



Study Report

P3-C1-009

DARWIN EU[®] - CGRP antagonists - treatment patterns and user characteristics

25/10/2024

Version 3.0

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	Author(s): J. Politi, K. Verhamme	Version: 3.0
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Study Title	DARWIN EU® - CGRP antagonists - treatment patterns and users characteristics
Study Report Version	3.0
Date	25/10/2024
EU PAS number	EUPAS1000000240
Active substance	• Erenumab • Eptinezumab • Fremanezumab • Galcanezumab Therapeutic Drug class: N02CD
Medicinal product	Aimovig; Vyepti; Ajovy; Emgality
Research question and objectives	The aim of this study was to characterise individuals treated with CGRP antagonists for migraine. The specific study objectives were: 1. Characterisation of individuals newly treated with CGRP antagonists (i.e. new user cohort) in terms of demographics, risk factors for erectile dysfunction, insomnia and hypertension and concomitant medications taken at index date. This characterisation was stratified by sex. 2. Characterisation of treatment with CGRP antagonists in a cohort of new users in terms of duration of treatment. 3. Incidence rate of erectile dysfunction, insomnia, and hypertension in a newly diagnosed migraine population (irrespective of treatment) stratified by age groups and sex. 4. Incidence rate of erectile dysfunction, insomnia, and hypertension in a newly diagnosed migraine population initiating treatment with CGRP antagonists or other prophylactic treatments (anti-epileptics, TCA, Beta-blockers, calcium channel blockers), stratified by age groups and sex. 5. Incidence rate of erectile dysfunction, insomnia, and hypertension in the general population (as reference) stratified by age groups and sex.
Country(-ies) of study	Finland, Germany, Croatia, Spain
Author	Julieta Politi (j.politi@darwin-eu.org) Katia Verhamme (k.verhamme@darwin-eu.org)

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1. DESCRIPTION OF STUDY TEAM

The description of the Study team is available in [Table 1](#).

Table 1. Description of study team.

Study team role	Names	Organisation
Study Project Manager/Principal Investigator	Julieta Politi Katia Verhamme	Erasmus MC
Data Scientist	Ross Williams Maarten van Kessel Cesar Barbosa Ger Inberg	Erasmus MC
Epidemiologist/ Clinical Domain Expert	Julieta Politi Guido van Leeuwen Katia Verhamme	Erasmus MC
Data Partner*	Names	Organisation
FinOMOP – HILMO	Tuomo Nieminen Tiina Wahlfors	Finnish Care Register for Health Care
IQVIA DA Germany	James Brash Isabella Kaczmarczyk Dina Vojinovic	IQVIA
NAJS	Jakov Vukovic	Croatian Institute of Public Health
VID	Gabriel Sanf��lix Gimeno Francisco S��nchez S��ez	La Fundaci��n para el Fomento de la Investigaci��n Sanitaria y Biom��dica de la Comunitat Valenciana (FISABIO)

*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

This study used routinely collected health data from 4 databases in the DARWIN EU[®] network of data partners from 4 European countries. All databases were previously mapped to the OMOP CDM.

Data sources

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1. Finnish Care Register for Health Care (FinOMOP-HILMO), Finland
2. IQVIA Disease Analyzer Germany (DA Germany), Germany
3. Croatian National Public Health Information System (NAJS), Croatia
4. Valencia Health System Integrated Dataset (VID), Spain

These databases fulfilled the criteria required for patient-level drug utilisation, characterisation, and population-level study, allowing for large-scale characterisation while covering different regions of Europe. The selection of databases was based on the availability of data on the selected drugs of interest, the conditions of interest, and other variables needed to perform the described analyses. Furthermore, 3 out of 4 are population-wide data sources, providing a reliable denominator for the incidence rate calculation. Detailed information on the selected data sources is described in [Table 2](#).

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Table 2. Description of data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active individuals	Data lock for the last update	Ability to answer study objectives
FI	FinOMOP-HILMO	Adequate number of individuals exposed to CGRP, availability of medical history for patient characterisation, reliable denominator for estimation of rates. Covers inpatient and outpatient care	Primary care, outpatient specialist care, and inpatient care	EHR and Registries	7.33 million	2024-04-16	1, 2, 3, 4, and 5
DE	IQVIA DA Germany	Adequate number of individuals exposed to CGRP, availability of medical history for cohort characterisation	Primary care and outpatient specialist care	EHR	43.1 million	2023-09-30	1, 2, 3, 4, and 5
HR	NAJS	Adequate number of individuals exposed to CGRP, availability of medical history for patient characterisation, reliable denominator for estimation of rates. Covers inpatient and outpatient care	Primary care, outpatient specialist care, and inpatient care	EHR and registries	5.4 million	2023-11-17	1, 2, 3, 4, and 5
ES	VID	Adequate number of individuals exposed to CGRP, availability of medical history for patient characterisation, reliable denominator for estimation of rates. Covers inpatient and outpatient care	Primary care, outpatient specialist care, and inpatient care	EHR, and registries	1.96 million	2022-01-01	1, 2, 3, 4, and 5 This database only included female individuals aged 12-55 years

DE = Germany, ES = Spain, HR = Croatia, FI = Finland.

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3. ABSTRACT

Title

DARWIN EU® - CGRP antagonists - treatment patterns and users characteristics

Rationale and Background

Galcanzumab, fremanezumab, erenumab, and eptinezumab are monoclonal antibodies that interfere with the signalling pathway of the Calcitonin-Gene-Related Peptide (CGRP), which is involved in the pathophysiology of migraine. These novel therapies are indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month. The PRAC is currently investigating signals on a potential association between the use of these drugs and insomnia, erectile dysfunction, and increased blood pressure.

Through this study, we aimed to characterise individuals with migraine newly treated with these drugs, in order to contextualise the signal assessments. In addition, we aimed to investigate the incidence rate of erectile dysfunction, insomnia and increased blood pressure in a population with newly diagnosed migraine, and in the general population.

Research Question and Objectives

The aim of this study was to characterise individuals treated with CGRP antagonists for migraine.

The specific study objectives were:

1. To characterise individuals newly treated with CGRP antagonists (i.e. new user cohort) in terms of demographics, risk factors for erectile dysfunction, insomnia, hypertension, and concomitant medications taken at index date, overall and stratified by sex.
2. To characterise treatment with CGRP antagonists in a cohort of new initiators in terms of duration of treatment.
3. To calculate the incidence rate of erectile dysfunction, insomnia, and hypertension in a newly diagnosed migraine population (irrespective of treatment), overall and stratified by age groups and sex.
4. To calculate the incidence rate of erectile dysfunction, insomnia, and hypertension in a newly diagnosed migraine population initiating treatment with CGRP antagonists or other prophylactic treatments (anti-epileptics, Tricyclic antidepressants (TCA), Beta-blockers, and calcium channel blockers), overall and stratified by age groups and sex.
5. To calculate the incidence rate of erectile dysfunction, insomnia, and hypertension in the general population (as reference), overall and stratified by age groups and sex

Research Methods

Study design

Patient-level drug utilisation study.

Study Period

From January 1st, 2018 (first EU approval) to 31st December 2023 (or last available date)

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Population

For this study, 3 different cohorts were defined, namely:

1. Population of individuals newly initiating any of the CGRP antagonists of interest (objectives 1 and 2).
2. Population of individuals with newly diagnosed migraine (objectives 3 and 4).
3. General population, consisting of all individuals observable during the study period with at least 365 days of database history (objective 5).

Follow up

For individuals newly initiating CGRP antagonists (objective 2), follow-up began at the start of the first CGRP antagonist treatment and continued until the end of the first drug era. The incident migraine population (objective 3) was followed from the date of first diagnosis until the end of the study period or censoring (due to loss to follow-up, death, or the occurrence of the outcomes of interest). Individuals with incident migraine who initiated prophylactic treatments (objective 4) were followed for one year after treatment initiation. The general population cohort was followed from the date of inclusion until the end of the study period or censoring.

Data sources

- Finnish Care Register for Health Care (FinOMOP-HILMO), Finland
- IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
- Croatian National Public Health Information System (NAJS), Croatia
- Valencia Health System Integrated Dataset (VID), Spain, contributing with a female-only cohort

Exposure of interest

CGRP antagonist use specifically, erenumab, eptinezumab, fremanezumab, and galcanezumab.

Other migraine prophylactic treatments were also assessed (anti-epileptics, tricyclic antidepressants, Beta-blockers, and calcium channel blockers).

Exposure to other drugs of interest in the year before the start of CGRP antagonists was assessed to better contextualise CGRP antagonist use.

Outcomes of interest

- Erectile dysfunction: Incident events during the study period
- Insomnia: Incident events during the study period
- Hypertension: Incident events during the study period (only clinical diagnosis was considered; no blood pressure measurement-based diagnosis was used)

Covariates of interest

Comorbidities of interest, related to the outcomes of interest (i.e. erectile dysfunction, insomnia, and hypertension) were assessed during the year prior to the index date.

Data analyses

Characterisation of individuals newly initiating treatment with CGRP antagonists was assessed using the “*CohortCharacteristics*” and “*CohortDiagnostics*” R packages.

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For the second objective, we used the DrugUtilisation analytical pipeline to characterise CGRP antagonist use, including counts (%) for each substance, duration of treatment, and concomitant medications taken at index date. Use of prior medication of interest was assessed for windows 0-30, 31-90, and 91-365 days prior to the index date. For the calculation of the incidence rates of the outcomes of interest, the “*IncidencePrevalence*” R package was used, stratified by age and sex.

Outcomes of interest (i.e. erectile dysfunction, hypertension, and insomnia) were assessed over the entire study period in the incident migraine population and the general population (objectives 3 & 5), while for the individuals treated with CGRP antagonist-or treated with other specific prophylactic treatments (objective 4), outcomes were assessed within one year following treatment initiation. Erectile dysfunction was only reported for males.

Minimum cell count of 5 was used when reporting results, with any smaller count reported as “Supp”. All analyses were reported by country/database, overall and stratified by sex and age groups.

Results

Characterisation of individuals newly initiating CGRP antagonists

Individuals newly initiating CGRP antagonists (with or without explicit migraine diagnosis) were characterised. Overall, new initiators of CGRP antagonists were mostly female (female to male ratio 6:1), except in VID, which contributed to a female-only cohort. The median age ranged between 42-48 years.

The proportion of individuals newly initiating CGRP antagonists with an explicit migraine diagnosis ranged between 75.6-94.6%. In terms of the outcomes of interest for this study, the prevalence of hypertension ranged between 10.0-25.3%, and insomnia between 4.5-19.5%, while for erectile dysfunction, the number of events was very low. In terms of comorbidities of interest, mental health disorders were highly prevalent, ranging between 39.6-46.0% across databases. Other prevalent conditions were heart disease, between 2.9-18.6%; asthma, between 3.1-10.7%; and gastroesophageal reflux disease (GERD), between 0.7% and 33.9%.

The highest use of migraine-specific treatments was observed during the 91-365 days prior to index window and varied by database. In particular, drugs in which the prevalence of use was above 10.0% in any database included antiepileptics, ranging between 0-15.4%; TC antidepressants, between 7.0-11.5%; and triptans, between 5.4-13.0%. For other comedications assessed (not specifically anti-migraine treatments), antidepressant use during the 91-365 days window ranged between 3.2-12.4%. For the remaining medication categories, use was generally low, except for some drugs used for hypertension (mainly beta-blockers and angiotensin II receptor blockers) and drugs used for sleep disorders (benzodiazepines).

Large-scale characterisation was used to assess the 10 most prevalent conditions and prescriptions recorded in the year before the index date. In terms of conditions, headaches and pain in different body parts were among the most prevalent. The most frequently administered drugs (in addition to the previously reported predefined medications) included pain relievers such as dextketoprofen, dipyrone, ibuprofen, and acetaminophen.

The duration of treatment of the first drug era in new initiators of CGRP antagonists ranged between 31-233 days. Duration was notably shorter in VID, and when VID was excluded, the median duration of the first drug era increased, ranging between 220-233 days. Duration was not available for FinOMOP-HILMO.

Incidence rates for outcomes of interest

Incidence rates for outcomes of interest in individuals with incident migraine

Throughout the entire period, the (unadjusted) incidence rates of erectile dysfunction in men with incident migraine ranged between 1-6 per 1,000 person-years (PY). The incidence rates for hypertension in the

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incident migraine population for the entire period ranged between 23-34 per 1,000 PY. For Insomnia, incidence rates ranged between 15-45 per 1,000 PY in the incident migraine population.

Incidence rates for outcomes of interest in the general population

Similarly, outcomes of interest were also assessed for the general population over the entire study period. Rates for erectile dysfunction in males ranged between 0-3 per 1,000 PY. Hypertension ranged between 11-25 per 1,000 PY across databases and over the entire period. The incidence rate of insomnia for the entire study period ranged between 5-17 per 1,000 PY.

Incidence rates for outcomes of interest within one year after the start of the different prophylactic treatments in individuals with incident migraine

Incidence rates of erectile dysfunction in males with incident migraine, within one year after the start of prophylactic treatment, were consistently low across treatment classes. Initiators of CGRP antagonists, antiepileptic drugs, and calcium channel blockers had rates of 0 per 1,000 PY. TCA initiators had a rate of 9 per 1,000 PY, and the rate in Beta-blocker initiators ranged from 0 to 7 per 1,000 PY.

Incidence rates of hypertension one year after the initiation of prophylactic migraine therapy varied widely by treatment class. Beta-blocker initiators showed the broadest range of 28-253 per 1,000 PY, while calcium channel blocker initiators had the narrowest range, from 0 to 13 per 1,000 PY. Incidence rates of hypertension were comparable for individuals initiating treatment with CGRP antagonists, antiepileptics, and TCA (8-33, 0-43, and 19-49 per 1,000 PY, respectively).

For insomnia, rates within one year after the initiation of prophylactic migraine treatment were variable across treatment groups. Rates ranged between 6-45 per 1,000 PY for CGRP antagonist initiators, 0-36 per 1,000 PY for antiepileptic initiators, 20-64 per 1,000 PY for TCA initiators, 9-57 per 1,000 PY for beta-blocker initiators, and 0 per 1,000 PY for calcium channel blocker initiators.

Conclusion

This study describes the use of CGRP antagonists in a real-world setting across four European countries. Most individuals newly initiating CGRP antagonists were females with a median age of 42-48 years. The most frequently prescribed drug was erenumab and median treatment duration (first drug era) ranged between one to seven months.

While no formal comparisons were made, the (unadjusted) incidence rates of the outcomes of interest over the entire period were generally higher in individuals with incident migraine than in the general population. This difference was particularly high for insomnia, with incidence rates at least 2.5 times higher in those with incident migraine than in the general population.

Incidence rates of the outcomes of interest across the different prophylactic treatment classes within one year following treatment initiation were consistently low for erectile dysfunction for all treatment classes. The incidence rate of hypertension amongst individuals with incident migraine, initiating migraine prophylactic treatment showed the widest variability across classes, and rates were notoriously wide among beta-blocker initiators. Insomnia rates also varied across treatment classes, being highest among individuals initiating treatment with TCA.

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4. LIST OF ABBREVIATIONS

Abbreviation	Name
CC	Coordinating centre
CDM	Common Data Model
CGRP	Calcitonin gene related peptide
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DOI	Declaration Of Interests
DQD	Data Quality Dashboard
DRE	Digital Research Environment
DUS	Drug Utilisation Study
ED	Erectile dysfunction
EHR	Electronic Health Record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FinOMOP-HILMO	Finnish Care Register for Health Care
GDPR	General Data Protection Regulation
GP	General Practitioner
ICD	International Classification of Diseases
NAJS	Croatian National Public Health Information System
OMOP	Observational Medical Outcomes Partnership
PCT	Primary Care Teams
PDE5	Phosphodiesterase-5
PRAC	Pharmacovigilance Risk Assessment Committee
PTSD	Post-traumatic stress disorder
PY	Person-years
RxNorm	Medical prescription normalized
SNOMED	Systematized Nomenclature of Medicine
SNRI	Serotonin and norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressants
VID	Valencia Health System Integrated Dataset

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5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	08/08/2024	8.8 Analysis	No sensitivity analysis was initially planned. However, it was decided to add an Erectile dysfunction “broad” concept set as a sensitivity analysis.	Given that counts for the Erectile dysfunction outcome were low, we generated a broader definition of erectile dysfunction, which incorporated two additional concepts: ‘4152169’ (failure of genital response) and ‘4250163’ (sexual arousal disorder).
2	02/09/2024	8.8 Analysis	Erectile dysfunction is only reported for the male sex stratum.	This phenotype was specifically designed for men, with erectile dysfunction as the primary outcome of interest. However, the inclusion of codes such as sexual arousal disorder may lead to include some women in the erectile dysfunction outcome. Therefore, the outcome is reported exclusively for men.

6. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINES (actual)
Draft Study Protocol	7/06/2024	07/06/2024
Final Study Protocol	1/07/2024	01/07/2024
Creation of Analytical code	June 2024	June-mid July 2024
Execution of Analytical Code on the data	July/August 2024	26/07/2024
Draft Study Report	19/08/2024	21/08/2024
Final Study Report	20/09/2024	22/10/2024
Draft Manuscript	November 2024	
Final Manuscript (if agreed on)	December 2024	

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7. RATIONALE AND BACKGROUND

Migraine is a chronic and often debilitating disease affecting around 15% of adult individuals ([1-3](#)), and one of the top 20 causes of disability worldwide ([1](#)). It is typically characterised by recurrent disabling attacks of headache, accompanied by photo- and phonophobia and/or severe nausea and/or vomiting and other accompanying symptoms, including aura ([4](#)).

The aetiology of migraine is considered multifactorial. Some monogenic variants have been described, although rare. Spreading depolarisation probably causes aura and possibly also triggers trigeminal sensory activation, the underlying mechanism for the headache. The pathophysiology is not completely understood, although calcitonin gene-related peptide (CGRP) has been identified to play a major role ([5](#)).

CGRP is known to be a potent vasodilator ([5](#)). In addition to its role in migraine, CGRP is involved in other physiological processes, such as regulating blood pressure ([6, 7](#)), having chronotropic and inotropic effects on the heart, and maintaining cerebral and cardiovascular homeostasis ([8](#)).

Management of migraine attacks usually requires drugs to relieve pain. Still, in some individuals, because of frequency, severity and impact on quality of life, preventive treatment is required to reduce the occurrence of acute attacks and the need for pain relief medication. Preventive treatments include calcium-channel antagonists, antidepressants, antiepileptics, and anti-hypertensives developed for indications other than migraine and subsequently repurposed for migraine based on clinical studies ([9-12](#)). However, efficacy is often insufficient, and there is a delay between the start of therapy and its effect. Poor tolerability and side effects are important limitations of available preventive treatments and may hinder treatment adherence. In this sense, treatment adherence is low, dropping to 20% after one year ([13](#)). Additionally, comorbidities, such as depression, epilepsy, stroke and myocardial infarction, limit the use of some prophylactic drugs.

Monoclonal antibodies acting on the CGRP or on its receptor are new drugs used to prevent migraine by interfering in the signalling pathway of the CGRP, which is involved in the pathophysiology of migraine. These drugs, approved for their use in migraine prophylaxis in adults who have at least 4 migraine days per month, target either the calcitonin gene-related peptide receptor (erenumab) or the calcitonin gene-related peptide (eptinezumab, fremanezumab, and galcanezumab) ([14-16](#)). Galcanezumab, erenumab, and fremanezumab are available in pre-filled pens for subcutaneous use once a month (every 4 weeks), while eptinezumab is formulated as a concentrate for intravenous infusion and administered once every three months in an outpatient setting.

Erectile dysfunction (ED) is the inability to get and keep a penis erection; it is a complex event involving the psychological, neurological, endocrine, vascular, and anatomical systems aspects. Neither ED nor any sexual dysfunctions are listed in the Summaries of Product Characteristics of any CGRP antagonists. There is some biological plausibility about the relation of these molecules with ED in the scientific literature, with a small number of case reports in males, while in females, there are some reports of sexual dysfunction ([17, 18](#)).

Insomnia most often represents an individual's report of difficulty with sleep, which could entail difficulties falling asleep, staying asleep, or experiencing nonrestorative sleep despite adequate sleep circumstances, which can impact daily activities. Sleep disorders such as insomnia can affect migraine attack frequency. Insomnia is not listed in the Summaries of Product Characteristics of any CGRP antagonists. Erenumab does not cross the blood-brain barrier, so a directly mediated effect would be unlikely ([19](#)). Some literature even suggests an improvement in sleep quality among CGRP antagonist users ([19, 20](#)).

Elevated blood pressure, also referred to as hypertension, occurs when the force of blood flowing through the blood vessels is consistently too high. The normal range is usually less than 120mmHg for systolic blood pressure and less than 80mmHg for diastolic blood pressure. Elevated blood pressure can lead to serious

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health problems, including heart attack or stroke. Elevated blood pressure is not listed in the Summaries of Product Characteristics of any CGRP antagonists. However, some literature suggests increased systolic blood pressure (compared to baseline) in individuals treated with erenumab ([21](#)).

The PRAC is evaluating signals on a potential association between the use of these drugs and insomnia, erectile dysfunction, and increased blood pressure, all based on spontaneous case reports. Through this study, we aimed to characterise individuals with migraine newly treated with this drug class, including the prevalence of risk factors for these events. In addition, we aimed to investigate the incidence rate of erectile dysfunction, insomnia and hypertension in a population of individuals with newly diagnosed migraine and the general population to contextualise the signal assessment.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this study was to characterise individuals treated with CGRP antagonists for migraine.

The specific study objectives were:

1. To characterise individuals newly treated with CGRP antagonists (i.e. new user cohort) in terms of demographics, risk factors for erectile dysfunction, insomnia and hypertension and concomitant medications taken at index date, overall and stratified by sex.
2. To characterise treatment with CGRP antagonists in a cohort of new initiators in terms of duration of treatment.
3. To calculate the incidence rate of erectile dysfunction, insomnia, and hypertension in a newly diagnosed migraine population (irrespective of treatment), overall and stratified by age groups and sex.
4. To calculate the Incidence rate of erectile dysfunction, insomnia, and hypertension in a newly diagnosed migraine population initiating treatment with CGRP antagonists or other prophylactic treatments (anti-epileptics, TCA, Beta-blockers, and calcium channel blockers), overall and stratified by age groups and sex.
5. To calculate the Incidence rate of erectile dysfunction, insomnia, and hypertension in the general population (as reference), overall and stratified by age groups and sex.

9. RESEARCH METHODS

9.1 Study type and study design

The proposed design for this study was a patient-level DUS study, classified as “off-the-shelf”, as described in the DARWIN EU® Complete Catalogue of Standard Data Analyses. We also performed a patient-level characterisation. Additionally, the incidence of the events of interest described in objectives 3, 4, and 5 was assessed using a population-level descriptive epidemiology design.

9.2 Study setting and data sources

This study used routinely collected health data from 4 databases in the DARWIN EU® network of data partners from 4 European countries. All databases were previously mapped to the OMOP CDM.

1. Finnish Care Register for Health Care (FinOMOP-HILMO), Finland
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

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These databases fulfilled the criteria required for patient-level drug utilisation, characterisation, and population-level study, allowing for large-scale characterisation while covering different regions of Europe. The selection of databases was based on the availability of data on the selected drugs of interest, the conditions of interest, and other variables needed to perform the described analyses. Furthermore, 3 out of 4 are population-wide data sources, providing a reliable denominator for the incidence rate calculation. Detailed information on the selected data sources is described in [Table 2](#).

To assess the reliability of data sources, data partners are asked to describe their internal data quality process on the source data as part of the DARWIN EU onboarding procedure. To further ensure data quality, we utilise the Achilles software tool (<https://ohdsi.github.io/TheBookOfOhdsi/DataQuality.html#data-quality-checks>), which systematically characterises the data and presents it in a dashboard format that is inspected. The generated data characteristics such as age distribution, condition prevalence per year, data density, and measurement value distribution can be compared against expectations for the data. Additionally, the data quality dashboard (DQD) consistently provides more objective checks on plausibility across data sources. Regarding relevance, a more general-purpose diagnostic software tool, CohortDiagnostics, was developed. This package evaluates phenotype algorithms for OMOP CDM datasets, offering a standard set of analytics for understanding patient capture, including data generation. It provides additional insights into cohort characteristics, record counts and index event misclassification. Furthermore, timeliness is guarded by extracting the release dates for each dataset in the network and monitoring when data are out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it is important to clearly understand the time period covered by each released database, as this can vary across different domains. To facilitate this, the CdmOnboarding (and Achilles) packages contain a 'data density' plot that is checked. This plot displays the number of records per OMOP domain monthly. This allows us to get insights into when data collection started, when new data sources were added and until when data was included.

FINOMOP-HILMO, Finland

This database covers both public and private, primary and specialised inpatient and outpatient health care encounters in Finland starting from 2011. The entire public sector and private inpatient encounters have been included since 2011, while private outpatient encounters, including occupational care, are included since 2020. The main content of the THL CDM is The Finnish Care Register for Health Care, which is a continuation of the former Hospital Discharge Register, which originally gathered data on individuals discharged from hospitals. The Care Register has comprehensive data on the use of services and service users from Finnish public inpatient and outpatient primary and specialised care nationwide. Since 1998, the register has covered both public outpatient and inpatient specialised care and private inpatient care (TerveysHilmo). From 2011 the register has covered public primary care (AvoHilmo). From 2020 the register has covered private outpatient care and occupational care. In addition, the CDM also contains the vaccination data from the Finnish National Vaccination Register, the vaccination data from the Finnish National Vaccination Register, and COVID-19 test results from the Finnish National Infectious Diseases Register, which is maintained by THL. The CDM includes all the above-mentioned data sources and is limited to observation periods commencing after 1.1.2011. The National Population is used to form the base population. This ensures up-to-date location (municipality of residence) of individuals and complete death occurrences (although not the cause of death). Using the complete population as a basis for the person table also facilitates calculations on a population level, e.g. incidence rates. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.

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IQVIA Disease Analyser (DA) Germany, Germany

IQVIA Disease Analyzer (DA) Germany is a database of de-identified electronic medical records from specialised and general primary practices (GP) in Germany since 1992. This dataset encompasses approximately 3% of all outpatient practices within Germany, ensuring a substantial representation of the national healthcare landscape ([22](#), [23](#)). The sampling methods used for practice selection, taking into account physician's demographics, specialty focus, community size category and federal state location, was instrumental in constructing a database that accurately mirrors the diverse spectrum of healthcare providers in the country ([22](#)). Consequently, data within IQVIA DA Germany database has been demonstrated to be representative of general and specialised practices throughout Germany.

The database contains demographics records, basic medical data, disease diagnosis according to International Classification of Diseases, 10th revision (ICD-10), and prescription records ([23](#)). While the database partly records information on deaths and procedures, it currently does not support linkage with external data sources and therefore, information on mortality is incomplete. Routine updates are conducted at regular intervals. Data quality is assessed based on several criteria, including completeness of information and correctness (e.g. linkage between diagnosis and prescriptions).

No registration or approval is required for drug utilisation studies. As previously demonstrated, IQVIA DA Germany is suitable for pharmacoepidemiologic and pharmaco-economic studies ([23-25](#)).

NAJS, Croatia

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by the Croatian Institute of Public Health (CIPH). This database was established in 1998, with nationwide coverage, representing approximately 5.4 million inhabitants. Settings covered include public primary, secondary/outpatient, and inpatient care. Data is retrieved primarily from EHR and holds information on demographics, inpatient and outpatient visits, conditions and procedures, drugs (outpatient and inpatient prescriptions), measurements, and inpatient and outpatient dates of death. NAJS provides linkage between medical and public health data collected and stored in health registries and other health data collections, including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse and others. The CDM population comprises all publicly insured persons residing in Croatia starting in 2015.

VID, Valencia, Spain

The Valencia Health System Integrated Dataset (VID) is a set of multiple, public, population-wide electronic databases for the Valencia Region, the fourth most populated Spanish region, with about 5 million inhabitants and an annual birth cohort of 48 000 new-borns, representing 10.7% of the Spanish population and around 1% of the European population. The VID provides exhaustive longitudinal information, including sociodemographic and administrative data (sex, age, nationality, etc.), clinical (diagnoses, procedures, diagnostic tests, imaging, etc.), pharmaceutical (prescription, dispensing) and healthcare utilisation data from hospital care, emergency departments, specialised care (including mental and obstetrics care), primary care and other public health services. It also includes a set of associated population databases and registries of significant care areas such as cancer, rare diseases, vaccines, congenital anomalies, microbiology (including COVID-19 test results registry), and public health databases from the population screening programmes. All the information in the VID databases can be linked individually through a single personal identification code. The databases were initiated at different times, but overall, the VID provides comprehensive individual-level data fed by all the databases from 2008 to 2022. However, for this study, this database participated with

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data of women aged 12-55 years, from 01/01/2018 to 01/01/2022, representing the data that was currently mapped and readily available for study purposes.

9.3 Study period

The study period was from 01/01/2018 (the first EU approval of a CGRP antagonist) up to 31/12/2023. When the study end date was not reached in a data source, the study end for that source was the last date of available data ([Table 2](#)).

9.4 Follow-up

For objective 2, study individuals were followed up from the start of the first CGRP antagonist treatment to the end of the first exposure era (to estimate treatment duration).

For objectives 3 and 4, individuals were followed up as follows:

Incident migraine population: from their date of first diagnosis (incident migraine cohort) until the earliest of the following: 1) censoring (loss to follow-up or death), 2) end of data availability, or 3) the first occurrence of outcomes of interest.

For stratification by prophylactic treatment class among incident migraine cohort: from the date of first prophylactic treatment initiation, until the earliest of the following: 1) censoring (loss to follow-up or death), 2) end of data availability, 3) the first occurrence of outcomes of interest, or 4) 1-year follow-up time. Individuals could contribute to different cohorts (if different types of prophylactic treatment were used).

For objective 5, overall population were followed up from the date of fulfilling inclusion criteria for the study (cohort of general population), until the earliest of the following: 1) censoring (loss to follow-up or death), 2) end of data availability, or 3) first occurrence of outcomes of interest.

Operational definitions on index date are specified in [Table 3](#).

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Table 3. Operational definition of time 0 (index date) and other primary time anchors.

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting ¹	Code Type	Diagnosis position	Incident with respect to...	Measurement characteristics/ validation	Source of algorithm
Individuals initiating treatment with any CGRP antagonist of interest (objective 1 & 2)	Date of first treatment with CGRP antagonist during study period	Single entry	Incident	Any time prior to study entry date	OP	Time	n/a	Prior CGRP antagonist use	n/a	n/a
Individuals with incident migraine diagnosis (objective 3,)	Date of diagnosis (incident diagnosis)	Single entry	Incident	Any time prior to study entry date	OP	Clinical finding, time	n/a	Prior migraine diagnosis	n/a	n/a
Individuals with incident migraine diagnosis initiating treatment with any of the selected prophylactic drugs of interest	Date of first treatment with any of the selected prophylactic treatments classes	Single entry	Incident	Any time prior to study entry date	OP	Clinical finding, time	n/a	Prior selected prophylactic treatment class, prior migraine diagnosis	n/a	n/a
All individuals present in the database (i.e. general population cohort)	Date of first fulfilment of inclusion criteria from the start of the observation period	Single entry	Incident	n/a	OP	Time	n/a	Fulfilment of inclusion criteria	n/a	n/a

¹ IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

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An example of entry and exit into the denominator population is shown in [Figure 1](#). In this example, person ID 1 already has sufficient prior history before the study start date and the observation period ends after the study end date, so this person contributed during the complete study period. Person IDs 2 and 4 enter the study only when they have sufficient prior history. Person ID 3 leaves when exiting the database (the end of the observation period). Lastly, person ID 5 has two observation periods in the database. The first period contributes time from study start until end of observation period, and the second starts contributing time again once sufficient prior history is reached and exits at study end date.

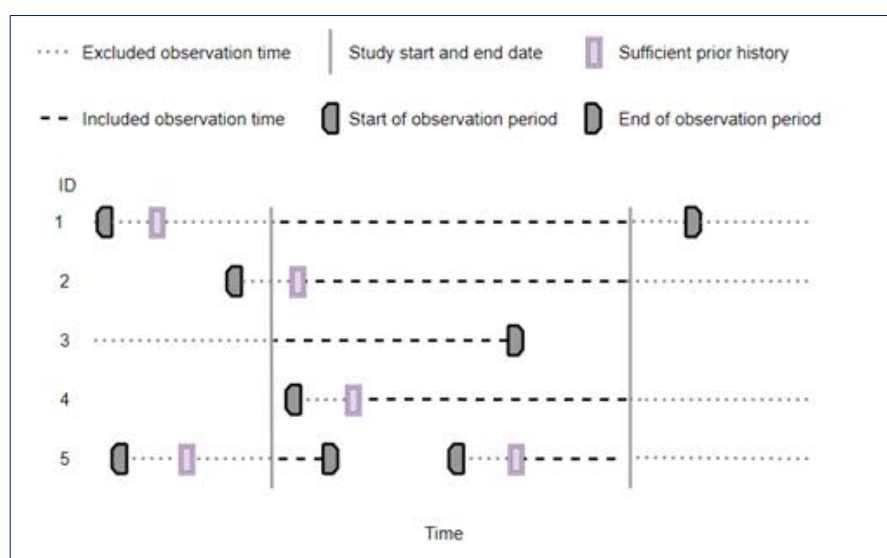


Figure 1. Included observation time for the denominator population.

9.5 Study population with inclusion and exclusion criteria

The general population cohort consisted of all individuals with observable time during study period and with at least one year of database history.

Two additional cohorts were defined within this population: a cohort of individuals initiating treatment with any of the CGRP antagonists of interest (objectives 1 and 2) and a cohort of individuals with newly diagnosed migraine (objective 3). Within this cohort of individuals with newly diagnosed migraine, we nested a cohort of individuals initiating prophylactic treatment class for the first time (objective 4) (CGRP antagonists, Beta-Blockers, Anti-epileptics, TCA, or Calcium channel blockers).

The concept definitions of migraine and CGRP antagonists are described in [Appendix I. Table S1](#). The operational definitions of the inclusion and exclusion criteria are described in [Table 4](#) and [Table 5](#), respectively.

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Table 4. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings ¹	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Observation period in the database during the period 2018-2023 (or the latest date available)	All individuals present in the period 2018-2023 (or the latest date available)	After	n/a	OP, OT	n/a	n/a	All individuals within selected databases	n/a	n/a
Prior database history	Individuals were required to have 365 days of prior history observed before contributing observation time	Prior	[-365, -1]	OP, OT	n/a	n/a	All individuals within selected databases	n/a	n/a

¹ IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

Table 5. Operational definitions of exclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings	Code Type	Diagnosis position ²	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

n/a = not applicable

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9.6 Variables

9.6.1 Exposures

The operational definition of exposures is described in [Table 6](#).

Drugs of interest are CGRP antagonists and other migraine prophylactic drugs ([26-29](#)), along with the use of medicines that help contextualise exposure to CGRP antagonists (see also section 9.6.3. – Other covariates of interest). The drugs of interest were defined based on the respective RxNorm codes (see also [Appendix I. Table S1](#)).

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Table 6. Operational definitions of exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting ¹	Code Type	Diagnosis position	Applied to study populations	Incident with respect to	Measurement characteristics/algorithm validation	Source of
Erenumab, Eptinezumab, Fremanezumab, Galcanezumab	Preliminary code lists provided in Appendix I	[-Inf, -1] *	Anytime post start of the study period	IP, OP, and OT	RxNorm	n/a	Individuals newly treated with CGRP antagonists Incident migraine population	Any of the specified drugs, within class of interest	n/a	n/a
Antiepileptics (Valproate, Topiramate)	Preliminary code lists provided in Appendix I	[-Inf, -1] *	Anytime post start of the study period	IP, OP, and OT	RxNorm	n/a	Incident migraine population	Any of the specified drugs, within class of interest	n/a	n/a
Beta-blockers (Metoprolol, Propranolol, timolol)	Preliminary code lists provided in Appendix I	[-Inf, -1] *	Anytime post start of the study period	IP, OP, and OT	RxNorm	n/a	Incident migraine population	Any of the specified drugs, within class of interest	n/a	n/a
Tricyclic antidepressants (Amitriptyline)	Preliminary code lists provided in Appendix I	[-Inf, -1] *	Anytime post start of the study period	IP, OP, and OT	RxNorm	n/a	Incident migraine population	Any of the specified drugs,	n/a	n/a

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Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting ¹	Code Type	Diagnosis position	Applied to study populations	Incident with respect to	Measurement characteristics/algorithm validation	Source of algorithm
								within class of interest		
Calcium antagonists (Flunarizine)	Preliminary code lists provided in Appendix I	[-Inf, -1] *	Anytime post start of the study period	IP, OP, and OT	RxNorm	n/a	Incident migraine population	Any of the specified drugs, within class of interest	n/a	n/a
Other medications of interest	Preliminary code lists provided in Appendix I	n/a	365 days prior to the start of the study period	IP, OP, and OT	RxNorm	n/a	Individuals newly treated with CGRP antagonists	n/a	n/a	n/a

¹ IP = inpatient, OP = outpatient, OT = other, n/a = not applicable, *= for incident use only

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9.6.2 Outcomes

The operational definition of the outcomes is presented in [Table 7](#).

All lists of codes used to identify the outcomes of interest are available in [Appendix I. Table S1](#).

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Table 7. Operational definitions of outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings ¹	Code Type	Diagnosis Position	Applied to study populations	Measurements/characteristics/ validation	Source of algorithm
Erectile dysfunction	Incident cases during the study period	Yes	Count	[∞, 0)	IP, OP, and OT	SNOMED	n/a	All eligible individuals within the database considered for objectives 3, 4, and 5 (cohorts: newly diagnosed migraine, and general population)	n/a	n/a
Insomnia	Incident cases during the study period	Yes	Count	[∞, 0)	IP, OP, and OT	SNOMED	n/a	All eligible individuals within the database considered for objectives 3, 4, and 5 (cohorts: newly diagnosed migraine, and general population)	n/a	n/a
Hypertension	Incident cases during the study period	Yes	Count	[∞, 0)	IP, OP, and OT	SNOMED	n/a	All eligible individuals within the database considered for objectives 3, 4, and 5 (cohorts: newly diagnosed migraine, and general population)	n/a	n/a

¹ IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

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

The operational definition of the covariates is described in [Table 8](#).

Covariates for the patient-level characterisation (Objective 1) to describe new initiators of CGRP antagonist drugs included:

- age at the index date (i.e. first prescription of CGRP antagonist) (<18, 18-44, 45-64, 65-79, and ≥80)
- sex (male/ female).
- Comorbidities considered risk factors for ED, insomnia and hypertension were assessed within 365 days before the index date. These comorbidities were identified based on the presence of disease codes. The code list for each condition of interest is available in [Appendix I. Table S2](#).

- Endocrine/metabolism:
 - Diabetes
 - Hyperthyroidism
 - Hypopotassaemia
 - Obesity and overweight
- Cardiovascular:
 - Heart disease
- Urinary system:
 - Chronic kidney disease
 - Injuries of pudendal arteries, veins, or nerves
 - Prostate surgery or radiation treatment for cancer
- Oncological:
 - Cancer
- Respiratory:
 - Asthma
- Gastrointestinal:
 - Gastroesophageal reflux disease (GERD)
- Neurological disorders:
 - Parkinson's disease and dementia (including Alzheimer's disease)
 - Migraine
- Mental health disorders:
 - Anxiety, depression, PTSD
- Sleep-related disorders:
 - Sleep apnoea, restless legs syndrome

- Comedications: Prior use of these medications of interest was assessed in different time windows before the index date (0-30 days, 31-90 days, 91-365 days). The list of codes for drugs of interest is available in [Appendix I. Table S3](#).

Briefly, the comedications of interest were classified into:

- Other anti-migraine treatments (focusing on prophylactic treatments):
 - Anti-epileptics (Valproate, topiramate)
 - Beta-blockers (i.e., propranolol, metoprolol, and timolol)
 - TCA (Amitriptyline)
 - Calcium antagonists (flunarizine)
 - Triptans
- Drugs used as treatment for with erectile dysfunction:
 - PDE5 inhibitors and alprostadil

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- Drugs used as treatment for insomnia:
 - Zolpidem and zopiclone
 - Benzodiazepines
 - Antidepressants:
 - SSRI
 - SNRI
 - Others
- Drugs used as treatment for hypertension:
 - Diuretics
 - Beta-blockers
 - ACE inhibitors
 - Angiotensin II receptor blockers
 - Calcium channel blockers
 - Alpha-blockers
 - Alpha-2 receptor agonists
 - Combined Alpha and Beta-blockers
 - Vasodilators

Large-scale characterisation was used to complement the patient characterisation: Any drug (by RxNorm code) and condition (by standard SNOMED code) were assessed within predefined windows (at index date and 365 days to 1 day before the index date). While all conditions and medications above 1% were recorded, only the 10 most frequent conditions and drugs are described in this report.

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Table 8. Operational definitions of covariates.

Characteristic details		Type of variable	Assessment window	Care Settings ¹	Code type	Diagnosis Position	Applied to study populations	Measurement characteristics/ validation	Source for algorithm
Demographics	Age at index date and sex	Numeric, continuous, binary	All history	IP, OP, and OT	n/a	n/a	All first users of the selected CGRP antagonists of interest	n/a	n/a
Risk factors (Health conditions of interest)	Prespecified conditions of interest prior to index date	Count, Binary	[-365, -1],	IP, OP, and OT	SNOMED	n/a	All first users of the selected CGRP antagonists of interest	n/a	n/a
Other medicines of interest	Prespecified Drug prescriptions prior to index date	Count, Binary	[-365, -91], [-90, -31], [-30, -1], [at index]	IP, OP, and OT	RxNorm	n/a	All first users of the selected CGRP antagonists of interest	n/a	n/a
Health Conditions, medication use	All history prior to the index date (for large-scale characterisation)	Count, Binary	[-365, -1],	IP, OP, and OT	SNOMED	n/a	All first users of the selected CGRP antagonists of interest	n/a	n/a

¹ IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

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9.7 Study size

No sample size was calculated as this was a descriptive Drug Utilisation Study (DUS) to assess the characteristics of all new (incident) users of CGRP antagonists in each database.

9.8 Data transformation

Drug exposure calculation

Drug eras were defined as follows: Exposure starts at date of the first prescription, e.g., the index date the person entered the cohort. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM, using the start and end date of the exposure. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications:

Two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era was ≤ 90 day. The time between the two joined eras was considered as exposed by the first era as shown in [Figure 2](#), first row.

<i>Gap era joint mode</i>	Schematics	Dose in between	Cumulative dose	Cumulative time
“first”		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
“second”		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
“zero”		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
“join”	 first exposure time = x_1, dose = d_1 gap time = x_{12} second exposure time = x_2, dose = d_2	NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 2. Gap-era joint mode.

As previously stated, for each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM, using the start and end date of the exposure, and calculated as the duration of the first treatment era of the CGRP antagonist of interest during the study period. Treatment duration was summarised providing the minimum, p25, median, p75, and maximum treatment duration. For databases in which duration could not be calculated, treatment duration is not provided.

9.9 Statistical methods

9.9.1 Main summary measures

Results were presented by counts, proportions, mean, median, SD, IQR, and incidence rates.

9.9.2 Main statistical methods

The type of analysis used in this study is described in [Table 9](#).

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Table 9. Description of study types and types of analysis.

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
Patient Level DUS	Off-the-shelf	- characterisation of patient-level features - Frequency and % of indication/s - Estimation of minimum, p25, median, p75, and maximum treatment duration
Population-level descriptive epidemiology	Off-the-shelf	- Incidence rates of the condition of interest

R-packages

We used the R package “*IncidencePrevalence*” for the calculation of the outcomes of interest. We used the “*DrugUtilisation*” R package to calculate the duration of treatment (first drug era) interest and the “*CohortCharacteristics*” and “*CohortDiagnostics*” R packages to describe the characteristics of individuals initiating treatment with GCRP antagonists.

Population-level incidence calculations

Incidence rates of the outcomes of interest, for the incident migraine and the general population, were calculated as the number of newly diagnosed individuals with the outcome of interest divided by the person-years as contributed by the population at risk of the outcome during the period for each calendar year. Follow-up was censored upon the end of the observation period, the outcome of interest or upon death whichever came first. Incidence rates were provided together with 95% Poisson confidence intervals.

Figure 3 Represents an example of incidence rate estimation.

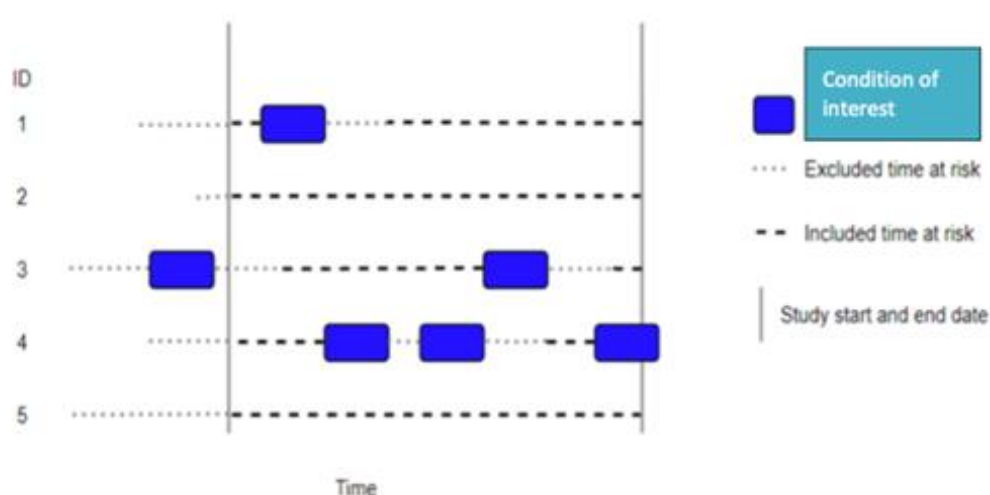


Figure 3. Example of incidence rate estimation.

Patient ID 1 and 4 contribute time at risk between the study start until they have an incident outcome of interest. Patient ID 2 and 5 contribute time at risk between the study start and end date as no outcome of interest is observed between this period nor before the study start date. Patient ID 3 was excluded from

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the analysis and does not contribute time at risk since a previous diagnosis was observed before the study start date.

For the calculation of incidence rates in the cohort of individuals newly diagnosed with migraine and initiating treatment with prophylactic treatment, the numerator consisted of individuals with the outcome of interest occurring within one year following index date (i.e. date of first prescription of the prophylactic treatment of interest) and the denominator consisted of person time from index date until the end of observation period, outcome of interest, mortality or one year following the index date whichever came first.

Follow-up in individuals initiating treatment with prophylactic treatment is described in

Figure 4. As observed, individuals might have contributed to multiple exposure cohorts as individuals were possibly exposed to different classes of prophylactic drugs.

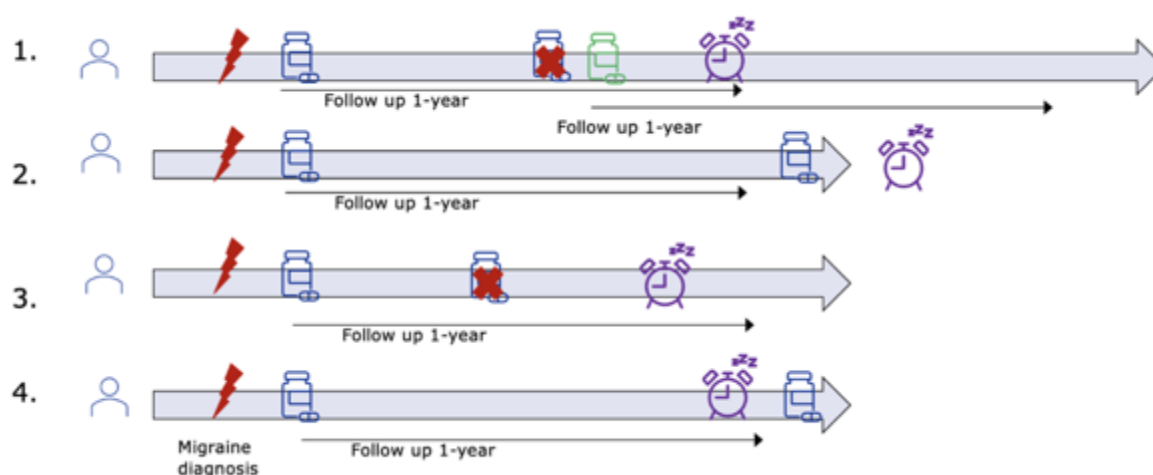


Figure 4. Example of follow-up time contribution for incidence rate estimation.

Patient 1 contributes to time at risk of drugs “blue” and “green” for a maximum of one year or until they have an incident outcome of interest (whichever occurs first). Index date is different for drug “blue” and drug “green” as the start date of the first prescription of the different drugs is different. The event (in this case, an alarm clock representing insomnia) would be counted in both cohorts (drugs blue and green). Patients 2, 3, and 4 only contribute time at risk for drug “blue”, from the start of the drug up to a year or until they have the event (if event occurs <= within one year following treatment initiation). Patients 3 and 4 have an incident outcome (an alarm clock representing insomnia) within one year, so they would be counted in the numerator for drug “blue”. Patient 2 has the event outside the one-year maximum follow-up, so the event is not counted.

Patient-level characteristics on/before index date

Characterisation of individuals newly treated with CGRP antagonists: We used the R package “PatientsProfiles” for the patient-level characterisation of demographics and predefined clinical characteristics, as well as large-scale characterisation. The co-variables used to summarise baseline characteristics have been described in section 9.6.3. Prior use of comedications of interest was described for different time windows before the index date (0-30 days, 31-90 days, 91-365 days). The large-scale patient-level characterisation was conducted to describe medical history and prior medication use (365 days to 1 day before the index date).

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Objective 2. Characterisation of treatment with CGRP antagonists in a cohort of new users: The “DrugUtilisation” package was used to characterise the use of CGRP antagonists. The number and % of individuals receiving each of a pre-specified list of CGRP antagonist treatments was described. Treatment duration (first drug era) was also described.

9.9.3 Missing values

All missing values were assumed to occur at random.

Regarding follow-up, to estimate incidence rates of outcomes of interest, individuals were followed up from the date until the earliest of the following: 1) loss to follow-up, 2) end of data availability, 3) date of death, or 4) one year after index date.

Individuals with missing part of their follow-up were censored at the time of loss to follow-up or end of data availability and the reported incidence rates implicitly assumed that censoring occurred at random.

9.9.4 Sensitivity analysis

Given that the counts for the Erectile dysfunction outcome were low, we generated a broader definition for erectile dysfunction, which incorporated two additional concepts: ‘4152169’ (failure of genital response) and ‘4250163’ (sexual arousal disorder).

10. DATA MANAGEMENT

Data management

All databases were mapped to the OMOP common data model. This enabled the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is 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 returned the results set which only contained aggregated data. The results from each of the contributing data sites was then combined in tables and figures for the study report.

Data storage and protection

For this study, participants from various EU member states processed personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person-level data and performing only a central analysis, local analyses were run, which generated non-identifiable aggregate summary results.

The output files were stored in the DARWIN Digital Research Environment. These output files do not contain any data that allows identification of individuals included in the study. The DRE implements further security

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measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/2016 in the various member states.

11. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI <http://book.ohdsi.org/DataQuality.html>). In particular, data partners have run the OHDSI Data Quality Dashboard tool (<https://github.com/OHDSI/DataQualityDashboard>). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining specific drugs, conditions, and co-morbidities, a systematic search of possible codes for inclusion was previously identified using “*CodelistGenerator*” R package (<https://github.com/darwin-eu/CodelistGenerator>). This software allows the user to define a search strategy and, using this will then query the vocabulary tables of the OMOP CDM to find potentially relevant codes. The codes returned were then reviewed by two clinical epidemiologists to consider their relevance. In addition, the “*CohortDiagnostics*” R package (<https://github.com/OHDSI/CohortDiagnostics>) was run to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. This allowed for a consideration of the validity of the study cohort of individuals with the selected conditions, drugs, and co-morbidities in each of the databases and informed decisions around whether multiple definitions were required.

12. RESULTS

All results are available in a web application (“Shiny app”) at <https://data-dev.darwin-eu.org/P3-C1-009-DUS-CGRP-Antagonists/>.

12.1 Descriptive Data

Details on attrition and the number of individuals contributing to each study cohort by database are described in **Table 10**.

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Table 10. Study attrition of individuals included in each cohort per database.

	IQVIA DA Germany	VID Spain	FinOMOP- HILMO Finland	NAJS Croatia
Entire database population	43,058,712	2,177,318	7,113,980	5,448,809
Population active in the database between 01/01/2018 and 31/12/2023, with at least 365 days of prior observation	12,910,707	1,604,141	6,563,599	4,485,136
Incident migraine diagnosis	147,961	63,066	177,000	36,480
First initiation of CGRP antagonist treatments (with or without explicit migraine diagnosis)	2,565	1,341	7,894	5,620

The final number of individuals with incident migraine by prophylactic treatments is not presented in this table. This information is available in [Table 17](#).

During the study period, the number of individuals newly initiating CGRP antagonists ranged between 1,341 (VID) and 7,894 (FinOMOP-HILMO) ([Table 10](#)). Erenumab was the most frequently prescribed CGRP antagonist drug, ranging between 46.8% (VID) to 69.7% (IQVIA DA Germany) of all CGRP antagonist prescriptions ([Table 11](#)). Eptinezumab use was only observed in one database (FinOMOP-HILMO), and its use was low at 0.35%.

Table 11. Total number and distribution of CGRP antagonists by database.

CGRP antagonist	IQVIA DA Germany N=2,565		VID N=1,341		FinOMOP-HILMO N=7,894		NAJS N=5,620	
	N	%	N	%	N	%	N	%
Erenumab	1,788	69.7	627	46.8	4,378	55.5	2,951	52.5
Eptinezumab	0	0.0	0	0.0	28	0.35	0	0.0
Fremanezumab	589	23.0	156	11.6	2,895	36.7	2314	41.2
Galcanezumab	192	7.5	565	42.1	662	8.4	356	6.3

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Percentages and the number of individuals in each category may not sum to 100% as prescription of more than one CGRP antagonists' drug or different formulations of the same drug (such as a loading dose) could occur at index date, as categories were not mutually exclusive.

12.1.1 Characterisation of patients

Individuals at first initiation of CGRP antagonist treatments (with or without explicit migraine diagnosis) were characterised. In all databases, except VID, the proportion of females was higher than males ($\geq 86\%$), with an approximate 6:1 ratio (**Table 12**). The median age ranged between 42-48 years. VID participated in this study with a woman-only cohort, aged 15-55 years; therefore, the demographics were influenced by this preselection.

Explicit migraine diagnoses among new initiators of CGRP antagonists ranged between 75.6-94.6%. In terms of the outcomes of interest for this study, the prevalence of hypertension ranged between 10.0-25.3%, and insomnia between 4.5-19.5%, while for erectile dysfunction, the number of events was very low and could only be estimated in FinOMOP-HILMO, at 0.2%. In terms of comorbidities of interest, mental health disorders were the most prevalent, ranging between 39.6-46.0% across all databases. Other prevalent conditions were heart disease (including valvular, coronary artery disease, and cardiomyopathies, among others) (between 2.9-18.6%), asthma (3.1-14.1%), and gastroesophageal reflux disease (0.7-33.9%), which was notably higher in NAJS compared to other databases.

Table 12. Demographic characteristics and conditions of interest in individuals newly initiating CGRP antagonists by database

Variable		IQVIA DA Germany N=2,565	VID N=1,341	FinOMOP- HILMO N=7,894	NAJS N=5,620
Sex					
Female	N (%)	2,216 (86.4)	1,341 (100.0)	6,831 (86.5)	5,092 (90.6)
Male	N (%)	348 (13.6)		1,063 (13.5)	528 (9.4)
Age					
	Median [Q25 - Q75]	48 [38 - 56]	46 [38 - 51]	43 [33 - 51]	42 [34 - 49]
	Mean (SD)	46.80 (12.7)	43.78 (9.8)	42.42 (12.8)	41.70 (11.6)
	Range (min- max)	18 - 88	16 - 59	12 - 87	6 - 85
Migraine diagnosis					
Yes	N (%)	2,427 (94.6)	1,243 (92.7)	6,774 (85.8)	4,251 (75.6)

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Variable		IQVIA DA Germany	VID	FinOMOP- HILMO	NAJS
		N=2,565	N=1,341	N=7,894	N=5,620
Outcomes of interest					
Erectile dysfunction**	N (%)	0		Supp	Supp
Erectile dysfunction broad**	N (%)	Supp		12 (0.2)	Supp
Hypertension	N (%)	271 (10.6)	174 (13.0)	791 (10.0)	1,423 (25.3)
Insomnia	N (%)	115 (4.5)	261 (19.5)	1,300 (16.5)	625 (11.1)
Endocrine/metabolism					
Diabetes	N (%)	39 (1.5)	41 (3.1)	539 (6.8)	461 (8.2)
Hyperthyroidism	N (%)	0	0	12 (0.2)	288 (5.1)
Hypokalaemia	N (%)	Supp	Supp	31 (0.4)	28 (0.5)
Overweight and obesity	N (%)	46 (1.8)	96 (7.2)	486 (6.2)	270 (4.8)
Urinary/Reproductive system					
Chronic kidney disease	N (%)	5 (0.2)	13 (1.0)	23 (0.3)	16 (0.3)
Pudendal injury	N (%)	0	0	0	0
Prostate surgery, radiation, others	N (%)	0	0	15 (0.2)	0
Respiratory					
Asthma	N (%)	80 (3.1)	101 (7.5)	1,111 (14.1)	602 (10.7)
Oncological					
Cancer	N (%)	59 (2.3)	40 (3.0)	269 (3.4)	276 (4.9)
Gastrointestinal					
Gastroesophageal reflux disease	N (%)	18 (0.7)	107 (8.0)	443 (5.6)	1,903 (33.9)

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Variable		IQVIA DA Germany N=2,565	VID N=1,341	FinOMOP- HILMO N=7,894	NAJS N=5,620
Cardiovascular					
Heart disease*	N (%)	74 (2.9)	65 (4.8)	1,101 (13.9)	1,044 (18.6)
Neurological					
Parkinson, dementia	N (%)	15 (0.6)	Supp	18 (0.2)	30 (0.5)
Sleep-related					
Sleep related disorders	N (%)	40 (1.6)	47 (3.5)	588 (7.4)	65 (1.2)
Mental health					
Mental health disorders (anxiety, depression, PTSD)	N (%)	1,127 (43.9)	617 (46.0)	3,124 (39.6)	2,419 (43.0)

Supp= indicates data suppressed for confidentiality (values ≥ 1 and < 5). 0 indicates no occurrences. Empty cells = Not identified. PTSD=Post-traumatic stress disorder. For definitions of conditions, please refer to Annex I. Table S2. *Heart disease includes a variety of conditions such as valvular, coronary artery disease, cardiomyopathies, and arrhythmias, among others. **Erectile dysfunction was only reported in males, although percentages shown in this table were based on total N.

The highest use of prior migraine-specific treatments was observed during the 91-365 window and varied by database (**For the** remaining medication categories, use was generally low, except for some drugs used in hypertension, specifically beta-blockers (which ranged between 1.3-8.7%) and angiotensin II receptor blockers (which ranged between 0.7-14.1%), as well as drugs used in sleep disorders, in which benzodiazepine use ranged between 0.7-6%.

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Table 13). For this window, drugs in which the prevalence of use was above 10% in any database included antiepileptics, which ranged between 0.0% (VID) and 15.4% (IQVIA DA Germany); TCA, which ranged between 7.0% (VID) and 11.5% (FinOMOP-HILMO); and triptans, which ranged between 5.4 % (VID) and 13.0% (NAJS). For other comedications assessed (not specifically anti-migraine treatments), antidepressant use other than TCA during the 91-365 days window ranged between 3.2-12.4%. For the remaining medication categories, use was generally low, except for some drugs used in hypertension, specifically beta-blockers (which ranged between 1.3-8.7%) and angiotensin II receptor blockers (which ranged between 0.7-14.1%), as well as drugs used in sleep disorders, in which benzodiazepine use ranged between 0.7-6%.

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Table 13. Prior use of medications of interest assessed at different time windows (0-30, 31-90, 91-365 days prior to the index date) in individuals newly initiating CGRP antagonists, by database.

	IQVIA DA Germany			VID			FinOMOP-HILMO			NAJS		
	N=2,565			N=1,341			N=7,894			N=5,620		
	0-30	31-90	91-365	0-30	31-90	91-365	0-30	31-90	91-365	0-30	31-90	91-365
Other anti-migraine treatments (focusing on prophylactic treatments) [N (%)]												
Antiepileptics	128 (5.0)	164 (6.4)	396 (15.4)	0	0	0	229 (2.9)	221 (2.8)	414 (5.2)	16 (0.3)	15 (0.3)	51 (0.9)
Beta-blockers	70 (2.7)	91 (3.5)	207 (8.1)	14 (1.0)	15 (1.1)	58 (4.3)	142 (1.8)	176 (2.2)	441 (5.6)	57 (1.0)	106 (1.9)	270 (4.8)
Calcium antagonists	118 (4.6)	154 (6.0)	207 (8.1)	0	0	0	Supp	Supp	Supp			
TCA	77 (3.0)	116 (4.5)	270 (10.5)	9 (0.7)	17 (1.3)	94 (7.0)	300 (3.8)	386 (4.9)	906 (11.5)			
Triptans	79 (3.1)	42 (1.6)	165 (6.4)	16 (1.2)	15 (1.1)	73 (5.4)	373 (4.7)	317 (4.0)	926 (11.7)	658 (11.7)	267 (4.8)	728 (13.0)
Drugs used for erectile dysfunction [N (%)]												

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	IQVIA DA Germany			VID			FinOMOP-HILMO			NAJS		
	N=2,565			N=1,341			N=7,894			N=5,620		
	0-30	31-90	91-365	0-30	31-90	91-365	0-30	31-90	91-365	0-30	31-90	91-365
PDE5 inhibitors	0	0	Supp	0	0	0	6 (0.1)	7 (0.1)	29 (0.4)	0	0	13 (0.2)
Antidepressants												
Antidepressants other than TCA	77 (3.0)	108 (4.2)	294 (11.5)	15 (1.1)	18 (1.3)	106 (7.9)	290 (3.7)	374 (4.7)	982 (12.4)	48 (0.9)	61 (1.1)	192 (3.4)
Drugs used in hypertension [N (%)]												
Ace inhibitors	Supp	Supp	Supp	0	0	0	51 (0.6)	56 (0.7)	168 (2.1)	53 (0.9)	58 (1.0)	119 (2.1)
Alpha 2 receptor agonists	0	0	0	0	0	0	0	0	0	0	0	0
Alpha-blockers	0	0	0	0	0	Supp	Supp	Supp	0	Supp	Supp	5 (0.1)
Angiotensin II receptor blockers	11 (0.4)	10 (0.4)	26 (1.0)	Supp	Supp	10 (0.7)	382 (4.8)	503 (6.4)	1,115 (14.1)	19 (0.4)	22 (0.4)	50 (0.9)

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	IQVIA DA Germany			VID			FinOMOP-HILMO			NAJS		
	N=2,565			N=1,341			N=7,894			N=5,620		
	0-30	31-90	91-365	0-30	31-90	91-365	0-30	31-90	91-365	0-30	31-90	91-365
Beta-blockers	79 (3.1)	97 (3.8)	223 (8.7)	14 (1.0)	16 (1.2)	62 (4.6)	224 (2.8)	302 (3.8)	661 (8.4)	33 (0.6)	39 (0.7)	72 (1.3)
Calcium channel blockers	Supp	Supp	11 (0.4)	Supp	Supp	11 (0.8)	45 (0.6)	44 (0.6)	111 (1.4)	100 (1.8)	120 (2.1)	340 (6.0)
Combined Alpha and Beta-blockers	0	0	0	0	Supp	Supp	Supp	Supp	Supp	Supp	0	Supp
Diuretics	Supp	Supp	8 (0.3)	Supp	Supp	8 (0.6)	14 (0.2)	11 (0.1)	36 (0.5)	Supp	Supp	11 (0.2)
Vasodilators	0	0	0	0	0	Supp	7 (0.1)	7 (0.1)	21 (0.3)	Supp	Supp	62 (1.1)
Drugs used for insomnia [N (%)]												
Benzodiazepine derivatives	9 (0.4)	8 (0.3)	18 (0.7)	7 (0.5)	13 (1.0)	75 (5.6)	110 (1.4)	108 (1.4)	287 (3.6)	148 (2.6)	112 (2.0)	337 (6.0)
Zolpidem, zopiclone	7 (0.3)	7 (0.3)	13 (0.5)	6 (0.4)	6 (0.4)	19 (1.4)	69 (0.9)	55 (0.7)	136 (1.7)	22 (0.4)	33 (0.6)	97 (1.7)

Supp= indicates data suppressed for confidentiality (values ≥1 and <5). 0 indicates no occurrences. Empty cells = Not identified.

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12.1.2 Characterisation by sex

Sex-based differences at first initiation of CGRP antagonist treatments (with or without explicit migraine diagnosis) were observed across databases ([Appendix II. Table S1](#)). For example, women had a higher rate of explicit migraine diagnoses in all databases. In terms of outcomes of interest, the prevalence of hypertension was consistently higher in males (range: 11.7-31.8%) than in females (range: 9.4-24.6%). Insomnia showed variable sex-based differences depending on the database. Regarding comorbidities, males had a higher prevalence of sleep-related disorders across all databases, while females generally had a higher prevalence of mental health disorders—except in IQVIA DA Germany, where the opposite was observed. For the other prespecified comorbid conditions that were assessed, any sex-based differences observed varied by database.

In terms of comedications in the 91-365 period, differences by sex were modest and varied across databases ([Appendix II. Table S2](#)).

12.1.3 Large-scale characterisation

In addition to predefined conditions, we checked the 10 most prevalent conditions and prescriptions recorded within the year prior to index date. From this exploratory analysis, headaches, and pain in different body parts were among the most prevalent conditions (all results are available in the Shiny app). Additionally, a high prevalence of complicated migraine (18.5%) was identified in FinOMOP-HILMO.

The most frequently administered drugs, in addition to the previously reported comedications of interest, were pain medications, such as dextetoprofen, dipyrone, ibuprofen, and acetaminophen ([Table 14](#)).

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Table 14. Large-scale characterisation of medications in the year prior to index date of individuals newly initiating CGRP antagonists.

IQVIA DA Germany			VID			FinOMOP-HILMO			NAJS		
Drug	N=2,565	%	Drug	N=1,341	%	Drug	N=7,894	%	Drug	N=5,620	%
Sumatriptan 100 MG Oral Tablet	202	7.9	Dexketoprofen 25 MG Oral Tablet	492	36.7	Influenza A virus / Influenza B virus Injectable Suspension	2,121	26.9	Ibuprofen 600 MG Oral Granules	2,078	37.0
0.1 ML zolmitriptan 50 MG/ML Topical Solution	157	6.1	rizatriptan 10 MG Oral Tablet	395	29.5	amitriptyline	2,068	26.2	Rizatriptan 10 MG Oral Tablet	1,353	24.1
topiramate 25 MG Delayed Release Oral Tablet	129	5.0	SARS-COV-2 (COVID-19) vaccine, UNSPECIFIED	339	25.3	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein	2,034	25.8	COVID-19 vaccine Injectable Solution	1,214	21.6
naratriptan 2.78 MG Delayed Release Oral Tablet	105	4.1	Dipyron 500 MG Oral Tablet	326	24.3	Acetaminophen 1000 MG Oral Tablet	1,574	19.9	diazepam / metoclopramide / simethicone Oral Tablet	1,149	20.4
rizatriptan 10 MG Oral Tablet Glenmark	84	3.3	influenza virus vaccine	232	17.3	Ibuprofen 600 MG Oral Tablet	996	12.6	Azithromycin 500MG Oral Tablet	1,075	19.1
Botulinum Toxin Type A 200 UNT	81	3.2	Naproxen 550 MG Oral Tablet	228	17.0	frovatriptan 2.5 MG Oral Tablet	934	11.8	Zolmitriptan Oral Tablet	987	17.6

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IQVIA DA Germany			VID			FinOMOP-HILMO			NAJS		
Drug	N=2,565	%	Drug	N=1,341	%	Drug	N=7,894	%	Drug	N=5,620	%
Flunarizine 5 MG Oral Capsule	74	2.9	eletriptan 40 MG Oral Tablet	220	16.4	Ibuprofen 800 MG Oral Tablet	838	10.6	pantoprazole 40 MG Delayed Release Oral Tablet	902	16.1
rizatriptan 10 MG Oral Tablet	70	2.7	zolmitriptan 5 MG Oral Tablet	200	14.9	Metoclopramide 10 MG Oral Tablet	789	10.0	Eletriptan 40 MG Oral Tablet	754	13.4
Amitriptyline 10 MG Oral Tablet	66	2.6	1 ACTUAT zolmitriptan 5 MG/ACTUAT Nasal Spray	153	11.4	acetaminophen	788	10.0	Diazepam / Verapamil Oral Tablet	726	12.9
topiramate 25 MG Oral Tablet	66	2.6	Amitriptyline 10 MG Oral Tablet Box of 20	152	11.3	candesartan 8 MG Oral Tablet Box of 98	752	9.5	naproxen / sumatriptan Oral Tablet	663	11.8

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12.1.4 Treatment duration

Overall, median duration of the first drug era in individuals newly initiating CGRP antagonists was longest in IQVIA DA Germany, with a median of 233 days (IQR: 81-477), followed by NAJS, with a median of 220 days (IQR: 75-423), and was notably shorter for VID, with a median of 31 days (31-103) (**Table 15**). Duration was not available for FinOMOP-HILMO. When results for VID were excluded, the median duration of the first drug era increased, and ranged between 220-233 days.

Table 1515. CGRP antagonist treatment duration (first drug era), by database.

Variable	Format	IQVIA DA Germany	VID	NAJS
Number of individuals		2,565	1,341	5,620
Duration of first drug era (number of days)				
	Range (min – max)	1 - 1,882	2 - 694	3 - 1,400
	Range (Q25 - Q75)	81 - 477	31 - 103	75 - 423
	Median	233	31	220

Duration refers to the duration of the first drug era, allowing a treatment gap of 90 days. Duration was not available for FinOMOP-HILMO.

12.2 Incidence rates of outcomes of interest

In this section, we present the incidence rates for outcomes of interest: erectile dysfunction, insomnia, and hypertension. These outcomes were assessed in an incident migraine population, as well as following first exposure to different migraine prophylactic treatment classes (among individuals with an incident migraine diagnosis), and in the general population. Due to low numbers of the erectile dysfunction outcome, only the erectile dysfunction “broad” category is reported, which is only reported in men. Incidence rates for outcomes of interest are presented by year in **Appendix II. Table S3**.

12.2.1 Migraine population

The incidence rates of erectile dysfunction in men with incident migraine and for the entire period ranged between 1-6 per 1,000 PY across databases (**Table 16**). Due to low numbers, no figure by age group is shown.

Incidence rates for hypertension in the incident migraine population for the entire period ranged between 23-34 per 1,000 PY (**Table 16**). Yearly rates were highest at the start of the study period and behaved similarly across databases, decreasing in 2020, and remaining stable for the rest of the years, except for a slight upward trend in IQVIA DA Germany towards the end of the study period (**Appendix II. Table S3**). As expected, incidence rates increased with age (

NAJS_ HZJZ_CRO=NAJS, THL_OMOP=FinOMOP-HILMO. Dots represent actual incidence rate estimate for that category, while whiskers represent 95% CI.

Figure 5).

The incidence of insomnia for the entire period, in individuals with incident migraine, ranged between 15-45 per 1,000 PY across databases (**Table 16**). Yearly rates increased during 2019-2021 for FinOMOP-HILMO,

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remaining stable at 2021 values from there on ([Appendix II. Table S3](#)). By contrast, rates in other databases decreased during that same period, with a slight uptrend for IQVIA DA Germany towards the end of the observation period. In NAJS, the incidence rate increased by age, while for the other DPs, incidence peaked in the 45-64 age group, and in some, a bimodal pattern was observed affecting the >80 age group in addition to the former age group ([NAJS_HZJZ_CRO=NAJS, THL_OMOP=FinOMOP-HILMO](#)). Dots represent actual incidence rate estimate for that category, while whiskers represent 95% CI.

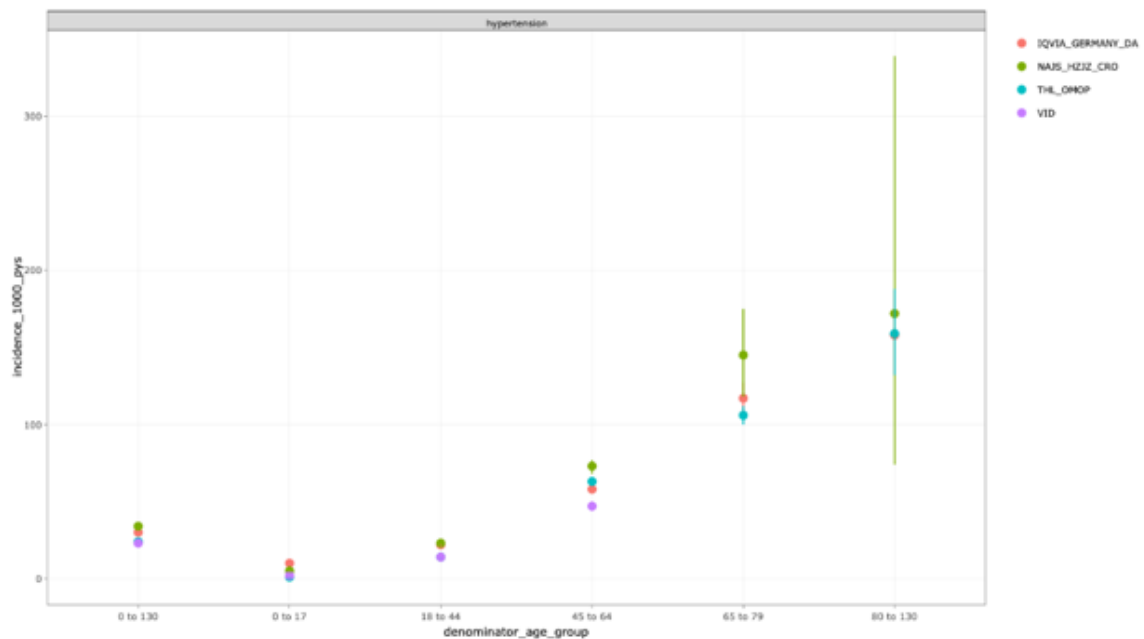
Figure 6).

Differences in rates by sex for hypertension were only observed in IQVIA DA Germany, with a slightly higher rate among males than females ([Appendix II. Figure S1](#)). For insomnia, sex-based differences were observed in FinOMOP-HILMO; rates were higher in females, at 49 per 1,000 PY (95%CI: 48-50), compared with men at 32 per 1,000 PY (31-34) ([Appendix II. Figure S2](#)).

Table 16. Incidence rates for outcomes of interest in the incident migraine population for the entire study period and by database.

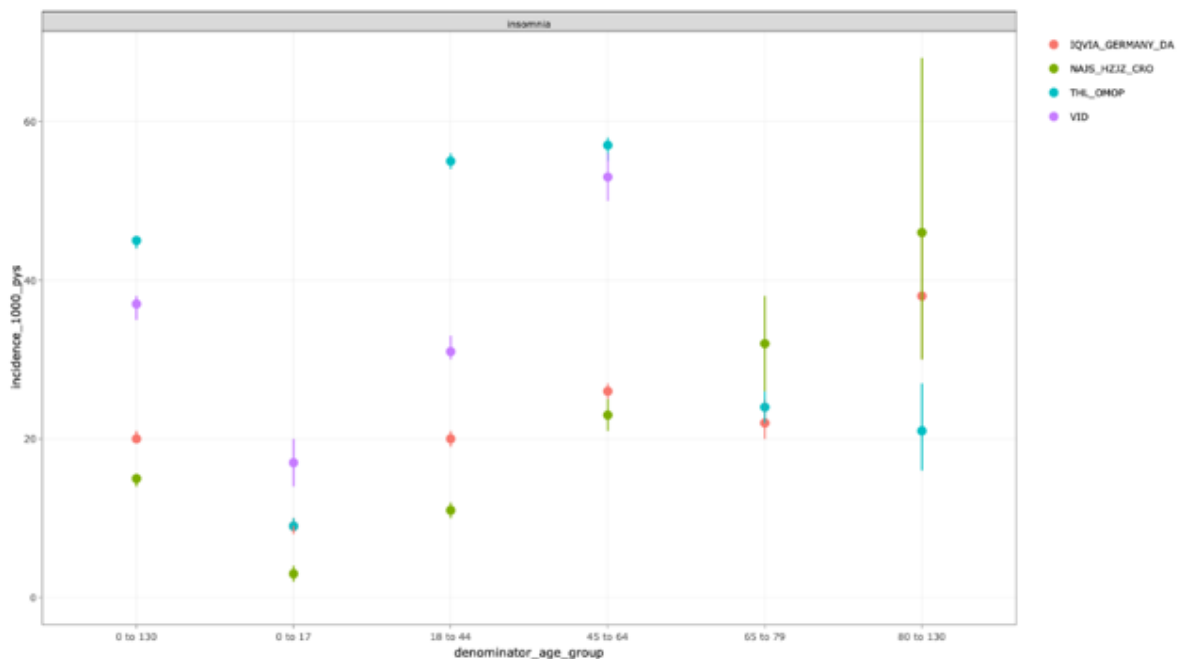
Database name	Outcome of Interest	Interval	N events	N persons	Person years	Incidence (1,000 PYs)	95% CI
IQVIA DA Germany	Erectile dysfunction (broad)	overall	258	42,116	81,867	3	(3 , 4)
FinOMOP-HILMO	Erectile dysfunction (broad)	overall	615	44,841	110,973	6	(5 , 6)
NAJS	Erectile dysfunction (broad)	overall	13	6,788	20,043	1	(0 , 1)
IQVIA DA Germany	hypertension	overall	7,176	128,149	235,759	30	(30 , 31)
VID	hypertension	overall	2,049	58,241	90,722	23	(22 , 24)
FinOMOP-HILMO	hypertension	overall	9,192	160,128	390,012	24	(23 , 24)
NAJS	hypertension	overall	2,667	28,266	78,930	34	(33 , 35)
IQVIA DA Germany	insomnia	overall	5,346	137,305	261,567	20	(20 , 21)
VID	insomnia	overall	3,279	57,801	89,639	37	(35 , 38)
FinOMOP-HILMO	insomnia	overall	16,763	155,409	375,836	45	(44 , 45)
NAJS	insomnia	overall	1,442	33,903	98,527	15	(14 , 15)

Erectile dysfunction (broad) rates are only reported in men. VID: overall period between 01/01/2019-01/01/2022.



NAJS_HZIZ_CRO=NAJS, THL_OMOP=FinOMOP-HILMO. Dots represent actual incidence rate estimate for that category, while whiskers represent 95% CI.

Figure 5. Incidence rates for hypertension in the incident migraine population for the entire period by age group and database.



NAJS_HZIZ_CRO=NAJS, THL_OMOP=FinOMOP-HILMO. Dots represent actual incidence rate estimate for that category, while whiskers represent 95% CI.

Figure 6. Incidence rates for insomnia in the incident migraine population for the entire period, by age group and database.

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12.2.2 Migraine population receiving prophylactic treatment

This section presents incidence rates of events of interest among individuals with an incident migraine diagnosis following initiation of migraine prophylactic treatments. Incidence rates were assessed one year after initiation of the different prophylactic treatment classes. Due to low numbers, stratification per year or sex is not presented, and only relevant results are mentioned below (these results are available in Shiny App). Values below report on rates that were 0 (zero occurrences) or above sufficient values to provide estimates.

Incidence rates of erectile dysfunction in males with incident migraine within one year after the start of prophylactic treatment were as follows: 0 per 1,000 PY (NAJS) for CGRP antagonist initiators, 0 per 1,000 PY (NAJS) for antiepileptic initiators, 9 per 1,000 PY (FinOMOP-HILMO) for TCA initiators, 0 (NAJS) to 7 per 1,000 PY (FinOMOP-HILMO) for beta-blocker initiators, and 0 per 1,000 PY for calcium channel blocker initiators (IQVIA DA Germany, FinOMOP-HILMO, and NAJS) ([Table 17](#)).

Hypertension rates within one year after the initiation of prophylactic migraine treatment ranged as follows: 8-33 per 1,000 PY for CGRP antagonist initiators, 0-43 per 1,000 PY for antiepileptic initiators, 19-49 per 1,000 PY for TCA initiators, 28-253 per 1,000 PY for Beta-blocker initiators, and 0 (VID, FinOMOP-HILMO, and NAJS) to 13 (IQVIA DA Germany) per 1,000 PY for calcium channel blocker initiators ([Table 17](#)).

For Insomnia, rates within one year after the initiation of prophylactic migraine treatment ranged as follows: 6-45 per 1,000 PY for CGRP antagonist initiators, 0-36 per 1,000 PY for antiepileptic initiators, 20-64 per 1,000 PY for TCA initiators, 9-57 per 1,000 PY for Beta-blocker initiators, and 0 per 1,000 PY for calcium channel blocker initiators (VID, FinOMOP-HILMO, and NAJS) ([Table 17](#)).

Sex-based differences in hypertension rates were observed for some prophylactic treatments and databases. For CGRP antagonists, hypertension rates were higher in males compared to females in FinOMOP-HILMO (46 vs. 17 per 1,000 PY). Similarly, higher rates in males were noted for TCAs (75 vs. 34 in IQVIA DA Germany and 37 vs. 22 per 1,000 PY in FinOMOP-HILMO), and for Beta-blockers (420 vs. 215 per 1,000 PY in IQVIA DA Germany) (these results are available in the Shiny App).

Regarding insomnia, sex-based differences were identified only for beta-blockers in FinOMOP-HILMO, where females had higher rates than males (61 vs. 37 per 1,000 PY) (these results are available in the Shiny App).

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Table 17. Incidence rates of outcomes of interest within one year following initiation of migraine prophylactic treatments, by prophylactic treatment class and database.

Outcome of Interest	Migraine prophylactic treatment	Database name	Interval	N events	N persons	Person years	Incidence Per 1,000 PYs (95%CI)
Erectile dysfunction (broad)							
	CGRP antagonists	IQVIA DA Germany	Overall	Supp	166	116.22	Supp
	CGRP antagonists	FinOMOP-HILMO	Overall	Supp	507	438.63	Supp
	CGRP antagonists	NAJS	Overall	0	339	272.89	0 (0 , 14)
	Antiepileptics	IQVIA DA Germany	Overall	Supp	421	314.07	Supp
	Antiepileptics	FinOMOP-HILMO	Overall	Supp	486	430.47	Supp
	Antiepileptics	NAJS	Overall	0	88	78.21	0 (0 , 47)
	TCA	IQVIA DA Germany	Overall	Supp	675	501.07	Supp
	TCA	FinOMOP-HILMO	Overall	21	2,810	2,419.73	9 (5, 13)
	TCA	NAJS	Overall	Supp	195	164.08	Supp
	Beta-blockers	IQVIA DA Germany	Overall	Supp	850	673.04	Supp
	Beta-blockers	FinOMOP-HILMO	Overall	15	2,682	2,265.11	7 (4 , 11)
	Beta-blockers	NAJS	Overall	0	241	221.57	0 (0 , 17)
	Calcium channel blockers	IQVIA DA Germany	Overall	0	126	99.35	0 (0 , 37)
	Calcium channel blockers	FinOMOP-HILMO	Overall	0	Supp	Supp	Supp
	Calcium channel blockers	NAJS	Overall	0	0	0	0
Hypertension							
	CGRP antagonists	IQVIA DA Germany	Overall	6	1,087	784.36	8 (3 , 17)
	CGRP antagonists	VID	Overall	Supp	157	110.46	Supp
	CGRP antagonists	FinOMOP-HILMO	Overall	53	2,891	2,460.69	22 (16 , 28)
	CGRP antagonists	NAJS	Overall	62	2332	1858.93	33 (26 , 43)
	Antiepileptics	IQVIA DA Germany	Overall	30	1,827	1,368.85	22 (15 , 31)
	Antiepileptics	VID	Overall	0	14	7.36	0 (0 , 501)
	Antiepileptics	FinOMOP-HILMO	Overall	19	1,801	1,603.74	12 (7 , 19)
	Antiepileptics	NAJS	Overall	11	284	255	43 (22 , 77)
	TCA	IQVIA DA Germany	Overall	89	3,027	2,162.08	41 (33 , 51)

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Outcome of Interest	Migraine prophylactic treatment	Database name	Interval	N events	N persons	Person years	Incidence Per 1,000 PYs (95%CI)
	TCA	VID	Overall	45	3,180	2,425.47	19 (14 , 25)
	TCA	FinOMOP-HILMO	Overall	309	14,520	12,415.6	25 (22 , 28)
	TCA	NAJS	Overall	30	735	614.26	49 (33 , 70)
	Beta-blockers	IQVIA DA Germany	Overall	441	2,691	1,745.9	253 (230, 277)
	Beta-blockers	VID	Overall	17	748	585.28	29 (17 , 47)
	Beta-blockers	FinOMOP-HILMO	Overall	322	13,904	11,608.6	28 (25 , 31)
	Beta-blockers	NAJS	Overall	86	1362	1207.81	71 (57 , 88)
	Calcium channel blockers	IQVIA DA Germany	Overall	6	620	470.42	13 (5 , 28)
	Calcium channel blockers	VID	Overall	0	0	0	0
	Calcium channel blockers	FinOMOP-HILMO	Overall	0	0	0	0
	Calcium channel blockers	NAJS	Overall	0	0	0	0
Insomnia							
	CGRP antagonists	IQVIA DA Germany	Overall	8	1,112	796.83	10 (4 , 20)
	CGRP antagonists	VID	Overall	Supp	141	100.42	Supp
	CGRP antagonists	FinOMOP-HILMO	Overall	108	2,802	2,382	45 (37 , 55)
	CGRP antagonists	NAJS	Overall	15	2905	2347.41	6 (4 , 11)
	Antiepileptics	IQVIA DA Germany	Overall	17	1,934	1,466.04	12 (7 , 19)
	Antiepileptics	VID	Overall	0	11	5.64	0 (0 , 654)
	Antiepileptics	FinOMOP-HILMO	Overall	57	1,817	1,594.23	36 (27 , 46)
	Antiepileptics	NAJS	Overall	7	393	354	20 (8 , 41)
	TCA	IQVIA DA Germany	Overall	106	3,447	2,491.98	43 (35 , 51)
	TCA	VID	Overall	92	3,025	2,297.91	40 (32 , 49)
	TCA	FinOMOP-HILMO	Overall	764	14,167	11,903.4	64 (60 , 69)
	TCA	NAJS	Overall	18	1092	920.61	20 (12 , 31)
	Beta-blockers	IQVIA DA Germany	Overall	39	3,623	2,812.59	14 (10 , 19)
	Beta-blockers	VID	Overall	29	714	558.36	52 (35 , 75)
	Beta-blockers	FinOMOP-HILMO	Overall	621	13,240	10,987.8	57 (52 , 61)
	Beta-blockers	NAJS	Overall	15	1873	1716.45	9 (5 , 14)

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Outcome of Interest	Migraine prophylactic treatment	Database name	Interval	N events	N persons	Person years	Incidence Per 1,000 PYs (95%CI)
	Calcium channel blockers	IQVIA DA Germany	Overall	Supp	637	485.29	Supp
	Calcium channel blockers	VID	Overall	0	0	0	0
	Calcium channel blockers	FinOMOP-HILMO	Overall	0	Supp	Supp	Supp
	Calcium channel blockers	NAJS	Overall	0	0	0	0

Supp = indicates data suppressed for confidentiality (values ≥ 1 and < 5). 0 indicates no occurrences. Empty cells = Not identified. VID: overall period between 01/01/2019-01/01/2022. Erectile dysfunction (broad) rates are only reported in men. Erectile dysfunction was not reported for VID since it is a female-exclusive database. The final denominators for each prophylactic treatment class and outcome of interest show differences between them because, after selecting first exposure for each prophylactic class following migraine diagnosis, individuals with a prior history of the event of interest were excluded from the analysis for each specific outcome.

12.2.3 General population

Rates for erectile dysfunction for males in the general population and over the entire period ranged between 0-3 per 1,000 PY ([Table 18](#)). Due to low numbers, no figure by age group is shown.

Hypertension in the general population ranged between 11-25 per 1,000 PY across databases and over the entire period ([Table 18](#)). By year, a slight decrease in rates was noted in 2020 for VID and NAJS, while FinOMOP-HILMO increased between 2019-2021, remaining at 2021 values from there ([Appendix II. Table S4](#)). For IQVIA DA Germany, rates increased towards the end of the period. As expected, incidence rates increased with age ([Figure 1](#)).

The incidence rate of insomnia for the entire study period and in the general population ranged between 5-17 per 1,000 PY ([Table 18](#)). Similar to the trend observed in hypertension, rates increased between 2019-2021 for FinOMOP-HILMO, remaining near 2021 values for the rest of the period, while for IQVIA DA Germany, there was an increasing trend towards the end of the period ([Appendix II. Table S4](#)). No clear age-related pattern was noted, except for VID, where the incidence rate of insomnia was the highest among the 45-64 age group, and in NAJS, where the highest incidence was noted in those aged ≥ 80 ([NAJS_HZJZ](#)__{CRO}=NAJS, _{THL}_OMOP=FinOMOP-HILMO. Dots represent actual incidence rate estimate for that category, while whiskers represent 95% CI.

Figure 8).

Differences in rates by sex for hypertension showed a slightly higher rate in males for IQVIA DA Germany and NAJS compared with females, while the opposite was observed for FinOMOP-HILMO ([Appendix II. Figure S3](#)). For insomnia, sex-based differences were more notorious, with higher rates observed for females in NAJS and FinOMOP-HILMO, compared with men ([Appendix II. Figure S4](#)), while no sex-based differences were observed for IQVIA DA Germany.

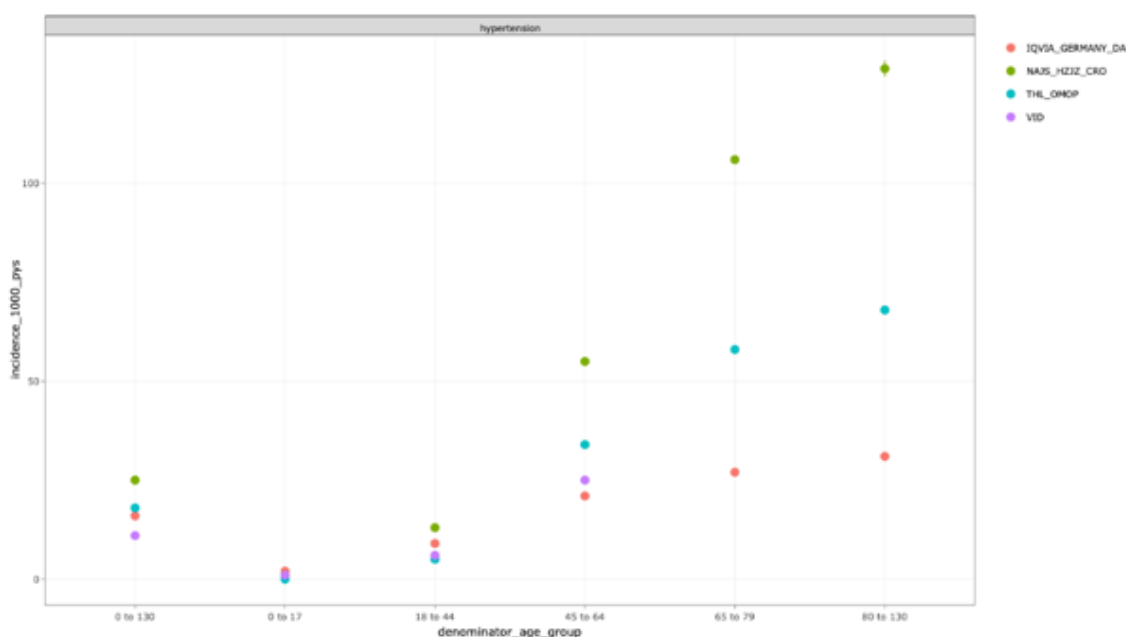
Table 18. Incidence rates for outcomes of interest in the General population for the entire study period by database.

Database name	Outcome of Interest	Interval	N events	N persons	Person years	Incidence (1,000 PYs)	95% CI
IQVIA DA Germany	Erectile dysfunction (broad)	overall	52,781	5,490,726	17,323,336	3	(3, 3)

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Database name	Outcome of Interest	Interval	N events	N persons	Person years	Incidence (1,000 PYs)	95% CI
FinOMOP-HILMO	Erectile dysfunction (broad)	overall	44,143	3,338,967	18,652,343	2	(2, 2)
NAJS	Erectile dysfunction (broad)	overall	4,514	2,187,767	11,788,500	0	(0, 0)
IQVIA DA Germany	hypertension	overall	546,438	10,953,439	33,284,732	16	(16, 16)
VID	hypertension	overall	48,180	1,531,545	4,232,373	11	(11, 11)
FinOMOP-HILMO	hypertension	overall	571,735	5,739,977	30,927,087	18	(18, 19)
NAJS	hypertension	overall	410,363	3,213,597	16,487,349	25	(25, 25)
IQVIA DA Germany	insomnia	overall	198,119	12,617,690	39,961,435	5	(5, 5)
VID	insomnia	overall	72,191	1,561,336	4,285,576	17	(17, 17)
FinOMOP-HILMO	insomnia	overall	418,111	6,354,870	34,688,816	12	(12, 12)
NAJS	insomnia	overall	217,749	4,314,963	23,038,099	9	(9, 9)

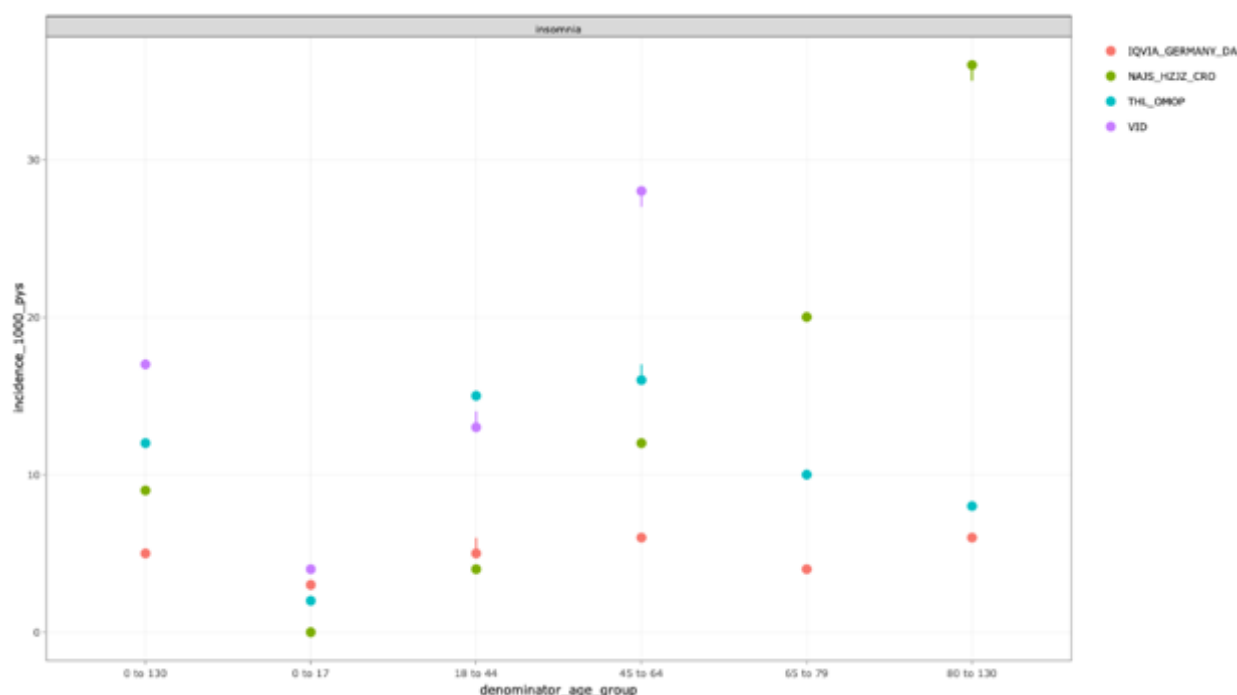
Erectile dysfunction (broad) rates are only reported in men. VID: overall period between 01/01/2019-01/01/2022.



NAJS_HZIZ_CRO=NAJS, THL_OMOP=FinOMOP-HILMO. Dots represent actual incidence rate estimate for that category, while whiskers represent 95% CI.

Figure 7. Incidence rates for hypertension in the general population for the entire period, by age groups and database.

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NAJS_HZIZ_CRO=NAJS, THL_OMOP=FinOMOP-HILMO. Dots represent actual incidence rate estimate for that category, while whiskers represent 95% CI.

Figure 8. Incidence rates for insomnia in the general population for the entire period, by age groups and database

12.3 Other analysis

None.

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions were not 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.

14. DISCUSSION

14.1 Key results

During the study period, 17,420 individuals newly initiating CGRP antagonists were identified (2,565 in IQVIA DA Germany, 1,341 in VID, 7,894 in FinOMOP-HILMO, and 5,620 in NAJS). By CGRP antagonist type, erenumab was the most frequently prescribed drug, ranging between 46.5 (VID) to 69.2% (IQVIA DA Germany). Eptinezumab use was only identified in one database (FinOMOP-HILMO), and use was minimal (<1%).

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In all databases (except VID, a female-exclusive database), the proportion of females was higher than males, with an approximate 6:1 ratio. The median age ranged between 42-48 years.

Characterisation

Individuals at first initiation of CGRP antagonist treatments (with or without explicit migraine diagnosis) were characterised.

At first initiation of CGRP antagonists, migraine diagnoses ranged between 75.6-94.6%. The prevalence of hypertension ranged between 10.0-25.3% and insomnia 4.5-19.5%, while for erectile dysfunction, the number of events was very low. In terms of comorbidities of interest during the year before index date, mental health disorders were highly prevalent, ranging between 39.6-46% across databases. Other prevalent conditions were heart disease, between 2.9-18.6%; asthma, between 3.1-14.1%; and GERD, between 0.7% and 33.9%.

The highest use of migraine-specific treatments (in individuals newly initiating CGRP antagonists) during the year prior to index date was observed in the 91-365 window, with variation across databases. Drugs in which the prevalence of use was above 10% in any database included antiepileptics, ranging between 0.0-15.4%; TCA, between 7-11.5%; and triptans, between 5.4-13.0%. For other comedications assessed (not specifically anti-migraine treatments), antidepressant use during the 91-365 days window ranged between 3.2-12.4%. For the remaining medication categories, use was generally low, except for some drugs used in hypertension (mainly Beta-blockers and Angiotensin II receptor blockers) and drugs used in sleep disorders (benzodiazepines).

Large-scale characterisation was exploratory and assessed the 10 most prevalent conditions and prescriptions recorded the year before index. Headaches and pain in different body parts were among the most prevalent conditions. The most frequently administered drugs (in addition to the previously reported predefined medications) included pain medications, such as dexketoprofen, dipyrone, ibuprofen, and acetaminophen.

The duration of treatment of the first drug era in individuals newly initiating CGRP antagonists ranged between 31-233 days. Duration was notably shorter in VID [median: 31 days (IQR: 31-103)]. When results from VID were excluded, the median duration of the first drug era increased, ranging between 220-233 days. Duration was not available in FinOMOP-HILMO.

Incidence rates of the outcomes of interest

Outcomes of interest (erectile dysfunction, hypertension, and insomnia) were assessed over the entire study period among the incident migraine and general populations.

Erectile dysfunction rates for the entire period were markedly low, oscillating between 1 and 6 per 1,000 PY in the male incident migraine cohort, compared to 0-3 per 1,000 PY in the general population. For hypertension, the incidence rate ranged between 23 and 34 per 1,000 PY and between 11-25 per 1,000 PY in the general population. For Insomnia, incidence ranged between 15-45 per 1,000 PY and between 5-17 per 1,000 PY in the general population.

Outcomes of interest were assessed among individuals with incident migraine within one year after initiating different prophylactic treatments.

Incidence rates in males with incident migraine within one year after the start of prophylactic treatment were consistently low across treatment classes. CGRP antagonist, antiepileptic, and calcium channel blocker initiators had rates of 0 per 1,000 PY. TCA initiators had a 9 per 1,000 PY rate, and Beta-blocker initiators ranged from 0 to 7 per 1,000 PY.

Hypertension rates within one year after the initiation of prophylactic migraine varied widely by treatment class. Beta-blocker initiators showed the broadest range of 28-253 per 1,000 PY, while calcium channel

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blocker initiators had the narrowest range, from 0 (VID, FinOMOP-HILMO, and NAJS) to 13 (IQVIA DA Germany) per 1,000 PY. CGRP antagonists, antiepileptics, and TCA initiators had similar ranges (8-33, 0-43, and 19-49 per 1,000 PY, respectively).

For Insomnia, rates within one year after the initiation of prophylactic migraine treatment were variable across treatment groups. Rates ranged between 6-45 per 1,000 PY for CGRP antagonist initiators, 0-36 per 1,000 PY for antiepileptic initiators, 20-64 per 1,000 PY for TCA initiators, 9-57 per 1,000 PY for Beta-blocker initiators, and 0 per 1,000 PY for calcium channel blocker initiators (VID, FinOMOP-HILMO, and NAJS).

14.2 Limitations of the research methods

As for all observational research, several limitations must be addressed. First, the recording of a prescription or dispensation does not imply actual intake or adherence to the drug. Assumptions around the duration of drug use, particularly with a 90-day gap era, may have led to an overestimation of the treatment duration. Additionally, the identification of CGRP antagonist users, recording of drug prescription drugs, and the prescriptions themselves may vary across databases and healthcare settings and lead to differences. For example, in VID, treatment duration was notably shorter than in other data sources and shorter than clinically expected, suggesting potential issues such as incomplete recording of refills, or treatment continued in private settings. In FinOMOP-HILMO, we could not estimate duration because key variables required for estimation (namely drug end data and days of supply) were unavailable.

Stratification of the incident migraine cohort by prophylactic treatment class may have introduced some overlap between drug exposures, as an intention-to-treat approach was used without a washout period between treatments. Also, the analytical pipeline used did not allow to account for drug exposure time, discontinuation, or treatment switch.

Differences in database characteristics may have affected patient characterisation and outcomes of interest. For example, VID database contained only a preselected population of women, preventing the assessment of erectile dysfunction. Additionally, some events may have occurred in healthcare settings not represented in the database, with country-specific healthcare practices further influencing the results. For instance, outcomes potentially treated by specialists, such as erectile dysfunction or insomnia, might be underreported in databases with lower specialist representation, such as IQVIA DA Germany. Furthermore, in IQVIA DA Germany, even when healthcare settings are included in the database, events may be missed due to a lack of patient-level cross-identification between practices, resulting in fragmented and incomplete data capture. In this context, if specialists prescribe CGRP antagonists, conditions generally managed by GPs and primary care could be underreported. In NAJS, the coexistence of confirmed conditions and working diagnoses for conditions could lead to an overestimation of the prevalence of conditions generally diagnosed and managed by GPs and primary care.

Regarding incidence rates, several database-specific considerations must be noted. In IQVIA DA Germany, the observation periods are defined based on the last recorded healthcare interaction. When the end of the study period is close to the data lock for the last update of the database this leads to overestimating incidence rates toward the end of the study period, since individuals with less frequent healthcare interaction and no visits during the last years before the data lock point are not observed in the denominator for those years and that version (data lock point) of the database although they do contribute to the denominator for the same years in future versions of the database based on visits in the coming years. In FinOMOP-HILMO, the inclusion of private practice consultation data in 2020 increased the number of recorded events per individual, particularly for conditions typically managed by GPs and primary care, without changes in the total population, leading to higher rates. Additionally, the study period coincided with the COVID-19 pandemic, which likely affected rates for some outcomes, possibly due to factors such as mobility restrictions and changes in healthcare-seeking behaviours.

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The assessment of outcomes based on a one-year follow-up from the initiation of prophylactic treatments was guided by existing literature. However, duration may be insufficient for some outcomes to be observed. Moreover, the use of an intention-to-treat approach, coupled with the short treatment duration observed in certain data sources, and the small sample sizes—particularly among male patients—may further contribute to underestimating the true rates of these outcomes. Additionally, while exposure to CGRP antagonists was likely indicated as prophylactic treatment for migraine, this may not always be the case for the other prophylactic treatments assessed (especially Beta-blockers and antiepileptics), which could have been prescribed for conditions other than migraine and may influence the risk of the outcomes of interest. (e.g. higher rate of hypertension in individuals treated with Beta-blockers)

The initial phenotype for erectile dysfunction retrieved very low counts and led to a broader definition to be developed and used to address the possibility of low counts arising from differences in coding practices. However, this adjustment did not significantly improve the counts for erectile dysfunction cases, suggesting that coding variability or underreporting could remain a limitation.

Lifestyle factors, such as previous exposure to smoking, drugs, and alcohol, although of interest for the outcomes of this study, were not assessed because these are not systematically recorded in the participating DPs.

Small cell counts may have affected the analysis for some subgroup strata. When counts were too low, counts were not disclosed for governance reasons.

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14.3 Interpretation

Characterisation

Overall, the characteristics of CGRP antagonist users seem consistent with prior literature in terms of age, sex, and low prevalence of co-occurrent comorbidities (30-32). While mental health disorders in prior literature are generally co-occurrent, their prevalence is generally lower (<33%) than in our study (30, 32).

From the CGRP antagonists, Erenumab was the most frequently used drug, and its higher use could be influenced by its earlier approval in Europe (33). Eptinezumab use was minimal (<1%) and only observed in one country (Finland).

The recommended treatment duration with CGRP antagonists to assess an initial clinical response is 12 to 24 weeks (33). When excluding limited data from one database (VID, 2019-2021), the median duration of the first drug era meets this recommendation (193-233 days). However, this duration remains notably shorter than the recommended treatment period before considering discontinuation, which suggests 12–18 months of continued treatment (33).

Incidence rates of the outcomes of interest

Estimates for erectile dysfunction rates in the general population are scarce. One study based on a population of white males in the US estimated incident rates at 26 cases per 1,000 PY (34). In Europe, a study from the Netherlands reported clinically relevant erectile dysfunction, defined as causing concern to the individual, was reported at 11.4 per 1,000 PY (35). Although our findings are lower than those previously reported in the literature, these are likely explained by methodological differences between our study and prior research, particularly because prior studies were based on survey data. Additional factors, such as provider or patient stigma surrounding diagnosis, may also contribute to underdiagnosis, further explaining the variations (36). Notably, in the context of migraine, prior literature suggests that males with migraine may be at higher risk of erectile dysfunction than the general population (37). In our study, while direct comparisons were not made, erectile dysfunction rates in patients with migraine were twice as high as those observed in the general population.

Regarding hypertension, incidence rates in the general population have been reported at 41 per 1,000 PY in past studies (38), and some literature suggests that individuals with migraine may be at increased risk of developing hypertension compared to the general population (39). We found slightly higher rates of hypertension in the migraine population, although no formal comparison was made.

Insomnia is a common condition with varying incidence rates reported in the general population. Rates have been reported to occur in 15 % at one year and 15% after five years (40, 41). Among individuals with migraine, sleep disorders often coexist, reporting lower sleep quality than individuals without migraine, and poorer sleep quality may trigger migraine attacks (41). We found higher rates of insomnia in the migraine population, although again no formal comparison was made. These findings are consistent with previous literature, which suggests that individuals with migraine have a two-fold increased risk of experiencing insomnia (42).

We observed (unadjusted) low incidence rates of erectile dysfunction within one year following treatment initiation of different prophylactic treatments. However, limitations related to underreporting or coding variability may have affected the validity of our estimates. For hypertension, the highest estimates were identified for Beta-blockers (243 per 1,000 PY), which could be related to their use in hypertension management, in addition to migraine. For other drugs, hypertension rates were mostly lower and similar across classes. Regarding insomnia, rates were highest for TCAs (64 per 1,000 PY), followed by beta-blockers (57 per 1,000 PY). For TCAs, this finding contrasts with their expected sedative effect. However, TCAs have been associated with restless leg syndrome and periodic limb movements, which could contribute to sleep

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disruption in some individuals (43). Alternatively, it is possible that insomnia rates reflect TCA use for anxiety or depression rather than migraine, among which sleep disturbances might be more prevalent.

These rates must be interpreted with caution since they could be influenced by a lack of adjustment for confounders, differences in baseline characteristics between treated groups, and low counts in some categories, among several other limitations.

14.4 Generalisability

This study included data from 4 databases from 4 different European countries/regions (Croatia, Finland, Germany, and Spain (Valencia)) and healthcare systems (primary care and specialist care in IQVIA DA Germany and in-patient and out-patient hospital care for FinOMOP, NAJS, and VID).

While these results may be considered largely representative of individuals newly diagnosed with migraine and newly treated with CGRP antagonist drugs in the respective countries/regions, results should not be completely generalised to the entire European population. Differences in population characteristics, small sample sizes—particularly among male patients—and differences in how individuals are diagnosed and treated for migraine may vary by country. Furthermore, incomplete data from certain data sources, such as those from IQVIA DA Germany, may limit the generalizability of these findings across all regions.

14.5 Other information

None.

15. CONCLUSION

This study describes the use of CGRP antagonists in a real-world setting across 4 European countries. Most individuals newly initiating CGRP antagonists were females with a median age of 42-48. The most frequently prescribed drug was erenumab and median treatment duration (first drug era) ranged between one to seven months.

While no formal comparisons were made, the (unadjusted) incidence rates of the outcomes of interest over the entire period were generally higher in individuals with incident migraine than in the general population. This difference was particularly high for insomnia, with incidence rates at least 2.5 times higher among those with incident migraine than in the general population.

Incidence rates of the outcomes of interest across the different prophylactic treatment classes within one year following treatment initiation were consistently low for erectile dysfunction for all treatment classes. Hypertension rates showed the widest variability across classes, and rates were notoriously wide and highest among Beta-blocker initiators. Insomnia rates also varied across treatment classes, being highest among TCA.

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17. ANNEXES

Appendix I: Concept sets for conditions and drugs of interest

Appendix II: Supplemental tables and figures

Appendix I. Table S1. Code list for drugs and conditions of interest.

Concept set name	IDs
Erenumab	1510467
Eptinezumab	37499031
Fremanezumab	35200577
Galcanezumab	35200800
Migraine	318736
Erectile dysfunction	
Absolute erectile dysfunction	3655358
Erectile dysfunction	3655355
Erectile dysfunction caused by drug	3655356
Erectile dysfunction co-occurrent and due to arterial insufficiency	37016340
Erectile dysfunction due to arterial disease	3655360
Erectile dysfunction due to diabetes mellitus	35626763
Erectile dysfunction due to endocrine disease	3655361
Erectile dysfunction due to fibrosis of corpus cavernosum	606412
Erectile dysfunction due to injury	606410
Erectile dysfunction due to neuropathy	3655362
Erectile dysfunction due to psychophysiologic disorder	3655359
Erectile dysfunction due to type 1 diabetes mellitus	43531565
Erectile dysfunction due to type 2 diabetes mellitus	4177050
Erectile dysfunction due to venous disorder	606407
Erectile dysfunction unresponsive to phosphodiesterase-5 inhibitor	45772922
Exacerbation of erectile dysfunction	1340324
Absolute erectile dysfunction	3655358
Erectile dysfunction	3655355
Erectile dysfunction caused by drug	3655356
Erectile dysfunction co-occurrent and due to arterial insufficiency	37016340
Erectile dysfunction due to arterial disease	3655360
Erectile dysfunction due to diabetes mellitus	35626763
Erectile dysfunction due to endocrine disease	3655361
Erectile dysfunction due to fibrosis of corpus cavernosum	606412
Erectile dysfunction due to injury	606410
Erectile dysfunction due to neuropathy	3655362
Erectile dysfunction due to psychophysiologic disorder	3655359
Erectile dysfunction due to type 1 diabetes mellitus	43531565
Erectile dysfunction due to type 2 diabetes mellitus	4177050
Erectile dysfunction due to venous disorder	606407
Erectile dysfunction unresponsive to phosphodiesterase-5 inhibitor	45772922
Exacerbation of erectile dysfunction	1340324
Ligation of penile veins for impotence	4019657
Male erectile disorder due to corporovenous occlusion	37109304
Management of erectile dysfunction	44808863

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Concept set name	IDs
Neurogenic erectile dysfunction due to diabetes mellitus type 2	760989
Penile revascularization for impotence	4343129
Primary erectile dysfunction	43021236
Relative erectile dysfunction	3655357
Revascularization for impotence	4022799
Secondary erectile dysfunction	43021237
Vasculopathic erectile dysfunction	45769867
Insomnia	
Acute insomnia	42538607
Cannot sleep at all	4086851
Chronic insomnia	37110488
Difficulty sleeping	4115402
Difficulty sleeping with sedation	42689991
Difficulty sleeping without sedation	42689992
Disorders of initiating and maintaining sleep	439708
Disruptions of 24 hour sleep-wake cycle	43530738
Disturbance in sleep behavior	4204989
Does not sleep	42690122
Does not sleep with sedation	42690123
Does not sleep without sedation	42690715
Drug induced central sleep apnea	43530616
Drug-induced insomnia	44784625
Drug-induced sleep disorder	435792
Dyssomnia	435657
Exacerbation of insomnia	1340379
Hyposomnia co-occurrent and due to psychological disorder	37395584
Initial insomnia	4243368
Insomnia	436962
Insomnia co-occurrent and due to medical condition	37117120
Insomnia co-occurrent and due to nocturnal myoclonus	37397765
Insomnia disorder related to another mental disorder	439013
Insomnia disorder related to known organic factor	436681
Insomnia due to anxiety and fear	763092
Insomnia with sleep apnea	434172
Irregular sleep-wake pattern	436522
Late insomnia	4012514
Menopausal sleeplessness	4113205
Middle insomnia	4282607
Mixed insomnia	4182361
Non-organic sleep disorder	374905
Nonorganic insomnia	4102985
Not getting enough sleep	4087475
Organic sleep disorder	443544
Persistent insomnia	440082
Poor sleep hygiene	3173994
Poor sleep pattern	4200883
Primary hyposomnia	43020415
Primary insomnia	4215402

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Concept set name	IDs
Primary insomnia	4215402
Psychophysiologic insomnia	4138617
Rebound insomnia	4228217
Sleep deprivation	4305303
Sleep disorder	435524
Sleep dysfunction with arousal disturbance	40482260
Sleep dysfunction with sleep stage disturbance	40480927
Sleep pattern disturbance	4132137
Sleep state misperception	4175644
Symptoms interfere with sleep	4093843
Terminal insomnia	4283230
Transient insomnia	434918
Unable to sleep with sedation	42690379
Unable to sleep without sedation	42690380
Acute insomnia	42538607
Cannot sleep at all	4086851
Chronic insomnia	37110488
Difficulty sleeping	4115402
Difficulty sleeping with sedation	42689991
Difficulty sleeping without sedation	42689992
Hypertension	
Benign essential hypertension	312648
Benign hypertension	4028741
Benign secondary hypertension	314958
Benign secondary renovascular hypertension	4249016
Diastolic hypertension	4167358
Diastolic hypertension and systolic hypertension	42538697
Essential hypertension	320128
Exacerbation of hypertensive disorder	1340364
Exertional hypertension	4179379
High-renin essential hypertension	4058987
Hypertension associated with transplantation	4322735
Hypertension due to gain-of-function mutation in mineralocorticoid receptor	35624277
Hypertension in chronic kidney disease due to type 1 diabetes mellitus	45771067
Hypertension in chronic kidney disease due to type 2 diabetes mellitus	45771064
Hypertension in chronic kidney disease stage 2 due to type 2 diabetes mellitus	45757447
Hypertension in chronic kidney disease stage 3 due to type 2 diabetes mellitus	45757446
Hypertension in chronic kidney disease stage 4 due to type 2 diabetes mellitus	45757445
Hypertension in chronic kidney disease stage 5 due to type 2 diabetes mellitus	45757444
Hypertension resistant to drug therapy	44809548
Hypertension secondary to drug	4108213
Hypertension secondary to endocrine disorder	4110948
Hypertension secondary to kidney transplant	4178312
Hypertension with albuminuria	4262182
Hypertension with apparent mineralocorticoid excess	3169253
Hypertension with hyperadrenergic findings	3191244
Hypertensive crisis	45768449
Hypertensive disorder	316866

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Concept set name	IDs
Hypertensive emergency	43020424
Hypertensive urgency	40481896
Intermittent hypertension	44783643
Labile diastolic hypertension	4276511
Labile essential hypertension	4159755
Labile hypertension due to being in a clinical environment	44783644
Labile systemic arterial hypertension	36713024
Low-renin essential hypertension	4263067
Malignant essential hypertension	317898
Malignant hypertension	4289933
Malignant secondary hypertension	318437
Malignant secondary renovascular hypertension	4110947
Multiple drug intolerant hypertension	37208293
Nocturnal hypertension	44811110
Parenchymal renal hypertension	4212496
Paroxysmal hypertension	4049389
Rebound hypertension	4221991
Renal arterial hypertension	4305599
Renal hypertension	443771
Renal sclerosis with hypertension	4032952
Renovascular hypertension	317895
Resistant hypertensive disorder	37208172
Secondary diastolic hypertension	4253928
Secondary hypertension	319826
Severe hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	44809027
Stage 1 hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	44809026
Stage 1 hypertension (NICE 2011) with evidence of end organ damage	44811933
Stage 1 hypertension (NICE 2011) without evidence of end organ damage	44811932
Stage 2 hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	44809569
Supine hypertension	37016726
Sustained diastolic hypertension	4242878
Systolic essential hypertension	4180283
Systolic hypertension	4209293
Transient hypertension	4199306

Appendix I. Table S2. Code list for conditions representing risk factors of interest.

Concept set name	IDs
Diabetes	201820
Heart disease	321588
Chronic renal disease	46271022
Cancer diagnosis	443392
Asthma	317009
Gastroesophageal reflux disease (GERD)	318800
Hyperthyroidism	4142479
Hypotatasaemia	437833
Neurological disorders (Parkinson's disease and Dementia)	
Parkinson's disease	381270

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Concept set name	IDs
Alzheimer's or other dementias	4182210
Mental health disorders (anxiety, depression, PTSD)	
PTSD	436676
Depression	440383
Anxiety	442077
Anxiety disorders	441542
Sleep disorders (sleep apnoea and restless leg syndrome)	
Sleep apnoea	313459
Restless leg syndrome	35626941
Prostate surgery and cancer radiation treatment	
Operation on prostate	4250917
Ultrasound guided brachytherapy of prostate	44812239
Pudendal nerve or artery lesions	
Pudendal nerve neuropathy	4196277
Injury of pelvic blood vessel	36686418
Obesity and overweight	
Obesity	4215968
Overweight	437525

Appendix I. Table S3. Code list for identifying prior exposure to drugs of interest.

Concept set name	IDs
Triptans and ditans	21604375
Antiepileptics used in migraine (topiramate, valproate)	
Topiramate	742267
Valproate	745466
Tricyclic antidepressants used in migraine (amitriptyline)	710062
Beta-blockers used in migraine (e.g., propranolol, metoprolol, timolol)	
Timolol	902427
Propranolol	1353766
Metoprolol	1307046
Calcium channel blockers used in migraine (flunarizine)	19055183
PDE5 inhibitors (e.g., sildenafil, vardenafil, tadalafil and avanafil) and Alprostadil	21602645
Zolpidem and zopiclone	
Zolpidem	744740
Zopiclone	19044883
Benzodiazepines	21604565
Antidepressant drugs (SSRIs, SNRIs, others)	
SSRI antidepressants	724149
SNRI antidepressants	724150
sibutramine	739363
Selective serotonin reuptake inhibitors	21604709
Other antidepressants	21604729
Non-selective monoamine reuptake inhibitors (excluding 710062)	21604687
Monoamine oxidase inhibitors, non-selective	21604719
Monoamine oxidase A inhibitors	21604726
levomilnacipran	43560354
Diuretics	21601461

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Beta-blockers	21601664
ACE inhibitors	21601784
Angiotensin II receptor blockers	21601823
Calcium channel blockers	21601744
Alpha-blockers	21600410
Alpha-2 receptor agonists	21600416
Combined Alpha and Beta-blockers	21601698
Vasodilators	21600316

Some concept sets included within this table represent the fourth level of ATC codes, indicating the chemical/ therapeutic/ pharmacological subgroup. However, this code was used to identify all descendants to be included within each concept set.

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Appendix II. Supplemental tables and figures

Appendix II. Table S1. Demographic characteristics and conditions of interest in individuals newly initiating CGRP antagonists by database and sex.

Variable		IQVIA DA Germany		VID	FinOMOP-HILMO		NAJS	
		Females	Males	Females	Females	Males	Females	Males
		N=2,216	N=348	N=1,341	N=6,831	N=1,063	N= 5,092	N=528
Age								
	Median [Q25 - Q75]	48 [38 - 56]	52 [39 - 58]	46 [38 - 51]	43 [33 - 51]	44 [34 - 55]	42 [34 - 49]	42 [33 - 49]
	Mean (SD)	46.46 (12.67)	49.03 (12.79)	43.78 (9.79)	42.09 (12.47)	44.54 (14.27)	41.66 (11.51)	42.12 (12.06)
	Range (min - max)	18 - 88	19 - 81	16 - 59	12 - 87	15 - 87	6 - 85	18 - 83
Migraine diagnosis								
	N (%)	2,119 (95.6)	308 (88.5)	1,243 (92.7)	5,944 (87.0)	830 (78.1)	3,897 (76.5)	354 (67.0)
Yes								
Outcomes of interest								
Erectile dysfunction*	N (%)		0			Supp		Supp
Erectile dysfunction (Broad)*	N (%)		Supp			12 (1.1)		Supp
Hypertension	N (%)	208 (9.4)	63 (18.1)	174 (13.0)	667 (9.8)	124 (11.7)	1,255 (24.6)	168 (31.8)
Insomnia	N (%)	94 (4.2)	21 (6.0)	261 (19.5)	1,167 (17.1)	133 (12.5)	571 (11.2)	54 (10.2)
Endocrine/metabolism								
Diabetes	N (%)	32 (1.4)	7 (2.0)	41 (3.1)	495 (7.2)	44 (4.1)	422 (8.3)	39 (7.4)
Hyperthyroidism	N (%)	0	0	0	11 (0.2)	Supp	279 (5.5)	9 (1.7)
Hypokalemia	N (%)	Supp	0	Supp	30 (0.4)	Supp	28 (0.5)	0
Overweight and obesity	N (%)	38 (1.7)	8 (2.3)	96 (7.2)	437 (6.4)	49 (4.6)	258 (5.1)	12 (2.3)
Urinary/Reproductive system								
Chronic kidney disease	N (%)	Supp	Supp	13 (1.0)	18 (0.3)	5 (0.5)	12 (0.2)	Supp

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Variable		IQVIA DA Germany		VID	FinOMOP-HILMO		NAJS	
		Females	Males	Females	Females	Males	Females	Males
		N=2,216	N=348	N=1,341	N=6,831	N=1,063	N= 5,092	N=528
Pudendal injury	N (%)	0	0	0	0	15 (1.4)	0	0
Prostate surgery, radiation, others	N (%)	0	0	0	0	0	0	0
Respiratory								
Asthma	N (%)	66 (3.0)	14 (4.0)	101 (7.5)	991 (14.5)	120 (11.3)	56 (10.6)	86 (16.3)
Oncological								
	N (%)	47 (2.1)	12 (3.4)	40 (3.0)	225 (3.3)	44 (4.1%)	250 (4.9)	26 (4.9)
Cancer								
Gastrointestinal								
Gastroesophageal reflux disease	N (%)	13 (0.6)	5 (1.4)	107 (8.0)	397 (5.8)	46 (4.3)	1,746 (34.3)	157 (29.7)
Cardiovascular								
Heart disease **	N (%)	53 (2.4)	21 (6.0)	65 (4.8)	952 (13.9)	149 (14.0)	958 (18.8)	86 (16.3)
Neurological								
Parkinson, dementia	N (%)	10 (0.5)	5 (1.4)	Supp	17 (0.2)	Supp	26 (0.5)	Supp
Sleep-related								
Sleep related disorders	N (%)	22 (1.0)	18 (5.2)	47 (3.5)	413 (6.0)	175 (16.5)	40 (0.8)	25 (4.7)
Mental health								
Mental health disorders (anxiety, depression, PTSD)	N (%)	968 (43.7)	158 (45.4)	617 (46.0)	2,834 (41.5)	290 (27.3)	2,259 (44.4)	160 (30.3)

Supp = indicates data suppressed for confidentiality (values ≥1 and <5). 0 indicates no occurrences. Empty cells = Not identified. *Erectile dysfunction is only reported for males, so cells are empty for females. PTSD=Post-traumatic stress disorder. For definitions of conditions, please refer to Annex I. Table S2. **Heart disease includes a variety of conditions such as valvular, coronary artery disease, cardiomyopathies, and arrhythmias, among others.

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Appendix II. Table S2. Prior use of medications of interest during between at 91-365 days before the index date in individuals newly initiating CGRP antagonists by database and sex.

		IQVIA DA Germany	FinOMOP-HILMO	NAJS
Comedication of interest	Sex	91-365 days	91-365 days	91-365 days
Other anti-migraine treatments (focusing on prophylactic treatments)				
Antiepileptics migraine prophylaxis	Female [N (%)]	344 (15.5)	369 (5.4)	43 (0.8)
	Male	52 (14.9)	45 (4.2)	8 (1.5)
Beta-blockers migraine prophylaxis	Female	171 (7.7)	387 (5.7)	245 (4.8)
	Male	36 (10.3)	54 (5.1)	25 (4.7)
Calcium antagonists migraine prophylaxis	Female	175 (7.9)	Supp	
	Male	32 (9.2)	0	
TCA migraine prophylaxis	Female	237 (10.7)	784 (11.5)	
	Male	33 (9.5)	122 (11.5)	
Drugs used for erectile dysfunction				
Pde5 inhibitors	Female	Supp	0	13 (0.3)
	Male	0	29 (2.7)	0
Antidepressants				
Antidepressants	Female	259 (11.7)	834 (12.2)	172 (3.4)
	Male	35 (10.1)	148 (13.9)	20 (3.8)
Drugs used in hypertension				
Ace inhibitors	Female	Supp	153 (2.2)	105 (2.1)
	Male	0	15 (1.4)	14 (2.7)
Alpha 2 receptor agonists	Female	0	0	0
	Male	0	0	0
Alpha-blockers	Female	0	0	Supp
	Male	0	0	Supp
Angiotensin II receptor blockers	Female	21 (0.9)	956 (14.0)	43 (0.8)
	Male	5 (1.4)	159 (15.0)	7 (1.3)
Beta-blockers	Female	182 (8.2)	575 (8.4)	68 (1.3)
	Male	41 (11.8)	86 (8.1)	Supp
Calcium channel blockers	Female	8 (0.4)	88 (1.3)	302 (5.9)
	Male	Supp	23 (2.2)	38 (7.2)
	Female	0	Supp	Supp

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Combined Alpha and Beta-blockers	Male	0)	0	0
Diuretics	Female	8 (0.4)	35 (0.5)	11 (0.2)
	Male	0	Supp	0
Vasodilators	Female	0	15 (0.2)	59 (1.2)
	Male	0	6 (0.6)	Supp
Drugs used for insomnia				
Benzodiazepine derivatives	Female	14 (0.6)	258 (3.8)	304 (6.0)
	Male	Supp	29 (2.7)	33 (6.2)
Zolpidem zopiclone	Female	9 (0.4)	116 (1.7)	91 (1.8)
	Male	Supp	20 (1.9)	6 (1.1)

Supp = indicates data suppressed for confidentiality (values ≥1 and <5). 0 indicates no occurrences. Empty cells = Not identified.

Appendix II. Table S3. Incidence rates for outcomes of interest in the overall Incident migraine population by year and database

Database name	Outcome of Interest	Year	N events	N persons	Person years	Incidence (1,000 PYs)	95% CI
IQVIA DA Germany	Erectile dysfunction (broad)	2018	11	6,432	2,957	4	(2 , 7)
IQVIA DA Germany	Erectile dysfunction (broad)	2019	26	12,845	8,639	3	(2 , 4)
IQVIA DA Germany	Erectile dysfunction (broad)	2020	33	18,164	13,787	2	(2 , 3)
IQVIA DA Germany	Erectile dysfunction (broad)	2021	41	23,342	18,049	2	(2 , 3)
IQVIA DA Germany	Erectile dysfunction (broad)	2022	65	26,971	20,570	3	(2 , 4)
IQVIA DA Germany	Erectile dysfunction (broad)	2023	82	27,761	17,864	5	(4 , 6)
FinOMOP-HILMO	Erectile dysfunction (broad)	2018	5	4,540	2,314	2	(1 , 5)
FinOMOP-HILMO	Erectile dysfunction (broad)	2019	Supp	9,038	6,831	Supp	Supp
FinOMOP-HILMO	Erectile dysfunction (broad)	2020	31	15,361	11,679	3	(2 , 4)
FinOMOP-HILMO	Erectile dysfunction (broad)	2021	88	25,526	20,559	4	(3 , 5)
FinOMOP-HILMO	Erectile dysfunction (broad)	2022	198	34,955	30,146	7	(6 , 8)
FinOMOP-HILMO	Erectile dysfunction (broad)	2023	291	44,312	39,444	7	(7 , 8)

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Database name	Outcome of Interest	Year	N events	N persons	Person years	Incidence (1,000 PYs)	95% CI
NAJS	Erectile dysfunction (broad)	2018	Supp	1,190	630	Supp	Supp
NAJS	Erectile dysfunction (broad)	2019	Supp	2,385	1,782	Supp	Supp
NAJS	Erectile dysfunction (broad)	2020	Supp	3,287	2,837	Supp	Supp
NAJS	Erectile dysfunction (broad)	2021	Supp	4,375	3,795	Supp	Supp
NAJS	Erectile dysfunction (broad)	2022	Supp	5,560	4,910	Supp	Supp
NAJS	Erectile dysfunction (broad)	2023	7	6,669	6,090	1	(0 , 2)
IQVIA DA Germany	hypertension	2018	509	19,958	8,868	57	(53 , 63)
IQVIA DA Germany	hypertension	2019	887	38,792	25,609	35	(32 , 37)
IQVIA DA Germany	hypertension	2020	1,077	54,733	40,346	27	(25 , 28)
IQVIA DA Germany	hypertension	2021	1,425	69,197	52,738	27	(26 , 28)
IQVIA DA Germany	hypertension	2022	1,527	78,309	58,661	26	(25 , 27)
IQVIA DA Germany	hypertension	2023	1,751	79,538	49,537	35	(34 , 37)
VID	hypertension	2019	478	23,896	12,114	39	(36 , 43)
VID	hypertension	2020	675	39,776	31,494	21	(20 , 23)
VID	hypertension	2021	896	56,734	47,115	19	(18 , 20)
FinOMOP-HILMO	hypertension	2018	340	16,576	8,250	41	(37 , 46)

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Database name	Outcome of Interest	Year	N events	N persons	Person years	Incidence (1,000 PYs)	95% CI
FinOMOP-HILMO	hypertension	2019	529	32,723	24,310	22	(20 , 24)
FinOMOP-HILMO	hypertension	2020	945	56,361	41,927	23	(21 , 24)
FinOMOP-HILMO	hypertension	2021	1,981	92,417	73,517	27	(26 , 28)
FinOMOP-HILMO	hypertension	2022	2,391	123,608	106,077	23	(22 , 23)
FinOMOP-HILMO	hypertension	2023	3,006	153,485	135,930	22	(21 , 23)
NAJS	hypertension	2018	128	4,976	2,545	50	(42 , 60)
NAJS	hypertension	2019	267	9,800	7,212	37	(33 , 42)
NAJS	hypertension	2020	333	13,414	11,371	29	(26 , 33)
NAJS	hypertension	2021	542	17,673	15,078	36	(33 , 39)
NAJS	hypertension	2022	648	22,087	19,253	34	(31 , 36)
NAJS	hypertension	2023	749	26,292	23,471	32	(30 , 34)
IQVIA DA Germany	insomnia	2018	316	21,469	9,713	33	(29 , 36)
IQVIA DA Germany	insomnia	2019	589	42,013	28,111	21	(19 , 23)
IQVIA DA Germany	insomnia	2020	846	59,514	44,357	19	(18 , 20)
IQVIA DA Germany	insomnia	2021	1,068	75,347	58,052	18	(17 , 20)
IQVIA DA Germany	insomnia	2022	1,136	85,623	64,873	18	(17 , 19)

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Database name	Outcome of Interest	Year	N events	N persons	Person years	Incidence (1,000 PYs)	95% CI
IQVIA DA Germany	insomnia	2023	1,391	87,744	56,460	25	(23 , 26)
VID	insomnia	2019	604	24,137	12,244	49	(45 , 53)
VID	insomnia	2020	1,047	39,633	31,297	33	(31 , 36)
VID	insomnia	2021	1,628	55,814	46,098	35	(34 , 37)
FinOMOP-HILMO	insomnia	2018	203	16,814	8,464	24	(21 , 28)
FinOMOP-HILMO	insomnia	2019	541	33,335	24,810	22	(20 , 24)
FinOMOP-HILMO	insomnia	2020	1,361	56,940	42,404	32	(30 , 34)
FinOMOP-HILMO	insomnia	2021	3,697	91,474	72,366	51	(49 , 53)
FinOMOP-HILMO	insomnia	2022	4,680	119,100	101,446	46	(45 , 47)
FinOMOP-HILMO	insomnia	2023	6,281	144,245	126,346	50	(48 , 51)
NAJS	insomnia	2018	64	6,005	3,122	20	(16 , 26)
NAJS	insomnia	2019	147	11,887	8,885	17	(14 , 19)
NAJS	insomnia	2020	168	16,442	14,084	12	(10 , 14)
NAJS	insomnia	2021	277	21,726	18,819	15	(13 , 17)
NAJS	insomnia	2022	347	27,222	24,073	14	(13 , 16)
NAJS	insomnia	2023	439	32,716	29,542	15	(14 , 16)

Erectile dysfunction was not reported for VID since it is a female-exclusive database. Supp = indicates data suppressed for confidentiality (values ≥ 1 and < 5). 0 indicates no occurrences. Empty cells = Not identified.

Appendix II. Table S44

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	Author(s): J. Politi, K. Verhamme	Version: 3.0
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Appendix II. Table S44. Incidence rates of outcomes of interest in the general population by year, overall period, and database

Database name	Outcome of Interest	Year	N events	N persons	Person years	Incidence (1,000 PYs)	95% CI
IQVIA DA Germany	Erectile dysfunction (broad)	2018	7,743	3,785,201	3,358,850	2	(2 , 2)
IQVIA DA Germany	Erectile dysfunction (broad)	2019	8,304	3,770,392	3,345,396	2	(2 , 3)
IQVIA DA Germany	Erectile dysfunction (broad)	2020	9,230	3,759,819	3,287,506	3	(3 , 3)
IQVIA DA Germany	Erectile dysfunction (broad)	2021	8,712	3,604,045	3,102,867	3	(3 , 3)
IQVIA DA Germany	Erectile dysfunction (broad)	2022	9,520	3,197,892	2,594,155	4	(4 , 4)
IQVIA DA Germany	Erectile dysfunction (broad)	2023	9,272	2,418,219	1,634,561	6	(6 , 6)
FinOMOP-HILMO	Erectile dysfunction (broad)	2018	1,997	3,147,817	3,109,419	1	(1 , 1)
FinOMOP-HILMO	Erectile dysfunction (broad)	2019	1,906	3,150,777	3,113,219	1	(1 , 1)
FinOMOP-HILMO	Erectile dysfunction (broad)	2020	5,094	3,153,648	3,123,767	2	(2 , 2)
FinOMOP-HILMO	Erectile dysfunction (broad)	2021	1,0276	3,152,129	3,110,607	3	(3 , 3)
FinOMOP-HILMO	Erectile dysfunction (broad)	2022	11,666	3,147,380	3,101,518	4	(4 , 4)
FinOMOP-HILMO	Erectile dysfunction (broad)	2023	13,204	3,142,228	3,093,814	4	(4 , 4)
NAJS	Erectile dysfunction (broad)	2018	703	1,945,902	1,895,386	0	(0 , 0)

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Database name	Outcome of Interest	Year	N events	N persons	Person years	Incidence (1,000 PYs)	95% CI
NAJS	Erectile dysfunction (broad)	2019	745	1,977,297	1,936,381	0	(0 , 0)
NAJS	Erectile dysfunction (broad)	2020	678	2,000,838	1,968,023	0	(0 , 0)
NAJS	Erectile dysfunction (broad)	2021	776	2,014,508	1,977,358	0	(0 , 0)
NAJS	Erectile dysfunction (broad)	2022	801	2,040,964	1,995,528	0	(0 , 0)
NAJS	Erectile dysfunction (broad)	2023	811	2,048,519	2,015,825	0	(0 , 0)
IQVIA DA Germany	hypertension	2018	87,069	7,500,026	6,604,648	13	(13 , 13)
IQVIA DA Germany	hypertension	2019	89,973	7,417,853	6,530,660	14	(14 , 14)
IQVIA DA Germany	hypertension	2020	87,609	7,340,549	6,358,918	14	(14 , 14)
IQVIA DA Germany	hypertension	2021	92,265	7,001,091	5,959,470	15	(15 , 16)
IQVIA DA Germany	hypertension	2022	92,882	6,139,367	4,909,699	19	(19 , 19)
IQVIA DA Germany	hypertension	2023	96,640	4,542,385	2,921,336	33	(33 , 33)
VID	hypertension	2019	18,768	1,451,661	1,403,765	13	(13 , 14)
VID	hypertension	2020	13,741	1,458,176	1,418,542	10	(10 , 10)
VID	hypertension	2021	15,671	1,455,093	1,410,067	11	(11 , 11)
FinOMOP-HILMO	hypertension	2018	75,752	5,376,044	5,279,070	14	(14 , 14)
FinOMOP-HILMO	hypertension	2019	73,782	5,336,637	5,243,032	14	(14 , 14)

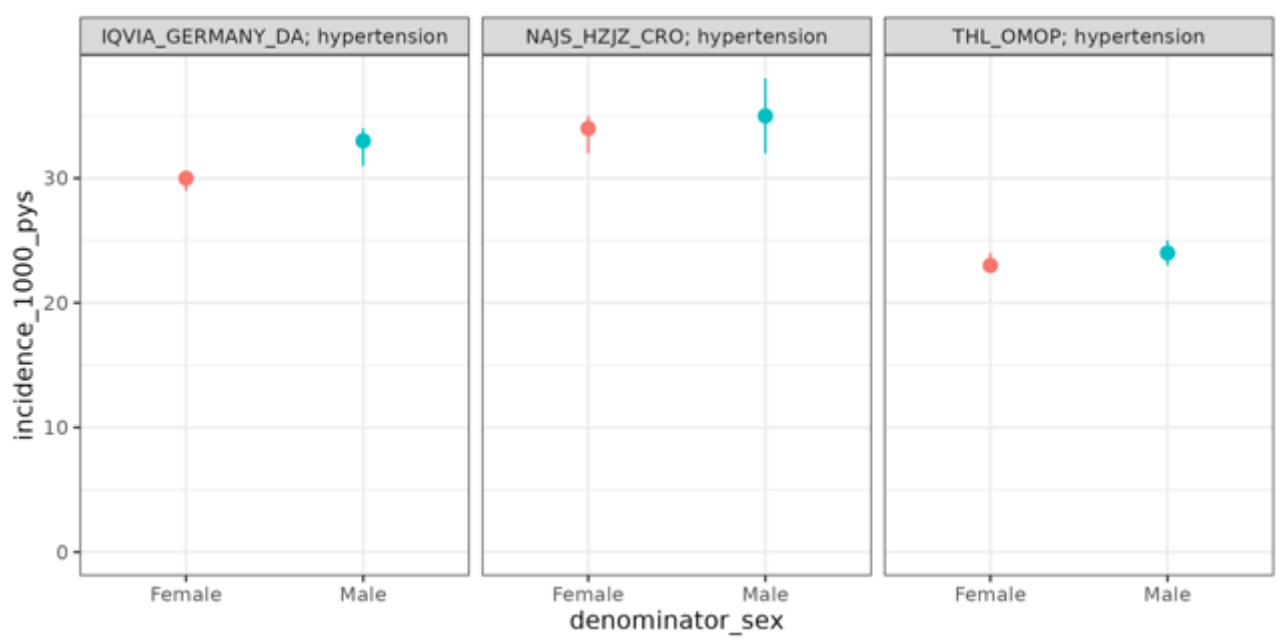
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Database name	Outcome of Interest	Year	N events	N persons	Person years	Incidence (1,000 PYs)	95% CI
FinOMOP-HILMO	hypertension	2020	91,885	5,300,696	5,219,187	18	(17 , 18)
FinOMOP-HILMO	hypertension	2021	118,524	5,246,047	5,131,094	23	(23 , 23)
FinOMOP-HILMO	hypertension	2022	105,914	5,170,869	5,057,638	21	(21 , 21)
FinOMOP-HILMO	hypertension	2023	105,878	5,113,435	4,997,067	21	(21 , 21)
NAJS	hypertension	2018	78,871	2,835,444	2,732,574	29	(29 , 29)
NAJS	hypertension	2019	71,760	2,832,669	2,747,036	26	(26 , 26)
NAJS	hypertension	2020	58,924	2,827,531	2,760,287	21	(21 , 22)
NAJS	hypertension	2021	69,717	2,824,975	2,749,332	25	(25 , 26)
NAJS	hypertension	2022	66,972	2,834,569	2,748,184	24	(24 , 25)
NAJS	hypertension	2023	64,119	2,821,057	2,749,935	23	(23 , 23)
IQVIA DA Germany	insomnia	2018	32,239	8,785,479	7,812,396	4	(4 , 4)
IQVIA DA Germany	insomnia	2019	33,198	8,712,176	7,745,072	4	(4 , 4)
IQVIA DA Germany	insomnia	2020	33,677	8,650,439	7,575,678	4	(4 , 4)
IQVIA DA Germany	insomnia	2021	34,782	8,288,343	7,136,676	5	(5 , 5)
IQVIA DA Germany	insomnia	2022	31,356	7,333,915	5,961,337	5	(5 , 5)
IQVIA DA Germany	insomnia	2023	32,867	5,551,119	3,730,275	9	(9 , 9)
VID	insomnia	2019	25,949	1,480,662	1,429,278	18	(18 , 18)

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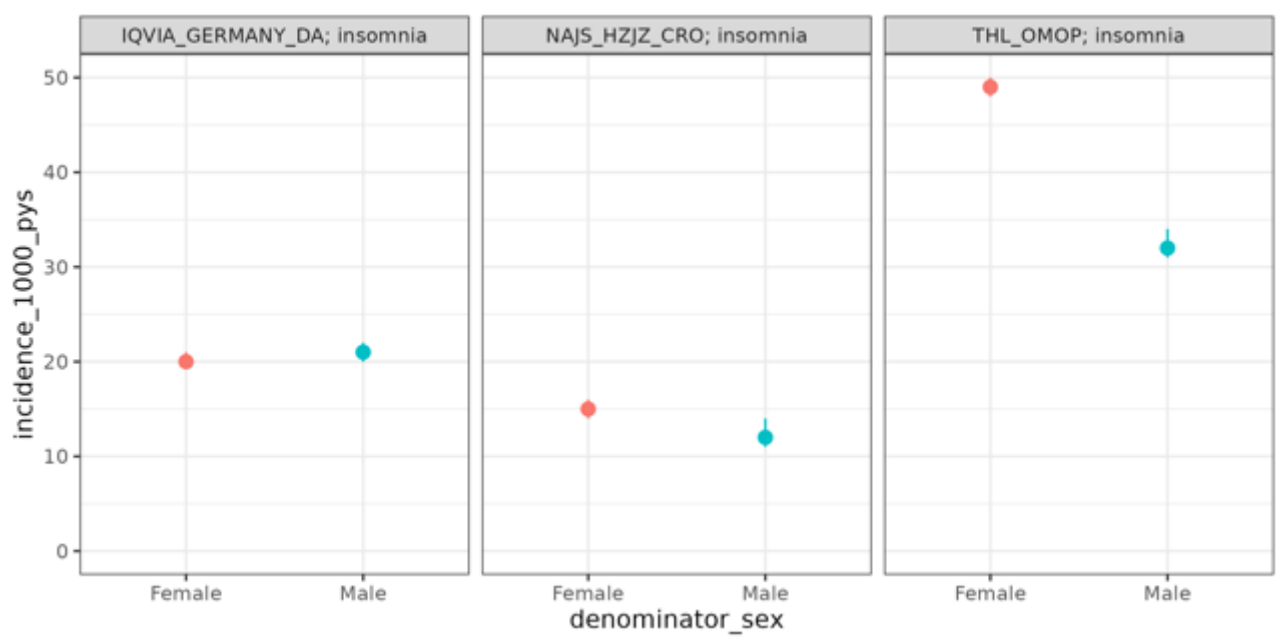
Database name	Outcome of Interest	Year	N events	N persons	Person years	Incidence (1,000 PYs)	95% CI
VID	insomnia	2020	21,332	1,480,321	1,436,285	15	(15 , 15)
VID	insomnia	2021	24,910	1,469,960	1,420,013	18	(17 , 18)
FinOMOP-HILMO	insomnia	2018	33,008	5,991,788	5,903,297	6	(6 , 6)
FinOMOP-HILMO	insomnia	2019	36,805	5,967,289	5,879,388	6	(6 , 6)
FinOMOP-HILMO	insomnia	2020	62,007	5,940,266	5,860,727	11	(10 , 11)
FinOMOP-HILMO	insomnia	2021	96,055	5,885,866	5,769,108	17	(17 , 17)
FinOMOP-HILMO	insomnia	2022	90,996	5,801,657	5,680,537	16	(16 , 16)
FinOMOP-HILMO	insomnia	2023	99,240	5,724,040	5,595,758	18	(18 , 18)
NAJS	insomnia	2018	38,235	3,910,487	3,808,575	10	(10 , 10)
NAJS	insomnia	2019	36,241	3,924,399	3,838,473	9	(9 , 10)
NAJS	insomnia	2020	34,652	3,929,720	3,860,146	9	(9 , 9)
NAJS	insomnia	2021	36,604	3,921,627	3,842,396	10	(9 , 10)
NAJS	insomnia	2022	34,881	3,931,745	3,842,005	9	(9 , 9)
NAJS	insomnia	2023	37,136	3,920,160	3,846,503	10	(10 , 10)

Erectile dysfunction was not reported for VID since it is a female-exclusive database. Supp = indicates data suppressed for confidentiality (values ≥ 1 and < 5). 0 indicates no occurrences. Empty cells = Not identified.



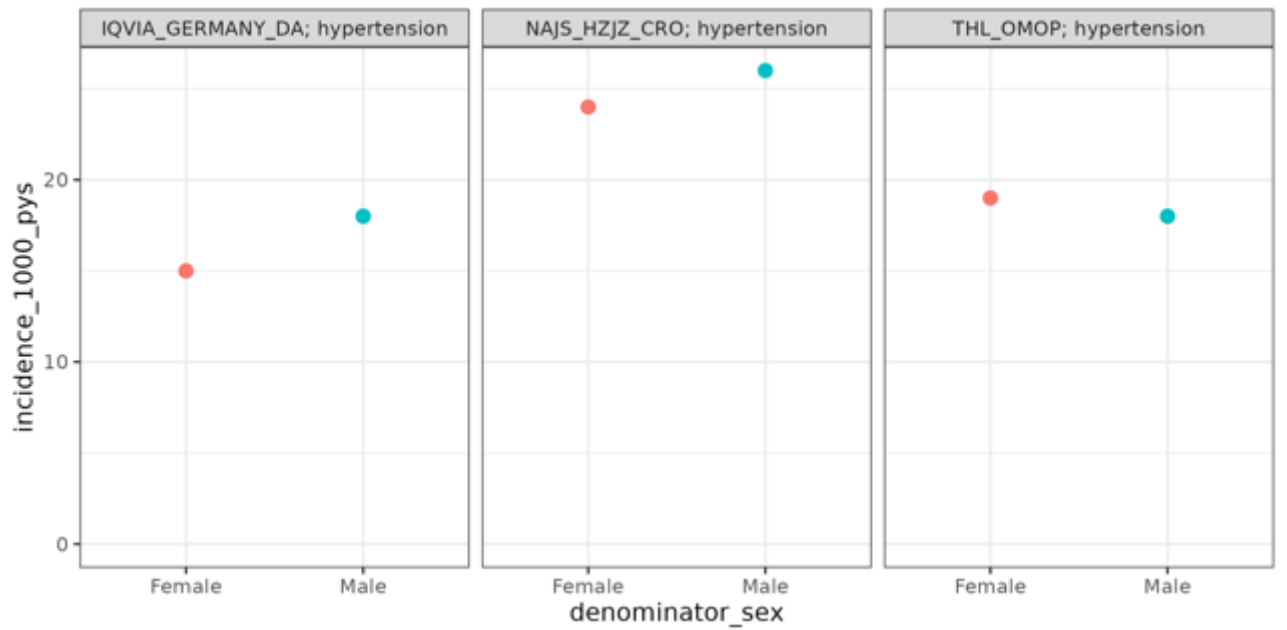
NAJS_HZJZ_CRO=NAJS, THL_OMOP=FinOMOP-HILMO. Dots represent actual incidence rate estimate for that category, while whiskers represent 95% CI. PYS=Person Years.

Appendix II. Figure S1. Incidence rates for hypertension in the incident migraine population for the entire study period, stratified by sex.



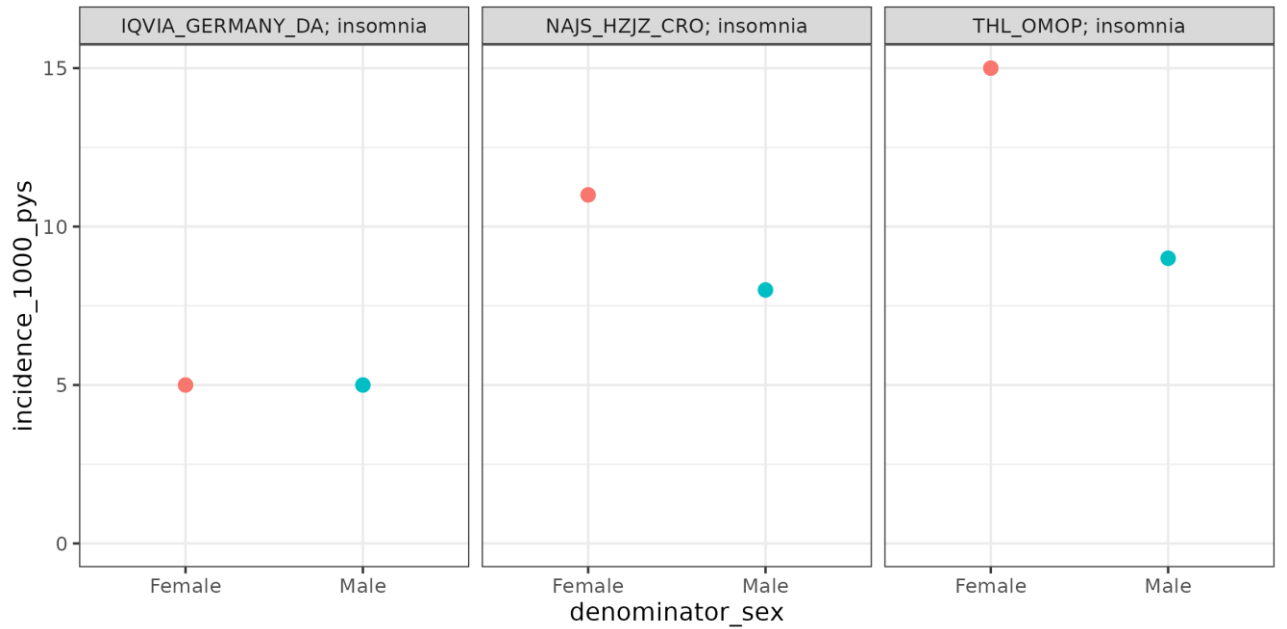
NAJS_HZJZ_CRO=NAJS, THL_OMOP=FinOMOP-HILMO. Dots represent actual incidence rate estimate for that category, while whiskers represent 95% CI. PYS=Person Years.

Appendix II. Figure S2. Incidence rates for insomnia in the incident migraine population for the entire study period, stratified by sex.



NAJS_HZJZ_CRO=NAJS, THL_OMOP=FinOMOP-HILMO. Dots represent actual incidence rate estimate for that category, while whiskers represent 95% CI. PYS=Person Years.

Appendix II. Figure S3. Incidence rates for hypertension in the general population for the entire study period, stratified by sex.



NAJS_HZJZ_CRO=NAJS, THL_OMOP=FinOMOP-HILMO. Dots represent actual incidence rate estimate for that category, while whiskers represent 95% CI. PYS=Person Years.

Appendix II. Figure S4. Incidence rates for insomnia in the general population for the entire study period, stratified by sex .