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LCZ696 / sacubitril/valsartan / Entresto®

LCZ696B2015
Non-interventional Study Final Report

Non-interventional post-authorization multi-database safety study to assess the risk of myotoxicity, hepatotoxicity, and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto® (sacubitril/valsartan)

Author(s) [redacted]

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Research question and objectives	With this non-interventional, multi-database case-control study, real-world data was gathered on the potential impact of co-administration of an HMG-CoA reductase inhibitor (statin) together with sacubitril/valsartan on the risk of statin-associated toxicity, namely of myotoxicity, hepatotoxicity, and acute pancreatitis
Country(-ies) of study	Denmark, Germany, Italy, the Netherlands, Spain, United Kingdom

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Marketing authorization holder

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1 Abstract

Title

Non-interventional post-authorization multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto® (sacubitril/valsartan)

Version and date

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Keywords

Sacubitril/valsartan; statins, drug-drug interaction, safety, case-control study

Rationale and background

LCZ696 (sacubitril/valsartan; Entresto®) was approved in the European Union (EU) for the treatment of adult patients with symptomatic chronic heart failure (HF) and a reduced ejection fraction (HFrEF) in November 2015.

Based on the observation that sacubitril inhibits the organic anion-transporting polypeptides OATP1B1 and OATP1B3 transporters *in vitro*, a drug-drug interaction (DDI) study with atorvastatin (an HMG-CoA reductase inhibitor [statin]) was conducted. An increase in the maximal plasma concentrations (C_{max}) of the OATP1B1 and OATP1B3 substrates (atorvastatin and its metabolites) by up to 2-fold was noted with sacubitril/valsartan. However, the areas under the curve (AUCs) for atorvastatin and its metabolites were not increased to a clinically significant extent (< 1.3-fold). This suggests that the impact of sacubitril on the pharmacokinetics of atorvastatin is limited to C_{max}. Therefore, the EU SmPC recommends that "caution should be exercised when co-administering sacubitril/valsartan with statins".

To further understand the impact of interactions between sacubitril/valsartan and OATP1B1 and OATP1B3 substrates, another clinical DDI study was undertaken. Sacubitril/valsartan was shown to have no clinically significant impact on exposures of both simvastatin and simvastatin acid when simvastatin was co-administered with sacubitril/valsartan.

Based on findings from the atorvastatin DDI study and given the high proportion of patients expected to be on a concomitant statin post-marketing, the Committee for Medicinal Products for Human Use (CHMP) requested that Novartis consider further evaluation of this potential DDI in the post-marketing setting. Novartis therefore committed to perform a non-imposed, non-interventional post-authorization safety study (NIS PASS) to assess specific statin-associated safety events (myotoxicity, hepatotoxicity, or acute pancreatitis) in association with concomitant use of statins and sacubitril/valsartan in patients with HF (Study LCZ696B2015).

Research question and objectives

For this NIS, real-world data were gathered on the potential impact of co-administration of a statin together with sacubitril/valsartan on the risk of myotoxicity, hepatotoxicity, or acute pancreatitis in patients with HF.

The primary objective of the study was:

To separately assess the relative risk of the above outcome events associated with concomitant exposure of sacubitril/valsartan and statins compared with statin exposure alone in patients with HF.

The secondary objectives of the study were:

1. To assess the impact of duration of use of sacubitril/valsartan on the association of concomitant exposure to sacubitril/valsartan and statins on the outcome events.
2. To assess the impact of recency of cessation of sacubitril/valsartan on the association of exposure to sacubitril/valsartan and statins on the outcome events.
3. To determine if any potential association of concomitant exposure of sacubitril/valsartan and statins on the outcome events is dependent on the type of statin.
4. To determine if any potential association of concomitant exposure of sacubitril/valsartan and statins on the outcome events is dependent on the statin dose.

Study design

LCZ696B2015 is a non-interventional, multi-database, post-authorization safety study (PASS) category 3, using a case-control design nested in a dynamic population of patients with HF exposed to statins.

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 at the latest, 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 and secondary analyses (including primary and secondary 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 base is the source population at risk that gave rise to the cases for this study and was constructed per database. The study base consisted of all patients who were registered in their respective database during the study period, i.e., after the launch of sacubitril/valsartan. The study base included adult patients (≥ 18 years of age) exposed to statins during the study period, with a valid database history of ≥ 365 days and a diagnosis of HF at any time, i.e., throughout the entire available history in patients' electronic health records/claims data. In GePaRD, HF was identified by a predefined confirmation algorithm.

The observation period for each patient ended at the date of data availability, death, or the end data of the study period. Patients were censored on the end date of the last period of treatment with statins.

For each outcome of interest (myotoxicity, hepatotoxicity, or acute pancreatitis), controls were sampled from the study base, which resulted in separate case-control risk sets. Cases were patients who had a recorded outcome event of interest which was identified using the database-specific coding systems for recorded inpatient and/or outpatient 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)). Additional natural language processing (NLP) terms were used in PHARMO to further differentiate ICPC codes. In GePaRD, the outcome events were identified by a predefined confirmation algorithm. The first recorded event date of the outcome event of interest within the study period during follow-up (once all inclusion criteria were fulfilled) was defined as 'index date'.

Patients with the following events during follow-up were censored if these events occurred before the outcome event of interest:

- Myotoxicity: myotoxic events for which external causes (other than poisoning by drugs or medicaments) have been recorded.
- Hepatotoxicity: events indicating hepatic morbidity without defined cause (e.g., "hepatitis unspecified"), or indicating hepatic morbidity suggestive of another etiology ("other specified disorders of liver", including hepatitis C, or HIV, or biliary or alcohol-induced hepatotoxicity). These events were excluded by the specification 'exclude' and all diagnostic codes for hepatic morbidity including prescriptions of HCV drugs (a proxy for hepatitis C) and HIV.
- Acute pancreatitis: Alcohol-induced or biliary acute pancreatitis, other diseases of the pancreas, or pancreatic cancer events.

Up to 100 controls were sampled for each case from the study base of patients at risk (the set of eligible controls) in the same database by matching on age (year of birth [±2 years]), sex, index date (actual event date of the corresponding case), and category of duration of statin exposure at index date, using incidence density sampling. For PHARMO, SIDIAP, and CPRD, eligibility for linked hospital data was added as a matching criterion.

Inclusion and exclusion criteria were applied to the matched case-control risk sets as specified in the study protocol.

Variables and data sources

Exposure information such as sacubitril/valsartan and statins, was identified using prescription or dispensing data using the database-specific coding systems.

Episodes of uninterrupted use of sacubitril/valsartan and statins (on class-level) were separately constructed based on the calculated durations per prescription. Each prescription was extended with a grace period, which was the maximum of either seven days or half the calculated duration of the prescription (Catalan et al 2000). Stockpiling was not considered, i.e., durations were truncated on the day that a patient had a subsequent fill. If the next prescription occurred before the last day of this extended duration (duration + grace period) continuous use was assumed, otherwise the episode of uninterrupted use ended at the end of the calculated duration without the grace period.

For the *primary objective*, concomitant sacubitril/valsartan use (yes/no) was determined as an episode of sacubitril/valsartan use that covered the index date or stopped at most seven days before the index date. The same definition of concomitant sacubitril/valsartan use was also applied for *secondary objective 3 and 4*.

For the *secondary objective 1* investigating the duration of sacubitril/valsartan exposure, duration for patients with concomitant sacubitril/valsartan use was calculated as the index date minus the start of the episode of sacubitril/valsartan use that covered the index date or stopped at most seven days before. The duration of sacubitril/valsartan exposure was further classified in the following categories relative to index date: short (30 days prior to index date), medium (31 - 90 days prior), long (> 90 days prior) duration of concomitant sacubitril/valsartan use.

For the *secondary objective 2* investigating recency of cessation of sacubitril/valsartan use, only the episode that covered the index date or stopped at most 90 days before was considered in the classification of recent sacubitril/valsartan exposure. Recency of use was defined relative to index date as follows: Concomitant use (covers index date and stops at most seven days prior to index date), recent use (exposure ended between eight and 90 days prior), non-use (never used sacubitril/valsartan or use ended > 90 days prior).

Patient characteristics/demographics were assessed with a look-back period of one year prior and including the index date. Evaluation of comorbidities were done ever before index date and assessment of co-medications was conducted 365 days prior to index date. Concomitant use with statins and risk factors were assessed for all outcome events in the 90 days, within one year, or any time before or at index date, respectively.

Statistical methods

Statistics of patient demographic and clinical characteristics were described for cases and controls, using contingency tables for categorical variables, and mean (±SD), median (IQR), and minimum, maximum for continuous variables per database in the pre-COVID (primary and secondary analyses) and full study period (sensitivity analysis), and for the analysis where cases of myotoxicity were defined as patients with diagnostic codes other than myalgia alone (sensitivity analysis).

For each database or subset, the relative risk of myotoxicity, hepatotoxicity, or acute pancreatitis was expressed as an odds ratio (OR; crude and adjusted) with its corresponding 95% CIs for concomitant exposure of sacubitril/valsartan with statins versus statin exposure alone are estimated in patients with HF per database (as feasible) and in all databases. Estimates were calculated in the pre-COVID period and full study period. In a sensitivity analysis, cases of myotoxicity were defined as patients with diagnostic codes other than myalgia alone. Furthermore, sensitivity analyses excluding data from SIDIAP were conducted for all outcomes.

For all outcomes of interest (myotoxicity, hepatotoxicity, and acute pancreatitis) database- or subset-specific and pooled ORs with corresponding 95% CIs were calculated as follows: the crude and adjusted ORs (parameter estimates and standard errors (SEs)) estimated with the conditional logistic regression models in each database were combined in a two-stage meta-analysis, using fixed- and random-effects models employing the Mantel-Haenszel (Robins et al 1986, Higgins et al 2011) and DerSimonian and Laird method (DerSimonian et al 1986), respectively. This was performed for the primary objective, secondary objectives, and all sensitivity analyses.

Reporting information on small-cell-counts had to be adhered to for some databases (small-cell-count policy): cell counts below five such as the number of cases or concomitant users of sacubitril/valsartan and statins in cases or controls in Aarhus and CPRD, could not be displayed. However, Aarhus can share information when there are zero outcome events of interest as long as patients are not traceable. This information was relevant for estimating the pooled ORs and their SEs using the Mantel-Haenszel method. To deal with the small-cell-counts, two scenarios were introduced: the highest and lowest exposed scenarios. For the lowest exposed scenario, zero (only when database- or subset-specific ORs were <0.01 in CPRD) otherwise one user per database or subset (for Aarhus and/or CPRD) was assumed, and for the highest exposed scenario, four users per database or subset (for Aarhus and/or CPRD) were assumed.

Both meta-analysis methods used in this study, handle databases or subsets with zero exposure to sacubitril/valsartan among cases, i.e., ‘single arm zero study’ or ‘single zero-counts’ in databases or subsets (Xu et al 2021), differently: The fixed-effect model considers data from single zero-counts by including the weight of each database or subset in the meta-analysis whereas the random-effects model deals with these single zero-counts by giving those databases or subsets zero weight, i.e., by excluding it. The weights of databases or subsets with single zero-counts tend to go to zero because these databases or subsets have a large SE. In the random-effects model, the database- or subset-specific SEs were directly included in the between-database or subsets variance. In scenarios where both cases and controls were not exposed to sacubitril/valsartan (i.e., ‘double zero-counts’), the affected comparison category in a given database or subset was not included in the analysis.

Given the poor performance of the significance tests for statistical heterogeneity, no such testing was used. Rather, heterogeneity of the fixed- and random-effects model was assessed based on I^2. Meta-analysis of pooled data was performed if heterogeneity did not exceed 50% (Cochrane Collaboration 2011). Otherwise, the cells were blank in tables presenting the results of the primary, secondary, and sensitivity analyses. Negative values of heterogeneity were truncated at zero.

A sensitivity analysis for the outcome event of myotoxicity was performed to assess the potential bias due to a low specificity of identifying myotoxicity. For this analysis, a more specific definition of myotoxicity was used, excluding cases with only a diagnostic code for myalgia in all databases, except for ARS and HSD, which use the ICD-9 coding system that does not have a specific code for myalgia.

In another sensitivity analysis the impact of the COVID-pandemic was examined. In this analysis, the primary objective was examined for the full period, including the period in which the COVID-19 pandemic occurred.

In SIDIAP, the date of the dispensing was defined as the first day of the month because only the month and year of dispensing is captured in this database. Patients, therefore, may not have been correctly defined as concomitant users of sacubitril/valsartan and statins or statins alone at the date of the outcome event of interest. Furthermore, the duration of statin use, as well as the duration or patient exposure to sacubitril/valsartan at index date would be overestimated. Because the direction and magnitude of bias which may have been introduced by this measurement error is difficult to predict, post-hoc sensitivity analyses were conducted that excluded SIDIAP for the estimation of pooled ORs and corresponding 95% CIs for the primary analysis (primary objective).

Results

Subjects

A total source population of 41,383,318 patients from seven European electronic healthcare databases was utilized in this study. After the application of all exclusion criteria, a total of 922,199 patients were included in the study base. For each of the outcomes of interest, the number of patients at risk slightly differed, since they were not allowed to have a history of the outcome event of interest. Of these patients at risk, cases with the outcome event of interest were identified and then controls were sampled, using incident density sampling.

Myotoxicity

For the primary objective, across all databases, 2,634 cases of myotoxicity and 200,556 matched controls were included in the primary analysis (pre-COVID period). In this analysis, the database- or subset-specific adjusted ORs comparing concomitant use of sacubitril/valsartan and statins with statin use alone ranged from <0.01 (Aarhus and HSD) to 1.78 (PHARMO without linked hospital data). The CIs were wide and covered the null effect of no association. Meta-analyses based on the fixed-effects model for the primary analysis of myotoxicity showed adjusted ORs of 1.17 (95% CI 0.86-1.58) for the lowest exposed scenario and 1.17 (95% CI 0.87-1.56) for the highest exposed scenario. The random-effects model resulted in an adjusted OR of 1.21 (95% CI 0.88-1.66) based on eight databases or subsets excluding Aarhus and HSD due to zero cases exposed to sacubitril/valsartan.

The two sensitivity analyses including the full study period and excluding SIDIAP data showed similar results compared to the primary analysis.

For secondary objective 1 on duration of concomitant use of sacubitril/valsartan and statins, only four of ten databases or subsets had an adequate number of cases and controls concomitantly using sacubitril/valsartan and statins in all categories of duration of use (short: 30 days, medium: 31 to 90 days, long: >90 days prior index) to perform an analysis. Database- or subset-specific adjusted ORs ranged from <0.01 to 20.09 with no consistent pattern for any duration category. The CIs were wide and covered the null effect indicating no association for most databases and duration categories, except for CPRD without linked hospital data and short duration ($OR_{adjusted}$ 5.77, 95% CI 1.31-25.52) and PHARMO without linked hospital data and medium duration ($OR_{adjusted}$ 20.09, 95% CI 1.66-243.54). In the meta-analysis using the fixed-effects model, the adjusted ORs for short, medium, and long duration of concomitant use of sacubitril/valsartan and statins were 1.78 (95% CI 0.98-3.24), 1.16 (95% CI 0.60-2.24), and 1.01 (95% CI 0.66-1.54) for the lowest exposure scenario and 1.77 (95% CI 1.09-2.87), 1.15 (95% CI 0.65-2.05), and 1.01 (95% CI 0.68-1.50) for the highest exposure scenario, respectively. Adjusted ORs based on the random-effects model for short, medium, and long duration of concomitant use of sacubitril/valsartan and statins were 2.37 (95% CI 1.31-4.30), 1.42 (95% CI 0.71-2.81), and 1.11 (95% CI 0.72-1.71), respectively.

The analysis addressing secondary objective 2 on recency of use of sacubitril/valsartan included four cases with recent use (i.e., treatment episode ending between eight and 90 days before the index date) from GePaRD and both subsets of SIDIAP. Database- or subset-specific adjusted ORs ranged from <0.01 to 2.48 with wide CIs covering the null effect of no association. For the meta-analysis of recent use, the fixed-effects model resulted in adjusted ORs of 1.12 (95% CI 0.42-3.01) and 1.10 (95% CI 0.41-2.95) for the lowest and highest exposed scenarios, respectively. The random-effects model showed an adjusted OR of 1.55 (95% CI 0.57-4.23).

For secondary objective 3 on specific types of statins, 1,135 cases of myotoxicity and 75,532 matched controls were included in the analysis comparing concomitant use of sacubitril/valsartan and atorvastatin at index date with atorvastatin use alone. Database- or subset-specific adjusted ORs ranged from <0.01 to 2.20 with wide CIs covering the null effect of no association. In the meta-analysis using the fixed-effect model, adjusted ORs were 0.90 (95% CI 0.58-1.41) and 0.90 (95% CI 0.61-1.34) for the lowest and highest exposed scenario, respectively. The random-effect model resulted in an adjusted OR of 1.02 (95% CI 0.64-1.61) based on six of ten databases or subsets. For simvastatin, 1,148 cases and 77,948 matched controls were included in the meta-analysis; data from Aarhus did not further contribute to the analysis because less than five cases using simvastatin were identified. Database- or subset-specific adjusted ORs ranged from <0.01 to 5.29 with wide CIs covering the null effect of no association. In the meta-analysis using the fixed-effects model, adjusted ORs were 1.28 (95% CI 0.77-2.15) and 1.27 (95% CI 0.82-1.97) for the lowest and highest exposed scenario, respectively. The random-effects model showed an adjusted OR of 1.56 (95% CI 0.92-2.64) based on five databases or subsets.

For secondary objective 4 on statin dose, there were 1,602 cases of myotoxicity and 114,227 matched controls included in the analysis of high dose statins. Database- or subset-specific adjusted ORs ranged from <0.01 to 1.65 with wide CIs covering the null effect of no association. In the meta-analysis using the fixed-effects model, adjusted ORs were 1.02 (95% CI 0.70-1.48) and 1.02 (95% CI 0.72-1.43) for the lowest and highest exposed scenario, respectively. The random-effects model resulted in an adjusted OR of 1.13 (95% CI 0.78-1.66) based on seven databases or subsets. For low dose statins, 1,037 cases and 72,149 matched controls were included in the analysis; data from Aarhus did not further contribute to the analysis because less than five cases on lose dose of statins were identified. Database- or subset-specific adjusted ORs ranged from <0.01 to 2.65 with wide CIs covering the null effect of no association. In the meta-analysis using the fixed-effects model, adjusted ORs were 1.53 (95% CI 0.90-2.61) and 1.53 (95% CI 0.98-2.40) for the lowest and highest exposed scenario, respectively. Using the random-effect model, the adjusted OR was 1.62 (95% CI 0.92-2.85) based on six databases or subsets.

A sensitivity analysis was conducted utilizing a more specific definition of myotoxicity that excluded non-specific myalgia cases, resulting in 311 cases and 23,174 matched controls in the analysis. ARS and HSD did not contribute to this analysis because the ICD-9 coding system lacks specific codes for myalgia. Database- or subset-specific and pooled adjusted ORs were mainly numerically higher and consistent with the primary analysis. However, confidence intervals (CIs) overlapped and included the null effect. Excluding SIDIAP data from this analysis, resulted in higher adjusted ORs based on data from GePaRD and PHARMO with linked hospital data: using the fixed-effect model, adjusted ORs were with SIDIAP data 1.52 (95% CI 0.78-2.98) and 1.51 (95% CI 0.77-2.95) and without SIDIAP data 2.48 (95% CI 1.01-6.11) and 2.42 (95% CI 0.98-5.95) for the lowest and highest exposed scenario, respectively. The random-effect model yielded adjusted ORs of 1.93 (95% CI 0.95-3.92) based on four databases/subsets including SIDIAP data and of 3.11 (95% CI 1.18-8.14) based on data from GePaRD and PHARMO with linked hospital data only.

Hepatotoxicity

For the primary objective a total of 329 cases of hepatotoxicity and 30,636 matched controls were included in the primary analysis (pre-COVID period). Of the seven databases or subsets included in this analysis, GePaRD and SIDIAP with linked hospital data, had cases concomitantly exposed to sacubitril/valsartan and statins. The other five databases included less than five cases (CPRD) or no cases exposed to sacubitril/valsartan. The ORs for SIDIAP with linked hospital data and GePaRD were below one (SIDIAP: $OR_{adjusted}$ 0.87, 95% CI 0.19-4.04 and GePaRD: $OR_{adjusted}$ 0.85, 95% CI 0.30-2.36), and were based on two and four cases with concomitant sacubitril/valsartan and statin exposure out of

29 and 253 cases, respectively. The meta-analysis showed for the fixed-effects model adjusted ORs of 0.76 (95% CI 0.33-1.72) and 0.75 (95% CI 0.33-1.70) for the lowest and highest exposed scenario, respectively. The random-effects model resulted in an adjusted OR of 0.86 (95% CI 0.37-2.01) based on two databases or subsets excluding Aarhus, ARS, both PHARMO and CPRD with linked hospital data, and SIDIAP without linked hospital data due to zero cases exposed to sacubitril/valsartan.

The sensitivity analyses including the full-study period and where SIDIAP data were excluded showed similar results compared to the primary analysis. No result for the meta-analysis of the random-effects model in the sensitivity analysis without SIDIAP data was presented as only GePaRD provided data for this model.

For secondary objective 1 on duration of concomitant use of sacubitril/valsartan and statins, only GePaRD had a sufficient number of cases and controls concomitantly using sacubitril/valsartan and statins in each category of the duration of concomitant use (short, medium, or long) of sacubitril/valsartan and statins, while there were two cases for medium and long duration in SIDIAP with linked hospital data. Adjusted ORs for low, medium, and long duration of concomitant sacubitril/valsartan and statin exposure in GePaRD were 1.17 (95% CI 0.16-8.67), 1.96 (95% CI 0.47-8.16), and 0.35 (95% CI 0.05-2.54) and in SIDIAP the adjusted ORs for medium and long duration were 2.42 (95% CI 0.30-19.81) and 0.82 (95% CI 0.10-6.55), respectively. In all other databases and subsets less than a total of five cases were present, or no case was concomitantly using sacubitril/valsartan and statins in one of the categories of duration of use. In the meta-analysis, using the fixed-effects model, the adjusted ORs for short, medium, and long duration of concomitant sacubitril/valsartan and statin use were 0.54 (95% CI 0.07-3.85),1.97 (95% CI 0.62-6.29), and 0.44 (95% CI 0.11-1.81) for lowest exposed scenario and 0.50 (95% CI 0.07-3.56),1.89 (95% CI 0.59-6.04), and 0.44 (95% CI 0.11-1.81) for the highest exposed scenario, respectively. Adjusted ORs based on the random-effects model for medium and long duration of concomitant sacubitril/valsartan and statin use were, 2.09 (95% CI 0.64-6.82) and 0.52 (95% CI 0.12-2.20), respectively. For short duration, a meta-analysis of the random-effects model was not needed as GePaRD only contributed data for this analysis.

Regarding the secondary objective 2 on recency of sacubitril/valsartan use, none of the cases (less than five for CPRD) was recently exposed to sacubitril/valsartan in any of the databases. A meta-analysis, using the fixed- or random-effects model, was not conducted for recent use of sacubitril/valsartan and the risk of hepatotoxicity.

For secondary objective 3 on specific types of statins, there were 123 cases of hepatotoxicity and 10,482 matched controls included in the analysis of atorvastatin. Cases and controls were concomitantly exposed to sacubitril/valsartan and atorvastatin in GePaRD and SIDIAP with linked hospital data, whereas no case and control were exposed to sacubitril/valsartan (double zero exposed) in SIDIAP without linked hospital data and CPRD with linked hospital data. In all other databases, less than five cases of hepatotoxicity were present among patients using atorvastatin. The adjusted OR was 0.33 (95% CI 0.04-2.47) and 1.39 (95% CI 0.17-11.55) in GePaRD and SIDIAP with linked hospital data, which was based on one case exposed to sacubitril/valsartan in both databases. In the meta-analysis, using the fixed-effects model the adjusted OR was 0.62 (95% CI 0.15-2.56) for the lowest and highest exposed scenario, respectively. The random-effects model showed an adjusted OR of 0.65 (95% CI 0.15-2.81), which was based on two databases. For simvastatin, 160 cases of hepatotoxicity and 14,944 matched controls were included in the analysis. Only cases and controls were concomitantly using sacubitril/valsartan at index date in GePaRD and SIDIAP with linked hospital data. In Aarhus none of the cases was exposed to sacubitril/valsartan. Other databases did not contribute data to this analysis. The adjusted ORs were 1.18 (95% CI 0.36-3.89) and 3.53 (95% CI 0.37-33.71) in GePaRD and SIDIAP with linked hospital data, respectively. Using the fixed-effects model, the adjusted ORs were 1.63 (95% CI 0.59-4.50) and 1.58 (95% CI 0.58-4.36) for the lowest and highest exposed scenario, respectively. The random-effects model showed an adjusted OR of 1.50 (95% CI 0.52-4.30), which was based on two databases.

For secondary objective 4 on statin dose, there were 163 cases of hepatotoxicity and 14,022 matched controls included in the analysis of high dose statin use. Database- or subset-specific adjusted ORs ranged from <0.01 to 1.05 with wide CIs covering the null effect indicating no association. All other

databases with less than five cases did not contribute data for this objective. The meta-analysis showed for the fixed-effects model, adjusted ORs of 0.51 (95% CI 0.19-1.40) and 0.51 (95% CI 0.24-1.10) for the lowest and highest exposed scenario, respectively. The random-effects model showed an adjusted OR of 0.65 (95% CI 0.19-2.24), which was based on two databases or subsets. For low dose of statins,157 cases and 14,950 matched controls were included in the analysis. Aarhus, GePaRD, and SIDIAP with linked hospital data contributed data to this analysis and the adjusted ORs were <0.01 (Aarhus and SIDIAP with linked hospital data) and 1.24 (GePaRD), respectively. In the meta-analysis, using the fixed-effects model adjusted ORs were 1.00 (95% CI 0.31-3.17) and 0.97 (95% CI 0.30-3.06) for the lowest and highest exposed scenario, respectively. No meta-analysis of the random-effects model was performed as the results were based on GePaRD data only,

Acute pancreatitis

For the primary objective, across nine databases or subsets, a total of 1,265 cases of acute pancreatitis and 115,042 matched controls were included in the primary analysis (pre-COVID period). Data from PHARMO without linked hospital data were not included in any of the analyses for acute pancreatitis (less than five cases). Database- or subset-specific adjusted ORs comparing concomitant use of sacubitril/valsartan and statins with statin use alone ranged from <0.01 (Aarhus, HSD, and both subsets of CPRD) to 1.96 (PHARMO with linked hospital data). The CIs were wide and covered the null effect indicating no association. Meta-analyses based on the fixed-effects model showed adjusted ORs of 0.82 (95% CI 0.47-1.42) for the lowest and highest exposed scenario. The adjusted OR for the random-effects model was 0.98 (95% CI 0.55-1.72) which was based on five databases (Aarhus, HSD, and both subsets of CPRD had no cases with exposure to sacubitril/valsartan).

The two sensitivity analyses including the full study period and excluding SIDIAP data showed similar results compared to the primary analysis.

For secondary objective 1 on duration of concomitant use of sacubitril/valsartan and statins, there was no database or subset with adequate number of cases and controls concomitantly using sacubitril/valsartan and statins in all categories of duration of use (short, medium, or long) to perform an analysis. Database- or subset-specific adjusted ORs ranged from <0.01 to 7.02 with no consistent pattern of any duration category of concomitant use of sacubitril/valsartan and statins. The CIs were large and included the null effect, indicating no association. In the meta-analysis, using the fixed-effects model, the adjusted ORs for short, medium, and long duration of concomitant sacubitril/valsartan and statin use were 0.89 (95% CI 0.28-2.77), 1.29 (95% CI 0.41-4.04), and 0.71 (95% CI 0.34-1.50) for the lowest exposure scenario and 0.87 (95% CI 0.28-2.70), 1.27 (95% CI 0.41-3.98), and 0.71 (95% CI 0.34-1.50) for the highest exposure scenario, respectively. Adjusted ORs based on the random-effect model for short, medium, and long duration of concomitant sacubitril/valsartan and statin use were 1.16 (95% CI 0.37-3.65), 4.37 (95% CI 1.35-14.17), and 1.13 (95% CI 0.52-2.47), respectively.

For secondary objective 2 on recency of use of sacubitril/valsartan, an analysis was performed in ARS, GePaRD, and SIDIAP without linked hospital data. Apart from PHARMO without linked hospital data, all other databases had at least five cases to perform an analysis. Database- or subset-specific adjusted ORs ranged from <0.01 to 4.79 with wide CIs covering the null effect indicating no association. For the meta-analysis of recent use, the fixed-effects model resulted in adjusted ORs of 2.26 (95% CI 1.00-5.10) and 2.23 (95% CI 0.99-5.02) for the lowest and highest exposed scenario, respectively. The random-effects model showed an adjusted OR of 2.61 (95% CI 1.12-6.07), which was based on three databases or subsets.

For secondary objective 3 on specific types of statins, 529 cases of acute pancreatitis and 42,608 matched controls were included in the analysis comparing concomitant use of sacubitril/valsartan and atorvastatin at index date with atorvastatin use alone. Database- or subset-specific adjusted ORs ranged from <0.01 to 3.59 with wide CIs that included the null effect, indicating no association. The meta-analysis showed, when using the fixed-effects model, adjusted ORs of 0.91 (95% CI 0.43-1.93) for the lowest and highest exposed scenario. The random-effects model resulted in an adjusted OR of 1.29 (95% CI 0.59-2.80) and was based on five databases. For simvastatin, 628 cases and 53,516 matched controls were included in the analysis. Only GePaRD had cases and controls that were concomitantly

using sacubitril/valsartan and simvastatin at index date. Apart from PHARMO without linked hospital data, in all other databases none of the cases was exposed to sacubitril/valsartan. The adjusted OR for the comparison between concomitant use of sacubitril/valsartan and simvastatin and the risk of acute pancreatitis in GePaRD was 1.35 (95% CI 0.54-3.37). Similar results were observed for the random-effects model as GePaRD contributed only data for this analysis. Using the fixed-effects model, the ORs were 1.01 (95% CI 0.42-2.45) and 0.98 (95% 0.41-2.38) for the lowest and highest exposed scenario, respectively.

For secondary objective 4 on statin dose, there were 650 cases of acute pancreatitis and 53,913 matched controls included in the analysis of high dose of statins. Database- or subset-specific ORs ranged from <0.01 to 2.96. The CIs were wide and covered the null effect indicating no association. In the meta-analysis using the fixed-effects model, adjusted ORs were 0.94 (95% CI 0.48-1.82) for the lowest and highest exposed scenario. The random-effects model resulted in an adjusted OR of 1.17 (95% CI 0.59-2.33) based on five databases or subsets. For low dose of statins, 617 cases of acute pancreatitis and 53,024 matched controls were included in the analysis; data from PHARMO without linked hospital data did not further contribute to the analysis because less than five cases on low dose of statins were identified. Except for GePaRD, in all other databases including CPRD, (potentially) none of the cases was exposed to sacubitril/valsartan. The adjusted OR for the comparison between concomitant use of sacubitril/valsartan and low dose of statins and the risk of acute pancreatitis was 0.88 (95% CI 0.32-2.40). The same results were observed in the random-effects model, as results from GePaRD were only included, and therefore no meta-analysis was conducted. The fixed-effects model yielded adjusted ORs of 0.72 (95% CI 0.27-1.93) and 0.70 (95% CI 0.26-1.88) for the lowest and highest exposed scenario, respectively.

Discussion

The present study aimed to assess whether concomitant use of sacubitril/valsartan and statins versus statins alone, increased the risk of myotoxicity, hepatotoxicity, or acute pancreatitis in patients with HF. Database- or subset-specific analyses, for each of the three outcome events, were limited due to the low number of cases, as well as the low number of cases concomitantly exposed to sacubitril/valsartan and statins. In addition, there was an increased risk of chance findings due to multiplicity in terms of providing CIs for multiple outcomes and analyses. The more comparisons that are made, the more likely it is that at least one comparison will be statistically significant by chance alone, even if the treatment has no true effect. Therefore, all results presented for the secondary objectives should be interpreted with caution.

Myotoxicity

No significant increased risk of myotoxicity for concomitant use of sacubitril/valsartan and statins was observed when comparing it with users of statin alone in the primary analysis. Results were comparable for the fixed- and random-effects models for pooling. The results of the meta-analysis were largely driven by GePaRD and SIDIAP. Excluding the results from SIDIAP from the primary analysis in the post-hoc sensitivity analysis showed similar pooled adjusted ORs of 1.17 (95% CI 0.78-1.76) and 1.17 (95% CI 0.78-1.76) in the fixed-effects model for the lowest exposed scenario and pooled adjusted ORs from 1.21 (95% CI 0.88-1.66) to 1.25 (95% CI 0.82-1.90) in the random-effects model.

The pre-planned sensitivity analysis, excluding myalgia cases only, from myotoxicity, showed a higher (non-significant) risk of myotoxicity for the primary analysis, including SIDIAP data (pooled $OR_{adjusted}$ from 1.17, 95%CI 0.86-1.58 to 1.52, 95% CI 0.78-2.98 for the lowest exposed scenario and pooled $OR_{adjusted}$ from 1.21, 95%CI 0.88-1.66 to 1.93, 95% CI 0.95-3.92 using the fixed- and random-effects model, respectively). When SIDIAP data were excluded from this sensitivity analysis, the pooled adjusted ORs increased to 3.11 (95% CI 1.18-8.14) in the random-effects model and increased to 2.48 (95% CI 1.01-6.11) in the fixed-effects model for the lowest exposed scenario. This may suggest an association between concomitant use of sacubitril/valsartan and statins and the risk of myotoxicity that is more specifically defined and not based on myalgia alone, although the associated risk was not observed for the highest exposed scenario from the fixed effects model. However, this analysis should

be interpreted with caution due to the low number of cases (n=5) that were concomitantly exposed to sacubitril/valsartan and statins.

The secondary analyses focused on exploring the potential association of concomitant use of sacubitril/valsartan and statins further, by investigating whether the duration of concomitant use, recency of use of sacubitril/valsartan, type and dose of statins, had an impact. This reduced the number of exposed in each exposure category substantially, resulting in an increased uncertainty around the ORs. No significant associations were found, although some isolated statistically significant associations were shown for some exposure categories (one in PHARMO without linked hospital data and one in CPRD without linked hospital data), with wide CI's which were not consistent nor explainable. These analyses were all conducted using the broadly defined outcome of myotoxicity.

No statistically significant evidence of an association between myotoxicity and concomitant exposure to sacubitril/valsartan and atorvastatin compared to atorvastatin alone was observed. This corroborates the idea that any pharmacokinetic interaction between sacubitril and atorvastatin does not necessarily and directly imply a higher risk of muscular disorders. The lack of evidence of a higher risk with concomitant use of sacubitril/valsartan and simvastatin also indicates against the existence of the risk of broadly defined myotoxicity. Although there is an inconsistent pattern in the risk of myotoxicity for concomitant use of sacubitril/valsartan and simvastatin across databases, the results are in line with the studies that showed no pharmacokinetic interaction between sacubitril/valsartan and simvastatin or its active metabolite (Ayalasomayajula et al 2017, Ayalasomayajula et al 2018). A pharmacokinetic interaction exists between sacubitril/valsartan and atorvastatin but not between sacubitril/valsartan and simvastatin. Observing no association either with one or with other types of statins using broadly defined myotoxicity, points against the clinical significance of such a potential interaction.

Hepatotoxicity

There was no association between concomitant use of sacubitril/valsartan and statins and the risk of hepatotoxicity when compared to statin use alone, using the fixed-effects model for the meta-analysis, in which all databases are included. No effects of duration of use and recency of sacubitril/valsartan or type and dose of statins were observed. Excluding SIDIAP data from the meta-analysis did not affect the primary analysis.

Acute pancreatitis

No association between concomitant use of sacubitril/valsartan and statins and an increased risk of acute pancreatitis was found when comparing it with users of statin alone. This was consistent for the fixed- and random-effects models. When the results from SIDIAP were excluded, the pooled weights of the other databases increased, however, the findings of this analysis were similar to the results of the primary analysis.

A statistically significant association was found for medium duration (i.e., 31 to 90 days prior to index date) of concomitant use of sacubitril/valsartan and statins and an increased risk of acute pancreatitis, using the random-effects model. This finding was not observed in the fixed-effects model where cases and controls from six other databases or subsets were included. This suggests that the results of the random-effects model were biased towards an increased risk of acute pancreatitis when databases with single zero-counts were ignored. There is no database that contributed data to all three categories of sacubitril/valsartan duration, but for the analysis with medium duration only data from ARS and both subsets of SIDIAP were included, which all showed risk effects in the same direction. The results of SIDIAP should be considered with caution as patients may have been wrongly defined as exposed at index date if their first dispensing of sacubitril/valsartan occurred in the same month as the index date or were incorrectly categorized as medium duration of use.

Recent use of sacubitril/valsartan showed also a statistically significant increased risk of acute pancreatitis, using the fixed- and random-effects model. In ARS, GePaRD, and SIDIAP without linked hospital data, which all showed an increased risk of acute pancreatitis, the analyses included overall six cases who discontinued treatment with sacubitril/valsartan more than eight days before the index date, at the latest, by which time the drugs should be eliminated (the estimated half-life of valsartan is 9.9

hours and that of sacubitril (prodrug) 1.4 hours, and for sacubitrilat (the active metabolite of the prodrug sacubitril) 11.5 hours (Entresto CDS/USPI)). It is anticipated that at the time of the event, patients were likely on single treatment with statin, as sacubitril/valsartan should have been eliminated based on their half-lives. The clinical manifestations of acute pancreatitis may sometimes start insidiously, and some days may elapse before the diagnosis can be established. Vomiting and poor oral intake are frequent and can lead to dehydration and electrolyte disturbances, which are to be avoided in HF patients. Prescribers of sacubitril/valsartan were likely more familiar with it than with the standard of care at that time and may therefore have been more cautious and willing to discontinue sacubitril/valsartan as soon as those manifestations appeared, compared with other medications. These discontinuations, in turn, may have occurred some days before the diagnosis of acute pancreatitis was established, reflecting in the recency that is addressed in this analysis. Regarding recent use, it is questionable whether the risk of the outcome event of interest among recent users of sacubitril/valsartan can be assessed in a nested case-control design. This design can be misleading for the analysis of lagged exposures such as recent use of sacubitril/valsartan (Deubner et al 2007).

All other secondary objectives (i.e., atorvastatin, simvastatin, high and low dose of statins) showed similar results as the primary analysis. As the sacubitril/valsartan users with a medium duration or recent use were small, the Bayesian method of meta-analysis should have been considered, but due to data protection regulations using patient-specific data from each database was not possible. The results of both meta-analyses should be interpreted with caution owing to the limited number of cases exposed to sacubitril/valsartan.

Pooling of data

Meta-analyses based on the fixed-effects model were conducted using the Mantel-Haenszel method (Robins et al 1986) for which calculation of the weight of each database requires knowledge about the actual number of cases and controls, which was challenging for small numbers in Aarhus and CPRD, since these were redacted. This required that sometimes a lowest exposed and highest exposed scenario analysis had to be performed for the fixed-effects model of the meta-analysis since the weight in this model is based on the absolute number of cases and controls. While the true OR is unknown, these scenarios provide an understanding of the variation when applying different assumptions. For the random-effects model, the DerSimonian and Laird method was used, using the SEs of the database- or subset-specific estimates (DerSimonian et al 1986). Databases or subsets with single zero-counts received zero weight and were therefore excluded from the random-effects model. Both DerSimonian and Laird and Mantel-Haenszel have been found to produce biased effect estimates when evaluating rare events, especially in instances of double zero exposure encountered in many secondary analyses in this study (Efthimiou 2018). Thus, the results of such analyses need to be interpreted with caution. Both fixed-effects and random-effects models were provided to transparently show the difference.

The EU SmPC of sacubitril/valsartan recommends that "caution should be exercised when co-administering sacubitril/valsartan with statins". This recommendation was based on in vitro data. No previous observational studies have explored the interaction between sacubitril/valsartan and statins and the risk of myotoxicity, hepatotoxicity, or acute pancreatitis, which makes it challenging to put these results into clinical context. Regular monitoring is warranted when treatment with sacubitril/valsartan is initiated in patients starting treatment with statins at the same time or patients at risk for these three outcome events.

Conclusion

This study is the first to evaluate a potential drug-drug interaction between sacubitril/valsartan and statins and the risk of myotoxicity, hepatotoxicity, or acute pancreatitis using real-world data.

No association was found between concomitant use of sacubitril/valsartan and statins versus statins alone and the risk of myotoxicity, hepatotoxicity, or acute pancreatitis. No consistent pattern of database- or subset-specific risks was observed for any outcome event, which supports the overall finding that indicates no association. Furthermore, no evidence of an association was observed for any outcome event of interest and concomitant use of sacubitril/valsartan with atorvastatin or simvastatin, individually, and high or low dose of statins. Statistically significant associations were found in some analyses for the

secondary objectives investigating duration of use and recency of use, however, these results were based on very low numbers of cases concomitantly exposed to sacubitril/valsartan and statins and are more likely chance findings due to the multiplicity of comparisons.

Study findings should be interpreted with caution given the limitations of this real-world study.

Marketing Authorization Holder(s)

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

[redacted]

2 List of abbreviations

ACEI	Angiotensin Converting Enzyme Inhibitor
ARB	Angiotensin Receptor Blocker
ARS	Agenzia Regionale di Sanità della Toscana
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BCRP	Breast Cancer Resistant Protein
BIPS	Leibniz Institute for Prevention Research and Epidemiology
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CK	Creatinine Kinase
CKD	Chronic Kidney Disease
CM	Clinical Modification
C_{max}	Maximal Plasma Concentration
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	The disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
CPRD	Clinical Practice Research Datalink
CYP	Cytochrome P450 Enzyme
DDD	Defined Daily Dose
DDI	Drug–Drug Interaction
DE	Deutschland (Germany)
DK	Denmark
Dx	Diagnosis
EED	Eligibility Entry Date
EHR	Electronic Healthcare Record
ERCP	Endoscopic Retrograde Cholangio-Pancreatography
EMR	Electronic Medical Record
ES	Spain
EU	European Union
EU PAS register	European Union electronic Register of Post-Authorization Studies
FU	Follow-up
GePaRD	German Pharmacoepidemiological Research Database
GM	German Modification
GP	General Practitioner
HCV	Hepatitis C virus
HES	Hospital Episode Statistics
HF	Heart Failure
HFrEF	Heart Failure with Reduced Ejection Fraction
HIV	Human Immunodeficiency Virus
HSD	Health Search Database
ICD-9	The International Classification of Diseases, 9th Revision
ICD-10	The International Classification of Diseases, 10th Revision
ICPC	International Classification of Primary Care
IQR	Interquartile Range
IT	Italy

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
MRI	Magnetic Resonance Imaging
NIS	Non-Interventional Study
NL	The Netherlands
NLP	Natural Language Processing
NSAID	Non-Steroidal Anti-Inflammatory Drug
OATP	Organic Anion-Transporting Polypeptide
OR	Odds Ratio
PASS	Post-Authorization Safety Study
PDD	Prescribed Daily Dose
PPV	Positive Predictive Value
PRAC	Pharmacovigilance Risk Assessment Committee
PYs	Person Years
Q	Calendar Quarter
QC	Quality check
R	R programming language
RAAS	Renin–Angiotensin–Aldosterone–System
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software package from SAS Institute Inc.
SD	Standard Deviation
SE	Standard Error
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SHI	Statutory Health Insurance
SmPC	Summary of Product Characteristics
TIA	Transient Ischemic Attack
UK	United Kingdom
US	United States
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	09-Jul-2024	None
Registration in the EU PAS register	After PRAC/CHMP endorsement of the protocol	Apr 2017	None
ISAC approval (CPRD)	Dec 2017	Dec 2017	None
Study progress report 1	Q4 2017 or with PBRER in 2018	06-Apr-2018	None
Study progress report 2	Q1 2019	06-Feb-2019	None
Study progress report 3	Q1 2020	30-Mar-2020	None
Study progress report 4	Q3 2021	30-Sep-2021	None
Final report	31-Dec-2024§	03-Oct-2024	None

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

*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 December 31, 2024 due to the implementation of additional quality assurance measures.

6 Rationale and background

6.1 Rationale and background

LCZ696 (sacubitril/valsartan; Entresto®) is a treatment approved in the United States, the European Union (EU) and a number of other countries globally since 2015. In the EU, Entresto® is indicated in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

Based on the observation that sacubitril inhibits the organic anion-transporting polypeptides OATP1B1 and OATP1B3 *in vitro*, Novartis conducted a drug–drug interaction (DDI) study with atorvastatin (an HMG-CoA reductase inhibitor [statin]) in which sacubitril/valsartan increased the maximal plasma concentrations (C_{max}) of the OATP1B1 and OATP1B3 substrates atorvastatin and its metabolites by up to 2-fold (Ayalasomayajula et al 2017). However, the areas under the curve (AUCs) of atorvastatin and its metabolites were not increased to a clinically significant extent (<1.3-fold), suggesting that the impact of sacubitril on the pharmacokinetics of atorvastatin is limited to C_{max}. Therefore, the EU Summary of Product Characteristics (SmPC) recommends "that caution should be exercised when co-administering Entresto with statins".

To further elucidate the potential of sacubitril/valsartan to interact with OATP1B1 and OATP1B3 substrates, Novartis conducted another clinical DDI study – completed after the Entresto® EU submission – using simvastatin. Simvastatin is a prodrug and metabolized to the active metabolite simvastatin acid, which is a more sensitive OATP1B1 and OATP1B3 substrate. Sacubitril/valsartan had no clinically significant impact on exposures of both simvastatin and simvastatin acid when simvastatin was co-administered with sacubitril/valsartan (Ayalasomayajula et al 2016).

Based on the atorvastatin study and given the high proportion of patients expected to be on a concomitant statin post-marketing, the Committee for Medicinal Products for Human Use (CHMP) requested that Novartis consider further evaluation of this potential DDI in the post-marketing setting. In the Entresto® EU Risk Management Plan (RMP Version 1.4), Novartis therefore committed to perform a (non-imposed) non-interventional post-authorization safety study (PASS, category 3) dedicated to assessing specific statin-associated outcome events, namely myotoxicity, and hepatotoxicity, in association with concomitant use of sacubitril/valsartan and statins in patients with heart failure (HF) (study LCZ696B2015). In addition, in the Pharmacovigilance Risk Assessment Committee (PRAC) RMP Assessment Report from September 2015, Novartis was asked by the PRAC Rapporteur to "consider including pancreatitis to the list of statin-related events".

Considering the above, the non-interventional DDI study (LCZ696B2015) focuses on concomitant use of sacubitril/valsartan and statins, and the occurrence of myotoxicity, hepatotoxicity, or acute pancreatitis in the real-world.

7 Research question and objectives

The goal of this study was to provide real-world evidence on the potential impact of co-administration of a statin together with sacubitril/valsartan to separately evaluate the potential for an increased risk of myotoxicity, hepatotoxicity, or acute pancreatitis. The objectives below were assessed for each of these outcomes separately, referred to as 'the outcome events of interest'.

The objectives of the study were:

Primary objective

To separately assess the relative risk of the above outcome events associated with concomitant exposure of sacubitril/valsartan together with statins compared with statin exposure alone in patients with HF.

Secondary objectives

1. To assess the impact of duration of use of sacubitril/valsartan on the association of concomitant exposure to sacubitril/valsartan and statins on the outcome events
2. To assess the impact of recency of cessation of sacubitril/valsartan on the association of exposure to sacubitril/valsartan and statins on the outcome events
3. To determine if any potential association of concomitant exposure of sacubitril/valsartan and statins on the outcome events is dependent on the type of statin
4. To determine if any potential association of concomitant exposure of sacubitril/valsartan and statins on the outcome events is dependent on the statin dose.

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
LCZ696B2015 v01 amendments				
1	06 June 2019	4 'Milestones'	Amendment	The recalculated sample size requires an extension of the study timelines by one year and an additional progress report.
2	06 June 2019	6 'Research question and objectives'	Amendment	Addition of Section 6.2 'Secondary objectives' to specifically reflect secondary analyses already planned originally.
3	06 June 2019	7.3.3 'Covariates'	Update	Addition of various general covariates.
4	06 June 2019	7.4 'Data sources' (and other sections	Amendment	Due to the low number of sacubitril/valsartan-exposed patients

		throughout the protocol where applicable)		identified in the first two progress reports, GePaRD and ARS are added to complement the initially included five databases.
5	06 June 2019	7.5 Study size/power calculation'	Amendment	Recalculation of the sample size with lower assumptions of the sacubitril/valsartan exposure prevalence in controls now varying from 0.2% to 5% (instead of 10% and 20% as in the original v0.0 protocol version).
6	06 June 2019	7.6 'Data management'	Update	To reflect necessary revisions in the methodology (Jerboa© won't be used anymore and is replaced by SAS) – due to the change in the coordinating center from Erasmus MC to the PHARMO Institute for Drug Outcomes Research.
LCZ696B2015 v02 amendments				
7	18 March 2021	4 'Milestones'	Amendment	Extension of the study timeline and inclusion of an additional 4th progress report.
8	18 March 2021	6.2 Secondary objectives	Amendment	Secondary objective number two was rephrased to better address a potential DDI of sacubitril/valsartan with individual statins or dose intensity of statins.
9	18 March 2021	7.2.2.4.2 'Exclusion'	Update	Minor modification of the exclusion criteria (regarding exposure to sacubitril/valsartan prior to the country-specific launch date [e.g., through exposure in a clinical trial, or in a patient access program]). Further clarifications/ specifications of exclusion criteria for myotoxicity, hepatotoxicity, and acute pancreatitis added.
10	18 March 2021	7.3.1	Update	Clarifications added for the definition of statin dose intensity.
11	18 March 2021	7.3.1	Update	Clarifications added regarding necessary separate matching steps to assess the impact of sacubitril/valsartan on individual statins.
12	18 March 2021	7.3.3	Update	Order of covariates presentation revised to follow the LCZ696B2015 SAP.
13	18 March 2021	7.3.3.1	Update	Categorization of general covariates of interest revised.
14	18 March 2021	7.3.3.2	Update	Obesity was deleted as covariate for myotoxicity (as low body mass index is a risk factor for myotoxicity rather than obesity); surgery and trauma were removed as covariates but included as exclusion criteria for myotoxicity (see Section 7.2.2.4.2); metabolic disorders were removed as covariate (as

				carnitine palmitoyltransferase II deficiency, myophosphorylase deficiency, coQ10 deficiency or myoadenylate deaminase deficiency do not have specific diagnostic codes in the databases and therefore cannot be determined).
15	18 March 2021	7.7.2.5	Update	Additional sensitivity analysis proposed due to the COVID-19 pandemic.
16	18 March 2021	12.3.3 Table 12-1	Update	Definitions of low, medium, and high statin dose added to the table.

ARS = Agenzia Regionale di Sanità della Toscana; DDI = drug-drug interaction; GePaRD = German Pharmacoepidemiological Research Database; SAP = statistical analysis plan.

An updated LCZ696B2015 study protocol v02 – amendment 2, dated from March 18, 2021, was approved by the PRAC on June 24, 2021 ([redacted]; see Section 15.1.1). The deviations from the LCZ696B2015 study protocol v02 – amendment 2 specified analysis for the final study execution are described in Table 8-2. Most deviations resulted from findings of the validation study. These 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 originally 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 how the final analyses deviate from the analyses specified in LCZ696B2015 protocol amendment v0.2 – amendment 2

Topic/ Section no	Specified in protocol	Decision for final SAP	Rationale for deviation from the protocol
Application of exclusion criteria/ Section 9.3.2.3	For the acute pancreatitis outcome event, patients with recorded pancreatitis (acute or chronic, other diseases of the pancreas or pancreatic cancer) will be excluded, as well as myotoxicity prior to start of follow-up (as myalgia or rhabdomyolysis have been reported before development of acute pancreatitis [Jones et al 2015]).	For the acute pancreatitis outcome event, patients with recorded pancreatitis (acute or chronic, other diseases of the pancreas, or pancreatic cancer) prior to start of follow-up (= eligibility entry date of patients) will be excluded.	In view of the rare occurrence of myotoxicity preceding acute pancreatitis, and the expected low specificity of the case finding algorithm for myotoxicity as assessed in the validation study ([redacted]), the exclusion of prior myalgia or rhabdomyolysis for the outcome event of acute pancreatitis is dropped.
Exposures of interest/ Section 9.4.1	Statin dose was originally defined as low, medium, and high, based on DDDs.	Dose will be categorized as low or high, based on DDDs and frequency of use in real life.	DDDs are not always based on available dosing units, and qualifications of medium and high may differ across countries, therefore a dichotomous categorization is chosen

Topic/ Section no	Specified in protocol	Decision for final SAP	Rationale for deviation from the protocol
Outcome events of interest/ Section 9.4.2	To ensure high specificity of the outcome event (i.e., to minimize outcome misclassification) the primary analysis will focus on the validated outcome events of each database (or subset): if the PPV determined per outcome event in the validation study was <80%, only confirmed cases were included for that database (or subset); if the PPV was ≥80%, all cases were included.	The primary analyses will be conducted without validation of all outcome events as has been concluded in the validation report ([redacted]).	The validation study ([redacted]) demonstrated that the exclusion of a substantial amount of (potentially) true cases due to a significant proportion of critical clinical information being missing in the databases. This would then result in a large decrease in study power without relevant improvement of the internal validity of the study.
Comparative analyses/ Section 9.9.2.4	Matching.	An additional matching criterion has been added based on duration of statin use prior to index date.	Represents time at risk for a potential drug-drug interaction.
Primary analysis/ Section 9.9.2.5	Additional adjustments based on the change in estimate method as proposed by Maldonado and Greenland (Maldonado et al 1993).	Matching variables plus predefined potential confounders (number of potential confounding variables plus one (for the exposure variable of concomitant sacubitril/valsartan [yes/no]) does not exceed the number of cases/10), all predefined potential confounders will be included (Peduzzi 1996). If the number of predefined potential confounders exceeds this threshold, a step-by-step approach of adjustment was applied, using selection algorithm adapted for case-control setting (Schneeweiss et al 2009, Arah et al 2008).	Change in estimate method not generally justifiable to compare different regression models (Karp 2013).
Sensitivity analyses/ Section 9.9.4	Effect of missing first prescriptions of sacubitril/valsartan.	Not possible (result of feasibility analysis) and has been removed.	If the first prescription is not captured in the database, and an outcome event was triggered by the exposure, exposure is likely to have stopped. Therefore, the exposed patients cannot not be identified in the database. In the unlikely event that exposure was continued, and exposure identified, artificially extending the exposure by assuming an earlier start will not contribute to the primary analysis and will likely overestimate exposure in secondary objective 1.

Topic/ Section no	Specified in protocol	Decision for final SAP	Rationale for deviation from the protocol
Sensitivity analyses/ Section 9.9.4	Impact of misclassification of the outcome event.	Repeat primary analysis with cases of myotoxicity, thereby excluding cases with only the unspecific term of myalgia.	The sensitivity analysis to assess the potential bias due to a low specificity of identifying myotoxicity was recommended in the validation report ([redacted]).
Sensitivity analyses/ Section 9.9.4	Study objectives were assessed both in the full population (i.e., patients without or with linked hospital data available [PHARMO, SIDIAP, and CPRD]), as well as in patients with linked hospital data (a stratified analysis).	No real sensitivity analysis. Analyses are stratified for each database with partial hospital linkage into mutually exclusive subsets: without and with linked hospital data (two subsets each for PHARMO, SIDIAP, and CPRD).	The stratification will optimally show the differences between patients without and with linked hospital data. Inclusion of patients with linked hospital data into the full study population results in a duplication of these patients for the meta-analyses.
Sensitivity analyses/ Primary analysis/ Section 9.9.4 / Section 9.9.2.5	Sensitivity analysis where the study period ends on December 31, 2019, the time at which the COVID-19 pandemic may started to have an impact.	The primary analysis is restricted to the pre-COVID period. The sensitivity analysis is without restriction to pre-COVID period.	Primary analysis and sensitivity analysis are exchanged due to the assumption that pre-COVID data represent a more reliable period.
Sensitivity analyses/ exposures of interest/ /Section 9.9.4/Section 9.4.1	Impact of SIDIAP data on pooled results (day of dispensing not known) was not specified.	Included a sensitivity analysis for estimation of pooled odds ratios without SIDIAP data.	First, in SIDIAP, the date of the dispensing was defined as the first day of the month because only the month and year of dispensations were available for this study (a limitation not known at the design stage of the study). The direction and magnitude of bias potentially caused by the misclassified exposure start (systematically set to first day of the month) is difficult to predict.

CPRD = Clinical Practice Research Datalink; DDDs = defined daily doses; PHARMO = PHARMO Institute for Drug Outcomes Research; 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

LCZ696B2015 is a non-interventional, multi-database, post-authorization safety study (PASS) category 3, using a case-control design nested in a dynamic population of patients with HF exposed to statins.

Cases were identified from the study base of adult patients with HF using statins during follow-up and having at least one year of look-back data i.e., at least one year of database history was available for patients, meaning the patient was registered in the database for at least one year with an end date after the launch date of sacubitril/valsartan in each country of interest. The

recorded diagnosis date of the outcome event of interest (either myotoxicity, hepatotoxicity, or acute pancreatitis) was defined as the 'index date.' Controls (cases without a recorded outcome event of interest prior to index date of the [matched] case) were matched to cases based on age (year of birth at index date [±2 years]), sex, category of duration of statin use [four categories: 1–30 days, 31–90 days, 91–180 days and >180 days], and index date (= calendar date). Cases and matched controls within a certain risk period prior to index date were assessed for exposure to sacubitril/valsartan together with statins or exposure to statins alone. Further, concomitant exposure to sacubitril/valsartan and simvastatin or atorvastatin, or high or low dose of statins was assessed (see Section 9.4.1). This resulted in three separate matched case-control analyses per objective, one each for the outcome events of myotoxicity, hepatotoxicity, and acute pancreatitis, nested in the population of patients with HF using statins within the study base.

A nested case-control study is an efficient method to assess the relative risk of potential DDIs on a population-based, real-world level using electronic healthcare information. It is efficient to assess concomitant drug use at one point in time (i.e., at the index date) over the risk period rather than the entire period of follow-up, especially in this population that uses many different types of drugs. This type of design has been applied many times for assessing various DDIs on a population-level, using electronic healthcare databases (Cressman et al 2015, Pincus et al 2012, Jobski et al 2011, Juurlink et al 2011, Schellemann et al 2011, Juurlink et al 2009, Schellemann et al 2008).

Codes and Feasibility Study

All outcome events of interest were identified using outcome-specific codes based on the coding system(s) used in the database(s) of interest. The differences between database specific coding were studied and have been harmonized to the best extent possible by benchmarking in the feasibility study ([redacted]). The findings of the feasibility study demonstrated that the incidence rates for the outcome events of interest in the general population based on codes alone were markedly higher in GePaRD compared to the other databases ([redacted]). Consequently, all outcome events of interest, comorbidities, and inclusion and exclusion criteria were identified using specific algorithms in GePaRD. The algorithms are described in Section 9.4.2.4.

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 the General Practitioner (GP) medical records and the interpretation thereof by various medical doctors led to a 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 exclusion of a substantial amount of (potentially) true cases, an underestimation of absolute event rates, and a large decrease in study power. With endorsement from PRAC, the final analyses were conducted with all events of myotoxicity, hepatotoxicity, and acute pancreatitis identified in each database.

9.2 Setting

The study made use of secondary electronic health data from seven European electronic healthcare databases, from Denmark (DK), Germany (DE), Italy (IT), the Netherlands (NL),

Spain (ES) and the United Kingdom (UK). The databases were: the Aarhus University Prescription Database and Danish National Patient Registry (Aarhus [DK]); the Agenzia Regionale di Sanità della Toscana (ARS [IT]); the Clinical Practice Research Datalink (CPRD [UK]), the German Pharmacoepidemiological Research Database (GePaRD [DE]); the Health Search Database (HSD [IT]); the PHARMO Database Network (PHARMO [NL]); and the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP [ES]). See Table 9-2 and Table 9-3 for details on the data sources used in this study.

The study period of the study base started at the launch date of sacubitril/valsartan in the countries of interest (see launch dates in Table 9-1). The study periods of the study base by database are displayed in the table below.

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 transferred data to Medicines and Healthcare products Regulatory Agency (MHRA) is December 26, 2020.

The period over which information and medical information was retrieved for each patient started at an individual's database entry or enrollment date, which was before or after (i.e., to define the outcome event of interest) the sacubitril/valsartan launch date. Each patient was captured for one period of continuous enrollment in the study, i.e., gaps in enrollment were not allowed. If gaps existed in enrollment, only the last period of enrollment was included. 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 and secondary analyses ended on December 31, 2019 for all databases, since early 2020 the COVID-19 pandemic was declared. Specifically, only patients with the outcome event of interest prior to December 31, 2019 (i.e., during the pre-COVID

period) were considered for the primary and secondary analyses (see Section 9.9.2). For the sensitivity analyses the full study period was used.

9.3 Subjects

9.3.1 Source population

The source population included all patients in the databases during the study period. Three databases have linkage with hospital data limited to a subset of the source population, i.e., PHARMO, SIDIAP, and CPRD. All these three databases have linkage with hospital data to the GP data and only two databases with outpatient pharmacy data (PHARMO and SIDIAP). Since this linkage with hospital data is only partial, analyses were stratified based on this eligibility (=subgroup analyses) and are referred to as "with linked hospital data" and "without linked hospital data" in the rest of this document. 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. For details on individual databases, see LCZ696B2015 protocol v02 – amendment 2 ([redacted], Section 15.1.1) and Table 9-2 and Table 9-3.

Table 9-2 Provenances of the data use per database

Database	Provenance (data sources)
Aarhus	Secondary outpatient care data Hospitalizations Emergency department Laboratory data
ARS[*]	Hospitalizations Emergency department Death registry
GePaRD	Primary care data Secondary outpatient care data Hospitalizations
HSD	Primary care data Laboratory data
PHARMO	Primary care data Hospitalizations (linked for approximately 90% of patients of the database) Laboratory data
SIDIAP	Primary care data Hospitalizations (linked for approximately 35% of patients in the database) Laboratory data
CPRD	Primary care data Hospitalizations (linked for approximately 55% patients of the database) Laboratory data

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 = the PHARMO Database Network; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Assessment and diagnostic codes for the identification of the outcome events of interest are displayed in Section 15.2.1-Table 2-2 to Section 15.2.1-Table 2-7. Primary care databases will contain information reported back from secondary care and hospitalizations.

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

Table 9-3 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 back by patient)	Yes, partial through linkage	Yes, partial through linkage	Yes, partial through 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.

Input files were constructed based on a tailored common data model (see Section 9.8 and Section 15.2.1-Table 5-1 to Section 15.2.1-Table 5-6), from which the study base was constructed.

9.3.2 Study population

9.3.2.1 Study base

The study base was the source population that gave rise to the cases. The study base was constructed per database and was defined by the following inclusion criteria, applied to all patients who were registered in the respective database during the study period, i.e., after launch of sacubitril/valsartan:

- Non-missing data on age and sex

- At least one year of look-back data (i.e., at least one year of database history available for a patient, meaning the patient was registered in the database for at least one year, ending after launch of sacubitril/valsartan)
- Aged ≥ 18 years during the study period
- A recorded diagnosis of HF in the database at any time (i.e., assessment window for HF was the entire available history in the patient's electronic health records [EHRs]/claims data) (see Section 15.2.1-Table 2-1 for diagnosis codes of HF)
- No record of sacubitril/valsartan exposure prior to country-specific launch date
- Statin exposure at any time during the study period with the start date of follow-up (see definition below) (see Section 15.2.1-Table 2-8 for medication codes)

Note: To identify individuals with a HF diagnosis with the status 'assured' in the claims data of GePaRD, patients needed to have at least one hospital discharge diagnosis of HF (irrespective of whether it was a main or secondary diagnosis at hospital discharge) or two outpatient diagnoses (no time limit applied). The rationale for this approach in GePaRD was that a diagnosis from outpatient care may be either an unconfirmed (suspected) diagnosis, or a confirmed diagnosis coded for claims purposes. Therefore, confirmation of outpatient diagnoses by a second diagnosis is usually required, especially for chronic conditions (see also Section 9.4.2.4 for more details) to not overestimate the frequency of those conditions. In all cases, the first recorded claims date in the assessment period of an HF diagnosis was considered the 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.

Generally, if the exact date of birth was not known, January 1st of the calendar year the patient turned 18 years was the start date of the study when only the year was known, and the first date of the month when the month and year were known.

Follow-up was defined as the time window in which EHR were assessed for the study base of patients at risk. Follow-up for each patient in the study base started at the latest date of the following points in time:

- Launching of sacubitril/valsartan (as defined in Table 9-1).
- Reaching age 18 years.
- Having at least one year of continuous look-back data in the database from the date of enrollment in the database ending after launch of sacubitril/valsartan (to include only patients who were enrolled in the relevant time-period).

For programming purposes, eligibility periods were defined for each patient in the study base, since only time periods during follow-up where a HF diagnosis was made before and during statin use were eligible for inclusion as either case or control. This way, time without statin use was excluded for efficiency purposes in identifying cases and sampling controls. The eligibility period for being included as cases or controls started at the latest date of the above-mentioned bullet points or the latest of the following points in time (referred in this report as the eligibility entry date [see Figure 9-1]):

- Start of follow-up (see previous bullet points);
- A recorded diagnosis of HF;

- Starting treatment with statins.

Note: For example, in case of patients aged 18 years or older with a diagnostic code for HF who started treatment of statins prior to launch date of sacubitril/valsartan, the launch date was the eligibility entry date (EED).

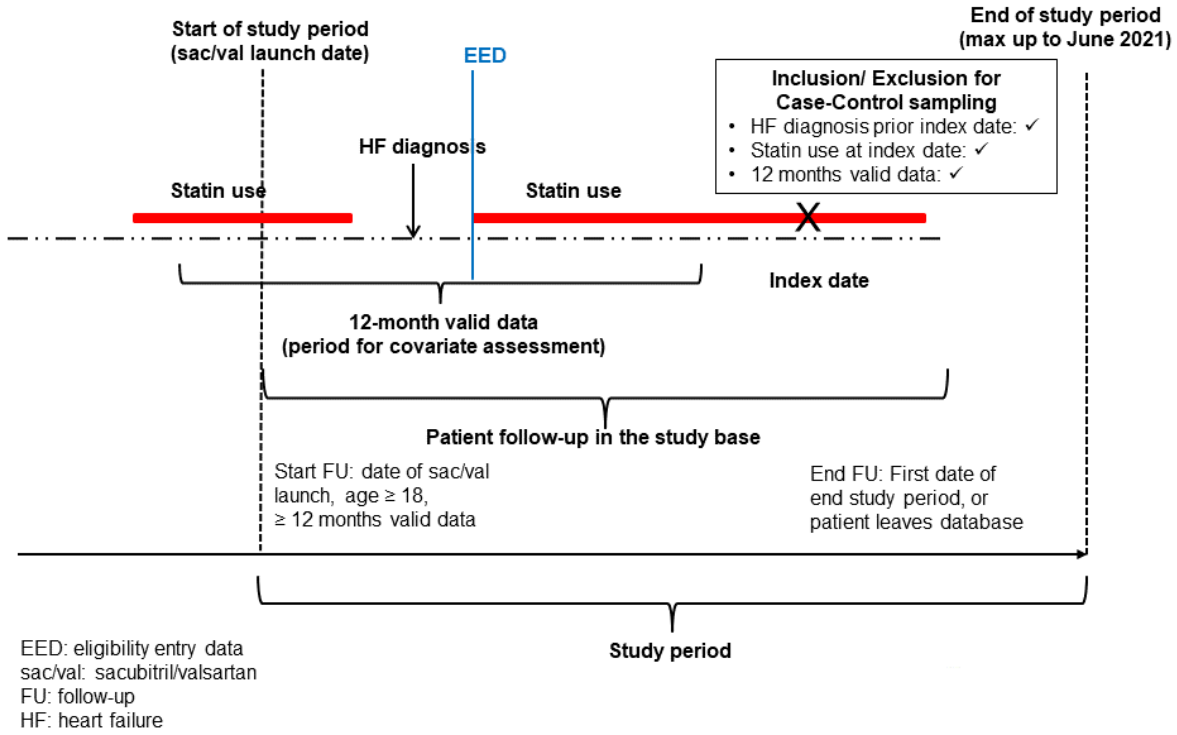
The observation period for each patient in the study base ended at the earliest of the following dates:

- Last data supply from hospital, general practitioner (GP) practice, pharmacy, or insurance company to the database
- Date that the patient transferred to a region, GP practice, pharmacy or insurance company from which data are not captured in the database, i.e., the patient transferred to a different
  - Region: Aarhus, ARS;
  - GP practice: HSD, PHARMO, SIDIAP, CPRD;
  - Pharmacy: PHARMO, SIDIAP;
  - Insurance company: SIDIAP (only data from one company are captured), GePaRD (data from four statutory health insurance [SHI] companies are captured, patients were followed for the last recorded insurance period only, patients were also followed if there was a gap in insurance within one company);
  - Date of death.

Other data sources may have been available for the databases (hospitalization, emergency department, secondary care out-patient or laboratory data), but these did not determine the follow-up of a patient.

A graphical display of the study design of the study base including information on start of study period, follow-up of patients in the study base and end of study etc. can be found in Figure 9-1.

Figure 9-1 Graphical display of the study design of the study base



Index date = date of outcome event of interest; eligibility entry date = latest date of either the launch date of sacubitril/valsartan, or date of turning 18 years old, or date of the first prescription of statins, or the first diagnostic code of HF during the study follow-up.
The assessment window for HF was the entire available history in the patient's electronic health records, not limited to the study period, but prior to index date. Statin use may have extended beyond the index date.

9.3.2.2 Sets of Case-controls

Cases and controls were identified from the study base, which complies with all eligibility criteria. Outcome events of interest were myotoxicity, hepatotoxicity, and acute pancreatitis (see Section 15.2.1-Table 2-2, Section 15.2.1-Table 2-3, and Section 15.2.1-Table 2-6 for diagnosis codes, for further details regarding database-specific considerations see Section 9.3). For each outcome, a separate set of cases and matched controls was selected from each individual study base within the same database. For the secondary objectives investigating whether a drug–drug interaction may depend on the type of statin or statin dose (=secondary analyses), additional sets of case-controls were selected as described in Section 9.3.2.2.2.

9.3.2.2.1 Definition of cases

The first recorded event date of the outcome event of interest (see Section 9.4.2) within the study period (once all inclusion criteria were fulfilled) was defined as 'index date'. To qualify

as a case (= patient with the outcome event of interest in the study base) – in addition to a recorded outcome event of interest – a patient needed to have:

(i) a HF diagnosis at any time during their recorded history prior to index date;

(ii) statin exposure (for definition, see Section 9.4.1.1) at index date;

(iii) no prior event or condition listed as an exclusion criterion (Section 9.3.2.3).

Because follow-up in the study base started after 12 months of enrollment, all cases had at least 12 months of continuous look-back data before the index date (see Figure 9-1).

Cases were classified by their duration of statin exposure at index date, which was used as matching criterion for control selection. The start of the period of statin exposure that encompassed the index date was defined as the start of statin episode (see Section 9.4.1.1). The duration of statin exposure at the time of the outcome event of interest was determined as: index date – start of statin episode (= start of person-time exposed to statins), and was categorized as 1–30 days, 31–90 days, 91–180 days, and >180 days. The index date is within an episode of statin use, and the start date of this episode can be prior to, at, or after the EED.

9.3.2.2.2 Sampling of controls

For each case up to 100 controls were sampled from the study base of patients at risk (the set of eligible controls) in the same database by matching on age (year of birth [±2 years; used to relax matching on year of birth]), sex, index date (event date of the corresponding case), and category of duration of statin exposure at index date. For PHARMO, SIDIAP, and CPRD, eligibility for linked hospital data was added as a matching criterion. Matching on index date in a dynamic population ensured that controls were sampled from a period with the same density of exposure to sacubitril/valsartan in the study base as the case and accounted for potential seasonal factors. Matching on duration of statin exposure ensured a similar risk of developing the outcome events of interest associated with statin exposure, allowing investigation of a drug interaction of statin exposure with sacubitril/valsartan exposure. Matching on eligibility for linked hospitalization data ensured that stratification into subsets without or with linked hospital data was executed for the selection of the matched sets (= matched cases and controls). The number of controls was maximized to 100 to ensure sufficient power, while limiting the required computational memory for analyses to a manageable size.

Because follow-up of any patient in the study base started after 12 months of enrollment, and sampling of controls was limited to the follow-up period, all controls had at least 12 months of continuous look-back data to determine the matching variables. All patients from the study base (except the exact case being matched) were eligible controls, provided they had:

(i) A HF diagnosis at any time during their recorded history prior to index date;

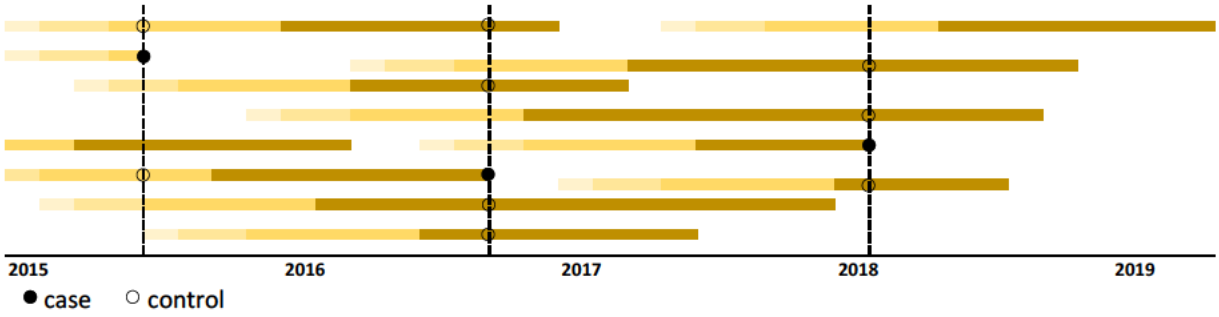
(ii) statin exposure (for definition, see Section 9.4.1.1) of similar duration at index date;

(iii) no prior event or condition listed as an exclusion criterion (Section 9.3.2.3).

A patient who became a case could be a control earlier to another case. Sampling of controls was performed based on the dynamic cohort assumption (Vandenbroucke et al 2012), using an adapted version of the Statistical Analysis System (SAS) macro described by Richardson (Richardson 2004). Periods of person-time exposed to statins in patients with an HF

diagnosis – during which the patients were at risk – were constructed for the incidence density sampling procedure. Eligibility periods of person-time at risk (i.e., person-time exposed to statins) started at EED during follow-up (see Section 9.4.1 for definition of "continuous use") and ended at either one day before the outcome event of interest, or end of statin exposure, or end of follow-up in the study base, whichever came first. Multiple periods at risk were possible for one patient if statin exposure was interrupted. Within the periods of continuous statin exposure, additional segmentation into periods of use of predefined durations of statin exposure (see Section 9.4.1.1) was applied before sampling of controls. The macro published by Richardson (Richardson 2004) was adapted to include multiple matching criteria. A graphical representation of the sampling method is given in Figure 9-2 (modified from Vandenbroucke et al 2012).

Figure 9-2 Sampling controls in a dynamic population



Adapted from Vandenbroucke et al 2012: Incidence density case-control sampling in a dynamic population (= study base of patients at risk) when a control is sampled each time a case occurs: matching on calendar time Patients moved in or out of the population by mechanisms such as birth or death or moved in or out from statin exposure to non-exposure as depicted. Person-time is indicated by horizontal-colored lines (exposed to statins). The sampling of the control was 'matched on calendar time': each time a case occurred (=index date); controls were sampled. Cases and controls could be either exposed or unexposed to sacubitril/valsartan at index date (not shown here). A patient who became a case could be a control earlier, multiple controls could be drawn for each case, and controls may have been matched to multiple cases. The figure was adapted to include duration of statin exposure as an additional matching criterion: increasing hues of color indicate categories of increasing duration of statin use (1–30 days, 31–90 days, 91–180 days, and >180 days). The matching criteria of age and sex are not included in the graphical display but were also considered.

Sampling of up to 100 controls (from the same database) was intended to increase the precision of the risk estimates (expressed as "odds ratios" [ORs]). If more eligible controls were available for each case, random sampling was performed. If the matching criteria were too restrictive to identify at least 20 eligible matches for all cases, sampling for those patients was repeated, but this time the matching on duration of statin exposure was relaxed to include only two categories: <30 days and longer. If that was still too restrictive, matching on year of birth was relaxed to include ±2 years. The incidence density sampling was done *separately* for all three outcome events of interest, i.e., separately for myotoxicity (cases of myotoxicity without solely diagnostic codes for myalgia [sensitivity analysis]), hepatotoxicity, and acute pancreatitis, resulting in four individual matched case-control sets, to be used for the primary objective and the secondary objectives 1 and 2. Any number of controls up to 100 was accepted after relaxation of the matching criteria.

For the secondary objective 3 investigating whether an interaction with sacubitril/valsartan depended on the type of statin (i.e., atorvastatin and simvastatin), separate control sampling (on

the same matching variables per database) was performed per outcome event, once within a subset of cases and eligible controls exposed to atorvastatin at index date, and once within a subset exposed to simvastatin at index date in the pre-COVID period. These were the two most frequently prescribed/dispensed statins in all participating countries. Sampling of eligible controls required defining time at risk during statin exposure based on the same type of statin as used by the case. Similarly, for the secondary objective 4 investigating whether an interaction with sacubitril/valsartan depended on the statin dose, separate control sampling on the same matching variables per database was performed per outcome event: once within a subset of cases and eligible controls exposed to high dose of statins at index date; and once within a subset exposed to low dose of statins at index date in the pre-COVID period (for exposure definitions, see Section 9.4.1). Sampling of eligible controls required defining time at risk during statin exposure based on the same statin dose as used by the case.

In each database, irrespective of eligibility for linked hospital data (i.e., PHARMO, SIDIAP, CPRD), each of the above matched control samples was generated if at least five cases of the study outcome event of interest were available. With less than five cases, no adjustment for covariates would be possible, and the unadjusted analyses would unlikely contribute relevant data to the objective(s). Furthermore, information of less than five cases could not be disclosed as it could potentially identify patients involved (e.g., in Aarhus, PHARMO, and CPRD).

9.3.2.3 Application of exclusion criteria

Exclusion criteria were applied at different stages of the analysis: before selection of cases and controls (i.e., for the selection of patients at risk for the outcome event of interest) and after selection of cases and controls (post-hoc exclusion criteria added based on insights from the validation study (Heintjes et al 2022)).

For each selection of patients at risk for the outcome event of interest, the following exclusion criteria were applied:

- No recorded HF diagnosis prior to index date (using all available records) for cases and assigned index date for controls;
- Non-use of statins (see Section 9.4.1.1) at index date (applicable for cases) and assigned index date for controls;
- Exposure to sacubitril/valsartan prior to country-specific launch date of sacubitril/valsartan (e.g., through exposure in a clinical trial, or in a patient access program).

  After applying these three exclusion criteria, the number of patients with HF who were using statins after the country-specific launch date of sacubitril/valsartan were considered as the patients at risk for the outcome event of interest. The date when the patients at risk fulfilled all these criteria was the eligibility entry date.
- History of the particular outcome event of interest prior to eligibility entry date (see Section 15.2.1-Section 2 Selected Study Codes for diagnosis codes).

  For *myotoxicity*, patients with a history of myotoxicity or myotoxic events for which external causes (other than poisoning by drugs or medicaments) have been recorded prior to eligibility entry date were excluded. These patients were defined as myotoxicity with the specification ‘narrow’ and ‘exclude’ (see (Section 15.2.1-Table 2-2) Codes used to identify cases of myotoxicity). Patients with a diagnostic code for

hereditary muscle disease any time during the study period (i.e., prior to, at, or after eligibility entry date) were excluded as well (see Section 15.2.1-Table 2-14).

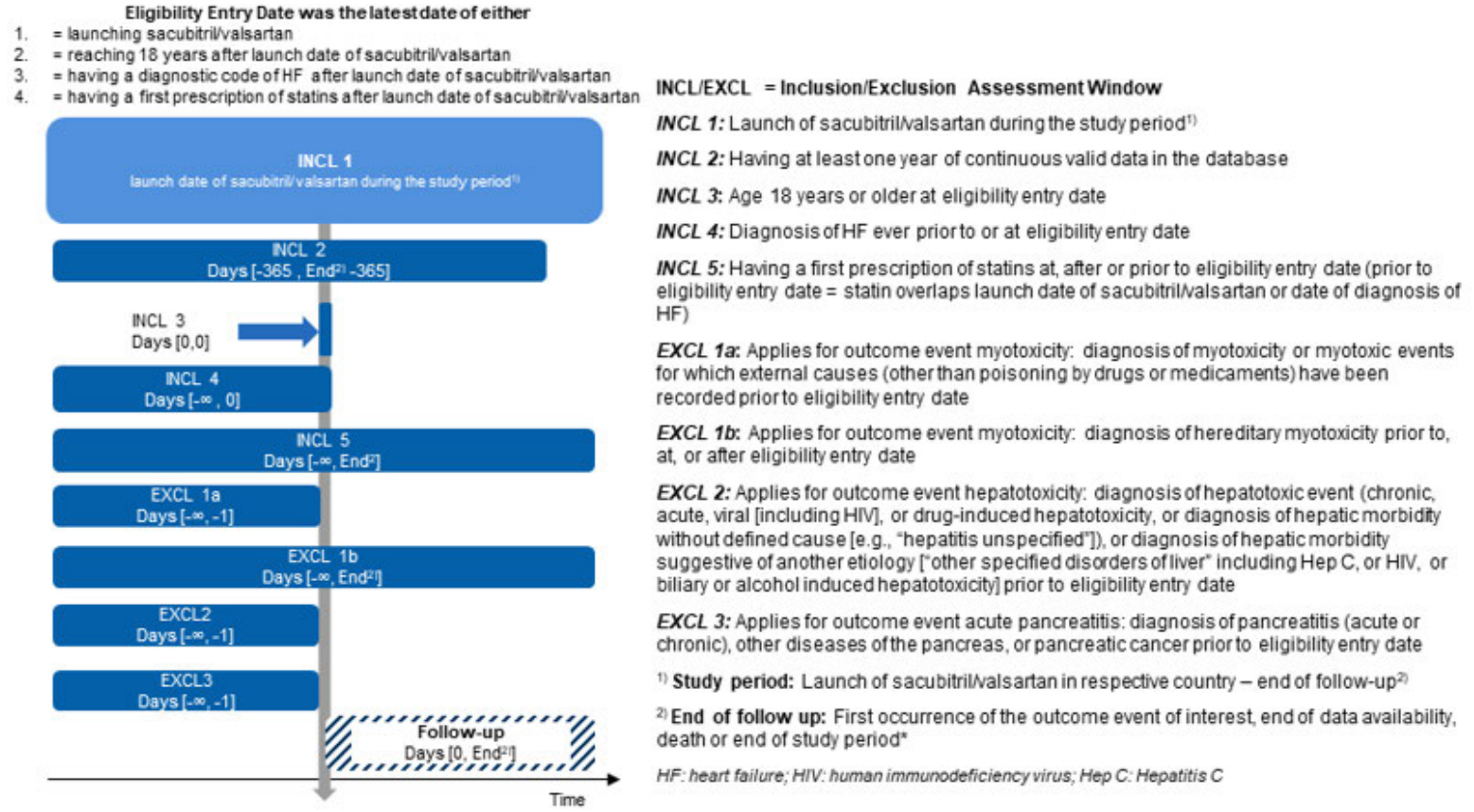
For *hepatotoxicity*, patients with a hepatotoxic event (chronic, acute, viral [including human immunodeficiency virus, or HIV], or drug-induced hepatotoxicity, or diagnostic codes indicating hepatic morbidity without defined cause [e.g., "hepatitis unspecified"]), or diagnostic codes indicating hepatic morbidity suggestive of another etiology ("other specified disorders of liver", including hepatitis C, or HIV, or biliary or alcohol-induced hepatotoxicity) prior to eligibility entry date were excluded. These patients were defined as hepatotoxicity with the specification 'narrow' and 'exclude' (see Section 15.2.1-Table 2-3 Codes used to identify case of hepatotoxicity), and defined by all diagnostic and drug codes for hepatic morbidity, including hepatitis C virus (HCV) drugs which serve as a proxy for hepatitis C (see Section 15.2.1-Table 2-4Codes used for identification of chronic hepatic disease and Section 15.2.1-Table 2-13 Codes used for identification of HCV drugs) and HIV (see Section 15.2.1-Table 2-5 Codes used for identification of HIV). The diagnostic and drug codes for hepatic morbidity were defined by chronic hepatic disease which includes HCV drugs, or HIV.

For *acute pancreatitis*, patients with recorded pancreatitis (acute or chronic), other diseases of the pancreas, or pancreatic cancer prior to eligibility entry date were excluded. These patients were defined as acute pancreatitis with the specification 'narrow' and 'exclude' (Section 15.2.1-Table 2-6 Codes used to identify cases of acute pancreatitis).

All exclusion criteria applied at eligibility entry date are depicted in Figure 9-3.

Note: In GePaRD, for all outcome events of interest only confirmed diagnoses were excluded by using algorithms based on records with a confirmed 'assured' diagnosis status. All these algorithms were examined in the feasibility study which was conducted prior to the final analysis ([redacted]).

Figure 9-3 Design diagram at eligibility entry date



The study period for the primary analyses was restricted to December 31, 2019, the time at which COVID-19 pandemic may have started having an impact. The study period for the sensitivity analysis is the full study period which was defined as the period with the last available date in each database (see Table 9-1).

The following exclusion criteria were applied after identifying cases and sampling of controls:

For *myotoxicity*, patients were defined as having myotoxicity with only the specification 'narrow' (see Section 15.2.1-Table 2-2 Codes used to identify cases of myotoxicity). Myotoxic events for which external causes (other than poisoning by drugs or medicaments) have been recorded at or in the seven days after the index date (in order to allow diagnostics revealing etiology to be recorded) were excluded as cases of myotoxicity. These patients were defined as myotoxicity with the specification 'exclude' (Section 15.2.1-Table 2-2 Codes used to identify cases of myotoxicity). Patients with a history of e.g., traumatic events or surgery leading to myalgia or rhabdomyolysis in the 90 days prior to index date were excluded as well. These patients were defined as myotoxicity with the specification 'narrow' who had diagnostic code for trauma or surgery (see Section 15.2.1-Table 2-15 and Section 15.2.1-Table 2-16 Codes used to identify case of myotoxicity) in the 90 days prior to index date.

For *hepatotoxicity*, patients were defined as having hepatotoxicity with only the specification 'narrow' (see Section 15.2.1-Table 2-3 Codes used to identify cases of hepatotoxicity). Patients with diagnostic codes indicating hepatic morbidity suggestive of another etiology ("other specified disorders of liver", including hepatitis C, or HIV, or biliary or alcohol-induced hepatotoxicity) at or in the seven days after the index date were excluded. This took into account late recording of the excluded etiology of the same event. These patients were defined as hepatotoxicity with the specification 'exclude' (see Section 15.2.1-Table 2-3 Codes used to identify cases of hepatotoxicity) and defined by all diagnostic codes for hepatic morbidity (Section 15.2.1-Table 2-4 Codes used for identification of chronic hepatic disease), HIV (see Section 15.2.1-Table 2-5 Codes used for identification of HIV), or by records of HCV drugs (see Section 15.2.1-Table 2-13 Codes used for identification of HCV drugs).

For *acute pancreatitis*, patients were defined as having acute pancreatitis with only the specification 'narrow' (see Section 15.2.1-Table 2-6 Codes used to identify cases of acute pancreatitis). Patients with alcohol-induced or biliary acute pancreatitis, other diseases of the pancreas, or pancreatic cancer at or in the seven days after the index date were excluded. This considered late recording of the excluded etiology of the same event. These patients were defined as having acute pancreatitis with the specification 'exclude' (Section 15.2.1-Table 2-6 Codes used to identify cases of acute pancreatitis).

All exclusion criteria applied at index date are depicted in Figure 9-4.

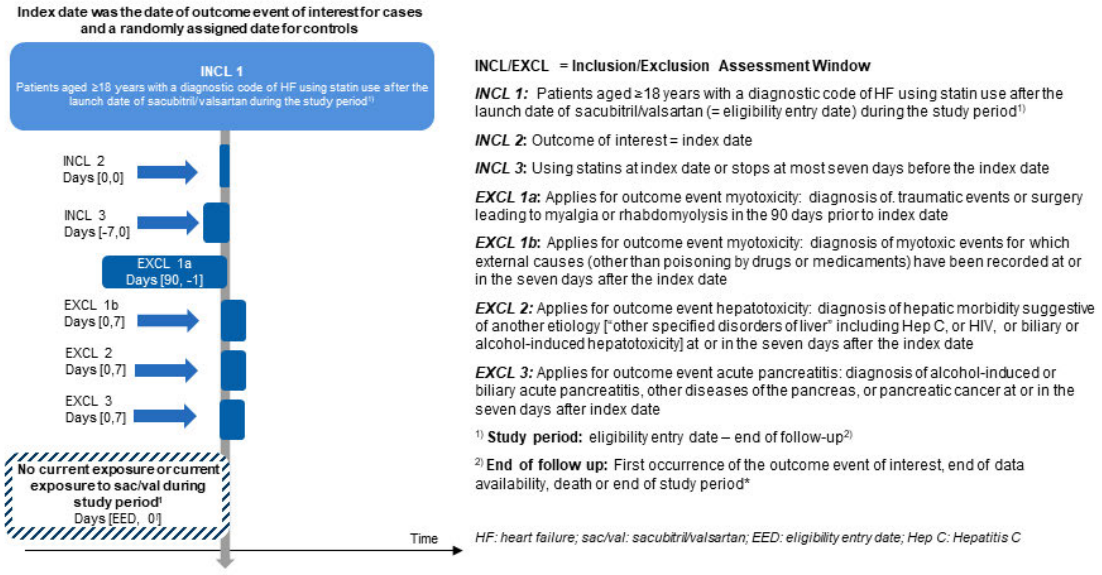
Note: Patients with myotoxicity (specification 'narrow') without statin use at index date were censored in the selection of patients at risk for myotoxicity. The same approach applied for hepatotoxicity and acute pancreatitis.

Note: Patients with the following events during follow-up were censored if these events occurred before the outcome event of interest:

- Myotoxicity: myotoxic events for which external causes (other than poisoning by drugs or medicaments) have been recorded. These events were specified by the specification 'exclude'.

- Hepatotoxicity: events indicating hepatic morbidity without defined cause (e.g., "hepatitis unspecified"), or indicating hepatic morbidity suggestive of another etiology ("other specified disorders of liver", including hepatitis C, or HIV, or biliary or alcohol-induced hepatotoxicity). These events were excluded by the specification 'exclude' and all diagnostic codes for hepatic morbidity including prescriptions of HCV drugs (a proxy for hepatitis C) and HIV. The latter events were specified by 'chronic hepatic disease' and 'HIV', respectively.
- Acute pancreatitis: Alcohol-induced or biliary acute pancreatitis, other diseases of the pancreas, or pancreatic cancer events. These events were specified by the specification 'exclude'.

Figure 9-4 Design diagram at index date



*The study period for the primary analyses was restricted to December 31, 2019, the time at which COVID-19 pandemic may have started having an impact. The study period for the sensitivity analysis is the full study period which was defined as the period with the last available date in each database (see Table 9-1).

9.4 Variables

9.4.1 Exposures of interest

9.4.1.1 Episodes of continuous exposure

Drug exposures of primary interest were sacubitril/valsartan and statins. Exposure information was identified using prescription or dispensing data using the database-specific coding system (Anatomical Therapeutic Chemical [ATC] Classification; which were mapped to Gemscript coding for CPRD). ATC code C09DX04 was used to identify sacubitril/valsartan; for codes used to identify statins see Section 15.2.1-Table 2-8.

Based on the common data model (Section 9.8), the duration of each prescription/dispensing 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 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 and statins 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 (see Section 15.2.1-Table 3-1 for the DDDs of statins). 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 provide this in the common data model (see Section 9.8). For the data sources that contain records of medications dispensed in a pharmacy (Aarhus, ARS, GePaRD, PHARMO, SIDIAP), the actual date or the first date of the month (SIDIAP only) associated with the dispensing in the pharmacy was used; for other databases, the GP prescription dates were used (CPRD, HSD) (see Table 9-4). Both are referred to as prescriptions in this document. For SIDIAP, dates of dispensing were set to the first of the month.

Table 9-4 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 by either the prescribed (if available) or DDD equivalent	DDD	Dosing description derived from labels on package	DDD	DDD	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; GP = general practitioner; HSD = Health Search Database; PHARMO = PHARMO Institute for Drug Outcomes Research; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

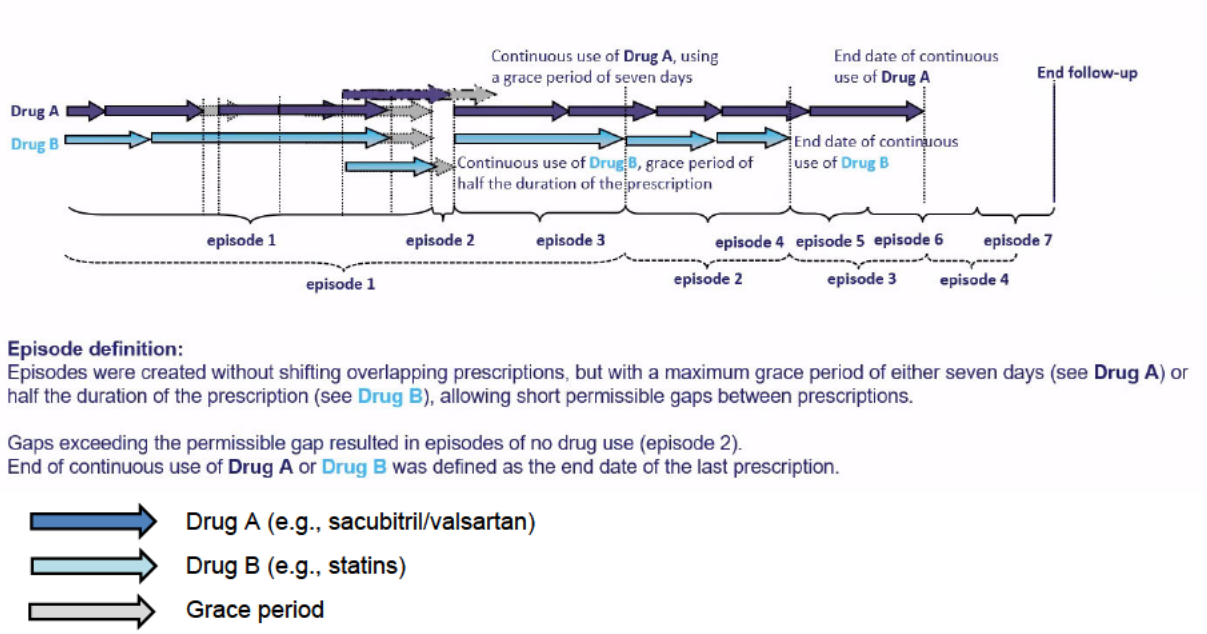
[#]Pharmacy records include any drugs dispensed and reimbursed via public pharmacies, and do not include in-patient drug dispensings.

[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.

Episodes of uninterrupted use of sacubitril/valsartan and statins (on class-level) were separately constructed based on the calculated durations per prescription. Each prescription was extended with a grace period, which was the maximum of either seven days or half the calculated duration of the prescription (Catalan et al 2000). Stockpiling was not considered, i.e., durations were truncated on the day that a patient had a subsequent fill (see Figure 9-6). If the next prescription occurred before the last day of this extended duration (duration + grace period) continuous use was assumed (see Figure 9-5). If the next prescription occurred after the last day of this extended duration, the prior episode of uninterrupted use ended at the end of the calculated duration without the grace period. The next prescription was considered the "first prescription" of a new episode of uninterrupted exposure. When the last prescription of statins or sacubitril/valsartan ended before the end date of data availability, death, or the end date of the study period (see Section 9.3.2.1), patients were censored on the end date of the episode and grace period of seven days. The grace period was only applied in patients that did not re-initiate statins or sacubitril/valsartan.

Figure 9-5 Episodes of uninterrupted use of sacubitril/valsartan or statins

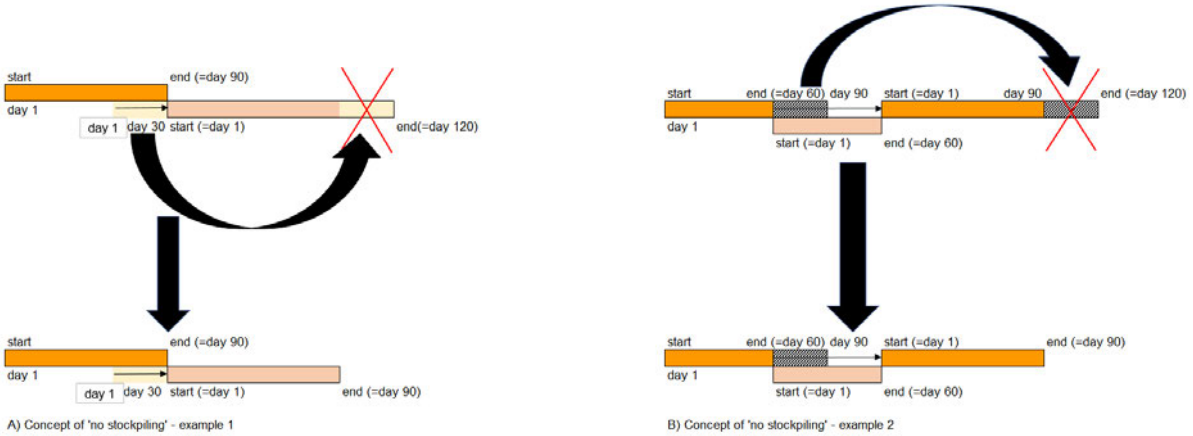


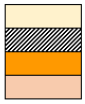
Episode definition:
Episodes were created without shifting overlapping prescriptions, but with a maximum grace period of either seven days (see **Drug A**) or half the duration of the prescription (see **Drug B**), allowing short permissible gaps between prescriptions.

Gaps exceeding the permissible gap resulted in episodes of no drug use (episode 2).
End of continuous use of **Drug A** or **Drug B** was defined as the end date of the last prescription.

Drug A (e.g., sacubitril/valsartan)
Drug B (e.g., statins)
Grace period

Figure 9-6 Concept of 'no stockpiling' and discontinuation of treatment





A. Concept of 'no stockpiling' where the overlap of prescriptions of sacubitril/valsartan or statins (depicted in yellow) was disregarded by not moving it to the end date of the consecutive prescription.
B. Concept of 'no stockpiling' where the overlap of prescriptions of sacubitril/valsartan or statins (depicted by stripes) was disregarded by not moving it to the end date of the last prescription.

For the secondary objective 3 of statin type, the episodes of use were subdivided into episodes per type of statin, and only those of simvastatin and atorvastatin were considered in the respective study sets of cases and matched controls for that objective. For the secondary objective 4 of statin dose, episodes of use were subdivided into episodes of high and low doses (Section 15.2.1-Table 3-1), irrespective of type of statin. Combination preparations of statins and other drugs were assessed as statin only preparations; for the secondary objectives, this was based on the statin type or dose.

9.4.1.1 Statin exposure

For cases and controls, exposure to statins (see Section 15.2.1-Table 2-8 for details) was assessed at index date: the episode duration covered the index date or stopped at most seven days before the index date (see Figure 9-1, Figure 9-5, and Figure 9-6).

For each outcome event of interest, the person-time at risk based on the episodes of statin exposure was censored at index date, or the end of follow-up in the study base. For the purpose of matching cases and controls by duration of statin use, the statin episode overlapping with the index date was segmented relative to the episode start date as follows: 1–30 days, 31–90 days, 91–180 days and >180 days from index date. The index date is within an episode of statin use or grace period, and the start date of this episode can be prior to, at, or after the EED. These four categories of statin exposure were used as a matching criterion in the sampling of controls for each case (see also Section 9.3.2.2.1 and Section 9.3.2.2.2).

For the *secondary objective 3* on the type of statin, the individual statin that was used last before the index date determined the type of statin exposure at the time of the event. The type of statin of interest included atorvastatin and simvastatin, together estimated to cover 75–95% of all statin exposure across the databases based on the latest data update (see Table 9-1). Control sampling was performed in the time at risk defined by episodes of use of the same statin type (simvastatin or atorvastatin) as the case. Other types of statins (see Section 15.2.1-Table 2-8) are not commonly used, therefore no meaningful analyses can be performed.

For the *secondary objective 4* of statin dose, the daily dose of the most recent statin prescription prior to index date was determined and categorized as 'high' and 'low', applying the labels of high and low dose based on a combination of DDD and frequently used doses in daily practice as described in (Section 15.2.1-Table 3-1). Any dose below the most frequently used doses was considered low.

9.4.1.2 Sacubitril/valsartan exposure

For the *primary objective*, concomitant sacubitril/valsartan use (yes/no) was determined as an episode of sacubitril/valsartan use that covered the index date or stopped at most seven days before the index date (see Figure 9-1, Figure 9-5, and Figure 9-6).

For the *secondary objective 1* investigating the duration of sacubitril/valsartan exposure, duration for patients with concomitant sacubitril/valsartan use was calculated as the index date minus the start of the episode of sacubitril/valsartan use that covered the index date or stopped at most seven days before (see Figure 9-1, Figure 9-5, and Figure 9-6). The duration of sacubitril/valsartan exposure was further classified in the following categories relative to index date:

- *Short*: the episode of concomitant sacubitril/valsartan use started maximally 30 days prior to index date
- *Medium*: the episode of concomitant sacubitril/valsartan use started within 31–90 days prior to index date
- *Long*: the episode of concomitant sacubitril/valsartan use started more than 90 days prior to index date

For the *secondary objective 2* investigating recency of cessation of sacubitril/valsartan use, only the episode that covered the index date or stopped at most 90 days before was considered in the classification of recent sacubitril/valsartan exposure (Figure 9-5 and Figure 9-6).

Exposure to sacubitril/valsartan was assessed at index date and categorized in the following categories of recency of use:

- *Concomitant use*: the latest prescription covered the index date or stopped at most seven days before the index date
- *Recent use*: exposure ended between eight and 90 days before the index date, but within the person-time at risk as defined in Section 9.3.2.2.1.
- *Non-use*: never used sacubitril/valsartan or latest exposure ended more than 90 days before the index date

9.4.1.3 Other exposures of interest

Other exposures of interest were drugs that may confound or modify the potential association; these are listed under 'Covariates' (see Section 9.4.3). All drugs were extracted, using their 'Anatomical Therapeutic Chemical' (ATC) codes or Gemscript codes (CPRD only). Gemscript codes were mapped to ATC codes for the common data model (see Section 15.2.1-Table 2-8). Further processing of prescription records in all databases was based on ATC codes. Exposure duration was pragmatically set at a default of 90 days for the purpose of identification as a potential covariate. Only exposures covering the index date were considered as potential covariates.

9.4.2 Outcome events of interest

The outcome events of interest (i.e., myotoxicity, hepatotoxicity, acute pancreatitis) 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, International Classification of Diseases [ICD], 9th version [ICD-9-CM] for GP diagnoses in HSD and hospital diagnoses in PHARMO and ARS, or 10th revision [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, CPRD, and the death registry in ARS, ICD-10 German Modification (GM) codes for GePaRD diagnoses from GP, outpatient specialist or hospitalizations, International Classification of Primary Care [ICPC] v1993 and Werkgroep Coördinatie Informatisering en Automatisering [WCIA] for PHARMO GP diagnoses), as defined in the code list (see Section 15.2.1-Table 2-2 to Table 2-7). Furthermore, in PHARMO, additional text search of the GP EHRs diagnostic text fields was applied, either to identify events that were not coded, or to further specify the ICPC codes that were not granular enough to differentiate between inclusion and exclusion criteria. Applied terms for this natural language processing (NLP) are described with the code list (see Section 15.1.5). Further algorithms to identify confirmed diagnoses in GePaRD have been developed (see Section 15.2.1-Table 4-1) and were tested in the feasibility study ([redacted]). The rationale for using the selected algorithm in the final analysis is described in Section 9.4.2.4 The sources used by each database for identification of the outcome events are shown in Table 9-2.

Several efforts such as code harmonization, benchmarking/feasibility and validation of the outcome events of interest have been undertaken to define these outcome events of interest appropriately. Code harmonization took place until the feasibility study was finalized. Code harmonization started with drafting the code list for all outcome events of interest to ensure the same or equivalent code requirements in each database. This drafted code list was reviewed by two independent medical doctors and discussed with all data partners.

The best approach of how to capture and harmonize diagnosis codes and to select confirmation algorithms (see Section 9.4.2.4) for detecting the outcome event of interest in each of the databases were examined in the feasibility study ([redacted]). In the process of code harmonization, some codes identified in the original code list were excluded because they were too unspecific. Code harmonization also resulted in the exclusion of diagnosis codes indicative of a specific underlying cause for the outcome event of interest (e.g., "alcohol-induced hepatotoxic") to focus more on potential 'idiopathic' events ([redacted]). Code harmonization aimed at minimizing the coding differences between the databases, but cannot

take away all variation, due to differences in the granularity of coding systems and local use of the codes. Selected diagnoses and drug codes are listed in code lists available in the final study report Section 15.2.1-Table 2-1 to Section 15.2.1-Table 2-35; complete study code list with additional attributes is available upon request (see Section 15.1.5). .

For each outcome event of interest and covariate, benchmarking of database-specific frequencies for the outcome event of interest and covariates was conducted in the feasibility analysis ([redacted]). The observed frequencies were compared to frequencies from previous database studies and literature.

Outcome events of interest were not identified based on laboratory data alone to avoid inclusion of asymptomatic cases that were coincidentally detected because of screening that happened for other purposes.

As part of the validation study, the PPV of the identified cases in databases that had not performed validation before for the outcome event of interest was assessed in a sample of cases. In this validation study, the initial plan was to perform a full case validation in case the PPV was lower than 80%. The laboratory tests and magnetic resonance imaging to confirm cases of myotoxicity, hepatotoxicity, and acute pancreatitis were not included in most databases, thus leading to low PPVs. The proportion of potential cases that were unconfirmed was high for all outcome events of interest. The validation study concluded that validating all cases and restricting the sets of cases and controls only to cases confirmed by validation would lead to exclusion of most cases (likely including a few true positive cases) and thus to a substantially reduced sample size. The final analysis was therefore conducted without validation of all outcome events of interest. The PPVs determined in the validation study are shown in Table 9-5 ([redacted]).

Table 9-5 Positive predictive values for myotoxicity, hepatotoxicity, and acute pancreatitis by database from the validation study*

	Confirmed cases / total validated	Myotoxicity	Confirmed cases / total validated	Hepatotoxicity	Confirmed cases / total validated	Acute pancreatitis
Database	n/N	PPV (95% CIs)	n/N	PPV (95% CIs)	n/N	PPV (95% CIs)
Aarhus	11/14	79% (49;95)	NA	NA	NA	NA
ARS	73/73	100% (95;100)	1/1	100% (3;100)	0/2	0% (0;84)
GePaRD	48/54	89% (77;96)	43/54	80% (66;89)	27/36	75% (58;88)
HSD	0/86	0% (0;4)	1/2	50% (1;99)	0/9	0% (0;34)
PHARMO§	36/98	37% (27;47)	9/33	27% (13;46)	19/19	100% (82;100)
SIDIAP§	3/86	3% (1;10)	1/5	20% (1;72)	40/92	43% (33;54)
CPRD§	5/93	5% (2;12)	8/17	47% (23;72)	19/53	36% (23;50)

Aarhus = Aarhus University Prescription Database and Danish National Patient Registry, ARS = Agenzia Regionale di Sanità della Toscana; CIs = confidence intervals; CPRD = Clinical Practice Research Datalink; GePaRD = German Pharmacoepidemiological Research Database; HSD = Health Search Database; NA = not applicable; PHARMO = PHARMO Institute for Drug Outcomes Research; PPV = positive predictive value; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

*Validation study by Heintjes et al 2022.

§Databases with partial linkage to hospital data.

9.4.2.1 Myotoxicity

Myotoxicity was identified from inpatient and outpatient diagnoses of myalgia, myositis, rhabdomyolysis, and myopathy. Database-specific identification based on codes and NLP (PHARMO) was developed in the feasibility study ([redacted]). Individual terms to identify cases of myotoxicity and related exclusion criteria are presented in Section 15.2.1-Table 2-2. Codes and NLP used to identify cases (see Section 9.3.2.2.1) are described in the complete code list with additional attributes, available upon request (see Section 15.1.5).

Myalgia (muscle pain) is a common symptom of myotoxicity, often associated with excessive exercise, trauma, or other morbidities than myotoxicity. The likelihood of having myotoxicity is small in patients identified by a sole diagnostic code of myalgia as patients with myotoxicity often have a diagnosis of myalgia accompanied with elevated levels of creatinine kinase (CK) or the presence of myoglobinuria. In the validation study ([redacted]) most cases had no data on recorded CK levels within three months prior to or after the date of diagnosis, and none of the cases had data on the presence of myoglobinuria. Based on these findings, a sensitivity analysis was conducted where cases with only a diagnostic code for myalgia were excluded as a case of myotoxicity.

9.4.2.2 Hepatotoxicity

Hepatotoxicity was identified from inpatient and outpatient diagnoses indicating acute hepatic failure, liver injury, or hepatotoxicity. Database-specific identification based on codes and NLP (PHARMO) was developed in the feasibility study ([redacted]). Individual terms to identify cases of hepatotoxicity and related exclusion criteria are presented in (Section 15.2.1-Table 2-3). Codes and NLP terms used to identify cases and exclusion criteria for cases (see Section 9.3.2.2.1) are described in the complete code list with additional attributes, available upon request(seeSection 15.1.5).

9.4.2.3 Acute pancreatitis

Acute pancreatitis was identified from inpatient and outpatient diagnosis codes, except for GePaRD where only inpatient diagnoses were considered (see Section 9.4.2.4). Database-specific identification of acute pancreatitis based on codes and NLP (PHARMO) was developed in the feasibility study ([redacted]). Individual terms to identify cases of acute pancreatitis and related exclusion criteria are presented in (Section 15.2.1-Table 2-6). Codes and NLP used to identify cases and exclusion criteria for cases (see Section 9.3.2.2.1) are described in the complete code list with additional attributes, available upon request (see Section 15.1.5).

9.4.2.4 German database outcome event selection algorithms

The German database (GePaRD) contains claims records for both primary and secondary outpatient care and hospitalizations. Hospitalization diagnoses are always considered as confirmed diagnoses, and they comprise primary diagnoses (reason for admission) and secondary diagnoses (co-existing conditions).

Results from the feasibility analyses using any diagnostic code showed that the inclusion of outpatient diagnoses with status 'confirmed' that were only recorded once ever and not confirmed by a second recording in GePaRD caused higher frequencies of conditions compared to 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 a status marked as '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 higher number of cases due to misclassification. Therefore, confirmation of 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 outcome event of interests when the date of onset was before the EED. 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 an outcome event but may have been used in the confirmation of an outcome 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 4-1) and 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 ([redacted]). The final algorithms are listed in (Section 15.2.1-Table 4-1).

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

Myotoxicity

- Final algorithm: One main discharge diagnosis or two outpatient diagnoses with both the status ‘assured’ within three months (of any physician).
- Rationale: Outpatient diagnoses were likely to capture less severe events of myotoxicity, which likely reflected most cases. Using only one outpatient diagnosis seemed to overestimate the occurrence of the outcome event; therefore, a second outpatient diagnosis within three months by another physician was required, as the diagnostics was challenging. Physicians could potentially ask a colleague to investigate the case to rule out an alternative diagnosis. Only main discharge diagnoses were selected because the main reason for treatment should be myotoxicity. Only acute events of myotoxicity should be considered.

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 another 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, which led 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.

Acute pancreatitis

- Final algorithm: One main discharge diagnosis
- Rationale: As acute pancreatitis is a potentially lethal event (which results in hospitalization for almost all cases), no outpatient diagnoses were considered. Only main discharge diagnoses were considered because the main reason for treatment should be acute pancreatitis. In this case, pancreatitis is an acute event.

9.4.3 Covariates

Variables that were used for descriptive analyses and evaluated as risk factors or potential confounding variables for the analytical analyses are listed below.

Covariates were defined as variables that could be associated with statin exposure, could increase the systemic concentrations of statins, or could be considered as proxies for HF severity (Section 9.4.3.1 ‘Patient characteristics/demographics’), or that could be risk factors and potential confounders for the specific outcome event of interest (Section 9.4.3.2 ‘Covariates for specific outcome events’). Patients’ demographics and clinical characteristics may have served as covariates in the comparative analyses (see Section 9.9.2.5 ‘Primary analysis’).

9.4.3.1 Patient characteristics/demographics

9.4.3.1.1 Demographics and clinical characteristics

For categorical characteristics listed here, all categories (including one for missing information, where indicated) were included in one categorical variable in the analyses. For potential use as covariates in the statistical modeling, reference categories are indicated.

Patient characteristics were summarized at index date for each outcome separately, including:

- Age (continuous, categorical: 18–44, 45–64, 65–74, ≥75 years). Matching variable (actually: year of birth), not used as covariate, no reference.
- Sex (female, male). Matching variable, not used as covariate, no reference.
- Duration of statin exposure at index date (1-30 days, 31-90 days, 91-180 days, >180 days). Matching variable, not used as covariate, no reference.
- Statin type (simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin). Stratified analyses were performed for simvastatin and atorvastatin, and therefore not used as covariate, no reference.
- Statin dose (high dose, low dose). Stratified analyses were performed for high dose and low dose, and therefore not used as covariate, no reference (see Section 15.2.1-Table 3-1).
- Comorbidities (i.e., diseases/conditions already prevalent before the index date, using the in- and outpatient medical records within the entire available history (=look-back period) of patients' EHRs); (yes/no [no = reference]),
  - Obesity (in the year prior to index date) based on available diagnostic coding or body mass index (BMI) ≥ 30 kg/m^2– if available; for consistency across databases, in absence of a diagnostic code or a BMI value ≥ 30 kg/m^2, obesity was assumed to be absent (absence of obesity code or BMI < 30 kg/m^2 = reference). BMI is not available for ARS and GePaRD (was not presented for the set of cases and matched controls for myotoxicity and hepatotoxicity, and acute pancreatitis as it is listed as a covariate specifically for this outcome event (see Section 9.4.3.2.3).
  - 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)
  - Chronic kidney disease (CKD) (look-back period), is not presented for the set of cases and matched controls for myotoxicity because CKD in the year prior to index date is used as covariate for this specific outcome event (see Section 9.4.3.2.1)
  - Chronic hepatic disease (entire available history), is not presented for the set of cases and matched controls for hepatotoxicity (exclusion criterion) and myotoxicity (assessed

in the year prior index date as covariate specifically for this outcome event (see Section 9.4.3.2.2).

Note: 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.

- Smoking status (in the year prior to index date: current, prior smoker, never-smoker [reference], unknown/missing). Available in HSD, PHARMO, SIDIAP, and CPRD only.
- Number of different ATC codes (full codes) in the year prior to index date, as a proxy for the number of comorbid conditions/frailty of a patient (continuous variable).
- Co-medication (yes/no [no = reference]) to characterize the case and control populations (use based on prescriptions within the year prior to index date) (see Section 15.2.1-Table 2-17 for medication codes):
  - Angiotensin-converting enzyme inhibitors (ACEIs)
  - Angiotensin receptor blockers (ARBs)
  - Other Renin–Angiotensin–Aldosterone–System (RAAS) targeting drugs (e.g., aliskiren/remikiren)
  - Beta-blockers
  - Calcium channel blockers
  - Mineralocorticoid receptor antagonists (MRAs)
  - Diuretics (thiazides, loop, potassium-sparing diuretics, others [excluding MRAs])
  - Digoxin
  - Ivabradine
  - Nitrates
  - Hydralazine
  - Antiarrhythmic agents
  - Anticoagulants
  - Antiplatelets (including prescription aspirin)
  - Lipid lowering drugs (excluding statins)
  - Antidiabetics
  - Non-steroidal anti-inflammatory drugs (NSAIDs)

9.4.3.1.2 Concomitant drug use

Drugs that may increase the risk of any of the outcome events of interest when used concomitantly with statins were assessed for all outcome events in the 90 days before the index date and were based on the Summaries of Product Characteristics (SmPCs) of the various statins. Concomitant use was defined as "prescription duration covering the index date". The duration of prescriptions of these drugs was set to a default of 90 days (see Section 9.4.1.3).

- Concomitant use of drugs potentially increasing systemic statin concentrations (below drug classes were included as one covariate in the model) (yes/no [no = reference])
  - Cytochrome P450 CYP3A4 enzyme inhibitors or substrates with effects on simvastatin, lovastatin, pravastatin, and atorvastatin
  - CYP2C9 enzyme inhibitors or substrates with effects on fluvastatin and pravastatin
  - OATP1B1 inhibitors with effects on atorvastatin, simvastatin, pravastatin, lovastatin, and rosuvastatin
  - Breast Cancer Resistant Protein (BCRP) inhibitors with effect on rosuvastatin

Individual drugs for each of the specified groups of medications are listed in (Section 15.2.1-Table 2-9).

9.4.3.2 Covariates for specific outcome events

In addition to the general characteristics, some additional characteristics may have influenced the rates of specific outcome events. The presence of the following variables was assessed at index date. These are presented per relevant outcome event as additional characteristics. Codes, drugs, and algorithms to identify these covariates are described in Section 15.2.1-Section 2 and the procedure identification methods per database are listed in (Section 15.2.1-Table 2-7).

9.4.3.2.1 Covariates for myotoxicity

- Hypothyroidism (in the year prior to index date)
- Hypovitaminosis D (in the year prior to index date)
- Chronic renal insufficiency (any time prior to index date, i.e., CKD)
- Infection (in the 90 days prior to index date) based on a proxy of anti-infectives use (defined as ATC codes J01 – J05)
- Liver impairment (in the year prior to index date, i.e., chronic hepatic disease (Turner et al 2019, Fernandes et al 2016)
- Alcohol abuse (in the year prior to index date)
- Drugs associated with an increased risk of myotoxicity (prescription/ within 90 days before and including index date): bezafibrate, gemfibrozil, ciprofibrate, nicotinic acid, ciclosporin, fusidic acid, colchicine, ezetimibe, and amiodarone. These were combined into one covariate (no [reference], yes)

Codes, drugs and algorithms to identify these covariates are listed in Section 15.2.1-Table 2-4, Section 15.2.1-Table 2-10, Section 15.2.1-Table 2-27 to Section 15.2.1-Table 2-30, and Section 15.2.1-Table 2-32.

9.4.3.2.2 Covariates for hepatotoxicity

- Drugs causing acute hepatocellular or cholestatic hepatotoxicity (within 90 days before the index date) (based on Devarbhavi et al 2014, Teschke 2018, Andrade et al 2011, and (Section 15.2.1-Table 2-11)). These were combined into one covariate (no [reference], yes)
- Alcohol abuse (in the year prior to index date) (see Section 15.2.1-Table 2-28).

9.4.3.2.3 Covariates for acute pancreatitis

- Alcohol abuse (in the year prior to index date)
- Obesity (in the year prior to index date) based on available diagnostic coding or BMI ≥ 30 kg/m^2 – if available; for consistency across databases, in absence of a diagnostic code or a BMI value ≥ 30 kg/m^2, obesity is assumed to be absent (absence of obesity code or BMI < 30 kg/m^2 = reference). BMI is not available for ARS and GePaRD.
- Hypercalcemia (in the year prior to index date)
- Hypertriglyceridemia (in the year prior to index date)
- Gallbladder disease (gallstones) (in the year prior to index date)
- Endoscopic retrograde cholangio-pancreatography (ERCP) (90 days prior to index date)7
- Cholecystectomy (90 days prior to index date)
- Trauma (90 days prior to index date)
- Drugs associated with acute pancreatitis including ACEIs (90 days prior to index date) (Jones et al 2015, European Medicines Agency 2023). These were combined into one covariate (no [reference], yes).

Codes, drugs, and algorithms to identify these covariates are listed in Section 15.2.1-Table 2-7, Section 15.2.1-Table 2-12, Section 15.2.1-Table 2-16, Section 15.2.1-Table 2-28, Section 15.2.1-Table 2-31, Section 15.2.1-Table 2-33 to Section 15.2.1-Table 2-35.

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.

9.5 Data sources and measurement

This study used European databases comprising routine healthcare data. This reflected 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 maximize 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 National Research Council, and from GePaRD provided by BIPS.

All the databases comply with EU guidelines on the use of medical data for medical research and have been validated for pharmaco-epidemiological 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, Garcia-Gil et al 2011, Ohlmeier et al 2016, Trifirò et al 2019).

Table 9-6 provides an overview of database characteristics including available data. 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.

Table 9-6 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)	Every month with a lag-time of 3-4 months	Yearly (Q4)	Twice a year: (30/06 and 31/12)	Yearly (October)	Yearly (April/May)	Yearly (May/June)
Prescriptions							
Outpatient Rx	Yes	Yes	Yes	Yes (incomplete specialist prescriptions)	Yes	Yes (specialist incomplete)	No (only prescriptions recorded by GPs)

	Database						
Characteristics	**Aarhus**	**ARS**	**GePaRD**	**HSD**	**PHARMO**	**SIDIAP**	**CPRD**
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)
Outcome 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 GPs and specialists diagnoses recorded by GPs)	Yes (diagnoses made by GPs and specialists diagnoses 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)
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 worldometers.info/ (accessed February 13, 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 LCZ696B2015 study protocol v02 – amendment 2 (see 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

Observational studies do not randomize and as such bias and confounding need to be addressed. Multiple approaches are used in this study to address confounding: first matching. With this approach controls were matched to cases on age (year of birth), sex and index date (same calendar date) and duration of statin use. A second approach to deal with confounding was adjustment in the analysis phase. In this study an applied approach for covariate selection for controlling the confounders in the comparative analyses was introduced (see Section 9.9.2.5).

Misclassification of the outcome and exposure may occur, especially because validation of outcomes could not be done, due to lack of access to adequate source data. Specifically, misclassification of cases of myotoxicity may have occurred, as it is likely that patients with myotoxicity were identified by a sole diagnostic code of myalgia without accompanied elevated levels of CK or the presence of myoglobinuria. A sensitivity analysis utilizing a more specific definition of myotoxicity cases, excluding cases with non-specific terms of myalgia was conducted.

Heterogeneity introduced by the use of different data sources may have played a role in this study. To ensure that the outcome event of interest and covariates identified in each database were as expected or were comparable between all databases, benchmarking of data were performed before the data analysis of the study.

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 sample size was calculated following a non-inferiority approach (Wang et al 2007), with the intent to demonstrate that the increased risk due to sacubitril/valsartan exposure was less than 3-fold for hepatotoxicity and less than 5-fold for myotoxicity and acute pancreatitis.

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

A total of 647 cases with hepatotoxicity would allow ruling out a 3-fold increased risk with a one-sided test (80% power, 5% type I error), assuming a conservative case:control ratio of 1:4 and that 1% of the statin-exposed HF patients concomitantly use sacubitril/valsartan in the control group (Table 9-7). As per second progress report, approximately 1% of the study population was exposed to sacubitril/valsartan during follow-up ([redacted]).

A total of 302 cases with a myotoxic event or acute pancreatitis would allow ruling out a 5-fold increased risk (Table 9-7).

Table 9-7 Sample size scenarios for a one-sided non-inferiority test (80% power, 5% type 1 error)

Risk (odds ratio) to be ruled out	No of cases needed (as per LCZ696 exposure prevalence in controls)				
	with 0.2% LCZ696 use	with 0.5% LCZ696 use	with 1% LCZ696 use	with 2% LCZ696 use	with 5% LCZ696 use
5	1,495	600	302	153	63
3	3,208	1,288	647	327	135
2	8,059	3,234	1,625	821	339

9.8 Data transformation

Due to the different database structures, characteristics, and coding systems, it was not possible to use one single data program to the native data for all databases. To overcome this and harmonize the analysis, a study-specific 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, i.e., standardized patient, drug, diagnosis, and assessment files, linkable via a patient unique identifier (see Figure 9-7), 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 outcome 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 was adapted by each data partner as needed to reflect database-specific coding system requirements.

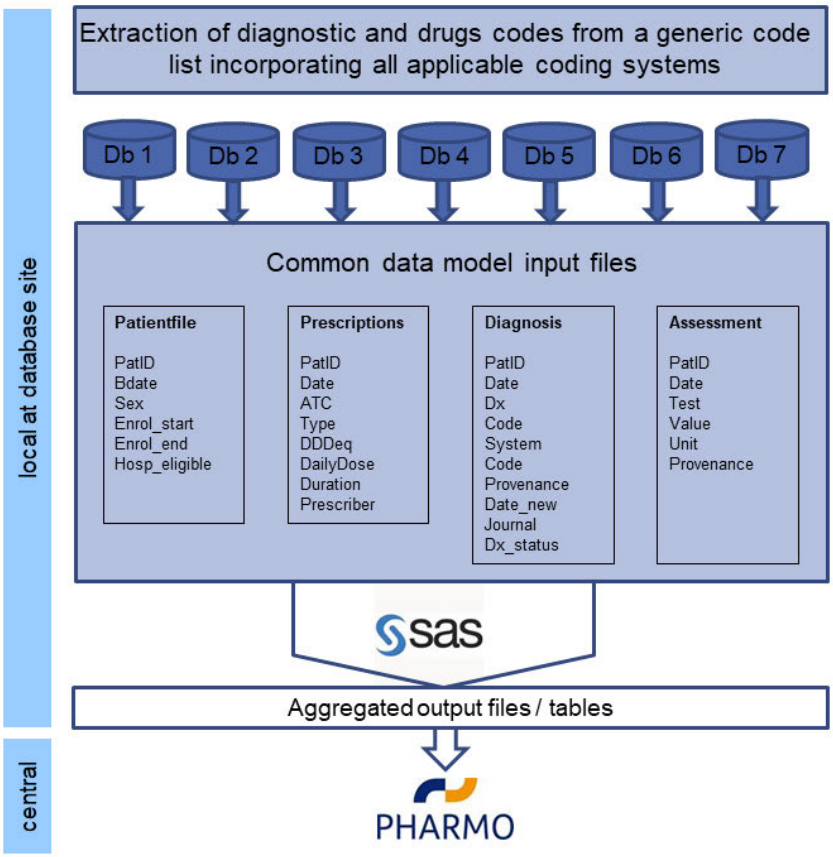
The feasibility study, validation study, and benchmarking of the data for the final analysis were finalized in Q1 2021 ([redacted]), Q2 2022 ([redacted]), and Q1 2022, respectively, and informed the SAP of the final LCZ696B2015 study.

Programming for data transformation of the input files into relevant evidence 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 outcome 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 the results of the primary, secondary, and sensitivity analyses, if necessary. PHARMO combined all aggregated data into the final report. The process of data collection, programming, and reporting is summarized in Figure 9-7.

For all data partners, SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) was available for data processing and analysis. For the final report, ARS used SAS version 9.4 instead of R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), which was used for the previous progress reports.

Figure 9-7 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 9-7 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 and secondary analyses 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 pre-COVID period.

Based on the results of the validation study ([redacted]), all analyses for the primary and secondary analyses were conducted without validation for all outcome events that were identified in each database. The outcome event of myotoxicity, hepatotoxicity, and acute pancreatitis was based on a total number of patients identified by the recorded diagnostic codes as described in Section 15.2.1-Table 2-2, Section 15.2.1-Table 2-3, and Section 15.2.1-Table 2-6.

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 linked hospital data. 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 9-2). 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 (= patients without and with linked hospital data) was not analyzed. This stratification by eligibility for linked hospital data gives insight into the added value of hospital data in addition to primary care data in the various countries.

Small-cell-counts

Due to regulations regarding data sharing, CPRD is not allowed to report information on cell counts below five, which therefore are presented as '<5' in this study 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 outcome events of interest as long as patients are not traceable. While cell counts below five can be provided for PHARMO, detailed information on small subsets including less than five patients cannot be disclosed as it could potentially identify patients involved.

When actual cell counts were not known due to redaction, a range of possible values ranging from zero to four for CPRD and from one to four for Aarhus was assumed for the presentation of the number of cases in each study.

9.9.1 Main summary measures

This study report includes the following summary measures:

Descriptive summary measures

- The size of the study base per database for the full study period is presented in an attrition table.
- For each outcome event of interest (myotoxicity, hepatotoxicity, acute pancreatitis, and myotoxicity defined as diagnostic codes other than myalgia alone [sensitivity analysis]), the number of cases and matched controls using statins, irrespective of type or dose, from the study base is presented per database as absolute number of patients in the pre-COVID (primary analysis) and full study period (sensitivity analysis).

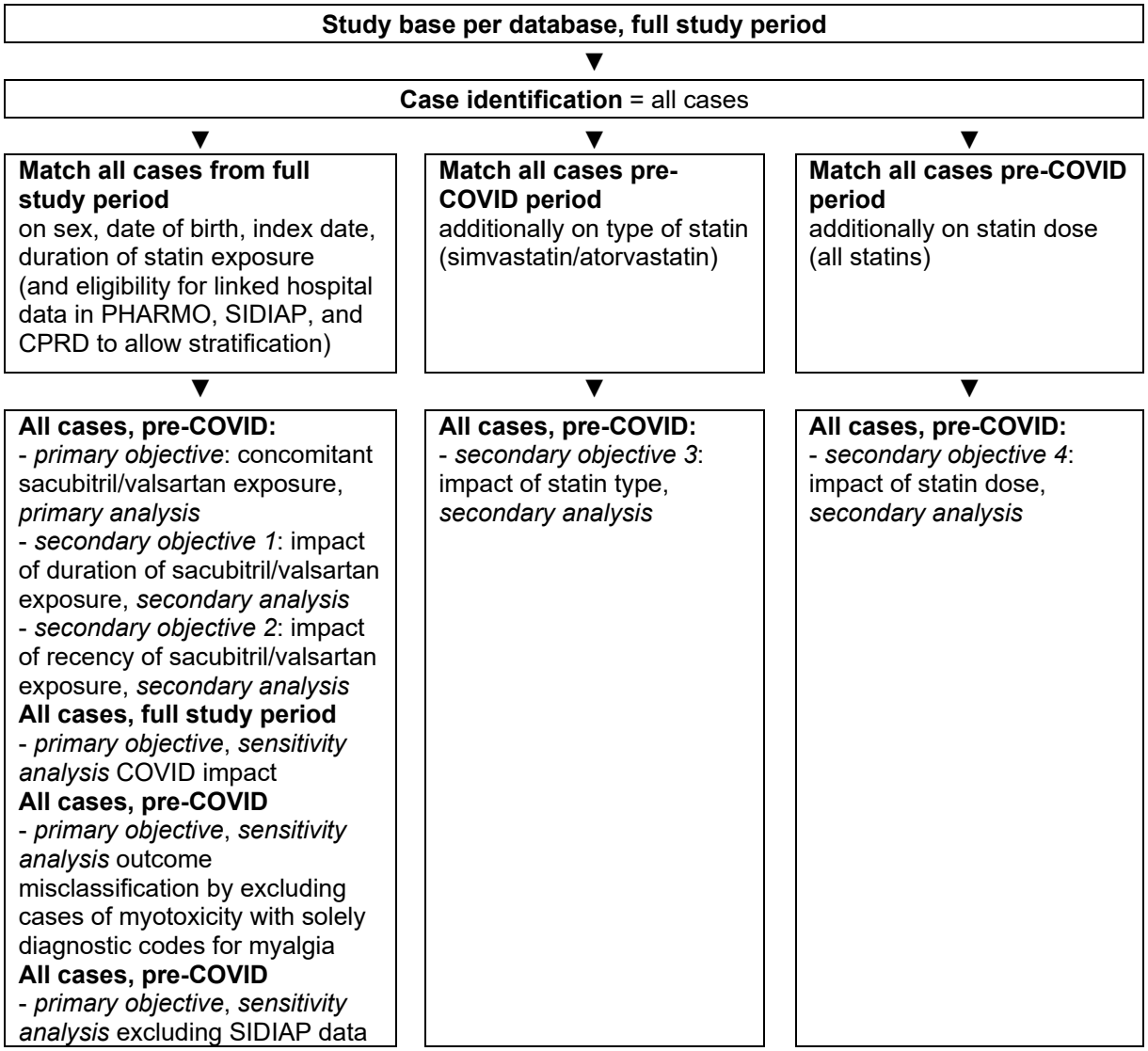
- For the additional set of cases and matched controls using simvastatin, atorvastatin, high or low dose of statins, the number of cases and controls from the study base is presented per database as absolute numbers in the pre-COVID (secondary analyses) and full study period (sensitivity analysis).
- Patient demographic and clinical characteristics are provided for cases and controls in the pre-COVID and full study period, including:
  - Age,
  - Sex,
  - Duration, type, and dose of statin exposure,
  - Duration and recency of sacubitril/valsartan exposure,
  - Smoking status
  - Comorbidities (ever prior to (=look-back period) or at index date),
  - Co-medications (in the year prior to index date),
  - Concomitant use of statins (90 days prior to index date)
  - Risk factors for myotoxicity, hepatotoxicity, and acute pancreatitis (90 days or within one year prior to or at index date).

Statistics of patient demographic and clinical characteristics were described for cases and controls in the primary and secondary analyses, using contingency tables for categorical variables, and mean (±SD), median (IQR), and min, max for continuous variables per database in the pre-COVID and full study period, and for the analysis where cases of myotoxicity were defined as patients with diagnostic codes other than myalgia alone (sensitivity analysis).

Inferential summary measures

- The relative risk of myotoxicity, hepatotoxicity, acute pancreatitis, or myotoxicity defined as diagnostic codes other than myalgia alone [sensitivity analysis] was expressed as an odds ratio (OR; crude and adjusted) with its corresponding 95% confidence intervals (CIs) for concomitant exposure of sacubitril/valsartan with statins versus statin exposure alone are estimated in patients with HF per database (as feasible) and in all databases or all databases without SIDIAP data (sensitivity analysis) in the pre-COVID period (primary analysis) and full study period (sensitivity analysis).
- The relative risk of myotoxicity, hepatotoxicity, or acute pancreatitis for concomitant exposure of sacubitril/valsartan with simvastatin, atorvastatin, high and low dose of statins versus simvastatin, atorvastatin, high and low dose of statin exposure alone are estimated in patients with HF per database (as feasible) and in all databases in the pre-COVID period (secondary analyses). The definitions of low and high dose (mg) of each type of statins are described in (Section 15.2.1-Table 3-1). The relative risk for all these secondary analyses were expressed as ORs with its corresponding 95% CIs.
- The diagram in Figure 9-8 shows which analyses were conducted based on which selection of a matched case-control set.

Figure 9-8 Overview of which matched case-control sets were used for which objectives and analyses



CPRD = Clinical Practice Research Datalink; PHARMO = PHARMO Institute for Drug Outcomes Research; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

9.9.2 Main statistical methods

9.9.2.1 Number of patients in the study base

The size of the study base population is presented in an attrition table (see Section 15.2.1-Table 1-1) with numbers included and excluded in each subsequent step. Exclusions are reported as absolute numbers, as well as percentages (%) of the population size immediately prior to the applied exclusion in the attrition table.

9.9.2.2 Number of patients in the matched, nested case-control sets for each outcome event of interest

From the study base cases were identified and then sampled and matched to controls, and the matched case-control sets are presented per database in an attrition table with numbers of patients included or excluded in each step of the patient selection (see Section 15.2.1-Table 1-1 for the selection of the study base; and the tables in Section 15.2.1-Table 1-2 to Section 15.2.1-Table 1-16 for the selection of the sets of cases and controls per outcome event of interest). Exclusions were summarized as the number of patients and percentage of the population size immediately prior to exclusion according to the attrition table. Section 15.2.1-Table 1-17 shows the composition of cases regarding severity based on hospitalizations, and for myotoxicity based on the occurrence of rhabdomyolysis in the pre-COVID period.

9.9.2.3 Demographic and baseline clinical characteristics

Demographics, matching variables, and potential covariates of matched cases and controls are described in contingency tables for categorical variables as counts and percentages, and mean, standard deviation (SD), range, median and interquartile range (IQR) values were given for continuous variables per outcome event of interest in each individual database (Tables in Section 15.2.1-Section 1.3). All demographics and clinical characteristics were assessed at index date, using different look-back periods (See Section 9.4.3)

To account for any variation in the number of controls per case between matched case-control risk sets, all mean, SD, range, median, IQR, counts, and percentages reported for controls were weighted by the inverse number of controls in each sample risk set (de Jong et al 2017). Cases had a weight of one whereas controls were weighted by the inverse number of matched controls in each case-control risk set.

For controls descriptive statistics of unweighted continuous and categorical variables are reported without decimals, whereas descriptive statistics of weighted continuous and categorical variables are reported with one decimal.

9.9.2.4 Comparative analyses

For each case, up to 100 controls from the same database were randomly selected, matched by age, sex, index date, and duration of statin exposure (and eligibility for linked hospital data in PHARMO, SIDIAP, and CPRD) at and prior to outcome event of interest by incidence density sampling (see Section 9.3.2.2.2).

The association between exposure to sacubitril/valsartan and the outcome events of myotoxicity, hepatotoxicity, and acute pancreatitis in a study base of patients with HF aged ≥ 18 years exposed to statins was determined, using conditional logistic regression analyses to estimate the OR as an approximation for the relative risk. In SAS, this was done with the PHREG procedure by using the discrete logistic model and forming a stratum for each matched set (matching ID includes age, sex, index date, and duration of statin exposure [and eligibility for linked to hospital data in PHARMO, SIDIAP, and CPRD]).

proc phreg data = *dataset* summary;

model *time***event*(0)= *exposure and covariates* /ties=discrete risklimits;

strata *matching ID*;

run;

Dummy survival times were assigned value 1 for cases and 2 for controls, so that all cases in a matched set had the same event time value, and the corresponding controls were censored at later times. The matching ID was entered into the strata statement, identifying the matched case-control risk sets. Exposure variables and covariates used for each objective, including definition of the reference category, are defined in Section 9.4.1 and Section 9.4.3.2. All analyses applied dummy coding (i.e., 1 = yes and 0 = no).

Per 10 cases, one covariate could be added to the model in addition to the sacubitril/valsartan exposure variable. If fewer than 20 cases were identified for the analysis only unadjusted estimates are reported. The modeling steps are described in the following sections. In each database, the order in which covariates were added to the models was determined by the amount of bias that may have been introduced. The same covariates order was applied to the sensitivity and secondary analyses.

All conditional logistic analyses for each outcome event of interest (including sensitivity analyses [see Section 9.9.4]) were executed in each database based on common SAS programs prepared by PHARMO.

9.9.2.5 Primary analysis

The primary analysis evaluated the primary objective, i.e., the comparison between concomitant sacubitril/valsartan exposure with statins and no concomitant sacubitril/valsartan exposure with statins (the reference category). Past and recent exposure to sacubitril/valsartan were included in the group with no sacubitril/valsartan exposure.

The primary analysis adjusted for potential confounders beyond the matching factors (i.e., database, age, sex, index date, statin duration, linked hospital data [only PHARMO, SIDIAP, and CPRD]). To build the adjusted model for the primary analysis per database (or subset regarding linked hospital data), the following conditional logistic regression models were applied separately for each outcome event of interest.

- Model 0: Base model: exposure: concomitant sacubitril/valsartan(yes/no), covariates: none, strata: matching ID (see Section 9.4) for the case-control risk sets with identical matching variables
- Model 1: Base model + predefined potential confounders (as specified in Section 9.4.3.1 and Section 9.4.3.2): If the number of potential confounding variables plus one (for the exposure variable of concomitant sacubitril/valsartan [yes/no] which was present in each model) did not exceed one variable per ten cases, all predefined potential confounders were included (Peduzzi 1996). If the number of predefined potential confounders exceeded this threshold, the following selection algorithm was applied:
  a. Derive the maximal number of covariates for each database based on the number of valid cases and the one variable per ten cases rule. Let K denote the maximal number of allowed covariates: $K = \lfloor \max(n_{cases} - 10, 0)\ /10 \rfloor$, where $\lfloor ... \rfloor$ denotes the floor function (which resolves into the next smaller integer).
  b. Calculate $|log\ (Bias)|$ for each potential confounder, similar to the approach used for variable identification for the high-dimensional propensity score (Schneeweiss et al

2009) adapted to the case-control setting according to equation (12) in Arah et al 2008 and corresponding simplification for binary covariates:

$$\boldsymbol{Bias = \frac{P_{C1}(OR_{CD}-1)+1}{P_{C0}(OR_{CD}-1)+1}}, \text{ where}$$

OR_{CD}: OR of confounder C for outcome D in unexposed,

P_{C1}: Prevalence of controls having confounder C in exposed,

P_{C0}: Prevalence of controls having confounder C in unexposed, and $log()$ refers to the natural logarithm.

For estimating the $|log\ (Bias)|$ smoking was categorized as current and non-current smokers (= prior smoker and never-smoked).

The OR_{CD}, P_{C1}, P_{C0}, and *log (Bias)* are presented in Section 15.2.1-Table 1-108 to Table 1-117; Section 15.2.1-Table-1-129 to Table 1-138, Section 15.2.1-Table 1-159 to Table 1-168; Section 15.2.1-Table 1-188 to Table 1-197. To show the covariates with a *log (Bias)* that were included in the model ($|log\ (Bias)| \geq 0.05$) the *log (Bias)* of each covariate is displayed as three decimal places.

c. Covariate selection: Among the potential confounders specific to the outcome event of interest (as specified in Section 9.4.3) dismiss those with $|log\ (Bias)| < 0.05$ (corresponding to approx. 5% bias).
   - If the number of covariates left ($K1$) is still $\geq K$, select K covariates with largest $|log\ (Bias)|$.
   - If the number of covariates left ($K1$) $< K$, include the $K1$ covariates in the model and select remaining $(K - K1)$ covariates from the other potential covariates based on the largest $|log\ (Bias)|$.

Lack of information on smoking may occur. If more than 20% of the patients had missing data, then the covariate was not included in the model.

In case the model did not converge after addition of a potential confounder, the potential confounders were removed.

All results of the primary analyses are described in tables and depicted in forest plots as presented in Section 15.2.1-Section 1.4 (Primary analyses of myotoxicity), Section 15.2.1-Section 1.7 (Primary analyses of hepatotoxicity) and Section 15.2.1-Section 1.10 (Primary analyses of acute pancreatitis).

9.9.2.6 Secondary analyses

Secondary analyses were performed to assess the potential impact of duration of sacubitril/valsartan exposure and recency of cessation of sacubitril/valsartan exposure on the association of concomitant sacubitril/valsartan exposure and statins on the outcome event of myotoxicity, hepatotoxicity, and acute pancreatitis. Furthermore, the impact of statin type and statin dose on the association of concomitant exposure to sacubitril/valsartan and statins was assessed. Each analysis should contain at least five cases per database (or subset based on linked hospital data); otherwise, findings could not be presented.

Secondary objective 1 – duration of use of sacubitril/valsartan

- To assess the potential impact of duration of sacubitril/valsartan exposure on the association between concomitant sacubitril/valsartan and statin exposure and each outcome event of interest (*secondary objective 1*), the exposure variable contained four categories of concomitant sacubitril/valsartan exposure:
  - no concomitant exposure (same reference as the primary analysis)
  - short concomitant exposure
  - medium concomitant exposure
  - long concomitant exposure

No concomitant sacubitril/valsartan exposure was the reference category.

Secondary objective 2 – recency of use of sacubitril/valsartan

- To assess the potential impact of the recency of cessation of sacubitril/valsartan exposure on the association between concomitant sacubitril/valsartan and statin exposure and each outcome event of interest (*secondary objective 2*), the exposure variable contained three categories:
  - concomitant sacubitril/valsartan exposure
  - recent sacubitril/valsartan exposure
  - non-use (i.e., no recent [i.e., latest exposure ended more than 90 days before the index date] or no sacubitril/valsartan exposure [i.e., never exposed to sacubitril/valsartan]).

The latter category was used as reference and may contain past sacubitril/valsartan use that was not deemed recent. Limiting incidence density sampling to time at risk due to exposure to statins, ensured that recent exposure to sacubitril/valsartan coincided with statin exposure to allow studying the drug-drug interaction.

Secondary objective 3 – specific types of statins

- To assess the potential impact of the type of statins on the association between concomitant exposure to sacubitril/valsartan and statins and each outcome event of interest (*secondary objective 3*), the exposure variable contained categories based on:
  - concomitant sacubitril/valsartan exposure
  - no concomitant sacubitril/valsartan exposure (reference)
- The analyses were performed in separately created matched case-control sets:
  - one restricted to simvastatin exposure at index date (the statin deemed first choice in most countries)
  - one restricted to atorvastatin exposure at index date (the second most often used statin type)

The restriction to type of statin restricted the number of cases per analysis, and thus the number of covariates per analysis.

Secondary objective 4 – dose of statins

- To assess the potential impact of the statin dose on the association between concomitant exposure to sacubitril/valsartan and statins and each outcome event of interest (*secondary objective 4*), the exposure variable contained categories based on:
  - concomitant sacubitril/valsartan exposure
  - no concomitant sacubitril/valsartan exposure (reference)

The analyses were performed in separately created sets of cases and matched controls for high dose and low dose of statins used at index date (see Section 9.4.1.1).

The restriction to statin dose restricted the number of cases per analysis, and thus the number of covariates per analysis.

For all secondary analyses, the same prioritization of covariates (identified by the $|log\ (Bias)|$ term in the primary analyses) was used for each outcome event of interest in Section 9.9.2.5, however, the number included covariates varied based on the number of cases per analysis. However, for the sensitivity analysis where the full study period, including the period in which the COVID-19 pandemic occurred (from 2020 onward), was used, the number of covariates were the same as the primary analysis.

All results of the secondary analyses are presented in tables and forest plots as described in Section 15.2.1-Section 1.6 (Secondary analyses of myotoxicity), Section 15.2.1-Section 1.9 (Secondary analyses of hepatotoxicity) and Section 15.2.1-Section 1.12 (Secondary analyses of acute pancreatitis).

9.9.2.7 Data pooling

Matching was performed per outcome event of interest and per database. Individual-level data could not be shared due to governance restrictions for the databases. The study-specific effect estimates such as the ORs and corresponding 95% CIs (parameter estimates and standard errors (SEs)) received from the database partners were pooled in a meta-analysis (see Section 9.9.2.8) and are presented in tables and forest plots as described in Section 15.2.1-Section 1.4 to 15.2.1-Section 1.12.

9.9.2.8 Meta-analysis

All ORs and corresponding 95% CIs were calculated per database and pooled as follows: the crude and adjusted ORs (parameter estimates and SEs) estimated with the conditional logistic regression models in each database were combined in a two-stage meta-analysis, using fixed-effects and random-effects models employing the Mantel-Haenszel (Robins et al 1986, Higgins et al 2011) and DerSimonian and Laird method (DerSimonian et al 1986), respectively.

Each meta-analysis estimate was based on treatment effect estimates arising from models that were conditioned on different covariates per database (or subset). The estimates are presented as outcomes of the fixed-effects and random-effects models, respectively.

Fixed-effects model

For the fixed-effects model, the database- or subset-specific ORs adjusted for confounders and the corresponding SEs, and the given weight of each database- or subset-specific OR were used for estimating the pooled ORs, using the Mantel-Haenszel method (Robins et al 1986, Higgins et al 2011). When the number of concomitant users of sacubitril/valsartan and statins was less than five in Aarhus and CPRD, the actual number of users could not be displayed due to the small-cell-count policy. This information is relevant for estimating the pooled ORs and their SEs using the Mantel-Haenszel method. The actual number of sacubitril/valsartan users was used when this number was traced based on all results presented in this study, otherwise a range of the number of concomitant users of sacubitril/valsartan and statins was assumed: For the

lowest exposed scenario, zero (only when database- or subset-specific ORs were <0.01 in CPRD) otherwise one user per database or subset (for Aarhus and/or CPRD) was assumed, and for the highest exposed scenario, four users per database or subset (for Aarhus and/or CPRD) were assumed.

Random-effects model

For the random-effects model, the database- or subset-specific ORs adjusted for confounders and the corresponding SEs (which were derived from the 95% CIs), and the given weight of each database- or subset-specific OR were used for estimating the pooled ORs where the between-database or subsets variance was included by using the DerSimonian and Laird method (DerSimonian et al 1986).

The Mantel-Haenszel method was introduced post-hoc to mitigate the limitation of the DerSimonian and Laird method with respect to handling data situations where cases were zero exposed to sacubitril/valsartan in databases or subsets. Both methods deal differently with the so-called 'single arm zero study' or 'single zero-counts' (Xu et al 2021). The fixed-effects model considers data from single zero-counts by including the weight for each database or subset in the meta-analysis whereas the random-effects model deals with these single zero-counts by giving those databases or subsets zero weight, i.e., by excluding them. The weights of databases or subsets with single zero-counts tend to go to zero because these databases or subsets have a large SE. In the random-effects model, however, the database- or subset-specific SEs were directly included in the between-database or subsets variance.

It is not likely that both cases and controls were not exposed to sacubitril/valsartan (a 'double arm zero study' or 'double zero-counts'). However, it occurred for some analyses when the recency of use and duration of exposure to sacubitril/valsartan was assessed. For these databases or subsets, recent use, medium and/or long duration of sacubitril/valsartan was/were not included in the analysis.

Heterogeneity

Given the poor performance of the significance tests for statistical heterogeneity, no such testing was used. Rather, heterogeneity of the fixed- and random-effects model was assessed based on I^2. Meta-analysis of pooled data was performed if heterogeneity did not exceed 50% (Cochrane Collaboration 2011). Otherwise, the cells were blank in tables presenting the results of the primary, secondary, and sensitivity analyses in Section 15.2.1-Section 1.4 to 15.2.1-Section 1.12. Negative values of heterogeneity were truncated at zero.

A planned separate analysis of heterogeneity in subsets of databases comprising records of primary care and hospital data, only primary care data, or only hospital data was not conducted because of the limited sample size in some databases or subsets and related small-cell-count policy issues.

The pooled ORs and their corresponding CIs were considered as the main estimates for all analyses and are presented in tables and forest plots as described in Section 15.2.1.

9.9.3 Missing values

Since the underlying data represent attended medical care, it was assumed that absence of clinical information of a condition meant absence of that condition. Lack of information on

smoking may have occurred, but this was unlikely differential. No data imputations were performed.

9.9.4 Sensitivity analyses

The sensitivity analyses focused on the impact of potential outcome misclassification and on the impact of the COVID-19 pandemic (e.g., through differences in health-seeking behavior, healthcare resource utilization, compliance with statin therapy by patients, or prescribing of types or doses of statins by physicians, recording of outcome event of interest). For the latter sensitivity analysis, the adjusted model from the primary objective for each outcome event of interest was used. For the first sensitivity analysis, an adjusted model was built as described in Section 9.9.2.5. For the sensitivity analysis where the impact of SIDIAP data on the study results was examined, the results of SIDIAP were not included in the meta-analysis.

9.9.4.1 Sensitivity Analysis: Potential outcome misclassification

Because of the inability to validate cases of myotoxicity, hepatotoxicity, and acute pancreatitis, specificity of the outcome event of interest could not be guaranteed. This could have led to an attenuation of the treatment effect assuming that the misclassification was non-differential between the exposure groups of concomitant sacubitril/valsartan and statins exposure and no concomitant sacubitril/valsartan exposure.

To assess the potential bias due to a low specificity of identifying myotoxicity, a sensitivity analysis for the outcome event of myotoxicity was performed, based on a more specific definition of myotoxicity cases that excluded cases with only unspecific terms of myalgia. This sensitivity analysis was conducted in all databases except for ARS and HSD which use the ICD-9 coding system that does not have a specific code for myalgia. For each case, up to 100 controls were sampled from the set of eligible controls in the same database by matching on age, sex, index date, category of duration of statin exposure, and eligibility for linked hospital data (only applicable for PHARMO, SIDIAP, and CPRD) at index date (see Section 9.3.2.2.2).

9.9.4.2 Sensitivity Analysis: Impact of the COVID-19 pandemic

The primary analysis was censored at the time of the COVID-19 pandemic. To examine the impact of the COVID-19 pandemic, sensitivity analyses were conducted where the primary objective was examined for the full period, including the period in which the COVID-19 pandemic occurred.

9.9.4.3 Sensitivity Analysis: Impact of SIDIAP data on the study results

In SIDIAP, the date of the dispensing is defined as the first day of the month because only the month and year of dispensing is captured in this database. This leads to inaccuracy of exposure and patients, may not have been correctly defined as concomitant users of sacubitril/valsartan and statins or statins alone at the date of the outcome event of interest. Furthermore, the duration of statin use, as well as the duration or patient exposure to sacubitril/valsartan at index date would be overestimated. Because the direction and magnitude of bias which may have been introduced by this measurement error is difficult to predict, post-hoc sensitivity analyses were conducted that excluded SIDIAP data for the estimation of pooled ORs and corresponding 95% CIs for the primary analysis (primary objective).

9.9.5 Amendments to the statistical analysis plan

For the final 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 using 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 based on the pre-specified SAP version 3.0 for the final report (see Section 15.1.4) and using SAS. During double programming, necessary changes to the SAP were documented in SAP version 3.0. Double-programming based on stated principles (available on request) provided additional quality control of the results. Specifically, double programming in SAS also allowed checking each step in the data analysis to examine if both programs provided the same number of patients in the study base and number of exposed or non-exposed cases and controls with the same data. Both SAS programs were then implemented by the data partners to generate aggregated data files to fill the final report.

The LCZ696B2015 study was double programmed by programmers that were not involved in either the LCZ696B2015 or LCZ696B2014 study at any time during the project. The programmers performed double programming with no access to the location where all statistical programs of the LCZ696B2015 and LCZ696B2014 studies 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 the input files. These input files served as the basis for the diagnosis of HF, outcome events of interest, and comorbidities selection algorithms (see Section 9.3.2.1 for the HF selection algorithm, Section 9.4.2.4 for the outcome event selection algorithms, and Section 9.4.3.1.1 for the comorbidity selection algorithm).

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 LCZ696B2015 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

Small-cell-counts

Due to regulations regarding data sharing, CPRD is not allowed to report information on cell counts below five, which therefore are presented as '<5' in this study 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 outcome events of interest as long as patients are not traceable. While cell counts below five can be provided for PHARMO, detailed information on small subsets including less than five patients cannot be disclosed as it could potentially identify patients involved (see Section 15.2.1-Table 1-17).

When actual cell counts were not known due to redaction, a range of possible values ranging from zero to four for CPRD and from one to four for Aarhus is assumed for the presentation of the number of cases in each study.

10.1 Participants

A total of 41,383,318 patients were potentially eligible for inclusion in the study base during the study period. This total included all patients in each database regardless of linkage with hospital data. The databases with only primary care data (HSD, PHARMO, SIDIAP, and CPRD [N=10,872,860]) represent 26% of the country specific total population. After applying all inclusion and exclusion criteria, the study base included 922,199 patients, irrespective of linkage with hospital data. The majority of the patients were excluded due to no recorded HF diagnosis (92-99%) and an absence of statin exposure during the study period (36-54%). GePaRD contributed the largest proportion of patients to the study base (72% of all patients in the study base), followed by SIDIAP (8%) and ARS (8%). HSD contributed the smallest number/proportion of patients (1%). A subset of patients in PHARMO, SIDIAP, and CPRD has been linked with hospital data. Restricting the study base to those with linked hospital data in PHARMO, SIDIAP, and CPRD resulted in a total of 70,284 patients (46% of all patients in the study base for these three databases [n=152,281]). As CPRD received hospital data (for linkage) from patients 18 years or older only, there were differences observed in the proportion of excluded patients due to age <18 years between the subgroups with and without linked hospital data in the CPRD database. In HSD patients younger than 18 years were not enrolled with a GP and did not appear in this database.

The selection of the study base, from which cases per database for the matched nested case-control study were selected, is presented in attrition (Section 15.2.1-Table 1-1).

10.1.1 Myotoxicity

Selection of matched nested case-control sets
Within the study base of 922,199 patients (irrespective of linked hospital data), a total of 872,839 patients were at risk of myotoxicity (full study period) (see Section 15.2.1-Table 1-2).

Primary objective and secondary objectives 1 – duration of use of sacubitril/valsartan, and 2 – recency of use of sacubitril/valsartan
Among patients at risk, a total of 3,557 cases of myotoxicity were identified in all databases in the full study period. Almost all cases of myotoxicity could be matched with controls. After excluding patients with a history of trauma or surgery, and patients who experienced myotoxic events from causes other than drug-related events in the seven days after the index date, 2,634 cases of myotoxicity and 200,556 matched controls in the pre-COVID period were included in the study, ranging from 14 cases and 995 controls in Aarhus to 1,135 cases and 91,298 controls in GePaRD (see Table 10-1 and Section 15.2.1-Table 1-2). Hence, GePaRD contributed 43% of cases and 46% of the controls to the matched case-control sample of all databases in the pre-COVID period. Of the myotoxicity cases, 23% (607 to 611 patients) were identified from hospital data, of which 2% to 3% were exposed to sacubitril/valsartan. Cases of rhabdomyolysis were only identified in ARS (47 patients) and SIDIAP (29 patients with linked hospital data and 2 patients without linked hospital data), only one of them (from SIDIAP) had concomitant exposure to sacubitril/valsartan and statins (see Section 15.2.1-Table 1-17). Due to small-cell-count redaction, it is not known if rhabdomyolysis cases were found in CPRD.

Primary objective – sensitivity analysis excluding myalgia
The sensitivity analysis using a more specific definition of myotoxicity that excluded cases with only a diagnostic code for myalgia was conducted in all databases except in ARS and HSD, since they did not have specific myalgia codes in the ICD-9 coding system. Based on this definition, 88% (n=2,319 out of 2,634) of all cases in the databases, with exception of ARS and HSD, were excluded. A total of 315 cases with a more specific definition of myotoxicity were identified in the databases contributing to this analysis, ranging from four cases in PHARMO without linked hospital data to 137 cases in GePaRD. For these 315 cases, a total of 23,298 controls were sampled and matched in the pre-COVID period (see Table 10-1 and Section 15.2.1-Table 1-2). Of these 315 myotoxicity cases, 53% to 55% (167 to 174 patients) were identified in the hospital data. Of those, 4% to 9% were exposed to sacubitril/valsartan. There were 31 cases of rhabdomyolysis, in SIDIAP (29 patients with linked hospital data and 2 patients without linked hospital data), of whom one had concomitant exposure to sacubitril/valsartan and statins. Due to small-cell-count redaction it is not known if rhabdomyolysis cases were found in CPRD. No case of rhabdomyolysis was identified in any other database (see Section 15.2.1-Table 1-17).

Secondary objective 3 – specific types of statins
Within the 872,839 patients at risk of myotoxicity in the study base, 386,217 (44%) and 505,830 (58%) patients were treated with atorvastatin and simvastatin during the pre-COVID period, respectively. Among atorvastatin users, a total of 1,135 cases of myotoxicity and 75,532 controls were identified in all databases after applying the same exclusion criteria as used for the primary objective and secondary objectives 1 and 2, ranging from 10 cases and 595 controls

in Aarhus to 440 cases and 34,630 controls in GePaRD. Among those treated with simvastatin, a total of 1,149 to 1,152 cases of myotoxicity and 78,165 controls were identified in all databases after exclusions, ranging from less than five cases and 217 controls in Aarhus to 595 cases and 47,240 controls in GePaRD (see Table 10-1 and Section 15.2.1-Table 1-3 and Section 15.2.1-Table 1-4). Because the number of cases of myotoxicity was lower than 5 in Aarhus, further analyses were not performed in that database.

Secondary objective 4 – dose of statins

Of the 872,839 patients at risk for myotoxicity in the study base, 465,623 (53%) and 531,192 (61%) were treated with a high and low dose of statins during the pre-COVID period, respectively. Among the high dose statin users, a total of 1,602 cases of myotoxicity and 114,227 controls were identified in all databases after exclusions of trauma or surgery within three months prior to index date, or myotoxic events other than drug-related events prior to or seven days after the index date, ranging from 10 cases and 566 controls in Aarhus to 514 cases and 40,368 controls in GePaRD. After all exclusions, a total of 1,038 to 1,041 cases of myotoxicity and 72,369 controls were identified among low dose statin users in all databases, with a lowest number of less than 5 cases and 220 controls in Aarhus and highest number of 624 cases and 49,527 controls in GePaRD (see Table 10-1 and Section 15.2.1-Table 1-5 and Section 15.2.1-Table 1-6). Further analyses were not conducted in Aarhus as there were less than five cases of myotoxicity among low dose statin users.

Table 10-1 Selection of matched nested case-control sets for myotoxicity in each database – primary and secondary analyses

Myotoxicity[§]	Aarhus (DK)	ARS (IT)	GePaRD (DE)	HSD (IT)	PHARMO (NL)		SIDIAP (ES)		CPRD (UK)	
					Without linked hospital data	With linked hospital data	Without linked hospital data	With linked hospital data	Without linked hospital data	With linked hospital data
Primary objective and Secondary objectives 1 and 2										
Matched cases, n	14	85	1,135	25	80	297	358	332	190	118
Matched controls, n	995	7,079	91,298	1,008	2,975	24,667	28,091	22,436	14,937	7,070
Primary objective – sensitivity analysis (myotoxicity cases excluding only myalgia)										
Matched cases, n	7	-*	137	-*	4≠	19	22	108	7	11
Matched controls, n	540	-	10,900	-	124	1,330	1,678	7,659	508	559
Secondary objective 3										
Atorvastatin										
Matched cases, n	10	53	440	14	27	93	152	171	107	68
Matched controls, n	595	3,803	34,630	439	1,028	3,597	12,034	9,563	7,144	2,699
Simvastatin										
Matched cases, n	#	20	595	10	34	128	147	120	56	38
Matched controls, n	217	870	47,240	466	1,352	7,639	9,568	5,620	3,396	1,797
Secondary objective 4										
High dose of statins										
Matched cases, n	10	59	514	14	55	200	262	261	144	83
Matched controls, n	566	4,443	40,368	439	1,904	14,730	18,807	18,130	10,632	4,208
Low dose of statins										
Matched cases, n	#	26	624	11	25	97	97	72	48	37
Matched controls, n	220	1,247	49,527	611	986	4,078	8,105	4,021	2,208	1,366

[§]Statin exposure was based on single agents or fixed combination therapies of statins. Each prescription of statins was extended with a grace period, which was the maximum of either seven days or half the calculated duration of the prescription.

*No sensitivity analysis focusing on the primary objective which included all outcome events of myotoxicity with a more specific definition of myotoxicity cases, that excluded cases with only unspecific terms of myalgia in the pre-COVID period was performed, because the ICD-9 coding system does not have a specific code for myalgia.

≠No analyses were conducted when the number of cases was less than five.

#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.

10.1.2 Hepatotoxicity

Selection of matched nested case-control sets

Within the study base of 922,199 patients (irrespective of linked hospital data), a total of 727,355 patients were at risk of hepatotoxicity (full study period) (see Section 15.2.1-Table 1-7).

Primary objective and secondary objectives 1 – duration of use of sacubitril/valsartan, and 2 – recency of use of sacubitril/valsartan

Among 727,355 patients at risk, a total of 576 hepatotoxic events were identified across all databases in the full study period. Nearly all cases could be matched with controls. Hepatotoxic events were excluded if patients had an indicated hepatic morbidity suggestive of another etiology at or in the seven days after the index date, leaving 329 to 333 matched cases and 30,890 matched controls across all databases in the pre-COVID period, ranging from no case in HSD and PHARMO (without linked hospital data) to 253 cases and 25,179 controls in GePaRD (see Table 10-2 and Section 15.2.1-Table 1-7). Hence, GePaRD contributed 76% to 77% of cases and 82% of the controls to the matched case-control sample of all databases in the pre-COVID. In CPRD without linked hospital data less than five cases of hepatotoxicity were identified and further analyses were not conducted. Of the hepatotoxicity cases, 247 patients (74% to 75%) were identified from hospital data. Of those, six to ten cases were exposed to sacubitril/valsartan and statins (see Section 15.2.1-Table 1-17).

Secondary objective 3 – specific types of statins

Within the 727,355 patients at risk of hepatotoxicity in the study base, there were a total of 324,585 (45%) and 413,891 (57%) patients who had been treated with at least one prescription of atorvastatin and simvastatin in the pre-COVID period across all databases, respectively. Among patients using atorvastatin, there were a total of 142 to 149 cases of hepatotoxicity and 11,871 matched controls identified across all databases after applying the same exclusion criterion as employed for the primary and secondary objectives 1 and 2. The lowest number of cases and controls was observed in HSD and PHARMO without linked hospital data (zero cases) and the highest number in GePaRD (101 cases and 9,311 controls). Only in GePaRD, both subsets of SIDIAP, and CPRD with linked hospital data there were more than five cases for performing further analyses.

Among those treated with simvastatin, sufficient number of cases were only observed in Aarhus (8 cases and 425 controls), GePaRD (143 cases and 14,140 controls), and SIDIAP with linked hospital data (9 cases and 379 controls), respectively. A total of 160 cases of hepatotoxicity and 14,944 controls were identified in these three databases together after exclusions (see Table 10-2 and Section 15.2.1-Table 1-8 and Section 15.2.1-Table 1-9).

Secondary objective 4 – dose of statins

Among the 727,355 patients at risk of hepatotoxicity in the study base, 395,597 (54%) and 433,610 (60%) patients were treated with a high and low dose of statins, respectively, during the pre-COVID period. Among high dose statin users there were a total of 167 to 171 hepatotoxic events and 14,700 matched controls across all databases. Hepatotoxic events and matched controls ranged from 0 cases and controls in HSD and PHARMO without linked hospital data to 111 cases and 10,400 controls in GePaRD. Adequate numbers of cases for further analyses were noticed in Aarhus, GePaRD, both subsets of SIDIAP, PHARMO and

CPRD with linked hospital data. After all exclusions 8, 144, and 5 cases of hepatotoxicity and 440, 14,249, and 261 controls were identified among low dose statin users in Aarhus, GePaRD, and SIDIAP with linked hospital data, respectively. Further analyses were not conducted in all other databases as there were less than five cases of hepatotoxicity (see Table 10-2 and Section 15.2.1-Table 1-10 and Section 15.2.1-Table 1-11).

Table 10-2 Selection of matched nested case-control sets for hepatotoxicity in each database – primary and secondary analyses

Hepatotoxicity[§]	Aarhus (DK)	ARS (IT)	GePaRD (DE)	HSD (IT)	PHARMO (NL)		SIDIAP (ES)		CPRD (UK)	
					Without linked hospital data	With linked hospital data	Without linked hospital data	With linked hospital data	Without linked hospital data	With linked hospital data
Primary objective and Secondary objectives 1 and 2										
Matched cases, n	15	6	253	0	0	8	6	29	<5	12
Matched controls, n	1,157	538	25,179	0	0	705	414	1844	254	799
Secondary objective 3										
Atorvastatin										
Matched cases, n	#	3[≠]	101	0	0	4	5	17	<5	11
Matched controls, n	164	237	9,311	0	0	197	306	865	342	449
Simvastatin										
Matched cases, n	8	2	143	0	0	4	1	9	<5	<5
Matched controls, n	425	32	14,140	0	0	167	37	379	<5	<5
Secondary objective 4										
High dose of statins										
Matched cases, n	7	4	111	0	0	6	6	24	<5	9
Matched controls, n	535	354	10,400	0	0	462	413	1,712	324	500
Low dose of statins										
Matched cases, n	8	2	144	0	0	2	0	5	<5	<5
Matched controls, n	440	48	14,249	0	0	74	0	261	<5	138

[§]Statin exposure was based on single agents or fixed combination therapies of statins. Each prescription of statins was extended with a grace period, which was the maximum of either seven days or half the calculated duration of the prescription.

<5 less than five patients cannot be displayed due to specific database regulations.

[≠]No analyses were conducted when the number of cases was less than five.

#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.

10.1.3 Acute pancreatitis

Selection of matched nested case-control sets

Within the study base of 922,199 patients (irrespective of linked hospital data), a total of 875,518 patients were at risk of acute pancreatitis (full study period) (see Section 15.2.1-Table 1-12).

Primary objective and secondary objectives 1 – duration of use of sacubitril/valsartan, and 2 – recency of use of sacubitril/valsartan

A total of 1,404 to 1,407 cases of acute pancreatitis were identified in 875,518 patients at risk in the full study period. Almost all cases could be matched with controls. After excluding patients with alcohol-induced or biliary acute pancreatitis, other diseases of the pancreas, or pancreatic cancer at or within the seven days after the index date, 1,267 cases of acute pancreatitis and 115,163 matched controls in the pre-COVID period remained in the study, ranging from 2 cases and 121 controls in PHARMO without linked hospital data to 697 cases and 69,231 controls in GePaRD (see Table 10-3 and Section 15.2.1-Table 1-12). Hence, GePaRD contributed 55% of cases and 60% of the controls to the matched case-control sample of all databases in the pre-COVID. Of the acute pancreatitis cases, 79% (997 to 1,001 patients) identified from hospital data sources. In GePaRD all cases were identified from hospital data (n=697). Of cases identified in hospital, 10 to 18 cases were concomitantly exposed to sacubitril/valsartan and statins (see Section 15.2.1-Table 1-17). Because the number of cases of acute pancreatitis was below 5 in PHARMO without linked hospital data, further analyses were not performed in this subset of PHARMO.

Secondary objective 3 – specific types of statins

Within the 875,518 patients at risk of acute pancreatitis in the study base, 388,277 (44%) and 505,893 (58%) patients were treated with atorvastatin and simvastatin during the pre-COVID period, respectively. Among atorvastatin users, a total of 540 cases of acute pancreatitis and 43,037 controls were identified across all databases after applying the same exclusion criteria as described above (the primary and secondary objectives 1 and 2), ranging from 2 cases and 79 controls in PHARMO without linked hospital data to 231 cases and 22,380 controls in GePaRD. Among those treated with simvastatin, a total of 628 cases of acute pancreatitis and 53,516 controls were identified in all databases after exclusions, ranging from 0 cases and controls in PHARMO without linked hospital data to 431 cases and 42,518 controls in GePaRD (see Table 10-3 and Section 15.2.1-Table 1-13 and Section 15.2.1-Table 1-14). Because the number of cases of acute pancreatitis was below five among in PHARMO without linked hospital data, further analyses were not conducted in this subset of the database.

Secondary objective 4 – dose of statins

Of the 875,518 patients at risk of acute pancreatitis in the study base, 469,415 (54%) and 531,015 (61%) were treated with a high and low dose of statins during the pre-COVID period, respectively. Of high dose statin users, a total of 652 patients experienced an acute pancreatitis event and were matched to 54,076 controls across all databases after applying exclusions, ranging from 2 cases and 163 matched controls in PHARMO without linked hospital data to 258 cases and 25,160 matched controls in GePaRD. After exclusions, a total of 617 cases of acute pancreatitis and 53,024 controls were identified among low dose statin users in all databases, with a lowest number of 0 cases and controls in PHARMO without linked hospital

data and highest number of 440 cases and 43,483 controls in GePaRD (see Table 10-3 and Section 15.2.1-Table 1-15 and Section 15.2.1-Table 1-16). Because the number of cases of acute pancreatitis was below 5 in PHARMO without linked hospital data, further analyses were not conducted in this subset of the database.

Table 10-3 Selection of matched nested case-control sets for acute pancreatitis in each database – primary and secondary analyses

Acute pancreatitis[§]	Aarhus (DK)	ARS (IT)	GePaRD (DE)	HSD (IT)	PHARMO (NL)		SIDIAP (ES)		CPRD (UK)	
					Without linked hospital data	With linked hospital data	Without linked hospital data	With linked hospital data	Without linked hospital data	With linked hospital data
Primary objective and Secondary objectives 1 and 2										
Matched cases, n	42	270	697	15	2[≠]	31	75	56	49	30
Matched controls, n	3,398	22,987	69,231	717	121	2,791	6,316	4,145	3,464	1,993
Secondary objective 3										
Atorvastatin										
Matched cases, n	20	172	231	9	2	14	26	26	21	19
Matched controls, n	1,286	11,959	22,380	350	79	773	2,318	1,635	1,369	888
Simvastatin										
Matched cases, n	18	73	431	5	0	10	34	21	25	11
Matched controls, n	941	3,574	42,518	295	0	744	2,479	934	1,664	367
Secondary objective 4										
High dose of statins										
Matched cases, n	25	185	258	10	2	24	51	44	35	18
Matched controls, n	1,672	13,594	25,160	461	163	2,034	4,130	3,382	2,473	1,007
Low dose of statins										
Matched cases, n	17	86	440	5	0	7	24	12	14	12
Matched controls, n	894	4,341	43,483	267	0	362	2,009	667	628	373

[§]Statin exposure was based on single agents or fixed combination therapies of statins. Each prescription of statins was extended with a grace period, which was the maximum of either seven days or half the calculated duration of the prescription.

<5 less than five patients cannot be displayed due to specific database regulations.

[≠]No analyses were conducted when the number of cases was less than five.

#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.

10.2 Descriptive data

10.2.1 Myotoxicity

Primary objective and secondary objectives 1– duration of use of sacubitril/valsartan, and 2 – recency of use of sacubitril/valsartan

Median age of cases and controls with myotoxicity exposed to statins at index date was between 67 and 79 years across all databases in the pre-COVID period. Patients from Aarhus had the lowest median age (67 years for cases and controls). The highest median age was observed in the SIDIAP subset of the database without linked hospital data (79 years in cases and controls, respectively) and the ARS database (78 and 79 years in cases and controls, respectively). By design, the median age was similar for cases and matched controls. Of patients included, 48% to 68% were 75 years of age or older in all databases.

The proportion of women ranged from 38% to 51% across all databases, except in HSD where the proportion of women was 28%. Across all databases, the median duration of statin use at index date was over one year, apart from cases and controls in ARS, GePaRD, and SIDIAP without linked hospital data (median duration was 97 and 145 days in ARS, 317 and 326 days in GePaRD, and 117 and 230 days in SIDIAP without linked hospital data, respectively). By design, matching variables age, sex, duration of study use at index date were equally distributed among cases and controls. The most commonly used statin at index date across the different databases was atorvastatin, except in GePaRD and PHARMO, where the most common statin was simvastatin, and in SIDIAP without linked hospital data where atorvastatin and simvastatin were used equally often. Apart from GePaRD, cases and controls were more often treated with a high dose of statins at index date than low dose of statins.

Approximately 2% of cases (43 to 47 of 2,634 patients) and matched controls (3,035 to 3,038 of 200,556 patients) concomitantly used sacubitril/valsartan and statins at index date, of whom approximately 81% came from GePaRD and SIDIAP. In SIDIAP and CPRD without linked hospital data, 3% of cases were concomitantly using sacubitril/valsartan and statins whereas in all other databases it was about 1%. No concomitant use of sacubitril/valsartan and statins was observed among cases in Aarhus and HSD.

The most frequently recorded comorbidities across all databases, in both cases and controls, were hypertension, myocardial infarction, atrial fibrillation, angina pectoris, stroke or transient ischemic attack (TIA), and diabetes mellitus. No clear pattern in difference in these frequently recorded comorbidities were observed in cases and controls.

Co-medication use in the year prior to or at index date seemed to be high in cases and controls; the median number of different drugs was between 7 and 11 across all databases. Co-medication use was particularly high for beta blockers, diuretics, ACEIs, antiplatelets, and anticoagulants among cases and controls. In GePaRD, these frequently used co-medications were almost equally distributed between cases and controls.

Of the predefined risk factors for myotoxicity, chronic renal insufficiency any time prior to index date and infections in the 90 days prior to index date were often present among cases and controls.

The patient demographics and characteristics of cases and matched controls using all types of statins at index date in the pre-COVID period are presented in Section 15.2.1-Table 1-18 to Section 15.2.1-Table 1-27.

Primary objective – sensitivity analysis excluding myalgia
The patient demographics and characteristics of cases with a more specific definition of myotoxicity (i.e., excluded cases with only unspecific terms of myalgia) and matched controls were not markedly different when compared to cases and controls in the main analysis. Only in SIDIAP without linked hospital data, the median duration of statin use at index date decreased from 117 and 230 days to 30 and 19 days in cases and controls (primary objective [see Section 15.2.1-Table 1-18 to Section 15.2.1-1-27).

Secondary objective 3 – specific types of statins
Apart from HSD, in all databases another type of statin than atorvastatin was used in the seven days prior to (=grace period) index date by cases of myotoxicity and matched controls. This other type of statins included simvastatin (1 to 9 cases and 29 to 40 controls). Across all databases, above 79% of cases and matched controls had a high dose of statins at index date. Approximately, 2 % of cases (18 to 26 of 1,135 patients) and matched controls (1,641 of 75,532 patients) concomitantly used sacubitril/valsartan and atorvastatin at index date. In PHARMO without linked hospital data and SIDIAP with linked hospital data, 4% of cases were concomitantly using sacubitril/valsartan and atorvastatin at index date whereas in SIDIAP without linked hospital data it was 3% and in GePaRD 1%. No concomitant use of sacubitril/valsartan and atorvastatin in cases was observed in Aarhus, ARS, HSD, and PHARMO with linked hospital data, and potentially in CPRD. Patient demographics and characteristics of cases and matched controls using atorvastatin in the pre-COVID period are presented in Section 15.2.1-Table 1-28 to Section 15.2.1-1-37.

Of cases using simvastatin at index date, 4 to 12 cases and 54 to 62 matched controls used atorvastatin in the grace period around index date in GePaRD and PHARMO with linked data. Of cases and matched controls using simvastatin, the majority were considered as low dose of statins in ARS, GePaRD, and HSD.
In cases 1% to 2% (13 to 21 of 1,148 patients) and in matched controls 1% (787 of 77, 948 patients) were concomitantly using sacubitril/valsartan and simvastatin at index date, of whom 62% to 100% of cases and 87% of matched controls were present in GePaRD and SIDIAP. In both subsets of SIDIAP 2% of cases were concomitantly using sacubitril/valsartan and simvastatin whereas in GePaRD it was 1%. There was no concomitant use of sacubitril/valsartan and simvastatin at index date among cases observed in ARS, HSD, and PHARMO, and potentially in CPRD.
Patient demographics and characteristics of cases and matched controls using simvastatin in the pre-COVID period are presented in Section 15.2.1-Table 1-28 to Section 15.2.1-1-37.

Secondary objective 4 – dose of statins
Besides ARS, more than 50% of cases and matched controls used high dose of statins for more than 180 days prior to index date across all databases. Atorvastatin was the most frequently used statin at index date across all databases. In Aarhus, ARS, GePaRD, and HSD, around 80 % or higher were using atorvastatin among cases and matched controls using high dose of statins. There were 2% of cases (26 to 34 of 1,602 patients) and matched controls (2,348 of 114,227 patients) concomitantly using sacubitril/valsartan and high dose of statins at index date, of which approximately 50% to 65% were present in SIDIAP (with/without linked hospital data). In SIDIAP, 3% to 4% of cases were concomitantly using sacubitril/valsartan and high dose of statins in the subsets without and with linked hospital data, respectively, whereas in all other

databases it was 1% to 2%. There was no recorded concomitant use of sacubitril/valsartan and high dose of statins at index date in cases observed in Aarhus, HSD, and PHARMO with linked hospital data, and potentially in CPRD.
Patient demographics and characteristics of cases and matched controls using high dose of statins in the pre-COVID period are presented in Section 15.2.1-Table 1-38 to Section 15.2.1-1-47.
In PHARMO and SIDIAP without linked hospital data, and CPRD with linked hospital data, the proportion of women was higher in cases and matched controls using low dose statins, however, in HSD the proportion of women was lower than in cases and controls using high dose of statins. Simvastatin was the most frequently used statin at index date across all databases. In GePaRD, HSD, and both subsets of SIDIAP around 75% or higher were using simvastatin among cases and matched controls using low dose of statins.
Across all databases, except Aarhus, 1% to 2% of cases (12 to 20 of 1,037 patients) and matched controls (657 of 72,149 patients) were concomitantly using sacubitril/valsartan and statins at the index date. In SIDIAP without linked hospital data 2% of cases were concomitantly using sacubitril/valsartan and high dose of statins, whereas in all other databases it was 1%. No concomitant use of sacubitril/valsartan and low dose statins was observed among cases in ARS, HSD, and PHARMO without linked hospital data, and potentially in CPRD.
Patient demographics and characteristics of cases and matched controls using low dose of statins in the pre-COVID period are presented in Section 15.2.1-Table 1-38 to Section 15.2.1-1-47.

10.2.2 Hepatotoxicity

Primary objective and secondary objectives 1 – duration of use of sacubitril/valsartan, and 2 – recency of use of sacubitril/valsartan
Cases of hepatotoxicity and controls using statins at index date had a similar median age, ranging from 68 to 84 years of age across all databases in the pre-COVID period. The proportion of women ranged from 21% to 50% across all databases. By design, matching variables age, sex, duration of statin use at index date were equally distributed among cases and controls. The proportion of cases and controls using statins for more than 180 days at index date ranged from 33% and 40 % in ARS to 75% and 96% in PHARMO with linked hospital data, respectively. In all other databases than GePaRD, the proportion of controls exposed to statins for more than 180 days was higher than cases. Apart from GePaRD, cases and controls were more often treated with a high dose of statins at index date than a low dose of statins.
There were approximately 2% cases (6 to 10 of 329 cases) and 1% matched controls (402 to 406 of 30,636 controls) concomitantly using sacubitril/valsartan and statins at index date in GePaRD and SIDIAP with linked hospital data, whereas in all other databases no case or an unknown number of cases (due to redaction of data) used sacubitril/valsartan at index date. In SIDIAP with linked hospital data 7% of cases were concomitantly using sacubitril/valsartan and statins whereas in GePaRD it was about 2%.
The most frequently recorded comorbidities differed between databases but was often based on a small number of cases. In GePaRD the distribution of comorbidities was almost balanced between cases and controls and hypertension and diabetes mellitus were most frequent. Co-medication use in the year prior to or at index date was high; the median number of different

drugs was between 8 and 12. Co-medication use was particularly high for beta blockers, diuretics, ACEIs, antiplatelets, anticoagulants and antidiabetics.
Of the predefined risk factors for hepatotoxicity, drugs potentially causing acute hepatocellular or cholestatic hepatotoxicity were often recorded in both cases and controls.
The patient demographics and characteristics of cases and matched controls using statins at index date in the pre-COVID period are presented in Section 15.2.1-Table 1-48 to Section 15.2.1-1-57.

Secondary objective 3 – specific types of statins
In GePaRD and SIDIAP with linked hospital data, there was about 1 to 2% of cases of hepatotoxicity (2 to 6 of 134 patients) and matched controls (203 to 207 of 10,931 patients) in which sacubitril/valsartan was concomitantly used with atorvastatin, whereas in SIDIAP without linked hospital data and CPRD with linked hospital data potentially had no case using sacubitril/valsartan.
Patient demographics and characteristics of cases and matched controls using atorvastatin in the pre-COVID period are presented in Section 15.2.1-Table 1-58 to Section 15.2.1-1-67.

In cases and matched controls using simvastatin, myocardial infarction, and angina pectoris were generally less often recorded than in patients using any statin irrespective of the type. Four of 160 cases of hepatotoxicity (3% [in GePaRD and SIDIAP with linked hospital data]) and 159 to 162 of 14,944 (1%) matched controls were concomitantly using sacubitril/valsartan and simvastatin at index date, whereas in Aarhus, no case was concomitantly using sacubitril/valsartan and simvastatin at index date.
Patient demographics and characteristics of cases and matched controls using simvastatin in the pre-COVID period are presented in Section 15.2.1-Table 1-58 to Section 15.2.1-1-67.

Secondary objective 4 – dose of statins
Atorvastatin was the most frequently used statin at index date among cases and matched controls using high dose of statins in Aarhus, GePaRD, both subsets of SIDIAP, and CPRD with linked hospital data. In PHARMO with linked hospital data atorvastatin was only the most frequently used statin in cases.
Across all these databases, 3 to 7 hepatotoxicity cases among 163 patients, and 262 to 266 among 14,022 matched controls concomitantly exposed to sacubitril/valsartan and high dose of statins at index date were identified. In the other three datasets (potentially) no case concomitantly used sacubitril/valsartan with high dose of statins. Patient demographics and characteristics of cases and matched controls using high dose of statins in the pre-COVID period are presented in Section 15.2.1-Table 1-68 to Section 15.2.1-Table 1-77.

Compared to cases and matched controls who were using statins irrespective of dose, the median duration of statin use tended to be shorter in cases and matched controls using low dose of statins in GePaRD and SIDIAP with linked hospital data. Simvastatin was the most frequently used statin (above 80%) at index date in both datasets.
There were 3 of 157 cases of hepatotoxicity (2%) and 145 to 148 of 14,950 matched controls (1%) using sacubitril/valsartan together with low dose of statins at index date in all databases with sufficient number of cases. No case concomitantly used sacubitril/valsartan and low dose of statins was observed in Aarhus and SIDIAP with linked hospital data.

Patient demographics and characteristics of cases and matched controls using high dose of statins in the pre-COVID period are presented in Section 15.2.1-Table 1-68 to Section 15.2.1-Table 1-77.

10.2.3 Acute pancreatitis

Primary objective and secondary objectives 1 – duration of use of sacubitril/valsartan and 2 – recency of use of sacubitril/valsartan

Median age of cases of acute pancreatitis and controls at index date ranged between 71 and 82 years of age across all databases in the pre-COVID period. Patients from Aarhus had the lowest median age (71 years for cases and 72 years for controls). The highest median age was observed in SIDIAP, without linked hospital data (82 years for cases and 81 years for controls). Of patients included, more than 50% were 75 years of age or older in all databases, with exception of Aarhus where only 41% of patients were 75 years of age or older.

The proportion of women was above 30% in all databases, except for HSD, and PHARMO and CPRD with linked data where the proportion of women was 20% to 27%.

Across all databases, approximately 60% of cases and controls used statins for more than 90 days at index date, ranging from 55% in SIDIAP without linked hospital data to 87% and 93% in PHARMO with linked hospital data, respectively. By design, matching variables age, sex, duration of statin use were equally distributed among cases and matched controls. The most commonly used statin at index date across all databases was atorvastatin, except for GePaRD, PHARMO (with linked hospital data), both subsets of SIDIAP, and CPRD without linked hospital data, in which the most common statin was simvastatin or there was no clear pattern regarding the type of statin. Except for GePaRD, cases and controls were more often treated with a high dose of statins at index date.

Approximately 1% to 2% of cases (13 to 21 of 1,265 patients) and 1% of matched controls (1,495 of 115,042 patients) concomitantly used sacubitril/valsartan and statins at index date, of which more than 60% were present in GePaRD, considering that no case was exposed to sacubitril/valsartan in CPRD. In PHARMO and SIDIAP with linked hospital data, 2% to 3% of cases were concomitantly exposed to sacubitril/valsartan and statins whereas in all other databases it was about 1%. No case was concomitantly using sacubitril/valsartan and statins in Aarhus, HSD, and potentially CPRD.

The most frequently recorded comorbidities were hypertension, myocardial infarction, and atrial fibrillation across all databases. No clear pattern was observed from the recorded comorbidities for both cases and controls.

Co-medication use in the year prior to or at index date was high in cases and controls; the median number of different drugs was between 8 and 11 across all databases. Co-medication use was particularly high for beta blockers, diuretics, ACEIs, antiplatelets, and anticoagulants among cases and controls.

Of the predefined risk factors for acute pancreatitis, the use of drugs associated with acute pancreatitis including ACEIs was reported in approximately 90% in both cases and controls, due to the design of the study.

The patient demographics and characteristics of cases and matched controls using statins at index date in the pre-COVID period are presented in Section 15.2.1-Table 1-78 to Section 15.2.1-Table 1-87.

Secondary objective 3 – specific types of statins

Among atorvastatin users in the matched case control set, more than 80% were users of high dose of statins in all databases.
Across all databases and subsets including HSD, there were 7 to 15 of 538 cases of acute pancreatitis (1% to 3%) and 691 to 694 of 42,958 matched controls (2%) in which sacubitril/valsartan was concomitantly used with atorvastatin. In PHARMO with linked hospital data and both subsets of SIDIAP, 4% to 7% of cases were concomitantly using sacubitril/valsartan and atorvastatin at index date, respectively, whereas in all other databases it was 1%. No concomitant use of sacubitril/valsartan and atorvastatin in cases was observed in Aarhus and HSD, and in CPRD (numbers less than five). Patient demographics and characteristics of cases and matched controls using atorvastatin in the pre-COVID period are presented in Section 15.2.1-Table 1-88 to Section 15.2.1-Table 1-97.

In cases and matched controls using simvastatin, the proportion of women was higher compared to cases and matched controls using atorvastatin, apart from GePaRD. In cases and matched controls using simvastatin, myocardial infarction was generally less often recorded when compared with cases and matched controls using atorvastatin. Of cases and matched controls using simvastatin, the majority were considered as low dose of statins in Aarhus, ARS, GePaRD, and HSD. For acute pancreatitis, 5 to 13 of 628 cases (1% to 2% [all in GePaRD]) and 500 to 507 of 53,516 matched controls (1%) were concomitantly using sacubitril/valsartan and simvastatin at index date. In all other databases and potentially in CPRD, no concomitant use of sacubitril/valsartan and simvastatin was observed. Patient demographics and characteristics of cases and matched controls using simvastatin in the pre-COVID period are presented in Section 15.2.1-Table 1-88 to Section 15.2.1-Table 1-97.

Secondary objective 4 – dose of statins
In GePaRD, the proportion of women was higher in cases of acute pancreatitis and matched controls exposed to high dose of statins compared to cases and matched controls using any type of statins. In Aarhus, ARS, GePaRD, and HSD atorvastatin was more frequently used among cases and controls using high dose of statins, whereas it was less pronounced in all other databases.
Approximately 1% to 3% of acute pancreatitis cases (9 to 17 of 650 patients) and 2% of matched controls (851 to 854 of 53,913 patients concomitantly using sacubitril/valsartan and high dose of statins at index date, of which most were present in GePaRD (4 cases and 468 controls). In PHARMO with linked hospital data, 4% of cases were concomitantly using sacubitril/valsartan and atorvastatin at index date, respectively, whereas in both subsets of SIDIAP and GePaRD it was 2% and in ARS 1%. There was no case concomitantly using sacubitril/valsartan and high dose of statins at index data in Aarhus and HSD, and potentially none in CPRD (less than five). Patient demographics and characteristics of cases and matched controls using high dose of statins in the pre-COVID period are presented in Section 15.2.1-Table 1-98 to Section 15.2.1-Table 1-107.

History of myocardial infarction was less frequently recorded among cases and matched controls using low dose of statins than cases and controls using high dose of statins, except the cases in CPRD without linked hospital data. Across all databases simvastatin was the most frequently used statin at index date, but this was less pronounced in PHARMO and CPRD.
There were 4 to 12 of 617 acute pancreatitis cases (1% to 2% [potentially all in GePaRD]) and 516 to 520 of 53,024 matched controls (1% [88 to 89%(from GePaRD]) concomitantly using

sacubitril/valsartan and statins at index date in low dose of statin users. No concomitant use of sacubitril/valsartan and statins was observed among cases in all other databases, including potentially in CPRD.
Patient demographics and characteristics of cases and matched controls using low dose of statins in the pre-COVID period are presented in Section 15.2.1-Table 1-98 to Section 15.2.1-Table 1-107.

10.3 Outcome data

Outcome data during the pre-COVID period are included in Section 15.2.1-Section 1.4 to (Section 15.2.1-Section 1.12).

10.4 Main results

Important considerations for results

Due to privacy regulations regarding data sharing, Aarhus and CPRD are not permitted to show any number less than five and these data are redacted as # or <5, In Aarhus, zero-counts can be presented, while this cannot be shown in CPRD. Therefore, the ORs and 95% CIs are presented for the lowest and highest exposed scenarios in the fixed-effects model for the meta-analysis. For the lowest and highest exposed scenarios, a range of possible values is presented, ranging from zero (only when database- or subset-specific ORs were <0.01) otherwise one to four for CPRD and from one to four for Aarhus. This was not needed for the random-effects model as the used weight in the analysis was based on SEs and not on the number of patients.

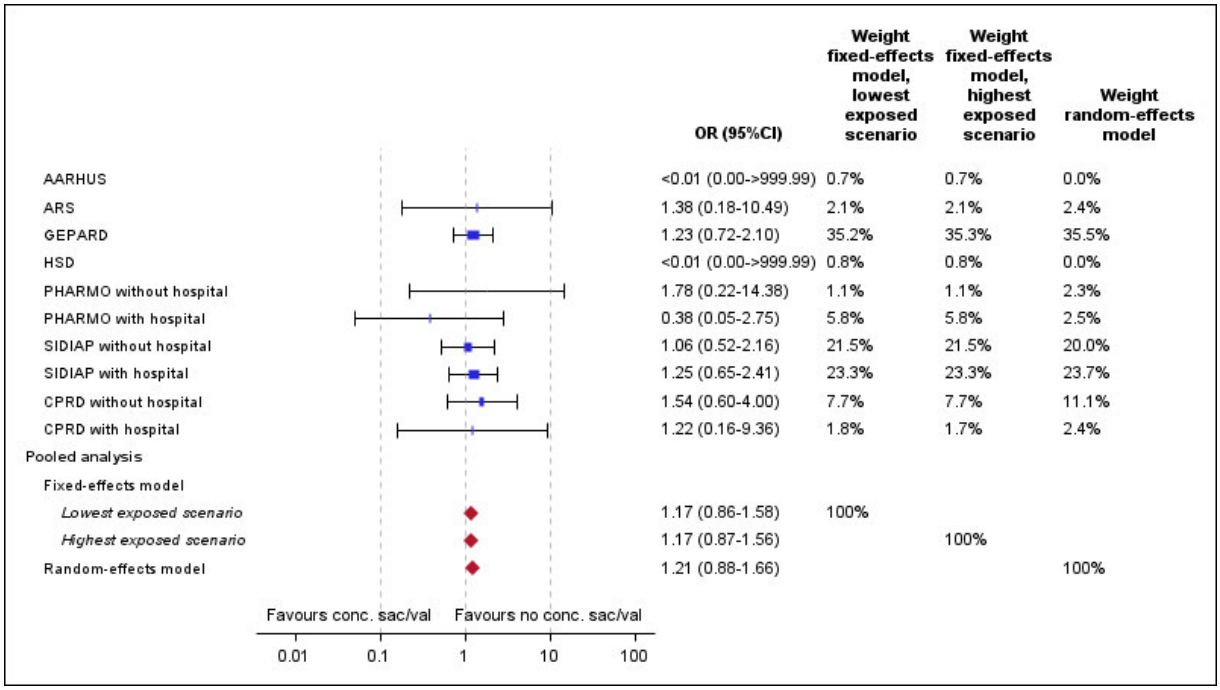
Note: ORs estimated across each database and pooled databases for the outcome event of interests in the full study period are presented in Section 10.5 'Other analyses'.

10.4.1 Myotoxicity

Primary objective
The covariates of interest for the primary analysis of statins and the risk of myotoxicity were specified in the LCZ696B2015 study protocol v02 – amendment 2 (see Section 15.1.1). If the number of cases hindered the inclusion of all covariates of interest in the primary analysis model, the priority of inclusion was determined by the estimated $|log\ (Bias)|$ for each covariate. All modeling steps for the inclusion of covariates are described in Section 15.2.1-Table 1-108 to Section 15.2.1-Table 1-117. Based on the modeling steps the number of covariates that were included in each model for adjustment differed across databases, ranging from 7 covariates in ARS and PHARMO without linked hospital data to 33 in SIDIAP without linked hospital data (see Section 15.2.1-Table 1-118 to Section 15.2.1-Table 1-127).
Database- or subset-specific adjusted ORs comparing concomitant use of sacubitril/valsartan and statins at index date with statin use alone ranged from <0.01 (Aarhus and HSD) to 1.78 (PHARMO without linked hospital data). The CIs were wide and covered the null effect indicating no association (Figure 10-1 and Section 15.2.1-Table 1-128 and Section 15.2.1-Figure 1-1.
The crude, unadjusted ORs are presented for each database or subset in Section 15.2.1-Table 1-128.
The meta-analysis with the fixed-effects model showed an adjusted ORs of 1.17 (95% CI 0.86-1.58) for the lowest exposed scenario and 1.17 (95% CI 0.87-1.56) for the highest exposed

scenario. The adjusted OR for the random-effects model was 1.21 (95% CI 0.88-1.66) based on eight databases or subsets (Aarhus and HSD were not included due to cases who were zero exposed to sacubitril/valsartan). Results for the analysis of association between concomitant sacubitril/valsartan and statin use and myotoxicity are shown in Figure 10-1 and Section 15.2.1-Table 1-128 and(Section 15.2.1-Figure 1-1.

Figure 10-1 Forest plot of myotoxicity primary objective – Adjusted Odds ratios for concomitant sacubitril/valsartan and statin use versus statin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-1.

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).

The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant users of sacubitril/valsartan and statins among cases and controls was redacted in Aarhus and CPRD with linked hospital data due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of CPRD, and based on need for masking, the lowest exposed scenario assumes one case with concomitant use of sacubitril/valsartan and statins and the highest exposed scenario assumes four cases with concomitant use of sacubitril/valsartan and statins; due to the traceability as part of the small-cell-count policy, the number of controls with concomitant use of sacubitril/valsartan and statins was the same for low and high exposed scenario in Aarhus.

For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

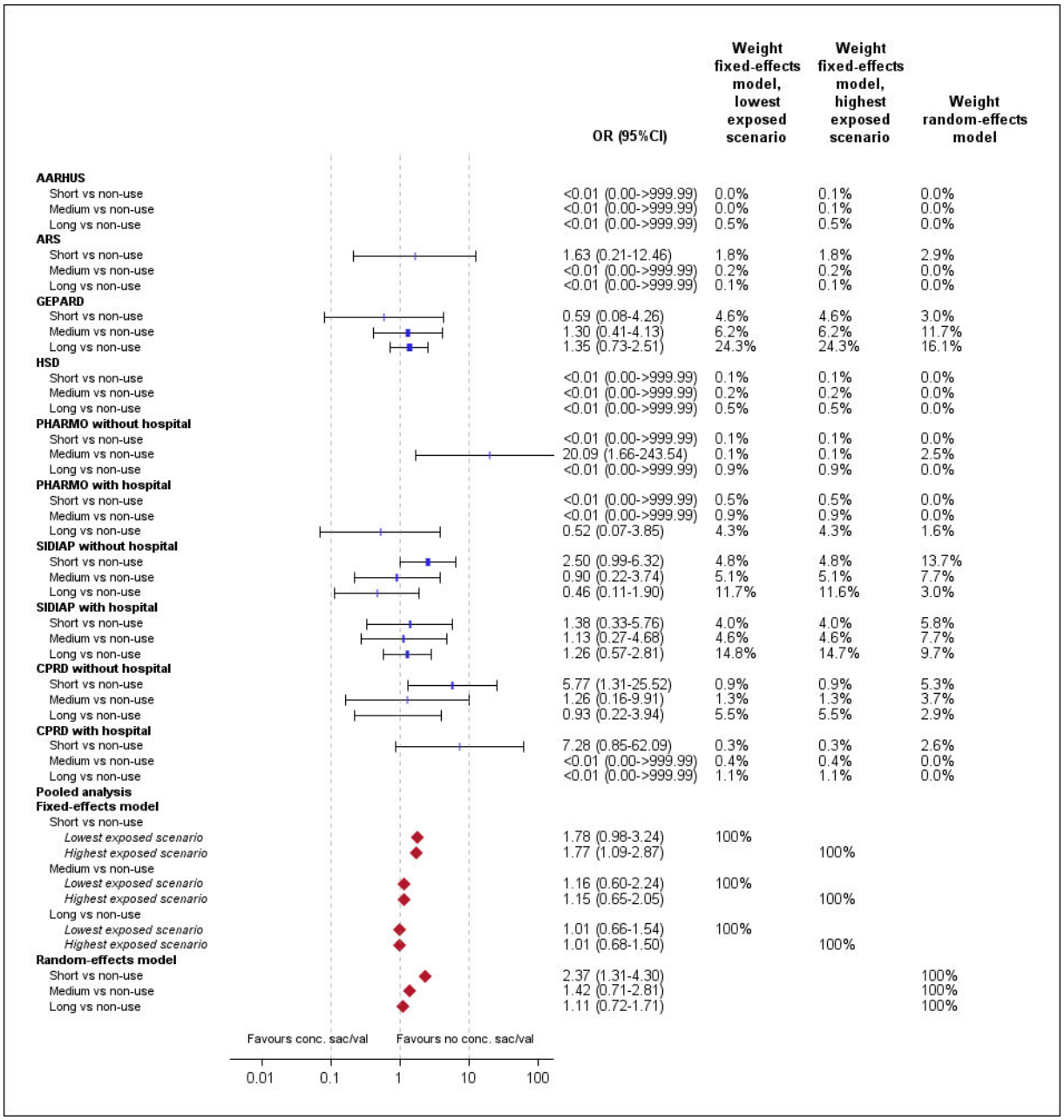
Secondary objective 1 – duration of use of sacubitril/valsartan

Four of ten databases or subsets had sufficient numbers of cases and controls concomitantly using sacubitril/valsartan and statins in all categories of the duration of use (short, medium, or long) to perform an analysis by duration of use: GePaRD, SIDIAP with and without linked hospital data, and CPRD without linked hospital data. In CPRD without linked hospital data, an association was observed between short duration of concomitant use of sacubitril/valsartan

and statins (start of episode maximally 30 days prior to index date) and myotoxicity ($OR_{adjusted}$ 5.77, 95% CI 1.31-25.52). The $OR_{adjusted}$ for myotoxicity and short duration of concomitant use of sacubitril/valsartan and statins was below one in Aarhus, HSD, both subsets of PHARMO (all three databases had an adjusted OR of <0.01), and GePaRD ($OR_{adjusted}$ 0.59 (95% CI 0.08-4.26), however, in ARS, both subsets of SIDIAP, and CPRD with linked hospital data, the $OR_{adjusted}$ was above one, ranging from 1.38 (SIDIAP with linked hospital data) to 7.28 (CPRD with linked hospital data). For all other databases than CPRD without linked hospital data, the CIs were wide and covered the null effect indicating no association. In PHARMO without linked hospital data, an association was observed between myotoxicity and medium duration of concomitant use of sacubitril/valsartan and statins (31 to 90 days; $OR_{adjusted}$ 20.09, 95% CI 1.66-243.54). Database-or subset-specific adjusted ORs comparing medium and long duration of concomitant sacubitril/valsartan and statins at index date versus non-use of sacubitril/valsartan ranged from <0.01 (Aarhus, ARS, HSD, both subsets of PHARMO, and CPRD with linked hospital data) to 1.30 and 1.35 (GePaRD), respectively. Except for PHARMO without linked hospital data, the CIs were large and included the null effect for medium and long duration of concomitant sacubitril/valsartan and statin use, indicating no association. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-153, and only adjusted ORs in Figure 10-2 and Section 15.2.1-Figure 1-6.

In the meta-analysis, using a fixed-effects model, the adjusted ORs for short, medium, and long duration of concomitant sacubitril/valsartan and statin use were 1.78 (95% CI 0.98-3.24), 1.16 (95% CI 0.60-2.24), and 1.01 (95% CI 0.66-1.54) for the lowest exposure scenario and 1.77 (95% CI 1.09-2.87), 1.15 (95% CI 0.65-2.05), and 1.01 (95% CI 0.68-1.50) for the highest exposure scenario, respectively. Adjusted ORs from the random-effect model for short, medium, and long duration of concomitant sacubitril/valsartan and statin use were 2.37 (95% CI 1.31-4.30), 1.42 (95% CI 0.71-2.81), and 1.11 (95% CI 0.72-1.71), respectively. The analysis for short duration of concomitant sacubitril/valsartan and statin use was based on six databases or subsets, whereas for medium and long duration of concomitant use it was five. Databases that were not included in the analysis had zero sacubitril/valsartan exposed cases. Results for the analysis of association between duration of concomitant sacubitril/valsartan and statin use and myotoxicity are shown in Figure 10-2 and Section 15.2.1-Table 1-153 and Section 15.2.1-Figure 1-6.

Figure 10-2 Forest plot of myotoxicity secondary objective – Adjusted Odds ratios for the duration of concomitant sacubitril/valsartan and statin use versus statin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-6

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).
Short duration was that the episode of concomitant sacubitril/valsartan use started maximally 30 days prior to index date.
Medium duration was that the episode of concomitant sacubitril/valsartan use started within 31-90 days prior to index date.
Long duration was that the episode of concomitant sacubitril/valsartan use started more than 90 days prior to index date.

The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of short, medium, and long duration concomitant users of sacubitril/valsartan and statins among cases and controls was redacted in Aarhus and both subsets of CPRD due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of Aarhus (i.e., database- or subset-specific ORs were <0.01) and CPRD, the lowest exposed scenario assumes one case or control with short (Aarhus and both subsets of CPRD), medium (Aarhus and CPRD without linked hospital data), or long (CPRD without linked hospital data) duration of concomitant use of sacubitril/valsartan and the highest exposed scenario assumes four cases or controls with short, medium, or long duration of concomitant use of sacubitril/valsartan. Cases were zero exposed to sacubitril/valsartan in medium and long duration categories (i.e., database- or subset-specific ORs were <0.01) in CPRD with linked hospital data.

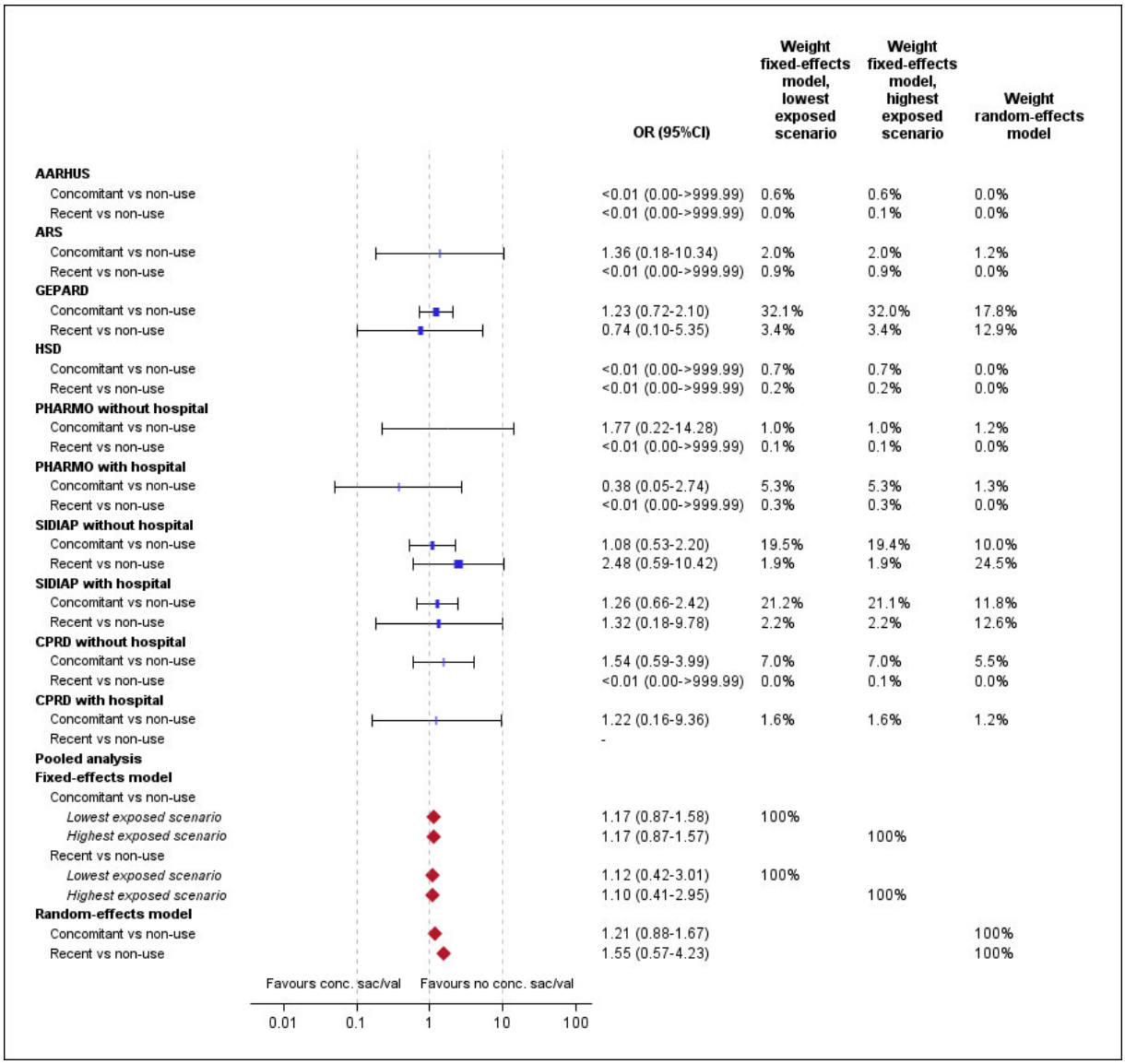
For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

Secondary objective 2 – recency of use of sacubitril/valsartan

The analysis by recency of sacubitril/valsartan use included four cases with recent use (i.e., treatment episode ending between eight and 90 days before the index date) from GePaRD and both subsets of SIDIAP. In all other databases, none of the cases was recently exposed to sacubitril/valsartan. The range of adjusted ORs of myotoxicity for recent use was <0.01 (in Aarhus, ARS, HSD, both subsets of PHARMO, and CPRD without linked hospital data) to 2.48 in SIDIAP without linked hospital data. The CIs were wide and covered the null effect indicating no association. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-154, and only adjusted ORs in Figure 10-3 and Section 15.2.1-Figure 1-7.

The meta-analysis based on the fixed-effects model resulted in an $OR_{adjusted}$ of 1.12 (95% CI 0.42-3.01) for the lowest exposed scenario and an $OR_{adjusted}$ of 1.10 (95% CI 0.41-2.95) for the highest exposed scenario. The random-effects model showed an adjusted OR of 1.55 (95% CI 0.57-4.23), which was based on three databases or subsets with at least one case of recent exposure (n=4). Neither cases nor controls with recent use of sacubitril/valsartan were identified in CPRD with linked hospital data (double zero-counts in the meta-analysis), and this database subset was not included in the fixed- and random-effects models. Results for the analysis of associations between the recency of concomitant sacubitril/valsartan and statin use and myotoxicity are shown in Figure 10-3 and Section 15.2.1-Table 1-154 and Section 15.2.1-Figure 1-7.

Figure 10-3 Forest plot of myotoxicity secondary objective – Adjusted Odds ratios for the recency of concomitant sacubitril/valsartan and statin use versus statin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-7

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).

Recent sacubitril/valsartan use was the episode of sacubitril/valsartan use that ends between eight and 90 days before the index date.

The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant and recent users of sacubitril/valsartan and statins among cases and controls was redacted in Aarhus and both subsets of CPRD due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of Aarhus and CPRD (database- or subset-specific OR for recent use of sacubitril/valsartan was <0.01 and no database- or subset-specific OR for recent use of sacubitril/valsartan was presented [double zero exposed]), the lowest and highest exposed scenario assumes zero cases and/or controls with recent use of sacubitril/valsartan and statins in both subsets of CPRD,

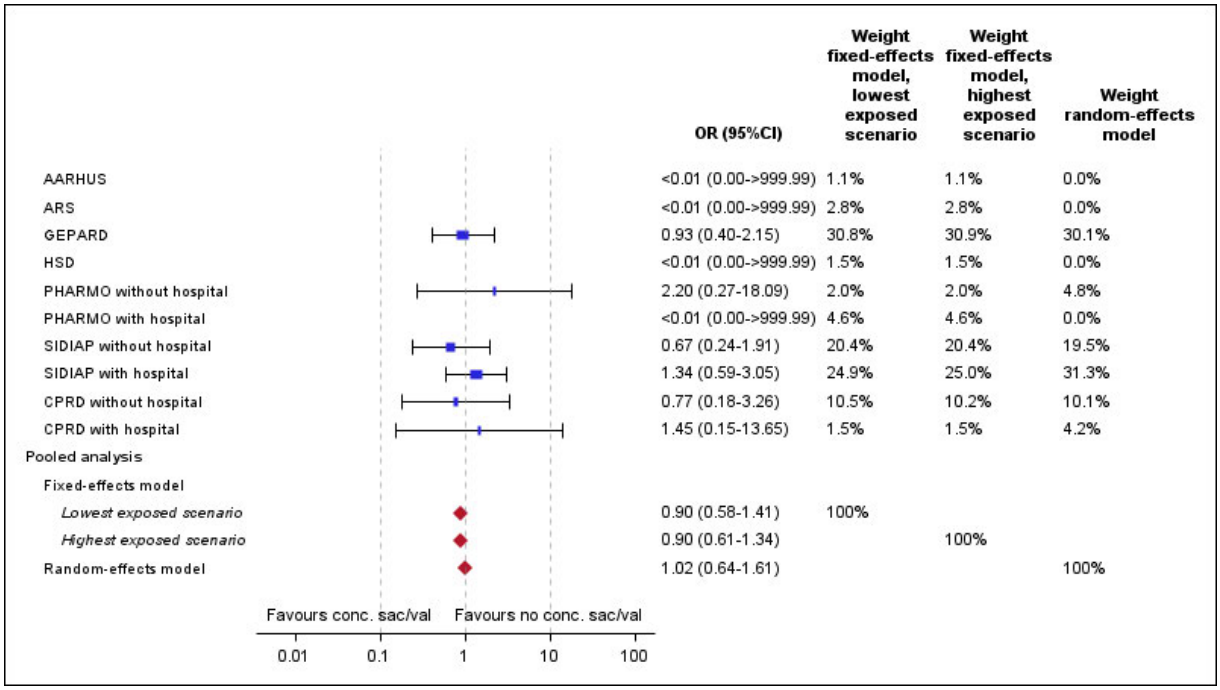
and the lowest exposed scenario assumes one control with recent use of sacubitril/valsartan and statins and the highest exposed scenario assumes four controls with recent use of sacubitril/valsartan and statins in Aarhus and CPRD without linked hospital data. For concomitant use of sacubitril/valsartan and statins (i.e., cases were zero [Aarhus] or were exposed [CPRD with linked hospital data] to sacubitril/valsartan), the lowest exposed scenario assumes one case (CPRD with linked hospital data) or control (Aarhus) with concomitant use of sacubitril/valsartan and statins and the highest exposed scenario assumes four cases or controls with concomitant use of sacubitril/valsartan and statins.
For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

Secondary objective 3 – specific types of statins

Aarhus, ARS, HSD, and PHARMO with linked hospital data had no case of myotoxicity in patients who were concomitantly using atorvastatin and sacubitril/valsartan at index date. Thus, database- or subset-specific adjusted ORs comparing concomitant use of sacubitril/valsartan and statins at index date with atorvastatin use alone ranged from <0.01 (Aarhus, ARS, HSD, PHARMO with linked hospital data) to 2.20 (PHARMO without linked hospital data). The CIs were large and included the null effect, indicating no association. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-155, and only adjusted ORs in Figure 10-4 and Section 15.2.1-Figure 1-8.

The meta-analysis showed, when using the fixed-effects model, an adjusted OR of 0.90 (95% CI 0.58-1.41) for the lowest exposed scenario and 0.90 (95% CI 0.61-1.34) for the highest exposed scenario, respectively. The random-effects model resulted in OR of 1.02 (95% CI 0.64-1.61) based on six databases or subsets. Results for the analysis of associations between the concomitant sacubitril/valsartan and atorvastatin use and myotoxicity are shown in Figure 10-4 and Section 15.2.1-Table 1-155 and Section 15.2.1-Figure 1-8.

Figure 10-4 Forest plot of myotoxicity secondary objective – Adjusted Odds ratios for concomitant sacubitril/valsartan and atorvastatin use versus atorvastatin use alone based on all cases in the pre-COVID period



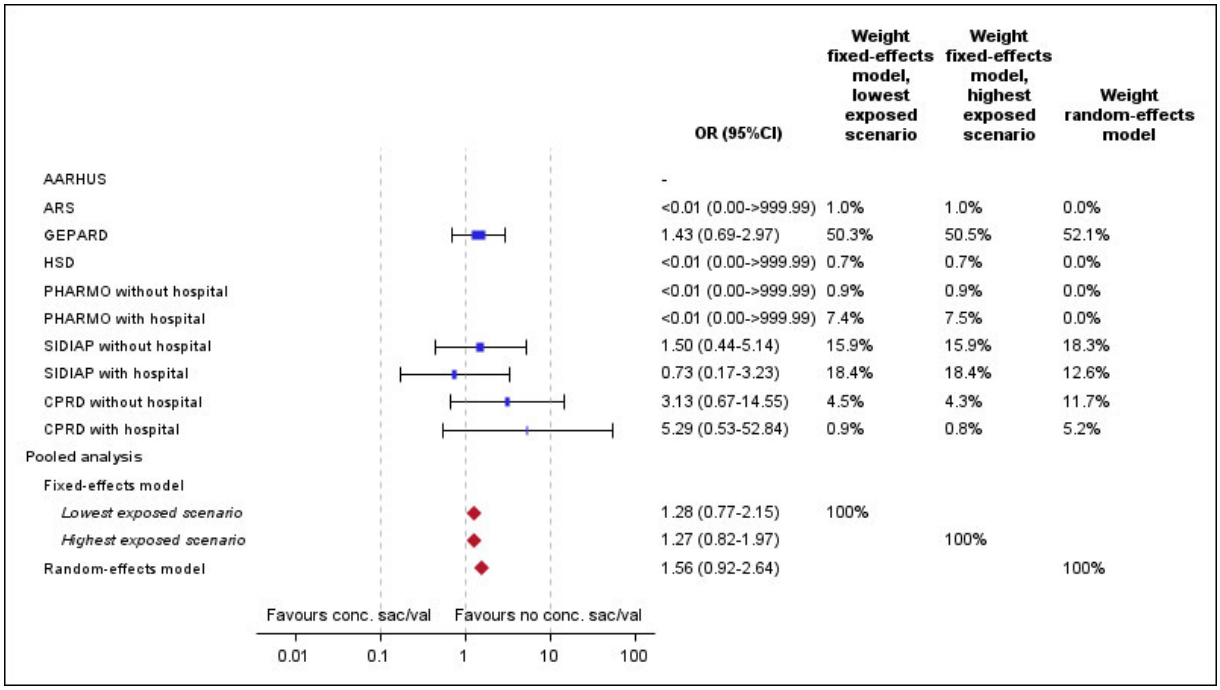
Source: Section 15.2.1-Figure 1-8

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).
The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant users of sacubitril/valsartan and atorvastatin among cases was redacted in both subsets of CPRD due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of Aarhus and CPRD, the lowest exposed scenario assumes one case with concomitant use of sacubitril/valsartan and atorvastatin and the highest exposed scenario assumes four cases with concomitant use of sacubitril/valsartan and atorvastatin.
For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

No analysis between concomitant use of sacubitril/valsartan and simvastatin and the risk of myotoxicity was conducted in Aarhus as there were less than five cases identified. In ARS, HSD, and both subsets of PHARMO none of the cases was concomitantly exposed to sacubitril/valsartan and simvastatin. The database- or subset-specific adjusted ORs ranged from <0.01 (ARS, HSD, and both subsets of PHARMO) to 5.29 (CPRD with linked hospital data). The CIs were large and included the null effect, indicating no association. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-156, and only adjusted ORs in Figure 10-5 and Section 15.2.1-Figure 1-9.

In the meta-analysis based on the fixed-effects model, the adjusted ORs were 1.28 (95% CI 0.77-2.15) for the lowest exposed scenario and 1.27 (95% CI 0.82-1.97) for the highest exposed scenario, respectively. Using the random-effects model showed an adjusted OR of 1.56 (95% CI 0.92-2.64) based on five databases or subsets. Results for the analysis of associations between concomitant sacubitril/valsartan and simvastatin use and myotoxicity can be found in Figure 10-5 and Section 15.2.1-Table 1-156 and Section 15.2.1-Figure 1-9.

Figure 10-5 Forest plot of myotoxicity secondary objective – Adjusted Odds ratios for concomitant sacubitril/valsartan and simvastatin use versus simvastatin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-9

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).

The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant users of sacubitril/valsartan and simvastatin among cases was redacted in both subsets of CPRD due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of CPRD, the lowest exposed scenario assumes one case with concomitant use of sacubitril/valsartan and simvastatin and the highest exposed scenario assumes four cases with concomitant use of sacubitril/valsartan and simvastatin.

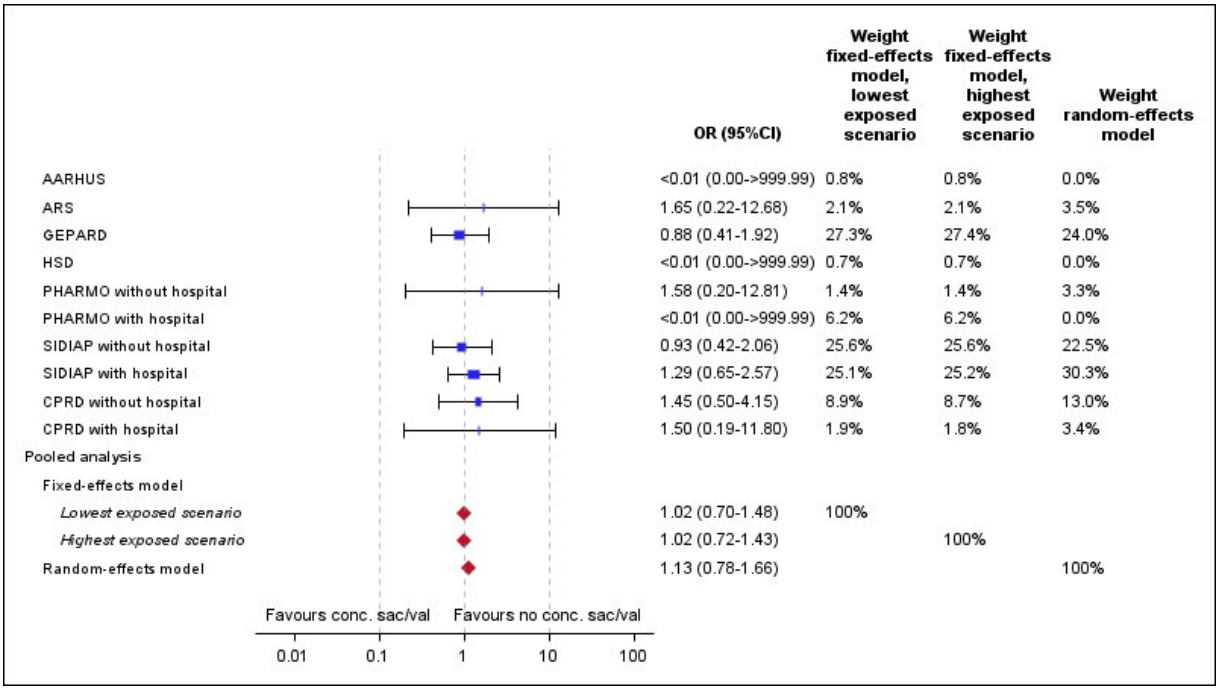
For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

Secondary objective 4 – dose of statins

For the database- or subset-specific ORs, the lowest adjusted OR was observed in Aarhus, HSD, and PHARMO with linked hospital data (OR: <0.01) and the highest in ARS (OR: 1.65). The CIs were wide and covered the null effect indicating no association. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-157, and only adjusted ORs in Figure 10-6 and Section 15.2.1-Figure 1-10.

For the meta-analysis based on the fixed-effects model, the adjusted ORs were 1.02 (95% CI 0.70-1.48) for the lowest exposed scenario and 1.02 (95% CI 0.72-1.43) for the highest exposed scenario, respectively. The adjusted OR from the random-effects model was 1.13 (95% CI 0.78-1.66) based on seven databases or subsets. Results for the analysis of associations between concomitant sacubitril/valsartan use and high dose of statins and myotoxicity are detailed in Figure 10-6 and Section 15.2.1-Table 1-157 and Section 15.2.1-Figure 1-10.

Figure 10-6 Forest plot of myotoxicity secondary objective – Adjusted Odds ratios for concomitant sacubitril/valsartan and high dose of statin use versus high dose of statin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-10

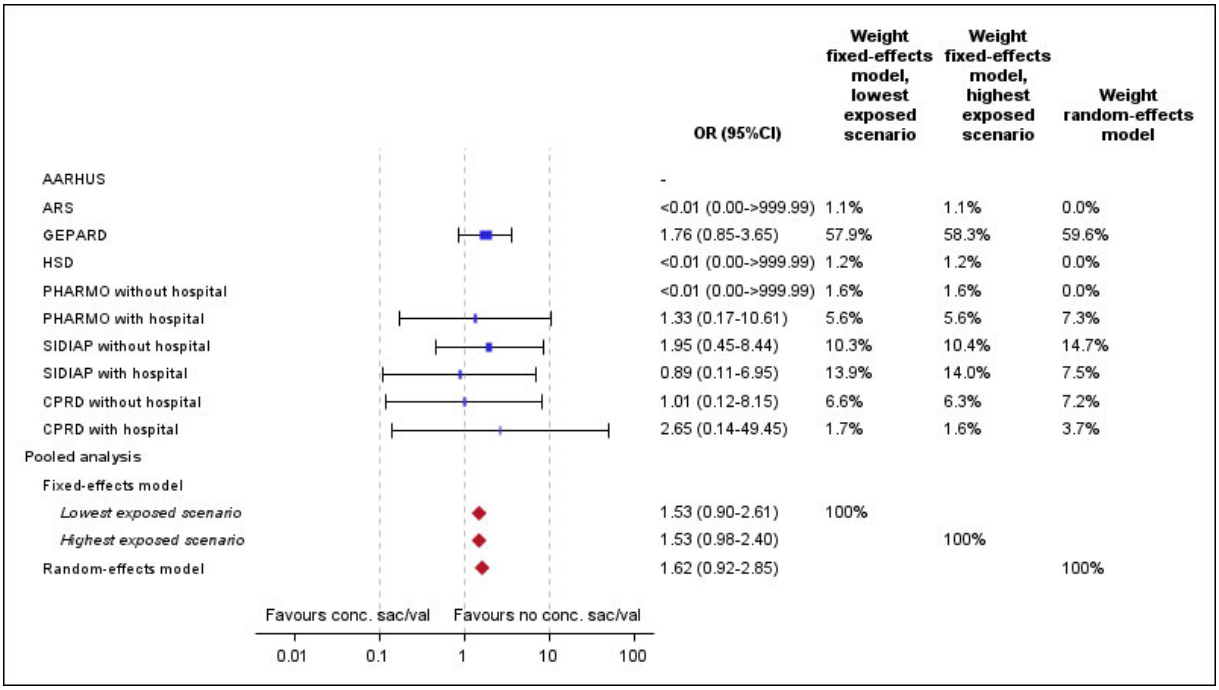
Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).

The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant users of sacubitril/valsartan and high dose of statins among cases was redacted in both subsets of CPRD due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of CPRD, the lowest exposed scenario assumes one case with concomitant use of sacubitril/valsartan and high dose of statins and the highest exposed scenario assumes four cases with concomitant use of sacubitril/valsartan and high dose of statins.

For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

No analysis between concomitant use of sacubitril/valsartan and low dose of statins and the risk of myotoxicity was conducted in Aarhus as there were less than five cases identified. The database- or subset-specific adjusted ORs ranged from <0.01 in ARS, HSD, and PHARMO without linked hospital data to 2.65 in CPRD with linked hospital data. The CIs were wide and covered the null effect indicating no association. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-158, and only adjusted ORs in Figure 10-7 and Section 15.2.1-Figure 1-11. The fixed-effects model of the meta-analysis gave adjusted ORs of 1.53 (95% CI 0.90-2.61) for the lowest exposed scenario and 1.53 (95% CI 0.98-2.40) for the highest exposed scenario, respectively. Using the random-effects model, the adjusted OR was 1.62 (95% CI 0.92-2.85) based on six databases or subsets. Results for the analysis of associations between the concomitant sacubitril/valsartan and low dose of statin use and myotoxicity are presented in Figure 10-7 and Section 15.2.1-Table 1-158 and Section 15.2.1-Figure 1-11.

Figure 10-7 Forest plot of myotoxicity secondary objective – Adjusted Odds ratios for concomitant sacubitril/valsartan and low dose of statin use versus low dose of statin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-11

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).

The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant users of sacubitril/valsartan and low dose of statins among cases was redacted in both subsets of CPRD due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of CPRD, the lowest exposed scenario assumes one case with concomitant use of sacubitril/valsartan and low dose of statins and the highest exposed scenario assumes four cases with concomitant use of sacubitril/valsartan and low dose of statins.

For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

10.4.2 Hepatotoxicity

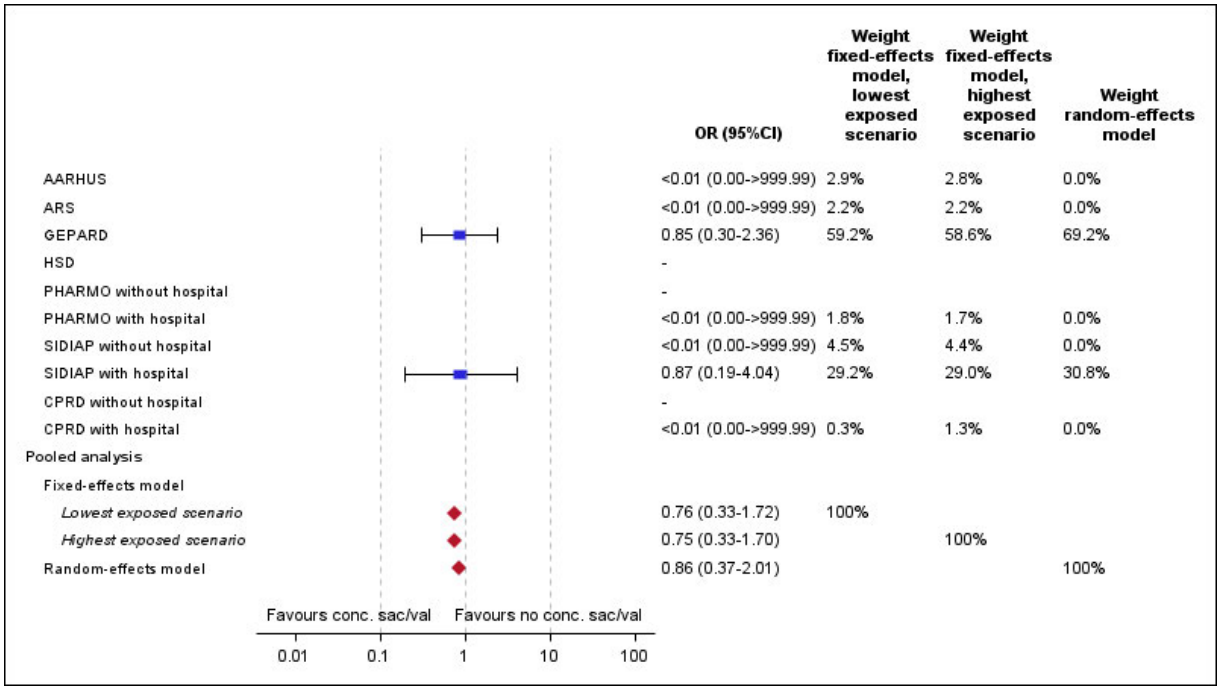
Primary objective

In the LCZ696B2015 study protocol v02 – amendment 2 (see Section 15.1.1) covariates of interest for the primary analysis of statins and the risk of hepatotoxicity were listed. If the number of cases were too low to allow inclusion of all covariates of interest in the primary analysis model, the priority of inclusion was determined by the estimated $|log\ (Bias)|$ for each covariate. All modeling steps for the inclusion of covariates are described in Section 15.2.1-Table 1-159 to Section 15.2.1-1-168. The number of covariates in the adjusted model was 24 in GePaRD, 1in SIDIAP with linked hospital data one covariate, whereas in all other databases no covariate was included in the model (see Section 15.2.1-Table 1-169 to Section 15.2.1-1-178). The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-179.

Of the seven databases or subsets included in this analysis, only GePaRD and SIDIAP with linked hospital data contributed to the six cases concomitantly exposed to sacubitril/valsartan and statins. The other five databases or subsets included no or less than five cases (CPRD) who were zero exposed to sacubitril/valsartan. The ORs for SIDIAP with linked hospital data and GePaRD were below one (SIDIAP: $OR_{adjusted}$ 0.87, 95% CI 0.19-4.04 and GePaRD: $OR_{adjusted}$ 0.85, 95% CI 0.30-2.36), and was based on two and four cases with concomitant sacubitril/valsartan and statin exposure out of 29 and 253 cases, respectively (Figure 10-8 and Section 15.2.1-Table 1-179 and Section 15.2.1-Figure 1-12).

The meta-analysis showed for the fixed-effects model, an adjusted OR of 0.76 (95% CI 0.33-1.72) for the lowest exposed scenario and 0.75 (95% CI 0.33-1.70) for the highest exposed scenario, respectively. The random-effects model resulted in an adjusted OR of 0.86 (95% CI 0.37-2.01) based on two databases or subsets excluding Aarhus, ARS, both PHARMO and CPRD with linked hospital data, and SIDIAP without linked hospital data due to cases who were zero exposed to sacubitril/valsartan. Results for the analysis of associations between concomitant sacubitril/valsartan and statin use and hepatotoxicity are shown in Figure 10-8 and Section 15.2.1-Table 1-179 and Section 15.2.1-Figure 1-12.

Figure 10-8 Forest plot of hepatotoxicity primary objective – Adjusted Odds ratios for concomitant sacubitril/valsartan and statin use versus statin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-12

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date). The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant users of sacubitril/valsartan and statins among cases and controls was redacted in CPRD with linked hospital data due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of CPRD (i.e., database- or subset-specific ORs were <0.01), the lowest exposed scenario assumes one control with concomitant use of sacubitril/valsartan and statins and the highest exposed scenario assumes four controls with

concomitant use of sacubitril/valsartan and statins. Cases were assumed to be zero exposed to sacubitril/valsartan (i.e., database- or subset-specific ORs were <0.01) in CPRD with linked hospital data.
For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

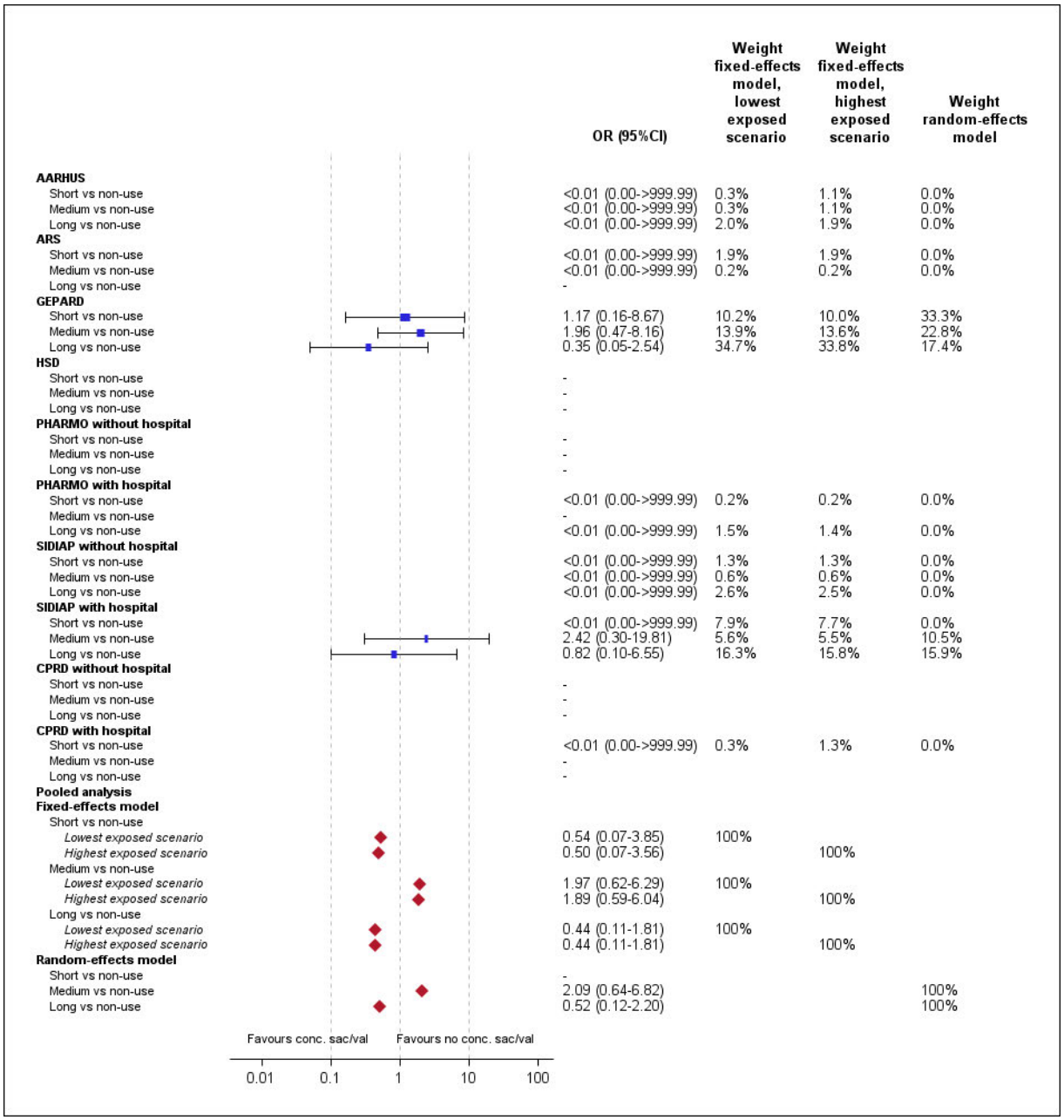
Secondary objective 1 – duration of use of sacubitril/valsartan

Only GePaRD had cases and controls concomitantly using sacubitril/valsartan and statins in each category of the duration of use (short, medium, or long). Adjusted ORs for low, medium, and long duration of concomitant sacubitril/valsartan and statin exposure in GePaRD were 1.17, 1.96, and 0.35, respectively. In SIDIAP with linked hospital data, the adjusted ORs for medium and long duration of concomitant use of sacubitril/valsartan and statins were 2.42 and 0.82, respectively. No other database contributed information on duration of use. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Tables 1-182, and only adjusted ORs in Figure 10-9 and Section 15.2.1-Figure 1-15.

In the meta-analysis, using the fixed-effects model, the adjusted ORs for the short, medium, and long duration of concomitant sacubitril/valsartan and statins use versus statins alone were 0.54 (95% CI 0.07-3.85), 1.97 (95% CI 0.62-6.29), and 0.44 (95% CI 0.11-1.81) for the lowest exposed scenario and 0.50 (95% CI 0.07-3.56), 1.89 (95% CI 0.59-6.04), and 0.44 (95% CI 0.11-1.81) for the highest exposed scenario, respectively. For the random-effects model, the adjusted ORs of the medium and long duration of concomitant sacubitril/valsartan and statin use versus statins alone were 2.09 (95% CI 0.64-6.82) and 0.52 (95% CI 0.12-2.20), respectively. For short duration of concomitant sacubitril/valsartan and statins, a meta-analysis of the random-effects model was not estimated, as only GePaRD contributed data for this analysis.

Moreover, data from cases and controls that were not exposed to sacubitril/valsartan in any of categories of sacubitril/valsartan duration (so called double zero exposed) were not included in the fixed- and random-effects model of the meta-analysis. Double zero exposed appeared for short duration of concomitant use of sacubitril/valsartan and statins in CPRD with linked hospital data, for medium duration in PHARMO with linked hospital data, and for long duration in ARS. Results for the analysis of associations between the duration of concomitant sacubitril/valsartan and statin use and hepatotoxicity are shown in Figure 10-9 and Section 15.2.1-Table 1-182 and Section 15.2.1-Figure 1-15.

Figure 10-9 Forest plot of hepatotoxicity secondary objective – Adjusted Odds ratios for the duration of concomitant sacubitril/valsartan and statin use versus statin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-15

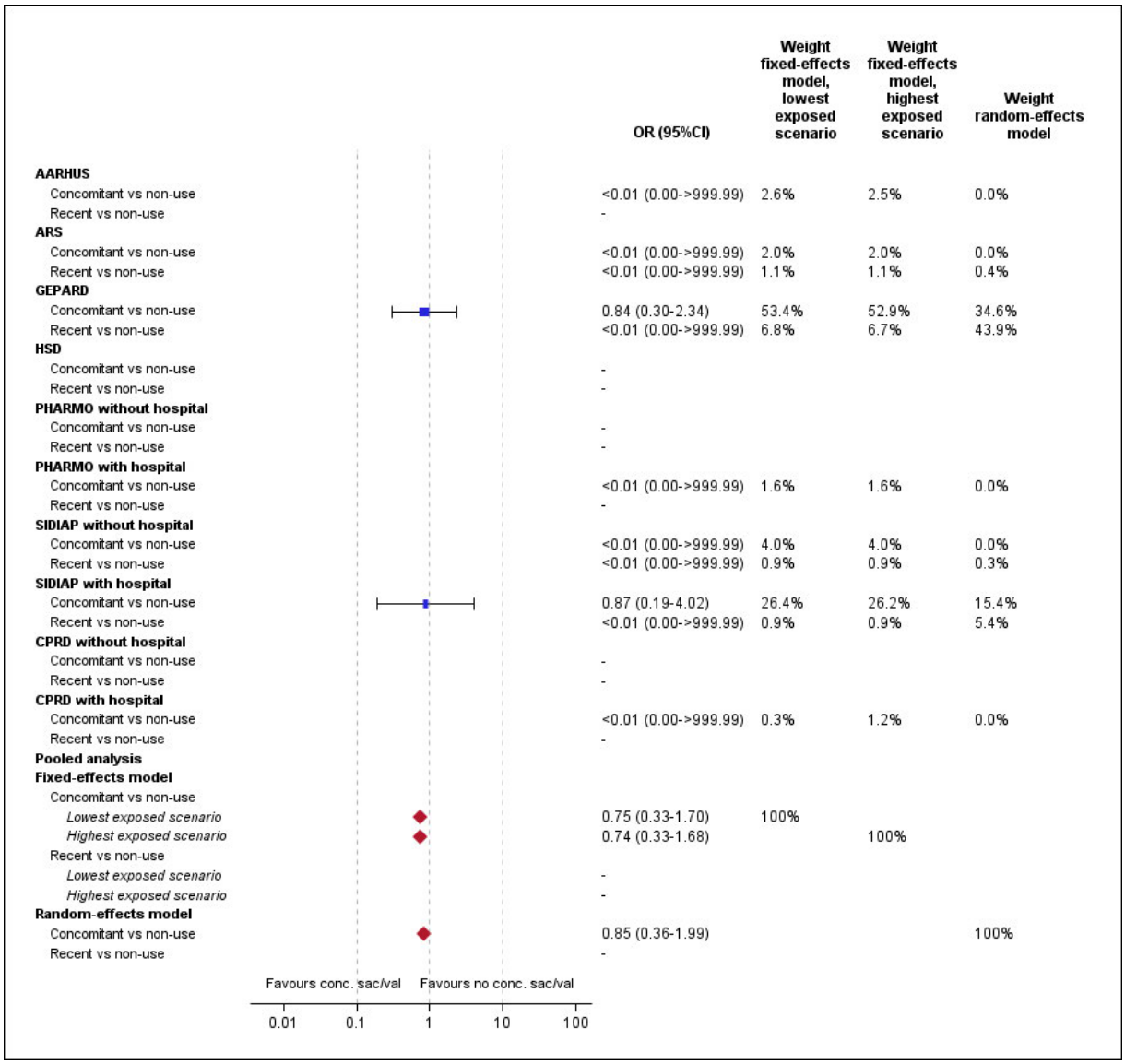
Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).
Short duration was that the episode of concomitant sacubitril/valsartan use started maximally 30 days prior to index date.
Medium duration was that the episode of concomitant sacubitril/valsartan use started within 31-90 days prior to index date.
Long duration was that the episode of concomitant sacubitril/valsartan use started more than 90 days prior to index date.

The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986).
Since the number of short, medium, and long duration concomitant users of sacubitril/valsartan and statins among cases and controls were redacted in Aarhus and CPRD with linked hospital data due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of Aarhus and CPRD (i.e., database- or subset-specific ORs were <0.01), the lowest exposed scenario assumes one control with short (Aarhus and CPRD with linked hospital data) or medium (Aarhus) duration of concomitant use of sacubitril/valsartan and the highest exposed scenario assumes four controls with short or medium duration of concomitant use of sacubitril/valsartan. Cases were zero exposed to sacubitril/valsartan (i.e., database- or subset-specific ORs were <0.01) in CPRD with linked hospital data.
For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

Secondary objective 2 – recency of use of sacubitril/valsartan

Regarding the analysis by recency of sacubitril/valsartan use, none of the cases (less than five for CPRD) was recently exposed to sacubitril/valsartan in any of the databases. Therefore, no meta-analysis was conducted for recent use of sacubitril/valsartan and the risk of hepatotoxicity. Results for the analysis of associations between the recency of sacubitril/valsartan use and hepatotoxicity are reported in Figure 10-10 and Section 15.2.1-Table 1-183 and Section 15.2.1-Figure 1-16.

Figure 10-10 Forest plot of hepatotoxicity secondary objective – Adjusted Odds ratios for the recency of concomitant sacubitril/valsartan and statin use versus statin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-16

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).

Recent sacubitril/valsartan use was the episode of sacubitril/valsartan use that ends between eight and 90 days before the index date.

A meta-analysis, using the fixed- or random-effects model, was not conducted for recent use of sacubitril/valsartan and the risk of hepatotoxicity.

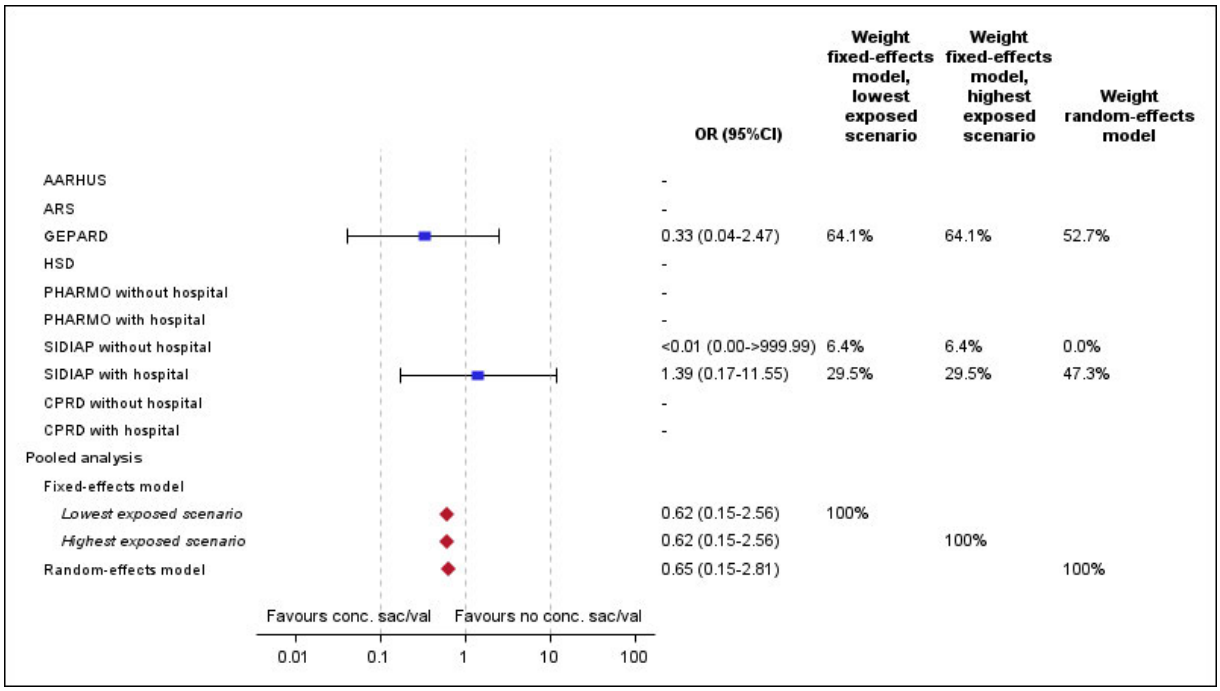
The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant users of sacubitril/valsartan and statins among cases and controls was redacted in CPRD with linked hospital data due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of CPRD (i.e., cases were zero exposed to sacubitril/valsartan [i.e., database- or subset-specific ORs were <0.01]), the lowest exposed scenario assumes one

control with concomitant use of sacubitril/valsartan and statins and the highest exposed scenario assumes four controls with concomitant use of sacubitril/valsartan and statins.
For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

Secondary objective 3 – specific types of statins

In all databases except for GePaRD, both subsets of SIDIAP, and CPRD with linked hospital data, less than five cases of hepatotoxicity were present among patients using atorvastatin, excluding them from further analyses. In GePaRD and SIDIAP with linked hospital data, cases and controls were exposed to sacubitril/valsartan and atorvastatin, whereas in SIDIAP without linked hospital data, no case was exposed to sacubitril/valsartan and atorvastatin but controls were exposed. In CPRD with linked hospital data it is likely that no case and control were concomitantly exposed to sacubitril/valsartan and atorvastatin (double zero exposed). The adjusted OR was 0.33 (95% CI 0.04-2.47) and 1.39 (95% CI 0.17-11.55) in GePaRD and SIDIAP with linked hospital data, which was based on one case exposed to sacubitril/valsartan in both databases. In the meta-analysis, using the fixed-effects model the adjusted OR was 0.62 (95% CI 0.15-2.56) for the lowest and highest exposed scenario, respectively. The random-effects model showed an adjusted OR of 0.65 (95% CI 0.15-2.81), which was based on two databases. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-184, and only adjusted ORs in Figure 10-11 and Section 15.2.1-Table 1-184 and Section 15.2.1-Figure 1-17.

Figure 10-11 Forest plot of hepatotoxicity secondary objective – Adjusted Odds ratios for concomitant sacubitril/valsartan and atorvastatin use versus atorvastatin use alone based on all cases in the pre-COVID period



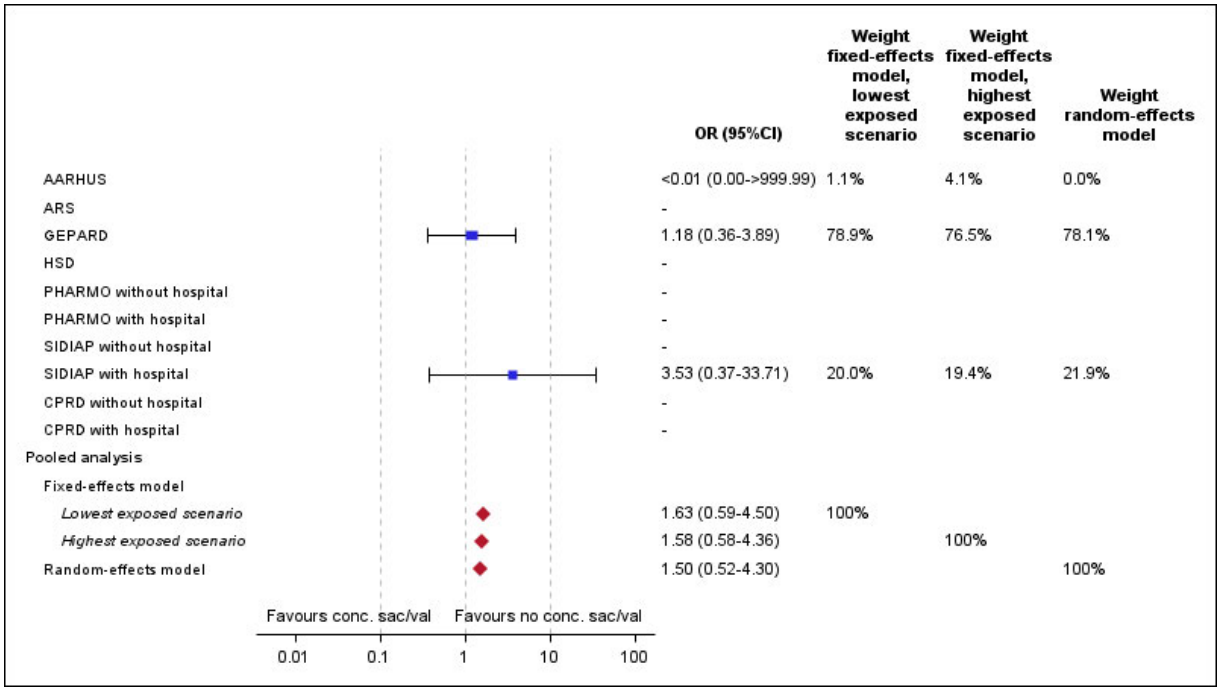
Source: Section 15.2.1-Figure 1-17

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).

The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant users of sacubitril/valsartan and atorvastatin among cases was redacted in CPRD with linked hospital data due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of CPRD (no database- or subset-specific OR was presented [double zero exposed]), the lowest and highest exposed scenario assumes zero cases and controls with concomitant use of sacubitril/valsartan and atorvastatin in CPRD with linked hospital data.
For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

GePaRD and SIDIAP with linked hospital data had cases and controls that were concomitantly using sacubitril/valsartan and simvastatin at index date. In Aarhus none of the cases was exposed to sacubitril/valsartan. Other databases did not contribute data to this analysis. The adjusted ORs for the comparison between concomitant use of sacubitril/valsartan and simvastatin and the risk of hepatotoxicity in GePaRD and SIDIAP with linked hospital data were 1.18 (95% CI 0.36-3.89) and 3.53 (95% CI 0.37-33.71), respectively. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-185, and only adjusted ORs in Figure 10-12 and Section 15.2.1-Figure 1-18.
Using the fixed-effects model, the ORs were 1.63 (95% CI 0.59-4.50) for the lowest exposed scenario and 1.58 (95% CI 0.58-4.36) for the highest exposed scenario, respectively. The random-effects model showed an adjusted OR of 1.50 (95% CI 0.52-4.30), which was based on two databases. Results for the analysis of associations between concomitant sacubitril/valsartan and simvastatin use and hepatotoxicity can be found in Figure 10-12 and Section 15.2.1-Table 1-185 and Section 15.2.1-Figure 1-18.

Figure 10-12 Forest plot of hepatotoxicity secondary objective – Adjusted Odds ratios for concomitant sacubitril/valsartan and simvastatin use versus simvastatin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-18

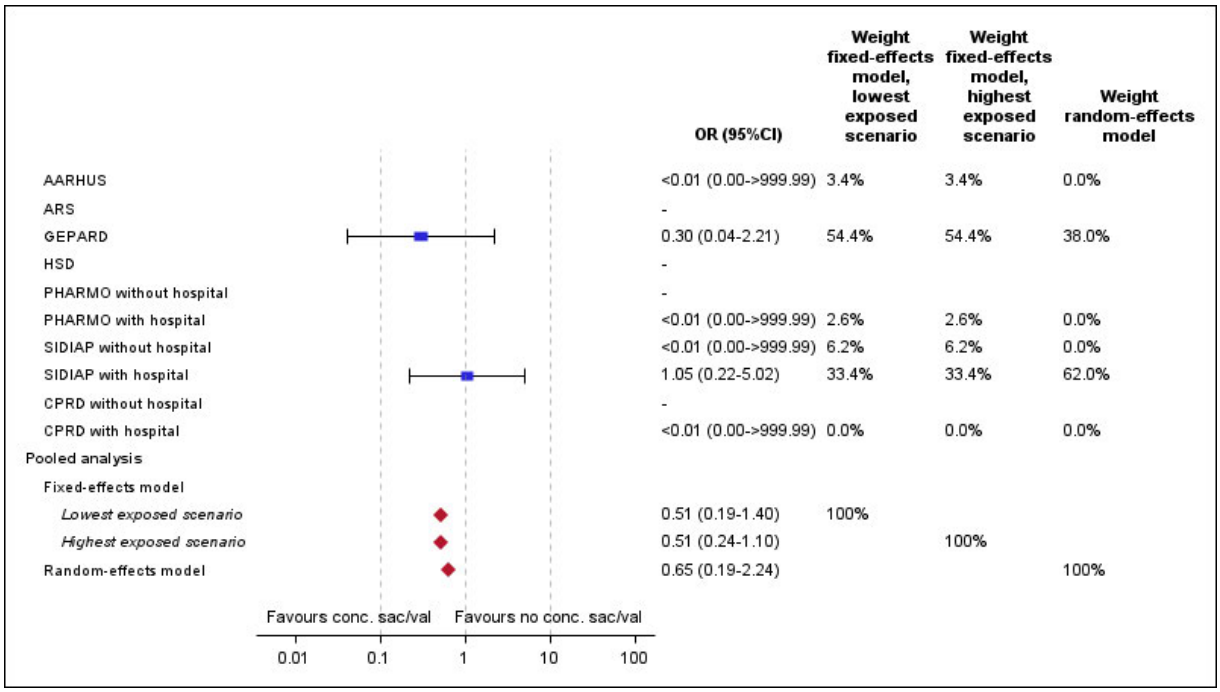
Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).
The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant users of sacubitril/valsartan and simvastatin among controls was redacted Aarhus due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of Aarhus (i.e., cases were zero exposed to sacubitril/valsartan), the lowest exposed scenario assumes one control with concomitant use of sacubitril/valsartan and simvastatin and the highest exposed scenario assumes four controls with concomitant use of sacubitril/valsartan and simvastatin.
For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

Secondary objective 4 – dose of statins

Database- or subset-specific adjusted ORs ranged from <0.01 in Aarhus, PHARMO and CPRD with linked hospital data, SIDIAP without linked hospital data to 1.05 in SIDIAP with linked hospital data. The CIs were wide and covered the null effect indicating no association. All other databases with less than five cases did not contribute data for this objective. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-186, and only adjusted ORs in Figure 10-13 and Section 15.2.1-Figure 1-19.

The meta-analysis showed for the fixed-effects model, adjusted ORs of 0.51 (95% CI 0.19-1.40) for the lowest exposed scenario and 0.51 (95% CI 0.24-1.10) for the highest exposed scenario, respectively. The random-effects model showed an adjusted OR of 0.65 (95% CI 0.19-2.24), which was based on two databases or subsets. Results for the analysis of associations between concomitant sacubitril/valsartan and high dose of statin use and hepatotoxicity can be found in Figure 10-13 and Section 15.2.1-Table 1-186 and Section 15.2.1-Figure 1-19.

Figure 10-13 Forest plot of hepatotoxicity secondary objective – Adjusted Odds ratios for concomitant sacubitril/valsartan and high dose of statin use versus high dose of statin use alone based on all cases in the pre-COVID period

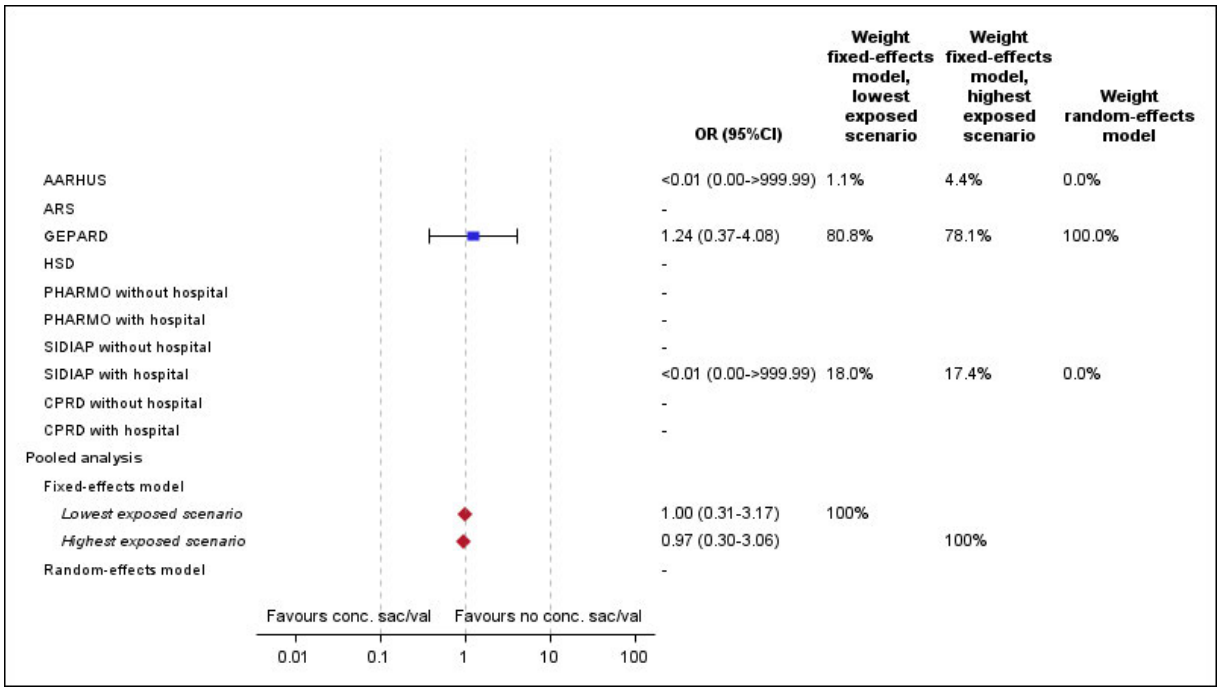


Source: Section 15.2.1-Figure 1-19

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).
The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant users of sacubitril/valsartan and high dose of statins among cases and controls were redacted in CPRD with linked hospital data due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of CPRD (i.e., database- or subset-specific ORs were <0.01), the lowest exposed scenario assumes one control with concomitant use of sacubitril/valsartan and high dose of statins and the highest exposed scenario assumes four controls with concomitant use of sacubitril/valsartan and high dose of statins. Cases were assumed to be zero exposed to sacubitril/valsartan (i.e., database- or subset-specific ORs were <0.01) in CPRD with linked hospital data.
For the random-effects model, estimated standard errors (derived from the 95% CIs) of OR of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

Aarhus, GePaRD, and SIDIAP with linked hospital data contributed data to the analysis and the adjusted ORs were <0.01 (Aarhus and SIDIAP with linked hospital data) and 1.24 (GePaRD), respectively. Other databases did not contribute data for this analysis as there were less than five cases. The adjusted OR for the association between concomitant use of sacubitril/valsartan and low dose of statins and the risk of hepatotoxicity in GePaRD was 1.24 (95% CI 0.37-4.08). The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Tables 1-187, and only adjusted ORs in Figure 10-14 and Section 15.2.1-Figure 1-20.
Using the fixed-effects model, adjusted ORs for the comparison between concomitant use of sacubitril/valsartan and low dose of statins and the risk of hepatotoxicity were 1.00 (95% CI 0.31-3.17) for the lowest exposed scenario and 0.97 (95% CI 0.30-3.06) for the highest exposed scenario, respectively. No meta-analysis of the random-effects model was performed as the results were based on GePaRD data only, and hence produced equal results. Results for the analysis of associations between concomitant sacubitril/valsartan use and low dose of statins and hepatotoxicity can be found in Figure 10-14 and Section 15.2.1-Table 1-187 and Section 15.2.1-Figure 1-20.

Figure 10-14 Forest plot of hepatotoxicity secondary objective – Adjusted Odds ratios for concomitant sacubitril/valsartan and low dose of statin use versus low dose of statin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-20

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).
The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant users of sacubitril/valsartan and low dose of statins among controls was redacted in Aarhus due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database-specific results of Aarhus (i.e., cases were zero exposed to sacubitril/valsartan), the lowest exposed scenario assumes one control with concomitant use of sacubitril/valsartan and low dose of statins and the highest exposed scenario assumes four controls with concomitant use of sacubitril/valsartan and low dose of statins.
For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

10.4.3 Acute pancreatitis

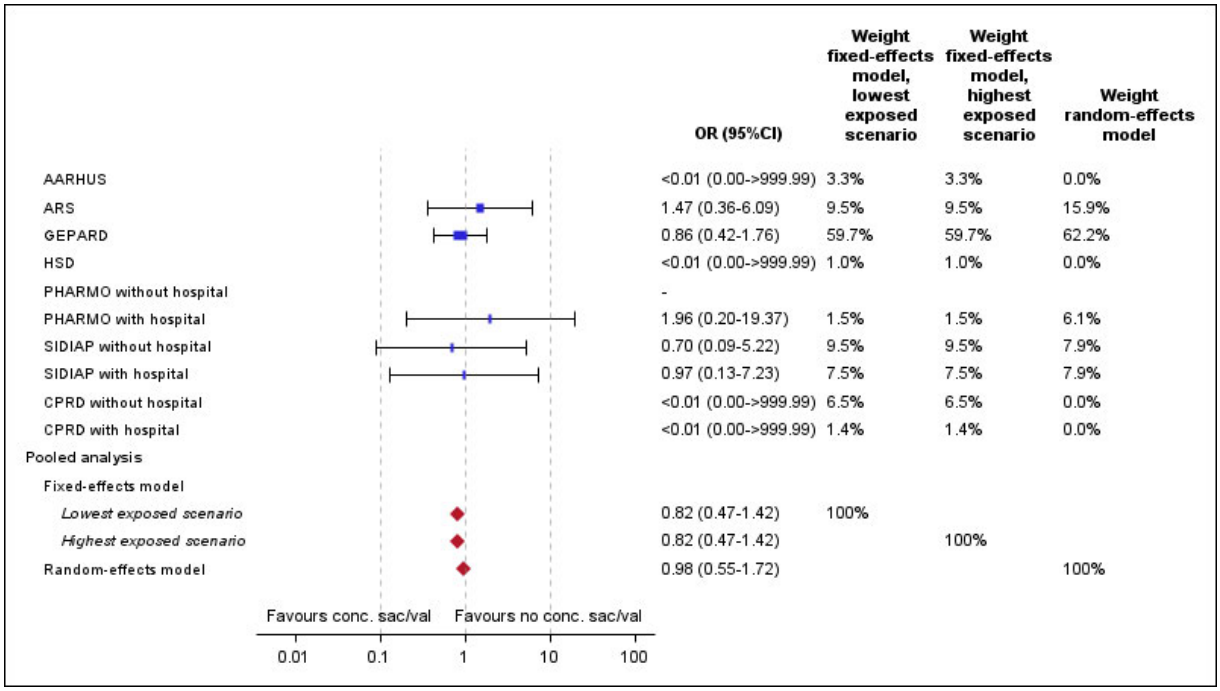
Primary objective

The covariates of interest for the primary analysis of statins and the risk of acute pancreatitis were specified in the LCZ696B2015 study protocol v02 – amendment 2 (see Section 15.1.1). If the number of cases prevented the inclusion of all covariates of interest in the primary analysis model, the priority of inclusion was determined by the estimated $|log\,(Bias)|$ for each covariate. All modeling steps for the inclusion of covariates are described in Section 15.2.1-Table 1-188 to Section 15.2.1-Table 1-197). The number of covariates that were included in each model for adjustment differed across databases, ranging from no covariates in HSD to 35 in GePaRD (see Section 15.2.1-Table 1-198 to Section 15.2.1-Table 1-207).
The crude, unadjusted ORs are presented in Section 15.2.1-Table 1-208.

Data from PHARMO without linked hospital data was not included in any of the analyses for acute pancreatitis, since there were less than five cases. Database- or subset-specific adjusted ORs comparing concomitant use of sacubitril/valsartan and statins at index date with statin use alone ranged from <0.01 (Aarhus, HSD, and both subsets of CPRD) to 1.96 (PHARMO with linked hospital data). The CIs were wide and covered the null effect indicating no association (Figure 10-15 and Section 15.2.1-Table 1-208 and Section 15.2.1-Figure 1-21).

The fixed-effects model for the meta-analysis showed for the comparison between concomitant use of sacubitril/valsartan and statins and acute pancreatitis adjusted ORs of 0.82 (95% CI 0.47-1.42) for the lowest and highest exposed scenario. The adjusted OR for the random-effects model was 0.98 (95% CI 0.55-1.72) which was based on five of the nine databases or subsets (Aarhus, HSD, and both subsets of CPRD had cases who were zero exposed to sacubitril/valsartan). Results for the analysis of associations between concomitant sacubitril/valsartan and statin use and acute pancreatitis are shown in Figure 10-15 and Section 15.2.1-Table 1-208 and Section 15.2.1-Figure 1-21.

Figure 10-15 Forest plot of acute pancreatitis primary objective – Adjusted Odds ratios concomitant sacubitril/valsartan use versus statin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-21

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).

The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant users of sacubitril/valsartan and statins among cases was redacted in both subsets of CPRD data due to the small-cell-count policy, cases were assumed to be zero exposed to sacubitril/valsartan (i.e., database- or subset-specific ORs were <0.01) in both subsets of CPRD.

For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

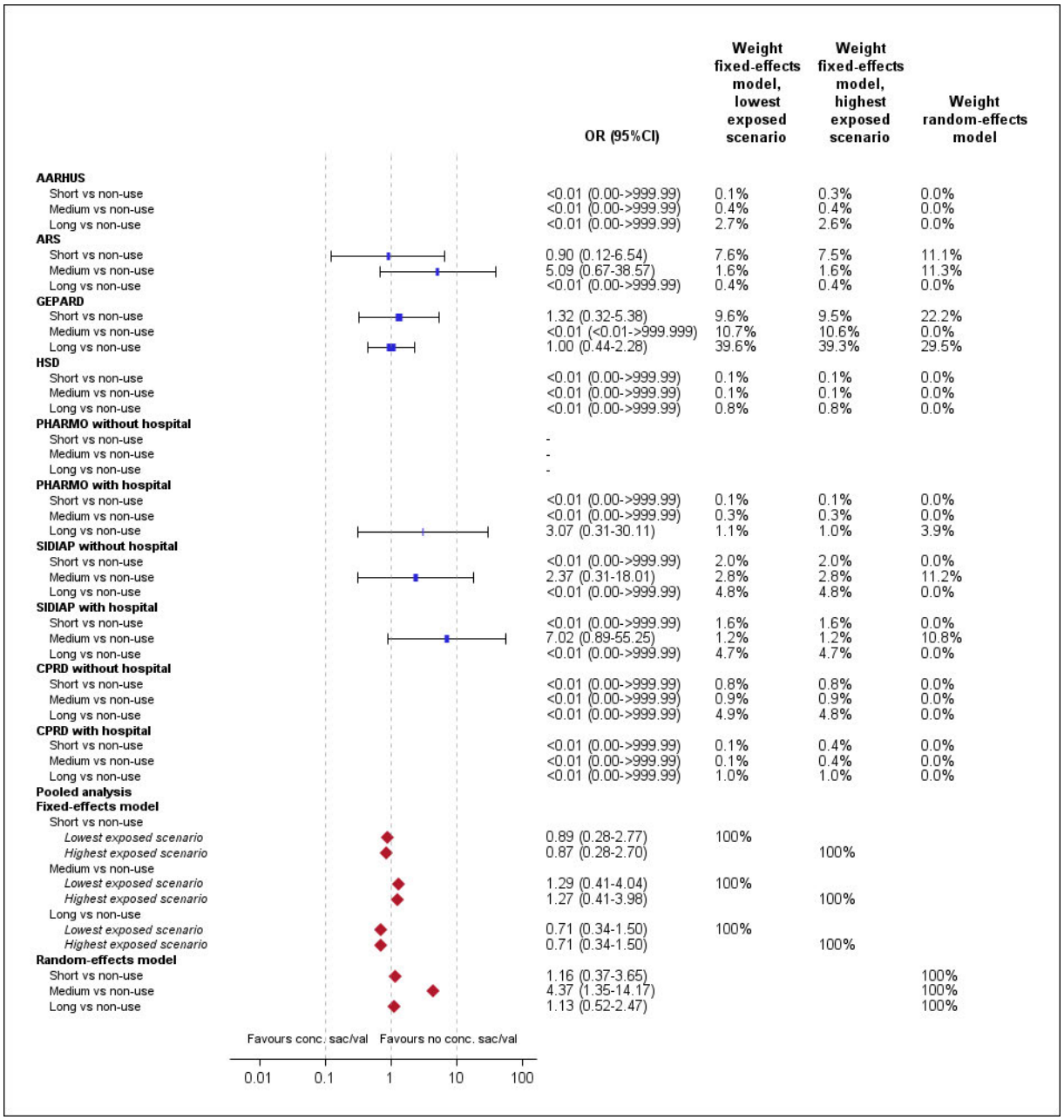
Secondary objective 1 – duration of use of sacubitril/valsartan

In none of the databases, cases with acute pancreatitis and controls concomitantly using sacubitril/valsartan and statins in all categories of duration of use (short, medium, or long) were present. Adjusted ORs for short duration of concomitant sacubitril/valsartan and statin use at index date and the risk of acute pancreatitis across nine databases or subsets ranged from <0.01 (Aarhus, HSD, PHARMO with linked hospital data, and both subsets of SIDIAP and CPRD) to 1.32 (GePaRD). For medium duration of concomitant sacubitril/valsartan and statin use, database- or subset-specific adjusted ORs ranged from <0.01 (Aarhus, GePaRD, HSD, PHARMO with linked hospital data, and both subsets of CPRD) to 7.02 (SIDIAP with linked hospital data). Comparing long duration of concomitant sacubitril/valsartan and statin use and statins versus statins alone across nine databases or subsets, adjusted ORs ranged from <0.01 (Aarhus, ARS, HSD, and both subsets of SIDIAP and CPRD) to 3.07 (PHARMO with linked hospital data). For all database-or subset-specific adjusted ORs for short, medium, and long duration of concomitant use of sacubitril/valsartan and statins, the CIs were large and included the null effect, indicating no association.

The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-211, and only adjusted ORs in Figure 10-16 and Section 15.2.1-Figure 1-24.

In the meta-analysis, using a fixed-effects model, adjusted ORs for short, medium, and long duration of concomitant sacubitril/valsartan and statin use were 0.89 (95% CI 0.28-2.77), 1.29 (95% CI 0.41-4.04), and 0.71 (95% CI 0.34-1.50) for the lowest exposure scenario and 0.87 (95% CI 0.28-2.70), 1.27 (95% CI 0.41-3.98), and 0.71 (95% CI 0.34-1.50) for the highest exposure scenario, respectively. Adjusted ORs from the random-effects model for short, medium, and long duration of concomitant sacubitril/valsartan and statin use were 1.16 (95% CI 0.37-3.65), 4.37 (95% CI 1.35-14.17), and 1.13 (95% CI 0.52-2.47), respectively. The analysis for low, medium, and long duration of concomitant sacubitril/valsartan and statin use was based on two (ARS and GePaRD), three (ARS and both subsets of SIDIAP), and two (GePaRD and PHARMO with linked hospital data) databases or subsets. Results for the analysis of associations between the duration of concomitant sacubitril/valsartan and statin use and acute pancreatitis are shown in Figure 10-16 and Section 15.2.1-Table 1-211 and Section 15.2.1-Figure 1-24.

Figure 10-16 Forest plot of acute pancreatitis secondary objective – Adjusted Odds ratios for the duration of concomitant sacubitril/valsartan and statin use versus statin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-24

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).
Short duration was that the episode of concomitant sacubitril/valsartan use started maximally 30 days prior to index date.
Medium duration was that the episode of concomitant sacubitril/valsartan use started within 31-90 days prior to index date.
Long duration was that the episode of concomitant sacubitril/valsartan use started more than 90 days prior to index date.

The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of short, medium, and long duration concomitant users of sacubitril/valsartan and statins among cases and controls were redacted in Aarhus and both subsets of CPRD due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of Aarhus (only applicable for short duration of concomitant use of sacubitril/valsartan) and CPRD (i.e., database- or subset-specific ORs were <0.01), the lowest exposed scenario assumes one control with concomitant use of sacubitril/valsartan and statins and the highest exposed scenario assumes four controls with concomitant use of sacubitril/valsartan and statins; due to the traceability as part of the small-cell-count policy, the number of controls with concomitant use of sacubitril/valsartan and statins were the same for low and high exposed scenario (only applicable for medium duration of concomitant use of sacubitril/valsartan) in Aarhus. Cases were assumed to be zero exposed to sacubitril/valsartan (i.e., database- or subset-specific ORs were <0.01) in both subsets of CPRD.

For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

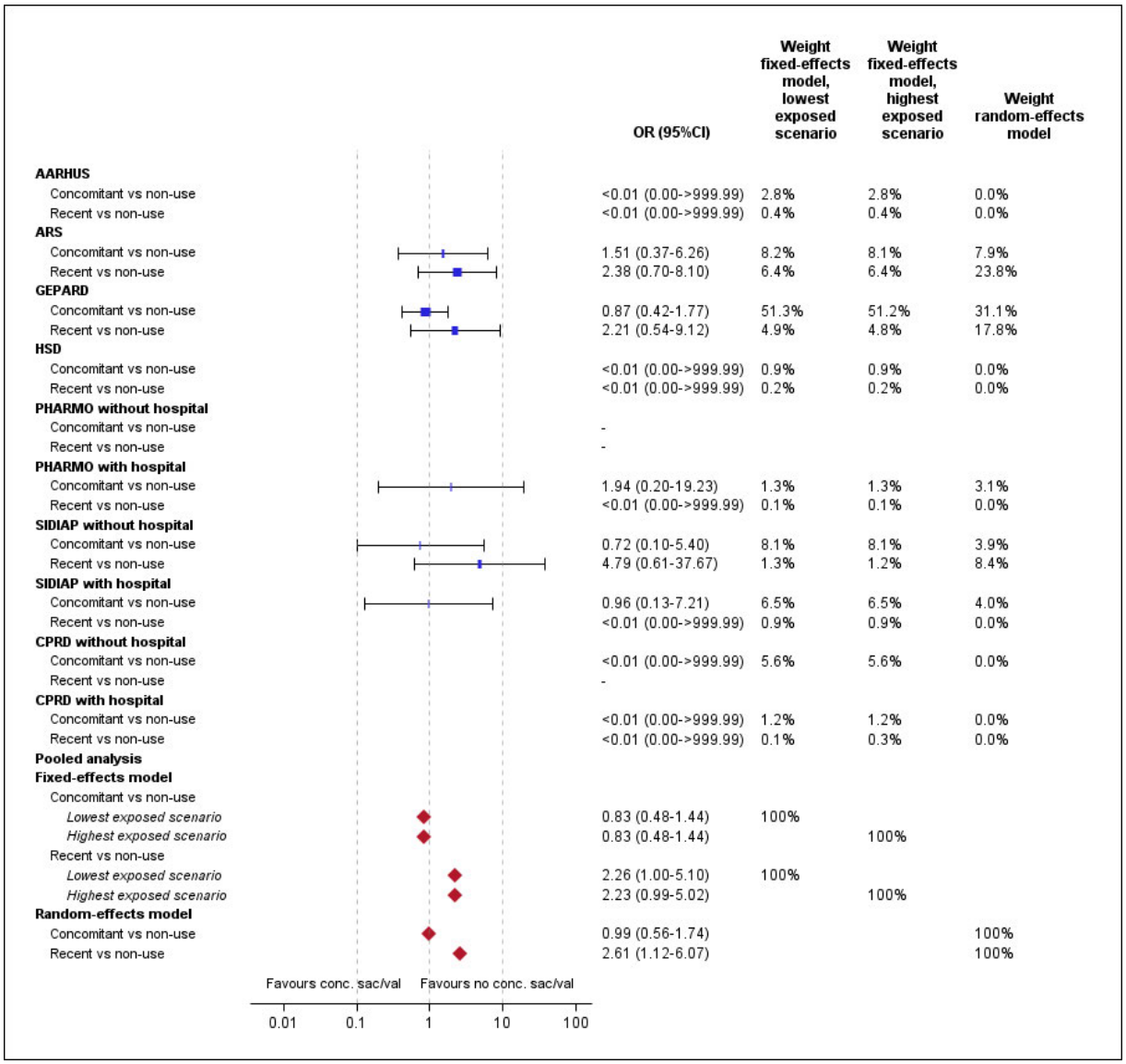
Secondary objective 2 – recency of use of sacubitril/valsartan

The analysis by recency of sacubitril/valsartan use included six cases with recent use (i.e., treatment episode ended between eight and 90 days before the index date) from ARS, GePaRD, and SIDIAP without linked hospital data. In all other databases, none of the cases was recently exposed to sacubitril/valsartan.

Apart from PHARMO without linked hospital data, all other databases had at least five cases to perform an analysis. The range of the adjusted ORs of acute pancreatitis for recent use was <0.01 (in Aarhus, HSD, and the subset of PHARMO, SIDIAP, and CPRD with linked hospital data) to 4.79 in SIDIAP without linked hospital data. The CIs were wide and covered the null effect indicating no association. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-212, and only adjusted ORs in Figure 10-17 and Section 15.2.1-Figure 1-25.

The meta-analysis based on the fixed-effects model resulted in an $OR_{adjusted}$ of 2.26 (95% CI 1.00-5.10) for the lowest exposed scenario and an $OR_{adjusted}$ of 2.23 (95% CI 0.99-5.02) for the highest exposed scenario, respectively. The random-effects model showed an adjusted OR of 2.61 (95% CI 1.12-6.07), which was based on three databases or subsets. It seems that neither cases or controls had recent use of sacubitril/valsartan in CPRD without linked hospital data (double zero-counts in the meta-analysis) and this database subset was not included in the fixed- and random-effects model. Results for the analysis of associations between the recency of concomitant sacubitril/valsartan and statin use and acute pancreatitis are reported in Figure 10-17 and Section 15.2.1-Table 1-212 and Section 15.2.1-Figure 1-25.

Figure 10-17 Forest plot of acute pancreatitis secondary objective – Adjusted Odds ratios for the recency of concomitant sacubitril/valsartan and statin use versus statin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-25

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).

Recent sacubitril/valsartan use was the episode of sacubitril/valsartan use that ends between eight and 90 days before the index date.

The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant and recent users of sacubitril/valsartan and statins among cases and controls were redacted in both subsets of CPRD due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of CPRD (i.e., database- or subset-specific OR for recent use was <0.01 and no database- or subset-specific OR for recent use of sacubitril/valsartan was presented [double zero exposure]), the lowest exposed scenario assumes zero or one control with concomitant use of sacubitril/valsartan and statins and the highest exposed scenario assumes four controls with concomitant use of

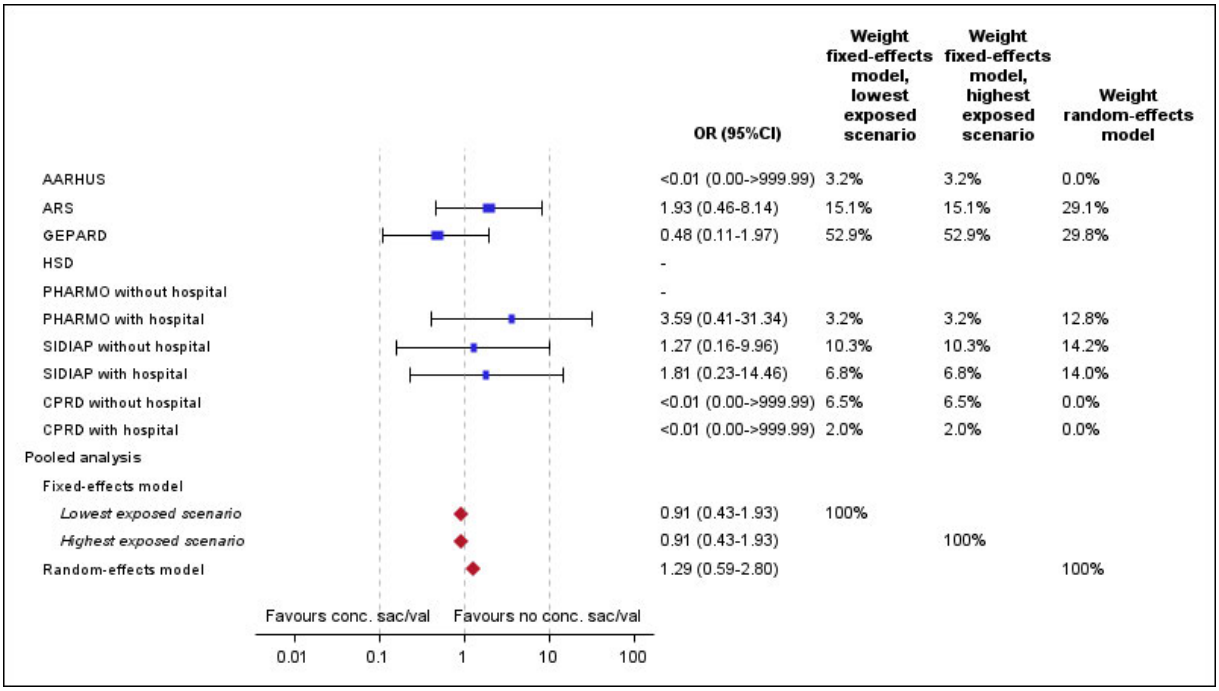
sacubitril/valsartan and statins. Cases were assumed to be zero exposed to sacubitril/valsartan (i.e., database- or subset-specific ORs were <0.01 or when no database- or subset-specific OR was presented [double zero exposure]) in both subsets of CPRD.
For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

Secondary objective 3 – specific types of statins

Database- or subset-specific adjusted ORs comparing concomitant use of sacubitril/valsartan and atorvastatin at index date with the use of atorvastatin alone ranged from <0.01 (Aarhus and both subsets of CPRD) to 3.59 (PHARMO with linked hospital data). The CIs were large and included the null effect, indicating no association. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-213, and only adjusted ORs in Figure 10-18 and Section 15.2.1-Figure 1-26.

The meta-analysis showed, when using the fixed-effects model, an adjusted OR of 0.91 (95% CI 0.43-1.93) for the lowest and highest exposed scenario. The random-effects model resulted in an adjusted OR of 1.29 (95% CI 0.59-2.80) and was based on five databases or subsets. Double zero-counts appeared for concomitant use of sacubitril/valsartan and statins in HSD, and this database was not included in the fixed- and random-effects models. Results for the analysis of associations between the concomitant sacubitril/valsartan and atorvastatin use and acute pancreatitis are shown in Figure 10-18 and Section 15.2.1-Table 1-213 and Section 15.2.1-Figure 1-26.

Figure 10-18 Forest plot of acute pancreatitis secondary objective – Adjusted Odds ratios for concomitant sacubitril/valsartan and atorvastatin use versus atorvastatin use alone based on all cases in the pre-COVID period



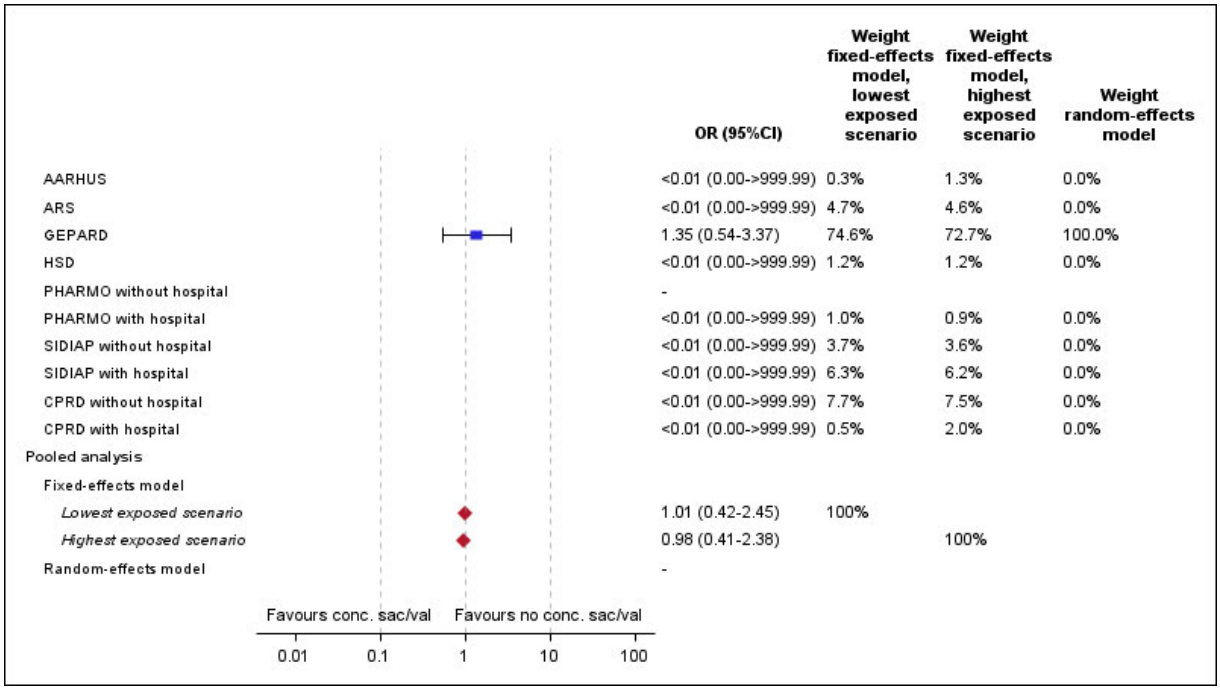
Source: Section 15.2.1-Figure 1-26

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).

The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). The number of concomitant users of sacubitril/valsartan and atorvastatin among cases and controls were redacted in Aarhus and both subsets of CPRD due to the small-cell-count policy. Since the number of concomitant users of sacubitril/valsartan and atorvastatin among cases and controls was redacted in Aarhus and both subsets of CPRD due to the small-cell-count policy, however, due to traceability as part of the small-cell-count policy in Aarhus, the number of controls with concomitant use of sacubitril/valsartan and atorvastatin were the same for low and high exposed scenario in the fixed-effects model. Cases were assumed to be zero exposed to sacubitril/valsartan (i.e., database- or subset-specific ORs were <0.01) in both subsets of CPRD.
For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

No analysis between concomitant use of sacubitril/valsartan and simvastatin and the risk of acute pancreatitis was conducted in PHARMO without linked hospital data as there was no case identified. Only GePaRD had cases and controls that were concomitantly using sacubitril/valsartan and simvastatin at index date, and in all other databases none of the cases was exposed to sacubitril/valsartan. The adjusted OR for the comparison between concomitant use of sacubitril/valsartan and simvastatin and the risk of acute pancreatitis in GePaRD was 1.35 (95% CI 0.54-3.37). The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-214, and only adjusted ORs in Figure 10-19 and Section 15.2.1-Figure 1-27.
Using the fixed-effects model, adjusted ORs were 1.01 (95% CI 0.42-2.45) for the lowest exposed scenario and 0.98 (95% 0.41-2.38) for the highest exposed scenario, respectively. No meta-analysis of the random-effects model was performed as it was based on GePaRD data only, and hence provided the same results. Results for the analysis of associations between concomitant sacubitril/valsartan and simvastatin use and acute pancreatitis can be found in Figure 10-19 and Section 15.2.1-Table 1-214 and Section 15.2.1-Figure 1-27.

Figure 10-19 Forest plot of acute pancreatitis secondary objective – Adjusted Odds ratios for concomitant sacubitril/valsartan and simvastatin use versus simvastatin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-27

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).

The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant users of sacubitril/valsartan and simvastatin among cases and controls was redacted in Aarhus and both subsets of CPRD due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of Aarhus and CPRD (i.e., database- or subset-specific ORs were <0.01), the lowest exposed scenario assumes one control with concomitant use of sacubitril/valsartan and simvastatin and the highest exposed scenario assumes four controls with concomitant use of sacubitril/valsartan and simvastatin in CPRD with linked hospital data; due to the traceability as part of the small-cell-count policy, the number of controls with concomitant use of sacubitril/valsartan and simvastatin were the same for low and high exposed scenario in Aarhus. Cases were assumed to be zero exposed to sacubitril/valsartan (i.e., database- or subset-specific ORs were <0.01) in both subsets of CPRD.

For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

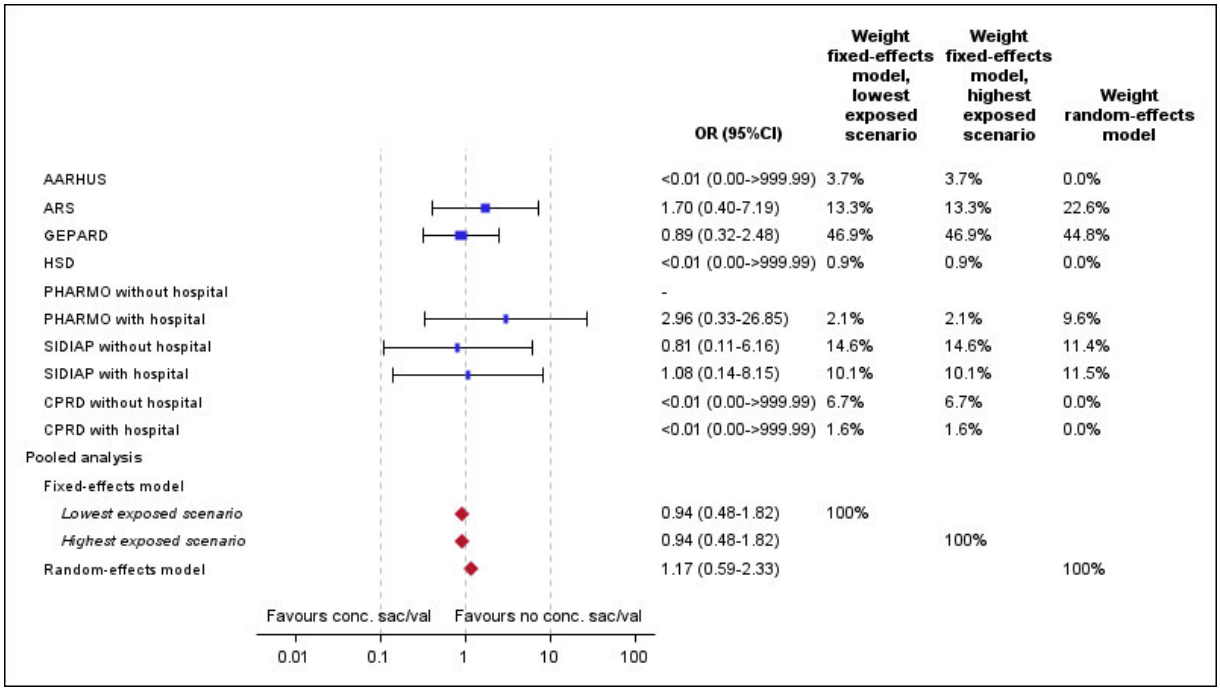
Secondary objective 4 – dose of statins

For the database- or subset-specific ORs, the lowest adjusted OR was observed in Aarhus, HSD, and both subsets of CPRD (OR: <0.01) and the highest in PHARMO with linked hospital data (OR: 2.96). The CIs were wide and covered the null effect indicating no association. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-215, and only adjusted ORs in Figure 10-20 and Section 15.2.1-Figure 1-28.

For the meta-analysis based on the fixed-effects model, the adjusted OR was 0.94 (95% CI 0.48-1.82) for the lowest and highest exposed scenario. The adjusted OR from the random-effects model was 1.17 (95% CI 0.59-2.33) based on five databases or subsets. Results for the analysis

of associations between concomitant sacubitril/valsartan and high dose of statin use and acute pancreatitis are detailed in Figure 10-20 and Section 15.2.1-Table 1-215.

Figure 10-20 Forest plot of acute pancreatitis secondary objective – Adjusted Odds ratios for concomitant sacubitril/valsartan and high dose of statin use versus high dose of statin use alone based on all cases in the pre-COVID period



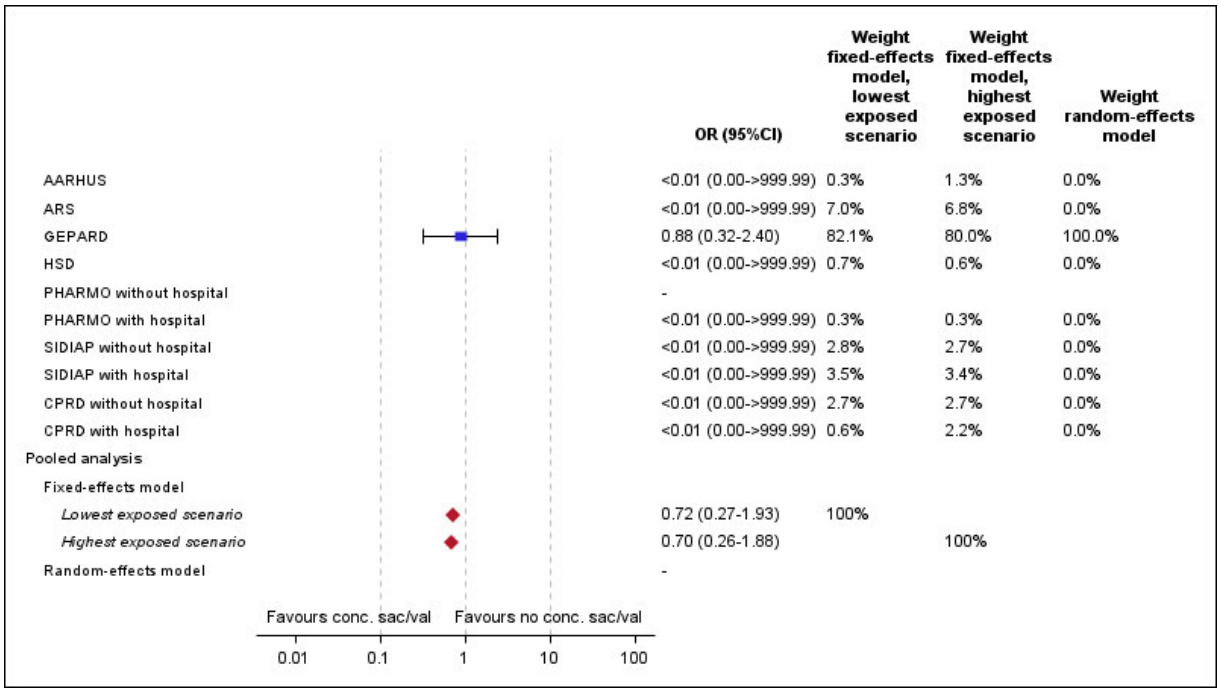
Source: Section 15.2.1-Figure 1-28

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).
The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). The number of concomitant users of sacubitril/valsartan and high dose of statins among cases and controls was redacted in Aarhus and both subsets of CPRD due to the small-cell-count policy. Due to traceability as part of the small-cell-count policy, the number of controls with concomitant use of sacubitril/valsartan and high dose of statins were the same for low and high exposed scenario in Aarhus. Cases were assumed to be zero exposed to sacubitril/valsartan (i.e., database- or subset-specific ORs were <0.01) in both subsets of CPRD.
For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

No analysis between concomitant use of sacubitril/valsartan and low dose of statins and the risk of acute pancreatitis was conducted in PHARMO without linked hospital data as there were less than five cases identified. Only in GePaRD cases of acute pancreatitis were concomitantly using sacubitril/valsartan and low dose of statins at index date. In all other databases including CPRD, (potentially) none of the cases was exposed to sacubitril/valsartan. The adjusted OR for the comparison between concomitant use of sacubitril/valsartan and low dose of statins and the risk of acute pancreatitis was 0.88 (95% CI 0.32-2.40) in GePaRD. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-216, and only adjusted ORs in Figure 10-21 and Section 15.2.1-Figure 1-29.

For the meta-analysis the same results were observed in the random-effects model, as results from GePaRD were only included in this model. The fixed-effects model of the meta-analysis gave adjusted ORs of 0.72 (95% CI 0.27-1.93) for the lowest exposed scenario and 0.70 (95% CI 0.26-1.88) for the highest exposed scenario, respectively. The random-effects model was only based on GePaRD data and hence produced equal results. Results for the analysis of associations between concomitant sacubitril/valsartan and low dose of statin use and acute pancreatitis can be found in Figure 10-21 and Section 15.2.1-Table 1-216 and Section 15.2.1-Figure 1-29.

Figure 10-21 Forest plot of acute pancreatitis secondary objective – Adjusted Odds ratios for concomitant sacubitril/valsartan and low dose of statin use versus low dose of statin use alone based on all cases in the pre-COVID period



Source: Section 15.2.1-Figure 1-29

Concomitant sacubitril/valsartan use was the episode of sacubitril/valsartan use that covered the index date (or stopped at most seven days before the index date).

The pooled fixed-effects OR was estimated using the Mantel-Haenszel method based on the database- or subset-specific adjusted ORs and cell counts for the calculation of weights and standard errors (Robins et al 1986). Since the number of concomitant users of sacubitril/valsartan and low dose of statins among cases and controls was redacted in Aarhus and both subsets of CPRD due to the small-cell-count policy, two scenarios were implemented for the fixed-effects model: Based on the database- or subset-specific results of Aarhus and CPRD (i.e., database- or subset-specific ORs were <0.01), the lowest exposed scenario assumes one control with concomitant use of sacubitril/valsartan and low dose of statins and the highest exposed scenario assumes four controls with concomitant use of sacubitril/valsartan and low dose of statins in CPRD with linked hospital data; due to traceability as part of the small-cell-count policy, the number of controls with concomitant use of sacubitril/valsartan and low dose of statins were the same for low and high exposed scenario in Aarhus. Cases were assumed to be zero exposed to sacubitril/valsartan (i.e., database- or subset-specific ORs were <0.01) in both subsets of CPRD.

For the random-effects model, estimated standard errors (derived from the 95% CIs) of adjusted ORs of databases or subsets were used for estimating the pooled OR, using the DerSimonian and Laird method (DerSimonian et al 1986).

10.5 Other analyses

10.5.1 Sensitivity analysis: Misclassification of outcome events

Mitigating potential misclassification of myotoxicity by excluding non-specific terms of myalgia

A sensitivity analysis using a more specific definition of myotoxicity that excluded cases with only a diagnostic code for myalgia was conducted in all databases except for ARS and HSD, that do not have myalgia codes in the ICD-9 coding system. Following the application of the same exclusion criteria as for the outcome event of myotoxicity, a total of 315 cases with a more specific definition of myotoxicity (i.e., excluded cases with only unspecific terms of myalgia) were identified in all databases, ranging from four cases in PHARMO without linked hospital data to 137 cases in GePaRD. There was a total of 23,298 matched controls in the pre-COVID period that were also included (see Section 15.2.1-Table 1-2). The patient demographics and characteristics of these cases and controls were not markedly different when compared to cases and controls in the analysis for the primary analysis (see Section 15.2.1-Table 1-18 to Section 15.2.1-Table 1-27). Database- or subset-specific adjusted ORs of the comparison between concomitant use of sacubitril/valsartan and statins versus statins alone ranged from <0.01 (Aarhus and both subsets of CPRD) to 7.25 (PHARMO with linked hospital data). The CIs were wide and covered the null effect indicating no association (Section 15.2.1-Table 1-149 and Section 15.2.1-Figure 1-2). Modeling steps including the covariate selection per database and the crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-129 to Section 15.2.1-Table 1-138, Section 15.2.1-Table 1-139 to Section 15.2.1-Table 1-148 and Section 15.2.1-Table 1-149.

The meta-analysis based on the fixed-effects model resulted in adjusted ORs of 1.52 (95% CI 0.78-2.98) for the lowest scenario and 1.51 (95% CI 0.77-2.95) for the highest exposed scenario, respectively. Using the random-effects model, the adjusted OR was 1.93 (95% CI 0.95-3.92) based on four databases or subsets (Aarhus and both subsets of CPRD were not included because no cases were exposed to sacubitril/valsartan). Except for SIDIAP with linked hospital data, all ORs obtained from this analysis were numerically higher and in the same direction as those from the primary analysis, however, the CIs of both analyses were widely overlapping and included the null effect; see Section 15.2.1-Table 1-149 and Section 15.2.1-Figure 1-2).

10.5.2 Sensitivity analysis: Impact of the COVID-19 pandemic

Myotoxicity

The number of cases of myotoxicity and matched controls for the full study period are presented in Section 15.2.1-Table 1-2. The patient demographics and characteristics of cases and controls included in the full study period were similar to the demographics and characteristics of cases and controls in the primary analysis (see Section 15.2.1-Table 1-18 to Section 15.2.1-Table 1-27).

The range of database- or subset-specific adjusted ORs of the comparison between concomitant use of sacubitril/valsartan and statins and myotoxicity was <0.01 (Aarhus and HSD) to 1.37 (PHARMO without linked hospital data). The CIs were wide and covered the null effect

indicating no association. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-150, and only adjusted ORs in Section 15.2.1-Figure 1-3.
In the meta-analysis, using the fixed-effects model, the adjusted OR was 1.12 (95% CI 0.88-1.43) for the lowest and highest exposed scenario. Using a random-effects model, the adjusted OR was 1.15 (95% CI 0.88-1.49) based on eight databases or subsets (Aarhus and HSD were not included because no cases were exposed to sacubitril/valsartan). Both models showed similar results as the ones for the primary analysis; see Section 15.2.1-Table 1-150 and Section 15.2.1-Table 1-3.

Hepatotoxicity

The number of cases of hepatotoxicity and matched controls in the full study period are presented in Section 15.2.1-Table 1-7. The patient demographics and characteristics of these cases and controls were similar to the demographics and characteristics of cases and controls in the primary analysis for the primary objective (see Section 15.2.1-Table 1-48 to Section 15.2.1-Table 1-57).
Similar to this primary analysis, most databases, except GePaRD and SIDIAP with linked hospital data, had no case concomitantly exposed to sacubitril/valsartan and statins, which resulted in ORs of zero. The OR for SIDIAP was one ($OR_{adjusted}$ 1.00, 95% CI 0.28-3.56, which was based on three cases with concomitant sacubitril/valsartan statin exposure out of 40 cases overall. For GePaRD, the same results were found because the end date of follow-up is December 31, 2019. For both databases, the CIs were wide and covered the null effect indicating no association. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-180, and only adjusted ORs in Section 15.2.1-Figure 1-13.
The meta-analysis showed for the fixed-effects model similar results as the primary analysis for the primary objective. The analysis resulted in an adjusted OR of 0.76 (95% CI 0.35-1.62) for the lowest exposed scenario and 0.75 (95% CI 0.35-1.61) for the highest exposed scenario. Using a random-effects model, the adjusted OR from the random-effects model was 0.91 (95% CI 0.41-2.01) based on two databases or subsets (Aarhus, ARS, HSD, PHARMO and CPRD with linked hospital data, and SIDIAP without linked hospital data were not included because no cases were exposed to sacubitril/valsartan) (see Section 15.2.1-Table 1-180 and Section 15.2.1-Table 1-13).

Acute pancreatitis

The number of cases of acute pancreatitis and matched controls in the full study period are presented in Section 15.2.1-Table 1-12. The patient demographics and characteristics of these cases and controls were similar to the demographics and characteristics of cases and controls in the primary analysis for the primary objective (see Section 15.2.1-Table 1-78 to Section 15.2.1-Table 1-87).
The range of database- or subset-specific adjusted ORs of the comparison between concomitant use of sacubitril/valsartan and statins and acute pancreatitis was <0.01 (Aarhus and both subsets of CPRD) to 2.93 (HSD). The CIs were wide and covered the null effect indicating no association. The crude, unadjusted and adjusted ORs are presented in Section 15.2.1-Table 1-209, and only adjusted ORs in Section 15.2.1-Figure 1-22.
In the meta-analysis, using the fixed-effects model, the adjusted OR was 0.70 (95% CI 0.42-1.17) for the lowest and highest exposed scenario. Using a random-effects model, the adjusted

OR was 0.88 (95% CI 0.52-1.50) based on six databases or subsets (Aarhus, and both subsets of CPRD were not included because no cases were exposed to sacubitril/valsartan and less than five cases were presented in PHARMO without linked hospital data). Both models showed similar results as that from the primary analysis (Section 15.2.1-Table 1-209 and Section 15.2.1-Figure 1-22).

10.5.3 Sensitivity analysis: Impact of SIDIAP data on study results

The sensitivity analysis which excluded SIDIAP data from the meta-analysis for primary objectives showed results that were similar to the primary analysis results for myotoxicity, hepatotoxicity, and acute pancreatitis, with wide and overlapping CIs (Section 15.2.1-Table 1-151, Section 15.2.1-Table 1-181, Section 15.2.1-Table 1-210, and Section 15.2.1-Figure 1-4, Section 15.2.1-Figure 1-14, Section 15.2.1-Figure 1-23).

In the sensitivity analysis using a more specific definition of myotoxicity (i.e., excluding cases with unspecific terms of myalgia), the adjusted ORs were higher in the analysis without SIDIAP data compared to the analysis with SIDIAP data in GePaRD and PHARMO with linked hospital data. The fixed-effects model for the analysis without SIDIAP data was based on only five exposed cases and resulted in adjusted ORs of 2.48 (95% CI 1.01-6.11) for the lowest exposed scenario and 2.42 (95% CI 0.98-5.95) for the highest exposed scenario, respectively. For the random-effects model, the adjusted OR was 3.11 (95% CI 1.18-8.14), which was based on two databases (GePaRD and PHARMO with linked hospital data). See Section 15.2.1-Table 1-152 and Section 15.2.1-Figure 1-15 for detailed results.

10.6 Adverse events/adverse reactions

Not applicable.

11 Discussion

11.1 Key results

The study aimed to provide real-world evidence on the potential impact of co-administration of a statin together with sacubitril/valsartan on the risk of myotoxicity, hepatotoxicity, or acute pancreatitis in adult patients with HF. To address the primary and secondary objectives, data from seven European electronic healthcare databases with data on a source population of 41,383,318 patients were utilized in this study.

After the application of all exclusion criteria, a total of 922,199 patients were included in the study base. Of these patients at risk, cases with the outcome event of interest were identified and then controls were sampled. For each of the outcomes of interest, the number of patients at risk differed slightly, since they were not allowed to have a history of the outcome event of interest.

The key results for each outcome event are listed and discussed below by objective.

Myotoxicity

Primary objective

Across all databases, a total of 2,634 cases of myotoxicity and 200,556 matched controls were included in the pre-COVID period. The meta-analysis showed no significant association between concomitant use of sacubitril/valsartan and statins and myotoxicity in the fixed-effects model for the lowest exposed scenario ($OR_{adjusted}$ 1.17, 95% CI 0.86-1.58) in the random-effects model ($OR_{adjusted}$ 1.21, 95% CI 0.88-1.66) compared to use of statins alone. Two databases had zero exposure to sacubitril/valsartan among cases and contributed an OR of <0.01 to the fixed-effects model. Additionally, one subset of PHARMO had an adjusted OR below one whereas seven other databases showed an OR above one. The findings from SIDIAP should be considered with caution because of potential misclassification of sacubitril/valsartan and statin use at index date. However, when the sensitivity analysis was conducted that excluded SIDIAP data from the meta-analysis, the adjusted ORs were almost the same and were 1.17 (95% CI 0.78-1.76) in the fixed-effects model for the lowest exposed scenario and 1.25 (95% CI 0.82-1.90) in the random-effects model.

Secondary objective 1– duration of use of sacubitril/valsartan

Analyses stratified by duration of concomitant use had only few cases in each database. Exposure of less than 30-day use of sacubitril/valsartan (short duration) concomitant with statins showed a statistically significant association with myotoxicity in the random-effects model ($OR_{adjusted}$ 2.37, 95% CI 1.31-4.30) compared to use of statins alone. However, this is based mostly on few cases in CPRD ($OR_{adjusted}$ 5.77, 95% CI 1.31-25.52), as databases with zero cases exposed to sacubitril/valsartan were disregarded in the random-effects model. In the fixed-effects model, the adjusted OR was elevated but not significant. In contrast, an opposite trend between increasing duration of concomitant use of sacubitril/valsartan and statins and the risk of myotoxicity was found in GePaRD as compared with the results of the meta-analysis. The CIs were wide and covered the null effect in GePaRD. The fixed-effect and random-effects models both show no significant association between medium and long duration of concomitant use of sacubitril/valsartan and statins at index date. In PHARMO without linked hospital data

an isolated adjusted OR of 20.09 (95% CI 1.66-243.54) for medium concomitant use of sacubitril/valsartan and the risk of myotoxicity was observed, based on one exposed case and two exposed controls, leading to a wide CI, this elevation was not observed in other databases. The results of SIDIAP should be considered with caution as exposure duration may have been misclassified as a result of setting dispensing dates to the first of the month.

Secondary objective 2 – recency of use of sacubitril/valsartan

No association between recent use of sacubitril/valsartan and statins and the risk of myotoxicity was found, but this was based on few exposed cases. In the random-effects model, the adjusted OR of myotoxicity for recent use of sacubitril/valsartan with statins compared to no concomitant use of sacubitril/valsartan and statins was 1.55 (95% CI 0.57-4.23), and the fixed-effects ORs were lower. The risk of myotoxicity for recent use varied between 0.74 (95% CI 0.10-5.35) in GePaRD and 2.48 (95% CI 0.59-10.42) in SIDIAP without linked hospital data. However, data from SIDIAP should be regarded with caution due to setting dispensing dates to the first of the month, resulting in potential misclassification of exposure.

Secondary objective 3 – specific types of statins

Concomitant use of sacubitril/valsartan and atorvastatin versus atorvastatin alone was not associated with myotoxicity ($OR_{adjusted}$ 0.90, 95% CI 0.58-1.41 for the lowest exposed scenario) in the fixed-effects model or ($OR_{adjusted}$ 1.02, 95% CI 0.64-1.61) in the random-effects model but was based on a few exposed cases. The random-effects model excluded information from four databases where there were no concomitant users of sacubitril/valsartan and atorvastatin. A variable pattern of database- or subset-specific adjusted ORs was shown. Seven databases or subsets had an adjusted OR below one and three others had an OR above one. The absence of evidence of the association of interest might be due to the small number of patients with concomitant exposure to sacubitril/valsartan and atorvastatin.

Concomitant use of sacubitril/valsartan and simvastatin versus simvastatin alone was not associated with myotoxicity in the fixed-effects model ($OR_{adjusted}$ 1.28, 95% CI 0.77-2.15 for the lowest exposed scenario) nor in random-effects model ($OR_{adjusted}$ 1.56, 95% CI 0.92-2.64). Similar to atorvastatin, four databases had no cases were exposed to sacubitril/valsartan that resulted in adjusted ORs of less than 0.01. There was one other database that had an adjusted OR below one whereas there were four databases or subsets that showed an OR above one.

Secondary objective 4 – dose of statins

No association was observed between concomitant use of sacubitril/valsartan and high dose of statins and the risk of myotoxicity ($OR_{adjusted}$ 1.02, 95% CI 0.70-1.48 for the lowest exposed scenario) compared to high dose of statins alone in the fixed-effects model nor in the random-effects model ($OR_{adjused}$ of 1.13 (95% CI 0.78-1.66).

Concomitant use of sacubitril/valsartan and low dose of statins versus low dose of statins alone elevated the risk of myotoxicity in the fixed-effects model using both the lowest and highest number of patients exposed to sacubitril/valsartan ($OR_{adjusted}$ 1.53, 95% CI 0.90-2.61 versus $OR_{adjusted}$ 1.53, 95% 0.98-2.40). This was due to the redacted number of cases exposed to sacubitril/valsartan and statin dose categories in CPRD, where the number of cases exposed to sacubitril/valsartan was changed from zero to one (lowest exposed scenario) or to four (highest exposed scenario) exposed cases. In the lowest exposed scenario 14 cases were exposed to sacubitril/valsartan whereas for the highest exposed scenario 20 cases were exposed. Changing

the number of cases concomitantly using sacubitril/valsartan did not change the risk of myotoxicity, but influenced the precision of the results (i.e., the CIs became narrower). The random-effects model of concomitant sacubitril/valsartan and low dose of statins showed an adjusted OR of 1.62 (95% CI 0.92-2.85). Database- or subset-specific ORs showed an inconsistent pattern as four databases or subsets had an adjusted OR below one and five databases had an OR above one and were all based on small numbers of exposed cases.

Sensitivity Analysis: using a more specific definition of myotoxicity

Using a more specific definition of myotoxicity, the exclusion of cases with only unspecific terms of myalgia resulted in an increase in the adjusted ORs for myotoxicity of 1.52 (95% CI 0.78-2.98) in the fixed-effects model for the lowest exposed scenario, and an adjusted OR of 1.93 (95% CI 0.95-3.92) in the random-effects model, compared to those from the primary analysis for the primary objective. This is consistent with non-differential misclassification that may be expected when false positive cases are included, which is more likely to be myalgia. However, in both analyses the CIs included the null-effect. When data from SIDIAP (which may suffer from misclassification of exposure) were excluded from this sensitivity analysis, the risk of myotoxicity associated with concomitant use of sacubitril/valsartan and statins increased to an adjusted OR of 2.48, 95% CI 1.01-6.11 in the fixed-effects model for the lowest exposed scenario. Noteworthy, GePaRD contributed almost exclusively to this analysis, with a small number of cases with concomitant use of sacubitril/valsartan and statins. Aarhus and both subsets of CPRD had no case that were concomitantly exposed to sacubitril/valsartan and statins resulting in zero weights in the random-effects model and an adjusted OR of 3.11 (95% CI 1.18-8.14).

Hepatotoxicity

Primary objective

A total of 329 cases of hepatotoxicity and 30,636 matched controls in the pre-COVID period were identified for inclusion in the analysis (based on lowest and highest count assumptions for redacted numbers of controls who were exposed to sacubitril/valsartan). Of cases of hepatotoxicity more than 75% were contributed by GePaRD. No association between concomitant use of sacubitril/valsartan and statins versus statins alone and hepatotoxicity was found in the fixed-effects model for the meta-analysis ($OR_{adjusted}$ 0.76, 95% CI 0.33-1.72; lowest exposed scenario) in the pre-COVID period. In SIDIAP with linked hospital data and GePaRD, the adjusted ORs were below one for two and four exposed cases out of 29 and 253 cases, respectively. The adjusted ORs for SIDIAP was 0.87 (95% CI 0.19-4.04) and for GePaRD 0.85 (95% CI 0.30-2.36). The random-effects model for the meta-analysis resulted in an adjusted OR of 0.86 (95% CI 0.37-2.01), based on these two databases. Four databases or subsets had cases who were not exposed to sacubitril/valsartan and were not included in the meta-analysis of the random-effects model. The findings from SIDIAP should be considered with caution because of potential misclassification of sacubitril/valsartan and statin use at index date. When the results from SIDIAP were excluded, the results of the analysis were driven by GePaRD and were similar to that of the primary analysis.

Secondary objective 1– duration of use of sacubitril/valsartan

There were insufficient numbers to analyze the effect of duration of concomitant sacubitril/valsartan and statin use in many databases, and results were heterogeneous. The

findings in the random-effects model were mainly driven by the results of GePaRD (short duration) and showed small elevations of risk but no statistical significance.

Secondary objective 2 – recency of use of sacubitril/valsartan

None of the databases included cases that were recently exposed to sacubitril/valsartan, and therefore the analysis could not be conducted.

Secondary objective 3 – specific types of statins

Cases of hepatotoxicity and matched controls from GePaRD and CPRD without linked hospital data were used for the analysis of atorvastatin. In CPRD, it seems that no case and control were concomitantly exposed to sacubitril/valsartan and atorvastatin, and consequently no results were presented. In GePaRD and SIDIAP with linked hospital data, there were no associations between concomitant use of sacubitril/valsartan and atorvastatin use and hepatotoxicity (GePaRD: $OR_{adjusted}$ 0.33, 95% CI 0.04-2.47; SIDIAP: $OR_{adjusted}$ 1.39, 95% CI 0.17-11.55) versus atorvastatin alone. Both analyses included one case that concomitantly used sacubitril/valsartan and atorvastatin, which indicates uncertainties in the result.

Data from Aarhus, SIDIAP with linked hospital data, and GePaRD could be included in the meta-analysis of concomitant sacubitril/valsartan and simvastatin use versus simvastatin alone and hepatotoxicity. No significant association was found. The results of the meta-analyses were mainly driven by the results of GePaRD and SIDIAP with linked hospital data, which included 152 cases and 14,519 matched controls of whom approximately one percent were concomitantly exposed to sacubitril/valsartan and simvastatin (GePaRD: $OR_{adjusted}$ 1.18, 95% CI 0.36-3.89; SIDIAP with linked hospital data: $OR_{adjusted}$ 3.53, 95% CI 0.37-33.71).

Secondary objective 4 – dose of statins

Of all databases or subsets (Aarhus, GePaRD, PHARMO, and both SIDIAP and CPRD subsets with linked hospital data), GePaRD and SIDIAP with linked hospital data had sufficient cases of hepatotoxicity exposed to sacubitril/valsartan and high dose of statins. No associations were found between patients concomitantly using sacubitril/valsartan and high dose of statins (GePaRD: $OR_{adjusted}$ 0.30, 95% CI 0.04-2.21; SIDIAP with linked hospital data: $OR_{adjusted}$ 1.05, 95% CI 0.22-5.02) versus high dose of statins alone and the risk of hepatotoxicity. The results of the meta-analysis included data from GePaRD and SIDIAP with linked hospital data. Three cases were concomitantly using sacubitril/valsartan and high dose of statins in GePaRD and SIDIAP, showing the lack of power.

No association was found between among patients concomitantly using sacubitril/valsartan and low dose of statins versus low dose alone and the risk of hepatotoxicity in the fixed-effects model ($OR_{adjusted}$ 1.00, 95% CI 0.31-3.17 and $OR_{adjusted}$ 0.97, 95% CI 0.30-3.06) for the lowest and highest exposed scenario, respectively. No meta-analysis of the random-effects was performed as the results were only driven by the results of GePaRD ($OR_{adjusted}$ 1.24, 95% CI 0.37-4.08), and hence produced equal results.

Acute pancreatitis

Primary objective

Across nine databases or subsets (PHARMO without linked hospital data was not included as there were less than five cases), a total of 1,265 cases of acute pancreatitis and 115,042 matched controls in the pre-COVID period were included in the analysis. Of these cases, 13 were

concomitantly exposed to sacubitril/valsartan and statins. The fixed-effects model for the meta-analysis showed no association between concomitant use of sacubitril/valsartan and statins and acute pancreatitis ($OR_{adjusted}$ of 0.82 95% CI 0.47-1.42 – same values for lowest and highest exposed scenario). Four databases or subsets had no concomitant exposure to sacubitril/valsartan and statins. Three other databases or subsets had an adjusted OR below one whereas two other databases showed ORs above one. The adjusted OR was nearly one when pooling was conducted with a random-effects model (0.98, 95% CI 0.55-1.72). The sensitivity analysis where the results from SIDIAP were excluded from the meta-analysis showed similar results as that of the primary analysis ($OR_{adjusted}$ 0.82, 95% CI 0.45-1.49 in the fixed-effects model for both exposed scenarios; $OR_{adjusted}$ 1.01, 95% CI 0.54-1.87 in the random-effects model).

Secondary objective 1– duration of use of sacubitril/valsartan

The association between duration of concomitant use of sacubitril/valsartan and statins and the risk of acute pancreatitis showed inconsistent patterns in the meta-analysis. Patients with 31 to 90 days (medium duration) of concomitant sacubitril/valsartan and statin use prior to index date showed a statistically significant association between this medium duration of use and the risk of acute pancreatitis, using the random-effects model ($OR_{adjusted}$ 4.37, 95% CI 1.35-14.17). In this random-effects model data from Aarhus, GePaRD, HSD, PHARMO with linked hospital data, and both subsets of CPRD were not included because no cases were exposed to sacubitril/valsartan. The fixed-effects models that include these databases, did not show an increased risk for medium duration of concomitant use of sacubitril/valsartan and statins versus non-use of sacubitril/valsartan. This suggests that leaving databases with single zero-counts results out of the random-effects model biased results towards an increased risk of acute pancreatitis. The number of cases and controls with medium duration of concomitant sacubitril/valsartan and statin use was very small in the databases or subsets, resulting in wide CIs which were also overlapping each other, and therefore these results should be interpreted with caution. An increased risk of acute pancreatitis and medium duration of concomitant sacubitril/valsartan and statin use was found in ARS and both subsets (without and with linked hospital data) of SIDIAP. The results of SIDIAP should be considered with caution as patients may have been defined as exposed at index date while there were not exposed to sacubitril/valsartan or should have been allocated to another exposure category than medium duration of use.

Secondary objective 2 – recency of use of sacubitril/valsartan

A statistically significant association between recent use of sacubitril/valsartan and statins and the risk of acute pancreatitis was found for recent use but not for concomitant use. The fixed-effects model from the meta-analysis showed an adjusted OR of 2.26 (95% CI 1.00-5.10) for the lowest exposed scenario and 2.61 (95% CI 1.12-6.07) in the random-effects model. The analysis was mainly driven by the findings from ARS, GePaRD, and SIDIAP without linked hospital data, which all provided the largest number of cases and controls, that is three cases who were recently exposed to sacubitril/valsartan in ARS, two cases in GePaRD, and one case in SIDIAP without linked hospital data. As the results of the single zero-counts databases or subsets were disregarded in the random-effects model, the risk of acute pancreatitis was higher than using the fixed-effects model. Recent users discontinued their treatment with sacubitril/valsartan more than eight days before the index date, at the latest, by which time the drugs should be eliminated [the estimated half-life of valsartan is 13.6 hours, that of sacubitril

(prodrug) 6.0 hours, and for sacubitrilat (activated form) 13.0 hours (Ayalasomayajula et al 2018)].

Secondary objective 3 – specific types of statins

No statistically significant association was found between sacubitril/valsartan and atorvastatin use versus atorvastatin alone and acute pancreatitis in the fixed-effects model for the lowest and highest exposed scenario ($OR_{adjusted}$ 0.91, 95% CI 0.43-1.93) and in the random-effects model ($OR_{adjusted}$ 1.29, 95% CI 0.59-2.80). There were three databases or subsets that did not have cases with concomitant use of sacubitril/valsartan and atorvastatin. Including these three databases or subsets led to four databases or subsets with an adjusted OR below one, and four databases or subsets with an OR above one. Despite the existence of a pharmacokinetic interaction between sacubitril/valsartan and atorvastatin, no statistically significant association between concomitant use of sacubitril/valsartan and atorvastatin and acute pancreatitis was observed. The small number of patients with concomitant exposure to sacubitril/valsartan and atorvastatin likely contributed to this finding.

There was no association between concomitant use of sacubitril/valsartan and simvastatin versus simvastatin alone and acute pancreatitis in the fixed-effects model for the lowest exposed scenario ($OR_{adjusted}$ 1.01, 95% CI 0.42-2.45). No meta-analysis of the random-effects model was performed, because the potential results of this model will be the same as the results of GePaRD. This is because all other databases showed no information on concomitant use of sacubitril/valsartan and simvastatin. The results of both models are consistent with the studies examining the effects of sacubitril/valsartan on the pharmacokinetics of simvastatin and its active metabolite (Ayalasomayajula et al 2017, Ayalasomayajula et al 2018).

Secondary objective 4 – dose of statins

No statistically significant association was found between concomitant sacubitril/valsartan use and acute pancreatitis ($OR_{adjusted}$ 0.94, 95% CI 0.48-1.82) for the lowest and highest exposed scenario of the fixed-effects model and for the random-effects model ($OR_{adjusted}$ 1.17, 95% CI 0.59-2.33) in users of high dose of statins. In 4 databases or subsets no cases were exposed to sacubitril/valsartan. Besides these, two others had also an adjusted OR below one, whereas there were 3 databases or subsets with an OR above one.

For low dose of statins (cases and controls from PHARMO without linked data were not included), no associated risk of acute pancreatitis was found in concomitant users of sacubitril/valsartan in the fixed-effects model for the lowest exposed scenario ($OR_{adjusted}$ 0.72, 95% CI 0.27-1.93). All databases or subsets showed an adjusted OR of <0.01, apart from GePaRD where the OR was 0.88. The random-effects model was only based on GePaRD data, because all other databases had no concomitant users of sacubitril/valsartan and low dose of statins, and therefore a meta-analysis of the random-effects model was not needed.

Sensitivity analysis: Impact of the COVID-19 pandemic

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 of all three outcome events, which had a study end date of December 31, 2019. The COVID-19 pandemic and change in healthcare utilization had no effect on the results of this study. Due to the longer period of follow-up, this sensitivity analysis had more power.

11.2 Limitations

This study has several limitations.

For all databases, it should be noted that the primary purpose of data collection is for patient management or administration, it was not collected primarily for medical research.

Databases from different healthcare settings and with heterogeneous vocabularies for coding of diagnoses were used for these analyses. The codes were mapped using the Unified Medical Language System Meta-thesaurus and refined with the database partners during the quality reviews. Differences in the granularity of coding systems (i.e., between ICD-9, ICD-10, ICPC, and READ) were present. In spite of using a common protocol, a common data model and common analytics, differences due to the provenance of data (hospital based in Denmark (Aarhus) and Italy (ARS), versus only primary care data in HSD, or both in other databases, or claims data as used in GePaRD), were not avoidable, which may lead to differences in false positive or negative rates. Heterogeneity across databases also existed because of differences in the information they hold: GePaRD and ARS do not contain laboratory test results, and ARS does not capture diagnosis information from the outpatient setting but does contain diagnoses from the emergency room and hospital admissions. In GP databases information relies on reporting back of diagnoses made by specialists, which may lead to misclassification if information is not shared, delayed, or interpretated differently. This is the rationale why databases between those that could link to hospital data and those that cannot, were split. In databases that could link to hospital data, recordings of diagnoses by GPs were present in both the GP and GP+hospital subsets. GPs may record a diagnosis based on their knowledge and experiences or communications with specialists, instead of the diagnosis being made directly by GPs.

For example, there are uncertainties in the READ codes for hepatotoxicity. READ codes for liver failure may also cover liver dysfunction by elevated liver enzymes in blood, a liver biopsy, or by imaging. Without further information from medical charts from specialists, the accuracy of GP diagnoses such as acute or chronic hepatotoxicity cannot be assessed.

In the present study exclusion criteria were applied at or in the seven days after the diagnosis date of hepatotoxicity (when an indicated hepatic morbidity was suggestive of another etiology, i.e., “other specified disorders of the liver”, including hepatitis C, or HIV, or biliary or alcohol-induced hepatotoxicity) to minimize that cases of acute hepatotoxicity due to other causal agents were included in the study. We cannot exclude the possibility of outcome misclassification.

The PHARMO database includes ICPC coding in the GP data, which is less granular than the ICD-10 or READ coding used in other databases. To compensate for that, additional text evaluation was applied to comments reported alongside the higher-level codes. Using this method, ICD-10 codes were assigned to the corresponding records, as far as the data allowed. Comparisons of ORs between subsets with linked hospital data and without linked hospital data for CPRD, SIDIAP, and PHARMO in general showed higher ORs for the subset with linked hospital data, although in certain subsets ORs could not be obtained due to the limited number of exposed cases.

Outcome misclassification

A full validation of all cases was planned for this study, but the validation study demonstrated that most of the databases did not have access to adequate data to validate them (e.g., laboratory

values or discharge letters), resulting in large variations of the PPVs between automated and medical assessor assignment ([redacted]). Because of the lack of access to adequate source data to validate, it was agreed to not validate further and include all cases of myotoxicity, hepatotoxicity, or acute pancreatitis in the current study. False positive cases of myotoxicity, hepatotoxicity, or acute pancreatitis may therefore have been included in the study results. Although such misclassification is often non-differential (leading to underestimation) there is a possibility that physicians who were aware of the potential interaction may better monitor and/or diagnose concomitantly exposed patients. Validation could reduce the false positive rate but the findings of the validation study ([redacted]) showed that a substantial amount of (potentially) true cases would be excluded due to a significant proportion of critical clinical information being missing in the databases that could not be retrieved. This would have reduced the power substantially.

For myotoxicity, a sensitivity analysis was conducted of the primary analysis with a more specific definition of myotoxicity, namely by excluding cases for which myalgia was the sole identifying diagnostic code ([redacted]). This analysis using the more specific definition resulted in higher adjusted ORs, however, the number of cases, especially of cases exposed to sacubitril/valsartan, was too low to draw firm conclusions. Furthermore, in the CPRD, data is derived mainly from UK primary care general practices. Diagnosis made in this outpatient settings are mainly done by general practitioners, not by specialists or consultants. Thus, general practitioners in this setting are more unlikely to use specific read codes meant for complex diagnosis. This implies that definitive diagnosis of complex conditions such as hepatotoxicity using specific read codes is most likely captured/recorded following an inpatient assessment by specialists rather than in an outpatient (primary care) setting. Consequently, any missed specific read code for hepatotoxicity is likely to have minimal impact on our findings.

Exposure misclassification

Aarhus, ARS, PHARMO, SIDIAP, and GePaRD have information on dispensing of drugs from outpatient pharmacy data, the remaining databases have information on GP prescriptions only. None of these databases has information on actual drug intake. This means that there is no certainty whether the patient actually took the drug or not; however, this is likely to be non-differential between cases and controls prior to index date, which may lead to an underestimation of risks. Such misclassification may be differential, which may have biased the results in an unpredictable direction.

Information on the prescribed or dispensed dose was not available in all databases (Aarhus, ARS, GePaRD, and SIDIAP), therefore duration was estimated based on the dosing regimen for an adult recommended in the SmPC of the relevant medicinal product or DDDs. This may have led to misclassification of the duration of exposure and statin dose for the analyses evaluating recency of use of sacubitril/valsartan and dose of statins. Both misclassifications were likely to be non-differential and would have biased the results towards the null hypothesis. The direction of this misclassification cannot be predicted, and therefore the results of dose and recency of use should be reviewed in light of these limitations for these databases.

A few databases may not have fully captured (initial) specialist prescriptions (see Table 9-4), and therefore may have missed the first prescription of sacubitril/valsartan, leading to potential exposure misclassification of the duration of use. If the first prescription is missed, patients who

recently started sacubitril/valsartan may have been included in the non-exposed group, however, this probability is low.

In SIDIAP, only the month and year were known for the medications dispensed in SIDIAP, and not the exact dispensing day. For each dispensing date the first day of the month was imputed, when only month and year were known. Because of this the timing of exposure is misclassified, which may have an unknown direction of impact. To study the impact on the overall result (the primary objective), a sensitivity analysis (post-hoc) was conducted where SIDIAP data was excluded from the meta-analysis. Exclusion of SIDIAP did not change the ORs but did impact power.

Confounding and covariates

Matching was used to deal with the strongest confounders, age and sex, as well as calendar time and duration of statin use. After matching the distribution of characteristics was fairly well balanced between cases and controls. Other confounders were controlled by adjustment using a step-by-step approach (Schneeweiss et al 2009, Arah et al 2008). Due to low numbers of exposed cases, and the fact that confounders may not be measured completely, residual confounding cannot be excluded. For example, lifestyle factors such as smoking and alcohol use are not well captured, and the latter is a well-known risk factor for myopathy, hepatotoxicity, and acute pancreatitis.

The approach of using the *log (Bias)* for covariate selection for the comparative analyses has advantages as well as disadvantages, as compared to forward and backward selections, the main advantage being that it considers the association of covariate with both exposure and the outcome event of interest (VanderWeele 2019).

Pooling of data

The number of exposed cases was limited in each of the databases or subsets, except for GePaRD. The low number of cases was most pronounced in the analyses for the secondary objectives, when specific categories of exposure by duration of concomitant sacubitril/valsartan use, recency, type of statin and dose of statin were further examined. No cases were exposed to sacubitril/valsartan for some analyses in the smaller databases or subsets, which were excluded in the random-effects model. Because of the large number of controls that were sampled (up to 100), it was less likely that zero controls were exposed to sacubitril/valsartan.

Meta-analyses based on the fixed-effects model were conducted using the Mantel-Haenszel method (Robins et al 1986) for which calculation of the weight of each database requires knowledge about the actual number of cases and controls, which was challenging for small numbers in Aarhus and CPRD, since these were redacted. This required that sometimes a lowest exposed and highest exposed scenario analysis had to be performed for the fixed-effects model of the meta-analysis since the weight in this model is based on the absolute number of cases and controls. While the true OR is unknown, these scenarios provide an understanding of the variation when applying different assumptions. For the random-effects model, the DerSimonian and Laird method was used, using the SEs of the database specific estimates (DerSimonian et al 1986). Databases or subsets with single zero-counts received zero weight and were therefore excluded from the random-effects model. Both DerSimonian and Laird and Mantel-Haenszel have been found to produce biased effect estimates when evaluating rare events, especially in instances of double zero exposure encountered in many secondary analyses in this study

(Efthimiou 2018). Thus, the results of such analyses need to be interpreted with caution. Both fixed-effects and random-effects models were provided to transparently show the difference.

11.3 Interpretation

This study aimed to assess whether concomitant use of sacubitril/valsartan and statins versus statins alone, increased the risk of myotoxicity, hepatotoxicity, or acute pancreatitis in patients with HF. Database- or subset-specific analyses, for each of the three outcome events, were limited due to the low number of cases, as well as the low number of cases concomitantly exposed to sacubitril/valsartan and statins. In addition, there was an increased risk of chance findings due to multiplicity in terms of providing CIs for multiple outcomes and analyses.

Myotoxicity

No significant increased risk of myotoxicity for concomitant use of sacubitril/valsartan and statins was observed when comparing it with users of statin alone in the primary analysis. Results were comparable for the fixed- and random-effects models for pooling. The results of the meta-analysis were largely driven by GePaRD and SIDIAP. Excluding the results from SIDIAP from the primary analysis in the post-hoc sensitivity analysis showed similar ORs of 1.17 (95% CI 0.86-1.58) and 1.17 (95% CI 0.78-1.76) in the fixed-effects model for the lowest exposed scenario and adjusted ORs of 1.21 (95% CI 0.88-1.66) and 1.25 (95% CI 0.82-1.90) in the random-effects model. Although all databases or subsets had no case or limited number of cases concomitantly using sacubitril/valsartan and statins at index date, a two-fold increased risk of myotoxicity can be excluded. This observation was based on the upper confidence limits of both models from the meta-analysis of the primary analysis.

The pre-planned sensitivity analysis, excluding myalgia cases only, from myotoxicity, showed a higher (non-significant) risk of myotoxicity for the primary analysis, including SIDIAP data (pooled $OR_{adjusted}$ from 1.17, 95%CI 0.86-1.58 to 1.52, 95% CI 0.78-2.98 for the lowest exposed scenario and pooled $OR_{adjusted}$ from 1.21, 95%CI 0.88-1.66 to 1.93, 95% CI 0.95-3.92 using the fixed- and random-effects model, respectively). When SIDIAP data were excluded from this sensitivity analysis the adjusted OR increased to 3.11 (95% CI 1.18-8.14) in the random-effects model, and increased to 2.48 (95% CI 1.01-6.11) in the fixed-effects model for the lowest exposed scenario. This may suggest an association between concomitant use of sacubitril/valsartan and statins and the risk of myotoxicity that is more specifically defined and not based on myalgia alone, although the associated risk was not observed for the highest exposed scenario from the fixed effects model. However, this analysis should be interpreted with caution due to the low number of cases (n=5) that were concomitantly exposed to sacubitril/valsartan and statins.

The secondary analyses focused on exploring the potential association of concomitant use of sacubitril/valsartan and statins further by investigating whether the duration of concomitant use, recency of use of sacubitril/valsartan, type and dose of statins, had an impact. This reduced the number of exposed in each exposure category substantially, resulting in an increased uncertainty around the ORs. No specific effects were found, although some isolated statistically significant associations were shown in some databases or subsets for some exposure categories, which were not consistent nor explainable. These analyses were all conducted using the broadly defined outcome of myotoxicity.

No statistically significant evidence of an association between myotoxicity and concomitant exposure to sacubitril/valsartan and atorvastatin compared to atorvastatin alone was observed. This corroborates the idea that any pharmacokinetic interaction between sacubitril and atorvastatin does not necessarily and directly imply a higher risk of muscular disorders. The lack of evidence of a higher risk with concomitant use of sacubitril/valsartan and simvastatin also indicates against the existence of the risk of broadly defined myotoxicity. Although there is an inconsistent pattern in the risk of myotoxicity for concomitant use of sacubitril/valsartan and simvastatin across databases, the results are in line with the studies that showed no pharmacokinetic interaction between sacubitril/valsartan and simvastatin or its active metabolite (Ayalasomayajula et al 2017, Ayalasomayajula et al 2018). A pharmacokinetic interaction exists between sacubitril/valsartan and atorvastatin but not between sacubitril/valsartan and simvastatin. Observing no association either with one or with other types of statins using broadly defined myotoxicity, points against the clinical significance of such a potential interaction.

Hepatotoxicity

There was no association between concomitant use of sacubitril/valsartan and statins and the risk of hepatotoxicity when compared to statin use alone, using the fixed-effects model for the meta-analysis, in which all databases are included. No effects of duration of use and recency of sacubitril/valsartan or type and dose of statins were observed. Excluding SIDIAP data from the meta-analysis did not affect the primary analysis.

In this study, large proportion hepatotoxicity cases were not validated in GePaRD, it seems that the confirmation algorithm selected certain cases of hepatotoxicity, even though GePaRD did not have recorded liver enzyme values. With a limited number of cases of hepatotoxicity exposed to sacubitril/valsartan in the present study, a three-fold increased risk for hepatotoxicity was excluded.

Acute pancreatitis

No association between concomitant use of sacubitril/valsartan and statins and an increased risk of acute pancreatitis was found when comparing it with users of statin alone. This was consistent for the fixed- and random-effects models. When the results from SIDIAP were excluded, the weights of the other databases increased, however, the findings of this analysis were similar to the results of the primary analysis. Although all databases or subsets had no case or limited number of cases concomitantly using sacubitril/valsartan and statins at index date, a two-fold increased risk of acute pancreatitis can be excluded with the acquired sample size.

No validation of cases of acute pancreatitis was performed because almost all potential cases were classified as unconfirmed in the validation study ([redacted]) due to the lack of access to adequate data (i.e., laboratory tests/results (amylase and/or lipase), symptoms, diagnostic imaging tests and/or results). However, 65% to 100% of cases with acute pancreatitis in the present study were identified in hospital data in the databases (GePaRD and ARS) that contributed the most to the meta-analysis. It is most likely that these cases had laboratory tests and diagnostic imaging to diagnose acute pancreatitis. In addition, the medical assessor assessment showed that 75% to 100% were confirmed cases, although small numbers of cases were validated in GePaRD and ARS ([redacted]). This suggest that actual cases of acute pancreatitis were included in the study, and it is not conceivable that the results will change that much.

A statistically significant association was found for medium duration (i.e., 31 to 90 days prior to index date) of concomitant use of sacubitril/valsartan with statins and an increased risk of acute pancreatitis, using the random-effects model. This finding was not observed in the fixed-effects model where cases and controls from six other databases or subsets were included. This suggests that the results of the random-effects model were biased towards an increased risk of acute pancreatitis when databases with single zero-counts were ignored. None of the databases contributed data to all three categories of sacubitril/valsartan duration, but for the analysis with medium duration only data from ARS and both subsets of SIDIAP were included, which all showed risk effects in the same direction. The results of SIDIAP should be considered with caution as patients may have been wrongly defined as exposed at index date if their first dispensing of sacubitril/valsartan occurred in the same month as the index date or were incorrectly categorized as medium duration of use.

Recent use of sacubitril/valsartan showed also a statistically significant increased risk of acute pancreatitis, using the fixed- and random-effects model. In ARS, GePaRD, and SIDIAP without linked hospital data, which all showed an increased risk of acute pancreatitis, the analyses included overall six cases who discontinued treatment with sacubitril/valsartan more than eight days before the index date, at the latest, by which time the drugs should be eliminated (the estimated half-life of valsartan is 9.9 hours and that of sacubitril (prodrug) 1.4 hours, and for sacubitrilat (the active metabolite of the prodrug sacubitril) 11.5 hours (Entresto CDS/USPI)). It is anticipated that at the time of the event, patients were likely on single treatment with statin, as sacubitril/valsartan should have been eliminated based on their half-lives. The clinical manifestations of acute pancreatitis may sometimes start insidiously, and some days may elapse before the diagnosis can be established. Vomiting and poor oral intake are frequent and can lead to dehydration and electrolyte disturbances, which are to be avoided in HF patients. Prescribers of sacubitril/valsartan were likely more familiar with it than with the standard of care at that time and may therefore have been more cautious and willing to discontinue sacubitril/valsartan as soon as those manifestations appeared, compared with other medications. These discontinuations, in turn, may have occurred some days before the diagnosis of acute pancreatitis was established, reflecting in the recency that is addressed in this analysis. Regarding recent use, it is questionable whether the risk of the outcome event of interest among recent users of sacubitril/valsartan can be assessed in a nested case-control design. This design can be misleading for the analysis of lagged exposures such as recent use of sacubitril/valsartan (Deubner et al 2007).

All other secondary objectives (i.e., atorvastatin, simvastatin, high and low dose of statins) showed similar results as the primary analysis. As the sacubitril/valsartan users with a medium duration or recent use were small, the Bayesian method of meta-analysis should have been considered, but due to data protection regulations using patient-specific data from each database was not possible. The results of both meta-analyses should be interpreted with caution owing to the limited number of cases exposed to sacubitril/valsartan.

Based on patients' characteristics, patients with high dose statin use were almost exclusively atorvastatin users and patients with low dose were likely to be simvastatin users. The results of the meta-analysis including patients with sacubitril/valsartan and high dose of statin use reflect those from the analysis including patients with sacubitril/valsartan and atorvastatin.

Across the full study period, the ORs for myotoxicity, hepatotoxicity, or acute pancreatitis with concomitant use of sacubitril/valsartan and statins at index date were similar to those calculated

in all primary analyses, which were conducted in the pre-COVID period. The impact of the COVID-19 pandemic was limited on the relative measure of association. It has been shown that the number of primary diagnoses of HF reduced by 43 % compared with the number of previous years. On the hand, complications of COVID-19 infection affected the cardiovascular system and included mild myocardial injury to more severe conditions such as myocardial infarction, HF, and cardiogenic shock (Bashir et al 2023), and may have increased the number of patients with HF. This may have influenced the number of eligible patients in the study. The number of identified cases using statins at the date of the outcome event did not increase that much when at least one year of data were included. During the COVID-19 pandemic the healthcare utilization decreased, showing larger reductions among patients with less severe conditions (Moynihan et al 2021). This may have resulted in a reduction of prescribing statins and sacubitril/valsartan by physicians or the recording of outcome event of interest, but in this study patients with HF, a more severe condition, were selected. It is therefore not likely that the healthcare utilization changed substantially in these patients.

The EU SmPC of sacubitril/valsartan recommends that "caution should be exercised when co-administering sacubitril/valsartan with statins". This recommendation was based on in vitro data. No previous observational studies have explored the interaction between sacubitril/valsartan and statins and the risk of myotoxicity, hepatotoxicity, or acute pancreatitis, which makes it challenging to put these results into clinical context. Regular monitoring is warranted when treatment with sacubitril/valsartan is initiated in patients starting treatment with statins at the same time or patients at risk for these three outcome events.

11.4 Generalizability

All databases used in this study comply with EU guidelines (European Commission 2022) 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 (Catalonia, Spain), and the CPRD (UK) have been shown to be representative of the general populations of these countries. All these listed countries are situated in Western Europe and, therefore, may not be generalizable to the entire EU.

The number of cases of myotoxicity, hepatotoxicity, or acute pancreatitis that were concomitantly exposed to sacubitril/valsartan and statins were limited especially considering the stratified secondary analyses, and therefore the results of each comparative analysis should be interpreted with caution.

11.5 Other

11.5.1 Data comparability across databases / reasons for differences in outcome events

There were differences between the databases in monitoring programs and related registration policies for the regular assessment of comorbid conditions. There was also variability in the types of data held within the database such as claims data requiring regular claims for chronic conditions in GePaRD, or exemptions from copayment for chronic conditions in ARS, which were both contrary to the other databases that used electronic healthcare records.

Differences between the databases were highlighted in the validation study (see below; Heintjes et al 2022).

Myotoxicity

In the absence of laboratory test results in hospital or GP databases, cases of myotoxicity were identified based on diagnoses recorded by specialists (hospital or outpatient) or GPs, respectively. Diagnosing myotoxicity in clinical practice can be challenging, particularly milder cases of myotoxicity, and are often related to alternative diagnoses or were unreported (Janssen et al 2020). Cases of myotoxicity were identified in all databases, but the reliance on those diagnoses were made on clinical grounds, best surrounded by a certain amount of uncertainty.

In the validation study it was shown that the use of different data sources influenced the validation of myotoxicity PPV ([redacted]). PHARMO was the only database that relied on text searches due to less granular ICPC coding system, and unilateral or localized myalgia due to exercise or other causes were excluded upfront, resulting in an increased specificity of myotoxicity detection. The PPV of myotoxicity in PHARMO was below 30%. Severe cases of myotoxicity such as rhabdomyolysis are rare and infrequently reported. In all databases rhabdomyolysis was rare, although ARS and SIDIAP cases of rhabdomyolysis were identified. These patients were likely to be admitted as an emergency, and ARS is the only database that includes this type of data. The PPV of myotoxicity was 100%.

Hepatotoxicity

Despite a lack of results from laboratory tests in the databases, cases of hepatotoxicity are mostly identified based on diagnoses by specialists, and consequently the number of cases were lower in primary care databases. The numbers of hepatotoxicity cases were lower in databases which included only primary care data, such as HSD, PHARMO, SIDIAP, and CPRD without linked hospital data, than in the other databases.

The diagnosis of hepatotoxicity is a complicated task due to a lack of reliable markers for use in general clinical practice, so the diagnosis is based on physicians' judgement. Diagnosis requires a high degree of suspicion, compatible chronology, awareness of the drug's hepatotoxic potential, the exclusion of alternative causes of liver damage, and the ability to detect the presence of subtle data that favors a toxic etiology to incriminate a specific therapy (Andrade et al 2007). Although determining the diagnosis by physicians was challenging, additional exclusion criteria were applied at or in the seven days after the diagnosis date of hepatotoxicity (an indicated hepatic morbidity suggestive of another etiology, i.e., "other specified disorders of the liver", including hepatitis C, or HIV, or biliary or alcohol-induced hepatotoxicity) to ensure that cases of hepatotoxicity were included in the study.

Acute pancreatitis

Acute pancreatitis is most likely to be diagnosed in a hospital setting, and therefore specific data related to its diagnosis (all related clinical symptoms, amylase and/or lipase tests, and diagnostic imaging) are not usually reported in primary care databases. This also applies to the management of acute pancreatitis. Patients with acute pancreatitis were more likely to be treated in a hospital setting due to the uncertainties around whether it was a mild or severe case. Data on clinical tests and diagnostic imaging from hospitals were not present, or were limited, in all databases, which may have resulted in an underestimated number of true cases of acute

pancreatitis. It is therefore likely that these cases were diagnosed by laboratory tests and diagnostic imaging ordered by physicians.

12 Other information

Not applicable.

13 Conclusion

The present study is the first to evaluate a potential drug-drug interaction between sacubitril/valsartan and statins and the risk of myotoxicity, hepatotoxicity, or acute pancreatitis using real-world data.

Overall, no association was found between concomitant use of sacubitril/valsartan and statins and an increased risk of myotoxicity, hepatotoxicity, or acute pancreatitis. No consistent pattern of database- or subset-specific risks was observed for any outcome event, which supports the overall finding that indicates no association. Furthermore, no evidence of an association was observed for any outcome event of interest and concomitant use of sacubitril/valsartan with atorvastatin or simvastatin, individually, and high or low dose of statins.

Statistically significant associations were found in some analyses for the secondary objectives investigating duration of use and recency of use; however, these results were based on very low numbers of cases concomitantly exposed to sacubitril/valsartan and statins and are more likely chance findings due to the multiplicity of comparisons.

Study findings should be interpreted with caution given the limitations of this real-world study.

14 References (available upon request)

Andrade RJ and Tulkens PM (2011) Hepatic safety of antibiotics used in primary care. J Antimicrob Chemother; 66:1431-46.

Andrade RJ, Robles M, Fernández-Castañer A, et al. (2007) Assessment of drug-induced hepatotoxicity in clinical practice: A challenge for gastroenterologists. World J Gastroenterol; 13(3): 329-40.

Arah OA, Chiba Y, Greenland S (2008) Bias Formulas for External Adjustment and Sensitivity Analysis of Unmeasure Confounders. Ann Epidemiol; 18: 637-46.

Ayalasomayajula S, Han Y, Langenickel T, et al (2016) In vitro and clinical evaluation of OATP-mediated drug interaction potential of sacubitril/valsartan (LCZ696). J Clin Pharm Ther; 41(4):424-31.

Ayalasomayajula S, Pan W, Han Y, et al (2017) Assessment of drug–drug interaction potential between atorvastatin and LCZ696, a novel angiotensin receptor neprilysin inhibitor, in healthy Chinese male subjects. Eur J Drug Metab Pharmacokinet; 42(2):309-18.

Ayalasomayajula S, Langenickel T, Pal P, et al (2018) Erratum to: Clinical Pharmacokinetics of sacubitril/valsartan (LCZ696): a novel angiotensin receptor-neprilysin inhibitor. Clin Pharmacokinet; 57:105-23.

Bashir H, Yildiz M, Cafardi J, et al (2023) A review of heart failure in patients with COVID-19. Heart Fail Clin; 19(2): e1-e8.

Benichou C (1990) Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol; 11: 272-6.

Bross ID (1966) Spurious effects from an extraneous variable. J Chron Dis; 19:637-47.

Catalan V, LeLorier J (2000) Predictors of long term persistence on statins in a subsidized clinical population. Value Health; 3(6):417-26.

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.

Cochrane Collaboration (2011) Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011. Section 9.5.2 Identifying and measuring heterogeneity Available from: <https://handbook-5-1.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm> (accessed 16 June 2021)

Cressman AM, Mcdonald EM, Fernandes KA, et al (2015) A population-based study of the drug interaction between clopidogrel and angiotensin converting enzyme inhibitors. Br J Clin Pharmacol; 80(4):662-9.

de Jong HJI, Kingwell E, Shirani A et al (2017) Evaluating the safety of β-interferons in MS. A series of nested case-control studies. Neurology; 88:2310-20.

Devarbhavi H (2012) An update on drug-induced liver injury. J Clin Exp Hepatol; 2: 247-9.

Devarbhavi H, Andrade RJ (2014) Drug-induced liver injury due to antimicrobials, central nervous system agents, and nonsteroidal anti-inflammatory drugs. Semin Liver Dis; 34(2):145-61.

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

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

Efthimiou O (2018) Practical guide to the meta-analysis of rare events. Evidence-Based Mental Health; 21:72-6.

European Commission (2022) eHealth: Digital health and care. EU Health Data Space. Available from https://health.ec.europa.eu/ehealth-digital-health-and-care/european-health-data-space_en (accessed 5 April 2024).

European Medicines Agency (2023) Revestine: EPAR – Risk-management-plan summary. Available from https://www.ema.europa.eu/en/documents/overview/revestive-epar-summary-public_en.pdf (accessed 17 July 2023).

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).

Fernandes V, Santos MJ, Antonio Pérez A (2016) Statin-related myotoxicity. Endocrinol Nutr; 63(5):239-49.

Frossard LJ, Steer ML, Pastor CM (2008) Acute pancreatitis. Lancet; 371: 143-52.

[redacted]

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.

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.

Janssen L, Allard NAE, Saris CGJ, et al (2020) Muscle toxicity of drugs: when drugs turn physiology into pathophysiology. Physiol Rev 100: 633-72.

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

Jobski K, Behr S, Garbe E (2011) Drug interactions with phenprocoumon and the risk of serious haemorrhage: a nested case-control study in a large population-based German database. Eur J Clin Pharmacol; 67:941-51.

Jones MR, Hall OM, Kaye AM, et al (2015) Drug-induced acute pancreatitis: a review. Ochsner J; 15(1):45-51.

Juurlink DN, Gomes T, Ko DT, et al (2009) A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. Can Med J; 180(7):713-8.

Juurlink DN, Gomes T, Mamdani MM, et al (2011) The safety of proton pump inhibitors and clopidogrel in patients after stroke. Stroke; 42:128-32.

Karp I (2013) Irrelevance of non-collapsibility in case-control studies. Epidemiology; 24(1):173-4.

[redacted]

Deubner DC, Roth HD, Levy PS (2007) Empirical evaluation of complex epidemiologic study designs: workplace exposure and cancer. J Occup Environ Med; 49(9):953-9.

Maldonado G and Greenland S (1993) Simulation study of confounder-selection strategies. Am J Epidemiol; 138(11):923-36.

Moynihan R, Sanders S, Michaleff ZA et al (2021) Impact of COVID-19 pandemic on utilisation of healthcare services: a systematic review. BMJ Open;11:e045343.

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.

Pearce N (2016) Analysis of matched case-control studies. BMJ; 352:i969.

Peduzzi (1996) A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol; 49(12):1373-9.

PHARMO (2019) Data Dictionary. Common data model specifications for Entresto feasibility study and progress reports for studies LCZ696B2014 and LCZ696B2015 Version 9.1, 1-Nov-2019.

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.

Pincus D, Gomes T, Hellings C, et al (2012) A population-based assessment of the drug interaction between levothyroxine and warfarin. Clin Pharmacol Ther; 92(6):766-70.

Richardson DB (2004) An incidence density sampling program for nested case-control analyses. Occup Environ Med; 61(12):e59.

Robins J, Greenland S, Breslow NE (1986) A general estimator for the variance of the Mantel-Haenszel odds ratio. Am J Epidemiol; 124:719-23.

Schelleman H, Bilker WB, Brensinger CM, et al (2008) Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: Interactions and the risk of hospitalization for gastrointestinal bleeding. Clini Pharmacol Ther; 84(5):581-8.

Schelleman H, Brensinger CM, Bilker WB, et al (2011) Antidepressant-warfarin interaction and associated gastrointestinal bleeding risk in a case-control study. PLoS ONE; 6(6):e21447.

Schneeweiss S, Rassen JA, Glynn RJ, et al (2009) High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology; 20(4):512-22.

[redacted]

[redacted]

Teschke R (2018) Top-ranking drugs out of 3312 drug-induced liver injury cases evaluated by the Roussel Uclaf Causality Assessment Method. Expert Opin Drug Metab Toxicol 14(11): 1169-87.

Turner RM and Pirmohamed M (2019) Statin-Related Myotoxicity: A Comprehensive Review of Pharmacokinetic, Pharmacogenomic and Muscle Components. J Clin Med; 9(1):22.

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.

Vandenbroucke JP, Pearce N (2012) Case-control studies: basic concepts. Int J Epidemiol; 41(5): 1480-9.

VanderWeele TJ (2019) Principles of confounder selection. Eur J Epidemiol; 34(3):211-9.

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.

Xu C, Furuya-Kanamori L, Zorzela L, et al (2021) A proposed framework to guide evidence synthesis practice for meta-analysis with zero-events studies. J Clin Epidemiol; 135:70-8.

Wang H and Chow SC (2007) Sample size calculations for comparing proportions. Wiley Encyclopedia Clin Trials; 1-11.

Wiley LK, Moretz JD, Denny JC, et al (2015) Phenotyping adverse drug reactions: Statin-related myotoxicity. AMIA Jt Summits Transl Sci Proc; 2015:466-70.

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