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Quantitative Safety & Epidemiology

NVA237 / Glycopyrronium bromide
Non-interventional Study Report
NVA237A2402T

Multinational, multi-database cohort study to assess adverse cardiovascular and cerebrovascular outcomes and mortality in association with inhaled NVA237 in Europe Final Report

Redacted Report

Author [redacted]

Document Status	Final
Date of final version of the study report	17-Nov-2017
EU PAS register number	ENCEPP/SDPP/5035

NIS Report Template Version 2.0 August-13-2014

PASS information

Title	Multinational, multi-database cohort study to assess adverse cardiovascular and cerebrovascular outcomes and mortality in association with inhaled NVA237 in Europe –Final Report
Version identifier of the Final report	Version 1.0 (final)
Date of last version of the final report	17 November 2017
EU PAS register number	ENCEPP/SDPP/5035
Active substance	Glycopyrronium bromide (R03BB06)
Medicinal product	Seebri® Breezhaler®, Tovanor® Breezhaler®, Enurev® Breezhaler®
Product reference	NVA237
Procedure number	Seebri Breezhaler: EMEA/H/C/0002430 Tovanor Breezhaler: EMEA/H/C/0002690 Enurev Breezhaler: EMEA/H/C0002691
Marketing authorization holder	Novartis Europharm Ltd
Joint PASS	No
Research question and objectives	Use of inhaled anticholinergics has been associated with an increased risk of cardiovascular and cerebrovascular events. In the context of the NVA237 marketing application in Europe, the Committee for Medicinal Products for Human Use (CHMP) required the conduct of a post-authorization safety study (PASS) to assess the association between the use of NVA237 and cardiovascular and cerebrovascular events. The objectives of this study are to assess the incidence rates and relative risks of 1) cardiovascular and cerebrovascular outcomes and 2) mortality among new users of NVA237 with COPD compared to new users of comparator drugs (long-acting antimuscarinic antagonists [LAMAs] excluding NVA237) or long-acting β_2 agonists (LABAs)
Country(-ies) of study	United Kingdom, Denmark, Italy, The Netherlands, Spain
Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	[redacted]
MAH contact person	[redacted]

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1 Abstract

Title

Multinational, multi-database cohort study to assess adverse cardiovascular and cerebrovascular outcomes and mortality in association with inhaled NVA237 in Europe – Final Report

Version and date

Version 1.0; 17 November 2017

Name and affiliation of main author:

[redacted]

Keywords

Chronic obstructive pulmonary disease, glycopyrronium bromide, long-acting muscarinic antagonist, long acting β2-agonist, safety

Rationale and background

NVA237 (glycopyrronium bromide) is a long-acting muscarinic antagonist (LAMA) which was approved in the European Union in September 2012 as maintenance bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease (COPD). In the context of the NVA237 marketing authorization application in 2012, the Committee for Medicinal Products for Human Use (CHMP) requested Novartis, the marketing authorization holder of NVA237, to conduct a post-authorization safety study (PASS) to examine cardio- and cerebrovascular safety concerns related to the use of NVA237.

Research question and objectives

To assess the risk of cardio- and cerebrovascular outcomes and mortality in patients using NVA237 compared to patients using LAMAs (excluding NVA237) or long-acting β2-agonists (LABAs).

Study design

Multinational, multi-database cohort study in new users of NVA237 vs. new users of two comparator drug classes (LABA, LAMA [other than NVA237]) with secondary use of data derived from various European health care databases.

Setting

The study is based on data derived from five European electronic health care databases, namely from The Netherlands (NL) (Integrated Primary Care Information Project [IPCI]), Italy (IT) (Health Search Database [HSD]), United Kingdom (UK) (The Health Improvement Network [THIN]), Denmark (DK) (Aarhus University Prescription Database [Aarhus]), and Spain (ES) (System d'Informació per al Desenvolupament de la Investigació en Atenció Primària [SIDIAP]).

This final report describes the results of 39 months of data collection, from 1st November 2012 until 1st February 2016.

Subjects and study size, including dropouts

All COPD patients aged 40 years or older with at least one year of database history, a first-time prescription/dispensing for NVA237, LABA, or LAMA (other than NVA237) and enrolled in the database during the study period (i.e., 01-Nov-2012 to 01-Feb-2016) were selected for inclusion. Follow-up time for each patient started at first-time prescription of NVA237, LABA, or LAMA (other than NVA237) (= index date) and ended at end of treatment, switch to/from/or add-on of other study drugs, end of study (i.e., date of database-specific data cut for the last interim report), death, or

disenrollment from the database. For calculation of incidence rates for the outcomes of interest, follow-up time was censored upon occurrence of the respective outcome.

Variables and data sources

The outcomes of interest were 1) Major adverse cardiovascular events (MACE) including myocardial infarction, stroke, and hospitalizations due to acute coronary syndromes and/or heart failure , 2) ischemic heart disease (IHD) including myocardial infarction or (unstable) angina pectoris, 3) cardiac arrhythmias (atrial fibrillation/flutter, atrioventricular (AV) block, premature depolarization, sick sinus, supraventricular tachycardia and ventricular arrhythmia including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes/Long QT syndrome), 4) cerebrovascular disorders (ischemic and hemorrhagic stroke, transient ischemic attack [TIA]) and 5) mortality (all-cause). In addition, demographic factors, lifestyle circumstances, concomitant medication use and history of underlying comorbidities were assessed at index date.

Results

During the overall study period three COPD cohorts were studied: new users of NVA237 (n=8,772), new users of LABA (n=17,890) and new users of LAMA (n=58,852).

All three exposure cohorts were comparable in terms of age distribution. The mean age at cohort inception was approximately 70 years. The proportion of males was similar in the LABA exposure cohort (63%) compared to the NVA237 (62%) and the LAMA (62%) cohort.

In the pooled dataset, history of COPD hospitalization in the year prior to the index date was present in 5.9% of NVA237, 4.0% of LABA, and 6.1% of other (non-NVA237) LAMA patients. In the pooled dataset, use of systemic corticosteroids for the treatment of COPD in the one year prior to the index date varied between the three exposure cohorts, ranging from 8.4 to 12.6%, while use of antibiotics for treatment of lower respiratory tract infection/COPD exacerbation in the year prior to the index date ranged from 18.4 to 21.1%. For those patients where COPD severity was assessed by spirometry, the majority of patients in the pooled dataset had either moderate (range 51.8-60.4%) or severe COPD (range 21.0-32.7%). The proportions of patients with very severe COPD were highest in the NVA237 (4.8%) and LAMA (3.4%) cohort and lowest in the LABA (2.3%) cohort.

Amongst all exposure cohorts, a substantial proportion of patients presented with cardiovascular (range 60.1-61.6% pooled dataset) and/or cerebrovascular (8.9-9.7%) co-morbidity at baseline. Also, the number of patients with a history of diabetes mellitus and hyperlipidemia was high (19.9-20.7%). These important underlying (cardiovascular, cerebrovascular and metabolic) comorbidities were mirrored by high use of antihypertensive (pooled 61.6-64.7%), lipid lowering (pooled 42.0-44.8%), antithrombotic (pooled 37.0-40.9%) and antidiabetic medications (pooled 16.3-17.1%) across exposure cohorts.

The median duration of follow-up on treatment was short (95 days for NVA237, 62 days for LABA and 91 days for non-NVA237 LAMA in the pooled dataset) and the number of events was low (<3%). Among the pre-specified study end-points, events with the highest incidence of occurrence in the pooled dataset were mortality (range 42.3-46.5/1,000 patient-years [PY]) and MACE (25.8-46.5/1,000 PY).

In addition to crude hazard ratios (HR), adjusted hazard ratios were calculated by two methods: (i) by including treatment and potential confounders as covariates in the outcome regression model, and (ii) via inverse probability of treatment weighting (IPTW). Because of the large number of covariates requiring adjustment and few events-per-variable for some end-points, the latter was considered as the main statistical model and HRs discussed below are referring to that model.

For all outcomes, the pooled adjusted HR estimates of NVA237 versus LABA or versus LAMA were close to or below 1.

The relative risk for NVA237 exposed patients (as defined by HR) to develop MACE in comparison to LABA use was 0.61 (95% confidence interval [CI] 0.47-0.79) with similar findings in comparison to LAMA use (HR 0.56, 95% CI 0.44-0.71). The HR for NVA237 exposed patients for IHD events was

0.74 (95% CI 0.46-1.17) in comparison to LABA use and HR 0.67(95% CI 0.46-0.99) in comparison to LAMA use.

The HR for NVA237 exposed patients for cardiac arrhythmia in comparison to LABA use was 0.84 (95% CI 0.62-1.14). This risk was 0.69 (95% CI 0.53-0.90) in comparison to LAMA use.

The HR for cerebrovascular events in NVA237 exposed patients, in comparison to LABA exposed patients was 0.82 (95% CI 0.54-1.23) with similar results for the comparison with LAMA (HR 0.80, 95% CI 0.54-1.19).

No association between use of NVA237 and risk of mortality was observed with an HR in comparison to LABA of 0.88 (95% CI 0.71-1.11) and a HR in comparison to LAMA of 0.95 (95% CI 0.79-1.15).

For all of these endpoints, the meta-analysis of the HRs provided similar estimates as for the pooled analysis, both for the random- and fixed-effect model.

Sensitivity analyses did not show important differences compared to the main analyses. Effect modification by gender was suggested where the inverse association between use of NVA237 and risk of MACE and IHD was larger in absolute magnitude in women compared with men.

In the sensitivity analysis using complete follow-up time in the pooled data, for all outcomes the age-and-gender adjusted HRs shifted towards 1 compared to the HRs of the main analysis, both for the comparison of NVA237 with LABA and NVA237 with LAMA. Still, an inverse association between use of NVA237, in comparison to LABA (HR 0.80, 95% CI 0.66-0.96) and LAMA (HR 0.69, 95% CI 0.59-0.82) and risk of MACE remained.

Discussion

For this final report, more than 8,700 patients treated with NVA237 were included providing more than 4,200 person-years of follow-up. Of the patients that were included in this study, the majority had moderate COPD and in general, the proportion of patients with very severe COPD tended to be the lowest in the LABA cohort.

The median duration of follow-up on treatment was short resulting in a low number of events. Events with the highest incidence of occurrence in the pooled dataset, in all exposure cohorts, were mortality and MACE

We observed no association between NVA237 and all-cause mortality and cerebrovascular events. A negative association between the use of NVA237 and risk of MACE (in comparison to LABA and LAMA), IHD and cardiac arrhythmia (in comparison to LAMA) was observed. This inverse association must be interpreted with caution. Because it does not seem very likely that this association represents a true protective biological effect, it may be an indication of residual confounding by unmeasured covariates, or other form of bias in favor of NVA237. From a pharmacological point of view, it is unlikely that NVA237 protects against cardiovascular events. Channeling bias where GPs are more reluctant to prescribe new drugs in patients at risk of cardiovascular endpoints is more likely but this is not confirmed by baseline characteristics as the prevalence of cardiovascular and cerebrovascular comorbidity is comparable amongst exposure cohorts. The product labels of glycopyrronium bromide, LAMA and LABA advice against the use of these drugs in patients underlying cardiovascular conditions. The negative association between use of NVA237 and risk of cardiovascular events can thus not be explained by a difference in label, however, instruction guidelines might be better adhered to for new drugs.

Conclusion

We observed no association between NVA237 and all-cause mortality and cerebrovascular events. The negative associations between the use of NVA237 and risk of MACE (in comparison to LABA and LAMA), IHD and cardiac arrhythmia (in comparison to LAMA) must be interpreted with caution, as it may be an indication of bias in favor of NVA237.

Marketing Authorization Holder(s)

Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, United Kingdom

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

[redacted]

2 List of abbreviations

AB	Antibiotics
ACE	Angiotensin-Converting Enzyme
ACS	Acute Coronary Syndrome
ADM	Administrative
(A)MI	(Acute) Myocardial Infarction
AP	Angina Pectoris
ATC	Anatomical Therapeutic Chemical Classification system
AUH	Aarhus University Hospital
AV	Atrioventricular
BNF	British National Formulary
BPH	Benign Prostatic Hyperplasia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
DK	Denmark
HER	Electronic Health Record
EMA	European Medicines Agency
EMC	Erasmus Medical Center
ES	Spain (Espania)
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GFR	Glomerular Filtration Rate
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practice
HF	Heart Failure
HSD	Health Search Database
HR	Hazard Ratio
ICD-9	International Classification of Disease, 9th revision
ICD-10	International Classification of Disease, 10th revision
ICPC	International Classification of Primary Care
ICS	Inhaled Corticosteroid
IHD	Ischemic Heart Disease
IPCI	Integrated Primary Care Information
IPTW	Inversed Probability Weighting
IQR	Interquartile Range
IR	Incidence Rate
IT	Italy
LABA	Long-Acting β2 Agonist

LAMA	Long-Acting Muscarinic Antagonist
LRTI	Lower Respiratory Tract Infection
LTRA	Leukotriene Receptor Antagonist
MACE	Major Adverse Cardiovascular Event
MR	Medical Record
Nap	Not Applicable
NL	The Netherlands
NOS	Not otherwise specified
NS	Not Significant
NSAID	Nonsteroidal Anti-inflammatory Drug
OTC	Over-the-counter
PS	Propensity Score
PAI	Platelet Aggregation Inhibitor
PAS	Post-Authorization Safety
PASS	Post-Authorization Safety Study
PDE	Phosphodiesterase
PPV	Positive Predictive Value
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PY	Patient-Year
RCT	Randomized Controlled Trial
RRE	Remote Research Environment
SABA	Short-Acting β2 Agonist
SAC	Scientific Advisory Committee
SAMA	Short-Acting Muscarinic Antagonist
SD	Standard Deviation
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SmPC	Summary of Product Characteristics
SSRI	Selective Serotonin Reuptake Inhibitor
SVT	Supraventricular Tachycardia
TIA	Transient Ischemic Attack
THIN	The Health Improvement Network
UK	United Kingdom
UMLS	Unified Medical Language System
WHO	World Health Organization

3 Investigators

Role	Name
Project lead	[redacted]
Principal investigators (PI)	[redacted]
Sub-investigators	[redacted]

4 Other responsible parties

Role	Name
Marketing authorization holder contact person	[redacted]
Scientific advisory committee (SAC)	[redacted]

5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	01-Nov-2012	01-Nov- 2012	None
Registration in the EU PAS register	25-Oct-2013	25-Oct-2013	None
End of data collection for Interim Report 1	IPCI (NL): 01-Jul-2013; Aarhus (DK): 31-Dec-2012; THIN (UK): Jan 2013	IPCI (NL): 01-Jul-2013; Aarhus (DK): 31-Dec-2012; THIN (UK): 30-May-2013	None
Interim Report 1	With PSUR 2	10-Dec-2013	None
End of data collection for Interim Report 2	IPCI (NL): 01-May-2014; Aarhus (DK): 31-Dec-2013; HSD (IT): 31-Dec-2013; SIDIAP (ES): 31-Dec-2013; THIN (UK): 01-Jan-2014	IPCI (NL): 01-May-2014; Aarhus (DK): 31-Dec-2013; HSD (IT): 31-Dec-2013; SIDIAP (ES): 31-Dec-2013; THIN (UK): 31-Dec-2013	None
Interim Report 2	Nov-2014	10-Nov-2014	None

Milestone	Planned date	Actual date	Comments
End of data collection for Interim Report 3	IPCI (NL): 01-Mar-2015; Aarhus (DK): 31-Dec-2014; HSD (IT): 31-Dec-2014; SIDIAP (ES): 31-Dec-2014; THIN (UK): 01-Mar-2015	IPCI (NL): 01-Mar-2015; Aarhus (DK): 31-Dec-2014; HSD (IT): 31-Dec-2014; SIDIAP (ES): 31-Dec-2014; THIN (UK): 01-Mar-2015	None
Interim Report 3	Nov-2015	4-Nov-2015	None
End of data collection for Interim Report 4	IPCI (NL): 01-Feb-2016; Aarhus (DK): 31-Dec-2015; HSD (IT): 31-Dec-2015; SIDIAP (ES): 31-Dec-2015; THIN (UK): 01-Feb-2016	IPCI (NL): 01-Feb-2016 Aarhus (DK): 31-Dec-2015; HSD (IT): 31-Dec-2015; SIDIAP (ES): 31-Dec-2015; THIN (UK): 01-Feb-2016	None
Interim Report 4	Q4 2016	10-Nov-2016	None
End of data collection for Final Study Report*	IPCI (NL): 01-Feb-2016 Aarhus (DK): 31-Dec-2015; HSD (IT): 31-Dec-2015; SIDIAP (ES): 31-Dec-2015; THIN (UK): 01-Feb-2016	IPCI (NL): 01-Feb-2016 Aarhus (DK): 31-Dec-2015; HSD (IT): 31-Dec-2015; SIDIAP (ES): 31-Dec-2015; THIN (UK): 01-Feb-2016 Final pooled analytical dataset available: 25-Aug-2017	None
Final Study Report	Q4 2017	17-Nov-2017	None

*Date from which the analytical dataset is completely available (European Medicines Agency 2012)

6 Rationale and background

In the context of the NVA237 marketing authorization, the Committee for Medicinal Products for Human Use (CHMP) requested Novartis to perform a post-authorization safety study (PASS) to determine the cardio- and cerebrovascular risk of inhaled NVA237.

Glycopyrronium bromide (NVA237) is a synthetic, quaternary ammonium, long-acting muscarinic antagonist (LAMA) that acts through competitive antagonism of acetylcholine at the muscarinic receptors. NVA237 is a dry powder formulation (44mcg delivered dose of glycopyrronium) developed as a once-daily inhalation treatment for patients with chronic obstructive pulmonary disease (COPD). COPD is characterized by a progressive decline in lung function which cannot be reversed by treatment. Bronchodilators are the mainstay of symptomatic management of COPD and include β_2 agonists, long-acting muscarinic antagonists (LAMAs), methylxanthines and phosphodiesterase-4 inhibitors, used alone or in combination (Pauwels et al 2001). NVA237 is indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

In 2008, based on data from a pooled analysis of 29 trials as well as results from a meta-analysis, concerns were raised on the cardio- and cerebrovascular safety of tiotropium, the first available LAMA (Lee et al 2008, Singh, Loke and Furberg 2008). A later meta-analysis also suggested an increased mortality in association with tiotropium (Michele, Pinheiro and Iyasu 2010). In January 2010, the FDA's public health alert on the use of inhaled tiotropium

was updated based on data from the UPLIFT study and updated meta-analysis (including the UPLIFT study) and the FDA stated that the available data no longer supported an association between the use of inhaled tiotropium Handihaler and an increased risk of stroke, heart attack or death from cardiovascular causes (Michele, Pinheiro and Iyasu 2010). However, the evidence on the safety of tiotropium remains conflicting and new concerns were raised based on two meta-analyses of randomized controlled trials (RCTs), showing an increased risk of mortality of inhaled tiotropium Respimat compared to placebo and a new user cohort study reporting an increased risk of cardiovascular endpoints (stroke, angina and myocardial infarction) in patients treated with tiotropium Handihaler vs. LABA (Singh et al 2011, Jara et al 2012, [redacted] Dong et al 2013). The TIOSPIR study, showed no increased risk of cardiovascular endpoints and mortality in patients treated with tiotropium Respimat compared to tiotropium Handihaler (Wise et al 2013).

7 Research question and objectives

To assess the risk of cardiovascular and cerebrovascular outcomes and mortality in COPD patients using NVA237 compared to COPD patients using LAMA (excluding NVA237) or LABA.

7.1 Main objective

To assess the incidence rates (IRs) and hazard ratios (HRs) of cardiovascular and cerebrovascular outcomes and of mortality among new users of inhaled NVA237 with COPD compared to new users of LAMA (non-NVA237) or new users of LABA in patients with COPD.

The outcomes of interest include:

- Major adverse cardiovascular events (MACE) including myocardial infarction and stroke, and hospitalizations due to acute coronary syndrome and/or heart failure
- Ischemic heart disease including myocardial infarction and (unstable) angina pectoris
- Cardiac arrhythmias (atrial fibrillation/flutter, atrioventricular (AV) block, premature depolarization, sick sinus, supraventricular tachycardia and ventricular arrhythmia including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes/Long QT syndrome)
- Cerebrovascular disorders (ischemic and hemorrhagic stroke and transient ischemic attack)
- Mortality

8 Amendments and updates to the protocol

Table 8-1 Protocol amendments

Number	Date	Section of study protocol	Amendment or update	Reason
1	29 May 2013	4 Abstract	Abstract was updated to reflect changes in the body of the protocol	Based on PRAC comments

Number	Date	Section of study protocol	Amendment or update	Reason
2	29 May 2013	6 Milestones	End of data-collection: 30-Apr-2017 Final study report: maximum 5 years after launch of NVA237	Based on PRAC comments
3	29 May 2013	9.2.2 Study period	Removed “maximum of 5 years following the first launch” End of data collection added Added that the progress of identification of NVA237 within all databases will be monitored closely Launch dates updated	Based on PRAC comments
4	29 May 2013	9.2.3 In - and exclusion criteria	Missing age and gender has been added as exclusion criteria	Based on PRAC comments
5	29 May 2013	9.3.1 Endpoints of interest and Annex 2 – Validation algorithm	Clarified how mortality data will be collected Clarification on validation of outcomes added (= blinded to exposure + free text validation algorithms added to protocol)	Based on PRAC comments
6	29 May 2013	9.3.5 Demography, life style factors and comorbidity	Atrial fibrillation and flutter have been added to the list of underlying comorbidity Further details on collection of hospitalization data have been added.	Based on PRAC comments
7	29 May 2013	9.4 Data sources	Details on the average follow-up time per patient (2.5 – 11 years) and completeness of data of the databases have been added.	Based on PRAC comments
8	29 May 2013	9.5 Study Size	A sample size justification, together with a range of sample sizes at different risk levels has been added	Based on PRAC comments

Number	Date	Section of study protocol	Amendment or update	Reason
9	29 May 2013	9.6 Data management	The data management section in the protocol was expanded to include further details on the methods used for pooling of data	Based on PRAC comments
10	29 May 2013	9.7 Data analysis	This section has been updated as following: clarification of analysis in case of 3-fold increase of IR of the different outcomes adding hospitalization for COPD exacerbation as confounder additional details and codes in relation to the propensity score have been added list of endpoints has been clearly defined further details on sensitivity analyses and stratified analyses have been added information on handling of missing data was updated	Based on PRAC comments
11	29 May 2013	Annex 3 – Event definitions	A definition of the codes used in the evaluation of MACE has been added	Based on PRAC comments
12	05 September 2013	7 Background	Results from more recent publications have been added and reference list has been updated accordingly (including Section 13)	More recent literature added
13	05 September 2013	9.2.3 In - and exclusion criteria	Clarified the plan for assessing the effect of non-cardiovascular life-threatening conditions on the final results	Based on PRAC comments (Sep-13)
14	05 September 2013	9.7 Data analysis	Clarified that ‘full analysis’ includes all details mentioned in section 9.7.2 Plan for stratified analysis in patients with or without non-cardiovascular life-threatening conditions was added	Based on PRAC comments (Sep-13)

Number	Date	Section of study protocol	Amendment or update	Reason
15	05 September 2014	Not applicable	Transcription of the entire protocol into the Novartis protocol template for non-interventional PASS	To follow Novartis-internal guidelines
16	05 September 2014	9.2.3 In - and exclusion criteria	Patients with COPD diagnosed (via disease codes) within 6 months after the first prescription of any of the exposure categories of interest will also be included within the study. Thus not only considering patients with COPD diagnosed prior to the first prescription of any of the exposure categories of interest	Based on comments from the Scientific Advisory Committee
17	05 September 2014	8.1 Main objective and 9.3.1 Endpoints of interest	Clarification that ventricular arrhythmia also includes AV block (this has been added to Annex 3 – event definition)	Based on comments from the Scientific Advisory Committee
18	05 September 2014	9.3.3 COPD and COPD severity	Manual validation has been clarified and use of spirometry has been limited to patients for whom date of spirometry and index date is less than 5 years	Based on comments from the Scientific Advisory Committee
19	05 September 2014	9.3.5 Demography, life style factors and comorbidity	Chronic kidney disease has been added to comorbidity	Based on comments from the Scientific Advisory Committee
20	05 September 2014	9.7 Data analysis	A sensitivity analysis will be conducted only considering the first treatment episode during follow-up in patients who are naïve to both NVA237 and all of the comparator drugs.	Based on comments from the Scientific Advisory Committee

Number	Date	Section of study protocol	Amendment or update	Reason
21	18 December 2014	8.1 Objective, 9.3.1 endpoints, 9.3.5 demography, 9.7 Data analysis, 9.7.1 Yearly analysis for study progress reports and yearly reports, Annex 3.1.5 and Annex 4.3	Cardiac arrhythmia as endpoint and as comorbidity has been clarified, based on the comments by PRAC	Based on PRAC comments/questions (Dec 2014)

9 Research methods

9.1 Study design

Multinational, multi-database, new-user cohort study with secondary use of data from five electronic health care databases in Europe, namely from The Netherlands (Integrated Primary Care Information [IPCI] Project), Italy (Health Search Database [HSD]), United Kingdom (The Health Improvement Network [THIN]), Denmark (Aarhus University Prescription Database [Aarhus {AUH}]) and Spain (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària [SIDIAP]); for further information about these databases, see Section 9.5 (‘Data sources and measurement’).

Since the start of data collection in November 2012 until the end of data collection (February 2016), follow-up data for the initially selected patients, as well as data for newly selected patients were retrieved from the annual updates of the aforementioned databases. However, it should be noted that patients selected for inclusion in the first interim analysis (report dated from December 2013) may have been excluded from the second, third or fourth interim analyses in cases where general practitioners (GPs) decided to discontinue contribution of patient data to the respective database or if practices changed their software and the minimum requirement of 1 year of database history was re-set. This occurrence is low and will not have an impact on the safety data as the decisions made by the GPs are unrelated to drug exposure.

For this final analysis, patients with COPD were selected from the aforementioned databases; each patient was subsequently allocated to one of the following three new-user exposure cohorts: NVA237 or LABA or LAMA (excluding NVA237). Individuals from these exposure cohorts were followed from the start of the first prescription of NVA237, LABA or LAMA (excluding NVA237) until the end of treatment episode (+30 days), switching or add-on therapy (see Section 9.4.2 for details), end of the study period, disenrollment from the database or death, whichever came first. End of treatment was defined as the discontinuation of use of NVA237, LAMAs (excluding NVA237) or LABAs for the respective treatment cohorts. For the calculation of incidence rates for the various endpoints of interest, follow-up time was censored upon occurrence of the endpoint. As multiple endpoints were studied, different follow-up times were used per patient and per endpoint.

9.2 Setting

The study used secondary data from five European electronic health care databases (from The Netherlands, Italy, UK, Denmark and Spain). This final report presents results for 39 months of patient accrual, namely from [redacted] (note: not all data sources had a total of 39 months of patient accrual; for more details by database, see Section 9.5).

This study covers data starting from the date of the first launch of NVA237 in the five European countries (i.e., Denmark and UK in November 2012) up to one year after inclusion of the 3,000th patient in the NVA237 new-user cohort. Based on the size of the databases and the expected market uptake of NVA237, the end of study was estimated to be approximately 4.5 years after drug launch, i.e., around April 2017 (estimated 1 year follow-up date of 3,000th patient enrolled in the NVA237 cohort).

The launch dates of NVA237 in the countries of the different databases are shown below:

Table 9-1 Launch dates for NVA237 in the five participating countries

Country	Launch date
Denmark	26 November 2012
Italy	15 April 2013
Netherlands	01 February 2013
Spain	15 April 2013
United Kingdom	02 November 2012

9.3 Subjects

9.3.1 In- and exclusion criteria

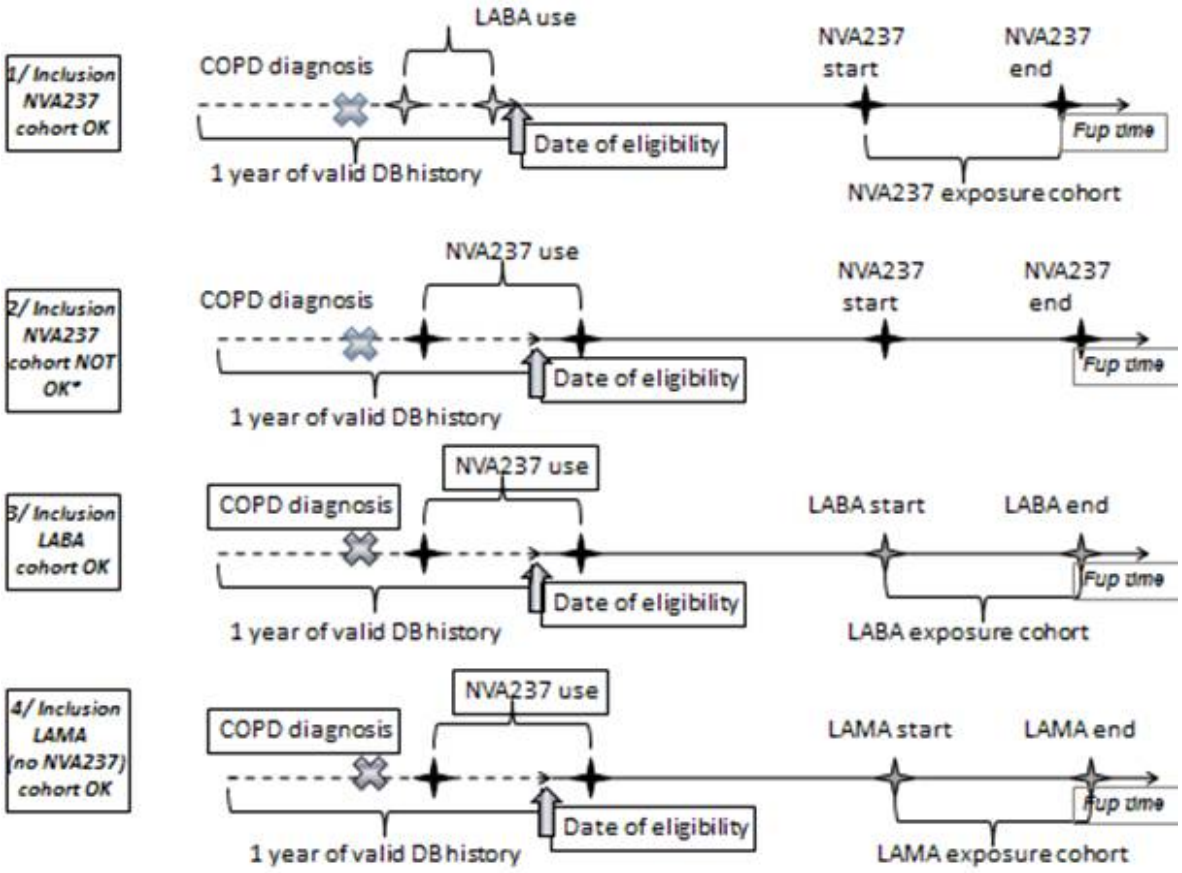
Inclusion criteria

All patients aged 40 years or older who were diagnosed with COPD and had at least one year of database history and a first time prescription/dispensing for one of the following medications after 01 November 2012 were included in the study: NVA237 or a single-ingredient LAMA (other than NVA237) or a single-ingredient LABA.

Exclusion criteria

Patients with 1) missing data on age or gender, 2) a recorded diagnosis of asthma only and thus, no recorded diagnosis of COPD prior to or within six months after the first prescription/dispensing of any of the drugs of interest, or 3) who received the study drug of interest (NVA237, LAMA [excluding NVA237] or LABA) in the one year prior to the index date (= time of first prescription) of the respective study cohorts were excluded (see Figure 9-1). Patients thus needed to be treatment-naïve to the exposure of interest for a minimum of one year. In addition, patients treated with both LABA and LAMA at the time of first prescription/dispensing of the study drug of interest were excluded from the study.

Figure 9-1 In- or exclusion in the study based on previous exposure of study drugs



DB = database; Fup = follow-up

(* In the second example, inclusion in the NVA237 exposure cohort would be valid if the time window between date of eligibility and start of NVA237 would be > 1 year)

As this was a non-interventional study using real-world data, it was decided to not exclude patients with non-cardiovascular life-threatening conditions (i.e., defined as patients with underlying cancer

9.3.2 Follow-up

For the primary analysis, namely the risk of overall mortality as well as the risk of the different endpoints of interest among new users of NVA237 compared to single-agent LABA and single-agent LAMA, patients initiating NVA237 or any single-ingredient comparator drug (LABA or LAMA [excluding NVA237]) were followed from the time of first prescription (index date) until the earliest of (i) end of treatment episode +30 days (see Section 9.4.2) or (ii) switching to another study treatment (see Section 9.4.2), (iii) end of study period or disenrollment from the database, or (iv) death. For the calculation of the incidence rates of the different endpoints of interest, follow-up time was censored upon occurrence of the respective endpoints. As multiple endpoints were studied, different follow-up times were applied (thus, patients might have different follow-up times in case of different endpoints).

End of treatment was defined as the discontinuation of use of NVA237, LAMA (excluding NVA237) or LABA for the respective treatment cohorts. This implies that follow-up, for the respective cohorts, ended when a patient discontinued treatment, received add-on therapy with another long-acting bronchodilator or switched treatment.

9.4 Variables

9.4.1 Endpoints of interest

During exposure to the different study drugs of interest, patients were followed for a new diagnosis of any of the following endpoints:

- MACE including myocardial infarction, stroke, and hospitalizations due to acute coronary syndromes and/or heart failure
- Ischemic heart disease including myocardial infarction or (unstable) angina pectoris
- Cardiac arrhythmias (atrial fibrillation/flutter, atrioventricular (AV) block, premature depolarization, sick sinus, supraventricular tachycardia and ventricular arrhythmia including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes/Long QT syndrome)
- Cerebrovascular disorders (ischemic and hemorrhagic stroke, transient ischemic attack [TIA])
- Mortality (all-cause)

As each endpoint was studied separately, patients who experienced more than one endpoint during the study were included in the analysis of each endpoint.

With regard to the combined endpoints (MACE, ischemic heart disease, cardiac arrhythmia and cerebrovascular disorders), the individual components (in the report further named as "additional events" of these combined endpoints were described separately with regard to numbers and crude incidence rates.

The definitions of the endpoints are described under Annex 2.2 – 'Event definition and corresponding codes'.

Prior to analysis, for each patient of the exposure cohorts, all endpoints were identified in the database based on searches on disease specific coding. As different data sources were used with different coding dictionaries (International Classification of Primary Care [ICPC], International Classification of Disease 9th or 10th version [ICD-9, ICD-10] and READ codes) concepts of diseases were mapped through the Unified Medical Language System (UMLS) for the different outcomes (see Annex 2.2 – 'Event definition and corresponding codes'). For details on which coding system was used by the different databases, see Table 9-2.

Patients with a medical history of any of these endpoints (apart from mortality) were not excluded from the study.

9.4.2 Exposure

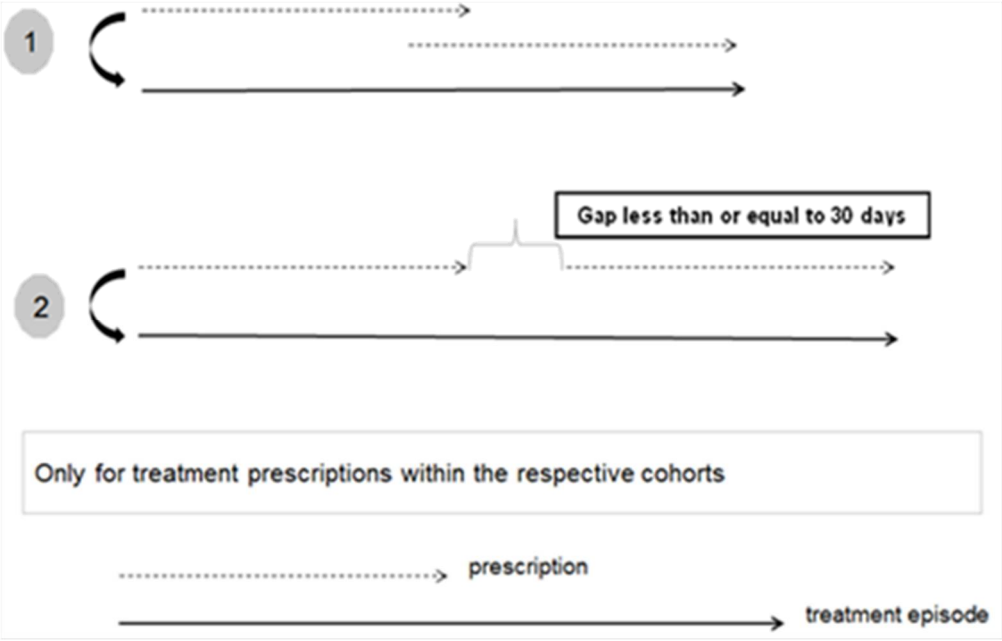
Patients prescribed NVA237, single-ingredient LAMA (excluding NVA237) or single-ingredient LABA were identified in the individual databases by an automated search on the respective anatomical therapeutic chemical classification system (ATC) codes, product names

or Multilex codes of the prescription records in the respective databases (see Annex 2.3– 'Exposure definition').

From the prescriptions, episodes of drug exposure were created. First of all, for each drug prescription, the end date of the prescription was calculated based on the amount of drug prescribed and the actual dosing regimen of the individual patient. If dosing information was missing, the total amount (per prescription) was divided by the recommended dose according to the Summary of Product Characteristics (SmPC) of the respective drug (i.e. NVA237, or other respiratory drugs/drug classes of interest). This duration of use was then added to the start date of the prescription resulting in a stop date for each prescription.

From the individual prescriptions, episodes of use were created taking into account potential overlap and gaps (Figure 9-2). If the subsequent prescription overlapped with the previous prescription, the two prescriptions were combined into one episode and the stop date of that episode was the stop date of the second prescription ((1) in Figure 9-2). In case of a gap between two prescriptions, these prescriptions were only combined into one episode if the duration of the gap was less than or equal to 30 days ((2) in Figure 9-2).

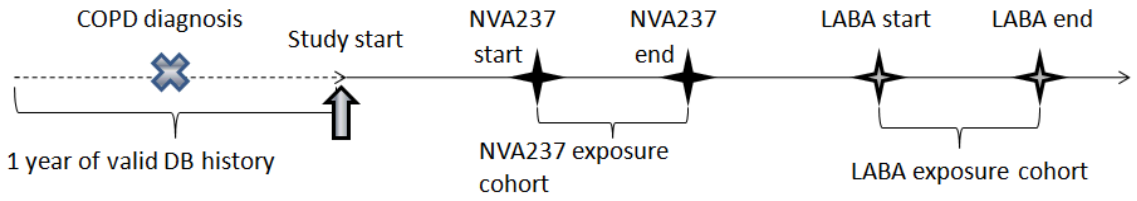
Figure 9-2 Creation of treatment episodes for NVA237 and comparators



Patients were classified as "exposed" to study medication (NVA237, LABA or LAMA [excluding NVA237]) for the duration of the first treatment episode plus 30 days. This 30-day grace period was chosen as patients are considered not to be 100% compliant, especially in case of chronic therapy (Huetsch et al 2013). Patients were censored upon treatment stop date + 30 days of the exposure of interest. Subsequent treatment episodes of the exposure of interest were thus not taken into account (unless if gap in between episodes was ≤ 30days, see above). To avoid misclassification of the endpoints, the 30-day extension window was not considered when treatment was discontinued because of switching to another treatment cohort.

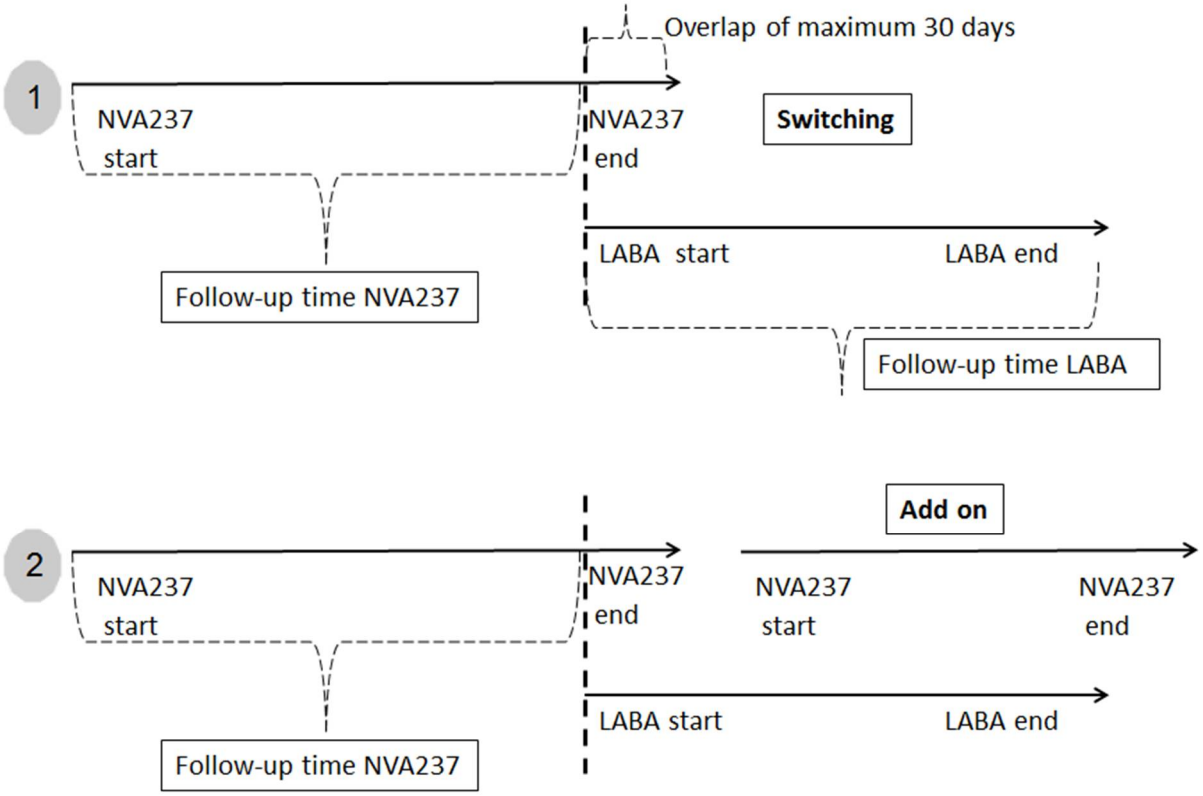
Patients who discontinued treatment and later restarted (the same cohort drug class) were only considered for their first episode of continuous use (+30 days). Upon discontinuation of exposure attributed to one of the treatment cohorts, patients were still eligible to be enrolled in the other treatment cohorts (Figure 9-3).

Figure 9-3 Eligibility to different exposure cohorts



Follow-up, for the respective cohorts, ended when a patient discontinued treatment, received add-on therapy with another long-acting bronchodilator or switched treatment. Switching was defined as start of another comparator drug with maximum overlap of prescriptions of 30 days. Add-on therapy was defined as start of prescriptions of comparator drugs combined with repeated prescriptions of first exposure cohort (Figure 9-4).

Figure 9-4 Switching and add-on therapy



Note: patient-time for LABA exposure in example 2 is disregarded

9.4.3 COPD severity

As COPD severity is an important confounder and/or effect modifier for the association between use of NVA237 or comparator drug and the risk of cardiovascular and/or cerebrovascular endpoints or mortality, COPD severity was quantified where possible.

Based on the suggestions made by the Scientific Advisor Committee (SAC) during review of previous interim reports of study NVA237A2402T, COPD severity based on spirometry data was assessed in all patients with recorded FEV_1 measurements, and not limited to patients with $FEV_1/FVC<70\%$.

COPD severity was assessed by spirometry, where spirometry data maximum 5 years prior to the index date was used using data closest to the index date.
Mild COPD was defined as FEV_1 predicted >= 80%, moderate COPD as $50\% \leq FEV_1 <80\%$ predicted, severe COPD as $30\% \leq FEV_1 <50\%$ predicted and very severe as $FEV_1<30\%$ predicted

In addition, in all patients, COPD severity by proxy was categorised according to published algorithms (Soriano et al 2001, Eisner et al 2005, Curkendall et al 2006). Information on COPD severity closest to the index date was considered as a covariate in the analysis. For further details on COPD severity, see Annex 2.4 – 'COPD definition'.

9.4.4 Concomitant drug use

Concomitant drug use was assessed either in the one year prior to or on the index date. The following classes of concomitant drugs were considered:

9.4.4.1 Concomitant use of respiratory products

Information on the use of products for the treatment of COPD was retrieved from the prescription records through an automated search on either ATC, product names or Multilex codes (see Annex 2.3 – 'Exposure definition' and Annex 2.5 – 'Concomitant medication definition'). Concomitant use of respiratory products was assessed at and in the one year prior to the index date. The following types of bronchodilating and anti-inflammatory agents were considered respiratory products:

- Single-ingredient short-acting muscarinic agents (SAMAs)
- Single-ingredient short-acting β2 agonists (SABAs)
- Inhaled corticosteroids (ICS)
- Xanthines
- Fixed-combination therapy (LABA + ICS, anticholinergic agents + SABA, LABA+LAMA)
- Oral β2-agonists
- Leukotriene receptor antagonists (LTRAs)
- Systemic corticosteroids (oral, intravenous or intramuscular administration)
- Inhaled LABAs
- LAMAs

- Oral phosphodiesterase-4 (PDE-4) inhibitors

9.4.4.2 Other concomitant drug use

Exposure to the following drug classes, at the index date, was assessed via an automated search on either ATC, product names or Multilex codes (see Annex 2.5– 'Concomitant medication definition').

9.4.4.2.1 Central nervous system drugs (excluding drugs with anticholinergic effects)

Use of opioids, hypnotics and sedatives, anxiolytics, antiepileptic drugs, serotonin reuptake inhibitors.

9.4.4.2.2 Anticholinergic drugs

Use of drugs with anticholinergic effects (antipsychotic drugs, tricyclic and tetracyclic antidepressant agents, disopyramide, antispasmodics, anti-Parkinsonian agents, cholinesterase inhibitors, atropine, H1-antihistamines, and anticholinergics for treatment of overactive bladder.

9.4.4.2.3 Drugs affecting cerebrovascular and cardiovascular disease

Use of systemic corticosteroids, NSAIDs, antithrombotic agents, lipid lowering drugs, platelet aggregation inhibitors, nitrates, anti-arrhythmics, anti-diabetic drugs and anti-hypertensive drugs.

9.4.5 Demography, life-style factors and comorbidity

- For all patients, information on gender and age (at time of index date) was captured.
- If available, information on smoking status was retrieved from the databases, and patients were classified as "current smoker", "past smoker", "never-smoker" or "smoking status unknown" at the index date.
- Duration of COPD (from date of diagnosis of COPD until index date)
- COPD severity at index date
- Number of COPD exacerbations requiring hospitalization or need of oral corticosteroids in the year prior to the index date. Information on hospitalization was retrieved either via linkage with hospital admission/discharge database (SIDIAP and Aarhus), combination of disease codes with information from hospital referral and discharge letters (HSD and IPCI) or combination of disease codes with source codes (hospital discharge letters) (THIN).
- The number of GP (outpatient) visits (excluding telephone requests for repeat prescriptions only) in the year prior to the index date
- Use of each of the classes of the cardiovascular drugs, respiratory drugs, CNS drugs and analgesics in the year prior to the index date
- Underlying comorbidity or "history of" at time of the index date, namely:
  - Asthma
  - Cardiovascular disease (hypertension, angina pectoris, myocardial infarction, cardiac arrhythmia [including atrial flutter and atrial fibrillation, supraventricular tachycardia

(SVT), premature depolarization, sick sinus, ventricular tachycardia, ventricular fibrillation, Torsade de Pointes/Long QT syndrome and AV block], heart failure)
- Cerebrovascular disease (history of stroke and/or TIA at time of index date)
- Metabolic disorders including diabetes mellitus, and hyperlipidemia
- Lung cancer
- Malignancies (excluding lung cancer)
- Chronic kidney disease
- Hepatic impairment
- Benign prostatic hyperplasia (BPH)/bladder outflow obstruction

Underlying comorbidity or history of above conditions was identified via an automated search on disease specific codes (see Annex 2.2 – Event definition and corresponding codes and Annex 2.6 – Comorbidity definition).

9.5 Data sources and measurement

For this study, databases comprising routine health care data were used to provide a reflection of real-world circumstances and prescribing behaviors. The databases were selected based on their geographic location, the availability of population-based data on dispensation/prescription of medications (including strength and indication), and their recognized reputation in the area of drug-utilization and drug safety research. Multiple countries were included to provide international data and to guarantee sufficient exposure to NVA237. All participating databases are part of the "EU-ADR Alliance", a stable collaboration framework for running drug safety studies in a federated manner, especially when the participation of several electronic healthcare record databases is required (Molero et al 2015).

All chosen databases comply with European Union (EU) guidelines on the use of medical data for medical research and have been validated for pharmaco-epidemiologic research (Vlug et al 1999, Lewis et al 2007, Ehrenstein, Antonsen, and [redacted], Cazzola et al 2011, Garcia-Gil et al 2011).

The databases used for this study are: THIN (UK), HSD (IT), IPCI (NL), the Aarhus University Prescription Database (DK), and SIDIAP (ES). Table 9-2 provides an overview of the data sources included in this study. These databases have a mean follow-up ranging from 3.2 to 15 years. The databases are representative of the country-specific populations in terms of age and gender. They are primary care databases – except for the Aarhus database, which is a prescription database with linkage to the hospital and outpatient registry. The available data are complete as they originate from the GP's electronic primary care records. The primary care databases represent 3.0-13.0% of the country specific total population. As of 2015, the total number of active persons in the source population encompassing all five databases was around 14 million.

Table 9-2 Overview of databases

Database characteristics	IPCI	THIN	Aarhus	HSD	SIDIAP
Country	Netherlands	United Kingdom	Denmark	Italy	Spain

Database characteristics	IPCI	THIN	Aarhus	HSD	SIDIAP
Type of database	MR	MR	ADM	MR	MR
Number of patients, *millions*	2.2	3.8	1.4	1.1	5.6
Mean follow-up in the database (years)	3.2	7.3	15.0	11.5	7.7
Date in	Yes	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes	Yes
Date of death	Yes	Yes	Yes	Yes	Yes
Cause of death	Yes	Yes	Yes	No	No
Updates	Twice per year (January/July)	Three times per year (January/May/September)	Yearly (April)	Twice per year (June/December)	Yearly (April/May)
Prescriptions					
Outpatient Rx	Yes (specialist incomplete)	Yes (specialist incomplete)	Yes	Yes (specialist incomplete)	Yes (specialist incomplete)
Inpatient Rx	missing	Missing	missing	missing	missing
Coding of drugs	ATC	BNF/Multilex code	ATC	ATC	ATC
Dosing regimen	Yes	Yes	No	Yes (incomplete)	Yes
Outcomes					
Hospitalizations	Yes (might be incomplete as no linkage with hospital database)	Yes (might be incomplete as no linkage with hospital database)	Yes	Yes (might be incomplete as no linkage with hospital database)	Yes
Inpatient diagnoses	Yes (might be incomplete if missing discharge letter or if diagnosis not recorded by GP)	Yes (might be incomplete if missing discharge letter or if diagnosis not recorded by GP)	Yes	Yes (might be incomplete if missing discharge letter or if diagnosis not recorded by GP)	Yes
Outpatient diagnoses	Yes	Yes	Yes	Yes	Yes
Coding of diseases	ICPC	READ	ICD-10	ICD-9 CM	ICD-10

ADM = Administrative; ATC = Anatomical Therapeutic Chemical; BNF = British National Formulary; CM = Clinical Modification; GP = General Practitioner; ICD= International Classification of Disease, ICPC = International Classification of Primary Care; MR = Medical Records; Rx = Prescription

Data-cuts used for this final report are based on new-user exposure to NVA237 or defined comparators and availability of database updates, and are as follows:

- IPCI: 01 November 2012 to 01 February 2016
- THIN: 01 November 2012 to 01 February 2016
- Aarhus: 01 November 2012 to 31 December 2015
- HSD: 01 November 2012 to 31 December 2015
- SIDIAP: 01 November 2012 to 31 December 2015

For this final report, the same data-cuts were used as for the fourth interim report. The cohort sizes are identical to the cohort sizes of the fourth interim report, but outcomes have been validated where possible (IPCI, HSD and SIDIAP).

More detailed information on the databases is available under Annex 2.9 – 'Data sources'.

9.6 Bias

There is the potential for diagnostic bias – if disease coding is inconsistent or differential – as co-morbidity and endpoints were assessed via disease specific codes. Validation studies however have shown that coding is reliable in the databases being used and that these databases are suitable for pharmacoepidemiological research (Vlug et al 1999, Lewis et al 2007, Ehrenstein, Antonsen, and [redacted], Cazzola et al 2011, Garcia-Gil et al 2011). To control for selection bias in the detection of the outcomes of interest, all endpoints were searched for in the respective databases by an automatic search algorithm, where the researchers were blinded to the exposure status. For the final report, for those databases that have free text (IPCI, HSD and SIDIAP) available, validation of the outcomes and of a sample of COPD patients was done.

In addition, as data are obtained from electronic primary care databases and a prescriptions database (with linkage to the hospital and out-patient registry) (Aarhus), information on important covariates such as smoking status, spirometry results, and oxygen therapy might be missing or reported in an inconsistent manner. The potential for bias is further discussed in Section 11.2 – 'Limitations'.

COPD severity is an important confounder and/or effect modifier in the association between the use of NVA237 or comparator product and the risk of cardiovascular and/or cerebrovascular endpoints or mortality. For this reason, COPD severity was determined using spirometry data (if available) or based via proxy, i.e., according to published algorithms. COPD severity was adjusted for in the final analysis. More information on the assessment of COPD severity is described under Annex 2.4 – 'COPD definition'.

Channeling bias is a concern when new drugs are launched onto the market as differential/preferential prescribing might occur in view of the patient characteristics. (Petri and Urquhart 1991). To overcome the issue of channeling two methods were applied. Firstly, outcome regression models were fitted with treatment and potential confounders as covariates. Secondly, models were fitted to obtain for each patient the probability of receiving one treatment over the other (expressed as a function of potential confounders) and these propensity scores were used in an inversed probability of treatment weighting (IPTW) analysis (Lobo et al 2006).

The potential for confounding is further discussed under Section 11.2 – 'Limitations'.

9.7 Study size

Although there is conflicting evidence from the literature on the association between the use of LAMA (tiotropium) and the risk of cardiovascular events, those studies with positive associations, reported hazard ratios (HRs) varying from 1.5 to 2 and above (Singh, Loke and Furberg 2008, Jara et al 2012, Dong et al 2013). For this reason, sample size estimates were calculated assuming an incidence rate ratio (IRR) of 1.5 and 2. Considering the size of the

databases and the fact that the comparator groups are well established treatments in COPD and NVA237 being new to market, we assumed in the worst case a 1:4 ratio of NVA237 vs. LAMA, (excluding NVA237) or LABA.

Sample size calculation was based on a log rank test, with a power of 80% and a 2-sided test with a significance level of 0.05. Accrual time (= time between first patient and last patient entering the study) was set at 3 years and we assumed no additional follow-up time. Based on information from literature on the duration of LAMA treatment episodes, censoring was set after a median of 180 days, assuming most censoring will be caused by the end of treatment period (Breekveldt-Postma et al 2007, Jara et al 2012, [redacted]). To allow detecting an increased risk, if the risk is higher by at least a factor of two (IRR = 2.0), for an event with a background incidence rate of 10 per 1,000 person-years, and a worst case scenario of a 1:4 ratio of number of NVA237 vs. LAMA or LABA users, the group of NVA237 users were estimated to be at least 2,079 persons with at least 10,395 persons for both the LAMA and the LABA cohort.

9.8 Data transformation

For this final report, data from all five databases (Aarhus, IPCI, THIN, HSD and SIDIAP) were obtained after local extraction, validation and data cleaning. All databases use different coding schemes (e.g. ICD9-CM and ICD10, ICPC, READ) and their content comes from different data sources (e.g., general practitioners' records, hospital discharge diagnoses, and death registries). To reconcile the differences across terminologies, a shared semantic foundation was built for the definition of events under study by selecting disease concepts from the Unified Medical Language System (UMLS, V.2008AA). The sequential steps of this process are described below.

1) Identification of Unified Medical Language System® (UMLS®) concepts

A UMLS concept is identified by a Concept Unique Identifier (CUI) and describes a single medical notion that can be expressed using different synonyms (terms). For each event, a medical definition was created and, based on such definition; relevant UMLS concepts were identified and projected into the database-specific terminologies. In addition, for those databases where free text is available, the labels of the codes were selected for free text search of the events. In IPCI, HSD and SIDIAP validation of the events was done at the end of the study for the final analysis.

2) Definition of data extraction algorithm

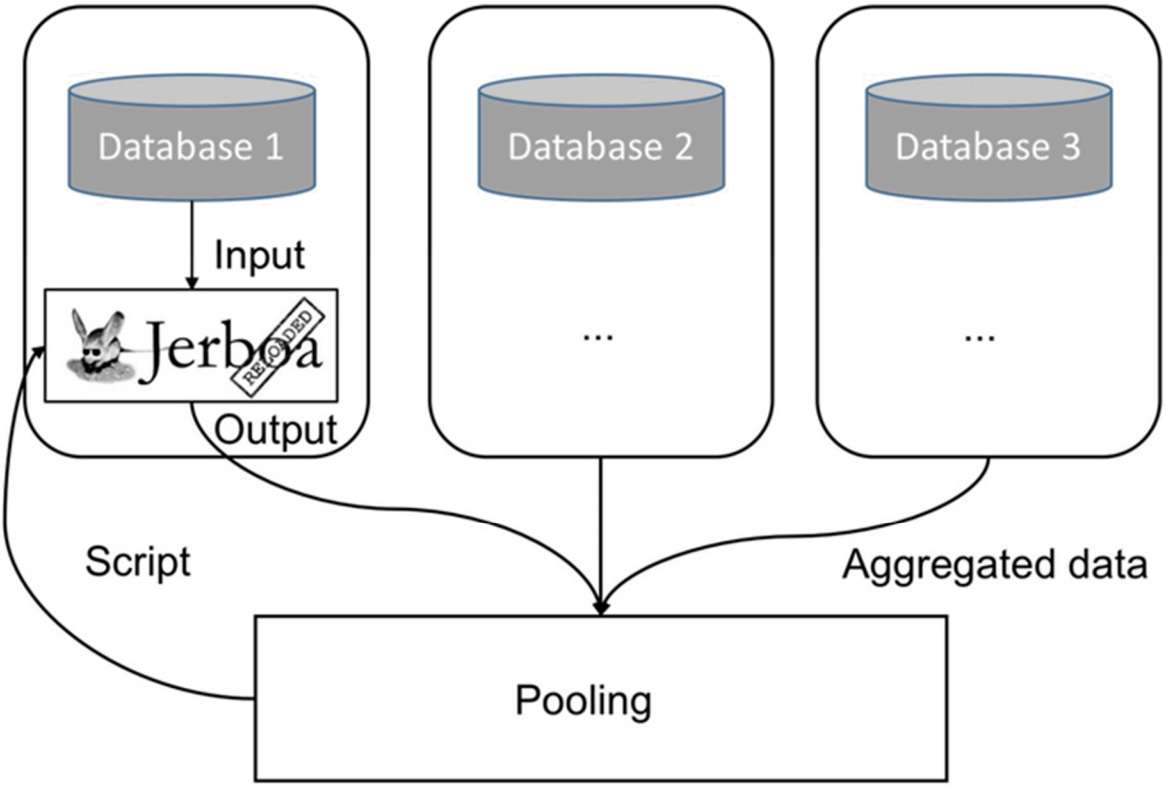
Based on the relevant diagnostic codes and key words (for free text search), a data extraction algorithm was constructed for each event based on the consensus of the data providers. This data extraction algorithm was then implemented by all databases.

3) Event data extraction

Subsequently, each database extracted data using a common data model, i.e. standardized patient, drug, and event files linkable via a patient unique identifier. These files were managed locally by purpose-built software called Jerboa, which transformed the input files in de-identified aggregated output files (see Figure 9-5). These output files were transmitted to a

central secured environment (remote research environment) for pooling and further processing. Jerboa has been developed for the EU-ADR FP7-ICT project (www.EU-ADR-project.org) that combines healthcare data of approximately 30 million individuals in Europe to detect adverse drug events. It has been used in many other EU funded projects and EMA tender protocols. (Ferrajolo et al. 2014, Coloma et al. 2013)

Figure 9-5 Model for data sharing and elaboration



Source: www.EU-ADR-project.org

9.9 Statistical methods

9.9.1 Main summary measures

In this final report, the following data are presented:

- Number of patients in the defined exposure cohorts (NVA237, LAMA [excluding NVA237] or LABA)
- Baseline characteristics in terms of comorbidity and concomitant drug use. For comorbidity, the complete history is considered and for concomitant drug use, the one year preceding the index date with index date included. These were described using contingency tables for categorical variables and mean, standard deviation (SD), median, with IQR and range for continuous variables
- Description of endpoints of interest (absolute count) among the three different exposure cohorts
- Incidence rates for all outcomes of interest across the three exposure cohorts.

9.9.2 Main statistical methods

9.9.2.1 Demographic and baseline characteristics of exposure cohorts

Demographic and baseline characteristics of the patients initiating NVA237 or new users of LAMA and LABA were described using contingency tables for categorical variables and mean, standard deviation (SD), median, with IQR and range for continuous variables for continuous variables in each database. Differences in demographic and baseline characteristics of NVA237 and the two comparator drug classes were assessed via the non-parametric Mann-Whitney U test for continuous variables, and the Chi-square test for categorical variables.

9.9.2.2 Incidence rates of different endpoints and Kaplan-Meier curves

To determine the risk of cardiovascular and cerebrovascular endpoints and mortality in new users of NVA237 and new users of LAMA (excluding NVA237) and LABA (two comparator groups), the IRs with 95% CIs were calculated for each outcome of interest in the three treatment cohorts. To calculate the IRs of the endpoints of interest, the number of patients (with the endpoint of interest) were summed among the different exposure cohorts and divided by the follow-up time. The 95% CIs were calculated using the negative binomial distribution. For this final report, data were pooled over all databases, but database-specific incidence rates are also reported.

For the main outcomes Kaplan-Meier curves were plotted by treatment cohort and by categories of the a priori confounders (age groups, gender, smoking status and COPD severity).

9.9.2.3 Hazard ratios of different endpoints

The relative risks (expressed as HRs with 95% CIs) were estimated for new users of NVA237 vs. new users of LAMA (excluding NVA237) and new users of LABA using Cox regression models (for each of the endpoints of interest). In these analyses, it is possible that patients contribute data to both the NVA237 cohort and the comparator cohort. Because occurrence will be limited and it will concern different time periods of the patient, data was analyzed as if all patients are independent. HRs were only estimated in case of at least 5 events per exposure cohort. Analyses in the pooled data were stratified by database, so each database had its own baseline hazard function.

First the crude HR was estimated. Subsequently, HRs were estimated adjusting for a priori confounders **(model 1).** This list of **a priori confounders** was restricted to: Age, Gender, Smoking status, COPD severity assessed by spirometry.

Next, the adjusted HRs were estimated by step-wise adding additional **potential confounders** (**model 2**). Selection of the potential confounders was done by checking the change in mean square error (MSE) (Greenland, Daniel, and Pearce 2016). One by one they were added to the model, adjusted for the a priori confounders. ΔMSE was determined comparing the estimate (B) of NVA237 and its standard error (SE) with and without adjustment for this confounder. The confounder with highest ΔMSE was added to the model. This selection step was repeated until none of the remaining potential confounders had a positive ΔMSE.

The following additional **potential confounders** were considered:

- Hospitalizations for COPD in the one year prior to the index date (Yes/No)
- Duration of COPD
- Number of GP visits at practice in the one year prior to the index date (categories 0,1,2, 3 or more, used as continuous variable)
- Number of GP visits at home in the one year prior to the index date (categories 0,1,2, 3 or more, used as continuous variable)
- History of cardiac arrhythmia
- History of cerebrovascular comorbidity
- History of ischemic heart disease
- History of diabetes mellitus
- History of cancer
- History of lung cancer
- History of asthma
- Chronic kidney disease (CKD), dichotomised into: 'mild or no CKD' = stage 1 or 2, stage unknown or no information on CKD and 'moderate or severe CKD' = stage 3 or higher.
- History of use of respiratory drugs in the one year prior to the index date
- History of use of CNS drugs in the one year prior to the index date
- History of use of anticholinergic drugs in the one year prior to the index date
- History of use of drugs affecting cerebrovascular and cardiovascular disease in the one year prior to the index date

In these models, interaction with treatment was tested for the following variables:

- Age
- Gender
- COPD severity assessed by spirometry
- History of cardiovascular or cerebrovascular disease

In each imputed dataset (see section 9.9.3) an interaction was marked if the P-value was below 0.1. If in at least three out of the five imputed sets the interaction was marked, a stratified analysis was done in categories of the variable. For age, categories used were: 1. age at cohort start below 70 years, and 2. age at cohort start 70 years or older.

In addition to adjusted regression (with confounders entered along with treatment as covariates in the outcome regression models, model 1 and 2), the analysis was repeated using inverse probability of treatment weighting (**IPTW**) using weights determined by a **propensity score model**. First, logistic regression models were fitted for outcome NVA237 treatment vs. LAMA (no NVA237) treatment and vs. LABA, respectively. For reason of efficiency, one propensity score model was fitted for different outcomes. The forward selection of all confounders as mentioned above was used, with P = 0.10.

Weight of each patient was calculated, defined as Pr(Z=1)(Z/e)+ Pr(Z=0) [(1-Z)/(1-e)] with Z=1 for NVA237 user and Z=0 for LAMA (or LABA), respectively, and e denotes the estimated propensity score. Tables with absolute standardized differences were provided to check the balancing of covariates after weighting. Cox models were fitted comparing NVA237 with LAMA and with LABA, respectively, while weighting by these IPTWs. The IPTW approach avoids the sparse-data problems that may arise in adjusted regression when the number of covariates is large and the number of events-per-covariate is small.

9.9.2.4 Meta-analysis

The estimated HRs comparing NVA237 with the comparator drugs were pooled over databases using fixed and random effect meta-analysis.

9.9.3 Missing values

Smoking status and COPD severity by spirometry has missing values. A multiple imputation procedure using SAS Proc MI with method FCS (fully conditional specification) with a logistic model was used. (van Buuren 2007) This imputation was done in each database separately. Next to the variables to be imputed, the imputation model also included the outcome variables, the covariates that were used in the models and variables thought to be related to smoking status or COPD severity.

Five imputed datasets were created. The HR estimate obtained by combining the estimates of the analyses on these imputed sets (SAS Proc MIAnalyze) was regarded as the final result for the database.

9.9.4 Sensitivity analyses

9.9.4.1 Sensitivity analysis 1 – Analysis in naïve patients and in patients without missing data with regard to COPD severity and smoking status

As part of the statistical analysis, from the initial exposure cohorts (which is called “total analysis population”), two additional sets of exposure cohorts were created namely the “naïve analysis population” and the “complete cases analysis population”. The naïve analysis population consists of patients naïve to any of the exposure treatments (also including fixed combination LABA+ICS and LABA+LAMA) in the year prior to study start. In this population, cohort time is not only censored if one of the other cohort drugs is started but also in case of a prescription of fixed LABA+ICS or fixed LABA+LAMA (including NVA237). The “complete cases analysis population” consists of patients without missing data with regard to COPD severity and smoking status. In these analysis populations, the association between use of NVA237 in comparison to LABA or LAMA use and risk of the different outcomes of interest was calculated adjusting for a priori confounders.

9.9.4.2 Sensitivity analysis 2 – No censoring at start of other drug

In the main analysis, patients were censored at start of other treatments. In a sensitivity analysis, patient’s follow-up time was not censored at initiation of other treatment and

endpoints occurring in the 30 days window upon switching or add-on therapy were attributed to the first treatment episode.

9.9.4.3 Sensitivity analysis 3 – Wash-out period 60 days

The use of a 30-day window after drug discontinuation to define "current exposure" is common in pharmacoepidemiological research within COPD. In a sensitivity analysis, the IPTW model was fitted now using follow-up with a wash-out period of 60 days instead of 30 days.

9.9.4.4 Sensitivity analysis 4 – Analysis of total follow-up time

On the 'total follow-up cohort' for each main outcome a Cox regression model was run with time-dependent variable 'NVA237 exposure', 'LAMA exposure' and 'LABA exposure'. This model was adjusted for age and gender. For each outcome, the first event following the first start of the treatment of interest was the outcome variable. Patients not experiencing the outcome were censored only at end of follow-up. From the parameter estimates for the time-dependent treatment variables, comparing exposure to non-exposure, the HRs comparing NVA237 exposure with LAMA exposure and with LABA exposure, respectively were derived.

9.9.5 Amendments to the statistical analysis plan

The analysis for this final report is described in the last version of the statistical analysis plan [redacted]

9.10 Quality control

The study was conducted according to the guidelines for Good Pharmacoepidemiology Practice (Epstein 2005) and according to the ENCePP code of conduct (European Medicines Agency 2011). All programs were programmed according to agreed coding standards and were validated by double programming or source code review with second programmer involvement. Only validated software (SAS version 9.2, SAS Institute Inc., Cary, NC) was used for statistical analyses.

10 Results

10.1 Participants

The individual study period for the respective databases is described in Table 10-1. These study periods are based on the most recent data releases of the respective databases. The overall study period was from 01 November 2012 until 01 February 2016.

In total, more than 14 million eligible patients were identified during the study period. Eligible patients are considered as patients with at least one year of medical history and still present in the database during the study period. The number of eligible patients per database is described in Table 10-1.

Table 10-1 Number of eligible patients during study period

Database	THIN database*	IPCI database	Aarhus database	HSD database	SIDIAP database
Study period	1st Nov 2012 – 1st Feb 2016	1st Nov 2012 – 1st Feb 2016	1st Nov 2012 – 31st Dec 2015	1st Nov 2012 – 31st Dec 2015	1st Nov 2012 – 31st Dec 2015
Number of eligible patients during study period	3,550,466	1,886,883	1,437,787	1,238,432	6,145,459

HSD = Health Search Database; IPCI = Integrated Primary Care Information; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; THIN = The Health Improvement Network
* = based on the THIN mid-year count in 2015

From each database, a cohort of COPD patients was identified who received a prescription of NVA237, LAMA (excluding NVA237), or LABA during study follow-up. From these COPD cohorts, three exposure cohorts were identified. These cohorts consisted of new users of either NVA237, or LAMA (other than NVA237), or LABA. Flowcharts with the number of patients by database and exposure cohort are presented in Annex 2.1 (Figure 15-1 to Figure 15-5). Patients were excluded if they were not naïve users of the exposure drug/drug classes of interest or concomitantly using a drug defined in one of the other exposure cohorts. Of patients that were excluded, in the majority of cases this was because of concomitant comparator drug use on the index date.

The target of 3,000 patients exposed to NVA327 was reached: a total of 8,277 new users of NVA237 were identified, of which 5,448 (62%) had at least 1 year of follow-up data (= database follow-up from start of NVA237 exposure until the end of study). The newly exposed LABA cohort included 17,890 patients; the newly exposed LAMA cohort was the largest and consisted of 58,852 patients. The numbers of patients by cohort and by database are presented in Table 10-2. The overall NVA237/LABA ratio was 1:2.0 and the overall NVA237/LAMA ratio was 1:6.7.

Table 10-2 Frequency distribution of patients by exposure cohort and database

Database	NVA237 (N=8,722)		LABA (N=17,890)		Other LAMA (N=58,852)	
	N	%	N	%	N	%
THIN (UK)	2,876	32.97%	3,410	19.06%	22,569	38.38%
IPCI (NL)	673	7.72%	1,942	10.85%	6,587	11.19%
Aarhus (DK)	468	5.37%	1,443	8.06%	3,890	6.61%
HSD (IT)	1,373	15.74%	1,144	6.39%	3,343	5.68%
SIDIAP (ES)	3,332	38.20%	9,951	55.61%	22,463	38.15%

DK = Denmark; ES = Spain (Espania); HSD = Health Search Database; IPCI = Integrated Primary Care Information; IT = Italy; NL = the Netherlands; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; THIN = The Health Improvement Network

The size of the naïve analysis population and the complete case analysis population is described below (by exposure cohort and by database) in Table 10-3 and Table 10-4. By design, all exposure cohorts dropped in size, but especially for NVA237 the reduction from total to naïve cohort was more than 70%.

Table 10-3 Frequency distribution of patients by exposure cohort and database – naïve analysis population

Database	NVA237 (N=2,603)		LABA (N=11,144)		Other LAMA (N=26,873)	
	N	%	N	%	N	%
THIN (UK)	830	31.89%	2,106	18.90%	10,710	39.85%
IPCI (NL)	187	7.18%	971	8.71%	3,360	12.50%
Aarhus (DK)	111	4.26%	741	6.65%	1,496	5.57%
HSD (IT)	403	15.48%	648	5.81%	1,407	5.24%
SIDIAP (ES)	1072	41.18%	6678	59.92%	9901	36.84%

DK = Denmark; ES = Spain (Espania); HSD = Health Search Database; IPCI = Integrated Primary Care Information; IT = Italy; NL = the Netherlands; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; THIN = The Health Improvement Network

Table 10-4 Frequency distribution of patients by exposure cohort and database – complete cases analysis population

Database	NVA237 (N=5,509)		LABA (N=10,587)		Other LAMA (N=37,224)	
	N	%	N	%	N	%
THIN (UK)	2,513	45.62%	2,861	27.02%	18,203	48.90%
IPCI (NL)	316	5.74%	1,045	9.87%	3,553	9.54%
Aarhus (DK)	173	3.14%	461	4.35%	1,327	3.56%
HSD (IT)	427	7.75%	318	3.00%	838	2.25%
SIDIAP (ES)	2,080	37.76%	5,902	55.75%	13,303	35.74%

DK = Denmark; ES = Spain (Espania); HSD = Health Search Database; IPCI = Integrated Primary Care Information; IT = Italy; NL = the Netherlands; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; THIN = The Health Improvement Network

For this final report, baseline characteristics are described for the total analysis population only.

The median duration of follow-up on treatment (NVA237, LABA, or other LAMA) within the different cohorts by database and pooled is presented in Table 10-5. The range of median durations of follow-up across the different sources or datasets was 70-120 days for NVA237, 60-90 for LABA and 69-125 days for LAMA.

Table 10-5 Median duration of follow-up on treatment (in days) by exposure cohort and database

Database	NVA237 (N=8,722)		LABA (N=17,895)		Other LAMA (N=58,880)	
	Median (IQR)	min-max	Median (IQR)	min-max	Median (IQR)	min-max
THIN (UK)	118 (60-280)	1-1,088	90 (60-168)	1-1,166	125 (60-308)	1-1,174
IPCI (NL)	98 (60-212)	4-1,047	80 (60-130)	1-1,119	120 (60-210)	1-1,149
Aarhus (DK)	120 (60-271)	1-1,130	90 (60-161)	1-1,123	119 (60-249)	1-1,156
HSD (IT)	70 (60-160)	1-932	63 (60-102)	1-1,151	90 (60-144)	1-1,107
SIDIAP (ES)	91 (60-211)	16-974	60 (60-120)	9-1,155	69 (60-151)	8-1,155
Pooled	95 (60-227)	1-1,130	62 (60-121)	1-1,166	91 (60-213)	1-1,174

DK = Denmark; ES = Spain (Espania); HSD = Health Search Database; IPCI = Integrated Primary Care Information; IT = Italy; NL = the Netherlands; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; THIN = The Health Improvement Network

10.2 Descriptive data

10.2.1 Baseline characteristics by exposure cohort and database

The baseline characteristics for age, gender, and smoking status of the pooled exposure cohorts are described in Table 10-6 (for more detailed information of baseline characteristics in study cohorts, both pooled and by database, see Annex 2.1 - Table 15-1).

Mean (pooled) age at the index date was comparable between exposure cohorts, namely 70.7 years for NVA237 compared to 70.1 years for both the LABA and LAMA cohorts. With regard to database specific characteristics, the mean age was the highest for HSD (72.5-74.1) and SIDIAP (70.6-71.1). (Annex 2.1 - Table 15-1).

The pooled proportion of males was similar in the NVA237 (62%) compared to the LABA (63%) and the LAMA (62%) cohort; however, gender distribution showed variations across the different data sources (e.g. for male NVA237A users ranging from 49.7% [THIN] to 75.4% [SIDIAP]). In HSD and SIDIAP, both representing Southern European populations, the majority prescribed these products were males . (Annex 2.1 - Table 15-1).

Distribution of smoking is described, using as denominator, all patients for whom smoking status is known. The proportion of current, past and non-smokers were balanced in all exposure cohorts with the highest proportion of current smokers (38.2%) in the LAMA exposure cohort. (Annex 2.1 - Table 15-1). In HSD (range 25.3-27.8% and SIDIAP (range 54.4-58.9%), the proportion of never-smokers was higher compared to the Northern European population (range 8.5-11.6%). The proportion of missing smoking status was the lowest for THIN (0.0-0.1%) and SIDIAP (range 2.4-3.4%), and highest for Aarhus (range 38.9-41.3%). (Annex 2.1 - Table 15-1 In preparation of the analysis, smoking status was imputed if missing. Results of imputation are described in Annex 2.1 - Table 15-1 and displayed in Annex 2.1 - Figure 15-6.

The median number of GP practice visits was higher for NVA237 (8 visits) compared to LABA (7 visits) or LAMA (7 visits). GP home visits were low in all exposure cohorts. Differences between databases were observed with the highest median number of GP practice visits for HSD (11-12 visits) and Aarhus (16.5-18 visits) (see Annex 2.1 - Table 15-1).

Table 10-6 Baseline characteristics of exposure cohorts (NVA237, LABA, LAMA [excl. NVA237]) - POOLED Total analysis population

	NVA237 N (%)	LABA N (%)	P comparing NVA237 to LABA	LAMA (excl. NVA) N (%)	P comparing NVA237 to LAMA
Total	8722 (100.0%)	17890 (100.0%)	.	58852 (100.0%)	.
Gender			0.0440		0.6970
Male	5396 (61.9%)	11297 (63.2%)	.	36278 (61.6%)	.
Female	3326 (38.1%)	6593 (36.9%)	.	22574 (38.4%)	.
Age at cohort entry (years)					
Mean (SD)	70.7 (10.5)	70.1 (11.2)	<.0001	70.1 (11.0).	<.0001
Smoking status					
Current smoker	2812 (34.3%)	5833 (35.0%)	.	21193 (38.2%)	.
Past smoker	2845 (34.7%)	4572 (27.4%)	.	18920 (34.1%)	.
Never smoker	2540 (31.0%)	6276 (37.6%)	.	15373 (27.7%)	.
Unknown	525 (6.0%)	1209 (6.8%)	.	3366 (5.7%)	.

SD = standard deviation

Note: Differences in Gender were tested with Chi-square test. Differences in Age were tested with Mann-Whitney test. For Smoking status the percentage of Unknown is based on the total number. Percentages of the other categories are based on the number with known Smoking status. Differences in Smoking status are not tested for these unimputed data. For test results in imputed data see .

10.2.2 COPD characteristics by exposure cohort and database

The pooled COPD characteristics are presented in Table 10-7 (and in more details [pooled and by database] in Annex 2.1 - Table 15-2, and Annex 2.1 - Table 15-7).

The pooled median duration of COPD was 4.3 years for NVA237, 2.9 years for LABA and 2.6 years for LAMA cohorts. In all databases, the pooled median duration of COPD was the highest in the NVA237 exposure cohort. When investigating database specific COPD duration, the median duration of COPD was highest for HSD (ranging from 6.4 to 7.0 years) in all 3 exposure cohorts (Annex 2.1 - Table 15-2).

With regard to COPD severity, spirometry data closest to the index date was analysed limiting the date of spirometry to a maximum of 5 years prior to the index date. FEV_1 (as percentage of predicted) was available for a subset of patients in THIN (80.4-87.0%), IPCI (47.1-54.4%), Aarhus (44.1-50.0%), HSD (27.1-33.0%) and SIDIAP (59.9-62.9%). The pooled median FEV_1 percentage of predicted was 62% for NVA237, 65% for LABA and 62.9% for LAMA. FEV_1 percentage of predicted was the lowest for Aarhus and SIDIAP, across exposure cohorts.

Based on spirometry data, the proportion of patients without COPD (i.e. defined as FEV1/FVC $\geq$ 70%) was 28.2% for the NVA237 exposure cohort, 31.6% for the LABA exposure cohort, and 27.2% for the LAMA exposure cohort. The proportion of patients without COPD confirmed by spirometry was highest for HSD (range 49.8-52.7%) (Annex 2.1 - Table 15-2).

For those patients where COPD severity was assessed by spirometry, a higher proportion of patients in the NVA237 and LAMA exposure cohort had ‘severe’ (32.7% NVA237 and 27.6% LAMA) and ‘very severe’ COPD (4.8% NVA237 and 3.4% LAMA) than patients in the LABA exposure cohort (21.0% ‘severe’ COPD; 2.3% ‘very severe’ COPD, respectively).

When assessing COPD severity in all patients with information on FEV_1 (as percentage of predicted), irrespective whether the patient had an FEV1/FVC < 70%, a higher prevalence was seen in patients treated with NVA237 and LAMA for ‘severe’ (26.0% for NVA237 and 23.0% for LAMA) and ‘very severe’ COPD (3.6% for NVA237 and 2.8% for LAMA) than for patients treated with LABA (‘severe’ 16.6%; ‘very severe’ 1.7%, respectively). Furthermore, as part of the analysis, COPD severity by spirometry was imputed if missing. Results of imputation are described in Annex 2.1 - Table 15-2, again showing a higher prevalence of ‘severe’ and ‘very severe’ COPD in NVA237 and LAMA cohorts, compared to LABA.

In addition, COPD severity was also assessed via previously published algorithms. In general, COPD severity by proxy resulted in a higher proportion of less severe COPD across all exposure cohorts and databases.

The proportion of patients with at least one COPD exacerbation requiring hospitalization in the 1 year prior to index date in the pooled dataset was less than 10.0% in all exposure cohorts. The proportion of patients with at least one COPD exacerbation requiring hospitalization was the highest for Aarhus across exposure cohorts (range 9.6-16.7%).

The proportion of patients requiring treatment with systemic corticosteroids for the treatment of COPD exacerbation in the year prior to and including the index date, was 12.6% for the

pooled NVA237 exposure cohort, 8.4% for the pooled LABA cohort, and 11.5% for the pooled LAMA cohort. The proportion of patients treated with antibiotics for COPD exacerbation/lower respiratory tract infection (LRTI) was 21.1% in the pooled NVA237 cohort, 18.4% for the pooled LABA cohort, and 20.1% for the pooled LAMA cohort. Use of corticosteroids and antibiotics was lowest for HSD (4.5-6.3% and 13.0-15.7%, respectively) and SIDIAP (4.4-4.9% and 16.8-17.3%, respectively) (see also Annex 2.1 - Table 15-2).

Table 10-7 COPD characteristics (NVA237, LABA, LAMA (excl. NVA237)) - POOLED Total analysis population

	NVA237 N (%) 8722	LABA N (%) 17890	P comparing NVA237 to LABA	LAMA (excl. NVA) N (%) 58852	P comparing NVA237 to LAMA
Duration of COPD (years)					
Median (IQR)	4.3 (0.7-8.9)	2.9 (0.1-7.5)	<.0001.	2.6 (0.1-7.3)	<.0001.
Patients with spirometry data recorded within 5 years prior to the index date	5614 (64.4%)	10854 (60.7%)		38039 (64.6%)	
FEV1 (percentage of predicted)					
Median (IQR)	62.0 (52.0- 71.0)	65.0 (56.5- 72.0)	<.0001.	62.9 (53.2- 70.7)	<.0001.
COPD severity assessed by spirometry					
No COPD	1424 (28.2%)	3128 (31.6%)	.	9198 (27.2%)	.
Mild	387 (10.7%)	1104 (16.3%)	.	3148 (12.8%)	.
Moderate	1881 (51.8%)	4096 (60.4%)	.	13780 (56.1%)	.
Severe	1189 (32.7%)	1425 (21.0%)	.	6793 (27.6%)	.
Very severe	175 (4.8%)	154 (2.3%)	.	847 (3.4%)	.
Unknown	3666 (42.0%)	7983 (44.6%)	.	25086 (42.6%)	
COPD severity assessed by spirometry (considering all FEV1 predicted – also if FEV1/FVC missing)					
Mild	919 (16.4%)	2477 (22.8%)	.	6823 (17.9%)	.
Moderate	3033 (54.0%)	6385 (58.8%)	.	21420 (56.3%)	.
Severe	1461 (26.0%)	1806 (16.6%)	.	8742 (23.0%)	.
Very severe	201 (3.6%)	186 (1.7%)	.	1054 (2.8%)	.
Unknown	3108 (35.6%)	7036 (39.3%)	.	20813 (35.4%)	.
COPD severity assessed by proxy			<.0001		<.0001

	NVA237 N (%) 8722	LABA N (%) 17890	P comparing NVA237 to LABA	LAMA (excl. NVA) N (%) 58852	P comparing NVA237 to LAMA
Mild	1653 (19.0%)	5181 (29.0%)	.	16226 (27.6%)	.
Moderate	5942 (68.1%)	11451 (64.0%)	.	36503 (62.0%)	.
Severe	918 (10.5%)	1158 (6.5%)	.	5540 (9.4%)	.
Very severe	209 (2.4%)	100 (0.6%)	.	583 (1.0%)	.
Number of hospitalizations for COPD exac (categorical)			<.0001		0.6820
None	8210 (94.1%)	17176 (96.0%)	.	55264 (93.9%)	.
1	393 (4.5%)	555 (3.1%)	.	2888 (4.9%)	.
2	69 (0.8%)	88 (0.5%)	.	485 (0.8%)	.
3 or more	50 (0.6%)	71 (0.4%)	.	215 (0.4%)	.

FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IQR = interquartile range; COPD exac = COPD exacerbation

Note: Continuous variables tested with Wilcoxon test and categorical variables tested with Chi-Square test. For COPD severity assessed by spirometry, percentages of ‘‘Unknown’ are based on total numbers in the corresponding cohort. Percentages of “No COPD” are based on all patients with a known COPD status. For the other categories, percentages are based on number of patients with COPD and with severity status known (i.e. those classified as either ‘mild’, ‘moderate’, ‘severe’, or ‘very severe’). Differences in COPD severity assessed by spirometry are not tested for these unimputed data. For test results in imputed data see Annex 2.1 - Table 15-2.

10.2.3 Co-morbidities by exposure cohort and database

Comorbidities by exposure cohort and database are presented in Annex 2.1 - Table 15-3 and Annex 2.1 - Figure 15-8 to Figure 15-21.

10.2.3.1 Cardiovascular and cerebrovascular comorbidity

In the pooled dataset, more than 50% had a medical history of arterial hypertension with the lowest proportion (50.9%) in the LAMA exposure cohort (Annex 2.1 - Figure 15-8).

The prevalence of prior myocardial infarction was 5.9% in the LABA cohort, 6.7% in the NVA237 cohort and 7.4% in the LAMA cohort (both $p<0.05$) (Annex 2.1 - Figure 15-9). The prevalence of angina pectoris was slightly higher with prevalences of 7.9% in the LABA cohort, 8.9% in the NVA237 cohort and 10.7% in the LAMA cohort, differences being statistically significant (both $p<0.05$) (Annex 2.1 - Figure 15-10). The prevalence of unstable angina pectoris was $\leq 2\%$ in all 3 exposure cohorts (Annex 2.1 - Figure 15-11).

The prevalence of heart failure was 7.5% in the LABA cohort, 8.9% in the LAMA cohort and 9.1% in the NVA237 cohort ($p<0.0001$ for difference between NVA237 and LABA). (Annex 2.1 - Figure 15-12).

Approximately 12% of the patients had a medical history of cardiac arrhythmia mainly dominated by a history of atrial fibrillation/flutter (range 9.9-11.1%, NS) (Annex 2.1 - Figure 15-13). The prevalence of other cardiac arrhythmia was below 2% in all exposure cohorts.

Approximately 10% of the patients had a history of cerebrovascular comorbidity with a prevalence of prior stroke of 6.4% in the LABA cohort, 7.3% in the LAMA cohort and 7.6% in the NVA237 cohort ($p<0.05$ for differences between NVA237 and LABA cohort) (Annex 2.1 - Figure 15-14). The proportion of patients with a medical history of TIA was 3.5% in the LABA cohort, 3.6% in the NVA237 cohort and 4.0% in the LAMA cohort (NS) (Annex 2.1 - Figure 15-15).

10.2.3.2 Diabetes mellitus, hyperlipidemia and hepatic impairment

In the pooled dataset, approximately 20% had a medical history of diabetes mellitus (Annex 2.1 - Figure 15-16) and slightly more a medical history of hyperlipidemia (Annex 2.1 - Figure 15-17). The prevalence of diabetes mellitus was comparable across exposure cohorts (range 19.9-20.7%) (NS). The prevalence of hyperlipidemia was 23.6% in the NVA237 exposure cohort, 22.4% in the LAMA cohort and 21.0% in the LABA cohort (both $p<0.05$). The proportion of patients with hepatic impairment was 3.2% and 3.0% in the NVA237 and LAMA cohort, respectively, and 2.2% in the LABA cohort ($p<0.0001$ for difference between NVA237 and LABA) (Annex 2.1 - Figure 15-18).

10.2.3.3 Cancer

In the pooled dataset, the proportion of lung cancer was 1.6%, both in the NVA237 and LAMA exposure cohorts, and 1.3% in the LABA cohort ($p<0.05$ for difference between NVA237 and LABA) (Annex 2.1 - Figure 15-19).

The proportion of cancer (excluding lung cancer) ranged between 13.6-14.0% (NS) (Annex 2.1 - Figure 15-20).

10.2.3.4 Asthma

The proportion of patients with asthma was 20.5% in the NVA237 and 19.5% in the LAMA exposure cohorts, whereas this proportion was 14.7% in the LABA exposure cohort (both $p<0.05$) (Annex 2.1 - Table 15-3) (Annex 2.1 - Figure 15-21).

10.2.3.5 Chronic kidney disease

CKD was assessed either via disease code or via creatinine clearance. Almost 50% of patients in the pooled dataset had a creatinine clearance between 60-89 mL/min/1.73 m^2 (stage 2) (46.9% in the NVA237 exposure cohort, 48.4% in the LABA cohort and 47.2% in the LAMA cohort). CKD stage 3 was also prevalent with the lowest proportion for LABA (20.8%) and the highest proportion for NVA23 (25.5%). The proportion of patients with CKD stage 1 and CKD stage 4 and 5 was below 2% (Annex 2.1 - Table 15-3).

10.2.3.6 Benign prostatic hyperplasia and bladder outflow obstruction

In the pooled dataset, the prevalence of BPH was 12.1 % in the LAMA cohort, 13.8% in the NVA237 exposure cohort and 14.8% in the LABA cohort (both $p<0.05$) (Annex 2.1 - Figure 15-22).

The prevalence of bladder obstruction/urinary retention was around 2% in all 3 exposure cohorts (2.1% NVA237, 1.7% LABA and 2.2% in the LAMA exposure cohort) ($p<0.05$ for difference between NVA237 and LABA) (Annex 2.1 - Figure 15-23).

10.2.3.7 Differences in comorbidities between databases

Differences in comorbidities between databases were observed with the lowest prevalence of arterial hypertension, diabetes mellitus and hyperlipidemia in Aarhus. A history of ischemic heart disease (i.e., unstable angina pectoris, angina pectoris and myocardial infarction) was more frequently reported in THIN, IPCI and Aarhus (range angina pectoris 12.1-23.8%, range myocardial infarction 6.8-9.7%) than in HSD and SIDIAP (range angina pectoris 2.5-3.4%, range myocardial infarction 3.9-6.1%).

Up to 15.8% of patients were diagnosed with heart failure at cohort inception, proportions were the highest for Aarhus, apart for the NVA237 cohort where the proportion was the highest for IPCI (14.9%).

The prevalence of stroke was almost twice as high for HSD compared to the other databases. The proportion of hepatic impairment was the lowest for Aarhus and SIDIAP. (range 0.5-2.1% vs. 2.7-7.2% in the other databases).

The proportion of patients with a medical history of asthma was the highest in IPCI and THIN across all exposure cohorts (range 23.3-32.6%) and lowest for HSD and SIDIAP (range 8.1-15.9%).

The proportion of patients with lung cancer was the highest for IPCI and Aarhus in all exposure cohorts with a high prevalence of 5.2% in the IPCI NVA237 exposure cohort.

Differences in prevalence of BPH were observed across databases, with highest prevalences in HSD (12.9-18.1%) and SIDIAP (21.0-22.2%), both of which have a male preponderance of COPD patients. In the other databases, the prevalence of BPH ranged between 4.7-7%.

10.2.4 Use of other respiratory medications by exposure cohort and database - assessed during the year prior to index date and on index date

Information on use of other respiratory medications at or during the year prior to index date are presented in Annex 2.1 - Table 15-4 and graphically in Annex 2.1 - Figure 15-24 to Annex 2.1 - Figure 15-30.

10.2.4.1 Use of other respiratory medications by exposure cohort – pooled dataset

With respect to single-ingredient short-acting bronchodilators in the year prior to the index date, the majority of patients from the pooled dataset received SABA (51.7% NVA237, 44.2% LABA and 50.2% in the LAMA exposure cohort, both $p<0.05$ for comparison between NVA237 and LABA and comparison between NVA237 and LAMA) (Annex 2.1 - Figure 15-24). Use of SAMA was markedly lower (19.1% NVA237, 22.0% LABA and 20.1% in the LAMA exposure cohort, both $p<0.05$) (Annex 2.1 - Figure 15-25).

Previous use of LABA was observed in 10.2% of the NVA237 exposure cohort and 6.1% of the LAMA cohort (Annex 2.1 - Figure 15-26). Previous use of LAMA was higher, namely 31.6% in the NVA237 exposure cohort and 17.7% of the LABA cohort (Annex 2.1 - Figure 15-27). Previous use of NVA237 was considerably lower, namely 1.2% in the LABA cohort and 1.3% in the LAMA cohort. (Annex 2.1 - Figure 15-28). According to the protocol, previous use of NVA237, LABA and LAMA in the one year prior to cohort start was absent in the respective exposure cohorts.

Fifteen to 20% of patients had used an ICS in the year prior to cohort start with the largest proportion for LABA (19.7%), 17.7% for NVA237 and 15.6% for the LAMA exposure cohort (both $p<0.0001$) (Annex 2.1 - Figure 15-29).

With regard to fixed combinations of respiratory drugs, 52.9% of the NVA237 exposure cohort had used a fixed dose combination of LABA+ICS in the year prior to cohort start. This proportion was 40.0% for the LAMA exposure cohort and much lower, namely 26.1% for the LABA exposure cohort (both $p<0.0001$) (Annex 2.1 - Figure 15-30). Previous use of a fixed LABA+LAMA combination was 1.3% for NVA237, 0.8% for LABA and 0.6% for the LAMA exposure cohort (both $p<0.05$). The fixed combination of SABA+SAMA ranged between 1.2-2.4%.

Up to almost 11% of patients had been treated with systemic corticosteroids for the treatment of COPD in the year prior to the index date with the highest proportion for NVA237 (11.6%), followed by LAMA (9.7%) and LABA (7.0%) (both $p<0001$).

Finally, use of oral β_2-agonists, xanthines, leukotriene receptor antagonists (LTRA) and oral phosphodiesterase-4 (PDE-4) inhibitors was low for all exposure cohorts.

Use of respiratory drugs assessed at index date is documented in Annex 2.1 - Table 15-5. In the NVA237 cohort, patients mainly switched from use of another LAMA (9.5%). Switching from LABA to NVA237 at index date occurred less frequently (1.6%). Switching from LAMA to LABA occurred in 4% of all patients in the LABA cohort. In the LAMA cohort, patients switched from LABA to LAMA in 1.1%. Switching from NVA237 to either LABA or LAMA was low namely 0.3% for both.

At cohort inception, use of ICS was the highest for the LABA exposure cohort (19.9%) whereas it was around 8% for the NVA237 and LAMA exposure cohort (p for comparison between NVA237 and LABA for the comparison between NVA237 and LAMA <0.0001) Use of fixed combination LABA+ICS was high, both in the NVA237 exposure cohort (45.5%) and the LAMA exposure cohort (40.9%), whereas this was much lower for the LABA exposure cohort (10.0%) (both p<0.0001). Use of systemic corticosteroids because of COPD at cohort inception was 4.6% for the NVA237 exposure cohort, 3.9% for the LABA cohort and 5.2% for the LAMA cohort (both p<0.05).

10.2.4.2 Differences in respiratory medication use between databases

Differences in proportions of SABA use compared to SAMA use in the one year prior to cohort entry was most pronounced in the UK (THIN), where at least 75.9% of patients had used a SABA (range 75.9-84.1%) whereas the cohort-specific proportions for SAMA use in the UK ranged from 7.2 to 10.4%. Use of SAMA was almost non-existing in Denmark (Aarhus), whereas in SIDIAP (Spain) the proportion of patients using SAMA (ranging from 33.5-37.6% across exposure cohorts) was similar to that of SABA (36.3-39.6%). In HSD (Italy) use of short-acting agents was lower than for the other databases namely between 4.8-6.0% for SAMA and 10.1-15.6% for SABA.

Large differences in use of fixed-combination of SABA+SAMA were observed with low use in THIN (UK) and SIDIAP (Spain), whereas use ranged from 2.2 to 9.7% in the other three databases).

Compared to LABA+ICS use, the use of single-ingredient ICS was lower (10.7-20.3%) in all databases except for HSD. In Italy (HSD), use of single-ingredient ICS was highest (27.2-34.4%) in all exposure cohorts.

Use of systemic corticosteroids for the treatment of COPD in the year prior to the index date was higher in THIN (UK) (range 11.1-18.1%), IPCI (The Netherlands) (range 18.9-32.8%) and Aarhus (Denmark) (range 11.3-15.7%) compared to HSD (Italy) (range 3.4-5.5%) and SIDIAP (Spain) (range 3.0-3.7%).

Two to 13.6% of patients were using systemic corticosteroids for the treatment of COPD at inception cohort with the highest proportions in IPCI (6.7-10.8%) and Aarhus (6.8-13.6%).

10.2.5 Use of non-respiratory medications by exposure cohort and database

Use of non-respiratory medications was assessed in the year prior to the index date, and is presented in Annex 2.1 - Table 15-6.

In line with the high frequency of underlying comorbidities, the frequencies of antihypertensive medication use in the pooled dataset were the highest (64.7% NVA237, 61.6%

LABA and 61.8% in the LAMA exposure cohort, p for difference between NVA237 and LABA and p for difference between NVA237 and LAMA<0.0001), followed by lipid-lowering (44.8% NVA237, 42.0% LABA and 44.1% in the LAMA exposure cohort) (p for difference between NVA237 and LABA <0.0001) and anti-diabetic medications (17.1% NVA237, 17.0% LABA and 16.3% in the LAMA exposure cohort, NS).

Use of NSAIDs was high (28.6% NVA237, 29.8% LABA and 24.9% in the LAMA exposure cohort, p<0.0001 for the comparison of NVA237 with LAMA), especially in HSD (40.6-46.9%) and SIDIAP (32.3-35.2%). Use of antithrombotics (including platelet aggregation inhibitors) was reported in around 37-41% of patients (40.9% NVA237, 37.0% LABA and 39.9% in the LAMA exposure cohort, p<0.0001 for the comparison of NVA237 with LABA).

In the pooled dataset, use of opioids, anxiolytics and SSRIs varied around 15% in all exposure cohorts. The use of tricyclic and tetracyclic antidepressants ranged between 10.9-12.7%. Differences by database were observed with low use of hypnotics and anxiolytics in Denmark (Aarhus) (0.4% for hypnotics, 0.5-0.6% for anxiolytics), whereas use of anxiolytics (25.6-28.0%) was highest in Spain (SIDIAP). Use of SSRIs was much lower in IPCI (Netherlands) (7.4-9.2%) whereas use ranged from 10.7-18.0% in the other databases. Use of opioids in the year prior to the index data was the highest in Aarhus (24.4-31.4%).

10.3 Outcome data

According to the protocol, validation of endpoints as identified for the 4th interim report was done for IPCI, HSD and SIDIAP. Upon validation, endpoints were classified as definite, probable, possible or non-event. The result of this validation is provided in Annex 2.1 - Table 15-7. Data are provided for the validation of both, COPD and the outcomes of interest.

The positive predictive value (PPV) of COPD was comparable between databases, namely 89.1% for SIDIAP, 93.5% for HSD and 96.7% for IPCI.

With regard to the outcomes of interest, huge ranges in PPV between outcomes and databases were observed mainly because of low number for certain outcomes. In IPCI, the range of PPV was between 76.9% (hospitalization for acute coronary syndrome [ACS]) and 100% (death, sick sinus, SVT and ventricular tachycardia). In HSD, the PPV ranged between 0% (AV block and unstable angina pectoris [AP]) and 100% (AP, death, longQT, premature depolarization, sick sinus, SVT and Torsade de Pointes). In HSD, PPV of stroke was also low (9.8%) because the search for stroke included an aspecific search code (= paresis) which in many cases was not confirmed as stroke upon validation. In SIDIAP, the PPV ranged between 100% (ventricular fibrillation) and 37.5% (unstable AP).

In IPCI, because of lack of granularity in the ICPC coding, a free text search on potential endpoints was in addition conducted for the final report. These endpoints included: myocardial infarction, (unstable) AP, stroke, TIA, atrial fibrillation/flutter, AV block, sick sinus, premature depolarization and SVT. No free text search on hospitalization for heart failure, hospitalization for acute coronary syndrome, ventricular tachycardia, ventricular fibrillation, Torsade de Pointes/Long QT syndrome and death was conducted for the final report as this search was already conducted to identify these endpoints for the interim reports. These additional events are not described in Annex 2.1 - Table 15-7.

For the analysis, definite, probable and possible endpoints were combined into one category.

10.3.1 Frequencies of main events in the pooled dataset

The number of main events of interest in the pooled data are presented in Table 10-8 below.

The number of main events for the outcomes of interest, by database and exposure cohort, is presented in Annex 2.1 - Table 15-8.

There were 182 patients (2.1%) who died in the NVA237 exposure cohort, 260 patients (1.5%) in the LABA exposure cohort, and 1,344 (2.3%) patients in the LAMA exposure cohort.

MACE (MI, stroke, hospitalization for ACS and hospitalization for heart failure) as endpoint occurred in 109 patients (1.3%) of the NVA237 exposure cohort, in 282 patients (1.6%) of the LABA cohort and in 1,247 (2.1%) of the LAMA cohort.

The number of patients developing cardiac arrhythmia during exposure time was 87 (1.0%) in the NVA237 cohort, 171 (1.0%) in the LABA cohort and 826 (1.4%) in the LAMA cohort.

With regard to ischemic heart disease (myocardial infarction and/or (unstable) angina pectoris) as endpoint, there were 36 events (0.4%) in the NVA237 exposure cohort, 79 (0.4%) in the LABA exposure cohort and 410 (0.7%) in the LAMA exposure cohort. Cerebrovascular events (stroke and/or TIA) were reported in 42 (0.5%) patients of the NVA237 exposure cohort, 80 (0.5%) of the LABA cohort and 381 (0.7%) of the LAMA cohort.

As can be observed in Table 10-8, the number of events dropped almost by half when considering complete cases only and naive cases only. The reduction in number of events was mainly observed in the NVA237 naïve category where up to 75% of patients and events were lost.

10.3.2 Frequencies of additional events in the pooled database

Number of additional events of interest in the pooled data are presented in Table 10-9 below.

The number of additional events for the outcomes of interest, by database and exposure cohort, is presented in Annex 2.1 - Table 15-9.

Additional events with the highest frequency of occurrence were atrial fibrillation (66 events (0.8%) in the NVA237 exposure cohort, 114 (0.6%) in the LABA cohort and 613 (1.0%) in the LAMA cohort), hospitalization for heart failure (63 (0.7%) events in the NVA237 exposure cohort, 181 (1.0%) events in the LABA cohort and 722 (1.2%) in the LAMA cohort). Stroke as event was reported in 28 (0.3%) patients of the NVA237 exposure cohort, in 53 (0.3%) of the LABA cohort and 276 (0.5%) of the LAMA cohort.

The other endpoints had a frequency below 0.5% and are not discussed individually.

Table 10-8 Total number of patients and number of patients with main events by exposure cohorts (NVA237, LABA, LAMA (excl. NVA237)) - POOLED - Total analysis population, Complete Cases, Naive analysis population

	NVA237			LABA			LAMA (excl. NVA237)		
Pooled	**Total**	**Complete cases**	**Naive**	**Total**	**Complete cases**	**Naive**	**Total**	**Complete cases**	**Naive**
Total	8722	5509	2603	17890	10587	11144	58852	37224	26874
MACE	109	62	24	282	147	149	1247	639	482
Ischemic heart disease (any event of)	36	16	7	79	42	49	410	247	154
Cardiac arrhythmia (any event of)	87	52	25	171	92	98	826	453	301
Cerebrovascular disorders (any event of)	42	29	10	80	41	44	381	219	168
Mortality	182	98	39	260	110	135	1344	706	396

MACE = major adverse cardiovascular event

Table 10-9 Total number of patients and number of patients with additional events by exposure cohorts (NVA237, LABA, LAMA (excl. NVA237)) - POOLED - Total analysis population, Complete Cases, Naive analysis population

	NVA237			LABA			LAMA (excl. NVA237)		
Pooled	**Total**	**Complete cases**	**Naive**	**Total**	**Complete cases**	**Naive**	**Total**	**Complete cases**	**Naive**
Total	8722	5509	2603	17890	10587	11144	58852	37224	26874
Cardiac arrhythmia									
Atrial fibrillation/flutter	66	42	19	114	65	63	613	335	216
AV block	10	5	3	27	15	16	86	48	41
Long QT	0	0	0	0	0	0	2	0	1
Premature depolarization	7	2	1	19	7	13	65	40	24
Sick sinus	1	1	1	5	0	4	10	6	2
Supraventricular tachycardia	5	2	2	7	2	4	52	28	17
Torsades de Pointes	0	0	0	0	0	0	2	0	1
Ventricular tachycardia	1	0	0	4	3	2	14	8	4
Ventricular fibrillation	1	1	0	1	1	0	11	5	4

	NVA237			LABA			LAMA (excl. NVA237)		
Pooled	**Total**	**Complete cases**	**Naive**	**Total**	**Complete cases**	**Naive**	**Total**	**Complete cases**	**Naive**
Ischemic heart disease									
Angina pectoris	22	13	5	33	15	22	183	121	62
Myocardial infarction	13	5	1	36	24	22	194	107	74
Unstable angina pectoris	6	2	1	16	7	9	65	36	28
Hospitalization for acute coronary syndrome	12	3	3	45	23	24	207	108	90
Cerebrovascular events									
Stroke	28	21	7	53	27	27	276	161	121
TIA	16	10	3	29	15	19	127	72	59
Hospitalization for heart failure	63	35	14	181	87	95	722	338	262

AV = atrioventricular; TIA = transient ischemic attack

10.4 Main results

10.4.1 Incidence rates of main events across exposure cohorts

Database-pooled, crude incidence rates (with 95% CIs) for the main events of interest are presented in Table 10-10 and Annex 2.1 - Figure 15-32.

The crude incidence rate of death was comparable across all exposure cohorts namely 42.8/1,000 PY for the NVA237 exposure cohort, 42.3/1,000 PY for the LABA exposure cohort and 46.5/1,000 PY for the LAMA cohort.

The incidence rate of MACE was 46.5/1,000 PY in the LABA exposure cohort, 43.8/1,000 PY in the LAMA exposure cohort but considerably lower in the NVA237 exposure cohort (25.8/1,000 PY).

The crude incidence rate of cardiac arrhythmia was very similar in the LABA (28.0/1,000 PY) and the LAMA exposure cohort (28.9/1,000 PY) and lower in the NVA237 exposure cohort (20.6/1,000 PY).

The incidence rate of cerebrovascular events (stroke and/or TIA) was the lowest in the NVA237 exposure cohort, namely 9.9/1,000 PY, 13.1/1,000 PY in the LABA exposure cohort and 13.3/1,000 PY in the LAMA exposure cohort.

Finally, the incidence of ischemic heart disease (myocardial infarction and/or (unstable) angina pectoris) was the lowest in the NVA237 exposure cohort, namely 8.5/1,000 PY, 12.9/1,000 PY in the LABA exposure cohort and 14.3/1,000 PY in the LAMA exposure cohort.

Crude incidence rates for the main events by database and by exposure cohort are presented in Annex 2.1 - Table 15-10.

10.4.2 Incidence rates of additional events across exposure cohorts

Database-pooled, crude incidence rates for the additional events of interest are presented in Table 10-11.

Additional events with incidence rates above 10/1,000 PY included atrial fibrillation/flutter (15.6/1,000 PY in the NVA237 cohort, 18.6/1.000 PY in the LABA cohort and 21.4/1,000 PY in the LAMA cohort) and hospitalization for heart failure (14.8/1,000 PY in the NVA237 cohort, 29.7/1,000 PY in the LABA cohort and 25.2/1,000 PY in the LAMA cohort).

Crude incidence rates for the additional events of interest by database and by exposure cohort are presented in Annex 2.1 – Table 15-11.

Differences in incidence rates by database were reported with for instance the highest incidence rates of hospitalization for acute coronary syndrome (19.4-25.5/1,000 PY) and hospitalization for heart failure (43.3-120/1,000 PY) in Aarhus and the lowest corresponding incidence rates in HSD (0/1,000 PY and 0-5.5/1,000 PY respectively).

Mortality rates in Aarhus (88.4 to 130/1,000 PY [for all exposure cohorts]) were also higher compared to the other databases (range between 25.1-57.6/1,000 PY [for all exposure cohorts]) (Annex 2.1 - Table 15-10).

The incidence of AV block, especially for the NVA237 exposure cohort, was higher in IPCI (15.3/1,000 PY) compared to the incidence of AV block in the NVA237 exposure cohort of the other databases (range 0-7.8/1,000 PY) (Annex 2.1 - Table 15-11).

Table 10-10 Database-pooled, crude incidence rates for main events of interest, by exposure cohort

	NVA237				LABA				LAMA			
Pooled	**Events**	**PY**	**IR***	**95% CI**	**Events**	**PY**	**IR***	**95% CI**	**Events**	**PY**	**IR***	**95% CI**
MACE	109	4225	25.8	[21.9,30.2]	282	6067	46.5	[42.1,51.2]	1247	28457	43.8	[41.8,45.9]
Ischemic heart disease (any event of)	36	4243	8.5	[6.3,11.2]	79	6115	12.9	[10.6,15.6]	410	28741	14.3	[13.1,15.5]
Cardiac arrhythmia (any event of)	87	4222	20.6	[17.1,24.6]	171	6098	28.0	[24.6,31.8]	826	28573	28.9	[27.3,30.6]
Cerebrovascular disorders (any event of)	42	4240	9.9	[7.5,12.8]	80	6121	13.1	[10.8,15.7]	381	28753	13.3	[12.2,14.4]
Mortality	182	4257	42.8	[37.8,48.2]	260	6146	42.3	[38.2,46.8]	1344	28910	46.5	[44.5,48.6]

CI = confidence interval; IR = incidence rate; MACE = major adverse cardiovascular event; PY = patient-year
Note: * = IR per 1,000 PY

Table 10-11 Database-pooled, crude incidence rates for additional events of interest, by exposure cohort

	NVA237				LABA				LAMA			
Pooled	**Events**	**PY**	**IR***	**95% CI**	**Events**	**PY**	**IR***	**95% CI**	**Events**	**PY**	**IR***	**95% CI**
Incidence rates of cardiac arrhythmia												
Atrial fibrillation/flutter	66	4232	15.6	[12.6,19.1]	114	6116	18.6	[15.9,21.7]	613	28663	21.4	[20.0,22.8]
AV block	10	4254	2.4	[1.3, 4.0]	27	6135	4.4	[3.1, 6.1]	86	28889	3.0	[2.5, 3.6]
Long QT	0	4259	0.0	[0.0, 0.7]	0	6148	0.0	[0.0, 0.5]	2	28926	0.1	[0.0, 0.2]
Premature depolarization	7	4254	1.6	[0.8, 3.1]	19	6144	3.1	[2.0, 4.5]	65	28889	2.3	[1.8, 2.8]
Sick sinus	1	4259	0.2	[0.0, 1.1]	5	6147	0.8	[0.3, 1.7]	10	28922	0.3	[0.2, 0.6]
Supraventricular tachycardia	5	4258	1.2	[0.5, 2.5]	7	6146	1.1	[0.5, 2.1]	52	28908	1.8	[1.4, 2.3]
Torsades de Pointes	0	4259	0.0	[0.0, 0.7]	0	6148	0.0	[0.0, 0.5]	2	28926	0.1	[0.0, 0.2]
Ventricular fibrillation	1	4259	0.2	[0.0, 1.1]	1	6148	0.2	[0.0, 0.8]	11	28924	0.4	[0.2, 0.6]
Ventricular tachycardia	1	4258	0.2	[0.0, 1.1]	4	6147	0.7	[0.2, 1.5]	14	28920	0.5	[0.3, 0.8]
Incidence rates of ischemic heart disease												

	NVA237				LABA				LAMA			
Pooled	**Events**	**PY**	**IR***	**95% CI**	**Events**	**PY**	**IR***	**95% CI**	**Events**	**PY**	**IR***	**95% CI**
Angina pectoris	22	4248	5.2	[3.5, 7.4]	33	6131	5.4	[3.9, 7.2]	183	28827	6.3	[5.6, 7.2]
Unstable angina pectoris	6	4257	1.4	[0.6, 2.8]	16	6143	2.6	[1.6, 4.0]	65	28902	2.2	[1.8, 2.8]
Myocardial infarction	13	4254	3.1	[1.8, 4.9]	36	6136	5.9	[4.4, 7.7]	194	28851	6.7	[6.0, 7.6]
Hospitalization for acute coronary syndrome	12	4256	2.8	[1.6, 4.6]	45	6136	7.3	[5.6, 9.4]	207	28845	7.2	[6.4, 8.0]
Incidence rates of cerebrovascular events												
Stroke	28	4246	6.6	[4.7, 9.0]	53	6132	8.6	[6.8,10.9]	276	28808	9.6	[8.7,10.6]
TIA	16	4252	3.8	[2.4, 5.7]	29	6137	4.7	[3.4, 6.4]	127	28857	4.4	[3.8, 5.1]
Hospitalization for heart failure	63	4243	14.8	[11.9,18.3]	181	6099	29.7	[26.2,33.5]	722	28672	25.2	[23.7,26.8]

AV = atrioventricular; TIA = transient ischemic attack

Note: * = IR per 1,000 PY

10.4.3 Kaplan Meier Curves

Kaplan Meier curves by treatment cohort for the main outcomes of interest in the pooled dataset are presented in Annex 2.1 - Figures 15-33 to 15-37. As the survival probabilities at one year are still high, the Y-axis does not start at 0.

Kaplan Meier curves by categories of the a priori confounders in the pooled data set as well as curves by treatment cohort in the different databases are presented in Annex 2.11.

10.4.4 Hazard ratios for NVA237 vs. LABA and NVA237 vs. LAMA

The HRs of NVA237 in comparison to LABA and to LAMA for the different outcomes of interest are described in Table 10-12 and Table 10-13, respectively.

For this report, both crude HR, HR upon adjustment for a priori confounders (age, gender, smoking status and COPD severity [model 1]) and HR from IPTW analysis are described.

The HR upon adjustment for selected confounders (model 2) are provided in Annex 2.10– Statistical table set. These HR are not described in this report as they provided similar estimates compared to model 1, and this analysis (model 2) was hampered by small numbers.

Because of the low number of events in relation to the high number of selected confounders in model 2, the IPTW analysis was considered as the main model.

10.4.4.1 Hazard ratios for MACE (major adverse cardiovascular events)

The crude HR of MACE (myocardial infarction, stroke, and hospitalizations because of acute coronary syndrome and/or heart failure) in NVA237 users in comparison to LABA was 0.70 (95% CI 0.55-0.89). Upon adjustment for a priori confounders, this HR was 0.67 (95% CI 0.52-0.86). The HR from the IPTW analysis was 0.61 (95% CI 0.47-0.79) (Table 10-12).

The crude HR of MACE in NVA237 users in comparison to LAMA was 0.55 (95% CI 0.45-0.69). Upon adjustment for a priori confounders, this HR remained 0.55 (95% CI 0.45-0.69). The HR from the IPTW analysis was 0.56 (95% CI 0.44-0.71) (Table 10-13).

Database specific HRs are described in Annex 2.1 – Table 15-12 (crude), Annex 2.1 - Table 15-13 (model 1), and Annex 2.1 – Table 15-14 (IPTW). When exploring results by database, in none of the databases, the HR of MACE for NVA237 in comparison to LABA or LAMA was above 1. In IPCI, the HR was the highest, namely with a crude HR of 0.97 (95% CI 0.49-1.92) for the comparison of NVA237 with LABA and a crude HR of 0.83 (95% CI 0.45-1.50) for the comparison between NVA237 and LAMA. The crude HR was the lowest in Aarhus, with a crude HR of 0.48 (95% CI 0.27-0.87) for the comparison of NVA237 to LABA and a crude HR of 0.35 (95% 0.20-0.62) for the comparison of NVA237 to LAMA. In HSD, no HR for MACE could be estimated because of few MACE events (<5) in the respective exposure cohorts. With regard to the database specific HRs, upon adjustment by a priori confounders and when applying the IPTW analysis, the HRs remained constant.

The meta-analysis of the hazard ratios of model 1 provided similar estimates as for the pooled analysis, both for the random- and fixed-effect model (Figures provided in Annex 2.11). The meta-analysis of the IPTW results provided similar estimates as the pooled IPTW analysis,

both for the fixed- and random-effect model (Annex 2.1 - Figure 15-38 [NVA237 vs. LABA], and Annex 2.1 - Figure 15-39 [NVA237 vs. LAMA]).

In the pooled dataset, because there was an indication of interaction (p for interaction <0.10 in at least 3 imputed sets), a stratified analysis, adjusted for a priori and selected potential confounders (model 2), by gender was conducted showing a reduced risk of MACE for NVA237 users in comparison to LABA in females only (HR_{adj_model2} 0.31, 95% CI 0.18-0.53 in females and HR_{adj_model2} 0.88, 95% CI 0.66-1.18 in males). Differences by gender were less pronounced in the comparison of NVA237 to LAMA (HR_{adj_model2} 0.39, 95% CI 0.24-0.63 in females and HR_{adj_model2} 0.69, 95% CI 0.54-0.89 in males). (Annex 2.10– Statistical table set)

In addition, stratified analyses were conducted by age (age <70 or age ≥70) and by history of cardiovascular and cerebrovascular which did not show important differences in HRs.

10.4.4.2 Hazard ratios for ischemic heart disease (IHD)

The crude HR of IHD (myocardial infarctions and/or [unstable] AP) in NVA237 users in comparison to LABA was 0.80 (95% CI 0.53-1.23). Upon adjustment for a priori confounders, this HR remained 0.80 (95% CI 0.52-1.24). In the IPTW analysis, this HR was 0.74 (95% CI 0.46-1.17) (Table 10-12).

The crude HR of IHD in NVA237 users in comparison to LAMA use was 0.71 (95% CI 0.50-1.02). The HR remained approximately constant upon adjustment for a priori confounders (HR_{adj} 0.72, 95% CI 0.50-1.03), while in the IPTW analysis it was 0.67 (95% CI 0.46-0.99) (Table 10-13).

When exploring results by database, the crude HR of IHD for NVA237 in comparison to LABA was around 1 (HR estimate range 1.00-1.19) for IPCI, Aarhus and SIDIAP whereas this crude HR was 0.34 (95% CI 0.14-0.80) for THIN. The crude HR of IHD for NVA237 in comparison to LAMA was 0.35 (95% CI 0.16-0.75) for THIN, 0.72 (95% CI 0.29-1.78) for IPCI and 1.39 (95% CI 0.66-2.95) and 1.12 (95% CI 0.59-2.14) for Aarhus and SIDIAP respectively (Annex 2.1 - Table 15-12). No HR could be estimated for HSD because of low numbers. With regard to the database specific HRs, upon adjustment by a priori confounders and when applying the IPTW analysis, the HRs remained constant (Annex 2.1 - Table 15-13 [model 1], and Annex 2.1 - Table 15-14 [IPTW]).

The meta-analysis of the HRs of model 1 provided similar estimates as for the pooled analysis, both for the random- and fixed-effect model. (Figures provided in Annex 2.11). The meta-analysis of the IPTW results provided similar estimates as the pooled IPTW analysis, both for the fixed- and random-effect model (Annex 2.1 - Figure 15-40 [NVA237 vs. LABA], Annex 2.1 - Figure 15-41 [NVA237 vs. LAMA]).

In the pooled dataset, because there was an indication of interaction (p interaction <0.10 in at least 3 imputed sets), a stratified analysis by gender was conducted showing a reduced risk of IHD for NVA237 users in comparison to LABA in females only (HR_{adj_model2} 0.33, 95% CI 0.13-0.82 in females, and HR_{adj_model2} 1.15, 95% CI 0.69-1.91 in males). Differences by gender were less pronounced in the comparison of NVA237 to LAMA (HR_{adj_model2} 0.39, 95% CI 0.17-0.88 in females and HR_{adj_model2} 0.90, 95% CI 0.60-1.35 in males). (Annex 2.10– Statistical table set)

In addition, a stratified analysis was conducted by history of cardiovascular and cerebrovascular risks for the comparison between NVA237 with LABA showing that the risk of IHD was lower in patients without a history (HR_{adj_model2} 0.63, 95% CI 0.33-1.21) than in patients with a history (HR_{adj_model2} 0.95, 95% CI 0.53-1.69). In both groups, the association was not significant.

10.4.4.3 Hazard ratios for cardiac arrhythmia

Cardiac arrhythmia was a combined endpoint of atrial fibrillation/flutter, atrioventricular (AV) block, premature depolarization, sick sinus, supraventricular tachycardia and ventricular arrhythmia namely ventricular tachycardia, ventricular fibrillation and Torsade de Pointes/Long QT syndrome.

The crude HR of cardiac arrhythmia in NVA237 users in comparison to LABA was 0.86 (95% CI 0.65-1.14). The HR remained approximately constant upon adjustment for a priori confounders (HR_{adj} 0.85, 95% CI 0.64-1.13) and in the IPTW analysis (HR_{IPTW} 0.84, 95% CI 0.62-1.14) (Table 10-14).

The crude HR of cardiac arrhythmia in NVA237 users in comparison to LAMA was 0.67 (95% CI 0.53-0.85). The HR remained constant upon adjustment for a priori confounders (HR_{adj} 0.67, 95% CI 0.53-0.85) and IPTW analysis (HR_{IPTW} 0.69, 95% CI 0.53-0.90) (Table 10-15).

Large differences between databases were observed with a reduced risk of cardiac arrhythmia in Aarhus (HR crude 0.35, 95% CI 0.12-0.98, HR_{adj} 0.38, 95% CI 0.13-1.09 and HR_{IPTW} 0.30, 95% CI 0.11-0.87) and an increased risk in IPCI (HR_{crude} 2.27, 95% CI 1.01-5.09, HR_{adj} 2.38, 95% CI 1.03-5.47 and HR_{IPTW} 2.5, 95% CI 1.04-5.99) in NVA237 users compared to LABA users. This reduced risk in the Aarhus database was also observed in the comparison between NVA237 and LAMA, whereas the HR was around 1 in IPCI. In the other databases, the HR for cardiac arrhythmia in users of NVA237 relative to LAMA users was also below 1 but not always statically significant (Annex 2.1 - Table 15-12 [crude], Annex 2.1 - Table 15-13 [model 1], and Annex 2.1 - Table 15-14 [IPTW]).

The meta-analysis of the HRs of model 1 provided similar estimates as for the pooled analysis, both for the random- and fixed- effect model. (Figures provided in Annex 2.11). The meta-analysis of the IPTW results provided similar estimates as the pooled IPTW analysis, both for the fixed and random effect model (Annex 2.1 - Figure 15-42 [NVA237 vs. LABA], Annex 2.1 - Figure 15-43 [NVA237 vs. LAMA]).

In the pooled dataset, because there was an indication of interaction (p interaction <0.10 in at least 3 imputed sets), a stratified analysis by age category was conducted showing a non-significant reduced risk of cardiac arrhythmia for NVA237 users in comparison to LABA patients in patients ≥70 years (HR_{adj_model2} 0.75, 95% CI 0.53-1.05). This HR_{adj_model2} was 1.32 (95% CI 0.78-2.25) in patients < 70 years. Differences by age were less pronounced in the comparison of NVA237 to LAMA (HR_{adj_model2} 0.59, 95% CI 0.44-0.79 in patients ≥ 70 years versus HR_{adj_model2} 0.94, 95% CI 0.62-1.42 in patients <70 years). (Annex 2.10– Statistical table set)

10.4.4.4 Hazard ratios for cerebrovascular events

The crude HR of cerebrovascular events (stroke and/or TIA) in NVA237 users in comparison to LABA was 0.82 (95% CI 0.54-1.26). The HR remained approximately constant upon adjustment for a priori confounders (HR_{adj} 0.85, 95% CI 0.65-1.30) and in the IPTW analysis (HR_{IPTW} 0.82, 95% CI 0.54-1.23) (Table 10-12).

The crude HR of cerebrovascular events in NVA237 users in comparison to LAMA was 0.82 (95% CI 0.58-1.18). The HR remained approximately constant upon adjustment for a priori confounders (HR_{adj} 0.84, 95% CI 0.59-1.21) and in the IPTW analysis (HR_{IPTW} 0.80, 95% CI 0.54-1.19) (Table 10-13).

When exploring results by database, differences between databases were observed with a non-significant increased risk in THIN for NVA237 users compared to LABA users in the crude (HR_{crude} 1.60, 95% CI 0.76-3.37), adjusted (HR_{adj} 1.78, 95% CI 0.84-3.77) and IPTW analysis (HR_{IPTW} 1.81, 95% CI 0.84-3.86). In SIDIAP the HR of cerebrovascular events for NVA237 users compared to LABA users was below 1 namely HR_{crude} 0.41 (95% CI 0.16-1.06) , HR_{adj} 0.41 (95% CI 0.16-1.09) and a HR of 0.34 (95% CI 0.13-0.89) for the IPTW analysis (Annex 2.1 - Table 15-12 [crude], Annex 2.1 - Table 15-13 [model 1], and Annex 2.1 - Table 15-14 [IPTW]).

With regard to differences in HR for NVA237 users compared to LAMA, a non significant reduced risk of cerebrovascular events was observed in SIDIAP (HR_{crude} 0.52, 95% CI 0.21-1.31, HR_{adj} 0.54, 95% CI 0.21-1.35 and HR_{IPTW} 0.46, 95% CI 0.18-1.15). In HSD and Aarhus, the number of cerebrovascular events within the NVA237 exposure cohort was below 5 and no analysis was conducted (Annex 2.1 - Table 15-12 [crude], Annex 2.1 - Table 15-13 [model 1], and Annex 2.1 - Table 15-14 [IPTW]).

The meta-analysis of the HRs of model 1 provided similar estimates as for the pooled analysis, both for the random- and fixed-effect model. (Figures provided in Annex 2.11). The meta-analysis of the IPTW results provided similar estimates as the pooled IPTW analysis, both for the fixed-and random-effect model (Annex 2.1 - Figure 15-44 [NVA237 vs. LABA], Annex 2.1 - Figure 15-45 [NVA237 vs. LAMA]).

In the pooled dataset, because there was an indication of interaction (p interaction <0.10 in at least 3 imputed sets), for the association between NVA237 in comparison to LABA, a stratified analysis by presence of underlying history of cardio or cerebrovascular disease was conducted. This showed a non-significant reduced risk of cerebrovascular events for NVA237 users in comparison to LABA users in patients without a history (HR_{adj_model2} 0.52, 95% CI 0.27-1.02). This HR_{adj_model2} was 1.21 (95% CI 0.66-2.22) in patients with a history.

For the association between NVA237 in comparison to LAMA, an interaction by age was observed. In patients < 70 years, the risk of cerebrovascular events in NVA237 users compared to LAMA was 0.55 (95% CI 0.25-1.19) whereas it was 1.04 (95% CI 0.69-1.56) in patients 70 years or older. (Annex 2.10– Statistical table set).

10.4.4.5 Hazard ratios for mortality

The crude HR of mortality in NVA237 users in comparison to LABA was 1.02 (95% CI 0.83-1.27). The HR remained approximately constant upon adjustment for a priori confounders

(HR_{adj} 0.94, 95% CI 0.75-1.17) and in the IPTW analysis (HR_{IPTW} 0.88, 95% CI 0.71-1.11) (Table 10-12).

The crude HR of mortality in NVA237 users in comparison to LAMA was 0.91 (95% CI 0.77-1.08). The HR remained approximately constant upon adjustment for a priori confounders (HR_{adj} 0.92, 95% CI 0.77-1.09) and IPTW analysis (HR_{IPTW} 0.95, 95% CI 0.79-1.15) (Table 10-13).

When exploring results by database, the crude HR of mortality in NVA237 users compared to LABA users ranged between 0.79 (95% CI 0.41-1.53) (IPCI) and 1.29 (95% CI 0.87-1.92) (THIN) (Annex 2.1 - Table 15-12). Upon adjustment for a priori confounders these HR estimates decreased to 0.68 (95% CI 0.35-1.36) (IPCI) and 1.18 (95% CI 0.79-1.77) (THIN) (Annex 2.1 - Table 15-13). Upon IPTW analysis, the HR was 0.51 (95% CI 0.25-1.03) for IPCI and 1.14 (0.75-1.74) for THIN (Annex 2.1 - Table 15-14).

The crude HR of mortality in NVA237 users compared to LAMA users ranged between 0.64 (95% CI 0.41-1.01) (Aarhus) and 1.15 (95% CI 0.61-2.17) (HSD). These HR estimates remained the same upon adjustment for confounders. Upon IPTW analysis, the HR in IPCI changed from 0.97 (HR_{crude} 95% CI 0.54-1.76) to 0.60 (HR_{IPTW} 95% CI 0.31-1.18).

The meta-analysis of the HRs of model 1 provided similar estimates as the pooled analysis, both for the random- and fixed-effect model. (Figures provided in Annex 2.11). The meta-analysis of the IPTW results provided similar estimates as the pooled IPTW analysis, both for the fixed-and random-effect model (Annex 2.1 - Figure 15-46 [NVA237 vs. LABA], Annex 2.1 - Figure 15-47 [NVA237 vs. LAMA]).

For outcome mortality, for the association between NVA237 in comparison to LAMA and in comparison to LAMA, no covariate-by-treatment interactions were found.

Table 10-12 Database-pooled, hazard ratios for main events – NVA237 compared to LABA

NVA237 compared to LABA Pooled	NVA237	LABA	Crude			adjusted for a priori confounders (Model 1)			IPTW analysis		
Outcome	**n**	**n**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
MACE	109	282	0.70	[0.55,0.89]	0.0043	0.67	[0.52,0.86]	0.0017	0.61	[0.47,0.79]	0.0002
Ischemic heart disease (any event of)	36	79	0.80	[0.53,1.23]	0.3084	0.80	[0.52,1.24]	0.3256	0.74	[0.46,1.17]	0.1970
Cardiac arrhythmia (any event of)	87	171	0.86	[0.65,1.14]	0.2948	0.85	[0.64,1.13]	0.2690	0.84	[0.62,1.14]	0.2577
Cerebrovascular disorders (any event of)	42	80	0.82	[0.54,1.26]	0.3622	0.85	[0.55,1.30]	0.4467	0.82	[0.54,1.23]	0.3337
Mortality	182	260	1.02	[0.83,1.27]	0.8205	0.94	[0.75,1.17]	0.5582	0.88	[0.71,1.11]	0.2823

Model 1: Adjusted for age, gender, smoking status and COPD severity

CI = confidence interval; HR = hazard ratio; IPTW = inversed probability weighting; MACE = major adverse cardiovascular event

Table 10-13 Database-pooled, hazard ratios for main events – NVA237 compared to LAMA

NVA237 compared to LAMA Pooled	NVA237	LAMA	Crude			adjusted for a priori confounders (Model 1)			IPTW analysis		
Outcome	**n**	**n**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
MACE	109	1247	0.55	[0.45,0.69]	<.0001	0.55	[0.45,0.69]	<.0001	0.56	[0.44,0.71]	<.0001
Ischemic heart disease (any event of)	36	410	0.71	[0.50,1.02]	0.0651	0.72	[0.50,1.03]	0.0748	0.67	[0.46,0.99]	0.0455
Cardiac arrhythmia (any event of)	87	826	0.67	[0.53,0.85]	0.0009	0.67	[0.53,0.85]	0.0010	0.69	[0.53,0.90]	0.0052
Cerebrovascular disorders (any event of)	42	381	0.82	[0.58,1.18]	0.2840	0.84	[0.59,1.21]	0.3509	0.80	[0.54,1.19]	0.2708
Mortality	182	1344	0.91	[0.77,1.08]	0.2852	0.92	[0.77,1.09]	0.3263	0.95	[0.79,1.15]	0.5873

Model 1: Adjusted for age, gender, smoking status and COPD severity

CI = confidence interval; HR = hazard ratio; IPTW = inversed probability weighting; MACE = major adverse cardiovascular event

10.5 Sensitivity analysis

10.5.1 Analysis in complete naïve patients and in patients without missing data with regard to COPD severity and smoking (= complete cases)

When considering naïve patients or patients with complete data only, an important drop in number of events per exposure cohort was observed (Table 10-14).

HRs were calculated adjusted for age, gender, smoking status and COPD severity. In general, the adjusted HRs [model1] in complete cases and in naïve patients were comparable except for ischemic heart disease. Indeed, the HR for the association between use of NVA237, in comparison to LABA use, and risk of ischemic heart disease dropped from 0.80 (95% CI 0.52-1.24) in the total dataset to 0.52 (95% CI 0.28-0.98) in the complete cases-set and 0.50 (95% CI 0.21-1.19) in the naïve exposure population however with overlapping 95% CIs.

Similar findings were observed for the comparison with LAMA where the HR_{adj} for ischemic heart disease decreased from 0.72 (95% CI 0.50-1.03) in the total exposure cohort to 0.51 (95% CI 0.30-0.88) in the complete cases-set and 0.51 (95% CI 0.23-1.17) in the naïve dataset.

This analysis was also conducted per database, but interpretation was hampered because of low numbers. (Annex 2.10– Statistical table set)

Table 10-14 Database-pooled, adjusted (model 1) hazard ratios for main events – NVA237 compared to LABA and LAMA (analysis in naïve and complete cases)

Pooled		NVA237 compared to LABA					NVA237 compared to LAMA (excl. NVA237)			
Outcome		NVA237 events	LABA events	Adj. HR (model 1)	95% CI	p	LAMA events	Adj. HR (model 1)	95% CI	p
MACE	Total	109	282	0.67	[0.52,0.86]	0.0017	1247	0.55	[0.45,0.69]	<.0001
	Complete cases	62	147	0.62	[0.45,0.88]	0.0065	639	0.57	[0.43,0.77]	0.0002
	Naive	24	149	0.69	[0.43,1.13]	0.1415	482	0.48	[0.31,0.77]	0.0020
Ischemic heart disease	Total	36	79	0.80	[0.52,1.24]	0.3256	410	0.72	[0.50,1.03]	0.0748
	Complete cases	16	42	0.52	[0.28,0.98]	0.0435	247	0.51	[0.30,0.88]	0.0163
	Naive	7	49	0.50	[0.21,1.19]	0.1187	154	0.51	[0.23,1.17]	0.1116
Cardiac arrhythmia	Total	87	171	0.85	[0.64,1.13]	0.2690	826	0.67	[0.53,0.85]	0.0010
	Complete cases	52	92	0.85	[0.58,1.24]	0.3903	453	0.72	[0.53,0.98]	0.0345
	Naive	25	98	1.10	[0.69,1.75]	0.6965	301	0.84	[0.55,1.30]	0.4405
Cerebrovascular disorders	Total	42	80	0.85	[0.55,1.30]	0.4467	381	0.84	[0.59,1.21]	0.3509
	Complete cases	29	41	0.98	[0.56,1.72]	0.9425	219	0.97	[0.62,1.52]	0.8897
	Naive	10	44	0.74	[0.32,1.68]	0.4695	168	0.60	[0.28,1.28]	0.1842
Mortality	Total	182	260	0.94	[0.75,1.17]	0.5582	1344	0.92	[0.77,1.09]	0.3263
	Complete cases	98	110	0.95	[0.70,1.31]	0.7721	706	0.86	[0.68,1.10]	0.2374
	Naive	39	135	1.09	[0.74,1.62]	0.6650	396	1.14	[0.80,1.63]	0.4644

Model 1: Adjusted for age, gender, smoking status and COPD severity

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular event

10.5.2 Sensitivity analysis 2 – No censoring at start of other drug

In the main analysis, patients were censored at start of other study treatments. In a sensitivity analysis, patient's follow-up time was not censored at initiation of other treatment and events of interest were attributed to the first prescribed treatment.

As could be expected, the number of events of interest increased (Annex 2.1 - Table 15-15), but the obtained HR_{IPTW} were similar to the HR_{IPTW} of the main analysis (Annex 2.1 - Table 15-16).

10.5.3 Sensitivity analysis 3 – Wash-out period of 60 days

Next, a wash-out period of 60 days instead of 30 days was used. Here again, the number of endpoints increased (Annex 2.1 - Table 15-15), but the obtained HR_{IPTW} were similar to the HR_{IPTW} of the main analysis (Annex 2.1 - Table 15-16).

Database specific results are included in the supplement table set (available upon request).

10.5.4 Sensitivity analysis 4 – Analysis of total follow-up time

For this analysis, all database follow-up from the patients was used namely from the start of the first prescription of any of the exposure cohorts of interest until the end of the study (last data-cut off, death or patient leaving the practice whichever came first)

On the 'total follow-up cohort' three Cox regression models were run. In the first model, the HR comparing NVA237 episodes to non-NVA237 episodes was estimated, using a time-dependent variable 'NVA237 exposure'. In the second model, the same was done for LABA episodes, and in the third model for LAMA (NVA237 excluded) episodes. No other variables were included in these models. For each outcome, the first event following the first start of the treatment of interest was the outcome variable. Patients not experiencing the outcome were censored only at end of follow-up. All analyses were adjusted for age and gender.

In the analysis of complete follow-up time in the pooled data, for all outcomes the HRs shifted towards 1 compared to the HR_{IPTW}, both, for the comparison NVA327 with LABA and NVA237 with LAMA (Table 10-12, 10-13 and 10-15).

Because the estimated HRs for MACE were below 1, this analysis was further explored by selecting from the 'total follow-up cohort' only patients with at least one NVA237 exposure period. This ensures that all patients in the analysis set were eligible to receive NVA237. In this set, the time-dependent variable 'NVA237 exposure' was estimated. The same was done selecting patients with at least one LABA exposure period and patients with at least one LAMA exposure period. In these analyses, the HR comparing episodes with NVA237 exposure to episodes without NVA237 exposure was 0.73 (95% CI 0.60 – 0.91), while for LABA exposure, the corresponding HR was 0.96 (95% CI 0.84 – 1.1) and for LAMA it was 0.92 (95% CI 0.85 – 0.99).

Table 10-15 Database-pooled, hazard ratios for NVA237 vs. LABA and NVA237 vs. LAMA (excl. NVA237) from analyses complete follow-up (POOLED - Total analysis population)

				NVA237 compared to LABA			NVA237 compared to LAMA (excl. NVA237)			
Outcome	**N events during unexposed time**	**N events during NVA237 exposure**	**N events during LABA exposure**	**HR_{adj}**	**95% CI**	**p**	**N events during LAMA exposure**	**HR_{adj}**	**95% CI**	**p**
MACE	1810	152	438	0.80	[0.66, 0.96]	0.0182	1660	0.69	[0.58, 0.82]	<.0001
Ischemic heart disease (any event of)	709	53	144	0.74	[0.55, 1.02]	0.0626	543	0.80	[0.61, 1.04]	0.0967
Cardiac arrhythmia (any event of)	1605	104	237	0.96	[0.79, 1.18]	0.7041	972	0.84	[0.71, 1.00]	0.0538
Cerebrovascular disorders (any event of)	829	68	140	0.87	[0.65, 1.17]	0.3519	553	0.93	[0.72, 1.19]	0.5511
Mortality	4398	188	405	1.01	[0.84, 1.21]	0.9198	1589	0.97	[0.84, 1.14]	0.7448

HR adjusted for age and gender

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular event

Note: Total follow-up in years (not censored by events) with exposure to NVA237 was 6,686, to LABA 13,012, and to LAMA 49,532.

Exposure times can overlap so events can be counted in more than one exposure period.

10.6 Adverse events/adverse reactions

According to guidelines on good pharmacovigilance practice (EMA/873138/2011) there is no requirement for reporting of adverse drug reactions from secondary use of data (such as electronic health care databases).

11 Discussion

11.1 Key results

During the overall study period (01 November 2012 to 01 February 2016) three COPD cohorts were studied: new users of NVA237 (n=8,772), new users of LABA (n=17,890) and new users of LAMA (n=58,852). Range over databases of median duration of follow-up on treatment was 70-120 days for NVA237, 60-90 for LABA and 69-125 days for LAMA.

All three exposure cohorts were comparable in terms of age distribution and the mean age at cohort inception was approximately 70 years. The majority of patients had moderate COPD and the proportion of patients with very severe COPD tended to be highest in the NVA237 and LAMA cohorts. Underlying cardiovascular comorbidity was highly prevalent which was reflected in high use of concomitant medications for cardiovascular-related treatments.

With this study, we aimed to investigate cardiovascular and cerebrovascular comorbidity as well as mortality in association with use of NVA237. The main outcomes of interest were MACE, IHD, cardiac arrhythmia, cerebrovascular events and mortality. Results are presented for the IPTW analysis in the pooled dataset as this was considered the main model.

The HR_{IPTW} for NVA237 exposed patients to develop MACE in comparison to LABA use was 0.61 (95% CI 0.47-0.79) with similar findings (HR_{IPTW} 0.56, 95% CI 0.44-0.71) in comparison to LAMA use. The HR_{IPTW} for NVA237 exposed patients for IHD events in comparison to LABA use was 0.74 (95% CI 0.46-1.17) with similar results (HR_{IPTW} 0.67, 95% CI 0.46-0.99) relative to LAMA use.

A stratified analysis in the pooled dataset showed that women treated with NVA237 – in comparison to women treated with LABA or women treated with LAMA – had the lowest risk of MACE and the lowest risk of new IHD events.

The HR_{IPTW} for NVA237 exposed patients for cardiac arrhythmia in comparison to LABA use was 0.84 (95% CI 0.62-1.14). This HR_{IPTW} was 0.69 (95% CI 0.53-0.90) in comparison to LAMA use.

The risk (HR_{IPTW}) for cerebrovascular events in NVA237 exposed patients relative to LABA exposed patients was 0.82 (95% CI 0.54-1.23) with similar results for the comparison with LAMA (HR_{IPTW} 0.80, 95% CI 0.54-1.19).

Use of NVA237 was not associated with an increased risk of mortality with a HR_{IPTW} in comparison to LABA of 0.88 (95% CI 0.71-1.11) and a HR_{IPTW} in comparison to LAMA of 0.95 (95% CI 0.79-1.15).

Sensitivity analyses did not show important differences compared to the main analysis. Effect modification by gender is suggested as in females, the risk of MACE and of IHD was observed to be lower with the use of NVA237 compared to the use of LABA or LAMA.

The interpretation of the findings of this report in relation to other evidence is further discussed in Section 11.3 – 'Interpretation'.

11.2 Limitations

11.2.1 Limitations with regard to exposure

For this final study report, data from all databases were used and a cohort of 8,772 new users of NVA237 was identified. Although the number of patients within the exposure cohorts of interest is large, the duration of follow-up is shorter than expected. This can be explained by the creation of treatment episodes, where a patient is considered to have interrupted treatment in case there are more than 30 days between prescriptions. In addition, according to the protocol, treatment in the NVA237 or LAMA cohort is interrupted when treatment with LABA is added, and for the LABA cohort when treatment with LAMA (including NVA237) is added. Combination therapy (either fixed or single agent) in patients with COPD is becoming increasingly popular, which was also observed in this analysis when creating the exposure cohorts: e.g., in Aarhus 75% of NVA237 users could not be included because of concomitant LABA use (see also Annex 2.1 - Figure 15-3). In principle, LABA and LAMA combination therapy is only recommended for patients with more severe COPD, however in practice, due to the availability of fixed-dose combinations, it is expected that the proportion of COPD patients on dual bronchodilating therapy will increase (Singh 2015). In this study, patients on fixed-dose combinations of LABA/LAMA were not included as an exposure cohort. However, Novartis is sponsoring a similar, ongoing safety outcomes study focusing on its marketed fixed-dose combination of indacaterol/glycopyrronium (Ultibro® Breezhaler) (study code CQVA149A2402).

The sensitivity analyses in the strictly naïve patients was hampered because of low numbers of events. Indeed, the cohort size of NVA237 (and reported endpoints) dropped by almost 75% when selecting completely naïve NVA237 users (no use of any long-acting bronchodilating drugs in the year prior to index date, nor use of fixed combination of either LABA+LAMA or LABA+ICS). Also for LABA and LAMA, a drop in size was observed but not as markedly as for NVA237. The results of the analysis of the strictly naïve cohort, were in line with the results of the complete dataset and there was no indication of an increased risk of main endpoints in NVA237 users compared to LABA and LAMA users.

All databases, with the exception of Aarhus and SIDIAP, contain prescription as opposed to dispensing data. Exposure data for SIDIAP is based on prescription and dispensing data. For chronic therapy, patients attend specialists or GPs for the first prescription; later on, follow-up medication is dispensed by the pharmacy without need of further prescriptions (the so called "electronic dispensation"). The exact date (day/month/year) of pharmacy dispensing is unknown in SIDIAP, dates are available as month/year with the potential of non-differential misclassification. For all databases, it is not known whether the patient actually took the prescribed or dispensed medication. However, as adherence to drugs is highest at initiation of

therapy, the risk of misclassification of exposure is likely to be less worrisome in a new-user design such as in this study. (Lareau and Yawn 2010)

The indication for use of medicinal products is not available in all databases. Only IPCI and HSD capture the indication of use within the prescription files. However, this is not 100% complete. To check the indication of use for systemic corticosteroids and antibiotics, the medical file was searched for relevant disease codes within a maximum of one month prior and one week after prescription start. The validity of this approach depends on appropriate coding. That is, the degree of underestimation of prescription indication (e.g., systemic corticosteroids for COPD exacerbation and antibiotics for lower respiratory tract infections) will correspond to the degree to which non-coding or coding of symptoms/diagnosis, has occurred.

11.2.2 Limitations with regard to COPD, comorbidity and endpoint identification

When using spirometry data to determine COPD severity, patients were considered not to have COPD if the FEV_1/FVC ratio was above 70%. When this criterion was applied, up to 30% of patients in THIN, IPCI, Aarhus and SIDIAP were considered not to have COPD. In HSD, around 50% of patients amongst all exposure cohorts were considered not to have COPD. It should be noted however, that the FEV_1/FVC ratio underestimates COPD in the young and overestimates COPD in the elderly. (Wollmer and Engstrom 2013) Ideally, we would have used the lower limit of normal of the FEV_1/FVC ratio, however this is not routinely available in primary care databases (Wollmer and Engstrom 2013).

As part of the final analysis, in IPCI, HSD and SIDIAP, a sample (500 per exposure cohort per database) of COPD patients was validated by medically trained personnel according to a predefined algorithm. The positive predictive value (PPV) of COPD (identified via disease codes) was high with a PPV of 89.1% for SIDIAP, 93.5% for HSD and 96.7% for IPCI. This is in contradiction to the spirometry results for HSD (although spirometry data were limited in size, as only available in up to 30% of the HSD population) suggesting that, in HSD, there might be a mix-up between FEV_1/FVC ratio and the FEV_1/FVC ratio as percentage of expected ratio.

Co-morbidity and endpoints were assessed via disease-specific codes. If disease coding is inconsistent or different across exposure cohorts, diagnostic bias could have affected the validity of results. Previous validation studies for these databases have shown that coding is reliable and that these databases are suitable for pharmaco-epidemiologic research (Vlug et al 1999, Lewis et al 2007, Ehrenstein, Antonsen, and [redacted], Cazzola et al 2011, Garcia-Gil et al 2011). However, these studies did not focus on respiratory epidemiology with the exception of the Cazzola paper which studied the prevalence of asthma and COPD in HSD (Cazzola et al 2011). Still, some differences in prevalences of underlying co-morbidity and differences in incidence rates were observed between the databases. In IPCI, the proportion of patients with a history of heart failure and lung cancer was higher than in the other databases. In IPCI, diseases are coded via the ICPC (International Classification of Primary Care) coding system, which is a relatively simple coding system but with the disadvantage that it lacks granularity to substantiate patient-specific diagnoses. Also the proportion of asthma was

higher in THIN and IPCI compared to the other databases. Large ranges were also observed for hepatic impairment. Although search codes have been defined based on UMLS, large variation might exist in the sensitivity and specificity of these codes. To account for this, for those databases where free-text is available (i.e., IPCI, HSD and SIDIAP), a sample of COPD patients and all endpoints were validated, according to a validation protocol. In addition, for IPCI, a free text search was conducted. Validation of certain outcomes proved to be difficult, first of all, because free text around the disease code was limited, especially in HSD and SIDIAP. Also in SIDIAP, because of new internal procedures with regard to data privacy, free text can only be searched in the 3 months around the disease code. If limited data was available it was difficult to investigate whether it considered a new event or an event referring to what happened in the past. If information was missing and the patient already had the disease code in the past, the event was classified as a "non-case" explaining the drop of events for the final report compared to the interim report. As validation was done blinded to exposure, this drop is suspected to be non-differential by exposure cohort. This drop of events was limited in IPCI, first of all, because IPCI contains a lot of free text and second because additional events were identified via free text searches.

For those databases where linkage with the hospital database registries is possible (i.e. Aarhus and SIDIAP), the number of patients with events for outcomes of interest, such as hospitalization for acute coronary syndrome and hospitalization for heart failure, is higher than in those databases where direct linkage is not possible (THIN, IPCI and HSD). In HSD, hospitalization is not well documented which is reflected in the results with lower proportions of hospitalization for COPD exacerbation, ACS and heart failure compared to the other databases.

Mortality rates were the highest in Aarhus across exposure cohorts which makes sense as COPD patients identified in Aarhus represented patients with more severe COPD. Also Aarhus is the only database which automatically links to the Danish death register, thus misclassification of death in Aarhus is unlikely.

Patients with a medical history of cardiovascular and cerebrovascular events were not excluded from this study. First, these patients were not excluded because many COPD patients do have underlying cardiovascular and cerebrovascular comorbidity and the aim was to select a group of patients which a representative of patients with COPD under real life circumstances. Second, these patients were not excluded in order not to jeopardize sample size. Indeed, in this report, up to 60% of the patients had a medical history of cardiovascular or cerebrovascular events. By keeping these patients in however, there is the potential of misclassification of outcomes, as for these patients it is much more difficult to assess whether we deal with a new event or whether it refers to an event that happened in the past. To overcome the issue of misclassification, all databases received clear instructions emphasizing that only new events during follow-up should be considered. In addition, interaction by underlying cardiovascular and cerebrovascular comorbidity was investigated and if needed, a stratified analysis was done. These stratified analyses (for the endpoints MACE, ischemic heart disease and cerebrovascular events) did not show an increased risk associated with NVA237 treatment for these endpoints in patients without a history of cardiovascular and/or cerebrovascular diseases.

11.2.3 Correction of potential confounders

As for all observational research, there is the potential of bias and confounding. Especially when investigating drugs newly introduced onto the market, channeling bias is a concern, where physicians prescribe drugs differently based on the patient's profile (Petri and Urquhart 1991).

We adjusted for confounding through adjustment of a priori defined confounders i.e. age, gender, smoking status and COPD severity. In addition, we conducted an analysis where we not only adjusted for a priori defined confounders but also added predefined potential confounders, selected in each model based on their influence on the estimated HR for treatment. This model however was hampered by low numbers and for this reason, the IPTW analysis was considered as the main model.

A sensitivity analysis was conducted considering treatment naïve patients only (naïve of all exposure cohort drugs and associated fixed combinations within the one year prior to treatment start). This analysis was chosen to reduce the risk of treatment tolerability and COPD status as this analysis was conducted in incident users of monotherapy with either a LABA or LAMA (including NVA237). Unfortunately, this analysis was hampered by low numbers and especially for the NVA237 exposure cohort, the number of patients which remained in the analysis dropped by more than 70%. This happened as many of the NVA237 users had used either LABA, LAMA and/or the fixed combination of LABA+ICS in the one year prior to the index date. The pooled HR_{adj_model1} (adjusted for age, gender, smoking status and COPD severity) provided comparable estimates to the pooled HR_{adj_model1}considering the complete dataset with even a more reduced risk for ischemic heart disease.

Because NVA237 was launched only recently, NVA237 exposure episodes may generally lay later in calendar time than LABA and LAMA episodes. This may introduce ascertainment bias where available follow-up time after end of cohort time (= end exposure) is shorter for NVA237 compared to LABA and LAMA. Therefore, a *post-hoc* analysis was done in the pooled data, for the outcome MACE, adjusting the IPTW analysis for 'follow-up time after cohort time', i.e. number of days of follow-up available after end of cohort time. The median of this characteristic was 273 days in the NVA237 cohort, 440 in the LABA cohort, and 289 days in the LAMA cohort. After adjustment for this variable, the HR for NVA237 compared to LABA was still 0.57 (95% CI 0.44 – 0.74) and the HR compared to LABA was 0.55 (95% CI 0.43 – 0.69).

Despite these efforts, we cannot rule out the potential of remaining unmeasured confounding. Indeed, based on the mechanism of action, it is unlikely to assume that the risk of MACE would be lower for NVA237 users compared to LABA and LAMA users, although this is what we observe in our data. Such a finding can be explained in case GPs prescribe NVA237 to younger, healthier patients with less severe COPD but this is not in line with our description of patient characteristics of NVA237 patients in comparison to LABA and LAMA.

11.3 Interpretation

This final report describes the risk of cardio- and cerebrovascular outcomes and mortality in COPD patients initiating therapy with NVA237 compared to COPD patients initiating LAMA (excluding NVA237) or LABA therapy. We observed negative associations between the use

of NVA237 and risk of MACE (in comparison to LABA and LAMA), IHD and cardiac arrhythmia (in comparison to LAMA) and no association between NVA237 and all-cause mortality and cerebrovascular events.

These data are in line with recent literature on the safety of LAMAs and glycopyrronium in particular.

In 2014, results from a pooled safety analysis of the fixed-dose combination of indacaterol and glycopyrronium (QVA149), its monocomponents and tiotropium versus placebo were published using data from 14 RCTs including more than 11,000 patients (Wedzicha et al 2014). Use of glycopyrronium, in comparison to placebo, was not associated with an increased risk of mortality or MACE. For serious cardiovascular and cerebrovascular events, even a (statistically not significant) negative association was observed (adjusted HR 0.56, 95% CI 0.29-1.09)

A recent meta-analysis investigated the safety of inhaled glycopyrronium (50 µg) compared to tiotropium (18 µg) or placebo (D'Urzo et al 2015). In total, data from 6 RCTs (> 4,000 COPD patients) were included. Apart from the RCT data, this study also evaluated spontaneous reports that were reported as part of the post-marketing surveillance phase of glycopyrronium bromide. The overall incidence of adverse events and deaths was similar across treatment arms and there were no new safety reports during the post-marketing surveillance phase that suggested an increased risk compared to results from the clinical trials. The IR of death (9.7/1,000 PY) in the glycopyrronium arm is lower than is reported in our data (42.8/1,000 PY), but the study by D'Urzo et al used data from RCTs whereas for this report, real-world data was used (D'Urzo et al 2015).

In 2016, the cardiovascular and cerebrovascular safety of inhaled long-acting bronchodilating drugs in patients with COPD were studied (Dong et al 2016). In that retrospective cohort study, data from a population-based health care database from Taiwan was used and safety of LABA, LAMA was compared to the combination of LABA and LAMA. MACE was defined as hospitalization for acute myocardial infarction, congestive heart failure, and stroke. Safety was comparable between LAMA and LABA with a crude incidence rate of MACE within the LAMA exposure cohort of 53/1,000 PY and in the LABA exposure cohort of 45.9/1,000 PY. These crude incidence rates of MACE are comparable to the crude incidence rates of LABA and LAMA as presented in this report except for the IR of MACE in the NVA237 exposure cohort which was lower (25.8/1,000 PY) (Dong et al 2016).

In 2017, results from a UK database cohort study were published investigating the risk of cardiovascular, cerebrovascular and pulmonary adverse events in tiotropium initiators (LAMA) vs. new users of LABA ([redacted]). In this cohort, 26,442 tiotropium initiators were matched (on propensity scores) to 26,442 initiators of LABA. No increased risk of myocardial infarction, stroke, arrhythmia and heart failure was observed for tiotropium relative to LABA with HRs around 1. Results from this study thus also suggest that the use of LAMA, in comparison to LABA, does not increase the risk of cardiovascular and cerebrovascular outcomes.

There have been reports on an increased risk of cardiac arrhythmia in patients treated with LAMA (including glycopyrronium bromide) (Lahousse et al 2016). In the pooled dataset of this PASS, no increased risk of cardiac arrhythmia was observed. However in IPCI, the risk of

cardiac arrhythmia was 2.5-fold higher in NVA237 users relative to LABA (HR_{IPTW} 2.50, 95% CI 1.04-5.99). This signal was not identified in the last interim report which is explained by the fact that in IPCI, in preparation of the final report, a free text search on cardiac arrhythmia was done. These additional events mainly considered first grade AV block reported as part of an automatic ECG reading. According to the previous version of the Dutch primary care guideline (which was in place at the time of data collection), LAMA relative to LABA was preferably prescribed to patients with underlying cardiovascular comorbidities (Smeele 2009).It is unclear whether the association is real or confounded by preferential ECG use in LAMA versus LABA users. If real, it is remarkable that no association was observed in the other databases.

We observed a negative association between use of NVA237 and risk of MACE (in comparison to LABA and LAMA), IHD and cardiac arrhythmia (in comparison to LAMA) was observed. Based on the mechanism of action, it is unlikely to assume that the risk of these cardiovascular events would be lower for NVA237 users compared to LABA or other LAMA users, although this is what we observe in our data. Such a finding can be explained in case GPs prescribe NVA237 to younger, healthier patients with less severe COPD but this is not in line with our description of patient characteristics of NVA237 patients in comparison to LABA. The NVA237 Summary of Product characteristics advices precaution when NVA237 is prescribed to patients with impaired kidney function (GFR<30 mL/min/1.73 m^2) and to patients with underlying cardiovascular disease (unstable ischemic heart disease, left heart failure, medical history of myocardial infarction and cardiac arrhythmia) but so does the label of tiotropium, the first LAMA which was introduced onto the market. Also the label of LABA advices precaution when LABA is initiated in patients with underlying cardiovascular disease. The negative association between use of NVA237 and risk of cardiovascular events can thus not be explained by a difference in label, however, instruction guidelines might be better adhered to for new drugs.

In our study, MACE was the composite endpoint of myocardial infarction, stroke, and hospitalizations due to acute coronary syndromes and/or heart failure. Especially the incidence of hospitalisation for heart failure (14.8/1,000 PY) and hospitalization for acute coronary syndrome (2.8/1,000 PY) was much lower for NVA237 compared to LABA (29.7 and 7.3/1,000 PY, respectively) and LAMA (25.2 and 7.2/1,000 PY, respectively). Also, the negative association was mainly observed for Aarhus and SIDIAP but these are the only databases that allow linkage with hospital data. Differential reporting of endpoints for NVA237 exposed patients compared to LABA or LAMA exposed patients is unlikely as endpoint validation was blinded to exposure status.

Effect modification by gender was reported where women treated with NVA237 had a reduced risk of MACE compared to women treated with LABA. This reduced risk was not observed in males. It is unclear whether this association is real or based on residual confounding. In May 2017, an article was published on gender-related responsiveness to pharmacological treatment in COPD reporting a higher ratio in gene expression for M3 muscarinic receptor compared to males (Calzetta 2017). This might potentially translate into higher efficacy of LAMAs in females but whether this would also translate into a reduced risk of cardiovascular endpoints is unclear.

For this final report, we reported results on patient demography, COPD characteristics, underlying comorbidity, previous use of respiratory drugs and concomitant use of both respiratory and non-respiratory drugs. Based on the results of these covariates, we made the following observations. Age at cohort entry was comparable across the five databases, but somewhat higher than reported in RCTs and a large prospective cohort study (Agusti et al 2010, D'Urzo et al 2011, Kerwin et al 2012, Wise et al 2013). In IPCI, THIN and Aarhus, smoking status was comparable amongst exposure cohorts and between databases. The proportion of never-smokers was the highest for HSD (Italy) and SIDIAP (Spain). It is known that smoking is one of the main risk factors of COPD however, it is estimated that 25-45% of patients with COPD have never smoked (Salvi and Barnes 2009, Lamprecht et al 2011). Although the proportion of never-smokers among COPD patients is likely to increase over the coming years, it is difficult to assume that this would only hold for Spain. In addition, the high proportion of COPD in never-smokers is mainly reported in non-European countries. Within the databases that were used in this study, data on smoking is not prospectively collected. The potential for misclassification of smoking, especially between "non-smoking" and "past-smoking", cannot be ruled out. The proportion of patients with missing information on smoking status was the lowest for SIDIAP and THIN and the highest for Aarhus. There is literature suggesting that those with missing data are more often non-smokers (Marston et al 2014).

Second, the proportion of patients with COPD exacerbations, requiring either hospitalization or the need of treatment with systemic corticosteroids or antibiotics, was lower (except for IPCI) than reported in the RCTs with glycopyrronium bromide (D'Urzo et al 2011) and the observational ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) cohort study (Agusti et al 2010). However, it must be noted that both the RCTs and the ECLIPSE study mainly recruited patients from secondary care, thereby having recruited patient populations with greater COPD severity than the COPD population in this study. In addition, as only Aarhus and SIDIAP are linked to hospital databases, we might underestimate hospitalization for COPD exacerbations in the other databases.

Third, the number of patients with underlying cardiovascular co-morbidities was high. We know from epidemiologic research that the prevalence of underlying cardiovascular co-morbidity is elevated in patients with COPD (Smith and Wrobel 2014). COPD and cardiovascular diseases share the same major risk factors, namely smoking and ageing (Maclay and MacNee 2013, Miller et al 2013), and according to recently updated GOLD definitions, COPD is a systemic disease characterized by extra-pulmonary manifestations and co-morbidities including cardiovascular diseases (GOLD 2017).

Fourth, the proportion of patients with a diagnosis of asthma in their medical records was high for all exposure cohorts, with the highest proportions in the UK (THIN) (32.5% in the NVA237 cohort) and The Netherlands (IPCI) (32.1% in the LABA cohort). High prevalence of asthma in patients with COPD are well documented in the respiratory literature, and we also know that the proportion of patients with asthma-COPD overlap syndrome (ACOS) increases with age (Gibson and Simpson 2009, van der Molen 2010). However, it is also known that GPs are frequently unable to make a differential diagnosis between asthma and COPD, especially in the elderly population [redacted]

Fifth, in all databases, the LAMA cohort was considerably larger than the LABA cohort. One explanation could be that, when GPs decide to prescribe a LABA to a COPD patient, they prefer to prescribe a fixed combination of LABA+ICS instead of LABA and ICS in 2 separate inhalers. In addition, RCTs have shown that LAMAs are more effective in the prevention of COPD exacerbations than LABAs (Vogelmeier et al 2011, Decramer et al 2013).

For this final report, more than 8,700 NVA237 patients were included. Although the cohort size is much higher than what was estimated for the sample size calculation (=2,079 NVA237 users), the median duration of follow-up on treatment (70-120 days) of the NVA237 cohort is lower than the 180 days that was anticipated. Because of the large sample size, we have in total more than 4,200 person-years of follow-up which fulfills the minimal criteria for the sample size calculation although the number of patients with a long duration of first treatment episode is limited.

11.4 Generalizability

We used real-world data from five European electronic primary care databases for this study. While the large sample size might allow for extrapolation of some of the results to the general population of COPD patients who initiate treatment with NVA237, LABA or LAMA in various European regions, generalizability may not be appropriate for results for which differences between the databases have been observed.

12 Other information

On 27nd October 2017 a SAC teleconference was held to discuss the final report.

The SAC suggested making clarifications with regard to the method, result and interpretation section which have been implemented. No request for additional analyses was made.

In addition, they made the following observations:

The median duration of follow-up on treatment was short (95 days for NVA237, 62 days for LABA and 91 days for LAMA [excl. NVA237] in the pooled dataset) and the number of events was low (<3%). This short follow-up time in the three exposure cohorts is probably due to the fact that the follow-up time for each patient ended not only at end of treatment, end of study or death, but also when there was a change in treatment (including a switch to other drugs, but also add-on of other study drugs). This implicates that this report can make only firm conclusions with respect to the short-term safety of NVA237 in patients with COPD in real life. To investigate the long-term safety of NVA237 (or other LAMA), further research would be needed such as observational cohort studies where the follow-up (time) continues even if additional drugs are added. Sensitivity analysis 4 investigated the safety of NVA237 in comparison to LABA or LAMA considering the complete patient's follow-up (not censoring upon treatment discontinuation or add-on therapy) since study start, but this analysis was only adjusted for age and gender.

The Hazard Ratio (HR) for MACE and cardiac arrhythmia was lower in NVA237 users compared to LAMA users (the most appropriate control group); however, the HR of mortality was not decreased. These data suggest that other causes of death (non-CV death) might be higher in NVA237 users than in LAMA users.

To control for prevalent use of any of the comparator drugs, a sensitivity analysis was conducted considering naïve patients only (patients naïve to any of the exposure treatments, also including fixed combination LABA+ICS and LABA+LAMA, in the 1 year prior to start of cohort treatment). This analysis was hampered by low numbers but the pooled HR_{adj_model1} provided comparable estimates to the pooled HR_{adj_model1}considering the complete dataset.

The SAC suggested revising the conclusion not making a general statement that for none of the outcomes, the risk was higher for the NVA237 exposure cohort compared to the LABA or the LAMA exposure cohort as this would imply that a protective effect (as observed for MACE and cardiac arrhythmia) would be interpreted in the same way as a HR around 1.The SAC also suggested to speak of observations in terms of "associations", with "risks" reserved when speaking specifically about a causal interpretation.

13 Conclusion

During the study period from 2012 to 2016, COPD patients identified in five European healthcare databases who were newly prescribed/dispensed with either NVA237 (n=8,772), LABA (n=17,890), or LAMA (n=58,852) were selected into corresponding cohorts.

Age and gender was comparable between pooled exposure cohorts and in terms of COPD severity, the majority of patients had moderate COPD and the proportion of patients with very severe COPD tended to be highest in the NVA237 and LAMA cohort. Underlying cardiovascular comorbidity was found in the majority of patients, across exposure cohorts, which in turn, was reflected in the high use of concomitant medications for cardiovascular comorbidities.

We observed no association between NVA237 and all-cause mortality and cerebrovascular events. The negative associations between the use of NVA237 and risk of MACE (in comparison to LABA and LAMA), IHD and cardiac arrhythmia (in comparison to LAMA) must be interpreted with caution, as it may be an indication of bias in favor of NVA237.

14 References (available upon request)

Agusti A, Calverley PM, Celli B, et al (2010) Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res; 11:122.

American Diabetes Association (2012) Diagnosis and classification of diabetes mellitus. Diabetes Care; 35 Suppl 1:S64-71.

Anon. (2007) Summary of the 2007 European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines for the management of arterial hypertension. Vasc Health Risk Manag; 3(6):783-95.

Bateman ED, Hurd SS, Barnes PJ, et al (2008) Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J; 31(1):143-78.

Breekveldt-Postma NS, Koerselman J, Erkens JA, et al (2007) Enhanced persistence with tiotropium compared with other respiratory drugs in COPD. Respir Med; 101(7):1398-1405.

Calzetta L, Puxeddu E, Rogliani P (2017) Gender-related responsiveness to the pharmacological treatment of COPD: A first step towards the personalized medicine. EBioMedicine; 19:14-5.

Camm AJ, Kirchhof P, Lip GY, et al (2010) Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J; 31(19):2369-429.

Casson RJ, Chidlow G, Wood JP, et al (2012) Definition of glaucoma: clinical and experimental concepts. Clin Experiment Ophthalmol; 40(4):341-9.

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.

Coloma PM, Valkhoff VE, Mazzaglia G, et al (2013) Identification of acute myocardial infarction from electronic healthcare records using different disease coding systems: a validation study in three European countries. BMJ Open; 3(6):e002862

Cricelli C, Mazzaglia G, Samani F, et al (2003) Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. J Public Health Med; 25(3):254-7.

[redacted].

D'Urzo A, Ferguson GT, van Noord JA, et al (2011) Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. Respir Res; 12:156.

D'Urzo AD, Kerwin EM, Chapman KR, et al (2015) Safety of inhaled glycopyrronium in patients with COPD: a comprehensive analysis of clinical studies and post-marketing data. Int J Chron Obstruct Pulmon Dis; 10:1599-612.

Decramer M, Chapman KR, Dahl R, et al (2013) Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. Lancet Respir Med; 1(7):524-33.

[redacted]

Dickstein K, Cohen-Solal KA, Filippatos G, et al (2008) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J; 29(19):2388-442.

Dong YH, Chang CH, Gagne JJ, et al (2016) Comparative cardiovascular and cerebrovascular safety of inhaled long-acting bronchodilators in patients with chronic obstructive pulmonary disease: A population-based cohort study. Pharmacotherapy; 36(1):26-37.

Dong YH, Lin HH, Shau WY, et al (2013) Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. Thorax; 68(1):48-56.

Easton JD, Saver JL, Albers GW, et al (2009) Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke; 40(6):2276-93.

[redacted]

Eisner MD, Trupin L, Katz PP, et al (2005) Development and validation of a survey-based COPD severity score. Chest; 127(6):1890-7.

Epstein M (2005) Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf; 14(8):589-95.

European Medicines Agency (2005) Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired heopatic function. Available from <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003122.pdf>.

European Medicines Agency (2011) The ENCePP Code of Conduct – for Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies. Available from: <http://www.encepp.eu/code_of_conduct/documents/CodeofConduct_Rev2.pdf> (Accessed 13 November 2015).

European Medicines Agency (2012) Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies. Available from: < http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500123204.pdf> (Accessed 31 August 2012).

[redacted]

Filippi A, Vanuzzo D, Bignamini AA, et al (2005) The database of Italian general practitioners allows a reliable determination of the prevalence of myocardial infarction. Ital Heart J; 6(4):311-4.

Fox K, Garcia MA, Ardissino D, et al (2006) Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J; 27(11):1341-81.

[redacted]

Gibson PG, Simpson JL (2009) The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax; 64(8):728-35.

GOLD (2016) Global Strategy for Diagnosis, Management, and Prevention of COPD - 2016. Available from <http://goldcopd.org>

GOLD (2017) Global Strategy for the Diagnosis, Management and Prevention of COPD. Available from <http://goldcopd.org> (accessed on 25 September 2017).

Goldstein LB, Bushnell CD, Adams RJ, et al (2011) Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke; 42(2):517-84.

Greenland S, Daniel R, Pearce N (2016). Outcome modelling strategies in epidemiology: traditional methods and basic alternatives. Int J Epidemiol; 45(2): 565-75.

Huetsch JC, Uman JE, Udris EM, et al (2013) Predictors of adherence to inhaled medications among veterans with COPD. J Gen Intern Med; 27(11):1506-12.

[redacted].

Kerwin E, Hebert J, Gallagher N, et al (2012) Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. Eur Respir J; 40(5):1106-14.

[redacted]

Lamprecht B, McBurnie MA, Vollmer WM, et al (2011) COPD in never smokers: results from the population-based burden of obstructive lung disease study. Chest; 139(4):752-63.

Lareau SC, Yawn BP (2010) Improving adherence with inhaler therapy in COPD. Int J Chron Obstruct Pulmon Dis; 5:401-6.

Lee TA, Pickard AS, Au DH, et al (2008) Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. Ann Intern Med; 149(6): 380-90.

Levey AS, Coresh J (2012) Chronic kidney disease. Lancet; 379(9811):165-80.

Levey AS, Stevens LA, Schmid CH, et al (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med; 150(9):604-12.

Lewis JD, Schinnar R, Bilker WB, et al (2007). Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. Pharmacoepidemiol Drug Saf; 16(4):393-401.

Lobo FS,Wagner S, Gross CR, et al (2006) Addressing the issue of channeling bias in observational studies with propensity scores analysis. Res Social Adm Pharm; 2(1):143-51.

Maclay JD, MacNee W (2013) Cardiovascular disease in COPD: mechanisms. Chest; 143(3):798-807.

Marston L, Carpenter JR, Walters KR, et al (2014) Smoker, ex-smoker or non-smoker? The validity of routinely recorded smoking status in UK primary care: a cross-sectional study. BMJ Open; 4(4):e004958.

Michele TM, Pinheiro S, Iyasu S (2010) The safety of tiotropium – the FDA's conclusions. N Engl J Med; 363(12):1097-9.

Miller J, Edwards LD, Agusti A, et al (2013) Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. Respir Med; 107(9):1376-84.

Molero E, Diaz C, Sanz F, et al (2015) The EU ADR Alliance: A federated collaborative network for drug safety studies. Available from <http://synapse-pi.com/new_web/wp-content/uploads/2013/12/EU-ADR-alliance1.pdf> (accessed 13 November 2015).

Pauwels RA, Buist AS, Ma P, et al (2001) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. Respir Care; 46(8):798-825.

Petri H, Urquhart J (1991) Channeling bias in the interpretation of drug effects. Stat Med; 10(4):577-81.

[redacted].

Salvi SS, Barnes PJ (2009) Chronic obstructive pulmonary disease in non-smokers. Lancet; 374(9691):733-43.

Singh S, Loke YK, Enright PL, et al (2011) Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. BMJ; 342:d3215.

Singh S, Loke YK, Furberg CD (2008) Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA; 300(12):1439-50.

Smeele IJM (2009) NHG-Standaard COPD, Bohn Stafleu van Loghum, Houten.

Smith MC, Wrobel JP (2014) Epidemiology and clinical impact of major comorbidities in patients with COPD. Int J Chron Obstruct Pulmon Dis; 9:871-88.

Sorensen HT, Larsen BO (1994) A population-based Danish data resource with possible high validity in pharmacoepidemiological research. J Med Syst; 18(1):33-8.

Soriano JB, Maier WC, Visick G, et al (2001) Validation of general practitioner-diagnosed COPD in the UK General Practice Research Database. Eur J Epidemiol; 17(12):1075-80.

[redacted]

Thygesen K, Alpert JS, Jaffe AS, et al (2012) Third universal definition of myocardial infarction. Eur Heart J; 33(20):2551-67.

van Buuren, S. (2007) Multiple Imputation of Discrete and Continuous Data by Fully Conditional Specification, Statistical Methods in Medical Research: 16:219–242.

van der Molen T (2010) Co-morbidities of COPD in primary care: frequency, relation to COPD, and treatment consequences. Prim Care Respir J; 19(4):326-34.

[redacted]

Vlug AE, van der Lei J, Mosseveld BM, et al (1999) Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med; 38(4-5):339-44.

Vogelmeier C, Hederer B, Glaab T, et al (2011) Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med; 364(12):1093-103.

Wedzicha JA, Dahl R, Buhl R, et al (2014) Pooled safety analysis of the fixed-dose combination of indacaterol and glycopyrronium (QVA149), its monocomponents, and tiotropium versus placebo in COPD patients. Respir Med; 108(10):1498-507.

WHO (2008) The selection and use of essential medicines. World Health Organ Tech Rep Ser; (950):backcover, vii-174.

Wise RA, Anzueto A, Cotton D, et al (2013) Tiotropium Respimat inhaler and the risk of death in COPD. N Engl J Med; 369(16):1491-1501.

Wollmer P, Engstrom G (2013) Fixed ratio or lower limit of normal as cut-off value for FEV1/VC: an outcome study. Respir Med; 107(9):1460-2.

Zipes DP, Camm AJ, Borggrefe M, et al (2006) ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol; 48(5):e247-346.

15 Appendices

Annex 1 – List of stand-alone documents

There are no stand-alone documents.

Annex 2 – Additional information

Annex 2.1 Post-text results (figures and tables)

Figure 15-1 Flowchart for THIN (UK) patient selection

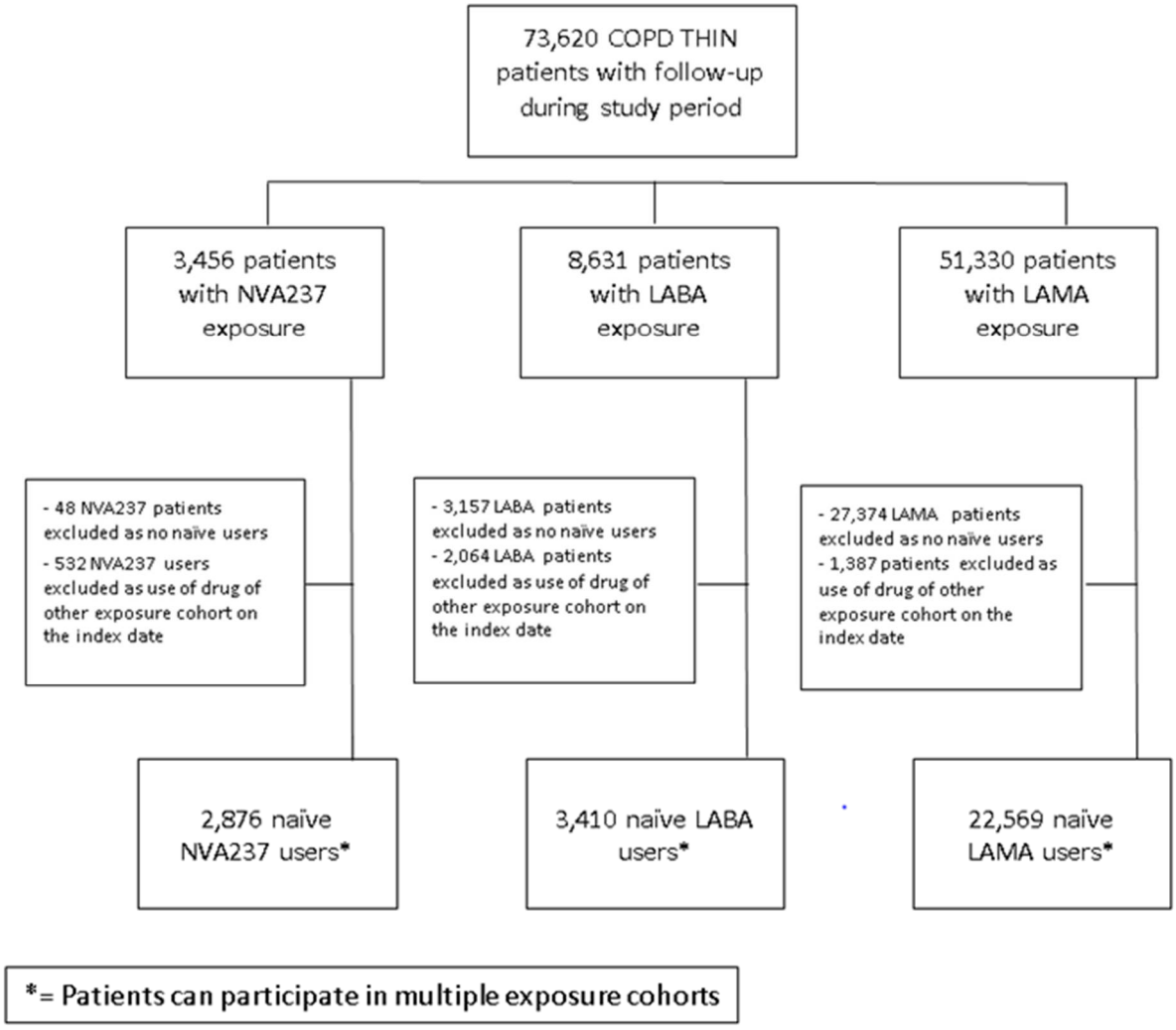


Figure 15-2 Flow chart for IPCI (NL) patient selection

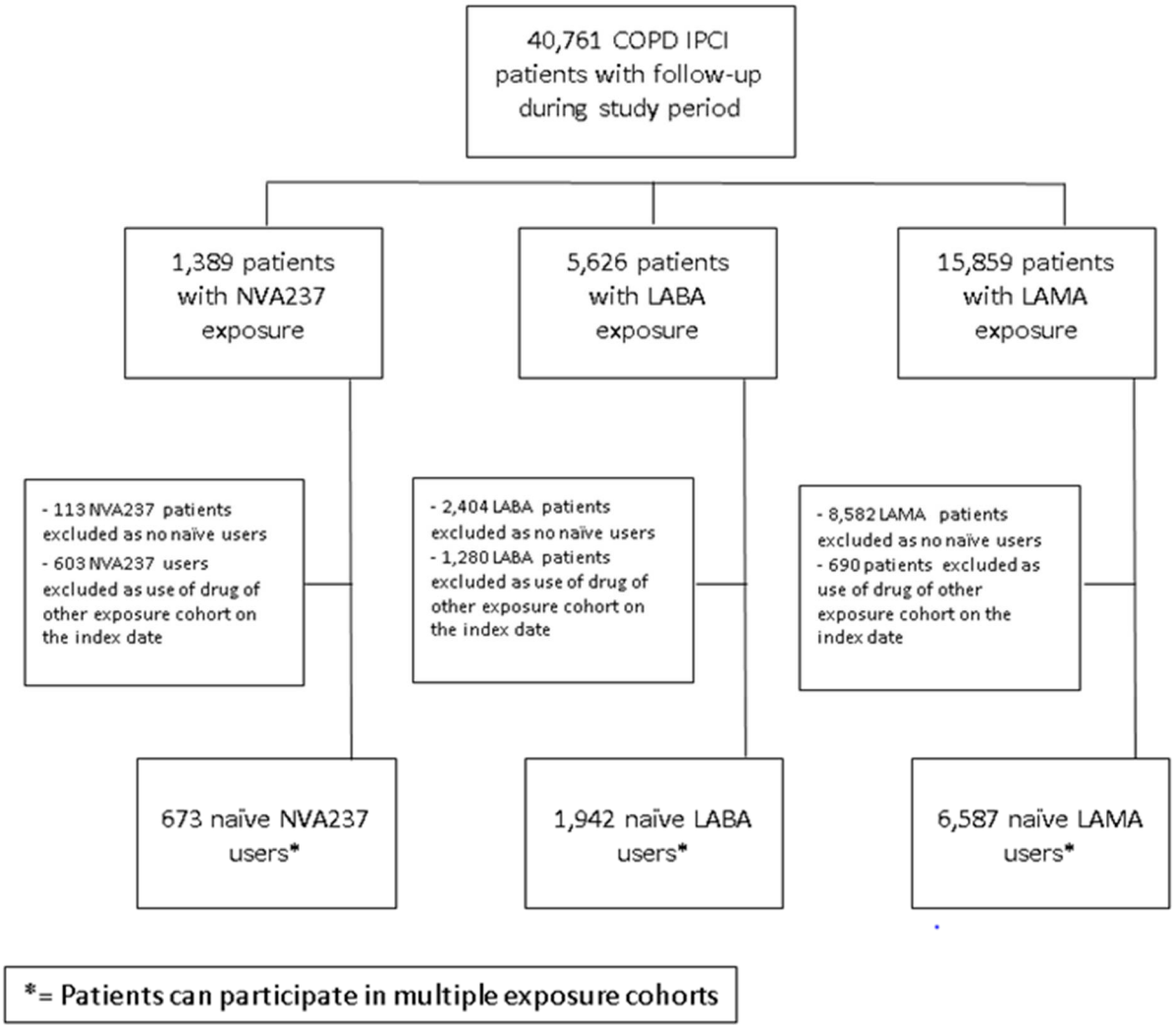


Figure 15-3 Flow chart for Aarhus (DK) patient selection

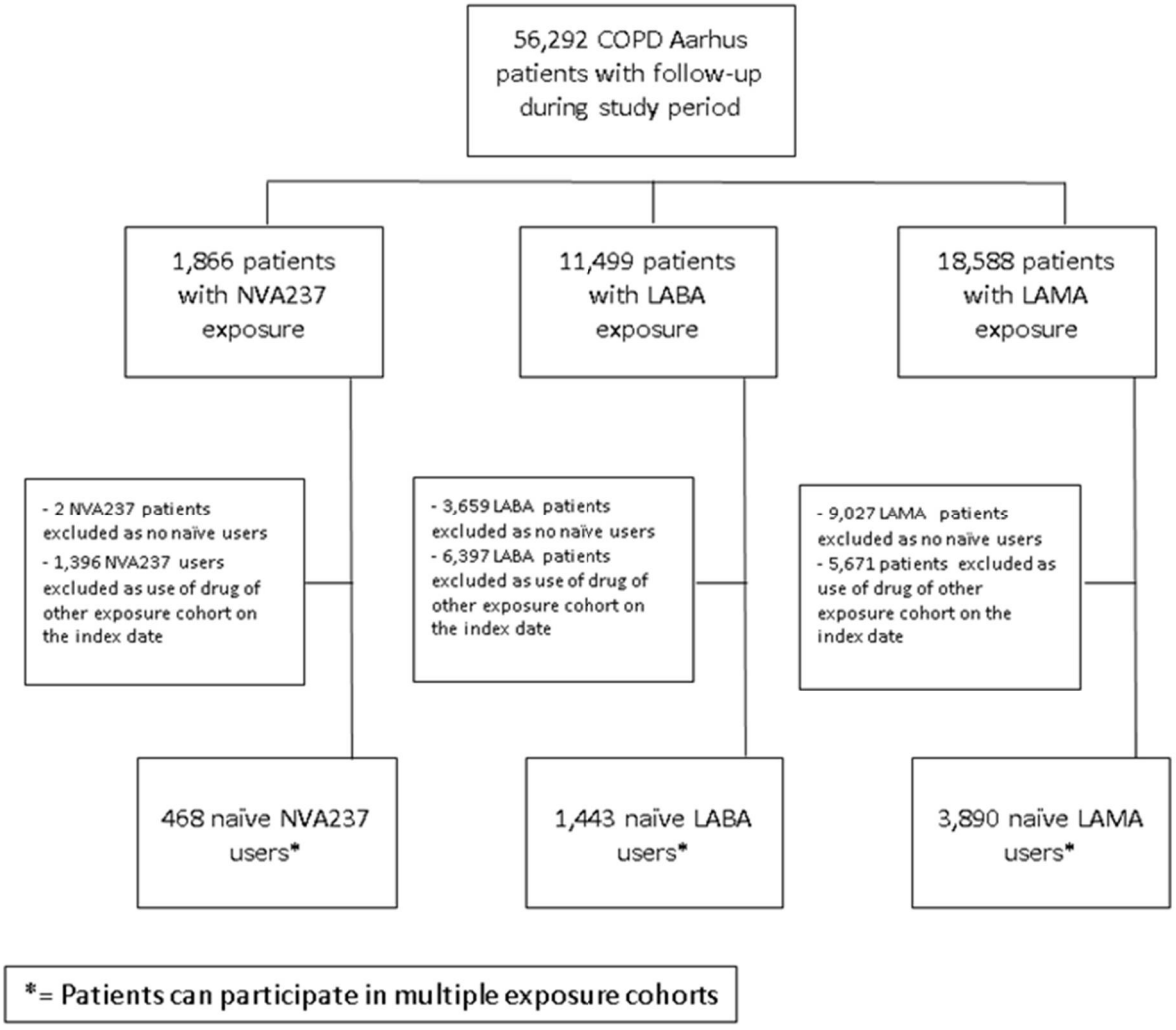


Figure 15-4 Flow chart for HSD (IT) patients

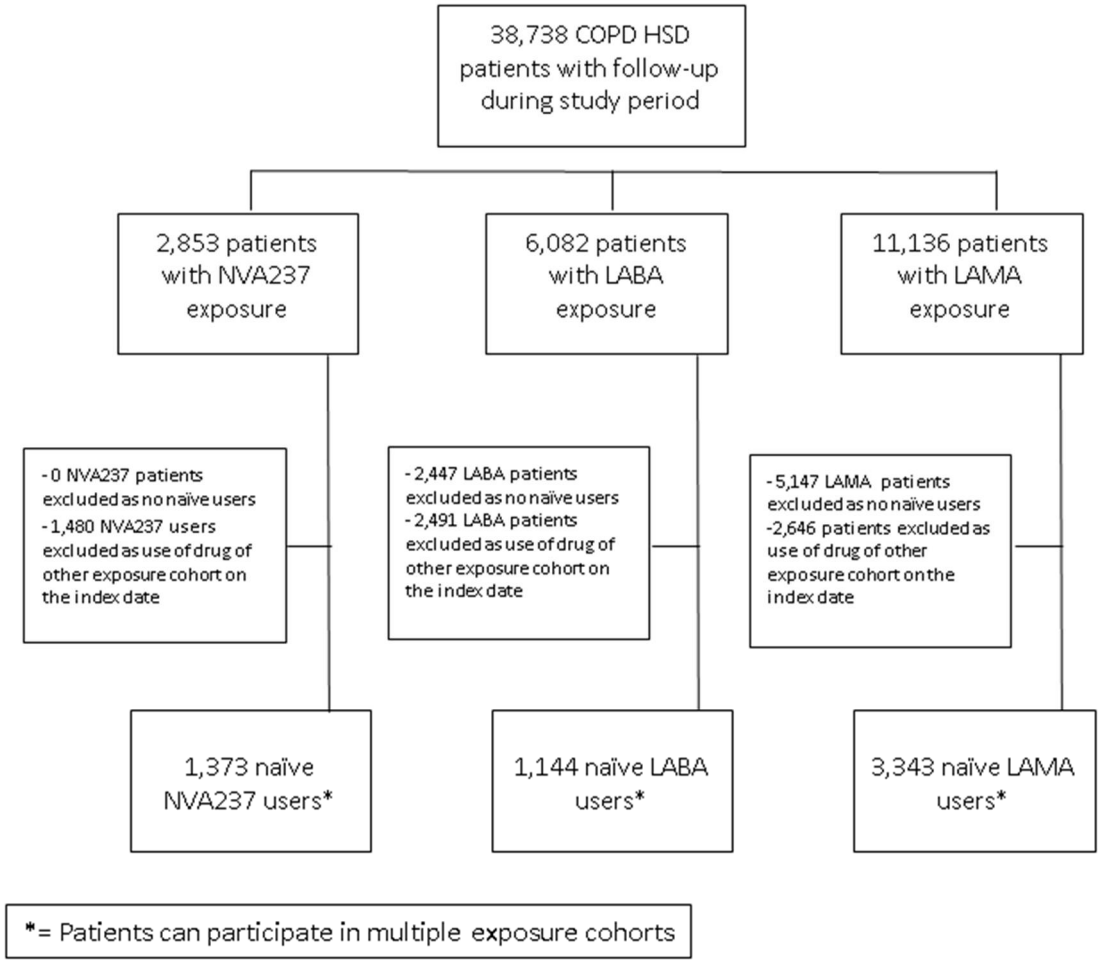


Figure 15-5 Flow chart for SIDIAP (ES) patients

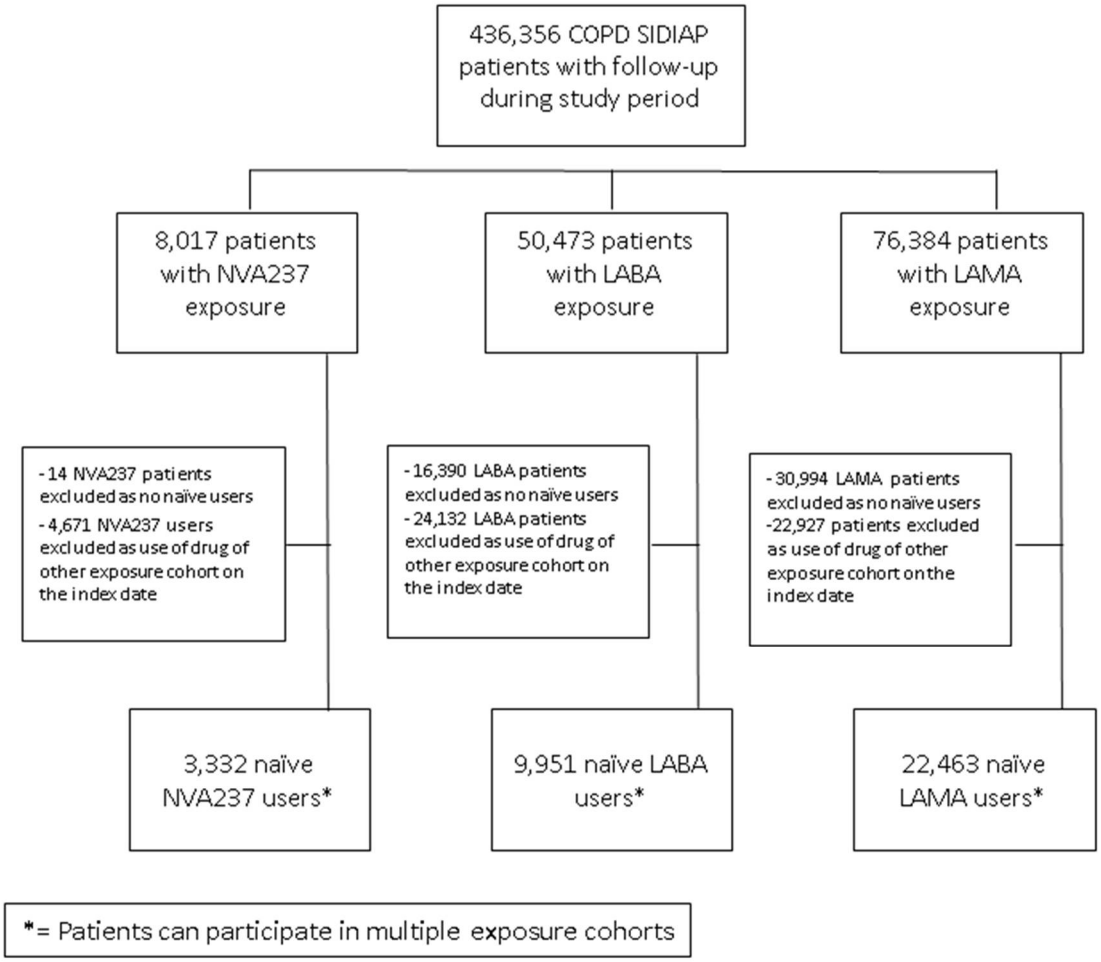
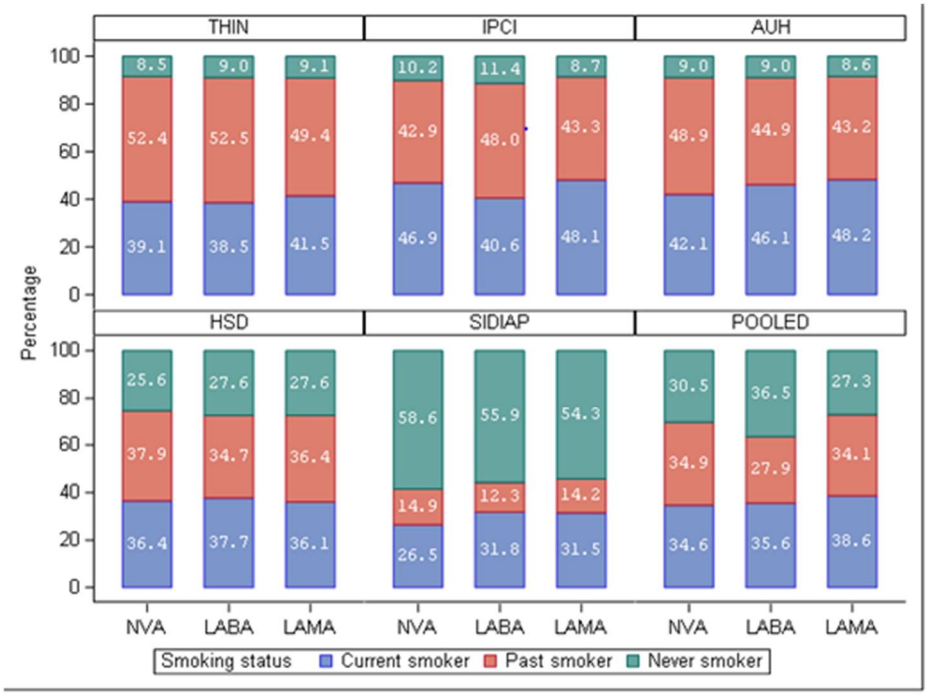
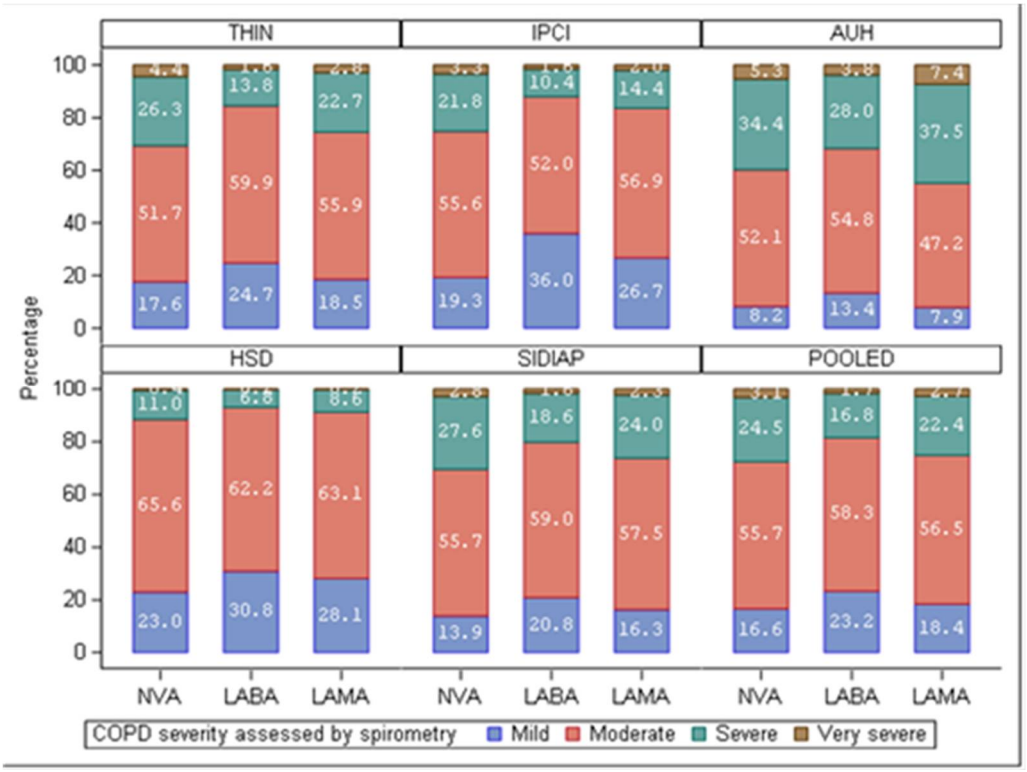


Figure 15-6 Smoking status (imputed) – pooled dataset and by database



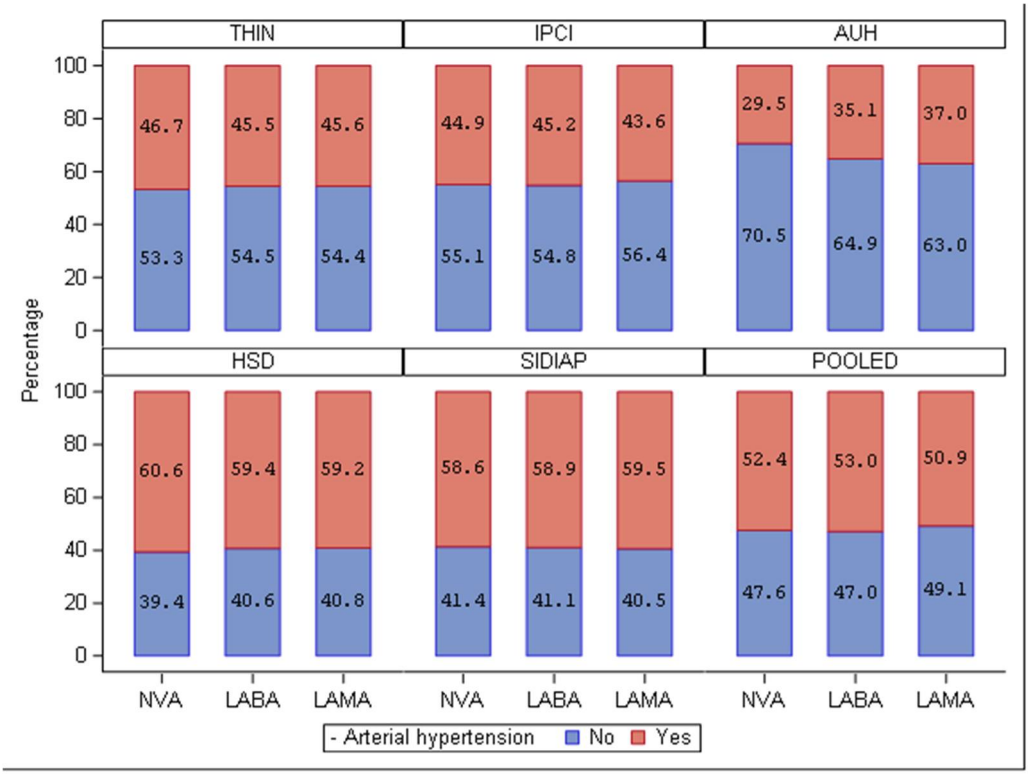
AUH = Aarhus University Hospital

Figure 15-7 COPD severity via spirometry considering all FEV1 percentage predicted – pooled dataset and by database



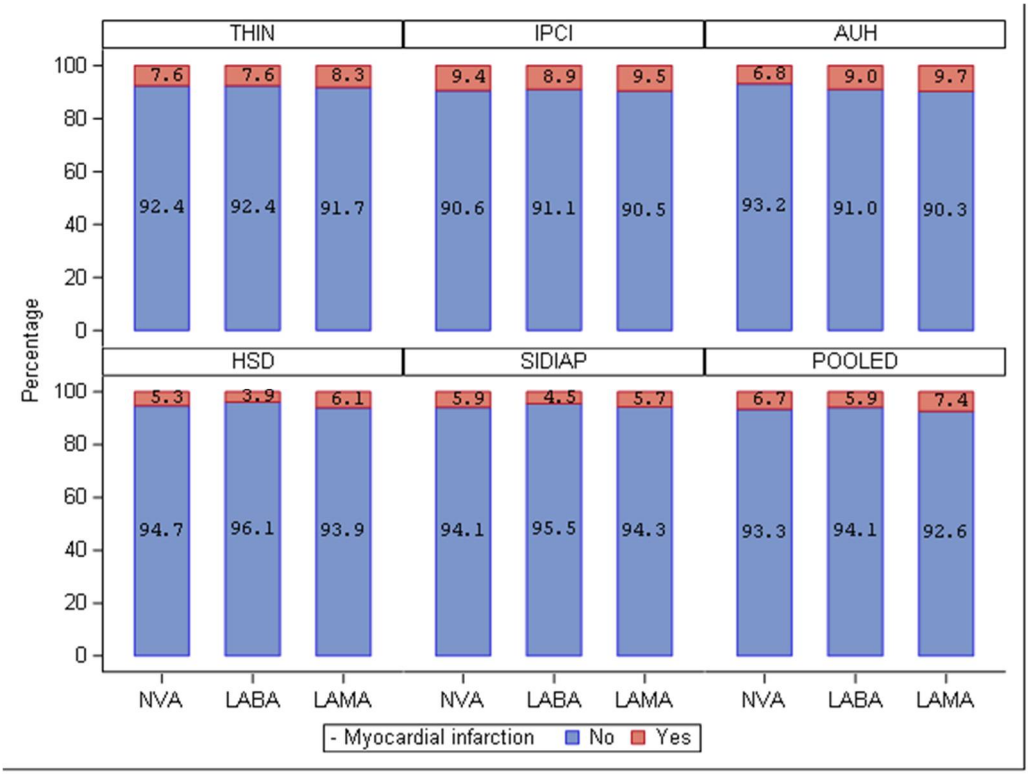
AUH = Aarhus University Hospital

Figure 15-8 Arterial hypertension as comorbidity – pooled dataset and by database



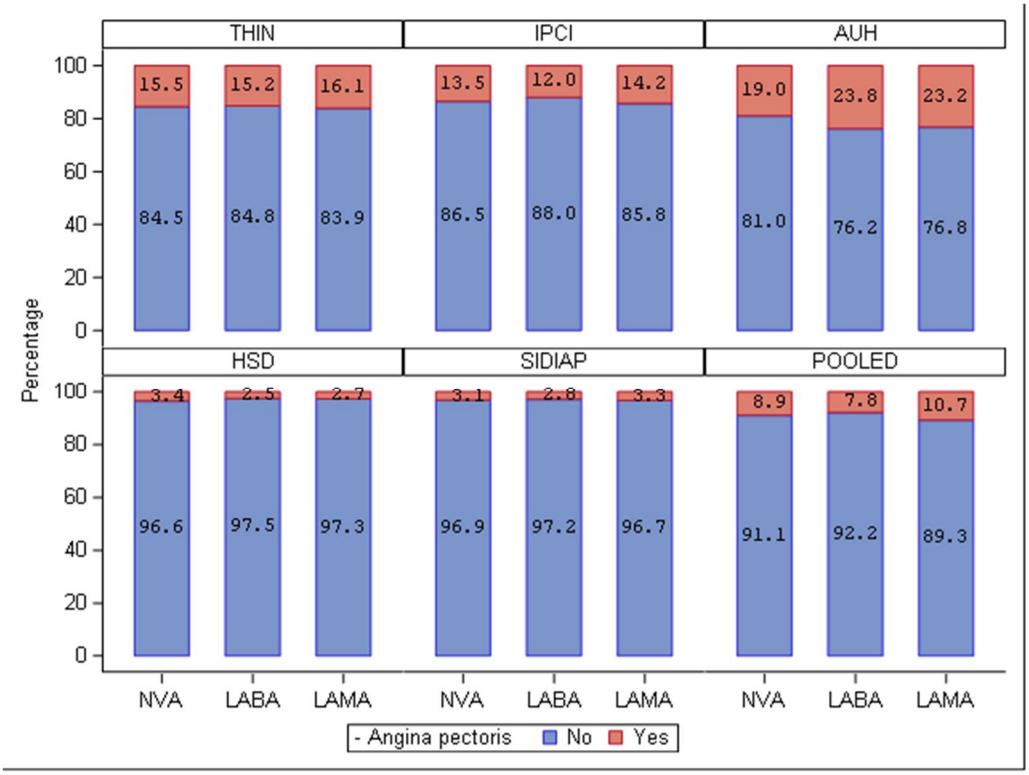
AUH = Aarhus University Hospital

Figure 15-9 Myocardial infarction as comorbidity – pooled dataset and by database



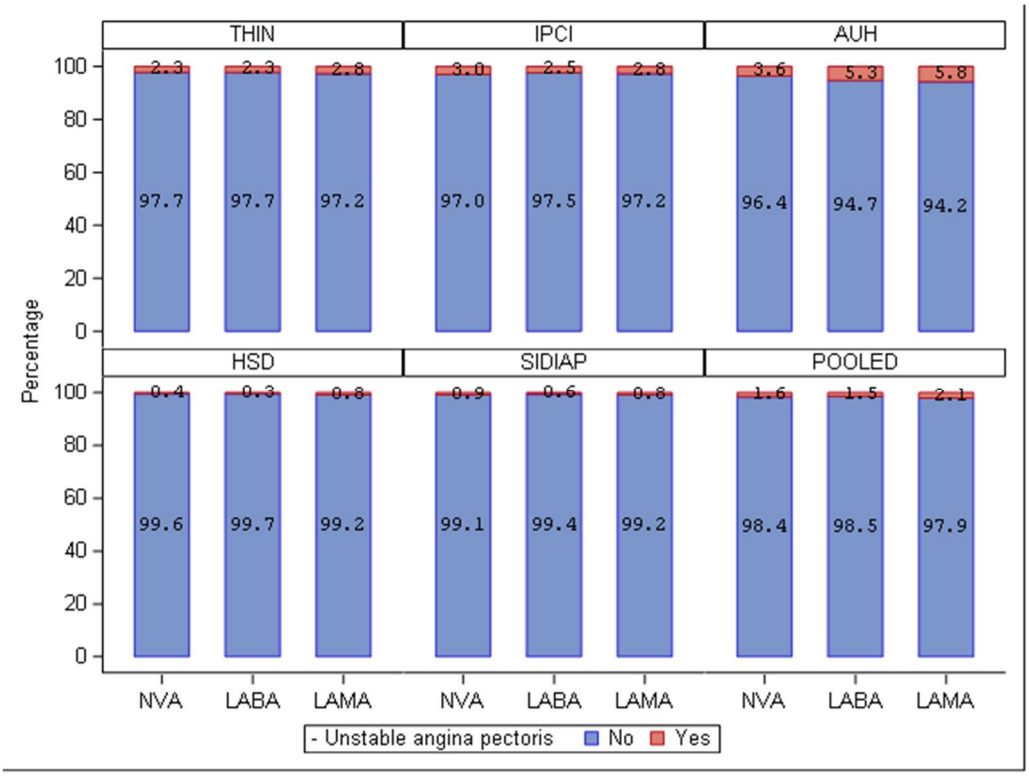
AUH = Aarhus University Hospital

Figure 15-10 Angina pectoris as comorbidity – pooled dataset and by database



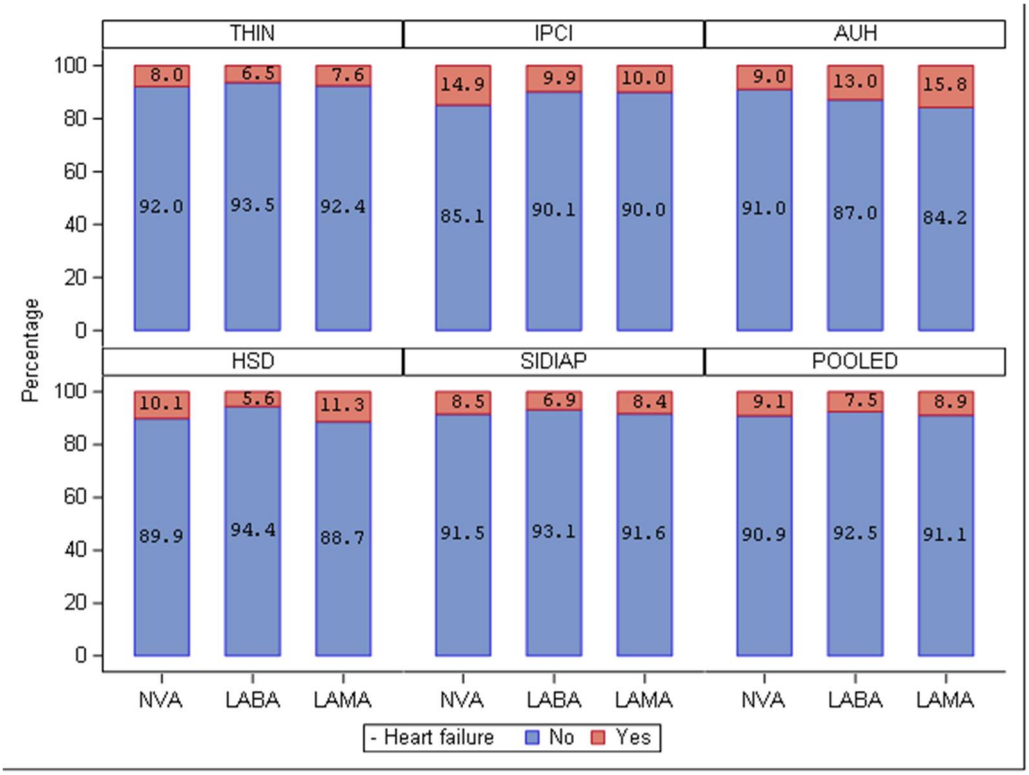
AUH = Aarhus University Hospital

Figure 15-11 Unstable angina pectoris as comorbidity – pooled dataset and by database



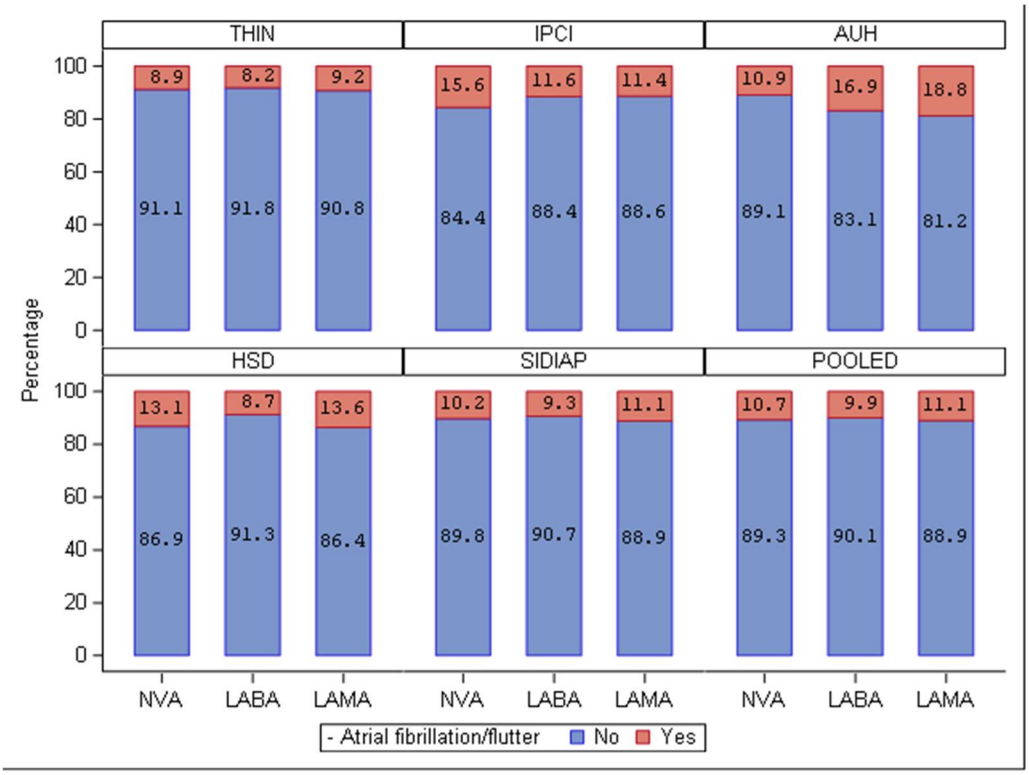
AUH = Aarhus University Hospital

Figure 15-12 Heart failure as comorbidity – pooled dataset and by database



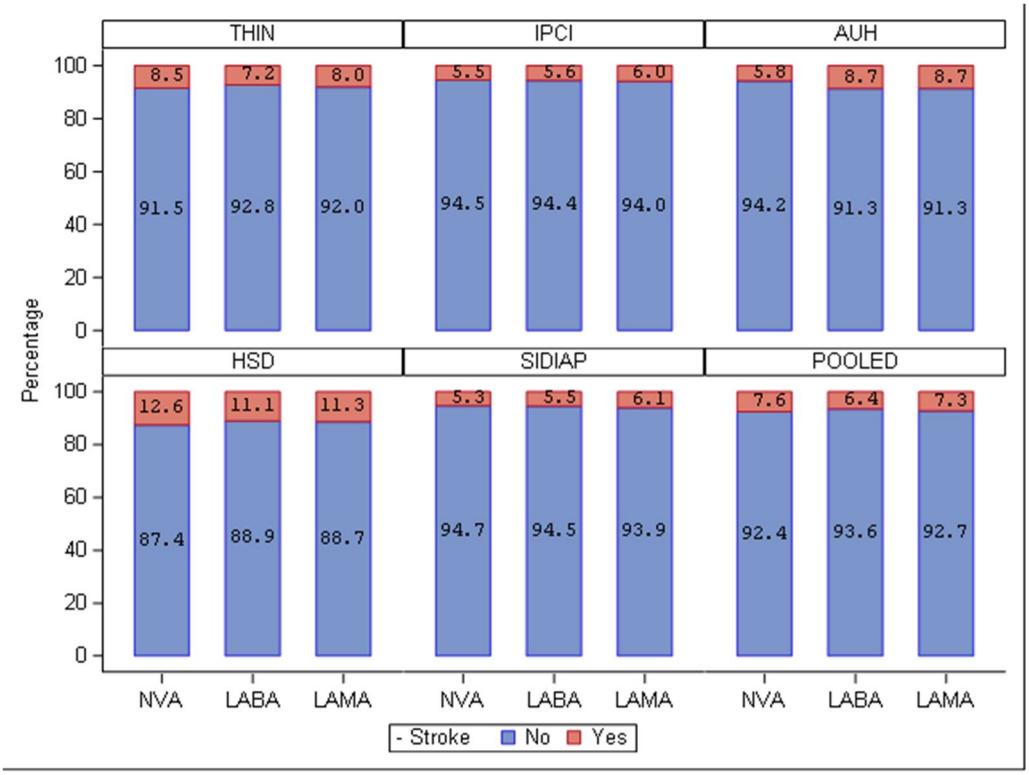
AUH = Aarhus University Hospital

Figure 15-13 Atrial fibrillation/flutter as comorbidity – pooled dataset and by database



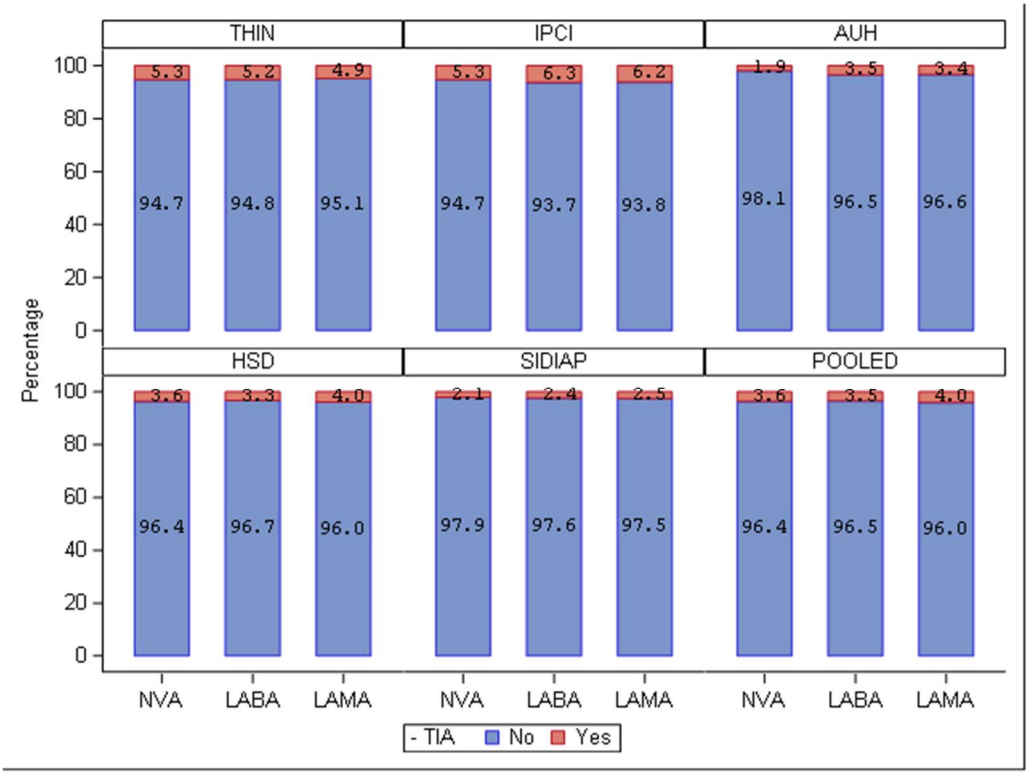
AUH = Aarhus University Hospital

Figure 15-14 Stroke as comorbidity – pooled dataset and by database



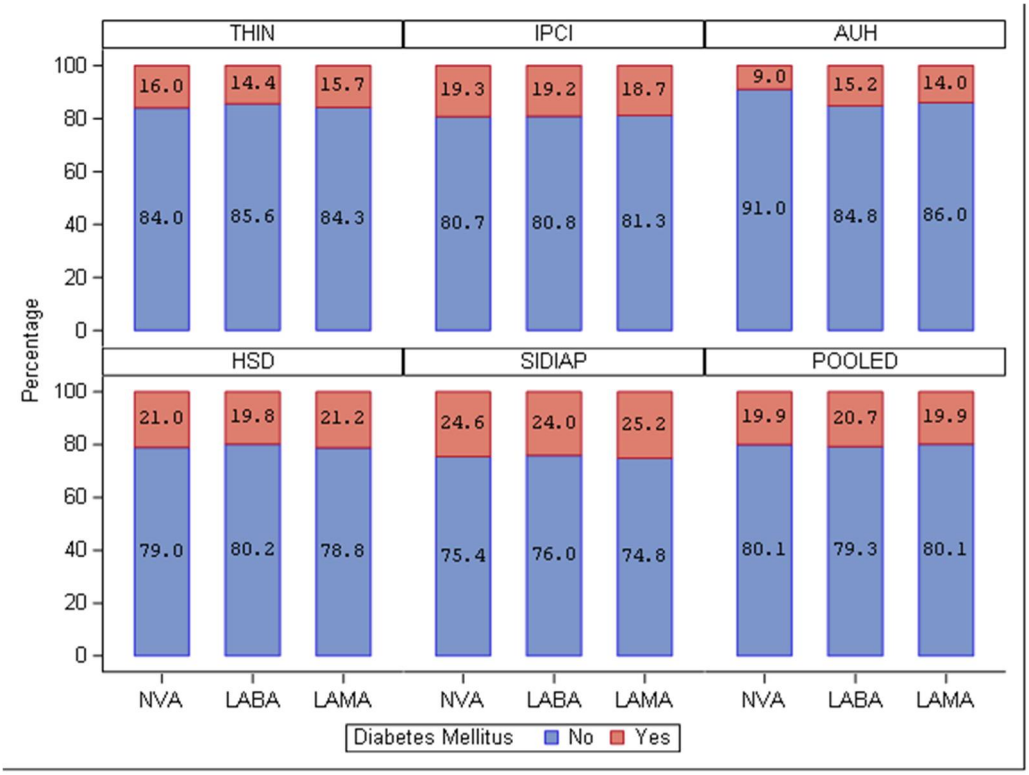
AUH = Aarhus University Hospital

Figure 15-15 TIA as comorbidity – pooled dataset and by database



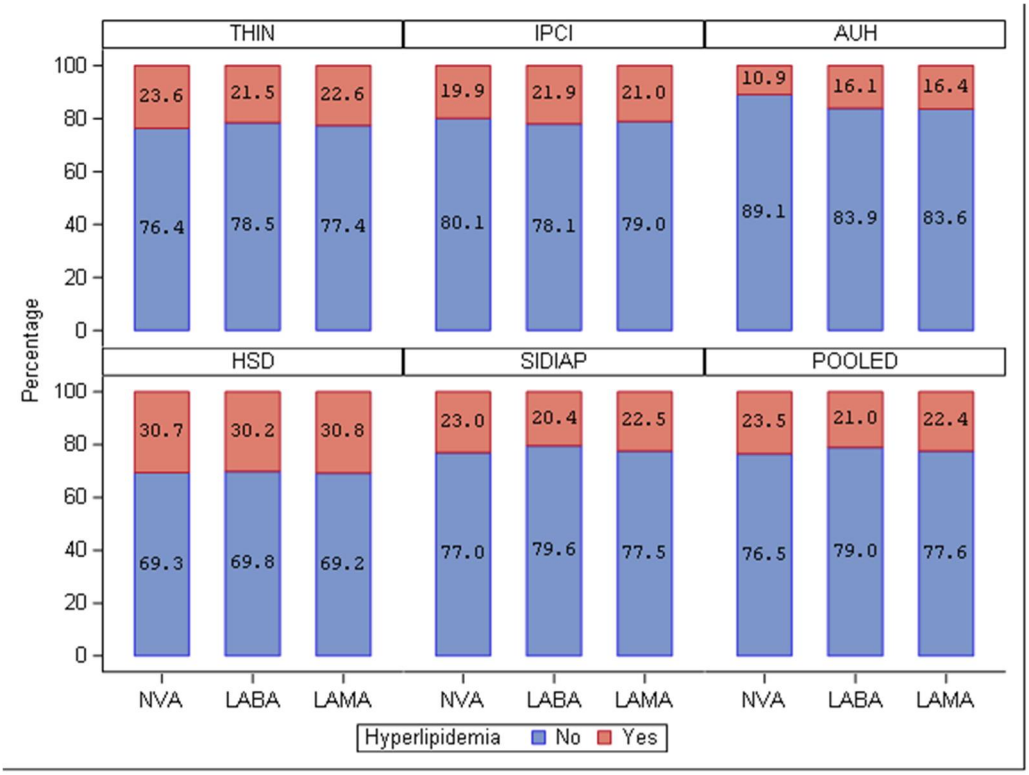
AUH = Aarhus University Hospital

Figure 15-16 Diabetes mellitus as comorbidity – pooled dataset and by database



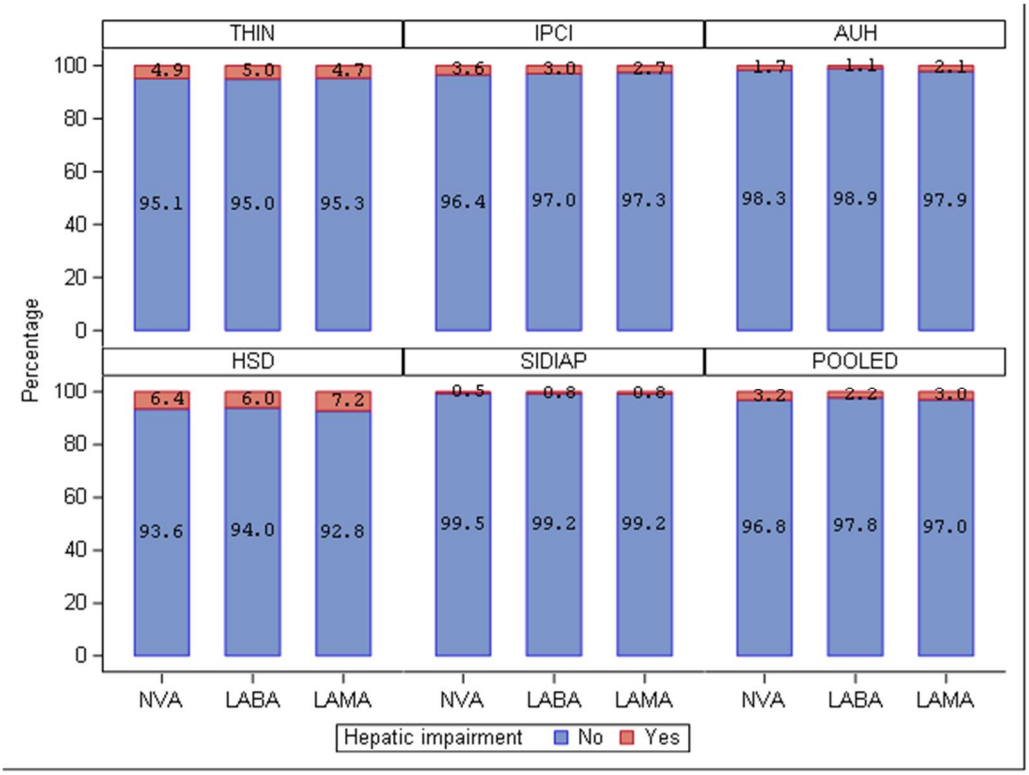
AUH = Aarhus University Hospital

Figure 15-17 Hyperlipidemia as comorbidity – pooled dataset and by database



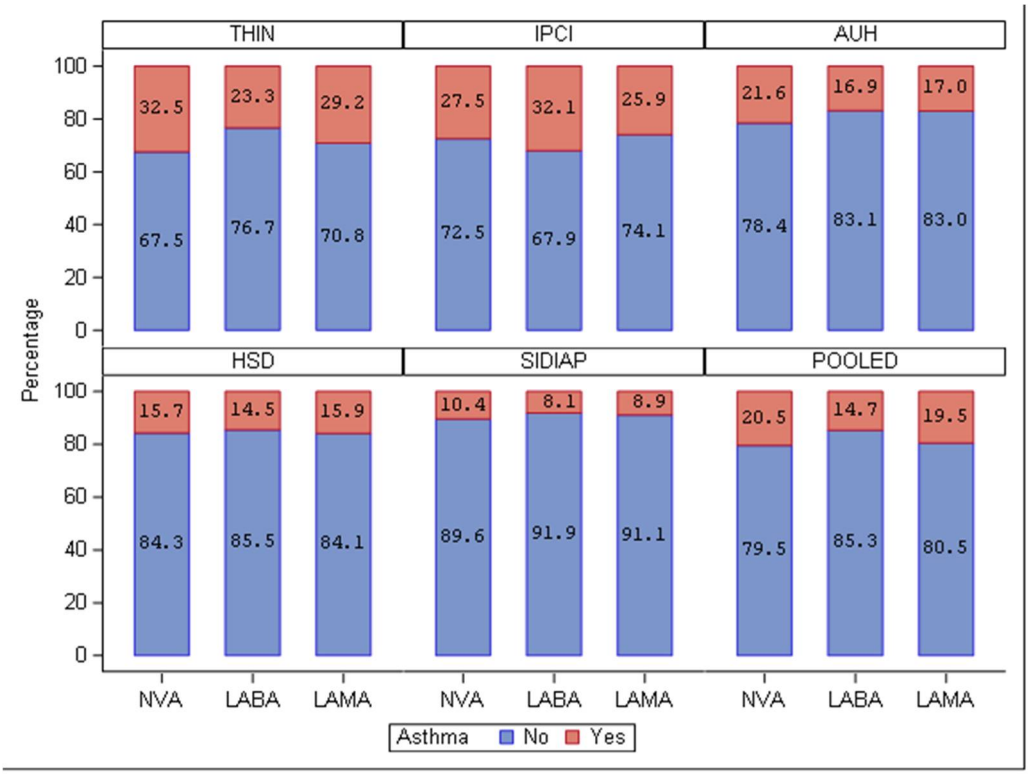
AUH = Aarhus University Hospital

Figure 15-18 Hepatic impairment as comorbidity – pooled dataset and by database



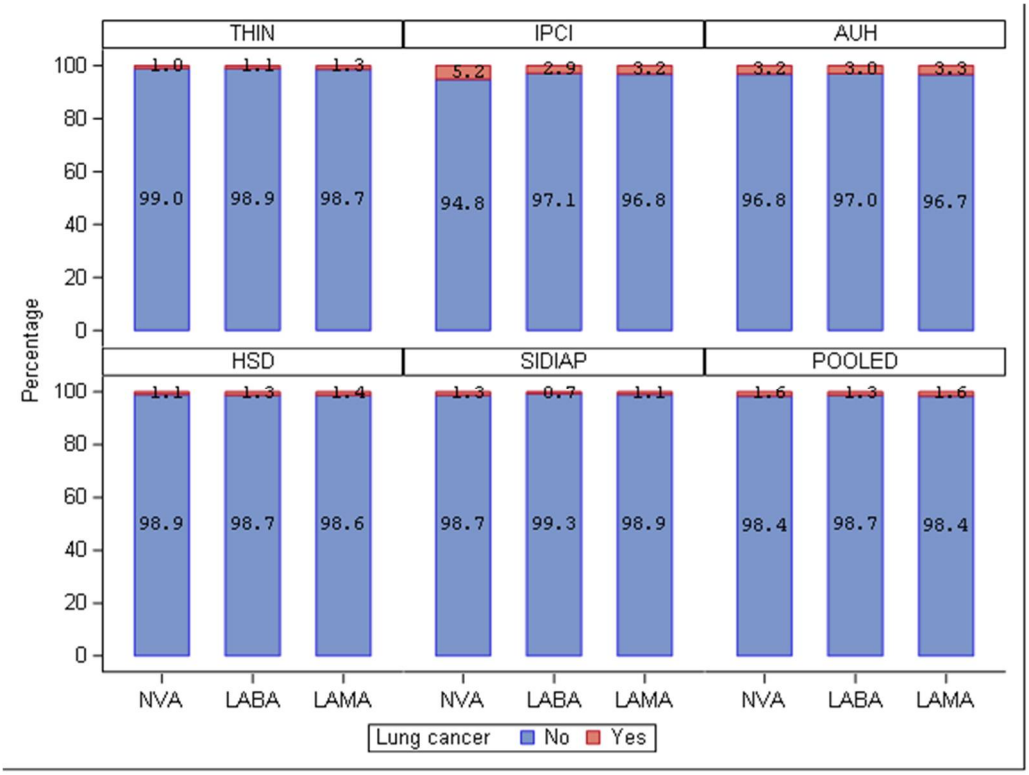
AUH = Aarhus University Hospital

Figure 15-19 Asthma as comorbidity – pooled dataset and by database



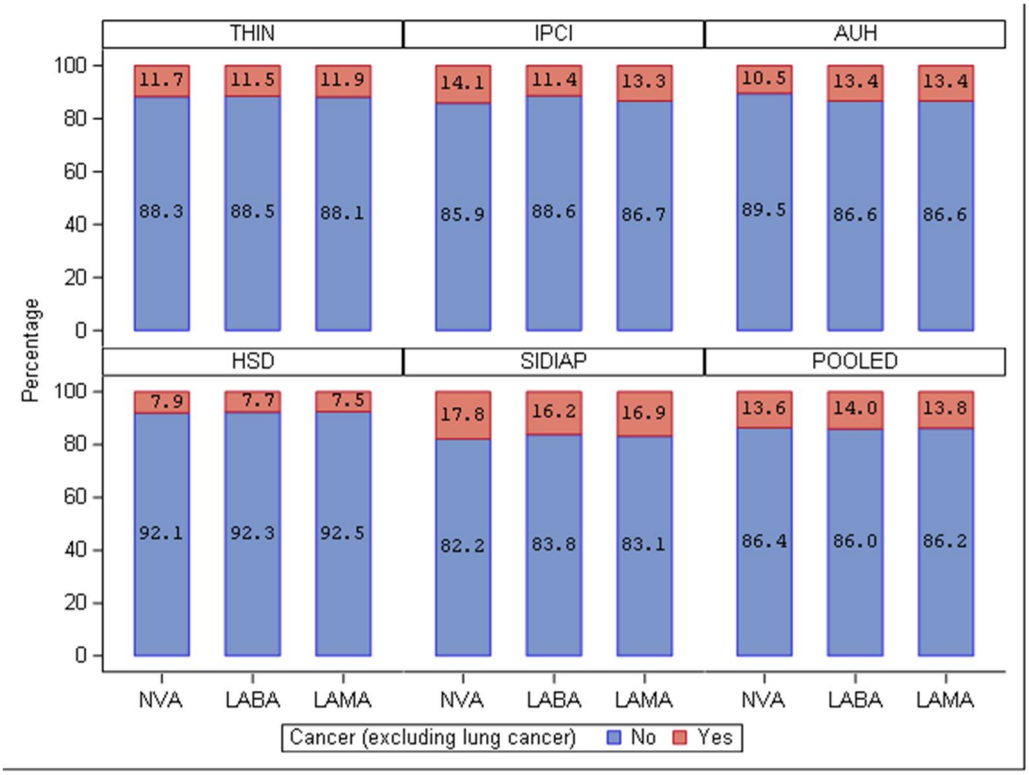
AUH = Aarhus University Hospital

Figure 15-20 Lung cancer as comorbidity – pooled dataset and by database



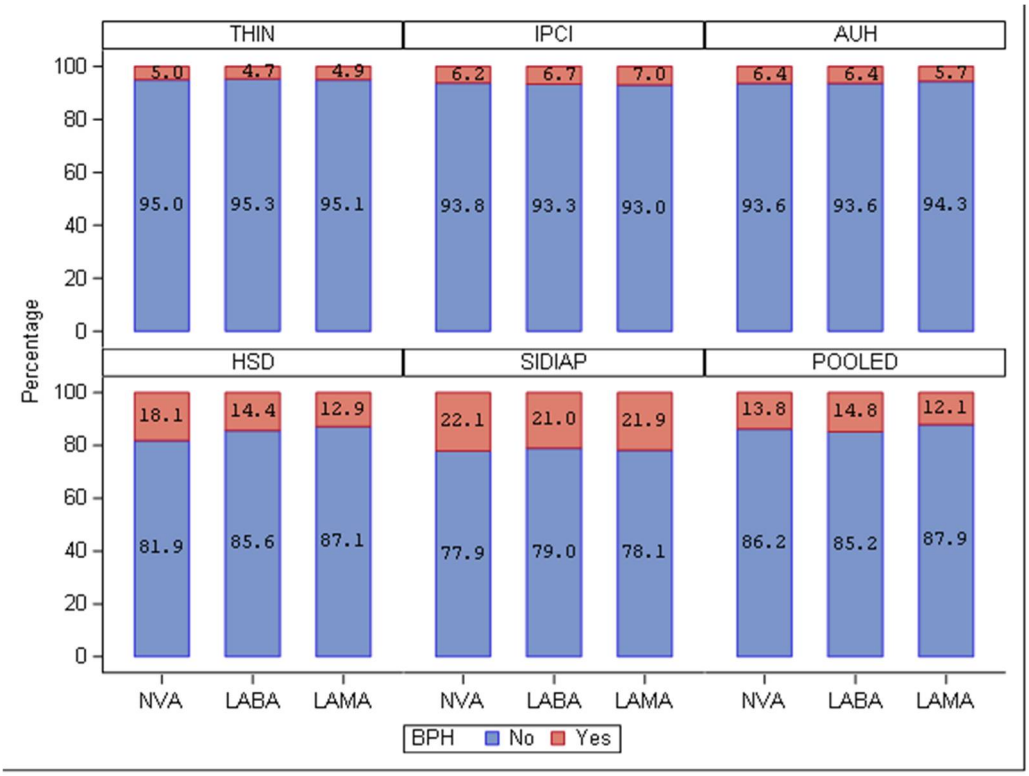
AUH = Aarhus University Hospital

Figure 15-21 Cancer as comorbidity – pooled dataset and by database



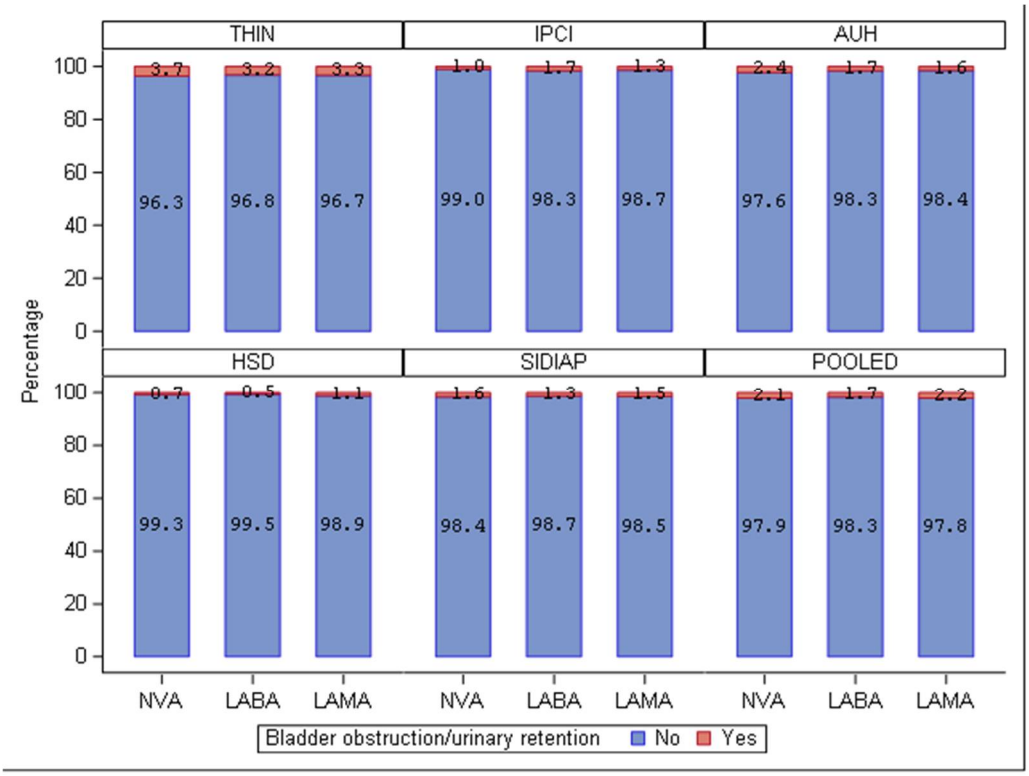
AUH = Aarhus University Hospital

Figure 15-22 Benigh prostatic hyperplasia (BPH) as comorbidity – pooled dataset and by database



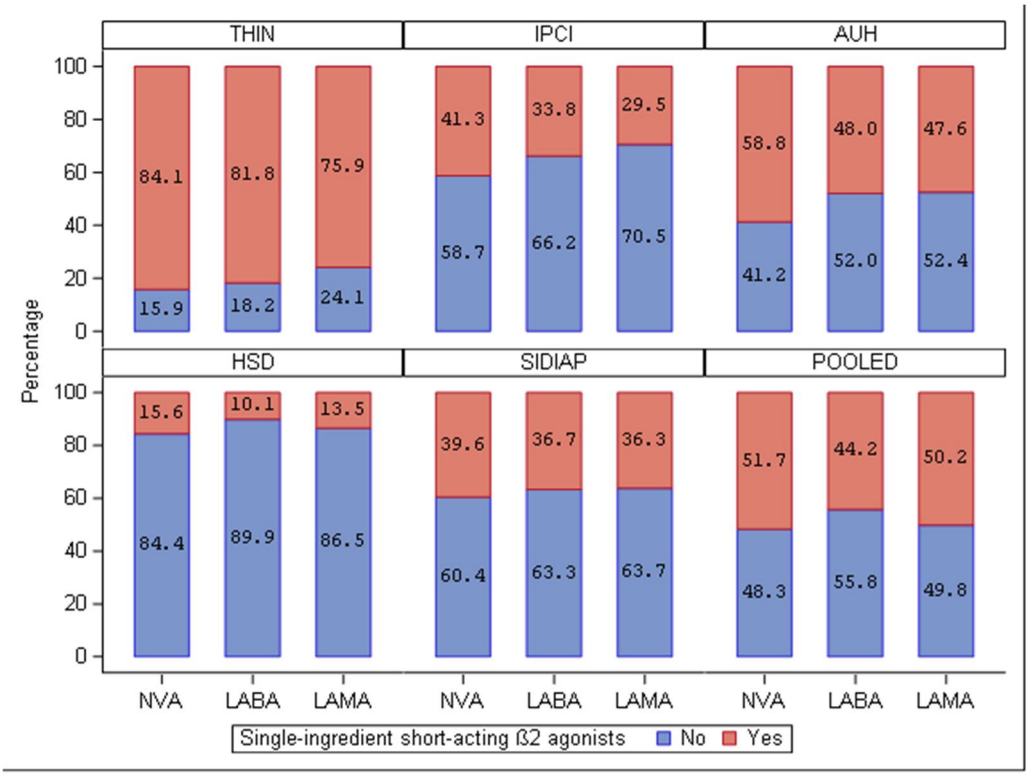
AUH = Aarhus University Hospital

Figure 15-23 Bladder obstruction/Urinary retention as comorbidity – pooled dataset and by database



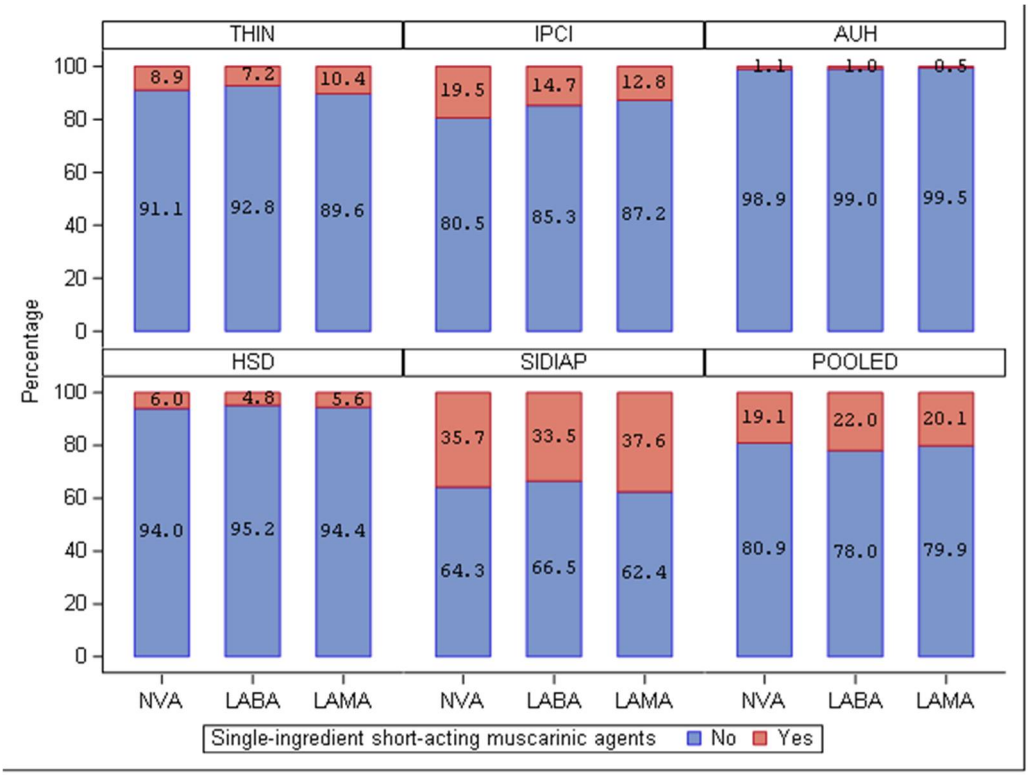
AUH = Aarhus University Hospital

Figure 15-24 Use of SABA in the year prior to the index date – pooled dataset and by database



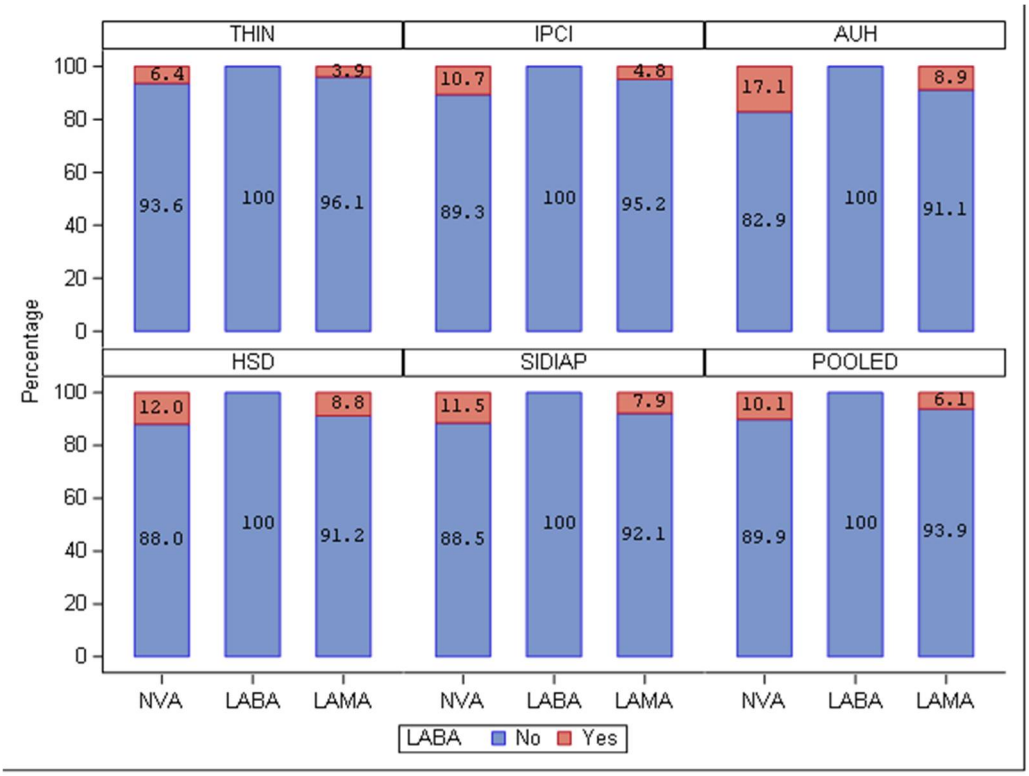
AUH = Aarhus University Hospital

Figure 15-25 Use of SAMA in the year prior to the index date – pooled dataset and by database



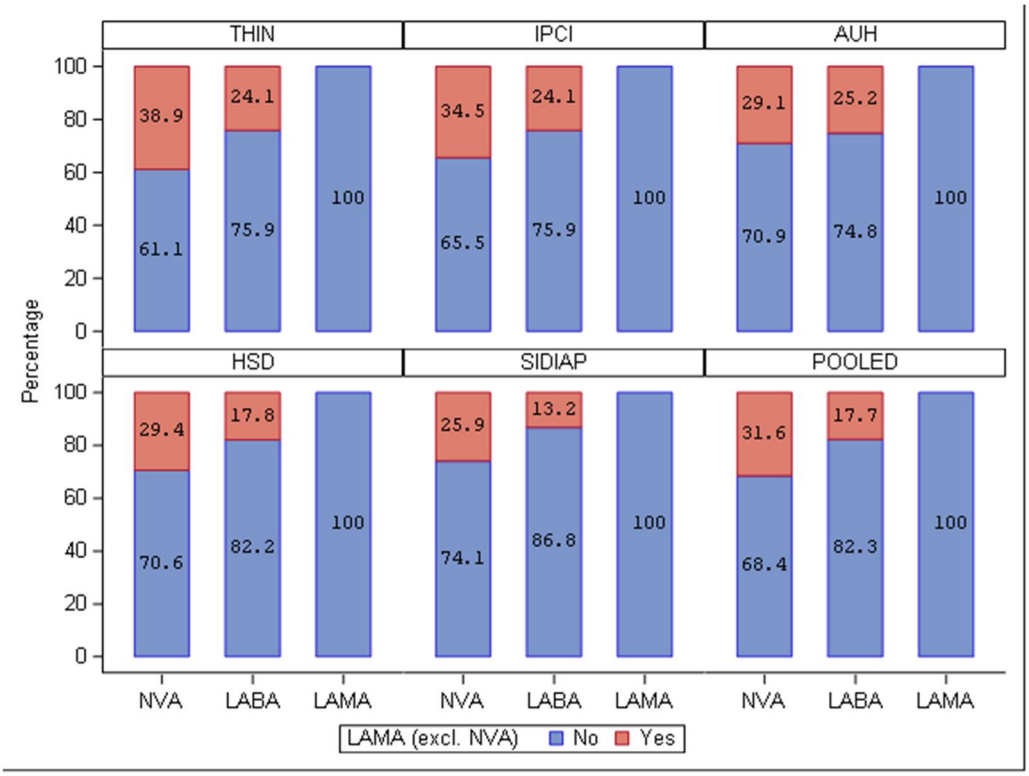
AUH = Aarhus University Hospital

Figure 15-26 Use of LABA in the year prior to the index date – pooled dataset and by database



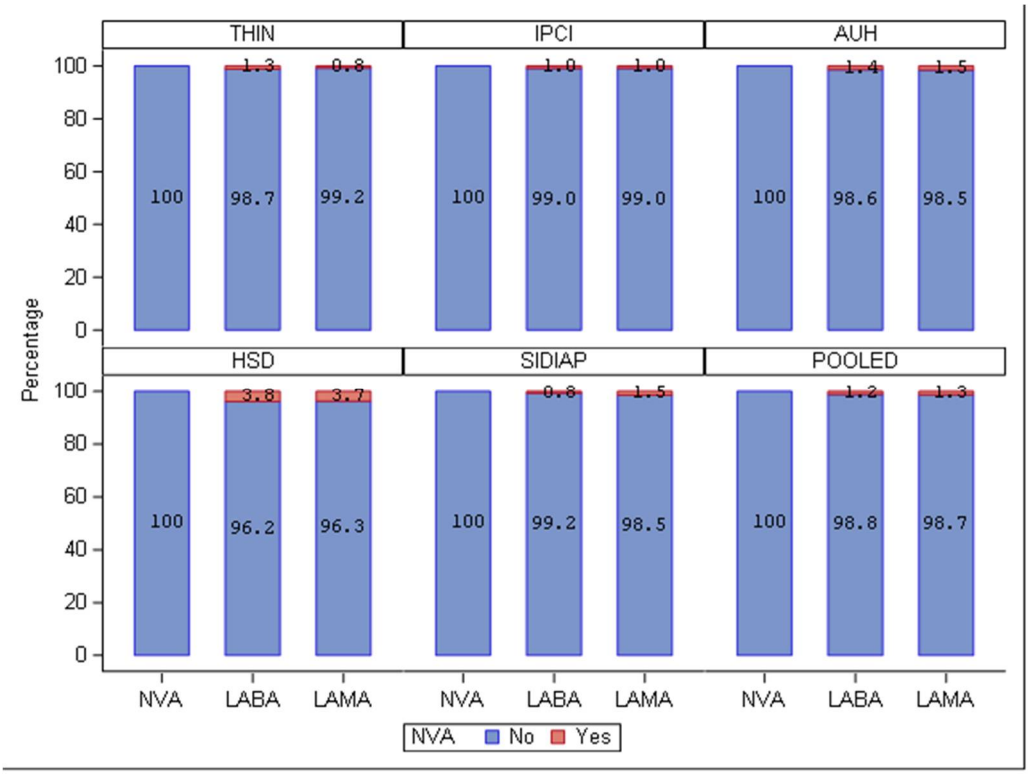
AUH = Aarhus University Hospital

Figure 15-27 Use of LAMA in the year prior to the index date – pooled dataset and by database



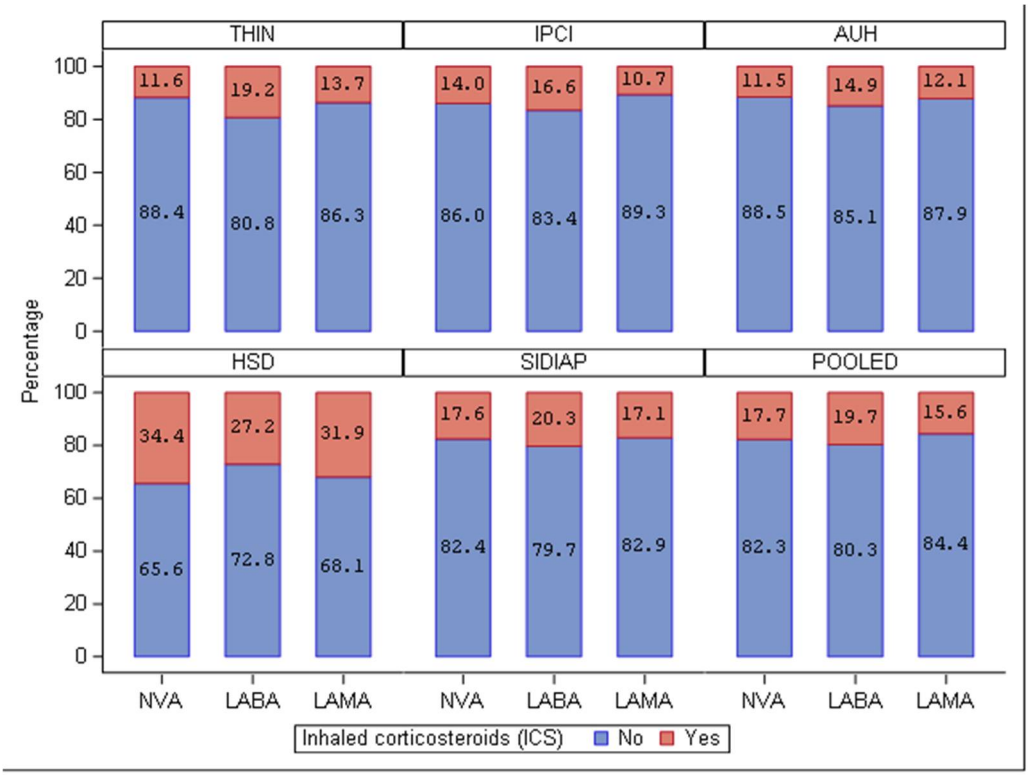
AUH = Aarhus University Hospital

Figure 15-28 Use of NVA237 in the year prior to the index date – pooled dataset and by database



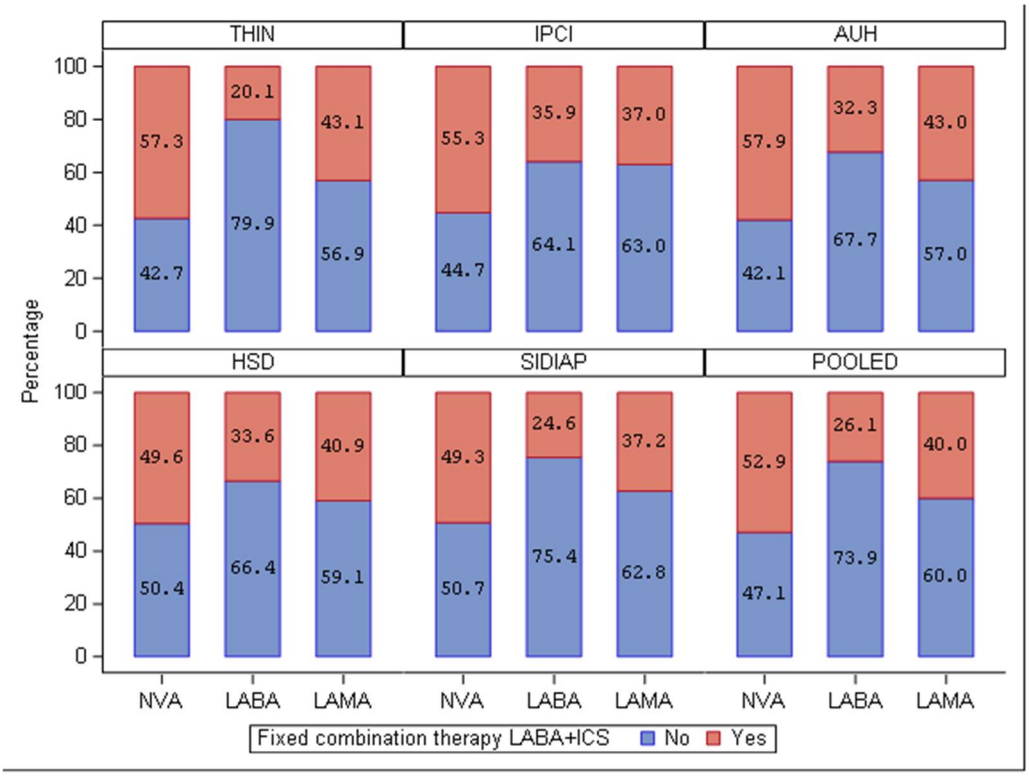
AUH = Aarhus University Hospital

Figure 15-29 Use of ICS in the year prior to the index date – pooled dataset and by database



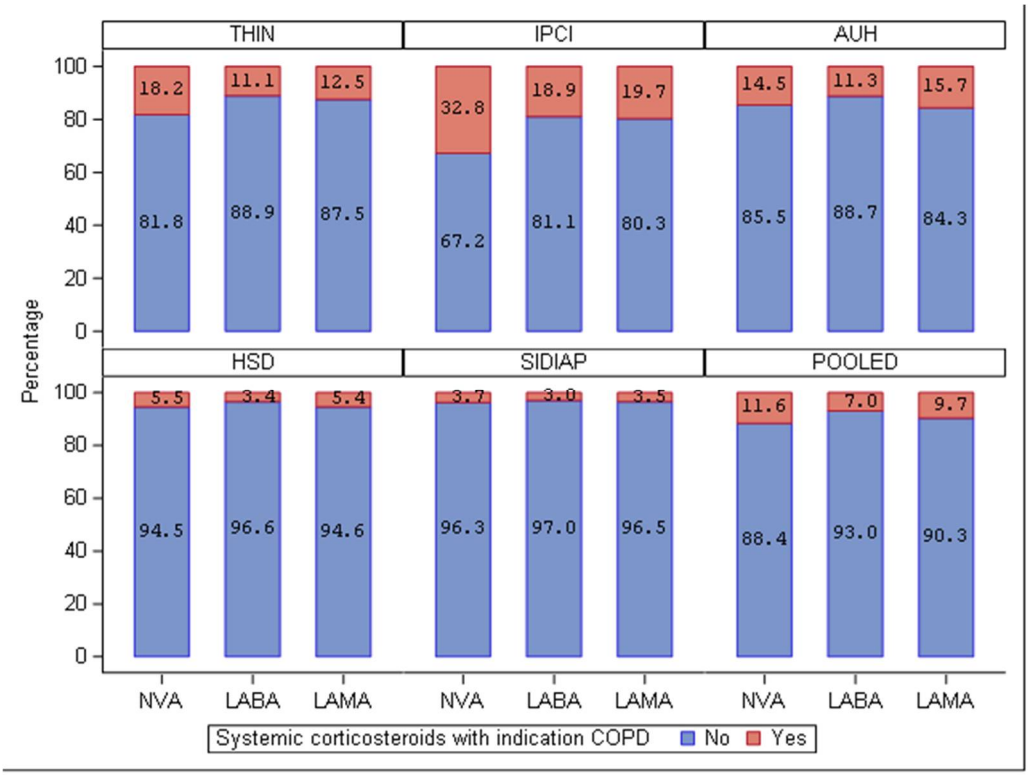
AUH = Aarhus University Hospital

Figure 15-30 Use of LABA+ICS in the year prior to the index date – pooled dataset and by database



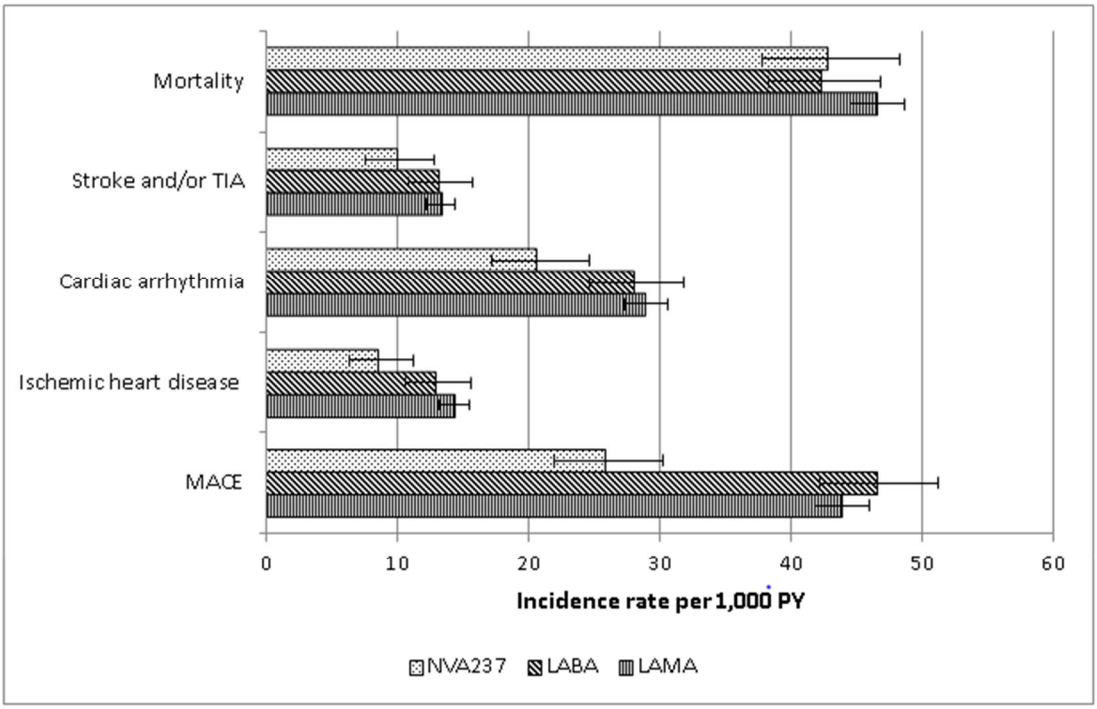
AUH = Aarhus University Hospital

Figure 15-31 Use of systemic corticosteroids for reason of COPD exacerbation at the index date – pooled dataset and by database



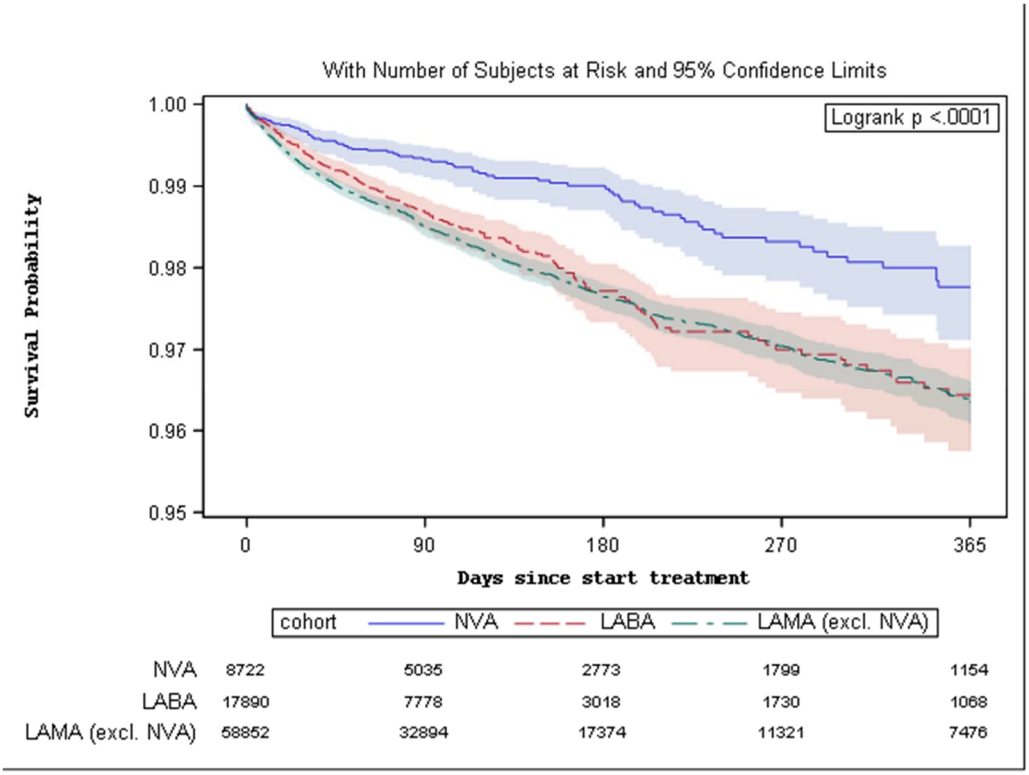
AUH = Aarhus University Hospital

Figure 15-32 Incidence rates of main outcomes



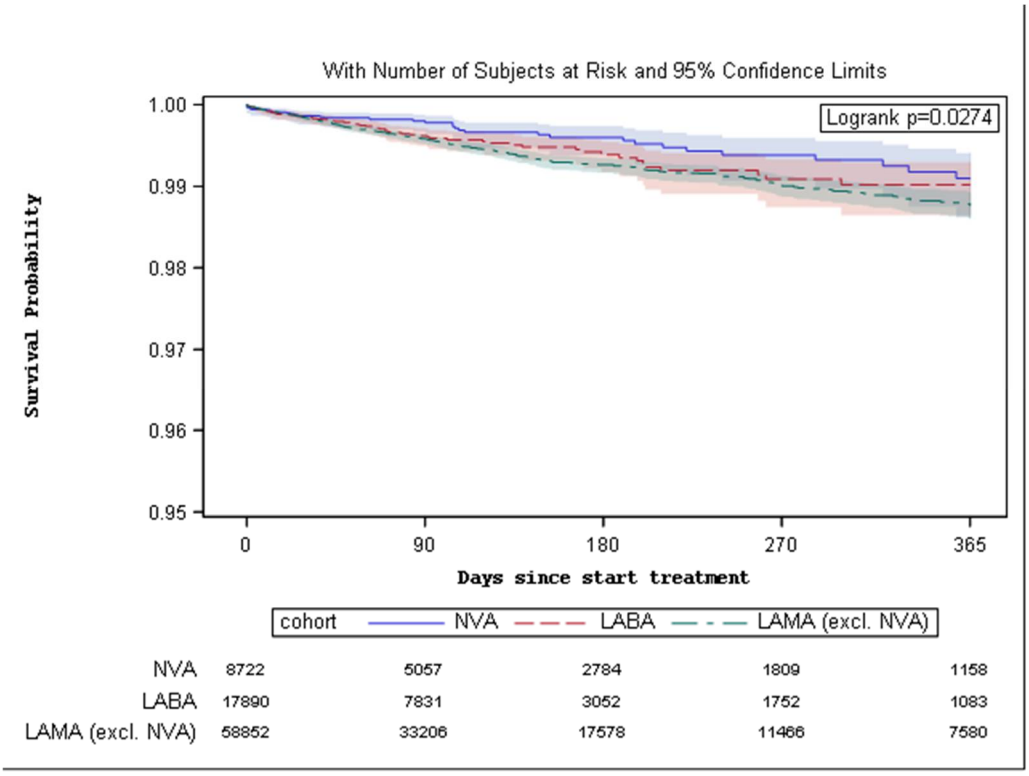
= 95% CI

Figure 15-33 Survival up to event of MACE by cohort – Total analysis population



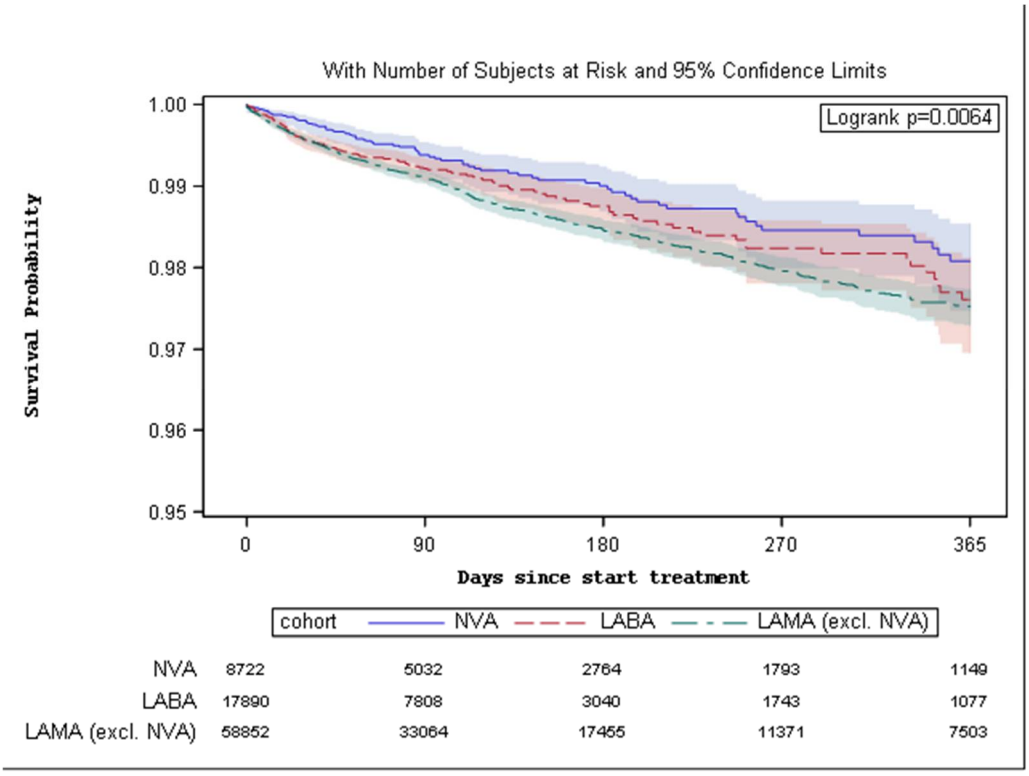
Y-axis does not start at zero

Figure 15-34 Survival up to event of IHD by cohort – Total analysis population



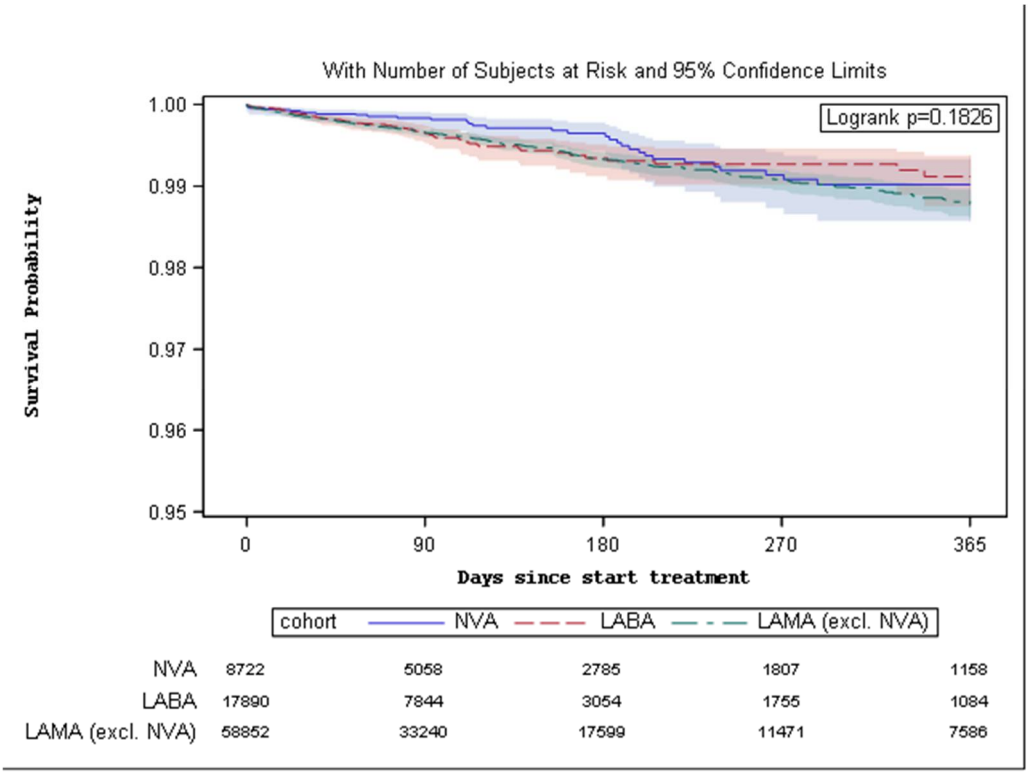
Y-axis does not start at zero

Figure 15-35 Survival up to event of Cardiac Arrhythmia by cohort – Total analysis population



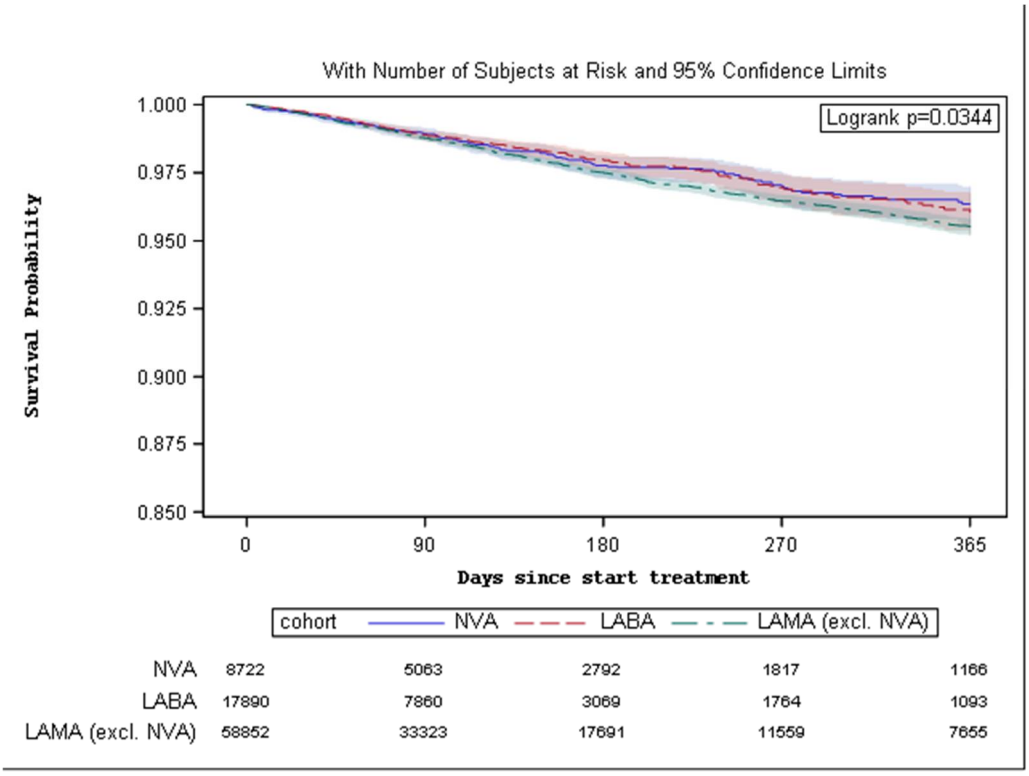
Y-axis does not start at zero

Figure 15-36 Survival up to event of Cerebrovascular disorders by cohort – Total analysis population



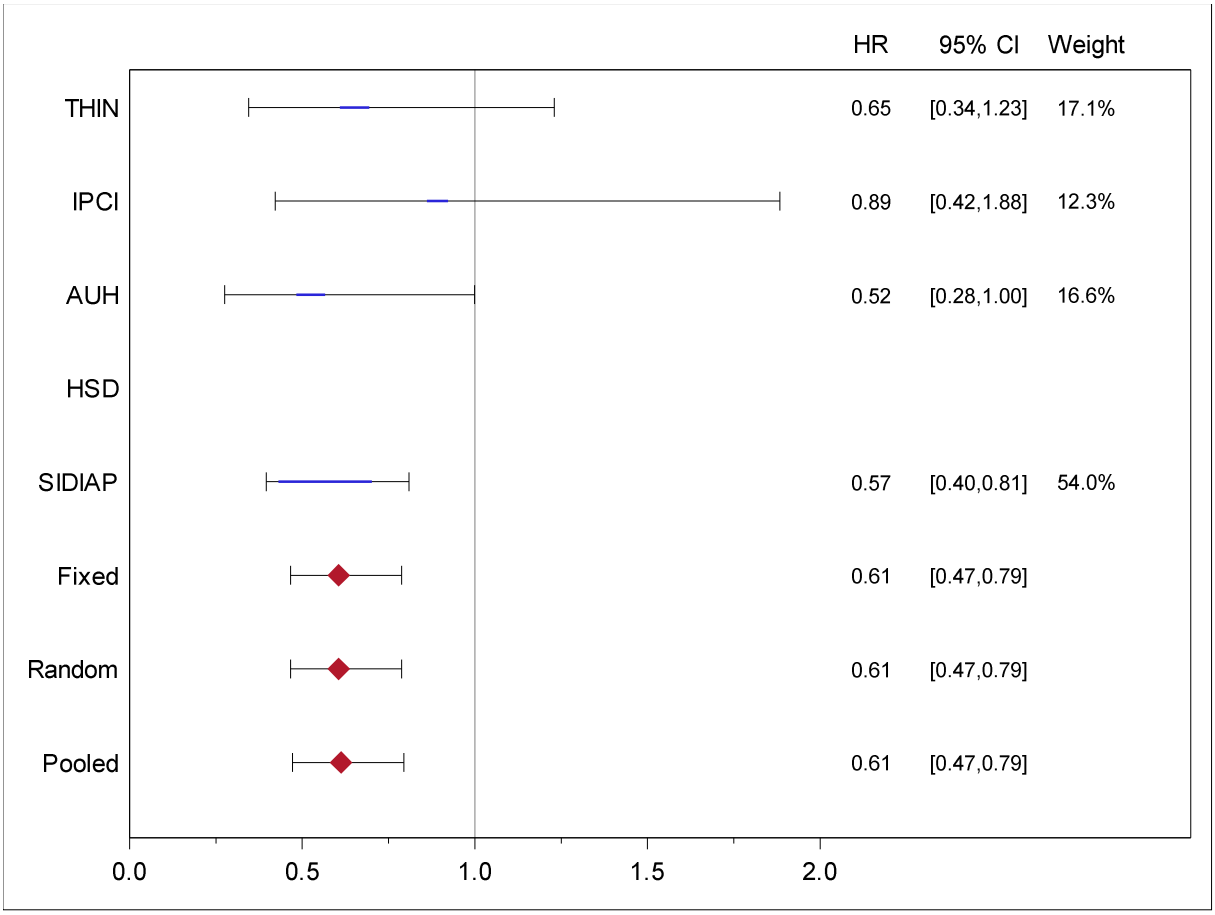
Y-axis does not start at zero

Figure 15-37 Survival up to Mortality by cohort – Total analysis population



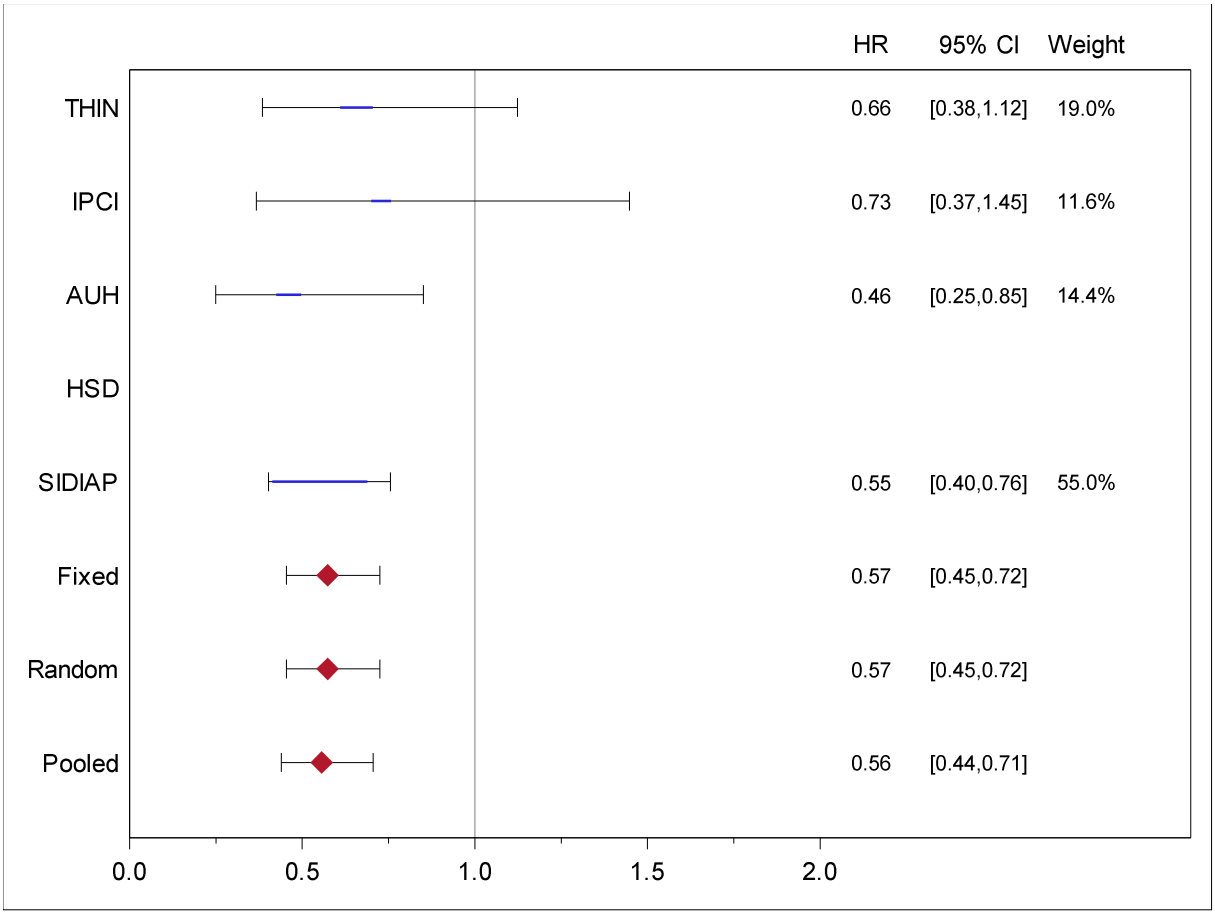
Y-axis does not start at zero

Figure 15-38 Forest plot results Model IPTW NVA237 versus LABA, outcome MACE – Total analysis population



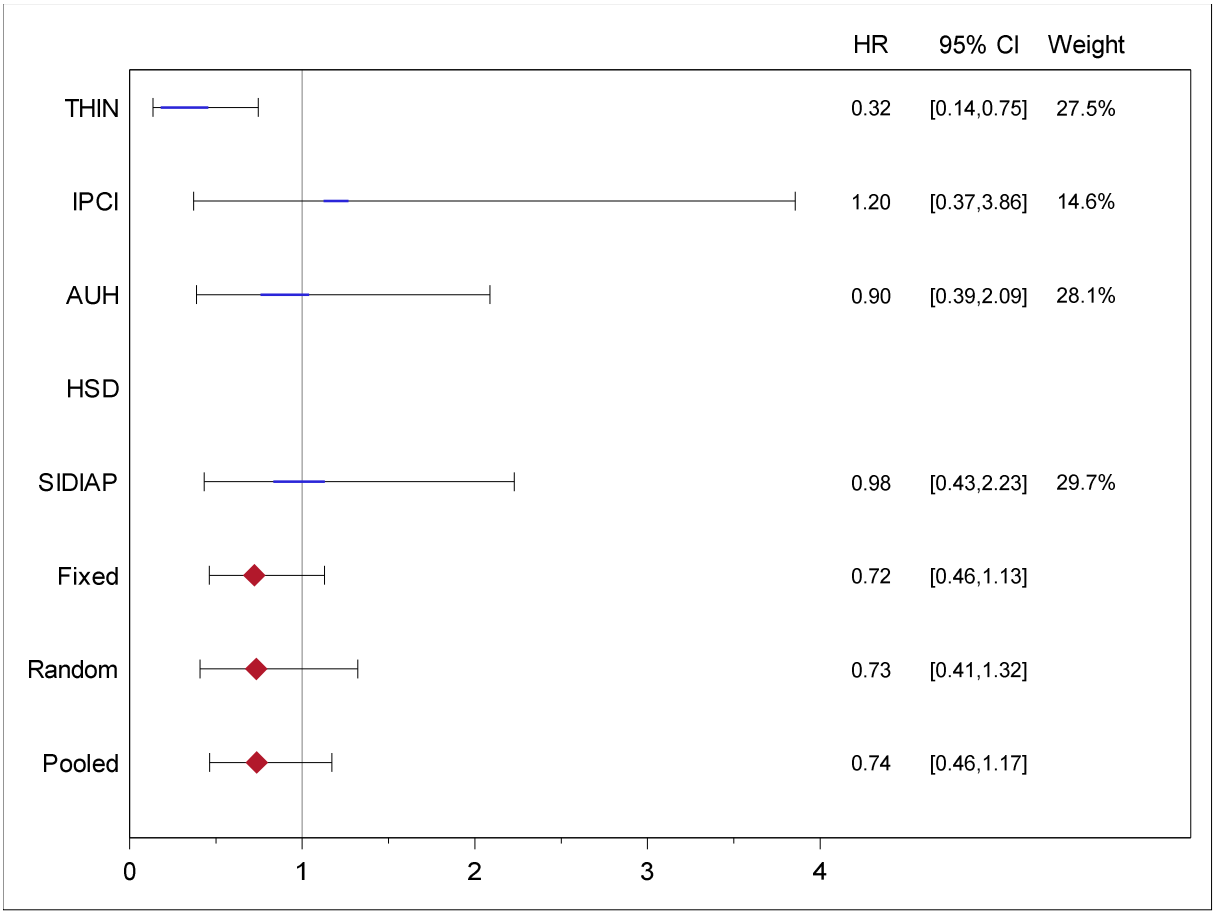
No plot for HSD as less than 5 events in one of the exposure categories

Figure 15-39 Forest plot results Model IPTW NVA237 versus LAMA, outcome MACE – Total analysis population



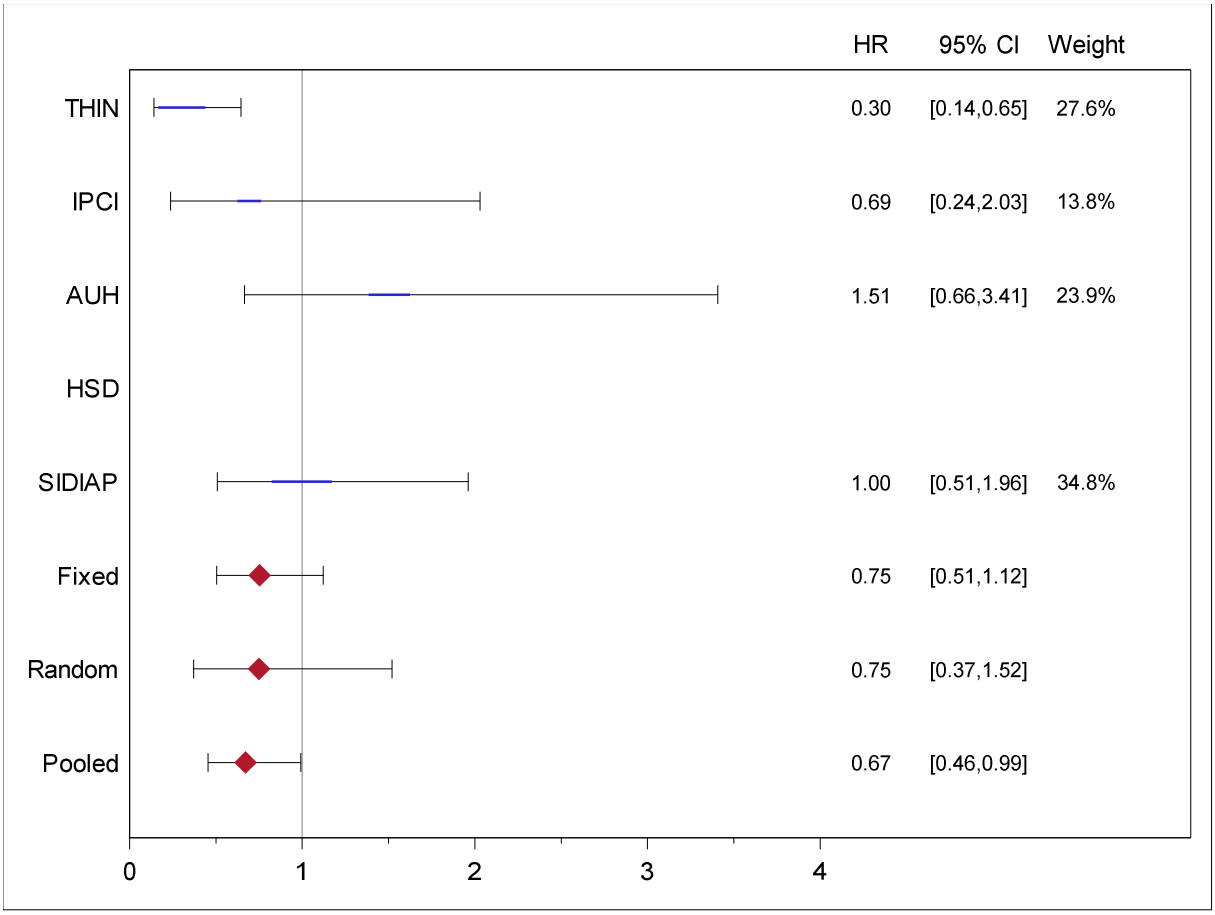
No plot for HSD as less than 5 events in one of the exposure categories

Figure 15-40 Forest plot results Model IPTW NVA237 versus LABA, outcome ischemic heart disease – Total analysis population



No plot for HSD as less than 5 events in one of the exposure categories

Figure 15-41 Forest plot results Model IPTW NVA237 versus LAMA, outcome ischemic heart disease – Total analysis population



No plot for HSD as less than 5 events in one of the exposure categories

Figure 15-42 Forest plot results Model IPTW NVA237 versus LABA, outcome cardiac arrhythmia – Total analysis population

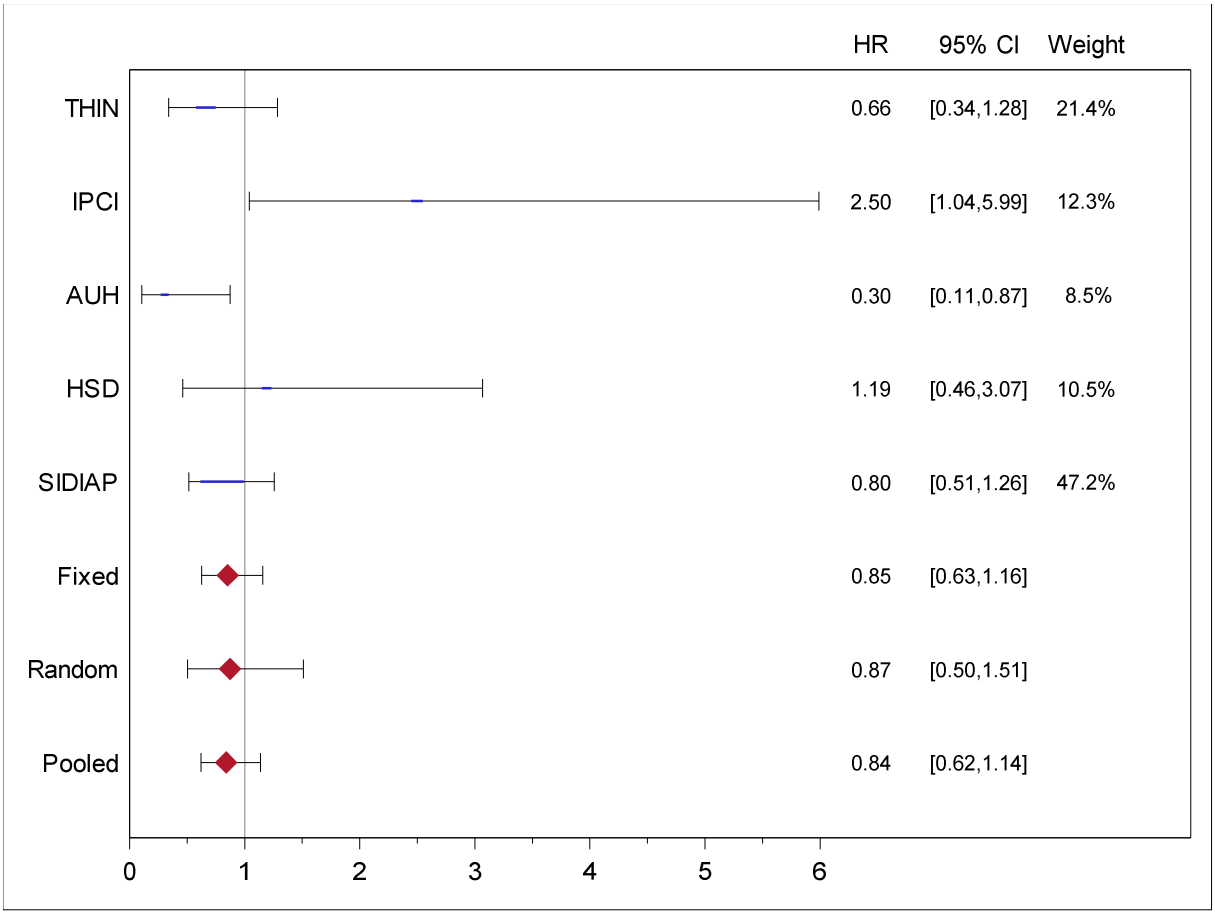


Figure 15-43 Forest plot results Model IPTW NVA237 versus LAMA, outcome cardiac arrhythmia – Total analysis population

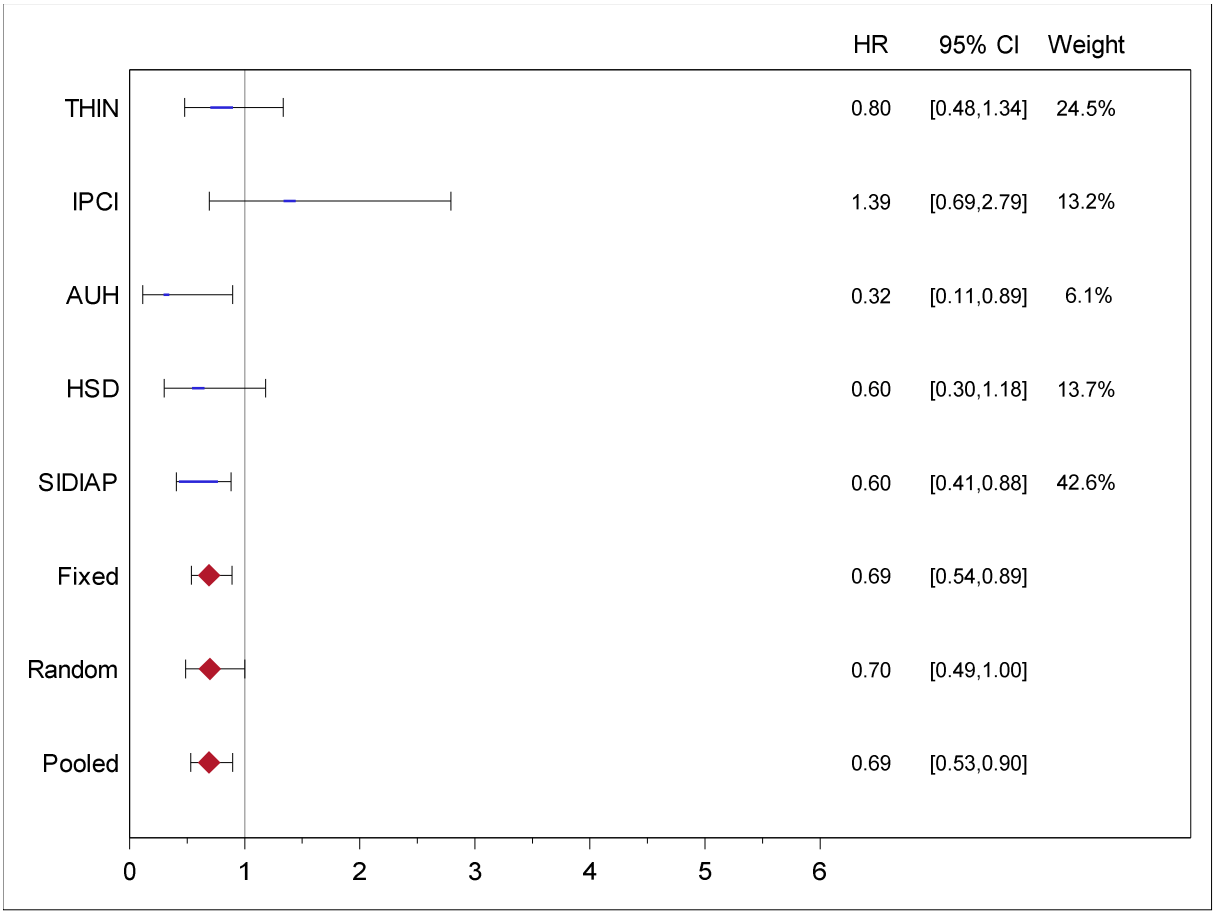
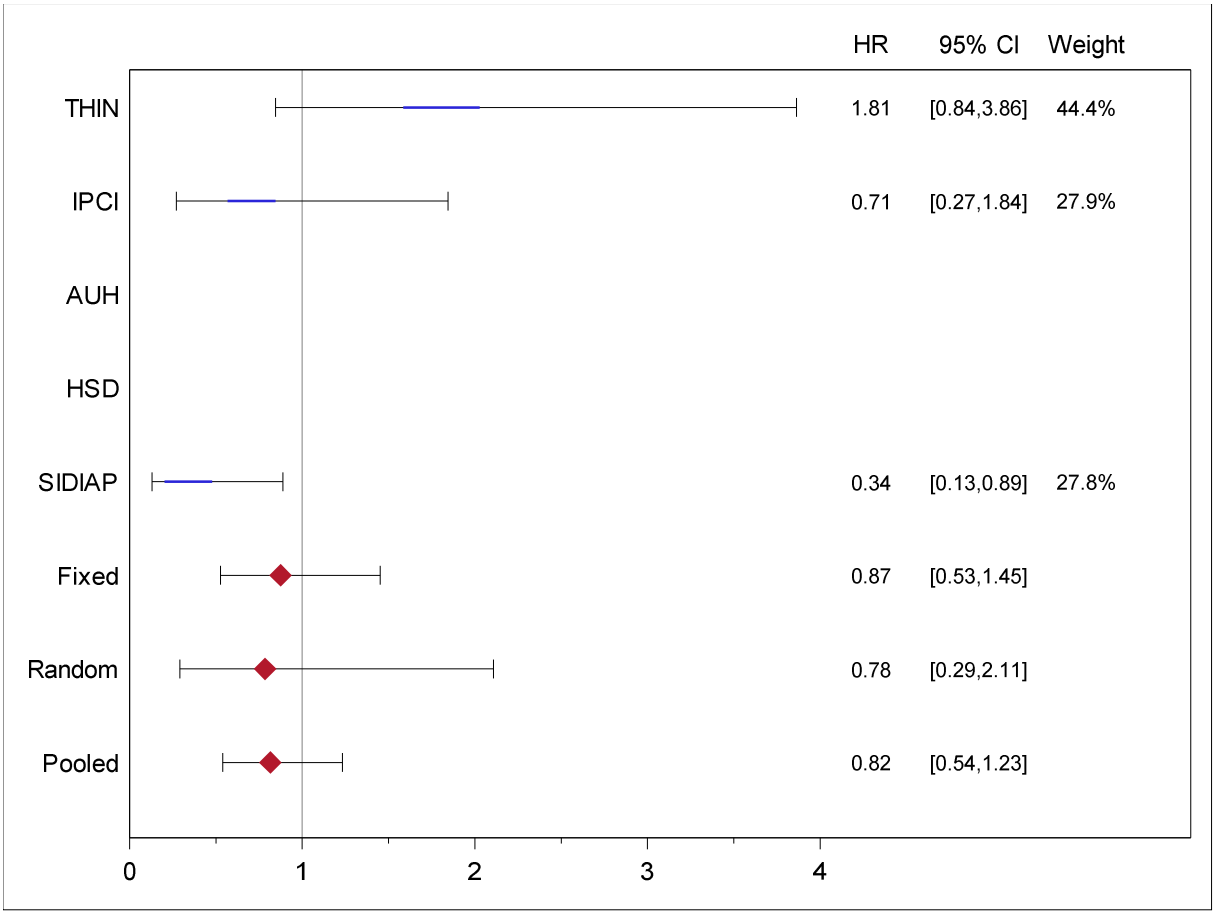
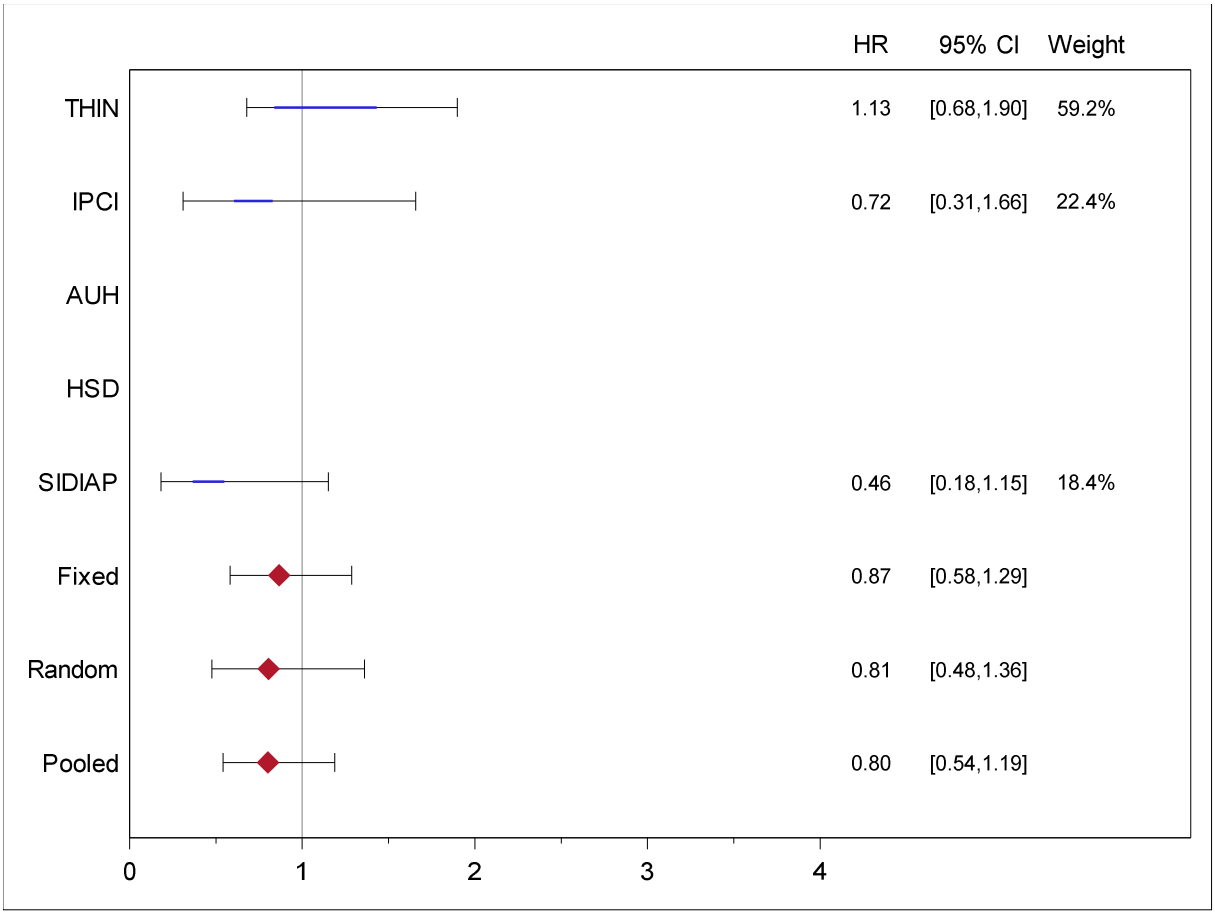


Figure 15-44 Forest plot results Model IPTW NVA237 versus LABA, outcome cerebrovascular events – Total analysis population



No plot for AUH and HSD as less than 5 events in one of the exposure categories

Figure 15-45 Forest plot results Model IPTW NVA237 versus LAMA, outcome cerebrovascular events – Total analysis population



No plot for AUH and HSD as less than 5 events in one of the exposure categories

Figure 15-46 Forest plot results Model IPTW NVA versus LABA, outcome Mortality – Total analysis population

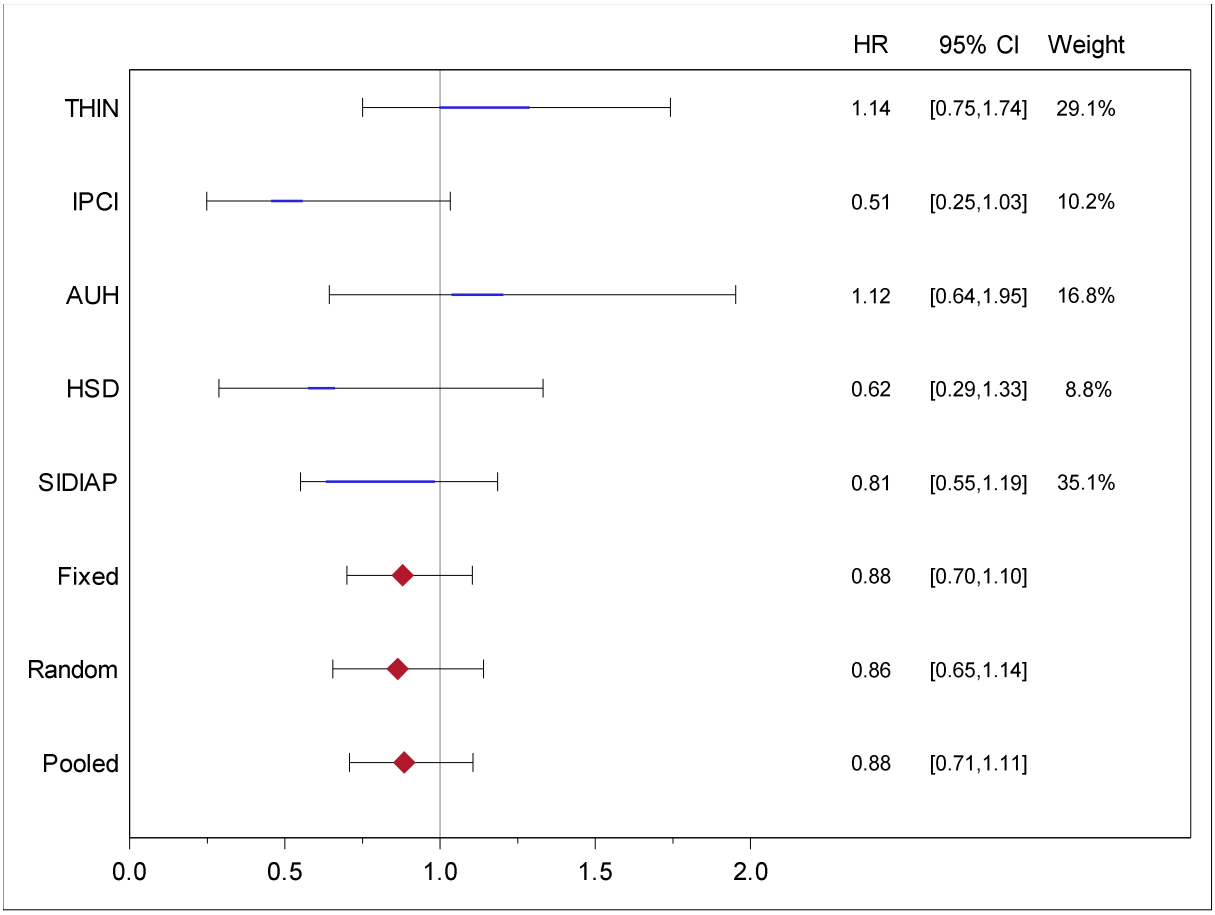


Figure 15-47 Forest plot results Model IPTW NVA versus LAMA, outcome Mortality – Total analysis population

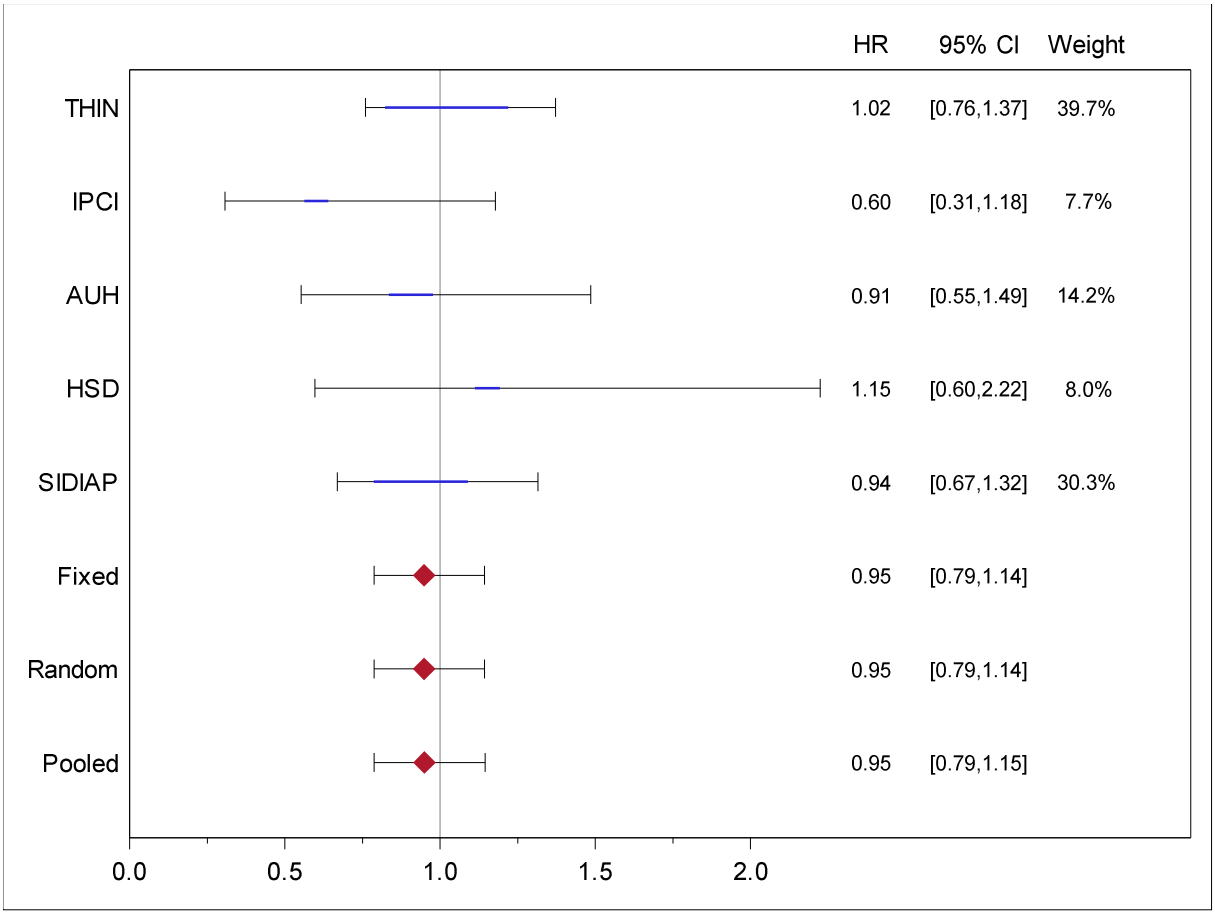


Table 15-1 Baseline characteristics of study cohorts (pooled and by database)

Pooled	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Total	8722 (100.0%)	17890 (100.0%)	.	58852 (100.0%)	.
Gender			0.0440		0.6970
Male	5396 (61.9%)	11297 (63.2%)	.	36278 (61.6%)	.
Female	3326 (38.1%)	6593 (36.9%)	.	22574 (38.4%)	.
Age at cohort entry					
Mean (SD)	70.7 (10.5)	70.1 (11.2)	<.0001	70.1 (11.0).	<.0001
Median (IQR)	71.3 (63.6- 78.8)	70.5 (62.5- 78.5)	.	70.6 (62.5- 78.5)	.
Min-Max	40.0-102.1	40.0-101.1	.	40.0-101.8	.
Age at cohort entry (categorical)			<.0001		0.0007
40-<60	1479 (17.0%)	3506 (19.6%)	.	11188 (19.0%)	.
60-<80	5406 (62.0%)	10715 (59.9%)	.	35493 (60.3%)	.
>=80	1837 (21.1%)	3669 (20.5%)	.	12171 (20.7%)	.
Number of contacts with GP at practice	8722	17890	<.0001	58852	<.0001
Mean (SD)	10.2 (9.1)	9.6 (8.6)	.	9.3 (8.5)	.
Median (IQR)	8.0 (4.0- 13.0)	7.0 (4.0- 12.0)	.	7.0 (4.0- 12.0)	.
Min-Max	0.0-144.0	0.0-112.0	.	0.0-179.0	.
Number of contacts with GP at home	8722	17890	0.0106	58852	0.3215
Mean (SD)	0.5 (2.2)	0.5 (2.0)	.	0.5 (2.4)	.

Pooled	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 47.0	0.0- 56.0	.	0.0-216.0	.
Smoking status			<.0001		<.0001
Current smoker	2812 (34.3%)	5833 (35.0%)	.	21193 (38.2%)	.
Past smoker	2845 (34.7%)	4572 (27.4%)	.	18920 (34.1%)	.
Never smoker	2540 (31.0%)	6276 (37.6%)	.	15373 (27.7%)	.
Unknown	525 (6.0%)	1209 (6.8%)	.	3366 (5.7%)	.
Smoking status (imputed)			<.0001		<.0001
Current smoker	-- (34.6%)	-- (35.6%)	.	-- (38.6%)	.
Past smoker	-- (34.9%)	-- (27.9%)	.	-- (34.1%)	.
Never smoker	-- (30.5%)	-- (36.5%)	.	-- (27.4%)	.

THIN	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Total	2876 (100.0%)	3410 (100.0%)	.	22569 (100.0%)	.
Gender			0.6141		0.0082
Male	1428 (49.7%)	1716 (50.3%)	.	11801 (52.3%)	.
Female	1448 (50.4%)	1694 (49.7%)	.	10768 (47.7%)	.
Age at cohort entry	2876	3410	0.0007	22569	0.1381
Mean (SD)	69.6 (10.6)	68.6 (10.8)	.	69.2 (10.9)	.
Median (IQR)	70.0 (62.3- 77.5)	69.1 (61.5- 76.5)	.	69.6 (61.9- 77.3)	.
Min-Max	40.3-102.1	40.2- 95.2	.	40.0-100.0	.

THIN	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Age at cohort entry (categorical)	2876	3410	0.0007	22569	0.1381
40-<60	557 (19.4%)	737 (21.6%)	.	4617 (20.5%)	.
60-<80	1819 (63.3%)	2158 (63.3%)	.	14050 (62.3%)	.
>=80	500 (17.4%)	515 (15.1%)	.	3902 (17.3%)	.
Number of contacts with GP at practice	2876	3410	0.4064	22569	0.0059
Mean (SD)	8.3 (7.5)	7.9 (6.5)	.	7.9 (6.8)	.
Median (IQR)	7.0 (4.0- 11.0)	7.0 (4.0- 11.0)	.	6.0 (3.0- 10.0)	.
Min-Max	0.0-144.0	0.0- 92.0	.	0.0-110.0	.
Number of contacts with GP at home	2876	3410	0.0784	22569	0.3257
Mean (SD)	0.4 (1.7)	0.4 (1.6)	.	0.5 (2.5)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 32.0	0.0- 31.0	.	0.0-216.0	.
Smoking status					
Current smoker	1123 (39.1%)	1313 (38.5%)	.	9364 (41.5%)	.
Past smoker	1506 (52.4%)	1789 (52.5%)	.	11138 (49.4%)	.
Never smoker	245 (8.5%)	307 (9.0%)	.	2062 (9.1%)	.
Unknown	2 (0.1%)	1 (0.0%)	.	5 (0.0%)	.
Smoking status (imputed)			0.7644		0.0082
Current smoker	-- (39.1%)	-- (38.5%)	.	-- (41.5%)	.
Past smoker	-- (52.4%)	-- (52.5%)	.	-- (49.4%)	.

THIN	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Never smoker	-- (8.5%)	-- (9.0%)	.	-- (9.1%)	.

IPCI	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Total	673 (100.0%)	1942 (100.0%)	.	6587 (100.0%)	.
Gender			0.2328		0.1946
Male	343 (51.0%)	936 (48.2%)	.	3535 (53.7%)	.
Female	330 (49.0%)	1006 (51.8%)	.	3052 (46.3%)	.
Age at cohort entry	673	1942	0.4017	6587	0.0811
Mean (SD)	68.2 (10.6)	67.9 (11.3)	.	67.6 (10.9)	.
Median (IQR)	68.7 (61.2- 76.4)	68.1 (59.6- 76.3)	.	67.3 (59.7- 75.8)	.
Min-Max	41.6- 92.7	40.2- 97.8	.	40.0- 97.9	.
Age at cohort entry (categorical)			0.7480		0.4137
40-<60	151 (22.4%)	504 (26.0%)	.	1691 (25.7%)	.
60-<80	429 (63.7%)	1119 (57.6%)	.	3909 (59.3%)	.
>=80	93 (13.8%)	319 (16.4%)	.	987 (15.0%)	.
Number of contacts with GP at practice	673	1942	0.7844	6587	0.2242
Mean (SD)	7.6 (6.1)	7.5 (6.0)	.	7.2 (5.7)	.
Median (IQR)	6.0 (3.0- 10.0)	6.0 (3.0- 10.0)	.	6.0 (3.0- 10.0)	.
Min-Max	0.0- 37.0	0.0- 64.0	.	0.0- 64.0	.

IPCI	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Number of contacts with GP at home	673	1942	<.0001	6587	<.0001
Mean (SD)	1.3 (3.3)	1.1 (3.2)	.	0.9 (2.9)	.
Median (IQR)	0.0 (0.0- 1.0)	0.0 (0.0- 1.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 30.0	0.0- 56.0	.	0.0- 49.0	.
Smoking status					
Current smoker	293 (46.6%)	721 (40.4%)	.	2975 (48.1%)	.
Past smoker	271 (43.1%)	857 (48.0%)	.	2671 (43.2%)	.
Never smoker	65 (10.3%)	207 (11.6%)	.	536 (8.7%)	.
Unknown	44 (6.5%)	157 (8.1%)	.	405 (6.2%)	.
Smoking status (imputed)			0.0179		0.4847
Current smoker	-- (46.9%)	-- (40.6%)	.	-- (48.1%)	.
Past smoker	-- (42.9%)	-- (48.0%)	.	-- (43.3%)	.
Never smoker	-- (10.2%)	-- (11.4%)	.	-- (8.7%)	.

Aarhus	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Total	468 (100.0%)	1443 (100.0%)	.	3890 (100.0%)	.
Gender			0.2269		0.0630
Male	245 (52.4%)	707 (49.0%)	.	1855 (47.7%)	.
Female	223 (47.7%)	736 (51.0%)	.	2035 (52.3%)	.
Age at cohort entry	468	1443	0.0515	3890	0.0142

Aarhus	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Mean (SD)	69.9 (10.5)	70.9 (10.9)	.	71.1 (11.2)	.
Median (IQR)	70.6 (62.4- 77.8)	71.7 (63.7- 78.8)	.	71.8 (63.5- 79.5)	.
Min-Max	43.6- 96.1	40.3- 97.7	.	40.2- 99.8	.
Age at cohort entry (categorical)			0.1197		0.0164
40-<60	93 (19.9%)	245 (17.0%)	.	680 (17.5%)	.
60-<80	288 (61.5%)	898 (62.2%)	.	2289 (58.8%)	.
>=80	87 (18.6%)	300 (20.8%)	.	921 (23.7%)	.
Number of contacts with GP at practice	468	1443	0.8071	3890	0.1269
Mean (SD)	20.3 (15.3)	20.6 (15.5)	.	21.3 (15.6)	.
Median (IQR)	16.0 (10.0- 28.0)	17.0 (10.0- 27.0)	.	18.0 (10.0- 28.0)	.
Min-Max	0.0-143.0	0.0-112.0	.	0.0-179.0	.
Number of contacts with GP at home	468	1443	0.0605	3890	<.0001
Mean (SD)	0.9 (2.8)	1.2 (3.2)	.	1.5 (3.5)	.
Median (IQR)	0.0 (0.0- 1.0)	0.0 (0.0- 1.0)	.	0.0 (0.0- 1.0)	.
Min-Max	0.0- 30.0	0.0- 41.0	.	0.0- 54.0	.
Smoking status					
Current smoker	123 (43.0%)	383 (45.2%)	.	1116 (47.7%)	.
Past smoker	140 (49.0%)	388 (45.8%)	.	1021 (43.7%)	.
Never smoker	23 (8.0%)	76 (9.0%)	.	202 (8.6%)	.
Unknown	182 (38.9%)	596 (41.3%)	.	1551 (39.9%)	.

Aarhus	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Smoking status (imputed)			0.7853		0.3651
Current smoker	-- (42.1%)	-- (46.1%)	.	-- (48.2%)	.
Past smoker	-- (48.9%)	-- (45.0%)	.	-- (43.3%)	.
Never smoker	-- (9.0%)	-- (9.0%)	.	-- (8.6%)	.

HSD	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Total	1373 (100.0%)	1144 (100.0%)	.	3343 (100.0%)	.
Gender			0.1043		0.0336
Male	869 (63.3%)	687 (60.1%)	.	2003 (59.9%)	.
Female	504 (36.7%)	457 (40.0%)	.	1340 (40.1%)	.
Age at cohort entry	1373	1144	0.0017	3343	0.2334
Mean (SD)	73.8 (9.7)	72.5 (10.4)	.	74.1 (10.1)	.
Median (IQR)	74.5 (67.9- 81.0)	73.3 (65.5- 80.2)	.	75.0 (67.5- 81.5)	.
Min-Max	44.1- 96.1	41.6- 97.5	.	43.6- 99.7	.
Age at cohort entry (categorical)	1373	1144	0.0135	3343	0.0002
40-<60	131 (9.5%)	137 (12.0%)	.	322 (9.6%)	.
60-<80	837 (61.0%)	713 (62.3%)	.	1967 (58.8%)	.
>=80	405 (29.5%)	294 (25.7%)	.	1054 (31.5%)	.
Number of contacts with GP at practice	1373	1144	0.0135	3343	0.0002
Mean (SD)	14.0 (11.1)	12.8 (10.0)	.	12.8 (10.7)	.

HSD	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Median (IQR)	11.0 (6.0- 19.0)	10.0 (5.0- 18.0)	.	10.0 (5.0- 18.0)	.
Min-Max	0.0- 77.0	0.0- 61.0	.	0.0- 80.0	.
Number of contacts with GP at home	1373	1144	0.0242	3343	0.7738
Mean (SD)	0.7 (3.2)	0.5 (2.3)	.	0.6 (3.1)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 47.0	0.0- 29.0	.	0.0- 53.0	.
Smoking status					
Current smoker	421 (36.5%)	363 (37.7%)	.	977 (36.1%)	.
Past smoker	442 (38.3%)	332 (34.5%)	.	980 (36.2%)	.
Never smoker	292 (25.3%)	268 (27.8%)	.	748 (27.7%)	.
Unknown	218 (15.9%)	181 (15.8%)	.	638 (19.1%)	.
Smoking status (imputed)			0.3462		0.3959
Current smoker	-- (36.4%)	-- (37.7%)	.	-- (36.1%)	.
Past smoker	-- (37.9%)	-- (34.7%)	.	-- (36.4%)	.
Never smoker	-- (25.6%)	-- (27.6%)	.	-- (27.6%)	.

SIDIAP	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Total	3332 (100.0%)	9951 (100.0%)	.	22463 (100.0%)	.
Gender			0.0051		0.3937
Male	2511 (75.4%)	7251 (72.9%)	.	17084 (76.1%)	.

SIDIAP	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Female	821 (24.6%)	2700 (27.1%)	.	5379 (24.0%)	.
Age at cohort entry	3332	9951	0.0340	22463	0.8223
Mean (SD)	71.1 (10.5)	70.6 (11.3)	.	71.0 (11.0)	.
Median (IQR)	71.7 (64.0- 79.3)	71.2 (62.8- 79.3)	.	71.6 (63.4- 79.5)	.
Min-Max	40.0- 96.4	40.0-101.1	.	40.0-101.8	.
Age at cohort entry (categorical)			0.0453		0.8591
40-<60	547 (16.4%)	1883 (18.9%)	.	3878 (17.3%)	.
60-<80	2033 (61.0%)	5827 (58.6%)	.	13278 (59.1%)	.
>=80	752 (22.6%)	2241 (22.5%)	.	5307 (23.6%)	.
Number of contacts with GP at practice	3332	9951	<.0001	22463	<.0001
Mean (SD)	9.5 (7.2)	8.7 (6.5)	.	8.9 (6.7)	.
Median (IQR)	8.0 (5.0- 13.0)	7.0 (4.0- 12.0)	.	7.0 (4.0- 12.0)	.
Min-Max	0.0- 93.0	0.0- 65.0	.	0.0- 70.0	.
Number of contacts with GP at home	3332	9951	0.0959	22463	0.2421
Mean (SD)	0.3 (1.4)	0.3 (1.3)	.	0.3 (1.4)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 27.0	0.0- 25.0	.	0.0- 40.0	.
Smoking status					
Current smoker	852 (26.2%)	3053 (31.6%)	.	6761 (31.2%)	.
Past smoker	486 (14.9%)	1206 (12.5%)	.	3110 (14.3%)	.

SIDIAP	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
Never smoker	1915 (58.9%)	5418 (56.0%)	.	11825 (54.5%)	.
Unknown	79 (2.4%)	274 (2.8%)	.	767 (3.4%)	.
Smoking status (imputed)			<.0001		<.0001
Current smoker	-- (26.5%)	-- (31.8%)	.	-- (31.5%)	.
Past smoker	-- (14.9%)	-- (12.3%)	.	-- (14.2%)	.
Never smoker	-- (58.6%)	-- (55.9%)	.	-- (54.3%)	.

gender and smoking status tested with Chi-square test, others with trend test
For non-missing categories of smoking status, percentage is based on number of patients with information available, for category 'Unknown' it is based on total number of patients

Table 15-2 COPD characteristics (NVA237, LABA, LAMA (excl. NVA237)) - (pooled and by database)

Pooled	NVA N(%) 8722 (100.0%)	LABA N(%) 17890 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 58852 (100.0%)	P comparing NVA to LAMA
Duration of COPD	8722	17890	<.0001	58852	<.0001
Mean (SD)	5.6 (5.6)	4.6 (5.4)	.	4.5 (5.5)	.
Median (IQR)	4.3 (0.7- 8.9)	2.9 (0.1- 7.5)	.	2.6 (0.1- 7.3)	.
Min-Max	0.0- 44.5	0.0- 49.5	.	0.0- 49.9	.
FEV1 percentage	5614 (64.4%)	10854 (60.7%)	<.0001	38039 (64.6%)	<.0001
Mean (SD)	61.4 (19.7)	66.6 (18.7)	.	63.0 (19.1)	.
Median (IQR)	60.9 (47.1- 74.0)	66.7 (54.0- 78.4)	.	62.2 (49.1- 75.0)	.
Min-Max	10.0-277.8	12.6-379.8	.	13.0-332.1	.
COPD severity assessed by spirometry					
No COPD	1424 (28.2%)	3128 (31.6%)	.	9198 (27.2%)	.
Mild	387 (10.7%)	1104 (16.3%)	.	3148 (12.8%)	.
Moderate	1881 (51.8%)	4096 (60.4%)	.	13780 (56.1%)	.
Severe	1189 (32.7%)	1425 (21.0%)	.	6793 (27.6%)	.
Very severe	175 (4.8%)	154 (2.3%)	.	847 (3.4%)	.
COPD severity assessed by spirometry (considering all FEV1% predicted – also if FEV1/FVC missing)					
Mild	919 (16.4%)	2477 (22.8%)	.	6823 (17.9%)	.
Moderate	3033 (54.0%)	6385 (58.8%)	.	21420 (56.3%)	.
Severe	1461 (26.0%)	1806 (16.6%)	.	8742 (23.0%)	.

Pooled	NVA N(%) 8722 (100.0%)	LABA N(%) 17890 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 58852 (100.0%)	P comparing NVA to LAMA
Very severe	201 (3.6%)	186 (1.7%)	.	1054 (2.8%)	.
Unknown	3108 (35.6%)	7036 (39.3%)	.	20813 (35.4%)	.
COPD severity assessed by spirometry (imputed)			<.0001		0.0008
Mild	-- (16.6%)	-- (23.3%)	.	-- (18.4%)	.
Moderate	-- (55.7%)	-- (58.3%)	.	-- (56.5%)	.
Severe	-- (24.5%)	-- (16.8%)	.	-- (22.4%)	.
Very severe	-- (3.1%)	-- (1.7%)	.	-- (2.7%)	.
COPD severity assessed by proxy			<.0001		<.0001
Mild	1653 (19.0%)	5181 (29.0%)	.	16226 (27.6%)	.
Moderate	5942 (68.1%)	11451 (64.0%)	.	36503 (62.0%)	.
Severe	918 (10.5%)	1158 (6.5%)	.	5540 (9.4%)	.
Very severe	209 (2.4%)	100 (0.6%)	.	583 (1.0%)	.
Number of hospitalizations for COPD exacerbation	8722	17890	<.0001	58852	0.4407
Mean (SD)	0.1 (0.4)	0.1 (0.4)	.	0.1 (0.4)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 11.0	0.0- 16.0	.	0.0- 15.0	.
Number of hospitalizations for COPD exac (categorical)			<.0001		0.6820
None	8210 (94.1%)	17176 (96.0%)	.	55264 (93.9%)	.
1	393 (4.5%)	555 (3.1%)	.	2888 (4.9%)	.

Pooled	NVA N(%) 8722 (100.0%)	LABA N(%) 17890 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 58852 (100.0%)	P comparing NVA to LAMA
2	69 (0.8%)	88 (0.5%)	.	485 (0.8%)	.
3 or more	50 (0.6%)	71 (0.4%)	.	215 (0.4%)	.
Number of systemic steroids episodes	8722	17890	<.0001	58852	0.0006
Mean (SD)	0.2 (0.5)	0.1 (0.4)	.	0.1 (0.4)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 6.0	0.0- 6.0	.	0.0- 7.0	.
Number of systemic steroids episodes (categorical)			<.0001		<.0001
None	7621 (87.4%)	16395 (91.6%)	.	52097 (88.5%)	.
1	819 (9.4%)	1248 (7.0%)	.	5569 (9.5%)	.
2	185 (2.1%)	192 (1.1%)	.	909 (1.5%)	.
3 or more	97 (1.1%)	55 (0.3%)	.	277 (0.5%)	.
Number of Antibiotic courses	8722	17890	<.0001	58852	0.0060
Mean (SD)	0.3 (0.8)	0.3 (0.7)	.	0.3 (0.7)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 10.0	0.0- 13.0	.	0.0- 13.0	.
Number of Antibiotic courses (categorical)			<.0001		<.0001
None	6885 (78.9%)	14599 (81.6%)	.	47040 (79.9%)	.
1	1164 (13.4%)	2286 (12.8%)	.	8121 (13.8%)	.
2	384 (4.4%)	687 (3.8%)	.	2465 (4.2%)	.

Pooled	NVA N(%) 8722 (100.0%)	LABA N(%) 17890 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 58852 (100.0%)	P comparing NVA to LAMA
3 or more	289 (3.3%)	318 (1.8%)	.	1226 (2.1%)	.

THIN	NVA N(%) 2876 (100.0%)	LABA N(%) 3410 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22569 (100.0%)	P comparing NVA to LAMA
Duration of COPD	2876	3410	<.0001	22569	<.0001
Mean (SD)	5.4 (6.0)	3.9 (5.3)	.	3.9 (5.5)	.
Median (IQR)	3.8 (0.3- 8.4)	1.9 (0.1- 5.8)	.	1.7 (0.0- 6.1)	.
Min-Max	0.0- 43.5	0.0- 49.2	.	0.0- 49.4	.
FEV1 percentage	2514 (87.4%)	2862(83.9%)	<.0001	18204 (80.7%)	<.0001
Mean (SD)	61.5 (21.2)	68.0 (19.4)	.	63.2 (19.6)	.
Median (IQR)	60.3 (46.7- 74.1)	67.7 (55.7- 79.5)	.	62.2 (49.2- 75.2)	.
Min-Max	16.1-277.8	18.3-379.8	.	17.7-332.1	.
COPD severity assessed by spirometry					
No COPD	569 (25.5%)	662 (26.0%)	.	3809 (23.9%)	.
Mild	208 (12.5%)	369 (19.5%)	.	1603 (13.2%)	.
Moderate	818 (49.1%)	1178 (62.4%)	.	6730 (55.6%)	.
Severe	542 (32.6%)	309 (16.4%)	.	3349 (27.7%)	.
Very severe	97 (5.8%)	32 (1.7%)	.	426 (3.5%)	.
COPD severity assessed by spirometry (considering all FEV1% predicted – also if FEV1/FVC missing)					

THIN	NVA N(%) 2876 (100.0%)	LABA N(%) 3410 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22569 (100.0%)	P comparing NVA to LAMA
Mild	443 (17.6%)	692 (24.2%)	.	3303 (18.1%)	.
Moderate	1287 (51.2%)	1730 (60.5%)	.	10172 (55.9%)	.
Severe	668 (26.6%)	392 (13.7%)	.	4196 (23.1%)	.
Very severe	116 (4.6%)	48 (1.7%)	.	533 (2.9%)	.
Unknown	362 (12.6%)	548 (16.1%)	.	4365 (19.3%)	.
COPD severity assessed by spirometry (imputed)			<.0001		<.0001
Mild	-- (17.6%)	-- (24.7%)	.	-- (18.5%)	.
Moderate	-- (51.7%)	-- (59.9%)	.	-- (55.9%)	.
Severe	-- (26.3%)	-- (13.8%)	.	-- (22.7%)	.
Very severe	-- (4.4%)	-- (1.6%)	.	-- (2.9%)	.
COPD severity assessed by proxy			<.0001		<.0001
Mild	417 (14.5%)	698 (20.5%)	.	5209 (23.1%)	.
Moderate	1982 (68.9%)	2397 (70.3%)	.	14767 (65.4%)	.
Severe	411 (14.3%)	286 (8.4%)	.	2273 (10.1%)	.
Very severe	66 (2.3%)	29 (0.9%)	.	320 (1.4%)	.
Number of hospitalizations for COPD exacerbation	2876	3410	<.0001	22569	0.0055
Mean (SD)	0.1 (0.4)	0.1 (0.3)	.	0.1 (0.3)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 5.0	0.0- 5.0	.	0.0- 6.0	.

THIN	NVA N(%) 2876 (100.0%)	LABA N(%) 3410 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22569 (100.0%)	P comparing NVA to LAMA
Number of hospitalizations for COPD exac (categorical)			<.0001		0.0006
None	2672 (92.9%)	3259 (95.6%)	.	21258 (94.2%)	.
1	178 (6.2%)	139 (4.1%)	.	1194 (5.3%)	.
2	16 (0.6%)	9 (0.3%)	.	92 (0.4%)	.
3 or more	10 (0.4%)	3 (0.1%)	.	25 (0.1%)	.
Number of systemic steroids episodes	2876	3410	<.0001	22569	<.0001
Mean (SD)	0.3 (0.6)	0.2 (0.4)	.	0.2 (0.5)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 5.0	0.0- 4.0	.	0.0- 6.0	.
Number of systemic steroids episodes (categorical)			<.0001		<.0001
None	2325 (80.8%)	2985 (87.5%)	.	19303 (85.5%)	.
1	399 (13.9%)	350 (10.3%)	.	2673 (11.8%)	.
2	106 (3.7%)	62 (1.8%)	.	473 (2.1%)	.
3 or more	46 (1.6%)	13 (0.4%)	.	120 (0.5%)	.
Number of Antibiotic courses	2876	3410	<.0001	22569	<.0001
Mean (SD)	0.4 (1.0)	0.3 (0.7)	.	0.3 (0.7)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 10.0	0.0- 9.0	.	0.0- 11.0	.
Number of Antibiotic courses (categorical)			<.0001		<.0001

THIN	NVA N(%) 2876 (100.0%)	LABA N(%) 3410 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22569 (100.0%)	P comparing NVA to LAMA
None	2192 (76.2%)	2846 (83.5%)	.	18387 (81.5%)	.
1	408 (14.2%)	384 (11.3%)	.	2841 (12.6%)	.
2	143 (5.0%)	114 (3.3%)	.	843 (3.7%)	.
3 or more	133 (4.6%)	66 (1.9%)	.	498 (2.2%)	.

IPCI	NVA N(%) 673 (100.0%)	LABA N(%) 1942 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 6587 (100.0%)	P comparing NVA to LAMA
Duration of COPD	673	1942	0.0250	6587	<.0001
Mean (SD)	6.1 (5.4)	5.7 (5.6)	.	5.4 (5.7)	.
Median (IQR)	5.2 (1.7- 9.0)	4.7 (1.4- 8.1)	.	4.2 (0.7- 7.8)	.
Min-Max	0.0- 34.5	0.0- 47.0	.	0.0- 49.9	.
FEV1 percentage	317 (47.1%)	1056 (54.4%)	<.0001	3581 (54.4%)	<.0001
Mean (SD)	64.2 (19.9)	73.3 (19.1)	.	68.9 (18.8)	.
Median (IQR)	63.0 (50.0- 77.9)	73.9 (60.7- 86.0)	.	69.1 (56.4- 81.1)	.
Min-Max	10.0-125.9	12.6-131.2	.	13.0-165.3	.
COPD severity assessed by spirometry					
No COPD	41 (13.1%)	212 (20.3%)	.	560 (15.9%)	.
Mild	52 (19.2%)	239 (28.7%)	.	661 (22.3%)	.
Moderate	145 (53.5%)	474 (56.8%)	.	1771 (59.8%)	.
Severe	67 (24.7%)	108 (12.9%)	.	467 (15.8%)	.

IPCI	NVA N(%) 673 (100.0%)	LABA N(%) 1942 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 6587 (100.0%)	P comparing NVA to LAMA
Very severe	7 (2.2%)	13 (1.6%)	.	62 (2.1%)	.
COPD severity assessed by spirometry (considering all FEV1% predicted – also if FEV1/FVC missing)					
Mild	68 (21.5%)	388 (36.7%)	.	977 (27.3%)	.
Moderate	171 (53.9%)	546 (51.7%)	.	2046 (57.1%)	.
Severe	69 (21.8%)	107 (10.1%)	.	493 (13.8%)	.
Very severe	9 (2.8%)	15 (1.4%)	.	65 (1.8%)	.
Unknown	356 (52.9%)	886 (45.6%)	.	3006 (45.6%)	.
COPD severity assessed by spirometry (imputed)			<.0001		0.0002
Mild	-- (19.3%)	-- (36.0%)	.	-- (26.7%)	.
Moderate	-- (55.6%)	-- (52.0%)	.	-- (56.9%)	.
Severe	-- (21.8%)	-- (10.4%)	.	-- (14.4%)	.
Very severe	-- (3.3%)	-- (1.6%)	.	-- (2.0%)	.
COPD severity assessed by proxy			<.0001		<.0001
Mild	109 (16.2%)	413 (21.3%)	.	1944 (29.5%)	.
Moderate	380 (56.5%)	1274 (65.6%)	.	3801 (57.7%)	.
Severe	171 (25.4%)	239 (12.3%)	.	788 (12.0%)	.
Very severe	13 (1.9%)	16 (0.8%)	.	54 (0.8%)	.
Number of hospitalizations for COPD exacerbation	673	1942	<.0001	6587	<.0001

IPCI	NVA N(%) 673 (100.0%)	LABA N(%) 1942 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 6587 (100.0%)	P comparing NVA to LAMA
Mean (SD)	0.1 (0.4)	0.1 (0.3)	.	0.0 (0.2)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 3.0	0.0- 6.0	.	0.0- 6.0	.
Number of hospitalizations for COPD exac (categorical)			0.0002		<.0001
None	619 (92.0%)	1864 (96.0%)	.	6362 (96.6%)	.
1	38 (5.7%)	56 (2.9%)	.	196 (3.0%)	.
2	12 (1.8%)	16 (0.8%)	.	19 (0.3%)	.
3 or more	4 (0.6%)	6 (0.3%)	.	10 (0.2%)	.
Number of systemic steroids episodes	673	1942	<.0001	6587	<.0001
Mean (SD)	0.6 (1.0)	0.3 (0.7)	.	0.3 (0.7)	.
Median (IQR)	0.0 (0.0- 1.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 6.0	0.0- 6.0	.	0.0- 7.0	.
Number of systemic steroids episodes (categorical)			<.0001		<.0001
None	444 (66.0%)	1545 (79.6%)	.	5155 (78.3%)	.
1	131 (19.5%)	267 (13.8%)	.	1002 (15.2%)	.
2	56 (8.3%)	91 (4.7%)	.	295 (4.5%)	.
3 or more	42 (6.2%)	39 (2.0%)	.	135 (2.1%)	.
Number of Antibiotic courses	673	1942	<.0001	6587	<.0001
Mean (SD)	0.8 (1.2)	0.5 (1.0)	.	0.5 (1.0)	.
Median (IQR)	0.0 (0.0- 1.0)	0.0 (0.0- 1.0)	.	0.0 (0.0- 1.0)	.

IPCI	NVA N(%) 673 (100.0%)	LABA N(%) 1942 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 6587 (100.0%)	P comparing NVA to LAMA
Min-Max	0.0- 7.0	0.0- 13.0	.	0.0- 13.0	.
Number of Antibiotic courses (categorical)			<.0001		<.0001
None	392 (58.3%)	1354 (69.7%)	.	4450 (67.6%)	.
1	146 (21.7%)	363 (18.7%)	.	1341 (20.4%)	.
2	74 (11.0%)	143 (7.4%)	.	492 (7.5%)	.
3 or more	61 (9.1%)	82 (4.2%)	.	304 (4.6%)	.

Aarhus	NVA N(%) 468 (100.0%)	LABA N(%) 1443 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3890 (100.0%)	P comparing NVA to LAMA
Duration of COPD	468	1443	0.0236	3890	<.0001
Mean (SD)	5.2 (5.4)	4.6 (5.1)	.	3.9 (5.0)	.
Median (IQR)	3.6 (0.4- 8.4)	2.8 (0.1- 7.6)	.	1.7 (0.0- 6.5)	.
Min-Max	0.0- 21.3	0.0- 20.2	.	0.0- 21.5	.
FEV1 percentage	81 (17.3%)	177 (12.3%)	0.1409	397 (10.2%)	0.0052
Mean (SD)	54.2 (14.2)	56.7 (12.4)	.	59.1 (12.8)	.
Median (IQR)	53.0 (43.5- 65.0)	58.0 (48.0- 65.0)	.	59.0 (49.6- 68.2)	.
Min-Max	26.5- 97.0	24.9- 91.0	.	26.0- 98.5	.
COPD severity assessed by spirometry					
No COPD	10 (13.9%)	20 (12.7%)	.	76 (21.3%)	.

Aarhus	NVA N(%) 468 (100.0%)	LABA N(%) 1443 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3890 (100.0%)	P comparing NVA to LAMA
Mild	3 (4.8%)	15 (10.9%)	.	15 (5.3%)	.
Moderate	32 (51.6%)	71 (51.8%)	.	134 (47.7%)	.
Severe	20 (32.3%)	46 (33.6%)	.	110 (39.1%)	.
Very severe	7 (11.3%)	5 (3.6%)	.	22 (7.8%)	.
COPD severity assessed by spirometry (considering all FEV1% predicted – also if FEV1/FVC missing)					
Mild	19 (8.1%)	80 (12.6%)	.	144 (7.6%)	.
Moderate	120 (51.3%)	344 (54.0%)	.	889 (46.9%)	.
Severe	81 (34.6%)	187 (29.4%)	.	717 (37.8%)	.
Very severe	14 (6.0%)	26 (4.1%)	.	145 (7.7%)	.
Unknown	234 (50.0%)	806 (55.9%)	.	1995 (51.3%)	.
COPD severity assessed by spirometry (imputed)			0.0008		0.0534
Mild	-- (8.2%)	-- (13.4%)	.	-- (7.9%)	.
Moderate	-- (52.1%)	-- (54.8%)	.	-- (47.2%)	.
Severe	-- (34.4%)	-- (28.0%)	.	-- (37.5%)	.
Very severe	-- (5.3%)	-- (3.8%)	.	-- (7.4%)	.
COPD severity assessed by proxy			<.0001		0.0917
Mild	87 (18.6%)	477 (33.1%)	.	1221 (31.4%)	.
Moderate	316 (67.5%)	787 (54.5%)	.	1856 (47.7%)	.
Severe	65 (13.9%)	179 (12.4%)	.	813 (20.9%)	.

Aarhus	NVA N(%) 468 (100.0%)	LABA N(%) 1443 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3890 (100.0%)	P comparing NVA to LAMA
Very severe					
Number of hospitalizations for COPD exacerbation	468	1443	0.8055	3890	<.0001
Mean (SD)	0.2 (0.9)	0.2 (0.8)	.	0.2 (0.7)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 11.0	0.0- 16.0	.	0.0- 15.0	.
Number of hospitalizations for COPD exac (categorical)			0.9714		0.0009
None	423 (90.4%)	1310 (90.8%)	.	3240 (83.3%)	.
1	33 (7.1%)	93 (6.4%)	.	472 (12.1%)	.
2	5 (1.1%)	17 (1.2%)	.	118 (3.0%)	.
3 or more	7 (1.5%)	23 (1.6%)	.	60 (1.5%)	.
Number of systemic steroids episodes	468	1443	0.1470	3890	0.0193
Mean (SD)	0.2 (0.5)	0.1 (0.4)	.	0.2 (0.5)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 3.0	0.0- 3.0	.	0.0- 4.0	.
Number of systemic steroids episodes (categorical)			0.0380		0.1358
None	398 (85.0%)	1262 (87.5%)	.	3120 (80.2%)	.
1	55 (11.8%)	161 (11.2%)	.	684 (17.6%)	.
2	12 (2.6%)	17 (1.2%)	.	74 (1.9%)	.
3 or more	3 (0.6%)	3 (0.2%)	.	12 (0.3%)	.

Aarhus	NVA N(%) 468 (100.0%)	LABA N(%) 1443 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3890 (100.0%)	P comparing NVA to LAMA
Number of Antibiotic courses	468	1443	0.3841	3890	0.0005
Mean (SD)	0.3 (0.8)	0.3 (0.8)	.	0.4 (0.9)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 1.0)	.
Min-Max	0.0- 5.0	0.0- 8.0	.	0.0- 7.0	.
Number of Antibiotic courses (categorical)			0.4821		0.0066
None	371 (79.3%)	1172 (81.2%)	.	2772 (71.3%)	.
1	63 (13.5%)	165 (11.4%)	.	753 (19.4%)	.
2	17 (3.6%)	64 (4.4%)	.	230 (5.9%)	.
3 or more	17 (3.6%)	42 (2.9%)	.	135 (3.5%)	.

HSD	NVA N(%) 1373 (100.0%)	LABA N(%) 1144 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3343 (100.0%)	P comparing NVA to LAMA
Duration of COPD	1373	1144	0.0319	3343	0.0002
Mean (SD)	7.0 (4.4)	6.6 (4.2)	.	6.5 (4.3)	.
Median (IQR)	7.0 (3.5- 10.6)	6.4 (3.2- 9.9)	.	6.4 (3.0- 9.9)	.
Min-Max	0.0- 15.8	0.0- 15.6	.	0.0- 15.8	.
FEV1 percentage	453 (33.0%)	338 (29.1%)	0.0002	907 (27.1%)	0.0604
Mean (SD)	69.5 (17.3)	74.5 (16.6)	.	71.4 (17.0)	.
Median (IQR)	69.0 (58.0- 79.0)	74.0 (63.0- 82.0)	.	71.0 (60.0- 81.0)	.

HSD	NVA N(%) 1373 (100.0%)	LABA N(%) 1144 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3343 (100.0%)	P comparing NVA to LAMA
Min-Max	25.0-125.0	33.0-123.0	.	28.9-125.0	.
COPD severity assessed by spirometry					
No COPD	199 (49.8%)	159 (52.7%)	.	420 (51.8%)	.
Mild	8 (4.0%)	15 (10.5%)	.	32 (8.2%)	.
Moderate	150 (74.6%)	115 (80.4%)	.	295 (75.4%)	.
Severe	41 (20.4%)	13 (9.1%)	.	62 (15.9%)	.
Very severe	2 (1.0%)	0 (0.0%)	.	2 (0.5%)	.
COPD severity assessed by spirometry (considering all FEV1% predicted – also if FEV1/FVC missing)					
Mild	106 (23.4%)	101 (29.9%)	.	252 (27.8%)	.
Moderate	294 (64.9%)	221 (65.4%)	.	574 (63.3%)	.
Severe	50 (11.0%)	16 (4.7%)	.	79 (8.7%)	.
Very severe	3 (0.7%)		.	2 (0.2%)	.
Unknown	920 (67.0%)	806 (70.5%)	.	2436 (72.9%)	.
COPD severity assessed by spirometry (imputed)			0.0557		0.0615
Mild	-- (23.0%)	-- (30.8%)	.	-- (28.1%)	.
Moderate	-- (65.6%)	-- (62.2%)	.	-- (63.1%)	.
Severe	-- (11.0%)	-- (6.8%)	.	-- (8.6%)	.
Very severe	-- (0.4%)	-- (0.2%)	.	-- (0.2%)	.
COPD severity assessed by proxy			<.0001		<.0001

HSD	NVA N(%) 1373 (100.0%)	LABA N(%) 1144 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3343 (100.0%)	P comparing NVA to LAMA
Mild	281 (20.5%)	330 (28.9%)	.	878 (26.3%)	.
Moderate	923 (67.2%)	734 (64.2%)	.	2149 (64.3%)	.
Severe	39 (2.8%)	25 (2.2%)	.	107 (3.2%)	.
Very severe	130 (9.5%)	55 (4.8%)	.	209 (6.3%)	.
Number of hospitalizations for COPD exacerbation	1373	1144	0.3685	3343	0.4381
Mean (SD)	0.0 (0.1)	0.0 (0.0)	.	0.0 (0.1)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 2.0	0.0- 1.0	.	0.0- 2.0	.
Number of hospitalizations for COPD exac (categorical)			0.2007		0.9586
None	1368 (99.6%)	1142 (99.8%)	.	3325 (99.5%)	.
1	2 (0.2%)	2 (0.2%)	.	17 (0.5%)	.
2	3 (0.2%)		.	1 (0.0%)	.
3 or more					
Number of systemic steroids episodes	1373	1144	0.0378	3343	0.9051
Mean (SD)	0.1 (0.3)	0.0 (0.2)	.	0.1 (0.3)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 4.0	0.0- 2.0	.	0.0- 4.0	.
Number of systemic steroids episodes (categorical)			0.0149		0.6496
None	1286 (93.7%)	1093 (95.5%)	.	3134 (93.8%)	.

HSD	NVA N(%) 1373 (100.0%)	LABA N(%) 1144 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3343 (100.0%)	P comparing NVA to LAMA
1	74 (5.4%)	46 (4.0%)	.	181 (5.4%)	.
2	7 (0.5%)	5 (0.4%)	.	22 (0.7%)	.
3 or more	6 (0.4%)		.	6 (0.2%)	.
Number of Antibiotic courses	1373	1144	0.0583	3343	0.8657
Mean (SD)	0.3 (0.7)	0.2 (0.6)	.	0.2 (0.7)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 7.0	0.0- 6.0	.	0.0- 8.0	.
Number of Antibiotic courses (categorical)			0.0623		0.8129
None	1158 (84.3%)	995 (87.0%)	.	2827 (84.6%)	.
1	145 (10.6%)	102 (8.9%)	.	333 (10.0%)	.
2	37 (2.7%)	28 (2.5%)	.	123 (3.7%)	.
3 or more	33 (2.4%)	19 (1.7%)	.	60 (1.8%)	.

SIDIAP	NVA N(%) 3332 (100.0%)	LABA N(%) 9951 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22463 (100.0%)	P comparing NVA to LAMA
Duration of COPD	3332	9951	<.0001	22463	<.0001
Mean (SD)	5.0 (5.6)	4.4 (5.4)	.	4.5 (5.5)	.
Median (IQR)	3.3 (0.4- 8.4)	2.5 (0.0- 7.3)	.	2.5 (0.0- 7.6)	.
Min-Max	0.0- 44.5	0.0- 49.5	.	0.0- 49.4	.

SIDIAP	NVA N(%) 3332 (100.0%)	LABA N(%) 9951 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22463 (100.0%)	P comparing NVA to LAMA
FEV1 percentage	2096 (62.9%)	5961 (59.9%)	<.0001	13452 (59.9%)	<.0001
Mean (SD)	59.9 (17.9)	65.2 (17.9)	.	62.0 (18.1)	.
Median (IQR)	59.4 (46.4- 71.4)	65.0 (52.8- 77.0)	.	61.5 (49.0- 74.0)	.
Min-Max	25.0-125.0	25.0-124.8	.	25.0-125.0	.
COPD severity assessed by spirometry					
No COPD	605 (29.7%)	2075 (35.5%)	.	4333 (32.9%)	.
Mild	116 (8.1%)	466 (12.3%)	.	837 (9.5%)	.
Moderate	736 (51.4%)	2258 (59.8%)	.	4850 (54.9%)	.
Severe	519 (36.2%)	949 (25.1%)	.	2805 (31.8%)	.
Very severe	62 (4.3%)	104 (2.8%)	.	335 (3.8%)	.
COPD severity assessed by spirometry (considering all FEV1% predicted – also if FEV1/FVC missing)					
Mild	283 (13.5%)	1216 (20.4%)	.	2147 (16.0%)	.
Moderate	1161 (55.4%)	3544 (59.5%)	.	7739 (57.5%)	.
Severe	593 (28.3%)	1104 (18.5%)	.	3257 (24.2%)	.
Very severe	59 (2.8%)	97 (1.6%)	.	309 (2.3%)	.
Unknown	1236 (37.1%)	3990 (40.1%)	.	9011 (40.1%)	.
COPD severity assessed by spirometry (imputed)			<.0001		0.0007
Mild	-- (13.9%)	-- (20.8%)	.	-- (16.3%)	.
Moderate	-- (55.7%)	-- (59.0%)	.	-- (57.5%)	.

SIDIAP	NVA N(%) 3332 (100.0%)	LABA N(%) 9951 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22463 (100.0%)	P comparing NVA to LAMA
Severe	-- (27.6%)	-- (18.6%)	.	-- (24.0%)	.
Very severe	-- (2.8%)	-- (1.6%)	.	-- (2.3%)	.
COPD severity assessed by proxy			<.0001		<.0001
Mild	759 (22.8%)	3263 (32.8%)	.	6974 (31.1%)	.
Moderate	2341 (70.3%)	6259 (62.9%)	.	13930 (62.0%)	.
Severe	232 (7.0%)	429 (4.3%)	.	1559 (6.9%)	.
Very severe					
Number of hospitalizations for COPD exacerbation	3332	9951	<.0001	22463	0.9601
Mean (SD)	0.1 (0.4)	0.1 (0.3)	.	0.1 (0.4)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 5.0	0.0- 12.0	.	0.0- 12.0	.
Number of hospitalizations for COPD exac (categorical)			<.0001		0.4724
None	3128 (93.9%)	9601 (96.5%)	.	21079 (93.8%)	.
1	142 (4.3%)	265 (2.7%)	.	1009 (4.5%)	.
2	33 (1.0%)	46 (0.5%)	.	255 (1.1%)	.
3 or more	29 (0.9%)	39 (0.4%)	.	120 (0.5%)	.
Number of systemic steroids episodes	3332	9951	0.2431	22463	0.7666
Mean (SD)	0.1 (0.2)	0.0 (0.2)	.	0.1 (0.2)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 2.0	0.0- 2.0	.	0.0- 4.0	.

SIDIAP	NVA N(%) 3332 (100.0%)	LABA N(%) 9951 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22463 (100.0%)	P comparing NVA to LAMA
Number of systemic steroids episodes (categorical)			0.3166		0.9867
None	3168 (95.1%)	9510 (95.6%)	.	21385 (95.2%)	.
1	160 (4.8%)	424 (4.3%)	.	1029 (4.6%)	.
2	4 (0.1%)	17 (0.2%)	.	45 (0.2%)	.
3 or more			.	4 (0.0%)	.
Number of Antibiotic courses	3332	9951	0.6023	22463	0.6709
Mean (SD)	0.2 (0.6)	0.2 (0.6)	.	0.2 (0.6)	.
Median (IQR)	0.0 (0.0- 0.0)	0.0 (0.0- 0.0)	.	0.0 (0.0- 0.0)	.
Min-Max	0.0- 6.0	0.0- 7.0	.	0.0- 7.0	.
Number of Antibiotic courses (categorical)			0.9736		0.8296
None	2772 (83.2%)	8232 (82.7%)	.	18604 (82.8%)	.
1	402 (12.1%)	1272 (12.8%)	.	2853 (12.7%)	.
2	113 (3.4%)	338 (3.4%)	.	777 (3.5%)	.
3 or more	45 (1.4%)	109 (1.1%)	.	229 (1.0%)	.

All categorical variables tested with trend test. For non-missing categories of COPD severity, percentage is based on number of patients with information available, for category 'Unknown' it is based on total number of patients

Table 15-3 Co-morbidities (assessed at and prior to index date) by exposure cohort – pooled and by database

Pooled	NVA N(%) 8722 (100.0%)	LABA N(%) 17890 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 58852 (100.0%)	P comparing NVA to LAMA
Cardiovascular comorbidities	5373 (61.6%)	10752 (60.1%)	0.0192	35397 (60.2%)	0.0098
- Arterial hypertension	4569 (52.4%)	9479 (53.0%)	0.3642	29929 (50.9%)	0.0079
- Unstable angina pectoris	139 (1.6%)	264 (1.5%)	0.4925	1246 (2.1%)	0.0015
- Angina pectoris	775 (8.9%)	1404 (7.9%)	0.0041	6306 (10.7%)	<.0001
- Myocardial infarction	584 (6.7%)	1056 (5.9%)	0.0125	4361 (7.4%)	0.0178
- Heart failure	793 (9.1%)	1346 (7.5%)	<.0001	5246 (8.9%)	0.6003
Cardiac arrhythmia					
Major Cardiac arrhythmia	1038 (11.9%)	2065 (11.5%)	0.4042	7274 (12.4%)	0.2301
- Atrial fibrillation/flutter	931 (10.7%)	1774 (9.9%)	0.0575	6520 (11.1%)	0.2682
- Torsade de Pointes/Long QT	2 (0.0%)	3 (0.0%)	1.0000	14 (0.0%)	1.0000
- Ventricular fibrillation	5 (0.1%)	31 (0.2%)	0.0252	78 (0.1%)	0.0877
- Ventricular tachycardia	18 (0.2%)	42 (0.2%)	0.7484	164 (0.3%)	0.2692
- AV block	117 (1.3%)	294 (1.6%)	0.0685	807 (1.4%)	0.8617
Sick Sinus	24 (0.3%)	43 (0.2%)	0.6880	136 (0.2%)	0.5013
Supraventricular tachycardia	97 (1.1%)	199 (1.1%)	1.0000	766 (1.3%)	0.1558
Premature depolarization	150 (1.7%)	227 (1.3%)	0.0042	790 (1.3%)	0.0058
Cerebrovascular comorbidities	849 (9.7%)	1593 (8.9%)	0.0294	5678 (9.7%)	0.8146
- Stroke	659 (7.6%)	1150 (6.4%)	0.0007	4284 (7.3%)	0.3666

Pooled	NVA N(%) 8722 (100.0%)	LABA N(%) 17890 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 58852 (100.0%)	P comparing NVA to LAMA
- TIA	317 (3.6%)	627 (3.5%)	0.6158	2344 (4.0%)	0.1256
Other comorbidities					
Diabetes Mellitus	1740 (20.0%)	3700 (20.7%)	0.1693	11691 (19.9%)	0.8649
Hyperlipidemia	2054 (23.6%)	3764 (21.0%)	<.0001	13207 (22.4%)	0.0216
Hepatic impairment	277 (3.2%)	390 (2.2%)	<.0001	1746 (3.0%)	0.3003
Lung cancer	138 (1.6%)	227 (1.3%)	0.0448	929 (1.6%)	1.0000
Cancer (excluding lung cancer)	1182 (13.6%)	2504 (14.0%)	0.3336	8123 (13.8%)	0.5373
Asthma	1786 (20.5%)	2636 (14.7%)	<.0001	11502 (19.5%)	0.0422
BPH	1204 (13.8%)	2642 (14.8%)	0.0375	7138 (12.1%)	<.0001
Bladder obstruction/urinary retention	187 (2.1%)	297 (1.7%)	0.0065	1270 (2.2%)	0.9647
Chronic kidney disease			<.0001		<.0001
No CKD	1971 (22.6%)	4807 (26.9%)	.	14356 (24.4%)	.
Stage unknown	100 (1.2%)	224 (1.3%)	.	776 (1.3%)	.
Stage 1	75 (0.9%)	66 (0.4%)	.	208 (0.4%)	.
Stage 2	4090 (46.9%)	8665 (48.4%)	.	27797 (47.2%)	.
Stage 3	2226 (25.5%)	3726 (20.8%)	.	14024 (23.8%)	.
Stage 4	209 (2.4%)	339 (1.9%)	.	1420 (2.4%)	.
Stage 5	51 (0.6%)	63 (0.4%)	.	271 (0.5%)	.

THIN	NVA N(%) 2876 (100.0%)	LABA N(%) 3410 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22569 (100.0%)	P comparing NVA to LAMA
Cardiovascular comorbidities	1659 (57.7%)	1850 (54.3%)	0.0068	12623 (55.9%)	0.0776
- Arterial hypertension	1344 (46.7%)	1553 (45.5%)	0.3592	10285 (45.6%)	0.2475
- Unstable angina pectoris	66 (2.3%)	78 (2.3%)	1.0000	630 (2.8%)	0.1397
- Angina pectoris	445 (15.5%)	518 (15.2%)	0.7838	3638 (16.1%)	0.3883
- Myocardial infarction	220 (7.7%)	259 (7.6%)	0.9737	1862 (8.3%)	0.2842
- Heart failure	229 (8.0%)	220 (6.5%)	0.0233	1713 (7.6%)	0.5022
Cardiac arrhythmia					
Major Cardiac arrhythmia	268 (9.3%)	290 (8.5%)	0.2774	2160 (9.6%)	0.6893
- Atrial fibrillation/flutter	255 (8.9%)	279 (8.2%)	0.3552	2080 (9.2%)	0.5636
- Torsade de Pointes/Long QT	1 (0.0%)	1 (0.0%)	1.0000	7 (0.0%)	1.0000
- Ventricular fibrillation	1 (0.0%)	5 (0.2%)	0.3073	17 (0.1%)	0.6906
- Ventricular tachycardia	6 (0.2%)	4 (0.1%)	0.5569	45 (0.2%)	1.0000
- AV block	8 (0.3%)	5 (0.2%)	0.3870	51 (0.2%)	0.7322
Sick Sinus	1 (0.0%)	3 (0.1%)	0.7403	22 (0.1%)	0.4688
Supraventricular tachycardia	25 (0.9%)	32 (0.9%)	0.8771	262 (1.2%)	0.1933
Premature depolarization	22 (0.8%)	22 (0.7%)	0.6776	161 (0.7%)	0.8484
Cerebrovascular comorbidities	301 (10.5%)	332 (9.7%)	0.3597	2215 (9.8%)	0.2849
- Stroke	245 (8.5%)	246 (7.2%)	0.0610	1804 (8.0%)	0.3477
- TIA	153 (5.3%)	179 (5.3%)	0.9457	1112 (4.9%)	0.3859

THIN	NVA N(%) 2876 (100.0%)	LABA N(%) 3410 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22569 (100.0%)	P comparing NVA to LAMA
Other comorbidities					
Diabetes Mellitus	460 (16.0%)	490 (14.4%)	0.0790	3550 (15.7%)	0.7338
Hyperlipidemia	680 (23.6%)	733 (21.5%)	0.0452	5105 (22.6%)	0.2259
Hepatic impairment	140 (4.9%)	169 (5.0%)	0.9184	1064 (4.7%)	0.7502
Lung cancer	30 (1.0%)	39 (1.1%)	0.7950	301 (1.3%)	0.2271
Cancer (excluding lung cancer)	336 (11.7%)	392 (11.5%)	0.8480	2684 (11.9%)	0.7668
Asthma	936 (32.6%)	795 (23.3%)	<.0001	6592 (29.2%)	0.0002
BPH	145 (5.0%)	161 (4.7%)	0.5967	1117 (5.0%)	0.8654
Bladder obstruction/urinary retention	106 (3.7%)	109 (3.2%)	0.3205	744 (3.3%)	0.2990
Chronic kidney disease			0.4816		0.0030
No CKD	362 (12.6%)	466 (13.7%)	.	3301 (14.6%)	.
Stage unknown	26 (0.9%)	30 (0.9%)	.	219 (1.0%)	.
Stage 1	2 (0.1%)	1 (0.0%)	.	4 (0.0%)	.
Stage 2	1371 (47.7%)	1666 (48.9%)	.	10850 (48.1%)	.
Stage 3	1027 (35.7%)	1151 (33.8%)	.	7438 (33.0%)	.
Stage 4	84 (2.9%)	88 (2.6%)	.	678 (3.0%)	.
Stage 5	4 (0.1%)	8 (0.2%)	.	79 (0.4%)	.

IPCI	NVA N(%) 673 (100.0%)	LABA N(%) 1942 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 6587 (100.0%)	P comparing NVA to LAMA
Cardiovascular comorbidities	400 (59.4%)	1114 (57.4%)	0.3719	3784 (57.5%)	0.3403
- Arterial hypertension	302 (44.9%)	877 (45.2%)	0.9334	2869 (43.6%)	0.5379
- Unstable angina pectoris	20 (3.0%)	48 (2.5%)	0.5741	184 (2.8%)	0.8853
- Angina pectoris	91 (13.5%)	234 (12.1%)	0.3525	935 (14.2%)	0.6749
- Myocardial infarction	63 (9.4%)	173 (8.9%)	0.7832	628 (9.5%)	0.9389
- Heart failure	100 (14.9%)	193 (9.9%)	0.0006	660 (10.0%)	0.0001
Cardiac arrhythmia					
Major Cardiac arrhythmia	114 (16.9%)	276 (14.2%)	0.0992	873 (13.3%)	0.0094
- Atrial fibrillation/flutter	105 (15.6%)	225 (11.6%)	0.0084	753 (11.4%)	0.0018
- Torsade de Pointes/Long QT	1 (0.2%)	2 (0.1%)	1.0000	7 (0.1%)	1.0000
- Ventricular fibrillation	2 (0.3%)	21 (1.1%)	0.1014	43 (0.7%)	0.3888
- Ventricular tachycardia	1 (0.2%)	16 (0.8%)	0.1095	50 (0.8%)	0.1178
- AV block	11 (1.6%)	31 (1.6%)	1.0000	109 (1.7%)	1.0000
Sick Sinus	4 (0.6%)	8 (0.4%)	0.7853	23 (0.4%)	0.5074
Supraventricular tachycardia	16 (2.4%)	31 (1.6%)	0.2518	107 (1.6%)	0.1988
Premature depolarization	18 (2.7%)	36 (1.9%)	0.2572	162 (2.5%)	0.8322
Cerebrovascular comorbidities	69 (10.3%)	214 (11.0%)	0.6313	706 (10.7%)	0.7589
- Stroke	37 (5.5%)	109 (5.6%)	0.9884	395 (6.0%)	0.6631
- TIA	36 (5.4%)	123 (6.3%)	0.4080	406 (6.2%)	0.4490

IPCI	NVA N(%) 673 (100.0%)	LABA N(%) 1942 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 6587 (100.0%)	P comparing NVA to LAMA
Other comorbidities					
Diabetes Mellitus	130 (19.3%)	372 (19.2%)	0.9724	1235 (18.8%)	0.7588
Hyperlipidemia	134 (19.9%)	426 (21.9%)	0.2941	1385 (21.0%)	0.5301
Hepatic impairment	24 (3.6%)	59 (3.0%)	0.5852	175 (2.7%)	0.2104
Lung cancer	35 (5.2%)	56 (2.9%)	0.0068	208 (3.2%)	0.0071
Cancer (excluding lung cancer)	95 (14.1%)	222 (11.4%)	0.0767	877 (13.3%)	0.6014
Asthma	185 (27.5%)	623 (32.1%)	0.0298	1709 (26.0%)	0.4107
BPH	42 (6.2%)	131 (6.8%)	0.7157	458 (7.0%)	0.5384
Bladder obstruction/urinary retention	7 (1.0%)	33 (1.7%)	0.3084	87 (1.3%)	0.6639
Chronic kidney disease			0.0996		0.3102
No CKD	269 (40.0%)	676 (34.8%)	.	2506 (38.0%)	.
Stage unknown	4 (0.6%)	20 (1.0%)	.	61 (0.9%)	.
Stage 1	0 (0.0%)	0 (0.0%)		0 (0.0%)	
Stage 2	301 (44.7%)	944 (48.6%)	.	3096 (47.0%)	.
Stage 3	96 (14.3%)	280 (14.4%)	.	848 (12.9%)	.
Stage 4	3 (0.5%)	17 (0.9%)	.	65 (1.0%)	.
Stage 5		5 (0.3%)	.	11 (0.2%)	.

Aarhus	NVA N(%) 468 (100.0%)	LABA N(%) 1443 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3890 (100.0%)	P comparing NVA to LAMA
Cardiovascular comorbidities	210 (44.9%)	739 (51.2%)	0.0198	2135 (54.9%)	<.0001
- Arterial hypertension	138 (29.5%)	507 (35.1%)	0.0286	1440 (37.0%)	0.0016
- Unstable angina pectoris	17 (3.6%)	76 (5.3%)	0.1921	225 (5.8%)	0.0698
- Angina pectoris	89 (19.0%)	343 (23.8%)	0.0382	903 (23.2%)	0.0469
- Myocardial infarction	32 (6.8%)	130 (9.0%)	0.1707	377 (9.7%)	0.0553
- Heart failure	42 (9.0%)	187 (13.0%)	0.0261	615 (15.8%)	0.0001
Cardiac arrhythmia					
Major Cardiac arrhythmia	57 (12.2%)	266 (18.4%)	0.0022	803 (20.6%)	<.0001
- Atrial fibrillation/flutter	51 (10.9%)	244 (16.9%)	0.0023	732 (18.8%)	<.0001
- Torsade de Pointes/Long QT	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
- Ventricular fibrillation	0 (0.0%)	2 (0.1%)	1.0000	8 (0.2%)	0.6815
- Ventricular tachycardia	4 (0.9%)	6 (0.4%)	0.4384	24 (0.6%)	0.7627
- AV block	8 (1.7%)	31 (2.2%)	0.6925	107 (2.8%)	0.2400
Sick Sinus	7 (1.5%)	23 (1.6%)	1.0000	61 (1.6%)	1.0000
Supraventricular tachycardia	22 (4.7%)	60 (4.2%)	0.7097	195 (5.0%)	0.8566
Premature depolarization	8 (1.7%)	19 (1.3%)	0.6891	50 (1.3%)	0.5872
Cerebrovascular comorbidities	34 (7.3%)	157 (10.9%)	0.0295	439 (11.3%)	0.0104
- Stroke	27 (5.8%)	125 (8.7%)	0.0559	337 (8.7%)	0.0404
- TIA	9 (1.9%)	51 (3.5%)	0.1131	133 (3.4%)	0.1131

Aarhus	NVA N(%) 468 (100.0%)	LABA N(%) 1443 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3890 (100.0%)	P comparing NVA to LAMA
Other comorbidities					
Diabetes Mellitus	42 (9.0%)	219 (15.2%)	0.0009	546 (14.0%)	0.0031
Hyperlipidemia	51 (10.9%)	233 (16.2%)	0.0069	638 (16.4%)	0.0026
Hepatic impairment	8 (1.7%)	16 (1.1%)	0.4383	83 (2.1%)	0.6633
Lung cancer	15 (3.2%)	43 (3.0%)	0.9269	130 (3.3%)	0.9845
Cancer (excluding lung cancer)	49 (10.5%)	193 (13.4%)	0.1183	522 (13.4%)	0.0866
Asthma	101 (21.6%)	244 (16.9%)	0.0268	663 (17.0%)	0.0176
BPH	30 (6.4%)	92 (6.4%)	1.0000	221 (5.7%)	0.5930
Bladder obstruction/urinary retention	11 (2.4%)	24 (1.7%)	0.4442	62 (1.6%)	0.3104
Chronic kidney disease			0.1594		0.0370
No CKD	159 (34.0%)	414 (28.7%)	.	1175 (30.2%)	.
Stage unknown	2 (0.4%)	10 (0.7%)	.	28 (0.7%)	.
Stage 1	0 (0.0%)	0 (0.0%)		0 (0.0%)	
Stage 2	224 (47.9%)	700 (48.5%)	.	1744 (44.8%)	.
Stage 3	75 (16.0%)	288 (20.0%)	.	831 (21.4%)	.
Stage 4	8 (1.7%)	27 (1.9%)	.	98 (2.5%)	.
Stage 5		4 (0.3%)	.	14 (0.4%)	.

HSD	NVA N(%) 1373 (100.0%)	LABA N(%) 1144 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3343 (100.0%)	P comparing NVA to LAMA
Cardiovascular comorbidities	953 (69.4%)	745 (65.1%)	0.0249	2297 (68.7%)	0.6623
- Arterial hypertension	832 (60.6%)	679 (59.4%)	0.5528	1978 (59.2%)	0.3812
- Unstable angina pectoris	6 (0.4%)	4 (0.4%)	0.9771	27 (0.8%)	0.2321
- Angina pectoris	47 (3.4%)	29 (2.5%)	0.2381	90 (2.7%)	0.2068
- Myocardial infarction	73 (5.3%)	45 (3.9%)	0.1236	204 (6.1%)	0.3300
- Heart failure	138 (10.1%)	64 (5.6%)	<.0001	379 (11.3%)	0.2176
Cardiac arrhythmia					
Major Cardiac arrhythmia	190 (13.8%)	111 (9.7%)	0.0018	487 (14.6%)	0.5463
- Atrial fibrillation/flutter	180 (13.1%)	100 (8.7%)	0.0007	453 (13.6%)	0.7216
- Torsade de Pointes/Long QT	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
- Ventricular fibrillation	0 (0.0%)	0 (0.0%)	.	1 (0.0%)	1.0000
- Ventricular tachycardia	1 (0.1%)	1 (0.1%)	1.0000	5 (0.2%)	0.8244
- AV block	17 (1.2%)	12 (1.1%)	0.7984	44 (1.3%)	0.9414
Sick Sinus	11 (0.8%)	8 (0.7%)	0.9500	30 (0.9%)	0.8802
Supraventricular tachycardia	7 (0.5%)	10 (0.9%)	0.3861	15 (0.5%)	0.9644
Premature depolarization	68 (5.0%)	50 (4.4%)	0.5531	168 (5.0%)	0.9756
Cerebrovascular comorbidities	208 (15.2%)	149 (13.0%)	0.1432	480 (14.4%)	0.5133
- Stroke	173 (12.6%)	127 (11.1%)	0.2741	378 (11.3%)	0.2279
- TIA	50 (3.6%)	38 (3.3%)	0.7443	133 (4.0%)	0.6447

HSD	NVA N(%) 1373 (100.0%)	LABA N(%) 1144 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3343 (100.0%)	P comparing NVA to LAMA
Other comorbidities					
Diabetes Mellitus	289 (21.1%)	227 (19.8%)	0.4859	709 (21.2%)	0.9341
Hyperlipidemia	421 (30.7%)	345 (30.2%)	0.8174	1029 (30.8%)	0.9641
Hepatic impairment	88 (6.4%)	69 (6.0%)	0.7584	241 (7.2%)	0.3594
Lung cancer	15 (1.1%)	15 (1.3%)	0.7497	46 (1.4%)	0.5216
Cancer (excluding lung cancer)	109 (7.9%)	88 (7.7%)	0.8770	251 (7.5%)	0.6559
Asthma	216 (15.7%)	166 (14.5%)	0.4268	530 (15.9%)	0.9518
BPH	249 (18.1%)	165 (14.4%)	0.0144	432 (12.9%)	<.0001
Bladder obstruction/urinary retention	10 (0.7%)	6 (0.5%)	0.6973	38 (1.1%)	0.2672
Chronic kidney disease			0.5716		0.0110
No CKD	149 (10.9%)	146 (12.8%)	.	447 (13.4%)	.
Stage unknown	3 (0.2%)	2 (0.2%)	.	7 (0.2%)	.
Stage 1	73 (5.3%)	65 (5.7%)	.	204 (6.1%)	.
Stage 2	544 (39.6%)	458 (40.0%)	.	1176 (35.2%)	.
Stage 3	490 (35.7%)	394 (34.4%)	.	1156 (34.6%)	.
Stage 4	74 (5.4%)	56 (4.9%)	.	233 (7.0%)	.
Stage 5	40 (2.9%)	23 (2.0%)	.	120 (3.6%)	.

SIDIAP	NVA N(%) 3332 (100.0%)	LABA N(%) 9951 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22463 (100.0%)	P comparing NVA to LAMA
Cardiovascular comorbidities	2151 (64.6%)	6304 (63.4%)	0.2182	14558 (64.8%)	0.7904
- Arterial hypertension	1953 (58.6%)	5863 (58.9%)	0.7721	13357 (59.5%)	0.3618
- Unstable angina pectoris	30 (0.9%)	58 (0.6%)	0.0669	180 (0.8%)	0.6238
- Angina pectoris	103 (3.1%)	280 (2.8%)	0.4422	740 (3.3%)	0.5734
- Myocardial infarction	196 (5.9%)	449 (4.5%)	0.0017	1290 (5.7%)	0.7773
- Heart failure	284 (8.5%)	682 (6.9%)	0.0015	1879 (8.4%)	0.7836
Cardiac arrhythmia					
Major Cardiac arrhythmia	409 (12.3%)	1122 (11.3%)	0.1254	2951 (13.1%)	0.1763
- Atrial fibrillation/flutter	340 (10.2%)	926 (9.3%)	0.1350	2502 (11.1%)	0.1147
- Torsade de Pointes/Long QT	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
- Ventricular fibrillation	2 (0.1%)	3 (0.0%)	0.7998	9 (0.0%)	0.9433
- Ventricular tachycardia	6 (0.2%)	15 (0.2%)	0.9069	40 (0.2%)	1.0000
- AV block	73 (2.2%)	215 (2.2%)	0.9719	496 (2.2%)	1.0000
Sick Sinus	1 (0.0%)	1 (0.0%)	1.0000	0 (0.0%)	0.2689
Supraventricular tachycardia	27 (0.8%)	66 (0.7%)	0.4465	187 (0.8%)	0.9767
Premature depolarization	34 (1.0%)	100 (1.0%)	1.0000	249 (1.1%)	0.7141
Cerebrovascular comorbidities	237 (7.1%)	741 (7.5%)	0.5485	1838 (8.2%)	0.0372
- Stroke	177 (5.3%)	543 (5.5%)	0.7834	1370 (6.1%)	0.0808
- TIA	69 (2.1%)	236 (2.4%)	0.3490	560 (2.5%)	0.1573

SIDIAP	NVA N(%) 3332 (100.0%)	LABA N(%) 9951 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22463 (100.0%)	P comparing NVA to LAMA
Other comorbidities					
Diabetes Mellitus	819 (24.6%)	2392 (24.0%)	0.5424	5651 (25.2%)	0.4866
Hyperlipidemia	768 (23.1%)	2027 (20.4%)	0.0011	5050 (22.5%)	0.4779
Hepatic impairment	17 (0.5%)	77 (0.8%)	0.1466	183 (0.8%)	0.0777
Lung cancer	43 (1.3%)	74 (0.7%)	0.0048	244 (1.1%)	0.3368
Cancer (excluding lung cancer)	593 (17.8%)	1609 (16.2%)	0.0308	3789 (16.9%)	0.1907
Asthma	348 (10.4%)	808 (8.1%)	<.0001	2008 (8.9%)	0.0054
BPH	738 (22.2%)	2093 (21.0%)	0.1813	4910 (21.9%)	0.7217
Bladder obstruction/urinary retention	53 (1.6%)	125 (1.3%)	0.1718	339 (1.5%)	0.7772
Chronic kidney disease			0.6368		0.6428
No CKD	1032 (31.0%)	3105 (31.2%)	.	6927 (30.8%)	.
Stage unknown	65 (2.0%)	162 (1.6%)	.	461 (2.1%)	.
Stage 1	0 (0.0%)	0 (0.0%)		0 (0.0%)	
Stage 2	1650 (49.5%)	4897 (49.2%)	.	10931 (48.7%)	.
Stage 3	538 (16.2%)	1613 (16.2%)	.	3751 (16.7%)	.
Stage 4	40 (1.2%)	151 (1.5%)	.	346 (1.5%)	.
Stage 5	7 (0.2%)	23 (0.2%)	.	47 (0.2%)	.

* CKD=Chronic kidney disease; CKD stage based on both disease codes and lab results. If CKD stage based on both disease codes and lab results were available, CKD stage closest and most severe to the index date is reported; ≈Stage 1 based on disease codes for CKD stage 1 only; ±Defined as no event of CKD available OR serum creatinine results in a GFR ≥90 mL/min/1.73m2;

Table 15-4 Use of other respiratory medications (assessed during the year prior to the index date), by exposure cohort – pooled and by database

Pooled	NVA N(%)	LABA N(%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%)	P comparing NVA to LAMA
	8722 (100.0%)	17890 (100.0%)		58852 (100.0%)	
Single-ingredient short-acting muscarinic agents	1665 (19.1%)	3940 (22.0%)	<.0001	11832 (20.1%)	0.0279
Single-ingredient short-acting ß2 agonists	4506 (51.7%)	7909 (44.2%)	<.0001	29520 (50.2%)	0.0091
NVA	0 (0.0%)	206 (1.2%)	<.0001	765 (1.3%)	<.0001
LABA	885 (10.2%)	0 (0.0%)	<.0001	3615 (6.1%)	<.0001
LAMA (excl. NVA)	2754 (31.6%)	3166 (17.7%)	<.0001	0 (0.0%)	<.0001
Inhaled corticosteroids (ICS)	1542 (17.7%)	3520 (19.7%)	0.0001	9167 (15.6%)	<.0001
Xanthines	341 (3.9%)	258 (1.4%)	<.0001	1065 (1.8%)	<.0001
Fixed combination therapy LABA+ICS	4615 (52.9%)	4675 (26.1%)	<.0001	23556 (40.0%)	<.0001
Fixed combination therapy LABA+LAMA	110 (1.3%)	139 (0.8%)	0.0002	378 (0.6%)	<.0001
Fixed combination therapy SABA+SAMA	211 (2.4%)	220 (1.2%)	<.0001	832 (1.4%)	<.0001
Oral ß2-agonists	28 (0.3%)	65 (0.4%)	0.6612	171 (0.3%)	0.7008
Leukotriene receptor antagonists (LTRA)	308 (3.5%)	328 (1.8%)	<.0001	1530 (2.6%)	<.0001
Systemic corticosteroids	3358 (38.5%)	4672 (26.1%)	<.0001	18880 (32.1%)	<.0001
Systemic corticosteroids with indication COPD	1009 (11.6%)	1252 (7.0%)	<.0001	5689 (9.7%)	<.0001
Oral phosphodiesterase-4 (PDE-4) inhibitors	56 (0.6%)	49 (0.3%)	<.0001	152 (0.3%)	<.0001

THIN	NVA N(%) 2876 (100.0%)	LABA N(%) 3410 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22569 (100.0%)	P comparing NVA to LAMA
Single-ingredient short-acting muscarinic agents	256 (8.9%)	247 (7.2%)	0.0179	2347 (10.4%)	0.0137
Single-ingredient short-acting ß2 agonists	2420 (84.1%)	2789 (81.8%)	0.0149	17128 (75.9%)	<.0001
NVA	0 (0.0%)	44 (1.3%)	<.0001	181 (0.8%)	<.0001
LABA	184 (6.4%)	0 (0.0%)	<.0001	889 (3.9%)	<.0001
LAMA (excl. NVA)	1119 (38.9%)	821 (24.1%)	<.0001	0 (0.0%)	<.0001
Inhaled corticosteroids (ICS)	335 (11.7%)	655 (19.2%)	<.0001	3096 (13.7%)	0.0024
Xanthines	125 (4.4%)	42 (1.2%)	<.0001	486 (2.2%)	<.0001
Fixed combination therapy LABA+ICS	1648 (57.3%)	685 (20.1%)	<.0001	9719 (43.1%)	<.0001
Fixed combination therapy LABA+LAMA	13 (0.5%)	9 (0.3%)	0.2966	37 (0.2%)	0.0022
Fixed combination therapy SABA+SAMA	11 (0.4%)	2 (0.1%)	0.0112	85 (0.4%)	1.0000
Oral ß2-agonists	4 (0.1%)	4 (0.1%)	1.0000	47 (0.2%)	0.5756
Leukotriene receptor antagonists (LTRA)	86 (3.0%)	51 (1.5%)	<.0001	660 (2.9%)	0.8898
Systemic corticosteroids	1408 (49.0%)	1209 (35.5%)	<.0001	9124 (40.4%)	<.0001
Systemic corticosteroids with indication COPD	522 (18.2%)	380 (11.1%)	<.0001	2819 (12.5%)	<.0001
Oral phosphodiesterase-4 (PDE-4) inhibitors	2 (0.1%)	1 (0.0%)	0.8826	3 (0.0%)	0.1867

IPCI	NVA N(%) 673 (100.0%)	LABA N(%) 1942 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 6587 (100.0%)	P comparing NVA to LAMA
Single-ingredient short-acting muscarinic agents	131 (19.5%)	286 (14.7%)	0.0046	843 (12.8%)	<.0001

IPCI	NVA N(%) 673 (100.0%)	LABA N(%) 1942 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 6587 (100.0%)	P comparing NVA to LAMA
Single-ingredient short-acting ß2 agonists	278 (41.3%)	656 (33.8%)	0.0005	1944 (29.5%)	<.0001
NVA	0 (0.0%)	19 (1.0%)	0.0208	64 (1.0%)	0.0187
LABA	72 (10.7%)	0 (0.0%)	<.0001	318 (4.8%)	<.0001
LAMA (excl. NVA)	232 (34.5%)	468 (24.1%)	<.0001	0 (0.0%)	<.0001
Inhaled corticosteroids (ICS)	94 (14.0%)	322 (16.6%)	0.1245	702 (10.7%)	0.0107
Xanthines	11 (1.6%)	12 (0.6%)	0.0282	35 (0.5%)	0.0015
Fixed combination therapy LABA+ICS	372 (55.3%)	697 (35.9%)	<.0001	2436 (37.0%)	<.0001
Fixed combination therapy LABA+LAMA	10 (1.5%)	19 (1.0%)	0.3844	43 (0.7%)	0.0292
Fixed combination therapy SABA+SAMA	40 (5.9%)	56 (2.9%)	0.0004	145 (2.2%)	<.0001
Oral ß2-agonists	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
Leukotriene receptor antagonists (LTRA)	20 (3.0%)	44 (2.3%)	0.3806	114 (1.7%)	0.0333
Systemic corticosteroids	320 (47.6%)	621 (32.0%)	<.0001	2032 (30.9%)	<.0001
Systemic corticosteroids with indication COPD	221 (32.8%)	368 (19.0%)	<.0001	1298 (19.7%)	<.0001
Oral phosphodiesterase-4 (PDE-4) inhibitors	0 (0.0%)	1 (0.1%)	1.0000	0 (0.0%)	.

Aarhus	NVA N(%) 468 (100.0%)	LABA N(%) 1443 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3890 (100.0%)	P comparing NVA to LAMA
Single-ingredient short-acting muscarinic agents	5 (1.1%)	14 (1.0%)	1.0000	20 (0.5%)	0.2396
Single-ingredient short-acting ß2 agonists	275 (58.8%)	693 (48.0%)	<.0001	1850 (47.6%)	<.0001

Aarhus	NVA N(%) 468 (100.0%)	LABA N(%) 1443 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3890 (100.0%)	P comparing NVA to LAMA
NVA	0 (0.0%)	20 (1.4%)	0.0215	57 (1.5%)	0.0155
LABA	80 (17.1%)	0 (0.0%)	<.0001	345 (8.9%)	<.0001
LAMA (excl. NVA)	136 (29.1%)	364 (25.2%)	0.1142	0 (0.0%)	<.0001
Inhaled corticosteroids (ICS)	54 (11.5%)	215 (14.9%)	0.0818	472 (12.1%)	0.7654
Xanthines	7 (1.5%)	12 (0.8%)	0.3220	31 (0.8%)	0.2030
Fixed combination therapy LABA+ICS	271 (57.9%)	466 (32.3%)	<.0001	1672 (43.0%)	<.0001
Fixed combination therapy LABA+LAMA	27 (5.8%)	45 (3.1%)	0.0132	73 (1.9%)	<.0001
Fixed combination therapy SABA+SAMA	45 (9.6%)	103 (7.1%)	0.1004	376 (9.7%)	1.0000
Oral ß2-agonists	10 (2.1%)	9 (0.6%)	0.0094	44 (1.1%)	0.1017
Leukotriene receptor antagonists (LTRA)	24 (5.1%)	38 (2.6%)	0.0125	112 (2.9%)	0.0123
Systemic corticosteroids	189 (40.4%)	442 (30.6%)	0.0001	1436 (36.9%)	0.1568
Systemic corticosteroids with indication COPD	68 (14.5%)	163 (11.3%)	0.0745	609 (15.7%)	0.5703
Oral phosphodiesterase-4 (PDE-4) inhibitors	0 (0.0%)	5 (0.4%)	0.4506	7 (0.2%)	0.7584

HSD	NVA N(%) 1373 (100.0%)	LABA N(%) 1144 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3343 (100.0%)	P comparing NVA to LAMA
Single-ingredient short-acting muscarinic agents	82 (6.0%)	55 (4.8%)	0.2324	186 (5.6%)	0.6304
Single-ingredient short-acting ß2 agonists	214 (15.6%)	116 (10.1%)	<.0001	451 (13.5%)	0.0669
NVA	0 (0.0%)	44 (3.9%)	<.0001	124 (3.7%)	<.0001

HSD	NVA N(%) 1373 (100.0%)	LABA N(%) 1144 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3343 (100.0%)	P comparing NVA to LAMA
LABA	165 (12.0%)	0 (0.0%)	<.0001	295 (8.8%)	0.0010
LAMA (excl. NVA)	403 (29.4%)	204 (17.8%)	<.0001	0 (0.0%)	<.0001
Inhaled corticosteroids (ICS)	472 (34.4%)	311 (27.2%)	0.0001	1067 (31.9%)	0.1090
Xanthines	143 (10.4%)	105 (9.2%)	0.3323	291 (8.7%)	0.0734
Fixed combination therapy LABA+ICS	681 (49.6%)	384 (33.6%)	<.0001	1368 (40.9%)	<.0001
Fixed combination therapy LABA+LAMA	3 (0.2%)	2 (0.2%)	1.0000	2 (0.1%)	0.3037
Fixed combination therapy SABA+SAMA	107 (7.8%)	42 (3.7%)	<.0001	160 (4.8%)	<.0001
Oral ß2-agonists	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
Leukotriene receptor antagonists (LTRA)	47 (3.4%)	30 (2.6%)	0.2958	122 (3.7%)	0.7691
Systemic corticosteroids	490 (35.7%)	371 (32.4%)	0.0942	1145 (34.3%)	0.3635
Systemic corticosteroids with indication COPD	75 (5.5%)	39 (3.4%)	0.0178	182 (5.4%)	1.0000
Oral phosphodiesterase-4 (PDE-4) inhibitors	2 (0.2%)	2 (0.2%)	1.0000	2 (0.1%)	0.7119

SIDIAP	NVA N(%) 3332 (100.0%)	LABA N(%) 9951 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22463 (100.0%)	P comparing NVA to LAMA
Single-ingredient short-acting muscarinic agents	1191 (35.7%)	3338 (33.5%)	0.0216	8436 (37.6%)	0.0458
Single-ingredient short-acting ß2 agonists	1319 (39.6%)	3655 (36.7%)	0.0034	8147 (36.3%)	0.0002
NVA	0 (0.0%)	79 (0.8%)	<.0001	339 (1.5%)	<.0001
LABA	384 (11.5%)	0 (0.0%)	<.0001	1768 (7.9%)	<.0001

SIDIAP	NVA N(%) 3332 (100.0%)	LABA N(%) 9951 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22463 (100.0%)	P comparing NVA to LAMA
LAMA (excl. NVA)	864 (25.9%)	1309 (13.2%)	<.0001	0 (0.0%)	<.0001
Inhaled corticosteroids (ICS)	587 (17.6%)	2017 (20.3%)	0.0009	3830 (17.1%)	0.4320
Xanthines	55 (1.7%)	87 (0.9%)	0.0002	222 (1.0%)	0.0007
Fixed combination therapy LABA+ICS	1643 (49.3%)	2443 (24.6%)	<.0001	8361 (37.2%)	<.0001
Fixed combination therapy LABA+LAMA	57 (1.7%)	64 (0.6%)	<.0001	223 (1.0%)	0.0003
Fixed combination therapy SABA+SAMA	8 (0.2%)	17 (0.2%)	0.5704	66 (0.3%)	0.7132
Oral ß2-agonists	14 (0.4%)	52 (0.5%)	0.5584	80 (0.4%)	0.6757
Leukotriene receptor antagonists (LTRA)	131 (3.9%)	165 (1.7%)	<.0001	522 (2.3%)	<.0001
Systemic corticosteroids	951 (28.5%)	2029 (20.4%)	<.0001	5143 (22.9%)	<.0001
Systemic corticosteroids with indication COPD	123 (3.7%)	302 (3.0%)	0.0707	781 (3.5%)	0.5631
Oral phosphodiesterase-4 (PDE-4) inhibitors	52 (1.6%)	40 (0.4%)	<.0001	140 (0.6%)	<.0001

Table 15-5 Use of other respiratory medications (assessed at the index date), by exposure cohort and pooled and by database

Pooled	NVA N(%) 8722 (100.0%)	LABA N(%) 17890 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 58852 (100.0%)	P comparing NVA to LAMA
Single-ingredient short-acting muscarinic agents	931 (10.7%)	3406 (19.0%)	<.0001	6894 (11.7%)	0.0049
Single-ingredient short-acting ß2 agonists	3350 (38.4%)	5330 (29.8%)	<.0001	24120 (41.0%)	<.0001
NVA	8722 (100.0%)	57 (0.3%)	<.0001	159 (0.3%)	<.0001
LABA	141 (1.6%)	17890 (100.0%)	<.0001	632 (1.1%)	<.0001
LAMA (excl. NVA)	826 (9.5%)	710 (4.0%)	<.0001	58852 (100.0%)	<.0001
Inhaled corticosteroids (ICS)	693 (8.0%)	3558 (19.9%)	<.0001	4934 (8.4%)	0.1732
Xanthines	227 (2.6%)	153 (0.9%)	<.0001	765 (1.3%)	<.0001
Fixed combination therapy LABA+ICS	3966 (45.5%)	1784 (10.0%)	<.0001	24095 (40.9%)	<.0001
Fixed combination therapy LABA+LAMA	50 (0.6%)	79 (0.4%)	0.1746	156 (0.3%)	<.0001
Fixed combination therapy SABA+SAMA	86 (1.0%)	119 (0.7%)	0.0062	457 (0.8%)	0.0476
Oral ß2-agonists	6 (0.1%)	9 (0.1%)	0.7480	71 (0.1%)	0.2422
Leukotriene receptor antagonists (LTRA)	247 (2.8%)	245 (1.4%)	<.0001	1184 (2.0%)	<.0001
Systemic corticosteroids with indication COPD	398 (4.6%)	694 (3.9%)	0.0091	3055 (5.2%)	0.0139
Oral phosphodiesterase-4 (PDE-4) inhibitors	38 (0.4%)	22 (0.1%)	<.0001	112 (0.2%)	<.0001

THIN	NVA N(%) 2876 (100.0%)	LABA N(%) 3410 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22569 (100.0%)	P comparing NVA to LAMA

THIN	NVA N(%) 2876 (100.0%)	LABA N(%) 3410 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22569 (100.0%)	P comparing NVA to LAMA
Single-ingredient short-acting muscarinic agents	162 (5.6%)	181 (5.3%)	0.6105	1524 (6.8%)	0.0255
Single-ingredient short-acting ß2 agonists	2135 (74.2%)	2362 (69.3%)	<.0001	15856 (70.3%)	<.0001
NVA	2876 (100.0%)	25 (0.7%)	<.0001	86 (0.4%)	<.0001
LABA	53 (1.8%)	3410 (100.0%)	<.0001	266 (1.2%)	0.0034
LAMA (excl. NVA)	546 (19.0%)	289 (8.5%)	<.0001	22569 (100.0%)	<.0001
Inhaled corticosteroids (ICS)	186 (6.5%)	532 (15.6%)	<.0001	1904 (8.4%)	0.0003
Xanthines	114 (4.0%)	32 (0.9%)	<.0001	415 (1.8%)	<.0001
Fixed combination therapy LABA+ICS	1496 (52.0%)	348 (10.2%)	<.0001	9796 (43.4%)	<.0001
Fixed combination therapy LABA+LAMA	10 (0.4%)	4 (0.1%)	0.0965	25 (0.1%)	0.0031
Fixed combination therapy SABA+SAMA	2 (0.1%)	2 (0.1%)	1.0000	49 (0.2%)	0.1484
Oral ß2-agonists	1 (0.0%)	1 (0.0%)	1.0000	27 (0.1%)	0.3201
Leukotriene receptor antagonists (LTRA)	67 (2.3%)	30 (0.9%)	<.0001	490 (2.2%)	0.6316
Systemic corticosteroids with indication COPD	168 (5.8%)	157 (4.6%)	0.0316	1363 (6.0%)	0.7051
Oral phosphodiesterase-4 (PDE-4) inhibitors	2 (0.1%)	1 (0.0%)	0.8826	2 (0.0%)	0.0979

IPCI	NVA N(%) 673 (100.0%)	LABA N(%) 1942 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 6587 (100.0%)	P comparing NVA to LAMA
Single-ingredient short-acting muscarinic agents	73 (10.9%)	221 (11.4%)	0.7593	491 (7.5%)	0.0022
Single-ingredient short-acting ß2 agonists	193 (28.7%)	428 (22.0%)	0.0006	1408 (21.4%)	<.0001

IPCI	NVA N(%) 673 (100.0%)	LABA N(%) 1942 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 6587 (100.0%)	P comparing NVA to LAMA
NVA	673 (100.0%)	4 (0.2%)	<.0001	16 (0.2%)	<.0001
LABA	8 (1.2%)	1942 (100.0%)	<.0001	79 (1.2%)	1.0000
LAMA (excl. NVA)	69 (10.3%)	130 (6.7%)	0.0035	6587 (100.0%)	<.0001
Inhaled corticosteroids (ICS)	55 (8.2%)	449 (23.1%)	<.0001	448 (6.8%)	0.2097
Xanthines	10 (1.5%)	8 (0.4%)	0.0085	25 (0.4%)	0.0003
Fixed combination therapy LABA+ICS	297 (44.1%)	366 (18.9%)	<.0001	2328 (35.3%)	<.0001
Fixed combination therapy LABA+LAMA	6 (0.9%)	9 (0.5%)	0.3315	24 (0.4%)	0.0863
Fixed combination therapy SABA+SAMA	24 (3.6%)	41 (2.1%)	0.0517	112 (1.7%)	0.0011
Oral ß2-agonists	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
Leukotriene receptor antagonists (LTRA)	18 (2.7%)	30 (1.5%)	0.0863	75 (1.1%)	0.0014
Systemic corticosteroids with indication COPD	73 (10.9%)	148 (7.6%)	0.0120	441 (6.7%)	<.0001
Oral phosphodiesterase-4 (PDE-4) inhibitors	0 (0.0%)	1 (0.1%)	1.0000	0 (0.0%)	.

Aarhus	NVA N(%) 468 (100.0%)	LABA N(%) 1443 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3890 (100.0%)	P comparing NVA to LAMA
Single-ingredient short-acting muscarinic agents	4 (0.9%)	9 (0.6%)	0.8378	10 (0.3%)	0.0843
Single-ingredient short-acting ß2 agonists	165 (35.3%)	398 (27.6%)	0.0019	1547 (39.8%)	0.0660
NVA	468 (100.0%)	6 (0.4%)	<.0001	15 (0.4%)	<.0001
LABA	18 (3.9%)	1443 (100.0%)	<.0001	87 (2.2%)	0.0470

Aarhus	NVA N(%) 468 (100.0%)	LABA N(%) 1443 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3890 (100.0%)	P comparing NVA to LAMA
LAMA (excl. NVA)	45 (9.6%)	98 (6.8%)	0.0553	3890 (100.0%)	<.0001
Inhaled corticosteroids (ICS)	24 (5.1%)	181 (12.5%)	<.0001	239 (6.1%)	0.4418
Xanthines	5 (1.1%)	6 (0.4%)	0.2041	23 (0.6%)	0.3605
Fixed combination therapy LABA+ICS	220 (47.0%)	226 (15.7%)	<.0001	1851 (47.6%)	0.8522
Fixed combination therapy LABA+LAMA	14 (3.0%)	32 (2.2%)	0.4380	27 (0.7%)	<.0001
Fixed combination therapy SABA+SAMA	23 (4.9%)	45 (3.1%)	0.0932	188 (4.8%)	1.0000
Oral ß2-agonists	2 (0.4%)	3 (0.2%)	0.7742	20 (0.5%)	1.0000
Leukotriene receptor antagonists (LTRA)	14 (3.0%)	26 (1.8%)	0.1687	74 (1.9%)	0.1589
Systemic corticosteroids with indication COPD	32 (6.8%)	103 (7.1%)	0.9072	529 (13.6%)	<.0001
Oral phosphodiesterase-4 (PDE-4) inhibitors	0 (0.0%)	2 (0.1%)	1.0000	3 (0.1%)	1.0000

HSD	NVA N(%) 1373 (100.0%)	LABA N(%) 1144 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3343 (100.0%)	P comparing NVA to LAMA
Single-ingredient short-acting muscarinic agents	29 (2.1%)	27 (2.4%)	0.7762	84 (2.5%)	0.4763
Single-ingredient short-acting ß2 agonists	65 (4.7%)	38 (3.3%)	0.0929	179 (5.4%)	0.4229
NVA	1373 (100.0%)	18 (1.6%)	<.0001	28 (0.8%)	<.0001
LABA	28 (2.0%)	1144 (100.0%)	<.0001	54 (1.6%)	0.3738
LAMA (excl. NVA)	102 (7.4%)	53 (4.6%)	0.0048	3343 (100.0%)	<.0001
Inhaled corticosteroids (ICS)	156 (11.4%)	193 (16.9%)	<.0001	441 (13.2%)	0.0952

HSD	NVA N(%) 1373 (100.0%)	LABA N(%) 1144 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3343 (100.0%)	P comparing NVA to LAMA
Xanthines	66 (4.8%)	66 (5.8%)	0.3229	159 (4.8%)	1.0000
Fixed combination therapy LABA+ICS	558 (40.6%)	146 (12.8%)	<.0001	1298 (38.8%)	0.2605
Fixed combination therapy LABA+LAMA	0 (0.0%)	2 (0.2%)	0.4011	0 (0.0%)	.
Fixed combination therapy SABA+SAMA	34 (2.5%)	20 (1.8%)	0.2639	64 (1.9%)	0.2642
Oral ß2-agonists	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
Leukotriene receptor antagonists (LTRA)	38 (2.8%)	19 (1.7%)	0.0847	78 (2.3%)	0.4404
Systemic corticosteroids with indication COPD	33 (2.4%)	23 (2.0%)	0.5962	86 (2.6%)	0.8149
Oral phosphodiesterase-4 (PDE-4) inhibitors	1 (0.1%)	0 (0.0%)	1.0000	0 (0.0%)	0.6457

SIDIAP	NVA N(%) 3332 (100.0%)	LABA N(%) 9951 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22463 (100.0%)	P comparing NVA to LAMA
Single-ingredient short-acting muscarinic agents	663 (19.9%)	2968 (29.8%)	<.0001	4785 (21.3%)	0.0673
Single-ingredient short-acting ß2 agonists	792 (23.8%)	2104 (21.1%)	0.0016	5130 (22.8%)	0.2414
NVA	3332 (100.0%)	4 (0.0%)	<.0001	14 (0.1%)	<.0001
LABA	34 (1.0%)	9951 (100.0%)	<.0001	146 (0.7%)	0.0223
LAMA (excl. NVA)	64 (1.9%)	140 (1.4%)	0.0448	22463 (100.0%)	<.0001
Inhaled corticosteroids (ICS)	272 (8.2%)	2203 (22.1%)	<.0001	1902 (8.5%)	0.5782
Xanthines	32 (1.0%)	41 (0.4%)	0.0004	143 (0.6%)	0.0443

SIDIAP	NVA N(%) 3332 (100.0%)	LABA N(%) 9951 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22463 (100.0%)	P comparing NVA to LAMA
Fixed combination therapy LABA+ICS	1395 (41.9%)	698 (7.0%)	<.0001	8822 (39.3%)	0.0046
Fixed combination therapy LABA+LAMA	20 (0.6%)	32 (0.3%)	0.0385	80 (0.4%)	0.0492
Fixed combination therapy SABA+SAMA	3 (0.1%)	11 (0.1%)	0.9942	44 (0.2%)	0.2630
Oral ß2-agonists	3 (0.1%)	5 (0.1%)	0.6874	24 (0.1%)	1.0000
Leukotriene receptor antagonists (LTRA)	110 (3.3%)	140 (1.4%)	<.0001	467 (2.1%)	<.0001
Systemic corticosteroids with indication COPD	92 (2.8%)	263 (2.6%)	0.7612	636 (2.8%)	0.8632
Oral phosphodiesterase-4 (PDE-4) inhibitors	35 (1.1%)	18 (0.2%)	<.0001	107 (0.5%)	<.0001

. * 100% use as assessed at index date

Table 15-6 Use of (non-respiratory) concomitant medications (assessed during the year prior to index date) by exposure cohort and pooled and by database

Pooled	NVA N(%) 8722 (100.0%)	LABA N(%) 17890 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 58852 (100.0%)	P comparing NVA to LAMA
CNS drugs					
Opioids	1392 (16.0%)	2619 (14.6%)	0.0050	9460 (16.1%)	0.7977
Hypnotics and sedatives	761 (8.7%)	1574 (8.8%)	0.8612	5240 (8.9%)	0.5981
Anxiolytics	1478 (17.0%)	3261 (18.2%)	0.0108	9362 (15.9%)	0.0143
Anti-epileptic drugs	826 (9.5%)	1640 (9.2%)	0.4365	5459 (9.3%)	0.5728
SSRI	1335 (15.3%)	2451 (13.7%)	0.0005	8278 (14.1%)	0.0021
Anticholinergic drugs					
Antipsychotic drugs	479 (5.5%)	931 (5.2%)	0.3397	3422 (5.8%)	0.2374
Antidepressant agents (tricyclic and tetracyclic)	1032 (11.8%)	1944 (10.9%)	0.0200	7467 (12.7%)	0.0256
Disopyramide	0 (0.0%)	1 (0.0%)	1.0000	9 (0.0%)	0.5106
Antispasmodics	116 (1.3%)	195 (1.1%)	0.0991	918 (1.6%)	0.1129
Antiparkinson drugs	29 (0.3%)	47 (0.3%)	0.3795	183 (0.3%)	0.8156
Cholinesterase inhibitors	9 (0.1%)	13 (0.1%)	0.5579	46 (0.1%)	0.5730
Atropine	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
H1 antihistamines	1340 (15.4%)	2601 (14.5%)	0.0785	7921 (13.5%)	<.0001
Anticholinergics for treatment of overactive bladder	254 (2.9%)	552 (3.1%)	0.4615	2034 (3.5%)	0.0096
Drugs affecting cerebrovascular and cardiovascular disease					
NSAIDs	2497 (28.6%)	5331 (29.8%)	0.0510	14641 (24.9%)	<.0001
Antithrombotic agents	3569 (40.9%)	6617 (37.0%)	<.0001	23469 (39.9%)	0.0656

Pooled	NVA N(%) 8722 (100.0%)	LABA N(%) 17890 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 58852 (100.0%)	P comparing NVA to LAMA
Lipid lowering drugs	3905 (44.8%)	7514 (42.0%)	<.0001	25931 (44.1%)	0.2167
Platelet Aggregation Inhibitor (PAI)	2856 (32.7%)	5350 (29.9%)	<.0001	18690 (31.8%)	0.0667
Nitrates	828 (9.5%)	1437 (8.0%)	<.0001	5992 (10.2%)	0.0486
Anti-arrhythmics	244 (2.8%)	378 (2.1%)	0.0006	1217 (2.1%)	<.0001
Anti-diabetic drugs	1489 (17.1%)	3049 (17.0%)	0.9672	9567 (16.3%)	0.0566
Anti-hypertensive drugs	5640 (64.7%)	11016 (61.6%)	<.0001	36364 (61.8%)	<.0001
- Diuretics	3241 (37.2%)	6493 (36.3%)	0.1734	20863 (35.5%)	0.0020
- B-blockers	1878 (21.5%)	3656 (20.4%)	0.0402	12855 (21.8%)	0.5203
- Calcium channel blockers	2076 (23.8%)	3710 (20.7%)	<.0001	13522 (23.0%)	0.0902
- ACE inhibitors	2570 (29.5%)	5177 (28.9%)	0.3814	16948 (28.8%)	0.2034
- Angiotensin II inhibitors	1799 (20.6%)	3343 (18.7%)	0.0002	9975 (17.0%)	<.0001

THIN	NVA N(%) 2876 (100.0%)	LABA N(%) 3410 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22569 (100.0%)	P comparing NVA to LAMA
CNS drugs					
Opioids	494 (17.2%)	497 (14.6%)	0.0053	3935 (17.4%)	0.7500
Hypnotics and sedatives	270 (9.4%)	286 (8.4%)	0.1777	2201 (9.8%)	0.5566
Anxiolytics	252 (8.8%)	262 (7.7%)	0.1313	2029 (9.0%)	0.7125
Anti-epileptic drugs	279 (9.7%)	347 (10.2%)	0.5591	2314 (10.3%)	0.3741
SSRI	519 (18.1%)	536 (15.7%)	0.0153	3675 (16.3%)	0.0177
Anticholinergic drugs					

THIN	NVA N(%) 2876 (100.0%)	LABA N(%) 3410 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22569 (100.0%)	P comparing NVA to LAMA
Antipsychotic drugs	209 (7.3%)	215 (6.3%)	0.1430	1645 (7.3%)	0.9967
Antidepressant agents (tricyclic and tetracyclic)	522 (18.2%)	570 (16.7%)	0.1437	4113 (18.2%)	0.9434
Disopyramide	0 (0.0%)	0 (0.0%)	.	5 (0.0%)	0.9267
Antispasmodics	88 (3.1%)	117 (3.4%)	0.4506	706 (3.1%)	0.8873
Antiparkinson drugs	10 (0.4%)	14 (0.4%)	0.8436	80 (0.4%)	1.0000
Cholinesterase inhibitors	4 (0.1%)	3 (0.1%)	0.8214	23 (0.1%)	0.7852
Atropine	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
H1 antihistamines	425 (14.8%)	454 (13.3%)	0.1030	3042 (13.5%)	0.0597
Anticholinergics for treatment of overactive bladder	131 (4.6%)	140 (4.1%)	0.4170	1020 (4.5%)	0.9692
Drugs affecting cerebrovascular and cardiovascular disease					
NSAIDs	482 (16.8%)	562 (16.5%)	0.7937	3845 (17.0%)	0.7290
Antithrombotic agents	1065 (37.0%)	1196 (35.1%)	0.1131	8522 (37.8%)	0.4596
Lipid lowering drugs	1357 (47.2%)	1529 (44.8%)	0.0668	10474 (46.4%)	0.4444
Platelet Aggregation Inhibitor (PAI)	889 (30.9%)	1001 (29.4%)	0.1892	7014 (31.1%)	0.8722
Nitrates	311 (10.8%)	366 (10.7%)	0.9508	2718 (12.0%)	0.0592
Anti-arrhythmics	28 (1.0%)	28 (0.8%)	0.6127	214 (1.0%)	0.9760
Anti-diabetic drugs	328 (11.4%)	346 (10.2%)	0.1175	2581 (11.4%)	0.9852
Anti-hypertensive drugs	1675 (58.2%)	1898 (55.7%)	0.0421	12964 (57.4%)	0.4258
- Diuretics	902 (31.4%)	900 (26.4%)	<.0001	6458 (28.6%)	0.0024
- B-blockers	520 (18.1%)	628 (18.4%)	0.7562	4455 (19.7%)	0.0368
- Calcium channel blockers	751 (26.1%)	828 (24.3%)	0.1013	5761 (25.5%)	0.5117
- ACE inhibitors	768 (26.7%)	870 (25.5%)	0.2972	6065 (26.9%)	0.8645

THIN	NVA N(%) 2876 (100.0%)	LABA N(%) 3410 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22569 (100.0%)	P comparing NVA to LAMA
- Angiotensin II inhibitors	351 (12.2%)	373 (10.9%)	0.1268	2483 (11.0%)	0.0575

IPCI	NVA N(%) 673 (100.0%)	LABA N(%) 1942 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 6587 (100.0%)	P comparing NVA to LAMA
CNS drugs					
Opioids	123 (18.3%)	308 (15.9%)	0.1628	1017 (15.4%)	0.0613
Hypnotics and sedatives	98 (14.6%)	290 (14.9%)	0.8645	873 (13.3%)	0.3733
Anxiolytics	117 (17.4%)	301 (15.5%)	0.2761	1052 (16.0%)	0.3705
Anti-epileptic drugs	50 (7.4%)	109 (5.6%)	0.1083	311 (4.7%)	0.0028
SSRI	62 (9.2%)	155 (8.0%)	0.3594	485 (7.4%)	0.0980
Anticholinergic drugs					
Antipsychotic drugs	17 (2.5%)	59 (3.0%)	0.5834	258 (3.9%)	0.0902
Antidepressant agents (tricyclic and tetracyclic)	62 (9.2%)	149 (7.7%)	0.2372	533 (8.1%)	0.3493
Disopyramide	0 (0.0%)	1 (0.1%)	1.0000	3 (0.1%)	1.0000
Antispasmodics	14 (2.1%)	44 (2.3%)	0.8968	121 (1.8%)	0.7678
Antiparkinson drugs	3 (0.5%)	3 (0.2%)	0.3715	16 (0.2%)	0.5585
Cholinesterase inhibitors	0 (0.0%)	0 (0.0%)	.	4 (0.1%)	1.0000
Atropine	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
H1 antihistamines	80 (11.9%)	222 (11.4%)	0.8036	652 (9.9%)	0.1176
Anticholinergics for treatment of overactive bladder	13 (1.9%)	51 (2.6%)	0.3897	167 (2.5%)	0.4070
Drugs affecting cerebrovascular and cardiovascular disease					

IPCI	NVA N(%) 673 (100.0%)	LABA N(%) 1942 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 6587 (100.0%)	P comparing NVA to LAMA
NSAIDs	157 (23.3%)	441 (22.7%)	0.7820	1375 (20.9%)	0.1509
Antithrombotic agents	283 (42.1%)	702 (36.2%)	0.0074	2508 (38.1%)	0.0479
Lipid lowering drugs	249 (37.0%)	742 (38.2%)	0.6092	2487 (37.8%)	0.7304
Platelet Aggregation Inhibitor (PAI	198 (29.4%)	516 (26.6%)	0.1676	1859 (28.2%)	0.5404
Nitrates	59 (8.8%)	152 (7.8%)	0.4907	542 (8.2%)	0.6823
Anti-arrhythmics	18 (2.7%)	36 (1.9%)	0.2572	122 (1.9%)	0.1833
Anti-diabetic drugs	105 (15.6%)	260 (13.4%)	0.1728	897 (13.6%)	0.1730
Anti-hypertensive drugs	401 (59.6%)	1082 (55.7%)	0.0891	3611 (54.8%)	0.0200
- Diuretics	214 (31.8%)	542 (27.9%)	0.0617	1680 (25.5%)	0.0005
- B-blockers	214 (31.8%)	541 (27.9%)	0.0582	1956 (29.7%)	0.2753
- Calcium channel blockers	113 (16.8%)	314 (16.2%)	0.7524	1078 (16.4%)	0.8189
- ACE inhibitors	146 (21.7%)	413 (21.3%)	0.8584	1348 (20.5%)	0.4831
- Angiotensin II inhibitors	118 (17.5%)	309 (15.9%)	0.3573	1093 (16.6%)	0.5694

Aarhus	NVA N(%) 468 (100.0%)	LABA N(%) 1443 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3890 (100.0%)	P comparing NVA to LAMA
CNS drugs					
Opioids	114 (24.4%)	429 (29.7%)	0.0293	1223 (31.4%)	0.0020
Hypnotics and sedatives	2 (0.4%)	6 (0.4%)	1.0000	15 (0.4%)	1.0000
Anxiolytics	3 (0.6%)	8 (0.6%)	1.0000	19 (0.5%)	0.9244
Anti-epileptic drugs	46 (9.8%)	103 (7.1%)	0.0738	354 (9.1%)	0.6663

Aarhus	NVA N(%) 468 (100.0%)	LABA N(%) 1443 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3890 (100.0%)	P comparing NVA to LAMA
SSRI	80 (17.1%)	243 (16.8%)	0.9550	680 (17.5%)	0.8856
Anticholinergic drugs					
Antipsychotic drugs	37 (7.9%)	100 (6.9%)	0.5431	301 (7.7%)	0.9704
Antidepressant agents (tricyclic and tetracyclic)	69 (14.7%)	230 (15.9%)	0.5855	666 (17.1%)	0.2179
Disopyramide	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
Antispasmodics	1 (0.2%)	0 (0.0%)	0.5529	0 (0.0%)	0.2047
Antiparkinson drugs	1 (0.2%)	6 (0.4%)	0.8503	13 (0.3%)	0.9976
Cholinesterase inhibitors	0 (0.0%)	1 (0.1%)	1.0000	1 (0.0%)	1.0000
Atropine	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
H1 antihistamines	35 (7.5%)	98 (6.8%)	0.6868	246 (6.3%)	0.3891
Anticholinergics for treatment of overactive bladder	13 (2.8%)	48 (3.3%)	0.6633	127 (3.3%)	0.6703
Drugs affecting cerebrovascular and cardiovascular disease					
NSAIDs	104 (22.2%)	289 (20.0%)	0.3396	813 (20.9%)	0.5464
Antithrombotic agents	177 (37.8%)	715 (49.6%)	<.0001	1893 (48.7%)	<.0001
Lipid lowering drugs	182 (38.9%)	659 (45.7%)	0.0119	1693 (43.5%)	0.0624
Platelet Aggregation Inhibitor (PAI	143 (30.6%)	594 (41.2%)	<.0001	1531 (39.4%)	0.0003
Nitrates	39 (8.3%)	148 (10.3%)	0.2597	441 (11.3%)	0.0597
Anti-arrhythmics	4 (0.9%)	26 (1.8%)	0.2231	80 (2.1%)	0.1077
Anti-diabetic drugs	45 (9.6%)	226 (15.7%)	0.0015	543 (14.0%)	0.0115
Anti-hypertensive drugs	300 (64.1%)	966 (66.9%)	0.2831	2742 (70.5%)	0.0053
- Diuretics	177 (37.8%)	601 (41.7%)	0.1583	1789 (46.0%)	0.0009
- B-blockers	109 (23.3%)	436 (30.2%)	0.0047	1244 (32.0%)	0.0002

Aarhus	NVA N(%) 468 (100.0%)	LABA N(%) 1443 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3890 (100.0%)	P comparing NVA to LAMA
- Calcium channel blockers	112 (23.9%)	400 (27.7%)	0.1216	1094 (28.1%)	0.0628
- ACE inhibitors	96 (20.5%)	349 (24.2%)	0.1163	984 (25.3%)	0.0273
- Angiotensin II inhibitors	92 (19.7%)	274 (19.0%)	0.8007	716 (18.4%)	0.5515

HSD	NVA N(%) 1373 (100.0%)	LABA N(%) 1144 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3343 (100.0%)	P comparing NVA to LAMA
CNS drugs					
Opioids	224 (16.3%)	219 (19.1%)	0.0714	581 (17.4%)	0.4007
Hypnotics and sedatives	73 (5.3%)	52 (4.6%)	0.4267	224 (6.7%)	0.0871
Anxiolytics	172 (12.5%)	141 (12.3%)	0.9264	440 (13.2%)	0.5883
Anti-epileptic drugs	108 (7.9%)	96 (8.4%)	0.6834	270 (8.1%)	0.8549
SSRI	170 (12.4%)	122 (10.7%)	0.2016	387 (11.6%)	0.4662
Anticholinergic drugs					
Antipsychotic drugs	47 (3.4%)	30 (2.6%)	0.2958	103 (3.1%)	0.6053
Antidepressant agents (tricyclic and tetracyclic)	98 (7.1%)	89 (7.8%)	0.5925	245 (7.3%)	0.8667
Disopyramide	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
Antispasmodics	10 (0.7%)	15 (1.3%)	0.2054	39 (1.2%)	0.2339
Antiparkinson drugs	4 (0.3%)	5 (0.4%)	0.7836	7 (0.2%)	0.8433
Cholinesterase inhibitors	2 (0.2%)	0 (0.0%)	0.5612	0 (0.0%)	0.1531
Atropine	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
H1 antihistamines	155 (11.3%)	118 (10.3%)	0.4725	340 (10.2%)	0.2773

HSD	NVA N(%) 1373 (100.0%)	LABA N(%) 1144 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 3343 (100.0%)	P comparing NVA to LAMA
Anticholinergics for treatment of overactive bladder	9 (0.7%)	7 (0.6%)	1.0000	23 (0.7%)	1.0000
Drugs affecting cerebrovascular and cardiovascular disease					
NSAIDs	610 (44.4%)	537 (46.9%)	0.2225	1359 (40.7%)	0.0185
Antithrombotic agents	743 (54.1%)	528 (46.2%)	<.0001	1749 (52.3%)	0.2754
Lipid lowering drugs	545 (39.7%)	398 (34.8%)	0.0128	1276 (38.2%)	0.3451
Platelet Aggregation Inhibitor (PAI	618 (45.0%)	467 (40.8%)	0.0382	1464 (43.8%)	0.4636
Nitrates	135 (9.8%)	77 (6.7%)	0.0066	377 (11.3%)	0.1623
Anti-arrhythmics	93 (6.8%)	44 (3.9%)	0.0017	183 (5.5%)	0.0972
Anti-diabetic drugs	291 (21.2%)	213 (18.6%)	0.1193	666 (19.9%)	0.3436
Anti-hypertensive drugs	1052 (76.6%)	823 (71.9%)	0.0084	2549 (76.3%)	0.8141
- Diuretics	487 (35.5%)	317 (27.7%)	<.0001	1237 (37.0%)	0.3372
- B-blockers	401 (29.2%)	268 (23.4%)	0.0013	977 (29.2%)	1.0000
- Calcium channel blockers	359 (26.2%)	269 (23.5%)	0.1405	876 (26.2%)	0.9969
- ACE inhibitors	492 (35.8%)	352 (30.8%)	0.0084	1108 (33.1%)	0.0821
- Angiotensin II inhibitors	455 (33.1%)	374 (32.7%)	0.8455	1117 (33.4%)	0.8829

SIDIAP	NVA N(%) 3332 (100.0%)	LABA N(%) 9951 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22463 (100.0%)	P comparing NVA to LAMA
CNS drugs					
Opioids	437 (13.1%)	1166 (11.7%)	0.0346	2704 (12.0%)	0.0807
Hypnotics and sedatives	318 (9.5%)	940 (9.5%)	0.8948	1927 (8.6%)	0.0700

SIDIAP	NVA N(%) 3332 (100.0%)	LABA N(%) 9951 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22463 (100.0%)	P comparing NVA to LAMA
Anxiolytics	934 (28.0%)	2549 (25.6%)	0.0065	5822 (25.9%)	0.0102
Anti-epileptic drugs	343 (10.3%)	985 (9.9%)	0.5316	2210 (9.8%)	0.4290
SSRI	504 (15.1%)	1395 (14.0%)	0.1207	3051 (13.6%)	0.0171
Anticholinergic drugs					
Antipsychotic drugs	169 (5.1%)	527 (5.3%)	0.6476	1115 (5.0%)	0.8215
Antidepressant agents (tricyclic and tetracyclic)	281 (8.4%)	906 (9.1%)	0.2541	1910 (8.5%)	0.9196
Disopyramide	0 (0.0%)	0 (0.0%)	.	1 (0.0%)	1.0000
Antispasmodics	3 (0.1%)	19 (0.2%)	0.3204	52 (0.2%)	0.1469
Antiparkinson drugs	11 (0.3%)	19 (0.2%)	0.2098	67 (0.3%)	0.8859
Cholinesterase inhibitors	3 (0.1%)	9 (0.1%)	1.0000	18 (0.1%)	1.0000
Atropine	0 (0.0%)	0 (0.0%)	.	0 (0.0%)	.
H1 antihistamines	645 (19.4%)	1709 (17.2%)	0.0046	3641 (16.2%)	<.0001
Anticholinergics for treatment of overactive bladder	88 (2.6%)	306 (3.1%)	0.2228	697 (3.1%)	0.1633
Drugs affecting cerebrovascular and cardiovascular disease					
NSAIDs	1144 (34.3%)	3502 (35.2%)	0.3796	7249 (32.3%)	0.0187
Antithrombotic agents	1301 (39.1%)	3476 (34.9%)	<.0001	8797 (39.2%)	0.9127
Lipid lowering drugs	1572 (47.2%)	4186 (42.1%)	<.0001	10001 (44.5%)	0.0043
Platelet Aggregation Inhibitor (PAI	1008 (30.3%)	2772 (27.9%)	0.0085	6822 (30.4%)	0.9062
Nitrates	284 (8.5%)	694 (7.0%)	0.0034	1914 (8.5%)	1.0000
Anti-arrhythmics	101 (3.0%)	244 (2.5%)	0.0790	618 (2.8%)	0.3898
Anti-diabetic drugs	720 (21.6%)	2004 (20.1%)	0.0728	4880 (21.7%)	0.8973
Anti-hypertensive drugs	2212 (66.4%)	6247 (62.8%)	0.0002	14498 (64.5%)	0.0393

SIDIAP	NVA N(%) 3332 (100.0%)	LABA N(%) 9951 (100.0%)	P comparing NVA to LABA	LAMA (excl. NVA) N(%) 22463 (100.0%)	P comparing NVA to LAMA
- Diuretics	1461 (43.9%)	4133 (41.5%)	0.0203	9699 (43.2%)	0.4780
- B-blockers	634 (19.0%)	1783 (17.9%)	0.1582	4223 (18.8%)	0.7717
- Calcium channel blockers	741 (22.2%)	1899 (19.1%)	<.0001	4713 (21.0%)	0.1017
- ACE inhibitors	1068 (32.1%)	3193 (32.1%)	0.9877	7443 (33.1%)	0.2227
- Angiotensin II inhibitors	783 (23.5%)	2013 (20.2%)	<.0001	4566 (20.3%)	<.0001

Table 15-7 Details on validation by database (IPCI, HSD and SIDIAP)

IPCI	Cases to be validated	Definite Case	Probable Case	Possible Case	Non- Case	Not assessable[$]	PPV
COPD[#]	1500	1385	Nap*	Nap*	48	67	96.7%[$]
AFIFLUT	77	67	2	3	5	Nap	93.5%
AP	30	23	1	0	6	Nap	80.0%
AVBLOCK	6	4	0	1	1	Nap	83.3%
DEATH	195	195	0	0	0	Nap	100.0%
HOSPACS	52	40	0	0	12	Nap	76.9%
HOSPHF	83	77	1	0	5	Nap	94.0%
MI	29	24	0	0	5	Nap	82.8%
LONGQT	No cases	Nap	Nap	Nap	Nap	Nap	
PREMATDEP	5	4	0	0	1	Nap	80.0%
SICKSINUS	1	1	0	0	0	Nap	100.0%
STROKE	53	32	9	1	11	Nap	79.2%

IPCI	Cases to be validated	Definite Case	Probable Case	Possible Case	Non- Case	Not assessable[$]	PPV
SVT	12	9	1	2	0	Nap	100.0%
TIA	43	26	4	4	9	Nap	79.1%
TORSPOINT	No cases	Nap	Nap	Nap	Nap	Nap	
UNSTABLEAP	11	10	0	0	1	Nap	90.9%
VENTTACH	4	4	0	0	0	Nap	100.0%
VENTFIBR	11	7	2	1	1	Nap	90.9%

HSD	Cases to be validated	Definite Case	Probable Case	Possible Case	Non- Case	Not assessable[$]	PPV
COPD[#]	1500	1403	Nap*	Nap*	97	0	93.5%
AFIFLUT	63	36	0	16	11	Nap	82.5%
AP	4	4	0	0	0	Nap	100.0%
AVBLOCK	5	0	0	0	5	Nap	0.0%
DEATH	61	61	0	0	0	Nap	100.0%
HOSPACS	No cases	Nap	Nap	Nap	Nap	Nap	Nap
HOSPHF	15	6	0	5	4	Nap	73.3%
MI	13	0	0	10	3	Nap	76.9%
LONGQT	2	2	0	0	0	Nap	100.0%
PREMATDEP	9	8	0	1	0	Nap	100.0%
SICKSINUS	5	4	0	1	0	Nap	100.0%
STROKE	41	0	0	4	37[¥]	Nap	9.8%[¥]
SVT	1	0	0	1	0	Nap	100.0%

HSD	Cases to be validated	Definite Case	Probable Case	Possible Case	Non- Case	Not assessable[$]	PPV
TIA	9	0	0	8	1	Nap	88.9%
TORSPOINT	2	2	0	0	0	Nap	100.0%
UNSTABLEAP	3	0	0	0	3	Nap	0.0%
VENTTACH	2	1	0	0	1	Nap	50.0%
VENTFIBR	No cases	Nap	Nap	Nap	Nap	Nap	Nap

SIDIAP	Cases to be validated	Definite Case	Probable Case	Possible Case	Non- Case	Not assessable[$]	PPV
COPD[#]	1500	1313	Nap*	Nap*	160	27	87.5%
AFIFLUT	353	264	5	45	39	Nap	89.1%[$]
AP	58	26	5	13	14	Nap	75.9%
AVBLOCK	80	60	0	11	9	Nap	88.8%
DEATH	Not validated	Nap	Nap	Nap	Nap	Nap	Nap
HOSPACS	Not validated	Nap	Nap	Nap	Nap	Nap	Nap
HOSPHF	Not validated	Nap	Nap	Nap	Nap	Nap	Nap
MI	74	54	2	11	7	Nap	90.5%
LONGQT	No Cases	Nap	Nap	Nap	Nap	Nap	Nap
PREMATDEP	49	38	0	6	5	Nap	89.8%
SICKSINUS	No cases	Nap	Nap	Nap	Nap	Nap	Nap
STROKE	92	50	2	19	21	Nap	77.2%
SVT	21	10	1	5	5	Nap	76.2%

SIDIAP	Cases to be validated	Definite Case	Probable Case	Possible Case	Non- Case	Not assessable[$]	PPV
TIA	34	28	0	4	2	Nap	94.1%
TORSPOINT	No Cases	Nap	Nap	Nap	Nap	Nap	Nap
UNSTABLEAP	16	5	1	0	10	Nap	37.5%
VENTTACH	5	3	0	1	1	Nap	80.0%
VENTFIBR	1	1	0	0	0	Nap	100.0%

[$] Not assessable only for COPD validation. If insufficient information for other endpoints, these were classified as none

[#] COPD only classified as definite or none

[¥] Upon validation, many of potential stroke cases classified as non-case as “outcome search” for HSD included “paresis” which is a sensitive but not specific search

[$] For calculation of PPV for COPD, non-assessable cases removed from the denominator

Table 15-8 Number of main events, by exposure cohort (pooled and by database)

Pooled	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Total	8722	5509	2603	17890	10587	11144	58852	37224	26874
MACE	109	62	24	282	147	149	1247	639	482
Ischemic heart disease (any event of)	36	16	7	79	42	49	410	247	154
Cardiac arrhythmia (any event of)	87	52	25	171	92	98	826	453	301
Cerebrovascular disorders (any event of)	42	29	10	80	41	44	381	219	168
Mortality	182	98	39	260	110	135	1344	706	396

THIN	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Total	2876	2513	830	3410	2861	2106	22569	18203	10710
MACE	22	19	5	34	26	24	314	242	118
Ischemic heart disease (any event of)	8	7	1	22	19	16	208	164	67
Cardiac arrhythmia (any event of)	24	18	7	25	19	15	237	184	76
Cerebrovascular disorders (any event of)	24	21	7	18	14	14	201	153	95
Mortality	75	58	18	47	34	31	623	445	165

IPCI	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Total	673	316	187	1942	1045	971	6587	3553	3360
MACE	15	3	4	31	15	10	148	53	76

IPCI	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Ischemic heart disease (any event of)	5	0	0	11	4	5	75	38	45
Cardiac arrhythmia (any event of)	13	5	5	14	9	2	128	60	59
Cerebrovascular disorders (any event of)	8	3	2	21	11	8	65	23	32
Mortality	15	3	3	37	15	19	141	41	62

Aarhus	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Total	468	173	111	1443	461	741	3890	1327	1496
MACE	15	8	5	75	36	37	315	118	129
Ischemic heart disease (any event of)	9	3	2	23	7	15	54	18	15
Cardiac arrhythmia (any event of)	5	3	0	30	4	16	108	30	42
Cerebrovascular disorders (any event of)	2	1	1	9	3	4	46	9	17
Mortality	26	12	4	56	24	24	281	97	79

HSD	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Total	1373	427	403	1144	318	648	3343	838	1407
MACE	2	0	0	1	0	0	18	2	5
Ischemic heart disease (any event of)	2	0	1	1	0	0	11	1	3
Cardiac arrhythmia (any event of)	11	7	2	8	2	3	50	12	20
Cerebrovascular disorders (any event of)	2	0	0	2	0	1	8	2	2
Mortality	15	2	5	14	1	4	32	3	11

SIDIAP	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Total	3332	2080	1072	9951	5902	6678	22463	13303	9901
MACE	55	32	10	141	70	78	452	224	154
Ischemic heart disease (any event of)	12	6	3	22	12	13	62	26	24
Cardiac arrhythmia (any event of)	34	19	11	94	58	62	303	167	104
Cerebrovascular disorders (any event of)	6	4	0	30	13	17	61	32	22
Mortality	51	23	9	106	36	57	267	120	79

Table 15-9 Number of additional events, by exposure cohort (pooled and by database)

Pooled	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Total	8722	5509	2603	17890	10587	11144	58852	37224	26874
Cardiac arrhythmia									
Atrial fibrillation/flutter	66	42	19	114	65	63	613	335	216
AV block	10	5	3	27	15	16	86	48	41
Long QT	0	0	0	0	0	0	2	0	1
Premature depolarization	7	2	1	19	7	13	65	40	24
Sick sinus	1	1	1	5	0	4	10	6	2
Supraventricular tachycardia	5	2	2	7	2	4	52	28	17
Torsades de Pointes	0	0	0	0	0	0	2	0	1
Ventricular tachycardia	1	0	0	4	3	2	14	8	4
Ventricular fibrillation	1	1	0	1	1	0	11	5	4
Ischemic heart disease									
Angina pectoris	22	13	5	33	15	22	183	121	62
Myocardial infarction	13	5	1	36	24	22	194	107	74
Unstable angina pectoris	6	2	1	16	7	9	65	36	28
Hospitalization for acute coronary syndrome	12	3	3	45	23	24	207	108	90
Cerebrovascular events									
Stroke	28	21	7	53	27	27	276	161	121

Pooled	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
TIA	16	10	3	29	15	19	127	72	59
Hospitalization for heart failure	63	35	14	181	87	95	722	338	262

THIN	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Total	2876	2513	830	3410	2861	2106	22569	18203	10710
Cardiac arrhythmia									
Atrial fibrillation/flutter	22	17	7	21	16	14	205	159	66
AV block	0	0	0	0	0	0	4	4	0
Long QT	0	0	0	0	0	0	0	0	0
Premature depolarization	1	0	0	1	1	1	11	10	5
Sick sinus	0	0	0	0	0	0	1	1	0
Supraventricular tachycardia	1	1	0	2	1	0	13	9	3
Torsades de Pointes	0	0	0	0	0	0	0	0	0
Ventricular tachycardia	0	0	0	1	1	0	5	3	2
Ventricular fibrillation	0	0	0	0	0	0	1	1	0
Ischemic heart disease									
Angina pectoris	7	6	1	8	6	5	114	92	40
Myocardial infarction	2	2	0	13	12	10	83	64	26
Unstable angina pectoris	0	0	0	4	3	3	30	24	8

THIN	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Hospitalization for acute coronary syndrome	1	0	1	9	8	5	57	46	13
Cerebrovascular events									
Stroke	17	16	4	13	9	10	152	116	71
TIA	9	7	3	6	6	5	64	49	32
Hospitalization for heart failure	2	1	0	7	3	5	62	48	18

IPCI	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Total	673	316	187	1942	1045	971	6587	3553	3360
Cardiac arrhythmia									
Atrial fibrillation/flutter	4	3	2	10	6	1	69	31	34
AV block	5	1	1	3	2	1	23	13	12
Long QT	0	0	0	0	0	0	0	0	0
Premature depolarization	3	0	0	2	1	0	13	8	4
Sick sinus	1	1	1	0	0	0	0	0	0
Supraventricular tachycardia	2	0	1	0	0	0	16	8	7
Torsades de Pointes	0	0	0	0	0	0	0	0	0
Ventricular tachycardia	0	0	0	0	0	0	4	1	0
Ventricular fibrillation	0	0	0	0	0	0	10	4	4

IPCI	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Ischemic heart disease									
Angina pectoris	1	0	0	1	0	1	20	13	12
Myocardial infarction	2	0	0	5	3	1	33	16	19
Unstable angina pectoris	2	0	0	5	1	3	22	9	14
Hospitalization for acute coronary syndrome	4	1	1	11	4	4	57	25	36
Cerebrovascular events									
Stroke	4	2	2	14	7	5	36	12	19
TIA	4	1	0	7	4	3	32	12	15
Hospitalization for heart failure	7	0	1	9	4	2	60	17	25

Aarhus	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Total	468	173	111	1443	461	741	3890	1327	1496
Cardiac arrhythmia									
Atrial fibrillation/flutter	2	1	0	19	4	9	87	21	36
AV block	2	1	0	4	0	2	12	5	5
Long QT	0	0	0	0	0	0	0	0	0
Premature depolarization	0	0	0	3	0	3	3	0	0

Aarhus	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Sick sinus	0	0	0	4	0	3	5	3	2
Supraventricular tachycardia	1	1	0	3	0	2	8	3	3
Torsades de Pointes	0	0	0	0	0	0	0	0	0
Ventricular tachycardia	0	0	0	0	0	0	1	1	1
Ventricular fibrillation	1	1	0	0	0	0	0	0	0
Ischemic heart disease									
Angina pectoris	7	3	1	15	4	11	27	7	5
Myocardial infarction	2	1	0	4	2	3	26	9	7
Unstable angina pectoris	4	2	1	7	3	3	12	3	5
Hospitalization for acute coronary syndrome	5	2	1	16	7	9	43	14	16
Cerebrovascular events									
Stroke	2	1	1	6	3	2	40	8	15
TIA	0	0	0	3	0	2	9	1	3
Hospitalization for heart failure	11	6	4	59	27	30	248	100	106

HSD	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Total	1373	427	403	1144	318	648	3343	838	1407

HSD	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Cardiac arrhythmia									
Atrial fibrillation/flutter	9	6	2	5	2	1	37	8	15
AV block	0	0	0	0	0	0	2	0	2
Long QT	0	0	0	0	0	0	2	0	1
Premature depolarization	1	1	0	2	0	1	6	4	2
Sick sinus	0	0	0	1	0	1	4	2	0
Supraventricular tachycardia	0	0	0	0	0	0	1	0	0
Torsades de Pointes	0	0	0	0	0	0	2	0	1
Ventricular tachycardia	1	0	0	0	0	0	0	0	0
Ventricular fibrillation	0	0	0	0	0	0	0	0	0
Ischemic heart disease									
Angina pectoris	2	0	1	0	0	0	2	0	0
Myocardial infarction	0	0	0	1	0	0	9	1	3
Unstable angina pectoris	0	0	0	0	0	0	0	0	0
Hospitalization for acute coronary syndrome	0	0	0	0	0	0	0	0	0
Cerebrovascular events									
Stroke	1	0	0	0	0	0	3	0	0
TIA	1	0	0	2	0	1	5	2	2

HSD	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Hospitalization for heart failure	1	0	0	0	0	0	7	2	2

SIDIAP	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Total	3332	2080	1072	9951	5902	6678	22463	13303	9901
Cardiac arrhythmia									
Atrial fibrillation/flutter	29	15	8	59	37	38	215	116	65
AV block	3	3	2	20	13	13	45	26	22
Long QT	0	0	0	0	0	0	0	0	0
Premature depolarization	2	1	1	11	5	8	32	18	13
Sick sinus	0	0	0	0	0	0	0	0	0
Supraventricular tachycardia	1	0	1	2	1	2	14	8	4
Torsades de Pointes	0	0	0	0	0	0	0	0	0
Ventricular tachycardia	0	0	0	3	2	2	4	3	1
Ventricular fibrillation	0	0	0	1	1	0	0	0	0
Ischemic heart disease									
Angina pectoris	5	4	2	9	5	5	20	9	5
Myocardial infarction	7	2	1	13	7	8	43	17	19
Unstable angina pectoris	0	0	0	0	0	0	1	0	1
Hospitalization for acute coronary syndrome	2	0	0	9	4	6	50	23	25

SIDIAP	NVA			LABA			LAMA (excl. NVA)		
	Total	Complete cases	Naive	Total	Complete cases	Naive	Total	Complete cases	Naive
Cerebrovascular events									
Stroke	4	2	0	20	8	10	45	25	16
TIA	2	2	0	11	5	8	17	8	7
Hospitalization for heart failure	42	28	9	106	53	58	345	171	111

Table 15-10 Incidence rate of main endpoints, by exposure cohort (by database)

THIN	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
MACE	22	1617	13.6	[9.2,19.4]	34	1418	24.0	[17.7,31.8]	314	14132	22.2	[20.2,24.4]
Ischemic heart disease (any event of)	8	1626	4.9	[2.5, 8.9]	22	1422	15.5	[10.5,22.0]	208	14177	14.7	[13.0,16.4]
Cardiac arrhythmia (any event of)	24	1619	14.8	[10.2,20.8]	25	1419	17.6	[12.3,24.5]	237	14153	16.7	[15.0,18.6]
Cerebrovascular disorders (any event of)	24	1617	14.8	[10.3,20.8]	18	1422	12.7	[8.2,18.7]	201	14174	14.2	[12.6,15.9]
Mortality	75	1627	46.1	[37.8,55.6]	47	1429	32.9	[25.5,41.8]	623	14259	43.7	[40.9,46.6]

IPCI	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
MACE	15	326	46.0	[28.6,69.9]	31	637	48.7	[35.4,65.1]	148	3180	46.5	[40.6,53.2]
Ischemic heart disease (any event of)	5	328	15.2	[6.0,31.8]	11	640	17.2	[9.7,28.3]	75	3195	23.5	[19.2,28.4]
Cardiac arrhythmia (any event of)	13	323	40.2	[23.9,63.2]	14	637	22.0	[13.3,34.1]	128	3180	40.3	[34.7,46.5]
Cerebrovascular disorders (any event of)	8	325	24.6	[12.3,44.0]	21	637	33.0	[22.2,47.1]	65	3204	20.3	[16.4,24.9]
Mortality	15	329	45.5	[28.3,69.3]	37	643	57.6	[43.2,75.1]	141	3229	43.7	[37.9,50.0]

Aarhus	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
MACE	15	253	59.2	[36.8,89.7]	75	608	123	[102, 147]	315	2037	155	[142, 168]
Ischemic heart disease (any event of)	9	255	35.3	[18.5,60.8]	23	620	37.1	[25.5,52.2]	54	2142	25.2	[19.9,31.5]

Aarhus	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
Cardiac arrhythmia (any event of)	5	257	19.4	[7.7,40.5]	30	625	48.0	[34.8,64.5]	108	2115	51.1	[43.4,59.7]
Cerebrovascular disorders (any event of)	2	258	7.8	[1.4,24.2]	9	630	14.3	[7.5,24.8]	46	2151	21.4	[16.5,27.3]
Mortality	26	258	101	[71.6, 137]	56	633	88.4	[70.6, 109]	281	2169	130	[118, 142]

HSD	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
MACE	2	523	3.8	[0.7,12.0]	1	374	2.7	[0.1,12.6]	18	1266	14.2	[9.2,21.0]
Ischemic heart disease (any event of)	2	523	3.8	[0.7,12.0]	1	374	2.7	[0.1,12.6]	11	1268	8.7	[4.9,14.3]
Cardiac arrhythmia (any event of)	11	520	21.2	[11.9,34.8]	8	373	21.4	[10.7,38.3]	50	1253	39.9	[31.2,50.3]
Cerebrovascular disorders (any event of)	2	523	3.8	[0.7,12.0]	2	372	5.4	[1.0,16.8]	8	1271	6.3	[3.1,11.3]
Mortality	15	523	28.7	[17.7,43.8]	14	375	37.4	[22.7,57.8]	32	1273	25.1	[18.4,33.6]

SIDIAP	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
MACE	55	1505	36.6	[28.9,45.5]	141	3029	46.6	[40.4,53.4]	452	7843	57.6	[53.4,62.1]
Ischemic heart disease (any event of)	12	1511	7.9	[4.6,12.8]	22	3059	7.2	[4.9,10.3]	62	7960	7.8	[6.2, 9.6]
Cardiac arrhythmia (any event of)	34	1503	22.6	[16.7,30.0]	94	3044	30.9	[25.9,36.5]	303	7873	38.5	[35.0,42.2]
Cerebrovascular disorders (any event of)	6	1518	4.0	[1.7, 7.8]	30	3059	9.8	[7.1,13.3]	61	7954	7.7	[6.1, 9.5]
Mortality	51	1519	33.6	[26.3,42.2]	106	3068	34.6	[29.3,40.5]	267	7980	33.5	[30.2,37.0]

Table 15-11 Incidence rate of additional endpoints, by exposure cohort (by database)

THIN	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
Incidence rates of cardiac arrhythmia												
Atrial fibrillation/flutter	22	1620	13.6	[9.2,19.3]	21	1419	14.8	[9.9,21.2]	205	14171	14.5	[12.9,16.2]
AV block	0	1629	0.0	[0.0, 1.8]	0	1430	0.0	[0.0, 2.1]	4	14270	0.3	[0.1, 0.6]
Long QT	0	1629	0.0	[0.0, 1.8]	0	1430	0.0	[0.0, 2.1]	0	14274	0.0	[0.0, 0.2]
Premature depolarization	1	1628	0.6	[0.0, 2.9]	1	1430	0.7	[0.0, 3.3]	11	14267	0.8	[0.4, 1.3]
Sick sinus	0	1629	0.0	[0.0, 1.8]	0	1430	0.0	[0.0, 2.1]	1	14274	0.1	[0.0, 0.3]
Supraventricular tachycardia	1	1629	0.6	[0.0, 2.9]	2	1430	1.4	[0.2, 4.4]	13	14268	0.9	[0.5, 1.4]
Torsades de Pointes	0	1629	0.0	[0.0, 1.8]	0	1430	0.0	[0.0, 2.1]	0	14274	0.0	[0.0, 0.2]
Ventricular fibrillation	0	1629	0.0	[0.0, 1.8]	0	1430	0.0	[0.0, 2.1]	1	14274	0.1	[0.0, 0.3]
Ventricular tachycardia	0	1629	0.0	[0.0, 1.8]	1	1430	0.7	[0.0, 3.3]	5	14270	0.4	[0.1, 0.7]
Incidence rates of ischemic heart disease												
Angina pectoris	7	1626	4.3	[2.0, 8.1]	8	1428	5.6	[2.8,10.1]	114	14210	8.0	[6.8, 9.4]
Unstable angina pectoris	0	1629	0.0	[0.0, 1.8]	4	1429	2.8	[1.0, 6.4]	30	14265	2.1	[1.5, 2.9]
Myocardial infarction	2	1628	1.2	[0.2, 3.9]	13	1425	9.1	[5.4,14.5]	83	14241	5.8	[4.8, 7.0]
Hospitalization for acute coronary syndrome	1	1629	0.6	[0.0, 2.9]	9	1427	6.3	[3.3,11.0]	57	14249	4.0	[3.2, 5.0]
Incidence rates of cerebrovascular events												

THIN	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
Stroke	17	1619	10.5	[6.7,15.7]	13	1425	9.1	[5.4,14.5]	152	14198	10.7	[9.3,12.2]
TIA	9	1626	5.5	[2.9, 9.6]	6	1427	4.2	[1.8, 8.3]	64	14238	4.5	[3.6, 5.5]
Hospitalization for heart failure	2	1629	1.2	[0.2, 3.9]	7	1430	4.9	[2.3, 9.2]	62	14245	4.4	[3.5, 5.4]

IPCI	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
Incidence rates of cardiac arrhythmia												
Atrial fibrillation/flutter	4	328	12.2	[4.2,27.7]	10	639	15.7	[8.5,26.4]	69	3204	21.5	[17.5,26.2]
AV block	5	328	15.3	[6.0,31.8]	3	641	4.7	[1.3,12.0]	23	3218	7.1	[4.9,10.1]
Long QT	0	329	0.0	[0.0, 9.1]	0	643	0.0	[0.0, 4.7]	0	3230	0.0	[0.0, 0.9]
Premature depolarization	3	327	9.2	[2.5,23.5]	2	642	3.1	[0.6, 9.8]	13	3221	4.0	[2.4, 6.4]
Sick sinus	1	329	3.0	[0.2,14.3]	0	643	0.0	[0.0, 4.7]	0	3230	0.0	[0.0, 0.9]
Supraventricular tachycardia	2	329	6.1	[1.1,19.0]	0	643	0.0	[0.0, 4.7]	16	3226	5.0	[3.1, 7.5]
Torsades de Pointes	0	329	0.0	[0.0, 9.1]	0	643	0.0	[0.0, 4.7]	0	3230	0.0	[0.0, 0.9]
Ventricular fibrillation	0	329	0.0	[0.0, 9.1]	0	643	0.0	[0.0, 4.7]	10	3228	3.1	[1.7, 5.2]
Ventricular tachycardia	0	329	0.0	[0.0, 9.1]	0	643	0.0	[0.0, 4.7]	4	3229	1.2	[0.4, 2.8]
Incidence rates of ischemic heart disease												
Angina pectoris	1	329	3.0	[0.2,14.3]	1	642	1.6	[0.1, 7.4]	20	3218	6.2	[4.1, 9.0]

IPCI	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
Unstable angina pectoris	2	328	6.1	[1.1,19.1]	5	642	7.8	[3.1,16.3]	22	3221	6.8	[4.6, 9.7]
Myocardial infarction	2	329	6.1	[1.1,19.0]	5	640	7.8	[3.1,16.4]	33	3216	10.3	[7.5,13.7]
Hospitalization for acute coronary syndrome	4	329	12.2	[4.2,27.6]	11	640	17.2	[9.7,28.3]	57	3207	17.8	[14.1,22.1]
Incidence rates of cerebrovascular events												
Stroke	4	328	12.2	[4.2,27.7]	14	640	21.9	[13.3,34.0]	36	3220	11.2	[8.3,14.7]
TIA	4	326	12.3	[4.2,27.8]	7	640	10.9	[5.1,20.5]	32	3213	10.0	[7.3,13.4]
Hospitalization for heart failure	7	328	21.3	[10.1,39.7]	9	642	14.0	[7.3,24.4]	60	3210	18.7	[14.9,23.1]

Aarhus	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
Incidence rates of cardiac arrhythmia												
Atrial fibrillation/flutter	2	257	7.8	[1.4,24.3]	19	628	30.3	[19.9,44.1]	87	2127	40.9	[34.1,48.7]
AV block	2	258	7.8	[1.4,24.2]	4	632	6.3	[2.2,14.4]	12	2162	5.6	[3.2, 9.0]
Long QT	0	258	0.0	[0.0,11.5]	0	633	0.0	[0.0, 4.7]	0	2169	0.0	[0.0, 1.4]
Premature depolarization	0	258	0.0	[0.0,11.5]	3	633	4.7	[1.3,12.2]	3	2166	1.4	[0.4, 3.6]
Sick sinus	0	258	0.0	[0.0,11.5]	4	632	6.3	[2.2,14.4]	5	2165	2.3	[0.9, 4.8]
Supraventricular tachycardia	1	258	3.9	[0.2,18.3]	3	632	4.7	[1.3,12.2]	8	2166	3.7	[1.8, 6.7]

Aarhus	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
Torsades de Pointes	0	258	0.0	[0.0,11.5]	0	633	0.0	[0.0, 4.7]	0	2169	0.0	[0.0, 1.4]
Ventricular fibrillation	1	258	3.9	[0.2,18.3]	0	633	0.0	[0.0, 4.7]	0	2169	0.0	[0.0, 1.4]
Ventricular tachycardia	0	258	0.0	[0.0,11.5]	0	633	0.0	[0.0, 4.7]	1	2169	0.5	[0.0, 2.2]
Incidence rates of ischemic heart disease												
Angina pectoris	7	255	27.4	[12.9,50.9]	15	624	24.1	[14.9,36.8]	27	2153	12.5	[8.9,17.3]
Unstable angina pectoris	4	257	15.5	[5.3,35.2]	7	630	11.1	[5.2,20.8]	12	2163	5.5	[3.2, 9.0]
Myocardial infarction	2	258	7.8	[1.4,24.2]	4	632	6.3	[2.2,14.4]	26	2160	12.0	[8.4,16.7]
Hospitalization for acute coronary syndrome	5	257	19.4	[7.7,40.4]	16	628	25.5	[16.0,38.4]	43	2152	20.0	[15.3,25.7]
Incidence rates of cerebrovascular events												
Stroke	2	258	7.8	[1.4,24.2]	6	631	9.5	[4.1,18.7]	40	2154	18.6	[14.0,24.1]
TIA	0	258	0.0	[0.0,11.5]	3	632	4.7	[1.3,12.2]	9	2164	4.2	[2.2, 7.2]
Hospitalization for heart failure	11	254	43.3	[24.5,70.6]	59	613	96.2	[77.3, 118]	248	2067	120	[108, 132]

HSD	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
Incidence rates of cardiac arrhythmia												

HSD	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
Atrial fibrillation/flutter	9	521	17.3	[9.0,30.0]	5	374	13.4	[5.3,27.9]	37	1258	29.4	[22.0,38.5]
AV block	0	523	0.0	[0.0, 5.7]	0	375	0.0	[0.0, 8.0]	2	1272	1.6	[0.3, 4.9]
Long QT	0	523	0.0	[0.0, 5.7]	0	375	0.0	[0.0, 8.0]	2	1273	1.6	[0.3, 4.9]
Premature depolarization	1	523	1.9	[0.1, 9.0]	2	374	5.3	[1.0,16.7]	6	1269	4.7	[2.1, 9.3]
Sick sinus	0	523	0.0	[0.0, 5.7]	1	374	2.7	[0.1,12.6]	4	1272	3.1	[1.1, 7.2]
Supraventricular tachycardia	0	523	0.0	[0.0, 5.7]	0	375	0.0	[0.0, 8.0]	1	1273	0.8	[0.0, 3.7]
Torsades de Pointes	0	523	0.0	[0.0, 5.7]	0	375	0.0	[0.0, 8.0]	2	1273	1.6	[0.3, 4.9]
Ventricular fibrillation	0	523	0.0	[0.0, 5.7]	0	375	0.0	[0.0, 8.0]	0	1273	0.0	[0.0, 2.4]
Ventricular tachycardia	1	523	1.9	[0.1, 9.0]	0	375	0.0	[0.0, 8.0]	0	1273	0.0	[0.0, 2.4]
Incidence rates of ischemic heart disease												
Angina pectoris	2	523	3.8	[0.7,12.0]	0	375	0.0	[0.0, 8.0]	2	1270	1.6	[0.3, 4.9]
Unstable angina pectoris	0	523	0.0	[0.0, 5.7]	0	375	0.0	[0.0, 8.0]	0	1273	0.0	[0.0, 2.4]
Myocardial infarction	0	523	0.0	[0.0, 5.7]	1	374	2.7	[0.1,12.6]	9	1270	7.1	[3.7,12.3]
Hospitalization for acute coronary syndrome	0	523	0.0	[0.0, 5.7]	0	375	0.0	[0.0, 8.0]	0	1273	0.0	[0.0, 2.4]
Incidence rates of cerebrovascular events												
Stroke	1	523	1.9	[0.1, 9.0]	0	375	0.0	[0.0, 8.0]	3	1272	2.4	[0.6, 6.1]
TIA	1	523	1.9	[0.1, 9.0]	2	372	5.4	[1.0,16.8]	5	1272	3.9	[1.6, 8.2]

HSD	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
Hospitalization for heart failure	1	523	1.9	[0.1, 9.0]	0	375	0.0	[0.0, 8.0]	7	1270	5.5	[2.6,10.3]

SIDIAP	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
Incidence rates of cardiac arrhythmia												
Atrial fibrillation/flutter	29	1507	19.2	[13.8,26.2]	59	3057	19.3	[15.4,23.9]	215	7903	27.2	[24.3,30.4]
AV block	3	1516	2.0	[0.5, 5.1]	20	3057	6.5	[4.3, 9.5]	45	7967	5.6	[4.3, 7.2]
Long QT	0	1519	0.0	[0.0, 2.0]	0	3068	0.0	[0.0, 1.0]	0	7980	0.0	[0.0, 0.4]
Premature depolarization	2	1518	1.3	[0.2, 4.1]	11	3066	3.6	[2.0, 5.9]	32	7966	4.0	[2.9, 5.4]
Sick sinus	0	1519	0.0	[0.0, 2.0]	0	3068	0.0	[0.0, 1.0]	0	7980	0.0	[0.0, 0.4]
Supraventricular tachycardia	1	1519	0.7	[0.0, 3.1]	2	3067	0.7	[0.1, 2.1]	14	7976	1.8	[1.1, 2.7]
Torsades de Pointes	0	1519	0.0	[0.0, 2.0]	0	3068	0.0	[0.0, 1.0]	0	7980	0.0	[0.0, 0.4]
Ventricular fibrillation	0	1519	0.0	[0.0, 2.0]	1	3067	0.3	[0.0, 1.5]	0	7980	0.0	[0.0, 0.4]
Ventricular tachycardia	0	1519	0.0	[0.0, 2.0]	3	3067	1.0	[0.3, 2.5]	4	7979	0.5	[0.2, 1.1]
Incidence rates of ischemic heart disease												
Angina pectoris	5	1514	3.3	[1.3, 6.9]	9	3063	2.9	[1.5, 5.1]	20	7975	2.5	[1.7, 3.6]
Unstable angina pectoris	0	1519	0.0	[0.0, 2.0]	0	3068	0.0	[0.0, 1.0]	1	7980	0.1	[0.0, 0.6]
Myocardial infarction	7	1516	4.6	[2.2, 8.7]	13	3063	4.2	[2.5, 6.7]	43	7965	5.4	[4.1, 7.0]

SIDIAP	NVA				LABA				LAMA			
	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
Hospitalization for acute coronary syndrome	2	1518	1.3	[0.2, 4.1]	9	3066	2.9	[1.5, 5.1]	50	7965	6.3	[4.9, 7.9]
Incidence rates of cerebrovascular events												
Stroke	4	1518	2.6	[0.9, 6.0]	20	3061	6.5	[4.3, 9.5]	45	7964	5.7	[4.3, 7.2]
TIA	2	1519	1.3	[0.2, 4.1]	11	3066	3.6	[2.0, 5.9]	17	7969	2.1	[1.4, 3.2]
Hospitalization for heart failure	42	1509	27.8	[21.2,35.8]	106	3040	34.9	[29.6,40.9]	345	7880	43.8	[40.1,47.8]

Table 15-12 Crude hazard ratios for NVA237 vs. LABA and NVA237 vs. LAMA (excl. NVA237) - by database

THIN	NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome	HR	95% CI	P	HR	95% CI	P
MACE	0.63	[0.34,1.16]	0.1381	0.57	[0.35,0.94]	0.0270
Ischemic heart disease (any event of)	0.34	[0.14,0.80]	0.0138	0.35	[0.16,0.75]	0.0066
Cardiac arrhythmia (any event of)	0.76	[0.41,1.41]	0.3896	0.79	[0.50,1.27]	0.3335
Cerebrovascular disorders (any event of)	1.60	[0.76,3.37]	0.2181	1.05	[0.65,1.70]	0.8286
Mortality	1.29	[0.87,1.92]	0.2078	0.97	[0.74,1.27]	0.8226

IPCI	NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome	HR	95% CI	P	HR	95% CI	P
MACE	0.97	[0.49,1.92]	0.9272	0.83	[0.46,1.50]	0.5425
Ischemic heart disease (any event of)	1.19	[0.39,3.59]	0.7624	0.72	[0.29,1.78]	0.4768
Cardiac arrhythmia (any event of)	2.27	[1.01,5.09]	0.0469	1.15	[0.63,2.09]	0.6515
Cerebrovascular disorders (any event of)	0.88	[0.36,2.11]	0.7669	1.19	[0.54,2.61]	0.6633
Mortality	0.79	[0.41,1.53]	0.4906	0.97	[0.54,1.76]	0.9266

Aarhus	NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome	HR	95% CI	P	HR	95% CI	P
MACE	0.48	[0.27,0.87]	0.0156	0.35	[0.20,0.62]	0.0003
Ischemic heart disease (any event of)	1.00	[0.44,2.25]	0.9954	1.39	[0.66,2.95]	0.3846
Cardiac arrhythmia (any event of)	0.35	[0.12,0.98]	0.0462	0.35	[0.13,0.95]	0.0393
Cerebrovascular disorders (any event of)	Nap[#]			Nap[#]		
Mortality	1.04	[0.62,1.76]	0.8772	0.64	[0.41,1.01]	0.0565

HSD	NVA compared to LABA			NVA compared to LAMA (excl. NVA)		

Outcome	HR	95% CI	P	HR	95% CI	P
MACE	Nap[#]			Nap[#]		
Ischemic heart disease (any event of)	Nap[#]			Nap[#]		
Cardiac arrhythmia (any event of)	1.17	[0.45,3.02]	0.7496	0.53	[0.28,1.03]	0.0608
Cerebrovascular disorders (any event of)	Nap[#]			Nap[#]		
Mortality	0.80	[0.38,1.69]	0.5616	1.15	[0.61,2.17]	0.6699

SIDIAP	NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome	HR	95% CI	P	HR	95% CI	P
MACE	0.76	[0.54,1.07]	0.1148	0.61	[0.45,0.83]	0.0018
Ischemic heart disease (any event of)	1.16	[0.55,2.42]	0.6955	1.12	[0.59,2.14]	0.7342
Cardiac arrhythmia (any event of)	0.83	[0.55,1.25]	0.3612	0.63	[0.43,0.91]	0.0140
Cerebrovascular disorders (any event of)	0.41	[0.16,1.06]	0.0656	0.52	[0.21,1.31]	0.1664
Mortality	0.96	[0.67,1.39]	0.8371	0.95	[0.69,1.31]	0.7532

Nap[#]= Not applicable as number of events in NVA237 is below 5

Table 15-13 Hazard ratios for NVA237 vs. LABA and NVA237 vs. LAMA (excl. NVA237) – adjusted for a priori confounders (model 1) – pooled and by database

Pooled		NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome		**Adj. HR (model 1)**	95% CI	P	**Adj. HR (model 1)**	95% CI	P
MACE	Total	0.67	[0.52,0.86]	0.0017	0.55	[0.45,0.69]	<.0001
	Total, complete cases	0.62	[0.45,0.88]	0.0065	0.57	[0.43,0.77]	0.0002
	Naive	0.69	[0.43,1.13]	0.1415	0.48	[0.31,0.77]	0.0020

Pooled		NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome		**Adj. HR (model 1)**	95% CI	P	**Adj. HR (model 1)**	95% CI	P
Ischemic heart disease (any event of)	Total	0.80	[0.52,1.24]	0.3256	0.72	[0.50,1.03]	0.0748
	Total, complete cases	0.52	[0.28,0.98]	0.0435	0.51	[0.30,0.88]	0.0163
	Naive	0.50	[0.21,1.19]	0.1187	0.51	[0.23,1.17]	0.1116
Cardiac arrhythmia (any event of)	Total	0.85	[0.64,1.13]	0.2690	0.67	[0.53,0.85]	0.0010
	Total, complete cases	0.85	[0.58,1.24]	0.3903	0.72	[0.53,0.98]	0.0345
	Naive	1.10	[0.69,1.75]	0.6965	0.84	[0.55,1.30]	0.4405
Cerebrovascular disorders (any event of)	Total	0.85	[0.55,1.30]	0.4467	0.84	[0.59,1.21]	0.3509
	Total, complete cases	0.98	[0.56,1.72]	0.9425	0.97	[0.62,1.52]	0.8897
	Naive	0.74	[0.32,1.68]	0.4695	0.60	[0.28,1.28]	0.1842
Mortality	Total	0.94	[0.75,1.17]	0.5582	0.92	[0.77,1.09]	0.3263
	Total, complete cases	0.95	[0.70,1.31]	0.7721	0.86	[0.68,1.10]	0.2374
	Naive	1.09	[0.74,1.62]	0.6650	1.14	[0.80,1.63]	0.4644

THIN		NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome		**Adj. HR (model 1)**	95% CI	P	**Adj. HR (model 1)**	95% CI	P
MACE	Total	0.64	[0.34,1.19]	0.1562	0.58	[0.35,0.95]	0.0296
	Total, complete cases	0.67	[0.33,1.34]	0.2533	0.56	[0.33,0.97]	0.0387
	Naive	0.53	[0.18,1.57]	0.2498	0.52	[0.19,1.42]	0.2053

THIN		NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome		**Adj. HR (model 1)**	95% CI	P	**Adj. HR (model 1)**	95% CI	P
Ischemic heart disease (any event of)	Total	0.35	[0.15,0.85]	0.0201	0.35	[0.16,0.74]	0.0060
	Total, complete cases	0.35	[0.13,0.90]	0.0287	0.34	[0.15,0.78]	0.0107
	Naive	NA			NA		
Cardiac arrhythmia (any event of)	Total	0.68	[0.37,1.28]	0.2327	0.79	[0.49,1.26]	0.3235
	Total, complete cases	0.66	[0.32,1.36]	0.2614	0.75	[0.44,1.28]	0.2980
	Naive	1.00	[0.38,2.66]	0.9959	1.22	[0.53,2.83]	0.6360
Cerebrovascular disorders (any event of)	Total	1.78	[0.84,3.77]	0.1331	1.08	[0.67,1.74]	0.7642
	Total, complete cases	1.79	[0.79,4.08]	0.1656	1.13	[0.67,1.91]	0.6536
	Naive	1.70	[0.53,5.39]	0.3688	0.84	[0.34,2.07]	0.7016
Mortality	Total	1.18	[0.79,1.77]	0.4183	0.94	[0.72,1.23]	0.6577
	Total, complete cases	1.22	[0.76,1.97]	0.4081	0.88	[0.64,1.21]	0.4173
	Naive	1.26	[0.67,2.39]	0.4720	1.49	[0.87,2.54]	0.1431

IPCI		NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome		**Adj. HR (model 1)**	95% CI	P	**Adj. HR (model 1)**	95% CI	P
MACE	Total	0.93	[0.46,1.88]	0.8333	0.81	[0.45,1.47]	0.4877
	Total, complete cases	NA			NA		
	Naive	NA			NA		

IPCI		NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome		**Adj. HR (model 1)**	95% CI	P	**Adj. HR (model 1)**	95% CI	P
Ischemic heart disease (any event of)	Total	1.29	[0.39,4.29]	0.6768	0.76	[0.30,1.89]	0.5514
	Total, complete cases	NA			NA		
	Naive	NA			NA		
Cardiac arrhythmia (any event of)	Total	2.38	[1.03,5.47]	0.0418	1.15	[0.63,2.09]	0.6566
	Total, complete cases	1.38	[0.40,4.80]	0.6120	0.98	[0.35,2.73]	0.9694
	Naive	NA			1.88	[0.75,4.74]	0.1794
Cerebrovascular disorders (any event of)	Total	0.74	[0.29,1.89]	0.5320	1.17	[0.53,2.60]	0.6913
	Total, complete cases	NA			NA		
	Naive	NA			NA		
Mortality	Total	0.68	[0.35,1.36]	0.2785	0.93	[0.51,1.68]	0.8066
	Total, complete cases	NA			NA		
	Naive	NA			NA		

Aarhus		NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome		**Adj. HR (model 1)**	95% CI	P	**Adj. HR (model 1)**	95% CI	P
MACE	Total	0.48	[0.26,0.87]	0.0154	0.36	[0.20,0.62]	0.0003
	Total, complete cases	0.47	[0.21,1.08]	0.0746	0.48	[0.22,1.02]	0.0569
	Naive	0.83	[0.29,2.37]	0.7322	0.47	[0.17,1.29]	0.1432

Aarhus		NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome		**Adj. HR (model 1)**	95% CI	P	**Adj. HR (model 1)**	95% CI	P
Ischemic heart disease (any event of)	Total	1.06	[0.46,2.43]	0.8853	1.51	[0.71,3.24]	0.2857
	Total, complete cases	NA			NA		
	Naive	NA			NA		
Cardiac arrhythmia (any event of)	Total	0.38	[0.13,1.09]	0.0730	0.34	[0.13,0.93]	0.0352
	Total, complete cases	NA			NA		
	Naive	NA			NA		
Mortality	Total	1.02	[0.60,1.74]	0.9415	0.71	[0.45,1.12]	0.1361
	Total, complete cases	0.92	[0.41,2.05]	0.8372	0.79	[0.40,1.57]	0.4996
	Naive	NA			NA		

HSD		NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome		**Adj. HR (model 1)**	95% CI	P	**Adj. HR (model 1)**	95% CI	P
MACE	Total	NA			NA		
	Total, complete cases	NA			NA		
	Naive	NA			NA		
Ischemic heart disease (any event of)	Total	NA			NA		
	Total, complete cases	NA			NA		
	Naive	NA			NA		

HSD		NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome		**Adj. HR (model 1)**	95% CI	P	**Adj. HR (model 1)**	95% CI	P
Cardiac arrhythmia (any event of)	Total	1.13	[0.43,2.95]	0.8046	0.55	[0.28,1.05]	0.0710
	Total, complete cases	NA			1.11	[0.43,2.84]	0.8331
	Naive	NA			NA		
Mortality	Total	0.69	[0.32,1.48]	0.3437	1.11	[0.58,2.12]	0.7506
	Total, complete cases	NA			NA		
	Naive	NA			1.73	[0.59,5.08]	0.3203

SIDIAP		NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome		Adj. HR (model 1)	95% CI	P	Adj. HR (model 1)	95% CI	P
MACE	Total	0.71	[0.51,1.01]	0.0574	0.60	[0.44,0.82]	0.0012
	Total, complete cases	0.69	[0.43,1.11]	0.1236	0.60	[0.40,0.91]	0.0156
	Naive	0.62	[0.30,1.28]	0.1970	0.45	[0.22,0.91]	0.0260
Ischemic heart disease (any event of)	Total	1.07	[0.50,2.26]	0.8693	1.15	[0.60,2.20]	0.6713
	Total, complete cases	0.81	[0.28,2.38]	0.7016	1.07	[0.41,2.80]	0.8929
	Naive	NA			NA		
Cardiac arrhythmia (any event of)	Total	0.82	[0.54,1.25]	0.3552	0.63	[0.44,0.92]	0.0156
	Total, complete cases	0.70	[0.40,1.23]	0.2150	0.57	[0.35,0.94]	0.0284
	Naive	0.90	[0.46,1.76]	0.7615	0.83	[0.43,1.60]	0.5806

SIDIAP		NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome		Adj. HR (model 1)	95% CI	P	Adj. HR (model 1)	95% CI	P
Cerebrovascular disorders (any event of)	Total	0.41	[0.16,1.09]	0.0728	0.54	[0.21,1.35]	0.1865
	Total, complete cases	NA			NA		
	Naive	NA			NA		
Mortality	Total	0.92	[0.63,1.34]	0.6584	0.96	[0.69,1.33]	0.8029
	Total, complete cases	0.95	[0.53,1.69]	0.8509	0.86	[0.53,1.39]	0.5458
	Naive	1.00	[0.49,2.04]	0.9977	0.98	[0.49,1.96]	0.9502

Adjusted for age, gender, smoking status and COPD severity

NA= Not applicable as less than 5 events in one of the exposure categories

Table 15-14 Hazard ratios for NVA237 vs. LABA and NVA237 vs. LAMA (excl. NVA237) – IPTW analysis – pooled and by database

Pooled	NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome	HR_{adj_IPTW}	95% CI	P	HR_{adj_IPTW}	95% CI	P
MACE	0.61	[0.47,0.79]	0.0002	0.56	[0.44,0.71]	<.0001
Ischemic heart disease (any event of)	0.74	[0.46,1.17]	0.1970	0.67	[0.46,0.99]	0.0455
Cardiac arrhythmia (any event of)	0.84	[0.62,1.14]	0.2577	0.69	[0.53,0.90]	0.0052
Cerebrovascular disorders (any event of)	0.82	[0.54,1.23]	0.3337	0.80	[0.54,1.19]	0.2708
Mortality	0.88	[0.71,1.11]	0.2823	0.95	[0.79,1.15]	0.5873

THIN	NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome	HR_{adj_IPTW}	95% CI	P	HR_{adj_IPTW}	95% CI	P

THIN	NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome	HR_{adj_IPTW}	95% CI	P	HR_{adj_IPTW}	95% CI	P
MACE	0.65	[0.34,1.23]	0.1866	0.66	[0.38,1.12]	0.1249
Ischemic heart disease (any event of)	0.32	[0.14,0.75]	0.0084	0.30	[0.14,0.65]	0.0020
Cardiac arrhythmia (any event of)	0.66	[0.34,1.28]	0.2221	0.80	[0.48,1.34]	0.3930
Cerebrovascular disorders (any event of)	1.81	[0.84,3.86]	0.1274	1.13	[0.68,1.90]	0.6307
Mortality	1.14	[0.75,1.74]	0.5337	1.02	[0.76,1.37]	0.8907

IPCI	NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome	HR_{adj_IPTW}	95% CI	P	HR_{adj_IPTW}	95% CI	P
MACE	0.89	[0.42,1.88]	0.7635	0.73	[0.37,1.45]	0.3664
Ischemic heart disease (any event of)	1.20	[0.37,3.86]	0.7653	0.69	[0.24,2.03]	0.5041
Cardiac arrhythmia (any event of)	2.50	[1.04,5.99]	0.0403	1.39	[0.69,2.79]	0.3556
Cerebrovascular disorders (any event of)	0.71	[0.27,1.84]	0.4784	0.72	[0.31,1.66]	0.4365
Mortality	0.51	[0.25,1.03]	0.0616	0.60	[0.31,1.18]	0.1384

Aarhus[#]	NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome	HR_{adj_IPTW}	95% CI	P	HR_{adj_IPTW}	95% CI	P
MACE	0.52	[0.28,1.00]	0.0498	0.46	[0.25,0.85]	0.0134
Ischemic heart disease (any event of)	0.90	[0.39,2.09]	0.8038	1.51	[0.66,3.41]	0.3267
Cardiac arrhythmia (any event of)	0.30	[0.11,0.87]	0.0269	0.32	[0.11,0.89]	0.0299
Mortality	1.12	[0.64,1.95]	0.6879	0.91	[0.55,1.49]	0.6963

HSD[*]	NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome	HR_{adj_IPTW}	95% CI	P	HR_{adj_IPTW}	95% CI	P

HSD*	NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome	HR_{adj_IPTW}	95% CI	P	HR_{adj_IPTW}	95% CI	P
Cardiac arrhythmia (any event of)	1.19	[0.46,3.07]	0.7178	0.60	[0.30,1.18]	0.1384
Mortality	0.62	[0.29,1.33]	0.2193	1.15	[0.60,2.22]	0.6732

SIDIAP	NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome	HR_{adj_IPTW}	95% CI	P	HR_{adj_IPTW}	95% CI	P
MACE	0.57	[0.40,0.81]	0.0018	0.55	[0.40,0.76]	0.0002
Ischemic heart disease (any event of)	0.98	[0.43,2.23]	0.9653	1.00	[0.51,1.96]	0.9943
Cardiac arrhythmia (any event of)	0.80	[0.51,1.26]	0.3406	0.60	[0.41,0.88]	0.0095
Cerebrovascular disorders (any event of)	0.34	[0.13,0.89]	0.0278	0.46	[0.18,1.15]	0.0969
Mortality	0.81	[0.55,1.19]	0.2749	0.94	[0.67,1.32]	0.7100

No HR for cerebrovascular disorders calculated as less than 5 events in NVA237 exposure category

* No HR for MACE, ischemic heart disease and cerebrovascular disorders calculated as less than 5 events in NVA237 exposure category

Table 15-15 Total number of patients and number of patients with main events by exposure cohorts (NVA237, LABA, LAMA (excl. NVA237)) - POOLED - Total analysis population, Complete Cases, Naive analysis population

Pooled		Total analysis population				Complete cases	Naive analysis population
			Additional patients with event in case of				
		Number of patients	No censoring for other drugs	Extension to 60 days after end of prescription	Follow-up limited to 1 year	Number of patients	Number of patients
NVA	Total	8722	.	.	.	5509	2603
	MACE	109	11	12	89	62	24

Pooled		Total analysis population				Complete cases	Naive analysis population
			Additional patients with event in case of				
		Number of patients	No censoring for other drugs	Extension to 60 days after end of prescription	Follow-up limited to 1 year	Number of patients	Number of patients
	Ischemic heart disease (any event of)	36	4	5	33	16	7
	Cardiac arrhythmia (any event of)	87	11	16	77	52	25
	Cerebrovascular disorders (any event of)	42	7	8	34	29	10
	Mortality	182	13	34	147	98	39
LABA	Total	17890	.	.	.	10587	11144
	MACE	282	33	36	263	147	149
	Ischemic heart disease (any event of)	79	16	13	73	42	49
	Cardiac arrhythmia (any event of)	171	18	40	162	92	98
	Cerebrovascular disorders (any event of)	80	8	18	68	41	44
	Mortality	260	55	52	230	110	135

Table 15-16 Hazard ratios for NVA237 vs. LABA and NVA237 vs. LAMA (excl. NVA237), main and sensitivity analyses - IPTW analysis - POOLED - total analysis population

Pooled		NVA compared to LABA			NVA compared to LAMA (excl. NVA)		
Outcome	Analysis	HR_{adj_IPTW}	95% CI	P	HR_{adj_IPTW}	95% CI	P
MACE	Main	0.61	[0.47,0.79]	0.0002	0.56	[0.44,0.71]	<.0001
	No censoring at start other drug	0.62	[0.48,0.79]	0.0002	0.59	[0.47,0.74]	<.0001
	Wash-out period 60 days	0.65	[0.51,0.83]	0.0005	0.57	[0.46,0.71]	<.0001
Ischemic heart disease (any event of)	Main	0.74	[0.46,1.17]	0.1970	0.67	[0.46,0.99]	0.0455
	No censoring at start other drug	0.66	[0.42,1.03]	0.0645	0.70	[0.48,1.01]	0.0543
	Wash-out period 60 days	0.78	[0.51,1.19]	0.2499	0.70	[0.49,1.01]	0.0569
Cardiac arrhythmia (any event of)	Main	0.84	[0.62,1.14]	0.2577	0.69	[0.53,0.90]	0.0052
	No censoring at start other drug	0.85	[0.64,1.14]	0.2880	0.70	[0.55,0.90]	0.0057
	Wash-out period 60 days	0.81	[0.61,1.07]	0.1414	0.74	[0.58,0.95]	0.0156
Cerebrovascular disorders (any event of)	Main	0.82	[0.54,1.23]	0.3337	0.80	[0.54,1.19]	0.2708
	No censoring at start other drug	0.91	[0.62,1.33]	0.6122	0.87	[0.61,1.24]	0.4322
	Wash-out period 60 days	0.83	[0.57,1.21]	0.3214	0.86	[0.60,1.23]	0.4088
Mortality	Main	0.88	[0.71,1.11]	0.2823	0.95	[0.79,1.15]	0.5873
	No censoring at start other drug	0.84	[0.68,1.04]	0.1145	0.94	[0.78,1.12]	0.4883
	Wash-out period 60 days	0.95	[0.78,1.16]	0.6337	0.92	[0.78,1.09]	0.3257

Note: All analyses are IPTW analyses, using different follow-up periods

Annex 2.2 – Event definition

Major adverse cardiovascular events (MACE)

Note: The identified codes as documented in this annex were reviewed by all databases prior to data-extraction. As coding might change over time, relevant codes might be updated during the course of the project.

MACE includes the following:

- ***myocardial infarction***
- ***stroke***
- ***hospitalization due to acute coronary syndrome and/or heart failure***

The definitions of myocardial infarction and stroke (and relevant disease codes) are described under items 4 and 6 of this annex, respectively.

Hospitalization due to acute coronary syndrome is defined as patients being hospitalized for reasons of 1) unstable angina pectoris or 2) myocardial infarction (ST segment elevation or non-ST segment elevation). The definition and disease specific codes for (unstable) angina pectoris and myocardial infarction are described under items 3-4 of this annex.

Patients will be identified within the different databases based on a combination of disease specific codes for either unstable angina pectoris or myocardial infarction in combination with codes related to hospitalization. Hospitalization will be retrieved either via linkage with hospital admission/discharge database (SIDIAP and Aarhus), combination of disease codes with information from hospital referral and discharge letters) (HSD and IPCI) or combination of disease codes with source codes (hospital discharge letters) (THIN).

Hospitalization due to heart failure is defined as patients hospitalized for reasons of heart failure. The definition and disease specific codes for heart failure are described under item 4 of this annex

Patients will be identified within the different databases based on a combination of disease specific codes for heart failure in combination with codes related to hospitalization. Hospitalization will be retrieved either via linkage with hospital admission/discharge database (SIDIAP and Aarhus), combination of disease codes with information from hospital referral and discharge letters) (HSD and IPCI) or combination of disease codes with source codes (hospital discharge letters) (THIN).

Ischemic heart disease

Ischemic heart disease or myocardial ischemia, is a disease characterized by ischemia of the heart muscle, usually due to atherosclerosis of the coronary arteries.

For this study, ischemic heart disease as endpoint encompasses angina pectoris (both stable and unstable) and myocardial infarction.

Angina pectoris

According to the guidelines of the European Heart Association; angina pectoris is described as chest discomfort due to myocardial ischaemia associated with coronary artery disease. Anginal symptoms are regarded as stable if they have been occurring over several weeks without major deterioration. They typically occur in conditions associated with increased myocardial oxygen consumption. Angina is said to be unstable if pre-existing angina worsens abruptly for no apparent reason or when new angina develops at a relatively low work load or at rest (Fox et al 2006, Thygesen et al 2012).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of angina pectoris.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Angina pectoris	I20*	413*	G33..	K74
Angina pectoris, unspecified	I20.9	413.9	G33z.	
Angina of effort	I20.8			
Anginal syndrome	I20.9			
Cardiac angina	I20.9			
Ischemic chest pain	I20.9		G33z400	
Ischaemic heart disease			G3...00	
			G3...13	
			Gyu3.	
Dressler's syndrome			G310.11	
Other chronic ischaemic heart disease			G34..00	
Stenocardia			G33z100	
Unstable angina	I20.0		G311.	K74.01
Intermediate coronary syndrome	I20.0	411.1		K76.01
Acute coronary syndrome			G33z000	
Angina pectoris with documented spasm	I20.1		G31y000	
			G332.00	
Nocturnal angina			G330000	
Stable angina			G33z700	
Other forms of angina pectoris	I20.8		Gyu30	
Exercise induced angina			G33z300	
Refractory angina			G311300	
Frequency of angina			187..00	
H/O angina pectoris#			14A5.	
			14AJ.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Canadian Cardiovascular Society classification of angina			388E.00	
Cardiovascular Limitations and			388F.00	
Angina self-management plan agreed			661M000	
Angina self-management plan review			661N000	
Angina control			662K.00	
			662K000	
			662K100	
			662K200	
			662K300	
			662Kz00	
Admit ischaemic heart disease emergency			8H2V.00	

Not for acute event, will only be considered for angina pectoris as underlying comorbidity

Myocardial infarction

Definition of Acute Myocardial Infarction (AMI)

Myocardial infarction is defined as necrosis of the myocardium caused by an obstruction of the blood supply to the heart (coronary circulation). Blockage of a coronary artery deprives the heart muscle of blood and oxygen, causing injury to the heart muscle Therefore, acute myocardial infarction is defined by the evidence of myocardial necrosis - in a clinical setting consistent with a) myocardial ischemia, including ST elevation b) myocardial infarction and c) non-ST elevation myocardial infarction. In this study, an acute MI event will be ascertained using specific diagnoses codes for acute transmural myocardial infarction, acute subendocardial myocardial infarction, or unspecified acute myocardial infarction (Thygesen et al 2012).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of myocardial infarction.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Cardiac infarction	I22*		G30.	
Cardiac infarction	I21*			
Acute myocardial infarction	I21*	410.*	G30z.	K75
Acute myocardial infarction, unspecified	I21.9	410.9		
Myocardial infarction (acute) NOS	I21.3	410		
Acute myocardial infarction, unspecified site, episode of care unspecified		410.90		

Terms	ICD10	ICD9CM	Read Codes	ICPC
AMI NOS, unspecified		410.90		
Acute myocardial infarction, sub endocardial infarction		410.7		
Old myocardial infarction#	I25.2	412		
Healed myocardial infarction#			G32..11	
Old myocardial infarction#			G32..00	
Subsequent/recurrent myocardial infarction	I22		G35..	
Subsequent myocardial infarction of unspecified site	I22.9		Gyu36	
Subsequent myocardial infarction of other sites	I22.8		Gyu35 G353.	
Subsequent myocardial infarction of anterior wall	I22.0		G350.	
Subsequent myocardial infarction of inferior wall	I22.1		G351.]	
Subsequent acute sub endocardial myocardial infarction	I22.2			
Subsequent non transmural myocardial infarction NOS	I22.2			
Subsequent myocardial infarction (acute) NOS	I22.9		G35.	
Acute sub endocardial myocardial infarction	I21.4			
Acute myocardial infarction, sub endocardial infarction, episode of care unspecified		410.70		
Non transmural myocardial infarction	I21.4			
Acute myocardial infarction, of antero lateral wall		410.0	G300.	
Acute antero septal myocardial infarction			G3011	
Acute inferior myocardial infarction		410.4	G308.00	
Acute myocardial infarction, true posterior wall infarction		410.6		
True posterior myocardial infarction			G306.	
Acute myocardial infarction, of inferoposterior wall		410.3	G303.	
Other specified anterior myocardial infarction			G301.	
Acute transmural myocardial infarction of unspecified site	I21.3		Gyu34 G30X.00	
Acute transmural myocardial infarction of anterior wall	I21.0 122.0			
Acute transmural myocardial infarction of inferior wall	I21.1 I21.19			

Terms	ICD10	ICD9CM	Read Codes	ICPC
	122.1			
Acute transmural myocardial infarction of other sites	I21.2 I21.29 122.8			
ECG: old myocardial infarction#			3232.	
Anterior myocard. infarct NOS		410.8	G301z	
Other acute myocardial infarct			G30y.	
Other acute myocardial inf.NOS			G30yz	
Inferior myocard. infarct NOS			G308.	
Acute myocardial infarction, of infero lateral wall		410.2	G302.	
Acute lateral myocardial infarction		410.5		
Lateral myocardial infarct NOS			G305.	
Acute posterior myocardial infarction		410.60 410.61 410.62		
Posterior myocard. infarct NOS			G304.	
Silent myocardial infarct			G30..17	
ECG: myocardial infarction			323..	
ECG: myocardial infarct NOS			323Z.	
Postoperative myocardial infarction			G38..00 – G38z.00	
Acute anterior myocardial infarction		410.1		
Acute Q wave myocard infarct			G309.00	
Acute myocardial infarction, sub endocardial infarction		410.71 410.72	G307.	
Non-Q wave myocardial infarction NOS	I21.4 122.2		G307000	
Non-ST elevation (NSTEMI) myocardial infarction	I21.4 122.2		G307100	
History of MI#			14A3.00 14A4.00 14AH.00 14AT.00	K76.02
Diabetes mellitus insulin-glucose infuse acute myocardial infarct			889A.00	
Other acute and subacute ischemic heart disease			G31..00	
Haemopericardium/current comp folow acut myocard infarct			G360.00	
Atrial septal defect/curr comp folow acut myocardal infarct			G361.00	
Ventric septal defect/curr comp fol acut myocardal infarctn			G362.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI			G363.00	
Ruptur chordae tendinae/curr comp fol acute myocard infarct			G364.00	
Rupture papillary muscle/curr comp fol acute myocard infarct			G365.00	

Not for acute event, will only be considered for angina pectoris as underlying comorbidity

Heart failure

Definition of heart failure

HF is a syndrome in which the patients should have the following features: symptoms of HF, typically shortness of breath at rest or during exertion, and/or fatigue; signs of fluid retention such as pulmonary congestion or ankle swelling; and objective evidence of an abnormality of the structure or function of the heart at rest A clinical response to treatment directed at HF alone is not sufficient for the diagnosis, but is helpful when the diagnosis remains unclear after appropriate diagnostic investigations. Patients with HF would usually be expected to show some improvement in symptoms and signs in response to those treatments from which a relatively fast symptomatic improvement could be anticipated (e.g. diuretic or vasodilator administration) (Dickstein et al 2008).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for heart failure.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Heart failure	I50	428*	G58..	K77
Heart failure, unspecified	I50.9	428.9		
Congestive heart failure	I50.0	428.0	G580.00	
Congestive heart disease	I50.9			
Left ventricular failure	I50.1	428.1	G581.00	
Acute cor pulmonale			G400.00	
Acute heart failure			G582.	
			G5800	
Admit heart failure emergency			8H2S.00	
Chronic congestive heart failure#			G5801	
H/O: heart failure#			14A6.00	
			14AM.00	
Hypertensive heart disease with (congestive) heart failure	I11.0	402.01	G21z011	
		402.91		

Terms	ICD10	ICD9CM	Read Codes	ICPC
Hypertensive heart and renal disease with (congestive) heart failure	I13.0	402.11	G232.00	
Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	I13.2	404.01 404.91		
Heart failure confirmed			1O1..00	
Heart failure resolved#			2126400	
Heart failure management			661M500	
			661N500	
New York Heart Association classification - class I			662f.00	
New York Heart Association classification - class II			662g.00	
New York Heart Association classification - class III			662h.00	
New York Heart Association classification - class IV			662i.00	
New York Heart Assoc classification heart failure symptoms			ZRad.00	
Heart failure monitoring			662p.00	
			662T.00	
			662W.00	
			679W100	
			679X.00	
			67D4.00	
			8CL3.00	
			8CMK.00	
			8CMW800	
Cardiac failure therapy			8B29.00	
Heart failure follow-up			8HBE.00	
			8Hg8.00	
			8HgD.00	
			8HHb.00	
			8HHz.00	
			8Hk0.00	
			8HTL.00	
			8IB8.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			8IE0.00	
			8IE1.00	
			9N0k.00	
			9N2p.00	
Heart failure quality indicators			9hH..00	
			9hH0.00	
			9hH1.00	
Cardiomegaly			G5y3.00	
			G5y3411	
			G5y3600	
Post cardiac operation heart failure NOS			G5y4z00	
Heart failure confirmed via echography			G5yy900	
			G5yyA00	
			G5yyC00	
			G5yyB00	
			G5yyE00	
			P69..00	
			P6y3100	
Heart transplant failure and rejection			SP08400	
Heart failure as a complication of care			SP11111	
Impaired left ventricular function			33BA.00	
Rheumatic left ventricular failure			G1yz100	
Congestive cardiomyopathy			G554000	
Congestive obstructive cardiomyopathy			G554011	

not for acute event, will only be considered for heart failure as underlying comorbidity

Stroke

Stroke is defined as rapidly developed clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death), with no apparent cause other than a vascular origin: it includes patients presenting clinical signs and symptoms suggestive of intracerebral haemorrhage or cerebral ischemic necrosis. It does not include transient cerebral ischemia or stroke events in cases of blood disease (e.g. leukemia, polycythaemia vera), brain tumour or brain metastases. Secondary stroke caused by trauma should also be excluded.

In this study, a stroke event is defined as any form of stroke due to haemorrhage (intracerebral) or infarction (i.e. ischemic) and stroke not specified as haemorrhage or infarction. Potential cases of acute stroke will be ascertained by specific and unspecific diagnosis codes (Goldstein et al 2011).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of stroke.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Stroke, not specified as hemorrhage or	I64			
Stroke NOS	I63.9			K90
Intracerebral haemorrhage	I61	431	G61..	
Non-traumatic subarachnoidal bleeding	I60	430	G60..	
Cerebrovascular accident (CVA)			G66..13	
Stroke and cerebrovascular accident unspecified			G66..00	
Stroke NOS			G66..12	
Sequelae of stroke, not specified as hemorrhage or infarction	I69	342*	Gyu6C00	
[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs			Gyu6300	
[X]Other cerebral infarction			Gyu6400	
[X]Occlusion and stenosis of other cerebral arteries			Gyu6600	
[X]Sequelae of stroke,not specfd as h'morrhage or infarction			Gyu6C00	
[X]Intracerebral haemorrhage in hemisphere, unspecified			Gyu6F00	
[X]Cereb infarct due unsp occlus/stenos precerebr arteries			Gyu6G00	
Brain stem stroke syndrome	G46.3		G663.	
Cerebellar stroke syndrome	G46.4		G664.	
Other and unspecified intracranial haemorrhage	I62	432.*	G62..00	
			G62z.00	
Cerebral infarction	I63		G64..	
Personal history of stroke#			ZV125	
Sequelae of stroke NOS#	I69.3			
H/O: Stroke#			14A7.00	
			14A7.11	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			14A7.12	
			14AK.00	
Cerebral infarct due to thrombosis of precerebral arteries		433*	G63y000	
			G63y100	
Personal history of transient# ischemic attack (TIA), and cerebral infarction without residual deficits	Z86.73	V12.54		
Management/monitoring of stroke			661M700	
			661N700	
			662e.00	
			662e.11	
			662M.00	
			662M100	
			662M200	
			662o.00	
			9Om..00	
			9Om0.00	
			9Om1.00	
			9Om2.00	
			9Om3.00	
			9Om4.00	
Delivery of rehabilitation for stroke			7P24200	
Stroke referral			8HBJ.00	
			8HTQ.00	
			8IEC.00	
Seen in stroke clinic			9N0p.00	
Quality indicators stroke			9h2..00	
			9h21.00	
			9h22.00	
Sequelae of cerebral infarction#		438.*	G683.00	
Sequelae of stroke, not specified as haemorrhage or infarction#			G68X.00/Gyu6C00	
Cerebral infarction due unspecified occlusion/stenosis of pre-cerebral arteries		433.*	G6W..00/Gyu6300	
			G6X..00/Gyu6G00	
Cerebral infarction due to unspecified occlusion/stenosis of cerebral		434.*		

Terms	ICD10	ICD9CM	Read Codes	ICPC
arteries				
[X]Other cerebral infarction			Gyu6400	
[X]Occlusion and stenosis of other cerebral arteries			Gyu6600	
Hemiplegia and hemiparesis		342.*		
Acute, but ill-defined, cerebrovascular disease		436.*		
Cereb infarct due cerebral venous thrombosis, nonpyogenic			G676000	

not for acute event, will only be considered for stroke as underlying comorbidity

TIA

TIA is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (Easton et al 2009).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of TIA.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Transient cerebral ischemic attack, unspecified	G45.9			
TIA - Transient ischemic attack	G45	435.*	G65..12	K89
H/O: TIA*			14AB.00	
			ZV12D00	
Amaurosis fugax			F423600	
Retinal transient arterial occlusion NOS			F423700	
Other transient cerebral ischemic attacks and related syndromes	G45.8		Fyu55	
Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits#		V12.54		
Transient ischaemic attack clinical management plan			8CRB.00	
Transient cerebral ischaemia			G65..00	
Drop attack			G65..11	
Carotid territory transient ischaemic attack			G657.00	
Other transient cerebral ischaemia			G65y.00	
Transient cerebral ischaemia NOS			G65z.00	
Impending cerebral ischaemia			G65z000	
Intermittent cerebral ischaemia			G65z100	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Transient cerebral ischaemia NOS			G65zz00	

not for acute event, will only be considered for stroke as underlying comorbidity

Cardiac arrhythmia

Atrial flutter (AFL) (eventtype=AFIFLUT) is an abnormal heart rhythm that occurs in the atria of the heart. When it first occurs, it is usually associated with a fast heart rate or tachycardia (beats over 100 per minute). On ECG, AFL is defined as presence of flutter waves (Camm et al 2010).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of atrial flutter.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Atrial flutter		427.32	G5731	
Atrial fibrillation and flutter	I48	427.3	G573.	K78
Atrial fibrillation and flutter NOS			G573z	
Unspecified atrial fibrillation and atrial flutter	I48.9			
Type I atrial flutter	I48.3			
Type II atrial flutter	I48.4			
Atypical atrial flutter	I48.4			
Unspecified atrial flutter	I48.92			
ECG: atrial flutter			3273.00	
History of atrial flutter#			14AR.00	

Not for acute event, will only be considered for atrial flutter as underlying comorbidity

Atrial fibrillation (AF) (eventtype=AFIFLUT) is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population. It is often associated with palpitations, fainting, chest pain, or congestive heart failure. By definition, the heart rate will be greater than 100 beats per minute. According to the ESC guidelines, the ECG shows absence of P waves, with disorganized electrical activity in their place, and irregular R-R intervals due to irregular conduction of impulses to the ventricles (Camm et al 2010).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of atrial fibrillation.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Atrial fibrillation		427.31	G573000	
Atrial fibrillation and flutter	I48	427.3	G573.	K78
Atrial fibrillation and flutter NOS			G573z	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Unspecified atrial fibrillation and atrial flutter	I48.9			
AF - Paroxysmal atrial fibrillation			G573200	K79.01
Chronic atrial fibrillation#	I48.2			
Persistent atrial fibrillation#	I48.1		G573500	
Permanent atrial fibrillation#	I48.2		G573400	
Non-rheumatic atrial fibrillation			G573300	
ECG: atrial fibrillation			3272.00	
Atrial fibrillation resolved			212R.00	
Atrial fibrillation monitoring			662S.00	
			6A9..00	
			8HTy.00	
			9hF..00	
			9hF0.00	
			9hF1.00	
			9Os..	

Not for acute event, will only be considered for atrial fibrillation as underlying comorbidity

Ventricular tachycardia (*eventtype*=***VENTTACH***) is a rapid heartbeat that originates in one of the ventricles of the heart. To be classified as tachycardia, the heart rate is usually at least 100 beats per minute (Zipes et al 2006).

Ventricular fibrillation (*eventtype*=***VENTFIBR***) is a very rapid, uncoordinated, ineffective series of contractions throughout the ventricles of the heart. Unless stopped, these chaotic impulses are fatal (Zipes et al 2006).

Torsade de pointes *(eventtype=**TORSPOINT**)* is an uncommon and distinctive form of polymorphic ventricular tachycardia (VT) characterized by a gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line. Torsade de pointes, is associated with a prolonged QT interval, which may be congenital or acquired. Torsade usually terminates spontaneously but frequently recurs and may degenerate into ventricular fibrillation (Zipes et al 2006).

The following concepts of **ventricular arrhythmia** (ventricular tachycardia, ventricular fibrillation and Torsade de pointes) have been mapped through the Unified Medical Language System (UMLS).

Terms	ICD10	ICD9CM	Read Codes	ICPC
Ventricular tachycardia	I47.2		G571.11	K79.02
Paroxysmal ventricular tachycardia		427.1	G571.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
ECG: ventricular tachycardia			3282.	
Ventricular fibrillation and flutter	I49.0	427.4	G574.	
ECG: ventricular fibrillation			3282.00	

Long QT syndrome (LQTS) (eventtype = LONGQT) is a congenital disorder characterized by a prolongation of the QT interval on electrocardiograms (ECGs) and a propensity to ventricular tachyarrhythmias, such as Torsade de Pointes, which may lead to syncope, cardiac arrest, or sudden death.

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of long QT syndrome.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Long QT syndrome	I45.81	426.82	X202	
	I47.2E			
ECG: Q-T interval prolonged			32K3.00	

Supraventricular tachycardia (SVT) (eventtype =SVT) is a condition presenting as a rapid heart rhythm originating at or above the atrioventricular node. Supraventricular tachycardias can be contrasted with the potentially more dangerous ventricular tachycardias—rapid rhythms that originate within the ventricular tissue.

Although "SVT" can be due to any supraventricular cause, the term is most often used to refer to a specific example, paroxysmal supraventricular tachycardia (PSVT), two common types being atrioventricular reciprocating tachycardia and AV nodal reentrant tachycardia.

The following concepts of sinus tachycardia have been mapped through the Unified Medical Language System (UMLS).

Terms	ICD10	ICD9CM	Read Codes	ICPC
supraventricular tachycardia	I47.1			K79.01
paroxysmal supraventricular tachycardia		427.0		
paroxysmal tachycardia	147			K79
paroxysmal tachycardia, unspecified	147.9			
re-entry ventricular arrhythmia	147.0			
Wolf Parkinson White syndrome	145.6			
ECG: supraventricular arrhythmia			327..00	
Paroxysmal supraventricular tachycardia			G570.00	
ECG: paroxysmal atrial tachy.			3274.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
ECG: supraventric. arryth. NOS			327Z.00	
Wolff-Parkinson-White syndrome			G567400	
Paroxysmal atrial tachycardia			G570000	
Paroxysmal atrioventricular tachycardia			G570100	
Paroxysmal junctional tachycardia			G570200	
Paroxysmal nodal tachycardia			G570300	
Paroxysmal supraventricular tachycardia NOS			G570z00	
Supraventricular tachycardia NOS			G57y900	
Re-entry ventricular arrhythmia			G57yA00	

Not for acute event, will only be considered for SVT as underlying comorbidity

Sick Sinus Syndrome (eventtype=SICKSINUS) is characterized by dysfunction of the sinoatrial (SA) node that is often secondary to senescence of the SA node and surrounding atrial myocardium. It is characterized by chronic SA node dysfunction, a sluggish or absent SA nodal pacemaker after electrical electroversion, frequently depressed escape pacemakers, and/or atrioventricular (AV) nodal conduction disturbances. These abnormalities can result in profound sinus bradycardia, sinus pauses, sinus arrest, SA nodal exit block, and inappropriate responses to physiological demands during exercise or stress.

The following concepts of Sick Sinus Syndrome have been mapped through the Unified Medical Language System (UMLS).

Terms	ICD10	ICD9CM	Read Codes	ICPC
Sick sinus syndrome	149.5		G57y300	K79.02

Atrioventricular (AV) block (eventtype=AVBLOCK) is a partial or complete interruption of impulse transmission from the atria to the ventricles. The most common cause is idiopathic fibrosis and sclerosis of the conduction system. Diagnosis is by ECG; symptoms and treatment depend on degree of block (first, second or third degree AV block), but treatment, when necessary, usually involves pacing.

The following concepts of atrioventricular block have been mapped through the Unified Medical Language System (UMLS).

Terms	ICD10	ICD9CM	Read Codes	ICPC
Atrioventricular block, first degree	I44.0	426.11	G561100	
Atrioventricular block, complete	I44.2	426.0	G560.	
Partial atrioventricular block			G561.00	
Third degree atrioventricular block			G560.11	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Atrioventricular block, second degree	I44.1		G561400	
			G561311	
Other and unspecified atrioventricular block	I44.3	426.1	Gyu5U	
Unspecified atrioventricular block	I44.3	426.10	G561z	K84.02
			G5610	
Atrioventricular and left bundle-branch block	I44			
Mobitz (type) II atrioventricular block		426.12	G5612	
Other second degree atrioventricular block		426.13		
ECG: complete atrioventricular block			3298.	
Partial atrioventricular block			G561.	
ECG: partial atrioventricular block			3294.	
ECG: partial atrioventricular block - 2:1			3295.	
ECG: partial atrioventricular block - 3:1			3296.	
ECG: Wenckebach phenomenon			3297.00	
Electrocardiogram: Mobitz type 1 second degree AV block			3297.11	
Electrocardiogram: Mobitz type 2 second degree AV block			329H.00	

Premature depolarization (eventtype=PREMATDEP) will include atrial premature depolarization, junctional premature depolarization and ventricular premature depolarization.

The following concepts of premature depolarization have been mapped through the Unified Medical Language System (UMLS).

Terms	ICD10	ICD9CM	Read codes	ICPC
Extra systole	I49.4	427.6	G576z00	K80
	I49.40		G576011	
	I49.49			
Supraventricular extra systole		427.61	G576100	K80.01
Ventricular extra systole	I49.3		G576500	K80.02
			G576200	
Atrial premature depolarization	I49.1		G576300	
Junctional premature depolarization	I49.2		G576400	
[X]Other and unspecified premature depolarization			Gyu5Z00	
ECG: ectopic beats		427.6	326..00	
ECG: extra systole			3262.00	
ECG: ventricular ectopics			3263.00	

Terms	ICD10	ICD9CM	Read codes	ICPC
ECG: atrial ectopics			3264.00	
ECG: ectopic beats NOS			326Z.00	
Ectopic beats			G576.00	
Premature beats			G576.11	
Ectopic beats unspecified			G576000	

Mortality (all-cause)

Mortality will be assessed in the database either from the population table (death date and identification of death as reason for end of database follow-up) or via death specific codes. The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of death.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Dead				A96
Died				
Death				
Has died				
Dead NOS			22JZ.	
Instantaneous death	R96.0	798.1	R211.	
Unattended death	R98	798.9	R213.	
Unattended death NOS			R213z	
Sudden cardiac death, so described	I46.1		G5751	
Other sudden death, cause unknown	R96	798	RyuC1	
			R21..	
			R21z.	
Death occurring less than 24 hours from onset of symptoms, not otherwise explained	R96.1	798.2	R212.	
			R212z	
Death in hospital			8HG..11	

Annex 2.3 – Exposure definition – respiratory medication use

This list will be updated whenever new respiratory medications come to the market.

NVA237

	ATC code
NVA237	R03BB06

Concomitant use of other respiratory medications

Class of medication	ATC code	Description	UK	NL	DK	IT	SP
SAMA	R03BB01	Ipratropium bromide	x	x	x	x	x
	R03BB02	Oxitropium bromide	x	no	no	x	no
LAMA	R03BB04	Tiotropium bromide	x	x	x	x	x
	R03BB05	Aclidinium bromide	x	x	no	x	x
	R03BB06	Glycopyrronium bromide	x	x	x	x	x
	R03BB07	Umeclidinium bromide	x	no			
SABA	R03AC02	Salbutamol	x	x	x	x	x
	R03AC03	Terbutaline	x	x	x	x	x
	R03AC04	Fenoterol	x	no	x	x	no
	R03AC05	Rimiterol	x	no	no	no	no
	R03AC06	Hexoprenaline	no	no	no	no	no
	R03AC07	Isoetarine	no	no	no	no	no
	R03AC08	Pirbuterol	x	no	no	no	no
	R03AC09	Tretoquinol	no	no	no	no	no
	R03AC10	Carbuterol	no	no	no	no	no
	R03AC15	Reproterol	x	no	no	no	no
	R03AC16	Procaterol	no	no	no	no	no
	R03AC17	Bitolterol	no	no	no	no	no
LABA	R03AC11	Tulobuterol	no	no	no	no	no
	R03AC12	Salmeterol	x	x	x	x	x
	R03AC13	Formoterol	x	x	x	x	x
	R03AC14	Clenbuterol	no	no	no	no	no
	R03AC18	Indacaterol	x	x	x	x	x
	R03AC19	Olodaterol	no	x	no	no	no
SABA+SAMA	R03AL01 ***(R03AK03 in past)***	Fenoterol and ipratropium bromide	x	x	x	no	no
	R03AL02 ***(R03AK04 in past)***	Salbutamol and ipratropium bromide	x	x	x	no	x

Class of medication	ATC code	Description	UK	NL	DK	IT	SP
LABA+LAMA	R03AL03	Vilanterol and umeclidinium bromide	x	x	no	no	no
	R03AL04	Indacaterol and glycopyrronium bromide	x	x	x	x	x
	R03AL05	Formoterol and aclidinium bromide	x	x	no	no	no
LABA+ICS	R03AK06	Salmeterol and fluticasone	x	x	x	x	x
	R03AK07	Formoterol and budesonide	x	x	x	x	x
	R03AK08	Formoterol and beclomethasone	x	x	no	x	x
	R03AK09	Formoterol and momethasone	no	no	no	no	no
	R03AK10	Vilanterol and fluticasone furoate	x	x	no	no	no
	R03AK11	Formoterol and fluticasone	x	x	no	x	no
ICS	R03BA01	Beclometasone	x	x	x	x	x
	R03BA02	Budesonide	x	x	x	x	x
	R03BA03	Flunisolide	no	no	no	x	no
	R03BA04	Betamethasone	no	no	no	no	no
	R03BA05	Fluticasone	x	x	x	x	x
	R03BA06	Triamcinolone	no	no	no	no	no
	R03BA07	Mometasone	x	no	x	x	x
	R03BA08	Ciclesonide	x	x	x	x	x
	R03BA09	Fluticasone furoate		no			
other fixed combinations	R03AK01	Epinephrine and other drugs for obstructive airway diseases	no	no		no	no
	R03AK02	Isoprenaline and other drugs for obstructive airway diseases	no	no		no	no
	R03AK04	Salbutamol and sodium cromoglicate	x	no		no	x
	R03AK05	Reproterol and sodium cromoglicate	no	no		no	no
xanthines	R03DA01	Diprophylline	no	no	no	x	no
	R03DA02	Choline theophyllinate	x	no	no	no	no
	R03DA03	Proxyphylline	no	no	no	no	no
	R03DA04	Theophylline	x	x	x	x	x
	R03DA05	Aminophylline	x	no	x	x	no
	R03DA06	Etamiphylline	no	no	no	no	no
	R03DA07	Theobromine	x	no	no	no	no
	R03DA08	Bamifylline	no	no	no	x	no
	R03DA09	Acefylline piperazine	no	no	no	no	no
	R03DA10	Bufylline	no	no	no	no	no
	R03DA11	Doxofylline	no	no	no	x	no
	R03DA20	Combinations of xanthines	no	no	no	no	no

Class of medication	ATC code	Description	UK	NL	DK	IT	SP
	R03DA51	Diprophylline, combinations	no	no	no	x	no
	R03DA54	Theophylline, combinations excluding psycholeptics	no	no	no	no	x
	R03DA55	Aminophylline, combinations	no	no	no	no	no
	R03DA57	Theobromine, combinations	no	no	no	no	no
	R03DA74	Theophylline, combinations with psycholeptics	no	no	no	no	no
Leukotriene receptor antagonists (LTRA)	R03DC01	Zafirlukast	x	no	x	x	x
	R03DC02	Pranlukast	no	no	no	no	no
	R03DC03	Montelukast	x	x	x	x	x
	R03DC04	Ibudilast	no	no	no	no	no
Oral phosphodiesterase- 4 (PDE-4) inhibitors	R03DX07	roflumilast	x	x	x	x	x
Oral ß$_2$-agonists	R03CC02	Salbutamol	x	x	x	x	x
	R03CC03	Terbutaline	x	no	x	no	x
	R03CC04	Fenoterol	no	no	no	no	no
	R03CC05	Hexoprenaline	no	no	no	no	no
	R03CC06	Isoetarine	no	no	no	no	no
	R03CC07	Pirbuterol	x	no	no	no	no
	R03CC08	Procaterol	no	no	no	no	no
	R03CC09	Tretoquinol	no	no	no	no	no
	R03CC10	Carbuterol	no	no	no	no	no
	R03CC11	Tulobuterol	x	no	no	no	no
	R03CC12	Bambuterol	x	no	x	no	x
	R03CC13	Clenbuterol	no	no	no	x	no
	R03CC14	Reproterol	x	no	no	no	no
	R03CC53	Terbutaline, combinations	no	no	no	no	no
	R03CC90	Clenbuterol, combinations	no	no	no	no	no
Systemic glucocorticosteroids	H02AB01	Betamethasone	x	x	x	x	x
	H02AB02	Dexamethasone	x	x	x	x	x
	H02AB03	Fluocortolone	no	no	no	no	no
	H02AB04	Methylprednisolone	x	x	x	x	x
	H02AB05	Paramethasone	no	no	no	x	no
	H02AB06	Prednisolone	x	x	x	x	x
	H02AB07	Prednisone	x	x	x	x	x
	H02AB08	Triamcinolone	x	x	x	x	x
	H02AB09	Hydrocortisone	x	x	x	x	x
	H02AB10	Cortisone	x	x	no	x	no
	H02AB11	Prednylidene	no	no	no	no	no

Class of medication	ATC code	Description	UK	NL	DK	IT	SP
	H02AB12	Rimexolone	no	no	no	no	no
	H02AB13	Deflazacort	x	no	no	x	no
	H02AB14	Cloprednol	no	no	no	no	no
	H02AB15	Meprednisone	no	no	no	no	no
	H02AB17	Cortivazol	no	no	no	no	no
	H02AB30	Combinations of glucocorticoids	no	no	no	no	no
	H02AB56	Prednisolone, combinations	no	no	no	no	no
	H02AB57	Prednisone, combinations	no	no	no	no	no
	H02AB90	Flumetasone	no	no	no	no	no

Annex 2.4 – COPD definition

According to GOLD (Global initiative of lung disease), COPD is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production and/or a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis in this clinical context; the presence of a postbronchodilator FEV1/FVC < 0.70 confirms the presence of persistent airflow limitation and thus of COPD (Cazzola et al 2011).

COPD will be identified within the databases both by COPD disease specific codes and via free text search for those databases where free text is available.

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of COPD.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic obstructive pulmonary disease, unspecified	J44.9			R95
Chronic obstructive lung disease			H3...	
Chronic obstructive airways disease			H3z..	
Other chronic obstructive pulmonary disease	J44			
Other specified chronic obstructive pulmonary disease	J44.8		H3y..11	
Chronic obstructive pulmonary disease with acute exacerbation, unspecified	J44.1		H3y1.00	
Mild chronic obstructive pulmonary disease			H36..00	
Moderate chronic obstructive pulmonary disease			H37..00	
Severe chronic obstructive pulmonary disease			H38..00	
Very severe chronic obstructive pulmonary disease			H39..00	
End stage chronic obstructive airways disease			H3A..00	
chronic obstructive pulmonary disease and allied conditions		490-496.99		

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic obstructive pulmonary disease with acute lower respiratory infection	J44.0		H3y0.00	
Chronic obstructive pulmonary disease monitoring (QoFcode UK)			66YB.00 66YB000 66YB100 66Yf.00 66Yg.00 66Yh.00 66YI.00 66YL.00 66YL.11 66YL.12 66YM.00 66YS.00 66YT.00 9h5..00 9h51.00 9h52.00	
Chronic bronchitis (QoF code)			H31. (and subsequent codes)	
Emphysema			H32. (and subsequent codes)	

*Read codes selected based on QoF codes for COPD as applied in the UK

COPD severity will be assessed at the index date for the three different exposure cohorts on the basis of spirometry data or on the basis of a severity classification if spirometry is not available.

- If spirometry is available:

Severity of COPD will be determined by spirometry, according to GOLD guidelines:

I. Mild COPD (GOLD stage I): $FEV_1/FVC<70\%$ and FEV_1 predicted >= 80%
II. Moderate COPD (GOLD stage II): $FEV_1/FVC<70\%$ and $50\% \leq FEV_1 <80\%$ predicted
III. Severe COPD (GOLD stage III): $FEV_1/FVC<70\%$ and $30\% \leq FEV_1 <50\%$ predicted
IV. Very severe COPD (GOLD stage IV): $FEV_1/FVC<70\%$ and $FEV_1 <30\%$ predicted or $FEV_1<50\%$ predicted and chronic respiratory failure.

Based on the recommendations by the SAC, COPD severity was assessed in all patients with information on FEV1 expected, even in patients with $FEV_1/FVC>=0.70$ % or in patients with missing FVC. Severity was assessed as following:

I. Mild COPD: FEV_1 predicted >= 80%
II. Moderate COPD: 50% ≤ FEV_1 <80% predicted
III. Severe COPD: 30% ≤ FEV_1 <50% predicted
IV. Very severe COPD: FEV_1<30% predicted or FEV_1<50% predicted and chronic respiratory failure.

The most recently performed spirometry prior to the index date (for all 3 cohorts) will be considered. In addition, in accordance with the updated GOLD guidelines (GOLD 2016), patients will be further stratified upon the previous history of exacerbations (no, one or ≥ two exacerbations in the year prior to the index date [time of first prescription]) (Cazzola et al 2011). A moderate COPD exacerbation is defined as need for oral corticosteroids and/or systemic antibiotics for COPD. A severe COPD exacerbation is defined as hospitalisation because of COPD exacerbation.

Since the COPD Assessment Test (CAT) is not performed routinely in clinical practice, and since a CAT score < 10 occurs only in the setting of screening programs in general populations, all patients will be considered as COPD GOLD B or D patients: COPD GOLD B if FEV1 > 50% AND a history of ≤ 1 exacerbation in the previous year; COPD GOLD D if FEV1 ≤ 50% OR a history of ≥ 2 exacerbations in the previous year.

- If spirometry is not available:

COPD severity will be categorised according to published literature on COPD severity scores using data from GP or health care databases. The COPD severity assessed closed to the index date (for all 3 cohorts) will be considered.

1. Mild: Patients initially diagnosed with COPD
2. Moderate: Patients on regular treatment (defined as at least 2 prescriptions of the same drug group within 6 months) with inhaled/oral bronchodilators, xanthines or combination therapy. Patients are considered to have moderate COPD from the time of the second prescription on.
3. Severe: Patients with any of the following:
   - hospitalized for COPD during the past 365 days (prior to the index date)
   - requiring 3 or more courses of antibiotics for the treatment of respiratory infections in the past 365 days (prior to the index date)
   - two or more courses of systemic corticosteroids for the treatment of COPD exacerbations in the past 365 days (prior to the index date)
   - long term use of systemic corticosteroids in the past 365 days for the treatment of COPD (prior to the index date)
4. Very severe: Patients requiring chronic oxygen therapy.

Annex 2.5 – Concomitant medication use

- *Central nervous system drugs (excl drugs with anticholinergic effects)*

Use of opioids, hypnotics and sedatives, anxiolytics, antiepileptic drugs, serotonin reuptake inhibitors.

Opioids **(N02A)**

N02AA Natural opium alkaloids
N02AA01 Morphine
N02AA02 Opium
N02AA03 Hydromorphone
N02AA04 Nicomorphine
N02AA05 Oxycodone
N02AA08 Dihydrocodeine
N02AA09 Diamorphine
N02AA10 Papaveretum
N02AA51 Morphine, combinations
N02AA55 Oxycodone, combinations
N02AA58 Dihydrocodeine, combinations
N02AA59 Codeine, combinations excluding psycholeptics
N02AA79 Codeine, combinations with psycholeptics
N02AB Phenylpiperidine derivatives
N02AB01 Ketobemidone
N02AB02 Pethidine
N02AB03 Fentanyl
N02AB52 Pethidine, combinations excluding psycholeptics
N02AB53 Fentanyl, combinations excluding psycholeptics
N02AB72 Pethidine, combinations with psycholeptics
N02AB73 Fentanyl, combinations with psycholeptics
N02AC Diphenylpropylamine derivatives
N02AC01 Dextromoramide
N02AC03 Piritramide
N02AC04 Dextropropoxyphene
N02AC05 Bezitramide
N02AC52 Methadone, combinations excluding psycholeptics
N02AC54 Dextropropoxyphene, combinations excluding psycholeptics
N02AC74 Dextropropoxyphene, combinations with psycholeptics
N02AD Benzomorphan derivatives
N02AD01 Pentazocine
N02AD02 Phenazocine
N02AE Oripavine derivatives

N02AE01 Buprenorphine
N02AE90 Etorphine
N02AE99 Oripavine derivatives, combinations
Morphinan derivatives
N02AF01 Butorphanol
N02AF02 Nalbuphine
N02AG Opioids in combination with antispasmodics
N02AG01 Morphine and antispasmodics
N02AG02 Ketobemidone and antispasmodics
N02AG03 Pethidine and antispasmodics
N02AG04 Hydromorphone and antispasmodics
N02AX Other opioids
N02AX01 Tilidine
N02AX02 Tramadol
N02AX03 Dezocine
N02AX05 Meptazinol
N02AX06 Tapentadol
N02AX52 Tramadol, combinations

Hypnotics and sedatives **(N05C)**
N05CA Barbiturates, plain
N05CA01 Pentobarbital
N05CA02 Amobarbital
N05CA03 Butobarbital
N05CA04 Barbital
N05CA05 Aprobarbital
N05CA06 Secobarbital
N05CA07 Talbutal
N05CA08 Vinylbital
N05CA09 Vinbarbital
N05CA10 Cyclobarbital
N05CA11 Heptabarbital
N05CA12 Reposal
N05CA15 Methohexital
N05CA16 Hexobarbital
N05CA19 Thiopental
N05CA20 Ethallobarbital
N05CA21 Allobarbital
N05CA22 Proxibarbal
N05CB Barbiturates, combinations

N05CB01 Combinations of barbiturates
N05CB02 Barbiturates in combination with other drugs
N05CC Aldehydes and derivatives
N05CC01 Chloral hydrate
N05CC02 Chloralodol
N05CC03 Acetylglycinamide chloral hydrate
N05CC04 Dichloralphenazone
N05CC05 Paraldehyde
N05CD Benzodiazepine derivatives
N05CD01 Flurazepam
N05CD02 Nitrazepam
N05CD03 Flunitrazepam
N05CD04 Estazolam
N05CD05 Triazolam
N05CD06 Lormetazepam
N05CD07 Temazepam
N05CD08 Midazolam
N05CD09 Brotizolam
N05CD10 Quazepam
N05CD11 Loprazolam
N05CD12 Doxefazepam
N05CD13 Cinolazepam
N05CD90 Climazolam
N05CE Piperidinedione derivatives
N05CE01 Glutethimide
N05CE02 Methyprylon
N05CE03 Pyrithyldione
N05CF Benzodiazepine related drugs
N05CF01 Zopiclone
N05CF02 Zolpidem
N05CF03 Zaleplon
N05CF04 Eszopiclone
N05CH Melatonin receptor agonists
N05CH01 Melatonin
N05CH02 Ramelteon
N05CM Other hypnotics and sedatives
N05CM01 Methaqualone
N05CM02 Clomethiazole
N05CM03 Bromisoval
N05CM04 Carbromal

N05CM05 Scopolamine
N05CM06 Propiomazine
N05CM07 Triclofos
N05CM08 Ethchlorvynol
N05CM09 Valerianae radix
N05CM10 Hexapropymate
N05CM11 Bromides
N05CM12 Apronal
N05CM13 Valnoctamide
N05CM15 Methylpentynol
N05CM16 Niaprazine
N05CM18 Dexmedetomidine
N05CM90 Detomidine
N05CM91 Medetomidine
N05CM92 Xylazine
N05CM93 Romifidine
N05CM94 Metomidate
N05CX Hypnotics and sedatives in combination, excluding barbiturates
N05CX01 Meprobamate, combinations
N05CX02 Methaqualone, combinations
N05CX03 Methylpentynol, combinations
N05CX04 Clomethiazole, combinations
N05CX05 Emepronium, combinations
N05CX06 Dipiperonylaminoethanol, combinations

Anxiolytics **(N05B)**
N05BA Benzodiazepine derivatives
N05BA01 Diazepam
N05BA02 Chlordiazepoxide
N05BA03 Medazepam
N05BA04 Oxazepam
N05BA05 Potassium clorazepate
N05BA06 Lorazepam
N05BA07 Adinazolam
N05BA08 Bromazepam
N05BA09 Clobazam
N05BA10 Ketazolam
N05BA11 Prazepam
N05BA12 Alprazolam
N05BA13 Halazepam

N05BA14 Pinazepam
N05BA15 Camazepam
N05BA16 Nordazepam
N05BA17 Fludiazepam
N05BA18 Ethyl loflazepate
N05BA19 Etizolam
N05BA21 Clotiazepam
N05BA22 Cloxazolam
N05BA23 Tofisopam
N05BA56 Lorazepam, combinations
N05BB Diphenylmethane derivatives
N05BB01 Hydroxyzine
N05BB02 Captodiame
N05BB51 Hydroxyzine, combinations
N05BC Carbamates
N05BC01 Meprobamate
N05BC03 Emylcamate
N05BC04 Mebutamate
N05BC51 Meprobamate, combinations
N05BD Dibenzo-bicyclo-octadiene derivatives
N05BD01 Benzoctamine
N05BE Azaspirodecanedione derivatives
N05BE01 Buspirone
N05BX Other anxiolytics
N05BX01 Mephenoxalone
N05BX02 Gedocarnil
N05BX03 Etifoxine

Antiepileptics **(N03A)**
N03AA Barbiturates and derivatives
N03AA01 Methylphenobarbital
N03AA02 Phenobarbital
N03AA03 Primidone
N03AA04 Barbexaclone
N03AA30 Metharbital
N03AB Hydantoin derivatives
N03AB01 Ethotoin
N03AB02 Phenytoin
N03AB03 Amino(diphenylhydantoin) valeric acid
N03AB04 Mephenytoin

N03AB05 Fosphenytoin
N03AB52 Phenytoin, combinations
N03AB54 Mephenytoin, combinations
N03AC Oxazolidine derivatives
N03AC01 Paramethadione
N03AC02 Trimethadione
N03AC03 Ethadione
N03AD Succinimide derivatives
N03AD01 Ethosuximide
N03AD02 Phensuximide
N03AD03 Mesuximide
N03AD51 Ethosuximide, combinations
N03AE Benzodiazepine derivatives
N03AE01 Clonazepam
N03AF Carboxamide derivatives
N03AF01 Carbamazepine
N03AF02 Oxcarbazepine
N03AF03 Rufinamide
N03AF04 Eslicarbazepine
N03AG Fatty acid derivatives
N03AG01 Valproic acid
N03AG02 Valpromide
N03AG03 Aminobutyric acid
N03AG04 Vigabatrin
N03AG05 Progabide
N03AG06 Tiagabine
N03AX Other antiepileptics
N03AX03 Sultiame
N03AX07 Phenacemide
N03AX09 Lamotrigine
N03AX10 Felbamate
N03AX11 Topiramate
N03AX12 Gabapentin
N03AX13 Pheneturide
N03AX14 Levetiracetam
N03AX15 Zonisamide
N03AX16 Pregabalin
N03AX17 Stiripentol
N03AX18 Lacosamide
N03AX19 Carisbamate

N03AX21 Retigabine
N03AX22 Perampanel
N03AX30 Beclamide
N03AX90 Imepitoin

Serotonin reuptake inhibitors **(N06A)**
N06AB Selective serotonin reuptake inhibitors
N06AB02 Zimelidine
N06AB03 Fluoxetine
N06AB04 Citalopram
N06AB05 Paroxetine
N06AB06 Sertraline
N06AB07 Alaproclate
N06AB08 Fluvoxamine
N06AB09 Etoperidone
N06AB10 Escitalopram

- *Anticholinergic drugs*

Antipsychotic drugs **(N05A)**
N05AA Phenothiazines with aliphatic side-chain
N05AA01 Chlorpromazine
N05AA02 Levomepromazine
N05AA03 Promazine
N05AA04 Acepromazine
N05AA05 Triflupromazine
N05AA06 Cyamemazine
N05AA07 Chlorproethazine
N05AB Phenothiazines with piperazine structure
N05AB01 Dixyrazine
N05AB02 Fluphenazine
N05AB03 Perphenazine
N05AB04 Prochlorperazine
N05AB05 Thiopropazate
N05AB06 Trifluoperazine
N05AB07 Acetophenazine
N05AB08 Thioproperazine
N05AB09 Butaperazine
N05AB10 Perazine
N05AC Phenothiazines with piperidine structure
N05AC01 Periciazine

N05AC02 Thioridazine
N05AC03 Mesoridazine
N05AC04 Pipotiazine
N05AD Butyrophenone derivatives
N05AD01 Haloperidol
N05AD02 Trifluperidol
N05AD03 Melperone
N05AD04 Moperone
N05AD05 Pipamperone
N05AD06 Bromperidol
N05AD07 Benperidol
N05AD08 Droperidol
N05AD09 Fluanisone
N05AD90 Azaperone
N05AE Indole derivatives
N05AE01 Oxypertine
N05AE02 Molindone
N05AE03 Sertindole
N05AE04 Ziprasidone
N05AF Thioxanthene derivative
N05AF01 Flupentixol
N05AF02 Clopenthixol
N05AF03 Chlorprothixene
N05AF04 Thiothixene
N05AF05 Zuclopenthixol
N05AG Diphenylbutylpiperidine derivatives
N05AG01 Fluspirilene
N05AG02 Pimozide
N05AG03 Penfluridol
N05AH Diazepines, oxazepines, thiazepines and oxepines
N05AH01 Loxapine
N05AH02 Clozapine
N05AH03 Olanzapine
N05AH04 Quetiapine
N05AH05 Asenapine
N05AH06 Clotiapine
N05AK Neuroleptics, in tardive dyskinesia
N05AL Benzamides
N05AL01 Sulpiride
N05AL02 Sultopride

N05AL03 Tiapride
N05AL04 Remoxipride
N05AL05 Amisulpride
N05AL06 Veralipride
N05AL07 Levosulpiride
N05AN Lithium
N05AN01 Lithium
N05AX Other antipsychotics
N05AX07 Prothipendyl
N05AX08 Risperidone
N05AX10 Mosapramine
N05AX11 Zotepine
N05AX12 Aripiprazole
N05AX13 Paliperidone
N05AX14 Iloperidone
N05AX90 Amperozide

Tricyclic and tetracyclic antidepressant agents **(N06A)**
N06AA Non-selective monoamine reuptake inhibitors
N06AA01 Desipramine
N06AA02 Imipramine
N06AA03 Imipramine oxide
N06AA04 Clomipramine
N06AA05 Opipramol
N06AA06 Trimipramine
N06AA07 Lofepramine
N06AA08 Dibenzepin
N06AA09 Amitriptyline
N06AA10 Nortriptyline
N06AA11 Protriptyline
N06AA12 Doxepin
N06AA13 Iprindole
N06AA14 Melitracen
N06AA15 Butriptyline
N06AA16 Dosulepin
N06AA17 Amoxapine
N06AA18 Dimetacrine
N06AA19 Amineptine
N06AA21 Maprotiline
N06AA23 Quinupramine

N06AX Other antidepressants
N06AX01 Oxitriptan
N06AX02 Tryptophan
N06AX03 Mianserin
N06AX04 Nomifensine
N06AX05 Trazodone
N06AX06 Nefazodone
N06AX07 Minaprine
N06AX08 Bifemelane
N06AX09 Viloxazine
N06AX10 Oxaflozane
N06AX11 Mirtazapine
N06AX12 Bupropion
N06AX13 Medifoxamine
N06AX14 Tianeptine
N06AX15 Pivagabine
N06AX16 Venlafaxine
N06AX17 Milnacipran
N06AX18 Reboxetine
N06AX19 Gepirone
N06AX21 Duloxetine
N06AX22 Agomelatine
N06AX23 Desvenlafaxine
N06AX24 Vilazodone
N06AX25 Hyperici herba
N06AX90 Selegiline

Disopyramide **(C01BA)**
C01BA03 Disopyramide

Antispasmodics **(A03A)**
A03AA Synthetic anticholinergics, esters with tertiary amino group
A03AA01 Oxyphencyclimine
A03AA03 Camylofin
A03AA04 Mebeverine
A03AA05 Trimebutine
A03AA06 Rociverine
A03AA07 Dicycloverine
A03AA08 Dihexyverine
A03AA09 Difemerine

A03AA30 Piperidolate
A03AB Synthetic anticholinergics, quaternary ammonium compounds
A03AB01 Benzilone
A03AB02 Glycopyrronium
A03AB03 Oxyphenonium
A03AB04 Penthienate
A03AB05 Propantheline
A03AB06 Otilonium bromide
A03AB07 Methantheline
A03AB08 Tridihexethyl
A03AB09 Isopropamide
A03AB10 Hexocyclium
A03AB11 Poldine
A03AB12 Mepenzolate
A03AB13 Bevonium
A03AB14 Pipenzolate
A03AB15 Diphemanil
A03AB16 (2-benzhydryloxyethyl)diethyl-methylammonium iodide
A03AB17 Tiemonium iodide
A03AB18 Prifinium bromide
A03AB19 Timepidium bromide
A03AB21 Fenpiverinium
A03AB53 Oxyphenonium, combinations
A03AB90 Benzetimide
A03AB92 Carbachol
A03AB93 Neostigmin

Anti Parkinson drugs
N04A Anticholinergic agents
N04AA Tertiary amines
N04AA01 Trihexyphenidyl
N04AA02 Biperiden
N04AA03 Metixene
N04AA04 Procyclidine
N04AA05 Profenamine
N04AA08 Dexetimide
N04AA09 Phenglutarimide
N04AA10 Mazaticol
N04AA11 Bornaprine
N04AA12 Tropatepine

N04AB Ethers chemically close to antihistamines
N04AB01 Etanautine
N04AB02 Orphenadrine (chloride)
N04AC Ethers of tropine or tropine derivatives
N04AC01 Benzatropine
N04AC30 Etybenzatropine

Choline-esterase inhibitors **(N07A)**
N07AA Anticholinesterases
N07AA01 Neostigmine
N07AA02 Pyridostigmine
N07AA03 Distigmine
N07AA30 Ambenonium
N07AA51 Neostigmine, combinations

Atropine **(A03BA)**
A03BA01 Atropine

H1-antihistamines **(R06A)**
R06AA Aminoalkyl ethers
R06AA01 Bromazine
R06AA02 Diphenhydramine
R06AA04 Clemastine
R06AA06 Chlorphenoxamine
R06AA07 Diphenylpyraline
R06AA08 Carbinoxamine
R06AA09 Doxylamine
R06AA52 Diphenhydramine, combinations
R06AA54 Clemastine, combinations
R06AA56 Chlorphenoxamine, combinations
R06AA57 Diphenylpyraline, combinations
R06AA59 Doxylamine, combinations
R06AB Substituted alkylamines
R06AB01 Brompheniramine
R06AB02 Dexchlorpheniramine
R06AB03 Dimetindene
R06AB04 Chlorphenamine
R06AB05 Pheniramine
R06AB06 Dexbrompheniramine
R06AB07 Talastine

R06AB51 Brompheniramine, combinations
R06AB52 Dexchlorpheniramine, combinations
R06AB54 Chlorphenamine, combinations
R06AB56 Dexbrompheniramine, combinations
R06AC Substituted ethylene diamines
R06AC01 Mepyramine
R06AC02 Histapyrrodine
R06AC03 Chloropyramine
R06AC04 Tripelennamine
R06AC05 Methapyrilene
R06AC06 Thonzylamine
R06AC52 Histapyrrodine, combinations
R06AC53 Chloropyramine, combinations
R06AD Phenothiazine derivatives
R06AD01 Alimemazine
R06AD02 Promethazine
R06AD03 Thiethylperazine
R06AD04 Methdilazine
R06AD05 Hydroxyethylpromethazine
R06AD06 Thiazinam
R06AD07 Mequitazine
R06AD08 Oxomemazine
R06AD09 Isothipendyl
R06AD52 Promethazine, combinations
R06AD55 Hydroxyethylpromethazine, combinations
R06AE Piperazine derivatives
R06AE01 Buclizine
R06AE03 Cyclizine
R06AE04 Chlorcyclizine
R06AE05 Meclozine
R06AE06 Oxatomide
R06AE07 Cetirizine
R06AE09 Levocetirizine
R06AE51 Buclizine, combinations
R06AE53 Cyclizine, combinations
R06AE55 Meclozine, combinations
R06AK Combinations of antihistamines
R06AX Other antihistamines for systemic use
R06AX01 Bamipine
R06AX02 Cyproheptadine

R06AX03 Thenalidine
R06AX04 Phenindamine
R06AX05 Antazoline
R06AX07 Triprolidine
R06AX08 Pyrrobutamine
R06AX09 Azatadine
R06AX11 Astemizole
R06AX12 Terfenadine
R06AX13 Loratadine
R06AX15 Mebhydrolin
R06AX16 Deptropine
R06AX17 Ketotifen
R06AX18 Acrivastine
R06AX19 Azelastine
R06AX21 Tritoqualine
R06AX22 Ebastine
R06AX23 Pimethixene
R06AX24 Epinastine
R06AX25 Mizolastine
R06AX26 Fexofenadine
R06AX27 Desloratadine
R06AX28 Rupatadine
R06AX29 Bilastine
R06AX53 Thenalidine, combinations
R06AX58 Pyrrobutamine, combinations

Anticholinergics for treatment of overactive bladder
G04BD Urinary antispasmodics
G04BD01 Emepronium
G04BD02 Flavoxate
G04BD03 Meladrazine
G04BD04 Oxybutynin
G04BD05 Terodiline
G04BD06 Propiverine
G04BD07 Tolterodine
G04BD08 Solifenacin
G04BD09 Trospium
G04BD10 Darifenacin
G04BD11 Fesoterodine

- *Drugs affecting cerebrovascular and cardiovascular disease*

Systemic glucocorticosteroids
H02AB Glucocorticoids
H02AB01 Betamethasone
H02AB02 Dexamethasone
H02AB03 Fluocortolone
H02AB04 Methylprednisolone
H02AB05 Paramethasone
H02AB06 Prednisolone
H02AB07 Prednisone
H02AB08 Triamcinolone
H02AB09 Hydrocortisone
H02AB10 Cortisone
H02AB11 Prednylidene
H02AB12 Rimexolone
H02AB13 Deflazacort
H02AB14 Cloprednol
H02AB15 Meprednisone
H02AB17 Cortivazol
H02AB30 Combinations of glucocorticoids
H02AB56 Prednisolone, combinations
H02AB57 Prednisone, combinations
H02AB90 Flumetasone

NSAIDs **(M01A)**
M01AA Butylpyrazolidines
M01AA01 Phenylbutazone
M01AA02 Mofebutazone
M01AA03 Oxyphenbutazone
M01AA05 Clofezone
M01AA06 Kebuzone
M01AA90 Suxibuzone
M01AA99 Combinations
M01AB Acetic acid derivatives and related substances
M01AB01 Indometacin
M01AB02 Sulindac
M01AB03 Tolmetin
M01AB04 Zomepirac
M01AB05 Diclofenac
M01AB06 Alclofenac

M01AB07 Bumadizone
M01AB08 Etodolac
M01AB09 Lonazolac
M01AB10 Fentiazac
M01AB11 Acemetacin
M01AB12 Difenpiramide
M01AB13 Oxametacin
M01AB14 Proglumetacin
M01AB15 Ketorolac
M01AB16 Aceclofenac
M01AB17 Bufexamac
M01AB51 Indometacin, combinations
M01AB55 Diclofenac, combinations
M01AC Oxicams
M01AC01 Piroxicam
M01AC02 Tenoxicam
M01AC04 Droxicam
M01AC05 Lornoxicam
M01AC06 Meloxicam
M01AC56 Meloxicam, combinations
M01AE Propionic acid derivatives
M01AE01 Ibuprofen
M01AE02 Naproxen
M01AE03 Ketoprofen
M01AE04 Fenoprofen
M01AE05 Fenbufen
M01AE06 Benoxaprofen
M01AE07 Suprofen
M01AE08 Pirprofen
M01AE09 Flurbiprofen
M01AE10 Indoprofen
M01AE11 Tiaprofenic acid
M01AE12 Oxaprozin
M01AE13 Ibuproxam
M01AE14 Dexibuprofen
M01AE15 Flunoxaprofen
M01AE16 Alminoprofen
M01AE17 Dexketoprofen
M01AE18 Naproxcinod
M01AE51 Ibuprofen, combinations

M01AE52 Naproxen and esomeprazole
M01AE53 Ketoprofen, combinations
M01AE56 Naproxen and misoprostol
M01AE90 Vedaprofen
M01AE91 Carprofen
M01AE92 Tepoxalin
M01AG Fenamates
M01AG01 Mefenamic acid
M01AG02 Tolfenamic acid
M01AG03 Flufenamic acid
M01AG04 Meclofenamic acid
M01AG90 Flunixin
M01AH Coxibs
M01AH01 Celecoxib
M01AH02 Rofecoxib
M01AH03 Valdecoxib
M01AH04 Parecoxib
M01AH05 Etoricoxib
M01AH06 Lumiracoxib
M01AH90 Firocoxib
M01AH91 Robenacoxib
M01AH92 Mavacoxib
M01AH93 Cimicoxib
M01AX Other anti-inflammatory and antirheumatic agents, non-steroids
M01AX01 Nabumetone
M01AX02 Niflumic acid
M01AX04 Azapropazone
M01AX05 Glucosamine
M01AX07 Benzydamine
M01AX12 Glucosaminoglycan polysulfate
M01AX13 Proquazone
M01AX14 Orgotein
M01AX17 Nimesulide
M01AX18 Feprazone
M01AX21 Diacerein
M01AX22 Morniflumate
M01AX23 Tenidap
M01AX24 Oxaceprol
M01AX25 Chondroitin sulfate
M01AX26 Avocado and soyabean oil, unsaponifiables

M01AX52 Niflumic acid, combinations
M01AX68 Feprazone, combinations
M01AX90 Pentosan polysulfate
M01AX91 Aminopropionitrile
M01AX99 Combinations

Antithrombotic agents (B01A)
B01AA Vitamin K antagonists
B01AA01 Dicoumarol
B01AA02 Phenindione
B01AA03 Warfarin
B01AA04 Phenprocoumon
B01AA07 Acenocoumarol
B01AA08 Ethyl biscoumacetate
B01AA09 Clorindione
B01AA10 Diphenadione
B01AA11 Tioclomarol
B01AA12 Fluindione

B01AE Direct thrombin inhibitors
B01AE01 Desirudin
B01AE02 Lepirudin
B01AE03 Argatroban
B01AE04 Melagatran
B01AE05 Ximelagatran
B01AE06 Bivalirudin
B01AE07 Dabigatran etexilate

B01AF Direct factor Xa inhibitors
B01AF01 Rivaroxaban
B01AF02 Apixaban

B01AX Other antithrombotic agents
B01AX01 Defibrotide
B01AX04 Dermatan sulfate
B01AX05 Fondaparinux

Lipid lowering drugs **(C10A, C10B))**
C10AA HMG CoA reductase inhibitors
C10AA01 Simvastatin

C10AA02 Lovastatin
C10AA03 Pravastatin
C10AA04 Fluvastatin
C10AA05 Atorvastatin
C10AA06 Cerivastatin
C10AA07 Rosuvastatin
C10AA08 Pitavastatin
C10AB Fibrates
C10AB01 Clofibrate
C10AB02 Bezafibrate
C10AB03 Aluminium clofibrate
C10AB04 Gemfibrozil
C10AB05 Fenofibrate
C10AB06 Simfibrate
C10AB07 Ronifibrate
C10AB08 Ciprofibrate
C10AB09 Etofibrate
C10AB10 Clofibride
C10AB11 Choline fenofibrate
C10AC Bile acid sequestrants
C10AC01 Colestyramine
C10AC02 Colestipol
C10AC03 Colextran
C10AC04 Colesevelam
C10AD Nicotinic acid and derivatives
C10AD01 Niceritrol
C10AD02 Nicotinic acid
C10AD03 Nicofuranose
C10AD04 Aluminium nicotinate
C10AD05 Nicotinyl alcohol (pyridylcarbinol)
C10AD06 Acipimox
C10AD52 Nicotinic acid, combinations
C10AX Other lipid modifying agents
C10AX01 Dextrothyroxine
C10AX02 Probucol
C10AX03 Tiadenol
C10AX05 Meglutol
C10AX06 Omega-3-triglycerides
C10AX07 Magnesium pyridoxal 5-phosphate glutamate
C10AX08 Policosanol

C10AX09 Ezetimibe
C10AX10 Alipogene tiparvovec
C10AX11 Mipomersen
C10B Lipid modifying agents, combinations
C10BA HMG CoA reductase inhibitors in combination with other lipid modifying agents
C10BA01 Lovastatin and nicotinic acid
C10BA02 Simvastatin and ezetimibe
C10BA03 Pravastatin and fenofibrate
C10BX HMG CoA reductase inhibitors, other combinations
C10BX01 Simvastatin and acetylsalicylic acid
C10BX02 Pravastatin and acetylsalicylic acid
C10BX03 Atorvastatin and amlodipine
C10BX04 Simvastatin, acetylsalicylic acid and ramipril

Platelet aggregation inhibitors **(B01AC)**
B01AC Platelet aggregation inhibitors excluding heparin
B01AC01 Ditazole
B01AC02 Cloricromen
B01AC03 Picotamide
B01AC04 Clopidogrel
B01AC05 Ticlopidine
B01AC06 Acetylsalicylic acid
B01AC07 Dipyridamole
B01AC08 Carbasalate calcium
B01AC09 Epoprostenol
B01AC10 Indobufen
B01AC11 Iloprost
B01AC13 Abciximab
B01AC15 Aloxiprin
B01AC16 Eptifibatide
B01AC17 Tirofiban
B01AC18 Triflusal
B01AC19 Beraprost
B01AC21 Treprostinil
B01AC22 Prasugrel
B01AC23 Cilostazol
B01AC24 Ticagrelor
B01AC30 Combinations
B01AC56 Acetylsalicylic acid and esomeprazole

Nitrates **(C01DA)**
C01DA Organic nitrates
C01DA02 Glyceryl trinitrate
C01DA04 Methylpropylpropanediol dinitrate
C01DA05 Pentaerithrityl tetranitrate
C01DA07 Propatylnitrate
C01DA08 Isosorbide dinitrate
C01DA09 Trolnitrate
C01DA13 Erityl tetranitrate
C01DA14 Isosorbide mononitrate
C01DA20 Organic nitrates in combination
C01DA38 Tenitramine
C01DA52 Glyceryl trinitrate, combinations
C01DA54 Methylpropylpropanediol dinitrate, combinations
C01DA55 Pentaerithrityl tetranitrate, combinations
C01DA57 Propatylnitrate, combinations
C01DA58 Isosorbide dinitrate, combinations
C01DA59 Trolnitrate, combinations
C01DA63 Erityl tetranitrate, combinations
C01DA70 Organic nitrates in combination with psycholeptics

Cardiac glycosides **(C01AA, C01AB, C01AC, C01AX)**
C01AA Digitalis glycosides
C01AA01 Acetyldigitoxin
C01AA02 Acetyldigoxin
C01AA03 Digitalis leaves
C01AA04 Digitoxin
C01AA05 Digoxin
C01AA06 Lanatoside C
C01AA07 Deslanoside
C01AA08 Metildigoxin
C01AA09 Gitoformate
C01AA52 Acetyldigoxin, combinations
C01AB Scilla glycosides
C01AB01 Proscillaridin
C01AB51 Proscillaridin, combinations
C01AC Strophanthus glycosides
C01AC01 G-strophanthin
C01AC03 Cymarin
C01AX Other cardiac glycosides

C01AX02 Peruvoside

Anti-arrhythmics **(C01B)**
C01BA Antiarrhythmics, class Ia
C01BA01 Quinidine
C01BA02 Procainamide
C01BA03 Disopyramide
C01BA04 Sparteine
C01BA05 Ajmaline
C01BA08 Prajmaline
C01BA12 Lorajmine
C01BA51 Quinidine, combinations excluding psycholeptics
C01BA71 Quinidine, combinations with psycholeptics
C01BB Antiarrhythmics, class Ib
C01BB01 Lidocaine
C01BB02 Mexiletine
C01BB03 Tocainide
C01BB04 Aprindine
C01BC Antiarrhythmics, class Ic
C01BC03 Propafenone
C01BC04 Flecainide
C01BC07 Lorcainide
C01BC08 Encainide
C01BD Antiarrhythmics, class III
C01BD01 Amiodarone
C01BD02 Bretylium tosilate
C01BD03 Bunaftine
C01BD04 Dofetilide
C01BD05 Ibutilide
C01BD06 Tedisamil
C01BD07 Dronedarone
C01BG Other antiarrhythmics, class I and III
C01BG01 Moracizine
C01BG07 Cibenzoline
C01BG11 Vernakalant

Anti-hypertensive drugs **(C03, C07, C08, C09)**
C03AA Thiazides, plain
C03AA01 Bendroflumethiazide
C03AA02 Hydroflumethiazide

C03AA03 Hydrochlorothiazide
C03AA04 Chlorothiazide
C03AA05 Polythiazide
C03AA06 Trichlormethiazide
C03AA07 Cyclopenthiazide
C03AA08 Methyclothiazide
C03AA09 Cyclothiazide
C03AA13 Mebutizide
C03AA56 Trichlormethiazide, combinations
C03AB Thiazides and potassium in combination
C03AB01 Bendroflumethiazide and potassium
C03AB02 Hydroflumethiazide and potassium
C03AB03 Hydrochlorothiazide and potassium
C03AB04 Chlorothiazide and potassium
C03AB05 Polythiazide and potassium
C03AB06 Trichlormethiazide and potassium
C03AB07 Cyclopenthiazide and potassium
C03AB08 Methyclothiazide and potassium
C03AB09 Cyclothiazide and potassium
C03AH Thiazides, combinations with psycholeptics and/or analgesics
C03AH01 Chlorothiazide, combinations
C03AH02 Hydroflumethiazide, combinations
C03AX Thiazides, combinations with other drugs
C03AX01 Hydrochlorothiazide, combinations
C03B Low-ceiling diuretics, excluding thiazides
C03BA Sulfonamides, plain
C03BA02 Quinethazone
C03BA03 Clopamide
C03BA04 Chlortalidone
C03BA05 Mefruside
C03BA07 Clofenamide
C03BA08 Metolazone
C03BA09 Meticrane
C03BA10 Xipamide
C03BA11 Indapamide
C03BA12 Clorexolone
C03BA13 Fenquizone
C03BA82 Clorexolone, combinations with psycholeptics
C03BB Sulfonamides and potassium in combination
C03BB02 Quinethazone and potassium

C03BB03 Clopamide and potassium
C03BB04 Chlortalidone and potassium
C03BB05 Mefruside and potassium
C03BB07 Clofenamide and potassium
C03BC Mercurial diuretics
C03BC01 Mersalyl
C03BD Xanthine derivatives
C03BD01 Theobromine
C03BK Sulfonamides, combinations with other drugs
C03BX Other low-ceiling diuretics
C03BX03 Cicletanine
C03C High-ceiling diuretics
C03CA Sulfonamides, plain
C03CA01 Furosemide
C03CA02 Bumetanide
C03CA03 Piretanide
C03CA04 Torasemide
C03CB Sulfonamides and potassium in combination
C03CB01 Furosemide and potassium
C03CB02 Bumetanide and potassium
C03CC Aryloxyacetic acid derivatives
C03CC01 Etacrynic acid
C03CC02 Tienilic acid
C03CD Pyrazolone derivatives
C03CD01 Muzolimine
C03CX Other high-ceiling diuretics
C03CX01 Etozolin
C03D Potassium-sparing agents
C03DA Aldosterone antagonists
C03DA01 Spironolactone
C03DA02 Potassium canrenoate
C03DA03 Canrenone
C03DA04 Eplerenone
C03DB Other potassium-sparing agents
C03DB01 Amiloride
C03DB02 Triamterene
C03E Diuretics and potassium-sparing agents in combination
C03EA Low-ceiling diuretics and potassium-sparing agents
C03EA01 Hydrochlorothiazide and potassium-sparing agents
C03EA02 Trichlormethiazide and potassium-sparing agents

C03EA03 Epitizide and potassium-sparing agents
C03EA04 Altizide and potassium-sparing agents
C03EA05 Mebutizide and potassium-sparing agents
C03EA06 Chlortalidone and potassium-sparing agents
C03EA07 Cyclopenthiazide and potassium-sparing agents
C03EA12 Metolazone and potassium-sparing agents
C03EA13 Bendroflumethiazide and potassium-sparing agents
C03EA14 Butizide and potassium-sparing agents
C03EB High-ceiling diuretics and potassium-sparing agents
C03EB01 Furosemide and potassium-sparing agents
C03EB02 Bumetanide and potassium-sparing agents
C07A Beta blocking agents
C07AA Beta blocking agents, non-selective
C07AA01 Alprenolol
C07AA02 Oxprenolol
C07AA03 Pindolol
C07AA05 Propranolol
C07AA06 Timolol
C07AA07 Sotalol
C07AA12 Nadolol
C07AA14 Mepindolol
C07AA15 Carteolol
C07AA16 Tertatolol
C07AA17 Bopindolol
C07AA19 Bupranolol
C07AA23 Penbutolol
C07AA27 Cloranolol
C07AA57 Sotalol, combinations
C07AA90 Carazolol
C07AB Beta blocking agents, selective
C07AB01 Practolol
C07AB02 Metoprolol
C07AB03 Atenolol
C07AB04 Acebutolol
C07AB05 Betaxolol
C07AB06 Bevantolol
C07AB07 Bisoprolol
C07AB08 Celiprolol
C07AB09 Esmolol
C07AB10 Epanolol

C07AB11 S-atenolol
C07AB12 Nebivolol
C07AB13 Talinolol
C07AB52 Metoprolol, combinations
C07AB57 Bisoprolol, combinations
C07AG Alpha and beta blocking agents
C07AG01 Labetalol
C07AG02 Carvedilol
C07B Beta blocking agents and thiazides
C07BA Beta blocking agents, non-selective, and thiazides
C07BA02 Oxprenolol and thiazides
C07BA05 Propranolol and thiazides
C07BA06 Timolol and thiazides
C07BA07 Sotalol and thiazides
C07BA12 Nadolol and thiazides
C07BA68 Metipranolol and thiazides, combinations
C07BB Beta blocking agents, selective, and thiazides
C07BB02 Metoprolol and thiazides
C07BB03 Atenolol and thiazides
C07BB04 Acebutolol and thiazides
C07BB06 Bevantolol and thiazides
C07BB07 Bisoprolol and thiazides
C07BB12 Nebivolol and thiazides
C07BB52 Metoprolol and thiazides, combinations
C07BG Alpha and beta blocking agents and thiazides
C07BG01 Labetalol and thiazides
C07C Beta blocking agents and other diuretics
C07CA Beta blocking agents, non-selective, and other diuretics
C07CA02 Oxprenolol and other diuretics
C07CA03 Pindolol and other diuretics
C07CA17 Bopindolol and other diuretics
C07CA23 Penbutolol and other diuretics
C07CB Beta blocking agents, selective, and other diuretics
C07CB02 Metoprolol and other diuretics
C07CB03 Atenolol and other diuretics
C07CB53 Atenolol and other diuretics, combinations
C07CG Alpha and beta blocking agents and other diuretics
C07CG01 Labetalol and other diuretics
C07D Beta blocking agents, thiazides and other diuretics
C07DA Beta blocking agents, non-selective, thiazides and other diuretics

C07DA06 Timolol, thiazides and other diuretics
C07DB Beta blocking agents, selective, thiazides and other diuretics
C07DB01 Atenolol, thiazides and other diuretics
C07E Beta blocking agents and vasodilators
C07EA Beta blocking agents, non-selective, and vasodilators
C07EB Beta blocking agents, selective, and vasodilators
C07F Beta blocking agents and other antihypertensives
C07FA Beta blocking agents, non-selective, and other antihypertensives
C07FA05 Propranolol and other antihypertensives
C07FB Beta blocking agents, selective, and other antihypertensives
C07FB02 Metoprolol and other antihypertensives
C07FB03 Atenolol and other antihypertensives
C07FB07 Bisoprolol and other antihypertensives
C08C Selective calcium channel blockers with mainly vascular effects
C08CA Dihydropyridine derivatives
C08CA01 Amlodipine
C08CA02 Felodipine
C08CA03 Isradipine
C08CA04 Nicardipine
C08CA05 Nifedipine
C08CA06 Nimodipine
C08CA07 Nisoldipine
C08CA08 Nitrendipine
C08CA09 Lacidipine
C08CA10 Nilvadipine
C08CA11 Manidipine
C08CA12 Barnidipine
C08CA13 Lercanidipine
C08CA14 Cilnidipine
C08CA15 Benidipine
C08CA16 Clevidipine
C08CA55 Nifedipine, combinations
C08CX Other selective calcium channel blockers with mainly vascular effects
C08CX01 Mibefradil
C08D Selective calcium channel blockers with direct cardiac effects
C08DA Phenylalkylamine derivatives
C08DA01 Verapamil
C08DA02 Gallopamil
C08DA51 Verapamil, combinations
C08DB Benzothiazepine derivatives

C08DB01 Diltiazem
C08E Non-selective calcium channel blockers
C08EA Phenylalkylamine derivatives
C08EA01 Fendiline
C08EA02 Bepridil
C08EX Other non-selective calcium channel blockers
C08EX01 Lidoflazine
C08EX02 Perhexiline
C08G Calcium channel blockers and diuretics
C08GA Calcium channel blockers and diuretics
C08GA01 Nifedipine and diuretics
C09A ACE inhibitors, plain
C09AA ACE inhibitors, plain
C09AA01 Captopril
C09AA02 Enalapril
C09AA03 Lisinopril
C09AA04 Perindopril
C09AA05 Ramipril
C09AA06 Quinapril
C09AA07 Benazepril
C09AA08 Cilazapril
C09AA09 Fosinopril
C09AA10 Trandolapril
C09AA11 Spirapril
C09AA12 Delapril
C09AA13 Moexipril
C09AA14 Temocapril
C09AA15 Zofenopril
C09AA16 Imidapril
C09B ACE inhibitors, combinations
C09BA ACE inhibitors and diuretics
C09BA01 Captopril and diuretics
C09BA02 Enalapril and diuretics
C09BA03 Lisinopril and diuretics
C09BA04 Perindopril and diuretics
C09BA05 Ramipril and diuretics
C09BA06 Quinapril and diuretics
C09BA07 Benazepril and diuretics
C09BA08 Cilazapril and diuretics
C09BA09 Fosinopril and diuretics

C09BA12 Delapril and diuretics
C09BA13 Moexipril and diuretics
C09BA15 Zofenopril and diuretics
C09BB ACE inhibitors and calcium channel blockers
C09BB02 Enalapril and lercanidipine
C09BB03 Lisinopril and amlodipine
C09BB04 Perindopril and amlodipine
C09BB05 Ramipril and felodipine
C09BB06 Enalapril and nitrendipine
C09BB07 Ramipril and amlodipine
C09BB10 Trandolapril and verapamil
C09BB12 Delapril and manidipine
C09C Angiotensin II antagonists, plain
C09CA Angiotensin II antagonists, plain
C09CA01 Losartan
C09CA02 Eprosartan
C09CA03 Valsartan
C09CA04 Irbesartan
C09CA05 Tasosartan
C09CA06 Candesartan
C09CA07 Telmisartan
C09CA08 Olmesartan medoxomil
C09CA09 Azilsartan medoxomil
C09D Angiotensin II antagonists, combinations
C09DA Angiotensin II antagonists and diuretics
C09DA01 Losartan and diuretics
C09DA02 Eprosartan and diuretics
C09DA03 Valsartan and diuretics
C09DA04 Irbesartan and diuretics
C09DA06 Candesartan and diuretics
C09DA07 Telmisartan and diuretics
C09DA08 Olmesartan medoxomil and diuretics
C09DB Angiotensin II antagonists and calcium channel blockers
C09DB01 Valsartan and amlodipine
C09DB02 Olmesartan medoxomil and amlodipine
C09DB04 Telmisartan and amlodipine
C09DB05 Irbesartan and amlodipine
C09DB06 Losartan and amlodipine
C09DX Angiotensin II antagonists, other combinations
C09DX01 Valsartan, amlodipine and hydrochlorothiazide

C09DX02 Valsartan and aliskiren
C09DX03 Olmesartan medoxomil, amlodipine and hydrochlorothiazide
C09X Other agents acting on the renin-angiotensin system
C09XA Renin-inhibitors
C09XA01 Remikiren
C09XA02 Aliskiren
C09XA52 Aliskiren and hydrochlorothiazide
C09XA53 Aliskiren and amlodipine
C09XA54 Aliskiren, amlodipine and hydrochlorothiazide

Anti-diabetic drugs **(A10)**
A10A Insulins and analogues
A10AB Insulins and analogues for injection, fast-acting
A10AB01 Insulin (human)
A10AB02 Insulin (beef)
A10AB03 Insulin (pork)
A10AB04 Insulin lispro
A10AB05 Insulin aspart
A10AB06 Insulin glulisine
A10AB30 Combinations
A10AC Insulins and analogues for injection, intermediate-acting
A10AC01 Insulin (human)
A10AC02 Insulin (beef)
A10AC03 Insulin (pork)
A10AC04 Insulin lispro
A10AC30 Combinations
A10AD Insulins and analogues for injection, intermediate-acting combined with fast-acting
A10AD01 Insulin (human)
A10AD02 Insulin (beef)
A10AD03 Insulin (pork)
A10AD04 Insulin lispro
A10AD05 Insulin aspart
A10AD30 Combinations
A10AE Insulins and analogues for injection, long-acting
A10AE01 Insulin (human)
A10AE02 Insulin (beef)
A10AE03 Insulin (pork)
A10AE04 Insulin glargine
A10AE05 Insulin detemir
A10AE30 Combinations

A10AF Insulins and analogues for inhalation
A10AF01 Insulin (human)
A10B Blood glucose lowering drugs, excluding insulins
A10BA Biguanides
A10BA01 Phenformin
A10BA02 Metformin
A10BA03 Buformin
A10BB Sulfonamides, urea derivatives
A10BB01 Glibenclamide
A10BB02 Chlorpropamide
A10BB03 Tolbutamide
A10BB04 Glibornuride
A10BB05 Tolazamide
A10BB06 Carbutamide
A10BB07 Glipizide
A10BB08 Gliquidone
A10BB09 Gliclazide
A10BB10 Metahexamide
A10BB11 Glisoxepide
A10BB12 Glimepiride
A10BB31 Acetohexamide
A10BC Sulfonamides (heterocyclic)
A10BC01 Glymidine
A10BD Combinations of oral blood glucose lowering drugs
A10BD01 Phenformin and sulfonamides
A10BD02 Metformin and sulfonamides
A10BD03 Metformin and rosiglitazone
A10BD04 Glimepiride and rosiglitazone
A10BD05 Metformin and pioglitazone
A10BD06 Glimepiride and pioglitazone
A10BD07 Metformin and sitagliptin
A10BD08 Metformin and vildagliptin
A10BD09 Pioglitazone and alogliptin
A10BD10 Metformin and saxagliptin
A10BD11 Metformin and linagliptin
A10BF Alpha glucosidase inhibitors
A10BF01 Acarbose
A10BF02 Miglitol
A10BF03 Voglibose
A10BG Thiazolidinediones

A10BG01 Troglitazone
A10BG02 Rosiglitazone
A10BG03 Pioglitazone
A10BH Dipeptidyl peptidase 4 (DPP-4) inhibitors
A10BH01 Sitagliptin
A10BH02 Vildagliptin
A10BH03 Saxagliptin
A10BH04 Alogliptin
A10BH05 Linagliptin
A10BX Other blood glucose lowering drugs, excluding insulins
A10BX01 Guar gum
A10BX02 Repaglinide
A10BX03 Nateglinide
A10BX04 Exenatide
A10BX05 Pramlintide
A10BX06 Benfluorex
A10BX07 Liraglutide
A10BX08 Mitiglinide
A10BX09 Dapagliflozin
A10X Other drugs used in diabetes
A10XA Aldose reductase inhibitors
A10XA01 Tolrestat

- Antibiotics (if given for the treatment of lower respiratory tract infections = acute bronchitis, pneumonia) (J01)

J01AA Tetracyclines (J01A)
J01AA01 Demeclocycline
J01AA02 Doxycycline
J01AA03 Chlortetracycline
J01AA04 Lymecycline
J01AA05 Metacycline
J01AA06 Oxytetracycline
J01AA07 Tetracycline
J01AA08 Minocycline
J01AA09 Rolitetracycline
J01AA10 Penimepicycline
J01AA11 Clomocycline
J01AA12 Tigecycline
J01AA20 Combinations of tetracyclines
J01AA53 Chlortetracycline, combinations
J01AA56 Oxytetracycline, combinations

J01B Amphenicols (J01B)
J01BA
J01BA01 Chloramphenicol
J01BA02 Thiamphenicol
J01BA52 Thiamphenicol, combinations
J01BA90 Florfenicol
J01BA99 Amphenicols, combinations

J01C Beta-lactam antibacterials, penicillins (J01C)
J01CA Penicillins with extended spectrum
J01CA01 Ampicillin
J01CA02 Pivampicillin
J01CA03 Carbenicillin
J01CA04 Amoxicillin
J01CA05 Carindacillin
J01CA06 Bacampicillin
J01CA07 Epicillin
J01CA08 Pivmecillinam
J01CA09 Azlocillin
J01CA10 Mezlocillin
J01CA11 Mecillinam
J01CA12 Piperacillin
J01CA13 Ticarcillin
J01CA14 Metampicillin
J01CA15 Talampicillin
J01CA16 Sulbenicillin
J01CA17 Temocillin
J01CA18 Hetacillin
J01CA19 Aspoxicillin
J01CA20 Combinations
J01CA51 Ampicillin, combinations
J01CE Beta-lactamase-sensitive penicillin
J01CE01 Benzylpenicillin
J01CE02 Phenoxymethylpenicillin
J01CE03 Propicillin
J01CE04 Azidocillin
J01CE05 Pheneticillin
J01CE06 Penamecillin
J01CE07 Clometocillin

J01CE08 Benzathine benzylpenicillin
J01CE09 Procaine benzylpenicillin
J01CE10 Benzathine phenoxymethylpenicillin
J01CE30 Combinations
J01CE90 Penethamate hydroiodide
J01CE91 Benethamine penicillin
J01CF Beta-lactamase-resistant penicillins
J01CF01 Dicloxacillin
J01CF02 Cloxacillin
J01CF03 Methicillin
J01CF04 Oxacillin
J01CF05 Flucloxacillin
J01CF06 Nafcillin
J01CG Beta-lactamase inhibitors
J01CG01 Sulbactam
J01CG02 Tazobactam
J01CR Combinations of penicillins, including beta-lactamase inhibitors
J01CR01 Ampicillin and enzyme inhibitor
J01CR02 Amoxicillin and enzyme inhibitor
J01CR03 Ticarcillin and enzyme inhibitor
J01CR04 Sultamicillin
J01CR05 Piperacillin and enzyme inhibitor
J01CR50 Combinations of penicillins

J01D Other beta-lactam antibacterials (J01D)
J01DB First-generation cephalosporins
J01DB01 Cefalexin
J01DB02 Cefaloridine
J01DB03 Cefalotin
J01DB04 Cefazolin
J01DB05 Cefadroxil
J01DB06 Cefazedone
J01DB07 Cefatrizine
J01DB08 Cefapirin
J01DB09 Cefradine
J01DB10 Cefacetrile
J01DB11 Cefroxadine
J01DB12 Ceftezole
J01DC Second-generation cephalosporins
J01DC01 Cefoxitin

J01DC02 Cefuroxime
J01DC03 Cefamandole
J01DC04 Cefaclor
J01DC05 Cefotetan
J01DC06 Cefonicide
J01DC07 Cefotiam
J01DC08 Loracarbef
J01DC09 Cefmetazole
J01DC10 Cefprozil
J01DC11 Ceforanide
J01DC12 Cefminox
J01DC13 Cefbuperazone
J01DC14 Flomoxef
J01DD Third-generation cephalosporins
J01DD01 Cefotaxime
J01DD02 Ceftazidime
J01DD03 Cefsulodin
J01DD04 Ceftriaxone
J01DD05 Cefmenoxime
J01DD06 Latamoxef
J01DD07 Ceftizoxime
J01DD08 Cefixime
J01DD09 Cefodizime
J01DD10 Cefetamet
J01DD11 Cefpiramide
J01DD12 Cefoperazone
J01DD13 Cefpodoxime
J01DD14 Ceftibuten
J01DD15 Cefdinir
J01DD16 Cefditoren
J01DD17 Cefcapene
J01DD54 Ceftriaxone, combinations
J01DD62 Cefoperazone, combinations
J01DD90 Ceftiofur
J01DD91 Cefovecin
J01DE Fourth-generation cephalosporins
J01DE01 Cefepime
J01DE02 Cefpirome
J01DE03 Cefozopran
J01DE90 Cefquinome

J01DF Monobactams
J01DF01 Aztreonam
J01DF02 Carumonam
J01DH Carbapenems
J01DH02 Meropenem
J01DH03 Ertapenem
J01DH04 Doripenem
J01DH05 Biapenem
J01DH51 Imipenem and enzyme inhibitor
J01DH55 Panipenem and betamipron
J01DI Other cephalosporins and penems
J01DI01 Ceftobiprole medocaril
J01DI02 Ceftaroline fosamil
J01DI03 Faropenem

J01E Sulfonamides and trimethoprim (J01E)
J01EA Trimethoprim and derivatives
J01EA01 Trimethoprim
J01EA02 Brodimoprim
J01EA03 Iclaprim
J01EB Short-acting sulfonamides
J01EB01 Sulfaisodimidine
J01EB02 Sulfamethizole
J01EB03 Sulfadimidine
J01EB04 Sulfapyridine
J01EB05 Sulfafurazole
J01EB06 Sulfanilamide
J01EB07 Sulfathiazole
J01EB08 Sulfathiourea
J01EB20 Combinations
J01EC Intermediate-acting sulfonamides
J01EC01 Sulfamethoxazole
J01EC02 Sulfadiazine
J01EC03 Sulfamoxole
J01EC20 Combinations
J01ED Long-acting sulfonamides
J01ED01 Sulfadimethoxine
J01ED02 Sulfalene
J01ED03 Sulfametomidine
J01ED04 Sulfametoxydiazine

J01ED05 Sulfamethoxypyridazine
J01ED06 Sulfaperin
J01ED07 Sulfamerazine
J01ED08 Sulfaphenazole
J01ED09 Sulfamazon
J01ED20 Combinations
J01EE Combinations of sulfonamides and trimethoprim, including derivatives
J01EE01 Sulfamethoxazole and trimethoprim
J01EE02 Sulfadiazine and trimethoprim
J01EE03 Sulfametrole and trimethoprim
J01EE04 Sulfamoxole and trimethoprim
J01EE05 Sulfadimidine and trimethoprim
J01EE06 Sulfadiazine and tetroxoprim
J01EE07 Sulfamerazine and trimethoprim
J01EQ Sulfonamides
J01EQ01 Sulfapyrazole
J01EQ02 Sulfamethizole
J01EQ03 Sulfadimidine
J01EQ04 Sulfapyridine
J01EQ05 Sulfafurazole
J01EQ06 Sulfanilamide
J01EQ07 Sulfathiazole
J01EQ08 Sulfaphenazole
J01EQ09 Sulfadimethoxine
J01EQ10 Sulfadiazine
J01EQ11 Sulfamethoxazole
J01EQ12 Sulfachlorpyridazine
J01EQ13 Sulfadoxine
J01EQ14 Sulfatroxazol
J01EQ15 Sulfamethoxypyridazine
J01EQ16 Sulfazuinoxaline
J01EQ17 Sulfamerazine
J01EQ18 Sulfamonomethoxine
J01EQ19 Sulfalene
J01EQ21 Sulfacetamide
J01EQ30 Combinations of sulfonamides
J01EQ59 Sulfadimethoxine, combinations
J01EW Combinations of sulfonamides and trimethoprim, including derivatives
J01EW03 Sulfadimidine and trimethoprim
J01EW09 Sulfadimethoxine and trimethoprim

J01EW10 Sulfadiazine and trimethoprim
J01EW11 Sulfamethoxazole and trimethoprime
J01EW12 Sulfachlorpyridazine and trimethoprim
J01EW13 Sulfadoxine and trimethoprim
J01EW14 Sulfatroxazol and trimethoprim
J01EW15 Sulfamethoxypyridazine and trimethoprim
J01EW16 Sulfaquinoxaline and trimethoprim
J01EW17 Sulfamonomethoxine and trimethoprim
J01EW18 Sulfamerazine and trimethoprim
J01EW30 Combinations of sulfonamides and trimethoprim

J01F Macrolides, lincosamides and streptogramins (J01F)
J01FA Macrolides
J01FA01 Erythromycin
J01FA02 Spiramycin
J01FA03 Midecamycin
J01FA05 Oleandomycin
J01FA06 Roxithromycin
J01FA07 Josamycin
J01FA08 Troleandomycin
J01FA09 Clarithromycin
J01FA10 Azithromycin
J01FA11 Miocamycin
J01FA12 Rokitamycin
J01FA13 Dirithromycin
J01FA14 Flurithromycin
J01FA15 Telithromycin
J01FA90 Tylosin
J01FA91 Tilmicosin
J01FA92 Tylvalosin
J01FA93 Kitasamycin
J01FA94 Tulathromycin
J01FA95 Gamithromycin
J01FA96 Tildipirosin
J01FF Lincosamides
J01FF01 Clindamycin
J01FF02 Lincomycin
J01FF52 Lincomycin, combinations
J01FG Streptogramins
J01FG01 Pristinamycin

J01FG02 Quinupristin/dalfopristin
J01FG90 Virginiamycin

J01G Aminoglycoside antibacterials (J01G)
J01GA Streptomycins
J01GA01 Streptomycin
J01GA02 Streptoduocin
J01GA90 Dihydrostreptomycin
J01GB Other aminoglycosides
J01GB01 Tobramycin
J01GB03 Gentamicin
J01GB04 Kanamycin
J01GB05 Neomycin
J01GB06 Amikacin
J01GB07 Netilmicin
J01GB08 Sisomicin
J01GB09 Dibekacin
J01GB10 Ribostamycin
J01GB11 Isepamicin
J01GB12 Arbekacin
J01GB13 Bekanamycin
J01GB90 Apramycin
J01GB91 Framycetin

J01M Quinolone antibacterials (J01M)
J01MA Fluoroquinolones
J01MA01 Ofloxacin
J01MA02 Ciprofloxacin
J01MA03 Pefloxacin
J01MA04 Enoxacin
J01MA05 Temafloxacin
J01MA06 Norfloxacin
J01MA07 Lomefloxacin
J01MA08 Fleroxacin
J01MA09 Sparfloxacin
J01MA10 Rufloxacin
J01MA11 Grepafloxacin
J01MA12 Levofloxacin
J01MA13 Trovafloxacin
J01MA14 Moxifloxacin

J01MA15 Gemifloxacin
J01MA16 Gatifloxacin
J01MA17 Prulifloxacin
J01MA18 Pazufloxacin
J01MA19 Garenoxacin
J01MA21 Sitafloxacin
J01MA90 Enrofloxacin
J01MA92 Danofloxacin
J01MA93 Marbofloxacin
J01MA94 Difloxacin
J01MA95 Orbifloxacin
J01MA96 Ibafloxacin
J01MA97 Pradofloxacin
J01MB Other quinolones
J01MB01 Rosoxacin
J01MB02 Nalidixic acid
J01MB03 Piromidic acid
J01MB04 Pipemidic acid
J01MB05 Oxolinic acid
J01MB06 Cinoxacin
J01MB07 Flumequine
J01MQ Quinoxalines
J01MQ01 Olaquindox

J01R Combinations of antibacterials (J01R)
J01RA Combinations of antibacterials
J01RA01 Penicillins, combinations with other antibacterials
J01RA02 Sulfonamides, combinations with other antibacterials (excluding trimethoprim)
J01RA03 Cefuroxime, combinations with other antibacterials
J01RA04 Spiramycin, combinations with other antibacterials
J01RA90 Tetracyclines, combinations with other antibacterials
J01RA91 Macrolides, combinations with other antibacterials
J01RA92 Amphenicols, combinations with other antibacterials
J01RA94 Lincosamides, combinations with other antibacterials
J01RA95 Polymyxins, combinations with other antibacterials
J01RA96 Quinolones, combinations with other antibacterials
J01RA97 Aminoglycosides, combinations with other antibacterials
J01RV Combinations of antibacterials and other substances
J01RV01 Antibacterials and corticosteroids

J01X Other antibacterials (J01X)
J01XA Glycopeptide antibacterials
J01XA01 Vancomycin
J01XA02 Teicoplanin
J01XA03 Telavancin
J01XA04 Dalbavancin
J01XA05 Oritavancin
J01XB Polymyxins
J01XB01 Colistin
J01XB02 Polymyxin B
J01XC Steroid antibacterials
J01XC01 Fusidic acid
J01XD Imidazole derivatives
J01XD01 Metronidazole
J01XD02 Tinidazole
J01XD03 Ornidazole
J01XE Nitrofuran derivatives
J01XE01 Nitrofurantoin
J01XE02 Nifurtoinol
QJ01XE90 Furazolidine
QJ01XQ Pleuromutilins
QJ01XQ01 Tiamulin
QJ01XQ02 Valnemulin
J01XX Other antibacterials
J01XX01 Fosfomycin
J01XX02 Xibornol
J01XX03 Clofoctol
J01XX04 Spectinomycin
J01XX05 Methenamine
J01XX06 Mandelic acid
J01XX07 Nitroxoline
J01XX08 Linezolid
J01XX09 Daptomycin
J01XX10 Bacitracin
QJ01XX55 Methenamine, combinations
QJ01XX93 Furaltadone
QJ01XX95 Novobiocin

Annex 2.6 – Comorbidity definition

History of any of the endpoints of interest will also be considered as comorbidity. These events are described in Annex 2.2 In addition, the following diseases will also be captured under comorbidity:

Definition of asthma

According to the GINA (Global Initiative for Asthma) guidelines, asthma is a disorder defined by its clinical, physiological and pathological characteristics. The predominant feature of the clinical history is episodic shortness of breath, particularly at night often accompanied by cough (Bateman et al 2008).

The following concepts of disease have been mapped through the UMLS for the outcomes of asthma.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Asthma	J45*	493.*	H33..	R96
Asthma, unspecified	J45.9	493.90	H33z	
Nonallergic asthma	J45.1	493.1	H331z	
Intrinsic asthma			H331z	
Mixed asthma	J45.8		H332.	
Atopic asthma	J45			
extrinsic allergic asthma	J45	493.0	H330z	
Predominantly allergic asthma	J45.0			
Confirmed asthma			1O2..00	
Extrinsic asthma with asthma attack		493.02	663d.00	
			663m.00	
Intrinsic asthma + attack		493.12		
Number of asthma exacerbations in past year			663y.00	
Emergency admission, asthma			8H2P.00	
Status asthmaticus	J46	493.91		
Extrinsic asthma with status asthmaticus		493.01		
Intrinsic asthma NOS		493.10		
Intrinsic asthma with status asthmaticus		493.11		
chronic obstructive asthma		493.2		
Other forms of asthma		493.8		
Mild asthma			663V100	
Moderate asthma			663V200	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Severe asthma			663V300	
History of asthma			14B4.00	
Asthma quality indicators			9hA..00	
			9hA1.00	
			9hA2.00	

Definition of arterial hypertension

According to the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) Guidelines for the Management of Arterial Hypertension, a patient is defined as having hypertension when the systolic blood pressure is above 140 mm Hg and the diastolic blood pressure is above 90 mm Hg (Anon. 2007).

	Blood pressure (mmHg)				
Other risk factors, OD or Disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥ 180 or DBP ≥ 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors, MS, OD or Diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for arterial hypertension.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Hypertensive diseases	I10-I15.9	401-405.99	Gyu2.	
high blood pressure	I10			
Uncomplicated hypertension			G211.00	K86
Hypertension with involvement target organs				K87
Renovascular hypertension	I15.0			
Secondary hypertension	I15	405	G24..	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Secondary hypertension, unspecified	I15.9		G24z.	
Malignant essential hypertension		401.0	G200.	
Essential (primary) hypertension	I10	401		
Hypertension NOS		401.9		
Benign hypertension		401.1	G201.	
Other secondary hypertension	I15.8	405.99	Gyu20	
Malignant secondary hypertension		405.0	G240.	
		405.09	G240z	
Benign secondary hypertension		405.1	G241	
		405.19	G241z	
Malignant hypertension			G210	
			G200.00	

Definition of hyperlipidemia/dyslipidemia

Dyslipidemia is defined as an elevation of plasma cholesterol, triglycerides (TGs), or both, or a low high-density lipoprotein level that contributes to the development of atherosclerosis. Causes may be primary (genetic) or secondary. Diagnosis is by measuring plasma levels of total cholesterol, TGs, and individual lipoproteins.

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for hyperlipidemia.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Mixed hyperlipidaemia	E78.2	272.2		T93.03
Fam hyperlipoproteinaemia IIb Familial combined hyperlipidaemia Hyperapobetalipoproteinaemia				T93.04
Other hyperlipidemia	E78.4	272.4	Cyu8D	
hypercholesterolemia	E78.0	272.0	C32. (and subsequent codes)	T93.01
Abnormal lipids			44O4.00 44O6.00 44P3.00 44P4.00 44Q3.00	
Lipid disorder			66X (and	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			subsequent codes)	
Lipid lowering therapy			8B28.00 8BG2.00 8BL1.00 8CR3.00	
Other lipid storage disorders			Cyu8900	
[X]Other disorders of lipoprotein metabolism			Cyu8E00	

Definition of chronic kidney disease

Chronic kidney disease is defined as either kidney damage or glomerular filtration rate <60 mL/min/1.73 m2 for at least 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies (Levey and Coresh 2012).

The different stages of chronic kidney disease are described in the table below:

Stage	**Description**	**GFR (mL/min/1.73 m^2)**
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	< 15 or dialysis

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of chronic kidney disease.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic kidney disease	N18	585.9	1Z1..	U99
	N18.9	583*	K05..13	
		585*		
		586*		
Hypertensive chronic kidney disease	I12	403		
Chronic kidney disease, Stage I		585.1	1Z10.00	
			1Z17.00	
			1Z18.00	
			1Z18.11	
			K051.00	
End stage renal disease		585.6	K050.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			K0D..00	
Chronic kidney disease, Stage 5		585.5	1Z14.00	
			1Z1K.00	
			1Z1K.11	
			1Z1L.00	
			1Z1L.11	
			K055.00	
Hypertensive chronic kidney disease, malignant		403.0		
Hypertensive heart and chronic kidney disease	I13	404		
Chronic kidney disease, stage 2 (mild)	N18.2	585.2	1Z11.00	
			1Z19.00	
			1Z19.11	
			1Z1A.00	
			1Z1A.11	
			K052.00	
Chronic kidney disease, stage 3 (moderate)	N18.3	585.3	1Z12.00	
			1Z15.00	
			1Z16.00	
			1Z1B.00	
			1Z1B.11	
			1Z1C.00	
			1Z1C.11	
			1Z1D.00	
			1Z1D.11	
			1Z1E.00	
			1Z1E.11	
			1Z1F.00	
			1Z1F.11	
			1Z1G.00	
			1Z1G.11	
			K053.00	
Chronic kidney disease, stage 4 (severe)	N18.4	585.4	1Z13.00	
			1Z1H.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			1Z1H.11	
			1Z1J.00	
			1Z1J.11	
			K054.00	
Hypertensive heart and chronic kidney disease, malignant		404.0		
		403.xx, 404.xx		
Renal failure	N17-N19.9	586	D215.00	
			D215000	
			K05..00	
			K05..12	
			K050.00	
			K06..00	
			K06..12	
Other chronic renal failure	N18.8		Kyu21	
Chronic kidney diseases monitoring/self-management			661M200	
			661N200	
			66i..00	
			6AA..00	
			9Ni9.00	
			9Ot..00	
			9Ot0.00	
			9Ot1.00	
			9Ot2.00	
			9Ot3.00	
			9Ot4.00	
Dialysis		V45.1	7L1..	
		V56.0	SP06B00	
		V56.8	Z1A..	
			Z91A.00	
			Z91A100	
			ZV45100	
			ZV56..	
			ZVu3G00	
CKD quality indicators			9hE..00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			9hE0.00	
			9hE1.00	
Predicted stage chronic kidney			9Ot5.00	
Renal impairment			K060.00	
Impaired renal function			K060.11	
Acute-on-chronic renal failure			K0E..00	
Kidney transplantation		V42.0, 996.81	SP08300	
		250.4x	SP08C00	
			SP08D00	
			SP08E00	
			SP08F00	
			SP08G00	
			SP08H00	

If available, kidney function will be derived from the lab results (calculation of glomerular filtration rate = creatinine clearance) using the following formula:

$$GFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1 (Levey et al 2009).

Based on the actual value of the GFR, it will be possible to describe the stage of chronic kidney disease. In addition, code specific terms by stage (see above) will be used.

Definition of hepatic impairment

Hepatic function decreases with age, but due to the high capacity of the liver this is considered not to change the pharmacokinetics to a clinically relevant extent. Liver disease, however, is known to be a common cause of altered pharmacokinetics of drugs. Hepatic function can be decreased through different pathophysiological mechanisms. Worldwide, chronic infections with hepatitis B or C are the most common causes of chronic liver disease, whereas in the western world, chronic and excessive alcohol ingestion is one of the major causes of liver disease. Other causes are uncommon diseases such as primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune chronic active hepatitis. Ongoing destruction of the liver parenchyma in chronic liver diseases ultimately leads to liver cirrhosis and the development of portal hypertension. However, even if liver cirrhosis is established, the residual metabolic function of the liver may be rather well preserved for many years because

of regeneration of hepatocytes. Clinical symptoms related to hepato-cellular failure and portal hypertensions are most importantly ascites, oesophageal varices and encephalopathy. Serum markers of liver failure are low serum albumin and a prothrombin deficiency. Serum bilirubin as well as other liver tests may or may not be affected to a varying degree, e.g. depending on the liver disease (cholestatic versus hepatocellular). Liver cirrhosis is irreversible in nature, but progression can be modified by e.g. abstinence of alcohol in alcohol liver cirrhosis (European Medicines Agency 2005).

Terms	ICD10	ICD9CM	Read Codes	ICPC
Liver enzymes abnormal	R94.5	794.8	44G2.	
	R74		R148.	
			44D2.	
			44G3100	
			44G4100	
			44H5100	
			44H5200	
			R148.00	
Hepatic failure, unspecified	K72.9			
Liver failure			7L1f.00	
			7L1fy00	
			7L1fz00	
			J625.00	
			J625.11	
			J62y.11	
			J62y.12	
			J62y.13	
Cirrhosis; liver	K74.60	571.5	J615..	D97
Hepatic failure, unspecified				
Nonspecific elevation of levels of transaminase or LDH		790.4		
Inflammatory liver disease, unspecified	K75.9			
Hepatitis NOS		573.3	J633.	
Hepatitis unspecified				
Unspecified viral hepatitis	B19	070	A70z.	D72
Viral hepatitis	B19.9		A70..	
			A72x000	
			A785200	
			AyuB..	
			J63..	
Chronic hepatitis, unspecified	K73.9	571.4	J614..	
			J614y	
Alcoholic cirrhosis or fibrosis	K70.2			
	K70.3			
	K70.4			
Primary or secondary biliary cirrhosis	K74.3			
	K74.4			
	K74.5			

Terms	ICD10	ICD9CM	Read Codes	ICPC
History of hepatitis			141E.00	
			141F.00	
			2126700	
H/O: liver disease			14C5.00	
Hepatitis A - current infection			2J23.00	
Chronic hepatitis			9kR..00	
			9kR..11	
Hepatitis screening positive			9kV..00	
			9kV..11	
			9kZ..00	
			9kZ..11	
Sequelae of viral hepatitis			AE23.00	
			AyuJ900	
Acute liver failure			J600011	
Acute hepatitis - noninfective			J600100	
Necrosis of liver			J600z00	
			J601.00	
Cirrhosis and chronic liver disease			J61..	
Other sequelae of chronic liver			J62y.00	
[X]Diseases of the liver			Jyu7..	
Liver transplant failure and rejection			SP08600	
Liver failure as a complication of care			SP14211	

Definition of lung cancer

The definition of lung cancer is a cancer (malignancy) that originates in the tissues of the lungs or the cells lining the airways. Lung cancer originates when normal lung cells become abnormal, usually after a series of mutations, and begin to divide out of control.

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for lung cancer.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Lung cancer Malignant neoplasm of bronchus and lung	C34.9	162 162.9	B22.. Byu20	R84
Secondary malignant neoplasm of lung	C78.0	197.0	B570	
Malignant neoplasm of hilus of lung			B2211	
Malignant neoplasm of upper lobe of lung			B2221	
Malignant neoplasm of middle lobe of lung			B2231	
Malignant neoplasm of lower lobe of lung			B2241	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Malignant neoplasm of upper lobe, bronchus or lung	C34.1	162.3	B222z	
Malignant neoplasm of middle lobe, bronchus or lung	C34.2	162.4	B223. B223z	
Malignant neoplasm of lower lobe, bronchus or lung	C34.3	162.5	B224. B224z	
Malignant neoplasm of other parts of bronchus or lung		162.8	B22y.	
Malignant neoplasm overlapping bronchus and lung sites	C34.8		B225.	
Personal history of malignant neoplasm of lung			ZV101	

Definition of cancer

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for cancer. **For skin cancer, basocellular epithelioma and spinocellular epithelioma are excluded**

Terms	ICD10	ICD9CM	Read Codes	ICPC
Malignant neoplasm without specification of site	C80	199	ByuC8 B59..	A79
Cancer Malignant neoplasm			142..00	
Malignant neoplasm of bladder	C67	188	B49..	U76
Malignant neoplasm of breast Breast cancer Malignant tumor of breast	C50-C50.9		Byu6.	X76
Malignant neoplasm of colon Malignant tumour of colon	C18	153	B13..	D75
Malignant neoplasm of larynx	C32	161	B21..	
Carcinoma of the rectum			B14.	
Malignant neoplasm of skin	C44		Byu43 B33z.	S77
Malignant neoplasm of thyroid gland	C73	193	B53..	T71
Malignant neoplasm of cervix uteri	C53	180	B41z.	X75
Malignant neoplasm of stomach	C16	151	B11z.	D74

Terms	ICD10	ICD9CM	Read Codes	ICPC
Gastric cancer				
Malignant neoplasm of vagina	C52	184.0	B450.	
Malignant neoplasm of oropharynx	C10	146	B06..	
Malignant neoplasm of nasopharynx	C11	147	B07..	
Malignant neoplasm of pharynx	C14	149.0	B06.. B08.	
Malignant neoplasm of duodenum	C17	152.0	B120.	
Malignant neoplasm of caecum	C18.0	153.4	B134.	
Malignant neoplasm of peritoneum	C48.2	158.9	Byu57	
Malignant neoplasm of trachea	C33	162.0	B220.	
Malignant neoplasm of pleura	C38.4	163	B23..	
Bone cancer			B3	
Malignant neoplasm of liver	C22	155	B152.	
Malignant neoplasm of intestinal tract, part unspecified	C26.0	159.0	Byu12 B1z0.	
Malignant neoplasm of pancreas	C25	157	B17..	D76
Malignant neoplasm of vertebral column	C41.2		B302.	
Malignant neoplasm of prostate	C61	185	B46..	Y77
Malignant neoplasm of oesophagus	C15	150.9	B10..	
Malignant neoplasm of ovary	C56	183.0	B440.	
Malignant neoplasm of uterus	C55	179	B43..	
Malignant melanoma of skin	C43	172	Byu41 B32..	S77.03
Malignant neoplasm of brain	C71	191	B51z.	N74
Malignant tumor of kidney	C64	189.0	B4A	U75
Hodgkin's disease	C81	201	B61.. BBjA.	B72
Leukemia	C95	208	BBr00	B73

Glaucoma (narrow angle glaucoma and other)

Definition of narrow angle glaucoma

Narrow angle glaucoma, also called acute angle closure glaucoma or closed angle glaucoma, is a rare type of glaucoma in which symptoms usually come on suddenly. Unlike most glaucoma, people with narrow angle glaucoma usually have severe symptoms including pain, blurry vision, redness and nausea. Some people also complain of seeing halos around lights.

Narrow angle glaucoma is caused by an acute blockage of the drainage canal where fluid normally flows freely out of the eye. A buildup of fluid causes a sudden increase in intraocular pressure.

Narrow angle glaucoma requires a quick diagnosis and rapid treatment, as significantly decreased vision or blindness can result within hours (Casson et al 2012).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of narrow angle glaucoma.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Anatomical narrow angle borderline glaucoma		365.02	F450200	
Acute angle-closure glaucoma	H40.21	365.22	F452	F93.02
Primary angle-closure glaucoma	H40.2		F452.00	
Closed angle glaucoma			F452.11	
Primary angle-closure glaucoma			F452..	
Glaucoma due to chamber angle anomaly			F454000	

Definitions of other glaucoma

Open-angle glaucoma, the most common form of glaucoma, accounting for at least 90% of all glaucoma cases: It is caused by the slow clogging of the drainage canals, resulting in increased eye pressure. In contrast to narrow angle glaucoma, it has as wide and open angle between the iris and cornea. Open angle glaucoma develops slowly and is a lifelong condition and often has symptoms and eye damage that are not immediately noticed.

In normal tension glaucoma, the optic nerve is damaged even though the eye pressure is not very high.

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of glaucoma.

Terms	ICD10	ICD9CM	Read Codes	ICPC
glaucoma	H40-H42.9	365	F45	F93
Glaucoma - absolute			F404211	
Glaucomatocyclitic crises			F442100	
[X]Glaucoma			FyuG.00	

Bladder obstruction/urinary retention/BPH

Definition of bladder obstruction/urinary retention *(eventtype=URINRETENTION)*

Urinary retention describes a bladder that does not empty completely or does not empty at all. Historically, urinary retention has been classified as either acute or chronic the latter is generally classified as high pressure or low pressure according to the bladder filling pressure on urodynamic [redacted].

Bladder outlet obstruction (BOO) is a blockage at the base of the bladder that reduces or prevents the flow of urine into the urethra, the tube that carries urine out of the body.Bladder outlet obstruction (BOO) can have many different causes, including benign prostatic hyperplasia (BPH), bladder stones, bladder tumors (cancer), pelvic tumors (cervix, prostate, uterus, rectum) and urethral stricture (scar tissue)

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of urinary retention.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Urinary Retention	R33	788.2 788.20	R082..	U05.02
Cannot pass urine - retention			1A32.00	
Acute retention of urine			R0822	
Retention symptoms			1A32.11	
Micturition stream poor			1A33.00	
Hesitancy			1A34.00	
Hesitancy of micturition			1A34.11	
BOO - Bladder outflow obstruction			K160.13	
Bladder outflow obstruction			K165200	
Bladder neck obstruction	N32.0	596.0		

Definition of BPH *(eventtype=BPH)*

Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone. The enlarged gland has been proposed to contribute to the overall lower urinary tract symptoms (LUTS) complex via at least two routes: (1) direct bladder outlet obstruction (BOO) from enlarged tissue (static component) and (2) from increased smooth muscle tone and resistance within the enlarged gland (dynamic component). Voiding symptoms have often been attributed to the physical presence of BOO. Detrusor overactivity is thought to be a contributor to the storage symptoms seen in LUTS.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Benign prostatic hypertrophy/ Benign prostatic hyperplasia	N40	600.0	XE0e6 K20*	Y85
Prostatic hyperplasia			K20z. K200.	
Benign neoplasm of prostate			B7C2.00	

Diabetes mellitus

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories (discussed in greater detail below). In one category, type 1 diabetes, the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers.

In the other, much more prevalent category, type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response (American Diabetes Association 2012).

Criteria for the diagnosis of diabetes (based on lab results):

A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).

*In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for diabetes mellitus.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Diabetes mellitus	E10-E14.9	250	C10..]	T90
Unspecified diabetes mellitus	E14			
diabetes NOS	E11			
Insulin-dependent diabetes mellitus	E10			
Non-insulin-dependent diabetes mellitus	E11			
Diabetes mellitus with ketoacidosis			C101. C101z	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Diabetes with renal manifestations		250.4	C104z	
Nephrotic syndrome in diabetes mellitus			K01x1	
Diabetic foot			2G5.	
Unspecified diabetes mellitus without complications	E14.9	250.0	C100. C100z	
Secondary diabetes mellitus		249		
Diabetic polyneuropathy	G63.2	357.2 250.6	F372. F3y0.00	
Diabetes with ophthalmic manifestations		250.5	C105. C105z 2BB. F420	
Unspecified diabetes mellitus with unspecified complications	E14.8	250.9	C10z. C10zz	
Diabetic management			66A. 661N400 661M400 8CR2.00 8CS0.00 9h4..00 9h41.00 9h42.00 9h43.00 9OL	
[X]Diabetes mellitus			Cyu2.00	
[X]Other specified diabetes mellitus			Cyu2000	
[X]Malnutrit-relat diabetes mellitus with other spec comps			Cyu2100	
[X]Malnutrit-related diabetes mellitus with unspec complics			Cyu2200	
[X]Unspecified diabetes mellitus with renal complications			Cyu2300	
Diab insipidus,diab mell,optic atrophy and deafness			PKyP.00	

For those databases where information on lab results are available (THIN, HSD, SIDIAP and IPCI), a new diagnosis of diabetes mellitus will be made based on either the presence of diabetes mellitus disease codes and abnormal lab results (HbA1c, fasting plasma glucose, glucose tolerance test).

Annex 2.7 – COPD, chronic bronchitis and emphysema as indication of use of NVA237 or QVA149 + codes for COPD exacerbation as indication of use of systemic corticosteroids and antibiotics

For the DUS reports, we are interested in the indication of use of NVA237 and QVA149. As GPs often use the terms COPD, chronic bronchitis and emphysema interchangeably, we will also consider disease specific codes for chronic bronchitis and emphysema. Thus codes for indication of use related to COPD are broader than the codes used to define COPD ➔ list below shows the extra codes. For the COPD codes (for cohort definition) please see Annex 2.4.

Codes in Annex 2.4 can also be used to identify use of systemic corticosteroids or antibiotics for reason of "COPD exacerbation"

Terms	ICD10	ICD9CM	Read Codes	ICPC
COPD exacerbation	J44.0		66Yd.00	
	J44.1		66Ye.00	
			66Yf.00	
			8H2R.00	
			H3y1.00	
			H312200	
Chronic obstructive pulmonary disease disturbs sleep			66Yg.00	
Chronic obstructive pulmonary disease does not disturb sleep			66Yh.00	
Attends respiratory support group			66YH.00	
COPD self-management plan given			66YI.00	
Multiple COPD emergency hospitalisations			66Yi.00	
Chronic obstructive pulmonary disease follow-up/monitoring			66YL.00	
			66YL.11	
			66YL.12	
			66YM.00	
			66YS.00	
			66YT.00	
COPD quality indicators			9h5..00	
			9h51.00	
			9h52.00	
Chronic bronchitis		491*	H31..00	R91
Simple and mucopurulent chronic bronchitis	J41			
Unspecified chronic bronchitis	J42			
Simple chronic bronchitis			H310.00	
Simple chronic bronchitis NOS			H310z00	
Mucopurulent chronic bronchitis			H311.00	
Purulent chronic bronchitis			H311000	
Fetid chronic bronchitis			H311100	
Mucopurulent chronic bronchitis NOS			H311z00	
Obstructive chronic bronchitis			H312.00	
Chronic wheezy bronchitis			H312011	
Emphysematous bronchitis			H312100	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Mixed simple and mucopurulent chronic bronchitis			H313.00	
Other chronic bronchitis			H31y.00	
Other chronic bronchitis NOS			H31yz00	
Chronic bronchitis NOS			H31z.00	
Bronchitis, not specified as acute or chronic	J40	490		
Emphysema	J43	492*	H32..00	R95
interstitial emphysema		518.1		
Compensatory emphysema		518.2		
Chronic bullous emphysema			H320.00	
Segmental bullous emphysema			H320000	
Zonal bullous emphysema			H320100	
Giant bullous emphysema			H320200	
Bullous emphysema with collapse			H320300	
Chronic bullous emphysema NOS			H320z00	
Panlobular emphysema			H321.00	
Centrilobular emphysema			H322.00	
Other emphysema			H32y.00	
Acute vesicular emphysema			H32y000	
Atrophic (senile) emphysema			H32y100	
MacLeod's unilateral emphysema			H32y200	
Other emphysema NOS			H32yz00	
Emphysema NOS			H32z.00	

Annex 2.8 – Definition of LRTI (indication of use of antibiotics)

Definition of lower respiratory tract infection (eventname=LRTI)

Lower respiratory tract infection consists of both pneumonia and (acute) bronchitis

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for lower respiratory tract infection.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Pneumonia, (unspecified)	J18*		X100E	R81
			H2*	
Bacterial pneumonia, (unspecified)	J15.9	482.9	X100H	
			H22z.	
Atypical pneumonia	J16.8		H28.00	
Viral pneumonia	J12.9	480	XE0YG	
	J10.0	480.9	H2*.	
Acute bronchitis	J20	466	H06..	R78
Acute tracheo-bronchitis	J20.9	466.0	XE0Xr	
			H060z	
			H0605	

Annex 2.9 – Data sources

IPCI Database

In 1992 the Integrated Primary Care Information Project (IPCI) was started by the Department of Medical Informatics of the Erasmus University Medical Center. IPCI is a longitudinal observational database that contains data from computer-based patient records of a selected group of general practitioners (GPs) throughout The Netherlands, who voluntarily chose to supply data to the database. Collaborating practices are located throughout The Netherlands and the collaborating GPs are comparable to other GPs in the country according to age and gender. In the Netherlands, all citizens are registered with a GP practice, which forms the point of care and acts as a gatekeeper in a two-way exchange of information with secondary care. The medical records of each patient can therefore be assumed to contain all relevant medical information including medical findings and diagnosis from secondary care.

The database contains information on about 2.2 million patients. This is the cumulative amount of patients who have ever been part of the dynamic cohort of patients who have been registered. The International Classification of Primary Care (ICPC) is the coding system for patient complaints and diagnoses, but diagnoses and complaints can also be entered as free text. Prescription data such as product name, quantity prescribed, dosage regimens, strength and indication are entered into the computer (Vlug et al 1999). The National Database of Drugs, maintained by the Royal Dutch Association for the Advancement of Pharmacy, enables the coding of prescriptions, according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the WHO (WHO 2008).

As this is a primary care database, information on specialist prescribing, drug dispensing and actual drug intake is missing.

IPCI is listed under the ENCePP resources database. (www.encepp.eu/encepp/resourcesDatabase.jsp)

THIN Database

The Health Improvement Network (THIN) is a database of primary care medical records from the United Kingdom. General practitioners are trained to complete their medical records using the Vision general practice computer system (InPractice Systems, London, UK). This electronic record serves as the primary medical records for the practice.

Data recorded in THIN include demographics, details from general practitioners' visits such as medical diagnoses and prescriptions written by the general practitioners, diagnoses from specialist referrals and hospital admissions, some results of laboratory tests, some lifestyle characteristics and other measurements as taken in the practice. Within the database, diagnoses are recorded using READ codes. Prospective data collection for THIN began in September 2002, with electronic medical records that date back to 1985. In addition, practices may retrospectively enter significant medical events into the electronic medical record. Currently, the database has 2.7 million active patients registered. Recently a validation study was conducted by Lewis et al which concluded that "THIN data that are collected outside of

the Clinical Practice Research Datalink (CPRD) appear as valid as the data collected as part of the CPRD (Lewis et al 2007).

As the primary aim of the collection of data in the THIN database is patient management, data will reflect only those events that are deemed to be relevant to patient's care. In addition; use of THIN data is not appropriate in studies where individual ethnicity, occupation, employment, and/or socio-economic status are important variables. As for all prescription databases, OTC drug use and non-compliance to medication prescriptions might be an issue. As the average follow-up within the THIN database is 7.3 years, the THIN database is not suitable to conduct long-term follow-up studies.

THIN is listed under the ENCePP resources database. (www.encepp.eu/encepp/resourcesDatabase.jsp)

Aarhus Database

The Aarhus University Prescription Database comprises clinical and prescription data on the population of former North-Jutland, Aarhus, Rinkjebing and Viborg counties, which since 2007 are called the Central Denmark Region and the North Denmark Region. This population covers a total of 1.4 million inhabitants and is representative of the population of Denmark (Ehrenstein, Antonsen, [redacted] Data available on these subjects comprise their eligibility, dispensing data, hospitalizations and procedures and the population can also be linked to other National Danish registries. Dispensing data comprise the filled prescriptions for all ambulatory patients and contains information on name of the drug, ATC code, package identifier (strength and route of administration), and the date of refill. These data can be linked to the national registry of patients that comprises information on admissions to Danish somatic hospitals, emergency rooms and outpatient clinics, diagnosis codes and procedures are registered. These databases have been used in numerous studies and are proven valid for pharmacoepidemiological research (Sorensen and Larsen 1994).

Dose must be inferred from the strength, assuming a once daily administration for NVA237 and according the dosing regimens of the respective Summary of Product Characteristics of the other drugs. The main drawbacks of the Aarhus University Prescription Database are a lack of nationwide coverage and the absence of data of certain medication types (non-reimbursed drugs, OTC drugs or drugs dispensed directly to hospital patients or outpatient clinics).

HSD CSD Longitudinal Patient Database

The Italian arm of the study uses the Health Search CSD Longitudinal Patient Database (HSD), a longitudinal observational database that is representative of the Italian general population. It was established in 1998 by the Italian College of General Practitioners (Filippi 2005). The HSD contains data from computer-based patient records from a selected group of GPs (covering a total of 1.7 million patients) located throughout Italy. These GPs voluntarily agreed to collect data for the database and attend specified training courses. The database includes information on the age, gender, and identification of the patient, and GP registration information, which is linked to prescription information, clinical events and diagnoses,

hospital admission, and causes of death. All diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Drug names are coded according to the ATC classification system (WHO 2008). To be included in the study, GPs must have provided data for at least 1 year and meet standard quality criteria pertaining to: levels of coding, prevalence of well-known diseases, and mortality rates (Cricelli et al 2003). The HSD complies with EU, guidelines on the use of medical data for research. The HSD has been used as data source for a number of peer-reviewed publications on the prevalence of disease conditions, drug safety and prescription patterns in Italian primary care (Cazzola et al 2011). Approval for use of data is obtained from the Italian College of General Practitioners.

Dose must be inferred from the strength, assuming a once daily administration for NVA237 and according to the dosing regimens of the respective SmPC for the other drugs. Around 50% of prescription dosage is also imputed by GPs.

HSD is listed under the ENCePP resources database. (www.encepp.eu/encepp/resourcesDatabase.jsp)

SIDIAP Database

General practitioners (GPs) play an essential role in the public health care system of Spain, as they are responsible for primary health care, long-term prescriptions and specialist and hospital referrals. The Spanish public health care system covers more than 98% of the population. SIDIAP Database comprises of electronic medical records of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.6 million patients (about 80% of the total of 7.5 million population of Catalonia) from 274 primary care practices with 3,414 participating GPs. The SIDIAP data comprises the clinical and referral events registered by primary care health professionals (GPs and nurses) and administrative staff in electronic medical records, comprehensive demographic information, prescription and corresponding pharmacy invoicing data, specialist referrals, primary care laboratory test results, and hospital admissions and their major outcomes. Health professionals gather this information using ICD-10 codes, and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, blood and urine test results. Only GPs who meet quality control standards can participate in the SIDIAP database. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP Database. Recent reports have shown the SIDIAP data to be useful for epidemiological research (Garcia-Gil et al 2011).

Annex 2.10 – Statistical table set

Annex 2.11 – Additional figures