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Quantitative Safety and Epidemiology

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LCZ696B2014
Non-interventional Study Final Report

Non-interventional post-authorization multi-database safety study to characterize the risk of angioedema and other specific safety events of interest in association with the use of Entresto® (sacubitril/valsartan) in adult patients with heart failure

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Research question and objectives	With this non-interventional cohort study, real-world data were gathered on the risk of angioedema and other potential or identified risks as listed in the Entresto® Risk Management Plan (including hypotension, hyperkalemia, hepatotoxicity, and renal impairment) in association with sacubitril/valsartan as compared to ACE inhibitor use in adult patients with heart failure
Country(-ies) of study	Denmark, Germany, Italy, the Netherlands, Spain, United Kingdom

Main Author [redacted]

Marketing authorization holder

Marketing authorization holder(s)	Novartis Europharm Limited Vista Building Elm Park, Merrion Road Dublin 4 Ireland
MAH contact person	[redacted]

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1 Abstract

Title

Non-interventional post-authorization multi-database safety study to characterize the risk of angioedema and other specific safety events of interest in association with the use of Entresto® (sacubitril/valsartan) in adult patients with heart failure

Version and date

v01 (final report); 09-Oct-2024

NIS Type

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Key words

Sacubitril/valsartan; ACEIs; safety; multi-database; angioedema

Rationale and background

Sacubitril/valsartan (ATC code C09DX04; product name Entresto®) utilizes a novel mechanism of action in the treatment of heart failure (HF).

In the randomized controlled trial (RCT) PARADIGM-HF, > 8400 patients with HF were treated with sacubitril/valsartan or ACE inhibitor (ACEI), enalapril. Patients receiving sacubitril/valsartan had a significant reduction in cardiovascular mortality and in the number of hospitalizations for heart failure by 20%. Additionally, sacubitril/valsartan was superior to enalapril in reducing symptoms and physical limitation associated with HF. Both treatments had a similar safety profile (McMurray et al. 2014).

As a result of this pivotal trial, Entresto® was approved in the European Union (EU) for the treatment of adult patients with symptomatic chronic HF and a reduced ejection fraction (HFrEF) in November 2015.

This non-interventional study (NIS) (LCZ696B2014) aimed to assess the risk of angioedema associated with sacubitril/valsartan in a real-world setting as well as the risk of various other important identified or potential risks listed in the Entresto® Risk Management Plan (RMP), including hypotension, hyperkalemia, hepatotoxicity, and renal impairment.

Research question and objectives

For this NIS, real-world data were gathered on the risk of angioedema and other potential or identified risks currently listed in the Entresto® RMP (including hypotension, hyperkalemia, hepatotoxicity, and renal impairment) in association with sacubitril/valsartan versus ACEI use in adult patients with HF.

The primary objectives of the study were:

- To estimate the incidence of specific safety events of interest in adult patients with HF newly starting treatment with sacubitril/valsartan (regardless of prior exposure to ACEIs or angiotensin receptor blockers [ARBs]).
- To estimate the incidence of all safety events of interest in adult HF patients newly starting treatment with sacubitril/valsartan without prior exposure to ACEIs or ARBs.

The primary safety event of interest was angioedema, and secondary safety events of interest were hypotension, hyperkalemia, hepatotoxicity, and renal impairment.

The secondary objectives of the study were:

- To estimate the incidence of all primary and secondary safety events of interest in adult HF patients newly starting treatment with ACEIs (patients without prior exposure to ACEIs/ARBs).
- To estimate the incidence of all primary and secondary safety events of interest in adult HF patients with ACEIs exposure (regardless of prior use of ACEIs/ARBs).

The study also included the following exploratory objectives:

- To estimate the relative risk of angioedema in adult patients with HF newly starting treatment with sacubitril/valsartan (without prior exposure to ACEIs/ARBs) as compared to adult HF patients newly starting treatment with ACEIs (without prior ACEI/ARB exposure).
- To estimate the relative risk of angioedema in adult HF patients newly starting treatment with sacubitril/valsartan (regardless of prior exposure to ACEIs/ARBs), versus adult HF patients ACEI exposure (regardless of prior exposure to ACEIs/ARBs).
- To estimate the relative risk of angioedema in adult HF patients newly starting treatment with sacubitril/valsartan (regardless of prior exposure to ACEIs/ARBs), versus adult HF patients newly starting treatment with ACEIs (without prior exposure to ACEIs/ARBs).

Study design

LCZ696B2014 is a non-interventional, cohort study using European healthcare database information in a population of adult patients with prevalent or incident HF, newly starting treatment with sacubitril/valsartan (with or without prior exposure to ACEIs or ARBs), or ACEIs (as new users, and separately as prevalent users).

Setting

The data for the source population of this study were retrieved from seven European electronic healthcare databases: Aarhus (Aarhus University Prescription Database and Danish National Patient Registry) from Denmark (DK), GePaRD (German Pharmacoepidemiological Research Database) from Germany, HSD (Health Search Database) and ARS (Agenzia Regionale di Sanità della Toscana) from Italy, PHARMO (PHARMO Institute for Drug Outcomes Research) from the Netherlands, SIDIAP (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) from Spain (ES), and the CPRD (Clinical Practice Research Datalink) from the United Kingdom (UK). PHARMO, SIDIAP, and CPRD have linkage with hospital data limited to a subset of the source population. Data from these three databases were analyzed separately as without or with linked hospital data and were considered as individual subsets.

The study period began at the launch date of sacubitril/valsartan in the countries of interest (earliest: December 2015 (DK, UK); latest: October 2016 (ES)) and ended on December 31, 2020, depending on the individual data availability at the time of data extraction (e.g., December 31, 2019 for GePaRD and June 30, 2021 for SIDIAP).

Data recorded during the COVID-19 pandemic (from 2020 onward) are likely to reflect different healthcare utilization patterns; therefore, the study period for the primary analysis (including primary, secondary and exploratory objectives) ended on December 31, 2019. Data from 2020 onward was assessed in a sensitivity analysis to determine the impact of the COVID-19 pandemic.

Subjects and study size

The study population included adult patients (≥ 18 years of age) initiating sacubitril/valsartan or using ACEIs (=index date, date of first prescription/dispensing) during the study period, with a valid database history of ≥ 365 days and a diagnosis of HF prior to or within three months (90 days) after their first prescription/dispensing of sacubitril/valsartan or ACEIs. Patients with HF were identified using specific coding systems for recorded inpatient and/or outpatient HF diagnoses (i.e., READ, International Classification of Diseases (ICD) 9th version (ICD-9) or ICD-10th version (ICD-10), ICD-10 German

Modification (GM), the International Classification of Primary Care codes (ICPC) and "Werkgroep Coördinatie Informatisering en Automatisering" codes (WCIA)), used by individual databases. Additional natural language processing (NLP) terms were used in PHARMO to further differentiate ICPC codes. In GePaRD, HF was identified by a predefined confirmation algorithm.

Patients who had a recorded angioedema diagnosis or hereditary angioedema any time prior to index date were excluded. For the safety event of hepatotoxicity, patients with a hepatotoxic event or hepatic morbidity suggestive of another etiology prior to or up to seven days after the index date were excluded. For the assessment of the safety event of renal impairment, patients with a recorded history of chronic renal disease or renal impairment at any time prior to index date were excluded.

Variables and data sources

Exposure information was identified using prescription or dispensing data using the database-specific coding systems. Patients were classified into four exposure cohorts, two for sacubitril/valsartan, and two for ACEI users:

- Exposure cohort 1: Patients initiating sacubitril/valsartan, regardless of prior ACEIs/ARBs use
- Exposure cohort 2: Patients initiating sacubitril/valsartan, without use of ACEIs/ARBs in the 365 days prior to index date (patients naïve to ACEIs/ARBs; a subset of exposure cohort 1)
- Exposure cohort 3: Patients using ACEIs, regardless of prior ACEIs/ARBs use (prevalent and incident users).
- Exposure cohort 4: Patients initiating ACEIs without prior use of ACEIs/ARBs in the 365 days prior to index date (patients naïve to ACEI/ARBs; a subset of exposure cohort 3)

Eligible patients were followed up from their index date until the occurrence of the safety event of interest, death, the date of discontinuing treatment of sacubitril/valsartan or ACEIs, the date of switching or adding treatment with another renin-angiotensin-aldosterone system (RAAS) blocking agent, the last date of follow-up available in the data set, or the study end date for the primary analysis (December 31, 2019) and sensitivity analysis (date of last available data).

Safety events of interest are listed below and were identified by-specific codes from in- or outpatient electronic medical records (e.g., READ, ICD-9/-10-CM, ICD-10 GM, ICPC, WCIA codes), and/or abnormal laboratory values (for hyperkalemia), if available.

The safety events of interest included:

Primary and Secondary Objectives (primary analyses)

- Angioedema (specification: 'narrow') [a primary endpoint]
- Hypotension (specification: 'narrow') [a secondary endpoint]
- Hyperkalemia (specification: 'narrow') [a secondary endpoint]
- Hepatotoxicity (specification: 'narrow') [a secondary endpoint]
- Renal impairment (specification: 'narrow') [a secondary endpoint]

Sensitivity Analyses [to examine potential misclassification of angioedema and hypotension]

- Angioedema ('broad': included terms for 'narrow' angioedema and anaphylactic shock)
- Angioedema ('narrow' definition expanded to unconfirmed diagnoses in GePaRD) [to understand if the number of events of angioedema may have been underestimated due to the event confirmation algorithm in GePaRD).
- Hypotension ('broad': included 'narrow' terms, as well as terms indicative of potential hypotensive events (e.g., "postural dizziness", "presyncope") in addition to specific diagnostic codes for hypotension [i.e., 'narrow' definition of hypotension])

Patients' characteristics/demographics included age at index date, sex, and ethnicity. Comorbidities (ever recorded prior to index date = look-back period) and co-medications (within 365 days prior to index date) were assessed.

Statistical methods

Statistics of patient baseline demographic and clinical characteristics were described, using contingency tables for categorical variables, and mean (±SD), median (IQR), and minimum, maximum for continuous variables per database and for all databases together (when possible) in the pre-COVID and full study period.

Differences in demographic and baseline characteristics of patients initiating sacubitril/valsartan and patients using ACEIs were quantified via standardized mean differences (SMD).

Crude and age- and sex-standardized incidence rates (IRs) of all safety events of interest were estimated per 1,000 person years (PYs) per database and all databases together. The corresponding 95% confidence intervals (CIs) for the crude IRs were estimated based on formulas proposed by Sahai and Khushid and Ulm (Sahai et al 1993, Ulm 1990). The 95% CIs for the age- and sex-standardized IRs were based on the Dobson method (Dobson et al 1991). The Dobson method produces relatively accurate 95% CIs when ten or more safety events are observed. For less than ten events 95% CIs were therefore not presented. The same approach was applied for all sensitivity analyses to examine potential misclassification of angioedema and hypotension.

In SIDIAP, the date of the dispensing was defined as the first day of the month because month and year of dispensing were only available. This has implications: first, for diagnoses of interest (safety events of interest/ exclusion criteria) occurring in the first month of exposure to sacubitril/valsartan or ACEIs, the initiation of both treatments is always assumed to precede the diagnosis although the opposite may be true. This may lead to incorrectly counting a diagnosis as a safety event although it would have qualified, as exclusion criterion had the exact exposure date been known. Second, dispensings for sacubitril/valsartan and ACEIs within the same month at index date were excluded and assumed non-adherent to the 36-hour wash-out period. To examine the impact of SIDIAP data on combined IRs, sensitivity analyses were conducted where all crude and age- and sex-standardized IRs were combined without data of SIDIAP were examined. This sensitivity analysis was not prespecified in the protocol but added post-hoc, to examine the impact of measurement errors in this data source.

Because the precise number of safety events was not provided for Aarhus and CPRD in case of less than five events due to their small-cell-count policies, a range of the combined crude IRs was calculated, assuming the true event count was zero for calculating the lower bound of the combined crude IR (best-case scenario) and assuming four events per data set for calculating the upper bound of the combined crude IR (worst-case scenario). When essential information for determining the IR was missing for at least one database, two combined crude IRs (best-case and worst-case scenario) are shown. Age- and sex-standardized IRs were not impacted by the small-cell-count policies with the exception of database- or subset-specific IRs for CPRD in case no event was observed.

The relative risk of angioedema expressed as a hazard ratio (HR; crude and adjusted) with its corresponding 95% CIs for sacubitril/valsartan versus ACEI cohorts were estimated for each comparison specified in the exploratory objectives per database (as feasible) in the pre-COVID period. To control for confounding, potential confounders such as age, sex, pre-specified comorbidities, and co-medications were introduced in the Cox regression model with overlap weighting based on the propensity score (PS).

Results

The source population included 41,383,318 patients from all seven databases combined. Of these, 5,049,696 adult patients either initiated sacubitril/valsartan or used ACEIs during the study period. The number of patients with HF in the study base was 676,505. This resulted in 39,616 patients initiating sacubitril/valsartan in exposure cohort 1 in the pre-COVID period. Of patients included in exposure cohort 1, a total of 4,548 patients (11%) were naïve to ACEIs/ARBs and were included in exposure cohort 2. Exposure cohort 3, which included patients using ACEI regardless of prior use of ACEIs/ARBs, was the largest cohort with a total of 642,689 patients. Approximately 26% (n=164,088) of patients in exposure cohort 3 were naïve to ACEIs/ARBs and were included in exposure cohort 4. The German claims database GePaRD contributed the majority of information (> 75%) to all exposure cohorts.

Across all databases patients were on average 72 and 74 years old among patients initiating sacubitril/valsartan (exposure cohort 1) and patients using ACEIs (exposure cohort 3), respectively. The proportion of men was higher among patients initiating sacubitril/valsartan (71% male in exposure cohort 1 and 65% in exposure cohort 2) compared with those using ACEIs (53% male in exposure cohort 3 and 51% male in exposure cohort 4). Cardiovascular diseases, chronic kidney disease (CKD), diabetes mellitus, and the use of cardiovascular co-medications were more frequent in patients initiating sacubitril/valsartan (exposure cohorts 1 and 2) than in patients using ACEIs (exposure cohorts 3 and 4). Co-medication use at or in the year prior to index date was higher for mineralocorticoid receptor antagonists (MRAs), loop diuretics, and beta-blockers in patients initiating sacubitril/valsartan (exposure cohorts 1 and 2) than in patients using ACEIs (exposure cohorts 3 and 4).

Primary and secondary objectives

Angioedema

For the safety event angioedema ('narrow'), there were 22 cases in exposure cohort 1 in all databases combined (21 in GePaRD, one in ARS), with a combined crude IR of 0.6 (95% CI 0.4-0.9) per 1,000 PYs for the best-case scenario. For the worst-case scenario of eight additional cases in CPRD, the combined crude IR was 0.8 (95% CI 0.5-1.1) per 1,000 PYs. There were three to 11 angioedema events observed in exposure cohort 2 (IR 0.9, 95% CI 0.2-2.5 [best-case scenario] and IR 3.1, 95% CI 1.6-5.6 [worst-case scenario] per 1,000 PYs). Combined IRs for angioedema in the ACEI cohorts were 0.9 (95% CI 0.8-0.9) per 1,000 PYs in exposure cohort 3 and 1.2 (95% CI 1.0-1.4 [best-case scenario]) and 1.3 (95% CI 1.1-1.5 [worst-case scenario]) per 1,000 PYs in exposure cohort 4, based on 769 events in exposure cohort 3 and 138 (best-case scenario) to 146 (worst-case scenario) events in exposure cohort 4. Combined age- and sex standardized IRs were 0.6 (95% CI 0.4-0.9) per 1,000 PYs in exposure cohort 1, 0.9 in exposure cohort 2 (less than ten events) per 1,000 PYs, 0.9 (95% CI 0.8-0.9) per 1,000 PYs in exposure cohort 3, and 1.2 (95% CI 1.0-1.4) per 1,000 PYs in exposure cohort 4, respectively. Combined age- and sex-standardized IRs were equal to combined crude IRs of the best-case scenarios.

In a sensitivity analysis conducted to account for potential misclassification of angioedema, the definition of potential cases of angioedema was expanded with diagnostic codes of anaphylactic shock (angioedema 'broad'). Combined crude IRs of angioedema [narrow] and anaphylactic shock were 1.3 (95% CI 1.0-1.7 [best-case scenario]) and 1.6 (95% CI 1.2-2.1 [worst-case scenario]) per 1,000 PYs in exposure cohort 1, 1.4 (95% CI 0.5-3.3 [best-case scenario]) and 3.7 (95% CI 2.0-6.3 [worst-case scenario]) per 1,000 PYs in exposure cohort 2, 1.4 (95% CI 1.3-1.4) per 1,000 PYs in exposure cohort 3, and 1.9 (95% CI 1.7-2.2 [best-case scenario]) and 2.0 (95% CI 1.7-2.2 [worst-case scenario]) per 1,000 PYs in exposure cohort 4, respectively. Combined age- and sex standardized IRs were 1.3 (95% CI 1.0-1.8) per 1,000 PYs in exposure cohort 1, 1.4 in exposure cohort 2 (less than ten events) per 1,000 PYs, 1.4 (95% CI 1.3-1.4) per 1,000 PYs in exposure cohort 3, and 1.9 (95% CI 1.7-2.2) per 1,000 PYs in exposure cohort 4, respectively.

In the sensitivity analysis where angioedema defined by confirmed diagnoses was expanded with unconfirmed diagnoses in GePaRD, crude IRs were 1.1 (95% CI 0.7-1.5) per 1,000 PYs in exposure cohort 1, 0.7 (95% CI 0.1-2.6) per 1,000 PYs in exposure cohort 2, 1.9 (95% CI 1.8-2.1) per 1,000 PYs in exposure cohort 3, and 2.5 (95% CI, 2.2-2.9) per 1,000 PYs in exposure cohort 4, respectively. Age- and sex-standardized IRs with 95% CIs were not estimated.

Hypotension

For hypotension, combined crude IRs were 24.8 (95% CI 23.2-26.4) per 1,000 PYs for exposure cohort 1, 34.7 (95% CI 28.7-41.5 [best-case scenario]) and 37.0 (95% CI 30.8-44.0 [worst-case scenario]) per 1,000 PYs for exposure cohort 2, 11.7 (95% CI 11.5-12.0) per 1,000 PYs for exposure cohort 3, and 20.8 (95% CI 20.0-21.7) per 1,000 PYs for exposure cohort 4, respectively. Combined age- and sex standardized IRs were 25.9 (95% CI 24.3-27.7) per 1,000 PYs in exposure cohort 1, 38.3 (95% CI 31.7-45.9) per 1,000 PYs in exposure cohort 2, 12.1 (95% CI 11.8-12.3) per 1,000 PYs in exposure cohort 3, and 21.6 (95% CI 20.8-22.5) per 1,000 PYs in exposure cohort 4, respectively.

In the sensitivity analysis where the definition of hypotension was expanded with additional diagnostic codes indicative of potential clinical manifestations of hypotension, combined crude IRs were 85.9 (95%

CI 82.9-89.0) per 1,000 PYs, 98.1 (95% CI 87.7-109.5 [best-case scenario]) and 100.6 (95% CI 90.0-112.1 [worst-case scenario]) per 1,000 PYs, 68.9 (95% CI 68.3-69.4) per 1,000 PYs, and 97.9 (95% CI 96.1-99.8) per 1,000 PYs, in exposure cohort 1, 2, 3, and 4, respectively. Combined age- and sex standardized IRs were 93.4 (95% CI 90.0-96.8) per 1,000 PYs, 109.6 (95% 97.6-122.7) per 1,000 PYs, 72.1 (95% CI 71.5-72.7) per 1,000 PYs, and 103.6 (95% CI 101.6-105.6) per 1,000 PYs in exposure cohort 1, 2, 3, and 4, respectively.

Hyperkalemia

Hyperkalemia was the most frequently identified event in all four exposure cohorts with the highest combined crude IR estimate found in exposure cohort 1 (IR 76.1, 95% CI 73.3-79.0 per 1,000 PYs), followed by exposure cohort 2 (IR, 64.5 95% CI 56.3-73.7 [best-case scenario] and IR 65.7, 95% CI 57.4-74.9 [worst-case scenario] per 1,000 PYs), exposure cohort 4 (IR, 45.1 95% CI 43.9-46.4 per 1,000 PYs), and exposure cohort 3 (IR, 30.9 95% CI 30.5-31.3 per 1,000 PYs). The same pattern was observed for combined age- and sex-standardized IRs and was as follows: 79.4 (95% CI 76.4-82.4) per 1,000 PYs in exposure cohort 1, 68.6 (95% CI 59.7-78.5) per 1,000 PYs in exposure cohort 2, 46.3 (95% CI 45.0-47.6) per 1,000 PYs in exposure cohort 4, and 31.5 (95% CI 31.1-31.9) per 1,000 PYs in exposure cohort 3, respectively. Compared to combined crude IRs, combined age- and sex-standardized IRs were similar across all exposure cohorts.

Hepatotoxicity

Combined crude IRs of hepatotoxicity in exposure cohort 1 were 0.5 (95% CI 0.3-0.9) per 1,000 PYs for the best-case scenario and 0.8 (95% CI 0.5-1.2) per 1,000 PYs for the worst-case scenario. In exposure cohort 2 no events of hepatotoxicity were identified for the best-case scenario (IR, 0.0 (95% CI 0.0-1.3) and for the worst-case scenario the combined crude IR was 2.8 (95% 1.2-5.5) per 1,000 PYs when eight cases were added, because the events were redacted in both subsets of CPRD. The combined crude IR of hepatotoxicity for exposure cohort 3 was 0.4 (95% CI 0.3-0.4) per 1,000 PYs for both the best- and worst-case scenario. In exposure cohort 4, combined crude IRs were 0.6 (95% CI 0.4-0.7) per 1,000 PYs for the best-case scenario and 0.7 (95% CI 0.5-0.9) per 1,000 PYs for the worst-case scenario. Combined age- and sex standardized IRs were 0.6 (95% CI 0.3-0.9) per 1,000 PYs in exposure cohort 1, 0.0 in exposure cohort 2, 0.4 (95% CI 0.3-0.4) per 1,000 PYs in exposure cohort 3, and 0.7 (95% CI 0.5-0.8) per 1,000 PYs in exposure cohort 4, respectively. Combined age and sex-standardized IRs were the same as combined crude IRs of hepatotoxicity for the best-case scenario in exposure cohorts 1 to 3 and were equal to the crude combined IR of hepatotoxicity for the worst-case scenario in exposure cohort 4.

Renal impairment

Combined crude IRs of renal impairment in exposure cohort 1 were 24.2 (95% CI 22.3-26.2) per 1,000 PYs for the best-case scenario and 24.4 (95% CI 22.5-26.4) per 1,000 PYs for the worst-case scenario and in exposure cohort 2 were 23.6 (95% CI 18.0-30.3) per 1,000 PYs for the best-case scenario and 26.7 (95% CI 20.7-33.9) per 1,000 PYs for the worst-case scenario, respectively. In exposure cohort 3 the combined crude IR was 13.1 (95% CI 12.8-13.3) per 1,000 PYs and in exposure cohort 4 it was 18.4 (95% CI 17.6-19.3) per 1,000 PYs. Combined age- and sex standardized IRs were 27.4 (95% CI 25.2-29.8) per 1,000 PYs in exposure cohort 1, 26.9 (95% CI 20.2-35.1) per 1,000 PYs in exposure cohort 2, 14.1 (95% CI 13.8-14.4) per 1,000 PYs in exposure cohort 3, and 20.1 (95% CI 19.2-21.1) per 1,000 PYs in exposure cohort 4, respectively. Compared to combined crude IRs, combined age- and sex-standardized IRs were similar to combined IRs across all exposure cohorts, however, in exposure cohort 1 and 2 the IRs were similar to the worst-case scenario.

Other Sensitivity Analyses

In all sensitivity analyses examining the impact of the COVID-19 pandemic, the number of patients in each exposure cohort were higher in the full study period (=the latest date of data availability in each database) than in the pre-COVID period which ended on December 31, 2019 for all databases (1.0 to 1.2 times higher). In the full study period, a similar pattern of all results in each exposure cohort and database of the pre-COVID period was observed, although the IRs were lower in the full study period. In GePaRD (the largest database contributing data to this study) the end date of the study period is

December 31, 2019, and therefore the findings of this sensitivity analysis were the same as the primary analysis.

In SIDIAP, the date of the prescription was defined as the first day of the month (instead of the actual date which was not provided). The sensitivity analysis which excluded SIDIAP results from combined IRs showed similar results (crude and age- and sex-standardized IRs) as the primary analysis.

Exploratory objectives

Exploratory Objective 1: exposure cohort 2 versus exposure cohort 4

There were no angioedema events across almost all databases in exposure cohort 2 during follow-up, except for GePaRD which recorded three events. The number of events in exposure cohort 2 was too small for a meaningful comparative analysis between patients initiating sacubitril/valsartan without prior exposure to ACEIs/ARBs, and those initiating ACEI use without prior exposure.

Exploratory Objective 2: exposure cohort 1 versus exposure cohort 3

A comparative analysis between exposure cohorts 1 and 3 was only conducted in GePaRD due to low angioedema counts (less than five events in exposure cohort 1 in all other databases). When comparing patients initiating sacubitril/valsartan regardless of prior exposure to ACEIs/ARBs to patients using ACEIs regardless of prior exposure to ACEIs/ARBs, the $HR_{adjusted}$ was 0.9 (95% CI 0.5-1.7) based on the PS-weighted cohorts.

Exploratory Objective 3: exposure cohort 1 versus exposure cohort 4

An analysis comparing patients initiating sacubitril/valsartan regardless of prior exposure to ACEIs/ARBs with patients using ACEIs without prior exposure to ACEIs/ARBs was only conducted in GePaRD due to low angioedema counts (less than five events in exposure cohort 1 in all other databases). The $HR_{adjusted}$ for angioedema in the PS-weighted cohorts was 0.7 (95% CI 0.2-2.7).

Discussion

In the present study patients initiating sacubitril/valsartan or using ACEIs were of a similar age. However, patients who use sacubitril/valsartan and ACEIs in the real-world were older (mean age 72 and 74 years, respectively) than patients that were enrolled in randomized controlled trials of sacubitril/valsartan and ACEIs (mean age 64 years) (McMurray et al 2014).

More male patients received sacubitril/valsartan compared to patients using ACEIs/ARBs. This might be attributable to a higher proportion of male patients who had HFrEF. This is further supported by an observational study of patients initiating sacubitril/valsartan (Wachter et al 2018) and the proportion of male patients with HFrEF in the PARADIGM-HF study (79% in sacubitril/valsartan initiators versus 77% in ACEI users) (McMurray et al 2014).

Cardiovascular diseases, CKD, diabetes mellitus, and the use of cardiovascular co-medications (including those influencing the occurrence of some safety event of interest such as hypotension, hyperkalemia, and renal impairment) were more frequent in patients initiating sacubitril/valsartan than in patients using ACEIs. The substantially higher proportion of patients using MRAs in the sacubitril/valsartan cohorts (versus the ACEI cohorts) strongly suggests a higher proportion of patients with more severe HF among patients treated with sacubitril/valsartan. The use of three or more cardiac medications, which served as a proxy for HF severity, was much higher among patients initiating sacubitril/valsartan compared to patients using ACEIs. The use of ivabradine, a second-line treatment considered in patients that respond insufficiently to other HF treatments such as beta-blockers (heart rate > 70 beats per minute despite adequate doses/or do not tolerate them) was higher among patients initiating sacubitril/valsartan versus patients using ACEIs, which further supports the higher proportion of severe HF patients in the sacubitril/valsartan cohorts than in the ACEI cohorts (McDonagh et al 2021). This patient profile was expected, as the guideline for HF stated that sacubitril/valsartan was indicated for patients who remained symptomatic after therapy with ACEIs/ARBs, i.e., patients with high disease severity (Ponikowski et al 2016). The impact of the guideline was reflected in the baseline characteristics profile of the patients initiating sacubitril/valsartan. This is consistent with previous observational studies,

showing the characteristics of patients prescribed with sacubitril/valsartan after its launch (Wachter et al 2018, Wachter et al 2019, Maggioni et al 2022, Zeymer et al 2019, Klebs et al 2017).

Angioedema

The incidence rate of angioedema among patients initiating sacubitril/valsartan regardless of prior ACEI use (exposure cohort 1; IR 0.6) was lower than among patients initiating sacubitril/valsartan who were naïve to ACEIs/ARBs (exposure cohort 2; IR 0.9) across databases based on the combined crude IR (best-case scenario) and age- and sex-standardized IR. The rate is numerically higher in exposure cohort 2, which is what would be expected if depletion of susceptible patients caused bias in exposure cohort 1. However, exposure cohort 2 was very small with only three recorded angioedema events and CIs of IRs in both exposure cohorts overlapped widely. The IR of angioedema among ACEI patients in exposure cohort 3 (prevalent and new users; IR 0.9) was slightly lower (statistically significant) than in patients without prior ACEIs/ARBs use (cohort 4; IR 1.2).

Patients initiating sacubitril/valsartan and those initiating ACEI who were naïve to prior ACEIs/ARBs were to be compared in a comparative analysis. This new user design may minimize substantial bias that has been observed in prevalent user designs. However, the number of events in exposure cohort 2 was too small (n=3) for a comparative analysis between patients initiating sacubitril/valsartan without prior exposure to ACEIs/ARBs, and those initiating ACEI use without prior exposure to ACEIs/ARBs.

No indication of an increased risk for angioedema between patients initiating sacubitril/valsartan (regardless of prior exposure to ACEIs/ARBs) and patients using ACEIs (naïve or not naïve ACEIs /ARBs) was found in the exploratory comparative analyses, after controlling for confounding. The findings of the present study are in agreement with a meta-analysis of randomized controlled trials examining the efficacy and safety of patients initiating sacubitril/valsartan or ACEIs (Zhang et al 2020), which all showed no statistically significant increased risk of angioedema in large randomized controlled trials that compared similar treatment regimens (McMurray et al 2014, Velazquez et al 2019, Desai et al 2019). However, in the PARADIGM-HF trial, the double-blind exposure period of sacubitril/valsartan or enalapril was preceded by two single-blind active run-in periods, in which patients with angioedema were excluded (Shi et al 2018). Hence, depletion of susceptible patients based on the run-in period in this trial was not differential between sacubitril/valsartan and ACEIs, which cannot be guaranteed in this study. Therefore, the lower HR in this study could be due to prevalent user bias, even though adjustment for prior ACEIs/ARBs included in the PS, was applied.

Because angioedema events may have been missed when the ‘narrow’ definition was used, two sensitivity analysis assessing angioedema misclassification were conducted. They included 1) adding anaphylactic shock to the narrow terms used to identify angioedema events (angioedema ‘broad’) in all databases and 2) expanding of the ‘narrow’ definition of angioedema in GePaRD by including both confirmed and unconfirmed diagnoses of angioedema. The results of both sensitivity analyses did not differ substantially from the primary analysis.

Hypotension

The combined IR of hypotension in exposure cohort 2 was higher than in exposure cohort 4 (IR 34.7 for exposure cohort 2 versus IR 20.8 for exposure cohort 4). Increased IRs of hypotension among sacubitril/valsartan initiators compared to ACEI users were expected, and the data collected complements and extends those data from randomized controlled trials where patients assigned to sacubitril/valsartan were more likely to experience episodes of hypotension compared to enalapril patients (Zhang et al 2020). Neprilysin (NEP) inhibition causes potent vasodilation by itself. When NEP inhibition is combined with an ARB (such as in sacubitril/valsartan) or when it occurs along with ACE inhibition (such as in omapatrilat), hypotension may occur more often than when ARBs or ACEIs are administered without the NEP inhibition component. Compared to ACEI users, patients initiating sacubitril/valsartan had higher prevalences of myocardial infarction, atrial fibrillation, valvular disease, and CKD (exposure cohort 1 only). Moreover, sacubitril/valsartan initiators (as compared to ACEI users), were more likely to use beta-blockers, MRAs, loop diuretics, and anti-arrhythmic agents and the use of more than 3 cardiac medications, suggesting that these patients were more susceptible to hypotension because of their severe HF disease state.

Additional potential explanation for higher IR of hypotension in sacubitril/valsartan initiators compared to ACEI users is that for the first few years after launch sacubitril/valsartan prescribers were less familiar with it than they were with ACEI and therefore may have been much more cautious with sacubitril/valsartan initiators. It is likely that they monitored the sacubitril/valsartan patients' blood pressure much more intensively than ACEI users, which could have led to detection bias.

A sensitivity analysis using a 'broad' definition of hypotension, including symptoms indicative of hypotensive events, showed higher IRs across all exposure cohorts which were in line with the findings of PARADIGM-HF trial where the definition of hypotension included its clinical manifestations and surveillance was much more intensive (Ruilope et al 2010, Vardeny et al 2018, Velazquez et al 2019, McMurray et al 2014).

Hyperkalemia

Hyperkalemia was the most frequently identified safety event in all four exposure cohorts with the highest combined IR estimate found in exposure cohort 1 (IR 76.1), followed by exposure cohort 2 (IR 64.5), exposure cohort 4 (IR 45.1), and exposure cohort 3 (IR 30.9). Sacubitril/valsartan initiators have a more severe form of HF as they report using MRAs in much higher proportions than ACEI users. Hyperkalemia is a well-known adverse drug reaction of MRA therapy in HF patients (Vukadinović et al 2017), and together with the higher proportions of MRA use among sacubitril/valsartan users as compared to ACEI users, this likely explains the higher IRs of hyperkalemia among sacubitril/valsartan cohorts. Among sacubitril/valsartan initiators CKD and diabetes mellitus are more frequently reported. Patients with CKD typically present with hyperkalemia because of an extracellular shift of potassium induced by metabolic acidosis of renal failure (Einhorn et al 2009). Diabetes mellitus is a risk factor for hyperkalemia because of its association with hyporeninemic hypoaldosteronism. Beta-blockers were also more used by sacubitril/valsartan initiators than ACEI users, and they may have altered transmembrane potassium movement, which may have resulted in hyperkalemia in these patients (Ben Salem et al 2014, Nyirenda et al 2009).

Hepatotoxicity

Almost similar combined IRs of hepatotoxicity were found in exposure cohorts 1, 3, and 4 (IRs between 0.4 and 0.6 for best-case scenario). In exposure cohort 2, no case of hepatotoxicity was reported for the best-case scenario in any of the databases, which is consistent with the absence of such events in randomized controlled trials (McMurray et al 2014, Velazquez et al 2019, Desai et al 2019).

Renal impairment

Higher IRs of renal impairment were found in patients initiating sacubitril/valsartan (exposure cohort 2; IR 23.6), than in patients using ACEIs (exposure cohort 4; IR 18.4). However, the variability of individual IRs of renal impairment for all exposure cohorts across various databases was very large. At time of launch sacubitril/valsartan was recommended for patients who had failed the current standard of case (i.e., patients with high disease severity) (Ponikowski et al 2016). These patients with a higher severity of HF were more likely to be present in exposure cohort 1 and 2, although the baseline characteristics were not determined specifically in these cohorts for the safety event of renal impairment. HF patients with a higher disease severity were more susceptible to develop renal impairment (McAlister et al 2004). Patients with HF induce or aggravate renal dysfunctions, which may then further deteriorate cardiac function and so on (Deferrari et al 2021). Thus, it is expected that the IRs of renal impairment were higher in exposure cohort 1 and 2 than those in exposure cohort 3 and 4. However, in a study comprising patients with mild, moderate, and severe renal impairment and matched healthy subjects for each severity group, it was shown that sacubitril/valsartan was generally well tolerated in patients with renal impairment (Ayalasomayajula et al 2016). As patients in the sacubitril/valsartan cohorts seem to have a more severe disease course of HF more intensive monitoring of renal function may have been conducted, increasing the likelihood of detecting renal impairment. Patients with more severe HF may have had a higher prevalence of comorbidities, such as diabetes or hypertension, which in turn also contribute to the occurrence of renal impairment

Other Sensitivity analyses

The study period includes data during the COVID-19 pandemic (from 2020 onward), which led to nationwide disruptions in healthcare utilization. The primary analyses focused on pre-COVID data only. In a sensitivity analysis the study period was extended until the last available data. It showed similar results to the primary analysis. The COVID-19 pandemic therefore did not have a measurable effect on the results of this study.

Limitations

Several general study limitations should be considered including potential misclassification of outcome, misclassification of exposure as well as prevalent user bias of the conducted exploratory analyses and potential residual confounding in the exploratory comparative analyses.

Since the accurate date of dispensing is not available in SIDIAP, a sensitivity analysis was conducted in which SIDIAP data were excluded for the combined IRs. The results showed similar results as the primary analysis, showing this misclassification did not have a measurable impact on the overall study findings.

Two databases (Aarhus and CPRD) were not allowed to share cell counts with less than five events, which limited the use of pooling their data especially for the rarer safety events. This limitation had to be mitigated by estimating best-case and worst-case scenarios for combined crude IRs as the true number of safety events was unknown. An addition of four events per dataset for the worst-case scenarios unlikely reflected realistic scenarios and may have led to implausibly high IRs for the rare safety events of interest.

Conclusion

This was a large observational study involving 39,616 patients initiating sacubitril/valsartan across seven databases from six European countries, of which GePaRD contributed most of the data. It provided valuable real-world data on the important identified and potential risks as defined in the RMP (angioedema, hypotension, hyperkalemia, hepatotoxicity, and renal impairment). The study has achieved its stated objectives and contributed to the further understanding of the safety profile of sacubitril/valsartan.

The study findings indicate that the use of sacubitril/valsartan is considered to be safe: an increased risk of angioedema among patients initiating sacubitril/valsartan compared to patients initiating or using ACEIs was not found. The overall numbers of angioedema events found in the study were low in all exposure cohorts, especially among sacubitril/valsartan initiators. Additionally, the majority of the databases recorded no events of angioedema among patients initiating sacubitril/valsartan.

There appear to be no differences in IRs of hepatotoxicity between exposure cohorts of patients initiating sacubitril/valsartan and patients using ACEIs although the limited number of cases of hepatotoxicity did not allow any meaningful comparison.

IRs of hypotension, hyperkalemia, and renal impairment (to a much lesser extent) were higher in patients initiating sacubitril/valsartan compared to patients using ACEIs, but any comparison of crude IRs should be interpreted with great caution. The higher incidences of those safety events among patients initiating sacubitril/valsartan are likely due to imbalances in patients' characteristics, the presence of underlying diseases, and closer monitoring of patients. Increased IRs of hypotension were expected given the dual mechanism of action of sacubitril/valsartan, in line with the data from the pivotal randomized controlled trials.

Marketing Authorization Holder(s)

Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland

Name(s) and Affiliation(s) of Principal Investigator(s)

[redacted]

2 List of abbreviations

ACE(I)	Angiotensin Converting Enzyme (Inhibitor)
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor Neprilysin Inhibitor
ARS	Agenzia Regionale di Sanità della Toscana
ATC	Anatomical Therapeutic Chemical
BIPS	Leibniz Institute for Prevention Research and Epidemiology – BIPS
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIF	Cumulative Incidence Function
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CM	Clinical Modification
COVID-19	Corona Virus Disease-19: the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
CPRD	Clinical Practice Research Datalink
DDD	Defined Daily Dose according to the WHO
DE	Germany
DK	Denmark
Dx	Diagnosis
EHR	Electronic Health Record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ES	Spain
ESC	European Society of Cardiology
EU	European Union
EU PAS register	European Union electronic Register of Post-Authorization Studies
FNR	False Negative Rate
GePaRD	German Pharmacoepidemiological Research Database
GM	German Modification
GP	General Practitioner
HES	Hospital Episode Statistics
HCV	Hepatitis C virus
HF	Heart Failure
HFrEF	Heart Failure with Reduced Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HSD	Health Search Database
ICD-9	International Classification of Diseases, 9th Revision
ICD-10	International Classification of Diseases, 10th Revision
ICPC	International Classification of Primary Care
IQR	Interquartile Range
IR	Incidence Rate
IT	Italy
LBQ657	The active metabolite of the prodrug sacubitril
LCL	Lower Confidence Limit
LCZ696	Sacubitril/valsartan

LCZ696B2014	Sacubitril/valsartan Safety study number
LCZ696B2015	Sacubitril/valsartan Drug-Drug Interaction study number
MHRA	Medicines and Healthcare products Regulatory Agency
MRA	Mineralocorticoid Receptor Antagonist
NEP	Neutral Endopeptidase
NIS	Non-Interventional Study
NL	The Netherlands
NLP	Natural Language Processing
NSAID	Non-Steroid Anti-Inflammatory Drug
NYHA	New York Heart Classification
OW	Overlap Weights
PARADIGM-HF	Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PASS	Post-Authorization Safety Study
PDD	Prescribed Daily Dose
PPV	Positive Predictive Value
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity Score
PYs	Person Years
Q	Calendar Quarter
QC	Quality check
R	R programming language
RAAS	Renin-Angiotensin-Aldosterone System
RCT	Randomized Controlled Trial
RMP	Risk Management Plan
RWE	Real World Evidence
sac/val	Sacubitril/valsartan
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software package from SAS Institute Inc.
SD	Standard Deviation
SE	Standard Error
SIDIAP	Si'tema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SHI	Statutory Health Insurance
SMD	Standardized Mean Difference
SmPC	Summary of Product Characteristics
TIA	Transient Ischemic Attack
UCL	Upper Confidence Limit
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VIF	Variance Inflation Factor
WCIA	Werkgroep Coördinatie Informatisering en Automatisering
Yrs	Years

3 Investigators

Role	Name
[redacted]	

4 Other responsible parties

Role	Name
[redacted]	

5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	Q2 2017	Sep 2017	None
End of data collection*	Sep 2021	14-Jul-2024	None
Registration in the EU PAS register	After PRAC/CHMP endorsement of the protocol	16-Mar-2017	None
Study interim report 1	Q1 2018	14 Mar-2018	None
Study interim report 2	Q1 2019	18-Mar-2019	None

Milestone	Planned date	Actual date	Comments
Study interim report 3	Q1 2020	13-Mar-2020	None
Study interim report 4	Q1 2021	22-Mar-2021	None
Study interim report 5	Q1 2022	22-Mar-2022	None
Final report	31-Dec-2024§	09-Oct-2024	None

Q = calendar quarter; EU PAS register = European Union electronic Register of Post-Authorization Studies; PRAC = Pharmacovigilance Risk Assessment Committee; CHMP = Committee for Medicinal Products for Human Use; CPRD = Clinical Practice Research Datalink; ISAC = Independent Scientific Advisory Committee

*Date from which analytical dataset was completely available.

§The planned delivery date of the final report was December 31, 2022, which was subsequently postponed to June 30, 2024 and then to December 31, 2024 due to the implementation of additional quality assurance measures.

6 Rationale and background

6.1 Rationale and background

LCZ696 (active substances sacubitril and valsartan, ATC code C09DX04; product name Entresto®) provides a novel mechanism of action of an angiotensin receptor neprilysin inhibitor (ARNI) by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The complementary cardiovascular benefits of sacubitril/valsartan in heart failure (HF) patients are attributed to the LBQ657-mediated enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), and the simultaneous inhibition of the effects of angiotensin II by valsartan (Vardeny et al 2014).

In the main randomized controlled trial conducted for sacubitril/valsartan (the PARADIGM-HF trial) in more than 8,442 HF patients with New York Heart Association (NYHA) class II-IV (ejection fraction ≤ 40%, was changed to 35% or less in protocol amendment v.1.1), sacubitril/valsartan significantly reduced the risk of composite endpoint (time to cardiovascular mortality and the risk of first hospitalization due to HF) by 20%. It also significantly decreased the symptoms and physical limitations associated with HF compared with treatment with the angiotensin converting enzyme inhibitor (ACEI) enalapril, while showing a similar safety profile (McMurray et al 2014).

Based on this pivotal trial, LCZ696 (sacubitril/valsartan; Entresto®) was approved in the European Union (EU) in November 2015 for the treatment of adult patients with symptomatic chronic HF with reduced ejection fraction (HFrEF).

This non-interventional study (NIS) (LCZ696B2014) aimed to assess the risk of angioedema associated with sacubitril/valsartan in a real-world setting as well as the risk of various other important identified or potential risks listed in the Entresto® Risk Management Plan (RMP), including hypotension, hyperkalemia, hepatotoxicity, and renal impairment.

The purpose of this study was to provide additional safety data for the above RMP-defined important risks under real-world conditions, thereby complementing the large volume of safety data already available from randomized controlled trials (RCTs) encompassing > 15,000 sacubitril/valsartan-exposed HF patients, including the large, long-term outcome trials PARADIGM-HF (McMurray et al 2014) and PARAGON-HF (Solomon et al 2019).

In addition, the study provides real-world data on the above safety events of interest in the subset of ACEI-/ARB-naïve HF patients newly starting treatment with sacubitril/valsartan, a population for which safety information from RCTs is limited (and is therefore classified as 'missing information' in the Entresto® RMP).

7 Research question and objectives

For this NIS, real-world data were gathered on the risk of angioedema and other potential or identified risks currently listed in the Entresto® RMP (including hypotension, hyperkalemia, hepatotoxicity, and renal impairment) in association with sacubitril/valsartan versus ACEI use in adult patients with HF.

The objectives of the study were:

Primary objective

1. To estimate the incidence of specific safety events of interest in adult HF patients newly starting treatment with sacubitril/valsartan (regardless of prior exposure to ACEIs or angiotensin receptor blockers [ARBs]).

   The primary safety event of interest was:

   - Angioedema ('narrow' and 'narrow' + anaphylactic shock definition (see Section 9.4.2 for details))

   The secondary safety events of interest were:

   - Hypotension ('narrow' and 'broad' definition (see Section 9.4.2 for details))
   - Hyperkalemia
   - Hepatotoxicity
   - Renal impairment
2. To assess the incidence of all specific safety events (as mentioned above) in adult HF patients newly starting treatment with sacubitril/valsartan without prior exposure to ACEIs or ARBs

Secondary objectives

1. To estimate the incidence of all primary and secondary safety events of interest in adult HF patients newly starting treatment with ACEIs (patients without prior exposure to ACEIs/ARBs)
2. To estimate the incidence of all primary and secondary safety events of interest in adult HF patients with ACEIs exposure (regardless of prior use of ACEIs/ARBs)

Exploratory objectives

1. To estimate the relative risk of angioedema ('narrow' definition) in adult HF patients newly starting treatment with sacubitril/valsartan (without prior exposure to ACEIs/ARBs) as compared to adult HF patients newly starting treatment with ACEIs (without prior exposure to ACEIs/ARBs)
2. To estimate the relative risk of angioedema ('narrow' definition) in adult HF patients newly starting treatment with sacubitril/valsartan (regardless of prior exposure to

ACEIs/ARBs) versus adult HF patients with ACEI exposure (regardless of prior exposure to ACEIs/ARBs)

3. To estimate the relative risk of angioedema ('narrow' definition) in adult HF patients newly starting treatment with sacubitril/valsartan (regardless of prior exposure to ACEIs/ARBs) versus adult HF patients newly starting treatment with ACEIs (without prior exposure to ACEIs/ARBs)

All comparative analyses in this study were considered exploratory due to potential biases that existed related to selecting patients on ACEI treatment who were either treatment-naïve to ACEIs and ARBs or were on prevalent ACEI treatment as the comparator group (see Rationale Section 7.1.1 and Limitations Section 7.9 in amended protocol v01.1, [redacted] Section 15.1.1).

8 Amendments and updates to the protocol

Amendments and changes to the original study protocol are summarized in Table 8-1.

Table 8-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
Amendment v01				
1	09-Sep-2021	Various sections throughout the protocol	Amendment	ARS and GePaRD added to complement the five original databases
2	09-Sep-2021	Title page	Update	Addition of the EU PAS number
3	09-Sep-2021	Title page	Update	Updated affiliation and address of PI
4	09-Sep-2021	Section 1, Table 1-1	Update	Update of contact information of the main responsible parties
5	09-Sep-2021	Section 4, Table 4-1	Update	Milestone table was updated with an additional column on 'Actual dates'
6	09-Sep-2021	Section 5	Update	Additional, more recent references added
7	09-Sep-2021	Section 6.3	Update	Order of exploratory objectives was altered, as the naïve sacubitril/valsartan cohort was deemed underpowered and should not be considered the primary exploratory analysis
8	09-Sep-2021	Section 7.2.1	Amendment	Databases from which the source populations are identified were expanded to include ARS and GePaRD
9	09-Sep-2021	Section 7.2.3, Table 7-1	Update	Table 7-1 was expanded to also include the expected end of data availability and the duration of the study period by database

10	09-Sep-2021	Section 7.2.4 Exclusion criteria	Amendment	Patients with a prescription (or dispensing) for sacubitril/valsartan and ACEIs on the same day or in SIDIAP in the same month were added as an exclusion criterion For the safety event of hepatotoxicity the exclusion of chronic hepatic conditions was extended with hepatotoxic events of specific etiology prior to index date
11	09-Sep-2021	Section 7.2.5	Update	A minimal look back period of 365 days is applied because a fixed period is insufficient to capture chronic morbidity in all databases
12	09-Sep-2021	Section 7.3.1.2	Amendment	The exposure group of historical ACEI users (naïve to prior ACEI/ARB) was deleted as the 4th interim showed that cohort 4 is large enough and that there is no need for this cohort (former Section 7.3.1.2.3 was deleted)
13	09-Sep-2021	Figure 7-1	Update	Figure 7-1 was replaced by a more detailed figure
14	09-Sep-2021	Table 7-2	Update	Table 7-2 was revised to reflect the changes in the order of the exploratory objectives
15	09-Sep-2021	Section 7.3.2	Update	Clarification that for angioedema a 'narrow' (primary) definition is used, and events identified through the mapping terms that would allow identification of hypersensitivity reactions that may indicate angioedema were viewed as a 'broad' definition. Separate analysis of the 'narrow' definition (primary analysis) and/or anaphylactic shock (sensitivity analysis) will be performed. Validation of the hypersensitivity reactions will inform possible underestimation of angioedema events.
16	09-Sep-2021	Section 7.3.2	Update	Clarification of the definition of angioedema and hypotension that will be used. Angioedema includes the 'narrow' definition (primary) and/or anaphylactic shock (sensitivity) The definition of hypotension includes a 'narrow' (primary) and 'broad' (sensitivity analysis) definition.
17	09-Sep-2021	Section 7.3.3	Update	List of co-medications and comorbid conditions was updated, as was the proxy used for estimating HF severity and overall health status of the patient
18	09-Sep-2021	Section 7.4	Amendment	Subsections added to cover for ARS and GePaRD as additional databases
19	09-Sep-2021	Section 7.6	Amendment	Data management section revised to reflect the process applied by PHARMO

20	09-Sep-2021	Section 7.7.1.2.2	Amendment	The primary analysis of all objectives will be censored at 31 December 2019, i.e., limited to the pre-COVID period. Databases with partial linkage to hospitalization data will be analyzed stratified by the linkage for all objectives. The method of handling confounding by propensity score adjustment was specified
21	09-Sep-2021	Section 7.7.1.2.3	Amendment	The sensitivity analyses of sacubitril/valsartan misclassification and ethnicity were deleted, based on feasibility assessments showing that these were not possible. However, ethnicity will be included in the propensity score model for CPRD, including the missing values as a separate category Sensitivity analysis of the full study period (end of data availability) was added.
22	09-Sep-2021	Section 7.8	Update	Additional information added on operating procedures and quality control
23	09-Sep-2021	Section 7.9	Update	Limitations updated to reflect latest insights
24	09-Sep-2021	Section 7.10	Update	Other aspects updated to reflect latest insights
Amendment v01.1				
25	22-Mar-2022	Section 6.3	Update	Reverted order of exploratory objectives to initial order
26	22-Mar-2022	Section 7.1.2	Update	Summary of feasibility assessments added
27	22-Mar-2022	Table 7-2	Update	Table updated to reflect reverted order of exploratory objectives

An updated LCZ696B2014 protocol v01.1, dated from March 22, 2022, was approved by the PRAC on Jun 23, 2022 ([redacted] Section 15.1.1). The deviations from the LCZ696B2014 study amended protocol v01.1 specified analysis are described in Table 8-2. Most deviations resulted from findings of the validation study. They have been discussed and agreed with PRAC (Entresto EMEA/H/C/004062/MEA/002.9, Entresto EMEA/H/C/004062/MEA/004.12, Neparvis EMEA/H/C/004343/MEA/002.6, Neparvis EMEA/H/C/004343/MEA/003.9). A protocol amendment was not drafted because of limited time between the discussion with European Medicines Agency (EMA) and the original planned delivery date of the final report (December 31, 2022), which was subsequently postponed due to the implementation of additional quality assurance measures.

Table 8-2 Details on where the final analyses deviate from the analyses specified in LCZ696B2014 protocol amendment v01.1

Topic/ Section no	Specified in protocol	Decision for final SAP	Rationale for deviation from the protocol
Setting/ Section 9.2	With a data extraction date in December 2021, the end of data availability will range from December 2019 (GePaRD) through April 2021 (ARS).	The launch dates and study periods vary per database – with an assumed time of data extraction of June 30, 2021.	The latest date of data availability in SIDIAP was June 30, 2021 as has been described in Table 7-1 in amended protocol v01.1, [redacted] Section 15.1.1 and Table 9-1.
Setting/ Section 9.2	The expected end of data availability for ARS is April 1, 2021.	For ARS data were available until December 31, 2020.	In ARS data from all data sources until December 31, 2020 were available at the time when the final analysis was initiated.
Exclusion criteria/ Section 9.3.2.2	For the safety event of renal impairment, patients with chronic kidney disease and/or renal impairment prior to start of follow-up (= index date) will be excluded.	Besides patients with chronic kidney disease, patients with a recorded renal impairment prior to start of follow-up (= index date) will also be excluded for the safety event of renal impairment.	Pre-existing renal impairment often also represents a chronic condition, so that patients would not be at risk of developing this safety event of interest during follow-up (as the medical condition was already evident at the start of follow-up).
Safety events of interest/ Section 9.4.2	For angioedema, case validation of a random sample will be performed across databases (where possible) to assess the PPV of the identification algorithms. If the PPV is below 80%, all cases will be validated, if that is feasible and informative.	Irrespective of the PPV of angioedema, the primary analyses were based on total numbers of cases identified from the 'narrow' definition.	Based on the results of the validation study ([redacted]), which showed that considering only validated cases resulted in an underestimation of the incidence of angioedema, the primary analysis was based on total numbers of cases identified from the 'narrow' definition.
Sensitivity analysis/ Section 9.9.4	Angioedema (primary event of interest; as 'narrow' [primary analysis] and hypersensitivity reactions' [sensitivity analysis])	Cases coded as angioedema with the specification 'narrow' and anaphylactic shock were included as cases of angioedema in a sensitivity analysis. Cases with diagnostic codes for hypersensitivity reactions other than anaphylactic shock were not included in the sensitivity analysis.	The validation study demonstrated that it is more appropriate to consider only anaphylactic shock as potentially missed angioedema events ([redacted]). Thus, for angioedema sensitivity analysis "hypersensitivity reactions" were replaced by "anaphylactic shock" in addition to angioedema with specification "narrow".
Sensitivity analysis/ Section 9.9.4	For angioedema, an algorithm of one discharge diagnosis (main or secondary) or two outpatient diagnoses from different physicians within up to three	In a sensitivity analysis the identification of the safety event of angioedema by confirmed diagnoses (using two outpatient diagnoses from different physicians within up to three months) were expanded with	Generally, angioedema is not considered as a chronic condition, and because of this, two diagnostic codes from GP visits or outpatient visits for the confirmation algorithm of angioedema ('narrow' definition)

Topic/ Section no	Specified in protocol	Decision for final SAP	Rationale for deviation from the protocol
	months was considered to be the most reliable algorithm for a confirmed diagnosis of angioedema in GePaRD.	unconfirmed diagnoses of angioedema in GePaRD.	may not occur that often in GePaRD.
Exposure of interest/Sensitivity analyses)/ Section 9.4.1/ Section 9.9.4.4	Impact of SIDIAP data on combined IRs (month and year of dispensing were only known) was not specified.	Included a sensitivity analysis for estimation of combined IRs without SIDIAP data.	In SIDIAP, the date of the dispensing was defined as the first day of the month because only month and year of dispensations were available for this study (a limitation not known at the design stage of the study). This has several consequences which limit the interpretability of the data on context of this study: First, for diagnoses of interest (safety events of interest/ exclusion criteria) occurring in the first month of exposure to sacubitril/valsartan or ACEIs, the initiation of both treatments is always assumed to precede the diagnosis although the opposite may be true. This may lead to incorrectly counting a diagnosis as a safety event although it would have qualified, as exclusion criterion had the exact exposure date been known. Second, dispensings for sacubitril/valsartan and ACEIs within the same month at index date were excluded and assumed non-adherent to the 36-hour wash-out period.

ARS = Agenzia Regionale di Sanità della Toscana; GePaRD = German Pharmacoepidemiological Research Database; GP = general practice; IR = incidence rates; PPV = positive predictive value; SAP = Statistical Analysis Plan; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

9 Research methods

9.1 Study design

LCZ696B2014 is a non-interventional, multi-database, post-authorization safety study (PASS) category 3. The study is a non-interventional cohort study using European healthcare database information in a population of adult patients with prevalent or incident HF, newly starting treatment with sacubitril/valsartan or ACEIs. Using a new user design (Ray 2003, Food and Drug Administration 2013, Yoshida et al 2015) was proposed to minimize the risk of prevalent user bias and depletion of susceptibles for angioedema. This is of particular importance for ACEI users. Sacubitril/valsartan was newly introduced to the market and therefore the exposure cohort automatically consisted of new users. As indicated in the Entresto® 'Summary of Product Characteristics' (SmPC), it is contraindicated for patients with a known history of

angioedema related to previous ACEIs or ARBs use or with hereditary or idiopathic angioedema. The combination of sacubitril/valsartan with an ACEI is contraindicated due to the increased risk of angioedema. Sacubitril/valsartan must therefore not be initiated until 36 hours after taking the last dose of ACEI therapy.

Since the majority of sacubitril/valsartan initiators are expected to have been treated with an ACEI or ARB before starting sacubitril/valsartan, these patients are likely to have a lower baseline risk of angioedema, as susceptible patients have been depleted. ACEI initiators who are naïve to ACEIs and ARBs, however, are likely to have a higher baseline risk of angioedema since this population includes all patients who are susceptible to an angioedema event. As the risk of ACEI-associated angioedema is highest very shortly after treatment initiation and decreases over time (Kostis et al 2005, Miller et al 2008, Toh et al 2012), an exposure cohort of prevalent ACEI users would be biased towards a lower angioedema risk compared to ACEI naïve patients. The majority of patients experiencing angioedema while treated with ACEIs can be expected to discontinue ACEI treatment and would therefore unlikely be part of a prevalent ACEI user cohort. Thus, comparing sacubitril/valsartan initiators regardless of their prior exposure to ACEIs/ARBs, to ACEI initiators who are treatment-naïve to ACEIs and ARBs are likely to bias the comparative (explorative) analysis in favor of sacubitril/valsartan. Therefore, it has been considered that the optimal comparison is between sacubitril/valsartan initiators who are treatment-naïve to ACEIs/ARBs and ACEI initiators without prior ACEIs/ARBs use.

Accruing the sample size required for the comparison of patients initiating sacubitril/valsartan without prior exposure to ACEIs/ARBs with those newly initiating treatment with ACEIs/ARBs was not likely to occur within the timelines of this study. Many HF patients (both prevalent and incident) had been previously exposed to an ACEI as treatment for hypertension or other comorbid diseases prevalent in HF patients (e.g., acute myocardial infarction, diabetic nephropathy). A US study in patients with incident HF diagnosed between 2005 and 2008 from four sites participating in the Cardiovascular Research Network (CVRN) found an exposure prevalence to ACEIs or ARBs in patients with incident HF-rEF (n=3,941, mean age 69 years) of 43% (Goldberg et al 2013). In the European 'ESC-HF Long-Term Registry' a prospective cohort study with primary data collection, including over 7,400 patients with prevalent chronic HF (median age 66 years) were enrolled over two years. In the subgroup of patients with HF-rEF (n=4,792), 92.2% were treated with ACEIs or ARBs at baseline (Maggioni et al 2013). Thus, indicating that the absolute number of ACEI initiators who are treatment-naïve to ACEIs and ARBs were limited. Ultimately this resulted in four different exposure cohorts based on previous exposure to ACEIs or ARBs (with or without prior exposure to ACEIs or ARBs).

See Section 9.4.1 for more details on exposure cohort classifications.

Codes and Feasibility Study

All safety events of interest were identified using the event-specific codes based on the coding system(s) used in the database(s) of interest. The differences between database-specific coding were evaluated and harmonized to the best extent possible by benchmarking in the feasibility study ([redacted]). The findings of the feasibility study demonstrated that the IRs of the safety event of interest in the general population based on codes alone were markedly higher in GePaRD compared to the other databases ([redacted]). Consequently, all safety

events of interest, comorbidities, and inclusion and exclusion criteria were identified using specific algorithms in GePaRD. The algorithms are described in Section 9.4.2.2.

Outcome Validation

A validation study was undertaken to assess the positive predictive value (PPV) of the codes and case-finding algorithms ([redacted]). The validation study showed that absence of adequately recorded information in general practitioner (GP) medical records and emergency visits records. The interpretation thereof by various medical-trained personnel led to large heterogeneity in assessment. It was concluded that conducting a full validation of all cases in the absence of access to hospital records would lead to an exclusion of a substantial amount of potentially true cases, an underestimation of absolute event rates, and a large decrease in study power. After approval from PRAC, the final analyses were conducted with all events of angioedema identified in each database.

The study protocol was endorsed by each data partner and was approved by local authorities.

9.2 Setting

The data for this study were retrieved from seven healthcare databases from six European countries (see Section 9.5 for details), i.e., the 'Clinical Practice Research Datalink' (CPRD) from the United Kingdom (UK), t'e 'Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària' (SIDIAP) from Spain (ES), the 'Health Search Database' (HSD) from Italy (IT), the 'PHARMO Database Network' (PHARMO) from the Netherlands (NL), Aarhus from Denmark (DK), 'Agenzia Regionale di Sanità della Toscana' (ARS) (IT) and the 'German Pharmacoepidemiological Research Database' (GePaRD) (DE).

The study period for this final report started at the launch date of sacubitril/valsartan in the countries of interest. The total study time frame (including the beginning of a minimum of 365-day look back period before the index date or cohort entry date) began on December 01, 2014 at the earliest. Records before that time were included for assessment of prior morbidity. The launch dates and study periods by data source are displayed in Table 9-1. It ended at the date of the most recently updated data, at the time the databases downloaded their data for this final analysis (for details, see Table 9-1).

Table 9-1 Study periods for the final report

Database	Sacubitril/ valsartan launch date	Earliest start of data availability	Median* start of data availability	End of data availability	Duration of study period
Aarhus	December 2015	January 2011	January 2011	December 2020	61 months
ARS	April 2016 (reimbursement March 2017)	January 2003	January 2004	December 2020	57 months
GePaRD	January 2016	January 2004	January 2010	December 2019#	48 months
HSD	April 2016 (reimbursement March 2017)	January 1999	December 2001	December 2020	57 months
PHARMO	July 2016	January 2008	October 2012	December 2020	54 months
SIDIAP	October 2016	January 2006	January 2006	June 2021	57 months
CPRD	December 2015	January 1989	April 2007	December 2020§	61 months

Aarhus = Aarhus University Prescription Database and Danish National Patient Registry; ARS = Agenzia Regionale di Sanità della Toscana; CPRD = Clinical Practice Research Datalink; GePaRD = German Pharmacoepidemiological Research Database; HSD = Health Search Database; PHARMO = PHARMO Institute for Drug Outcomes Research; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

*Enrollment in the databases may be subject to migration or healthcare insurance membership. Therefore, the median duration of enrollment in the database per patient was used to estimate the median start of data availability in the database based on benchmarking information provided by the database partners.

#end of data availability for GePaRD is due to lack of data of two years.

§The date that GPs from general practices last transfer data to Medicines and Healthcare products Regulatory Agency (MHRA) is December 26, 2020.

The period over which medication and medical information was retrieved for each patient started at an individual's database entry or enrollment date, which was far before or after (i.e., to define the safety event of interest) the sacubitril/valsartan launch date. The study period ended at the date of the most recently updated data at the time that the databases downloaded their data for the study ("end of data availability" in Table 9-1). Data during the COVID-19 pandemic (from 2020 onward) were likely to reflect different patterns of healthcare utilization, the influence of which was assessed in a sensitivity analysis. The study period for the primary analyses (primary, secondary, and exploratory objectives) ended on December 31, 2019 for all databases, since early 2020 the COVID-19 pandemic was declared. Specifically, only patients with their first prescription (or dispensing) for sacubitril/valsartan or an ACEI prior to December 31, 2019 were considered for the primary analyses.

9.3 Subjects

9.3.1 Source population

The data for this final analysis were retrieved from seven European electronic healthcare databases: Aarhus from Denmark, GePaRD from Germany, HSD and ARS from Italy, PHARMO from the Netherlands, SIDIAP from Spain and the CPRD from the United Kingdom.

The source population included all patients in the study databases during the study period. For databases which have linkage with hospital data limited to a subset of the source population, i.e., PHARMO, SIDIAP, and CPRD, all analyses were stratified based on this eligibility and are referred to as "with linked hospital data" and "without linked hospital data" in the rest of this document. Because of this, person-time was mutually exclusive for these two subsets of patients. For the subsets with linked hospital data, the full information of the linked datasets was used for all study assessments. For the subsets without linked hospital data, data from all other provenances available in the databases was used (see Table 9-7). For details on individual databases, see LCZ696B2014 protocol amendment v01.1 Section 7.4 ([redacted] Section 15.1.1) and Table 9-2.

Table 9-2 Available information in each database

Database (country)	Aarhus (DK)	ARS* (IT)	GePaRD (DE)	HSD (IT)	PHARMO (NL)	SIDIAP (ES)	CPRD (UK)
Hospitalization discharge Dx registry/claims	Yes	Yes	Yes	No (only if reported	Yes, partial through linkage	Yes, partial through linkage	Yes, partial through

				back by patient)			linkage with HES
Emergency visits Dx registry/claims	Yes	Yes	Yes (incomplete only emergency visits to GPs)	Yes (incomplete)¥	No	No	No
GP diagnoses in GP medical records/claims	No	No	Yes	Yes	Yes	Yes	Yes
Outpatient specialist visits	Yes	No	Yes	No	No	No	No
Dispensings outpatient from pharmacy/claims	Yes (those reimbursed)	Yes (those reimbursed)	Yes	No	Yes	Yes	No
Prescriptions recorded by GP	No	No	No	Yes	Yes	Yes	Yes
Access to hospital charts for validation	No	No	No	No	No	No	No
Access to text in automated GP notes	No	No	No	Yes	Yes	Yes	No
Linked Death registry	Yes	Yes	No	No	No	No	No

Aarhus = Aarhus University Prescription Database and Danish National Patient Registry; ARS = Agenzia Regionale di Sanità della Toscana; CPRD = Clinical Practice Research Datalink; DE = Germany; DK = Denmark; Dx = diagnosis; ES = Spain; GePaRD = German Pharmacoepidemiological Research Database; GP = general practitioner; HES = Hospital Episode Statistics; HSD = Health Search Database; IT = Italy; NL = Netherlands; PHARMO = PHARMO Institute for Drug Outcomes Research; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; UK = United Kingdom.

*ARS also has an additional data source that includes information when patients receive an exemption from copayment due to a chronic condition.

¥Only includes emergency visits requested by GPs or reported by patients.

9.3.2 Study population

The overall study population per database (or subset based on linked hospital data) consisted of adult patients (≥ 18 years of age) initiating either sacubitril/valsartan or using an ACEI and who had a recorded diagnosis of HF prior to or within three months (90 days) after the first prescription (or dispensing) of sacubitril/valsartan or ACEIs during the study period.

Input files were constructed based on a tailored common data model (see Section 9.8 and Section 15.2.1-Table 4-1 to Section 15.2.1-Table 4-6), from which the study population and exposure cohorts were constructed. In the case of multiple enrollment periods per patient, only the last period of continuous enrollment was included in the input files (see Section 15.2.1-Table 4-1 to Section 15.2.1-Table 4-6). The study base referred to patients initiating either sacubitril/valsartan or ACEIs during the study period. Patients of whom there was evidence indicating concurrent use of sacubitril/valsartan and ACEIs during the 36-hour washout period as recommended in the Summary of Product Characteristics (SmPC) of sacubitril/valsartan were not included. Steps to derive the study population from the source data are described in

Section 9.3.2.1 and Section 9.3.2.2. Exposure cohorts were created from the study population as described in Section 9.4.1.

HF patients were identified by both recorded inpatient and/or outpatient diagnoses, based on the specific coding system used by the individual database (i.e., READ version 2 in CPRD for GP diagnoses; ICD-9th version for GP diagnoses in HSD and hospital diagnoses in ARS and PHARMO or ICD-10th revision [ICD-10-CM] for GP and hospital diagnoses in SIDIAP (after mapping of historic ICD-9-CM and ICD-10 codes), death registry in Aarhus and hospital diagnoses in Aarhus, PHARMO, and CPRD (HES); ICD-10 GM in GePaRD; International Classification of Primary Care codes (ICPC; v1993) and "Werkgroep Coördinatie Informatisering en Automatisering" codes [WCIA] in PHARMO). For codes used to identify patients with HF, see Section 15.2.1-Table 2-1.

9.3.2.1 Inclusion criteria

The overall study population consisted of all patients identified from the database- or subset-specific source populations, who met the following criteria:

- Initiating sacubitril/valsartan or using an ACEI during the study period (see Section 9.2)
- Be aged ≥ 18 years at the time of the first prescription (or dispensing) for sacubitril/valsartan or an ACEI. If the exact date of birth was not known, January 1st of the calendar year the patient turned 18 years was the start date when only the year was known, and the first date of the month when the month and year were known.
- Have a recorded diagnosis of HF in the database (ever) prior to, at, or within three months (90 days) after the first prescription (or dispensing) of sacubitril/valsartan or ACEIs in the study period (see Section 15.2.1-Table 2-1 Codes used to identify heart failure)
- Have ≥ 365 days of valid database history prior to the first prescription (or dispensing) for sacubitril/valsartan or ACEIs (i.e., the patient was registered in the database for at least one year)

Note: In GePaRD (which is a health insurance claims database, that may contain suspected diagnoses), only 'confirmed' diagnoses of HF were selected by using the following algorithm based on records with a confirmed diagnosis status (for more information on the rationale please see Section 9.4.2 Safety events of interest):

- At least one primary hospital discharge diagnosis of HF
- OR at least two outpatient HF diagnoses

For this algorithm, the first recorded claims date in the assessment period of a HF diagnosis was considered the HF diagnosis date in GePaRD. In all other databases, one diagnosis of HF from in- and/or outpatient registry data or electronic health records (EHRs) was sufficient. However, when multiple diagnostic codes for HF were present in these databases, the diagnostic code prior to index date was selected first for defining HF. If no diagnostic code was recorded prior to index date, the diagnostic code in the 90 days after the index date was selected.

9.3.2.2 Exclusion criteria

As described in the SmPC of sacubitril/valsartan, patients who previously used ACEIs at initiation of sacubitril/valsartan in actual clinical care settings are recommended to adhere to a

36-hour washout period. Patients with concurrent prescriptions/dispensing for sacubitril/valsartan and ACEI or vice versa (i.e., start date of prescription/dispensing is on the same day or in SIDIAP the dispensing was in the same month as the index date), indicating non-adherence to the 36-hour wash-out period, were excluded. Concurrent prescriptions/dispensings are the only reliable indicator of non-adherence to the 36-hour washout period, although in SIDIAP it is unknown if patients were excluded because of receiving both dispensings of sacubitril/valsartan and ACEI or vice versa on the same day. The proportion of patients with concurrent prescriptions is mentioned in the table describing the selection of the sacubitril/valsartan exposure cohort (see Section 15.2.1-Table 1-2 and Table 1-3).

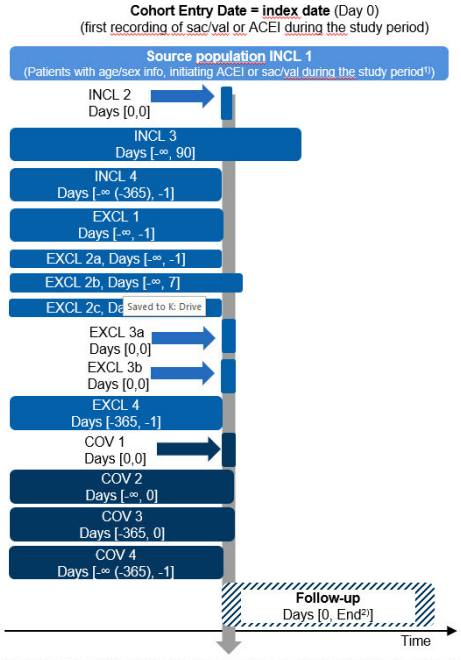
- For *all safety events of interest* (see Section 9.4.2): Use of sacubitril/valsartan in patients with prior angioedema history is contraindicated. Therefore, patients with a recorded angioedema diagnosis (specification 'narrow'), or hereditary angioedema (specification 'exclude') any time prior to index date (see Section 9.4.2 for definition of 'index date') were excluded from all exposure cohorts (see Section 15.2.1-Table 2-2 Codes used to identify angioedema).
- For *hepatotoxicity* as safety event of interest (see Section 9.4.2), patients with a hepatotoxic event (chronic, acute, viral [including human immunodeficiency virus, or HIV], or drug-induced hepatotoxicity, or diagnostic codes indicating hepatic morbidity without defined cause [e.g., "hepatitis unspecified"]) or diagnostic codes indicating hepatic morbidities suggestive of another etiology ["other specified disorders of liver", including hepatitis C, or HIV, or biliary or alcohol induced hepatotoxicity] at any time prior to, at, or up to seven days after the index date were excluded. Patients with a history of hepatotoxicity were defined as having a diagnostic code for hepatotoxicity with a specification 'narrow' and 'exclude' (see Section 15.2.1-Table 2-7 Codes used to identify hepatotoxicity) any time prior to, at, up to seven days after the index date. Excluding patients with a history of hepatic morbidity suggestive of another etiology any time prior to index date was defined as having a diagnostic or drug code for hepatic morbidity, including hepatitis C virus (HCV) drugs which serve as a proxy for hepatitis C (see Section 15.2.1-Table 2-8 Codes used to identify chronic hepatic disease and Section 15.2.1-Table 2-12 Codes used to identify of HCV drugs) before, at, or up to seven days after the index date. Liver conditions are common among patients with HIV and may have been caused by multiple factors, including coinfection with viral infection (Sulkowski et al 2000). In light of this, patients with HIV before, at, or up to seven days after the index date were excluded as well. These patients were defined as having a diagnostic code for HIV (see Section 15.2.1-Table 2-9 Codes used to identify HIV) before, at, or up to seven days after the index date.
- For *renal impairment* as safety event of interest (see Section 9.4.2), patients with a recorded history of chronic renal disease or renal impairment any time prior to index date were excluded. Patients with a history of renal impairment or chronic renal disease were defined as having a diagnostic code for renal impairment with the specification 'narrow' and 'exclude' (see Section 15.2.1-Table 2-10 Codes used to identify chronic renal disease or renal impairment) or chronic renal disease (see Section 15.2.1-Table 2-11 Codes used to identify chronic renal disease) at any time prior to index date.

For both events (hepatotoxicity and renal impairment) the proportion of patients that were excluded from the study population is mentioned in the table describing the selection of the study population (see Section 15.2.1-Table 1-1).

Note: In GePaRD, for all safety events of interest only confirmed diagnoses were excluded by using algorithms based on records with a confirmed diagnosis status. All these algorithms were examined in the feasibility study ([redacted]).

Figure 9-1 depicts the design diagram following the START-RWE template (Wang et al 2021). It reflects the order of operations to create the exposure cohorts (see Section 9.3.2) from the source databases. The temporality of assessment windows is clearly shown relative to the cohort entry ("index") date, which is considered day 0. Bracketed number ranges denote the inclusive time windows for inclusion/exclusion criteria and covariate assessment windows, as well as follow-up.

Figure 9-1 Design diagram



INCL/EXCL = Inclusion/Exclusion Assessment Window

INCL 1: Initiating sac/val or ACEI during the study period (=first prescription after the launch date of sac/val in respective country= index date)

INCL 2: Age 18 years or older at index date

INCL 3: Diagnosis of heart failure ever prior to, at, or within 90 days after the index date

INCL 4: Minimum of 365 days valid database history prior to index date

EXCL 1: Hereditary angioedema or angioedema ('narrow' definition) prior to index date

EXCL 2a: Applies only to the safety event hepatotoxicity: Hepatotoxicity prior to index date

EXCL 2b: Applies only to safety event hepatotoxicity: Diagnoses indicating hepatic morbidity of other etiology prior to or up to 7 days after the index date (to account for late determination)

EXCL 2c: Applies only to safety event renal impairment: Chronic renal disease or renal impairment prior to index date

EXCL 3a: Applies only to sac/val cohort: Concurrent prescription of ACEI at index date

EXCL 3b: Applies only to ACEI cohort: Concurrent prescription of sac/val

EXCL 4: Applies only to ACEI/ARB-naïve cohorts (cohort 2 + 4): ACEI or ARB use in the 365 days prior to index date

COV = Covariate Assessment Window

COV 1: Demographics (age, sex)

COV 2: race/ethnicity (only available in CPRD, but recording rather incomplete (Mathur et al 2014))

COV 3: Comedications (see Section 9.4.3) in the 365 days prior to or on the index date

COV 4: Comorbid conditions (see Section 9.4.3) ever prior to index date

1) **Study period:** Launch of sac/val in respective country – end of data availability in database

2) **End of follow up:** First occurrence of the safety event of interest (e.g., angioedema), discontinue sac/val or ACEI, addon or switch to other RAAS, stop contributing to database (due to death, left practice/insurance/health system, etc.), end of study period*

*The study period for the primary analyses will be restricted to December 31, 2019, the time at which COVID-19 pandemic might start having an impact.

9.3.2.3 Cohort start

The date of the first recorded prescription (or dispensing) for sacubitril/valsartan or an ACEI in the study period was defined as the index date (= start of follow-up or 'cohort entry date' or t=0).

A minimal look-back period of 365 days prior to index date was used to determine the use of ACEIs/ARBs, a recorded diagnosis of HF, baseline characteristics or the exclusion of angioedema, hepatotoxicity, hepatic morbidity of other etiology, chronic kidney disease, and renal impairment.

9.3.2.4 Follow-up

Eligible patients were followed from their index date until occurrence of the safety event of interest, death, the last date of follow-up available in the (linked) dataset, or the study end date for the primary analysis (December 31, 2019) and sensitivity analysis (the end date of data availability as described in Table 9-1). This resulted in four exposure cohorts of patients at risk for each safety event of interest (angioedema, hypotension, hyperkalemia, hepatotoxicity, or renal impairment).

Patients were censored in the respective exposure cohort if they:

- Had discontinued their treatment with sacubitril/valsartan or ACEIs (see Section 9.4.1)
- Added treatment with another renin-angiotensin-aldosterone system (RAAS) blocking agent at the start of the episode (i.e., at index date [e.g., use of another ARB and sacubitril/valsartan is not recommended on the same day in the SmPC of sacubitril/valsartan, because sacubitril/valsartan contains the ARB valsartan]) or within the episode (i.e., between the start date of the episode and the last date of the prescription to prevent it from being switched [see switched initial treatment]) of sacubitril/valsartan or ACEI (i.e., add-on of an ACEI [only for patients initiating sacubitril/valsartan], an ARB, or aliskiren/remikiren for sacubitril/valsartan or ACEIs).
- Switched initial treatment to another RAAS blocking agent after the last date of the episode of sacubitril/valsartan (i.e., sacubitril/valsartan to an ACEI, ARB or aliskiren/remikiren; ACEI to sacubitril/valsartan, an ARB, or aliskiren/remikiren [switching within the ACEIs class, however, was not censored]).
- Stopped contributing data to the database (e.g., patient died, or left the practice/health insurance, etc.), whichever occurred first.

Note: If the date of discontinuing treatment with sacubitril/valsartan or ACEIs was on the same day as adding or switching treatment with another RAAS blocking agent, the date of adding or switching treatment with another RAAS blocking agent was considered as the censor date.

Note: Patients switching from an ACEI to sacubitril/valsartan (but not the other way around) during the study period were allowed to enter both the ACEI exposure cohort and the sacubitril/valsartan exposure cohort, resulting in two index dates, one for each exposure cohort. The rationale for this is that most patients initiating sacubitril/valsartan (especially within the first years after launch) had prior use of ACEIs. To increase the number of patients in the sacubitril/valsartan exposure cohort and to better reflect real-world use, prior ACEIs/ARBs use in patients initiating sacubitril/valsartan was explicitly allowed.

See Section 9.4.1 for definitions regarding discontinuation of treatment.

9.4 Variables

9.4.1 Exposures of interest

Exposures of primary interest were sacubitril/valsartan, ACEIs, and ARBs (i.e., ARB exposure was used for determining previous treatment prior to index date, add-on treatment or switching to another RAAS blocking agent as well).

Exposure information was identified using prescription or dispensing data, using the database-specific coding system (Anatomical Therapeutic Chemical [ATC] Classification (see Table 9-4 and Section 15.2.1 Table 2-13); which were mapped to Gemscript coding for CPRD). Based on the common data model (see Section 9.8), the duration of prescriptions/dispensings was defined as the prescribed/dispensed quantity of tablets/units, divided by the number of tablets/units to be used per day (prescribed/dispensed quantity). If the prescribed quantity was not available, the assumed number of tablets per day based on the standard dosing regimen for an adult as described in the package insert or label of the package (prescribed daily dose, PDD) was used. When PDD in mg was not available from the prescription of sacubitril/valsartan, ACEIs, and ARBs, then the prescribed or dispensed dose strength per tablet was used as a proxy for PDD instead. As a last resort, the WHO defined daily dose (DDD) was used when PDD or dose strengths were not available. In case of assumed prescribed quantities which were based on the maintenance doses as described in Table 9-4, the calculated duration should be plausible, and the use of a local legal maximum or a maximum of 180 days was considered to prevent introduction of artefacts in the data. The data partners were responsible for estimating the dose and prescribed quantities and provided this in the common data model (see Section 9.8). For the data sources that contained records of medications dispensed in a pharmacy (Aarhus, ARS, GePaRD, PHARMO, SIDIAP), the date (month/year for SIDIAP) associated with the dispensing in the pharmacy was used; for other databases, the GP prescription dates were used (CPRD, HSD) (see Table 9-3 and Table 9-4). Both are referred to as prescriptions in this document.

Table 9-3 Details on exposure of interest per database

Type of information	Aarhus	ARS	GePaRD	HSD	PHARMO	SIDIAP	CPRD
Source of medication	Outpatient pharmacy records[#]	Outpatient pharmacy records[#]	Reimbursement from health insurance records/ pharmacy	GP prescriptions[*]	Outpatient pharmacy records[#]	Outpatient pharmacy records[#a]	GP prescriptions[*]
Start date per prescription based on	Date dispensed	Date dispensed	Date dispensed	Date prescribed	Date dispensed	Date dispensed	Date prescribed
Date accuracy	Actual date	Actual date	Actual date	Actual date	Actual date	*First day of the month*	Actual date
Duration based on dosing strength of tablet, amount, standard dose regimen or DDD	DDD	Dosing description derived from labels on package	DDD	Dosing description	Dosing description	DDD	Dosing description

Aarhus = Aarhus University Prescription Database and Danish National Patient Registry; ARS = Agenzia Regionale di Sanità della Toscana; CPRD = Clinical Practice Research Datalink; DDD = defined daily dose; GePaRD = German Pharmacoepidemiological Research Database; HSD = Health Search Database; PHARMO = PHARMO Institute for Drug Outcomes Research; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

[#]Pharmacy records include any drugs dispensed and reimbursed via public pharmacies, and do not include in-patient drug dispensings.

[a]SIDIAP captures outpatient pharmacy records from physicians within the Catalan Health institute (ICS) trust, which covers 85% of the GPs and 30% of hospitals.

*GP prescriptions may be missing the first specialist prescription but will include repeat prescriptions written by the GP.

Table 9-4 Defined daily dose and maintenance dose of exposure of interest per database

Databases*	ATC	DDD (mg)	Maintenance doses (mg)§		
			Aarhus	GePaRD	SIDIAP
Sacubitril/ valsartan	C09DX04	24/26	24/26 x 2 per day	24/26 x 2 per day	24/26 x 2 per day
		49/51	49/51 x 2 per day	49/51 x 2 per day	49/51 x 2 per day
		97/103	97/103 x 2 per day	97/103 x 2 per day	97/103 x 2 per day
ACEIs					
Captopril	C09AA01	50	75-150	100-150	50
Enalapril	C09AA02	10	20	20	10
Lisinopril	C09AA03	10	10-20	20	10
Perindopril	C09AA04	4	5	10	4
Ramipril	C09AA05	2.5	2.5-5	10	2.5
Quinapril	C09AA06	15	20-40	15	15
Benazepril	C09AA07	7.5	20-40	10	7.5
Cilazapril	C09AA08	2.5	5-7.5	2.5	2.5
Fosinopril	C09AA09	15	n/a	15	15
Trandolapril	C09AA10	2	1-2	2	2
Spirapril	C09AA11	6	n/a	10	6
Delapril	C09AA12	30	n/a	30	30
Moexipril	C09AA13	15	n/a	15	n/a
Temocapril	C09AA14	10	n/a	n/a	n/a
Zofenopril	C09AA15	30	n/a	30	n/a
Imidapril	C09AA16	10	n/a	10	10
ARBs					
Losartan	C09CA01	50	50-100	50	50
Eprosartan	C09CA02	600	600	600	600
Valsartan	C09CA03	80	80-160	80	80
Irbesartan	C09CA04	150	150-300	150	150
Candesartan	C09CA06	8	8-16	8	8
Telmisartan	C09CA07	40	40-80	40	40
Olmesartan medoxomil	C09CA08	20	n/a	20	20
Azilsartan medoxomil	C09CA09	40	n/a	40	n/a
Fimasartan	C09CA10	60	n/a	n/a	n/a

Aarhus = Aarhus University Prescription Database and Danish National Patient Registry; ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; ATC = Anatomical Therapeutic Chemical classification system; DDD = defined daily dose; GePaRD = German Pharmacoepidemiological Research Database; n/a = not applicable; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

*Only includes databases that uses DDDs for estimating the duration of each prescription/dispensing.

§Maintenance dose was derived from International and National guidelines.

After calculation of the treatment duration for each prescription, episodes of uninterrupted treatment were created for sacubitril/valsartan, ACEIs, ARBs, and other RAAS (aliskiren/remikiren) for all prescriptions in the same group, if there were less than 90 days between end of the previous prescription and the start of the new prescription. If multiple prescriptions of sacubitril/valsartan, ACEIs, ARBs, or aliskiren/remikiren irrespective of dose or ATC code appeared on the same day, the prescription with the longest duration was selected for the episode of uninterrupted treatment.

No stockpiling: Overlap in prescriptions of the same drug type (i.e., prescriptions of sacubitril/valsartan, ACEIs, ARBs, or aliskiren/remikiren, irrespective of dose or ATC code) was disregarded (i.e., no 'stockpiling').

Treatment discontinuation: Patients were considered as having discontinued treatment if there was a gap in a series of successive prescriptions of sacubitril/valsartan, ACEIs, or ARBs that was ≥ 90 days after the estimated treatment end of the last prescription preceding the gap, or when the last prescription ended before patients were censored on the criteria as described in Section 9.3.2.4. The calculated end date of the prescription preceding the gap or end of follow-up was defined as the date of discontinuation, at which point patients' follow-up time was censored. In other words, if patients restarted with sacubitril/valsartan or ACEIs > 90 days after date of discontinuation, patients were not considered in the study. In case follow-up ended before the 90 days were over, a patient was not considered to have discontinued.

ACEI- or ARB-naïve patients: Patients were considered as ACEI- or ARB-naïve if they did not have an episode of ACEIs or ARBs recorded within 365 days before the index date (see Figure 9-2).

Four different exposure cohorts were defined: two for patients initiating sacubitril/valsartan, and two for patients using ACEI (see Figure 9-2).

9.4.1.1 Sacubitril/valsartan initiator exposure cohorts

- Patients initiating sacubitril/valsartan regardless of prior ACEIs/ARBs use (exposure cohort 1) (see Section 9.3.2.3)

Exposure cohort 1 included all patients fulfilling the inclusion criteria (Section 9.3.2.1) who started using sacubitril/valsartan during the study period – regardless of prior exposure to ACEIs or ARBs.

- Patients initiating sacubitril/valsartan naïve to ACEIs/ARBs (exposure cohort 2)

Exposure cohort 2 was the subset of exposure cohort 1 without use of ACEIs/ARBs in the 365 days prior to index date. This sub-cohort corresponded to patients with new use of sacubitril/valsartan (being naïve to ACEIs/ARBs).

9.4.1.2 ACEI user exposure cohorts

- Patients using ACEIs regardless of prior ACEIs/ARBs use (exposure cohort 3) (see Section 9.3.2.3 cohort start)

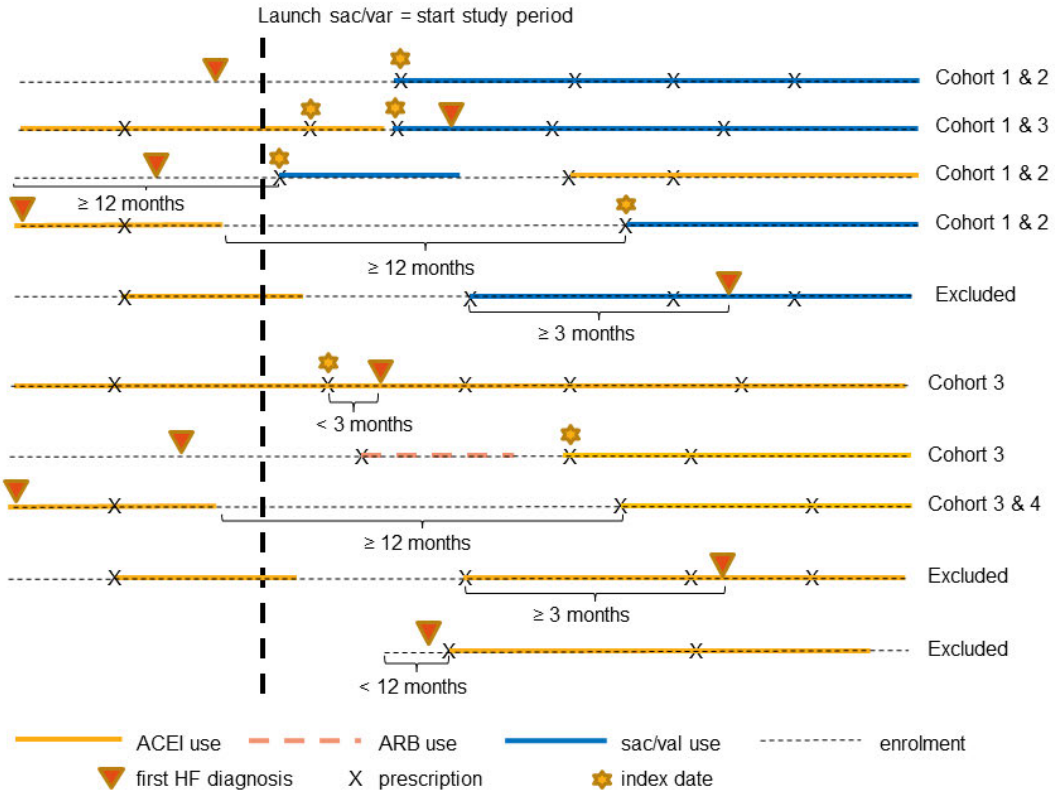
Exposure cohort 3 included all patients fulfilling the inclusion criteria (Section 9.3.2.1) who used ACEIs during the study period – regardless of prior exposure to ACEIs or ARBs. This exposure cohort was a mix of patients with prevalent and incident ACEI use.

- Patients initiating ACEIs without prior use of ACEIs/ARBs – ACEI/ARB treatment-naïve (exposure cohort 4)

Exposure cohort 4 was the subset of exposure cohort 3 without use of ACEIs/ARBs in the 365 days prior to index date. This sub-cohort corresponded to patients with new use of ACEIs (naïve to ACEIs/ARBs).

Switching: Patients switching from ACEIs to sacubitril/valsartan could be included in more than one exposure cohort. Those patients were first included in the ACEI exposure cohort and subsequently in the sacubitril/valsartan exposure cohort (only the first switch was considered). Patients changing from sacubitril/valsartan to an ACEI were censored at the date of start of ACEIs, or the end date of the prescription (whichever was earliest). A graphical display of inclusion, exclusion, determination of index date, and exposure cohort assignment is given in Figure 9-2.

Figure 9-2 Exposure cohort assignment and index date



ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; HF = heart failure (diagnosis must be recorded either any time prior to or within three months after the index date); index date = date of first prescription of sacubitril/valsartan (exposure cohort 1 & 2) or ACEI use (exposure cohort 3 & 4) (not shown for excluded patients); sac/val = sacubitril/valsartan.

9.4.2 Safety events of interest

The primary safety event of interest was angioedema and the secondary safety events of interest were hypotension, hyperkalemia, hepatotoxicity, and renal impairment. Safety events of interest were identified using the event-specific codes based on the coding system(s) used in the database(s) of interest (e.g., READ version 2 for CPRD GP diagnoses, ICD-9-CM for GP diagnoses in HSD and hospital diagnoses in PHARMO and ARS, or ICD-10-CM for GP diagnoses and hospital diagnoses in SIDIAP (after mapping of historic ICD-9-CM and ICD-10 codes), death registry in ARS, and hospital diagnoses in Aarhus, PHARMO, and CPRD, ICD-10 GM codes for GePaRD diagnoses from GP, outpatient specialist or hospitalizations, ICPC v1993 for PHARMO GP diagnoses, WCIA codes for PHARMO diagnostic assessments). Additional natural language processing (NLP) terms used in PHARMO to further differentiate within ICPC codes can be found in the code list (see Section 15.1.5). Recorded abnormal laboratory values for identification of hyperkalemia were also included for identification of safety events of interest, if available (not available for ARS and GePaRD).

Several efforts such as code harmonization, benchmarking/feasibility and validation of the safety events of interest have been undertaken to define these safety events of interest appropriately. Code harmonization took place until the feasibility study was finalized. Code harmonization was an intensive process starting with drafting the code list for all safety events of interest to ensure the same or equivalent code requirements in each database. This drafted code list was then meticulously reviewed by two independent medical doctors and discussed with all data partners. The best approach of how to capture of the safety event of interest and harmonization of the diagnosis codes and confirmation algorithms (see Section 9.4.2.2) used to detect the safety event of interest in each of the databases were then examined in the feasibility study ([redacted]). Code harmonization for the safety event of interest and diagnosis codes resulted in the exclusion of certain codes that were too unspecific for identification of the event of interest. Moreover, it resulted in the exclusion of diagnosis codes indicative of a specific underlying cause for the safety event of interest (e.g., “alcohol-induced hepatotoxic”) to focus more on potential ‘idiopathic’ events, as well as differentiation between ‘narrow’ and ‘broad’ diagnoses for angioedema and hypotension, to allow exploration of specificity and sensitivity of captured results in the final analysis ([redacted]). While code harmonization minimized the coding differences between the databases, differences in coding persisted. This is likely due to differences in the granularity of coding systems and local use of the codes. Selected diagnoses and prescriptions codes are listed in code lists available in Section 15.2.1-Table 2-1 to Section 15.2.1-Table 2-23; complete study code list with additional attributes is available upon request (see Section 15.1.5).

For each safety event of interest and covariate, benchmarking of database-specific frequencies for the safety event of interest and covariates was conducted. The observed frequencies were compared to frequencies from previous database studies and literature. Benchmarking data for the present study showed similar patterns in the frequencies of the safety event of interest in each database.

Table 9-5 Specification of safety event of interest in primary or sensitivity analysis

Safety event of interest	Specification	Type of analysis
Angioedema	'narrow'[§]	Primary
Angioedema and anaphylactic shock[*]	'narrow' + anaphylactic shock[§]	Sensitivity
Hypotension	'narrow'	Primary
Hypotension	'narrow' + 'broad'	Sensitivity
Hyperkalemia	'narrow'	Primary
Hepatotoxicity	'narrow'	Primary
renal impairment	'narrow'	Primary

[*]Defined by the diagnoses angioedema and anaphylactic shock as described in the code list in Section 15.2.1-Table 2-2 and Section 15.2.1-Table 2-3.

[§]Safety events with the specification 'narrow' were used in the primary analysis whereas the specification 'broad (only anaphylactic shock)' was used in the sensitivity analysis.

The safety event of interest (see Table 9-5) was identified based on a recorded diagnosis in the in- or outpatient EHRs files and included:

Angioedema (as 'narrow' [primary analysis]) and 'broad' definitions which included only anaphylactic shock [the latter addition was used as additional diagnosis ('narrow' and/or 'broad' (only anaphylactic shock)) for the sensitivity analysis to examine potential misclassification of angioedema]).

Narrow: events of angioedema identified through at least one diagnostic code [ICD-9/-10-CM/GM, ICPC v1993, READ version 2] specific for angioedema (= specification 'narrow' in code list in Section 15.2.1-Table 2-2 Codes used to identify angioedema)

Broad including anaphylactic shock: terms indicative of anaphylactic shock (e.g., "anaphylactic shock", "anaphylaxis", "other drug allergy") in addition to specific diagnostic codes for angioedema (i.e., 'narrow' definition of angioedema) (= specification 'narrow' and/or anaphylactic shock (in the code lists in Section 15.2.1-Table 2-2 and Section 15.2.1-Table 2-3 Codes used to identify angioedema). Based on the results of the validation study, the primary analysis was based on total numbers of cases identified from the 'narrow' definition (see Section 15.2.1-Table 2-2 for diagnostic codes with the specification 'narrow') without validation. Furthermore, the validation study demonstrated that it was more appropriate to consider anaphylactic shock as potentially missed angioedema events ([redacted]). Hence, cases coded as angioedema with the specification 'narrow' and/or anaphylactic shock were included as cases of angioedema in a sensitivity analysis (see Section 9.9.4.1) in this study. The positive predictive values of the validation study for angioedema ([redacted]) are shown in Table 9-6.

For GePaRD angioedema ('narrow' definition) was defined by an algorithm comprising of one discharge diagnosis for angioedema or two outpatient diagnoses from different physicians within up to three months). This algorithm for angioedema ('narrow' definition) may lead to an underestimation of angioedema events ('narrow' definition). Therefore, in a sensitivity analysis the identification of the safety events of angioedema was expanded with unconfirmed diagnoses of angioedema in GePaRD (see Section 9.9.4.1).

Hypotension (as 'narrow' [primary analysis] and 'broad' definition [the latter definition was used for the sensitivity analysis to examine potential misclassification of hypotension]) (see Section 15.2.1-Table 2-4 and Section 15.2.1-Table 2-5).

Narrow: events of hypotension identified through at least one diagnostic code [ICD-9/-10-CM/GM, ICPC v1993, READ version 2] specific for hypotension (= specification 'narrow' in the code list in Section 15.2.1-Table 2-4 Codes used to identify hypotension)

Broad: terms indicative of potential hypotensive events (e.g., "postural dizziness", "presyncope") in addition to specific diagnostic codes for hypotension (i.e., 'narrow' definition of hypotension) (= specification 'narrow' and 'broad' in Section 15.2.1-Table 2-4 and Section 15.2.1-Table 2-5 Codes used to identify hypotension)

The broad definition was added as a sensitivity analysis for misclassification of hypotensive events (see Section 9.9.4.1).

Hyperkalemia with the specification 'narrow' (see code list in Section 15.2.1-Table 2-6).

Hepatotoxicity with the specification 'narrow' (see code list in Section 15.2.1-Table 2-7).

Renal impairment with the specification 'narrow' (see code list in Section 15.2.1-Table 2-10).

Table 9-6 Positive predictive values for angioedema ('narrow' definition) by database from the validation study*

Database	Confirmed cases / total validated n/N	Angioedema PPV (95% CIs)
Aarhus	5/17	29% (10;56)
ARS	12/34	35% (20;54)
GePaRD	14/108	13% (7;21)
HSD	0/1	0% (0;98)
PHARMO§	14/23	61% (39;80)
SIDIAP§	55/79	70% (58;79)
CPRD§	2/17	12% (1;36)

*Validation study by [redacted]
§Databases with partial linkage to hospital data.

The sources used by each database for identification of the safety event of interest is shown in Table 9-7.

Table 9-7 Provenances of the data in the outcome identification algorithms for the safety event of interest per database

Database	Provenance
Aarhus	Secondary outpatient care data Hospitalizations Emergency department Laboratory data (for hyperkalemia only)
ARS	Hospitalizations Emergency department Death registry

Database	Provenance
GePaRD	Primary care data Secondary outpatient care data Hospitalizations
HSD	Primary care data Laboratory data (for hyperkalemia only)
PHARMO	Primary care data Hospitalizations (linked for approximately 90% of patients of the database) Laboratory data (for hyperkalemia only)
SIDIAP	Primary care data Hospitalizations (linked for approximately 35% of patients in the database) Laboratory data (for hyperkalemia only)
CPRD	Primary care data Hospitalizations (linked for approximately 55% patients of the database) Laboratory data (for hyperkalemia only)

Aarhus = Aarhus University Prescription Database and Danish National Patient Registry; ARS = Agenzia Regionale di Sanità della Toscana; CPRD = Clinical Practice Research Datalink; GePaRD = German Pharmacoepidemiological Research Database; HSD = Health Search Database; PHARMO = PHARMO Institute for Drug Outcomes Research; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

Assessment and diagnostic codes for the identification of the safety event of interest can be found in Section 15.2.1 Table 2-2 through 2-10). Primary care databases contained information reported back from secondary care and hospitalizations.

For each safety event of interest, the number of patients at risk for that specific safety event were reported, i.e., patients with no prior event of the safety event of interest at index date. In case of the safety event hepatotoxicity, patients with a history of hepatotoxic event or hepatic morbidity without a defined cause or suggestive of another etiology prior to, at, or seven days after the index date were excluded from all respective exposure cohorts. Similarly, for renal impairment, patients with a history of chronic renal disease or renal impairment prior to index date were excluded from all exposure cohorts (for details regarding exclusion criteria see Section 9.3.2.2).

9.4.2.1 Codes for event definition

The list of diagnostic codes that were used for the safety event definition is provided in Section 15.2.1 (Section 15.2.1-Table 2-2 to Table 2-10). Additional NLP terms used in PHARMO to further differentiate within ICPC codes v1993 are found in a Section 15.1.5. Recorded abnormal laboratory values for identification of hyperkalemia were also included for identification of safety events of interest, if available (were not available for ARS and GePaRD).

9.4.2.2 German database safety event selection algorithms

The German database (GePaRD) contains claims records for primary care, secondary outpatient care, and hospitalizations. Hospitalizations records always contain confirmed diagnoses and are subdivided into primary diagnoses (reason for admission) or secondary diagnoses (co-existing conditions).

Results from the feasibility analyses using any diagnostic code showed that the incidence rates (IRs) for the safety event of interest in the general population were markedly higher in GePaRD compared to the other databases ([redacted]). This was very likely due to the coding

practice in the German outpatient care setting where physicians code the status of diagnostic certainty in four categories: 'excluded diagnosis', 'assured diagnosis' (i.e., 'confirmed'), 'suspicion of diagnosis' (also used for ruling out stepwise), and 'status post diagnosis' (e.g., used in cancer patients or patients with a history of stroke). For this study, only outpatient diagnoses with status 'assured diagnosis' (or if information on status was missing, which applied to about 5% of outpatient diagnoses in GePaRD overall) were considered.

Because 'confirmed' status may be used as a default setting in some EHR systems, the diagnostic certainty has limited reliability. Studies with other events have shown that the inclusion of diagnoses with status 'confirmed' that are only recorded once ever and not confirmed by a second recording in GePaRD caused higher frequencies of conditions compared with other databases, which resulted in misleadingly high IRs due to misclassification. Therefore, confirmation of secondary outpatient diagnoses by a second diagnosis was usually required, especially for chronic conditions.

For all outpatient diagnoses, the day of diagnosis had to be estimated as outpatient diagnoses are only coded on a quarterly basis in Germany. However, the diagnoses are linked to the outpatient treatment case which includes an actual date of treatment related to the outpatient diagnosis. This treatment date was used as the date of diagnosis in the present study. When confirmation algorithms were applied based on one hospital diagnosis or at least two outpatient diagnoses with the status 'assured', the actual date of the first diagnostic code of the confirmed outpatient diagnoses was considered as the diagnosis date. The first diagnostic date of the confirmed diagnosis was used to depict disease onset and to avoid diagnoses potentially being erroneously counted as safety event of interests when the date of onset was before the index date. Diagnoses that were not confirmed by a subsequent diagnosis according to the algorithm-specific criteria were omitted.

For hospitalizations, pre-existing conditions may have been coded as secondary diagnoses, and these pre-existing conditions should not have been used for identification of a safety event but may have been used in the confirmation of a safety event recorded elsewhere. However, secondary diagnoses may also represent conditions that occurred during hospitalization, but that did not contribute to the need for admission or treatment. In a re-run of the feasibility study, different algorithms to identify the events were applied and a decision was made on the final choice of algorithm by GePaRD after discussion with both the Leibniz Institute for Prevention Research and Epidemiology (BIPS) investigators and German physicians with knowledge of the healthcare system and recording practices. For details on the algorithms that were identified, see Section 15.2.1-Table 3-1 and the final feasibility report ([redacted]). Ultimately, the choice of algorithm was determined based on comparable rates of events as identified in other databases as well as knowledge of the persistence and management of identified events.

The chosen rationale by BIPS for the final choice of the GePaRD algorithms to be used was as follows:

Angioedema

- Final algorithm: One discharge diagnosis or two outpatient diagnoses with both the status 'assured' from different physicians within up to three months (primary analysis).
  Generally, angioedema is not considered to be a chronic condition; because of this, the final algorithm for the primary analysis may have led to an underestimation of events of

angioedema ('narrow' definition). Therefore, in a sensitivity analysis, the identification of the safety events of angioedema by confirmed diagnoses (were confirmed by the final algorithm as described in this paragraph) was expanded with unconfirmed diagnoses (no confirmation algorithm was applied) of angioedema in each exposure cohort in GePaRD. In this analysis, patients with at least one recorded diagnosis of angioedema prior to index date in each exposure cohort were excluded.

- Rationale: Outpatient diagnoses were included to also capture less severe cases, in line with the other databases, but using one outpatient diagnosis with the status 'assured' only seems to overestimate the incidence rate. As angioedema is a rare condition and diagnostics are not easy, physicians potentially asked a colleague to also investigate the case to rule out alternative diseases and to ensure the diagnosis (and treatment) was correct. Angioedema may have been co-treated with other main causes of treatment that were the primary reason for hospitalization, therefore, it was necessary to also include secondary or ancillary diagnoses from the inpatient setting.

Hypotension

- Final algorithm: One main discharge diagnosis or two outpatient diagnoses with both the status 'assured' within three months (of any physician).
- Rationale: Historically in Germany, hypotension has had the status of a primary condition to be treated, rather than a symptom, as in other European countries. As a result, hypotension may be more readily diagnosed in Germany, and event rates may have been higher (Donner-Banzhoff et al 1994). As coding practice is additionally rather unspecific, with also rather unspecific causes like weather changes, heat, or an unknown, upcoming, or previous infection – all of which may have led to coding of hypotension – it was meaningful to require two outpatient diagnoses. However, they should be within a short time frame. This time frame was set to three months, as outpatient diagnoses are coded by the quarter only. Hospitalizations only capture severe cases and are therefore insufficient.

Hyperkalemia

- Final algorithm: Only one diagnosis of any type or provenance with the status 'assured'.
- Rationale: For hyperkalemia the broadest algorithm was chosen because a diagnosis of hyperkalemia was generally based on a laboratory assessment that did not need further confirmation.

Hepatotoxicity

- Final algorithm: One main discharge diagnosis or two outpatient diagnoses with both the status 'assured' from different physicians within up to three months.
- Rationale: Using one outpatient diagnosis only seemed to overestimate the incidence rate. A second outpatient diagnosis within three months by a different physician was required, as a second opinion to determine/confirm disease status and/or additional consultation to monitor disease progression of clinically relevant hepatotoxicity events might have been needed, leading to a second coding. Only main discharge diagnoses from hospital were selected because the main reason for treatment should be hepatotoxicity. Hepatotoxicity is an acute event.

Renal impairment

- Final algorithm: One main discharge diagnosis or two outpatient diagnoses with both the status 'assured' from different physicians within up to three months.

Rationale: A second outpatient diagnosis within three months by a second physician was required, as a second opinion was required to determine/confirm disease status and severity. Using only one outpatient diagnosis seemed to overestimate the incidence rate. When one main discharge diagnosis from a hospital was selected, the main reason for treatment should be renal impairment. Renal impairment is considered an acute event.

9.4.2.3 Person years of exposure

For patients in the four different exposure cohorts, person-years of exposure were calculated from the index date until end of exposure to sacubitril/valsartan or ACEIs for each specific safety event of interest. For this calculation of the persons-years of exposure, patients were, next to criteria for censoring as described in Section 9.3.2.4, censored at the time of the specific safety event of interest.

9.4.3 Patient characteristics/demographics

Patients' characteristics/demographics are summarized for the respective exposure cohort at index date. For categorical characteristics listed below, all categories (including one for missing information, where indicated) were included in one categorical variable for the analyses. For potential use as covariates in the statistical modeling, reference values are indicated below.

Patients' characteristics/demographics included:

- Age (continuous, categorical [18-44, 45-64, 65-74, ≥ 75] only for descriptive purposes, no reference needed as continuous was used for the propensity score weighting) were assessed at index date
- Sex (female as reference)
- Ethnicity (white, black, other, missing) assessed prior to index date (only available in CPRD, but recording rather incomplete (Mathur et al 2014)
- Comorbidities (i.e., diseases/conditions already prevalent before the index date) assessed using entire available history (= look back period) in patients' EHRs (in- and outpatient medical records) (yes/no [no = reference]) were identified using the event-specific codes based on the coding system(s) used in the database(s) of interest (e.g., READ version 2 for CPRD GP diagnoses, ICD-9-CM for GP diagnoses in HSD and hospital diagnoses in PHARMO and ARS, or ICD-10-CM for GP and hospital diagnoses in SIDIAP (after mapping of historic ICD-9-CM and ICD-10 codes) and hospital diagnoses for Aarhus, PHARMO, and CPRD, ICD-10-GM codes for GePaRD diagnoses from GP, outpatient specialist or hospitalizations, ICPC v1993 for PHARMO GP diagnoses, WCIA codes for PHARMO diagnostic assessments (see Section 15.2.1-Table 2-8, Table 2-11, Table 2-14 to Table 2-22 diagnosis codes):
  - Hypertension (look back period
  - Myocardial infarction (look back period)
  - Stroke or transient ischemic attack (TIA) (look back period)

- Angina pectoris (look back period)
- Atrial fibrillation (look back period)
- Valvular disease (look back period)
- Diabetes mellitus (look back period)
- Respiratory disease (asthma, chronic obstructive pulmonary disease [COPD]) (look back period)
- Allergic reactions (e.g., to food, seasonal allergies, drug rash, urticaria) (look back period)
- Chronic kidney disease (CKD) (look back period), is not presented for the respective exposure cohorts examining sacubitril/valsartan or ACEI use and the risk of renal impairment (exclusion criterion)
- Chronic hepatic disease (look back period), is not presented for the respective exposure cohorts examining sacubitril/valsartan or ACEI use and the risk of hepatotoxicity (exclusion criterion)

In GePaRD, only confirmed diagnoses for the comorbidities were selected by using the following algorithm:

- At least one primary discharge diagnosis from hospital
- OR at least two outpatient diagnoses with the status 'assured', of which the date of the first diagnostic code was considered as the diagnosis date.

- Co-medication (yes/no [no = reference] to characterize patients in the respective exposure cohorts) (use was based on prescription at index date or within 365 days prior to index date [i.e., the start date of the prescription of the co-medication is within 365 days prior to or at index date, which may have resulted in prescription overlapping the index date]) (see Section 15.2.1-Table 2-13 for medication codes):
  - ACEIs (*note:* assessed excluding index date)
  - ARBs (*note:* assessed excluding index date)
  - ACEIs and ARBs (note: assessed excluding index date)
  - Other RAAS targeting drugs (e.g., aliskiren/remikiren)
  - Beta-blockers
  - Calcium channel blockers
  - Mineralocorticoid receptor antagonists (MRAs)
  - Loop diuretics
  - Other diuretics (thiazides, potassium-sparing diuretics [excluding MRAs and loop diuretics])
  - Digoxin
  - Ivabradine
  - Nitrates
  - Hydralazine
  - Antiarrhythmic agents
  - Anticoagulants

- Antiplatelets (including prescription aspirin)
- Lipid lowering drugs (excluding statins)
- Statins
- Antidiabetics
- Fluoroquinolones
- Non-steroidal anti-inflammatory drugs (NSAIDs)

Fixed-dose combinations were split into single-agent drugs, and respective ATC codes of active compounds were assigned. Each drug type included in the combinations is represented in the classes as mentioned above.

- The number of cardiac drugs used in HF treatment at index date or within 365 days prior to index date other than ACEIs and sacubitril/valsartan (i.e., ARB [other than sacubitril/valsartan], direct renin inhibitors, ivabradine, beta-blockers, MRAs, hydralazine and isosorbide dinitrate, diuretics) counting the unique number of ATC codes of active compounds used in HF, dichotomized to use as a proxy for HF [≤ 3 (= reference), > 3])

9.5 Data sources and measurement

This study used European databases comprising routine healthcare data. This provided a reflection of real-world circumstances and prescribing behaviors. The databases were selected based on their geographic location, the availability of population-based data on drugs, plus their recognized reputation in the area of drug utilization, and safety research. Multiple countries were included to provide international data and to guarantee sufficient exposure to sacubitril/valsartan.

The data for this study were retrieved from the CPRD based on a license from the Basel Pharmacoepidemiology Unit, SIDIAP provided by IDIAP Jordi Gol, HSD provided by Società Italiana di Medicina Generale, PHARMO provided by the PHARMO Institute for Drug Outcomes Research, and Aarhus provided by Aarhus University. Consistent with the fourth interim report ([redacted]) data were also included from ARS provided by the Tuscany and the Region, and from GePaRD provided by the Leibniz Institute for Prevention Research and Epidemiology – BIPS (BIPS).

All databases comply with EU guidelines on the use of medical data for medical research and have been validated for pharmacoepidemiological research (Jick et al 2003, Pigeot et al 2008, Ehrenstein et al 2010, Herrett et al 2010, van Herk-Sukel et al 2010, Cazzola et al 2011, García-Gil et al 2011, Ohlmeier et al 2016, Trifirò et al 2019).

Table 9-8 provides an overview of database characteristics including available data. All databases had a mean timespan between look back and follow-up ranging from 2.5 to 11 years and were representative of the country-specific populations in terms of age and sex. Databases used in this study were mainly primary care databases (except for Aarhus from Denmark, which is a prescription database, and ARS, which is a database that comprises data on admissions to hospital and emergency care) and available data were complete, as it came from the general practitioners' (GPs') electronic primary care records. The primary care databases represent 3-

13% of the country specific total population. The total number of persons in the source population encompassing all seven databases was approximately 41.4 million in 2016.

Table 9-8 Overview of databases used in the study

	Database						
Characteristics	**Aarhus**	**ARS**	**GePaRD**	**HSD**	**PHARMO**	**SIDIAP**	**CPRD**
Country (population size 2019 in million inhabitants) †	Denmark (5.8)	Italy (59.2)	Germany (82.4)	Italy (59.2)	Netherlands (17.1)	Spain (46.4)	United Kingdom (66.8)
Type of database	ADM	ADM	Claims	EMR	EMR	EMR	EMR
Number of patients per database, millions	1.5	3.6	25	1.5	4.0 (approximately 1.2 million with both GP and outpatient pharmacy data available)	5.1 (about 35% linked to hospital data)	5.7 (approx. 55% linked to HES data)
Date in*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Date out±	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Date of death	Yes	Yes	Yes (date of in-hospital death is available. Date of out-of-hospital death can be estimated)	Yes	Yes	Yes	Yes
Cause of death	Yes	Yes	No	No	No	No	No (only available through linkage of data to the Office for National Statistics death registration data)
Updates	Yearly (April)	Monthly with a lag-time of 3-4 months	Yearly (mid-year)	Twice a year: (30/06 and 31/12)	Yearly (October)	Yearly (April/May)	Yearly (May/June)
Prescriptions							
Outpatient Rx	Yes	Yes	Yes	Yes (incomplete	Yes	Yes (specialist incomplete)	No (only prescriptions

	Database						
Characteristics	**Aarhus**	**ARS**	**GePaRD**	**HSD**	**PHARMO**	**SIDIAP**	**CPRD**
				specialist prescriptions)			recorded by GPs)
Coding of drugs	ATC	ATC and local Italian coding system	ATC and ATC GM	ATC and local Italian coding system	ATC	ATC	Gemscript codes
Dosing regimen	No	No (no posology, but dosing strength is available)	No (number of tablets/units and strength per tablet/unit are available)	Yes (incomplete)	Yes	No (number of tablets is available)	Yes (incomplete)
Safety events of interests							
Hospitalizations	Yes	Yes	Yes	No (only if reported to GP by patients)	Yes (for about 90%)	Yes (for about 35%)	Yes (for about 55%)
Emergency visits	Yes	Yes	Yes (incomplete, only emergency visits to GPs)	Yes (incomplete)	No	No	No
Outpatient diagnoses by specialists and GPs	Yes (diagnoses made by specialists in the outpatient departments of public and private hospitals)	No	Yes (diagnoses made by GPs and diagnoses made by specialists in the outpatient setting)	Yes (diagnoses made by GPs and specialists recorded by GPs)	Yes (diagnoses made by GPs and specialists diagnoses recorded by GPs)	Yes (diagnoses made by and specialists recorded by GPs)	Yes (diagnoses made by specialists and recorded by GPs)
Coding of disease	ICD-10-CM	ICD-9-CM	ICD-10-GM	ICD-9-CM	ICPC, ICD-10-CM	ICD-10-CM	READ (ICD-10-CM for HES data)

	Database						
Characteristics	**Aarhus**	**ARS**	**GePaRD**	**HSD**	**PHARMO**	**SIDIAP**	**CPRD**
Laboratory data	Yes	No	No (only information on date and type of test is recorded, results of tests are not available)	Yes	Yes	Yes	Yes

ADM = Administrative record linkage; ARS = Agenzia Regionale di Sanità della Toscana; ATC = Anatomical Therapeutic Chemical; BNF = British National Formulary; CM = Clinical Modification; CPRD = Clinical Practice Research Datalink; EMR = Electronic Medical Records; GePaRD = German Pharmacoepidemiological Research Database; GM = German Modification; GP = general practitioner; HES = Hospital Episode Statistics; HSD = Health Search Database; ICD= International Classification of Disease, ICPC = International Classification of Primary Care; Rx = prescription; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

[†]derived from http://www.worldometers.info/ (accessed February 19, 2019).

[*]Date in is the date when individuals entered the database.

[±]Date out is the date when individuals left the database.

All databases are listed in the HMA-EMA Catalogues of real-world data sources and studies (European Medicines Agency 2024); further details on individual databases are included in the amended LCZ696B2014 study protocol v01.1 ([redacted] Section 15.1.1).

Study approval

The study protocol was endorsed by each data partner and was approved by local authorities (see Section 15.1.2).

9.6 Bias

Prevalent-user bias

By design, a new user cohort was used, but this was impossible due to the fact that sacubitril/valsartan was a second line treatment at the time of this study. Many patients may have been treated with an ACEI/ARB before initiation, restricting to treatment-naïve patients would have limited the sample size and generalizability. Therefore, different exposure cohorts have been created.

Since the majority of patients initiating sacubitril/valsartan were expected to be treated with an ACEI or ARB before initiating sacubitril/valsartan, these patients were likely to have a lower baseline risk of angioedema as susceptible patients have been depleted. Patients using ACEI without prior exposure to ACEIs or ARBs, however, are likely to have a higher baseline risk of angioedema, since this population includes all patients who are susceptible to an angioedema event. Hence, the impact of depletion of susceptibles was explored by assessing the incidence rate of safety events among patients using ACEIs regardless of prior exposure to ACEIs/ARBs (exposure cohort 3) and initiators of ACEIs without prior use of ACEIs/ARBs (exposure cohort 4). In this study patients in exposure cohort 1 (initiators of sacubitril/valsartan with prior ACEIs/ARBs) were compared with patients in exposure cohort 3, which included prevalent ACEI users. Furthermore, because of the pathogenesis, the risk of angioedema should be the highest directly after treatment initiation of ACEIs and then decreases over time (Kostis et al 2005, Miller et al 2008, Toh et al 2012). A cohort of prevalent ACEI users would be biased towards a lower rate of angioedema during follow-up compared to ACEI-naïve patients. Patients experiencing angioedema while treated with ACEIs were expected to discontinue ACEI treatment and were, therefore, less likely to be included in exposure cohort 3 (prevalent ACEI user cohort). Thus, comparing patients initiating sacubitril/valsartan regardless of their prior exposure to ACEIs/ARBs to patients using ACEIs who were treatment-naïve to ACEIs and ARBs likely biased the comparative analysis in favor of sacubitril/valsartan. This hypothesis was explored by comparing the rate of angioedema events in exposure cohort 1 with patients in exposure cohort 4.

For comparability, patients in exposure cohort 2 (treatment-naïve to sacubitril/valsartan) were compared with patients newly initiating ACEIs (exposure cohort 4), since this was considered the most unbiased comparison.

Channeling

Prescribing of sacubitril/valsartan may be channeled to patients with more severe HF, especially in the UK, where The National Institute for Health and Care Excellence (NICE) guidance recommends sacubitril/valsartan for the treatment of chronic HFrEF in patients with NYHA Class II-IV symptoms and a left ventricular ejection fraction of 35% or less, or who took a stable dose of ACEIs or ARBs (National Institute for Health and Care Excellence 2016). Controlling for HF severity was difficult as the feasibility study showed that information on NYHA class or ejection fraction was not available in each database ([redacted]). A proxy measure of HF severity (less than three cardiac drugs used in HF treatment at index date) was introduced to address this kind of channeling bias. Residual confounding may have affected the comparative analyses for the relative risk assessment of angioedema (exploratory objectives, see Section 7). If channeling occurs, it is less likely that it would impact the results of the comparative analyses, as severity of HF may not have influenced the risk of angioedema.

Outcome Misclassification

Note that the main aim of data collection in real-world setting was patient management/administration, not medical research. This implies that only events were collected which were deemed to be relevant for patient care/reimbursement. In addition, information from specialists was incomplete in most of the databases. To assess the impact of using different data sources (hospital versus GP data), databases which have linkage with hospital data were limited to a subset of the source population, i.e., PHARMO, SIDIAP, and CPRD. In these three databases all analyses were stratified based on the eligibility for linkage to hospital data. A feasibility analysis with comparison of IRs and code harmonization was conducted. In addition, a validation study was performed which showed the heterogeneity in assessment due to lack of detailed clinical information and the interpretation thereof. Therefore, cases were not validated for this final analysis, mostly to avoid exclusion of false negatives.

In the validation study ([redacted]), a sensitivity analysis limiting the hypersensitivity reactions to codes for anaphylactic shock of up to 100 potential randomly sampled cases was performed, and the false negative rate (FNR) rose considerably. This sensitivity analysis showed that diagnostic codes for anaphylactic shock were much more likely to identify missed diagnoses of angioedema rather than using a broader definition of hypersensitivity reactions. This is why a sensitivity analysis with angioedema and anaphylactic reactions was conducted.

Exposure misclassification

Exposure of interests were obtained from prescriptions or dispensings. The only databases that capture both primary care and specialist prescriptions were Aarhus, GePaRD, and PHARMO. The other databases were primary care databases and did not capture (all) prescriptions from medical specialists. However, in all these countries (UK, Italy, and Spain), prescriptions initiated by the specialist were generally continued by the GP. The start of these prescriptions may have been missed, which was assessed in the feasibility analysis. In SIDIAP, the month and year of the dispensing were only available and the day of dispensing was set to the first day of the month (see Table 9-3). The impact of defining the dispensing date as the first day of the month of dispensings in SIDIAP may have several consequences which limit the interpretability of the data in context of this study. First, for diagnoses of interest (safety events of interest/

exclusion criteria) occurring in the first month of exposure to sacubitril/valsartan, the initiation of both treatments is always assumed to precede the diagnosis although the opposite may be true. This may lead to incorrectly counting a diagnosis as a safety event although it would have qualified, as exclusion criterion had the exact exposure date been known. Second, dispensings for sacubitril/valsartan and ACEIs within the same month at index date were excluded and assumed non-adherent to the 36-hour wash-out period. A sensitivity analysis was conducted where combined crude and age- and sex-standardized IRs of the primary and secondary objectives were estimated without data of SIDIAP (see Section 9.9.4.4 and Section 10.5.4). This sensitivity analysis was not prespecified in the protocol but added post-hoc, to examine the impact of measurement errors in this data source.

Remaining heterogeneity between data sources.

A common data model was used to overcome syntactic differences between databases. In addition, substantial benchmarking to harmonize semantic differences was conducted. However, bias due to heterogeneity in healthcare systems and capturing of different provenances of healthcare may not have been fully excluded. For the databases in which linkage of hospital data was limited to a subset of the full population (PHARMO, SIDIAP, CPRD), stratified analyses by eligibility for hospital linkage were conducted.

9.7 Study size

The initial sample size calculation was updated after the second interim report to reflect the lower-than-expected proportion of patients initiating sacubitril/valsartan in the study base.

Since the primary objective of the study was to estimate the IRs of angioedema and other safety events of interest with sacubitril/valsartan, Figure 9-3 presents confidence intervals (CIs) expected for angioedema, the rarest of all the events, given different sample sizes.

An IR of angioedema following sacubitril/valsartan was set to be 5.5 per 1,000 person years (PYs), based on an IR of 2.9 per 1,000 PYs following ACEI estimated via meta-analysis, using data up to one year from three observational retrospective cohort studies (Figure 9-5 and Table 9-9, random effect Poisson model using data from Burkhart and colleagues, Miller and colleagues, and Toh and colleagues), and assuming an incidence rate ratio sacubitril/valsartan : ACEI of 1.9, based on the results of the double-blind part of the pivotal phase III study PARADIGM (McMurray et al 2014, Burkhart et al 1996, Miller et al 2008, Toh et al 2012).

Figure 9-4 shows expected CIs for the hazard ratio (HR) of sacubitril/valsartan versus ACEI for angioedema (Exploratory objectives - see Section 7 and Relative risk for exploratory analyses – see Section 9.9.2.6) for different sample sizes. Additionally, to the previous assumptions on sacubitril/valsartan and ACEI IRs, the same exposure for sacubitril/valsartan and ACEIs was added.

With these assumptions, it was aimed to include approximately 24,000 PY of exposure with sacubitril/valsartan in the study, which would result in 132 observed angioedema cases and an estimated IR of 5.5 per 1,000 PYs with a 95% CI ranging from 4.6 to 6.5 per 1,000 PY. With this sample size and the assumed treatment effect of HR = 1.9, the power to detect a difference in the comparative analyses for the exploratory objectives (testing the null hypothesis HR = 1 versus the alternative hypothesis HR > 1) would be 99%.

Figure 9-3 Examples of confidence intervals (CIs) for the incidence rates (IRs) of angioedema following sacubitril/valsartan

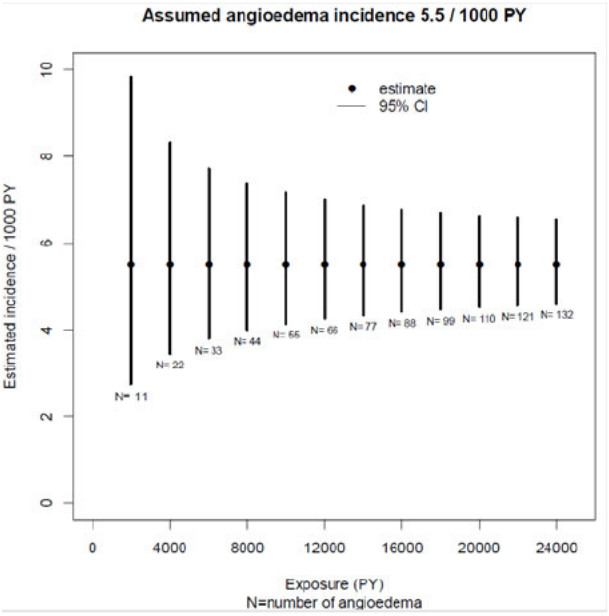


Figure 9-4 Examples of confidence intervals (CIs) for the hazard ratios (HRs) of angioedema following sacubitril/valsartan versus ACEI

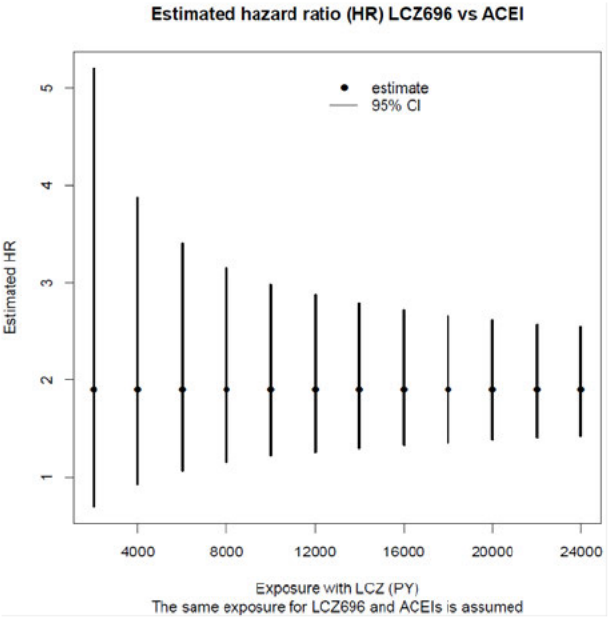
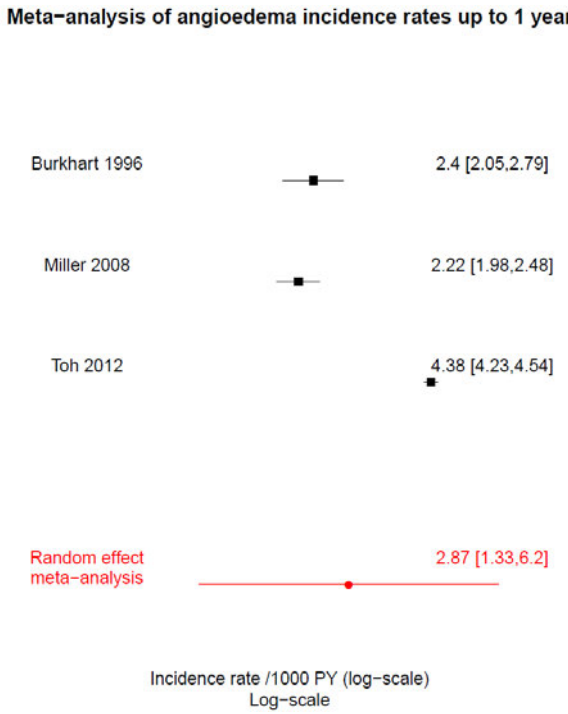


Table 9-9 Literature information for the meta-analysis of angioedema incidence rates (IRs) following ACEIs

Reference	Databases	Years	HF (%)	Number of Angioedema cases up to 1 year	Patients	Exposure Up to 1 year (PYs)	IR (per 1,000 PYs)	95% LCL	95% UCL
Toh et al 2012	Mini-sentinel	2001-2010	2.2	3301	1,845,138	753,105	4.38	4.24	4.54
Miller et al 2008	VA	1999-2000	20.3	319*	195,192	143,623	2.22*	1.98*	2.48*
Burkhart et al 1996	Medicaid	1986-1992	NA	168*	155,258	69,966	2.40*	2.05*	2.79*

ACEI = angiotensin converting enzyme inhibitor; IR = incidence rate; LCL = lower confidence limit; PY = patient-year; UCL = upper confidence limit; VA = Veterans Affairs; NA= not available; HF= patients with HF diagnosis
*Calculated from the published data

Figure 9-5 Meta-analysis of angioedema incidence rates (IRs) up to one year following ACEIs



Source data from: Burkhart et al 1996, Miller et al 2008, Toh et al 2012

9.8 Data transformation

Due to the different database structures, characteristics and coding systems, it was not possible to apply one single data program to the native data for all databases. To overcome this and harmonize the analysis, a common data model approach was used to analyze data in an efficient and distributed manner.

Each data partner extracted data locally and transformed them into a simple common data model that was maintained locally, including standardized patient, drug, diagnosis and assessment files, linkable via a patient-unique identifier (see Figure 9-6) as defined in a data dictionary. Based on the relevant diagnostic codes and keywords (for free text search), a data processing algorithm was constructed for each safety event of interest based on the consensus of the data partners, which led to the events in the input files. The common data model tables (also called input files) – as specified in the common data model specifically designed for this study – formed the basis for this study.

The study code list could be adapted by each data partner as needed to reflect database-specific coding system requirements.

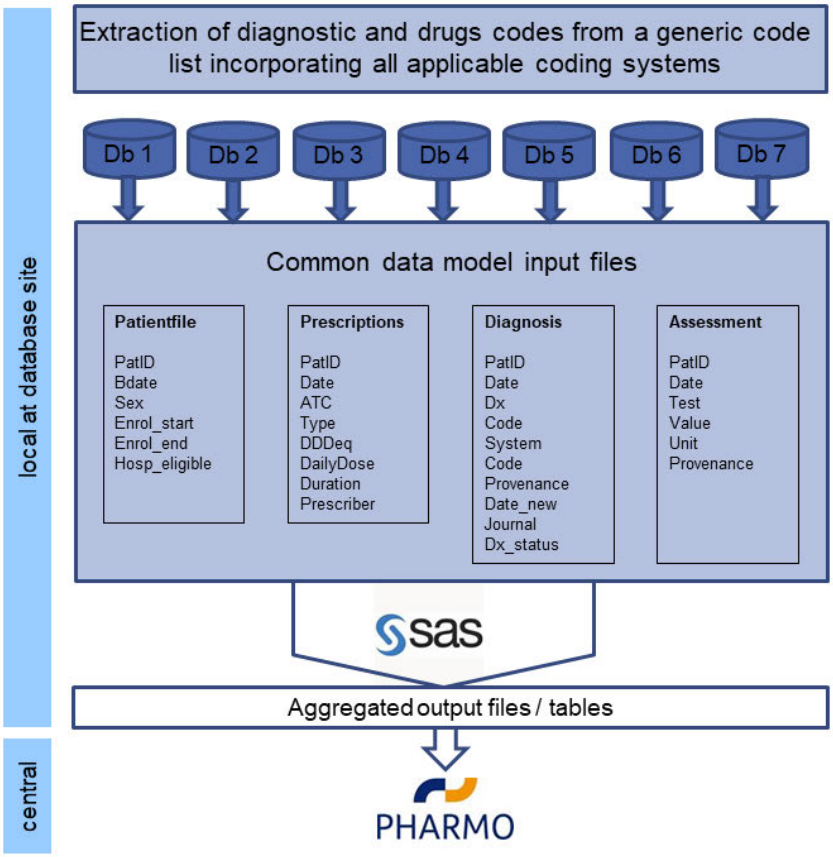
The feasibility study, validation study, and benchmarking of the data for the final analysis were finalized in Q1 2021 ([redacted]), Q2 2022 ([redacted]), and Q1 2022, respectively, and informed the SAP of the final LCZ696B2014 study.

Programming for data transformation of the input files into relevant elements for the study objectives was performed in SAS and produced by PHARMO (see SAP v3.0 in Section 15.1.4). Any confirmation algorithms necessary for the safety event of interest and diagnoses for comorbidities in GePaRD were performed on site, prior to inclusion of the confirmed diagnosis records in the common data model.

Aggregated data summaries as outlined in the table shells in SAP v3.0 in Section 15.1.4 were created on-site for each database using SAS programs shared by PHARMO. Using a secure file transfer protocol, aggregated data files were sent to PHARMO for further analysis, such as pooling of IRs or meta-analysis. PHARMO combined all aggregated data into the final report. The process of data collection, programming, and reporting is summarized in Figure 9-6.

For all data partners, SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) was used for data processing and final analysis. Note that although ARS used R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) for the previous interim reports, they used SAS version 9.4 for the final study report.

Figure 9-6 Common Data Model for data transformation



9.9 Statistical methods

All analyses were decided in collaboration between the scientific lead (MS) and the PHARMO Institute for Drug Outcomes Research, the coordinating center for the study. Aggregated data summaries were created on-site for each database using the programs shared by PHARMO. PHARMO combined all aggregated data into the final report. The process of data collection, programming and reporting is summarized above (see also Figure 9-6 for example overview).

At PHARMO, data management and statistical analysis and reporting were performed using the utility SAS Enterprise Guide version 7.1, an environment for SAS version 9.4 enabling the storage of syntaxes or codes belonging to a single study in one project file, subdivided into project flows for different aspects of a study.

Because of the potential impact of the COVID-19 pandemic, the study period for the primary analyses (primary, secondary, and exploratory objectives) ended on December 31, 2019, the time at which the COVID-19 pandemic might have started having an impact. All analyses in which this end date was used are referred to as the pre-COVID period. The full study period was defined as the latest date of data availability in each database, which included the period in which the COVID-19 pandemic occurred (from 2020 onward).

Based on the results of the validation study ([redacted]), all analyses for the primary and secondary objectives were conducted without validation for all safety events that were identified in each database. The primary analysis including the primary safety event of angioedema was therefore based on total number of patients identified from the 'narrow' definition (see Safety events of interest Section 9.4.2).

In the databases in which linkage of hospital data was limited to a subset of the full population (PHARMO, SIDIAP, CPRD), the study objectives were assessed and stratified by eligibility for hospital linkage. PHARMO, SIDIAP, and CPRD eligibility for linked hospital data was estimated at approximately 90% of the population with linked pharmacy and GP data in PHARMO, about 35% of the population in SIDIAP, and about 55% in CPRD (see Table 9-7). In the final analysis, for these three databases, all study objectives were examined in patients without and with linked hospital data, and the full population (i.e., patients without and with linked hospital data) was not analyzed. This stratification by eligibility for hospital linkage gives insight into the added value of hospital data in addition to primary care data in the various countries.

Small-cell-counts policies

Due to regulations regarding data sharing (i.e., small-cell-count policies), CPRD is not allowed to report information on cell counts below five, which are presented as '< 5' in this final report. Aarhus has to comply with Danish data protection regulations, and less than five patients per cell and data that can trace less than five patients per cell are therefore not shown but are presented as #. Aarhus can, however, share information when there are zero counts of safety events of interest, as long as patients are not traceable.

9.9.1 Main summary measures

The final report includes the following summary measures:

Descriptive summary measures

The size of the study population is presented in an attrition table. Exclusions are reported as absolute numbers, as well as percentages (%) of the population size immediately prior to the applied exclusion in the attrition table.

- The number of patients in each exposure cohort is presented by database as absolute numbers and relative (as percentage (%)) to the number of patients in the study population (for exposure cohorts 1 and 3) or relative to the numbers in exposure cohort 1 and 3 (for exposure cohorts 2 and 4).
- Patient baseline treatment characteristics are provided for patients in the pre-COVID and full study period, including:
  - Enrollment time to index date (defined as the time (=look back period) between the date of enrollment in the database and index date in weeks),
  - Duration of exposure to sacubitril/valsartan or ACEIs during follow-up are presented per database as patient-weeks of exposure (i.e., mean (± standard deviation (SD)), median (interquartile range (IQR)) and minimum (min), maximum (max), and pre-

defined duration categories, and the rationale for censoring patients discontinuing treatment during follow-up (presented as percentages (%)).

- Baseline demographic and clinical characteristics of patients initiating sacubitril/valsartan or using ACEIs are presented for patients in the pre-COVID (primary analysis) and full study period, including:
  - Age,
  - Sex,
  - Ethnicity (only for CPRD),
  - Comorbidities (ever prior to (=look back period) or at index date),
  - Co-medications (in the year prior to index date).

Statistics of patient baseline demographic and clinical characteristics were estimated, using contingency tables for categorical variables, and mean (±SD), median (IQR), and min, max for continuous variables per database and for all databases together (when possible) in the pre-COVID and full study period.

- Differences in demographic and baseline characteristics of patients initiating sacubitril/valsartan and patients using ACEIs were quantified via standardized mean differences (SMD).

Summary measures for primary and secondary objectives

- Crude and age- and sex-standardized IRs of all safety events of interest (i.e., angioedema [primary safety event of interest], hypotension [secondary safety event of interest], hyperkalemia [secondary safety event], hepatotoxicity [secondary safety event], and renal impairment [secondary safety event]) accompanied by 95% CIs are presented per 1,000 PYs.
- Cumulative incidence of events of interest per 1,000 patients at pre-defined time points (i.e., at Week 1, Week 4, Week 8, Week 26, and Week 52 after the index date) are presented as Kaplan–Meier curves.

Summary measures for exploratory objectives

- The relative risk of angioedema (‘narrow’) expressed as a hazard ratio (HR; crude and adjusted) with its corresponding 95% CIs for sacubitril/valsartan versus ACEI cohorts are estimated for each comparison specified in the exploratory objectives (as feasible) per database and all databases together in the pre-COVID period.

Sensitivity Analyses

- Misclassification of safety events
  - Angioedema (‘broad’ definition):
    - Expand the ‘narrow’ definition of angioedema by adding terms indicative of anaphylactic shock which were derived from the code list of angioedema with a ‘broad’ specification, to the specific terms for angioedema (‘narrow’) (see Section 9.4.2).

    - Use confirmed and unconfirmed diagnoses of angioedema in GePaRD (see Section 9.4.2.2).
  - Hypotension ('broad' definition):
    - Include symptoms indicative of potential hypotensive events from the code of hypotension with the specification 'broad' to the specific terms used for hypotension ('narrow').
- Potential impact of COVID-19 pandemic: analyses conducted for the full study period in addition to the pre-COVID study period (primary analysis)
- Impact of duration of prevalent ACEIs use.
- Impact of excluding SIDIAP data.

9.9.2 Main statistical methods

9.9.2.1 Demographic and baseline clinical characteristics

All differences in demographic and baseline characteristics of patients initiating sacubitril/valsartan and patients using ACEIs were quantified via standardized (mean) differences (SMD) (Austin 2009).

For continuous (e.g., age) and dichotomous variables, the SMD or standardized difference was defined by the formulas proposed by Austin (Austin 2009). For the categorial variable ethnicity the SMD was defined according to Dalton and Yang (Dalton et al 2012).

An SMD score under 0.1 (or 10%) generally indicates no difference (Austin 2009).

When data on demographic and baseline characteristics were combined across databases, mean (±SD), min, and max were estimated by implementing formulas by Higgins et al 2011.

As requested by the Pharmacovigilance Risk Assessment Committee (PRAC), the adherence to the 36-hour wash-out period recommended in the SmPC of sacubitril/valsartan for patients previously using ACEIs who started on sacubitril/valsartan in actual clinical care setting was investigated. This was assessed by the proportion of patients initiating sacubitril/valsartan with concurrent prescriptions (i.e., on the same day or in SIDIAP in the same month) of ACEIs and sacubitril/valsartan indicating non-adherence to the 36-hour wash-out period (see also Section 9.3.2.2, presented as an exclusion criterion in the selection of patients initiating sacubitril/valsartan and patients using ACEIs). Based on the electronic prescription records it was not possible to ascertain whether patients had stopped using ACEIs 36 hours prior to the start of sacubitril/valsartan, but it was likely that the instruction was given, and that the patient adhered to it. Durations of ACEIs prescriptions overlapping the index date therefore could not be construed as evidence of concurrent use of ACEIs and sacubitril/valsartan. Consequently, the proportion of patients initiating sacubitril/valsartan with concurrent prescriptions (i.e., on the same day or in SIDIAP in the same month) of ACEIs and sacubitril/valsartan indicating non-adherence to the 36-hour wash-out period were determined as sole indicator of violation of this recommendation.

9.9.2.2 Crude incidence rates for primary and secondary objectives

The risks of the safety event of interest (i.e., angioedema [primary safety event of interest], hypotension [secondary safety event of interest], hyperkalemia [secondary safety event], hepatotoxicity [secondary safety event], and renal impairment [secondary safety event]) were estimated as crude IRs, i.e., as the number of events of interest divided by PYs, along with 95% CIs, and are presented per 1,000 PYs in exposure cohorts 1 and 2 (patients initiating sacubitril/valsartan; primary objective) and exposure cohorts 3 and 4 (patients using ACEIs; secondary objective). All crude IRs per database and combined (pooled) crude IRs of all databases together are reported as the measure of absolute risk.

The sequence of first occurrences of a safety event of interest was modeled to follow approximately a Poisson process with constant intensity θ (Garwood 1936). The crude IRs and the accompanying 95% CIs were derived based on formulas proposed by Sahai et al and Ulm (Sahai et al 1993, Ulm 1990).

Due to data regulations, so-called small-cell-count policies at Aarhus and CPRD, the number of safety events of interest or patients at risk was not available when the number of events or patients was less than five (although in case of Aarhus zero counts of events could be reported, see Section 9.9.1). Therefore, crude IRs for Aarhus and CPRD are not reported for situations where the small-cell-count policies applied.

9.9.2.3 Age- and sex-standardized incidence rates for primary and secondary objectives

In addition, IRs were age- and sex-standardized per exposure cohort and database for all safety events. From each database, all patients categorized by age and across sex were merged to create a standard population. The standardized rates were calculated to understand potential differences in IRs between countries irrespective of country-specific differences in the age and sex distribution. Due to the small number of patients aged < 45 years, age categories below this age were merged into one age category. Above that age, 5-year age categories were created. Age- and sex-standardized IRs were determined using the direct method (Office for National Statistics 2016) (see Section 15.1.4 SAP v3.0 for formulas estimating the age-standardized mortality rate), replacing the European standard population (ESP) with the study-based standard population. For this method, the number of patients in each age category per sex per exposure cohort from each database were assessed and added up to a total number of patients per each category per sex per exposure cohort. Then the total number of patients were divided by the total number of patients per exposure cohort of all databases together and were then multiplied by 100,000.

For estimating the IRs per age category per sex, the number of safety events of interest in respective age- and sex-category divided by the person-time at risk in respective age- and sex-category.

These IRs were then multiplied with the age- and sex-standardized weights to estimate the age- and sex-standardized IRs (Morris et al 2018).

The corresponding 95% CIs were based on the Dobson method (Dobson et al 1991). The Dobson method produces relatively accurate 95% CIs when ten or more safety events are observed. For less than ten events 95% CIs were therefore not presented.

If the count of safety events was zero in CPRD, the age- and sex-standardized IRs are not displayed due to the small-cell-count policy. For all other databases, the crude and age- and sex-standardized IRs per database were estimated for all analyses, including all sensitivity analyses of the 'broad' definition (potential misclassification of angioedema and hypotension events), the potential impact of COVID-19 pandemic, and duration of prevalent ACEIs use.

9.9.2.4 Cumulative incidences of angioedema for primary and secondary objectives

For the safety event angioedema, cumulative incidences per 1,000 patients at pre-defined time points (i.e., at Week 1, Week 4, Week 8, Week 26, and Week 52 after the index date) up to the end of follow-up were determined for each exposure cohort of each database. Cumulative incidences per 1,000 patients were shown in the Kaplan–Meier curve (1-survival) at the pre-defined time-points for each exposure cohort, using the interval option in SAS proc lifetest and plotting cumulative incidence function (CIF) with arcsine transformed confidence bands using the equal precision formula (Borgan et al 1990). For each Kaplan-Meier curve, the at-risk table including the number of patients at risk, the number of events of angioedema, and the cumulative incidence estimates with its 95% CIs at the specified time points was displayed outside the body of the graph. The pooled cumulative incidence estimates (as described in the original protocol version 00 ([redacted])) were not calculated because of the inability to obtain meaningful estimates given sparse data and the lack of reported number of events from Aarhus and CPRD.

9.9.2.5 Combined incidence rates calculation for primary and secondary objectives

Individual-level data was not allowed to be shared due to governance restrictions for the databases; however, aggregated data could be shared. To avoid misconception of the term pooling, the term 'combined IR' was used rather than 'pooled IR' when referring to the estimate that combines data from all databases. Combined crude IRs were calculated by PHARMO, using the method described in Section 9.9.2.2. The number of safety events of interest (i.e., angioedema [primary safety event of interest], hypotension [secondary safety event of interest], hyperkalemia [secondary safety event], hepatotoxicity [secondary safety event], and renal impairment [secondary safety event]) and related PYs of each exposure cohort of each database were added up to estimate the total number of safety events of interest and PYs per exposure cohort of all databases together. Then the total number of events of interest were divided by the total PYs to estimate the combined crude IRs, along with 95% CIs, and were presented per 1,000 PYs (see Section 9.9.2.2). For the age- and sex-standardized combined IRs, the total number of events of interest were multiplied by the total number of patients in the study-based standardized population and then divided by the total number of PYs for each pre-defined 5-year age category and sex in each exposure cohort across all databases (see Section 9.9.2.3).

The method for estimating 95% CIs as proposed by Sahai and Khushid and Ulm (Sahai et al 1993, Ulm 1990, Section 9.9.2.2) was also used for estimating the 95% CIs for all combined

crude IRs. The CIs of combined age- and sex-standardized IRs were determined by the Dobson method (Dobson et al 1991) as described in Section 9.9.2.3.

Age- and sex-standardized IRs were also displayed graphically by safety event of interest, combined and stratified by exposure cohort and database and, on top of that, stratified by eligibility for linkage of hospital data in PHARMO, SIDIAP, CPRD in the pre-COVID and full study period.

Due to data regulations, so-called small-cell-count policies at Aarhus and CPRD, the number of safety events of interest or patients at risk was not available when the number of events or patients was less than five (although in case of Aarhus zero counts of events could be reported, see Section 9.9). Therefore, a range of the combined crude IRs was calculated, adding zero events to the number of events for calculating the lower combined crude IR (best-case scenario) and four events for the higher combined crude IR (worst-case scenario), when this was needed. For CPRD, up to eight events were included for the worst-case scenario in instances where cell counts were below five in both data subsets: without and with linked hospital data. In case the number of patients at risk were below five in a specific exposure cohort (in Aarhus or CPRD) but the PYs of these patients were available, the number of patients at risk were assumed to be four. When essential information for determining the IR is missing, two combined crude IRs (best-case and worst-case scenario) are shown. However, the number of safety events of interest and IRs for both these individual databases are not shown, if less than five events are registered. For calculation of combined age- and sex-standardized IRs, Aarhus and CPRD received aggregated data of the total number of patients (= the number of patients from all databases together) for each pre-defined 5-year age category and sex in each exposure cohort. With these data, Aarhus and CPRD calculated the study-based standard population and age- and sex-standardized rates for the safety event of interest per pre-defined 5-year age category per sex in each exposure cohort at their end. Both data partners provided PHARMO with the aggregated data to calculate the combined IRs as was described in Section 9.9.2.3. If the count of safety events was zero in CPRD, the age- and sex-standardized IRs were not allowed to be displayed.

9.9.2.6 Relative risk for exploratory analyses

The relative risk (HR and 95% CI) of angioedema ('narrow' definition, see Section 9.4.2) was estimated for sacubitril/valsartan versus ACEIs using the Cox regression model for each comparison specified in the exploratory objectives (see Section 7). The following comparisons between the exposure cohorts were performed in the pre-COVID period:

- Exposure cohort 2 versus exposure cohort 4 (patients initiating sacubitril/valsartan without prior exposure to ACEIs/ARBs versus patients using ACEIs without prior exposure to ACEIs/ARBs)
- Exposure cohort 1 versus exposure cohort 3 (patients initiating sacubitril/valsartan regardless of prior exposure to ACEIs/ARBs versus patients using ACEIs regardless of prior exposure to ACEIs/ARBs)
- Exposure cohort 1 versus exposure cohort 4 (patients initiating sacubitril/valsartan regardless of prior exposure to ACEIs/ARBs versus patients using ACEIs without prior exposure to ACEIs/ARBs)

Crude HRs and 95% CIs were only estimated in case of at least five events for the safety event angioedema ('narrow' definition) per comparison of exposure cohorts and database. Testing the proportional hazards assumption was not conducted as HRs from the Cox regression model can be interpreted as an average HR over the observed event time whenever the proportional hazards assumption is not satisfied. This is achieved through weighted estimation that allows suitable and interpretable average HRs to be obtained (Schemper et al 2009).

To control for confounding, potential confounders such as age, sex, pre-specified comorbidities, and co-medications (see Table 9-10) were introduced in the Cox regression model with overlap weighting (OW) based on propensity score (PS) (Li et al 2018, Li et al 2019, Mao et al 2018). Since the number of potential confounders was large relative to the expected number of the safety event of angioedema ('narrow' definition), PS rather than multivariable regression models were used for adjustment of the potential confounders. PS weighting was preferable over a PS matching approach as all patients were kept in the exposure cohorts of the study. With the PS matching approach, it was likely that patients would have been excluded due to unmatched controls (i.e., patients initiating sacubitril/valsartan without a matched patient using ACEIs). Consequently, these potential exclusions could have resulted in the exclusion of safety events of angioedema ('narrow' definition), and thereby a reduction in terms of precision and power.

Compared with other methods of PS weighting, the method of OWs has the following advantages:

1. The causal contrast estimated by this method is of natural interest because it emphasizes the portion of the population where the most treatment equipoise exists in clinical practice.
2. This method avoids the problem of instability of effect estimates due to extreme weights without excluding any patients from analysis.
3. OWs guarantee exact finite-sample balance of mean values of all covariates that will be included in the PS model even with model misspecification, thus reducing or eliminating the need for post-weighting balance diagnostics.
4. Treatment effect estimates based on the OWs have the smallest variance in the entire class of the PS-weighted estimators (Li et al 2018, Li et al 2019, Mao et al 2018).

To implement this approach, a logistic regression model was built to estimate the PS (i.e., probability to be treated with sacubitril/valsartan or ACEI) using the variables listed in Section 9.4.3 and Table 9-10.

Table 9-10 Predefined covariates for propensity score weighting

Characteristics	Details	Type of variables	Assessment window	Care settings	Databases	Pre-specified	Source for algorithm
Age	At index date – year of birth	Continuous	[0, 0]	n/a	All	Yes	n/a
Sex	Male, female	Categorical	[0, 0]	n/a	All	Yes	n/a
Ethnicity	White, Black, Other, Missing	Categorical	[-∞, 0]	n/a	CPRD	Yes	Mathur et al 2014
Hypertension	Present, not present	Binary	[-∞, 0]	out/in-patient	All	Yes	n/a

Characteristics	Details	Type of variables	Assessment window	Care settings	Databases	Pre-specified	Source for algorithm
Myocardial infarction	Present, not present	Binary	[-∞, 0]	out/in-patient	All	Yes	n/a
Stroke or TIA	Present, not present	Binary	[-∞, 0]	out/in-patient	All	Yes	n/a
Angina Pectoris	Present, not present	Binary	[-∞, 0]	out/in-patient	All	Yes	n/a
Atrial fibrillation	Present, not present	Binary	[-∞, 0]	out/in-patient	All	Yes	n/a
Valvular disease	Present, not present	Binary	[-∞, 0]	out/in-patient	All	Yes	n/a
Diabetes mellitus	Present, not present	Binary	[-∞, 0]	out/in-patient	All	Yes	n/a
Respiratory disease	Present, not present	Binary	[-∞, 0]	out/in-patient	All	Yes	n/a
Allergic reactions	Present, not present	Binary	[-∞, 0]	out/in-patient	All	Yes	n/a
CKD	Present, not present	Binary	[-∞, 0]	out/in-patient	All	Yes	n/a
Chronic hepatic disease	Use, no use	Binary	[-∞, 0]	out/in-patient	All	Yes	n/a
ACEIs	Use, no use; applicable for exposure cohort 1 and 3	Binary	[-365, -1]	Prescriptions	All	Yes	n/a
ARBs	Use, no use; Applicable for exposure cohort 1 and 3	Binary	[-365, -1]	Prescriptions	All	Yes	n/a
Other RAAS targeting drugs	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
Beta-blockers	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
CCBs	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
MRAs	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
Loop diuretics	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
Other diuretics	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
Digoxin	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
Ivabradine	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
Nitrates	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
Hydralazine	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
Antiarrhythmic agents	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
Anticoagulants	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
Antiplatelets	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
Lipid lowering drugs	Use, no use; Excluding statins	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
Statins	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
Antidiabetics	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
Fluoroquinolone	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a
NSAIDs	Use, no use	Binary	[-365, 0]	Prescriptions	All	Yes	n/a

Characteristics	Details	Type of variables	Assessment window	Care settings	Databases	Pre-specified	Source for algorithm
Number of cardiac drugs used in HF treatment	Number of cardiac drugs (based on ATC of active compounds) as proxy for the severity of HF; categorized as ≤ 3 and > 3	Categorical	[-365, 0]	Prescriptions	All	Yes	n/a

All databases = Aarhus, GePaRD, ARS, HSD, PHARMO, SIDIAP, and CPRD.

All safety events = angioedema [primary safety event of interest], hypotension [secondary safety event of interest], hyperkalemia [secondary safety event of interest], hepatotoxicity [secondary safety event of interest], renal impairment [secondary safety event of interest].

Note: All comorbidities were identified using specific codes based on coding system(s) used in each database(s) of interest (e.g., READ version 2, International Classification of Diseases, 9th or 10th revision [ICD-9-CM, or ICD-10-CM], ICD-10 German Modification [GM] codes, International Classification of Primary Care codes [ICPC]) v1993 and WCIA codes, as defined in the code list in Section 15.2.1-Table 2-8, Table 2-11, Table 2-14 to Table 2-22.

In PHARMO data, additional text searches of the GP electronic health records diagnostic text fields were applied, either to identify comorbidities that were not coded, or to further specify the ICPC codes that are not granular enough to differentiate between in- and exclusion criteria.

All medications were identified using the ATC codes from the Anatomical Therapeutic Chemical Classification and were mapped to Gemscript codes for CPRD.

Each patient was weighted by the method of OWs in which the weight was the probability of that patient being assigned to the opposite comparison exposure cohort (Li et al 2018, Li et al 2019) – i.e., the OWs for each patient were calculated as 1-PS for initiating sacubitril/valsartan and as PS for using ACEIs, respectively. A Cox regression model was then fitted comparing sacubitril/valsartan with ACEIs, while weighting by the OWs, and the HR (adjusted) was estimated. The 95% CIs for the HR (adjusted) was computed based on the robust variance estimator (Lin et al 1989, Lin 1994, Enders et al 2018).

For each exploratory objective, the diagnostics for assessing the balance of covariates (see Table 9-10) between patients initiating sacubitril/valsartan and patients using ACEIs was considered. All differences in these covariates of patients initiating sacubitril/valsartan and patients using ACEIs for the unweighted and weighted sample were quantified via SMDs or standardized differences as described in Section 9.9.2.1 (Austin 2009). A comparison of absolute standardized difference of unweighted means or proportions versus absolute standardized difference of weighted means or proportions is presented for each covariate for the comparative analyses conducted. By comparing diagnostics between the unweighted and weighted sample by the OWs an assessment was performed whether OW was implemented correctly, because OW would guarantee balance.

9.9.2.7 Meta-analysis of exploratory objectives

Comparisons between sacubitril/valsartan and ACEIs were performed per database. It was planned to conduct a meta-analysis for the comparative analyses if at least two databases contributed results. Since only one database delivered results no meta-analysis of the exploratory objectives was performed.

9.9.3 Missing values

Since the underlying data represent attended medical care, the assumption was that absence of information on clinical events or medication meant absence of that condition or medication. No imputations were done. Information on ethnicity was only available in CPRD, but still lacking for a large proportion of the patients (around 70%) and the proportion of black patients (relevant to the safety event angioedema) was < 0.5% of patients. Therefore, ethnicity was only included in the propensity score model for CPRD, including the missing values as a separate category.

9.9.4 Sensitivity Analyses

Sensitivity analyses were limited to the primary and secondary objectives, specifically the reporting of the crude and age- and sex-standardized IRs per database or combined for the safety event of interest.

9.9.4.1 Sensitivity Analysis: Misclassification of safety events

Safety events of interest were identified, using case-finding algorithms that included diagnostic codes (see Section 15.2.1-Table 2-2 to Table 2-7) for which coding systems differed per database and data source within a database), and NLP for the GP Database from the PHARMO Database Network (see Section 15.1.5). Additionally, confirmation algorithms were applied for codes identified in GePaRD (see Section 15.2.1-Table 3-1). As real-world data are not primarily collected for research purposes but for medical or administrative purposes, misclassification of safety events may have occurred and may have impacted the interpretation of the study results. Three sensitivity analyses were conducted to examine potential misclassification of angioedema and hypotensive events.

Angioedema

It is possible that not all events of angioedema were identified when using the 'narrow' definition of angioedema. In the validation study, the FNR of angioedema in hypersensitivity cases was ([redacted]) calculated as the proportion of hypersensitivity cases that were classified as confirmed angioedema cases based on the medical assessment). Based on the results of the validation study it seemed to be appropriate to consider patients with only a diagnostic code for anaphylactic shock as potentially missed angioedema cases. Cases coded as angioedema ('narrow' definition) and anaphylactic shock were therefore included as cases of angioedema in a sensitivity analysis.

Angioedema is not considered to be a chronic condition; because of this, the approach to consider only confirmed diagnoses (determined by one discharge diagnosis or two outpatient diagnoses from different physicians within up to three months) in GePaRD may have led to an underestimation of events of angioedema ('narrow' definition). Therefore, in a sensitivity analysis the identification of the safety events angioedema by confirmed diagnoses was expanded with unconfirmed diagnoses of angioedema in each exposure cohort in GePaRD, resulting in more potential cases of angioedema. In this analysis, patients with at least one recorded diagnosis of angioedema prior to index date in each exposure cohort were excluded. The unconfirmed diagnoses in this sensitivity analyses were applied to both: identification of the safety events of interest, as well as exclusion criteria.

Hypotension

The 'broad' definition of hypotension (see Section 9.4.2) was used in a sensitivity analysis to include symptoms indicative of potential hypotensive events.

9.9.4.2 Sensitivity Analysis: Potential COVID-19 pandemic impact

The primary analysis censored at the time of the COVID-19 pandemic on December 31, 2019. To examine the impact of the COVID-19 pandemic, sensitivity analyses were conducted where the primary and secondary objectives were examined for the full period, including the period in which the COVID-19 pandemic occurred (from 2020 onward).

9.9.4.3 Sensitivity Analysis: Impact of duration of prevalent ACEIs use on incidence rate of angioedema

In a subset of patients from exposure cohort 3 consisting of patients with prevalent ACEIs use at index date, a sensitivity analysis was conducted to calculate the IRs, thereby considering various prevalent ACEIs exposure periods prior to index date. Patients initiating ACEIs with prior exposure to ARBs were excluded from exposure cohort 3 for this analysis. The rationale for this analysis was that a shorter period of prior exposure to ACEIs may result in a higher risk of developing angioedema, because angioedema occurs most frequently shortly after start of a new treatment (Toh et al 2012). Longer exposure to ACEIs suggests that the patient is less likely susceptible for angioedema. The following periods of prevalent use prior to index date were assessed as mutually exclusive groups: 0< - < 8, 8 - < 26 weeks, and ≥ 26 weeks. From these categories, crude and age- and sex-standardized IRs were assessed from each database for the pre-COVID and the full study period. The same approach was applied to calculate these crude and age- and sex-standardized IRs and corresponding 95% CIs was used (see Section 9.9.2.2, Section 9.9.2.3, and Section 9.9.2.5).

9.9.4.4 Sensitivity Analysis: Impact of excluding SIDIAP data

In SIDIAP, the date of the dispensing was defined as the first day of the month. Because of this, there were implications: first, for diagnoses of interest (safety events of interest/ exclusion criteria) occurring in the first month of exposure to sacubitril/valsartan or ACEIs, the initiation of both treatments was assumed to precede the diagnosis although the opposite may be true. This may lead to incorrectly counting a diagnosis as a safety event although it would have qualified, as exclusion criterion had the exact exposure date been known. Second, dispensings for sacubitril/valsartan and ACEIs within the same month at index date were excluded and assumed non-adherent to the 36-hour wash-out period. To examine the impact of SIDIAP data on combined IRs, sensitivity analyses were conducted where combined crude and age- and sex-standardized IRs of the primary and secondary objectives were examined without data of SIDIAP. These sensitivity analyses were not prespecified in the protocol but added post-hoc.

9.9.5 Amendments to the statistical analysis plan

For the final LCZ696B2014 analysis, three versions of the statistical analysis plan (SAP v1.0 – 3.0) have been drafted. Changes in the SAPs have been documented by track changes. These changes have been included in SAP v2.0 and SAP v3.0 (see Section 15.1.4). The final analyses were conducted according to SAP v3.0.

9.10 Quality control

Standard operating procedures at each research center were used to guide the conduct of the study. These procedures included internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

Independent double programming of analyses was undertaken by Novartis based on the pre-specified SAP version 2.0 for the final report (see Section 15.1.4) and using SAS. During double programming process, necessary clarifications and changes to the SAP were documented in SAP version 3.0. Double-programming based on stated principles (available upon request) provided additional quality control of the results. Specifically, double programming in SAS also allowed checking each data step in the data analysis to examine if both programs provided the same number of patients in the study base and exposure cohorts, duration of exposure to sacubitril/valsartan or ACEIs, and the number of safety events of interest with the same data. Both SAS programs were then implemented by the data partners to generate aggregated data files for the final report.

The LCZ696B2014 study was double programmed by programmers that were not involved in either the LCZ696B2014 or LCZ696B2015 study at any time during the project. The programmers performed double programming with no access to the location where all statistical programs of the LCZ696B2014 study were stored, to ensure that the double programming was conducted independently. For the same reason, the programmer performing the product (main) programming had no access to the location where programs for the double programming activities were stored. All these locations were encrypted in such a way that the accessibility was limited to the programmer of interest (product versus quality check [QC] programmer). For creating the input files of the specific confirmed diagnoses in GePaRD, the BIPS team performed independent double programming of the inclusion of only confirmed diagnoses in these input files. These input files served as the basis for the diagnosis of HF, all safety events of interest, and comorbidities selection algorithms (see Section 9.3.2.1 for the HF selection algorithm, Section 9.4.3 for the comorbidity selection algorithm, and Section 9.4.2.2 for the safety event selection algorithms).

Results from the double programming were compared in a stepwise fashion, and any discrepancies in numbers were discussed and resolved between the data partner and an independent researcher from PHARMO, who was not the product or the QC programmer of the LCZ696B2014 study. Subsequently, the required changes were included in the product program and discussed with researchers from Novartis. Novartis could not influence these decisions, to avoid influence on the data analysis, but allowing quality control.

At PHARMO, all aggregated data files from each data partner were reviewed independently by a senior researcher with a statistical and programming background. The SAPs and the final report underwent quality control and senior scientific review.

10 Results

This section presents results of data from seven European electronic healthcare databases: Aarhus, ARS, GePaRD, HSD, PHARMO, SIDIAP, and CPRD. The study period for the

primary analyses (primary, secondary, and exploratory objectives) ended on December 31, 2019 for all databases (i.e., pre-COVID period).

10.1 Participants

Details regarding the size of the source populations, the size of the study bases, and the size of the populations included in the four exposure cohorts of interest across all databases can be found in Table 10-1 or Section 15.2.1-Table 1-6.

During the full study period, the source population included a total of 41,383,318 patients across seven databases. Three out of the seven databases (i.e., PHARMO, SIDIAP, CPRD) could partially link primary care with hospital records and these captured 9,467,308 patients (23% of the total source population) without linked hospital data and 4,906,147 with linked hospital data (12% of the total source population). For these three databases data is presented separately for these two subgroups (without linked hospital data and with hospital data).

The overall study base of adult patients either initiating sacubitril/valsartan or using an ACEI during the study period, included 5,049,696 patients (12% of the source population). After application of all exclusion criteria, the study base for the endpoints of angioedema, hypotension and hyperkalemia comprised a total of 676,505 patients. Most users of ACEIs or sacubitril/valsartan were excluded because of lack of a heart failure diagnosis. No patients younger than 18 years were excluded from GePaRD and CPRD with hospital linkage, as in CPRD only linked HES data and in GePaRD dispensing data from patients 18 years or older were received. The database subset without linked hospital data (PHARMO, SIDIAP, CPRD) included 54,390 patients and 43,430 patients were included in these database subsets with linked hospital data.

Of the 676,505 in the study base, 119,041 (18%) patients had a record of hepatotoxic event or hepatic morbidities without a defined cause [e.g., “hepatitis unspecified”] or suggestive of another etiology at any time prior to, at, or seven days after the index date. A record of chronic renal disease or renal impairment any time prior to index date was observed in 24% (n=165,477) of patients in the study base. These patients were excluded from the analysis of these respective safety events.

Of those in the study base, 39,616 (6%) patients initiating sacubitril/valsartan were included in exposure cohort 1 and less than one percent (n=4,548) in exposure cohort 2.
In exposure cohorts 3 and 4, 642,689 (95%) and 164,088 (24%) patients using ACEIs, respectively, were identified from the study base (see Table 10-1 or Section 15.2.1-Table 1-6).
The majorities of participants in exposure cohort 1 (76%), 2 (80%), 3 (75%), and 4 (76%) were from GePaRD, followed by ARS (6%, 6%, 8%, and 8%, respectively) and SIDIAP (9%, 10%, 7%, and 6% respectively for with and without linked hospital data combined).
More details on the selection of the study base in each database can be found in Section 15.2.1-Table 1-1.

10.1.1 Patients initiating sacubitril/valsartan

10.1.1.1 Patients initiating sacubitril/valsartan – regardless of prior exposure to ACEIs/ARBs (exposure cohort 1)

In the pre-COVID period, the total number of patients initiating sacubitril/valsartan (exposure cohort 1) in the study base across all databases was 39,616, of whom 30,160 (76%) were identified in GePaRD. A total of 19,036 patients (48%) in exposure cohort 1 were also included in exposure cohort 3 (ACEIs cohort) at an earlier time point during the study period. Patients were excluded due to potential non-adherence of the 36-hour washout period. From the study base, 851 patients (2% of patients initiating sacubitril/valsartan) were excluded because of concurrent prescriptions for sacubitril/valsartan and ACEI at the index date indicating non-adherence with the 36-hour washout period. Most patients (n=648; 76%) were contributed by SIDIAP where only the month and year of dispensing were known and dispensings issued in the same month were assumed to have occurred on the same day.

In the pre-COVID period, there were 31,815 patients with no diagnostic code for hepatotoxic event or hepatic morbidities without a defined cause [e.g., “hepatitis unspecified”] or suggestive of another etiology at any time prior to, at, or seven days after the index date and 25,690 patients with no diagnostic code for chronic renal disease or renal impairment any time prior to index date. Thus, these represent the sizes of sacubitril/valsartan cohorts for the endpoints of hepatotoxicity and renal impairment, respectively.

The total number of patients included in exposure cohort 1 for the full study period (including COVID time), and included in the sensitivity analysis, was 44,416. For details on the selection of the sacubitril/valsartan exposure cohort 1 by database for the pre-COVID and full study period, see Section 15.2.1-Table 1-2 and Section 15.2.1-Table 1-4.

10.1.1.2 Patients initiating sacubitril/valsartan – treatment-naïve to ACEIs/ARBs (exposure cohort 2)

Of the 39,616 patients included in the sacubitril/valsartan cohort 1 from all databases in the pre-COVID period, 4,548 (11% relative to exposure cohort 1; n=3,625 [80%] from GePaRD) were identified as treatment-naïve to ACEIs/ARBs (defined as no use in the 365 days prior to index date) and formed exposure cohort 2.

Details on the selection of patients qualifying for exposure cohort 2 by database for the pre-COVID period can be observed in Section 15.2.1-Table 1-4.

Table 10-1 Size of the source populations, study bases, and the four exposure cohorts of interest per database and combined in the pre-COVID period

		Aarhus (DK)[#]	ARS (IT)	GePaRD (DE)	HSD (IT)	PHARMO (NL)		SIDIAP (ES)		CPRD (UK)	
	Total All databases					**Without linked hospital data**	**With linked hospital data**	**Without linked hospital data**	**With linked hospital data**	**Without linked hospital data**	**With linked hospital data**
Source population – all patients in the database during the study period (N)	**41,383,318**	**1,664,972**	**3,967,325**	**19,972,014**	**1,405,552**	**248,105**	**1,561,697**	**4,711,743**	**1,822,508**	**4,507,460**	**1,521,942**
Study base[*]: Initiating either sac/ val or ACEIs during pre-COVID period[††] (N)	**676,505**	**15,193**	**57,514**	**497,082**	**8,896**	**2,070**	**12,598**	**30,005**	**17,169**	**19,465**	**11,967**
Exposure cohorts of interest (N)											
exposure cohort 1	**39,616**	**544**	**2,557**	**30,160**	**499**	**107**	**503**	**2,309**	**1,238**	**1,426**	**273**
exposure cohort 2	4,548	#	266	3,625	64	8	33	334	136	63	19
exposure cohort 3	**642,689**	**13,691**	**52,539**	**481,226**	**8,071**	**1,860**	**11,615**	**28,156**	**16,155**	**17,717**	**11,659**
exposure cohort 4	164,088	4,632	12,825	124,872	1,789	477	3,308	6,165	3,559	4,161	2,300

#To comply with Danish data protection regulations, the number of patients less than five per cell and data that can trace less than five patients per cell are not shown.

[††]Pre-COVID period is defined as the period with the end date of December 31, 2019.

[*]The number of patients after all exclusion criteria as described in Section 15.2.1 – Table 1-1 were applied.

10.1.2 Patients using ACEIs

10.1.2.1 Patients using ACEIs - regardless of prior exposure to ACEIs/ARBs (exposure cohort 3)

The total number of patients using ACEIs in the study base across all databases was 642,689 in the pre-COVID period. Of these patients 481,226 (75%) were identified in GePaRD. In exposure cohort 3 in the pre-COVID period, 528,921 patients had no diagnostic code for a hepatotoxic event or for hepatic morbidities without a defined cause [e.g., "hepatitis unspecified"] or suggestive of another etiology at any time prior to, at, or seven days after the index date, and 487,520 patients had no code for chronic renal disease or renal impairment any time prior to index date. Thus, these represent the sizes of ACEI cohorts for the endpoints of hepatotoxicity and renal impairment, respectively.

The total number of patients included in exposure cohort 3 for the full study period (including the COVID period), and included in the sensitivity analysis, was 652,689.

For full details on the selection of the ACEIs cohort 3 by database in the pre-COVID and full study period, see Section 15.2.1-Table 1-3 and Section 15.2.1-Table 1-5.

10.1.2.2 Patients using ACEIs – treatment-naïve to ACEIs/ARBs (exposure cohort 4)

Of the 642,689 patients using ACEIs qualifying for exposure cohort 3 identified in all databases in the pre-COVID period, 164,088 (26% relative to exposure cohort 3; 124,872 [76%] from GePaRD) were identified as treatment-naïve to ACEIs/ARBs (defined as no use in the 365 days prior to index date) and formed exposure cohort 4.

For details on the selection of the ACEIs cohort 4 by database, see Section 15.2.1-Table 1-5.

10.1.3 Enrollment and treatment duration, and reason for end of follow-up in the exposure cohorts – pre-COVID period

The enrollment time (defined as the time between the date of enrollment in the database and index date; the look-back period) and the duration of treatment during follow-up (weeks) in different exposure cohorts in the pre-COVID period are presented in Section 15.2.1-Table 1-7.

The mean enrollment time for the patients initiating sacubitril/valsartan (exposure cohort 1) in the pre-COVID period was approximately 13 years (676 weeks) across all databases. Among these patients the mean treatment duration during follow-up was 51 weeks in all databases, with the lowest mean duration (37 weeks) in HSD and the highest mean duration (57 weeks) in Aarhus. Across all databases, more than 81% of the patients in exposure cohort 1 were treated with sacubitril/valsartan for more than eight weeks and 61% were followed until the end of the follow-up period.

For patients initiating sacubitril/valsartan treatment who were naïve to ACEIs/ARBs (exposure cohort 2), the mean enrollment time was almost 13 years (662 weeks). In the 4,548 patients in this exposure cohort the mean sacubitril/valsartan treatment duration during follow-up was less than a year (40 weeks) in all databases, with the lowest mean duration (28 weeks) in HSD and

CPRD without linked hospital data, and the highest mean duration (111 weeks based on less than five patients) in Aarhus. The proportion of patients with a sacubitril/valsartan treatment duration shorter than eight weeks was 24%. Most patients in exposure cohort 2 were followed until the end of follow-up (57% in all databases).

The mean enrollment time in patients using ACEIs (prevalent or incident) in exposure cohort 3 from all databases was almost 12 years (608 weeks). The mean treatment duration of ACEIs in exposure cohort 3 was 71 weeks starting from index date until the end of follow-up across all databases, with the lowest mean duration (66 weeks) in GePaRD, and the highest mean duration (110 weeks) in CPRD without linked hospital data.

Approximately 57% of patients in exposure cohort 3 discontinued all RAAS treatment during follow-up. This was mainly driven by the high number of patients who discontinued RAAS treatment in GePaRD (63%).

In exposure cohort 4 (new users of ACEIs), the mean enrollment time was similar as in exposure cohort 3 (approximately 12 years; 643 weeks). The mean treatment duration among patients using ACEIs in exposure cohort 4 was 37 weeks during follow-up across all databases, with the lowest mean duration (33 weeks) in GePaRD, and the highest mean duration (62 weeks) in Aarhus and CPRD without linked hospital data.

The proportion of patients with a treatment duration shorter than eight weeks in exposure cohort 4 was 36%. In exposure cohort 4 almost 58% of the patients in all databases discontinued all RAAS treatment which was mainly driven by the high number of discontinuers in GePaRD (63%) (see Section 15.2.1-Table 1-7).

10.2 Descriptive data

10.2.1 Baseline characteristics in the pre-COVID period

The baseline characteristics in the four exposure cohorts in all databases combined and the corresponding SMD values for the various exposure cohort comparisons are presented in Table 10-2 and described in Sections 10.2.1.1 to Section 10.2.1.5. The age distribution per sex in each exposure cohort, separately per database, and combined in the pre-COVID period, is described in Section 15.2.1-Table 1-9 in pre-defined categories. Baseline characteristics of patients initiating sacubitril/valsartan and ACEIs in the defined exposure cohorts in the pre-COVID period are detailed, per database in Section 15.2.1-Table 1-11 to Section 15.2.1-Table 1-20.

Table 10-2 Baseline characteristics of patients initiating sacubitril/valsartan versus patients using ACEI in the combined databases – pre-COVID period

Pre-COVID period††	Exposure cohort 1* sac/val all N = 39,616	Exposure cohort 2*‡ sac/val naïve N = 4,548	Exposure cohort 3* ACEI all N = 642,689	Exposure cohort 4* ACEI naïve N = 164,088	SMD Exposure cohort 2 versus exposure cohort 4	SMD Exposure cohort 1 versus exposure cohort 3	SMD Exposure cohort 1 versus exposure cohort 4
Age (years), n (%)±							
18-44	997 (3)	219 (5)	10,490 (2)	4,835 (3)			
45-64	9,384 (24)	1,306 (29)	118,718 (18)	37,164 (23)			
65-74	10,312 (26)	971 (21)	145,246 (23)	35,295 (22)			
75+	18,923 (48)	2,044 (45)	368,235 (57)	86,794 (53)			
Mean (SD)	72 ± 12	70 ± 14	74 ± 12	73 ± 13	-0.04	-0.04	-0.02
Min, max	19-105	20-105	18-118	18-118			
Sex, n (%)					.	.	.
Male	28,066 (71)	2,968 (65)	342,377 (53)	83,734 (51)	0.29	0.37	0.41
Female	11,550 (29)	1,580 (35)	300,312 (47)	80,354 (49)			
Ethnicity, n (%)§	**N = 1,695**	**N = 78**	**N = 29,376**	**N = 6,461**	.	.	.
White	728 (43)	30 (38)	15884 (54)	3213 (50)	0.44	0.27	0.17
Black	5 (0)	0 (0)	159 (1)	37 (1)	.	.	.
Other	18 (1)	0 (0)	486 (2)	120 (2)	.	.	.
Missing	944 (56)	48 (62)	12847 (44)	3091 (48)	.	.	.
Comorbidities, n (%)					.	.	.
Hypertension	31,872 (80)	2,905 (64)	529,664 (82)	115,591 (70)	-0.14	-0.05	0.23
Myocardial infarction	14,473 (37)	1,197 (26)	139,124 (22)	32,335 (20)	0.16	0.33	0.38
Stroke or TIA	9,059 (23)	842 (19)	141,620 (22)	32,135 (20)	-0.03	0.02	0.08
Angina pectoris	8,349 (21)	640 (14)	100,282 (16)	20,743 (13)	0.04	0.14	0.23
Atrial fibrillation	19,012 (48)	1,934 (43)	206,544 (32)	48,942 (30)	0.27	0.33	0.38
Valvular disease	17,719 (45)	1,669 (37)	189,060 (29)	44,403 (27)	0.21	0.32	0.37
Diabetes mellitus	17,065 (43)	1,436 (32)	231,471 (36)	43,920 (27)	0.11	0.14	0.35
Asthma, COPD	11,199 (28)	1,167 (26)	148,481 (23)	38,040 (23)	0.06	0.12	0.12

Pre-COVID period††	Exposure cohort 1* sac/val all N = 39,616	Exposure cohort 2*‡ sac/val naïve N = 4,548	Exposure cohort 3* ACEI all N = 642,689	Exposure cohort 4* ACEI naïve N = 164,088	SMD Exposure cohort 2 versus exposure cohort 4	SMD Exposure cohort 1 versus exposure cohort 3	SMD Exposure cohort 1 versus exposure cohort 4
Allergic reactions	8,145 (21)	896 (20)	121,483 (19)	33,979 (21)	-0.03	0.04	0.00
CKD	13,084 (33)	1,189 (26)	142,986 (22)	28,157 (17)	0.22	0.24	0.37
Chronic hepatic disease	7,514 (19)	813 (18)	109,777 (17)	26,627 (16)	0.04	0.05	0.07
Co-medications in the year before the index date, n (%)					.	.	.
ACEIs (excluding index date)	21,587 (54)	0 (0)	431,893 (67)	0 (0)	n.a.	-0.26	n.a.
ARBs (excluding index date)	14,824 (37)	0 (0)	47,555 (7)	0 (0)	n.a.	0.77	n.a.
RAAS other	95 (<0.5)	48 (1)	875 (<0.5)	351 (<0.5)	0.11	0.02	0.01
Beta-blockers	36,142 (91)	3,776 (83)	449,336 (70)	107,715 (66)	0.41	0.56	0.65
Calcium channel blockers	8,935 (23)	534 (12)	196,241 (31)	34,212 (21)	-0.25	-0.18	0.04
MRAs	26,955 (68)	2,691 (59)	114,692 (18)	30,419 (19)	0.92	1.18	1.15
Loop diuretics	32,217 (81)	3,449 (76)	313,794 (49)	78,177 (48)	0.61	0.73	0.75
Other diuretics	11,672 (29)	698 (15)	207,906 (32)	30,152 (18)	-0.08	-0.06	0.26
Digoxin	1,636 (4)	137 (3)	21,774 (3)	4,579 (3)	0.01	0.04	0.07
Ivabradine	3,066 (8)	301 (7)	10,632 (2)	2,073 (1)	0.28	0.29	0.32
Nitrates	5,661 (14)	402 (9)	67,276 (10)	12,616 (8)	0.04	0.12	0.21
Hydralazine	181 (<0.5)	40 (1)	1,061 (<0.5)	285 (<0.5)	0.10	0.05	0.05
Antiarrhythmic agents	5,649 (14)	529 (12)	34,965 (5)	8,685 (5)	0.23	0.30	0.31
Anticoagulants	22,447 (57)	2,353 (52)	236,261 (37)	60,527 (37)	0.30	0.41	0.40
Antiplatelets	16,067 (41)	1,530 (34)	221,577 (34)	54,557 (33)	0.01	0.13	0.15
Statins	25,173 (64)	2,159 (47)	321,911 (50)	68,823 (42)	0.11	0.27	0.44
Lipid lowering drugs (excluding statins)	3,800 (10)	246 (5)	27,056 (4)	5,078 (3)	0.11	0.21	0.27
Cardiac medications (>3) used in the treatment of HF (proxy for HF severity)	17,464 (44)	771 (17)	53,817 (8)	8,642 (5)	0.38	0.89	1.01

Pre-COVID period††	Exposure cohort 1* sac/val all N = 39,616	Exposure cohort 2*‡ sac/val naïve N = 4,548	Exposure cohort 3* ACEI all N = 642,689	Exposure cohort 4* ACEI naïve N = 164,088	SMD Exposure cohort 2 versus exposure cohort 4	SMD Exposure cohort 1 versus exposure cohort 3	SMD Exposure cohort 1 versus exposure cohort 4
Antidiabetics	12,230 (31)	992 (22)	154,802 (24)	27,001 (16)	0.14	0.15	0.34
Fluoroquinolones	4,965 (13)	543 (12)	87,649 (14)	21,100 (13)	-0.03	-0.03	-0.01
NSAIDs	9,392 (24)	1,075 (24)	185,735 (29)	47,456 (29)	-0.12	-0.12	-0.12

ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; sac/val = sacubitril/valsartan; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CPRD = Clinical Practice Research Datalink; HF = heart failure; MRAs = mineralocorticoid receptor antagonists; n.a. = not applicable; NSAIDs = non-steroidal anti-inflammatory drugs; RAAS = renin-angiotensin-aldosterone system; SD = standard deviation; SMD = Standardized mean difference; TIA = transient ischemic attack.

*For assessing the characteristics of patients of all databases together, the characteristics of databases with less than five patients were considered as zero.

‡For assessing the total number of patients in exposure cohort 2, the number of patients in Aarhus was considered as zero.

§Ethnicity is partially available, only in CPRD.

°For one patient in the CPRD, the date of birth is disputable (see Section 15.2.1 – Table 1-21).

Source: Section 15.2.1 Table 1-21.

10.2.1.1 Baseline characteristics of patients initiating sacubitril/valsartan – regardless of prior exposure to ACEIs/ARBs (exposure cohort 1)

The 39,616 patients who initiated treatment with sacubitril/valsartan in exposure cohort 1 during the pre-COVID period were between 19 and 105 years of age across all databases. The mean age was 72 across databases and ranged from 67 in Aarhus to 72 years in GePaRD. Approximately 71% of patients in exposure cohort 1 were male, ranging from 70% in GePaRD to 81% in PHARMO for patients without linked hospital data. The most frequently recorded comorbidities across all databases were hypertension, atrial fibrillation, valvular disease, and myocardial infarction specifically in database subsets including hospital linkage. In addition, CKD and diabetes mellitus was frequently recorded but not specifically in databases including hospital data. Overall, the proportion of patients with a diagnosis of any of the pre-selected comorbidities was considerably higher in GePaRD compared to the other databases. This was particularly true for hypertension (89% versus 33-75% in the other databases) and chronic hepatic disease (23% versus 2-16%), but also for stroke or TIA (26% versus 11-17%). In ARS, HSD, and SIDIAP, lipid lowering drugs, excluding statins were more frequently used than in other databases. The use of co-medication in the year prior to or at index date was high, particularly for MRAs, loop diuretics, beta blockers, and statins (see Table 10-2 and per database in Section 15.2.1-Table 1-11 to Section 15.2.1-Table 1-20).

10.2.1.2 Baseline characteristics of patients initiating sacubitril/valsartan – treatment-naïve to ACEIs/ARBs (exposure cohort 2)

Information on the baseline characteristics for patients in exposure cohort 2 from Aarhus cannot be presented as the number of patients was below five. The restriction of patients initiating sacubitril/valsartan (exposure cohort 1) to those naïve to ACEIs/ARBs in the 365 days prior to index date (exposure cohort 2) did not alter the age range (20-105 years of age), however, it resulted in some changes in the distribution of certain covariates. Cardiovascular comorbidity was less frequently observed in exposure cohort 2 when compared to exposure cohort 1, but it is noteworthy that there was a difference in the sex distribution between exposure cohort 1 (71% male) and exposure cohort 2 (65% male). Regarding co-medications, a reduction was observed in the use of cardiovascular medications. Overall, among the most frequently used co-medication, their prescription was lower in exposure cohort 2 compared to exposure cohort 1: beta-blockers (83% versus 91%), MRAs (59% versus 68%), loop diuretics (76% versus 81%), anti-platelets (34% versus 41%), and statins (47% versus 64%) (see Table 10-2 and Section 15.2.1-Table 1-21 and per database in Section 15.2.1-Table 1-11 to Section 15.2.1-Table 1-20).

10.2.1.3 Baseline characteristics of patients using ACEIs regardless of prior exposure to ACEIs/ARBs (exposure cohort 3)

The age distribution of the 642,689 patients using ACEIs in exposure cohort 3 was between 18 and 118 years across all databases. Of that one patient aged 118 years, the date of birth is disputable. The mean age was 74 across databases and ranged from 70 in Aarhus to 78 years in SIDIAP without hospital linkage. Approximately 53% of patients were male, ranging from 48% in SIDIAP without hospital linkage, to 68% in Aarhus. The most frequently recorded comorbidities across all databases were hypertension and diabetes mellitus, with highest

proportions in GePaRD. In database subsets including hospital linkage, the most frequently recorded comorbidities tended to include atrial fibrillation in addition to hypertension. Besides the high use of ACEIs in the year prior to index date, co-medication use in the year prior to or at index date was high, particularly use of loop diuretics, beta blockers, and statins (see Table 10-2 and per database in Section 15.2.1-Table 1-11 to Section 15.2.1-Table 1-20).

10.2.1.4 Baseline characteristics of patients using ACEIs without prior use of ACEIs/ARBs (exposure cohort 4)

The restriction of patients using ACEIs in exposure cohort 3 to patients without prior use of ACEIs/ARBs in the 365 days prior to index date (exposure cohort 4; 164,088 patients) did not alter the age range (18-118 years of age) nor significantly altered the sex distribution (51% male) of the patients in the exposure cohort. In general, there were also no differences observed between exposure cohorts 3 and 4 regarding cardiovascular comorbidities prior to index date across all databases, though hypertension was less frequent in exposure cohort 4 (70% versus 82%). Patients in exposure cohort 4 had a similar frequency of use of most of the cardiovascular co-medications to patients in exposure cohort 3, but were less frequently using statins (42% versus 50% in exposure cohort 3), calcium channel blockers (21% versus 31%), other diuretics (18% versus 32%), and antidiabetic drugs (16% versus 24% in exposure cohort 3) (see Table 10-2 and per database in Section 15.2.1-Table 1-11 to Section 15.2.1-Table 1-20).

10.2.1.5 Comparison of patients from the sacubitril/valsartan (exposure cohort 1 and 2) to those in the ACEIs cohorts (exposure cohort 3 and 4)

There were differences in the distribution of some variables between patients initiating sacubitril/valsartan (exposure cohorts 1 and 2) and patients using ACEIs (exposure cohorts 3 and 4) and the extent of those differences varied by database. Generally, patients in the sacubitril/valsartan cohorts (compared to ACEI cohorts) tend to be younger, and were more often reported to be male, to have CKD, atrial fibrillation, valvular disease, and myocardial infarction. They were also more likely to use MRAs, loop diuretics, beta-blockers, antiarrhythmic agents, anticoagulants, ivabradine, statins, antidiabetic drugs, and lipid-lowering drugs. The imbalance in the distribution of these variables was the largest for MRAs, loop diuretics, and beta-blockers. There were no noteworthy differences in ethnicity between the sacubitril/valsartan cohorts (exposure cohort 1 and 2) and ACEIs cohorts (exposure cohort 3 and 4) in CPRD, although there was less missing information in exposure cohort 3 and 4 (Table 10-2).

Comparison of patients who newly started sacubitril/valsartan (exposure cohort 2) to those who newly started ACEIs (exposure cohort 4)

Differences were observed in the proportion of men, with exposure cohort 2 having a higher proportion of men than exposure cohort 4 across all databases (65% versus 51%; SMD = 0.29). There were also differences between the exposure cohorts in terms of comorbidities. Atrial fibrillation was more common in exposure cohort 2 than exposure cohort 4 (43% versus 30%; SMD = 0.27), particularly in Aarhus (SMD = 1.89) and GePaRD (SMD = 0.33) but was less common in exposure cohort 2 than in exposure cohort 4 in CPRD with linked hospital data (SMD = -0.23). Valvular disease was more common in exposure cohort 2 than in exposure

cohort 4 (37% versus 27%; SMD = 0.21), especially in GePaRD (SMD = 0.21), ARS (SMD = 0.33), SIDIAP with linked hospital data (SMD = 0.23), and in PHARMO without linked hospital data (SMD = 0.25), but in Aarhus and CPRD with linked hospital data this was the opposite (SMD = -0.54 and SMD = -0.21, respectively). In all databases, apart from CPRD and PHARMO without linked hospital data (SMD = 0.01, SMD = -0.30, and SMD = -0.94, respectively), myocardial infarction was more often reported in exposure cohort 2 than in exposure cohort 4 (26% versus 20%; SMD = 0.16). The greatest co-medication differences between exposure cohorts 2 and 4 were observed for MRAs (59% versus 19%; SMD = 0.92), loop diuretics (76% versus 48%; SMD = 0.61), and beta-blockers (83% versus 66%; SMD = 0.41) across all databases combined. Other co-medications with large differences between these exposure cohorts were anticoagulants, antiarrhythmic agents, and ivabradine (52% versus 37%; SMD = 0.30, 12% versus 5%; 0.23, 7% versus 1%; 0.28, respectively). In exposure cohort 2, more patients were prescribed with more than three cardiac medications than patients in exposure cohort 4 (17% versus 5%; SMD = 0.38) (see Table 10-2 and Section 15.2.1-Table 1-11 to Section 15.2.1-Table 1-20 for database- or subset-specific results).

Comparison of patients who newly started sacubitril/valsartan (regardless of prior exposure to ACEIs/ARBs; exposure cohort 1) to those with ACEIs exposure (exposure cohort 3)

Differences were also observed between exposure cohorts 1 and 3 in the proportions of males included (SMD =0.37); in all databases, exposure cohort 1 had 71% males, and exposure cohort 3 had 53% males. Aarhus had slightly more males in exposure cohort 1 (79%) and exposure cohort 3 (68%). The relative distributions of comorbid diagnoses were higher in exposure cohort 1 than 3, with myocardial infarction (37% versus 22%), atrial fibrillation (48% versus 32%), and valvular disease (45% versus 29%) showing SMDs around 0.30 The largest differences between exposure cohorts 1 and 3 were observed for co-medication variables, including MRAs (68% versus 18%; SMD = 1.18), HF severity (i.e., using more than 3 cardiac medications; 44% versus 8%; SMD = 0.89), ARBs (37% versus 7%; SMD = 0.77), loop diuretics (81% versus 49%; SMD = 0.73), and beta blockers (91% versus 70%; SMD = 0.56) (see Table 10-2 and Section 15.2.1-Table 1-11 to Section 15.2.1-Table 1-20).

Comparison of patients who newly started sacubitril/valsartan (regardless of prior exposure to ACEIs/ARBs; exposure cohort 1) to those who newly started ACEIs (exposure cohort 4)

Comparisons between patients from exposure cohort 1 and exposure cohort 4 show that the proportion of men was higher in exposure cohort 1 (overall 71% versus 51%; SMD = 0.41) and the mean age was similar for both exposure cohorts (exposure cohort 1, 72 years; exposure cohort 4, 73 years; SMD = -0.02). Compared to exposure cohort 4 there were more patients with valvular disease, myocardial infarction, and atrial fibrillation present in exposure cohort 1 across databases (45% versus 27%; SMD = 0.37, 37% versus 20%; SMD = 0.38, and 48% versus 30%; SMD = 0.38, respectively). These differences were not exhibited in all databases: with HSD, PHARMO without linked hospital data, SIDIAP without linked hospital data, and CPRD showing similar proportions for valvular disease (SMDs between -0.02 and 0.10), with HSD for myocardial infarction (SMD = 0.08), and with PHARMO, SIDIAP without linked hospital data, and CPRD with linked hospital data (SMDs between 0.04 and 0.09) for atrial

fibrillation. The presence of diabetes mellitus prior to index date was higher in exposure cohort 1 than in exposure cohort 4 in all databases (43% versus 27%; SMD = 0.35) except for PHARMO without linked hospital data (SMD = -0.05). Patients with CKD were more prevalent in exposure cohort 1 than in exposure cohort 4 (33% versus 17%; SMD = 0.37), although Aarhus, PHARMO, and SIDIAP without linked hospital data, showed similar proportions in both exposure cohorts (SMDs between 0.01 and 0.09). The largest differences between exposure cohort 1 and 4 were also observed in co-medication use; MRAs (68% versus 19%; SMD =1.15), HF severity (i.e., using more than 3 cardiac medications; 44% versus 5%; SMD = 1.01), loop diuretics (81% versus 48%; SMD = 0.75), and beta blockers (SMD = 0.65). Approximately 91% of patients used beta-blockers in exposure cohort 1, whereas beta-blocker use in exposure cohort 4 ranged from 56% in SIDIAP without linked hospital data to 73% in CPRD with linked hospital data. Statins, lipid lowering drugs, anticoagulants, antiarrhythmic agents, and antidiabetic drugs were also more often used in exposure cohort 1 than in exposure cohort 4 in all databases (64% versus 42%; SMD = 0.44, 10% versus 3%; SMD = 0.27, 57% versus 37%; SMD = 0.40, 14% versus 5%; SMD = 0.31, and 31% versus 16%; SMD = 0.34, respectively). Across the databases combined, observed differences in the use of MRAs and ivabradine between exposure cohort 1 and exposure cohort 4 (68% versus 19%, and 8% versus 1%, respectively) were more pronounced than the differences between exposure cohort 2 and exposure cohort 4 (59% versus 19% and 7% versus 1%, respectively) (see Table 10-2 and Section 15.2.1-Table 1-11 to Section 15.2.1-Table 1-20).

10.3 Outcome data

Outcome data during the pre-COVID period are included in Table 10-3 and Section 15.2.1-Table 1-33 to Section 15.2.1-Table 1-37. Because of their small-cell-count policies, Aarhus and CPRD are not permitted to show safety events of interest per exposure cohort and not patients at risk in exposure cohort 2, whenever cell counts are less than five. When this occurred, the numbers of less than five patients at risk or events are displayed as # in Aarhus and less than five in CPRD. Aarhus is permitted to show zero count of events whereas CPRD is not.

10.4 Main results

Based on the outcome data as presented in Table 10-3 and Section 15.2.1-Table 1-33, Section 15.2.1-Table 1-34 to Section 15.2.1-Table 1-37 (see Section 10.3), the crude and age- and sex-standardized IRs for each exposure cohort were calculated. Because of required concealing of small numbers of events in presenting data from Aarhus and CPRD, the crude combined IRs and 95% CIs are presented for the best-case and worst-case scenario. This was not performed for the age- and sex-standardized IRs as the actual numbers of the safety events of interest were not traceable.

Figures of age- and sex-standardized IRs by database and combined for the safety event of interests in the pre-COVID period are displayed in Figure 10-1 to Figure 10-5 (or Section 15.2.1-Figure 1-1 to Section 15.2.1-Figure 1-5).

Note: Crude and age- and sex-standardized IRs identified across each database and combined databases for the safety event of interests in the full study period were calculated as part of a sensitivity analysis and are presented in Section 10.5.

10.4.1 Primary and secondary objectives: incidence rates of angioedema ('narrow' definition)– [primary safety event of interest]

10.4.1.1 Incidence rates of angioedema ('narrow') in exposure cohort 1

In exposure cohort 1 (patients initiating sacubitril/valsartan regardless of prior ACEIs/ARBs use), there was a total of 22 (zero cases in CPRD [best-case scenario]) or 30 (eight cases in CPRD [worst-case scenario]) recorded events of angioedema across all databases, resulting in a combined crude IR of 0.6 (95% CI 0.4-0.9) per 1,000 PYs for the best-case scenario and 0.8 (95% CI 0.5-1.1) per 1,000 PYs for the worst-case scenario, respectively. There were 21 events of angioedema identified anytime during exposure in GePaRD, and one event in ARS, with corresponding crude IRs of 0.7 (95% CI 0.4-1.1) per 1,000 PYs and 0.4 (95% CI 0.0-2.5) per 1,000 PYs, respectively. In CPRD there were less than five events in both subsets (with and without linked hospital data), which were redacted due to small-cell-count policies. In all other databases no event of angioedema in exposure cohort 1 was observed. The combined age- and sex-standardized IR of angioedema was 0.6 (95% CI 0.4-0.9) per 1,000 PYs, corresponding to the combined crude IR of the best-case scenario. The age- and sex-standardized IRs of angioedema were almost similar in GePaRD and ARS and were 0.7 (95% CI 0.5-1.1) per 1,000 PYs in GePaRD and 0.5 per 1,000 PYs (less than ten events) in ARS, respectively (see Table 10-3, Figure 10-1, Section 15.2.1-Table 1-34, and Section 15.2.1-Figure 1-1).

10.4.1.2 Incidence rates of angioedema ('narrow') in exposure cohort 2

In exposure cohort 2 (patients initiating sacubitril/valsartan without prior exposure to ACEIs/ARBs), there were between three (zero cases in CPRD [best-case scenario]) and 11 (eight cases in CPRD [worst-case scenario]) angioedema events in all databases. Combined crude IRs of angioedema for the best-case and worst-case scenario were 0.9 (95% CI 0.2-2.5) and 3.1 (95% CI 1.6-5.6) per 1,000 PYs, respectively. In total, three events of angioedema were for certain identified anytime during exposure to sacubitril/valsartan, all within GePaRD. The corresponding crude IR was 1.1 (95% CI 0.2-3.1) per 1,000 PYs. The combined age- and sex-standardized IR was 0.9 (less than ten events), equal to the combined crude IR of the best-case scenario. The age- and sex-standardized IR of angioedema were almost similar in GePaRD was 1.2 per 1,000 PYs (see Table 10-3, Figure 10-1, Section 15.2.1-Table 1-35, and Section 15.2.1-Figure 1-1).

10.4.1.3 Incidence rates of angioedema ('narrow') in exposure cohort 3

In exposure cohort 3 (patients using ACEIs regardless of prior exposure to ACEIs/ARBs), a total of 769 events of angioedema were recorded, resulting in a combined crude IR of 0.9 (95% CI 0.8-0.9) per 1,000 PYs. The database- or subset-specific crude IRs ranged from 0.1 (95% CI 0.0-0.4) in HSD to 2.0 (95% CI 0.8-4.1) per 1,000 PYs in PHARMO without linked hospital data, and the age- and sex-standardized database- or subset-specific IRs were similar to the crude IRs. The combined age- and sex-standardized IR of angioedema was the same as the combined crude IR, 0.9 (95% CI 0.8-0.9) per 1,000 PYs. The database- or subset-specific age- and sex-standardized IRs were almost similar as the crude IRs and ranged from 0.1 in HSD to 2.1 per 1,000 PYs in PHARMO without linked hospital data (see Table 10-3, Figure 10-1, Section 15.2.1-Table 1-36, and Section 15.2.1-Figure 1-1).

10.4.1.4 Incidence rates of angioedema ('narrow') in exposure cohort 4

In exposure cohort 4 (patients initiating ACEIs without prior exposure to ACEIs/ARBs), between 138 (zero cases in CPRD [best-case scenario]) and 146 (eight cases in CPRD [worst-case scenario]) events of angioedema were recorded across all databases. This resulted in a combined crude IR of 1.2 (95% CI 1.0-1.4) for the best-case scenario and 1.3 (95% CI 1.1-1.5) per 1,000 PYs for the worst-case scenario, respectively. Database- or subset-specific IRs ranged from 0.0 in HSD to 4.7 (95% CI 0.6-17.1) per 1,000 PYs in PHARMO without linked hospital data. The database- or subset-specific IR of PHARMO without linked hospital data changed to 6.4 per 1,000 PYs when standardized for age and sex distribution. The combined age- and sex-standardized IR of angioedema was 1.2 (95% CI 1.0-1.4) per 1,000 PYs, corresponding to the combined crude IR of the best-case scenario (see Table 10-3, Figure 10-1, Section 15.2.1-Table 1-37, and Section 15.2.1-Figure 1-1).

10.4.1.5 Age- and sex-standardized incidence rates of angioedema ('narrow') stratified by exposure cohort and database

Age- and sex-standardized IRs of angioedema ('narrow' definition) for all four exposure cohorts by individual and combined databases are presented in Figure 10-1 (or Section 15.2.1-Figure 1-1).

Table 10-3 Incidence rates of the safety events of interest in patients initiating sacubitril/valsartan or using ACEIs in each exposure cohort – combined over all databases and range among databases (pre-COVID period)

Pre-COVID period††	Combined crude IR (95% CI) per 1,000 PY [database range of IRs per 1,000 PYs] *				Combined age-and-sex standardized IR (95% CI) per 1,000 PY‡‡ [database range of IRs per 1,000 PYs]			
Safety event of interest	Exposure cohort 1 (sac/val)	Exposure cohort 2§ (sac/val naïve)	Exposure cohort 3 (ACEI)	Exposure cohort 4 (ACEI naïve)	Exposure cohort 1 (sac/val)	Exposure cohort 2 (sac/val naïve)	Exposure cohort 3 (ACEI)	Exposure cohort 4 (ACEI naïve)
Angioedema ('narrow')	Best: 0.6 (0.4-0.9) Worst: 0.8 (0.5-1.1) [0.0 – 0.7]	Best: 0.9 (0.2-2.5) Worst: 3.1 (1.6-5.6) [0.0 – 1.1]	0.9 (0.8-0.9) [0.1 – 2.0]	Best: 1.2 (1.0-1.4) Worst: 1.3 (1.1-1.5) [0.0 – 4.7]	0.6 (0.4-0.9) [0.0 – 0.7]	0.9 [0.0 – 1.2]	0.9 (0.8-0.9) [0.1 – 2.1]	1.2 (1.0-1.4) [0.0 – 6.4]
Hypotension ('narrow')	24.8 (23.2-26.4) [5.3 – 45.1]	Best: 34.7 (28.7-41.5) Worst: 37.0 (30.8-44.0) [0.0 – 56.7]	11.7 (11.5-12.0) [2.3 – 33.5]	20.8 (20.0-21.7) [4.6 – 49.4]	25.9 (24.3-27.7) [5.7 – 51.6]	38.3 (31.7-45.9) [0.0 – 102.1]	12.1 (11.8-12.3) [2.4 – 35.8]	21.6 (20.8-22.5) [4.9 – 52.2]
Hyperkalemia	76.1 (73.3-79.0) [4.0 – 148.2]	Best: 64.5 (56.3-73.7) Worst: 65.7 (57.4-74.9) [0.0 – 296.2]	30.9 (30.5-31.3) [3.6 – 94.0]	45.1 (43.9-46.4) [4.9 –99.6]	79.4 (76.4-82.4) [4.9 – 166.1]	68.6 (59.7-78.5) [0.0 – 1,932]	31.5 (31.1-31.9) [3.5 – 99.6]	46.3 (45.0-47.6) [4.8 – 106.1]
Hepatotoxicity	Best: 0.5 (0.3-0.9) Worst: 0.8 (0.5-1.2) [0.0 – 2.8]	Best: 0.0 (0.0-1.3) Worst: 2.8 (1.2-5.5) [0.0 – 0.0]	Best: 0.4 (0.3-0.4) Worst: 0.4 (0.3-0.4) [0.0 – 1.2]	Best: 0.6 (0.4-0.7) Worst: 0.7 (0.5-0.9) [0.0 – 1.5]	0.6 (0.3-0.9) [0.0 – 2.9]	0.0 [0.0 – 0.0]	0.4 (0.3-0.4) [0.0– 1.3]	0.7 (0.5-0.8) [0.0 – 2.0]
Renal Impairment	Best: 24.2 (22.3-26.2) Worst: 24.4 (22.5-26.4) [3.7 –67.1]	Best: 23.6 (18.0-30.3) Worst: 26.7 (20.7-33.9) [0.0 – 48.1]	13.1 (12.8-13.3) [4.1 – 41.0]	18.4 (17.6-19.3) [6.8 – 49.7]	27.4 (25.2-29.8) [2.4 – 108.9]	26.9 (20.2-35.1) [0.0 – 116.4]	14.1 (13.8-14.4) [4.0 – 53.0]	20.1 (19.2-21.1) [6.6 – 67.7]

*Because the number of events and person years are not available for Aarhus and CPRD, a range of combined crude IRs was calculated, adding zero events to the number of events for calculating the lower combined crude IR (best-case scenario) and four events for the higher combined crude IR (worst-case scenario), when needed.

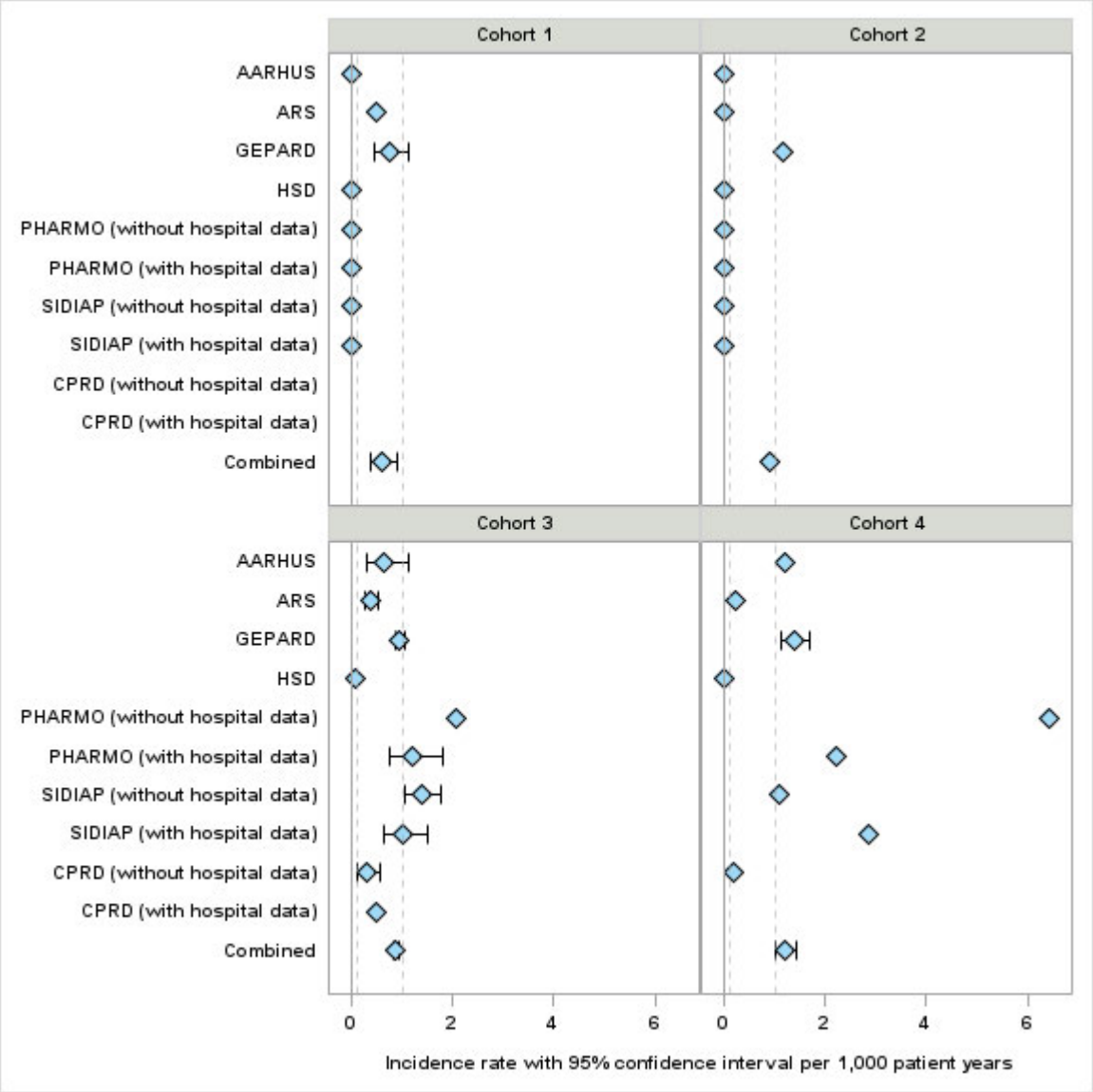
‡In case of combined age- and sex-standardized IRs, Aarhus and CPRD received aggregated data of the total number of patients (=the number of patients from all databases together) for each pre-defined 5-year age category and sex in each exposure cohort. With these data, Aarhus and CPRD estimated the study-based standard population and age- and sex-standardized rates for the safety event of interest per pre-defined 5-year age category per sex in each exposure cohort at their end. Both data partners provided PHARMO these aggregated data to calculate the combined IRs.

‡For assessing the total number of patients in exposure cohort 2, the number of patients in Aarhus was considered as four, as for the worst-case scenario four safety events of interest were considered.

‡For less than ten events, 95% CIs are not presented because the Dobson method produces relatively “accurate” 95% CIs only when ten or more safety events are observed (Dobson et al 1991).

Source: Section 15.2.1-Table 1-33, Section 15.2.1-Table 1-34 to Section 15.2.1-Table 1-37.

Figure 10-1 Age- and sex-standardized incidence rates of angioedema ('narrow' definition), stratified by exposure cohort and database – pre-COVID period



Age- and sex-standardized incidence rates with 95% confidence intervals per 1,000 person years, standardized to the combined study population.

Although crude IRs for Aarhus and CPRD are not available due to the small cell count redaction policy (for less than five events), age- and sex-standardized IRs are presented for Aarhus and CPRD as the number of safety events of interest cannot be traced due to standardization on age and sex distribution. However, if the safety event count is zero in CPRD, the age- and sex-standardized IR cannot be displayed.

For less than ten events, 95% CIs are not presented because the Dobson method produces relatively "accurate" 95% CIs only when ten or more safety events are observed (Dobson et al 1991).

For the readability of the age- and sex-standardized IRs grey dashed lines were added to the Figure at 0.1 and 1. For PHARMO without linked hospital data, the IR is 6.4 per 1,000 PYs in exposure cohort 4. The CI is not calculated because the IR is based on two events of angioedema. However, the CI for the crude IR of 4.7 is 0.6 to 17.1 in exposure cohort 4, indicating a large uncertainty.

Source: Section 15.2.1-Figure 1-1, Section 15.2.1-Table 1-33, Section 15.2.1-Table1-34 to Section 15.2.1-Table 1-37.

10.4.2 Primary and secondary objectives: incidence rates of hypotension ('narrow' definition) – [secondary safety event of interest]

10.4.2.1 Incidence rates of hypotension ('narrow') in exposure cohort 1

In exposure cohort 1 (patients initiating sacubitril/valsartan regardless of prior ACEIs/ARBs use), a total of 935 recorded events of hypotension ('narrow' definition) were present anytime during exposure, resulting in a combined crude IR of 24.8 (95% CI 23.2-26.4) per 1,000 PYs, with database- or subset-specific crude IRs ranging from 5.3 (95% CI 2.8-9.3) in ARS to 45.1 (95% CI 33.9-58.8) per 1,000 PYs in SIDIAP with linked hospital data. The age- and sex-standardized IR of hypotension was 25.9 (95% CI 24.3-27.7) per 1,000 PYs of exposure to sacubitril/valsartan for all databases combined. The database- or subset-specific age- and sex-standardized IRs ranged from 5.7 (95% CI 2.8-10.2) in ARS to 51.6 (95% CI 23.1-97.6) per 1,000 PYs in CPRD with linked hospital data (see Table 10-3, Figure 10-2, Section 15.2.1-Table 1-34, and Section 15.2.1-Figure 1-2).

10.4.2.2 Incidence rates of hypotension ('narrow') in exposure cohort 2

In exposure cohort 2 (patients initiating sacubitril/valsartan without prior exposure to ACEIs/ARBs), between 119 (zero cases in CPRD [best-case scenario]) and 127 (eight cases in CPRD [worst-case scenario]) hypotension events ('narrow' definition) were recorded across all databases. The combined crude IR of hypotension using the 'narrow' definition for the best-case scenario was 34.7 (95% CI 28.7-41.5) per 1,000 PYs, and for the worst-case scenario it was 37.0 (95% CI 30.8-44.0) per 1,000 PYs. The database- or subset-specific crude IRs ranged from 0.0 in Aarhus, HSD, and both subsets of PHARMO, to 56.7 (95% CI 20.8-123.5) per 1,000 PYs in SIDIAP with linked hospital data. The combined age- and sex-standardized IR of hypotension was 38.3 (95% CI 31.7-45.9) per 1,000 PYs, corresponding to almost the combined crude IR of the worst-case scenario. The range of database- or subset-specific age- and sex-standardized IRs was 0.0 in Aarhus, HSD, and both subsets of PHARMO to 102.1 per 1,000 PYs in SIDIAP with linked hospital data (see Table 10-3, Figure 10-2, Section 15.2.1-Table 1-35, and Section 15.2.1-Figure 1-2).

10.4.2.3 Incidence rates of hypotension ('narrow') in exposure cohort 3

In exposure cohort 3 (patients using ACEIs regardless of prior exposure to ACEIs/ARBs), a total of 10,242 hypotension events ('narrow' definition) was recorded, with a combined crude IR of 11.7 (95% CI 11.5-12.0) per 1,000 PYs. Database- or subset-specific crude IRs were between 2.3 (95% CI 1.6-3.3) in HSD and 33.5 (95% CI 30.8-36.4) per 1,000 PYs in CPRD with linked hospital data. The combined age- and sex-standardized IR of hypotension was 12.1 (95% CI 11.8-12.3) per 1,000 PYs, with the database- or subset-specific age- and sex-standardized IRs being similar as the crude database- or subset-specific IRs, ranging from 2.4 (95% CI 1.6-3.4) in HSD to 35.8 (95% CI 32.8-39.0) per 1,000 PYs in CPRD with linked hospital data (see Table 10-3, Figure 10-2, Section 15.2.1-Table 1-36, and Section 15.2.1-Figure 1-2).

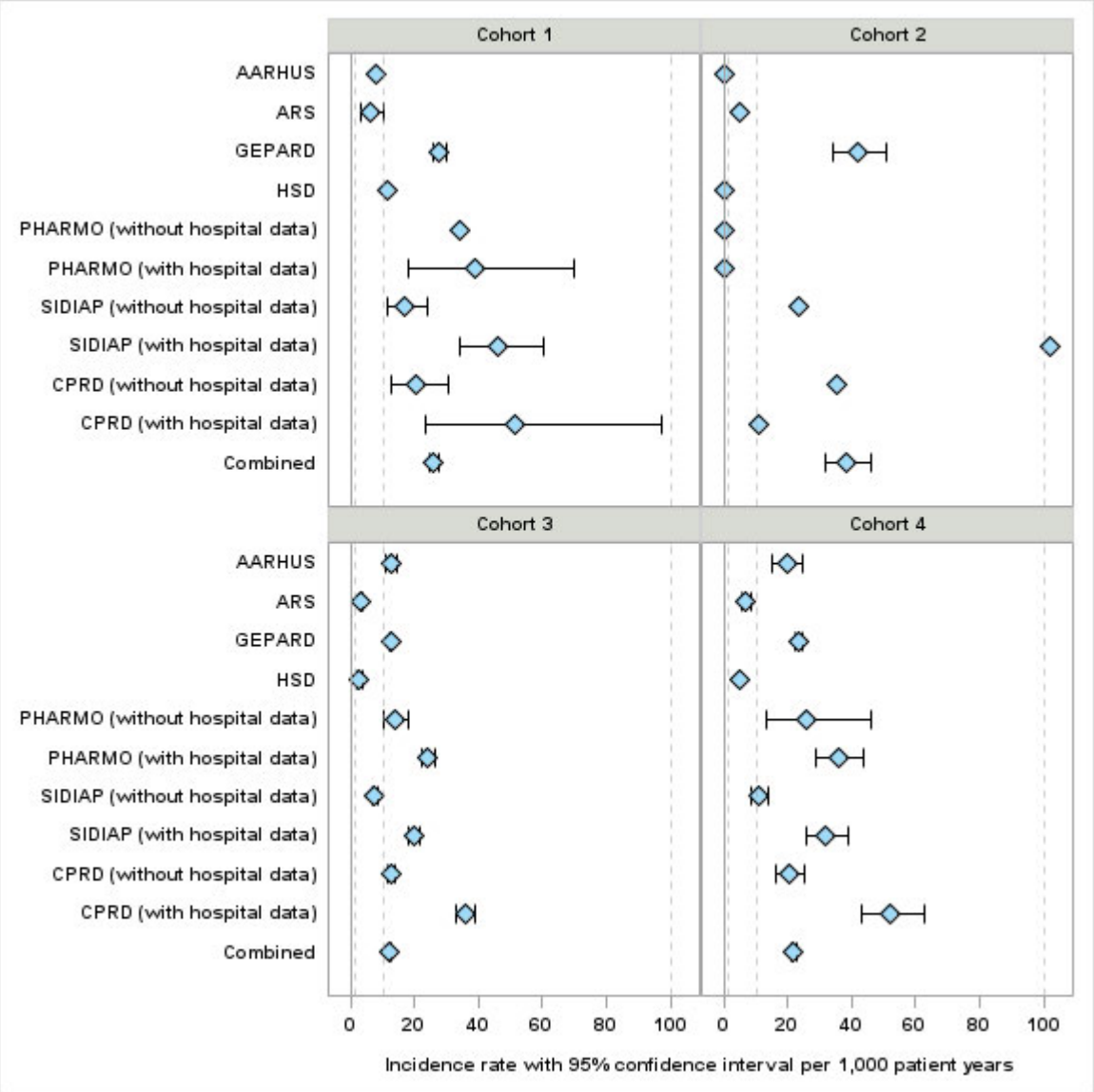
10.4.2.4 Incidence rates of hypotension ('narrow') in exposure cohort 4

In exposure cohort 4 (patients initiating ACEIs without prior exposure to ACEIs/ARBs), there were 2,360 hypotension events ('narrow' definition), resulting in a combined crude IR of 20.8 (95% CI 20.0-21.7) per 1,000 PYs. The range of database- or subset-specific crude IRs was 4.6 (95% CI 1.8-9.4) in HSD to 49.4 (95% CI 40.7-59.3) per 1,000 PYs in CPRD with linked hospital data. For this cohort of new ACEI users, the age- and sex-standardized combined IR of hypotension was 21.6 (95% CI 20.8-22.5) per 1,000 PYs. The range of database- or subset-specific standardized IRs was similar to the range of crude IRs, which was 4.9 (less than ten events) in HSD and 52.2 (95% CI 42.8-63.0) per 1,000 PYs in CPRD with linked hospital data (see Table 10-3, Figure 10-2, Section 15.2.1-Table 1-37, and Section 15.2.1-Figure 1-2).

10.4.2.5 Age- and sex-standardized incidence rates of hypotension ('narrow') stratified by exposure cohort and database

Age- and sex-standardized IRs of hypotension ('narrow' definition) for all four exposure cohorts by individual and combined databases are depicted in in Figure 10-2 (or Section 15.2.1-Figure 1-2).

Figure 10-2 Age- and sex-standardized incidence rates of hypotension ('narrow' definition), stratified by exposure cohort and database – pre-COVID period



Age- and sex-standardized incidence rates with 95% confidence intervals per 1,000 person years, standardized to the combined study population.

Although crude IRs for Aarhus and CPRD are not available due to the small cell count redaction policy (for less than five events), age- and sex-standardized IRs are presented for Aarhus and CPRD as the number of safety events of interest cannot be traced due to standardization on age and sex distribution.

For less than ten events, 95% CIs are not presented because the Dobson method produces relatively "accurate" 95% CIs only when ten or more safety events are observed (Dobson et al 1991).

For the readability of the age- and sex-standardized IRs grey dashed lines were added to the Figure at 1, 10 and 100.

For SIDIAP with linked hospital data, the IR is 102.1 per 1,000 PYs in exposure cohort 2. The CI is not calculated because the IR is based on six events of hypotension. However, the CI for the crude IR of 56.7 is 20.8 to 123.5 in exposure cohort 2, indicating a large uncertainty.

Source: Section 15.2.1-Figure 1-2, Section 15.2.1-Table 1-33, Section 15.2.1-Table 1-34 to Section 15.2.1-Table 1-37.

10.4.3 Primary and secondary objectives: incidence rates of hyperkalemia – [secondary safety event of interest]

10.4.3.1 Incidence rates of hyperkalemia in exposure cohort 1

In exposure cohort 1 (patients initiating sacubitril/valsartan regardless of prior ACEIs/ARBs use), there were 2,789 events of hyperkalemia with a combined crude IR of 76.1 (95% CI 73.3-79.0) per 1,000 PYs. The database- or subset-specific crude IRs were between 4.0 (95% CI 1.8-7.6) in ARS and 148.2 (95% CI 128.5-170.1) per 1,000 PYs in CPRD without linked hospital data. The age- and sex-standardized combined IR of hyperkalemia was 79.4 (95% CI 76.4-82.4) per 1,000 PYs, and the database- or subset- specific age- and sex-standardized IRs ranged from 4.9 in ARS (less than ten events) to 166.1 (95% CI 141.1-193.9) per 1,000 PYs in CPRD without linked hospital data (see Table 10-3, Figure 10-3, Section 15.2.1-Table 1-34, and Section 15.2.1-Figure 1-3).

10.4.3.2 Incidence rates of hyperkalemia in exposure cohort 2

In exposure cohort 2 (patients initiating sacubitril/valsartan without prior exposure to ACEIs/ARBs), there were between 219 (zero cases in CPRD [best-case scenario]) and 223 (four cases in CPRD [worst-case scenario]) hyperkalemia events across all databases, corresponding to combined crude IRs of 64.5 (95% CI 56.3-73.7) for the best-case scenario and 65.7 (95% CI 57.4-74.9) for the worst-case scenario per 1,000 PYs, respectively. The range of database- or subset-specific crude IRs was between 0.0 in Aarhus and both subsets of PHARMO to 296.2 (95% CI 127.9-583.7) per 1,000 PYs in CPRD without linked hospital data. For exposure cohort 2, the combined age- and sex-standardized IR was 68.6 (95% CI 59.7-78.5) per 1,000 PYs, corresponding to almost the combined crude IR of the worst-case scenario. The database- or subset-specific age- and sex-standardized IRs ranged from 0.0 per 1,000 PYs in Aarhus and both subsets of PHARMO to 1,932 per 1,000 PYs in CPRD without linked hospital data (less than ten events) (see Table 10-3, Figure 10-3, Section 15.2.1-Table 1-35, and Section 15.2.1-Figure 1-3).

10.4.3.3 Incidence rates of hyperkalemia in exposure cohort 3

In exposure cohort 3 (patients using ACEIs regardless of prior exposure to ACEIs/ARBs), the number of hyperkalemia events was 26,558 across all databases, resulting in a combined crude IR of hyperkalemia of 30.9 (95% CI 30.5-31.3) per 1,000 PYs. The range of database- or subset-specific crude IRs was 3.6 (95% CI 3.2-4.0) in ARS to 94.0 (95% CI 89.2-98.9) per 1,000 PYs in CPRD with linked hospital data. The combined age- and sex-standardized IR of hyperkalemia in this cohort was 31.5 (95% CI 31.1-31.9) per 1,000 PYs. For the database- or subset-specific age- and sex-standardized IRs of hyperkalemia, a similar pattern to the crude IRs was observed, and ranged from 3.5 (95% CI 3.1-4.0) in ARS to 99.6 (95% CI 94.3-105.1) per 1,000 PYs in CPRD with linked hospital data (see Table 10-3, Figure 10-3, Section 15.2.1-Table 1-36, and Section 15.2.1-Figure 1-3).

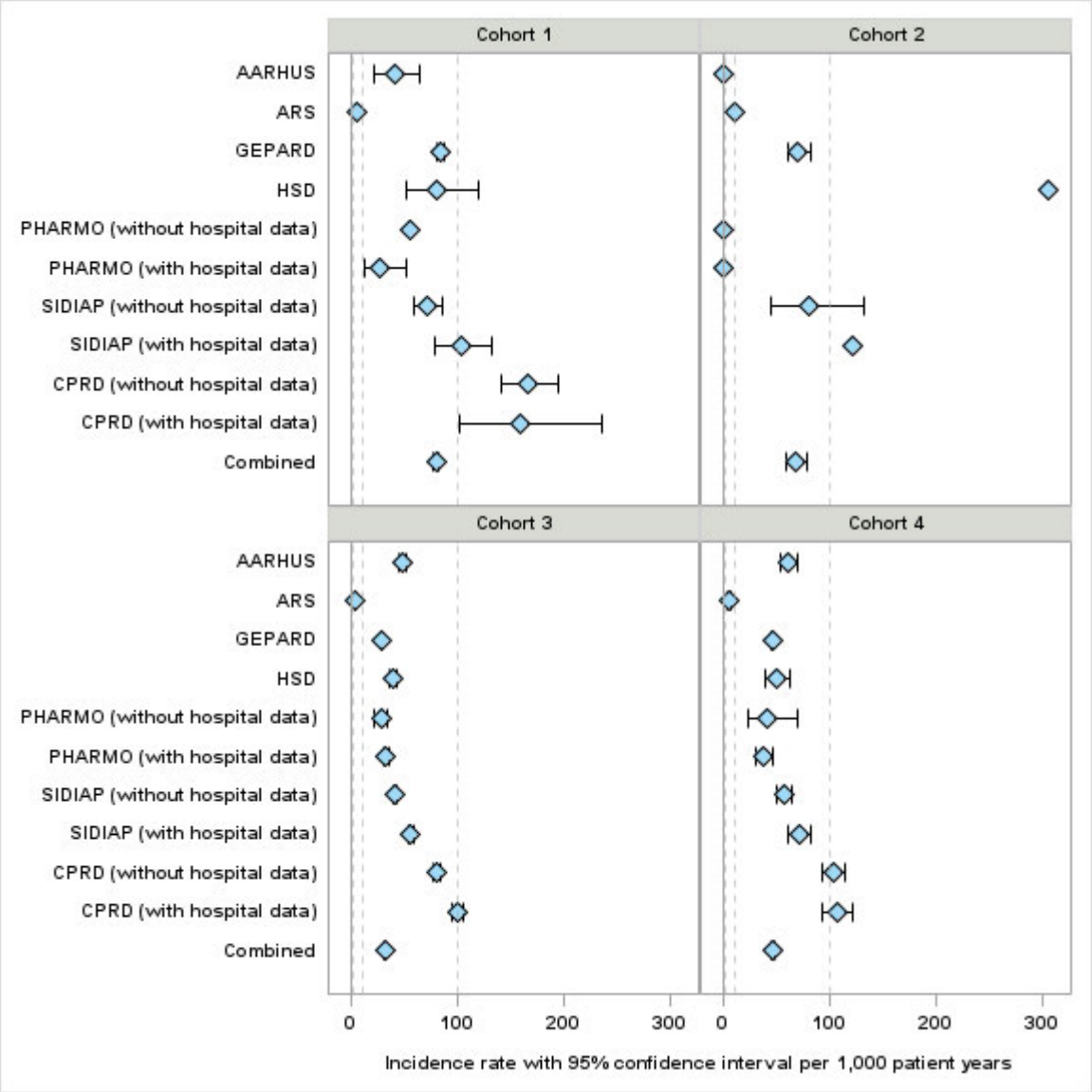
10.4.3.4 Incidence rates of hyperkalemia in exposure cohort 4

In exposure cohort 4 (patients initiating ACEIs without prior exposure to ACEIs/ARBs) there were 5,049 hyperkalemia events identified across all databases, and the corresponding combined crude IR of hyperkalemia was 45.1 (95% CI 43.9-46.4) per 1,000 PYs. The database- or subset- or subset-specific crude IRs ranged from 4.9 (95% CI 3.7-6.5) per 1,000 PYs in ARS to 99.6 (95% CI 90.5-109.3 [without linked hospital data], 95% CI 86.8-113.8 [with linked hospital data]) per 1,000 PYs in both subsets of CPRD. The combined age- and sex-standardized IR of hyperkalemia in this cohort was 46.3 (95% CI 45.0-47.6) per 1,000 PYs, and database-specific age- and sex-standardized IRs had a similar range to the crude IRs, and ranged from 4.8 (95% CI 3.6-6.4) in ARS to 106.1 (95% CI 92.0-121.8) per 1,000 PYs in CPRD with linked hospital data (see Table 10-3, Figure 10-3, Section 15.2.1-Table 1-37, and Section 15.2.1-Figure 1-3).

10.4.3.5 Age- and sex-standardized incidence rates of hyperkalemia stratified by exposure cohort and database

Age- and sex-standardized IRs of hyperkalemia for all four exposure cohorts by individual and combined databases are shown in Figure 10-3 (or Section 15.2.1-Figure 1-3).

Figure 10-3 Age- and sex-standardized incidence rates of hyperkalemia, stratified by exposure cohort and database – pre-COVID period



Age- and sex-standardized incidence rates with 95% confidence intervals per 1,000 person years, standardized to the combined study population.

Although crude IRs for Aarhus and CPRD are not available due to the small cell count redaction policy (for less than five events), age- and sex-standardized IRs are presented for Aarhus and CPRD as the number of safety events of interest cannot be traced due to standardization on age and sex distribution. However, if the safety event count is zero in CPRD, the age- and sex-standardized IR cannot be displayed.

For less than ten events, 95% CIs are not presented because the Dobson method produces relatively "accurate" 95% CIs only when ten or more safety events are observed (Dobson et al 1991).

For the readability of the age- and sex-standardized IRs grey dashed lines were added to the Figure at 10 and 100.

For HSD, the IR is 304.6 per 1,000 PYs in exposure cohort 2. The CI is not calculated because the IR is based on three events of hyperkalemia. However, the CI for the crude IR of 90.1 is 18.6 to 263.3 in exposure cohort 2, indicating a large uncertainty.

For CPRD without linked hospital data, the IR is 1,932 per 1,000 PYs in cohort 2, which cannot be displayed as all other results in the Figure become unreadable. The CI is not calculated because the IR is based on eight events of hyperkalemia.

Source: Section 15.2.1-Figure 1-3, Section 15.2.1-Table 1-33, Section 15.2.1-Table 1-34 to Section 15.2.1-Table 1-37.

10.4.4 Primary and secondary objectives: incidence rates of hepatotoxicity– [secondary safety event of interest]

10.4.4.1 Incidence rates of hepatotoxicity in exposure cohort 1

In exposure cohort 1 (patients initiating sacubitril/valsartan regardless of prior ACEIs/ARBs use), 17 events of hepatotoxicity were observed anytime during exposure in ARS, GePaRD, and both subsets of SIDIAP (zero cases in CPRD [best-case scenario]), and 25 events (eight cases in CPRD [worst-case scenario]). Combined crude IRs of hepatotoxicity for the best-case and worst-case scenario were 0.5 (95% CI 0.3-0.9) and 0.8 (95% CI 0.5-1.2) per 1,000 PYs, respectively. The database- or subset-specific crude IRs were ranging from 0.0 in Aarhus, HSD, and both subsets of PHARMO to 2.8 (95% CI 0.6-8.3) per 1,000 PYs in SIDIAP with linked hospital data. The combined age- and sex-standardized IR of hepatotoxicity was 0.6 (95% CI 0.3-0.9) per 1,000 PYs,. The data-specific age- and sex-standardized IR ranged from 0.0 in Aarhus, HSD, and both subsets of PHARMO to 2.9 per 1,000 PYs in SIDIAP with linked hospital data (less than ten events) (see Table 10-3, Figure 10-4, Section 15.2.1-Table 1-34, and Section 15.2.1-Figure 1-4).

10.4.4.2 Incidence rates of hepatotoxicity in exposure cohort 2

In exposure cohort 2 (patients initiating sacubitril/valsartan without prior exposure to ACEIs/ARBs), no events of hepatotoxicity were identified. Combined crude IRs were 0.0 (95% CI 0.0-1.3) for the best-case scenario and 2.8 (95% CI 1.2-5.5) per 1,000 PYs for the worst-case scenario, which was based on eight added events in CPRD. The combined age- and sex-standardized IR was 0.0 (see Table 10-3, Figure 10-4, Section 15.2.1-Table 1-35, and Section 15.2.1-Figure 1-4).

10.4.4.3 Incidence rates of hepatotoxicity in exposure cohort 3

In exposure cohort 3 (patients using ACEIs regardless of prior exposure to ACEIs/ARBs), between 265 (zero cases in CPRD [best-case scenario]) and 269 (four cases in CPRD [worst-case scenario]) events of hepatotoxicity were identified. The combined crude IR of hepatotoxicity was 0.4 (95% CI 0.3-0.4) per 1,000 PYs for both the best- and worst-case scenario. Database- or subset-specific crude IRs ranged from 0.0 in PHARMO without linked hospital data to 1.2 (95% CI 0.8-1.8) per 1,000 PYs in SIDIAP with linked hospital data. The combined age- and sex-standardized IR was the same as the combined crude IR of hepatotoxicity for both best- and worst-case scenarios. The data-specific age- and sex-standardized IR ranged from 0.0 in PHARMO without linked hospital data to 1.2 (95% CI 0.8-1.8) per 1,000 PYs in SIDIAP with linked hospital data (see Table 10-3, Figure 10-4, Section 15.2.1-Table 1-36, and Section 15.2.1-Figure 1-4).

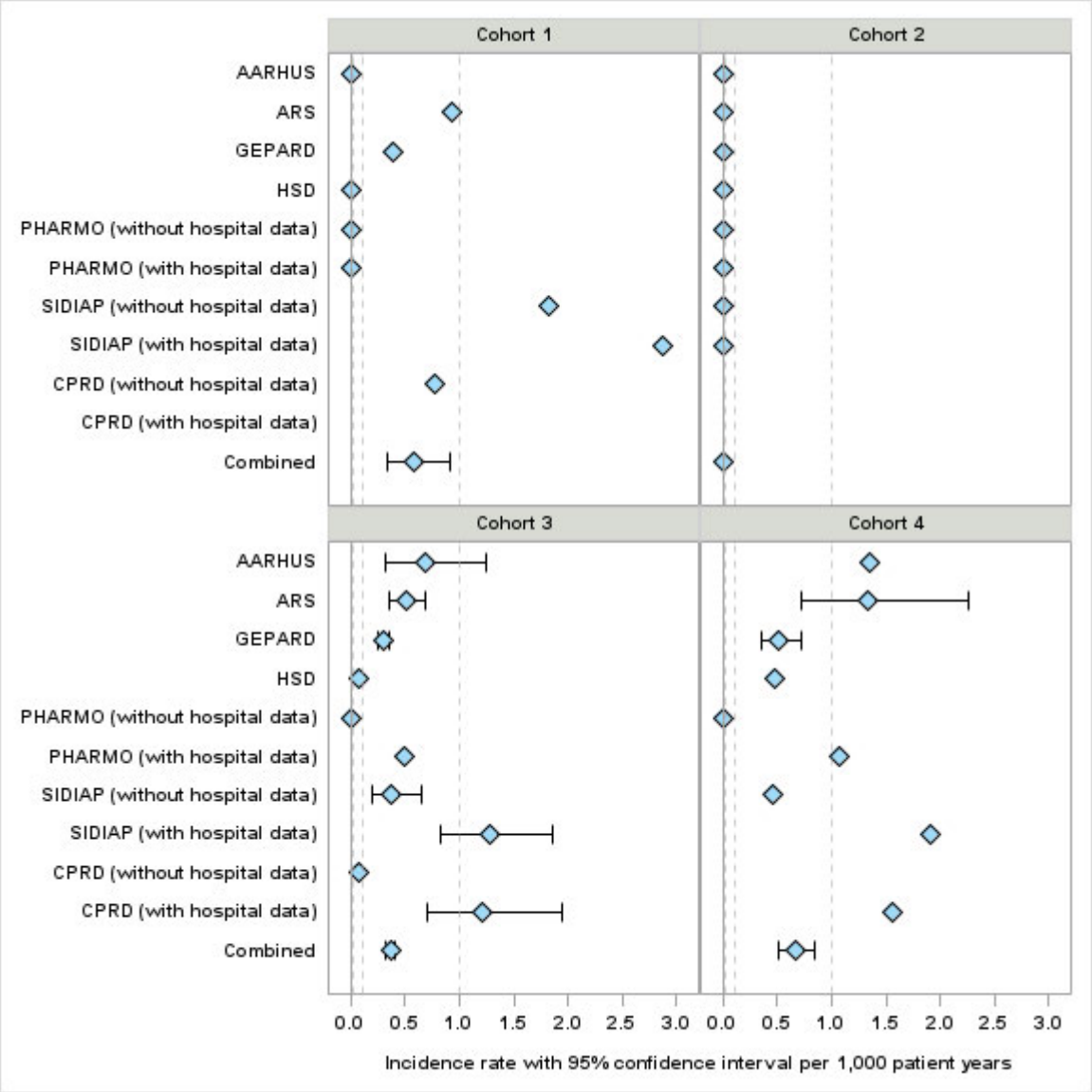
10.4.4.4 Incidence rates of hepatotoxicity in exposure cohort 4

In exposure cohort 4 (patients initiating ACEIs without prior exposure to ACEIs/ARBs), the number of hepatotoxicity events was between 56 (zero cases in Aarhus and CPRD [best-case scenario]) and 68 (12 cases in Aarhus and CPRD [worst-case scenario]). The combined crude IR of hepatotoxicity was 0.6 (95% CI 0.4-0.7) per 1,000 PYs for the best-case scenario and 0.7 (95% CI 0.5-0.9) per 1,000 PYs for the worst-case scenario, respectively. The range of database- or subset-specific crude IRs was 0.0 in PHARMO without linked hospital data to 1.5 per 1,000 PYs in ARS (95% CI 0.8-2.4) and in SIDIAP with linked hospital data (95% CI 0.4-3.9), respectively. The combined age- and sex-standardized IR was the same as the combined crude IR of hepatotoxicity for the worst-case scenario. The range of database- or subset-specific age- and sex-standardized IRs was 0.0 in PHARMO without linked hospital data to 1.9 per 1,000 PYs in SIDIAP with linked hospital data (less than ten events) (see Table 10-3, Figure 10-4, Section 15.2.1-Table 1-37, and Section 15.2.1-Figure 1-4).

10.4.4.5 Age- and sex-standardized incidence rates of hepatotoxicity stratified by exposure cohort and database

Age- and sex-standardized IRs of hepatotoxicity for all four exposure cohorts by individual and combined databases are depicted in Figure 10-4 (or Section 15.2.1-Figure 1-4).

Figure 10-4 Age- and sex-standardized incidence rates of hepatotoxicity, stratified by exposure cohort and database – pre-COVID period



Age- and sex-standardized incidence rates with 95% confidence intervals per 1,000 person years, standardized to the combined study population.

Although crude IRs for Aarhus and CPRD are not available due to the small cell count redaction policy (for less than five events), age- and sex-standardized IRs are presented for Aarhus and CPRD as the number of safety events of interest cannot be traced due to standardization on age and sex distribution. However, if the safety event count is zero in CPRD, the age- and sex-standardized IR cannot be displayed.

For less than ten events, 95% CIs are not presented because the Dobson method produces relatively “accurate” 95% CIs only when ten or more safety events are observed (Dobson et al 1991).

For the readability of the age- and sex-standardized IRs grey dashed lines were added to the Figure at 0.1 and 1.0.

Source: Section 15.2.1-Figure 1-4, Section 15.2.1-Table 1-33, Section 15.2.1-Table 1-34 to Section 15.2.1-Table 1-37.

10.4.5 Primary and secondary objectives: incidence rates of renal impairment – [secondary safety event of interest]

10.4.5.1 Incidence rates of renal impairment in exposure cohort 1

For exposure cohort 1 (patients initiating sacubitril/valsartan regardless of prior ACEIs/ARBs use), the combined crude IR of renal impairment was 24.2 (95% CI 22.3-26.2) for the best-case scenario based on 614 events (zero cases in CPRD) and 24.4 (95% CI 22.5-26.4) for the worst-case scenario per 1,000 PYs based on 618 events (four cases in CPRD), respectively. The range of database- or subset-specific crude IRs was from 3.7 (95% CI 0.1-20.6) in HSD to 67.1 (95% CI 21.8-156.5) per 1,000 PYs in PHARMO without linked hospital data. The combined age- and sex-standardized IR was slightly higher than the combined crude IR (27.4 [95% CI 25.2-29.8]) and was close to the crude IR of both the best- and worse-case scenario. The range of database- or subset-specific standardized age- and sex-standardized IRs was 2.4 in HSD to 108.9 per 1,000 PYs in PHARMO without linked hospital data (see Table 10-3, Figure 10-5, Section 15.2.1-Table 1-34, and Section 15.2.1-Figure 1-5).

10.4.5.2 Incidence rates of renal impairment in exposure cohort 2

In exposure cohort 2 (patients initiating sacubitril/valsartan without prior exposure to ACEIs/ARBs), there were 60 (zero cases in CPRD [best-case scenario]) to 68 (eight cases in CPRD [worst-case scenario]) events of renal impairment, resulting in combined crude IRs of 23.6 (95% CI 18.0-30.3) for the best-case scenario and 26.7 (95% CI 20.7-33.9) for the worst-case scenario per 1,000 PYs, respectively. Overall, there were seven events recorded anytime during exposure in ARS, five events in SIDIAP (both subsets combined), and 48 events in GePaRD. In CPRD events were redacted due to small-cell-count policies, but in all other databases no events of renal impairment were observed. Database- or subset-specific crude IRs ranged from 0.0 in Aarhus, HSD, and both subsets of PHARMO, to 48.1 (95% CI 9.9-140.6) per 1,000 PYs in SIDIAP with linked hospital data. The combined age- and sex-standardized IR of this cohort was almost the same as the combined crude IR of the worst-case scenario (26.9 [95% CI 20.2-35.1]). The range of database- or subset-specific standardized age- and sex-standardized IRs was 0.0 in Aarhus, HSD, and both subsets of PHARMO to 116.4 per 1,000 PYs in SIDIAP with linked hospital data (less than ten events) (see Table 10-3, Figure 10-5, Section 15.2.1-Table 1-35 and Section 15.2.1-Figure 1-5).

10.4.5.3 Incidence rates of renal impairment in exposure cohort 3

In exposure cohort 3 (patients using ACEIs regardless of prior exposure to ACEIs/ARBs), the number of events was 8,868 for renal impairment and the combined crude IR was 13.1 (95% CI 12.8-13.3) per 1,000 PYs. The database- or subset-specific crude IRs ranged from 4.1 (95% CI 3.4-4.9) per 1,000 PYs in SIDIAP without linked hospital data to 41.0 (95% CI 37.3-45.1) per 1,000 PYs in CPRD with linked hospital data. The combined age- and sex-standardized IR was 14.1 (95% CI 13.8-14.4) per 1,000 PYs. Database- or subset-specific age- and sex-standardized IRs ranged from 4.0 (95% CI 3.3-4.8) in SIDIAP without linked hospital data to 53.0 (95% CI 47.2-59.2) per 1,000 PYs in CPRD with linked hospital data (see Table 10-3, Figure 10-5, Section 15.2.1-Table 1-36 and Section 15.2.1-Figure 1-5).

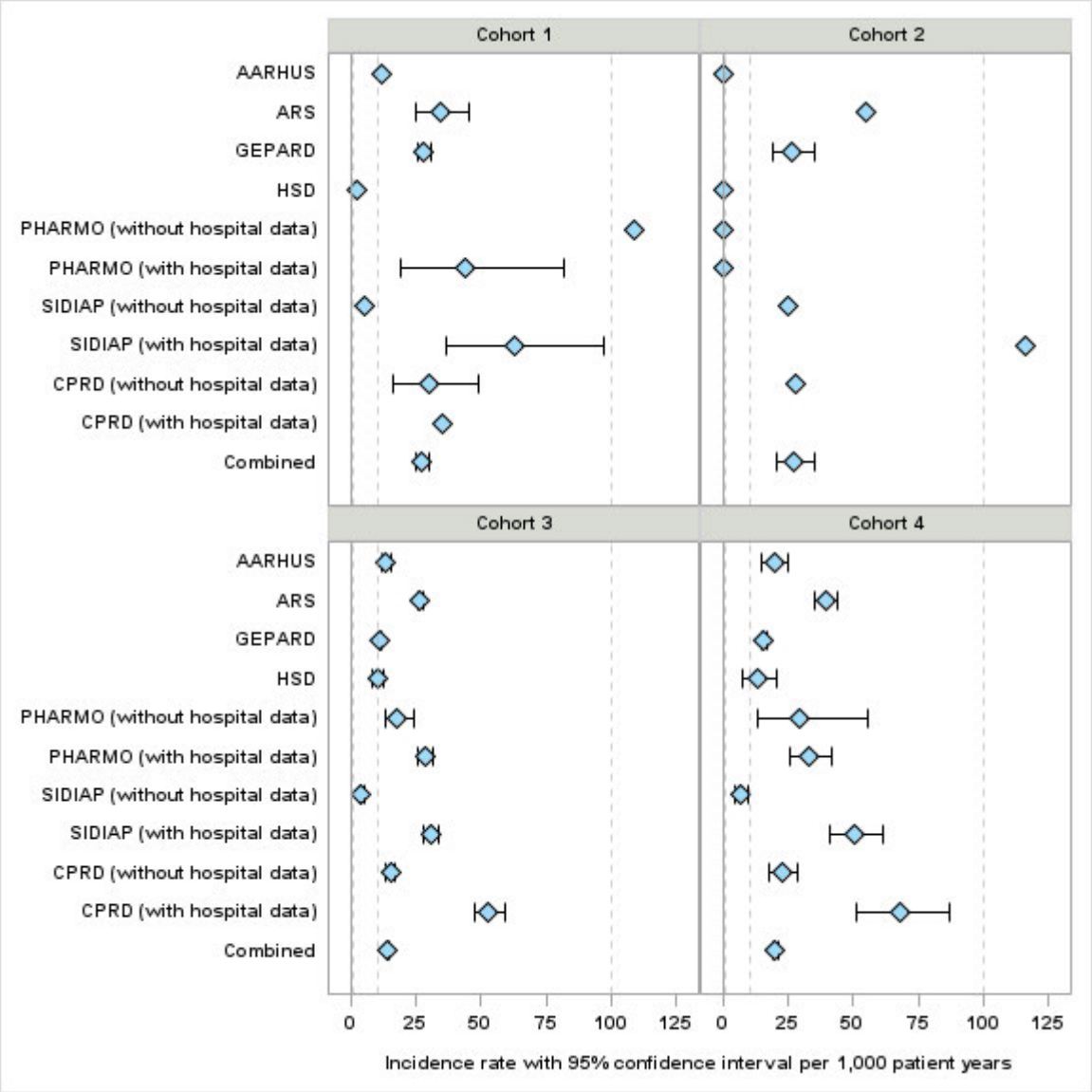
10.4.5.4 Incidence rates of renal impairment in exposure cohort 4

In exposure cohort 4 (patients initiating ACEIs without prior exposure to ACEIs/ARBs), there were 1,742 events of renal impairment, with a combined crude IR of 18.4 (95% CI 17.6-19.3) per 1,000 PYs. Database- or subset-specific crude IRs ranged from 6.8 (95% CI 4.4-10.0) in SIDIAP without linked hospital data to 49.7 (95% CI 39.7-61.4) per 1,000 PYs in CPRD with linked hospital data. The combined age- and sex-standardized IR of renal impairment was 20.1 (95% CI 19.2-21.1) per 1,000 PYs. The range of database- or subset-specific standardized age- and sex-standardized IRs was 6.6 (95% CI 4.2-9.7) in SIDIAP without linked hospital data to 67.7 (95% CI 51.4-86.8) per 1,000 PYs in CPRD with linked hospital data (see Table 10-3, Figure 10-5, Section 15.2.1-Table 1-37, and Section 15.2.1-Figure 1-5).

10.4.5.5 Age- and sex-standardized incidence rates of renal impairment stratified by exposure cohort and database

Age- and sex-standardized IRs of renal impairment for all exposure cohorts by individual and combined databases are shown in Figure 10-5 (or Section 15.2.1-Figure 1-5).

Figure 10-5 Age- and sex-standardized incidence rates of renal impairment, stratified by exposure cohort and database – pre-COVID period



Age- and sex-standardized incidence rates with 95% confidence intervals per 1,000 person years, standardized to the combined study population.

Although crude IRs for Aarhus and CPRD are not available due to the small cell count redaction policy (for less than five events), age- and sex-standardized IRs are presented for Aarhus and CPRD as the number of safety events of interest cannot be traced due to standardization on age and sex distribution. However, if the safety event count is zero in CPRD, the age- and sex-standardized IR cannot be displayed.

For less than ten events, 95% CIs are not presented because the Dobson method produces relatively “accurate” 95% CIs only when ten or more safety events are observed (Dobson et al 1991).

For the readability of the age- and sex-standardized IRs grey dashed lines were added to the Figure at 1, 10 and 100.

Source: Section 15.2.1-Figure 1-5, Section 15.2.1-Table 1-33, Section 15.2.1-Table 1-34 to Section 15.2.1-Table 1-37.

10.4.6 Primary and secondary objectives: cumulative incidence of angioedema ('narrow' definition) at pre-defined time points in each cohort of all databases together in the pre-COVID period

Section 15.2.1-Figure 1-8 to Section 15.2.1-Figure 1-17 display Kaplan-Meier curves of cumulative incidences of angioedema ('narrow' definition) at pre-defined time points, i.e., at Week 1, Week 4, Week 8, Week 26, and Week 52 after the index date in each exposure cohort for each database in the pre-COVID period.

10.4.6.1 Cumulative incidence of angioedema ('narrow') in exposure cohort 1

In GePaRD the cumulative incidence of angioedema with the definition 'narrow' was 0.1 (95% CI 0.0-0.3) per 1,000 patients by the first week, 0.2 (95% CI 0.1-0.4) per 1,000 patients by the fourth week, 0.6 (95% CI 0.3-0.9) per 1,000 patients by six months, and 0.7 (95% CI 0.4-1.1) per 1,000 patients by one year after starting treatment with sacubitril/valsartan. In ARS, the only angioedema event occurred between week 26 and week 52, hence, the cumulative incidence of angioedema in ARS stayed 0.0 per 1,000 patients until week 26 after initiation of sacubitril/valsartan and was 1.0 (0.0-3.9) per 1,000 patients at week 52. In all other databases, apart from CPRD no cumulative incidence of angioedema in the year after the index date was estimated as no angioedema event was observed in that year. In CPRD below five events were observed in the year after the index date (see Section 15.2.1-Figure 1-8 to Section 15.2.1-Figure 1-17).

10.4.6.2 Cumulative incidence of angioedema ('narrow') in exposure cohort 2

In GePaRD, the cumulative incidence of angioedema was 0.0 until week 8, and 0.9 (95% CI 0.1-2.5) per 1,000 patients by week 26 and week 52 after initiation of sacubitril/valsartan (based on two angioedema events). No events were observed in the other databases, except for CPRD where less than five events were observed (see Section 15.2.1-Figure 1-8 to Section 15.2.1-Figure 1-17).

10.4.6.3 Cumulative incidence of angioedema ('narrow') in exposure cohort 3

The one-week cumulative incidence of angioedema was 0.1 per 1,000 patients in GePaRD (95% CI 0.1-0.1) and PHARMO with linked hospital data (95% CI 0.0-0.3), the cumulative incidence at week 4 was 0.2 per 1,000 patients in both GePaRD (95% CI 0.1-0.2) and PHARMO (95% CI 0.0-0.5), and the cumulative incidence steadily increased to 1.1 (95% CI 0.9-1.2) per 1,000 patients in GePaRD and 1.4 (95% CI 0.7-2.3) per 1,000 patients in PHARMO with linked hospital data at one year after the index date. For all other databases, similar patterns in the cumulative incidences of angioedema in one year were observed. In PHARMO without linked hospital data, the cumulative incidence of angioedema was 0.0 per 1,000 patients at week one, four and eight, but changed to 2.7 (95% CI 0.7-5.9) per 1,000 patients at six months and 3.4 (95% CI 1.1-7.1) per 1,000 patients at 12 months after the index date (see Section 15.2.1- Figure 1-8 to Section 15.2.1-Figure 1-17).

10.4.6.4 Cumulative incidence of angioedema ('narrow') in exposure cohort 4

Similar patterns of the cumulative incidence of angioedema at week 1, 4, 8, 26, and 52 were observed in exposure cohort 4 in GePaRD and PHARMO with linked hospital data, but slightly

more pronounced than in exposure cohort 3. A similar observation was noticed in PHARMO without linked data where the cumulative incidence of angioedema was 0.0 per 1,000 patients at week one, four, and eight, but changed to 3.8 (95% CI 0.0-14.8) per 1,000 patients at six months and 9.0 (95% CI 0.8-25.8) per 1,000 patients at one year after starting ACEI treatment (see Section 15.2.1-Figure 1-8 to Section 15.2.1-Figure 1-17).

10.4.7 Exploratory objectives: relative risks of angioedema ('narrow') in adult patients with HF initiating sacubitril/valsartan as compared to adult patients with HF using ACEIs.

Comparative analyses of angioedema between patients initiating sacubitril/valsartan and patients using ACEI, with or without prior exposure to ACEIs/ARBs were only conducted if at least five events for the safety event angioedema ('narrow' definition) per comparison of exposure cohorts were available. This criterion was only fulfilled for GePaRD and the following comparisons were conducted:

- Exposure cohort 1 versus exposur` e cohort 3 (patients initiating sacubitril/valsartan regardless of prior exposure to ACEIs/ARBs versus patients using ACEIs regardless of prior exposure to ACEIs/ARBs) (exploratory objective 2)
- Exposure cohort 1 versus exposure cohort 4 (patients initiating sacubitril/valsartan regardless of prior exposure to ACEIs/ARBs versus patients using ACEIs without prior exposure to ACEIs/ARBs) (exploratory objective 3)

To control for confounding in each of these comparisons, propensity score with overlap weighting was applied in GePaRD. The overlap between the PS distribution of both exposure cohorts of interest for the safety event angioedema ('narrow' definition) are shown graphically in Section 15.2.1 –Figure 1-28 and Figure 1-29. For comparing exposure cohort 1 with exposure cohort 4, a limited overlap was shown, whereas an appropriate overlap between the PS distribution of exposure cohort 1 and 3 was observed in GePaRD.

For each exploratory objective, a comparison of absolute standardized difference of unweighted means or proportions versus absolute standardized difference of weighted means or proportions is presented for each covariate. The absolute standardized difference for the weighted means or proportions was zero for each objective in GePaRD, indicating an optimal balance of covariates between both exposure cohorts (see Section 15.2.1-Figure 1-30 and Section 15.2.1-Figure 1-31).

No meta-analyses of relative risks of angioedema ('narrow' definition) were conducted, as results from this comparative analysis were only available for GePaRD.

10.4.7.1 Exploratory Objective 1: relative risk of angioedema ('narrow') among patients initiating sacubitril/valsartan without prior exposure to ACEIs/ARBs (exposure cohort 2) versus patients using ACEIs without prior exposure to ACEIs/ARBs (exposure cohort 4)

Only three angioedema events were observed in exposure cohort 2 in GePaRD, which was below the specified threshold of five cases triggering the comparative analysis (see Section 15.2.1-Table 1-47).

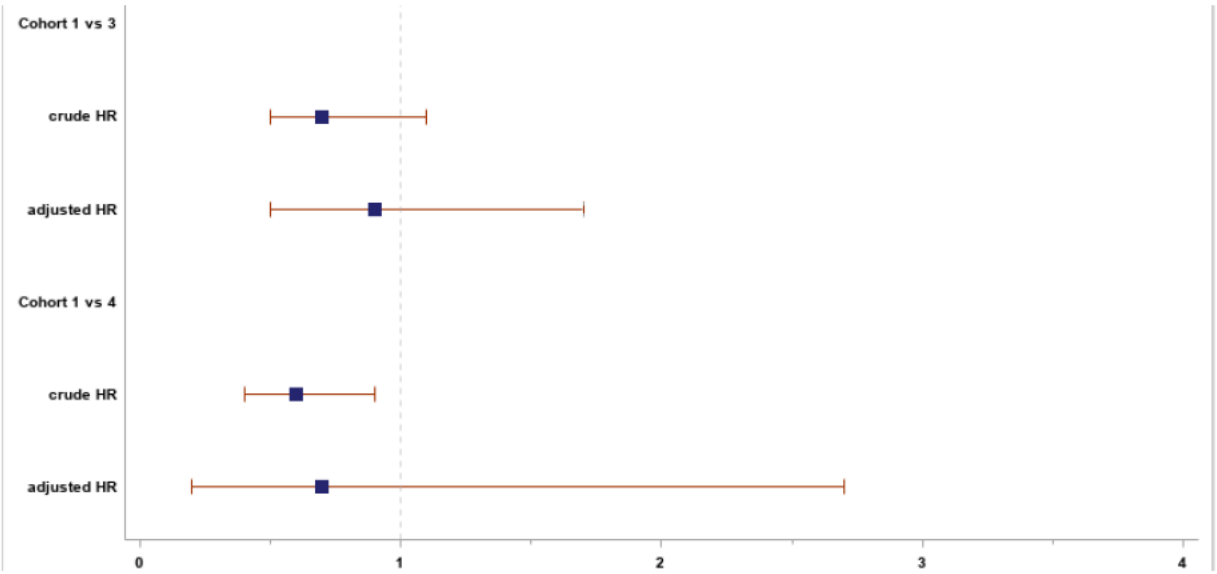
10.4.7.2 Exploratory Objective 2: relative risk of angioedema ('narrow') among patients initiating sacubitril/valsartan regardless of prior exposure to ACEIs/ARBs (exposure cohort 1) versus patients using ACEIs regardless of prior exposure to ACEIs/ARBs (exposure cohort 3)

The adjusted relative risk of angioedema in sacubitril/valsartan initiators regardless of prior exposure to ACEIs/ARBs (exposure cohort 1) compared to ACEIs users regardless of prior exposure to ACEIs/ARBs (exposure cohort 3) in GePaRD was $HR_{adjusted}$, 0.9 (95% CI 0.5-1.7) based on the PS-weighted cohorts; the respective crude HR was HR_{crude}, 0.7 (95% 0.5-1.1) (see Figure 10-6 and Section 15.2.1-Table 1-47 and Section 15.2.1-Figure 1-32).

10.4.7.3 Exploratory Objective 3: relative risk of angioedema among patients initiating sacubitril/valsartan regardless of prior exposure to ACEIs/ARBs (exposure cohort 1) versus patients using ACEIs without prior exposure to ACEIs/ARBs (exposure cohort 4)

The adjusted relative risk of angioedema in sacubitril/valsartan initiators regardless of prior exposure to ACEIs/ARBs (exposure cohort 1) compared to ACEIs users without prior exposure to ACEIs/ARBs (exposure cohort 4) in GePaRD was $HR_{adjusted}$, 0.7 (95% CI 0.2-2.7) based on the PS-weighted cohorts; the respective crude HR was HR_{crude}, 0.6 (95% 0.4-0.9) (see Figure 10-6 and Section 15.2.1-Table 1-47 and Section 15.2.1-Figure 1-32).

Figure 10-6 Relative risk of angioedema, comparative analyses of exposure cohort 1 versus exposure cohort 3 and exposure cohort 1 versus exposure cohort 4 in GePaRD



HR = hazard ratio

In the forest plot the relative risk of angioedema ('narrow' definition) between sacubitril/valsartan and ACEIs was plotted by hazards ratios and the corresponding 95% CIs.

Adjusted HR = to control for confounding, potential confounders such as age, sex, pre-specified comorbidities, and co-medications (see Table 9-10) were introduced in the Cox regression model with overlap weighting (OW) based on propensity score (PS).

Source: Section 15.2.1-Table 1-47, Section 15.2.1-Figure 1-32.

10.5 Other analyses

10.5.1 Sensitivity Analysis: misclassification of safety events

Mitigating potential misclassification of angioedema by adding anaphylactic shock

This sensitivity analysis expanded the definition of potential cases of angioedema ('narrow' definition) with diagnostic codes of anaphylactic shock. Combined crude IRs of angioedema and anaphylactic shock were 1.3 (95% CI 1.0-1.7) for the best-case scenario and 1.6 (95% CI 1.2-2.1) for the worst-case scenario per 1,000 PYs in exposure cohort 1, 1.4 (95% CI 0.5-3.3) for the best-case scenario and 3.7 (95% CI 2.0-6.3) for the worst-case scenario per 1,000 PYs in exposure cohort 2, 1.4 (95% CI 1.3-1.4) per 1,000 PYs in exposure cohort 3, and 1.9 (95% CI 1.7-2.2) for the best-case scenario and 2.0 (95% CI 1.7-2.2) for the worst-case scenario per 1,000 PYs in exposure cohort 4. Combined age- and sex-standardized IRs of angioedema and anaphylactic shock were 1.3 (95% CI 1.0-1.8) per 1,000 PYs in exposure cohort 1, 1.4 in exposure cohort 2 (less than ten events), 1.4 (95% CI 1.3-1.4) per 1,000 PYs in exposure cohort 3, and 1.9 (95% CI 1.7-2.2) per 1,000 PYs in exposure cohort 4, corresponding to combined crude IRs of the best-case scenario. (see Section 15.2.1-Table 1-34 to Section 15.2.1-Table 1-37).

Mitigating potential misclassification of angioedema by considering unconfirmed cases in GePaRD

A potential underestimation of angioedema events may have occurred in GePaRD, because of the confirmation algorithms that were used for event identification as well as exclusion criterion of prior angioedema events. Crude IRs of angioedema by considering unconfirmed cases were 1.1 (95% CI 0.7-1.5) per 1,000 PYs in exposure cohort 1, 0.7 (95% CI 0.1-2.6) per 1,000 PYs in exposure cohort 2, 1.9 (95% CI 1.8-2.1) per 1,000 PYs in exposure cohort 3, and 2.5 (95% CI 2.2-2.9) per 1,000 PYs in exposure cohort 4, respectively. Consequently, inclusion of unconfirmed diagnoses increased the crude IRs of angioedema with 'narrow' definition in exposure cohort 1, 3, and 4 by 57%, 90%, and 79%, respectively. However, consideration of unconfirmed angioedema events in addition to confirmed events resulted in the exclusion of more patients with prior angioedema (an exclusion criterion). Consequently, their angioedema events during follow-up were excluded as well, resulting in a crude IR decreased by 36% in exposure cohort 2. Age- and sex-standardized IRs with 95% CIs were not estimated. (see Section 15.2.1-Table 1-34 to Section 15.2.1-Table 1-37).

Mitigating potential misclassification of hypotension

In another sensitivity analysis, the safety event hypotension ('narrow' definition) was expanded with additional diagnostic codes indicative of potential clinical manifestations of hypotension. Combined crude IRs were 85.9 (95% CI 82.9-89.0) per 1,000 PYs in exposure cohort 1, 98.1 (95% CI 87.7-109.5) for the best-case scenario and 100.6 (95% CI 90.0-112.1 for the worst-case scenario) per 1,000 PYs in exposure cohort 2, 68.9 (95% CI 68.3-69.4) per 1,000 PYs in exposure cohort 3, and 97.9 (95% CI 96.1-99.8) per 1,000 PYs in exposure cohort 4, respectively. Patients with a 'broad' definition of hypotension had higher crude IRs (1.8 to 4.8

times) and age- and sex-standardized IRs (1.9 to 5.0 times) than patients with a 'narrow' definition of hypotension in each exposure cohort and database. The age- and sex-standardized IRs were almost similar to the crude IRs in each exposure cohort (in exposure cohort 2 the worst-case scenario), and were 93.4 (95% CI 90.0-96.8) per 1,000 PYs in exposure cohort 1, 109.6 (95% CI 97.6-122.7) per 1,000 PYs in exposure cohort 2, 72.1 (95% CI 71.5-72.7) per 1,000 PYs in exposure cohort 3, and 103.6 (95% CI 101.6-105.6) per 1,000 PYs in exposure cohort 4, respectively (see Section 15.2.1-Table 1-34 to Section 15.2.1-Table 1-37).

10.5.2 Sensitivity Analysis: Potential COVID-19 pandemic impact

In all analyses, the number of patients in each exposure cohort were higher in the full study period (=the latest date of data availability in each database) than in the pre-COVID period which ended on December 31, 2019 for all databases (1.0 to 1.2 times higher). In the full study period, a similar pattern of all results in each exposure cohort and database of the pre-COVID period was observed, although the IRs were lower in the full study period. In GePaRD (the largest database contributing data to this study) the end date of the study period is December 31, 2019, so the findings of this sensitivity analysis were the same as the primary analysis (see [Section 15.2.1-Table 1-38] to [Section 15.2.1-Table 1-41]).

10.5.3 Sensitivity Analysis: Impact of duration of prevalent ACEIs use on incidence rate of angioedema

The sensitivity analysis where patients with prevalent ACEIs use were stratified by ACEIs exposure duration prior to index date (a subset of exposure cohort 3) showed IRs of 1.2 (95% CI 0.7-2.0) per 1,000 PYs and 1.6 (95% CI 0.9-2.5) per 1,000 PYs for the best-case and worst-case scenario in the pre-COVID period, respectively for angioedema when patients were treated with ACEIs less than eight weeks prior to index date. The risk diminished over time when treatment continued (8 - < 26 weeks: 1.1 [95% CI 0.8-1.5] per 1,000 PYs for the best-case scenario and 1.3 [95% CI 1.0-1.7] per 1,000 PYs for the worst-case scenario and ≥ 26 weeks: 0.7 [95% CI 0.7-0.8] per 1,000 PYs). A similar pattern was observed in age- and sex-standardized IRs and for the full study period (see Section 15.2.1-Table 1-42).

10.5.4 Sensitivity Analysis: Impact of excluding SIDIAP data

The sensitivity analysis which excluded SIDIAP results from the combined IRs showed similar results (crude and age- and sex-standardized IRs) as the primary analysis (see Section 15.2.1-Table 1-43 to Section 15.2.1-Table 1-46).

10.6 Adverse events/adverse reactions

Not Applicable.

11 Discussion

11.1 Key results

The study aimed to provide real-world IRs of angioedema, hypotension, hyperkalemia hepatotoxicity, and renal impairment among patients with HF initiating sacubitril/valsartan or

using ACEIs, with a primary focus (as the primary safety event of interest) on angioedema. To address all study objectives, data from seven European electronic healthcare databases were utilized of a total source population of 41,383,318 patients.

11.1.1 Description of exposure cohorts

The total number of patients in the study base was 676,505 in the full study period, which was defined as the latest date of data availability in each database.

In the pre-COVID period (ended on 31 December 2019, before the COVID-19 pandemic was declared), exposure cohort 1 comprised 39,616 patients initiating sacubitril/valsartan regardless of prior exposure to ACEIs/ARBs. Of those patients in exposure cohort 1, 4,548 (11%) patients who initiated sacubitril/valsartan treatment and were naïve to ACEIs/ARBs were included in exposure cohort 2. Exposure cohort 3, which included patients using ACEIs regardless of prior use of ACEIs/ARBs, was the largest cohort with a total of 642,689 patients using ACEIs in the pre-COVID period. Approximately 26% (n=164,088) of these patients using ACEIs in exposure cohort 3 were naïve to ACEIs/ARBs and were included in exposure cohort 4.

In the pre-COVID period, GePaRD contributed most to the exposure cohorts, with > 75% of all users in all exposure cohorts as compared to the study base (30,160 sacubitril/valsartan initiators [exposure cohort 1] and 481,226 ACEI users [exposure cohort 3]), followed by ARS (2,557 exposure cohort 1 and 52,539 exposure cohort 3 [8%]), SIDIAP (3,547 exposure cohort 1 and 44,311 exposure cohort 3 [7%]), CPRD (1,699 exposure cohort 1 and 29,376 exposure cohort 3 [5%]), PHARMO (610 exposure cohort 1 and 13,475 exposure cohort 3 [2%]), Aarhus (544 exposure cohort 1 and 13,691 exposure cohort 3 [2%]), and HSD (499 exposure cohort 1 and 8,071 exposure cohort 3 [1%]).

11.1.2 Patient Characteristics

Across all databases and exposure cohorts, patients were on average of a similar age between 72 and 74 years old. The proportion of men was higher among patients initiating sacubitril/valsartan (71% male in exposure cohort 1 and 65% male in exposure cohort 2) compared with patients using ACEIs (53% male in exposure cohort 3 and 51% male in exposure cohort 4). Cardiovascular diseases, CKD, diabetes mellitus, and the use of cardiovascular co-medications (including those influencing the occurrence of some safety events of interest such as hypotension, hyperkalemia, and renal impairment) were more frequent in patients initiating sacubitril/valsartan (exposure cohorts 1 and 2) than in patients using ACEIs (exposure cohorts 3 and 4). Further, the proportion of three or more cardiac medications, used as a proxy for HF severity, was much higher in exposure cohorts 1 and 2 versus exposure cohort 3 and 4. The patient profile was as expected based on the German guideline (Bundesärztekammer (BÄK) Arbeitsgemeinschaft der Deutschen Ärztekammern et al 2019) and the 2016 European Society of Cardiology (ESC) guideline for HF (Ponikowski et al 2016), which stated that sacubitril/valsartan was indicated for patients with HFrEF and a left ventricular ejection fraction (LVEF) of 35% or less who remained symptomatic after therapy with ACEIs/ARBs, i.e., patients with high disease severity. The same guideline recommends the use of MRA in HF (Ponikowski et al 2016), which can be considered as a proxy for an advanced and severe disease course or stage of HF. The impact of the guideline was reflected in the baseline characteristics profile of patients in exposure cohort 1 and 2. The substantially higher proportion of patients

using MRAs in the sacubitril/valsartan cohorts (68% in exposure cohort 1) versus the ACEI cohorts (18% in exposure cohort 3) is therefore indicative of a higher proportion of patients with severe HF in those patients treated with sacubitril/valsartan. The observed higher proportion of patients receiving more than three cardiac medications for the treatment of HF, another proxy for HF severity, also reinforced this, with 44% of exposure cohort 1, 17% in exposure cohort 2, 8% in exposure cohort 3, and 5% in exposure cohort 4 taking three or more cardiac medications. In addition, the use of ivabradine, a second line treatment considered if patients respond insufficiently to other HF treatments such as beta-blockers (heart rate > 70 beats per minute despite adequate doses/or do not tolerate them) (Ponikowski et al 2016, McDonagh et al 2021) was higher in exposure cohorts 1 and 2 (8-7%) than in exposure cohorts 3 and 4 (2-1%), which further supports that the proportion of severe HF patients was higher in the sacubitril/valsartan cohorts than in the ACEI cohorts.

The baseline characteristics profile of patients in exposure cohort 1 and 2 is consistent with three previous observational studies, showing the characteristics of patients prescribed with sacubitril/valsartan after its launch in Germany (Maggioni et al 2022, Zeymer et al 2019, Klebs et al 2017), relevant as GePaRD contributed most patients to all exposure cohorts. The uptake of sacubitril/valsartan was relatively slow during the study period in Germany, not exceeding 3,000 initiations of sacubitril/valsartan treatment per month (Abdin et al 2022). It is likely that the profile of patients initiating sacubitril/valsartan did not change substantially from what was described by Wachter et al 2018 (Wachter et al 2018). Noteworthy, in this study by Wachter et al patients initiating sacubitril/valsartan had a lower systolic blood pressure, were more likely to present with some degree of renal impairment and had a more severe HF (Wachter et al 2018). Therefore, patients in exposure cohort 1 and 2 were more susceptible to hypotension and renal impairment.

Both studies from Wachter et al demonstrated that patients who use sacubitril/valsartan and ACEIs in the real-world tend to be older (mean age 72 and 74 years, respectively) (Wachter et al 2018, Wachter et al 2019) than patients that were enrolled in randomized controlled trials of sacubitril/valsartan and ACEIs, such as the pivotal PARADIGM-HF trial (mean age 64 years) (McMurray et al 2014).

The sex distribution of patients initiating sacubitril/valsartan was consistent with the sex distribution in a previous observational study (Wachter et al 2018). The observed difference in the proportion of men among patients receiving sacubitril/valsartan versus ACEIs/ARBs might be attributable to a higher proportion of patients who had HFrEF in the sacubitril/valsartan group, as men are substantially more likely to be diagnosed with HFrEF than women (Kenchaiah et al 2015). This is further supported by the proportion of males in each of the two exposure cohorts of patients recruited to the PARADIGM-HF study, which recruited patients with HFrEF, who were mostly male patients, with 79% in the sacubitril/valsartan cohort and 77% and in ACEI cohort (McMurray et al 2014).

There was variation in the prevalence of comorbidities between databases with considerably higher prevalences in GePaRD despite the applied confirmation algorithm for identifying comorbidities. This pattern was noticed in another multi-database study (Masclee et al 2018). A possible explanation may be that GePaRD covers almost the complete spectrum of healthcare utilization (results of laboratory test were not available) whereas other databases are partially lacking information from one provenance (e.g., specialist data, GP data, hospital data, or

emergency visits data - see Table 9-8). The contributions of different data provenances on the incidence of each safety event of interest in the general adult population was assessed in the feasibility study ([redacted]). Especially for those safety events that are typically diagnosed in GP settings (angioedema, hypotension, hyperkalemia) GePaRD showed the highest rates driven by the high rate of primary care diagnoses. Another explanation might be the coding practice in the German outpatient care setting as it is considered of lower accuracy compared to inpatient diagnoses, because outpatient diagnoses are not directly relevant for reimbursement and are not quality-checked by an independent party in Germany. This may have resulted in frequent repetition of diagnostic codes for reimbursement purposes. Studies with other events have shown that the inclusion of diagnoses with status 'confirmed' that are only recorded once ever and not confirmed by a second recording in GePaRD caused higher frequencies of conditions compared with other databases, which resulted in misleadingly high IRs due to misclassification. Therefore, confirmation of secondary outpatient diagnoses by a second diagnosis was usually required, especially for chronic conditions. Also, the introduction of the Morbi-RSA (a model that allocates more money to health insurances if their population shows certain type of diseases) may have contributed to more complete coding of some diagnoses in Germany.

11.1.3 Outcome data

Angioedema

The incidence rate of angioedema ('narrow' definition) among patients initiating sacubitril/valsartan regardless of prior ACEI use (exposure cohort 1) was 0.6 (95% CI 0.4-0.9) per 1,000 PYs across databases based on the combined crude IR of angioedema for the best-case scenario and age- and sex-standardized IR. To assess the potential bias due to prior ACEIs/ARBs use in exposure cohort 1, the incidence of angioedema was also estimated among the sub-cohort of patients initiating sacubitril/valsartan without prior exposure to ACEIs/ARBs in the 365 days prior to index date (exposure cohort 2), resulting in a crude IR of 0.9 (95% CI 0.2-2.5) per 1,000 PYs for the best-case scenario and an age- and sex-standardized IR of 0.9 (less than ten events). The rate is numerically higher in exposure cohort 2, which is what would be expected if depletion of susceptible patients caused bias in exposure cohort 1. However, exposure cohort 2 was very small with only three recorded angioedema events based on the best-case scenario and CIs of IRs in both exposure cohorts overlapped widely. As the number of angioedema events was redacted in both subsets of CPRD, eight events were included when estimating combined crude IRs of angioedema for the worst-case scenario, which were 0.8 (95% CI 0.5-1.1) per 1,000 PYs for exposure cohort 1 and 3.1 (95% CI 1.6-5.6) per 1,000 PYs for exposure cohort 2. Both combined crude for the best- and worst-case scenario and age- and sex-standardized IR of angioedema ('narrow' definition) among ACEI patients was 0.9 (95% CI 0.8-0.9) per 1,000 PYs in exposure cohort 3 (prevalent and new users) and was slightly higher in patients without prior ACEIs/ARBs use (cohort 4): 1.2 (95% CI 1.0-1.4) and 1.3 (95% CI 1.1-1.5) per 1,000 PYs. Concurrent prescriptions/dispensings were the only reliable indicator of non-adherence to the 36-hour washout period in this study. A relatively low percentage (2% in exposure cohort 1 and < 0.5% in exposure cohort 3) of patients with concurrent prescriptions/dispensing for sacubitril/valsartan and ACEIs or vice versa were excluded. In SIDIAP, the number patients with concurrent dispensings at index date was higher than in any

other database in exposure cohort 1. This was likely due to non-specific dates of dispensings as only the month and year were known and dispensings in the same month were assumed to occur on the same day.

Exploratory analyses comparing the incidence of angioedema between sacubitril/valsartan initiators and ACEI users with adjustment for covariates were performed, using different comparator cohorts of ACEI users. For the first exploratory objective, patients initiating sacubitril/valsartan and patients initiating ACEI (both naïve to prior ACEIs and ARBs use) were to be compared. This new user design may minimize substantial bias that has been observed in prevalent user designs. There were no angioedema events (with a 'narrow' definition) across almost all databases in exposure cohort 2 except for GePaRD that recorded three events. In exposure cohort 4, a total of 138 (best-case scenario) to 146 (worst-case scenario) angioedema events were recorded across all databases. The number of events in exposure cohort 2 was too small for a comparative analysis between patients initiating sacubitril/valsartan without prior exposure to ACEIs/ARBs, and those initiating ACEI use without prior exposure to ACEIs/ARBs. Thus, this most meaningful comparative analysis between exposure cohorts 2 and 4 could not be conducted.

For the second exploratory objective, exposure cohort 1 which includes initiators of sacubitril/valsartan with or without prior exposure to ACEIs/ARBs was compared to exposure cohort 3, which included a mix of patients with prevalent and incident ACEI use. It is likely that patients susceptible for angioedema have been depleted as a large proportion of patients were previously exposed with ACEIs in both cohorts. Two databases reported angioedema events among patients initiating sacubitril/valsartan, and most angioedema events among patients initiating sacubitril/valsartan were observed in GePaRD (n=21 out of 22). A comparative analysis between exposure cohorts 1 and 3 was therefore conducted only in GePaRD which controlled for confounding by weighting method based on propensity scores..

There was no indication of an increased risk of angioedema ('narrow' definition) with sacubitril/valsartan initiation compared to ACEI use regardless of prior exposure to ACEIs/ARBs (exposure cohort 1 compared to exposure cohort 3), when weighted ($HR_{adjusted}$, 0.9; 95% CI: 0.5-1.7). The results were in line with the results from the two randomized controlled trials, which all showed no statistically significant risk of angioedema (Velazquez et al 2019, Desai et al 2019). However, the large randomized controlled PARADIGM-HF trial where patients initiating sacubitril/valsartan were compared with ACEI enalapril (McMurray et al 2014, Shi et al 2018) found an increased relative risk of 1.9 (95% CI 0.8-4.5), which was not statistically significant. In this trial the double-blind exposure period of sacubitril/valsartan or enalapril was preceded by two single-blind active run-in periods. During these periods, patients were sequentially treated with sacubitril/valsartan (median duration: 29 days) and ACEIs (median duration: 15 days) before randomization to ACEIs and sacubitril/valsartan. Patients with angioedema during this run-in period were excluded (Shi et al 2018). Hence, depletion of susceptible patients based on the run-in period in this trial, was not differential between sacubitril/valsartan and ACEIs, which cannot be guaranteed in this present study. Therefore, the lower HR in this study could be due to prevalent user bias, even though adjustment for prior exposure to ACEIs/ARBs included in the PS, was applied.

Although a high potential of depletion of susceptible bias due to prior ACEI use in exposure cohort 1 may be present, a new user comparison analysis of patients initiating

sacubitril/valsartan regardless of prior exposure to ACEIs/ARBs (exposure cohort 1) with patients using ACEIs without prior exposure to ACEIs/ARBs (exposure cohort 4) was conducted in GePaRD. The result of this comparative analysis between exposure cohort 1 and 4 showed a lower risk of angioedema ('narrow' definition; $HR_{adjusted}$ was 0.7 [95% CI 0.2-2.7]) than the comparison of exposure cohort 1 and 3 ($HR_{adjusted}$ 0.9). Thus, comparing patients from exposure cohort 1 to 4 biased the analysis in favor of the sacubitril/valsartan initiators from exposure cohort 1. The lower risk of angioedema in this analysis may be due to prevalent user bias, and therefore biased the analysis in favor of the sacubitril/valsartan initiators in exposure cohort 1. However, a conclusion cannot be drawn from findings of comparative analyses where the CIs are widely overlapping, and HRs are close to each other. Because of this, it is considered that the optimal comparison would have been between sacubitril/valsartan initiators who were naïve to ACEIs/ARBs against new users of ACEIs. As indicated above, although this comparative analysis between exposure cohorts 2 and 4 was planned as part of the exploratory objective 1, it could not be conducted due to small number of angioedema events (n=3) among exposure cohort 2.

Because angioedema events may have been missed by the 'narrow' definition, two sensitivity analyses were conducted. A potential underestimation of angioedema events may have occurred in GePaRD due to the assumed temporary nature of angioedema leading to unconfirmed diagnoses, which was investigated in a sensitivity analysis. Inclusion of unconfirmed diagnoses increased the crude IR of angioedema with 'narrow' definition in exposure cohort 1, 3, and 4. In exposure cohort 2 the crude IR decreased, since the persons at risk decreased.

In another sensitivity analysis the diagnostic codes for angioedema ('narrow' definition) were expanded with those for anaphylactic shock to compose the 'broad' definition of angioedema and resulted in an increase of the IRs of 0.2 to 1.2 times relative to angioedema rates with a 'narrow' definition in all exposure cohorts across all databases together. This represents a likely upper bound of the estimate of the potential angioedema rates when underestimation is assumed to occur with angioedema codes only. This broader definition of angioedema is closer to the definition used in the PARADIGM-HF trial, although IRs of this sensitivity analysis are still lower. This may be due to different methods for case ascertainment. In randomized controlled trials safety events were adjudicated by assessors, which may have resulted in higher probability detecting cases of angioedema than in the present study. In this study recorded diagnostic codes for angioedema and/or anaphylactic shock were used without any standardized process for the assessment of these events.

As expected, the cumulative incidence of angioedema was estimated in each exposure cohort in GePaRD. The cumulative incidence of angioedema had a similar pattern until six months after the index date in all four exposure cohorts, however, the one year cumulative incidence of angioedema was lower in exposure cohort 1 and 2 than in exposure cohort 3 and 4. The one year cumulative incidence of angioedema was 0.7 per 1,000 (0.07%) patients in exposure cohort 1, 0.9 per 1,000 patients (0.09%) in exposure cohort 2, 1.1 per 1,000 patients (0.11%) in exposure cohort 3, and 1.6 per 1,000 patients (0.16%) in exposure cohort 4 in GePaRD (see Section 15.2.1-Figure 1-10). In the PARADIGM-HF trial (Shi at al 2018), the cumulative incidence of angioedema was higher (not statistically significant) for patients initiating sacubitril/valsartan than for patients initiating ACEIs with 0.07% and 0.05% at 30 days, 0.3% and 0.1% at six months, and 0.3% and 0.2% at one year after randomization. The patterns of

the cumulative incidences over time in the randomized controlled trial were roughly similar to what was observed in this study (see Section 15.2.1-Figure 1-8 to Section 15.2.1-Figure 1-17). Similar to PARADIGM-HF trial (Shi at al 2018), most of the cases of angioedema occurred in the first six months. However, the incidence estimates were lower than the ones from the trial, which may be due to close monitoring, resulting in a more complete capture of adverse events in the trial than in real-world data. Further, the cumulative incidences are not fully explained by the number of angioedema events at each time point but is partially caused by the low number of patients at risk at that time. This may have led to unreliable estimates, especially when a change in a small number of events occurred (e.g., one additional angioedema event can lead to a large increase in the cumulative incidence at that specific time point).

Hypotension

For hypotension ('narrow' definition), IRs were higher for sacubitril/valsartan cohorts compared to ACEI cohorts. Specifically, combined crude and age- and sex-standardized IRs were 24.8 (95% CI 23.2-26.4) per 1,000 PYs and 25.9 (95% CI 24.3-27.7) per 1,000 PYs for exposure cohort 1. For exposure cohort 2, combined crude IRs were 34.7 (95% CI 28.7-41.5) per 1,000 PYs for the best-case scenario and 37.0 (95% CI 30.8-44.0) per 1,000 PYs for the worst-case scenario, and the age- and sex-standardized IR of 38.3 (95% CI 31.7-45.9) per 1,000 PYs (those without prior exposure to ACEIs/ARBs). Combined IRs were notably lower in exposure cohort 3, with a combined crude IR of 11.7 (95% CI 11.5-12.0) per 1,000 PYs and age- and sex-standardized IR of 12.1 (95% CI 11.8-12.3) per 1,000 PYs. Similarly, in the ACEI cohort without prior exposure to ACEIs/ARBs (exposure cohort 4), combined crude and age- and sex-standardized IRs were 20.8 (95% CI 20.0-21.7) per 1,000 PYs and 21.6 (95% CI 20.8-22.5) per 1,000 PYs. The combined IRs were higher in sacubitril/valsartan and ACEI users naïve to ACEIs/ARBs compared to sacubitril/valsartan and ACEI users, regardless of prior ACEIs/ARBs use, due to depletion of susceptible bias.

Increased IRs of hypotension among sacubitril/valsartan initiators compared to ACEI users were expected, and data collected complements and extends those data from randomized controlled trials where patients assigned to sacubitril/valsartan were more likely to experience episodes of hypotension compared to enalapril patients (Zhang et al 2020). Neprilysin (NEP) inhibition causes potent vasodilation by itself. When NEP inhibition is combined with an ARB (such as in sacubitril/valsartan) or when it occurs along with ACE inhibition (such as in omapatrilat), hypotension may occur more often than when ARBs or ACEIs are administered without the NEP inhibition component.

Compared to ACEI users, patients initiating sacubitril/valsartan had higher prevalences of myocardial infarction, atrial fibrillation, valvular disease, and CKD (exposure cohort 1 only). Moreover, sacubitril/valsartan initiators (as compared to ACEI users), were more likely to use beta-blockers, MRAs, loop diuretics, and anti-arrhythmic agents and the use of more than 3 cardiac medications, suggesting that these patients were more susceptible to hypotension because of their severe HF disease state.

The high prevalence of pre-existent low systolic blood pressure and antihypertensive drugs in exposure cohort 1, as well as the daily doses used, may also have contributed to the observed difference with exposure cohort 3. This possibility is supported by an observational study of patients with HF prescribed sacubitril/valsartan in primary care who had lower systolic blood

pressure at the start of sacubitril/valsartan treatment (a known risk factor for hypotension), and a higher use of beta-blockers compared to the overall prevalent HF patients (Klebs et al 2017). The population of that German study likely overlapped with the population in GePaRD of the present study.

Additional potential explanation for higher IR of hypotension in sacubitril/valsartan initiators compared to ACEI users is that for the first few years after launch sacubitril/valsartan, prescribers were less familiar with it than they were with ACEIs and therefore may have been much more cautious with sacubitril/valsartan initiators. It is likely that they monitored the sacubitril/valsartan patients' blood pressure much more intensively than users of ACEIs, which could have led to detection bias.

In a sensitivity analysis, the definition of hypotension was expanded to the 'broad' definition to include symptoms indicative of hypotensive events. This definition closely aligns with the definition used in randomized controlled trials, where patients were more likely to manifest symptoms of hypotension and surveillance was much more intensive (Ruilope et al 2010, Vardeny et al 2018, Velazquez et al 2019, McMurray et al 2014). In the PARADIGM-HF trial (Vardeny et al 2018), IRs of hypotension were 140.4 per 1,000 patients (588/4,187 patients) and 92.1 (388/4,212 patients) for sacubitril/valsartan and ACEI initiators, respectively, who were both naïve to ACEIs, whereas in the present study IRs of hypotension ('broad' definition in exposure cohort 2) were 98.1 [best-case scenario] and 100.6 [worst-case scenario], and 97.9 per 1,000 PYs (exposure cohort 4), respectively. The IR of sacubitril/valsartan initiators for the best-case scenario is almost the same as the IR of new ACEI users, and the overlap in CIs is large, which indicates that there is no difference in IRs of symptomatic hypotension between sacubitril/valsartan and ACEI initiators. However, in the PARADIGM-HF trial an enalapril run-in phase was included, which means that no patients were naïve to ACEIs/ARBs, and therefore the IRs of exposure cohort 1 and 3 were more aligned. IRs of hypotension ('broad' definition) were 85.9 in exposure cohort 1 and 68.9 per 1,000 PYs in exposure cohort 3. Both IRs were lower than the ones estimated from the PARADIGM-HF trial, which may be due to the close monitoring of patients in randomized controlled trials.

Hyperkalemia

Hyperkalemia was the most frequently identified safety event in all four exposure cohorts. In exposure cohort 1, the combined crude IR was 76.1 (95% CI 73.3-79.0) per 1,000 PYs and the combined age- and sex-standardized IR was 79.4 (95% CI 76.4-82.4) per 1,000 PYs. In exposure cohort 2, combined crude IRs were slightly lower and were 64.5 (95% CI 56.3-73.7) per 1,000 PYs for the best-case scenario and 65.7 (95% CI 57.4-74.9) per 1,000 PYs for the worst-case scenario. Also, the combined age- and sex-standardized IR of 68.6 (95% CI 59.7-78.5) per 1,000 PYs was lower in exposure cohort 2 than in exposure cohort 1.

ACEI cohorts demonstrated lower combined IRs as compared to sacubitril/valsartan cohorts. For exposure cohort 3, combined crude and age- and sex-standardized IRs were 30.9 (95% CI 30.5-31.3) per 1,000 PYs and 31.5 (95% CI 31.1-31.9) per 1,000 PYs, respectively. In ACEI users without prior use of ACEIs/ARBs (exposure cohort 4), combined crude and age- and sex-standardized IRs were 45.1 (95% CI 43.9-46.4) per 1,000 PYs and 46.3 (95% CI 45.0-47.6) per 1,000 PYs. Sacubitril/valsartan initiators have a more severe form of HF as they report using MRAs in much higher proportions than ACEI users. Hyperkalemia is a well-known adverse

drug reaction of MRA therapy in HF patients (Vukadinović et al 2017), and together with higher proportions of MRA use among sacubitril/valsartan initiators as compared to ACEI users, this likely explains higher IRs of hyperkalemia among sacubitril/valsartan cohorts. Among sacubitril/valsartan initiators, CKD and diabetes mellitus were more frequently reported. Patients with CKD typically present with hyperkalemia because of an extracellular shift of potassium induced by metabolic acidosis of renal failure (Einhorn et al 2009). Diabetes mellitus is a risk factor for hyperkalemia because of its association with hyporeninemic hypoaldosteronism. This may occur because the sympathetic drive to renin secretion is decreased, the capacity to synthesize renin due to an injury to the juxtaglomerular apparatus is decreased, or the volume stimulus to renin release due to chronic renal salt retention is decreased (Hunter et al 2019, Sousa et al 2016). Beta-blockers were also more used by sacubitril/valsartan initiators than ACEI users, and they may have altered transmembrane potassium movement, which may have resulted in hyperkalemia in these patients (Ben Salem et al 2014, Nyirenda et al 2009). These imbalances in the baseline characteristics have also been observed in prior observational studies that described the characteristics of patients treated with sacubitril/valsartan or the conventional HF treatment (Klebs et al 2017, Maggioni et al 2022, Zeymer et al 2019), whose study populations largely overlap with the study population in GePaRD that contributed most data to this study. Sacubitril/valsartan and ACEI labels recommend a periodic monitoring of potassium, thereby increasing the likelihood of detecting hyperkalemia. However, as sacubitril/valsartan was a new drug in the market, its prescribers were less familiar with it than with the current standard of care, and hence they were more cautious with sacubitril/valsartan initiators. This led them to monitor sacubitril/valsartan initiators more intensively than ACEI users, which in turn could have led to detection bias. Moreover, a substantially larger proportion of patients in the sacubitril/valsartan cohorts were treated concomitantly with several other drugs affecting potassium levels for which monitoring of potassium is recommended (e.g., MRAs, beta-blockers and diuretics), which also resulted that the probability of detecting hyperkalemia increased. In the PARADIGM-HF trial, monitoring of the potassium levels was systematic, according to a pre-defined screening design and was followed regardless of any clinical manifestations that raised suspicions of hyperkalemia (McMurray et al 2014). This systematic monitoring allowed investigators to detect any hyperkalemia at their incipient stages, before they could become clinically significant. In contrast, potassium testing in real-world was performed less intensively as data in the databases or subsets were not primarily collected for research purposes but for medical or administrative purposes. Upon the occurrence of clinical triggers of hyperkalemia, making it more difficult to anticipate on time which may result in more severe episodes of hyperkalemia.

Hepatotoxicity

Combined crude IRs of hepatotoxicity in exposure cohort 1 for the best-case and worst-case scenario were 0.5 (95% CI 0.3-0.9) and 0.8 (95% CI 0.5-1.2) per 1,000 PYs, respectively, and the combined age- and sex-standardized IR was 0.6 (95% CI 0.3-0.9). In exposure cohort 2, those without prior use of ACEIs/ARBs, zero (best-case scenario) to eight cases were potentially found (worst-case scenario for both subsets of CPRD), resulting in combined crude IR of 0.0 (95% CI 0.0-1.3) per 1,000 PYs for the best-case scenario and 2.8 (95% CI 1.2-5.5) per 1,000 PYs for the worst-case scenario. The combined age- and sex-standardized IR was 0.0. The corresponding combined crude and age- and sex-standardized IRs of hepatotoxicity for

exposure cohort 3, containing a mix of patients using both prevalent and incident ACEI users, was both 0.4 (95% CI 0.3-0.4) per 1,000 PYs, and was similar to exposure cohort 1, in which it was 0.6 (95% CI 0.3-0.9) per 1,000 PYs. In ACEI users without prior ACEIs/ARBs use (cohort 4), combined crude IRs were 0.6 (95% CI 0.4-0.7) per 1,000 PYs for the best-case scenario and 0.7 (95% CI 0.5-0.9) per 1,000 PYs for both worst-case scenario. The age- and sex-standardized IR was similar and was estimated to be 0.7 (95% CI 0.5-0.8) per 1,000 PYs.

The limited number of cases of hepatotoxicity did not allow for any meaningful comparison between sacubitril/valsartan initiators and ACEI users. In several databases no event of hepatotoxicity was observed, which was supported by the notion that to date no event of hepatotoxicity has been noted in randomized controlled trials of sacubitril/valsartan (McMurray et al 2014, Velazquez et al 2019, Desai et al 2019).

Renal impairment

The highest combined IR of renal impairment was found in exposure cohort 1 and 2. Combined crude IRs were 24.2 (95% CI 22.3-26.2) per 1,000 PYs for the best-case scenario and 24.4 (95% CI 22.5-26.4) per 1,000 PYs for the worst-case scenario, respectively, and the combined age- and sex-standardized IR was 27.4 (95% CI 25.2-29.8) per 1,000 PYs for exposure cohort 1. For exposure cohort 2, combined crude IRs were 23.6 (95% CI 18.0-30.3) per 1,000 PYs for the best-case scenario) and 26.7 (95% CI 20.7-33.9) per 1,000 PYs for the worst-case scenario. The combined age- and sex-standardized IR was similar to the combined crude IR of the worst-case scenario. Combined crude and age- and sex-standardized IRs were lower in the ACEI users in exposure cohort 3 and 4 compared to exposure cohort 1. Specifically, in exposure cohort 3 the combined crude IR was 13.1 (95% CI 12.8-13.3) per 1,000 PYs and the combined age- and sex-standardized IR was 14.1 (95% CI 13.8-14.4) per 1,000 PYs. In exposure cohort 4 the combined crude IR was 18.4 (95% CI 17.6-19.3) per 1,000 PYs and the combined age- and sex-standardized IR was 20.1 (95% CI 19.2-21.1) per 1,000 PYs.

At time of launch, sacubitril/valsartan was recommended for patients who remained symptomatic despite the current standard of care (i.e., patients with higher disease severity) (Ponikowski et al 2016). These patients with a higher severity of HF were more likely to be present in exposure cohort 1 and 2, although the baseline characteristics were not determined specifically in these cohorts for the safety event of renal impairment. HF patients with a higher disease severity were more susceptible to develop renal impairment (McAlister et al 2004). Patients with HF induce or aggravate renal dysfunctions, which may then further deteriorate cardiac function and so on (Deferrari et al 2021). Thus, it is expected that the IRs of renal impairment were higher in exposure cohort 1 and 2 than those in exposure cohort 3 and 4. However, in a study comprising patients with mild, moderate, and severe renal impairment and matched healthy subjects for each severity group, it was shown that sacubitril/valsartan was generally well tolerated in patients with renal impairment (Ayalasomayajula et al 2016). As patients in the sacubitril/valsartan cohorts seem to have a more severe disease course of HF, more intensive monitoring of renal function may have been conducted, increasing the likelihood of detecting renal impairment. Patients with more severe HF may have had a higher prevalence of comorbidities, such as diabetes or hypertension, which in turn also contribute to the occurrence of renal impairment.

Sensitivity Analysis: Potential COVID-19 pandemic impact

This study includes data during the COVID-19 pandemic (from 2020 onward), which led to nationwide disruptions in healthcare utilization. Extending the study period until the last available data (see Table 9-1) showed similar results to the primary analysis, which had a study end date of December 31, 2019. The impact of the COVID-19 pandemic had no effect on the results of this study.

11.2 Limitations

This study has several limitations mostly pertaining to the availability of data in the underlying databases.

Safety event misclassification

Angioedema events were not validated and represent recorded diagnoses only. Although a full validation of all angioedema cases was planned for this study in case the PPV assessed in a validation study based on a random sample of 100 cases was below 80%, ultimately, validation was not conducted based on the results and recommendations from the validation study ([redacted]).

The conducted validation study applied two validation approaches, a pre-defined validation algorithm ('automated classification') as primary validation approach and general medical assessment based on the same electronic information that was used for the automated classification. A few of the databases reached the pre-specified cut-off value of 80% for the PPV assessment, ranging from 70% in PHARMO to 100% in GePaRD and HSD ([redacted]). A lack of recorded symptoms of angioedema was the main reason for classifying potential cases of angioedema as unconfirmed when using the automated classification. Indeed, the recording of symptoms is not required in any of the healthcare databases included in this study. Validation of all angioedema cases by the automated classification was not considered as being of value for this study because it could result in exclusion of potentially true cases which would result in underestimation of IRs. Using the total number of angioedema events in this study may have led to overestimation of IRs. Considering the PPVs according to the medical assessment from the validation study, rates in the sacubitril/valsartan cohorts were unlikely overestimated due to the high PPV in GePaRD whereas rates in the ACEI cohorts may be slightly overestimated (using the PPVs from the medical assessment changed the IR to 0.8/1,000 PYs (versus 0.9) in exposure cohort 3 and 1.1/1,000 PYs (versus 1.2) in exposure cohort 4).

To assess the risk of underestimating the incidence by missing angioedema cases, the validation study also assessed the FNR of potentially missed angioedema events among a random sample of patients with hypersensitivity events. Due to the limited information available to confirm angioedema, the FNR was low in most databases but the reliability of identifying true angioedema cases was also considered to be low ([redacted]). Instead of using a 'broad' definition including hypersensitivity to understand the potential impact of missing angioedema cases in this study, it appeared to be more appropriate to consider only anaphylactic shock as potentially missed angioedema events. Hence, a sensitivity analysis was conducted including cases coded as anaphylactic shock added those coded as angioedema with a 'narrow' definition.

This sensitivity analysis resulted in a slight increase in IRs of angioedema ('broad' definition i.e., 'narrow' definition and 'anaphylactic shock' definition) that was similar (on absolute scale) in all exposure cohorts.

Safety events of secondary interest were also not validated; hence, potential misclassification cannot be excluded.

Hypotension may be discussed with a GP, and may be observed by a GP, but would rarely lead to hospitalization. Therefore, it is likely that these events were less frequently observed or recorded in ARS and Aarhus, databases that do not capture primary care data.

Hepatotoxicity and renal impairment may not always result in hospitalizations, which may lead to events not being recorded in those databases that do not have linked hospital data.

Hyperkalemia requires laboratory assessments (where available) to identify events. ARS and GePaRD do not include laboratory results. In all exposure cohorts with ARS data, IRs of hyperkalemia were much lower compared with other databases, including GePaRD. This database could have underestimated hyperkalemia as it may only capture severe events identified in the inpatient/emergency setting. In the Netherlands (PHARMO), patients initiating sacubitril/valsartan are likely treated by specialists (de Boer et al 2021), but the laboratory results used for the identification of hyperkalemia were derived from GP records, which do not necessarily contain results of tests that are ordered by specialists. This may explain the lower frequency of hyperkalemia observed in PHARMO compared to other databases in which laboratory values of secondary care are available.

Databases across a range of countries with different healthcare practices and methods of disease coding were used for these analyses. The codes were mapped using the Unified Medical Language System and the Code mapper, and subsequently refined with database partners during quality reviews. However, it was not possible to eliminate the differences in granularity in various coding systems (i.e., between ICD-9, ICPC, and READ) and recording practices of, for instance, acute liver failure which may also cover liver dysfunction by elevated liver enzymes in blood, by a liver biopsy, or by imaging. It was also not possible to overcome differences due to the provenance of data (hospital based in Denmark and ARS, versus primary care data in other databases, or claims data, as used in GePaRD), but we tried to address it by stratification. In addition, PHARMO includes ICPC coding in GP data, which is less granular than the ICD-10 or READ coding used in other databases. To compensate for this, additional text evaluation was applied to comments reported with higher-level codes. Using this method, ICD-10 codes were able to be assigned to the corresponding records, as far as possible with the data available. However, sufficient detail was not always available to permit this in all cases. This aspect (differences between databases) can also be considered a strength because the study gives us a range of real-world data estimates across different healthcare systems and data provenances.

Two databases (Aarhus and CPRD) were not allowed to share cell counts with less than five events, which limited the use of their data especially for the rarer safety events. This limitation had to be mitigated by estimating best-case and worst-case scenarios for combined crude IRs as the true number of safety events was unknown. Addition of four safety events per database or subset for the worst-case scenarios unlikely reflected realistic scenarios and may have led to implausibly high IRs for the rare safety events of interest.

Exposure misclassification

The databases do not fully capture in- and outpatient specialist prescriptions and may have missed the first prescription of exposures of interest (in particular for sacubitril/valsartan), leading to potential exposure misclassification. The potential impact would depend on the situation. If the first prescription was missed but follow-up prescriptions were captured, the PYs at risk may have been underestimated to an unknown extent, and consequently, IRs may have been slightly overestimated if the safety event occurred during follow-up. If the first missed sacubitril/valsartan prescription led to the safety event of interest (e.g., angioedema), treatment was likely to be discontinued and exposure to sacubitril/valsartan may not have been captured at all. As a result, these patients would not contribute to either the number of events or PYs. Although the potential gap in sacubitril/valsartan prescriptions was assessed in a feasibility study ([redacted]), the impact of potential misclassification of exposure could not be captured in a sensitivity analysis.

In SIDIAP, only the month and year was known for prescriptions; for the analysis, the date of a prescription was defined as the first day of the month. Because of this, concurrent prescription for sacubitril/valsartan and ACEIs or vice versa at index date, indicating non-adherence to the 36-hour wash-out period were excluded within the same month. For diagnoses of interest (safety events of interest/ exclusion criteria) occurring in the first month of exposure to sacubitril/valsartan or ACEIs, the initiation of both treatments is always assumed to precede the diagnosis although the opposite may be true. In both circumstances, this resulted in more patients being excluded than needed, which may have led to an underestimation of IRs in case of acute events in SIDIAP. On the other hand, IRs may have been overestimated as patients in SIDIAP were censored at the first day of the month instead of the day when the patient had stopped their treatment, added or switched treatment, which likely has affected the duration of follow-up. The impact is considered to be non-differential across exposure cohorts. Nevertheless, a sensitivity analysis was conducted excluding SIDIAP data from combined IRs which showed generally similar results as the primary analysis (see Section 15.2.1 – Table 1-43 to Table 1-46).

Confounding and covariates

To control for all pre-defined confounders in a comparative analysis which included a small number of angioedema events, propensity score with overlap weighting was applied. However, not all potential confounders (e.g., lifestyle factors such as smoking and alcohol use, or body mass index [BMI] which is a very dynamic variable, and which is not well recorded at all [e.g., ethnicity]) were contained in several databases; this may have led to residual confounding.

The size of exposure cohort 2 was markedly lower than cohort 1, as only approximately 11% of patients initiating sacubitril/valsartan were identified to be naïve to ACEIs/ARBs in the pre-COVID period. This proportion corresponds well with the expectation outlined in the protocol (approximately 10% of patients initiating sacubitril/valsartan being naïve to ACEIs/ARBs; [redacted]). Due to a limited sample size, resulting in a low number of events, an exploratory analysis comparing exposure cohort 2 with exposure cohort 4 could not be performed. A comparative analysis between exposure cohort 1, including patients initiating sacubitril/valsartan regardless of previous ACEIs/ARBs use, and exposure cohort 4 was

conducted, although only in GePaRD. It was demonstrated that patients naïve to ACEIs/ARBs may not be an appropriate comparator group because there was limited overlap in PS.

The severity of HF could not be assessed as there was no information on NYHA class or LVEF was available. A proxy for HF severity was introduced to overcome this, and this was defined as the use of three or more cardiac medications within one year prior to index date. Although this proxy for HF severity was used, a distinction between HFpEF, HFrEF, and HFrEF could not be made, which may have resulted in patients with HFpEF and HFrEF being included among patients using ACEIs. Residual confounding by disease severity in the exploratory analysis cannot be excluded, however, HF severity is not known to increase the risk of angioedema. As discussed in Section 11.1, differences in disease severity plausibly explain the higher incidence rate of some safety events of interest in exposure cohort 1 and 2 as patients seemed to have a more severe disease course of HF, demonstrated by a higher proportion of MRA and beta-blocker use than in exposure cohorts 3 and 4 (Maggioni et al 2022, Zeymer et al 2019, Klebs et al 2017).

For the safety events of hepatotoxicity and renal impairment, separate exposure cohorts were constructed because patients with hepatotoxicity or hepatic morbidities at any time prior to, at, or up to seven days after the index date were excluded to estimate IRs of hepatotoxicity, and CKD and renal impairment anytime or at index date were excluded to estimate IRs of renal impairment. For the patients in these exposure cohorts, patients' characteristics/demographics were not described.

11.3 Interpretation

The present study contributed to the characterization of the safety events of interest based on real-world data. The study results did not indicate an increased risk of angioedema or hepatotoxicity among patients initiating sacubitril/valsartan compared to patients initiating or using ACEIs but did find a higher incidence rates of hypotension, hyperkalemia, and renal impairment. However, as discussed in Section 11.1.3 and below, those differences can be explained by the baseline characteristics of the sacubitril/valsartan initiators.

In the present study very low numbers of angioedema events were found using the 'narrow' definition in all exposure cohorts, especially among sacubitril/valsartan initiators. Angioedema events among patients initiating sacubitril/valsartan in both exposure cohorts were observed in GePaRD. No difference in the absolute risk between exposure cohorts of sacubitril/valsartan initiators and ACEI users was observed. However, IRs of angioedema of sacubitril/valsartan and ACEI users naïve to ACEIs/ARBs (exposure cohort 2 and 4) were higher than IRs of sacubitril/valsartan and ACEI users with a history of exposure to ACEIs/ARBs (exposure cohort 1 and 3). In addition, the exploratory comparative analyses in GePaRD did not identify a significant difference in the risk of angioedema between exposure cohorts of patients initiating sacubitril/valsartan and patients using or initiating ACEIs, which is in line with three randomized controlled trials including patients initiating sacubitril/valsartan or ACEIs (McMurray et al 2014, Velazquez et al 2019, Desai et al 2019). Although comparative analyses were limited to angioedema with the 'narrow' definition, there is no reason to assume that comparative analyses using angioedema events with the 'narrow' definition expanded with the diagnostic codes of anaphylactic shock would change that conclusion, because increased IRs followed a similar pattern across all cohorts in all databases.

For comparability, the new user design was intended to be used to compare patients initiating sacubitril/valsartan who were naïve to ACEIs/ARBs (exposure cohort 2) and patients using ACEIs without prior use of ACEIs/ARBs (exposure cohort 4). However, due to the small number of patients in exposure cohort 2, it was not possible to conduct this comparative analysis.

Exposure cohort 1, which included patients initiating sacubitril/valsartan regardless of prior exposure to ACEIs/ARBs, was not a suitable substitute for exposure cohort 2 when compared to patients naïve to ACEIs/ARBs (exposure cohort 4), as evidenced by a marginal overlap of the PS distribution between exposure cohorts 1 and 4. The difference between both cohorts may be due to the fact that patients in the ACEI cohort who were treatment-naïve to ACEIs/ARBs, were likely to have a higher baseline risk of angioedema due to the inclusion of all patients who were susceptible to an angioedema event. Therefore, a comparison between patients initiating sacubitril/valsartan, regardless of prior exposure to ACEIs/ARBs, with patients using ACEIs who had not previously received ACEIs/ARBs was likely to bias the comparative analysis in favor of sacubitril/valsartan. Besides the comparison of patients in exposure cohort 2 and exposure cohort 4, comparing patients from exposure cohort 1 with those from exposure cohort 3 explored the impact of depletion of susceptibles as well. PS weighting using overlap weights was applied to minimize any potential confounding for the comparison of patients initiating sacubitril/valsartan (exposure cohort 1) with patients using prevalent ACEIs or incident ACEI (exposure cohort 3). There was no association observed between sacubitril/valsartan initiation (regardless of prior exposure to ACEIs/ARBs) and angioedema with a 'narrow' definition. The risk of angioedema is likely to be highest shortly after treatment initiation and decreases over time (Owens et al 2017, Kostis et al 2005, Miller et al 2008, Toh et al 2012). The sensitivity analysis, where prior exposure to ACEIs in exposure cohort 3 was divided in three categories of follow-up duration, showed the highest IR when patients used ACEIs for less than eight weeks prior to index date. The risk then diminished over time. However, the follow-up time in all strata of prior ACEI use was different, which may also explain the difference in the results. Thus, a cohort of patients initiating sacubitril/valsartan regardless of prior exposure to ACEIs/ARBs could be biased against sacubitril/valsartan because exposure cohort 3 included more prevalent users of ACEIs than exposure cohort 1. The HR of this analysis was < 1 which indicated that there was bias towards the null hypothesis. Also, the follow-up time in exposure cohort 3 was substantially longer than in exposure cohort 1, indicating that the association could be biased in favor of ACEIs because the risk of angioedema reduced further over time.

For hepatotoxicity, no differences in combined IRs between any of the exposure cohorts have been observed. The limited number of cases of hepatotoxicity did not allow any comparison between sacubitril/valsartan initiators and ACEI users. In line with another study (McMurray et al 2014), no evidence of a potential risk of hepatotoxicity and sacubitril/valsartan was shown. Two databases (Aarhus and CPRD) were not allowed to share cell counts with less than five events, which limited the use of their data especially for the rarer safety events. This limitation had to be mitigated by estimating best-case and worst-case scenarios for combined crude IRs as the true number of safety events was unknown. Addition of four safety events per database or subset for the worst-case scenarios unlikely reflected realistic scenarios and may have led to high IRs for the rare safety events of interest.

Differences in combined IRs have been observed in hypotension with a 'narrow' definition but to a lesser extent for hypotension with a 'broad' definition. For the latter definition, IRs of

exposure cohort 2 and 4 were almost comparable, which was in line with the findings from the randomized controlled trials where patients were more likely to report symptoms of hypotension than low blood pressure (Ruilope et al 2010, Vardeny et al 2018, McMurray et al 2014). However, differences in combined IRs of hypotension (both definitions) between the exposure cohorts in each database should be interpreted with caution due to observed differences in baseline characteristics. These differences in IRs are likely explained because exposure cohort 1 and 2 included more patients with more severe HF, higher prevalence of comorbidities usually associated with hypotension, higher use of drugs causing low blood pressure (including antihypertensive drugs) and likely more prevalent pre-existing hypotension. As well, the combination of NEP inhibition with ARB blockade in sacubitril/valsartan naturally leads to higher incidence of low blood pressure than ACEI or ARB blockade alone. In the updated ESC guideline, it is stipulated that the use of target doses of evidence-based medications for the management of HFrEF should be attempted, even if patients experience slight hypotension (McDonagh et al 2021). The increased IRs of hypotension for patients initiating sacubitril/valsartan were expected based on the results from randomized controlled trials (Ruilope et al 2010, Vardeny et al 2018, McMurray et al 2014). Overall, hypotension is a listed reaction for sacubitril/valsartan, as increased IRs of hypotension (both definitions) for patients initiating sacubitril/valsartan were noticed in randomized controlled trials (Ruilope et al 2010, Vardeny et al 2018, McMurray et al 2014).

Differences in combined IRs of hyperkalemia between patients initiating sacubitril/valsartan (exposure cohorts 1 and 2) and those using ACEIs/ARBs (exposure cohorts 3 and 4) could be explained by confounding. The comorbidities CKD and diabetes mellitus, and beta-blocker use that were more often reported in exposure cohorts 1 and 2, have been shown to be associated with hyperkalemia (Einhorn et al 2009, Goia-Nishide et al 2022, Hunter et al 2019, Ben Salem et al 2014, Nyirenda et al 2009). Beta-blockers may alter transmembrane potassium movement, resulting in hyperkalemia in these patients (Ben Salem et al 2014, Nyirenda et al 2009). Hyperkalemia is a well-documented adverse event associated with MRA (Vukadinović et al 2017), beta-blocker, and loop diuretic treatment (Hollander-Rodriguez et al 2006), all of which were more frequently reported in patients using sacubitril/valsartan. As a substantially larger proportion of patients in the sacubitril/valsartan cohorts were treated concomitantly with several drugs affecting potassium levels for which monitoring of potassium is recommended, detection bias may have contributed to the higher IRs of hyperkalemia. The novelty to the market of sacubitril/valsartan likely steered its prescribers to monitor potassium more intensively in its initiators, which in turn may have led to detection bias. In addition, patients with HF are more likely to be on a high potassium diet, which can also lead to hyperkalemia. Evidence from the PARADIGM-HF study did not find a difference in hyperkalemia risk between the treatment groups (McMurray et al 2014). Overall, hyperkalemia is an identified risk of sacubitril/valsartan, and it is a listed reaction.

Differences in combined IRs of renal impairment between the exposure cohorts should be interpreted with caution. These differences were likely due to the higher severity of HF in sacubitril/valsartan initiators compared to ACEI users, as guidelines (Ponikowski et al 2016, McDonagh et al 2021) directed patients who remained symptomatic with ACEI use to initiating sacubitril/valsartan. Because of their more severe HF, these sacubitril/valsartan initiators were more likely to develop secondary renal impairment (McAlister et al 2004). Moreover, these

sacubitril/valsartan users with worse clinical conditions were more likely to have other comorbidities that often accompany HF, and which can also lead to renal impairment, such as diabetes and hypertension. Furthermore, these sacubitril/valsartan users were likely under a more intensive monitoring by their prescribers, who were less familiar with sacubitril/valsartan than with the standard of care at that time. This more intensive monitoring may have led to detection bias. Worsening of renal function is an identified risk of sacubitril/valsartan, and it is a listed reaction.

11.4 Generalizability

11.4.1 General databases

All databases in the present study comply with the EU guidelines on the use of medical data for medical research and have been validated for pharmaco-epidemiological research. Data from Aarhus (Denmark), GePaRD (Germany), HSD and ARS (Italy), the PHARMO Database Network (the Netherlands), SIDIAP (Spain), and the CPRD (UK) have been shown to be representative of the general populations of these countries. However, these countries are situated in Western Europe and may not be generalizable to the EU as a whole.

In this report, IRs of angioedema were slightly lower than rates observed in studies from the US where the proportion of Black patients were higher (Burkhart et al 1996, Miller et al 2008, Toh et al 2012), since Black patients initiating ACEIs are more susceptible to angioedema (Miller et al 2008). CPRD is the only database with information on ethnicity, although a few patients had data on race/ethnicity across all exposure cohorts. The impact of ethnicity could therefore not be assessed in this study.

There were differences in the incidence of safety events and the prevalence of comorbidities between the databases. This may have been due to differences in healthcare settings which may have influenced recording of diagnostics, as has been described in Section 11.1.3. For example, Aarhus and ARS capture hospitalizations and emergency visits, whereas other databases capture primary care information, or have data covering the entire continuum of care.

As Aarhus and ARS capture no information from GPs, recordings of allergic reactions were not that common in these databases, however, allergic reactions were captured from emergency visits which were more likely to be severe reactions. In addition, variability across databases may have been due to differences in the information they collect. For example, GePaRD and ARS do not collect laboratory results, and ARS does not capture information from the outpatient setting but has access to diagnoses from emergency visits. Sharing information between healthcare settings enabled the availability of data such as the comorbidities myocardial infarction and angina pectoris. These comorbidities, for example, were underreported in HSD, as there is no direct transfer of patients' information between secondary care (specialists) to primary care (i.e., communication from patient or specialist [highly exceptional] to GP). In PHARMO, however, information from specialists may have present in the notes from the GP.

Also, there were differences in national guidelines and policies in prescribing practice, monitoring programs, and related registration policies, such as the regular assessment of comorbid conditions. Finally, there were differences in types of data being collected by each database, such as exemption from copayment for chronic conditions as captured by ARS and

claims data requiring regular claims for chronic diseases in GePaRD, which was contrary to the other databases. Because of reimbursement, it is likely that (chronic) comorbidities were more reported in these databases than in others. For example, hypertension is much more present in GePaRD than in all other databases. This aspect (differences between databases) can also be considered as a strength, because the study gives us a range of real-world data estimates across different healthcare systems and data provenances.

11.4.2 Characteristics

The study population was on average between 72 and 74 years old and had a similar age as patients with a new onset of HFrEF, who were on average 68 to 72 years old (Maggioni et al 2022, Zeymer et al 2019, Klebs et al 2017). In a real-world setting, sacubitril/valsartan tends to be initiated mainly in prevalent patients with HFrEF awaiting a treatment alternative to their current, possibly suboptimal, therapy. In this study approximately 71 % of patients were men in exposure cohort 1, which was consistent with the sex distribution among patients with a new onset of HFrEF (Brouwers et al 2013, Maggioni et al 2022, Zeymer et al 2019).

11.4.3 Safety event of interest – primary objectives

Restriction of patients initiating sacubitril/valsartan to those naïve to ACEIs/ARBs (exposure cohort 2) had a large impact on the size of cohort 2, with just 11% of the patients initiating sacubitril/valsartan in exposure cohort 1 being naïve to ACEIs/ARBs in the pre-COVID period. Due to the small number of patients in exposure cohort 2, the results in this cohort should be interpreted with caution with respect to generalizability.

Patients who initiated sacubitril/valsartan in exposure cohort 2 had a less severe HF at baseline than the patients who initiated sacubitril/valsartan in exposure cohort 1 as determined by a proxy for HF severity (i.e., the number of cardiac medications for the treatment of HF). The proportions of patients with more than three cardiac medications for the treatment of HF was 17% in exposure cohort 2 whereas this was 44% in exposure cohort 1. It is possible that newly diagnosed patients with mild symptoms of HF were included in exposure cohort 2, as prescribers became more familiar with sacubitril/valsartan after its launch, but this should be interpreted with caution.

11.4.4 Safety event of interest – secondary objectives

The IR of angioedema, identified in exposure cohort 3 (an HF population representing a mix of patients using predominantly prevalent and to a lesser degree incident [new] ACEI) can be considered generalizable to a random sample of patients using ACEIs with underlying HF, but are not generalizable to a population of patients using incident ACEI for HF.

A large proportion of ACEI-associated angioedema cases tend to occur shortly after ACEI treatment initiation (Kostis et al 2005, Miller et al 2008, Toh et al 2012). A cohort of patients using prevalent ACEIs, such as exposure cohort 3, may have been depleted of patients with prior angioedema occurrence, thereby representing a population with a lower baseline angioedema risk in comparison to a cohort of patients using incident ACEI, such as exposure cohort 4. As with the other safety events of interest than angioedema in this study, the combined IRs identified in exposure cohort 3 were generally slightly lower compared to those observed in exposure cohort 4. It is conceivable that patients in exposure 3 were comparable to a random

sample of patients with HF. However, the restriction to patients using ACEIs who were naïve to ACEIs/ARBs had a large impact on the number of included patients and impacted the pattern of concomitant cardiovascular medications. It is likely that this exposure cohort 4 included newly diagnosed patients with HF.

12 Other information

Not applicable.

13 Conclusion

This was a large observational study involving 39,616 patients initiating sacubitril/valsartan across seven databases from six European countries, of which GePaRD contributed most of the data in the pre-COVID period. It provided valuable real-world data on the important identified and potential risks as defined in the RMP (angioedema, hypotension, hyperkalemia, hepatotoxicity, and renal impairment). The study has achieved its stated objectives and contributed to the further understanding of the safety profile of sacubitril/valsartan.

The study findings indicate that the use of sacubitril/valsartan is considered to be safe: an increased risk of angioedema among patients initiating sacubitril/valsartan compared to patients initiating or using ACEIs was not found. The overall numbers of angioedema events found in the study were low in all exposure cohorts, especially among sacubitril/valsartan initiators. There appears to be no differences in IRs of angioedema between sacubitril/valsartan and ACEI users, even though the IRs of angioedema of naïve sacubitril/valsartan and ACEI users were slightly higher than IRs of sacubitril/valsartan initiators and ACEI users with a history of ACEI exposure. In GePaRD, sufficient number of angioedema events were recorded among patients initiating sacubitril/valsartan to conduct two comparative analyses, specifically, patients initiating sacubitril/valsartan regardless of prior exposure to ACEIs/ARBs compared to patients using ACEIs regardless of or without prior exposure to ACEIs/ARBs. Both comparative analyses showed the impact of depletion of susceptibles and no (significant) increased risk of angioedema between exposure cohorts of patients initiating sacubitril/valsartan and patients using ACEIs.

There appear to be no differences in IRs of hepatotoxicity between exposure cohorts of patients initiating sacubitril/valsartan and patients using ACEIs although the limited number of cases of hepatotoxicity did not allow any meaningful comparison.

IRs of hypotension, hyperkalemia, and renal impairment (to a much lesser extent) were higher in patients initiating sacubitril/valsartan compared to patients using ACEIs, but any comparison of crude IRs should be interpreted with great caution. The higher incidences of those safety events are likely due to imbalances in patients' characteristics, the presence of underlying diseases, and closer monitoring of patients. Increased IRs of hypotension were expected given the dual mechanism of action of sacubitril/valsartan, in line with the data from the pivotal randomized controlled trials.

14 References (available upon request)

Abdin A, Schulz M, Riemer U, et al (2022) Sacubitril/valsartan in heart failure: efficacy and safety in and outside clinical trials. ESC Heart Fail; 9(6):3737-50.

Austin PC (2009) Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Simul Comput; 38(6):1228-34.

Ayalasomayajula SP, Langenickel TH, Jordaan P, et al (2016) Effect of renal function on the pharmacokinetics of LCZ696 (sacubitril/valsartan), an angiotensin receptor neprilysin inhibitor. Eur J Clin Pharmacol; 72(9):1065-73.

Ben Salem C, Badreddine A, Fathallah N, et al (2014) Drug-induced hyperkalemia. Drug Saf; 37(9):677-92.

Borgan O and Liestol K (1990) A note on confidence intervals and bands for the survival function based on transformations. Scand J Statist; 17:35-41.

Brouwers FP, de Boer RA, van der Harst P, et al (2013) Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. Eur Heart J; 34(19):1424-31.

Bundesärztekammer (BÄK), Arbeitsgemeinschaft der Deutschen Ärztekammern, Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) and A. d. D. A. (AMK), Eds. (2019). Nationale VersorgungsLeitlinie Chronische Herzinsuffizienz – Langfassung, 3. Auflage (German).

Burkhart DG, Brown NJ, Griffin MR, et al (1996) Angiotensin converting enzyme inhibitor associated angioedema: higher risk in blacks than whites. Pharmacoepidemiol Drug Saf; 5(3):149-54.

Cazzola M, Puxeddu E, Bettoncelli G, et al (2011) The prevalence of asthma and COPD in Italy: a practice-based study. Respir Med; 105(3):386-91.

Dalton JE and Yang D (2012) An unified approach to measuring the effect size between two groups using SAS. SAS Global Forum 2012. Statistics and data analysis. Paper 335-2012.

de Boer RA, Dieleman-Bij de Vaate AJ, Isfordink LM, et al (2021) Hartfalen NHG-STANDAARD KNR nummer M51, NHG, May 2021 (in Dutch).

Deferrari G, Cipriani A, La Porta E (2021) Renal dysfunction in cardiovascular diseases and its consequences. J Nephrol; 34(1):137-53.

Desai AS, Solomon SD, Shah AM, et al (2019) Effect of sacubitril‐valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA; 322: 1077-84.

DerSimionian R and Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials; 7(3):177-88.

Dobson AJ, Kuulasmaa K, Eberle E, et al (1991) Confidence intervals for weighted sums of Poisson parameters. Stat Med; 10:457-62.

Donner-Banzhoff N, Kreienbrock L, and Baum E (1994) Hypotension--does it make sense in family practice? Fam Pract; 11(4):368-74.

Ehrenstein V, Antonsen S, and Pedersen L (2010) Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol; 2:273-9.

Einhorn LM, Zhan M, Hsu VD, et al (2009) The Frequency of Hyperkalemia and Its Significance in Chronic Kidney Disease. Arch Intern Med;169(12):1156-62.

Enders D, Engel S, Linder R, et al (2018) Robust versus consistent variance estimators in marginal structural Cox models. Stat Med;37(24):3455-70.

European Medicines Agency (2024) HMA-EMA Catalogues of real-world data sources and studies. Available from https://catalogues.ema.europa.eu/ (accessed 5 July 2024).

Food and Drug Administration (2013) Guidance for Industry and FDA Staff. Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data. Available from <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm243537.pdf> (accessed 24 September 2021).

García-Gil MDM, Hermosilla E, Prieto-Alhambra D, et al (2011) Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). Inform Prim Care; 19(3):135-45.

Garwood F (1936) Fiducial limits for the Poisson distribution. Biometrika; 46:441-53.

Goia-Nishide K, Coregliano-Ring L, and Belvilagua Rangel E (2022) Hyperkalemia in diabetes mellitus setting. Diseases;10(2): 20.

Golberg RJ, Gurwitz JH, Saczynski JS, et al (2013) Comparison of medication practices in patients with heart failure and preserved versus those with reduced ejection fraction (from the Cardiovascular Research Network [CVRN]). Am J Cardiol; 111(9): 1324-9.

[redacted]

Herrett E, Thomas SL, Schoonen WM, et al (2010) Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol; 69(1):4-14.

Higgins JPT and Green S (2011) Cochrane handbook for systematic reviews of interventions. Part 2: General methods for Cochrane reviews. Version 5.1.0 The Cochrane Collaboration updated March 2011.

Hollander-Rodriguez JC and Calvert JF (2006) Hyperkalemia. Am Fam Physician 2006; 73:283-90.

Hunter RW and Bailey MA (2019) Hyperkalemia: pathophysiology, risk factors and consequences. Nephrol Dial Transplant; 34(3): iii2–iii11

Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al (2003) Validity of the general practice research database. Pharmacotherapy; 23(5):686-9.

Kenchaiah S and Vasan RS (2015) Heart failure in women—insights from the Framingham Heart Study. Cardiovasc Drugs Ther; 29:377-90.

Klebs S, Balas B, Grunow SS, et al (2017) P4395 – Characteristics of patients with heart failure prescribed sacubitril/valsartan in the primary care setting in Germany. Eur Heart J; 38(suppl1): 911.

Kostis JB, Kim HJ, Rusnak J, et al (2005) Incidence and characteristics of angioedema associated with enalapril. Arch Intern Med; 165(14):1637-42.

[redacted]

Li F, Morgan KL, and Zaslavsky AM (2018) Balancing covariates via propensity score weighting. J Am Stat Assoc;113(521):390-400.

Li F, Thomas LE, and Li F (2019) Addressing extreme propensity scores via the overlap weights. Am J Epidemiol;188(1):250-7.

Lin DY (1994) Cox regression analysis of multivariate failure time data: the marginal approach. Stat Med;13(21):2233-47.

Lin DY and Wei LJ (1989) The robust interference for the cox proportional hazards model. J Am Stat Assoc;84(408):1074-8.

Maggioni AP, Anker SD, Dahlström U, et al (2013) Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 15(10):1173-84.

Maggioni AP, Clark AL, Barrios V, et al (2022) Outcomes with sacubitril/valsartan in outpatients with heart failure and reduced ejection fraction: The ARIADNE registry. ESC Heart Fail; 9(6):4209-18.

Mao H, Li L, and Greene T (2018) Propensity score weighting analysis and treatment effect discovery. Stat Methods Med Res;28(8):2439-54.

Masclee GMC, Straatman H, Arfè A, et al (2018) Risk of acute myocardial infarction during use of individual NSAIDs: A nested case-control study from the SOS project. PLoS ONE; 13(11):e0204746.

Mathur R, Bhaskaran K, Chaturvedi N, et al (2014) Completeness and usability of ethnicity data in UK-based primary care and hospital databases. J Public Health; 36(4):684-92.

McAlister FA, Ezekowitz J, Tonelli M et al (2004) Renal Insufficiency and Heart Failure. Prognostic and Therapeutic Implications From a Prospective Cohort Study. Circulation; 109:1004-9.

McDonagh TA, Metra M, Adamo M, et al (2021) 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J; 42(36):3599-3726.

McMurray JJ, Packer M, Desai AS, et al (2014) Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med; 371(11):993-1004.

Miller DR, Oliveria SA, Berlowitz DR, et al (2008) Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. Hypertension; 51(6):1624-30.

Morris JK, Tan J, Fryers P, et al (2018) Evaluation of stability of directly standardized rates for sparse data using simulation methods. Popul Health Metr; 16(1):19.

National Institute for Health and Care Excellence (2016) Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. Technology appraisal guidance [TA388]. Available from < https://www.nice.org.uk/guidance/TA388/chapter/1-Recommendations > (accessed 16 October 2023).

Nyirenda MJ, Tang JI, Padfield PL, et al (2009) Hyperkalaemia. BMJ; 339:b4114.

Office for National Statistics (2016) Revised European Standard Population 2013 (2013 ESP) – "age standardized mortality rate calculation template using the 2013 ESP". Available from < https://webarchive.nationalarchives.gov.uk/ukgwa/20160106020035/http://www.ons.gov.uk/ons/guide-method/user-guidance/health-and-life-events/revised-european-standard-population-2013--2013-esp-/index.html > (Assessed 16 March 2022).

Ohlmeier C, Langner I, Garbe E, et al (2016) Validating mortality in the German Pharmacoepidemiological Research Database (GePaRD) against a mortality registry. Pharmacoepidemiol Drug Saf; 25(7):778-84.

Owens RE and Oliphant CS (2017) Angioedema Spotlight: a closer examination of sacubitril/valsartan safety results. J Am Board Fam Med; 30(4): 556-7.

Pigeot I and Ahrens W (2008) Establishment of a pharmacoepidemiological database in Germany: methodological potential, scientific value and practical limitations. Pharmacoepidemiol Drug Saf; 17(3):215-23.

Ponikowski P, Voors A., Anker S. et al (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur Heart J, 37 (27):2129–2200.

Ray WA (2003) Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol; 158(9):915-20.

Ruilope LM, Dukat A, Böhm M, et al (2010) Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. Lancet; 375:1255-66.

Sahai H and Khushid A (1993). Confidence intervals for the mean of a Poisson distribution: a review. Biom J ;35(7):857-67.

Schemper M, Wakounig S, and Heinze G (2009) The Estimation of Average Hazard Ratios by Weighted Cox Regression. Stat Med; 28:2473-89.

Shi V, Senni M, Streefkerk H, et al (2018) Angioedema in heart failure patients treated with sacubitril/valsartan (LCZ696) or enalapril in the PARADIGM-HF study. Int J Cardiol; 264:118-123.

Solomon SD, McMurray JJV, Anand IS, et al (2019) Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med; 381(17):1609-20.

Sousa AGP, de Sousa Cabral JV, El-Feghaly WB, et al (2016) Hyporeninemic hypoaldosteronism and diabetes mellitus: pathophysiology assumptions, clinical aspects and implications for management. World J Diab; 7:101-11.

Sulkowski MS, Thomas L, Chaisson RE, et al (2000). Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B Virus infection. JAMA; 283(1):74-80.

Toh S, Reichman ME, Houstoun M, et al (2012) Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. Arch Intern Med; 172(20):1582-9.

Trifirò G, Gini R, Barone-Adesi F, et al (2019) The role of European healthcare databases for post-marketing drug effectiveness, safety and value evaluation. Where does Italy stand? Drug Saf; 42(3):347-63.

Ulm K (1990). A simple method to calculate the confidence interval of a standard mortality ratio. Am J Epid; 131(2): 373-5.van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, et al (2010) New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. Eur J Cancer; 46(2): 395-404.

Vardeny O, Miller R, and Solomon SD (2014) Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. JACC Heart Fail; 2(6):663-70.

Vardeny O, Claggett B, Kachadourian J, et al (2018) Incidence, Predictors, and Outcomes Associated With Hypotensive Episodes Among Heart Failure Patients Receiving Sacubitril/Valsartan or Enalapril: The PARADIGM-HF Trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure). Circ Heart Fail; 11(4):e004745.

Velazquez EJ, Morrow DA, DeVore AD, et al (2019) Angiotensin-Neprilysin inhibition in acute decompensated heart failure. N Eng J Med; 380:539-38.

Vukadinović D, Lavall D, Vukadinović AN, et al (2017) True rate of mineralocorticoid receptor antagonists-related hyperkalemia in placebo-controlled trials: A meta-analysis. Am Heart J; 188:99-108.

Wachter R, Viriato D, Klebs S, et al (2018) Early insights into the characteristics and evolution of clinical parameters in a cohort of patients prescribed sacubitril/valsartan in Germany. Postgrad Med; 130(3):308-16.

Wachter R, Fonseca AF, Balas B, et al (2019) Real‐world treatment patterns of sacubitril/valsartan: a longitudinal cohort study in Germany. Eur J Heart Fail; 21(5):588-97.

Wang SV, Pinheiro S, Hua W, et al (2021) STaRT-RWE: structured template for planning and reporting on the implementation of real world evidence studies. BMJ. 12:372:m4856.

Yoshida K, Solomon DH, and Kim SC (2015) Active-comparator design and new-user design in observational studies. Nat Rev Rheumatol; 11(7):437-41.

Zhang H, Huang T, Shen W, et al (2020) Efficacy and safety of sacubitril/valsartan in heart failure: a meta-analysis of randomized controlled trials. ESC Heart Fail; 7:3841-50.

Zeymer U, Groves R, and Merkel T (2019) Treatment of patients with heart failure (HFrEF) in Germany: differences between cardiologists and primary care physicians. Abstracts of the heart failure 2019 and the world congress on acute heart failure, 25-28 May 2019, Megaron Athens international conference centre, Greece. Eur J Heart Fail;21(Suppl1): 3-592.

15 Appendices

15.1 Appendix 1 – List of stand-alone documents

Appendix	Appendix Title	Documents included
15.1.1	Protocol and protocol amendments	
15.1.2	List of IEC/IRBs	
15.1.3	Signature page of final report	
15.1.4	Documentation of statistical methods (SAP)	
15.1.5	Study code list with additional attributes (available upon request)	

15.2 Appendix 2 – Additional relevant statistical information

15.2.1 Result tables, Study Codes, GePaRD confirmation algorithms, and a description of input files