Study Report
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DARWIN EU® - Incidence of myoclonus in heart failure: a descriptive analysis in patients treated with sacubitril/valsartan and other treatments

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Contents

Study title	DARWIN EU® - Incidence of myoclonus in heart failure: a descriptive analysis in patients treated with sacubitril/valsartan and other treatments
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EU PAS number	EUPAS1000000351
Active substance	Sacubitril/valsartan Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers
Medicinal product	Entresto
Research question and objectives	What is the incidence rate of myoclonus among heart failure patients treated with sacubitril/valsartan and other commonly used heart failure treatments? Specific study objectives: 1. To calculate the incidence rate of myoclonus in the general population and in a newly diagnosed heart failure population, stratified by age groups and sex. 2. To calculate the incidence rate of myoclonus in the following heart failure treatment initiation cohorts: sacubitril/valsartan, angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARBs) (index date being the start of the treatment), stratified by age (at index date) groups and sex.
Country(-ies) of study	Germany, Spain, and the United Kingdom
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TITLE

DARWIN EU® - Incidence of myoclonus in heart failure: a descriptive analysis in patients treated with sacubitril/valsartan and other treatments

1. DESCRIPTION OF STUDY TEAM

Study team role(s)	Name(s)	Organisation(s)
Study Project Manager/Principal Investigator	Julieta Politi Talita Duarte-Salles	Erasmus MC
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Epidemiologist	Talita Duarte-Salles Julieta Politi Guido van Leeuwen	Erasmus MC
Clinical Domain Expert	Julieta Politi Guido van Leeuwen	Erasmus MC
Data partner name*	**Data Partner member name(s)**	**Organisation(s)**
CPRD GOLD	Antonella Delmestri	University of Oxford - CPRD
IQVIA DA Germany	Gargi Jadhav Isabella Kacmarczyl Akram Mendez Dina Vojinovic	IQVIA
SIDIAP	Anna Palomar-Cros Irene López-Sánchez Agustina Giuliodori	IDIAPJGol

*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 3 databases in the DARWIN EU® network of data partners from 3 European countries. All databases were previously mapped to the OMOP CDM.

The selection process was based on the size of the databases, the number of patients exposed to the selected treatments of interest, good capture of the outcome of interest, the suitability of the denominator population for population-level rates, geographical spread, and most importantly, the ability to access data and conduct the analysis in a timely manner (through expedited approvals or no IRB approval requirements).

Based on the feasibility assessment, the following data sources were considered a good fit:

1. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
3. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain

Specific descriptions of the data sources included in this study are shown in **Table 1**.

Table 1. Description of databases used for this study.

Country	Name of Database	Health Care setting	Type of Data	Number of active subjects	Calendar period covered by each data source
UK	CPRD GOLD	Primary care and outpatient specialist care	EHR	2.9 million	2015-01-01 to 2024-07-01
DE	IQVIA DA Germany	Primary care and outpatient specialist care	EHR	4.3 million	2015-01-01 to 2023-09-30
ES	SIDIAP	Primary care and outpatient specialist care	EHR	5.9 million	2015-01-01 to 2023-06-30

UK = United Kingdom, DE = Germany, ES = Spain. DA = Disease Analyzer, EHR = Electronic Health record. Active subjects are defined as the maximum number of persons in an observation period in the last 6 months.

3. ABSTRACT

Title

DARWIN EU® - Incidence of myoclonus in heart failure: a descriptive analysis in patients treated with sacubitril/valsartan and other treatments

Rationale and background

Sacubitril/valsartan (Entresto) is an angiotensin receptor-neprilysin inhibitor used to treat symptomatic chronic heart failure in both adults and children. Its dual mechanism of action involves inhibiting neprilysin and blocking the angiotensin II type-1 receptor, providing complementary cardiovascular benefits. The Pharmacovigilance Risk Assessment Committee (PRAC) is currently investigating a signal on a potential association between the use of sacubitril/valsartan and myoclonus.

To support PRAC signal evaluation, through this study, we aimed to investigate the incidence rate of myoclonus in the general population, in newly diagnosed heart failure patients, and in patients with heart failure newly initiating sacubitril/valsartan, angiotensin-converting enzyme inhibitors (ACEi), or angiotensin receptor blockers (ARBs).

Research question and objectives

What is the incidence rate of myoclonus among heart failure patients treated with sacubitril/valsartan and other commonly used heart failure treatments?

Specific study objectives:

1. To calculate the incidence rate of myoclonus in the general population and in a newly diagnosed heart failure population, stratified by age (at index date) groups and sex.
2. To calculate the incidence rate of myoclonus in the following heart failure treatment initiation cohorts: sacubitril/valsartan, angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARBs) (index date being the start of the treatment), stratified by age (at index date) groups and sex.

Methods

This population-level cohort study spanned from January 1st, 2015, to December 31st, 2023. Patients aged 18 and older with at least 365 days of database history were included. Two cohorts were defined: the general population and newly diagnosed heart failure patients. For objective 2, patients with a history of heart failure were categorized into treatment groups based on their first initiation of heart failure treatments.

The treatment groups included those who were new users of sacubitril/valsartan as a first line (with no prior exposure to sacubitril/valsartan or ACEi/ARB), new users of sacubitril/valsartan as a later line (with prior exposure to ACEi/ARB), new users of ACEi (with no prior exposure to ACEi), and new users of ARB (with no prior exposure to ARBs). The variables of interest were the exposure to sacubitril/valsartan, ACEi, and ARBs, and the outcomes of interest were incident myoclonus in line with the PRAC signal. Stratifications by age, sex, and predefined treatments were made. The general population cohort was followed from the first date of eligibility criteria fulfilment, while the incident heart failure population was followed from the date of first diagnosis. For objective 2, follow-up started at the initiation of the treatment of interest and continued. In all cohorts, follow-up continued until the first outcome event, the end of the study period, or censoring. Data sources included CPRD GOLD in the UK, IQVIA DA in Germany, and SIDIAP in Spain. Statistical analysis was conducted using the “IncidencePrevalence” R package to calculate the incidence rate of the outcome of interest (i.e. myoclonus). Incidence rates were reported by country/database and stratified by age and sex, with a minimum cell count of 5 for reporting results.

Incidence rates of the outcomes of interest were calculated as the number of newly diagnosed cases divided by the sum of person-years contributed by the at-risk population during follow-up. For the general population, rates were reported using monthly calendar rates. For the HF cohort and the HF cohort newly initiating treatments of interest, person-time was measured from the index date until the outcome of interest, loss to follow-up, death, or the end of the study period, whichever occurred first. Patients were censured at predefined time windows (0–30, 31–90, 91–180, 181–365 days, and >365 days) if no event occurred, with those who remained event-free continuing to contribute to the subsequent risk intervals. All rates were reported per 100,000 person-years (PY).

Results

Myoclonus rates

For myoclonus narrow, incidence rates were consistently low or zero across all three study populations (i.e., the general population, incident HF population, and HF population newly initiating treatments of interest) and databases. In the general population, rates ranged between 1 and 13 per 100,000 PY across all time windows. In the incident HF population, rates were generally negligible or not estimable due to low counts, with higher rates (655 per 1000,000 PY) observed in SIDIAP for the 0–30 day window. Among HF patients newly initiating treatments, myoclonus narrow incidence rates were close to zero for almost every time window and treatment of interest in all three databases.

For myoclonus broad, rates were consistently higher than narrow across all three populations and databases. In the general population, rates ranged between 60-120 per 100,000 PY for most of the study period, increasing to 100 and 200 per 100,000 PY in IQVIA DA Germany and SIDIAP, respectively, towards the end of the study period. In the incident HF population, myoclonus broad incidence rates were higher compared to myoclonus narrow incidence rates and to myoclonus broad incidence rates observed in the general population in all databases. Rates peaked in the earliest time windows, close to first HF diagnosis (ranging from 485-2818 per 100,000 PY during the 0–30 day window) and stabilised at lower values (212–645 per 100,000 PY) over later time windows. Among HF patients newly initiating treatments, ARBs consistently showed the highest rates, peaking at 893 per 100,000 PY in SIDIAP during the 0–30 day window (range 503-893 per 100,00 PY). Rates for ACEi and sacubitril-valsartan later line ranged between 579-667 and 729 per 100,000 PY, respectively, during the 0–30 day window. All treatments had higher rates of myoclonus in the earlier time windows after initiation compared to later on. For sacubitril/valsartan first-line initiators in all three databases, numbers were generally too low to estimate myoclonus incidence.

Myoclonus rates by Age

For myoclonus narrow, rates by age were generally zero or not estimable, and while they increased by age, differences were rather modest.

For myoclonus broad, rates increased with age. In the general population, the highest rates were observed in the >=80 age group, reaching 379 per 100,000 PY in SIDIAP. In the incident HF population, also the >=80 age group showed the highest rates during the 0–30 day window, ranging from 750 (CPRD GOLD) to 3164 (SIDIAP) per 100,000 PY, although differences between the 50-79 and >=80 age groups were modest across all databases. Among HF patients newly initiating treatments, rates generally increased with age for all treatments, the highest difference being between <50 and >=50 years of age.

Myoclonus rates by Sex

For myoclonus narrow, rates stratified by sex, when estimable, were mostly similar between sexes in all three populations.

For myoclonus broad, no sex differences were noted in the general population. In the incident HF population, rates showed minor variability by sex, with slightly higher rates in females in CPRD GOLD and

SIDIAP. Among HF patients newly initiating treatments, rates were generally higher in females than males for most time windows, treatments, and databases. However, the difference was rather small.

Conclusion

In this disease epidemiology study of myoclonus incidence in patients with incident heart failure, heart failure newly initiating treatments of interest (ACEi, ARBs, and sacubitril/valsartan first and later lines), and the general population in UK, Germany, and Spain, we found that patients with incident heart failure consistently exhibited higher incidence rates of myoclonus broad and narrow, when compared to both the general populations and with the heart failure newly initiating treatments of interest. For almost all cohorts, myoclonus narrow was estimated at zero (zero occurrences), or counts were >=1 and <5, so rates could not be estimated. For myoclonus broad, the highest rates in the incident heart failure cohort and treatment initiator cohorts occurred within the 0-30 days following the start of follow-up (i.e., heart failure debut or treatment initiation). Among new initiators of different heart failure treatments of interest, rates for myoclonus broad were highest among patients initiating ARBs, when estimable, and lower rates were observed among patients initiating sacubitril-valsartan (later line) and ACEi. For sacubitril/valsartan first-line initiators, numbers were generally too low to provide estimates.

4. LIST OF ABBREVIATIONS

ACEi	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin receptor blockers
CMD	Common Data Model
CPRD	Clinical Practice Research Datalink
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DOI	Declaration Of Interests
DQD	Data Quality Dashboard
DRE	Digital Research Environment
EHR	Electronic Health Record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GDPR	General Data Protection Regulation
GP	General Practitioner
HF	Heart Failure
ICD	International Classification of Diseases
OMOP	Observational Medical Outcomes Partnership
PRAC	Pharmacovigilance Risk Assessment Committee
PY	Person-Years
RxNorm	Medical Prescription Normalized
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SNOMED	Systematized Nomenclature of Medicine

5. AMENDMENTS AND UPDATES

The initial study was run on SIDIAP hospital-linked CDM. Results between SIDIAP and the other data sources used in the study revealed differences which we hypothesised were related to the linking to hospital data. In turn, we repeated the analysis for the three cohorts of interest in SIDIAP non-hospital-linked CDM data.

Results are presented as a sensitivity analysis under the **Section 12.3 Other analysis**.

Number	Date	Section of study protocol	Amendment or update	Reason
1	20/12/2024	8.8 Analysis	No sensitivity analysis was initially planned. However, it was decided to repeat the analysis only in SIDIAP, using their non-hospital linked-CDM.	Given the differences noted between SIDIAP and the other data sources used in this study we repeated the analysis using SIDIAP's non-hospital linked-CDM.

6. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Draft Study Protocol	14/10/2024	14/10/2024
Final Study Protocol	22/10/2024	10/12/2024
Creation of Analytical code	October/November 2024	October/November 2024
Execution of Analytical Code on the data	November/December 2024	December 2024
Draft Study Report	06/01/2025	06/01/2025
Final Study Report	13/01/2025	

7. RATIONALE AND BACKGROUND

Sacubitril/valsartan (Entresto) is an angiotensin receptor-neprilysin inhibitor used to treat symptomatic chronic heart failure (HF) in both adults and children. Its dual mechanism of action involves inhibiting neprilysin and blocking the angiotensin II type-1 receptor, providing complementary cardiovascular benefits. Sacubitril/valsartan has been shown to be superior to enalapril in reducing the risk of mortality and hospitalisation for HF in patients with reduced ejection fraction HF. (1) Current European guidelines recommend treatment with sacubitril/valsartan for patients with reduced ejection fraction HF, as first line or second line, to replace ACEi or ARBs. (2)

Myoclonus is characterised by sudden, involuntary muscle movements. Its epidemiology is not well known, mainly because it includes a wide spectrum of clinical manifestations and numerous causes. (3) These causes include neurodegenerative and metabolic conditions, central nervous system hypoxia, ischaemia, infections, or induced by drugs. (3)

The Pharmacovigilance Risk Assessment Committee (PRAC) is currently evaluating a potential safety signal of myoclonus with sacubitril/valsartan, detected based on spontaneous case reports in various countries. The causal association is under discussion.

Sacubitril/valsartan's central nervous system safety was assessed in preclinical pharmacology studies. (4) In repeated dose studies in rodents, increased locomotor activity, twitches, and sensitivity to touch were observed with sacubitril/valsartan, although this was not observed in primates. Given the sporadic nature of these findings, they were not deemed toxicologically significant. (4)

Due to the role of neprilysin in degrading enkephalins, sacubitril/valsartan has the potential to induce myoclonus. (5) To contextualise the signal assessment, we aimed to investigate the incidence rate of myoclonus in the general population, newly diagnosed HF patients and patients with HF newly initiating sacubitril/valsartan, angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARBs).

8. RESEARCH QUESTION AND OBJECTIVES

This study aimed to estimate incidence rates of myoclonus in different populations of interest.

Specific study objectives:

1. To calculate the incidence rate of myoclonus in the general population and in a newly diagnosed heart failure population, stratified by age groups and sex.
2. To calculate the incidence rate of myoclonus in the following heart failure treatment initiation cohorts: sacubitril/valsartan, angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARBs) (index date being the start of the treatment), stratified by age groups and sex.

9. RESEARCH METHODS

9.1 Study type and study design

We performed a population-level disease epidemiology study classified as "*off-the-shelf*" and as described in the DARWIN EU® Complete Catalogue of Standard Data Analyses (**Table 2**).

Table 2. Description study type and design.

Study type	Study design	Study classification
Population-level descriptive epidemiology	Population-level cohort	Off the shelf

9.2 Study setting and data sources

This study used routinely collected health data from 3 databases in the DARWIN EU® network of data partners from 3 European countries. All databases were previously mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) **(Table 3)**.

The selection process was based on the size of the databases, the number of patients exposed to the selected treatments of interest, good capture of the outcome of interest, the suitability of the denominator population for population-level rates, geographical spread, and most importantly, the ability to access data and conduct the analysis in a timely manner to meet the regulatory deadline (through expedited approvals or no IRB approval requirements).

Based on the feasibility assessment, the following data sources were considered a good fit:

1. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
3. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain

Specific descriptions of the data sources included and justification for their choice for inclusion in this study are shown in **Table 3**.

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.

In order to assess relevance, a more general-purpose diagnostic software tool, CohortDiagnostics, was developed. This package evaluates the study phenotype algorithms applied to OMOP CDM datasets, helps understanding patient capture and the cohort characteristics, including 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 relative to the expected refresh cycle (typically quarterly or half-yearly) and by encouraging expedited approvals or blanket approval among data partners. 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.

Table 3. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Calendar period covered by each data source
UK	CPRD GOLD	• Timeliness of data access. • Number of patients exposed to the selected treatments of interest. • Good capture of the outcome of interest. • Denominator population is representative of the target population • Geographical spread	Primary care and outpatient specialist care	EHR	2.9 million	2015-01-01 to 2024-07-01
DE	IQVIA DA Germany		Primary care and outpatient specialist care	EHR	4.3 million	2015-01-01 to 2023-09-30
ES	SIDIAP		Primary care and outpatient specialist care, hospital discharge.	EHR	5.9 million	2015-01-01 to 2023-06-30

UK = United Kingdom, DE = Germany, ES = Spain. DA = Disease Analyzer, EHR = Electronic Health record. Active subjects are defined as the maximum number of persons in an observation period in the last 6 months.

Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare Products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD comprises computerised records of all clinical and referral events in primary care, in addition to comprehensive demographic information and medication prescription data in a sample of UK patients. (6) In the regional distribution of currently contributing practices, the majority are from Scotland, accounting for 52% of all participating practices, while Wales contributes 28%. The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Primary care data quality is variable because GPs enter data during routine health care visits, not for research. Quality checks on patient and practice levels are applied during the initial processing. Data is

available for 20 million patients, including 3.2 million currently registered patients. Access to CPRD GOLD data requires approval via the Research Data Governance Process.

Research-quality-level validation covers the actual content of the data. CPRD provides a patient-level data quality metric as a binary 'acceptability' flag. This is based on recording and internal consistency of key variables, including date of birth, practice registration date, and transfer out date. The validity of diagnoses has been assessed for some diseases, and results show an overall high validity, including circulatory system diseases. (7) The database has been previously used to study heart failure.(8, 9) Research into data quality has shown large variations in the inter-practice recording of data, which should be considered when interpreting the results. Established linkages include, but are not limited to, Hospital Episode Statistics (hospitalisation data), Office for National Statistics (mortality data including causes of death), Index of Multiple Deprivation and Townsend scores (deprivation data), and disease registries.

CPRD GOLD is limited to GP records. General practitioners receive information about patient contacts with secondary care, although this must be manually entered into the patient records and could potentially affect information completeness.

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. Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patients visiting more than one provider are not cross identified for data protection reasons and, therefore, recorded as separate in the system. Observation time is defined by the first and last consultation dates. This dataset encompasses approximately 3% of all outpatient practices within Germany, ensuring a substantial representation of the national healthcare landscape.(10, 11) The sampling methods used for practice selection, taking into account physicians' demographics, speciality focus, community size category and federal state location, were instrumental in constructing a database that accurately mirrors the diverse spectrum of healthcare providers in the country. (10) Consequently, data within IQVIA DA Germany database has been demonstrated to be representative of general and specialised practices throughout Germany. Germany has no mandatory GP system, and patients have a free choice of specialists. As a result, data are collected from visits to GPs, Pediatric Medicine, Obstetrics / Gynecology, Orthopaedic Surgery, Dermatology, Otolaryngology, Diabetic medicine, Urology, Neuropsychiatry, Cardiology, Gastroenterology, Pulmonary Disease, Rheumatology, Neurology, Psychotherapy, Child and Adolescent Psychiatry and Psychiatry practices. Drugs are recorded as prescriptions of marketed products. The database contains demographics records, basic medical data, disease diagnosis according to International Classification of Diseases, 10th revision (ICD-10), and prescription records.(11) 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. As previously demonstrated, IQVIA DA Germany is suitable for pharmacoepidemiologic and pharmacoeconomic studies.(11-13)

Information System for Research in Primary Care (SIDIAP), Spain (IDIAP Jordi Gol)

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care teams consisting of GPs, nurses and non-clinical staff.(14) It is a regional database covering the region of Catalonia. The Catalan Health Institute manages 286 out of 370 such PCTs with a coverage of 5.6M patients out of 8M people in the Catalan population (75%).(15) The database started to collect data in 2006 and is updated every six months. The mean follow-up is 15.5 years. The observation period for a patient can be the start of the database (2006) or when a person is assigned to a Catalan Health Institute primary care centre. The exit date can be when a person is transferred out to a primary care centre that does not pertain

to the Catalan Health Institute, date of death, or date of end of follow-up in the database. The demographic composition within SIDIAP closely mirrors that of the broader Catalan population, encompassing a representative spectrum of geographic distribution, age, and sex proportions. SIDIAP obtains data from electronic health records. The dataset covers demographics, all-cause mortality, disease diagnoses, prescription and dispensation records of drugs, results of laboratory tests, socio-economic indicators, vaccination records, lifestyle information, parent-child linkage, and various clinical parameters. Diseases are classified under the International Classification of Diseases 10th revision (ICD-10).

Quality checks have been implemented, including central identification of duplicate patient IDs and visual inspection for temporal patterns in the registry of a certain variable. Furthermore, the data undergoes assessment for availability (longitudinally and reliability), plausibility (range checks and unusual values), and visualisation tools. Specifically, for biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed. SIDIAP is linked with numerous other databases. It integrates data from external sources, including laboratory biomarker data, drug prescription and dispensation records, hospital discharge records, mental health centres, and other specific disease registries. Drugs not prescribed in the GP setting might be underreported, and disease diagnoses made in specialist care settings are not included. Vital status (death date and cause) is collected through linkage with the civil registry. The main limitation is that SIDIAP covers only primary health care records. However, it is combined with data from various other sources through effective linkages. This study will use primary care data linked to hospital discharge data.

The quality of a wide number of data captured in SIDIAP has been demonstrated in validation studies, including vascular diseases and cardiovascular risk factors, and has been previously used to study heart failure.(15-18)

9.3 Study period

From January 1st, 2015 (first EU approval) to 31st December 2023 (or last available date).

9.4 Follow-up

The general population cohort was followed from the date of first eligibility criteria fulfilment (index date) until the end of the study period, censoring (due to loss to follow-up, death) or the occurrence of the outcome of interest, whichever occurred first (**Table 4**).

The incident HF population was followed from the date of first HF diagnosis (index date) until the end of the study period, censoring (due to loss to follow-up, death) or the occurrence of the outcome of interest, whichever occurred first.

The treated cohorts were followed from the time of treatment initiation until the end of the study period, censoring (due to loss to follow-up, death) or the occurrence of the outcome of interest, whichever occurred first.

Additionally, for all cohorts (except the general population), incidence rates were estimated at predefined consecutive time windows: 0–30 days, 31–90 days, 91–180 days, and 181–365 days post-index date. Patients were censored at the end of each time window if they had not experienced the event of interest, reflecting distinct periods at risk.

Table 4. 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	Incident with respect to…
General population	Study entry date	Single	n/a	n/a	OP	n/a	n/a
Incident Heart failure population	Date of heart failure diagnosis	Single	Incident	[-∞, ID]	OP	SNOMED	Heart failure diagnosis
Heart failure population newly initiating treatments of interest	Initiation of treatment with any of the treatments of interest	Single	Incident	[-∞, ID]	OP	SNOMED & RxNorm	Use of each drug of interest class

[1] OP = outpatient. n/a = not applicable

9.5 Study population with inclusion and exclusion criteria

The general population cohort included all patients in the database from January 1st, 2015 (first EU approval of sacubitril/valsartan) to December 31st, 2023 (or the last available date). All patients were required to have at least 365 days of observation time before the index date and be 18 years of age or above at index date.

Once eligibility to be included in the general population was met, a cohort of newly diagnosed HF patients was constructed by identifying patients with a diagnosis of HF after a minimum of one year of HF-free available historical data.

For the cohort of Heart failure population newly initiating treatments of interest, in addition to at least 365 days of observation time before the index date and being 18 years of age or above at index date**,** patients were required to have a history of HF, measured as at least one HF diagnosis, before index date.

For sacubitril/valsartan, two cohorts were created: First line and later line. First line represented use of the treatments as first line after diagnosis, while later line reflects the use of sacubitril/valsartan after ACEi and ARBs treatment (later line). Because of this, for the later line cohort, prior exposure to ACEi and/or ARBs treatment was required.

All cohorts were required not to have a history of myoclonus (event of interest) before index date.

The operational definitions of the inclusion and exclusion criteria are presented by means of **Table 5 and Table 6**, respectively. The concept sets used to define each cohort are presented in **Appendix I**.

Table 5. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings [1]	Code Type	Diagnosis position[2]	Applied to study populations:
Observation period during the study period	All individuals present in the period 01/01/2015-31/12/2023 (or last available date)	After	n/a	OP	n/a	n/a	All study populations
Prior database history	Study participants will be required to have 365 days of prior history observed before index date	Prior	[-365, 0]	OP	n/a	n/a	All study populations
Age >=18 years	Study participants will be required to be at least 18 years of age before index date	Prior	n/a	OP	n/a	n/a	All study populations
Prior diagnosis of heart failure	Individuals newly initiating study treatments will be required to have a history of heart failure before index date	Prior	[-Inf, -1]	OP	SNOMED	n/a	Heart failure population initiating any treatment

Prior exposure to ACEi and/or ARBs	Individuals diagnosed with heart failure and newly initiating sacubitril/valsartan later line, will be required to have previous exposure to ACEi and/or ARBs	Prior	[-Inf, -1]	OP	RxNorm	n/a	Heart failure population initiating treatment with sacubitril/valsartan – Later line

[1] IP = inpatient, OP = outpatient, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

Table 6. Operational definitions of exclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:
Washout window for myoclonus	Individual with previous history of myoclonus (prevalent) any time prior index date will be excluded	Prior	[-Inf, -1]	OP	SNOMED	n/a	Heart failure and General population Heart failure initiating treatments
Washout window for heart failure	Individuals with previous history of heart failure any time prior	Prior	[-Inf, -1]	OP	SNOMED	n/a	Heart failure population

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:
	index date will be excluded						
Washout window for exposure to heart failure treatments: Sacubitril/valsartan – First line	Individuals with previous exposure to Sacubitril/valsartan any time prior index date will be excluded. Additionally, first line will exclude patients with prior exposure to ACEi and ARBs	Prior	[-Inf, -1]	OP	RxNorm	n/a	Heart failure population initiating treatment with sacubitril/valsartan – First line
Washout window for exposure to heart failure treatments: Sacubitril/valsartan – Later line	Individuals with previous exposure to Sacubitril/valsartan any time prior index date will be excluded	Prior	[-Inf, -1]	OP	RxNorm	n/a	Heart failure population initiating treatment with sacubitril/valsartan – Later line
Washout window for exposure to heart failure treatments: ACEi	Individuals with previous exposure to ACEi any time prior	Prior	[-Inf, -1]	OP	RxNorm	n/a	Heart failure population initiating treatment with ACEi

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:
	index date will be excluded						
Washout window for exposure to heart failure treatments: ARBs	Individuals with previous exposure to ARBs any time prior index date will be excluded	Prior	[-Inf, -1]	OP	RxNorm	n/a	Heart failure population initiating treatment with ARBs

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

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

9.6 Variables

9.6.1 Exposure /s

To fulfil objective 2, different cohorts were defined within the HF population by the first initiation of HF treatments of interest, as specified below. For sacubitril/valsartan two cohorts were created: First line and later line. First line means that the first use of the drug was given after diagnosis with no prior use of ACEi or ARBs treatments, while later line reflects use of sacubitril/valsartan after ACEi and ARBs treatments.

Treatment groups (applied to patients with a history of HF, measured as at least one HF diagnosis):

- HF + New User sacubitril/valsartan - **first line**
    - Never exposed to sacubitril/valsartan or ACEi/ARB
- HF + New User sacubitril/valsartan - **later line**
    - Has been exposed to at least one ACEi/ARB any time up to the day before the index date
- HF + New User ACEi
    - No prior exposure to ACEi
- HF + New User ARB
    - No prior exposure to ARBs

The operational definition of exposure is described by means of Error! Reference source not found.**.** The list of concept sets for each exposure of interest is available in **Appendix I**.

Table 7. Operational definitions of exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Applied to study populations	Incident with respect to…
Sacubitril/valsartan – First line	Individuals diagnosed with heart failure and newly initiating sacubitril/valsartan without previous exposure to sacubitril/valsartan any time prior index date and without prior exposure to ACEi or ARBs	Prior	[-Inf, -1]	OP	Rx Norm	Heart failure treatment initiators	Sacubitril/valsartan initiation
Sacubitril/valsartan – Later line	Individuals diagnosed with heart failure and newly initiating sacubitril/valsartan without previous exposure to sacubitril/valsartan any time prior index date who have used ACEi or ARBs before index date	Prior	[-Inf, -1]	OP	Rx Norm	Heart failure treatment initiators	Sacubitril/valsartan initiation
ACEi	Individuals diagnosed with heart failure and newly initiating ACEi without previous exposure to any ACEi any time prior index date	Prior	[-Inf, -1]	OP	Rx Norm	Heart failure treatment initiators	ACEi initiation
ARBs	Individuals diagnosed with heart failure and newly initiating ARBs without previous exposure to any ARB any time prior index date	Prior	[-Inf, -1]	OP	Rx Norm	Heart failure treatment initiators	ARBs initiation

[1] OP = outpatient. n/a = not applicable

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

9.6.2 Outcome/s

Two definitions of the outcome were used. Myoclonus “narrow” focused strictly on myoclonus-related terms, while the “broad” definition included additional terms reflecting other involuntary movement disorders that are part of myoclonus’ differential diagnoses.

The operational definition of the outcome is presented in Error! Reference source not found.. The list of concept sets for each outcome of interest is available in **Appendix I**.

Table 8. Operational definitions of outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations
Myoclonus narrow	Incident cases during follow-up , using more specific terms, as specified in Appendix I. Individuals with prior history of myoclonus (prevalent definition – Appendix I), will be excluded.	Yes	Binary	[∞, 0)	OP	SNOMED	n/a	All eligible individuals within the database considered for objectives 1 and 2
Myoclonus broad	Incident cases during follow-up, using more sensitive terms, as specified in Appendix I. Individuals with prior history of myoclonus (prevalent definition – Appendix I), will be excluded.	Yes	Binary	[∞, 0)	OP	SNOMED	n/a	All eligible individuals within the database considered for objectives 1 and 2

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

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

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

The covariates for stratification were sex and age groups (18-49; 50-79; >=80).

Table 9. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations
Sex	Female, Male	Categorical	0	n/a	n/a	n/a	All
Age groups	18-49; 50-79; >=80	Categorical	0	n/a	n/a	n/a	All

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

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

9.7 Study size

Given its descriptive nature, no sample size was calculated for this study. From the counts obtained in the feasibility assessment, the expected number of patients exposed to sacubitril/valsartan was estimated to be between 10,000 and 40,000, depending on the data source. For the outcome, myoclonus counts were approximately 6,000. However, these counts were raw and represent the overall number of patients with a record of the medicine or condition of interest without considering inclusion/exclusion criteria. Therefore, final counts were expected to be lower.

9.8 Data transformation

None.

9.9 Statistical methods

9.9.1 Main summary measures

Main study measures are incidence rates and their corresponding 95% confidence intervals (95%CI).

9.9.2 Main statistical methods

The analysis used in this study is described in **(Table 10)**.

Table 10. Description of study type and type of analysis.

Study type	Study classification	Type of analysis
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 occurrence of the outcomes of interest (https://github.com/darwin-eu/IncidencePrevalence).

Population-level incidence calculations

Incidence rates of the outcomes of interest for HF and the general population were calculated as the number of patients newly diagnosed with the outcome of interest divided by the sum of person-years contributed by the population at risk of the outcome during the follow-up period. Follow-up was censored upon the first occurrence of outcome of interest, the end of the observation period, loss to follow-up, or upon death, whichever came first. Incidence rates are provided together with 95% Poisson confidence intervals. For the general population, monthly calendar rates were also calculated. For the incident HF cohort, rates were estimated using consecutive windows (0-30, 31-90, 91-180, 181-365, and the entire study period).

Figure 1 represents an example of incidence rate estimation.

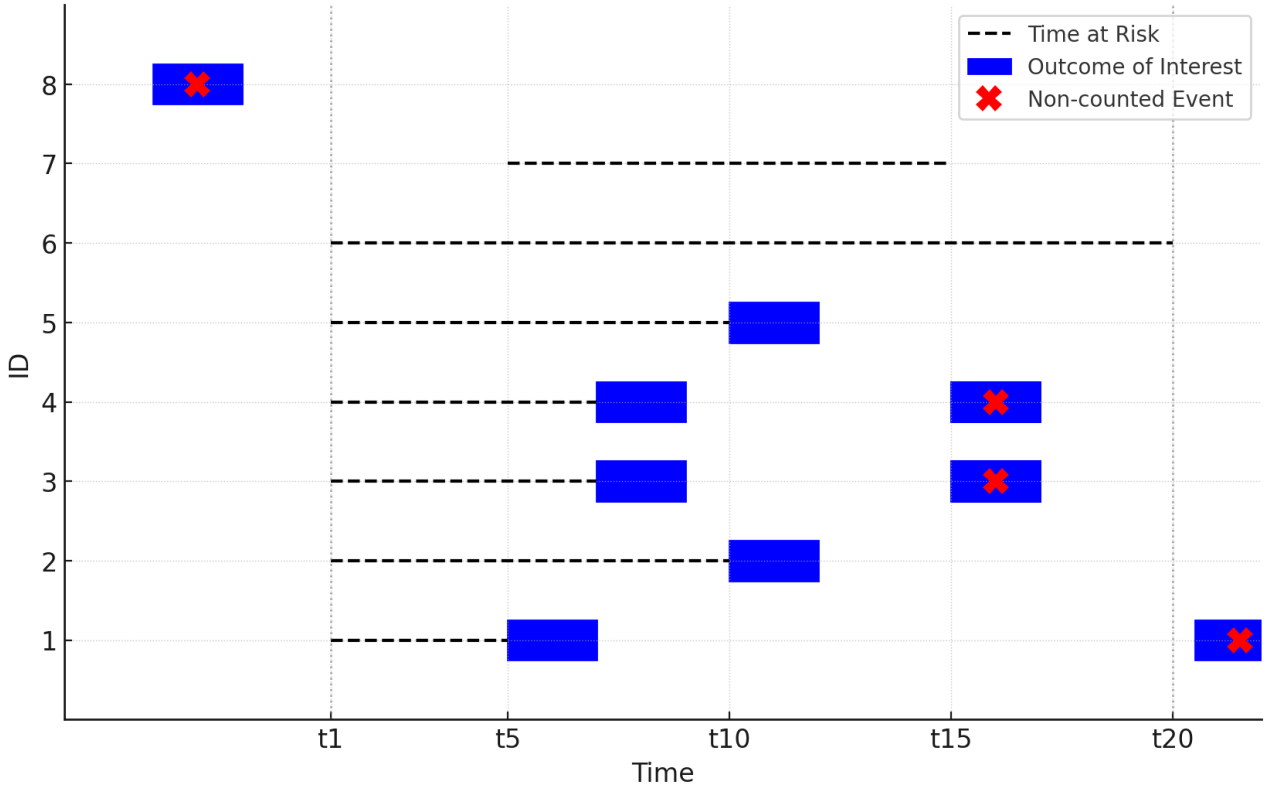


Figure 1. Example of incidence rate estimation.

Patient ID 1-5 contribute time at risk between the study start until they have an incident outcome of interest. Patient ID 6 contributes 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 8 was excluded from the analysis and did not contribute time at risk since a previous diagnosis was observed before the study start date. Patient IDs 1, 3, and 4 have a second event, which is not counted, as it is not an incident, and it also occurred outside the study period for patient 1.

For the calculation of incidence rates in the cohort of patients diagnosed with HF and newly initiating HF treatments of interest, the numerator consisted of the number of patients with the outcome of interest occurring within the different follow-up windows specified and to the end of the study period and the denominator consisted of the sum of person-time from index date until the end of observation period, outcome of interest, loss to follow-up, or death, whichever occurred first. Patients may have contributed to multiple drug exposure cohorts as they may have been exposed to different classes of drugs over time. The follow-up within a treatment cohort was not censored at treatment discontinuation or switch (i.e., intention-to-treat approach).

9.9.3 Missing values

For the disease epidemiology studies, we assume that the absence of a diagnosis record means that the person did not receive the diagnosis. All missing values were assumed to occur at random.

Regarding follow-up, to estimate incidence rates of outcomes of interest, patients 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

In the main analysis, the SIDIAP primary care data linked to hospital data was used. This CDM has the same population as the non-hospital linked CDM, with the benefit of hospital discharge data being captured. Differences in results between SIDIAP and the other data sources used in the study made us hypothesise they were related to the linking to hospital data. Therefore, we repeated the analysis for the three cohorts of interest in SIDIAP's non-hospital-linked data as a sensitivity analysis (specified as SIDIAP2 in the "Shiny app") to check if the results changed.

10. DATA MANAGEMENT

For this study, participants from various EU member states processed personal data from patients, which was collected in national/regional electronic health record databases. Due to the sensitive nature of this 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 DRE. These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

11. QUALITY CONTROL

General database quality control

Several 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 are expected to 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

Concepts and phenotypes of interest were developed and assessed using the following R packages: "CodelistGenerator", "CohortDiagnostics", and "DrugExposureDiagnostics". The study code was based on the R package to estimate incidence rates "IncidencePrevalence". Packages include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing.

12. RESULTS

All results are available in a web application ("Shiny app") at https://data-dev.darwin-eu.org/P3-C1-015-Myoclonus/.

12.1 Participants

Details on attrition and the number of patients contributing to each study cohort by database are described in **Table 11.**

Table 11. Study attrition of patients included in each cohort per database.

	CPRD GOLD UK	IQVIA DA Germany	SIDIAP Spain
Entire database population	17,521,504	43,058,712	8,553,325
General Population: • Population active in the database between 01/01/2015 and 31/12/2023 • aged>=18 years • At least 365 days of prior observation	6,152,493	13,119,798	5,960,331
Incident HF diagnosis	50,388	216,443	175,690
New-user ACEi in HF	9,167	35,724	18,713
New-user ARB in HF	4,522	35,166	12,175
New-user Sacubitril "first line" in HF	683	5,849	1,265
New-user Sacubitril "later line" in HF	5,747	13,674	13,297

HF=Heart failure. Incident HF diagnosis represents patients with a first occurrence of incident HF diagnostic codes during the study period, as specified in Appendix I. New-user refers to patients with first initiation of the treatment of interest applied to patients with a history of heart failure (measured as at least one heart failure diagnosis). Sacubitril "first line" represents de novo use of the drug (the drug was given as first choice), while sacubitril/valsartan "later line" reflects use of sacubitril/valsartan after ACEi and ARBs treatments (prior exposure to ACEi and/or ARBs treatments was required).

12.2 Incidence rate of myoclonus

12.2.1 Overall incidence rates

The incidence rates of myoclonus narrow and broad events were calculated in the general population by calendar month. For the incident HF population and the HF treatment newly initiator cohorts, rates were calculated in consecutive time at risk windows (0-30, 31-90, 91-180, 181-365, >365 days windows). **Appendix II. Tables 1-3 (Appendix II. Table 1, Appendix II. Table 2, Appendix II. Table 3)** describe the counts of outcome events, total time at risk, and incidence rates with 95% CI for each cohort and data source during the study period. It must be noted that for the general population, tables display calendar year rates instead of calendar month to improve readability of results (**Appendix II. Table 1**; monthly rates are available in the Shiny app).

General population

In the general population, the calendar month incidence rate of myoclonus narrow was between 1 and 13 events per 100,000 PY across all three databases (**Figure 2**).

Myoclonus broad range between 60-120 per 100,000 PYs in all three databases for most of the period, with some differences across databases. For CPRD GOLD, a decreasing trend was observed, starting near 130 per 100,000 PY and oscillating closer to 100 per 100,000 PY throughout the study period. In IQVIA DA Germany, rates started at 44 per 100,000 PY in 2015 and increased throughout the period, approaching 100 per 100,000 and reaching up to 200 per 100,000 PY towards the end of the study. In SIDIAP, rates ranged mostly between 75-140 per 100,000 PY for most of the period, increasing to around 150 per 100,000 towards the end of the study period (**Figure 2**).

Figure 2. Incidence rate of myoclonus narrow and broad in the general population by consecutive calendar month for each database, from 2015 to 2023.

Incident heart failure population

Myoclonus narrow rates were generally low across all databases. SIDIAP showed slightly higher rates compared to CPRD GOLD and IQVIA DA Germany. The highest rate was observed for SIDIAP during the 0-30 days window (655 per 1000,000 PY), while for the other databases, rates were negligible (0–36 per 100,000 PY) (**Figure 3**).

Myoclonus broad rates were higher compared to myoclonus narrow in all databases and to those observed in the general population. SIDIAP showed the highest rates, followed by IQVIA DA Germany and CPRD GOLD. Rates were highest across databases at the start of the period and decreased over time. For the 0-30 days window, rates ranged from 485 per 100,000 in CPRD GOLD to 2818 per 100,000 PY in SIDIAP. Over time, rates stabilised at 212-645 per 100,000 PY in all three databases (**Figure 3**).

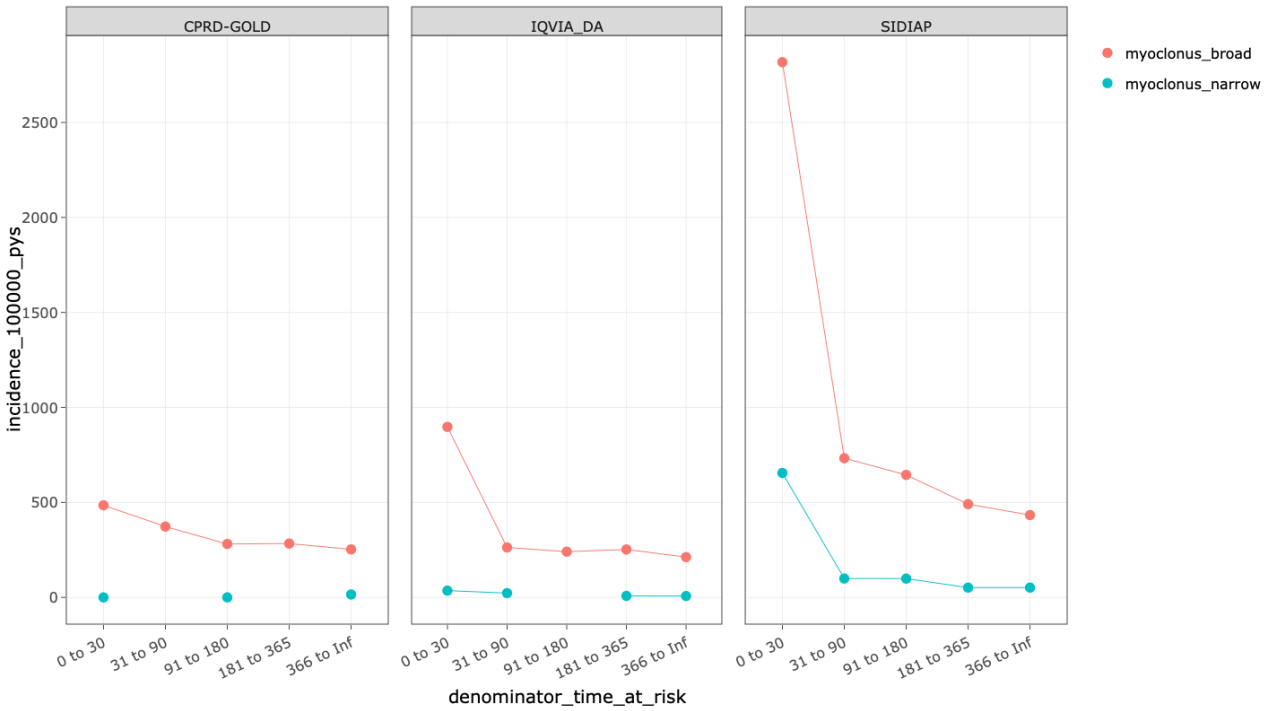


Figure 3. Incidence rate of myoclonus narrow and broad in the incident heart failure population using consecutive time-at-risk windows following heart failure diagnosis, by database during 2015-2023.

Heart failure population following first initiation treatments of interest

Myoclonus narrow rates could not be provided for some time windows and treatments due to low person-time and event counts (**Figure 4**). Even when the sample size was sufficient to identify more than five outcome events, the incidence rates were still close to zero for almost every time window and treatment of interest in all three databases.

Myoclonus broad rates were highest in the earliest time windows and showed variability by treatment and database (**Figure 4**). However, rates could not be provided for some time windows and treatments due to low counts (n<5). This issue was particularly noticeable in CPRD GOLD for practically all treatments and windows (except ACEi). Similarly, rates for sacubitril/valsartan first-line initiators were consistently low in all three databases (estimated between 0-79 per 100,000 PY when sufficient counts were reached). In the 0–30 day window, rates for ACEi, ARBs, and sacubitril/valsartan later line ranged from 579 to 893 and 667 to 713 per 100,000 person-years in SIDIAP and IQVIA DA Germany, respectively. ARBs consistently showed the highest rates, peaking at 893 per 100,000 PY in SIDIAP during the 0–30 day window (range 503-893 per 100,000 PY). Rates for ACEi and sacubitril-valsartan later line ranged between 579-667 and 729 per 100,000 PY, respectively, during the 0–30 day window. During the 31–90 day window, event rates ranged from 247–849 per 100,000 person-years for ACEi, ARBs, and sacubitril/valsartan later line, with consistently higher rates observed in the SIDIAP database and lower rates in IQVIA DA Germany and CPRD GOLD. Over longer time windows (e.g., 181–365 days and 366 days to infinity), rates declined slightly for most treatments, ranging between 182–528 per 100,000 person-years.

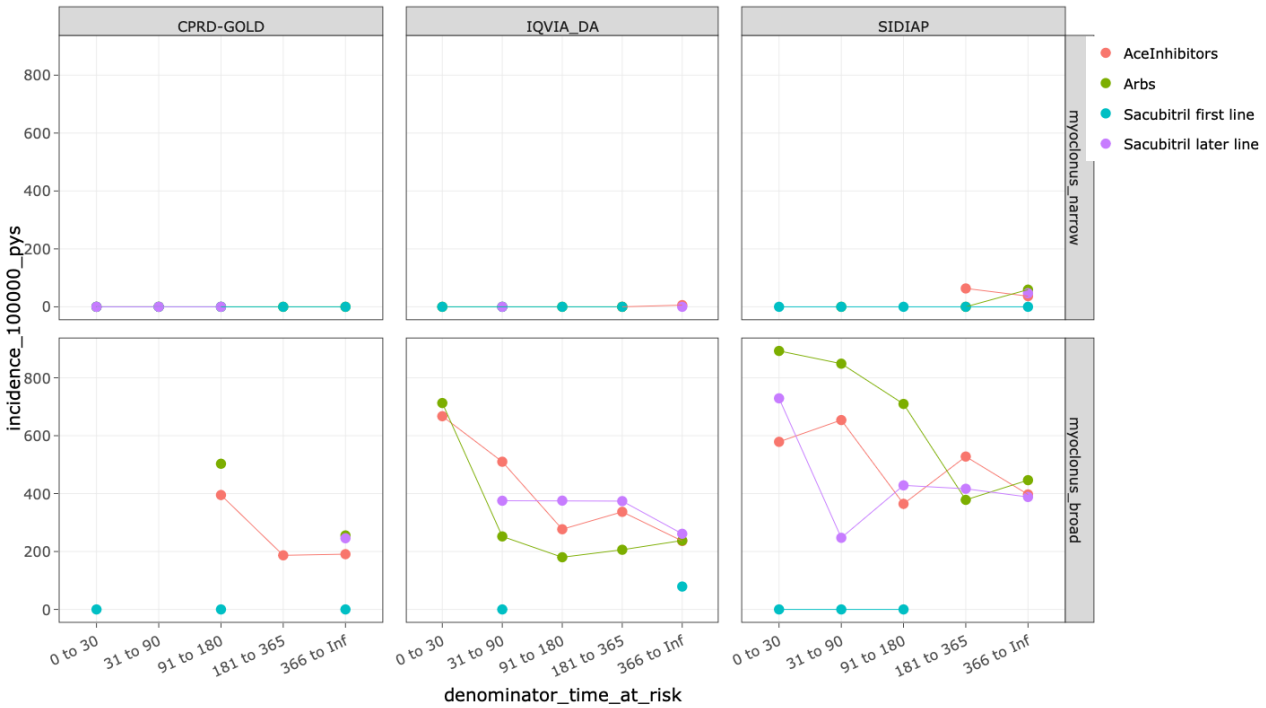
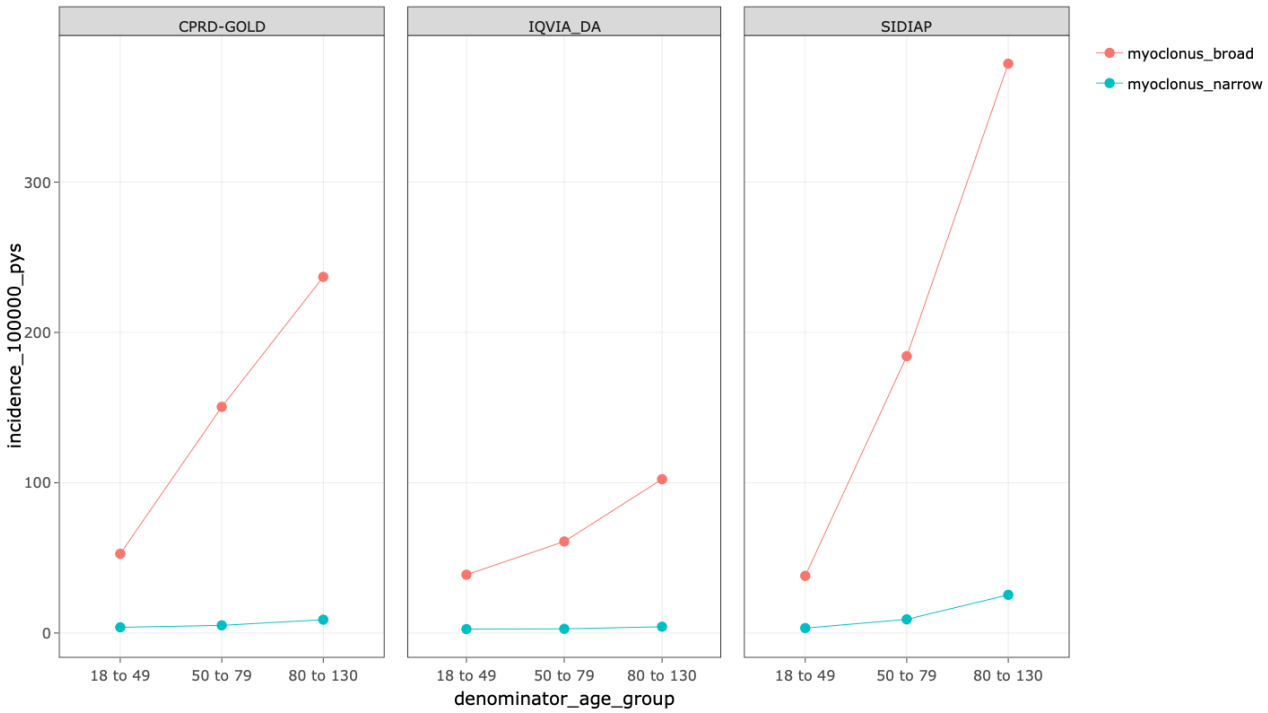


Figure 4. Incidence rate of myoclonus narrow and broad in the HF population newly initiating treatments using consecutive time-at-risk windows following treatment start, by database during 2015-2023.

12.2.2 Incidence rates by age

General population

In the general population, no differences by age were noted for myoclonus narrow across all databases. For myoclonus broad, rates increased with age in all databases. the highest rates were observed in the >=80 age group, reaching between 102-379, in IQVIA DA Germany and SIDIAP, respectively) (



Appendix II. Figure 1).

Incident heart failure population

Myoclonus narrow rates by age (when estimable) showed practically no differences in CRPD GOLD and IQVIA DA Germany. In SIDIAP, for the 50-79 and >=80 age groups, rates were highest within the 0-30 days window, with practically no differences thereafter (**Appendix II. Figure 2**).

For myoclonus broad, rates increased with age, although differences between the 50-79 and >=80 age groups were modest across all databases. The highest rates were observed for the >=80 age group during the 0-30 days window in all three databases (**Appendix II. Figure 2).**

Heart failure population following first initiation treatments of interest

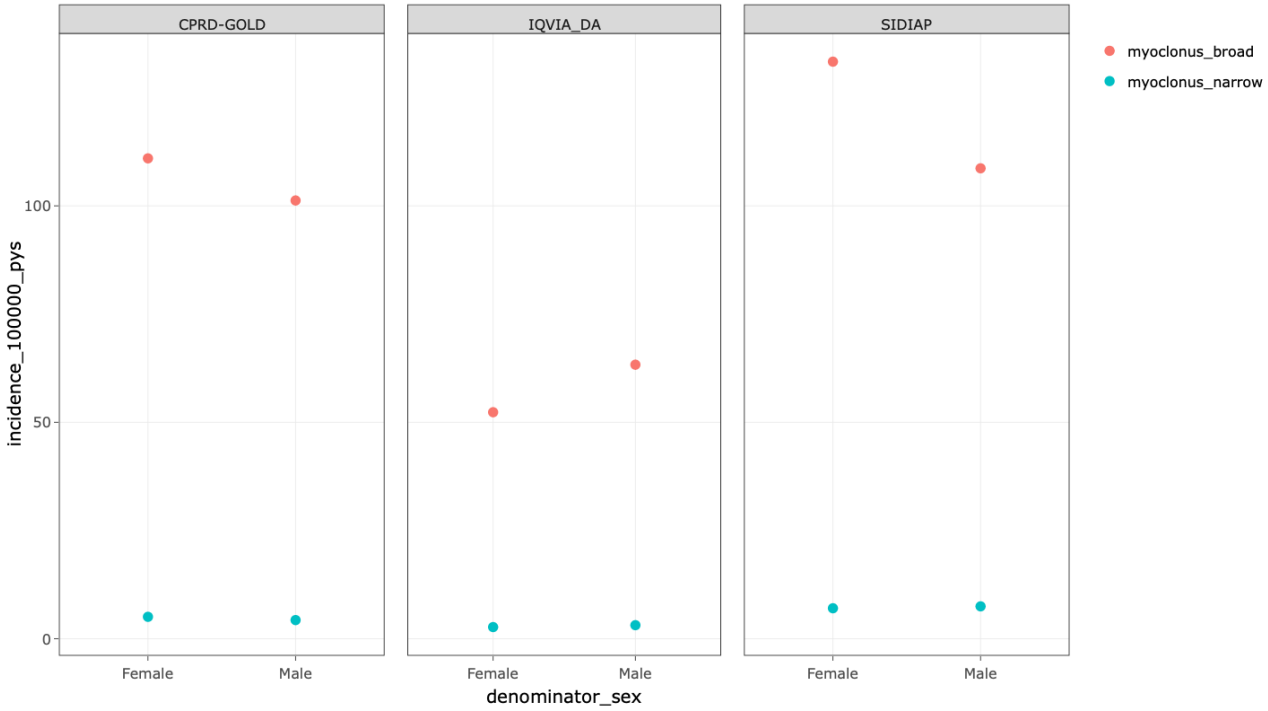
Myoclonus narrow rates by age were zero or not estimable for almost all time windows, databases, treatments, and age groups, except for ARBs in SIDIAP, where they were highest in the >=80 age group (**Appendix II. Figure 3a**).

Myoclonus broad rates increased with age (although were mostly zero or not estimable for almost all-time windows and treatments in CPRD GOLD and for sacubitril/valsartan first line in all databases). Differences were mostly between the 18–49 and the older age groups (50–79 and ≥80), although rates in the 18–49 group were predominantly zero or non-estimable. Between 50-79 and >=80 age group differences were modest, except for some time windows in SIDIAP among ARBs and sacubitril/valsartan later line treatments, where they were wider (**Appendix II. Figure 3b).**

12.2.3 Incidence rates by sex

General population

No differences by sex were noted for myoclonus narrow or broad in any of the three databases (



Appendix II. Figure 4).

Incident heart failure population

For myoclonus narrow, in CPRD and IQVIA DA Germany, when estimable, rates were mostly similar by sex. In SIDIAP, small differences between females and males were noted in the 0-30 window (569 vs 745) and remaining mostly similar thereafter (**Appendix II. Figure 5Error! Reference source not found.**).

For myoclonus broad, differences by sex were small. For CPRD and IQVIA DA Germany, rates were mostly similar by sex throughout all windows, while in SIDIAP, widest in the 0-30 and 31-90 days, in which rates in females surpassed males again in the 0-30 window (**Appendix II. Figure 5).**

Heart failure population following first initiation treatments of interest

For myoclonus narrow, rates stratified by sex in the HF patients newly initiating treatments showed no differences, except in SIDIAP for ARBs, sacubitril/valsartan later line during the 366 to infinity window, with rates higher in females compared to males (**Appendix II. Figure 6a**).

For myoclonus broad, rates were generally higher in females than males for most time windows, treatments, and databases, although differences were modest. For ACEi, the highest rates were noted in females during the 0-30 window (465 in males compared to 870 per 100,000 PY in females) (IQVIA DA Germany). ARBs were highest in males in IQVIA DA Germany (635 in females compared to 802 per 100,000 PY in males during the 0-30 window). However, in SIDIAP, the highest rates for ARBs were observed in females during the 31-90 window, at 1149 per 100,000 PY, while in males the highest rates were observed during the 0-30 window, at 1004 per 100,000 PY. For sacubitril/valsartan later line, rates were higher in females in CPRD GOLD and IQVIA DA Germany, with the highest rates ranging between 407-573 per 100,000 PY, compared to the highest rates in males, which ranged between 181-481 for males, while in SIDIAP, rates were higher in males compared to females, at 766 and 708 per 100,000 PY, respectively (**Appendix II. Figure 6b**).

12.3 Sensitivity analysis

In the main analysis, the SIDIAP primary care data linked to hospital data was used. This CDM has the same population as the non-hospital linked CDM, with the benefit of hospital discharge data being captured. Differences in results between SIDIAP and the other data sources used in the study made us hypothesise they were related to the linking to hospital data. Therefore, we repeated the analysis for the three cohorts of interest in SIDIAP's non-hospital-linked data as a sensitivity analysis (specified as SIDIAP2 in the "Shiny app") to check if the results changed.

This section describes the overall results for the three cohorts of interest (general population, incident HF population, and the HF population following first initiation treatments of interest) (Error! Reference source not found., **SIDIAP=hospital-linked CDM. SIDIAP2**=non-hospital-linked CDM.

Appendix II. Figure 8, SIDIAP=hospital-linked CDM. SIDIAP2=non-hospital-linked CDM.

Appendix II. Figure 9).

In the general population, myoclonus narrow ranged between 1 and7 per 100,000 PY (compared to 4-13 per 100,000 PY in the hospital-linked CDM). For myoclonus broad, rates ranged between 25 and 172 per 100,000 PY, although generally oscillated around 100 per 100,000 PY, compared to the hospital-linked CDM (ranging between 34-184 per 100,000 PY), where it oscillated near 125 Error! Reference source not found.).

The highest myoclonus narrow incidence rate was observed within the 0-30 days window in the incident HF population, at 52 per 100,000 PY (compared to 653 per 100,000 PY in the hospital-linked CDM). For myoclonus broad, during the 0-30 days time window, rates were calculated at 655 per 100,000 PY, compared to 2818 per 100,000 in the hospital-linked CDM. From there on, rates decreased, reaching 345 per 100,000 PY, and differences were less marked with the hospital-linked CDM, where the lowest rates were estimated at 433 per 100,000 PY (**SIDIAP=hospital-linked CDM. SIDIAP2**=non-hospital-linked CDM.

Appendix II. Figure 8).

For the first initiators of treatments of interest in the HF population, myoclonus narrow was estimated at 0 per 100,000 PY for all treatments, while for the hospital-linked CDM, when estimable, rates were <100 per 100,000 PY for all treatments. Myoclonus broad rates were higher in the earlier time windows: at 485 per 100,000 for ACEi (31-90 time window, compared to 654 per 100,000 PY in the hospital-linked CDM), 774 per 100,000 PY for ARBs (0-30 window, compared to 893 per 100,000 PY in the hospital-linked CDM), and 707 per 100,000 PY for sacubitril/valsartan later line (0-30 window, compared to 729 per 100,000 PY in the hospital-linked CDM), and decreased during the later time windows (**SIDIAP=hospital-linked CDM. SIDIAP2**=non-hospital-linked CDM.

Appendix II. Figure 9).

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions were not collected or analysed in this study. The nature of this non-interventional study, 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).

14. DISCUSSION

14.1 Key results

Incidence rate of Myoclonus

Overall myoclonus rates

For myoclonus narrow, incidence rates were consistently low or zero across all three populations and databases. In the general population, rates were between 1-13 per 100,000 person-years (PY) across all time windows. In the incident HF population, rates were generally negligible or not estimable due to low counts, with slightly higher rates (655 per 1000,000 PY) observed in SIDIAP for the 0–30 day window. Among HF patients newly initiating treatments, rates remained close to zero for almost every time window and treatment of interest in all three databases.

For myoclonus broad, rates were consistently higher than for myoclonus narrow across all three populations and databases. In the general population, rates ranged between 60 and 120 per 100,000 PY for most of the study period, increasing to 100 and 200 per 100,000 PY in IQVIA DA Germany and SIDIAP, respectively, towards the end. In the incident HF population, rates were higher than myoclonus narrow and those observed in the general population in all databases. Rates peaked in the earliest time windows, close to first HF diagnosis (ranging from 485-2818 per 100,000 PY during the 0–30 day window) and stabilised at lower values (212–645 per 100,000 PY) over later time windows.

Among HF patients newly initiating treatments, ARBs consistently showed the highest rates, peaking at 893 per 100,000 PY in SIDIAP during the 0–30 day window (range 503-893 per 100,00 PY). ACEi and sacubitril-valsartan later line rates ranged between 579-667 and 729 per 100,000 PY, respectively, during the 0–30 day window. All treatments had higher rates of myoclonus in the earlier time windows after initiation than later ones. Rates for sacubitril/valsartan first-line initiators were consistently low in all three databases (estimated between 0-79 per 100,000 PY when sufficient counts were reached).

Differences in rates by age

For myoclonus narrow, rates by age were generally zero or not estimable, and while they increased by age, differences were modest.

For myoclonus broad, rates increased with age. In the general population, the highest rates were observed in the >=80 age group, reaching 379 per 100,000 PY in SIDIAP. In the incident HF population, also the >=80 age group showed the highest rates during the 0–30 day window, ranging from 750 (CPRD GOLD) to 3164 (SIDIAP) per 100,000 PY, although differences between the 50-79 and >=80 age groups were modest across all databases. Among HF patients newly initiating treatments, rates generally increased with age for all treatments, the highest difference being between <50 and >=50 years of age.

Differences in rates by sex

For myoclonus narrow, rates stratified by sex, when estimable, were mostly similar by sex in all three populations.

For myoclonus broad, no sex differences were noted in the general population. In the incident HF population, rates showed minor variability by sex, with slightly higher rates in females in CPRD GOLD and SIDIAP. Among HF patients newly initiating treatments, rates were generally higher in females than males for most time windows, treatments, and databases, however the difference was rather small.

Sensitivity analysis

The initial study was run on SIDIAP's hospital-linked CDM. Results between SIDIAP and the other data sources used in the study revealed differences which we hypothesised were related to the linking to hospital data. In turn, we repeated the analysis for the three cohorts of interest in SIDIAP's non-hospital-linked CDM data.

In the general population, differences between the non-linked and hospital-linked CDM were small. The most remarkable difference was a less sustained increase in myoclonus broad towards the end of the study period.

The differences in rates in the incident HF population between the non-linked and hospital-linked CDM were especially pronounced for myoclonus broad during the 0-30 days time window, in which rates were calculated at 655 per 100,000 PY, compared to 2818 per 100,000 in the hospital-linked CDM. For all other periods, results were lower in the non-linked compared to the hospital-linked CDM, although differences were less marked.

For the first initiators of treatments of interest in the HF population, some differences in rates between the non-linked and hospital-linked CDM were noted for myoclonus broad, in which rates were lower. However, the number of time windows and treatments for which counts were insufficient to provide rates increased.

14.2 Limitations of the research methods

Data sources: This study used three different data sources from three countries. Results only reflect outcomes occurring in the healthcare settings covered by each database. Some differences across databases/countries can be related to how databases handle observation periods, which varies across different databases. For example, in IQVIA DA Germany, the observation periods are defined based on the last recorded healthcare interaction, which may have led to an overestimation of incidence rates toward the end of the study period since patients with no healthcare interactions will no longer be in the denominator, potentially leading to higher rates.

For IQVIA DA Germany, patients visiting multiple providers are not cross-identified (due to data protection reasons). Therefore, these consultations are recorded separately in the system and might lead to underreported events if specialists treating HF (cardiologists) are at clinics different from those diagnosing and treating myoclonus (neurologists).

The results estimated from this study only reflect the populations from the included data sources. Electronic health records have certain inherent limitations because they were collected for clinical use rather than primarily for research use.

The observed differences in myoclonus rates across databases (CPRD GOLD, IQVIA DA Germany, and SIDIAP) were marked and can be attributed to several factors inherent to the characteristics of each database and the healthcare systems they represent. Variations in data capture methods, such as the primary care focus of CPRD GOLD, (6) versus the integration of primary and secondary care data in SIDIAP, (15) may influence the recording and reporting of HF and myoclonus events. This was especially evident when we repeated the analysis in SIDIAP using the non-hospital-linked CDM and observed lower incidence rates, suggesting that hospital linkage plays a significant role in case identification.

While OMOP provides mappings to established vocabularies like SNOMED, inaccuracies or gaps in these mappings can occur, impacting the accuracy and completeness of data in different databases. There is also a possibility of outcome misclassification due to potential coding errors. Still, only databases that fulfil extensive data quality checks regarding mapping of source data to OMOP are eligible for participation in DARWIN EU®.

Heart failure phenotype: The HF phenotype did not distinguish between disease severity or reduced/preserved ejection fraction phenotype. Additionally, the recording of the diagnosis may not reflect the time of onset of the disease because HF often has a gradual onset with nonspecific symptoms, such as fatigue or mild dyspnea, which may mimic other conditions and lead to a diagnosis once the disease is advanced and chronic.

For the incident HF phenotype, the one-year observation period prior to index date may have helped accurately identify new diagnoses. However, the codes used to identify incident HF excluded incident diagnosis at chronic stages (even though the diagnosis may be truly incident). This approach may have skewed the population to more recently developed cases, potentially excluding incident cases identified at later stages.

Sacubitril/valsartan prescribing: The use of sacubitril/valsartan and all other treatments assessed were derived from prescription data, which may not reflect treatment compliance. An intention-to-treat approach was followed when estimating incidence rates for the different treatment classes. This may have introduced exposure misclassification since it assumed the index treatment continued throughout the follow-up. However, given the chronic nature of the disease, it is likely that most patients remain on each treatment for long periods. Particularly within the shorter follow-up windows of primary interest, where myoclonus onset was anticipated (since literature supports a short latency), misclassification may be somewhat mitigated. It must also be mentioned that the analysis did not account for the time between HF diagnosis and treatment start or for differences in HF severity, which could influence the occurrence of the outcome. In fact, no baseline characteristics between were measured of balanced between treatment cohorts. As a result, observed differences in the incidence across cohorts should not be interpreted as causal effects of the treatments.

Outcomes: Recording of the outcome event may vary across data sources. While relatively few false positives are expected, false negatives may be more likely, especially for data sources without patient-level linkage to secondary care data (such as IQVIA DA Germany or CPRD GOLD).

Small cell counts may have affected the analysis for some subgroup strata since counts are not disclosed for governance reasons when the number of events is >=1 and <5. This may have particularly impacted CPRD GOLD rates.

Study period: Part of the study period coincided with the COVID-19 pandemic (2020-2022), which likely affected rates for outcomes due to changes in healthcare use.

14.3 Interpretation

Myoclonus (narrow and broad) rates were estimated in the general, incident HF, and the HF population initiating treatments.

Myoclonus narrow (which focused on drug-induced myoclonus and idiopathic myoclonus) rates were generally low for all cohorts analysed, ranging from 1-13 per 100,000 PY in the general population and first initiators of treatments of interest in the HF population, while ranging from 0-655 per 100,000 PY in the incident HF population.

Literature on background rates of myoclonus is limited. One study reported an average annual incidence rate of pathologic and persistent myoclonus of approximately 1 per 100,000 PY, with rates increasing with age and being consistently higher in men.(19) However, this study focused solely on pathologic and persistent types, excluding physiologic or transient myoclonus. In contrast, the current study focused on drug-induced myoclonus and idiopathic myoclonus and mostly excluded progressive myoclonic syndromes. Nevertheless, the low rates of myoclonus observed in both studies likely reflect that myoclonus is challenging to diagnose due to its heterogeneous causes, overlapping symptoms with other movement disorders, and the lack of specific biomarkers. Drug-induced cases further complicate diagnosis, requiring detailed medication history and clinical awareness.(20, 21) Another potential cause could be the underestimation of myoclonus events. This was especially evident when we repeated the analysis in SIDIAP using the non-hospital-linked CDM and observed lower incidence rates, suggesting that hospital linkage plays a significant role in case identification/reporting.

In contrast, the broader category likely captured cases where diagnostic uncertainty or overlap with other conditions led to a less specific classification. Consequently, myoclonus broad rates were generally higher, with background rates in the general population consistently estimated at 60-120 per 100,000 PY. The highest rates for myoclonus broad were observed in the incident HF population within the 0–30 day window, ranging between 485-2818 per 100,000 PY across databases. In contrast, among first initiators of treatments of interest in the HF population, (unadjusted) rates were lower than the incident HF population. The increased risk of myoclonus following cardiac arrest and subsequent anoxic brain injury may explain the higher rates observed in the incident HF population.(22, 23) Additionally, drugs commonly used in intensive care settings, including cardiovascular agents (e.g., amiodarone, furosemide) and anaesthetics (e.g., propofol, enflurane), have been associated with drug-induced myoclonus.(24, 25)

A wide variety of drugs can cause myoclonus, but the clinical and pathophysiological heterogeneity of this phenomenon may mislead clinicians and result in underdiagnosis of drugs as a cause. The most commonly involved drug classes include opioids, antidepressants, antipsychotics, and antibiotics.(24-26) Correct identification is key for treatment since drug-induced myoclonus is often reversible. Importantly, the presentation of myoclonus can vary even within a drug class or for a single drug, meaning clinical characteristics alone should not rule out a drug-related cause.(26) In our analysis of newly initiators of various treatments in the HF population, we found no evidence of an increased myoclonus (unadjusted) rate in those treated with sacubitril/valsartan (first or later lines) compared to other treatments assessed. Existing case reports of sacubitril/valsartan-associated myoclonus describe events in males aged >=65 with low ejection fraction, and report a temporal relationship between drug intake and symptom onset (peak plasma concentration at 2 hours for sacubitril's active metabolite) and symptom resolution following drug withdrawal. (27) However, drug-drug interactions were considered for some cases.

While the absence of increased rates for sacubitril/valsartan-treated in our study may reflect the rarity of such events, it could also be related to differences in clinical populations or underreporting in databases. Nonetheless, results should be interpreted with caution, as low event counts in certain treatment groups and time windows may have limited the ability to estimate rates precisely or detect potential differences. Specifically, the infrequent use of sacubitril/valsartan as first line in our study, may have limited the ability to estimate rates in this treatment group accurately.

Variations in data capture methods, such as the primary care focus versus the integration of primary and secondary care data, and differences in healthcare delivery systems, including HF care or prescribing practices, can further influence the diagnosis and management of HF and myoclonus events. These factors collectively underscore the importance of interpreting database-specific results within the context of their healthcare and data recording environments.

14.4 Generalisability

This study included data from three data sources from four different European countries (United Kingdom, Germany, and Spain) and included primary and secondary healthcare data; therefore, they represent different aspects of the healthcare pathway, and each of the data sources has broad coverage, particularly the large primary care data sources.

While these results may be considered largely representative of patients newly diagnosed with HF, and HF patients following first initiation of treatments of interest (i.e. ACEi, ARBs, sacubitril/valsartan first and later lines), results should not be completely generalised to the entire Europe or regions outside of Europe, as differences in population characteristics and guidelines on diagnosis and treatment may vary by country.

14.5 Other information

There is no further information to report.

15. CONCLUSION

In this disease epidemiology study of myoclonus in patients with incident HF, HF newly initiating treatments of interest (ACEi, ARBs, and sacubitril/valsartan first and later lines), and the general population in UK, Germany, and Spain, we found that patients with incident HF consistently exhibited higher incidence rates of myoclonus broad and narrow outcomes, when compared to both the HF newly-initiating treatments of interest and general populations. For myoclonus broad, the highest rates for the incident HF and treatment initiator cohorts occurred within the 0-30 days following the start of follow-up. Among new initiators of different treatments of interest in the HF population, when estimable, rates for myoclonus broad were highest among ARBs initiators, and results do not support higher rates among sacubitril/valsartan (later line) treatment. While no significant increase in myoclonus rates was observed across treatment groups, findings should be interpreted with caution due to low event counts, especially for sacubitril/valsartan first-line initiators, where numbers were generally too low to provide precise estimates.

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17. ANNEXES

Appendix I: Code lists for drugs and conditions of interest

Appendix II: Other Additional Information

Appendix I: Code lists for drugs and conditions of interest

Heart Failure (Incident):

Concept ID	Concept name
44782718	Acute combined systolic and diastolic heart failure
4023479	Acute congestive heart failure
312927	Acute cor pulmonale
608954	Acute cor pulmonale due to septic pulmonary embolism
40481042	Acute diastolic heart failure
442310	Acute heart failure
764877	Acute heart failure co-occurrent with normal ejection fraction
4108245	Acute left ventricular failure
4327205	Acute left-sided congestive heart failure
4267800	Acute left-sided heart failure
36716182	Acute kidney injury due to circulatory failure
4215446	Acute right-sided congestive heart failure
4233424	Acute right-sided heart failure
40480603	Acute systolic heart failure
4193236	Ayerza's syndrome
439698	Benign hypertensive heart disease with congestive cardiac failure
4030258	Bernheim's syndrome
4242669	Biventricular congestive heart failure
4215802	Cardiac asthma
4205558	Cardiac failure after obstetrical surgery AND/OR other procedure including delivery
4177493	Cardiac insufficiency due to prosthesis
4233224	Cardiac insufficiency during AND/OR resulting from a procedure
4264636	Cardiac insufficiency following cardiac surgery
40482857	Cardiorenal syndrome
4259490	Cardiorespiratory failure
4108244	Compensated cardiac failure
319835	Congestive heart failure
44784345	Congestive heart failure as early postoperative complication
762002	Congestive heart failure as post-operative complication of cardiac surgery
762003	Congestive heart failure as post-operative complication of non-cardiac surgery
44782428	Congestive heart failure due to cardiomyopathy

4139864	Congestive heart failure due to left ventricular systolic dysfunction
4142561	Congestive heart failure due to valvular disease
36713488	Congestive heart failure stage B
36712928	Congestive heart failure stage B due to ischemic cardiomyopathy
43021826	Congestive heart failure stage C
36712927	Congestive heart failure stage C due to ischemic cardiomyopathy
43021825	Congestive heart failure stage D
44782713	Congestive heart failure with right heart failure
4307356	Cor pulmonale
4111554	Decompensated cardiac failure
4161569	Depression of left ventricular systolic function
443587	Diastolic heart failure
43021842	Diastolic heart failure stage C
43021841	Diastolic heart failure stage D
4037495	Dilated peripartum cardiomyopathy
316139	Heart failure
4124705	Heart failure as a complication of care
4215689	Heart failure confirmed
619797	Heart failure due to thyrotoxicosis
37311948	Heart failure with mid-range ejection fraction
40486933	Heart failure with normal ejection fraction
45766164	Heart failure with reduced ejection fraction
45766167	Heart failure with reduced ejection fraction due to cardiomyopathy
45766165	Heart failure with reduced ejection fraction due to coronary artery disease
45773075	Heart failure with reduced ejection fraction due to heart valve disease
45766166	Heart failure with reduced ejection fraction due to myocarditis
4004279	High output heart failure
439696	Hypertensive heart and renal disease with (congestive) heart failure
439694	Hypertensive heart and renal disease with both (congestive) heart failure and renal
314378	Hypertensive heart disease with congestive heart failure
444101	Hypertensive heart failure
4173819	Impaired left ventricular function
439846	Left heart failure
1126246	Left ventricular ejection fraction (lvef) less than or equal to 40% or documentation

4185565	Low cardiac output syndrome
4103448	Low output heart failure
3656094	Low output heart failure due to and following Fontan operation
316994	Malignant hypertensive heart disease with congestive heart failure
312383	Postpartum cardiomyopathy
4141124	Postvalvulotomy syndrome
764873	Reduced ejection fraction co-occurrent and due to acute heart failure
4199500	Refractory heart failure
4195785	Right heart failure secondary to left heart failure
4273632	Right ventricular failure
35615055	Saddle embolus of pulmonary artery with acute cor pulmonale
4079695	Sepsis-associated left ventricular failure
4079296	Sepsis-associated right ventricular failure
42598803	Spontaneous cardiomyopathy
44784442	Symptomatic congestive heart failure
443580	Systolic heart failure
43020421	Systolic heart failure stage C
36712929	Systolic heart failure stage C due to ischemic cardiomyopathy
43021840	Systolic heart failure stage D

Heart Failure (Prevalent):

Concept ID	Concept name
40481042	Acute diastolic heart failure
36684850	Cardiac volume overload
444031	Chronic heart failure
316139	Heart failure
4215689	Heart failure confirmed
4173819	Impaired left ventricular function

Exposures of Interest:

Sacubitril/valsartan:

Concept ID	Concept name
46275719	Sacubitril*

*Includes all descendants

ACEi:

Concept ID	Concept name
19102107	zofenopril
1342439	trandolapril
19040051	spirapril
1334456	ramipril
1331235	quinapril
1373225	perindopril
1310756	moexipril
1308216	lisinopril
19122327	imidapril
1363749	fosinopril
1342001	enalaprilat
1341927	enalapril
36878917	delapril hydrochloride
19050216	cilazapril
1340128	captopril
1335471	benazepril

*Includes all descendants

ARBs:

Concept ID	Concept name
40235485	azilsartan
1351557	candesartan
1346686	eprosartan
43009001	fimasartan potassium
1347384	irbesartan
1367500	losartan
40226742	olmesartan
1317640	telmisartan
1308842	valsartan*

*Excludes all sacubitril/valsartan containing products

Outcomes of Interest:

Incident Myoclonus (narrow):

Concept ID	Concept name

44784571	Brainstem myoclonus
44782838	Cerebral cortex myoclonus
4044065	Drug-induced myoclonus
37110510	Focal myoclonus
40481498	Hypnic jerk
4099899	Intention myoclonus
4133719	Myoclonic disorder
4207587	Myoclonic dystonia
441553	Myoclonus
43530739	Nocturnal myoclonus
4140601	Non-epileptic myoclonus
36716792	Segmental myoclonus
44782839	Spinal cord myoclonus
4047761	Symptomatic myoclonus

Incident Myoclonus (broad):

Concept ID	Concept name
4266977	Adiadochokinesia
37311988	Dissociative neurological symptom disorder co-occurrent with myoclonus
373185	Drug-induced dyskinesia
4046815	Dysdiadochokinesis
4319906	Dyskinesia
4141836	Dystonic tremor
37110510	Focal myoclonus
42596632	Head tremor
40481498	Hypnic jerk
4099899	Intention myoclonus
4148954	Intention tremor
4010355	Involuntary muscle contraction
4044064	Isolated vocal tremor
4151937	Medication-induced postural tremor
4219643	Muscle fasciculation
42572619	Muscle spasm
42596391	Muscle tremor
4133719	Myoclonic disorder

4207587	Myoclonic dystonia
4104714	Myoclonic encephalopathy
441553	Myoclonus
4334342	Orthostatic tremor
4138028	Physiological tremor
4096245	Resting tremor
4008895	Senile tremor
4329728	Spasticity
4209594	Static tremor
443782	Tremor
3178103	Tremor of hands and face
3663206	Tremor of tongue
4209594	Static tremor
4138992	Asterixis
3654239	Bilateral outstretched hands tremor
4302311	Coarse tremor
4222119	Continuous tremor
37311986	Dissociative neurological symptom disorder co-occurrent with tremor
4098315	Dissociative tremor
4141836	Dystonic tremor
37110508	Enhanced physiological tremor
3183493	Excessive physiologic tremor
4177049	Fine tremor
4278463	Intermittent tremor
4044063	Isolated facial tremor
4043397	Isolated head tremor
4100050	Massive tremor
4222566	Passive tremor
37396185	Primary orthostatic tremor
40483671	Psychogenic tremor
4145813	Trembles

Prevalent myoclonus:

Concept ID	Concept name
4266977	Adiadochokinesia

40483375	Chronic tremor
37311988	Dissociative neurological symptom disorder co-occurrent with myoclonus
373185	Drug-induced dyskinesia
4046815	Dysdiadochokinesis
4319906	Dyskinesia
4141836	Dystonic tremor
1340316	Exacerbation of dyskinesia
1340485	Exacerbation of tremor
37110510	Focal myoclonus
42596632	Head tremor
40481498	Hypnic jerk
4099899	Intention myoclonus
4148954	Intention tremor
4010355	Involuntary muscle contraction
4044064	Isolated vocal tremor
4151937	Medication-induced postural tremor
4219643	Muscle fasciculation
42572619	Muscle spasm
42596391	Muscle tremor
4133719	Myoclonic disorder
4207587	Myoclonic dystonia
4104714	Myoclonic encephalopathy
441553	Myoclonus
4334342	Orthostatic tremor
4163369	Persistent tremor
4138028	Physiological tremor
4232782	Post-hemiplegic tremor
4147501	Progressive myoclonic epilepsy
4096245	Resting tremor
4008895	Senile tremor
4329728	Spasticity
4209594	Static tremor
443782	Tremor
37110509	Tremor due to central nervous system disease

36716787	Tremor due to metabolic disorder
3178103	Tremor of hands and face
3663206	Tremor of tongue
4209594	Static tremor
4138992	Asterixis
3654239	Bilateral outstretched hands tremor
4302311	Coarse tremor
4222119	Continuous tremor
37311986	Dissociative neurological symptom disorder co-occurrent with tremor
4098315	Dissociative tremor
4141836	Dystonic tremor
37110508	Enhanced physiological tremor
3183493	Excessive physiologic tremor
4177049	Fine tremor
4278463	Intermittent tremor
4044063	Isolated facial tremor
4043397	Isolated head tremor
4100050	Massive tremor
4222566	Passive tremor
37396185	Primary orthostatic tremor
40483671	Psychogenic tremor
4145813	Trembles

Appendix II: Other Additional Information

Appendix II. Table 1. Incidence Rates of myoclonus narrow and myoclonus broad in the general population, by database and calendar year, from 2015 to 2023.

Database	Outcome	Year	Number of persons	Number of Events	Person years	Incidence per 100,000 PY	95%CI
CPRD GOLD	Myoclonus narrow	2015	4616164	228	4109670	5.55	(4.85, 6.32)
IQVIA DA Germany	Myoclonus narrow	2015	6934451	127	6254983	2.03	(1.69, 2.42)
SIDIAP	Myoclonus narrow	2015	4838903	271	4717132	5.74	(5.08, 6.47)
CPRD GOLD	Myoclonus narrow	2016	3959307	200	3574604	5.6	(4.85, 6.43)
IQVIA DA Germany	Myoclonus narrow	2016	7256017	150	6586419	2.28	(1.93, 2.67)

Database	Outcome	Year	Number of persons	Number of Events	Person years	Incidence per 100,000 PY	95%CI
SIDIAP	Myoclonus narrow	2016	4830768	293	4724098	6.2	(5.51, 6.95)
CPRD GOLD	Myoclonus narrow	2017	3582534	159	3257809	4.88	(4.15, 5.7)
IQVIA DA Germany	Myoclonus narrow	2017	7695506	167	6817163	2.45	(2.09, 2.85)
SIDIAP	Myoclonus narrow	2017	4843782	293	4723244	6.2	(5.51, 6.96)
CPRD GOLD	Myoclonus narrow	2018	3347715	152	3109314	4.89	(4.14, 5.73)
IQVIA DA Germany	Myoclonus narrow	2018	7935720	172	7102656	2.42	(2.07, 2.81)
SIDIAP	Myoclonus narrow	2018	4867120	303	4737167	6.4	(5.7, 7.16)
CPRD GOLD	Myoclonus narrow	2019	3237332	135	2986445	4.52	(3.79, 5.35)
IQVIA DA Germany	Myoclonus narrow	2019	7878579	187	7039988	2.66	(2.29, 3.07)
SIDIAP	Myoclonus narrow	2019	4900782	349	4764079	7.33	(6.58, 8.14)
CPRD GOLD	Myoclonus narrow	2020	3053801	98	2790324	3.51	(2.85, 4.28)
IQVIA DA Germany	Myoclonus narrow	2020	7826981	177	6882121	2.57	(2.21, 2.98)
SIDIAP	Myoclonus narrow	2020	4959823	346	4828796	7.16	(6.43, 7.96)
CPRD GOLD	Myoclonus narrow	2021	2799744	98	2527932	3.88	(3.15, 4.72)
IQVIA DA Germany	Myoclonus narrow	2021	7484587	216	6444941	3.35	(2.92, 3.83)
SIDIAP	Myoclonus narrow	2021	4968734	419	4836742	8.66	(7.85, 9.53)
CPRD GOLD	Myoclonus narrow	2022	2568073	97	2357968	4.11	(3.34, 5.02)
IQVIA DA Germany	Myoclonus narrow	2022	6530849	183	5252868	3.48	(3, 4.03)
SIDIAP	Myoclonus narrow	2022	4993349	446	4832296	9.23	(8.39, 10.13)
CPRD GOLD	Myoclonus narrow	2023	2446267	97	2284091	4.25	(3.44, 5.18)
IQVIA DA Germany	Myoclonus narrow	2023	4609285	190	2400150	7.92	(6.83, 9.13)
SIDIAP	Myoclonus narrow	2023	4906878	219	2396186	9.14	(7.97, 10.43)
CPRD GOLD	Myoclonus broad	2015	4616164	5438	4107177	132.4	(128.91, 135.97)
IQVIA DA Germany	Myoclonus broad	2015	6934451	2462	6253880	39.37	(37.83, 40.95)

Database	Outcome	Year	Number of persons	Number of Events	Person years	Incidence per 100,000 PY	95%CI
SIDIAP	Myoclonus broad	2015	4838890	5521	4714493	117.11	(114.04, 120.24)
CPRD GOLD	Myoclonus broad	2016	3954872	4504	3568502	126.22	(122.56, 129.96)
IQVIA DA Germany	Myoclonus broad	2016	7253907	2837	6583111	43.09	(41.52, 44.71)
SIDIAP	Myoclonus broad	2016	4825627	5810	4716249	123.19	(120.04, 126.4)
CPRD GOLD	Myoclonus broad	2017	3575138	3742	3249231	115.17	(111.51, 118.92)
IQVIA DA Germany	Myoclonus broad	2017	7691096	3340	6811449	49.03	(47.39, 50.73)
SIDIAP	Myoclonus broad	2017	4833506	5644	4710499	119.82	(116.71, 122.98)
CPRD GOLD	Myoclonus broad	2018	3338202	3433	3098673	110.79	(107.11, 114.56)
IQVIA DA Germany	Myoclonus broad	2018	7928776	3486	7094440	49.14	(47.52, 50.8)
SIDIAP	Myoclonus broad	2018	4852063	5098	4719972	108.01	(105.06, 111.02)
CPRD GOLD	Myoclonus broad	2019	3225717	3303	2974006	111.06	(107.31, 114.92)
IQVIA DA Germany	Myoclonus broad	2019	7869228	4008	7029272	57.02	(55.27, 58.81)
SIDIAP	Myoclonus broad	2019	4881644	5662	4742751	119.38	(116.29, 122.53)
CPRD GOLD	Myoclonus broad	2020	3040889	1839	2777532	66.21	(63.22, 69.31)
IQVIA DA Germany	Myoclonus broad	2020	7815022	3772	6868994	54.91	(53.17, 56.69)
SIDIAP	Myoclonus broad	2020	4936201	4302	4803792	89.55	(86.9, 92.27)
CPRD GOLD	Myoclonus broad	2021	2787376	2008	2515713	79.82	(76.36, 83.39)
IQVIA DA Germany	Myoclonus broad	2021	7470549	3974	6430141	61.8	(59.9, 63.75)
SIDIAP	Myoclonus broad	2021	4942433	6219	4808288	129.34	(126.14, 132.59)
CPRD GOLD	Myoclonus broad	2022	2555863	2175	2345464	92.73	(88.88, 96.71)
IQVIA DA Germany	Myoclonus broad	2022	6515652	3945	5237426	75.32	(72.99, 77.71)
SIDIAP	Myoclonus broad	2022	4962562	7071	4798975	147.34	(143.93, 150.82)
CPRD GOLD	Myoclonus broad	2023	2433541	2125	2270970	93.57	(89.64, 97.64)
IQVIA DA Germany	Myoclonus broad	2023	4594084	3299	2389618	138.06	(133.38, 142.85)

Database	Outcome	Year	Number of persons	Number of Events	Person years	Incidence per 100,000 PY	95%CI
SIDIAP	Myoclonus broad	2023	4871177	3649	2377861	153.46	(148.52, 158.52)

Incidence per 100,000 PY refers to the number of events per 100,000 person-years of follow-up. NA indicates values are not disclosed due to governance reasons. Myoclonus narrow represents a restrictive outcome definition, while myoclonus broad includes broader criteria. Rates are reported by calendar year and other rates (monthly, quarterly, and overall) are available in the shiny app. 95% CI = 95% confidence intervals (CIs). Variations across databases may reflect differences in population characteristics, data collection methods, or outcome definitions.

Appendix II. Table 2. Incidence Rates of myoclonus narrow and myoclonus broad in the incident heart failure population, by database and time-at-risk windows, during 2015-2023.

Database	Outcome	Time at risk window	Number of persons	Number of events	Person years	Incidence per 100,000 PY	95% CI
CPRD GOLD	Myoclonus narrow	0 to 30	50365	0	4165	0	(0, 88.57)
IQVIA DA Germany	Myoclonus narrow	0 to 30	216268	6	16817	35.68	(13.09, 77.66)
SIDIAP	Myoclonus narrow	0 to 30	175557	94	14353	654.92	(529.24, 801.46)
CPRD GOLD	Myoclonus narrow	31 to 90	48023	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus narrow	31 to 90	193576	7	31033	22.56	(9.07, 46.47)
SIDIAP	Myoclonus narrow	31 to 90	161188	25	25176	99.3	(64.26, 146.59)
CPRD GOLD	Myoclonus narrow	91 to 180	44454	0	10428	0	(0, 35.38)
IQVIA DA Germany	Myoclonus narrow	91 to 180	184183	NA	NA	NA	(NA, NA)
SIDIAP	Myoclonus narrow	91 to 180	146957	34	34336	99.02	(68.57, 138.37)
CPRD GOLD	Myoclonus narrow	181 to 365	40266	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus narrow	181 to 365	165794	6	77494	7.74	(2.84, 16.85)
SIDIAP	Myoclonus narrow	181 to 365	132492	32	62163	51.48	(35.21, 72.67)
CPRD GOLD	Myoclonus narrow	366 to Inf	33309	13	85035	15.29	(8.14, 26.14)
IQVIA DA Germany	Myoclonus narrow	366 to Inf	141901	28	398090	7.03	(4.67, 10.17)
SIDIAP	Myoclonus narrow	366 to Inf	114187	162	314248	51.55	(43.92, 60.13)
CPRD GOLD	Myoclonus broad	0 to 30	49872	20	4123	485.08	(296.3, 749.17)
IQVIA DA Germany	Myoclonus broad	0 to 30	215167	150	16716	897.37	(759.51, 1053.01)
SIDIAP	Myoclonus broad	0 to 30	172596	397	14090	2817.56	(2547.18, 3108.82)

Database	Outcome	Time at risk window	Number of persons	Number of events	Person years	Incidence per 100,000 PY	95% CI
CPRD GOLD	Myoclonus broad	31 to 90	47537	28	7510	372.81	(247.73, 538.82)
IQVIA DA Germany	Myoclonus broad	31 to 90	192381	81	30835	262.69	(208.61, 326.5)
SIDIAP	Myoclonus broad	31 to 90	158192	181	24701	732.76	(629.89, 847.63)
CPRD GOLD	Myoclonus broad	91 to 180	43994	29	10317	281.09	(188.25, 403.69)
IQVIA DA Germany	Myoclonus broad	91 to 180	182968	102	42388	240.64	(196.21, 292.12)
SIDIAP	Myoclonus broad	91 to 180	144129	217	33663	644.63	(561.71, 736.34)
CPRD GOLD	Myoclonus broad	181 to 365	39824	52	18349	283.39	(211.65, 371.63)
IQVIA DA Germany	Myoclonus broad	181 to 365	164615	194	76904	252.26	(218.01, 290.37)
SIDIAP	Myoclonus broad	181 to 365	129847	299	60884	491.1	(437, 550.04)
CPRD GOLD	Myoclonus broad	366 to Inf	32933	212	83894	252.7	(219.83, 289.1)
IQVIA DA Germany	Myoclonus broad	366 to Inf	140751	835	393547	212.17	(198.02, 227.07)
SIDIAP	Myoclonus broad	366 to Inf	111775	1328	306412	433.4	(410.4, 457.36)

Incidence per 100,000 PY refers to the number of events per 100,000 person-years of follow-up. NA indicates values are not disclosed due to governance reasons. Myoclonus narrow represents a restrictive outcome definition, while myoclonus broad includes broader criteria. Time-at-risk windows are defined as intervals following cohort entry: 0–30 days, 31–90 days, 91–180 days, 181–365 days, and beyond 366 days. 95% CI = 95% confidence intervals (CIs). Variations across databases may reflect differences in population characteristics, data collection methods, or outcome definitions.

Appendix II. Table 3. Incidence Rates of myoclonus narrow and myoclonus broad in the heart failure population following first initiation of treatments of interest, by database, treatment, and time-at-risk windows, during 2015-2023.

Database	Outcome	Treatment	Time at Risk window	Number of persons	Number of Events	Person years	Incidence per 100,000 PY	95% CI
CPRD GOLD	Myoclonus narrow	ACEi	0 to 30	9161	0	771	0	(0, 478.55)
IQVIA DA Germany	Myoclonus narrow	ACEi	0 to 30	35669	NA	NA	NA	(NA, NA)
SIDIAP	Myoclonus narrow	ACEi	0 to 30	18694	NA	NA	NA	(NA, NA)
CPRD GOLD	Myoclonus narrow	ARBs	0 to 30	4521	0	380	0	(0, 970.83)
IQVIA DA	Myoclonus narrow	ARBs	0 to 30	35130	0	2966	0	(0, 124.39)

Database	Outcome	Treatment	Time at Risk window	Number of persons	Number of Events	Person years	Incidence per 100,000 PY	95% CI
Germany								
SIDIAP	Myoclonus narrow	ARBs	0 to 30	12166	NA	NA	NA	(NA, NA)
CPRD GOLD	Myoclonus narrow	Sacubitril first line	0 to 30	683	0	57	0	(0, 6500.8)
IQVIA DA Germany	Myoclonus narrow	Sacubitril first line	0 to 30	5845	0	487	0	(0, 757.5)
SIDIAP	Myoclonus narrow	Sacubitril first line	0 to 30	1264	0	105	0	(0, 3507.11)
CPRD GOLD	Myoclonus narrow	Sacubitril later line	0 to 30	5743	0	483	0	(0, 764.27)
IQVIA DA Germany	Myoclonus narrow	Sacubitril later line	0 to 30	13663	NA	NA	NA	(NA, NA)
SIDIAP	Myoclonus narrow	Sacubitril later line	0 to 30	13287	NA	NA	NA	(NA, NA)
CPRD GOLD	Myoclonus narrow	ACEi	31 to 90	8991	0	1442	0	(0, 255.86)
IQVIA DA Germany	Myoclonus narrow	ACEi	31 to 90	35277	NA	NA	NA	(NA, NA)
SIDIAP	Myoclonus narrow	ACEi	31 to 90	18313	NA	NA	NA	(NA, NA)
CPRD GOLD	Myoclonus narrow	ARBs	31 to 90	4422	0	710	0	(0, 519.8)
IQVIA DA Germany	Myoclonus narrow	ARBs	31 to 90	34486	0	5592	0	(0, 65.97)
SIDIAP	Myoclonus narrow	ARBs	31 to 90	11923	0	1920	0	(0, 192.16)
CPRD GOLD	Myoclonus narrow	Sacubitril first line	31 to 90	655	0	103	0	(0, 3581.78)
IQVIA DA Germany	Myoclonus narrow	Sacubitril first line	31 to 90	5462	0	869	0	(0, 424.36)
SIDIAP	Myoclonus narrow	Sacubitril first line	31 to 90	1201	0	189	0	(0, 1956.42)
CPRD GOLD	Myoclonus narrow	Sacubitril later line	31 to 90	5615	0	897	0	(0, 411.28)
IQVIA DA	Myoclonus narrow	Sacubitril later line	31 to 90	13347	0	2153	0	(0, 171.32)

Database	Outcome	Treatment	Time at Risk window	Number of persons	Number of Events	Person years	Incidence per 100,000 PY	95% CI
Germany								
SIDIAP	Myoclonus narrow	Sacubitril later line	31 to 90	12879	NA	NA	NA	(NA, NA)
CPRD GOLD	Myoclonus narrow	ACEi	91 to 180	8556	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus narrow	ACEi	91 to 180	34509	NA	NA	NA	(NA, NA)
SIDIAP	Myoclonus narrow	ACEi	91 to 180	17492	NA	NA	NA	(NA, NA)
CPRD GOLD	Myoclonus narrow	ARBs	91 to 180	4218	0	1005	0	(0, 366.87)
IQVIA DA Germany	Myoclonus narrow	ARBs	91 to 180	33639	0	7829	0	(0, 47.12)
SIDIAP	Myoclonus narrow	ARBs	91 to 180	11389	NA	NA	NA	(NA, NA)
CPRD GOLD	Myoclonus narrow	Sacubitril first line	91 to 180	598	0	139	0	(0, 2652.86)
IQVIA DA Germany	Myoclonus narrow	Sacubitril first line	91 to 180	5145	0	1124	0	(0, 328.28)
SIDIAP	Myoclonus narrow	Sacubitril first line	91 to 180	1091	0	250	0	(0, 1475.29)
CPRD GOLD	Myoclonus narrow	Sacubitril later line	91 to 180	5294	0	1251	0	(0, 294.82)
IQVIA DA Germany	Myoclonus narrow	Sacubitril later line	91 to 180	12875	NA	NA	NA	(NA, NA)
SIDIAP	Myoclonus narrow	Sacubitril later line	91 to 180	12122	NA	NA	NA	(NA, NA)
CPRD GOLD	Myoclonus narrow	ACEi	181 to 365	7971	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus narrow	ACEi	181 to 365	31525	0	14966	0	(0, 24.65)
SIDIAP	Myoclonus narrow	ACEi	181 to 365	16388	5	7884	63.42	(20.59, 148)
CPRD GOLD	Myoclonus narrow	ARBs	181 to 365	3933	0	1846	0	(0, 199.88)
IQVIA DA	Myoclonus narrow	ARBs	181 to 365	30838	0	14677	0	(0, 25.13)

Database	Outcome	Treatment	Time at Risk window	Number of persons	Number of Events	Person years	Incidence per 100,000 PY	95% CI
Germany								
SIDIAP	Myoclonus narrow	ARBs	181 to 365	10692	0	5118	0	(0, 72.07)
CPRD GOLD	Myoclonus narrow	Sacubitril first line	181 to 365	528	0	235	0	(0, 1570.76)
IQVIA DA Germany	Myoclonus narrow	Sacubitril first line	181 to 365	4248	0	1915	0	(0, 192.63)
SIDIAP	Myoclonus narrow	Sacubitril first line	181 to 365	928	0	413	0	(0, 892.5)
CPRD GOLD	Myoclonus narrow	Sacubitril later line	181 to 365	4857	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus narrow	Sacubitril later line	181 to 365	11342	NA	NA	NA	(NA, NA)
SIDIAP	Myoclonus narrow	Sacubitril later line	181 to 365	10962	NA	NA	NA	(NA, NA)
CPRD GOLD	Myoclonus narrow	ACEi	366 to Inf	6950	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus narrow	ACEi	366 to Inf	27827	5	84876	5.89	(1.91, 13.75)
SIDIAP	Myoclonus narrow	ACEi	366 to Inf	14723	17	46157	36.83	(21.46, 58.97)
CPRD GOLD	Myoclonus narrow	ARBs	366 to Inf	3374	0	9936	0	(0, 37.13)
IQVIA DA Germany	Myoclonus narrow	ARBs	366 to Inf	27318	NA	NA	NA	(NA, NA)
SIDIAP	Myoclonus narrow	ARBs	366 to Inf	9508	17	28694	59.25	(34.51, 94.86)
CPRD GOLD	Myoclonus narrow	Sacubitril first line	366 to Inf	399	0	501	0	(0, 736.29)
IQVIA DA Germany	Myoclonus narrow	Sacubitril first line	366 to Inf	3395	NA	NA	NA	(NA, NA)
SIDIAP	Myoclonus narrow	Sacubitril first line	366 to Inf	717	0	981	0	(0, 376.15)
CPRD GOLD	Myoclonus narrow	Sacubitril later line	366 to Inf	4011	NA	NA	NA	(NA, NA)
IQVIA DA	Myoclonus narrow	Sacubitril later line	366 to Inf	9128	0	18234	0	(0, 20.23)

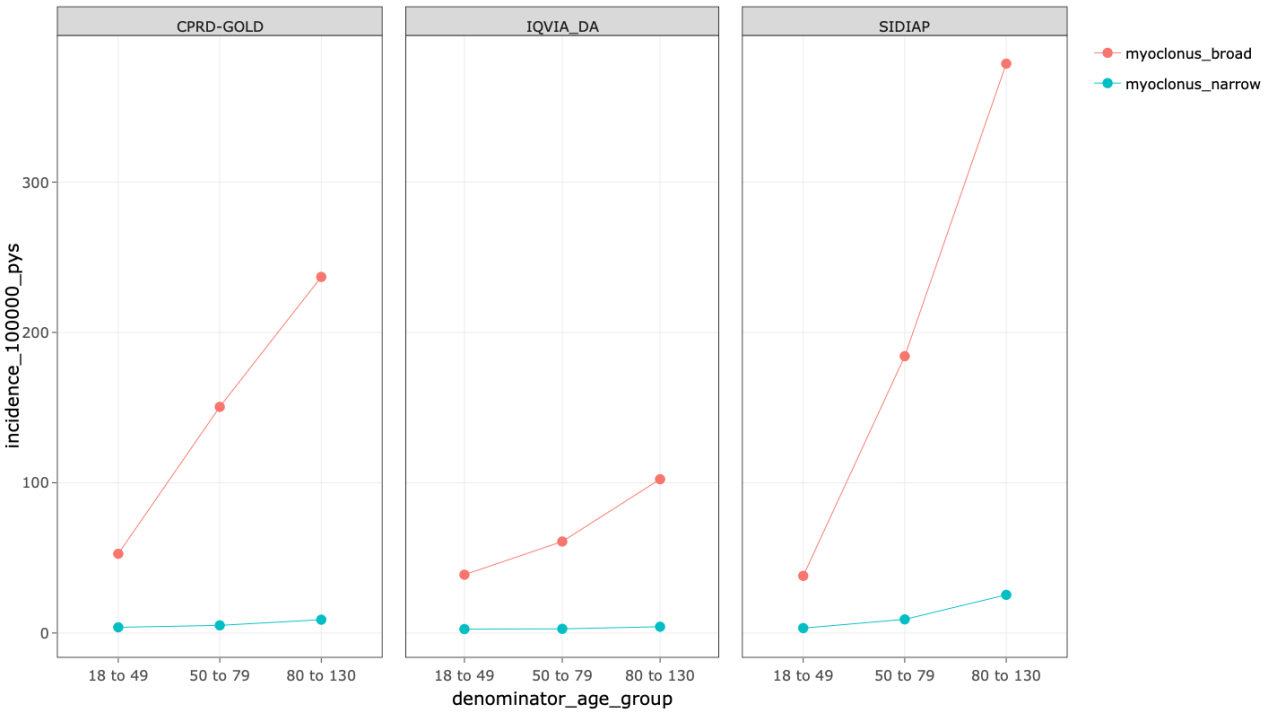
Database	Outcome	Treatment	Time at Risk window	Number of persons	Number of Events	Person years	Incidence per 100,000 PY	95% CI
Germany								
SIDIAP	Myoclonus narrow	Sacubitril later line	366 to Inf	9311	9	19152	46.99	(21.49, 89.2)
CPRD GOLD	Myoclonus broad	ACEi	0 to 30	9111	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus broad	ACEi	0 to 30	35447	20	2997	667.26	(407.58, 1030.53)
SIDIAP	Myoclonus broad	ACEi	0 to 30	18455	9	1555	578.79	(264.66, 1098.73)
CPRD GOLD	Myoclonus broad	ARBs	0 to 30	4479	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus broad	ARBs	0 to 30	34913	21	2946	712.78	(441.23, 1089.57)
SIDIAP	Myoclonus broad	ARBs	0 to 30	11955	9	1008	892.7	(408.2, 1694.62)
CPRD GOLD	Myoclonus broad	Sacubitril first line	0 to 30	678	0	56	0	(0, 6549.86)
IQVIA DA Germany	Myoclonus broad	Sacubitril first line	0 to 30	5831	NA	NA	NA	(NA, NA)
SIDIAP	Myoclonus broad	Sacubitril first line	0 to 30	1255	0	105	0	(0, 3529.89)
CPRD GOLD	Myoclonus broad	Sacubitril later line	0 to 30	5697	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus broad	Sacubitril later line	0 to 30	13536	NA	NA	NA	(NA, NA)
SIDIAP	Myoclonus broad	Sacubitril later line	0 to 30	13056	8	1097	729.05	(314.75, 1436.51)
CPRD GOLD	Myoclonus broad	ACEi	31 to 90	8940	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus broad	ACEi	31 to 90	35041	29	5686	510.04	(341.59, 732.51)
SIDIAP	Myoclonus broad	ACEi	31 to 90	18073	19	2905	653.94	(393.71, 1021.2)
CPRD GOLD	Myoclonus broad	ARBs	31 to 90	4380	NA	NA	NA	(NA, NA)
IQVIA DA	Myoclonus broad	ARBs	31 to 90	34250	14	5552	252.15	(137.85, 423.07)

Database	Outcome	Treatment	Time at Risk window	Number of persons	Number of Events	Person years	Incidence per 100,000 PY	95% CI
Germany								
SIDIAP	Myoclonus broad	ARBs	31 to 90	11714	16	1885	848.67	(485.09, 1378.19)
CPRD GOLD	Myoclonus broad	Sacubitril first line	31 to 90	650	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus broad	Sacubitril first line	31 to 90	5446	0	867	0	(0, 425.57)
SIDIAP	Myoclonus broad	Sacubitril first line	31 to 90	1194	0	188	0	(0, 1966.72)
CPRD GOLD	Myoclonus broad	Sacubitril later line	31 to 90	5569	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus broad	Sacubitril later line	31 to 90	13218	8	2132	375.3	(162.03, 739.48)
SIDIAP	Myoclonus broad	Sacubitril later line	31 to 90	12654	5	2022	247.34	(80.31, 577.2)
CPRD GOLD	Myoclonus broad	ACEi	91 to 180	8506	8	2025	395.11	(170.58, 778.52)
IQVIA DA Germany	Myoclonus broad	ACEi	91 to 180	34249	22	7946	276.87	(173.51, 419.19)
SIDIAP	Myoclonus broad	ACEi	91 to 180	17245	15	4115	364.55	(204.04, 601.27)
CPRD GOLD	Myoclonus broad	ARBs	91 to 180	4173	5	994	503.07	(163.35, 1174)
IQVIA DA Germany	Myoclonus broad	ARBs	91 to 180	33393	14	7769	180.2	(98.52, 302.34)
SIDIAP	Myoclonus broad	ARBs	91 to 180	11182	19	2678	709.61	(427.23, 1108.14)
CPRD GOLD	Myoclonus broad	Sacubitril first line	91 to 180	593	0	138	0	(0, 2676.57)
IQVIA DA Germany	Myoclonus broad	Sacubitril first line	91 to 180	5131	NA	NA	NA	(NA, NA)
SIDIAP	Myoclonus broad	Sacubitril first line	91 to 180	1087	0	249	0	(0, 1480.5)
CPRD GOLD	Myoclonus broad	Sacubitril later line	91 to 180	5245	NA	NA	NA	(NA, NA)
IQVIA DA	Myoclonus broad	Sacubitril later line	91 to 180	12740	11	2928	375.69	(187.54, 672.21)

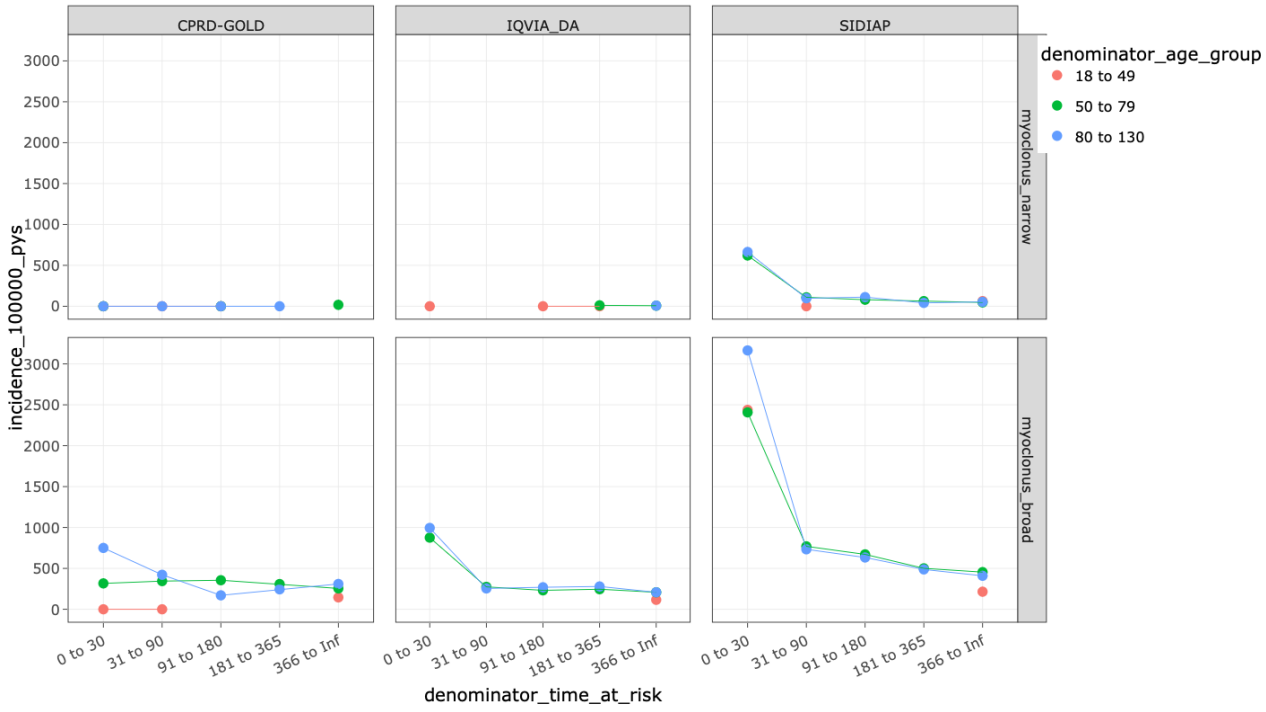
Database	Outcome	Treatment	Time at Risk window	Number of persons	Number of Events	Person years	Incidence per 100,000 PY	95% CI
Germany								
SIDIAP	Myoclonus broad	Sacubitril later line	91 to 180	11908	12	2801	428.44	(221.38, 748.39)
CPRD GOLD	Myoclonus broad	ACEi	181 to 365	7919	7	3747	186.82	(75.11, 384.93)
IQVIA DA Germany	Myoclonus broad	ACEi	181 to 365	31272	50	14837	337	(250.13, 444.3)
SIDIAP	Myoclonus broad	ACEi	181 to 365	16156	41	7766	527.92	(378.85, 716.18)
CPRD GOLD	Myoclonus broad	ARBs	181 to 365	3885	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus broad	ARBs	181 to 365	30604	30	14559	206.05	(139.02, 294.15)
SIDIAP	Myoclonus broad	ARBs	181 to 365	10491	19	5022	378.35	(227.79, 590.85)
CPRD GOLD	Myoclonus broad	Sacubitril first line	181 to 365	523	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus broad	Sacubitril first line	181 to 365	4236	NA	NA	NA	(NA, NA)
SIDIAP	Myoclonus broad	Sacubitril first line	181 to 365	925	NA	NA	NA	(NA, NA)
CPRD GOLD	Myoclonus broad	Sacubitril later line	181 to 365	4810	NA	NA	NA	(NA, NA)
IQVIA DA Germany	Myoclonus broad	Sacubitril later line	181 to 365	11217	19	5080	374.05	(225.2, 584.13)
SIDIAP	Myoclonus broad	Sacubitril later line	181 to 365	10764	21	5040	416.7	(257.94, 636.97)
CPRD GOLD	Myoclonus broad	ACEi	366 to Inf	6902	39	20437	190.83	(135.7, 260.88)
IQVIA DA Germany	Myoclonus broad	ACEi	366 to Inf	27572	198	83755	236.4	(204.62, 271.73)
SIDIAP	Myoclonus broad	ACEi	366 to Inf	14497	180	45330	397.09	(341.19, 459.52)
CPRD GOLD	Myoclonus broad	ARBs	366 to Inf	3330	25	9786	255.46	(165.32, 377.11)
IQVIA DA	Myoclonus broad	ARBs	366 to Inf	27089	194	81513	238	(205.68, 273.95)

Database	Outcome	Treatment	Time at Risk window	Number of persons	Number of Events	Person years	Incidence per 100,000 PY	95% CI
Germany								
SIDIAP	Myoclonus broad	ARBs	366 to Inf	9324	125	28000	446.42	(371.6, 531.89)
CPRD GOLD	Myoclonus broad	Sacubitril first line	366 to Inf	396	0	494	0	(0, 747.31)
IQVIA DA Germany	Myoclonus broad	Sacubitril first line	366 to Inf	3385	5	6327	79.02	(25.66, 184.41)
SIDIAP	Myoclonus broad	Sacubitril first line	366 to Inf	714	NA	NA	NA	(NA, NA)
CPRD GOLD	Myoclonus broad	Sacubitril later line	366 to Inf	3971	19	7729	245.83	(148, 383.89)
IQVIA DA Germany	Myoclonus broad	Sacubitril later line	366 to Inf	9019	47	17994	261.2	(191.92, 347.33)
SIDIAP	Myoclonus broad	Sacubitril later line	366 to Inf	9146	73	18799	388.32	(304.38, 488.25)

Incidence per 100,000 PY refers to the number of events per 100,000 person-years of follow-up. NA indicates values are not disclosed due to governance reasons. Myoclonus narrow represents a restrictive outcome definition, while myoclonus broad includes broader criteria. Time-at-risk windows are defined as intervals following cohort entry: 0–30 days, 31–90 days, 91–180 days, 181–365 days, and beyond 366 days. 95% CI = 95% confidence intervals (CIs). Variations across databases may reflect differences in population characteristics, data collection methods, or outcome definitions.

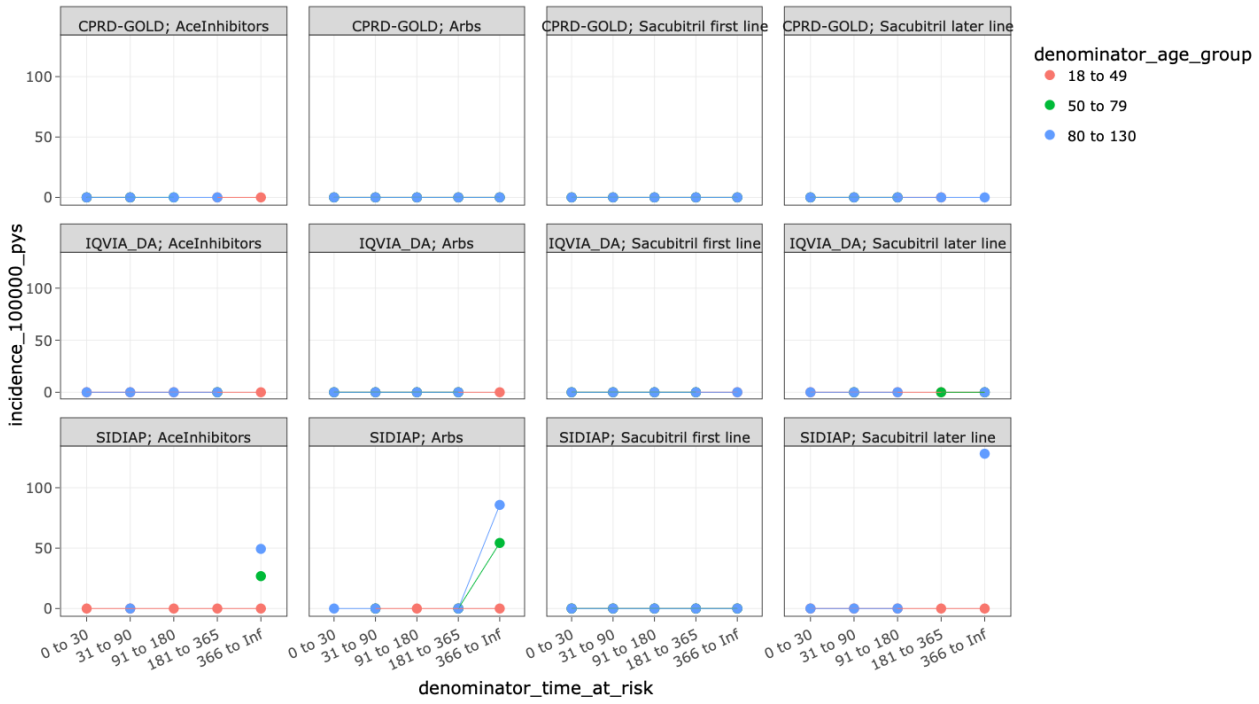


Appendix II. Figure 1. Overall incidence of myoclonus (narrow and broad) for the general population by age group and database, during 2015 to 2023.

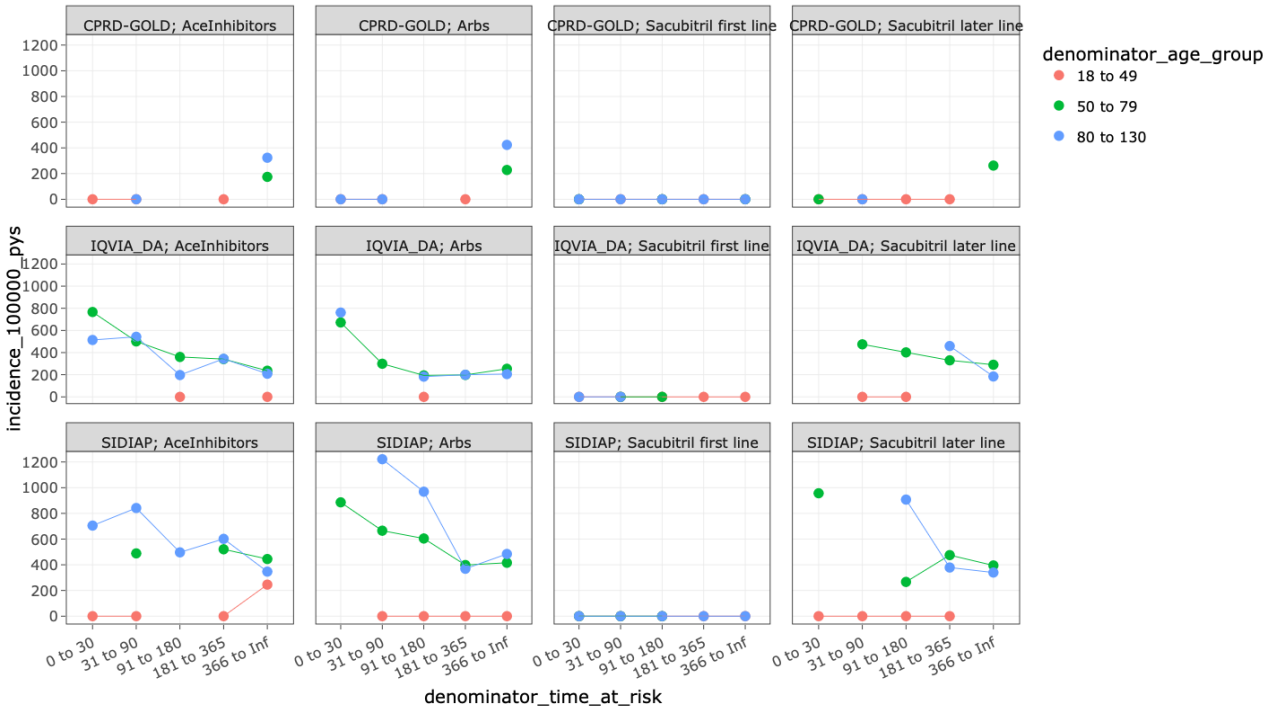


Appendix II. Figure 2. Incidence rate of myoclonus narrow and broad in the incident heart failure population using consecutive time-at-risk windows from heart failure diagnosis, by age group and database during 2015-2023.

a)

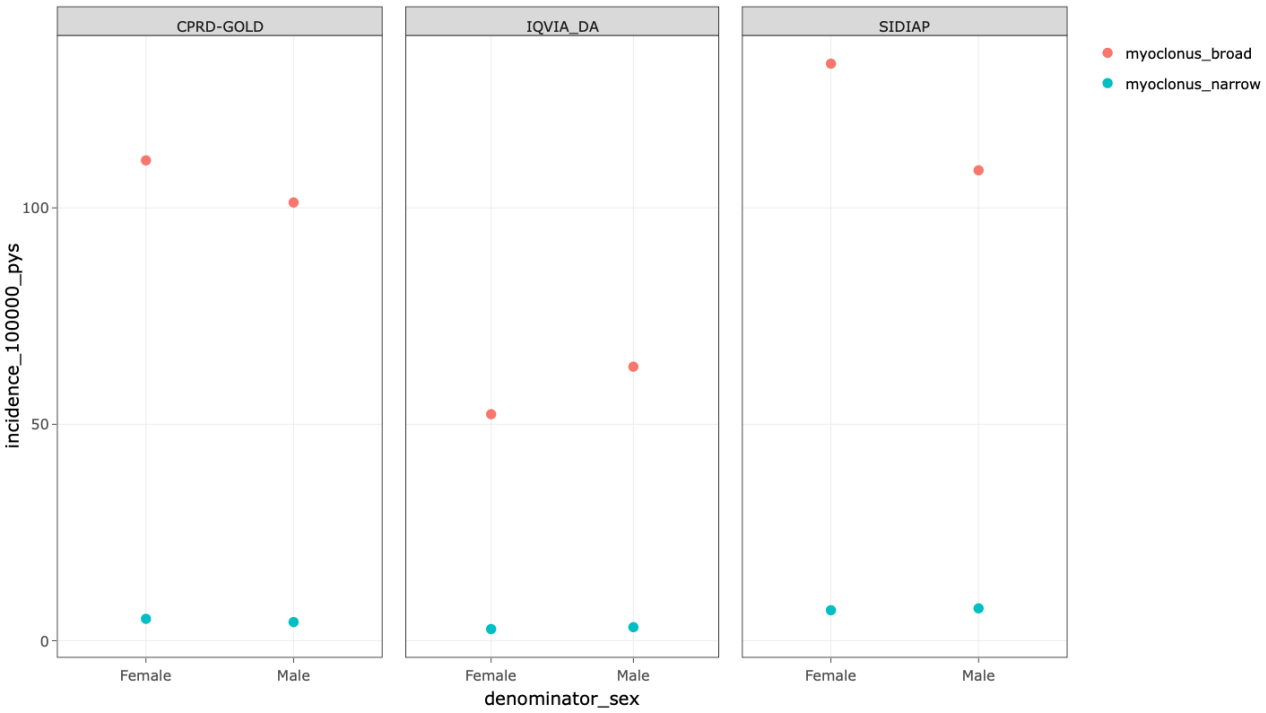


b)

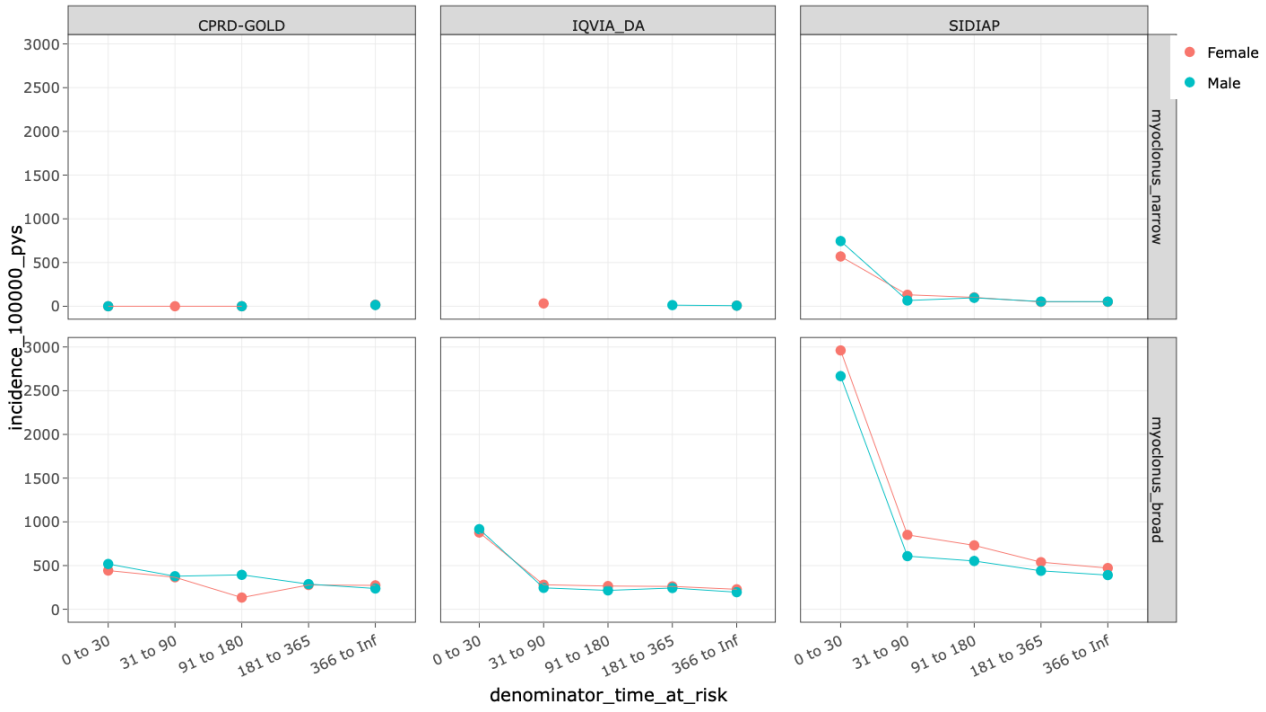


Axis scales differ between panels **a** and **b,** representing myoclonus narrow and broad outcomes, with each adjusted to best represent the range of data specific to that panel.

Appendix II. Figure 3. Incidence rate of myoclonus a) narrow and b) broad in the HF population newly initiating treatments using consecutive time-at-risk windows following treatment start, by age group and database during 2015-2023.

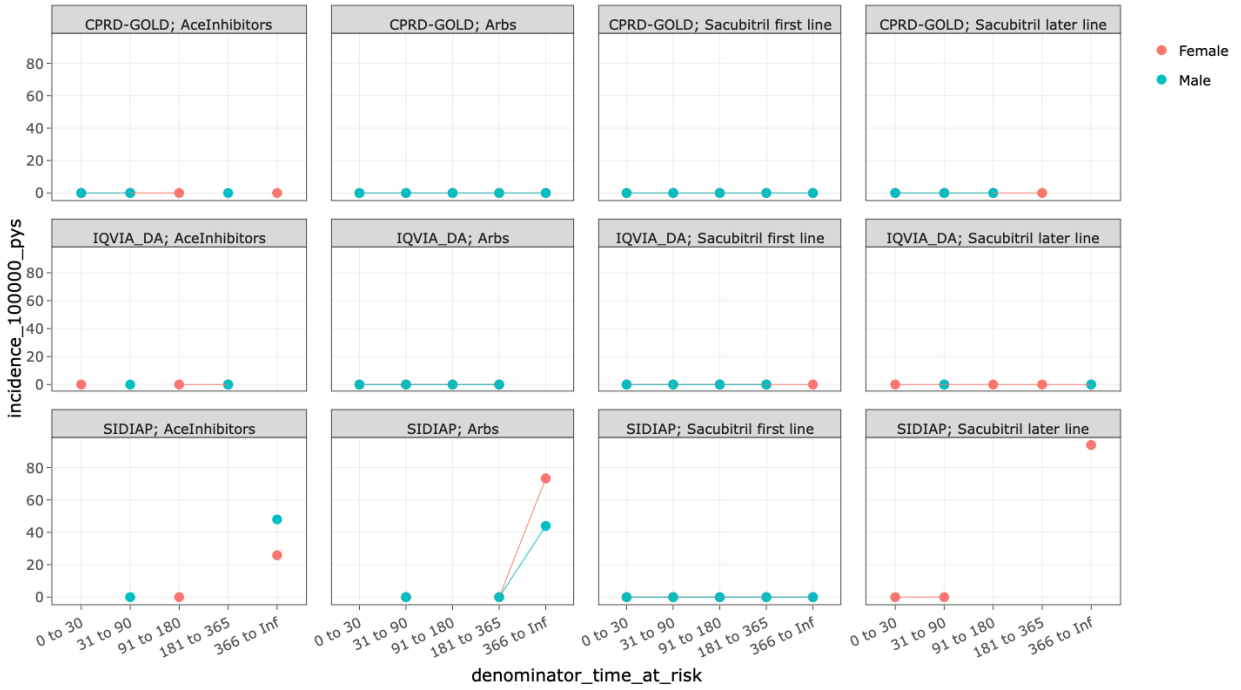


Appendix II. Figure 4. Overall incidence of myoclonus narrow and broad for the general population by sex and database, from 2015 to 2023.

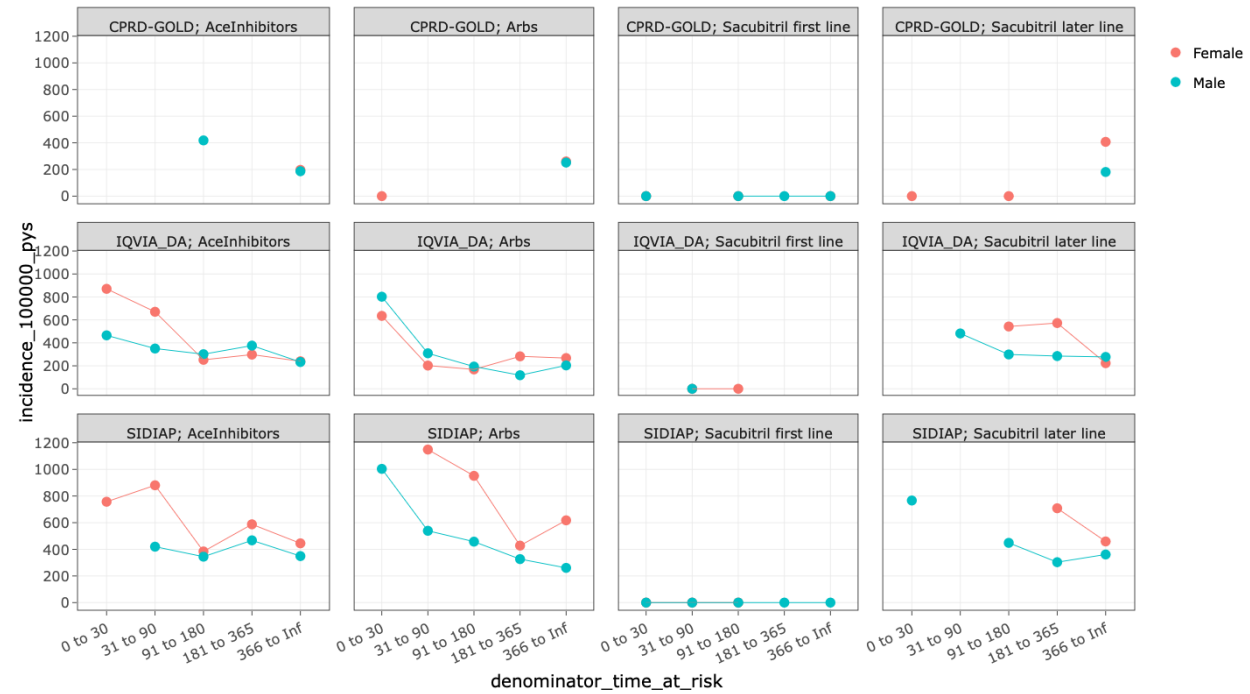


Appendix II. Figure 5. Incidence rate of myoclonus narrow and broad in the incident heart failure population using consecutive time-at-risk windows from heart failure diagnosis, by sex and database during 2015-2023.

a)



b)

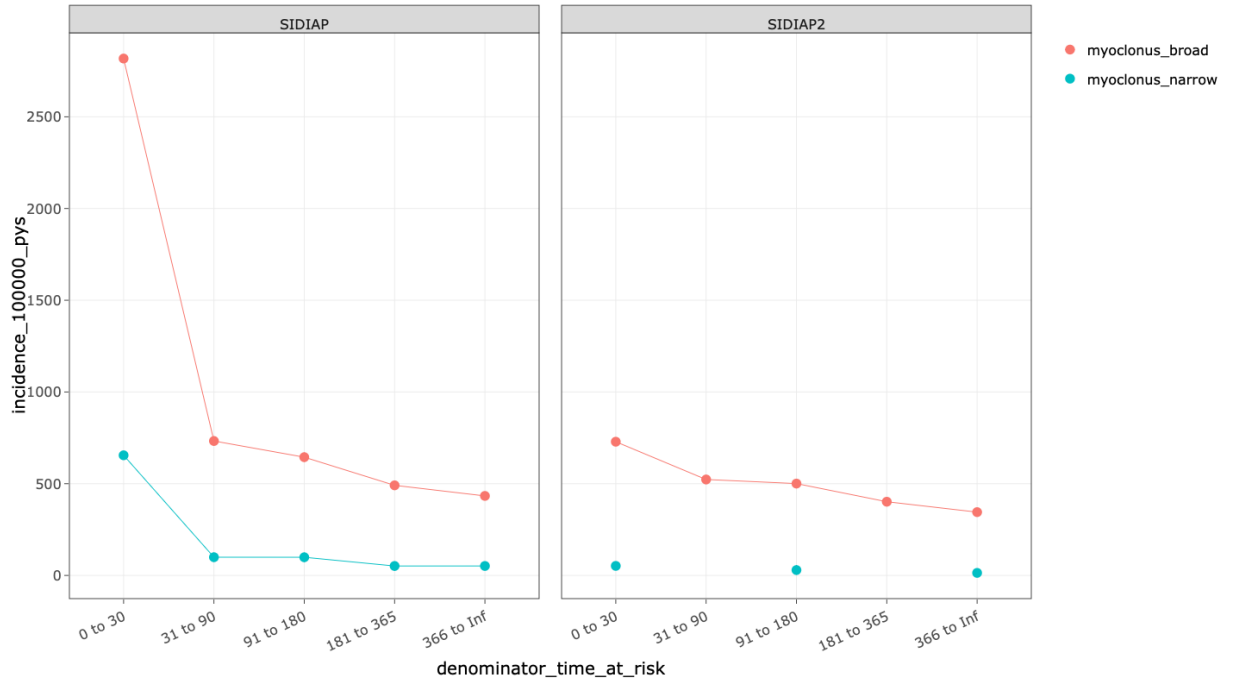


Axis scales differ between panels **a** and **b,** representing myoclonus narrow and broad outcomes, with each adjusted to best represent the range of data specific to that panel.

Appendix II. Figure 6. Incidence rate of myoclonus a) narrow and b) broad in the HF population newly initiating treatments using consecutive time-at-risk windows following treatment start, by sex and database during 2015-2023.

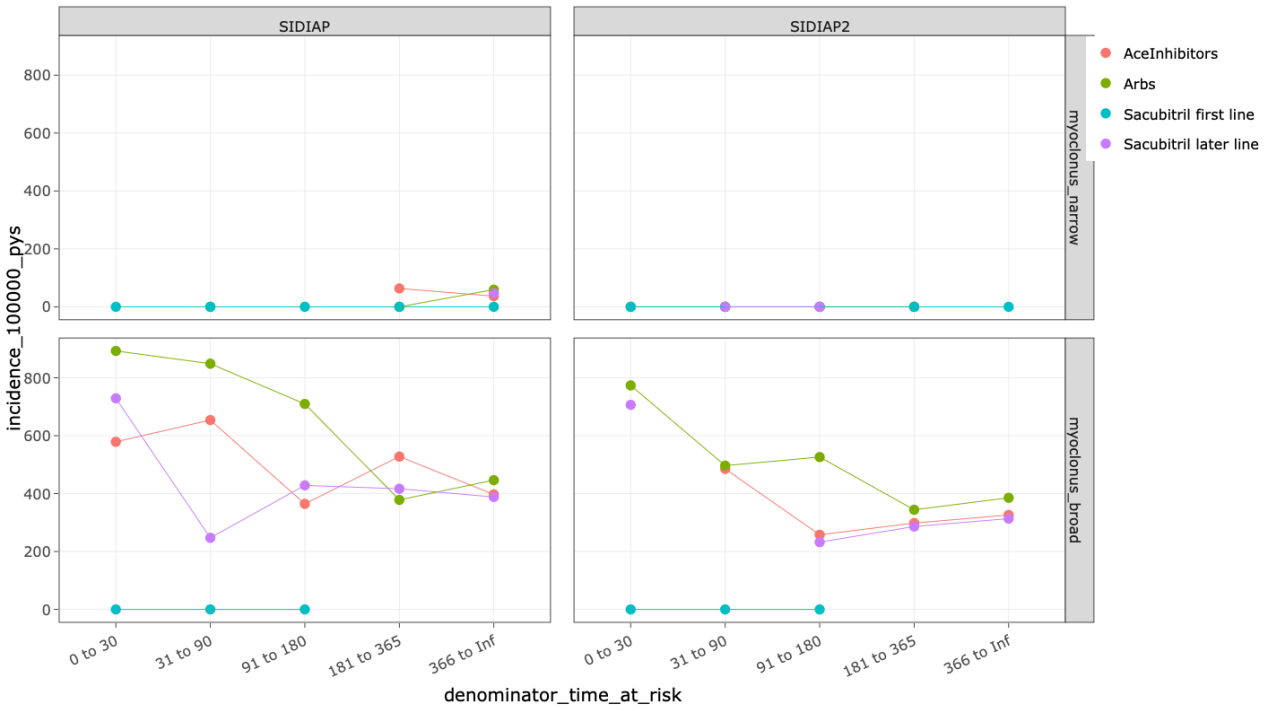
SIDIAP=hospital-linked CDM. SIDIAP2=non-hospital-linked CDM.

Appendix II. Figure 7. Incidence rate of myoclonus narrow and broad in the general population by consecutive calendar month in SIDIAP's hospital-linked (left) non-hospital-linked (right) CDM, from 2015 to 2023.



SIDIAP=hospital-linked CDM. SIDIAP2=non-hospital-linked CDM.

Appendix II. Figure 8. Incidence rate of myoclonus narrow and broad in the incident heart failure population using consecutive time-at-risk windows following heart failure diagnosis, in SIDIAP's hospital-linked (left) non-hospital-linked (right) CDM during 2015-2023.



SIDIAP=hospital-linked CDM. SIDIAP2=non-hospital-linked CDM.

Appendix II. Figure 9. Incidence rate of myoclonus narrow and broad in the HF population newly initiating treatments using consecutive time-at-risk windows following treatment start, in SIDIAP's hospital-linked (left) non-hospital-linked (right) CDM during 2015-2023.