision® software.[10] Consequently, there was an overall migration of patients that affected equally general and specific populations in the database (such as new users of a medicine of interest). Therefore, despite we observed a decrease when plotting the number of new users in CPRD, the IR should not have been impacted and presented the correct trends of incident use.

CPRD, IPCI and SIDIAP databases are based on primary care records and do not contain information in prescription of drugs given by specialists, which may also prescribe GLP-1 RA drugs. Mitigation action recommendations such as a requirement that the initial prescription should be issued by an endocrinologist could potentially had affected our results.[11] Potential effects of the implementation of such mitigation measures on the prescription of the drugs have not been taken into consideration in the current study but are likely to affect the results. Therefore, our results might be underestimating the use of the GLP-1 RA drugs in these three databases. In addition, the record size in the databases affects the ability to interpret the results. For example, IQVIA LPD Belgium covers 1.1 million patients from a total of 11.5 million Belgians which leads to a significant extrapolation in order to estimate the incidence rate and number of new users in respect to the entire population. As similar problem has been identified for IQVIA DA Germany, which covers a total of 43 million active subjects, but only 28.8% of the records are collected by general practitioners.

Another limitation of the current study is that the marketing status and reimbursement of the medicinal products in the individual countries has not been taken into consideration. The marketing status could have an influence on the prescription behaviour and availability of the products that could limit the interpretability.

IQVIA LPD Belgium, IQVIA DA Germany have a high percentage of patients without a BMI records (60.8% to 85.7%), while the percentage of individuals with missing BMI values in IPCI (<5% to 23.5%). The interpretation that GLP-1 RA users with a BMI ≤26 kg/m2 are infrequent in these three databases cannot be confirmed due to this high percentage of missing BMI records. Since BMI is less recorded among individuals who are younger or have less concomitant chronic conditions related to overweight,[12] we cannot rule out the possibility that a significant percentage of these patients with missing BMI records could have a BMI ≤26 kg/m2.

15.3. Interpretation

Prevalence of obesity has been increasing worldwide, whilst diabetes had become one of the most prevalent conditions among general population.[13-15] GLP-1 RA drugs are indicated for glucose control in DM2, for weight control under certain circumstances, or both.[16] The first GLP-1 RA product approved in the EU was the medicine containing exenatide as active substance in 2006, followed by liraglutide containing products in 2009, lixisenatide in 2013, dulaglutide in 2014 and semaglutide in 2018. Additionally, the indication to use a liraglutide containing medicinal product along with diet and increased physical activity to help manage weight for patients living with overweight or obesity was approved later than for the management of DM2. [14] All GLP-1 RA medicinal products approved in the EU/EEA are available as a solution for injection with the exception of one medicinal product containing semaglutide, which is for oral administration.

Since 2022, an increase in demand for some GLP-1 RAs, combined with manufacturing capacity constraints, has resulted in shortages throughout the EU/EEA.[1, 17] Mitigative actions put in place by EU/EEA countries, such as the publication of Direct Healthcare Professional Communication (DHPCs) and the publication of clinical practice guidelines and/or policy changes in individual countries may have an influence on the prescription and use of the medicinal products.[18, 19] For instance, the Netherlands allowed the reimbursement of GLP-1 RA drugs in 2022 upon adherence to a specified set of regulations , which could partially explain the increase in liraglutide use in IPCI in that year. Another example is the UK, where the guidelines for GLP-1 RA includes a reduction of 2.5 to 5kg/m2 in the BMI threshold for specific ethnic groups and could explain the marginally higher proportion of new GLP-1 RA users with a BMI between 27 and 29 kg/m2.[20, 21]

We found that GLP-1 RA were predominantly used by people living with type 2 diabetes, with or without obesity, which aligns with EU treatment recommendations that suggest prioritising these treatments for these conditions.[22] Exenatide usage was found to be higher among individuals with DM2, while liraglutide, dulaglutide and semaglutide were more commonly used in patients living with DM2 and obesity. Our study also found that there was a low proportion of new GLP-1 users who neither had a history of DM2 or obesity. This finding contrasts with a nationwide population study from Denmark that reported that up to a third of patients starting semaglutide in 2021 did not have an indication of DM2.[23]

Focussing further on the BMI categories, the majority of the new users of the current study had BMI values >30 kg/m2. Additionally, we observed that generally, individuals <18 are not prescribed GLP-1 RA drugs. The most common comorbidity in patients starting GLP-1 RA was hypertension, but the prevalence of this condition variated across the databases of the study (19.6% to 75.6%), showing the heterogeneity of the data. Multiple studies had shown this heterogeneity may be driven by the methodology used (called measurement heterogeneity), or by the clinical differences in the health-care systems, geographical regions and patients' behaviours (called true or clinical heterogeneity).[24] The use of the common data model minimises the impact of the measurement heterogeneity.[25] This study provides an overview of the current use of GLP-1 RA in the market in the selected databases. Future changes in the health policies and guidelines, such as the prioritisation of individuals accessing these medicines, may change the profile of patients starting GLP-1 RA medicines.

Lastly, information of the use of the other medicines used for the treatment of diabetes and weight management has limited significance in the current study as it reflects all prescriptions made for the respective medicine in the general population and not within the selected GLP-1 RA patient group. The data reflect solely the general prescribing behaviour for these substances for patient groups who may differ from GLP-1 RA users. For instance, metformin in monotherapy is commonly used as first line treatment for DM2 in EU.[26] However, there are other drug classes for the treatment of diabetes such as sulfonylureas or sodium-glucose co-transporter-2 inhibitors that were not included in this report and may be included in

a future study. Other than metformin, the prescription of the other medicines was generally very low. We could not rule out that the low prevalence of these other medicines might be specific to the selected databases of the study. In Denmark, initiation of orlistat and bupropion-naltrexone was very low over the study period (2018-2023), prevalence of bupropion-naltrexone use could not be assessed, and prevalence of orlistat use decreased.[23] However, a prior study in Norway reported a decrease in the use of orlistat from 2004 to 2022 but an increased use of bupropion-naltrexone between 2017 and 2022.[27] Further studies in other European databases may be considered to expand the understanding of GLP-1RA use in Europe. Moreover, future studies focusing on analysing the management of DM2 may be considered in order to explore whether there have been changes in the management of first-line treatments for DM2.

15.4. Generalisability

The study comprised all individuals using the GLP-1 RA of interest present in 5 databases from 5 different European countries. While we consider the results representative for the study population in the respective regions, the results should not be generalised to other countries or databases but only reflect the situation in the specific region and setting covered by the respective database. Nonetheless, this is the first study reporting trends of use of GLP-1 RA and the characteristics of the patients starting this medication in five databases from Europe simultaneously, providing a broader understanding of GLP-1 use. Further analyses expanding the current study to other databases may be considered to observe the use of GLP-1 RA in other countries.

16. CONCLUSION

We observed an increase in the incidence and prevalence of dulaglutide and semaglutide use since 2015 and 2019, respectively, and a contemporaneous decrease in the incidence and prevalence of exenatide and lixisenatide use since 2015. On the other hand, incidence of liraglutide use remained steady across different databases, but trends in prevalence of use exhibited variations, from an overall decrease in CPRD, to an increase in SIDIAP, IPCI and IQVIA DA Germany.

Stratification by indication revealed that most GLP-1 RA users had a history of type 2 diabetes, with or without obesity, which is in line with relevant European treatment recommendations.

The study also collected data on five non-GLP-1 receptor agonist medicines used for diabetes and weight control, but results were limited and could not be compared to GLP-1 RA use. We observed a low use in four of the five medicines (orlistat, naltrexone/bupropion, phentermine/topiramate, phentermine). Conversely, use of metformin seemed to remain generally stable over the past decade, likely as it remains a first line treatment for type 2 diabetes.

Patients' characteristics presented small variations across the databases of the study. Median BMI in patients with available data ranged between 31.6 and 36.6 kg/m2, where lowest values were observed in IQVIA LPD Belgium and highest in IPCI. However, IQVIA LPD Belgium presented the highest percentage of patients with no BMI records. When recorded, patients with BMI ≤26 km/m2 were a small minority (<4%) . Median age in GLP-1 RA users was similar at ingredient level across the different databases. Hypertension was the most frequent comorbidity, followed by chronic kidney disease and renal impairment. Additionally, users of GLP-1 RA <18 years old were infrequent.

17. REFERENCES

1. EMA. *Public information on medicine shortages*. 2024; Available from: .
2. Recalde, M., et al., *Data Resource Profile: The Information System for Research in Primary Care (SIDIAP).* Int J Epidemiol, 2022. **51**(6): p. e324-e336.
3. Raventos, B., et al., *Transforming the Information System for Research in Primary Care (SIDIAP) in Catalonia to the OMOP Common Data Model and Its Use for COVID-19 Research.* Clin Epidemiol, 2023. **15**: p. 969-986.
4. Herrett, E., et al., *Data Resource Profile: Clinical Practice Research Datalink (CPRD).* Int J Epidemiol, 2015. **44**(3): p. 827-36.
5. Rathmann, W., et al., *Basic characteristics and representativeness of the German Disease Analyzer database.* Int J Clin Pharmacol Ther, 2018. **56**(10): p. 459-466.
6. ChiCTR. *Chinese Clinical Trial Registry: A Multicenter, double-blinded, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of Beinaglutide therapy adjunctive with life style intervention in overweight/obesity adult. (ChiCTR1900023428)*. 2019; Available from: https://www.chictr.org.cn/showprojEN.html?proj=38105.
7. EMA. *Mounjaro - opinion on variation to marketing authorisation (tirzepatide)*. 2023 10/11/2023; Available from: https://www.ema.europa.eu/en/medicines/human/variation/mounjaro.
8. Burkard, T., et al., *Calculating daily dose in the Observational Medical Outcomes Partnership Common Data Model.* Pharmacoepidemiol Drug Saf, 2024. **33**(6): p. e5809.
9. Viitasalo, A., et al., *Changes in BMI and physical activity from youth to adulthood distinguish normal-weight, metabolically obese adults from those who remain healthy.* Front Endocrinol (Lausanne), 2022. **13**: p. 923327.
10. CPRD. *Primary care data for public health research*. 2024 02-09-2024; Available from: https://www.cprd.com/primary-care-data-public-health-research.
11. Schotte, S. *Session 2 - Sharing of good practice – examples from EUEEA countries*. 2024; Available from: https://www.ema.europa.eu/en/documents/presentation/presentation-session-2-sharing-good-practice-examples-eueea-countries-s-schotte_en.pdf.
12. Verberne, L.D.M., et al., *Recording of weight in electronic health records: an observational study in general practice.* BMC Fam Pract, 2018. **19**(1): p. 174.
13. World-Obesity-Federation. *World obesity atlas 2023.*; Available from: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2023.
14. Blind, E., et al., *The European Medicines Agency's approval of new medicines for type 2 diabetes.* Diabetes Obes Metab, 2018. **20**(9): p. 2059-2063.
15. Glovaci, D., W. Fan, and N.D. Wong, *Epidemiology of Diabetes Mellitus and Cardiovascular Disease.* Curr Cardiol Rep, 2019. **21**(4): p. 21.
16. EMA. *EU actions to tackle shortages of GLP-1 receptor agonists*. 2024 [cited 2024; Available from: https://www.ema.europa.eu/en/news/eu-actions-tackle-shortages-glp-1-receptor-agonists.
17. EMA. *Recommendations of the Executive Steering Group on Shortages and Safety of Medicinal Products on shortage of Glucagon-Like Peptide-1 (GLP-1) receptor agonists*. 2024; Available from: https://www.ema.europa.eu/en/documents/other/mssg-recommendations-shortage-glucagon-peptide-1-glp-1-receptor-agonists_en.pdf.
18. Zorginstituut-Nederland. *Verslag van de vergadering van de Wetenschappelijke Adviesraad (WAR) over liraglutide (Saxenda®)*. 2022 [cited 2024; Available from: https://www.zorginstituutnederland.nl/publicaties/verslag/2022/01/17/verslag-van-de-vergadering-van-de-wetenschappelijke-adviesraad-war-over-liraglutide-saxenda.
19. Zorginstituut-Nederland. *Advies - vergoed liraglutide (Saxenda®) voor een bepaalde groep patiënten met (ernstig) overgewicht*. 2022 [cited 2024; Available from:

https://www.zorginstituutnederland.nl/publicaties/adviezen/2022/02/24/gvs-advies-liraglutide-saxenda.

20. Board, N.H.a.W.E.I.C. *Prescribing guideline: The combination of a glucagon like peptide-1 receptor agonist (GLP-1 RA) or dual long acting Glucose-dependent Insulinotropic Polypeptide agonist (GIP) with GLP-1RA and insulin for adults who have poorly controlled type 2 diabetes (T2DM)*. 2024; Available from: https://www.hweclinicalguidance.nhs.uk/prescribing-guidance.
21. NICE. *NICE Guideline 28. Type 2 diabetes in adults: management.* 2015 2022; Available from: https://www.nice.org.uk/guidance/ng28.
22. EMA. *Recommendations of the executive steering group on shortages and safety of medicinal products on shortage of glucagon-like peptide-1 (GLP-1) receptor agonists*. 2024; Available from: https://www.ema.europa.eu/en/documents/other/mssg-recommendations-shortage-glucagon-peptide-1-glp-1-receptor-agonists_en.pdf.
23. Mailhac, A., et al., *Semaglutide (Ozempic((R))) Use in Denmark 2018 Through 2023 – User Trends and off-Label Prescribing for Weight Loss.* Clin Epidemiol, 2024. **16**: p. 307-318.
24. Deeks, J.J., J.P. Higgins, and D.G. Altman, *Analysing Data and Undertaking Meta-Analyses*, in *Cochrane Handbook for Systematic Reviews of Interventions*. 2008. p. 243-296.
25. Russek, M., et al., *Assessing heterogeneity of electronic health-care databases: A case study of background incidence rates of venous thromboembolism.* Pharmacoepidemiology and Drug Safety, 2023. **32**(9): p. 1032-1048.
26. Heintjes, E., et al., *Type 2 Diabetes Treatment Patterns Across Europe.* Value Health, 2014. **17**(7): p. A359.
27. Ruiz, P.L., et al., *Pharmacological treatment of obesity in adults in Norway 2004-2022.* Diabetes Obes Metab, 2024. **26**(6): p. 2102-2110.

18. ANNEXES

Appendix I

Preliminary code lists for GLP-1 RA and for medicines that help contextualise exposure to GLP-1 RA.

Objective	Substance Name	Class	ATC code	Ingredient ConceptID
1) GLP-1 RA	Exenatide	GLP-1 analogues	A10BJ01	1583722
1) GLP-1 RA	Liraglutide	GLP-1 analogues	A10BJ02	40170911
1) GLP-1 RA	Lixisenatide	GLP-1 analogues	A10BJ03	44506754
1) GLP-1 RA	Albiglutide	GLP-1 analogues	A10BJ04	44816332
1) GLP-1 RA	Dulaglutide	GLP-1 analogues	A10BJ05	45774435
1) GLP-1 RA	Semaglutide	GLP-1 analogues	A10BJ06	793143
1) GLP-1 RA	Beinaglutide	GLP-1 analogues	A10BJ07	36850844
1) GLP-1 RA	Tirzepatide	Other blood glucose lowering drugs, excl. insulins	A10BX16	779705
2) Other medicines used for the treatment of diabetes and weight management	Orlistat	Peripherally acting antiobesity products	A08AB01	741530
2) Other medicines used for the treatment of diabetes and weight management	Metformin	Biguanides	A10BA02	1503297
2) Other medicines used for the treatment of diabetes and weight management	Naltrexone/Bupropion (Mysimba)	Centrally acting antiobesity products	A08AA62	1714319 + 750982
2) Other medicines used for the treatment of diabetes and weight management	Phentermine/ topiramate (Qsiva)	Centrally acting antiobesity products	A08AA51	735340 + 742267
2) Other medicines used for the treatment of diabetes and weight management	Phentermine	Centrally acting antiobesity products	A08AA01	735340

GLP-1 = Glucagon-like peptide-1 receptor agonists

Appendix II

Characteristics of GLP-1 RA users as assessed at the beginning of each treatment episode (patients can contribute with more than one episode) are summarised in **Table 15-Table** 17:

In terms new episodes observed, semaglutide had the highest number of records in IPCI, IQVIA LPD Belgium and IQVIA DA Germany; liraglutide in CPRD and dulaglutide in SIDIAP. Sex distribution varied across the databases and the different GLP-1 RA, however most of men's proportion values were ranged between 49-59%, except lixisenatide in IQVIA LPD Belgium (60.1% were men). (**Table 15**)

Overall, there were very few users of GLP-1 RA younger than 18 years old. Median age was similar across the databases, but stratification by age groups showed certain databases preferred a specific GLP-1 RA for a specific age groups, such as larger number of users for semaglutide among 18-64 age group (proportion of semaglutide users aged 18-64 years were 67.7% and 67.8% in CPRD and IQVIA LPD Belgium, respectively) and lower number of users for individuals ≥65 years old (proportion of semaglutide users aged ≥65 years were 32.3% and 32.1% in CPRD and IQVIA LPD Belgium, respectively). (**Table 16**)

BMI values were poorly recorded in both IQVIA databases (61.7% to 87.1% of individuals did not have a BMI record in the last 5 years from starting their GP-1 RA drug), followed by IPCI (ranged between 11.5% to 27.9%). Missingness in BMI records was lower than 8.2% and 6% in SIDIAP and CPRD, respectively. In these two databases, users with a BMI ≤26 km/m2 were infrequent in all databases (<5%). IQVIA LPD Belgium presented the lowest median BMI (ranged between 30.03 to 32.9 kg/m2 across different GLP-1 RA), whilst the lowest median BMI estimated in the other databases were >33 kg/m2. However, the highest percentage of missingness in the BMI records limits the interpretation of BMI in IQVIA and IPCI. (**Table 17**)

Table 15. Description of users of new episodes of GLP-1 RA use: number of distinct subjects and records, and sex distribution in each database of the study.

Variable name		Number subjects					Number of records (episodes observed)					Sex [male] (respect to number of records)				
CDM name		CPRD	IPCI	IQVIA LPD Belgium	IQVIA DA Germany	SIDIAP	CPRD	IPCI	IQVIA LPD Belgium	IQVIA DA Germany	SIDIAP	CPRD	IPCI	IQVIA LPD Belgium	IQVIA DA Germany	SIDIAP
Estimate name		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cohort name	Dulaglutide	11,967 (29%)	1,536 (11%)	1,794 (20%)	36,340 (41%)	18,730 (36%)	20,547 (12%)	3,505 (11%)	10,159 (26%)	72,564 (30%)	21,588 (35%)	10,684 (52.0%)	1,720 (49.1%)	5,831 (57.4%)	39,438 (54.3%)	11,091 (51.4%)
	Liraglutide	14,205 (34%)	3,797 (27%)	1,567 (18%)	20,064 (23%)	16,513 (32%)	98,043 (57%)	12,869 (39%)	7,760 (20%)	52,791 (22%)	20,503 (33%)	49,572 (50.6%)	5,182 (40.3%)	3,772 (48.6%)	26,726 (50.6%)	8,830 (43.1%)
	Exenatide	4,321 (10%)	152 (1%)	551 (6%)	2,360 (3%)	2,697 (5%)	16,363 (9%)	444 (1%)	3,759 (9%)	9,420 (4%)	3,223 (5%)	8,453 (51.7%)	181 (40.8%)	2,150 (57.2%)	4,745 (50.4%)	1,586 (49.2%)
	Lixisenatide	2,038 (5%)	31 (0%)	317 (4%)	176 (0%)	-	4,483 (3%)	68 (0%)	1,358 (3%)	230 (0%)	-	2,224 (49.6%)	36 (52.9%)	816 (60.1%)	125 (54.3%)	-
	Semaglutide	8,727 (21%)	8,626 (61%)	4,597 (52%)	29,283 (33%)	13,809 (27%)	33,233 (19%)	16,469 (49%)	16,621 (42%)	107,407 (44%)	16,985 (27%)	16,933 (51.0%)	8,095 (49.2%)	7,223 (43.5%)	58,950 (54.9%)	8,133 (47.9%)

CDM, common data model.

Table 16. Description of users of new episodes of GLP-1 RA use: age distribution in each database of the study.

Variable name		Age (years)														
CDM name		CPRD			IPCI			IQVIA LPD Belgium			IQVIA DA Germany			SIDIAP		
Estimate name		Median [Q25 - Q75]	Mean (SD)	Range	Median [Q25 - Q75]	Mean (SD)	Range	Median [Q25 - Q75]	Mean (SD)	Range	Median [Q25 - Q75]	Mean (SD)	Range	Median [Q25 - Q75]	Mean (SD)	Range
Cohort name	Dulaglutide	60 [52 - 68]	59.70 (11.62)	16 to 94	61 [54 - 69]	60.91 (11.07)	24 to 99	65 [57 - 73]	64.45 (11.29)	0 to 95	62 [55 - 71]	62.08 (12.13)	1 to 98	62 [54 - 69]	61.17 (11.41)	17 to 93
	Liraglutide	61 [53 - 68]	60.04 (11.15)	6 to 93	60 [52 - 68]	59.48 (12.16)	7 to 90	63 [54 - 70]	61.66 (12.27)	13 to 106	62 [54 - 70]	61.32 (12.04)	0 to 98	58 [50 - 66]	57.37 (12.25)	12 to 93
	Exenatide	60 [53 - 68]	60.22 (10.42)	16 to 91	62 [56 - 68]	61.18 (8.91)	35 to 86	65 [59 - 72]	65.20 (10.17)	17 to 93	62 [55 - 70]	62.15 (10.83)	6 to 94	59 [52 - 66]	58.54 (11.14)	15 to 95
	Lixisenatide	59 [51 - 67]	58.65 (11.19)	21 to 93	63 [56 - 67]	62.29 (8.13)	44 to 78	65 [57 - 72]	63.72 (11.22)	10 to 93	61 [53 - 66.75]	60.03 (11.25)	30 to 89	-	-	-

	Semaglutide	59 [52 - 67]	58.73 (11.61)	12 to 89	61 [54 - 69]	60.80 (11.01)	15 to 92	58 [49 - 67]	57.24 (13.17)	6 to 98	62 [54 - 69]	61.04 (11.77)	6 to 96	60 [51 - 68]	58.95 (12.01)	14 to 98

Variable name		Age group														
CDM name		CPRD	IPCI	IQVIA LPD Belgium	IQVIA DA Germany	SIDIAP	CPRD	IPCI	IQVIA LPD Belgium	IQVIA DA Germany	SIDIAP	CPRD	IPCI	IQVIA LPD Belgium	IQVIA DA Germany	SIDIAP
Variable level		0 to 17	0 to 17	0 to 17	0 to 17	0 to 17	18 to 64	18 to 64	18 to 64	18 to 64	18 to 64	65 to 150	65 to 150	65 to 150	65 to 150	65 to 150
Estimate name		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cohort name	Dulaglutide	7 (0.0%)	-	8 (0.1%)	12 (0.0%)	<5 (<5%)	13,263 (64.5%)	2,109 (60.2%)	4,769 (46.9%)	41,119 (56.7%)	12,680 (58.7%)	7,277 (35.4%)	1,396 (39.8%)	5,382 (53.0%)	31,433 (43.3%)	8,906 (41.3%)
	Liraglutide	42 (0.0%)	10 (0.1%)	5 (0.1%)	33 (0.1%)	71 (0.3%)	62,314 (63.6%)	8,148 (63.3%)	4,157 (53.6%)	30,782 (58.3%)	14,402 (70.2%)	35,687 (36.4%)	4,711 (36.6%)	3,598 (46.4%)	21,976 (41.6%)	6,030 (29.4%)
	Exenatide	<5 (<5%)	-	<5 (<5%)	<5 (<5%)	<5 (<5%)	10,312 (63.0%)	269 (60.6%)	1,735 (46.2%)	5,404 (57.4%)	2,197 (68.2%)	6,047 (37.0%)	175 (39.4%)	2,023 (53.8%)	4,015 (42.6%)	1,024 (31.8%)
	Lixisenatide	-	-	<5 (<5%)	-	-	3,019 (67.3%)	40 (58.8%)	621 (45.7%)	143 (62.2%)	-	1,464 (32.7%)	28 (41.2%)	734 (54.1%)	87 (37.8%)	-
	Semaglutide	9 (0.0%)	<5 (<5%)	9 (0.1%)	23 (0.0%)	11 (0.1%)	22,493 (67.7%)	10,054 (61.0%)	11,276 (67.8%)	64,527 (60.1%)	11,102 (65.4%)	10,731 (32.3%)	6,412 (38.9%)	5,336 (32.1%)	42,857 (39.9%)	5,872 (34.6%)

CDM, common data model.

Table 17. Description of users of new episodes of GLP-1 RA use: body mass index and conditions in each database of the study.

Variable name	Variable level	CDM name	Estimate name	Cohort name				
				Dulaglutide	Liraglutide	Exenatide	Lixisenatide	Semaglutide
BMI Overall characteristics (kg/m2)	-	CPRD	Median [Q25 - Q75]	35 [31.1 - 39.8]	35.5 [31.6 - 40.2]	35.1 [31.1 - 40]	35.9 [31.0 - 41.4]	35 [31 - 40]
			Range	13 to 60	10.1 to 60	10.8 to 60	11.5 to 59.9	10.5 to 60
		IPCI	Median [Q25 - Q75]	34.2 [31.2 - 38.5]	35.6 [32.5 - 39.9]	36.7 [33.0 - 40.3]	34.3 [31 - 38]	33.4 [30.5 - 37.2]
			Range	20.3 to 58.7	20.3 to 60	26.4 to 56.9	25.4 to 47	16.8 to 59.9
		IQVIA LPD Belgium	Median [Q25 - Q75]	32.2 [29 - 35.8]	31.7 [28.7 - 34.9]	30.3 [26.8 - 35.9]	32.1 [29.7 - 36.7]	32.9 [29.7 - 36.6]

Variable name	Variable level	CDM name	Estimate name	Cohort name: Dulaglutide	Liraglutide	Exenatide	Lixisenatide	Semaglutide
			Range	20.8 to 53.9	19.7 to 57.8	21.3 to 54.3	22 to 54.7	16.9 to 57.9
		IQVIA DA Germany	Median [Q25 - Q75]	34 [30.3 - 38.8]	34.3 [30.3 - 39.3]	34.7 [30.9 - 40.8]	35.9 [29.6 - 40.8]	33.6 [29.6 - 38.5]
			Range	15 to 59.9	17.8 to 59.4	22.6 to 58.3	21.4 to 48.7	17.5 to 58.8
		SIDIAP	Median [Q25 - Q75]	34.7 [31.6 - 38.8]	36.4 [32.7 - 41.0]	36 [32.4 - 40.6]	-	35.3 [31.8 - 39.7]
			Range	10.4 to 59.9	12.8 to 60	18.3 to 59.8	-	12.5 to 60
BMI groups (kg/m2)	0 to 26	CPRD	N (%)	875 (4.3%)	3,373 (3.4%)	774 (4.7%)	134 (3.0%)	1,601 (4.8%)
		IPCI	N (%)	48 (1.4%)	218 (1.7%)	<5 (<5%)	<5 (<5%)	681 (4.1%)
		IQVIA LPD Belgium	N (%)	330 (3.2%)	299 (3.9%)	137 (3.6%)	15 (1.1%)	656 (3.9%)
		IQVIA DA Germany	N (%)	925 (1.3%)	746 (1.4%)	107 (1.1%)	7 (3.0%)	1,409 (1.3%)
		SIDIAP	N (%)	430 (2.0%)	370 (1.8%)	61 (1.9%)	-	416 (2.4%)
	27 to 29	CPRD	N (%)	2,099 (10.2%)	9,079 (9.3%)	1,653 (10.1%)	439 (9.8%)	3,498 (10.5%)
		IPCI	N (%)	266 (7.6%)	675 (5.2%)	21 (4.7%)	<5 (<5%)	1,690 (10.3%)
		IQVIA LPD Belgium	N (%)	626 (6.2%)	530 (6.8%)	171 (4.5%)	72 (5.3%)	884 (5.3%)
		IQVIA DA Germany	N (%)	1,544 (2.1%)	1,314 (2.5%)	171 (1.8%)	14 (6.1%)	1,929 (1.8%)
		SIDIAP	N (%)	1,683 (7.8%)	1,131 (5.5%)	183 (5.7%)	-	1,261 (7.4%)
	30 to 34	CPRD	N (%)	6,044 (29.4%)	28,669 (29.2%)	4,853 (29.7%)	1,180 (26.3%)	9,737 (29.3%)
		IPCI	N (%)	1,181 (33.7%)	3,123 (24.3%)	98 (22.1%)	20 (29.4%)	6,096 (37.0%)

Variable name	Variable level	CDM name	Estimate name	Cohort name: Dulaglutide	Liraglutide	Exenatide	Lixisenatide	Semaglutide
		IQVIA LPD Belgium	N (%)	1,227 (12.1%)	1,154 (14.9%)	231 (6.1%)	143 (10.5%)	2,436 (14.7%)
		IQVIA DA Germany	N (%)	3,909 (5.4%)	3,211 (6.1%)	618 (6.6%)	13 (5.7%)	4,244 (4.0%)
		SIDIAP	N (%)	7,956 (36.9%)	5,507 (26.9%)	947 (29.4%)	-	5,212 (30.7%)
	35 to 39	CPRD	N (%)	5,202 (25.3%)	26,577 (27.1%)	4,285 (26.2%)	1,161 (25.9%)	8,043 (24.2%)
		IPCI	N (%)	787 (22.5%)	3,282 (25.5%)	94 (21.2%)	15 (22.1%)	3,780 (23.0%)
		IQVIA LPD Belgium	N (%)	727 (7.2%)	533 (6.9%)	155 (4.1%)	90 (6.6%)	1,486 (8.9%)
		IQVIA DA Germany	N (%)	3,032 (4.2%)	2,455 (4.7%)	401 (4.3%)	22 (9.6%)	3,346 (3.1%)
		SIDIAP	N (%)	6,145 (28.5%)	5,971 (29.1%)	951 (29.5%)	-	4,660 (27.4%)
	40+	CPRD	N (%)	5,084 (24.7%)	26,762 (27.3%)	4,296 (26.3%)	1,407 (31.4%)	8,674 (26.1%)
		IPCI	N (%)	573 (16.3%)	2,606 (20.3%)	112 (25.2%)	9 (13.2%)	2,322 (14.1%)
		IQVIA LPD Belgium	N (%)	317 (3.1%)	229 (3.0%)	69 (1.8%)	39 (2.9%)	910 (5.5%)
		IQVIA DA Germany	N (%)	2,574 (3.5%)	2,480 (4.7%)	520 (5.5%)	26 (11.3%)	2,885 (2.7%)
		SIDIAP	N (%)	4,521 (20.9%)	6,100 (29.8%)	897 (27.8%)	-	4,046 (23.8%)
	NA	CPRD	N (%)	1,243 (6.0%)	3,583 (3.7%)	502 (3.1%)	162 (3.6%)	1,680 (5.1%)
		IPCI	N (%)	650 (18.5%)	2,965 (23.0%)	118 (26.6%)	19 (27.9%)	1,900 (11.5%)

Variable name	Variable level	CDM name	Estimate name	Cohort name: Dulaglutide	Liraglutide	Exenatide	Lixisenatide	Semaglutide
		IQVIA LPD Belgium	N (%)	6,932 (68.2%)	5,015 (64.6%)	2,996 (79.7%)	999 (73.6%)	10,249 (61.7%)
		IQVIA DA Germany	N (%)	60,580 (83.5%)	42,585 (80.7%)	7,603 (80.7%)	148 (64.3%)	93,594 (87.1%)
		SIDIAP	N (%)	853 (4.0%)	1,424 (6.9%)	184 (5.7%)	-	1,390 (8.2%)
Conditions	Chronic kidney disease	CPRD	N (%)	2,944 (14.3%)	14,628 (14.9%)	2,857 (17.5%)	715 (15.9%)	4,585 (13.8%)
		IPCI	N (%)	13 (0.4%)	25 (0.2%)	0 (0.0%)	0 (0.0%)	33 (0.2%)
		IQVIA LPD Belgium	N (%)	412 (4.1%)	192 (2.5%)	134 (3.6%)	23 (1.7%)	455 (2.7%)
		IQVIA DA Germany	N (%)	20,933 (28.8%)	14,648 (27.7%)	2,315 (24.6%)	42 (18.3%)	32,756 (30.5%)
		SIDIAP	N (%)	4,665 (21.6%)	2,904 (14.2%)	282 (8.7%)	-	3,690 (21.7%)
	Chronic kidney disease and renal impairment	CPRD	N (%)	2,958 (14.4%)	14,663 (15.0%)	2,907 (17.8%)	722 (16.1%)	4,628 (13.9%)
		IPCI	N (%)	374 (10.7%)	965 (7.5%)	19 (4.3%)	<5 (<5%)	1,605 (9.7%)
		IQVIA LPD Belgium	N (%)	413 (4.1%)	192 (2.5%)	134 (3.6%)	23 (1.7%)	457 (2.7%)
		IQVIA DA Germany	N (%)	20,948 (28.9%)	14,675 (27.8%)	2,315 (24.6%)	42 (18.3%)	32,797 (30.5%)
		SIDIAP	N (%)	4,665 (21.6%)	2,905 (14.2%)	282 (8.7%)	-	3,690 (21.7%)
	Heart failure	CPRD	N (%)	804 (3.9%)	3,762 (3.8%)	462 (2.8%)	133 (3.0%)	1,236 (3.7%)
		IPCI	N (%)	148 (4.2%)	456 (3.5%)	28 (6.3%)	0 (0.0%)	660 (4.0%)
		IQVIA LPD Belgium	N (%)	788 (7.8%)	357 (4.6%)	118 (3.1%)	87 (6.4%)	967 (5.8%)

Variable name	Variable level	CDM name	Estimate name	Cohort name				
				Dulaglutide	Liraglutide	Exenatide	Lixisenatide	Semaglutide
		IQVIA DA Germany	N (%)	9,426 (13.0%)	6,551 (12.4%)	992 (10.5%)	33 (14.3%)	13,193 (12.3%)
		SIDIAP	N (%)	1,780 (8.2%)	1,325 (6.5%)	183 (5.7%)	-	1,324 (7.8%)
	Hyper-tension	CPRD	N (%)	7,126 (34.7%)	35,793 (36.5%)	6,341 (38.8%)	1,550 (34.6%)	12,488 (37.6%)
		IPCI	N (%)	1,122 (32.0%)	3,713 (28.9%)	107 (24.1%)	35 (51.5%)	5,230 (31.8%)
		IQVIA LPD Belgium	N (%)	7,816 (76.9%)	5,420 (69.8%)	2,812 (74.8%)	1,010 (74.4%)	10,315 (62.1%)
		IQVIA DA Germany	N (%)	53,402 (73.6%)	38,985 (73.8%)	7,455 (79.1%)	181 (78.7%)	78,871 (73.4%)
		SIDIAP	N (%)	10,157 (47.0%)	8,495 (41.4%)	1,259 (39.1%)	-	7,808 (46.0%)
	Myocardial infarction	CPRD	N (%)	1,035 (5.0%)	4,537 (4.6%)	721 (4.4%)	225 (5.0%)	1,604 (4.8%)
		IPCI	N (%)	173 (4.9%)	438 (3.4%)	<5 (<5%)	<5 (<5%)	793 (4.8%)
		IQVIA LPD Belgium	N (%)	294 (2.9%)	193 (2.5%)	181 (4.8%)	38 (2.8%)	375 (2.3%)
		IQVIA DA Germany	N (%)	2,799 (3.9%)	1,739 (3.3%)	222 (2.4%)	8 (3.5%)	3,445 (3.2%)
		SIDIAP	N (%)	1,225 (5.7%)	862 (4.2%)	117 (3.6%)	-	989 (5.8%)
	MACE	CPRD	N (%)	1,564 (7.6%)	6,705 (6.8%)	1,174 (7.2%)	300 (6.7%)	2,386 (7.2%)
		IPCI	N (%)	253 (7.2%)	734 (5.7%)	16 (3.6%)	<5 (<5%)	1,363 (8.3%)
		IQVIA LPD Belgium	N (%)	557 (5.5%)	404 (5.2%)	315 (8.4%)	43 (3.2%)	711 (4.3%)
		IQVIA DA Germany	N (%)	5,959 (8.2%)	3,666 (6.9%)	450 (4.8%)	14 (6.1%)	6,937 (6.5%)
		SIDIAP	N (%)	2,261 (10.5%)	1,603 (7.8%)	226 (7.0%)	-	1,661 (9.8%)

Variable name	Variable level	CDM name	Estimate name	Cohort name				
				Dulaglutide	Liraglutide	Exenatide	Lixisenatide	Semaglutide
	Stroke	CPRD	N (%)	583 (2.8%)	2,329 (2.4%)	483 (3.0%)	85 (1.9%)	874 (2.6%)
		IPCI	N (%)	96 (2.7%)	338 (2.6%)	15 (3.4%)	<5 (<5%)	657 (4.0%)
		IQVIA LPD Belgium	N (%)	268 (2.6%)	215 (2.8%)	136 (3.6%)	6 (0.4%)	365 (2.2%)
		IQVIA DA Germany	N (%)	3,492 (4.8%)	2,089 (4.0%)	235 (2.5%)	6 (2.6%)	3,801 (3.5%)
		SIDIAP	N (%)	1,134 (5.3%)	801 (3.9%)	114 (3.5%)	-	732 (4.3%)

BMI, body mass index; CDM, common data model; MACE, composite outcome including myocardial infraction and stroke; NA, not available (no BMI value recorded in the last 5 years from first use of GLP-1 RA).

Characteristics of GLP-1RA patients by indication

Full characteristics of drug users of GLP-1 as assessed at the beginning of each treatment episode by indication (diagnosis of obesity, diagnosis of DM2, diagnosis of DM2 and obesity, or other indications) are available in the shiny app [*see Characteristics tab – use the Denominator Cohort sub-tab to select the GLP-1 RA user cohort/s of interest (ensure those are not the "_incident")*]. Given the large amount of results, we selected semaglutide as an example.

Table 18 presents the results for the users of new episodes of semaglutide overall, and by the four indication cohorts. The majority of new patients treated with semaglutide had the diagnosis of DM2 with obesity indication. Individuals in the Other indication (i.e., no diagnosis of obesity nor DM2) were the smallest group and had the largest proportion of patients with missing BMI.

Table 18. Description of users of new episodes of semaglutide use, overall and stratified by indication.

CDM name	Variable name	Variable level	Estimate name	Cohort name (indication)				
				Semaglutide (Overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
CPRD	Number of records	-	N	33,233	24,923	926	6,485	899
IPCI		-	N	16,469	12,613	2,393	932	531

CDM name	Variable name	Variable level	Estimate name	Cohort name (indication) Semaglutide (Overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
IQVIA LPD Belgium	(episodes observed)	-	N	16,621	9,271	5,959	595	796
IQVIA DA Germany		-	N	107,407	73,415	32,762	914	316
SIDIAP		-	N	16,985	16,042	891	45	7
CPRD	Number subjects	-	N	8,727	6,228	313	1,886	399
IPCI		-	N	8,626	6,504	1,354	628	434
IQVIA LPD Belgium		-	N	4,597	2,665	1,625	121	186
IQVIA DA Germany		-	N	29,283	18,940	9,977	253	113
SIDIAP		-	N	13,809	13,017	751	36	<5
CPRD	Sex distribution (respect number of records)	Male	N (%)	16,933 (51.0%)	12,726 (51.1%)	489 (52.8%)	3,221 (49.7%)	497 (55.3%)
IPCI		Male	N (%)	8,095 (49.2%)	6,174 (48.9%)	1,249 (52.2%)	413 (44.3%)	259 (48.8%)
IQVIA LPD Belgium		Male	N (%)	7,223 (43.5%)	3,791 (40.9%)	2,678 (44.9%)	297 (49.9%)	457 (57.4%)
IQVIA DA Germany		Male	N (%)	58,950 (54.9%)	39,416 (53.7%)	18,833 (57.5%)	489 (53.5%)	212 (67.1%)
SIDIAP		Male	N (%)	8,133 (47.9%)	7,695 (48.0%)	411 (46.1%)	22 (48.9%)	5 (71.4%)
CPRD	Age (years)	-	Median [Q25 - Q75]	59 [52 - 67]	59 [51 - 67]	60 [53 - 70]	60 [53 - 68]	58 [46 - 67]
			Mean (SD)	58.73 (11.61)	58.56 (11.46)	60.47 (11.81)	59.42 (11.70)	56.55 (14.01)
			Range	12 to 89	18 to 89	15 to 84	15 to 88	12 to 87

CDM name	Variable name	Variable level	Estimate name	Cohort name (indication) Semaglutide (Overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
IPCI			Median [Q25 - Q75]	61 [54 - 69]	61 [54 - 69]	62 [54 - 69]	61 [53 - 69]	61 [52 - 68]
			Mean (SD)	60.80 (11.01)	60.93 (10.69)	60.79 (12.03)	59.82 (11.64)	59.53 (12.22)
			Range	15 to 92	18 to 92	16 to 91	18 to 86	15 to 83
IQVIA LPD Belgium			Median [Q25 - Q75]	58.00 [49.00 - 67.00]	56.00 [47.00 - 65.00]	60.00 [51.00 - 69.00]	63.00 [56.00 - 69.00]	63.00 [57.00 - 70.00]
			Mean (SD)	57.24 (13.17)	55.27 (13.13)	59.17 (12.94)	61.09 (12.80)	62.79 (11.04)
			Range	6.00 to 98.00	15.00 to 95.00	6.00 to 98.00	22.00 to 92.00	22.00 to 89.00
IQVIA DA Germany			Median [Q25 - Q75]	62.00 [54.00 - 69.00]	61.00 [53.00 - 69.00]	63.00 [56.00 - 71.00]	55.00 [46.00 - 65.00]	55.00 [45.00 - 64.00]
			Mean (SD)	61.04 (11.77)	60.47 (11.64)	62.57 (11.77)	54.27 (14.10)	54.47 (13.10)
			Range	6.00 to 96.00	14.00 to 96.00	6.00 to 96.00	14.00 to 86.00	19.00 to 82.00
SIDIAP			Median [Q25 - Q75]	60 [51 - 68]	60 [52 - 68]	58 [48 - 65]	44 [35 - 56]	43 [36 - 66]
			Mean (SD)	58.95 (12.01)	59.14 (11.90)	56.38 (13.01)	45.00 (15.58)	48.29 (17.90)
			Range	14 to 98	14 to 93	17 to 98	18 to 78	24 to 66
CPRD	Age group [years] (respect number of records)	0 to 17	N (%)	9 (0.0%)	-	<5 (<5%)	6 (0.1%)	<5 (<5%)
IPCI		0 to 17	N (%)	<5 (<5%)	-	<5 (<5%)	-	<5 (<5%)
IQVIA LPD Belgium		0 to 17	N (%)	9 (0.1%)	6 (0.1%)	<5 (<5%)	-	-
IQVIA DA Germany		0 to 17	N (%)	23 (0.0%)	11 (0.0%)	9 (0.0%)	<5 (<5%)	-
SIDIAP		0 to 17	N (%)	11 (0.1%)	10 (0.1%)	<5 (<5%)	-	-
CPRD		18 to 64	N (%)	22,493 (67.7%)	17,145 (68.8%)	581 (62.7%)	4,157 (64.1%)	610 (67.9%)
IPCI		18 to 64	N (%)	10,054 (61.0%)	7,713 (61.2%)	1,440 (60.2%)	584 (62.7%)	317 (59.7%)

CDM name	Variable name	Variable level	Estimate name	Cohort name (indication) Semaglutide (Overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
IQVIA LPD Belgium		18 to 64	N (%)	11,276 (67.8%)	6,857 (74.0%)	3,694 (62.0%)	315 (52.9%)	410 (51.5%)
IQVIA DA Germany		18 to 64	N (%)	64,527 (60.1%)	45,570 (62.1%)	18,034 (55.0%)	681 (74.5%)	242 (76.6%)
SIDIAP		18 to 64	N (%)	11,102 (65.4%)	10,416 (64.9%)	643 (72.2%)	39 (86.7%)	<5 (<5%)
CPRD		65+	N (%)	10,731 (32.3%)	7,778 (31.2%)	343 (37.0%)	2,322 (35.8%)	288 (32.0%)
IPCI		65+	N (%)	6,412 (38.9%)	4,900 (38.8%)	951 (39.7%)	348 (37.3%)	213 (40.1%)
IQVIA LPD Belgium		65+	N (%)	5,336 (32.1%)	2,408 (26.0%)	2,262 (38.0%)	280 (47.1%)	386 (48.5%)
IQVIA DA Germany		65+	N (%)	42,857 (39.9%)	27,834 (37.9%)	14,719 (44.9%)	230 (25.2%)	74 (23.4%)
SIDIAP		65+	N (%)	5,872 (34.6%)	5,616 (35.0%)	247 (27.7%)	6 (13.3%)	<5 (<5%)
CPRD	BMI (kg/m2)	-	Median [Q25 - Q75]	35.00 [31.00 - 40.10]	35.50 [31.50 - 40.70]	25.80 [24.60 - 27.50]	34.60 [31.20 - 39.00]	26.95 [25.48 - 28.30]
			Range	10.50 to 60.00	10.50 to 60.00	18.60 to 29.90	15.00 to 60.00	18.40 to 29.90
IPCI			Median [Q25 - Q75]	33.40 [30.49 - 37.20]	33.81 [31.00 - 37.50]	28.07 [26.21 - 30.86]	34.08 [31.40 - 38.00]	30.30 [28.01 - 34.00]
			Range	16.80 to 59.93	21.20 to 59.93	16.80 to 55.47	22.70 to 58.62	19.92 to 57.55
IQVIA LPD Belgium			Median [Q25 - Q75]	32.87 [29.73 - 36.56]	33.71 [30.86 - 37.10]	26.88 [25.28 - 28.38]	35.79 [32.00 - 39.21]	28.16 [27.89 - 28.67]
			Range	16.90 to 57.86	18.52 to 57.86	16.90 to 29.83	20.42 to 50.78	18.69 to 29.65
IQVIA DA Germany			Median [Q25 - Q75]	33.60 [29.64 - 38.51]	35.07 [31.50 - 39.45]	26.92 [25.04 - 28.47]	33.94 [30.12 - 40.39]	27.58 [26.99 - 27.58]
			Range	17.45 to 58.82	17.45 to 58.82	18.61 to 29.99	20.44 to 50.75	22.77 to 28.93

CDM name	Variable name	Variable level	Estimate name	Cohort name (indication) Semaglutide (Overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
SIDIAP			Median [Q25 - Q75]	35.32 [31.83 - 39.73]	35.55 [32.19 - 39.95]	27.18 [25.48 - 28.31]	32.90 [30.83 - 36.82]	28.79 [27.68 - 29.39]
			Range	12.48 to 59.88	12.48 to 59.88	17.39 to 29.96	25.97 to 45.29	26.56 to 29.98
CPRD	BMI group [kg/m2] (respect number of records)	0 to 26	N (%)	1,601 (4.8%)	791 (3.2%)	423 (45.7%)	211 (3.3%)	176 (19.6%)
IPCI			N (%)	681 (4.1%)	261 (2.1%)	363 (15.2%)	19 (2.0%)	38 (7.2%)
IQVIA LPD Belgium			N (%)	656 (3.9%)	260 (2.8%)	368 (6.2%)	19 (3.2%)	9 (1.1%)
IQVIA DA Germany			N (%)	1,409 (1.3%)	448 (0.6%)	934 (2.9%)	19 (2.1%)	8 (2.5%)
SIDIAP			N (%)	416 (2.4%)	233 (1.5%)	182 (20.4%)	<5 (<5%)	-
CPRD		27 to 29	N (%)	3,498 (10.5%)	2,394 (9.6%)	282 (30.5%)	589 (9.1%)	233 (25.9%)
IPCI			N (%)	1,690 (10.3%)	1,038 (8.2%)	504 (21.1%)	63 (6.8%)	85 (16.0%)
IQVIA LPD Belgium			N (%)	884 (5.3%)	469 (5.1%)	382 (6.4%)	<5 (<5%)	31 (3.9%)
IQVIA DA Germany			N (%)	1,929 (1.8%)	815 (1.1%)	1,066 (3.3%)	21 (2.3%)	27 (8.5%)
SIDIAP			N (%)	1,261 (7.4%)	974 (6.1%)	280 (31.4%)	5 (11.1%)	<5 (<5%)
CPRD		30 to 34	N (%)	9,737 (29.3%)	7,521 (30.2%)	14 (1.5%)	2,175 (33.5%)	27 (3.0%)
IPCI			N (%)	6,096 (37.0%)	5,371 (42.6%)	235 (9.8%)	374 (40.1%)	116 (21.8%)
IQVIA LPD Belgium			N (%)	2,436 (14.7%)	2,248 (24.2%)	43 (0.7%)	144 (24.2%)	<5 (<5%)
IQVIA DA Germany			N (%)	4,244 (4.0%)	4,022 (5.5%)	162 (0.5%)	60 (6.6%)	-
SIDIAP			N (%)	5,212 (30.7%)	5,172 (32.2%)	23 (2.6%)	16 (35.6%)	<5 (<5%)
CPRD		35 to 39	N (%)	8,043 (24.2%)	6,341 (25.4%)	-	1,702 (26.2%)	-
IPCI			N (%)	3,780 (23.0%)	3,399 (26.9%)	104 (4.3%)	237 (25.4%)	40 (7.5%)

CDM name	Variable name	Variable level	Estimate name	Cohort name (indication) Semaglutide (Overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
IQVIA LPD Belgium			N (%)	1,486 (8.9%)	1,376 (14.8%)	-	110 (18.5%)	-
IQVIA DA Germany			N (%)	3,346 (3.1%)	3,309 (4.5%)	-	37 (4.0%)	-
SIDIAP			N (%)	4,660 (27.4%)	4,650 (29.0%)	-	10 (22.2%)	-
CPRD		40+	N (%)	8,674 (26.1%)	7,273 (29.2%)	-	1,401 (21.6%)	-
IPCI			N (%)	2,322 (14.1%)	2,047 (16.2%)	78 (3.3%)	168 (18.0%)	29 (5.5%)
IQVIA LPD Belgium			N (%)	910 (5.5%)	825 (8.9%)	-	85 (14.3%)	-
IQVIA DA Germany			N (%)	2,885 (2.7%)	2,826 (3.8%)	-	59 (6.5%)	-
SIDIAP			N (%)	4,046 (23.8%)	4,042 (25.2%)	-	<5 (<5%)	-
CPRD		NA	N (%)	1,680 (5.1%)	603 (2.4%)	207 (22.4%)	407 (6.3%)	463 (51.5%)
IPCI			N (%)	1,900 (11.5%)	497 (3.9%)	1,109 (46.3%)	71 (7.6%)	223 (42.0%)
IQVIA LPD Belgium			N (%)	10,249 (61.7%)	4,093 (44.1%)	5,166 (86.7%)	235 (39.5%)	755 (94.8%)
IQVIA DA Germany			N (%)	93,594 (87.1%)	61,995 (84.4%)	30,600 (93.4%)	718 (78.6%)	281 (88.9%)
SIDIAP			N (%)	1,390 (8.2%)	971 (6.1%)	406 (45.6%)	9 (20.0%)	<5 (<5%)
CPRD	Conditions (respect number of records)	Chronic kidney disease	N (%)	4,585 (13.8%)	3,720 (14.9%)	150 (16.2%)	653 (10.1%)	62 (6.9%)
IPCI			N (%)	33 (0.2%)	27 (0.2%)	<5 (<5%)	<5 (<5%)	<5 (<5%)
IQVIA LPD Belgium			N (%)	455 (2.7%)	214 (2.3%)	166 (2.8%)	41 (6.9%)	34 (4.3%)
IQVIA DA Germany			N (%)	32,756 (30.5%)	24,807 (33.8%)	7,547 (23.0%)	361 (39.5%)	41 (13.0%)
SIDIAP			N (%)	3,690 (21.7%)	3,505 (21.8%)	176 (19.8%)	8 (17.8%)	<5 (<5%)

CDM name	Variable name	Variable level	Estimate name	Cohort name (indication) Semaglutide (Overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
CPRD		Chronic kidney disease and renal impairment	N (%)	4,628 (13.9%)	3,760 (15.1%)	150 (16.2%)	656 (10.1%)	62 (6.9%)
IPCI			N (%)	1,605 (9.7%)	1,357 (10.8%)	167 (7.0%)	59 (6.3%)	22 (4.1%)
IQVIA LPD Belgium			N (%)	457 (2.7%)	215 (2.3%)	167 (2.8%)	41 (6.9%)	34 (4.3%)
IQVIA DA Germany			N (%)	32,797 (30.5%)	24,836 (33.8%)	7,559 (23.1%)	361 (39.5%)	41 (13.0%)
SIDIAP			N (%)	3,690 (21.7%)	3,505 (21.8%)	176 (19.8%)	8 (17.8%)	<5 (<5%)
CPRD		Heart failure	N (%)	1,236 (3.7%)	948 (3.8%)	10 (1.1%)	253 (3.9%)	25 (2.8%)
IPCI			N (%)	660 (4.0%)	547 (4.3%)	80 (3.3%)	29 (3.1%)	<5 (<5%)
IQVIA LPD Belgium			N (%)	967 (5.8%)	452 (4.9%)	370 (6.2%)	65 (10.9%)	80 (10.1%)
IQVIA DA Germany			N (%)	13,193 (12.3%)	9,717 (13.2%)	3,349 (10.2%)	100 (10.9%)	27 (8.5%)
SIDIAP			N (%)	1,324 (7.8%)	1,287 (8.0%)	32 (3.6%)	<5 (<5%)	<5 (<5%)
CPRD		Hyper-tension	N (%)	12,488 (37.6%)	11,025 (44.2%)	290 (31.3%)	1,098 (16.9%)	75 (8.3%)
IPCI			N (%)	5,230 (31.8%)	4,609 (36.5%)	432 (18.1%)	166 (17.8%)	23 (4.3%)
IQVIA LPD Belgium			N (%)	10,315 (62.1%)	5,307 (57.2%)	3,855 (64.7%)	500 (84.0%)	653 (82.0%)
IQVIA DA Germany			N (%)	78,871 (73.4%)	57,644 (78.5%)	20,430 (62.4%)	650 (71.1%)	147 (46.5%)
SIDIAP			N (%)	7,808 (46.0%)	7,505 (46.8%)	284 (31.9%)	15 (33.3%)	<5 (<5%)
CPRD		Myocardial infarction	N (%)	1,604 (4.8%)	1,315 (5.3%)	31 (3.3%)	244 (3.8%)	14 (1.6%)
IPCI			N (%)	793 (4.8%)	623 (4.9%)	132 (5.5%)	35 (3.8%)	<5 (<5%)
IQVIA LPD Belgium			N (%)	375 (2.3%)	132 (1.4%)	202 (3.4%)	25 (4.2%)	16 (2.0%)

CDM name	Variable name	Variable level	Estimate name	Cohort name (indication) Semaglutide (Overall)	Semaglutide (DM2+obesity)	Semaglutide (DM2)	Semaglutide (Obesity)	Semaglutide (Other)
IQVIA DA Germany			N (%)	3,445 (3.2%)	2,356 (3.2%)	1,034 (3.2%)	51 (5.6%)	<5 (<5%)
SIDIAP			N (%)	989 (5.8%)	937 (5.8%)	49 (5.5%)	<5 (<5%)	0 (0.0%)
CPRD		Myocardial infarction stroke	N (%)	2,386 (7.2%)	1,981 (7.9%)	52 (5.6%)	329 (5.1%)	24 (2.7%)
IPCI			N (%)	1,363 (8.3%)	1,087 (8.6%)	210 (8.8%)	57 (6.1%)	9 (1.7%)
IQVIA LPD Belgium			N (%)	711 (4.3%)	253 (2.7%)	386 (6.5%)	26 (4.4%)	46 (5.8%)
IQVIA DA Germany			N (%)	6,937 (6.5%)	4,773 (6.5%)	2,069 (6.3%)	81 (8.9%)	14 (4.4%)
SIDIAP			N (%)	1,661 (9.8%)	1,581 (9.9%)	75 (8.4%)	5 (11.1%)	0 (0.0%)
CPRD		Stroke	N (%)	874 (2.6%)	757 (3.0%)	21 (2.3%)	86 (1.3%)	10 (1.1%)
IPCI			N (%)	657 (4.0%)	513 (4.1%)	106 (4.4%)	32 (3.4%)	6 (1.1%)
IQVIA LPD Belgium			N (%)	365 (2.2%)	135 (1.5%)	199 (3.3%)	<5 (<5%)	30 (3.8%)
IQVIA DA Germany			N (%)	3,801 (3.5%)	2,606 (3.5%)	1,141 (3.5%)	44 (4.8%)	10 (3.2%)
SIDIAP			N (%)	732 (4.3%)	703 (4.4%)	26 (2.9%)	<5 (<5%)	0 (0.0%)

Abbreviations: BMI, body mass index; CDM, common data model; MACE, composite outcome including myocardial infraction and stroke; NA, not available (no BMI value recorded in the last 5 years from first use of GLP-1 RA).