Study Report

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DARWIN EU® - Characterisation of aliskiren users

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Version 2.0

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Public

CONTENTS

Study title	DARWIN EU® - Characterisation of aliskiren users
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Date	13/01/2026
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Active substance	Aliskiren
Medicinal product	Not applicable
Research question and objectives	The objective of this study was to characterise new users of aliskiren in order to inform the planning of potential future safety studies on aliskiren. The specific objectives were as follows: 1. To characterise new users of aliskiren in terms of demographics, comorbidities, duration of use, and potential indications for aliskiren use. 2. To assess the use of co-medication, both prior to and after new aliskiren treatment initiation. 3. To estimate the number of people with both at least one aliskiren prescription/dispensation record(s) and a record of pre-specified cardiac events.
Countries of study	Denmark, the Netherlands, Spain, United Kingdom
Authors	Amy Lam (a.lam@darwin-eu.org)

LIST OF ABBREVIATIONS

Acronyms/term	Description
ACEi	Angiotensin converting enzyme inhibitor
ALTITUDE	The Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints trial
ARB	Angiotensin II receptor blocker
ASTRONAUT	The Aliskiren Trial on Acute Heart Failure Outcomes study
ATC	Anatomical Therapeutic Chemical
CC	Coordinating centre
CDM	Common Data Model
CPRD GOLD	Clinical Practice Research Datalink GOLD
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DOI	Declaration of Interests
DQD	Data Quality Dashboard
DRE	Digital Research Environment
DTZ	Data Transfer Zone
ED	Emergency Department
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
GDPR	General Data Protection Regulation
GP	General Practitioner
ICD	International Classification of Diseases
IP	Inpatient
IPCI	Integrated Primary Care Information
IQR	Interquartile range
IRB	Institutional Review Board
NSAID	Non-steroidal anti-inflammatory drug
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
OP	Outpatient
RAAS	Renin-angiotensin aldosterone system
RxNorm	Medical prescription normalised
RCT	Randomised controlled trial

Acronyms/term	Description
SD	Standard deviation
SNOMED	Systematized Nomenclature of Medicine
SIDIAP	The Information System for Research on Primary Care
VA NEPHRON-D	Veterans Affairs Nephropathy in Diabetes study
VALIANT	Valsartan in Acute Myocardial Infarction Trial
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Characterisation of aliskiren users

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Amy Lam	University of Oxford
Data Scientist	Nuria Mercade-Besora Edward Burn	University of Oxford
Epidemiologist	Annika Jödicke	University of Oxford
Clinical Domain Expert	Anna Saura-Lazaro	University of Oxford
Study Manager	Natasha Yefimenko	Erasmus MC
Data source	**Names**	**Data Partner Organisation***
DK-DHR	Elvira Bräuner Susanne Bruun	Danish Medicines Agency
IPCI	Katia Verhamme Mees Mosseveld Guido van Leeuwen	Erasmus MC
SIDIAP	Agustina Giuliodori Picco Laura Granés González Irene López Sánchez Anna Palomar Cros	IDIAP JGol
CPRD GOLD	Antonella Delmestri	University of Oxford

*Data partners do not have an investigator role. Data partners execute code at their data source, review, and approve their results.

3. ABSTRACT

Title

DARWIN EU® - Characterisation of aliskiren users

Rationale and background

Existing evidence from case reports and preclinical data raised concerns regarding the atrial and ventricular proarrhythmic potential of aliskiren, especially with underlying risk of atrial fibrillation. However, little is known about the usage of aliskiren in clinical practice, in particular characteristics of aliskiren users.

This study aimed to characterise new aliskiren users to inform the planning and feasibility of a potential future safety study investigating risk of cardiac events.

Research question and objectives

Objectives

1. To characterise new aliskiren users in terms of demographics, comorbidities, duration of use, and potential indications for aliskiren use, overall and stratified by age and by sex, during the study period of 2007–2014 and 2015–2024.
2. To assess the use of co-medication, both prior to and after new aliskiren treatment initiation, overall and stratified by age and by sex, during the study period of 2007–2014 and 2015–2024.
3. To estimate the number of people with at least one aliskiren prescription/dispensation record(s) and a record of pre-specified cardiac events anytime during the study period of 2007–2014 and 2015–2024 (cross-cohort counts), overall and stratified by age and by sex.

Methods

Study design

Patient-level characterisation

Objective 1 and 2: Patient-level characterisation of new aliskiren users (new drug user cohort)

Population

The study population included all individuals who received a new aliskiren prescription/dispensation during the study period 01/01/2007 to 31/12/2014 and the study period 01/01/2015 to 31/12/2024 (or the end of available data), with at least 365 days of database history available prior to the first aliskiren prescription/dispensation, and with no aliskiren use in the prior 365 days.

Variables

Exposure: Aliskiren

Covariates for characterisation:

- Demographics: age, sex (Objective 1)
- Comorbidities: cardiac arrhythmia, cardiomyopathy, heart failure, ischemic heart disease, myocardial infarction, stroke and transient ischaemic attack, venous thromboembolism, anxiety, chronic kidney disease, chronic liver disease, dementia, depressive disorder, diabetes, obesity, metabolic syndrome, chronic obstructive pulmonary disease, hyperthyroidism, hypothyroidism, malignant neoplastic disease, dyslipidaemia, autoimmune diseases (Objective 1)
- Indication: hypertension (Objective 1)

- Co-medication: agents acting on the renin-angiotensin aldosterone system (RAAS) excluding aliskiren, beta blocking agents (systemic), calcium channel blockers, diuretics, other antihypertensive agents, antiarrhythmic agents, antithrombotic agents, digoxin, ivabradine, nicorandil, acetylcholinesterase inhibitor, antibacterials for systemic use (overall, macrolides, fluoroquinolones), antifungals for systemic use, antidepressants, antiemetics, antimalarial agents, antineoplastic agents, opioids, psycholeptics, psychostimulants, statins, antidiabetic agents, systemic corticosteroids, antihistamines for systemic use, and non-steroidal anti-inflammatory drugs for systemic use (Objective 2)

Covariates for stratification:

- Age groups
  - Below 18 years
  - 18–64 years
  - 65 years and above
- Sex

Statistical analysis

Patient level characteristics of new aliskiren users, including demographics, comorbidities, co-medication, and potential indication for aliskiren treatment were reported as counts and proportions. The statistical analyses were performed based on OMOP CDM mapped data using *Cohort Characteristics*. A minimum cell counts of 5 was used when reporting results, with any smaller count reported as "<5".

Objective 3: Patient-level characterisation of first-time aliskiren users (new drug user cohort, first-time user)

Population

The study population included all individuals who received a new aliskiren prescription/dispensation during the study period 01/01/2007 to 31/12/2014 and the study period 01/01/2015 to 31/12/2024 (or the end of available data), with at least 365 days of database history available prior to the first aliskiren prescription/dispensation, and without any prior exposure of aliskiren.

Variables

Exposure: Aliskiren

Covariate for characterisation:

- Cardiac events, as a composite of
  - Atrial fibrillation
  - Atrial arrhythmia other than atrial fibrillation
  - Ventricular arrhythmias
  - Sudden or unexplained death, sudden cardiac death, or unattended death
- Cardiac arrhythmia
- Atrial fibrillation
- Atrial arrhythmia other than atrial fibrillation
- Ventricular arrhythmias
- Sudden or unexplained death, sudden cardiac death, or unattended death

Covariates for stratification:

- Age groups
  - Below 18 years
  - 18–64 years
  - 65 years and above
- Sex

Statistical analysis

The number of individuals with both first-time aliskiren use and with cardiac events before/after aliskiren treatment was reported (person counts) at different assessment windows relative to the initiation of aliskiren. The statistical analyses were performed based on OMOP CDM mapped data using *CohortCharacteristics*. A minimum cell counts of 5 was used when reporting results, with any smaller count reported as "<5".

Data sources

1. Denmark: Danish Data Health Registries (DK-DHR)
2. The Netherlands: Integrated Primary Care Information (IPCI)
3. Spain: The Information System for Research on Primary Care (SIDIAP)
4. United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Study size

No sample size was calculated, as this was an exploratory study which did not test a specific hypothesis. Based on a preliminary feasibility assessment, the expected number of persons counts for aliskiren in the data sources included in this study ranged from 1,700 (IPCI) to 11,000 (SIDIAP).

Results

In the 2007–2014 study cohort, aliskiren use was identified ranging from 578 individuals (IPCI) to 10,593 individuals (SIDIAP). In the 2015–2024 study cohort, aliskiren use declined substantially, with only 45–314 individuals identified across each data source. Across both cohorts, aliskiren users were typically older adults (median age 65–69 years) with substantial cardiovascular comorbidity, particularly ischaemic heart disease and hypertension. Hypertension was frequently recorded both on or before aliskiren initiation, while resistant hypertension was identified in SIDIAP, IPCI, and CPRD GOLD, but not in DK-DHR.

Use of other antihypertensive agents was common, with medications acting on RAAS among the more frequently used drug classes, and antithrombotic therapy was also widely observed.

Cardiac events were captured in all data sources, with substantially more events observed in the 2007–2014 cohort due to larger aliskiren user populations. In the 2007–2014 cohort, cardiac events were observed in 27–465 aliskiren users within one year prior to initiation and in 19–512 users within one year after aliskiren initiation. Among the individual composite endpoints, atrial fibrillation was the most commonly observed outcome, except in DK-DHR, where atrial arrhythmia (excluding atrial fibrillation) was more frequently recorded. In the 2015–2024 cohort, cardiac events were less frequent but still present. Cardiac events were observed in 5–13 aliskiren users within one year prior to aliskiren initiation and in 7–15 users within one year after aliskiren initiation. No cardiac events were identified in CPRD GOLD.

Discussion

The study provided a detailed real-world profile of aliskiren users. Most aliskiren users were identified in the earlier period (2007–2014); consequently, more cardiac events were observed in this cohort. Within the predefined composite outcome of cardiac events, atrial fibrillation and atrial arrhythmia (excluding atrial fibrillation) were more commonly observed, whereas ventricular arrhythmia and sudden or unattended death were less common. These findings may support the feasibility of any future safety studies focusing on cardiac outcomes in aliskiren users.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Final Study Protocol	September 2025	9 September 2025
Creation of Analytical code	September 2025	10 October 2025
Execution of Analytical Code on the data	October 2025	30 October 2025
Draft Study Report	November 2025	28 November 2025
Final Study Report	To be confirmed by EMA	To be confirmed by EMA

6. RATIONALE AND BACKGROUND

Aliskiren is a direct renin inhibitor which acts to inhibit the renin activity in the renin-angiotensin aldosterone system (RAAS). Unlike the angiotensin converting enzyme inhibitor (ACEi) inhibiting the conversion of angiotensin I into angiotensin II, or the angiotensin II receptor blocker (ARB) competing with angiotensin II for the binding to angiotensin II type 1 receptor, aliskiren acts at the upstream of the RAAS axis to directly inhibit renin. It therefore prevents the conversion of angiotensinogen into angiotensin I. Aliskiren has been used for the treatment of hypertension. A Cochrane systematic review on randomised controlled trials (RCTs) with aliskiren monotherapy showed that aliskiren reduced blood pressure in adults with primary hypertension compared to placebo, with the blood pressure lowering effect being similar to ACEi and ARB.[1] The review also did not find significant difference in mortality and nonfatal serious adverse events with short term aliskiren monotherapy. Furthermore, aliskiren showed to be effective with or without amlodipine compared to hydrochlorothiazide.[2] Similar to ACEi and ARB, aliskiren increases risk of hyperkalaemia.[2]

The Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) was a randomised controlled trial evaluating the effectiveness of additional aliskiren use to the usual ACEi/ARB therapy in type 2 diabetic patients and investigating the safety of dual RAAS blockade.[3] However, study results failed to show benefit in cardiovascular events or renal outcome. There was increased risk of cardiac arrest with resuscitation, higher risk of hyperkalaemia, higher risk of renal impairment, and higher risk of hypotension with additional aliskiren use, leading to an early termination of trial. Despite being non-statistically significant when the study was terminated, the risk of stroke was increased within the aliskiren group during the interim study analysis.

Moreover, there has been a clinical case report on QT prolongation by aliskiren.[4] Animal studies showed conflicting results on aliskiren effect on cardiac electrophysiology and risk of atrial fibrillation. While one study demonstrated suppression of atrial remodelling in atrial fibrillation model with chronic aliskiren use, a more recent preclinical study published in 2020 showed an acute proarrhythmic property of aliskiren.[5]

To date, little is known about the use of aliskiren in real-world settings. Scarce literature is available on aliskiren usage and characteristics of aliskiren users, while most of the available evidence is dated.[6-11] A study using real-world data investigating use of aliskiren is warranted for a better and updated understanding of the drug user characteristics. This study described new aliskiren user's characteristics, including demographics, comorbidities, and use of co-medication of aliskiren users. The study also assessed the number of cardiac events in aliskiren users at any time to inform the feasibility of future safety study of aliskiren. Given the safety concerns, the European Medicine Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) issued restrictions on combination use of RAAS-acting agents in 2014.[12]

With this reason, study was conducted with two study periods to further distinguish aliskiren users characteristics pre- and post-implementation of restriction.

7. RESEARCH QUESTION AND OBJECTIVES

Research question

What are the characteristics of new aliskiren users in the real-world setting?

Research objectives

The objective of this study was to characterise new aliskiren users to inform the planning of potential future safety studies on aliskiren. The specific objectives were as follows:

1. To characterise new aliskiren users in terms of demographics, comorbidities, duration of use, and potential indications for aliskiren use, overall and stratified by age and by sex, during the study period of 2007–2014 and 2015–2024.
2. To assess the use of co-medication, both prior to and after new aliskiren treatment initiation, overall and stratified by age and by sex, during the study period of 2007–2014 and 2015–2024.
3. To estimate the number of people with both at least one aliskiren prescription/dispensation record(s) and a record of pre-specified cardiac events anytime during the study period of 2007–2014 and 2015–2024 (cross-cohort counts), overall and stratified by age and sex.

8. RESEARCH METHOD

8.1. Study design

A cohort study was conducted using routinely collected health data from 4 data sources from 4 countries across Europe and 3 EU member states.

The study comprised of 2 parts:

1. The patient-level characterisation of new aliskiren users (new drug user cohort) assessed baseline characteristics of new aliskiren users in terms demographics, comorbidities, duration of use, and potential indication for aliskiren use (objective 1), and described the use of co-medication prior to and after aliskiren treatment initiation (objective 2) during the study periods 01/01/2007 to 31/12/2014 and 01/01/2015 to 31/12/2024. Included aliskiren users were required to have at least 365 days of database history prior to first aliskiren prescription/dispensation. For each aliskiren prescription/dispensation, the duration of use was retrieved using the start and end date of the prescription/dispensation record. Subsequent prescription/dispensation records were combined into continuous exposure episodes (drug era) if the distance in days between end of the first exposure/era and start of the second exposure was less than 30 days. Multiple entries of the same individual into the patient-level characterisation study of new aliskiren users were allowed for individuals with multiple aliskiren drug eras, with a washout period of at least 365 days.
2. The patient-level characterisation of first-time aliskiren user (new drug user cohort, first-time user) estimated the number of first-time aliskiren users with cardiac events (any time) before/after aliskiren treatment (objective 3) during the study period 01/01/2007 to 31/12/2014 and 01/01/2015 to 31/12/2024. Included first-time aliskiren users were required to have with at least 365 days of prior database history.

Figure 1. to **Figure 3.** illustrate the HARPER diagrams corresponding to each objective, with the index date (Day 0) specified in each figure.

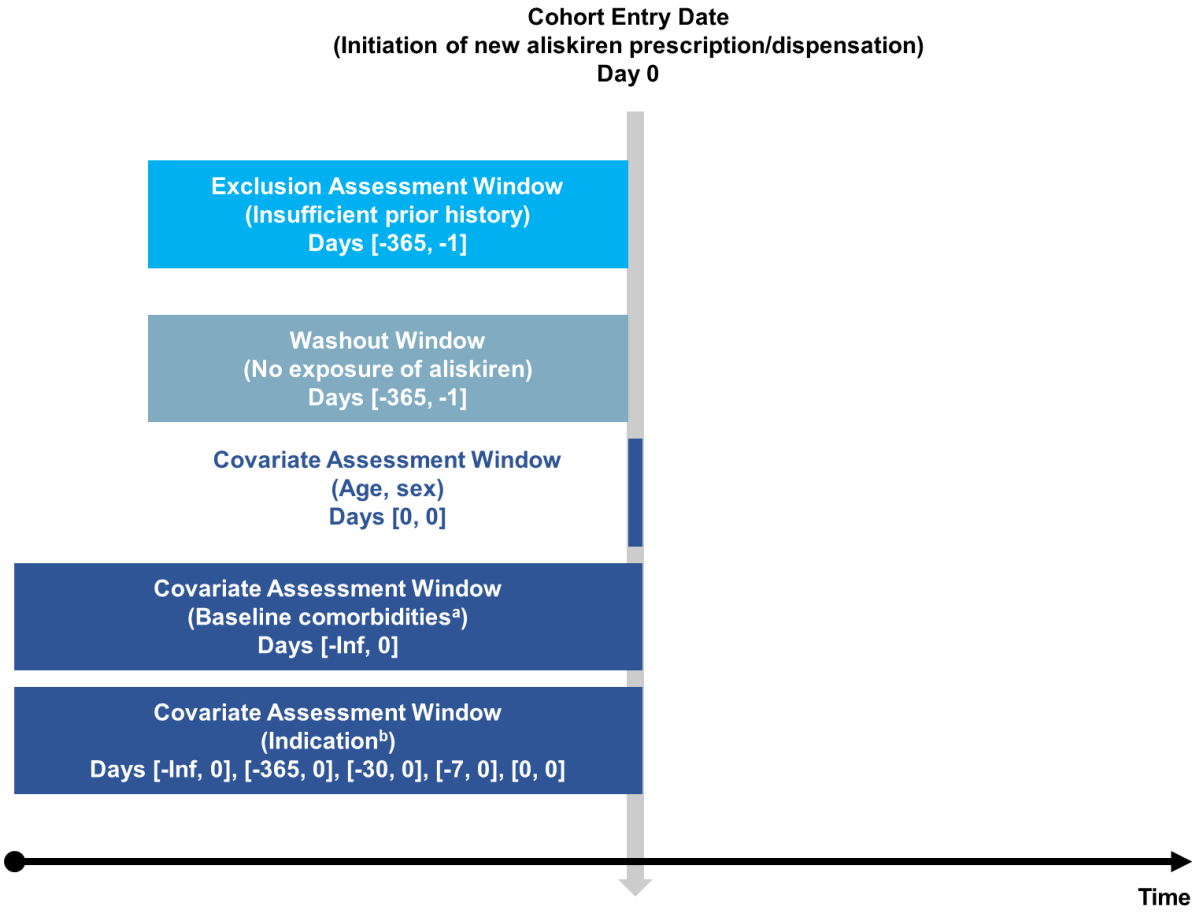

Figure 1. HARPER diagram for patient-level characterisation of new aliskiren users on baseline demographics, comorbidities, and indication (objective 1).

a. Conditions of interest for baseline comorbidities include arrhythmia, cardiomyopathy, heart failure, ischemic heart disease, myocardial infarction, stroke and transient ischaemic attach, venous thromboembolism, anxiety, chronic kidney disease, chronic liver disease, dementia, depressive disorder, diabetes, obesity, metabolic syndrome, chronic obstructive pulmonary disease, hyperthyroidism, hypothyroidism, malignant neoplastic disease, dyslipidaemia, and autoimmune diseases.
b. Conditions of interest for indication include hypertension, essential hypertension, and resistant hypertension.

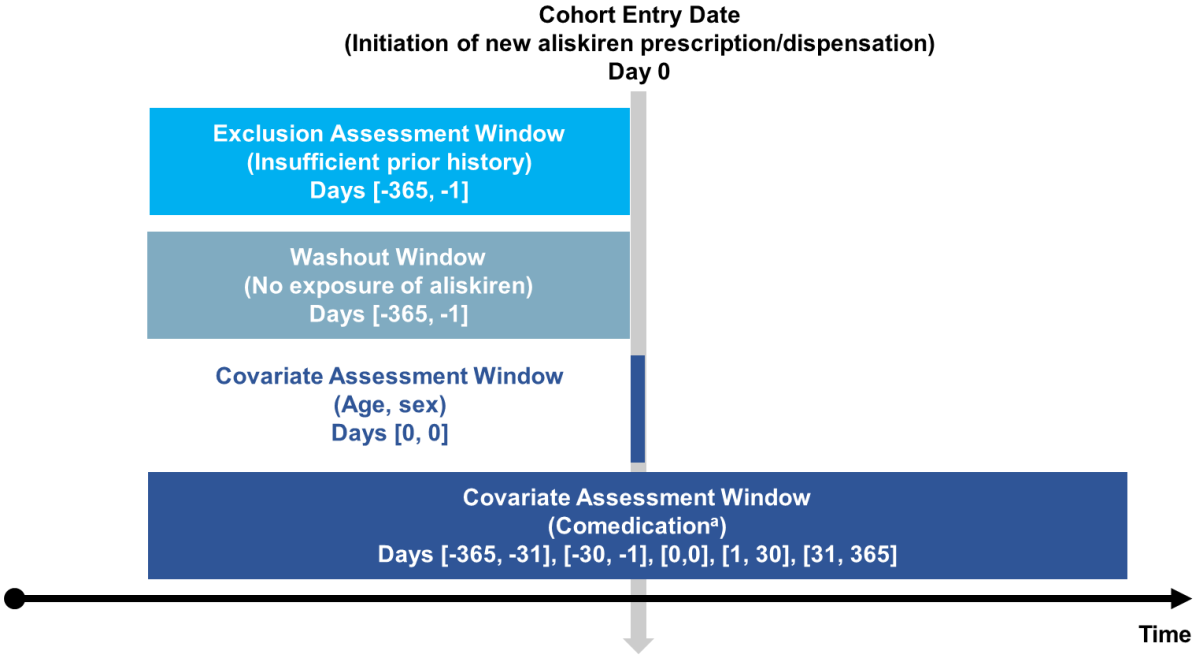

Figure 2. HARPER diagram for patient-level characterisation of new aliskiren users on use of medications (objective 2).

a. Medications of interest include agents acting on the renin-angiotensin system (excluding aliskiren), beta blocking agents (systemic), calcium channel blockers, diuretics, other antihypertensive agents, antiarrhythmic agents, antithrombotic agents, digoxin, ivabradine, nicorandil, acetylcholinesterase inhibitor, antibacterials for systemic use (overall, macrolides, fluoroquinolones), antifungals for systemic use, antidepressants, antiemetics, antimalarial agents, antineoplastic agents, opioids, psycholeptics, psychostimulants, statins, antidiabetic agents, systemic corticosteroids, antihistamines for systemic use, and non-steroidal anti-inflammatory drugs for systemic use.

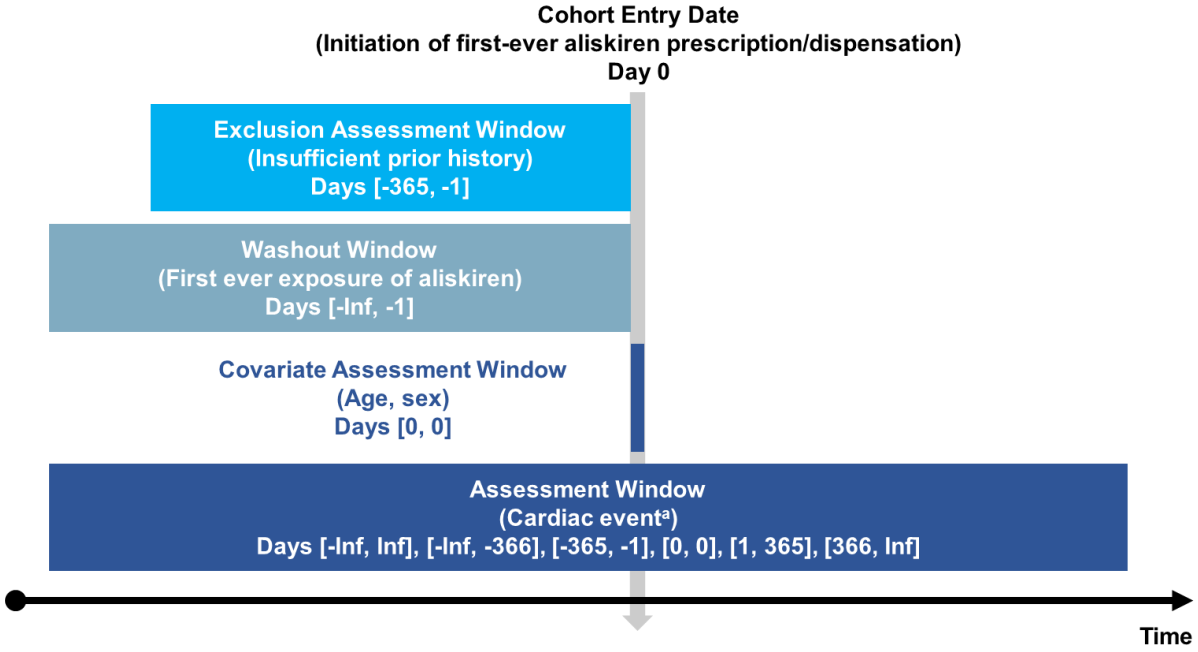

Figure 3. HARPER diagram for patient-level characterisation of first-time aliskiren users on cardiac events (objective 3).

a. Conditions of interest include cardiac events (defined as a composite of atrial fibrillation, atrial arrhythmias other than atrial fibrillation, ventricular arrhythmias, and sudden or unexplained death/sudden cardiac death/unattended death), individual outcomes of cardiac events, and cardiac arrhythmia.

8.2. Follow-up

None.

8.3. Study population with inclusion and exclusion criteria

All objectives

Inclusion criteria

- All individuals with an aliskiren prescription or dispensing record within the study periods: 01/01/2007 to 31/12/2014 and from 01/01/2015 to 31/12/2024 (or the latest available date)

Exclusion criteria

- Individuals starting first ever aliskiren with less than 365 days prior database history

8.4. Study setting and data sources

This study was conducted using routinely collected data from 4 primary care data sources in the DARWIN EU® network of data partners from 4 European countries in 3 EU member states. All data were a priori mapped to the OMOP CDM.

Data sources

1. Denmark: Danish Data Health Registries (DK-DHR)
2. The Netherlands: Integrated Primary Care Information (IPCI)
3. Spain: The Information System for Research on Primary Care (SIDIAP)
4. United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Table 1. Data sources.

Country	Name of Data source	Health Care setting	Type of Data	Number of active individuals	Calendar period covered by each data source	Contributing to
Denmark	Danish Data Health Registries (DK-DHR)	Primary care, secondary care, hospital care	EHR, registries	6.0 million	01/2007 – 11/2024 [a]	All objectives
The Netherlands	Integrated Primary Care Information (IPCI)	Primary care	EHR	1.3 million	01/2007 – 12/2024	All objectives
Spain	The Information System for Research on Primary Care (SIDIAP)	Primary care, hospital care	EHR	6.0 million	01/2007 – 06/2023	All objectives
United Kingdom	Clinical Practice	Primary care	EHR	2.6 million	01/2007 – 12/2024	All objectives

Country	Name of Data source	Health Care setting	Type of Data	Number of active individuals	Calendar period covered by each data source	Contributing to
	Research Datalink GOLD (CPRD GOLD)					

a. Observation period of DK-DHR was until 11/2024, while drug records were only available until 30/09/2024.

Data sources selection

These data sources fulfilled the criteria required in terms of data quality, completeness, timeliness, and representativeness for this cohort study while covering different regions of Europe.

When it came to assessing the reliability of data sources, the data partners were 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 utilised the *Achilles* tool, which systematically characterises the data and generates data characteristics such as age distribution, condition prevalence per year, and data density. Data density includes information on 1) monthly record counts by data domain (which offers insights into data collection patterns and the start date of each data source) and 2) measurement value distribution (i.e., min, max, quartiles for numeric values per measurement concept and per unit and counts for discrete measurement-value pairs). The latter can be compared against expectations for the data based on predefined standards, historical trends, or known epidemiological patterns to identify potential anomalies or inconsistencies. Additionally, the data quality dashboard (DQD) provides more objective checks on plausibility of data completeness, consistency, and conformity across the data sources.

In terms of relevance, the selection of data sources was based on the number of person counts with aliskiren use in the database and availability of records on cardiac outcome to perform the described analyses. In addition, the data sources were chosen considering their ability to support timely IRB approvals, thus ensuring alignment with the timeline established by stakeholders for the conduct of this study. Details on data source justification and key characteristics were given in the **ANNEX II Fitness for use assessment**.

The DARWIN EU® portal, as well as information from the onboarding documents, were used to assess whether data sources have information on aliskiren use and cardiac events. Data within the DARWIN EU® portal is maintained up to date by extracting the release dates for each dataset in the network and monitoring when data are out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it is important to have clear understanding of the time covered by each released data source, as this can vary across different domains. To facilitate this, the *CDMOnboarding* (and *Achilles*) packages contain a 'data density' plot. This plot displays the number of records per OMOP domain monthly. This allows to get insights when data collection started, when new sources of data were added and until when data was included. In addition, at time of inviting data partners, they were informed about study objectives and asked whether they could participate in the study.

More general-purpose diagnostic tools, *PhenotypeR[13]* and *DrugExposureDiagnostics[14]*, have been developed. The *PhenotypeR* package provides additional insights into cohort characteristics, record counts and index event misclassification.[13] The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records.[14] Upon finalisation of the study protocol and creation of the disease and drug cohorts of interest by DARWIN EU® Coordination Centre, these packages will be executed in each data sources by each data partners.

8.5. Study period

The study period was from 01/01/2007 to 31/12/2014 and from 01/01/2015 to 31/12/2024, or the most recent data available for each contributing data source.

8.6. Variables

8.6.1. Exposure

Objective 1 and 2: Patient-level characterisation of new aliskiren users (new drug user cohort)

In these objectives, exposure was defined as the aliskiren drug era. For each aliskiren prescription/dispensation, the duration of use was retrieved using the start and end date of the prescription/dispensation record. Subsequent prescription/dispensation records were combined into continuous exposure episodes (drug era) if the distance in days between end of the first exposure/era and start of the second exposure was less than 30 days. Multiple entries of the same individual into the patient-level characterisation study of new aliskiren users were allowed for those individuals with multiple aliskiren drug eras, if the second aliskiren era started at least 1 year after the first drug era ended (washout period of 365 days). Subsequent aliskiren drug era was regarded as new aliskiren user.

Objective 3: Patient-level characterisation of first-time aliskiren users (new drug user cohort, first time user)

In this objective, exposure was defined as the first-ever prescription/dispensation record of aliskiren (first-time aliskiren user).

The concept set used for the identification of exposure was described in **ANNEX IV Table S1**. These codes were refined during the study execution following the DARWIN EU® phenotyping standard processes, which involved the review of code lists by clinical experts, and the review of phenotypes after their execution in the participating data sources.

8.6.2. Outcome

None.

8.6.3. Covariates, including confounders, effect modifiers, intercurrent events, and other variables

Objective 1 and 2: Patient-level characterisation of new aliskiren users (new drug user cohort)

The following covariates were used to characterise new aliskiren users in terms of demographics, assessed on the index date [0,0]:

- Sex
- Age
- Age groups
    - Below 18 years
    - 18–64 years
    - 65 years and above

The following covariates were used to characterise new aliskiren users in terms of comorbidities, with the assessment window [-Inf, 0]:

- Cardiovascular- and cerebrovascular-related: cardiac arrhythmia, cardiomyopathy, heart failure, ischemic heart disease, myocardial infarction, stroke and transient ischaemic attack, venous thromboembolism

- Others: anxiety, chronic kidney disease, chronic liver disease, depressive disorder, dementia, diabetes, obesity, metabolic syndrome, chronic obstructive pulmonary disease, hyperthyroidism, hypothyroidism, malignant neoplastic disease, dyslipidaemia, autoimmune diseases.

The following covariates were used to characterise new aliskiren users in terms of potential indication of treatment, with the assessment window [-Inf, 0], [-365, 0], [-30, 0], [-7, 0], and [0, 0]:

- Hypertension, defined as:
    - (i) Condition or observation of hypertension (including essential hypertension, secondary hypertension, malignant hypertension, and resistant hypertension) AND not pregnancy-related, or (ii) Measurement of systolic blood pressure equal to or over 140 mmHg or diastolic blood pressure equal to or over 90 mmHg, on at least two different days within one year[15, 16] (if data available)
- Essential Hypertension, defined as:
    - (i) Condition or observation of essential hypertension, or (ii) Measurement of systolic blood pressure equal to or over 140 mmHg or diastolic blood pressure equal to or over 90 mmHg, on at least two different days within one year[15, 16] (if data available)
    - Excluding individuals with secondary hypertension
- Resistant hypertension, defined as:
    - (i) Condition or observation of resistant hypertension AND not pregnancy-related, or (ii) 'Hypertension' as described above AND measurement of systolic blood pressure equal to or over 140 mmHg or diastolic blood pressure equal to or over 90 mmHg while on three or more antihypertensive medications[17, 18]

The following covariates were used to characterise new aliskiren users in terms of indication of comedications, with the assessment window [-365, -31], [-30, -1], [0, 0], and [1, 30], [31, 365]:

- Agents acting on the renin-angiotensin aldosterone system (excluding aliskiren), beta blocking agents (systemic), calcium channel blockers, diuretics, other antihypertensive agents
- Antiarrhythmic agents, antithrombotic agents, digoxin, ivabradine, nicorandil
- Others: acetylcholinesterase inhibitor, antibacterials for systemic use (overall, macrolides, fluoroquinolones), antifungals for systemic use, antidepressants, antiemetics, antimalarial agents, antineoplastic agents, opioids, psycholeptics, psychostimulants, statins, antidiabetic agents, systemic corticosteroids, antihistamines for systemic use, and non-steroidal anti-inflammatory drugs for systemic use.

The following covariates were used to stratify results of characterisation in terms of comorbidities, indication of treatment, and comedications, assessed on the index date [0,0]:

- Sex
- Age groups
    - Below 18 years
    - 18–64 years
    - 65 years and above

Objective 3: Patient-level characterisation of first-time aliskiren users (new drug user cohort, first-time user)

The following covariates were used to characterise first-time aliskiren users in terms of cardiac events, with the assessment window [-Inf, Inf], [-Inf, -366], [-365, -1], [0, 0], [1, 365], [366, Inf]:

- Cardiac event, as a composite of:
    - Atrial fibrillation
    - Atrial arrhythmias other than atrial fibrillation
    - Ventricular arrhythmias
    - Sudden or unexplained death, sudden cardiac death, or unattended death
- Cardiac arrhythmia
- Atrial fibrillation
- Atrial arrhythmias other than atrial fibrillation
- Ventricular arrhythmias
- Sudden or unexplained death, sudden cardiac death, or unattended death

The following covariates were used to stratify results of characterisation in terms of cardiac events, assessed on the index date [0,0]:

- Sex
- Age groups
    - Below 18 years
    - 18–64 years
    - 65 years and above

The concept sets used for the identification of cardiac events were described in **ANNEX IV Table S2.** These codes were refined during the study execution following the DARWIN EU® phenotyping standard processes, which involved the review of code lists by clinical experts, and the review of phenotypes after their execution in the participating data sources.

8.7. Study size

No sample size was calculated, as this was a patient level characterisation study which did not test a specific hypothesis. In addition, we used already collected available data to estimate the number of aliskiren users. Based on a preliminary feasibility assessment, the expected number of persons counts for aliskiren in the data sources included in this study ranged from 1,700 (IPCI) to 11,000 (SIDIAP).

8.8. Data transformation

Analyses were conducted separately for each data source. Before study initiation, test runs of the analyses were performed on a subset of the data sources and quality control checks were performed. Once all the tests passed (see **Annex III**), the final study codes package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP CDM in R Studio and reviewed and approved the, by default, aggregated results.

The study results of all data sources were checked, after which they were made available to the team, and the dissemination phase started. All results were locked and timestamped for reproducibility and transparency.

8.9. Statistical methods

8.9.1. Main summary measures

Patient characterisation in terms of comorbidities, potential indications, comedications, and cardiac events were provided as overall and stratified by age and by sex. For each characteristic (unless otherwise specified), the number of persons (N, %) will be provided. Age will be provided both mean (SD) and median (IQR).

8.9.2. Main statistical methods

Drug era definition

Drug eras were defined as follows: exposure started at date of the first prescription after a washout of 365 days. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM, using the start and end date of the exposure. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) if the distance in days between end of the first exposure/era and start of the second exposure was ≤30 days.

Patient-level characterisation of new aliskiren users (Objective 1 and 2)

Patient characterisation for predefined conditions of interest before/on index date (start date of the new aliskiren prescription/dispensation) were provided for each new aliskiren prescription/dispensation after washout period (*Objective 1*). Covariates were extracted for the following time intervals: demographic information were assessed on the index date; predefined comorbidities were assessed from any time before index date to index date; predefined indications for aliskiren treatment were assessed from any time before index date to index date, from -365 days to index date, from -30 days to index date, from -7 days to index date, and on index date.

Patient characterisation by predefined medications of interest before/on/after index date were provided for each new aliskiren prescription/dispensation after the washout period *(Objective 2)*. Covariates on the predefined comedications were assessed from -365 days to -31 days, -30 days to -1 day, on index date, and 1 day to 30 days after index date, and 31 days to 365 days after index date.

List of pre-defined covariates of interest are given in **Section 8.6.3**.

Patient-level characterisation of first-time aliskiren users (Objective 3)

Patient characterisation by predefined cardiac events before/on/after index date (start date of the first-time aliskiren prescription/dispensation) were provided for the first aliskiren prescription/dispensation record of each aliskiren user *(Objective 3)*. Covariates on the predefined cardiac events were assessed from any time before to any time after index date, from any time before index date to -366 days, from -365 days to -1 day, on index date, from 1 day to 365 days, and from 366 days to any time after index date.

List of predefined covariates of interest are given in **Section 8.6.3**.

9. RESULTS

The full set of results for this study is available through an interactive web-application ShinyApp at EUPAS1000000768.

9.1. Participants

A total of 87,609 aliskiren drug records from 7,674 individuals (DK-DHR), 67,488 drug records from 3,377 individuals (IPCI), 26,789 drug records from 10,902 individuals (SIDIAP), and 51,984 drug records from 2,217 individuals (CPRD GOLD) were identified. 84 drug records from DK-DHR and 34,037 drug records from IPCI were excluded, as they were outside the observation period of 2007–2024. After excluding records outside observation period and calculating drug era, 31,902 drug era records from 7,663 individuals (DK-DHR), 4,739 drug era records from 1,979 individuals (IPCI), 13,480 drug era records from 10,902 individuals (SIDIAP), and 4,845 drug era records from 2,217 individuals (CPRD GOLD) were retained. Following the application of cohort requirements, including a prior observation period of 365 days and a washout period of 365 days, the final aliskiren new user cohorts consisted of 7,916 drug era records from 7,644 individuals (DK-DHR), 942 drug era records from 868 individuals (IPCI), 11,026 drug era records from 10,772 individuals (SIDIAP), and 2,058 drug era records from 2,022 individuals (CPRD GOLD).

9.2. Descriptive data

The characterisation of aliskiren users is presented in the section below: **9.3 Main results**.

9.3. Main results

Objective 1: Patient-level characterisation of new aliskiren users on baseline demographics, comorbidities, duration of use, and potential indication

Detailed results on the patient-level characterisation of baseline demographics, comorbidities, duration of use, and potential indication of new aliskiren users are provided in **Table 1**.

Study period 2007–2014

A total of 7,671 drug era records from 7,471 individuals (DK-DHR), 603 drug era records from 578 individuals (IPCI), 10,806 drug era records from 10,593 individuals (SIDIAP), and 2,012 drug era records from 1,983 individuals (CPRD GOLD) were identified for the 2007–2014 aliskiren new-user cohort. The median age ranged from 65 to 69 across the included data sources. A slightly higher proportion of females was observed in CPRD GOLD (55.3%) and IPCI (55.9%), but not in DK-DHR (47.2%) or SIDIAP (49.9%). The median duration of aliskiren use ranged from 80 days (DK-DHR) to 392 days (SIDIAP).

Approximately 10–20% of new aliskiren users had a medical history of ischaemic heart disease and 2.4–7.1% had myocardial infarction. A history of stroke was observed in 4.8–9.5% of new users and venous thromboembolism in 0.6–2.6%. History of cardiac arrhythmia at baseline was observed in 8.3–14.2%. Apart from cardiovascular and cerebrovascular comorbidities, 17.6–33.8% of new aliskiren users were diabetic. Obesity was observed in 10.4–13.7% of users in three data sources, but only 1.7% in IPCI. Malignant neoplastic disease was observed in 6.0–11.7%.

Potential indication for aliskiren use was assessed using different time windows. The study used both condition codes and measurement records to define hypertension. Hypertension was identified in 54.8–94.3% within one year prior to aliskiren initiation and in 77.3–98.7% when considering all medical history. Essential hypertension was observed in 21.6–92.5% of users within one year prior to aliskiren initiation and in 49.5–98.5% when considering all medical history. Resistant hypertension was observed in 21.1–62.9% of users in IPCI, SIDIAP, and CPRD GOLD within one year prior to initiation, and 26.6–78.2% when considering all medical history. No resistant hypertension was observed in DK-DHR.

Study period 2015–2024

A total of 245 drug era records from 230 individuals (DK-DHR), 339 drug era records from 314 individuals (IPCI), 220 drug era records from 213 individuals (SIDIAP), and 46 drug era records from 45 individuals (CPRD GOLD) were identified for the 2015–2024 aliskiren new-user cohort. The median age ranged from 66 to 69, with a slightly higher proportion of females in CPRD GOLD (52.2%) and IPCI (59.3%), but not in DK-DHR (49.4%) or SIDIAP (43.6%). Median duration of aliskiren use ranged from 56 days (CPRD GOLD) to 252 days (SIDIAP).

Common cardiovascular and cerebrovascular comorbidities included ischaemic heart disease (10.9–24.9%, excluding CPRD GOLD) and cardiac arrhythmia (9.4–20.8%, excluding CPRD GOLD). Prior history of stroke was observed in 5.5–14.7% of new aliskiren users. Diabetes (15.2–19.1%), obesity (4.1–28.6%), and chronic renal disease (1.8–23.2%) were more common among the other comorbidities. COPD was present in 6.5–13.1%, depressive disorder in 5.6–24.1%, anxiety in 11.4–28.3%, autoimmune disease in 9.1–22.9%, and malignant neoplastic disease in 10.9–18.4%.

Hypertension was recorded in 42.3–81.6% within one year prior, and up to 85.5–94.3% when considering all medical history before initiation.

Characteristics of aliskiren users stratified by age group and sex are available in the Shiny app EUPAS1000000768. A slightly higher proportion of cardiovascular and cerebrovascular comorbidities was observed in individuals aged 65 years or above than in younger individuals across all data sources, while patterns for other comorbidities were mostly similar.

When stratified by sex, median age was slightly higher among women, while duration of aliskiren use was slightly longer among men in CPRD GOLD, IPCI, and SIDIAP, but not in DK-DHR. Ischaemic heart disease and myocardial infarction were consistently more common in men, but other cardiovascular and cerebrovascular comorbidities showed inconsistent patterns. Diabetes was also more common in men, whereas hypothyroidism and autoimmune disease were more common in women. Depressive disorder and anxiety were significantly more common in women in CPRD GOLD, DK-DHR, and SIDIAP, with up to double the proportion observed in men, while the pattern was similar in IPCI. The ability to identify hypertension was slightly higher in women than in men.

Table 1: Baseline demographics, comorbidities of new aliskiren users, duration of use, and potential indication of aliskiren treatment.

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren users (2007–2014)				Aliskiren users (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
Number records	–	N	7,671	603	10,806	2,012	245	339	220	46
Number subjects	–	N	7,471	578	10,593	1,983	230	314	213	45
Age	–	Median [Q25–Q75]	65 [58–74]	67 [58–75]	69 [60–77]	69 [60–77]	68 [60–75]	69 [59–76]	66 [56–74]	66 [54–75]
		Mean (SD)	65.14 (11.82)	65.53 (12.35)	67.61 (12.34)	67.65 (12.54)	67.14 (11.02)	67.47 (12.25)	64.19 (14.64)	63.80 (14.17)
		Range	8 to 99	26 to 94	15 to 99	20 to 95	35 to 94	31 to 96	9 to 97	21 to 86
Age group	<18	N (%)	<5	–	6 (0.06%)	–	–	–	<5	–
	18 to 64	N (%)	3,552 (46.30%)	270 (44.78%)	4,010 (37.11%)	750 (37.28%)	88 (35.92%)	123 (36.28%)	99 (45.00%)	22 (47.83%)
	>=65	N (%)	4,116 (53.66%)	333 (55.22%)	6,790 (62.84%)	1,262 (62.72%)	157 (64.08%)	216 (63.72%)	120 (54.55%)	24 (52.17%)
Sex	Female	N (%)	3,620 (47.19%)	337 (55.89%)	5,387 (49.85%)	1,112 (55.27%)	121 (49.39%)	201 (59.29%)	96 (43.64%)	24 (52.17%)
	Male	N (%)	4,051 (52.81%)	266 (44.11%)	5,419 (50.15%)	900 (44.73%)	124 (50.61%)	138 (40.71%)	124 (56.36%)	22 (47.83%)
Duration of use	–	Median [Q25–Q75]	80 [30–185]	155 [62–450]	392 [91–826]	182 [56–667]	116 [28–420]	117 [38–381]	252 [61–1,034]	56 [28–110]
		Mean (SD)	177.44 (312.01)	366.78 (574.75)	614.76 (774.81)	490.78 (699.59)	372.13 (628.66)	351.42 (524.29)	652.76 (800.19)	226.00 (496.11)
Potential indications [-Inf, 0]	Hypertension	N (%)	5,932 (77.33%)	522 (86.57%)	9,025 (83.52%)	1,986 (98.71%)	231 (94.29%)	301 (88.79%)	186 (84.55%)	43 (93.48%)

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren users (2007–2014)				Aliskiren users (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	Essential hypertension	N (%)	3,794 (49.46%)	485 (80.43%)	8,928 (82.62%)	1,981 (98.46%)	167 (68.16%)	281 (82.89%)	181 (82.27%)	42 (91.30%)
	Resistant hypertension	N (%)	0 (0.00%)	251 (41.63%)	2,877 (26.62%)	1,573 (78.18%)	17 (6.94%)	123 (36.28%)	67 (30.45%)	31 (67.39%)
Potential indications [-365, 0]	Hypertension	N (%)	4,202 (54.78%)	470 (77.94%)	6,533 (60.46%)	1,897 (94.28%)	200 (81.63%)	257 (75.81%)	93 (42.27%)	34 (73.91%)
	Essential hypertension	N (%)	1,660 (21.64%)	418 (69.32%)	6,366 (58.91%)	1,861 (92.50%)	73 (29.80%)	228 (67.26%)	83 (37.73%)	31 (67.39%)
	Resistant hypertension	N (%)	0 (0.00%)	203 (33.67%)	2,275 (21.05%)	1,265 (62.87%)	<5	65 (19.17%)	32 (14.55%)	14 (30.43%)
Potential indications [-30, 0]	Hypertension	N (%)	2,450 (31.94%)	313 (51.91%)	3,278 (30.33%)	1,542 (76.64%)	167 (68.16%)	161 (47.49%)	36 (16.36%)	26 (56.52%)
	Essential hypertension	N (%)	743 (9.69%)	266 (44.11%)	3,189 (29.51%)	1,458 (72.47%)	39 (15.92%)	144 (42.48%)	35 (15.91%)	22 (47.83%)
	Resistant hypertension	N (%)	0 (0.00%)	92 (15.26%)	1,067 (9.87%)	815 (40.51%)	0 (0.00%)	30 (8.85%)	13 (5.91%)	9 (19.57%)
Potential indications [-7, 0]	Hypertension	N (%)	1,911 (24.91%)	264 (43.78%)	2,328 (21.54%)	1,333 (66.25%)	155 (63.27%)	130 (38.35%)	23 (10.45%)	18 (39.13%)
	Essential hypertension	N (%)	474 (6.18%)	220 (36.48%)	2,276 (21.06%)	1,219 (60.59%)	23 (9.39%)	114 (33.63%)	23 (10.45%)	14 (30.43%)
	Resistant hypertension	N (%)	0 (0.00%)	65 (10.78%)	742 (6.87%)	653 (32.46%)	0 (0.00%)	21 (6.19%)	8 (3.64%)	6 (13.04%)
Potential indications [0, 0]	Hypertension	N (%)	1,568 (20.44%)	239 (39.64%)	1,871 (17.31%)	1,211 (60.19%)	141 (57.55%)	108 (31.86%)	16 (7.27%)	17 (36.96%)

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren users (2007–2014)				Aliskiren users (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	Essential hypertension	N (%)	166 (2.16%)	194 (32.17%)	1,832 (16.95%)	1,081 (53.73%)	8 (3.27%)	93 (27.43%)	16 (7.27%)	11 (23.91%)
	Resistant hypertension	N (%)	0 (0.00%)	55 (9.12%)	582 (5.39%)	579 (28.78%)	0 (0.00%)	17 (5.01%)	5 (2.27%)	<5
Cardiovascular- and cerebrovascular-related comorbidities [-Inf, 0]	Ischemic heart disease	N (%)	1,401 (18.26%)	77 (12.77%)	1,047 (9.69%)	241 (11.98%)	61 (24.90%)	54 (15.93%)	24 (10.91%)	<5
	Myocardial infarction	N (%)	546 (7.12%)	26 (4.31%)	370 (3.42%)	48 (2.39%)	22 (8.98%)	22 (6.49%)	9 (4.09%)	0 (0.00%)
	Cardiac arrhythmia	N (%)	795 (10.36%)	50 (8.29%)	1,536 (14.21%)	172 (8.55%)	51 (20.82%)	32 (9.44%)	36 (16.36%)	<5
	Cardiomyopathy	N (%)	62 (0.81%)	<5	270 (2.50%)	8 (0.40%)	5 (2.04%)	<5	5 (2.27%)	0 (0.00%)
	Heart failure	N (%)	424 (5.53%)	43 (7.13%)	809 (7.49%)	63 (3.13%)	26 (10.61%)	15 (4.42%)	13 (5.91%)	<5
	Stroke	N (%)	732 (9.54%)	47 (7.79%)	516 (4.78%)	154 (7.65%)	36 (14.69%)	35 (10.32%)	12 (5.45%)	6 (13.04%)
	Venous thromboembolism	N (%)	68 (0.89%)	13 (2.16%)	62 (0.57%)	53 (2.63%)	<5	9 (2.65%)	5 (2.27%)	<5
Other comorbidities [-Inf, 0]	Diabetes mellitus	N (%)	2,595 (33.83%)	106 (17.58%)	2,599 (24.05%)	503 (25.00%)	45 (18.37%)	54 (15.93%)	42 (19.09%)	7 (15.22%)
	Dyslipidaemia	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Obesity	N (%)	798 (10.40%)	10 (1.66%)	1,254 (11.60%)	276 (13.72%)	36 (14.69%)	14 (4.13%)	63 (28.64%)	6 (13.04%)
	Metabolic syndrome	N (%)	0 (0.00%)	0 (0.00%)	9 (0.08%)	9 (0.45%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)
	Chronic renal disease	N (%)	172 (2.24%)	0 (0.00%)	1,319 (12.21%)	590 (29.32%)	13 (5.31%)	6 (1.77%)	51 (23.18%)	10 (21.74%)

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren users (2007–2014)				Aliskiren users (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	Chronic liver disease	N (%)	73 (0.95%)	7 (1.16%)	340 (3.15%)	11 (0.55%)	<5	6 (1.77%)	22 (10.00%)	<5
	Hyperthyroidism	N (%)	123 (1.60%)	6 (1.00%)	0 (0.00%)	17 (0.84%)	5 (2.04%)	<5	0 (0.00%)	<5
	Hypothyroidism	N (%)	365 (4.76%)	26 (4.31%)	426 (3.94%)	145 (7.21%)	25 (10.20%)	22 (6.49%)	23 (10.45%)	<5
	Chronic obstructive pulmonary disease	N (%)	573 (7.47%)	41 (6.80%)	693 (6.41%)	106 (5.27%)	32 (13.06%)	22 (6.49%)	17 (7.73%)	5 (10.87%)
	Dementia	N (%)	47 (0.61%)	<5	152 (1.41%)	5 (0.25%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)
	Depressive disorder	N (%)	1,169 (15.24%)	11 (1.82%)	647 (5.99%)	250 (12.43%)	59 (24.08%)	19 (5.60%)	30 (13.64%)	9 (19.57%)
	Anxiety	N (%)	382 (4.98%)	45 (7.46%)	699 (6.47%)	261 (12.97%)	28 (11.43%)	49 (14.45%)	48 (21.82%)	13 (28.26%)
	Autoimmune disease	N (%)	861 (11.22%)	31 (5.14%)	411 (3.80%)	254 (12.62%)	56 (22.86%)	31 (9.14%)	20 (9.09%)	9 (19.57%)
	Malignant neoplastic disease	N (%)	898 (11.71%)	50 (8.29%)	651 (6.02%)	168 (8.35%)	45 (18.37%)	62 (18.29%)	29 (13.18%)	5 (10.87%)

CPRD GOLD=Clinical Practice Research Datalink GOLD, DK-DHR=Danish Data Health Registries, IPCI=Integrated Primary Care Information, SIDIAP=The Information System for Research on Primary Care.

Objective 2: Patient-level characterisation of new aliskiren users on use of medications

Use of antihypertensive medication and cardiovascular-/cerebrovascular-related medication was characterised in new aliskiren users across different assessment windows (**Table 2**).

Study period 2007–2014

Use of other medication acting on RAAS decreased from 71.5–88.8% in the assessment window one year before to one month before aliskiren initiation ([-365, -31]), 57.2–75.4% within one month before aliskiren initiation ([-30, -1]), to 48.6–68.1% on the date of aliskiren initiation ([0, 0]), followed by an increase to 52.0–72.0% within one month after aliskiren initiation ([1, 30]), and further to 57.8–78.1% in the assessment window of one month to one year after aliskiren initiation ([31, 365]). A similar pattern was observed in beta blocker (26.4–51.6% in [-365, -31], 23.2–41.6% on [0, 0], 29.7–53.5% in [31, 365]), calcium channel blocker (41.8–66.7% in [-365, -31], 32.0–44.8% on [0, 0], 46.2–63.4% in [31, 365]), diuretics (58.0–80.1% in [-365, -31], 47.0–57.6% on [0, 0], 66.3–80.8% in [31, 365]), and other antihypertensives (9.8–47.5% in [-365, -31], 6.4–31.7% on [0, 0], 10.8–41.2% in [31, 365]).

Most data sources followed the general observed pattern. Exceptions were the slightly lower use of beta blockers, calcium channel blockers, diuretics, and other antihypertensives in [-30, -1] than on [0, 0] in IPCI, and lower use of diuretics in [-30, -1] than on [0 ,0] in SIDIAP.

Use of medication acting on RAAS excluding aliskiren was more common in [-365, -31] (71.5–88.8%) than in [31, 365] (57.8–78.1%), while a mixed pattern was observed in other antihypertensive classes.

Use of other cardiovascular- or cerebrovascular-related medication was less common, except for antithrombotic medication, which was observed in 32.7–46.8% of users in [-365, -31], 24.0–34.1% on [0, 0], and 39.5–50.6% in [31, 365]. Use of antithrombotic medication was more common in [31, 365] than in [-365, -31]. Antiarrhythmic medication was observed in only 0.3–2.7% of users, and digoxin in 1.9–3.1% on [0, 0]. Ivabradine and nicorandil use was rare.

Study period 2015-2024

A similar pattern in use of antihypertensive medication was observed across different assessment windows in the cohort of 2015–2024.

Use of medication acting on RAAS excluding aliskiren decreased from 54.9–73.5% in [-365, -31] to 26.4–57.1% on [0, 0], and increased to 33.2–64.9% in [31, 365]. That was also observed in beta blocker (27.3–58.4% in [-365, -31], 29.1–35.4% on [0, 0], and 34.4–58.0% in [31, 365]), calcium channel blocker (40.5–63.7% in [-365, -31], 31.0–53.1% on [0, 0], and 43.3–62.9% in [31, 365]), diuretics (52.2–73.1% in [-365, -31], 37.0–57.3% on [0, 0], 53.5–72.2% in [31, 365]), and in other antihypertensives (12.4–28.3% in [-365, -31], 8.0–14.3% on [0, 0], 10.1–30.2% in [31, 365]).

Use of other cardiovascular- or cerebrovascular-related medication remained uncommon among new aliskiren users during 2015–2024, except for antithrombotic medication, which was recorded in 21.7–37.6% in [-365, -31], 13.0–31.8% on [0, 0], and 27.9–42.0% in [31, 365]. The very low counts or suppressed results for some medications may be attributable to the small number of aliskiren users during this later period.

Table 2: Use of antihypertensive, cardiovascular, and cerebrovascular medications in new aliskiren users.

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren users (2007–2014)				Aliskiren users (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
Number records	–	N	7,671	603	10,806	2,012	245	339	220	46
Number subjects	–	N	7,471	578	10,593	1,983	230	314	213	45
Antihypertensive medications [-365, -31]	RAAS excl aliskiren	N (%)	6,813 (88.82%)	441 (73.13%)	7,722 (71.46%)	1,734 (86.18%)	180 (73.47%)	186 (54.87%)	124 (56.36%)	31 (67.39%)
	Beta blocker	N (%)	3,697 (48.19%)	311 (51.58%)	2,857 (26.44%)	877 (43.59%)	143 (58.37%)	127 (37.46%)	60 (27.27%)	18 (39.13%)
	Calcium channel blocker	N (%)	5,118 (66.72%)	269 (44.61%)	4,512 (41.75%)	1,325 (65.85%)	156 (63.67%)	158 (46.61%)	89 (40.45%)	20 (43.48%)
	Diuretics	N (%)	6,141 (80.05%)	373 (61.86%)	6,265 (57.98%)	1,447 (71.92%)	179 (73.06%)	177 (52.21%)	115 (52.27%)	32 (69.57%)
	Other antihypertensives	N (%)	984 (12.83%)	59 (9.78%)	1,371 (12.69%)	956 (47.51%)	44 (17.96%)	42 (12.39%)	29 (13.18%)	13 (28.26%)
Antihypertensive medications [-30, -1]	RAAS excl aliskiren	N (%)	4,781 (62.33%)	345 (57.21%)	7,326 (67.80%)	1,517 (75.40%)	146 (59.59%)	130 (38.35%)	107 (48.64%)	16 (34.78%)
	Beta blocker	N (%)	2,432 (31.70%)	241 (39.97%)	2,593 (24.00%)	744 (36.98%)	98 (40.00%)	95 (28.02%)	53 (24.09%)	13 (28.26%)
	Calcium channel blocker	N (%)	3,178 (41.43%)	189 (31.34%)	3,962 (36.66%)	1,017 (50.55%)	128 (52.24%)	103 (30.38%)	79 (35.91%)	14 (30.43%)
	Diuretics	N (%)	3,979 (51.87%)	277 (45.94%)	5,663 (52.41%)	1,182 (58.75%)	142 (57.96%)	121 (35.69%)	96 (43.64%)	21 (45.65%)
	Other antihypertensives	N (%)	623 (8.12%)	41 (6.80%)	1,206 (11.16%)	748 (37.18%)	36 (14.69%)	28 (8.26%)	23 (10.45%)	7 (15.22%)
Antihypertensive medications [0, 0]	RAAS excl aliskiren	N (%)	3,953 (51.53%)	324 (53.73%)	5,256 (48.64%)	1,371 (68.14%)	140 (57.14%)	122 (35.99%)	58 (26.36%)	21 (45.65%)

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren users (2007–2014)				Aliskiren users (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	Beta blocker	N (%)	1,916 (24.98%)	251 (41.63%)	2,503 (23.16%)	690 (34.29%)	83 (33.88%)	120 (35.40%)	64 (29.09%)	15 (32.61%)
	Calcium channel blocker	N (%)	2,623 (34.19%)	208 (34.49%)	3,460 (32.02%)	901 (44.78%)	130 (53.06%)	105 (30.97%)	78 (35.45%)	18 (39.13%)
	Diuretics	N (%)	3,608 (47.03%)	316 (52.40%)	6,221 (57.57%)	1,062 (52.78%)	133 (54.29%)	162 (47.79%)	126 (57.27%)	17 (36.96%)
	Other antihypertensives	N (%)	488 (6.36%)	45 (7.46%)	1,152 (10.66%)	637 (31.66%)	35 (14.29%)	27 (7.96%)	25 (11.36%)	6 (13.04%)
Antihypertensive medications [1, 30]	RAAS excl aliskiren	N (%)	4,762 (62.08%)	343 (56.88%)	5,617 (51.98%)	1,448 (71.97%)	143 (58.37%)	123 (36.28%)	69 (31.51%)	23 (50.00%)
	Beta blocker	N (%)	2,521 (32.86%)	263 (43.62%)	2,607 (24.13%)	754 (37.48%)	101 (41.22%)	126 (37.17%)	67 (30.59%)	16 (34.78%)
	Calcium channel blocker	N (%)	3,338 (43.51%)	222 (36.82%)	3,778 (34.96%)	985 (48.96%)	136 (55.51%)	114 (33.63%)	84 (38.36%)	19 (41.30%)
	Diuretics	N (%)	4,488 (58.51%)	339 (56.22%)	6,542 (60.54%)	1,169 (58.10%)	150 (61.22%)	178 (52.51%)	128 (58.45%)	19 (41.30%)
	Other antihypertensives	N (%)	628 (8.19%)	47 (7.79%)	1,241 (11.48%)	704 (34.99%)	37 (15.10%)	31 (9.14%)	28 (12.79%)	10 (21.74%)
Antihypertensive medications [31, 365]	RAAS excl aliskiren	N (%)	5,986 (78.09%)	348 (57.81%)	6,912 (64.05%)	1,450 (72.39%)	159 (64.90%)	112 (33.23%)	99 (45.41%)	21 (48.84%)
	Beta blocker	N (%)	3,710 (48.40%)	322 (53.49%)	3,207 (29.72%)	865 (43.19%)	142 (57.96%)	148 (43.92%)	75 (34.40%)	17 (39.53%)
	Calcium channel blocker	N (%)	4,863 (63.44%)	278 (46.18%)	5,087 (47.14%)	1,142 (57.01%)	154 (62.86%)	146 (43.32%)	97 (44.50%)	20 (46.51%)

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren users (2007–2014)				Aliskiren users (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	Diuretics	N (%)	6,194 (80.80%)	411 (68.27%)	7,575 (70.19%)	1,328 (66.30%)	177 (72.24%)	200 (59.35%)	141 (64.68%)	23 (53.49%)
	Other antihypertensives	N (%)	1,015 (13.24%)	65 (10.80%)	1,752 (16.23%)	826 (41.24%)	51 (20.82%)	34 (10.09%)	39 (17.89%)	13 (30.23%)
Cardiovascular- and cerebr ovascular medications [-365, -31]	Antiarrhythmics	N (%)	52 (0.68%)	25 (4.15%)	336 (3.11%)	56 (2.78%)	<5	8 (2.36%)	<5	0 (0.00%)
	Digoxin	N (%)	251 (3.27%)	17 (2.82%)	362 (3.35%)	69 (3.43%)	5 (2.04%)	<5	<5	0 (0.00%)
	Antithrombotics	N (%)	3,587 (46.76%)	236 (39.14%)	3,538 (32.74%)	880 (43.74%)	92 (37.55%)	103 (30.38%)	55 (25.00%)	10 (21.74%)
	Ivabradine	N (%)	7 (0.09%)	<5	100 (0.93%)	9 (0.45%)	<5	<5	<5	0 (0.00%)
	Nicorandil	N (%)	15 (0.20%)	<5	0 (0.00%)	34 (1.69%)	<5	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiovascular- and cerebr ovascular medications [-30, -1]	Antiarrhythmics	N (%)	28 (0.37%)	15 (2.49%)	272 (2.52%)	24 (1.19%)	<5	<5	<5	0 (0.00%)
	Digoxin	N (%)	177 (2.31%)	16 (2.65%)	319 (2.95%)	61 (3.03%)	5 (2.04%)	0 (0.00%)	<5	0 (0.00%)
	Antithrombotics	N (%)	2,270 (29.59%)	194 (32.17%)	3,261 (30.18%)	750 (37.28%)	79 (32.24%)	80 (23.60%)	50 (22.73%)	8 (17.39%)
	Ivabradine	N (%)	5 (0.07%)	0 (0.00%)	94 (0.87%)	8 (0.40%)	<5	<5	<5	0 (0.00%)
	Nicorandil	N (%)	12 (0.16%)	<5	0 (0.00%)	25 (1.24%)	<5	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiovascular- and cerebr ovascular medications [0, 0]	Antiarrhythmics	N (%)	20 (0.26%)	13 (2.16%)	287 (2.66%)	22 (1.09%)	<5	<5	<5	0 (0.00%)
	Digoxin	N (%)	144 (1.88%)	17 (2.82%)	323 (2.99%)	62 (3.08%)	<5	<5	<5	0 (0.00%)

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren users (2007–2014)				Aliskiren users (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	Antithrombotics	N (%)	1,842 (24.01%)	195 (32.34%)	3,426 (31.70%)	685 (34.05%)	78 (31.84%)	96 (28.32%)	59 (26.82%)	6 (13.04%)
	Ivabradine	N (%)	5 (0.07%)	<5	96 (0.89%)	7 (0.35%)	<5	<5	<5	0 (0.00%)
	Nicorandil	N (%)	7 (0.09%)	<5	0 (0.00%)	20 (0.99%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiovascular- and cerebr ovascular medications [1, 30]	Antiarrhythmics	N (%)	26 (0.34%)	15 (2.49%)	301 (2.79%)	24 (1.19%)	<5	5 (1.47%)	<5	0 (0.00%)
	Digoxin	N (%)	186 (2.42%)	16 (2.65%)	339 (3.14%)	64 (3.18%)	5 (2.04%)	<5	<5	0 (0.00%)
	Antithrombotics	N (%)	2,472 (32.23%)	214 (35.49%)	3,520 (32.57%)	765 (38.02%)	85 (34.69%)	101 (29.79%)	63 (28.77%)	8 (17.39%)
	Ivabradine	N (%)	5 (0.07%)	<5	97 (0.90%)	8 (0.40%)	<5	<5	<5	0 (0.00%)
	Nicorandil	N (%)	11 (0.14%)	<5	0 (0.00%)	26 (1.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiovascular- and cerebr ovascular medications [31, 365]	Antiarrhythmics	N (%)	60 (0.78%)	24 (3.99%)	390 (3.61%)	54 (2.70%)	<5	8 (2.37%)	<5	0 (0.00%)
	Digoxin	N (%)	257 (3.35%)	22 (3.65%)	407 (3.77%)	73 (3.64%)	9 (3.67%)	<5	<5	0 (0.00%)
	Antithrombotics	N (%)	3,882 (50.64%)	266 (44.19%)	4,258 (39.46%)	923 (46.08%)	103 (42.04%)	132 (39.17%)	69 (31.65%)	12 (27.91%)
	Ivabradine	N (%)	6 (0.08%)	5 (0.83%)	143 (1.33%)	11 (0.55%)	<5	6 (1.78%)	<5	0 (0.00%)
	Nicorandil	N (%)	13 (0.17%)	<5	0 (0.00%)	33 (1.65%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

CPRD GOLD=Clinical Practice Research Datalink GOLD, DK-DHR=Danish Data Health Registries, IPCI=Integrated Primary Care Information, RAAS=Renin-angiotensin aldosterone system, SIDIAP=The Information System for Research on Primary Care.

Use of other medications of interest in new aliskiren users was also examined. (**Table 3**)

On the date of aliskiren initiation during the study period 2007–2014, use of antidiabetic medication (18.1–29.6%), statins (25.0–43.4%), antidepressants (3.3–14.2%), psycholeptics (8.2–27.1%), systemic NSAIDs (6.5–26.7%), and opioids (5.3–12.8%) were commonly observed. Additionally, 1.8–6.6% of users received systemic antibacterials, 2.3–3.6% systemic corticosteroids, and 2.2–4.5% systemic antihistamines on the index date. The pattern of use of these medications before and after aliskiren initiation was similar to that observed for antihypertensive and cardiovascular medications in **Table 2**. Use of other medications of interest in new aliskiren users during 2015–2024 was similar to that observed during 2007–2014.

Table 3: Use of other medications of interest in new aliskiren users.

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren (2007–2014)				Aliskiren (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
Number records	–	N	7,671	603	10,806	2,012	245	339	220	46
Number subjects	–	N	7,471	578	10,593	1,983	230	314	213	45
Other medications [-365, -31]	Antidiabetics	N (%)	2,363 (30.80%)	131 (21.72%)	3,143 (29.09%)	433 (21.52%)	38 (15.51%)	52 (15.34%)	31 (14.09%)	<5
	Statin	N (%)	3,954 (51.54%)	250 (41.46%)	4,655 (43.08%)	1,030 (51.19%)	95 (38.78%)	105 (30.97%)	63 (28.64%)	11 (23.91%)
	Systemic antibacterials	N (%)	3,179 (41.44%)	213 (35.32%)	2,711 (25.09%)	917 (45.58%)	99 (40.41%)	104 (30.68%)	63 (28.64%)	18 (39.13%)
	Macrolides	N (%)	820 (10.69%)	50 (8.29%)	566 (5.24%)	190 (9.44%)	29 (11.84%)	19 (5.60%)	12 (5.45%)	<5
	Fluoroquinolones	N (%)	430 (5.61%)	42 (6.97%)	949 (8.78%)	104 (5.17%)	20 (8.16%)	18 (5.31%)	22 (10.00%)	<5
	Systemic antifungals	N (%)	111 (1.45%)	<5	19 (0.18%)	17 (0.84%)	<5	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Antimalarials	N (%)	248 (3.23%)	8 (1.33%)	9 (0.08%)	112 (5.57%)	<5	<5	<5	<5
	Acetylcholinesterase inhibitors	N (%)	16 (0.21%)	0 (0.00%)	55 (0.51%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)
	Antidepressants	N (%)	1,004 (13.09%)	44 (7.30%)	1,747 (16.17%)	366 (18.19%)	27 (11.02%)	31 (9.14%)	27 (12.27%)	9 (19.57%)
	Psycholeptics	N (%)	1,614 (21.04%)	134 (22.22%)	3,529 (32.66%)	383 (19.04%)	52 (21.22%)	59 (17.40%)	65 (29.55%)	9 (19.57%)
	Psychostimulants	N (%)	9 (0.12%)	<5	287 (2.66%)	<5	<5	<5	<5	0 (0.00%)

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren (2007–2014)				Aliskiren (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	Systemic NSAIDs	N (%)	2,585 (33.70%)	199 (33.00%)	5,112 (47.31%)	1,088 (54.08%)	128 (52.24%)	88 (25.96%)	96 (43.64%)	22 (47.83%)
	Opioids	N (%)	1,808 (23.57%)	147 (24.38%)	1,912 (17.69%)	703 (34.94%)	56 (22.86%)	65 (19.17%)	37 (16.82%)	13 (28.26%)
	Systemic corticosteroids	N (%)	796 (10.38%)	69 (11.44%)	967 (8.95%)	270 (13.42%)	11 (4.49%)	40 (11.80%)	30 (13.64%)	8 (17.39%)
	Antineoplastics	N (%)	24 (0.31%)	<5	86 (0.80%)	11 (0.55%)	<5	<5	<5	<5
	Systemic antihistamines	N (%)	633 (8.25%)	81 (13.43%)	1,185 (10.97%)	269 (13.37%)	41 (16.73%)	57 (16.81%)	40 (18.18%)	8 (17.39%)
	Antiemetics	N (%)	25 (0.33%)	<5	107 (0.99%)	<5	<5	<5	<5	0 (0.00%)
Other medications [-30, -1]	Antidiabetics	N (%)	2,127 (27.73%)	116 (19.24%)	3,059 (28.31%)	402 (19.98%)	27 (11.02%)	38 (11.21%)	31 (14.09%)	<5
	Statin	N (%)	2,295 (29.92%)	195 (32.34%)	4,406 (40.77%)	876 (43.54%)	66 (26.94%)	72 (21.24%)	63 (28.64%)	8 (17.39%)
	Systemic antibacterials	N (%)	789 (10.29%)	42 (6.97%)	549 (5.08%)	177 (8.80%)	20 (8.16%)	17 (5.01%)	18 (8.18%)	6 (13.04%)
	Macrolides	N (%)	153 (1.99%)	9 (1.49%)	98 (0.91%)	28 (1.39%)	5 (2.04%)	<5	<5	0 (0.00%)
	Fluoroquinolones	N (%)	77 (1.00%)	6 (1.00%)	184 (1.70%)	9 (0.45%)	<5	<5	<5	0 (0.00%)
	Systemic antifungals	N (%)	36 (0.47%)	<5	5 (0.05%)	7 (0.35%)	<5	<5	0 (0.00%)	0 (0.00%)
	Antimalarials	N (%)	92 (1.20%)	7 (1.16%)	<5	74 (3.68%)	0 (0.00%)	<5	0 (0.00%)	<5
	Acetylcholinesterase inhibitors	N (%)	15 (0.20%)	0 (0.00%)	49 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren (2007–2014)				Aliskiren (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	Antidepressants	N (%)	604 (7.87%)	25 (4.15%)	1,468 (13.59%)	244 (12.13%)	13 (5.31%)	15 (4.42%)	21 (9.55%)	<5
	Psycholeptics	N (%)	812 (10.59%)	72 (11.94%)	2,825 (26.14%)	190 (9.44%)	35 (14.29%)	27 (7.96%)	55 (25.00%)	<5
	Psychostimulants	N (%)	5 (0.07%)	<5	130 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)
	Systemic NSAIDs	N (%)	1,289 (16.80%)	61 (10.12%)	2,964 (27.43%)	518 (25.75%)	62 (25.31%)	26 (7.67%)	53 (24.09%)	10 (21.74%)
	Opioids	N (%)	737 (9.61%)	46 (7.63%)	853 (7.89%)	350 (17.40%)	18 (7.35%)	23 (6.78%)	18 (8.18%)	<5
	Systemic corticosteroids	N (%)	246 (3.21%)	20 (3.32%)	375 (3.47%)	67 (3.33%)	5 (2.04%)	18 (5.31%)	15 (6.82%)	<5
	Antineoplastics	N (%)	17 (0.22%)	<5	77 (0.71%)	9 (0.45%)	<5	<5	0 (0.00%)	<5
	Systemic antihistamines	N (%)	233 (3.04%)	30 (4.98%)	415 (3.84%)	114 (5.67%)	16 (6.53%)	25 (7.37%)	14 (6.36%)	<5
	Antiemetics	N (%)	<5	0 (0.00%)	26 (0.24%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Other medications [0, 0]	Antidiabetics	N (%)	1,961 (25.56%)	117 (19.40%)	3,198 (29.59%)	364 (18.09%)	21 (8.57%)	47 (13.86%)	38 (17.27%)	<5
	Statin	N (%)	1,919 (25.02%)	197 (32.67%)	4,687 (43.37%)	812 (40.36%)	64 (26.12%)	91 (26.84%)	93 (42.27%)	9 (19.57%)
	Systemic antibacterials	N (%)	507 (6.61%)	11 (1.82%)	372 (3.44%)	94 (4.67%)	9 (3.67%)	9 (2.65%)	16 (7.27%)	5 (10.87%)
	Macrolides	N (%)	97 (1.26%)	<5	72 (0.67%)	13 (0.65%)	<5	<5	<5	<5

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren (2007–2014)				Aliskiren (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	Fluoroquinolones	N (%)	39 (0.51%)	0 (0.00%)	133 (1.23%)	5 (0.25%)	<5	0 (0.00%)	<5	0 (0.00%)
	Systemic antifungals	N (%)	35 (0.46%)	<5	5 (0.05%)	6 (0.30%)	<5	<5	0 (0.00%)	0 (0.00%)
	Antimalarials	N (%)	68 (0.89%)	5 (0.83%)	5 (0.05%)	66 (3.28%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	<5
	Acetylcholinesterase inhibitors	N (%)	11 (0.14%)	0 (0.00%)	53 (0.49%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)
	Antidepressants	N (%)	480 (6.26%)	20 (3.32%)	1,535 (14.21%)	214 (10.64%)	14 (5.71%)	16 (4.72%)	26 (11.82%)	<5
	Psycholeptics	N (%)	661 (8.62%)	63 (10.45%)	2,925 (27.07%)	164 (8.15%)	23 (9.39%)	27 (7.96%)	71 (32.27%)	5 (10.87%)
	Psychostimulants	N (%)	6 (0.08%)	<5	138 (1.28%)	0 (0.00%)	0 (0.00%)	<5	<5	0 (0.00%)
	Systemic NSAIDs	N (%)	1,036 (13.51%)	39 (6.47%)	2,890 (26.74%)	382 (18.99%)	53 (21.63%)	24 (7.08%)	65 (29.55%)	7 (15.22%)
	Opioids	N (%)	596 (7.77%)	32 (5.31%)	810 (7.50%)	257 (12.77%)	10 (4.08%)	18 (5.31%)	18 (8.18%)	<5
	Systemic corticosteroids	N (%)	197 (2.57%)	15 (2.49%)	384 (3.55%)	47 (2.34%)	5 (2.04%)	13 (3.83%)	10 (4.55%)	<5
	Antineoplastics	N (%)	<5	<5	78 (0.72%)	8 (0.40%)	0 (0.00%)	<5	0 (0.00%)	<5
	Systemic antihistamines	N (%)	168 (2.19%)	26 (4.31%)	376 (3.48%)	90 (4.47%)	16 (6.53%)	24 (7.08%)	19 (8.64%)	<5
	Antiemetics	N (%)	0 (0.00%)	0 (0.00%)	21 (0.19%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Other medications [1, 30]	Antidiabetics	N (%)	2,223 (28.98%)	127 (21.06%)	3,253 (30.10%)	411 (20.43%)	25 (10.20%)	49 (14.45%)	38 (17.35%)	<5

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren (2007–2014)				Aliskiren (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	Statin	N (%)	2,595 (33.83%)	219 (36.32%)	4,791 (44.34%)	918 (45.63%)	71 (28.98%)	96 (28.32%)	95 (43.38%)	11 (23.91%)
	Systemic antibacterials	N (%)	914 (11.92%)	43 (7.13%)	695 (6.43%)	234 (11.63%)	20 (8.16%)	22 (6.49%)	26 (11.87%)	7 (15.22%)
	Macrolides	N (%)	169 (2.20%)	<5	123 (1.14%)	32 (1.59%)	<5	<5	<5	<5
	Fluoroquinolones	N (%)	85 (1.11%)	9 (1.49%)	254 (2.35%)	19 (0.94%)	<5	<5	5 (2.28%)	0 (0.00%)
	Systemic antifungals	N (%)	46 (0.60%)	<5	5 (0.05%)	8 (0.40%)	<5	<5	0 (0.00%)	0 (0.00%)
	Antimalarials	N (%)	124 (1.62%)	7 (1.16%)	5 (0.05%)	79 (3.93%)	0 (0.00%)	<5	0 (0.00%)	<5
	Acetylcholinesterase inhibitors	N (%)	18 (0.23%)	0 (0.00%)	59 (0.55%)	<5	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)
	Antidepressants	N (%)	646 (8.42%)	24 (3.98%)	1,599 (14.80%)	257 (12.77%)	14 (5.71%)	21 (6.19%)	28 (12.79%)	5 (10.87%)
	Psycholeptics	N (%)	882 (11.50%)	77 (12.77%)	3,104 (28.72%)	207 (10.29%)	33 (13.47%)	36 (10.62%)	73 (33.33%)	6 (13.04%)
	Psychostimulants	N (%)	9 (0.12%)	<5	154 (1.43%)	0 (0.00%)	0 (0.00%)	<5	<5	0 (0.00%)
	Systemic NSAIDs	N (%)	1,418 (18.49%)	66 (10.95%)	3,288 (30.43%)	566 (28.13%)	64 (26.12%)	33 (9.73%)	76 (34.70%)	12 (26.09%)
	Opioids	N (%)	853 (11.12%)	51 (8.46%)	992 (9.18%)	379 (18.84%)	20 (8.16%)	26 (7.67%)	23 (10.50%)	<5
	Systemic corticosteroids	N (%)	282 (3.68%)	22 (3.65%)	483 (4.47%)	77 (3.83%)	6 (2.45%)	19 (5.60%)	14 (6.39%)	<5

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren (2007–2014)				Aliskiren (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	Antineoplastics	N (%)	16 (0.21%)	<5	78 (0.72%)	10 (0.50%)	<5	<5	0 (0.00%)	<5
	Systemic antihistamines	N (%)	253 (3.30%)	35 (5.80%)	479 (4.43%)	121 (6.01%)	19 (7.76%)	31 (9.14%)	23 (10.50%)	5 (10.87%)
	Antiemetics	N (%)	<5	0 (0.00%)	27 (0.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Other medications [31, 365]	Antidiabetics	N (%)	2,551 (33.28%)	148 (24.58%)	3,646 (33.78%)	466 (23.27%)	44 (17.96%)	56 (16.62%)	44 (20.18%)	<5
	Statin	N (%)	4,228 (55.15%)	267 (44.35%)	5,506 (51.02%)	1,079 (53.87%)	100 (40.82%)	121 (35.91%)	100 (45.87%)	13 (30.23%)
	Systemic antibacterials	N (%)	3,172 (41.38%)	209 (34.72%)	3,133 (29.03%)	904 (45.13%)	95 (38.78%)	105 (31.16%)	69 (31.65%)	22 (51.16%)
	Macrolides	N (%)	805 (10.50%)	50 (8.31%)	606 (5.62%)	213 (10.63%)	23 (9.39%)	26 (7.72%)	18 (8.26%)	5 (11.63%)
	Fluoroquinolones	N (%)	472 (6.16%)	42 (6.98%)	1,114 (10.32%)	86 (4.29%)	15 (6.12%)	18 (5.34%)	25 (11.47%)	<5
	Systemic antifungals	N (%)	109 (1.42%)	<5	23 (0.21%)	22 (1.10%)	<5	<5	0 (0.00%)	0 (0.00%)
	Antimalarials	N (%)	287 (3.74%)	11 (1.83%)	<5	109 (5.44%)	<5	<5	<5	<5
	Acetylcholinesterase inhibitors	N (%)	25 (0.33%)	0 (0.00%)	81 (0.75%)	<5	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)
	Antidepressants	N (%)	1,124 (14.66%)	43 (7.14%)	2,096 (19.42%)	388 (19.37%)	31 (12.65%)	28 (8.31%)	39 (17.89%)	9 (20.93%)
	Psycholeptics	N (%)	1,674 (21.84%)	135 (22.43%)	4,003 (37.09%)	413 (20.62%)	51 (20.82%)	64 (18.99%)	84 (38.53%)	10 (23.26%)

Variable name	Variable level	Estimate name	Cohort name							
			Aliskiren (2007–2014)				Aliskiren (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	Psychostimulants	N (%)	15 (0.20%)	<5	330 (3.06%)	<5	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)
	Systemic NSAIDs	N (%)	2,943 (38.39%)	204 (33.89%)	5,884 (54.52%)	1,140 (56.91%)	125 (51.02%)	91 (27.00%)	114 (52.29%)	26 (60.47%)
	Opioids	N (%)	1,992 (25.98%)	136 (22.59%)	2,195 (20.34%)	739 (36.89%)	55 (22.45%)	68 (20.18%)	40 (18.35%)	11 (25.58%)
	Systemic corticosteroids	N (%)	857 (11.18%)	71 (11.79%)	1,199 (11.11%)	266 (13.28%)	20 (8.16%)	56 (16.62%)	38 (17.43%)	9 (20.93%)
	Antineoplastics	N (%)	48 (0.63%)	5 (0.83%)	101 (0.94%)	13 (0.65%)	<5	<5	<5	<5
	Systemic antihistamines	N (%)	642 (8.37%)	70 (11.63%)	1,282 (11.88%)	268 (13.38%)	35 (14.29%)	49 (14.54%)	34 (15.60%)	9 (20.93%)
	Antiemetics	N (%)	24 (0.31%)	<5	111 (1.03%)	<5	0 (0.00%)	<5	<5	0 (0.00%)

CPRD GOLD=Clinical Practice Research Datalink GOLD, DK-DHR=Danish Data Health Registries, IPCI=Integrated Primary Care Information, NSAID=Non-steroidal anti-inflammatory drug. SIDIAP=The Information System for Research on Primary Care.

Objective 3: Patient-level characterisation of first-time aliskiren users with respect to cardiac events

Results on cross-cohort counts of aliskiren users and cardiac events are provided in **Table 4**, with results from stratified analyses available in the Shiny app EUPAS1000000768.

Study period 2007–2014

Among first-ever aliskiren new users during the study period 2007–2014, a total of 2,377 users (31.8%) from DK-DHR, 87 (15.1%) from IPCI, 4,041 (38.2%) from SIDIAP, and 357 (18.0%) from CPRD GOLD had a record of a cardiac event at any time during the observation period. Among the individual composite endpoints, atrial fibrillation was the most commonly observed outcome in aliskiren users, except in DK-DHR where atrial arrhythmia (excluding atrial fibrillation) was more frequently recorded. A separate outcome of cardiac arrhythmia was also examined, which was observed more often than the composite cardiac event overall, ranging from 100 (17.3%) in IPCI to 5,182 (48.9%) in SIDIAP.

When examining the one-year period prior to first-ever aliskiren initiation, cardiac events were observed in 290 users (3.9%) in DK-DHR, 27 (4.7%) in IPCI, 465 (4.4%) in SIDIAP, and 32 (1.6%) in CPRD GOLD. Cardiac arrhythmia was observed in 335 (4.5%) in DK-DHR, 31 (5.4%) in IPCI, 697 (6.6%) in SIDIAP, and 37 (1.9%) in CPRD GOLD.

Within the first year after starting aliskiren, cardiac events were observed in 415 users (5.6%) in DK-DHR, 19 (3.3%) in IPCI, 512 (4.8%) in SIDIAP, and 28 (1.4%) in CPRD GOLD. Cardiac arrhythmia was recorded in 440 (5.9%) in DK-DHR, 23 (4.0%) in IPCI, 752 (7.1%) in SIDIAP, and 32 (1.6%) in CPRD GOLD.

Study period 2015–2024

Among first-ever aliskiren new users during the study period 2015–2024, 48 (27.8%) users in DK-DHR, 39 (13.5%) in IPCI, and 35 (19.6%) in SIDIAP experienced a cardiac event at any time during the observation period. No cardiac events were identified in CPRD GOLD during this period. Considering the one-year pre-initiation window, cardiac events ranged from 5 in SIDIAP to 13 in DK-DHR. In the one-year post-initiation window, cardiac events ranged from 7 in IPCI and SIDIAP to 15 in DK-DHR.

Across analyses stratified by age group, a higher proportion of cardiac events was consistently observed among older individuals in all data sources for both study periods (2007–2014 and 2015–2024). In analyses stratified by sex, the proportion of cardiac events was higher in female users compared with male users in CPRD GOLD, IPCI, and SIDIAP, but not in DK-DHR, during the 2007–2014 period.

Table 4: Cross-cohort count of aliskiren users and cardiac events.

Variable name	Variable level	Estimate name	Cohort name							
			First aliskiren (2007–2014)				First aliskiren (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
Number records	–	N	7,471	578	10,593	1,983	173	290	179	39
Number subjects	–	N	7,471	578	10,593	1,983	173	290	179	39
Cardiac events [-Inf, Inf]	Cardiac event	N (%)	2,377 (31.82%)	87 (15.05%)	4,041 (38.15%)	357 (18.00%)	48 (27.75%)	39 (13.45%)	35 (19.55%)	0 (0.00%)
	Cardiac arrhythmia	N (%)	2,576 (34.48%)	100 (17.30%)	5,182 (48.92%)	390 (19.67%)	53 (30.64%)	45 (15.52%)	57 (31.84%)	<5
	Atrial fibrillation	N (%)	537 (7.19%)	76 (13.15%)	3,152 (29.76%)	321 (16.19%)	17 (9.83%)	30 (10.34%)	26 (14.53%)	0 (0.00%)
	Atrial arrhythmia (excluding atrial fibrillation)	N (%)	2,091 (27.99%)	12 (2.08%)	745 (7.03%)	50 (2.52%)	41 (23.70%)	11 (3.79%)	8 (4.47%)	0 (0.00%)
	Ventricular arrhythmia	N (%)	253 (3.39%)	<5	316 (2.98%)	6 (0.30%)	7 (4.05%)	<5	<5	0 (0.00%)
	Sudden or unattended death	N (%)	78 (1.04%)	0 (0.00%)	958 (9.04%)	<5	0 (0.00%)	0 (0.00%)	6 (3.35%)	0 (0.00%)
Cardiac events [-Inf, -366]	Cardiac event	N (%)	584 (7.82%)	24 (4.16%)	632 (5.97%)	115 (5.80%)	24 (13.87%)	16 (5.52%)	14 (7.82%)	0 (0.00%)
	Cardiac arrhythmia	N (%)	663 (8.87%)	31 (5.37%)	961 (9.07%)	132 (6.66%)	27 (15.61%)	20 (6.90%)	27 (15.08%)	<5
	Atrial fibrillation	N (%)	0 (0.00%)	20 (3.47%)	576 (5.44%)	98 (4.94%)	<5	11 (3.79%)	12 (6.70%)	0 (0.00%)
	Atrial arrhythmia (excluding	N (%)	524 (7.01%)	<5	63 (0.59%)	22 (1.11%)	21 (12.14%)	6 (2.07%)	5 (2.79%)	0 (0.00%)

Variable name	Variable level	Estimate name	Cohort name							
			First aliskiren (2007–2014)				First aliskiren (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	atrial fibrillation)									
	Ventricular arrhythmia	N (%)	86 (1.15%)	0 (0.00%)	21 (0.20%)	<5	<5	<5	<5	0 (0.00%)
	Sudden or unattended death	N (%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac events [-365, -1]	Cardiac event	N (%)	290 (3.88%)	27 (4.67%)	465 (4.39%)	32 (1.61%)	13 (7.51%)	9 (3.10%)	5 (2.79%)	0 (0.00%)
	Cardiac arrhythmia	N (%)	335 (4.48%)	31 (5.36%)	697 (6.58%)	37 (1.87%)	15 (8.67%)	9 (3.10%)	11 (6.15%)	0 (0.00%)
	Atrial fibrillation	N (%)	<5	23 (3.98%)	418 (3.95%)	32 (1.61%)	<5	8 (2.76%)	<5	0 (0.00%)
	Atrial arrhythmia (excluding atrial fibrillation)	N (%)	278 (3.72%)	<5	63 (0.59%)	0 (0.00%)	10 (5.78%)	0 (0.00%)	<5	0 (0.00%)
	Ventricular arrhythmia	N (%)	14 (0.19%)	<5	17 (0.16%)	0 (0.00%)	<5	<5	0 (0.00%)	0 (0.00%)
	Sudden or unattended death	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)
Cardiac events [0, 0]	Cardiac event	N (%)	16 (0.21%)	9 (1.56%)	24 (0.23%)	0 (0.00%)	<5	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Cardiac arrhythmia	N (%)	17 (0.23%)	9 (1.56%)	42 (0.40%)	0 (0.00%)	<5	<5	0 (0.00%)	0 (0.00%)
	Atrial fibrillation	N (%)	0 (0.00%)	9 (1.56%)	20 (0.19%)	0 (0.00%)	<5	0 (0.00%)	0 (0.00%)	0 (0.00%)

Variable name	Variable level	Estimate name	Cohort name							
			First aliskiren (2007–2014)				First aliskiren (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	Atrial arrhythmia (excluding atrial fibrillation)	N (%)	16 (0.21%)	0 (0.00%)	<5	0 (0.00%)	<5	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Ventricular arrhythmia	N (%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Sudden or unattended death	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac events [1, 365]	Cardiac event	N (%)	415 (5.55%)	19 (3.29%)	512 (4.83%)	28 (1.41%)	15 (8.67%)	7 (2.41%)	7 (3.93%)	0 (0.00%)
	Cardiac arrhythmia	N (%)	440 (5.89%)	23 (3.98%)	752 (7.10%)	32 (1.61%)	16 (9.25%)	7 (2.41%)	10 (5.62%)	0 (0.00%)
	Atrial fibrillation	N (%)	<5	17 (2.94%)	450 (4.25%)	25 (1.26%)	6 (3.47%)	5 (1.72%)	7 (3.93%)	0 (0.00%)
	Atrial arrhythmia (excluding atrial fibrillation)	N (%)	384 (5.14%)	<5	74 (0.70%)	5 (0.25%)	11 (6.36%)	<5	<5	0 (0.00%)
	Ventricular arrhythmia	N (%)	16 (0.21%)	<5	10 (0.09%)	0 (0.00%)	<5	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Sudden or unattended death	N (%)	18 (0.24%)	0 (0.00%)	8 (0.08%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac events [366, Inf]	Cardiac event	N (%)	2,101 (28.80%)	65 (12.15%)	3,708 (35.83%)	230 (12.35%)	25 (15.43%)	26 (10.08%)	22 (13.25%)	0 (0.00%)
	Cardiac arrhythmia	N (%)	2,267 (31.07%)	72 (13.46%)	4,600 (44.45%)	243 (13.04%)	27 (16.67%)	28 (10.85%)	31 (18.67%)	0 (0.00%)

Variable name	Variable level	Estimate name	Cohort name							
			First aliskiren (2007–2014)				First aliskiren (2015–2024)			
			Data source							
			DK-DHR	IPCI	SIDIAP	CPRD GOLD	DK-DHR	IPCI	SIDIAP	CPRD GOLD
	Atrial fibrillation	N (%)	537 (7.36%)	58 (10.84%)	2,843 (27.47%)	205 (11.00%)	13 (8.02%)	20 (7.75%)	13 (7.83%)	0 (0.00%)
	Atrial arrhythmia (excluding atrial fibrillation)	N (%)	1,845 (25.29%)	9 (1.68%)	621 (6.00%)	27 (1.45%)	19 (11.73%)	6 (2.33%)	<5	0 (0.00%)
	Ventricular arrhythmia	N (%)	170 (2.33%)	0 (0.00%)	274 (2.65%)	<5	<5	<5	<5	0 (0.00%)
	Sudden or unattended death	N (%)	60 (0.82%)	0 (0.00%)	949 (9.17%)	<5	0 (0.00%)	0 (0.00%)	5 (3.01%)	0 (0.00%)

CPRD GOLD=Clinical Practice Research Datalink GOLD, DK-DHR=Danish Data Health Registries, IPCI=Integrated Primary Care Information, NSAID=Non-steroidal anti-inflammatory drug. SIDIAP=The Information System for Research on Primary Care.

10. DISCUSSION

10.1. Key results

For the 2007–2014 aliskiren new-user cohort, 7,471 individuals from DK-DHR, 578 individuals from IPCI, 10,593 individuals from SIDIAP, and 1,983 individuals from CPRD GOLD were identified. Median age of new aliskiren users ranged from 65 to 69 years, and median duration of aliskiren use ranged from 80 to 392 days. Most users had baseline cardiovascular comorbidities, particularly ischaemic heart disease. Hypertension was identified in 54.8–94.3% within one year prior to aliskiren initiation and in 77.3–98.7% when considering all medical history. Resistant hypertension was identified in SIDIAP, IPCI, and CPRD GOLD (21.1–62.9% within one year prior to initiation; 26.6–78.2% any time before initiation), but not in DK-DHR.

The number of individuals prescribed aliskiren between 2015–2024 was much smaller, with 230 individuals from DK-DHR, 314 individuals from IPCI, 213 individuals from SIDIAP, and 45 individuals from CPRD GOLD were identified. Median age ranged from 66 to 69 years, and median duration of use ranged from 56 to 252 days. Baseline ischaemic heart disease was common, affecting up to 25% of users. Hypertension was identified in 42.3–81.6% within one year prior and in 85.5–94.3% considering all medical history before initiation. Resistant hypertension was identified in SIDIAP, IPCI, and CPRD GOLD, but not in DK-DHR.

Use of other antihypertensive medications was frequent across all aliskiren users, with drugs acting on RAAS excluding aliskiren being the one of the most commonly used classes. Antithrombotic medications were also widely used.

Among first-ever aliskiren new users during 2007–2014, cardiac events occurred in 2,377 users (31.8%) from DK-DHR, 87 (15.1%) from IPCI, 4,041 (38.2%) from SIDIAP, and 357 (18.0%) from CPRD GOLD at any time during observation. Within the one-year period before initiation, cardiac events ranged from 27 (IPCI) to 465 (SIDIAP), and within the year after initiation, from 19 (IPCI) to 512 (SIDIAP). Among the individual composite endpoints, atrial fibrillation was the most commonly observed outcome, except in DK-DHR, where atrial arrhythmia (excluding atrial fibrillation) was more frequently recorded.

For the 2015–2024 cohort, 48 users (27.8%) from DK-DHR, 39 (13.5%) from IPCI, and 35 (19.6%) from SIDIAP experienced cardiac events during observation. Cardiac events within one year before initiation ranged from 5 (SIDIAP) to 13 (DK-DHR), and within one year after initiation ranged from 7 (IPCI and SIDIAP) to 15 (DK-DHR).

10.2. Strengths and limitations of the research methods

General limitations

The study was conducted in a federated manner, such that all analyses were performed separately for each data source locally, without sharing any patient-level data, to ensure compliance with data privacy regulations. However, as the study was based on routinely collected healthcare data, data quality issues must be taken into consideration.

The results estimated from this study reflect only the populations represented in the included data sources. EHR have certain inherent limitations because they are collected primarily for clinical purposes rather than for research use. In this study, misclassification is possible for drug exposures, as a recorded prescription or dispensation does not necessarily mean that the patient took the drug. In addition, assumptions regarding the duration of drug use are unavoidable. Nonetheless, we applied validated methods for estimating treatment duration, based on the concatenation of prescriptions and the handling of refill gaps.[19]

Study-specific limitations

A general limitation of DUS studies based on prescription or dispensing records is that actual drug intake cannot be confirmed. As we cannot capture whether aliskiren was taken as prescribed, or whether early

discontinuation occurred, estimates of treatment duration or medication use may reflect prescribing or dispensing patterns rather than true medication use. In addition, results related to the characterisation of medication use in aliskiren users should be interpreted with caution. The current approach identifies any recorded use of a medication within specific time windows before, on, or after the date of aliskiren initiation. However, this method does not provide information on whether the medications were used concurrently, as discontinuation of aliskiren treatment was not taken into account. Consequently, it is possible that some medications recorded after the initiation of aliskiren may actually reflect use that occurred after aliskiren discontinuation.

The actual indication for aliskiren use was not explicitly recorded in most of the data sources. Indications for drug use were only available in DK-DHR. To understand the potential indication for aliskiren use, we assessed the presence of diagnosis codes for hypertension, which is a known clinical indication of aliskiren. While we attempted to collect as much information as possible to define hypertension and supplement diagnosis codes with measurement-based definitions, this approach was limited by incomplete or missing records, as blood pressure values were not consistently available for all individuals.

A concept-based method was used to identify baseline comorbidities of aliskiren user. For the more complex conditions, these might not be well-captured with the current concept-based definition. For example, metabolic syndrome is defined by the presence of three or more conditions, including central obesity, high blood pressure, elevated blood glucose levels, high blood triglycerides, or low high-density lipoprotein cholesterol. However, in the current study, identification of metabolic syndrome among aliskiren users was based solely on diagnosis codes for metabolic syndrome, rather than on the concurrent presence of its individual components. This approach limited the ability to identify more complex comorbidities among aliskiren users.

10.3. Interpretation

The study was conducted across two periods (2007–2014 and 2015–2024). The separation of study periods was motivated by the restriction on combination use of RAAS-acting agents issued by the EMA CHMP in 2014,[12] following safety concerns raised by several landmark studies that reported increased risks of renal dysfunction and hyperkalaemia with dual RAAS blockade.[3, 20] Consistent with the regulatory action, a lower number of aliskiren users was observed during the 2015–2024 period compared with 2007–2014. Although an annual incidence analysis of aliskiren use would be more appropriate to fully assess the impact of the EMA CHMP recommendations on aliskiren prescribing practices, the current findings provide preliminary evidence suggesting that aliskiren has been less commonly prescribed in more recent years.

This study was motivated by the need to assess the feasibility of future safety studies evaluating the risk of cardiac events associated with aliskiren use. Cardiac events of interest include cardiac arrhythmia and cardiac arrest. Characterising aliskiren users in terms of use of medications that may increase the risk of cardiac arrhythmia, as well as identifying baseline comorbidities associated with elevated cardiac risk, is important for informing the design of future safety studies. Hyperkalaemia is also known to increase risk of cardiac arrest,[21] highlighting the relevance of understanding underlying comorbidities and the use of concomitant medications that may increase the risk of hyperkalaemia.

During the study period of 2007–2014, approximately 50–80% of aliskiren users received other RAAS-acting medications within one year after aliskiren initiation. This finding may suggest a high proportion of aliskiren users being exposed to dual RAAS blockade. However, as noted in the limitations section, the current approach to identify co-medication use did not account for discontinuation of aliskiren. Instead, it captured only the use of specific medications within pre-defined assessment windows. Therefore, results related to co-medication use should be interpreted with caution.

One of the objectives of the current study was to characterise aliskiren users in terms of treatment indication, specifically by identifying hypertension with different assessment windows at baseline. The

study attempted to define hypertension using both diagnosis records and blood pressure measurement data. Hypertension was identified in 55–94% of aliskiren users within one year prior to aliskiren initiation and in up to 77–99% when considering all available medical history during the 2007–2014 study period. The findings showed good alignment with the known clinical indication for aliskiren use. Similar results for hypertension and essential hypertension suggest that most hypertensive individuals were identified as having essential hypertension, consistent with the known epidemiology of hypertension.

Resistant hypertension, which was defined based on diagnosis records or blood pressure measurements during the antihypertensive treatment, was identified in up to 26.6–78.2% of aliskiren users in IPCI, SIDIAP, and CPRD GOLD when considering all available medical history. Resistant hypertension could not be identified in DK-DHR. In this data source, most blood pressure measurements were recorded on the same date, possibly reflecting a high proportion of ambulatory blood pressure monitoring, which limited the availability of distinct measurement records. Nonetheless, it should be also noted that treatment indication was directly available in DK-DHR. Therefore, this finding might be suggestive of the scenario that aliskiren was seldom prescribed for resistant hypertension in DK-DHR. Collectively, this demonstrates that defining hypertension based on blood pressure measurement data is feasible when data quality is sufficient and measurements are well captured.

We identified relevant diagnosis codes or hypertension flags derived from measurements across different assessment windows. Using this approach, hypertension was identified in 30–77% of aliskiren users within 30 days prior to initiation, 55–94% within 365 days, and up to 77–99% at any time before initiation. These findings may help refine the definition of target populations in future studies.

We characterised aliskiren users in terms of baseline demographics and comorbidities. The median age ranged from 65 to 69 years across data sources, with 10–20% having a history of ischaemic heart disease and up to 20–30% having diabetes, which aligns with the typical clinical profile of aliskiren use in older populations. However, no cases of chronic renal disease were identified in IPCI during the 2007–2014 study period. This should be interpreted carefully in the context of different coding practices, as chronic renal disease was recorded as ‘renal impairment’ in IPCI. For future studies using IPCI, the phenotype for chronic renal disease should be carefully reviewed and refined to better capture baseline prevalence, particularly in studies where renal function may influence medication use or outcomes.

Dyslipidaemia could not be characterised in most included data sources, with only scarce records observed in CPRD GOLD (count <5) during 2007–2014. In several data sources, hyperlipidaemia was used instead of dyslipidaemia, and hyperlipidaemia codes were not included in the dyslipidaemia definition. Therefore, future studies should consider incorporating both hyperlipidaemia and dyslipidaemia codes to improve condition capture. Statin use identified in Objective 2 may serve as a supplementary indicator of dyslipidaemia. However, it should also be noted that statins may be prescribed for patients with cardiovascular disease in the absence of true dyslipidaemia.

We aimed to characterise the occurrence of relevant clinical outcomes among aliskiren users to estimate cross-cohort counts and assess the feasibility of future safety study evaluating the risk of cardiac events in this population. When interpreting these findings, data availability and completeness should be considered in relation to the type of data source. The original composite outcome for cardiac events included specific types of cardiac arrhythmias and sudden or unattended death. To further assess data completeness and granularity, we additionally examined cardiac arrhythmia as a broader outcome. The results showed consistently higher counts for the broader cardiac arrhythmia definition than for the composite outcome of cardiac events. Cardiac arrhythmia was observed in 1.9–6.6% of aliskiren users, whereas the composite outcome of cardiac events was observed in 1.6–4.7% within one year prior to aliskiren initiation. These findings highlight the importance of carefully defining cardiac outcomes in future studies, particularly with respect to whether broader arrhythmia categories should be incorporated into composite outcomes or whether more granular definitions should be retained.

Atrial fibrillation is generally recognised as the most common form of atrial arrhythmia and would therefore be expected to contribute the highest counts within composite outcome. However, this pattern was not observed in DK-DHR. In this data source, atrial fibrillation and atrial flutter were frequently recorded and mapped to atrial arrhythmia. Improved differentiation between atrial fibrillation and other atrial arrhythmias should therefore be considered in future studies to enhance outcome specificity.

In addition to the clinical interpretation of the findings and their implications for the feasibility of future safety studies, it is also important to consider the impact of study design choices on the results. In the current study, we defined the new-user cohort of aliskiren using a washout period of 365 days. This means that if an individual received multiple aliskiren prescriptions/dispensations with a non-exposure period longer than 365 days between them, the same individual would be classified as a new user again. As a result, some individuals appeared with multiple records in the Objective 1 and Objective 2 characterisations. This approach allows us to pragmatically identify and characterise aliskiren users for potential self-controlled case series study designs, where multiple exposure periods may occur.

We observed a similar number of drug era records and individuals for new aliskiren users, suggesting that most individuals continued aliskiren treatment without long interruptions. However, when considering the number of records removed due to the 365-day washout requirement, more than half of the records in CPRD GOLD and IPCI, and around 75% in DK-DHR, were excluded. This suggests the presence of prescription/dispensation gaps longer than one month but shorter than twelve months, meaning these records were not concatenated into a single continuous treatment era. As a result, we may have underestimated the true duration of aliskiren treatment if these gaps represent the same treatment episode. One possible solution would be to test multiple gap durations in sensitivity analyses, although this was not feasible in the current off-the-shelf study. The choice of gap duration for drug era concatenation would be important as it determines whether individuals are classified as exposed or non-exposed to aliskiren. Misclassification of exposure periods could have important implications for risk estimation in future safety studies, particularly in self-controlled case series study design.

10.4. Generalisability

The study included data sources from 4 European countries (Denmark, the Netherland, Spain, and the United Kingdom), covering different regions across Europe. These data sources represented diverse healthcare settings, including two primary care data sources (IPCI, CPRD GOLD), one primary care data source with linked hospital data (SIDIAP), and one nationwide data source with linked registries (DK-DHR). However, the findings from this study reflect only the situation within the specific regions, settings, and time periods covered by each data source and should not be generalised to other countries or data sources.

11. CONCLUSION

The study provided a detailed real-world profile of aliskiren users. Most aliskiren users were identified in the earlier period (2007–2014); consequently, more cardiac events were observed in this cohort. Aliskiren users were typically older adults with substantial cardiovascular comorbidity. Hypertension was frequently recorded both on or before aliskiren initiation, while resistant hypertension was not consistently observed across all included data sources. Use of other antihypertensive agents was common, with medications acting on RAAS among the more frequently used drug classes. Within the predefined composite outcome of cardiac events, atrial fibrillation and atrial arrhythmia (excluding atrial fibrillation) were more commonly observed, whereas ventricular arrhythmia and sudden or unattended death were less common. These findings may support the feasibility of any future safety studies focusing on cardiac outcomes in aliskiren users.

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13. ANNEXES

ANNEX I. Description of data sources

Danish Data Health Registries (DK-DHR)

Danish health data (DK-DHR) is collected, stored, and managed in national health registers at the Danish Health Data Authority, and covers the entire population which makes it possible to study the development of diseases and their treatment over time. There are no gaps in terms of gender, age, and geography in Danish health data due to mandatory reporting on all patients from cradle to grave, in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers, so DK-DHR has data on all Danes throughout their lives, regardless of whether they have moved around the country. High data quality due to standardization, digitization, and documentation means that Danish health data is not based on interpretation. The Danish Health Data Authority is responsible for the national health registers and for maintaining and developing standards and classifications in the Danish healthcare system. Legislation ensures balance between personal data protection and use. In the present data base, DK-DHR has access to the following registries for the entire Danish population of 5.9 million persons from 1st January 1995: The central Person Registry (CPR), The National Patient Registry (LPR), The Register of Pharmaceutical Sales (LSR), The National Cancer Register (CAR), The Cause of Death registry (DAR), The Clinical Laboratory Information Register (LAB), COVID-19 test and vaccination Registries (SSI-OVD, SSI-DDV), The complete Vaccination registry (DDV_all). All data registered from 1st January 1995 will be included.

Integrated Primary Care Information (IPCI)

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

The Information System for Research in Primary Care (SIDIAP)

The Information System for Research in Primary Care (SIDIAP) is a clinical database of anonymized patient records in Catalonia, Spain. The Spanish public healthcare system covers more than 98% of the population, and more than two thirds of the Catalan population see their GP at least once a year. The computerisation of the primary care patient records of the Catalan Health Institute (CHI) was complete in 2005. SIDIAP was designed to provide a valid and reliable database of information from clinical records of patients registered in primary care centres for use in biomedical research. SIDIAP contains data of anonymized patients' healthcare records for nearly six million people (approximately 80% of the Catalan population) registered in 287 primary care practices throughout Catalonia since 2005. It includes data collected by health professionals during routine visits in primary care, including anthropometric measurements, clinical diagnoses (International Classification of Diseases 10th revision ICD-10), laboratory tests, prescribed and dispensed drugs, hospital referrals, demographic, and lifestyle information. It was previously shown that SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions. The high quality of these data has been previously documented, and SIDIAP has been

successfully applied to epidemiological studies of key exposures and outcomes. Quality checks to identify duplicate patient IDs are performed centrally at each SIDIAP database update. Checks for logical values and data harmonisation are performed. For biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

Clinical Practice Research Datalink GOLD (CPRD GOLD)

The Clinical Practice Research Datalink (CPRD) GOLD is a nation-wide database, with data collection since 1987.[22] CPRD GOLD consists of patients in contributing practices using Vision® software. Historically this covered the whole of the UK, but the number of contributing practices in the England is dropping. In January 2025 only 3 practices from England were a part of CPRD GOLD, while historical patient data were from the whole of the UK, and will continue to be so. In the future, no practices from England will be present, only practices from Scotland, Wales, and Northern Ireland. CPRD GOLD data covers primary care (both general practitioners and specialists, e.g. paediatricians), secondary care specialists (ambulatory or hospital outpatient care), and hospital inpatient care. Data includes patient demographics, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications. Data is entered by clinicians into the electronic health records and is processed by CPRD that provides data releases for research. CPRD GOLD has been assessed and found to be broadly representative of the UK general population in terms of age and sex. In CPRD GOLD January 2025 release there were 2,730,707 current acceptable patients (i.e. registered at currently contributing practices that use Vision software, excluding transferred out, deceased patients, and those flagged by CPRD as not acceptable for clinical research for data quality issues). This equals to 4.07%, based on the UK population estimates of 67,026,300 from the Office of National Statistics (mid-2023). Current patients are mainly from Scotland, Wales, and Northern Ireland. Historically, GOLD does contain data from England as well. Although CPRD GOLD contains information on referrals and discharge letters, it may not fully capture specific hospital information. Events from hospital and specialist care are not covered. The current study was run in CPRD GOLD 202501 release. The use of CPRD data was approved by CPRD's Research Data Governance process (24_004487).

ANNEX II. Fitness for use assessment

Data source justification and key characteristics

Danish Data Health Registries (DK-DHR)

DK-DHR was included in this study because it is a nation-wide registry data source with information from primary care, secondary care, and hospital care, which provided relevant information on aliskiren use and cardiac events in the general population.

Based on a preliminary feasibility assessment, the expected number of person counts for aliskiren use was 7,700 in DK-DHR.

Moreover, data availability and follow-up in DK-DHR was sufficient, as data availability in DK-DHR started in 1995, and the date of most recent data extraction was 11/2024 (as of 07/2025), which aligned with the study period. The median follow-up of the first observation period in DK-DHR was 7,920 days (IQR 2,610–10,900).

There was a study specific limitation present in DK-DHR, namely: due to data availability, the study period for DK-DHR was 01/2007 to 11/2024.

Lastly, DK-DHR has blanket IRB approval, which made the execution of this study feasible within the planned study timelines.

Integrated Primary Care Information (IPCI)

IPCI was included in this study because it is a nation-wide registry data source with information from primary care settings, which provided relevant information on the aliskiren use and cardiac events in the general population.

Based on a preliminary feasibility assessment, the expected number of person counts for aliskiren use was 1,700 in IPCI.

Moreover, data availability and follow-up in IPCI was sufficient, as data availability in IPCI started in 2006, and the date of most recent data extraction was 12/2024 (as of 09/2025), which aligned with the study period, and the median follow-up of the first observation period in IPCI was 1,730 days (IQR 791–3,070).

There were no study specific limitations present in IPCI.

Lastly, IPCI has blanket IRB approval, which made the execution of this study feasible within the planned study timelines.

The Information System for Research on Primary Care (SIDIAP)

SIDIAP was included in this study because it is a primary care data source with linked hospital data, which provided relevant information on aliskiren use and cardiac events in the general population.

Based on a preliminary feasibility assessment, the expected number of person counts for aliskiren use was 11,000 in SIDIAP.

Moreover, data availability and follow-up in SIDIAP was sufficient, as data availability in SIDIAP started in 2006, and the date of most recent data extraction was 06/2023 (as of 07/2025), which aligned with the study period, and the median follow-up of the first observation period in SIDIAP was 5,670 days (IQR 2,220–6,390).

There was study specific limitation present in SIDIAP, namely: due to data availability the study period for SIDIAP was 01/2007 to 06/2023.

Lastly, IRB approval for SIDIAP was estimated to take 1 month, which made the execution of this study feasible within the planned study timelines.

Clinical Practice Research Datalink GOLD (CPRD GOLD)

CPRD GOLD was included in this study because it is a nation-wide registry data source with information from primary care settings, which provided relevant information on the aliskiren use and cardiac events in the general population.

Based on a preliminary feasibility assessment, the expected number of person counts for aliskiren use was 2,300 in CPRD GOLD.

Moreover, data availability and follow-up in CPRD GOLD was sufficient, as data availability in CPRD GOLD started in 1987, and the date of most recent data extraction was 12/2024 (as of 07/2025), which aligned with the study period, and the median follow-up of the first observation period in CPRD GOLD was 2,150 days (IQR 727–4,930).

There was no study specific limitation present in CPRD GOLD.

Lastly, IRB approval for CPRD GOLD (protocol number: 24_004487) was estimated to take 1–2 months, which made the execution of this study feasible within the planned study timelines.

ANNEX III. Operational and reporting considerations

DATA MANAGEMENT

Data management

All data sources have previously mapped their data to the OMOP common data model. This enabled the use of standardised analytics and using DARWIN EU® tools across the network since the structure of the data and the terminology system was harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

The analytic code for this study was written in R and used standardized analytics wherever possible. Each data partner executed the study code against their data source containing individual data and then returned the results (csv files) which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

Data storage and protection

For this study, personal data from individuals in various EU member states were processed, using information collected from national/regional electronic health record data sources. 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 data sources used in this study were 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 were adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generate non-identifiable aggregate summary results.

QUALITY CONTROL

Data source quality control

When defining drug cohorts, non-systemic products were excluded from the list of included codes summarised on the ingredient level.

When defining cohorts for indications, a systematic search of possible codes for inclusion was identified using the *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This package allows the user to define a search strategy and will use this to query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the *PhenotypeR* (https://github.com/OHDSI/phenotypeR) and *DrugExposureDiagnostics* (https://cran.r-project.org/web/packages/DrugExposureDiagnostics/index.html) R packages were run to assess the use of different codes across the data sources contributing to the study and identify any codes potentially omitted in error. The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records.

The study code was based on DARWIN EU® R package *CohortCharacteristics* to characterise the cohort by indication. The package includes numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package was made publicly available via GitHub.

ANNEX IV: List of concept definitions

Table S1. List of definition for aliskiren.

Substance Name	Concept name	ATC code	Ingredient Concept ID	Include descendants
Aliskiren	Aliskiren	C09XA02	1317967	Yes

Table S2. List of definitions for cardiac events.

Phenotype	Concept id	Concept name	Domain	Vocabulary
atrial fibrillation	4139517	Transient cerebral ischemia due to atrial fibrillation	Condition	SNOMED
atrial fibrillation	4154290	Paroxysmal atrial fibrillation	Condition	SNOMED
atrial fibrillation	4199501	Rapid atrial fibrillation	Condition	SNOMED
atrial fibrillation	37208965	QOF (Quality and Outcomes Framework) atrial fibrillation quality indicator-related care invitation	Observation	SNOMED
atrial fibrillation	37310849	QOF (Quality and Outcomes Framework) atrial fibrillation quality indicator-related care invitation using preferred method of communication	Observation	SNOMED
atrial fibrillation	44782442	Atrial fibrillation with rapid ventricular response	Condition	SNOMED
atrial fibrillation	44804336	Atrial fibrillation monitoring invitation	Observation	SNOMED
atrial fibrillation	4064452	ECG: atrial fibrillation	Observation	SNOMED
atrial fibrillation	4108832	Atrial fibrillation and flutter	Condition	SNOMED
atrial fibrillation	4117112	Controlled atrial fibrillation	Condition	SNOMED
atrial fibrillation	4119601	Lone atrial fibrillation	Condition	SNOMED
atrial fibrillation	4119602	Non-rheumatic atrial fibrillation	Condition	SNOMED
atrial fibrillation	36717692	At high risk of atrial fibrillation	Observation	SNOMED
atrial fibrillation	40757907	Atrial fibrillation and other dysrhythmias in last 7 days [MDSv3]	Observation	LOINC
atrial fibrillation	40761370	Date of first episode of atrial fibrillation	Observation	LOINC
atrial fibrillation	40761371	Emergency room visit or hospitalized or saw doctor for atrial fibrillation	Observation	LOINC
atrial fibrillation	40761374	Taking any anticoagulants for treatment of atrial fibrillation	Observation	LOINC
atrial fibrillation	40761375	Taking any antiarrhythmics for treatment of atrial fibrillation	Observation	LOINC
atrial fibrillation	40768542	Atrial fibrillation 10Y risk [#] Framingham.Schnabel 2009	Observation	LOINC
atrial fibrillation	40768550	Stroke after atrial fibrillation 5 year risk [#] Framingham.Wang 2003	Observation	LOINC
atrial fibrillation	40768551	Stroke or death after atrial fibrillation 5 year risk [#] Framingham.Wang 2003	Observation	LOINC
atrial fibrillation	42539346	Preexcited atrial fibrillation	Condition	SNOMED
atrial fibrillation	42689664	Atrial fibrillation detected	Condition	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
atrial fibrillation	1340258	Exacerbation of atrial fibrillation	Condition	OMOP Extension
atrial fibrillation	313217	Atrial fibrillation	Condition	SNOMED
atrial fibrillation	605092	Paroxysmal atrial fibrillation with rapid ventricular response	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	314665	Atrial flutter	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	317302	Sinus node dysfunction	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	317893	Paroxysmal supraventricular tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	320425	Heart block	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	441872	Supraventricular premature beats	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606035	Right atrial non-cavotricuspid isthmus dependent macro re-entrant atrial tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606036	Non-scar mediated right atrial non-cavotricuspid isthmus dependent macro re-entrant atrial tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606049	Anticlockwise cavotricuspid isthmus dependent macroreentry tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606053	Antidromic atrioventricular reciprocating tachycardia utilizing atrio-ventricular accessory pathway with antegrade unidirectional conduction	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606054	Antidromic atrioventricular reciprocating tachycardia utilizing atrio-fascicular accessory pathway with antegrade unidirectional conduction	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606055	Non scar mediated left atrial non-cavotricuspid isthmus dependent macro re-entrant atrial tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606056	Antidromic atrioventricular reciprocating tachycardia utilizing accessory pathway with antegrade unidirectional conduction	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606057	Scar mediated left atrial non-cavotricuspid isthmus dependent macro re-entrant atrial tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606067	Clockwise cavotricuspid isthmus dependent macroreentry tachycardia	Condition	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
atrial arrhythmia (excluding atrial fibrillation)	606069	Left atrial non-cavotricuspid isthmus dependent macro re-entrant atrial tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606078	Antidromic atrioventricular reciprocating tachycardia utilizing nodo-fascicular accessory pathway with antegrade unidirectional conduction	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606079	Typical atrioventricular nodal re-entry tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606083	Sinus bradycardia caused by drug	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606087	Scar mediated right atrial non-cavotricuspid isthmus dependent macro re-entrant atrial tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606090	Atypical slow slow atrioventricular nodal re-entry tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606091	Atypical atrioventricular nodal re-entry tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606092	Atypical fast slow atrioventricular nodal re-entry tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606093	Orthodromic atrioventricular reciprocating tachycardia utilizing manifest accessory pathway	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606094	Atrioventricular nodal reentry tachycardia with twin atrioventricular nodes	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606095	Antidromic atrioventricular reciprocating tachycardia utilizing accessory pathway with bidirectional conduction	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	606139	Orthodromic atrioventricular reciprocating tachycardia utilizing concealed accessory pathway	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	36712986	Atypical atrial flutter	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	36714994	Typical atrial flutter	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	42536724	Macro re-entrant atrial tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	42536725	Cavotricuspid isthmus dependent macroreentry tachycardia	Condition	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
atrial arrhythmia (excluding atrial fibrillation)	42536726	Atrioventricular reciprocating tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	42539038	Non-cavotricuspid isthmus dependent atrial tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	40480216	Symptomatic sinus bradycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	42872924	Atrial standstill	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4275423	Supraventricular tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4277903	Sinoatrial block	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4302802	Right atrial incisional tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4303256	Sinoatrial nodal reentrant tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	37312595	Scar mediated macro re-entrant atrial tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4028322	Sinoatrial arrest with nodal/ventricular escape	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4064869	Electrocardiogram: paroxysmal atrial tachycardia	Observation	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4065288	EKG: atrial flutter	Observation	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4068155	Atrial arrhythmia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4081675	Atrioventricular tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4088210	Sinus arrest with junctional escape	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4088352	Sinus arrest with atrial escape	Condition	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
atrial arrhythmia (excluding atrial fibrillation)	4091446	Sinus arrest with ventricular escape	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4102252	Asymptomatic sinoatrial node dysfunction	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4108241	Paroxysmal atrioventricular tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4108830	Atrial paroxysmal tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4111698	Paroxysmal nodal tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4120084	Sinoatrial node tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4121479	Ectopic atrial tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4121480	Ectopic atrioventricular node tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4121481	Antidromic atrioventricular re-entrant tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4124696	Re-entrant atrial tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4124697	Incessant atrial tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4124698	Re-entrant atrioventricular node tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4124699	Re-entrant atrioventricular tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4124700	Orthodromic atrioventricular re-entrant tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	37017190	EKG: atrial tachycardia	Observation	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	37017191	EKG: multifocal atrial tachycardia	Observation	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
atrial arrhythmia (excluding atrial fibrillation)	37019050	EKG: focal atrial tachycardia	Observation	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4146580	Paroxysmal atrial flutter	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4169261	Severe sinus bradycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4171269	Atrial tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4171683	Sinus bradycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4171887	Left atrial incisional tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4176112	Multifocal atrial tachycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4190306	Paroxysmal atrial tachycardia with block	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4210313	Sinus arrest	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4218739	Junctional premature beats	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4254116	Tachycardia-bradycardia	Condition	SNOMED
atrial arrhythmia (excluding atrial fibrillation)	4261842	Sick sinus syndrome	Condition	SNOMED
ventricular arrhythmia	4303238	Catecholaminergic polymorphic ventricular tachycardia	Condition	SNOMED
ventricular arrhythmia	4305862	Fascicular ventricular tachycardia	Condition	SNOMED
ventricular arrhythmia	4325850	Sustained ventricular fibrillation	Condition	SNOMED
ventricular arrhythmia	4327066	Ventricular escape beat	Condition	SNOMED
ventricular arrhythmia	37017188	EKG ventricular tachycardia polymorphic	Observation	SNOMED
ventricular arrhythmia	37017189	EKG ventricular tachycardia monomorphic	Observation	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
ventricular arrhythmia	433225	Ventricular flutter	Condition	SNOMED
ventricular arrhythmia	437579	Paroxysmal ventricular tachycardia	Condition	SNOMED
ventricular arrhythmia	437894	Ventricular fibrillation	Condition	SNOMED
ventricular arrhythmia	606064	Congenital junctional ectopic tachycardia	Condition	SNOMED
ventricular arrhythmia	46272503	Mahaim fiber tachycardia	Condition	SNOMED
ventricular arrhythmia	40480274	Nonsustained ventricular tachycardia	Condition	SNOMED
ventricular arrhythmia	40484036	Bundle branch reentrant ventricular tachycardia	Condition	SNOMED
ventricular arrhythmia	40622721	Ventricular tachyarrhythmia	Condition	SNOMED
ventricular arrhythmia	4135823	Torsades de pointes	Condition	SNOMED
ventricular arrhythmia	4139206	Sustained ventricular tachycardia	Condition	SNOMED
ventricular arrhythmia	4141527	EKG: torsades de pointes	Observation	SNOMED
ventricular arrhythmia	4143407	ECG: paroxysmal ventricular tachycardia	Observation	SNOMED
ventricular arrhythmia	4171193	Idioventricular rhythm	Condition	SNOMED
ventricular arrhythmia	4185572	Ventricular arrhythmia	Condition	SNOMED
ventricular arrhythmia	4218242	Ventricular escape rhythm	Condition	SNOMED
ventricular arrhythmia	4233619	Pulseless ventricular tachycardia	Condition	SNOMED
ventricular arrhythmia	4244893	Ventricular parasystole	Condition	SNOMED
ventricular arrhythmia	4247537	Accelerated idioventricular rhythm	Condition	SNOMED
ventricular arrhythmia	37109917	Idiopathic ventricular fibrillation not Brugada type	Condition	SNOMED
ventricular arrhythmia	37110729	Torsades de pointe caused by drug	Condition	SNOMED
ventricular arrhythmia	37397458	Torsade de pointes with short coupling interval syndrome	Condition	SNOMED
ventricular arrhythmia	45771051	Recurrent ventricular tachycardia	Condition	SNOMED
ventricular arrhythmia	44782707	Nonsustained paroxysmal ventricular tachycardia	Condition	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
ventricular arrhythmia	4008580	Ventricular bigeminy	Condition	SNOMED
ventricular arrhythmia	4029303	Fusion beats	Condition	SNOMED
ventricular arrhythmia	4064453	EKG: ventricular arrhythmia	Observation	SNOMED
ventricular arrhythmia	4064455	EKG: ventricular fibrillation	Observation	SNOMED
ventricular arrhythmia	4064871	EKG: ventricular tachycardia	Observation	SNOMED
ventricular arrhythmia	4066289	Ventricular premature beats	Condition	SNOMED
ventricular arrhythmia	4088348	Wide QRS ventricular tachycardia	Condition	SNOMED
ventricular arrhythmia	4088349	Ventricular tachycardia, polymorphic	Condition	SNOMED
ventricular arrhythmia	4088350	Slow ventricular response	Condition	SNOMED
ventricular arrhythmia	4088501	Ventricular tachycardia, polymorphic without Q-T prolongation	Condition	SNOMED
ventricular arrhythmia	4088505	Ventricular trigeminy	Condition	SNOMED
ventricular arrhythmia	4088506	Ventricular quadrigeminy	Condition	SNOMED
ventricular arrhythmia	4088982	Narrow QRS ventricular tachycardia	Condition	SNOMED
ventricular arrhythmia	4088985	Multiple premature ventricular complexes	Condition	SNOMED
ventricular arrhythmia	4089462	Ventricular premature complex	Condition	SNOMED
ventricular arrhythmia	4089463	Multiple ventricular interpolated complexes	Condition	SNOMED
ventricular arrhythmia	4089464	Paired ventricular premature complexes	Condition	SNOMED
ventricular arrhythmia	4091900	Ventricular tachycardia, monomorphic	Condition	SNOMED
ventricular arrhythmia	4091904	Run of ventricular premature complexes	Condition	SNOMED
ventricular arrhythmia	4092010	Ventricular interpolated complexes	Condition	SNOMED
ventricular arrhythmia	4103295	Ventricular tachycardia	Condition	SNOMED
ventricular arrhythmia	4111552	Re-entry ventricular arrhythmia	Condition	SNOMED
ventricular arrhythmia	4111700	Ventricular fibrillation and flutter	Condition	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
ventricular arrhythmia	4119599	Ventricular tachycardia with normal heart	Condition	SNOMED
ventricular arrhythmia	4119600	Incessant infant ventricular tachycardia	Condition	SNOMED
ventricular arrhythmia	4120086	His bundle tachycardia	Condition	SNOMED
ventricular arrhythmia	4121482	Induced ventricular tachycardia	Condition	SNOMED
ventricular arrhythmia	4121483	Right ventricular outflow tract ventricular tachycardia	Condition	SNOMED
sudden or unattended death	42536727	Sudden arrhythmic death syndrome	Condition	SNOMED
sudden or unattended death	46272741	Sudden infant death with dysgenesis of testes syndrome	Condition	SNOMED
sudden or unattended death	4289171	Unexpected sudden death of adult	Observation	SNOMED
sudden or unattended death	4305552	Dead - unexpected	Observation	SNOMED
sudden or unattended death	4317150	Sudden cardiac death	Condition	SNOMED
sudden or unattended death	4145919	Sudden death of unknown cause during the puerperium	Observation	SNOMED
sudden or unattended death	4171903	Sudden death, cause unknown	Observation	SNOMED
sudden or unattended death	4177807	Unexpected death	Observation	SNOMED
sudden or unattended death	4233376	Unexplained sudden death	Observation	SNOMED
sudden or unattended death	4252573	Death unattended by physician	Observation	SNOMED
sudden or unattended death	37395454	Sudden infant death syndrome with mention of autopsy	Observation	SNOMED
sudden or unattended death	36714275	Sudden unexpected death in epilepsy	Observation	SNOMED
sudden or unattended death	4132309	Sudden death	Observation	SNOMED
sudden or unattended death	40480476	Unattended death of unknown cause	Observation	SNOMED
sudden or unattended death	441139	Instantaneous death	Observation	SNOMED
sudden or unattended death	441413	Death of unknown cause	Observation	SNOMED
sudden or unattended death	443584	Dead - sudden death	Observation	SNOMED
sudden or unattended death	443882	Unattended death	Observation	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
cardiac arrhythmia (incident)	46272503	Mahaim fiber tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	46284985	Holiday heart syndrome	Condition	SNOMED
cardiac arrhythmia (incident)	313209	Left bundle branch hemiblock	Condition	SNOMED
cardiac arrhythmia (incident)	313217	Atrial fibrillation	Condition	SNOMED
cardiac arrhythmia (incident)	313224	Anomalous atrioventricular excitation	Condition	SNOMED
cardiac arrhythmia (incident)	313780	Mobitz type II atrioventricular block	Condition	SNOMED
cardiac arrhythmia (incident)	313791	Bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	313792	Paroxysmal tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	314059	Right bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	314379	First degree atrioventricular block	Condition	SNOMED
cardiac arrhythmia (incident)	314664	Long QT syndrome	Condition	SNOMED
cardiac arrhythmia (incident)	314665	Atrial flutter	Condition	SNOMED
cardiac arrhythmia (incident)	315643	Tachyarrhythmia	Condition	SNOMED
cardiac arrhythmia (incident)	316135	Atrioventricular block	Condition	SNOMED
cardiac arrhythmia (incident)	316429	Premature beats	Condition	SNOMED
cardiac arrhythmia (incident)	316432	Right bundle branch block AND left anterior fascicular block	Condition	SNOMED
cardiac arrhythmia (incident)	316998	Left bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	316999	Conduction disorder of the heart	Condition	SNOMED
cardiac arrhythmia (incident)	317302	Sinus node dysfunction	Condition	SNOMED
cardiac arrhythmia (incident)	317893	Paroxysmal supraventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	318448	Second degree atrioventricular block	Condition	SNOMED
cardiac arrhythmia (incident)	320425	Heart block	Condition	SNOMED
cardiac arrhythmia (incident)	320744	Complete atrioventricular block	Condition	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
cardiac arrhythmia (incident)	321315	Trifascicular block	Condition	SNOMED
cardiac arrhythmia (incident)	321587	Bilateral bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	321590	Right bundle branch block AND left posterior fascicular block	Condition	SNOMED
cardiac arrhythmia (incident)	433225	Ventricular flutter	Condition	SNOMED
cardiac arrhythmia (incident)	437579	Paroxysmal ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	437894	Ventricular fibrillation	Condition	SNOMED
cardiac arrhythmia (incident)	441872	Supraventricular premature beats	Condition	SNOMED
cardiac arrhythmia (incident)	605092	Paroxysmal atrial fibrillation with rapid ventricular response	Condition	SNOMED
cardiac arrhythmia (incident)	606035	Right atrial non-cavotricuspid isthmus dependent macro re-entrant atrial tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	606036	Non-scar mediated right atrial non-cavotricuspid isthmus dependent macro re-entrant atrial tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	606049	Anticlockwise cavotricuspid isthmus dependent macroreentry tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	606053	Antidromic atrioventricular reciprocating tachycardia utilizing atrio-ventricular accessory pathway with antegrade unidirectional conduction	Condition	SNOMED
cardiac arrhythmia (incident)	606054	Antidromic atrioventricular reciprocating tachycardia utilizing atrio-fascicular accessory pathway with antegrade unidirectional conduction	Condition	SNOMED
cardiac arrhythmia (incident)	606055	Non scar mediated left atrial non-cavotricuspid isthmus dependent macro re-entrant atrial tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	606056	Antidromic atrioventricular reciprocating tachycardia utilizing accessory pathway with antegrade unidirectional conduction	Condition	SNOMED
cardiac arrhythmia (incident)	606057	Scar mediated left atrial non-cavotricuspid isthmus dependent macro re-entrant atrial tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	606064	Congenital junctional ectopic tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	606067	Clockwise cavotricuspid isthmus dependent macroreentry tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	606069	Left atrial non-cavotricuspid isthmus dependent macro re-entrant atrial tachycardia	Condition	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
cardiac arrhythmia (incident)	606078	Antidromic atrioventricular reciprocating tachycardia utilizing nodo-fascicular accessory pathway with antegrade unidirectional conduction	Condition	SNOMED
cardiac arrhythmia (incident)	606079	Typical atrioventricular nodal re-entry tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	606083	Sinus bradycardia caused by drug	Condition	SNOMED
cardiac arrhythmia (incident)	606087	Scar mediated right atrial non-cavotricuspid isthmus dependent macro re-entrant atrial tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	606090	Atypical slow slow atrioventricular nodal re-entry tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	606091	Atypical atrioventricular nodal re-entry tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	606092	Atypical fast slow atrioventricular nodal re-entry tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	606093	Orthodromic atrioventricular reciprocating tachycardia utilizing manifest accessory pathway	Condition	SNOMED
cardiac arrhythmia (incident)	606094	Atrioventricular nodal reentry tachycardia with twin atrioventricular nodes	Condition	SNOMED
cardiac arrhythmia (incident)	606095	Antidromic atrioventricular reciprocating tachycardia utilizing accessory pathway with bidirectional conduction	Condition	SNOMED
cardiac arrhythmia (incident)	606139	Orthodromic atrioventricular reciprocating tachycardia utilizing concealed accessory pathway	Condition	SNOMED
cardiac arrhythmia (incident)	4135823	Torsades de pointes	Condition	SNOMED
cardiac arrhythmia (incident)	4138545	Right bundle branch block, anterior fascicular block AND posterior fascicular block	Condition	SNOMED
cardiac arrhythmia (incident)	4138921	EKG: Mobitz type II atrioventricular block	Observation	SNOMED
cardiac arrhythmia (incident)	4138973	Right bundle branch block with left bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	4139206	Sustained ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4139517	Transient cerebral ischemia due to atrial fibrillation	Condition	SNOMED
cardiac arrhythmia (incident)	4141527	EKG: torsades de pointes	Observation	SNOMED
cardiac arrhythmia (incident)	4141820	ECG: sinus arrhythmia	Observation	SNOMED
cardiac arrhythmia (incident)	4143042	Ectopic beats	Condition	SNOMED
cardiac arrhythmia (incident)	4143407	ECG: paroxysmal ventricular tachycardia	Observation	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
cardiac arrhythmia (incident)	4146580	Paroxysmal atrial flutter	Condition	SNOMED
cardiac arrhythmia (incident)	4153404	Lev's syndrome	Condition	SNOMED
cardiac arrhythmia (incident)	4154290	Paroxysmal atrial fibrillation	Condition	SNOMED
cardiac arrhythmia (incident)	4154638	Stokes-Adams attack	Condition	SNOMED
cardiac arrhythmia (incident)	4164083	Ectopic rhythm	Condition	SNOMED
cardiac arrhythmia (incident)	4166380	Junctional escape beats	Condition	SNOMED
cardiac arrhythmia (incident)	4166844	Intraventricular conduction defect	Condition	SNOMED
cardiac arrhythmia (incident)	4169261	Severe sinus bradycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4171193	Idioventricular rhythm	Condition	SNOMED
cardiac arrhythmia (incident)	4171269	Atrial tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4171683	Sinus bradycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4171887	Left atrial incisional tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4175473	Atrioventricular dissociation	Condition	SNOMED
cardiac arrhythmia (incident)	4176112	Multifocal atrial tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4184950	Right bundle branch block AND incomplete left bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	4185572	Ventricular arrhythmia	Condition	SNOMED
cardiac arrhythmia (incident)	4188347	Stokes-Adams syndrome	Condition	SNOMED
cardiac arrhythmia (incident)	4190306	Paroxysmal atrial tachycardia with block	Condition	SNOMED
cardiac arrhythmia (incident)	4191222	Nonparoxysmal AV nodal tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4199501	Rapid atrial fibrillation	Condition	SNOMED
cardiac arrhythmia (incident)	4205137	Mobitz type I incomplete atrioventricular block	Condition	SNOMED
cardiac arrhythmia (incident)	4210313	Sinus arrest	Condition	SNOMED
cardiac arrhythmia (incident)	4217221	Nodal rhythm disorder	Condition	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
cardiac arrhythmia (incident)	4217860	Right bundle branch block, anterior fascicular block AND incomplete posterior fascicular block	Condition	SNOMED
cardiac arrhythmia (incident)	4218242	Ventricular escape rhythm	Condition	SNOMED
cardiac arrhythmia (incident)	4218739	Junctional premature beats	Condition	SNOMED
cardiac arrhythmia (incident)	4221549	Irregular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4226399	Fibrillation	Condition	SNOMED
cardiac arrhythmia (incident)	4228448	Bradyarrhythmia	Condition	SNOMED
cardiac arrhythmia (incident)	4228836	AV node arrhythmia	Condition	SNOMED
cardiac arrhythmia (incident)	4233619	Pulseless ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4236004	Ectopic atrial beats	Condition	SNOMED
cardiac arrhythmia (incident)	4243143	Interpolated ventricular premature complexes	Condition	SNOMED
cardiac arrhythmia (incident)	4244693	Right bundle branch block, anterior fascicular block AND incomplete left bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	4244893	Ventricular parasystole	Condition	SNOMED
cardiac arrhythmia (incident)	4247537	Accelerated idioventricular rhythm	Condition	SNOMED
cardiac arrhythmia (incident)	4248028	Supraventricular arrhythmia	Condition	SNOMED
cardiac arrhythmia (incident)	4249027	Right branch block, incomplete anterior fascicular block AND incomplete posterior fascicular block	Condition	SNOMED
cardiac arrhythmia (incident)	4250169	Bifascicular block	Condition	SNOMED
cardiac arrhythmia (incident)	4254116	Tachycardia-bradycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4261842	Sick sinus syndrome	Condition	SNOMED
cardiac arrhythmia (incident)	4262389	Tic-tac rhythm	Condition	SNOMED
cardiac arrhythmia (incident)	4267892	Complete left bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	4268046	Left posterior fascicular block	Condition	SNOMED
cardiac arrhythmia (incident)	4271464	Multifocal premature beats	Condition	SNOMED
cardiac arrhythmia (incident)	37017188	EKG ventricular tachycardia polymorphic	Observation	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
cardiac arrhythmia (incident)	37017189	EKG ventricular tachycardia monomorphic	Observation	SNOMED
cardiac arrhythmia (incident)	37017190	EKG: atrial tachycardia	Observation	SNOMED
cardiac arrhythmia (incident)	37017191	EKG: multifocal atrial tachycardia	Observation	SNOMED
cardiac arrhythmia (incident)	37019050	EKG: focal atrial tachycardia	Observation	SNOMED
cardiac arrhythmia (incident)	42536724	Macro re-entrant atrial tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	42536725	Cavotricuspid isthmus dependent macroreentry tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	42536726	Atrioventricular reciprocating tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	42536727	Sudden arrhythmic death syndrome	Condition	SNOMED
cardiac arrhythmia (incident)	42538755	Supraventricular bradyarrhythmia	Condition	SNOMED
cardiac arrhythmia (incident)	42539038	Non-cavotricuspid isthmus dependent atrial tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	42539346	Preexcited atrial fibrillation	Condition	SNOMED
cardiac arrhythmia (incident)	42689664	Atrial fibrillation detected	Condition	SNOMED
cardiac arrhythmia (incident)	40479264	Acquired long QT syndrome	Condition	SNOMED
cardiac arrhythmia (incident)	40480216	Symptomatic sinus bradycardia	Condition	SNOMED
cardiac arrhythmia (incident)	40480274	Nonsustained ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	40481891	Heart block caused by drug	Condition	SNOMED
cardiac arrhythmia (incident)	40482086	Left anterior fascicular block on electrocardiogram	Observation	SNOMED
cardiac arrhythmia (incident)	40482887	Right bundle branch block and left anterior fascicular block on electrocardiogram	Observation	SNOMED
cardiac arrhythmia (incident)	40482938	Trifascicular block on electrocardiogram	Observation	SNOMED
cardiac arrhythmia (incident)	40483798	Bifascicular block on electrocardiogram	Observation	SNOMED
cardiac arrhythmia (incident)	40484036	Bundle branch reentrant ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	40622721	Ventricular tachyarrhythmia	Condition	SNOMED
cardiac arrhythmia (incident)	42872924	Atrial standstill	Condition	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
cardiac arrhythmia (incident)	43020494	High degree second degree atrioventricular block	Condition	SNOMED
cardiac arrhythmia (incident)	36712986	Atypical atrial flutter	Condition	SNOMED
cardiac arrhythmia (incident)	36714994	Typical atrial flutter	Condition	SNOMED
cardiac arrhythmia (incident)	36717692	At high risk of atrial fibrillation	Observation	SNOMED
cardiac arrhythmia (incident)	45757098	Cardiac arrhythmia in mother complicating childbirth	Condition	SNOMED
cardiac arrhythmia (incident)	45771051	Recurrent ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	1340258	Exacerbation of atrial fibrillation	Condition	OMOP Extension
cardiac arrhythmia (incident)	44782442	Atrial fibrillation with rapid ventricular response	Condition	SNOMED
cardiac arrhythmia (incident)	44782643	Progressive familial heart block, type II	Condition	SNOMED
cardiac arrhythmia (incident)	44782707	Nonsustained paroxysmal ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	44782789	Nonsustained paroxysmal supraventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	44783731	Provision of written information about atrial fibrillation	Observation	SNOMED
cardiac arrhythmia (incident)	44784217	Cardiac arrhythmia	Condition	SNOMED
cardiac arrhythmia (incident)	44784220	Non-specific intraventricular conduction delay	Condition	SNOMED
cardiac arrhythmia (incident)	44784236	Short QT syndrome	Condition	SNOMED
cardiac arrhythmia (incident)	44804336	Atrial fibrillation monitoring invitation	Observation	SNOMED
cardiac arrhythmia (incident)	40757907	Atrial fibrillation and other dysrhythmias in last 7 days [MDSv3]	Observation	LOINC
cardiac arrhythmia (incident)	40761370	Date of first episode of atrial fibrillation	Observation	LOINC
cardiac arrhythmia (incident)	40761371	Emergency room visit or hospitalized or saw doctor for atrial fibrillation	Observation	LOINC
cardiac arrhythmia (incident)	40761374	Taking any anticoagulants for treatment of atrial fibrillation	Observation	LOINC
cardiac arrhythmia (incident)	40761375	Taking any antiarrhythmics for treatment of atrial fibrillation	Observation	LOINC
cardiac arrhythmia (incident)	40768542	Atrial fibrillation 10Y risk [#] Framingham.Schnabel 2009	Observation	LOINC
cardiac arrhythmia (incident)	40768550	Stroke after atrial fibrillation 5 year risk [#] Framingham.Wang 2003	Observation	LOINC

Phenotype	Concept id	Concept name	Domain	Vocabulary
cardiac arrhythmia (incident)	40768551	Stroke or death after atrial fibrillation 5 year risk [#] Framingham.Wang 2003	Observation	LOINC
cardiac arrhythmia (incident)	4008580	Ventricular bigeminy	Condition	SNOMED
cardiac arrhythmia (incident)	4023336	Multifocal premature ventricular complexes	Condition	SNOMED
cardiac arrhythmia (incident)	4028322	Sinoatrial arrest with nodal/ventricular escape	Condition	SNOMED
cardiac arrhythmia (incident)	4029303	Fusion beats	Condition	SNOMED
cardiac arrhythmia (incident)	4032785	Right bundle branch block, posterior fascicular block AND incomplete left bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	4034164	Monofascicular block	Condition	SNOMED
cardiac arrhythmia (incident)	4038688	AV junctional rhythm	Condition	SNOMED
cardiac arrhythmia (incident)	4057008	Accelerated atrioventricular conduction	Condition	SNOMED
cardiac arrhythmia (incident)	4064451	ECG: extrasystole	Observation	SNOMED
cardiac arrhythmia (incident)	4064452	ECG: atrial fibrillation	Observation	SNOMED
cardiac arrhythmia (incident)	4064453	EKG: ventricular arrhythmia	Observation	SNOMED
cardiac arrhythmia (incident)	4064455	EKG: ventricular fibrillation	Observation	SNOMED
cardiac arrhythmia (incident)	4064457	EKG: heart block	Observation	SNOMED
cardiac arrhythmia (incident)	4064459	Mobitz type I second degree atrioventricular block on electrocardiogram	Observation	SNOMED
cardiac arrhythmia (incident)	4064460	EKG: right bundle branch block	Observation	SNOMED
cardiac arrhythmia (incident)	4064612	ECG: ventricular ectopics	Observation	SNOMED
cardiac arrhythmia (incident)	4064614	EKG: left bundle branch block	Observation	SNOMED
cardiac arrhythmia (incident)	4064867	ECG: ectopic beats	Observation	SNOMED
cardiac arrhythmia (incident)	4064869	Electrocardiogram: paroxysmal atrial tachycardia	Observation	SNOMED
cardiac arrhythmia (incident)	4064871	EKG: ventricular tachycardia	Observation	SNOMED
cardiac arrhythmia (incident)	4064873	ECG: partial atrioventricular block - long PR	Observation	SNOMED
cardiac arrhythmia (incident)	4064874	EKG: complete atrioventricular block	Observation	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
cardiac arrhythmia (incident)	4065285	EKG: atrial ectopics	Observation	SNOMED
cardiac arrhythmia (incident)	4065287	EKG: supraventricular arrhythmia	Observation	SNOMED
cardiac arrhythmia (incident)	4065288	EKG: atrial flutter	Observation	SNOMED
cardiac arrhythmia (incident)	4065290	ECG: partial atrioventricular block - 2:1	Observation	SNOMED
cardiac arrhythmia (incident)	4066289	Ventricular premature beats	Condition	SNOMED
cardiac arrhythmia (incident)	4068155	Atrial arrhythmia	Condition	SNOMED
cardiac arrhythmia (incident)	4081675	Atrioventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4088210	Sinus arrest with junctional escape	Condition	SNOMED
cardiac arrhythmia (incident)	4088332	Intermittent second degree atrioventricular block	Condition	SNOMED
cardiac arrhythmia (incident)	4088336	Incomplete left bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	4088337	Complete right bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	4088338	Incomplete right bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	4088347	Marked sinus arrhythmia	Condition	SNOMED
cardiac arrhythmia (incident)	4088348	Wide QRS ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4088349	Ventricular tachycardia, polymorphic	Condition	SNOMED
cardiac arrhythmia (incident)	4088350	Slow ventricular response	Condition	SNOMED
cardiac arrhythmia (incident)	4088351	Junctional premature complex	Condition	SNOMED
cardiac arrhythmia (incident)	4088352	Sinus arrest with atrial escape	Condition	SNOMED
cardiac arrhythmia (incident)	4088496	Minor intraventricular conduction defect	Condition	SNOMED
cardiac arrhythmia (incident)	4088501	Ventricular tachycardia, polymorphic without Q-T prolongation	Condition	SNOMED
cardiac arrhythmia (incident)	4088502	AV junctional (nodal) arrest	Condition	SNOMED
cardiac arrhythmia (incident)	4088503	AV junctional (nodal) tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4088504	Atrial bigeminy	Condition	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
cardiac arrhythmia (incident)	4088505	Ventricular trigeminy	Condition	SNOMED
cardiac arrhythmia (incident)	4088506	Ventricular quadrigeminy	Condition	SNOMED
cardiac arrhythmia (incident)	4088507	Ventricular escape complex	Condition	SNOMED
cardiac arrhythmia (incident)	4088982	Narrow QRS ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4088983	AV-junctional (nodal) bradycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4088984	Blocked premature atrial contraction	Condition	SNOMED
cardiac arrhythmia (incident)	4088985	Multiple premature ventricular complexes	Condition	SNOMED
cardiac arrhythmia (incident)	4088986	Atrial escape complex	Condition	SNOMED
cardiac arrhythmia (incident)	4088987	Atrial parasystole	Condition	SNOMED
cardiac arrhythmia (incident)	4089459	AV nodal re-entry tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4089460	Multiple atrial premature complexes	Condition	SNOMED
cardiac arrhythmia (incident)	4089461	Run of atrial premature complexes	Condition	SNOMED
cardiac arrhythmia (incident)	4089462	Ventricular premature complex	Condition	SNOMED
cardiac arrhythmia (incident)	4089463	Multiple ventricular interpolated complexes	Condition	SNOMED
cardiac arrhythmia (incident)	4089464	Paired ventricular premature complexes	Condition	SNOMED
cardiac arrhythmia (incident)	4091446	Sinus arrest with ventricular escape	Condition	SNOMED
cardiac arrhythmia (incident)	4091899	Junctional ectopic tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4091900	Ventricular tachycardia, monomorphic	Condition	SNOMED
cardiac arrhythmia (incident)	4091901	Aberrant premature complexes	Condition	SNOMED
cardiac arrhythmia (incident)	4091902	Supraventricular bigeminy	Condition	SNOMED
cardiac arrhythmia (incident)	4091903	Atrial trigeminy	Condition	SNOMED
cardiac arrhythmia (incident)	4091904	Run of ventricular premature complexes	Condition	SNOMED
cardiac arrhythmia (incident)	4092010	Ventricular interpolated complexes	Condition	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
cardiac arrhythmia (incident)	4092011	Aberrantly conducted complex	Condition	SNOMED
cardiac arrhythmia (incident)	4099778	Unifocal premature ventricular complexes	Condition	SNOMED
cardiac arrhythmia (incident)	4102252	Asymptomatic sinoatrial node dysfunction	Condition	SNOMED
cardiac arrhythmia (incident)	4103295	Ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4106715	Vagal autonomic bradycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4108241	Paroxysmal atrioventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4108828	Ventricular pre-excitation	Condition	SNOMED
cardiac arrhythmia (incident)	4108830	Atrial paroxysmal tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4108832	Atrial fibrillation and flutter	Condition	SNOMED
cardiac arrhythmia (incident)	4109365	Premature atrial contraction	Condition	SNOMED
cardiac arrhythmia (incident)	4111543	Left main stem bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	4111546	Paroxysmal junctional tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4111552	Re-entry ventricular arrhythmia	Condition	SNOMED
cardiac arrhythmia (incident)	4111570	Partial atrioventricular block	Condition	SNOMED
cardiac arrhythmia (incident)	4111698	Paroxysmal nodal tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4111700	Ventricular fibrillation and flutter	Condition	SNOMED
cardiac arrhythmia (incident)	4115173	Atrial premature complex	Condition	SNOMED
cardiac arrhythmia (incident)	4117112	Controlled atrial fibrillation	Condition	SNOMED
cardiac arrhythmia (incident)	4119599	Ventricular tachycardia with normal heart	Condition	SNOMED
cardiac arrhythmia (incident)	4119600	Incessant infant ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4119601	Lone atrial fibrillation	Condition	SNOMED
cardiac arrhythmia (incident)	4119602	Non-rheumatic atrial fibrillation	Condition	SNOMED
cardiac arrhythmia (incident)	4120084	Sinoatrial node tachycardia	Condition	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
cardiac arrhythmia (incident)	4120085	Supraventricular tachycardia with functional bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	4120086	His bundle tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4120087	Unidirectional retrograde accessory pathway	Condition	SNOMED
cardiac arrhythmia (incident)	4121479	Ectopic atrial tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4121480	Ectopic atrioventricular node tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4121481	Antidromic atrioventricular re-entrant tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4121482	Induced ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4121483	Right ventricular outflow tract ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4124696	Re-entrant atrial tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4124697	Incessant atrial tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4124698	Re-entrant atrioventricular node tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4124699	Re-entrant atrioventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4124700	Orthodromic atrioventricular re-entrant tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4124702	Permanent junctional reciprocating tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4275423	Supraventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4277903	Sinoatrial block	Condition	SNOMED
cardiac arrhythmia (incident)	4280348	Right bundle branch block, posterior fascicular block AND incomplete anterior fascicular block	Condition	SNOMED
cardiac arrhythmia (incident)	4295336	Left anterior fascicular block	Condition	SNOMED
cardiac arrhythmia (incident)	4296729	Anterior fascicular block, posterior fascicular block AND incomplete right bundle branch block	Condition	SNOMED
cardiac arrhythmia (incident)	4298806	Incomplete atrioventricular block with atrioventricular response	Condition	SNOMED
cardiac arrhythmia (incident)	4302802	Right atrial incisional tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4303238	Catecholaminergic polymorphic ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4303256	Sinoatrial nodal reentrant tachycardia	Condition	SNOMED

Phenotype	Concept id	Concept name	Domain	Vocabulary
cardiac arrhythmia (incident)	4304839	Diffuse intraventricular block	Condition	SNOMED
cardiac arrhythmia (incident)	4305210	Atrioventricular conduction disorder	Condition	SNOMED
cardiac arrhythmia (incident)	4305862	Fascicular ventricular tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4313053	Normal sinus arrhythmia	Condition	SNOMED
cardiac arrhythmia (incident)	4320474	Idiojunctional tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	4325850	Sustained ventricular fibrillation	Condition	SNOMED
cardiac arrhythmia (incident)	4327066	Ventricular escape beat	Condition	SNOMED
cardiac arrhythmia (incident)	37108582	Arrhythmia during surgery	Condition	SNOMED
cardiac arrhythmia (incident)	37109917	Idiopathic ventricular fibrillation not Brugada type	Condition	SNOMED
cardiac arrhythmia (incident)	37110729	Torsades de pointe caused by drug	Condition	SNOMED
cardiac arrhythmia (incident)	37116420	Acquired complete atrioventricular block	Condition	SNOMED
cardiac arrhythmia (incident)	37208965	QOF (Quality and Outcomes Framework) atrial fibrillation quality indicator-related care invitation	Observation	SNOMED
cardiac arrhythmia (incident)	37310849	QOF (Quality and Outcomes Framework) atrial fibrillation quality indicator-related care invitation using preferred method of communication	Observation	SNOMED
cardiac arrhythmia (incident)	37312140	Acquired Brugada syndrome	Condition	SNOMED
cardiac arrhythmia (incident)	37312595	Scar mediated macro re-entrant atrial tachycardia	Condition	SNOMED
cardiac arrhythmia (incident)	37396235	Long QT syndrome caused by drug	Condition	SNOMED
cardiac arrhythmia (incident)	37397458	Torsade de pointes with short coupling interval syndrome	Condition	SNOMED

ANNEX V: Glossary

Additional definitions are available in the EMA Glossary of terms https://www.ema.europa.eu/en/about-us/glossaries.

Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g., side effects).

Common Data Model (CDM)

A standardized data structure that enables data from multiple sources to be harmonized, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

Complex Studies (C3)

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Centre in Rotterdam, the Netherlands.

Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

Data Source

A database or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

DARWIN EU®

The European Medicines Agency's (EMA) federated network of real-world data sources designed to generate evidence to support regulatory decision-making.

EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

Evidence Generation

The process of analysing real-world data to produce scientific information that can inform healthcare or regulatory decisions.

Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

Metadata

Descriptive information about a data source (e.g., its content, quality, and structure), essential for identifying relevant databases in DARWIN EU® studies.

Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

Patient-Level Data

Data related to individuals, de-identified, used for longitudinal or detailed analyses.

OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in real-world evidence generation.

Real-World Data (RWD)

Data relating to individual health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

Study Protocol

A detailed plan describing how a specific real-world study will be conducted, including objectives, design, data sources, and analyses.

Very Complex Studies (C4)

Studies which cannot rely only on electronic health care databases, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.