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Quantitative Safety & Epidemiology

QVA149

(Indacaterol/glycopyrronium bromide)

Non-Interventional Study Final Report
CQVA149A2402

Multinational database cohort study to assess RMP-specified safety outcomes in association with indacaterol/glycopyrronium bromide in Europe

Author

Document Status	Final (Redacted Report)
Date of final version of the study report	03-Dec-2018
EU PAS register number	EUPAS7674

NIS Report Template Version 3.0 dated 14-August-2017

Title	Multinational database cohort study to assess RMP specified safety outcomes in association with indacaterol/glycopyrronium bromide in Europe
Version identifier of the final study report	V1
Date of last version of the final study report	03-Dec-2018
EU PAS register number	EUPAS7674
Active substance	Indacaterol/Glycopyrronium bromide (QVA149) (R03AL04)
Medicinal product	Ultibro® Breezhaler® Xoterna® Breezhaler® Ulunar® Breezhaler®
Product reference	QVA149
Procedure number	EMEA/H/C/002679 EMEA/H/C/003755 EMEA/H/C/003875

Marketing authorization holder	Novartis Europharm Ltd Frimley Business Park Camberley GU16 7SR United Kingdom
Joint PASS	No
Research question and objectives	To assess the incidence rates and relative risks of various adverse events among new users of inhaled fixed-dose indacaterol/glycopyrronium bromide (QVA149) with COPD compared to new users of comparator medications
Country(-ies) of study	United Kingdom, Denmark, Italy, The Netherlands, Spain
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Marketing authorization holder

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1 Abstract

Title

Multinational database cohort study to assess Risk Management Plan (RMP)-specified safety outcomes in association with indacaterol/glycopyrronium bromide in Europe.

Keywords

Chronic obstructive pulmonary disease, glycopyrronium bromide, long-acting muscarinic antagonist, indacaterol, long-acting β_2-adrenergic agonist, safety.

Rationale and background

Indacaterol/glycopyrronium bromide (QVA149, registered as Ultibro® Breezhaler® and related products) is a once-daily, inhaled fixed-dose combination (FDC) of indacaterol maleate (QAB149, registered in EU as Onbrez® Breezhaler® and related products) and glycopyrronium bromide (NVA237, registered in EU as Seebri® Breezhaler® and related products) for the maintainance bronchodilator treatment to relieve symtoms in adult patients with chronic obstructive pulmonary disease (COPD). In the context of the QVA149 marketing authorization application in 2013, Novartis proposed to conduct a post-authorization safety study (PASS) to assess specific safety outcomes as specified in the risk management plan (RMP) in association with QVA149 exposure.

Research question and objectives

To assess the incidence rates and relative risks of selected endpoints in association with QVA149 exposure in a broader, real-world COPD population.

Study design

Multinational, multi-database observational cohort study in new users of QVA149 vs. new users of comparator medications: (1) a free combination of long-acting β_2-adrenergic agonist (LABA) and a long-acting muscarinic antagonist (LAMA) without inhaled corticosteroids (ICS) (anchor), (2) a free combination of LABA/LAMA with ICS, (3) a free combination of LABA/ICS (no LAMA), (4) a fixed combination of LABA+ICS (with or without LAMA), (5) a fixed combination of LABA+LAMA other than QVA149 (with or without ICS), (6) LABA monotherapy (no LAMA, no ICS), (7) LAMA with or without ICS (no LABA).

Setting

The study is based on data derived from five European electronic health care databases, namely from 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]).

Results from this final report are based on a 50-month data accrual period, namely from 1 November 2013 until 31 December 2017.

Subjects and study size, including dropouts

From the respective five databases, patients older than 40 years of age were selected with COPD who were enrolled in the databases during the study period and had at least one year of prior medical history. The follow-up of each patient started with the first prescription of a medication of interest (=index date) and ended at end of treatment, switch between or add-on of other study medications, end of study (date of database cut for the final analysis), disenrollment from the database or death, whichever came first. In the final analysis, sample size for the QVA149 cohort was n=9,798 patients. Final sample sizes for the comparator cohorts were as follows: (1) free combination of LAMA/LABA, no ICS n=9,619; (2) free combination of LAMA/LABA/ICS n=3,192; (3) free combination of LABA/ICS, no LAMA n=4,628; (4) fixed combination of LABA+ICS with or without LAMA n=58,332; (5) fixed combination of LABA/LAMA (excl. QVA149) with or without ICS n=9,150 patients; (6) LABA monotherapy cohort, no LAMA or ICS n=12,364; and (7) LAMA with or without ICS, no LABA n=42,972.

Variables and data sources

The primary endpoints of interest were 1) Major adverse cardiovascular events (MACE), defined as myocardial infarction (MI), stroke, and hospitalisations due to acute coronary syndrome (ACS) and/or heart failure (HF), 2) Ischemic heart disease (IHD) including MI and angina pectoris, 3) cerebrovascular events (ischemic stroke and hemorrhagic stroke and transient ischemic attack (TIA)), 4) Cardiac arrhythmias (atrial fibrillation/flutter, ventricular arrhythmia (= ventricular tachycardia, ventricular fibrillation and torsade de pointes (TDP))).

The secondary endpoints of interest were 1) (Narrow-angle) Glaucoma; 2) Bladder obstruction/urinary retention/incident and Benign prostatic hyperplasia (BPH); 3) Diabetes mellitus; 4) (paradoxical) Bronchospasm and 5) all-cause mortality.

Free-text validation of primary and secondary outcomes was performed in databases with available free text (IPCI, HSD, and SIDIAP), and non-confirmed events were excluded from analysis.

Demographic factors, lifestyle circumstances, COPD severity, concomitant medication use and underlying comorbidity were assessed as confounding factors.

Statistical Methods

For each study endpoint, covariate-adjusted hazard ratios (HRs) were estimated for new users of QVA149 versus each comparator cohort, with adjustment for baseline covariates using Cox regression modelling with inverse probability of treatment weighting (IPTW). Database-specific HRs were calculated in a given pairwise comparison (QVA149 versus a comparator cohort) if there were at least 5 events in both comparison groups. Database-pooled analysis was also performed for each pairwise comparison by calculating covariate-adjusted HR, pooling data from all five databases, including data from the databases with < 5 events per comparison cohort (with database as a stratification variable in the Cox model). Variability of estimated hazard ratios across databases in each pairwise comparison (QVA149 versus a comparator cohort) was assessed based on Cochran's Q-test. No adjustment for multiple comparisons was performed in this analysis.

Results

Mean (database-pooled) age at the index date was comparable between exposure cohorts, namely 71.1 years for QVA149 compared to 71.3 years for the anchor (free LABA/LAMA combination) and 69.8-72.3 years for the other exposure cohorts.

The database-pooled proportion of males in QVA149 was 69.9%, 67.2% in the anchor and between 56.6-68.1% in the other exposure cohorts.

Among patients for which COPD severity was assessed by spirometry (60.2-72.9% of patients), the database-pooled proportion of patients with severe and very severe COPD was the highest for the QVA149 cohort (31.9% severe COPD – 4.3% very severe COPD), 24.0% (severe COPD) and 2.6% (very severe COPD) for the anchor and ranged between 14.2-31.5% (severe COPD) and 1.4-5.0% (very severe COPD) for the other pooled exposure cohorts.

The database-pooled proportion of patients with at least one hospitalization for COPD exacerbations in the year prior to index date was (10.4% for QVA149, 6.2% for the anchor and between 3.4-9.2% for the other exposure cohorts).

Among all exposure cohorts in the database-pooled analysis, a substantial proportion of patients presented with cardiovascular (range 57.5-65.2%) and/or cerebrovascular (9.0-10.0%) co-morbidities at baseline. Almost one patient in 5 had a history of diabetes mellitus and also the proportion of patients with hyperlipidemia was high (20.8-23.1%). These important underlying (cardiovascular, cerebrovascular and metabolic) comorbidities were mirrored by high use of antihypertensive (61.9-69.8%), lipid lowering (42.5-47.6%), antithrombotic (37.6-44.9%) and antidiabetic medications (14.5-20.3%) across exposure cohorts.

With regard to the most prominent differences in baseline characteristics between databases, a history of ischemic heart disease was the lowest in HSD (IT) and SIDIAP (ES) (range of cohort specific percentages for angina pectoris 2.2-4.2%, for myocardial infarction 3.4-6.6%) and highest in Aarhus (21.5-25.9% for angina pectoris and 8.7-11.6% for myocardial infarction). The prevalence of asthma was the highest in THIN (UK) across all exposure cohorts (range 23.4-63.6%) and the lowest for HSD (Italy) and SIDIAP (Spain) (range 4.9-19.0%).

The median duration of follow-up on treatment was 120 days for QVA149, 60 days for the anchor and between 50-113 days for the other exposure cohorts. Among the pre-specified study end-points, events with the highest incidence of occurrence in the database-pooled dataset were mortality (range of cohort-specific estimates 27.5-61.4/1,000 patient-years [PY]) and major adverse cardiovascular events (range of cohort-specific estimates: 38.6-58.8/1,000 PY).

Database-pooled hazard ratios are presented for all primary and secondary endpoints in Table 1-1. Database-specific hazard ratios are shown in Figures 15-14 through 15-69.

Primary endpoints

No statistically significant increase in the rates of any of the primary safety endpoints was seen on QVA149 relative to any of the comparators in the pooled analysis. However, for some endpoints in some comparisons, individual databases showed conflicting results with opposite directions of association and statistically significant treatment-by-database interactions (Cochran's Q test, see Table 1-1 footnotes). Specifically, for the endpoint of ischemic heart disease in the comparison of QVA149 vs. fixed LABA+LAMA, the covariate-adjusted event

rate was significantly increased on QVA149 in AUH and (marginally) in THIN, but it was significantly decreased on QVA149 in SIDIAP (Cochran's Q p=0.005) (Figure 15-25 in the Full Report).

Table 1-1 Covariate-adjusted (IPTW) hazard ratios (95% CIs) for primary and secondary endpoints in the pooled analysis (QVA149 versus each comparator)

	Free LABA LAMA (no ICS) (anchor)	**Free LABA LAMA ICS**	**Free LABA/ICS (no LAMA)**	**Fixed LABA + ICS (+/- LAMA)**	**Fixed LABA + LAMA (+/- ICS)**	**LABA (no LAMA, no ICS)**	**LAMA (+/- ICS, no LABA)**
	n= 9,619	**n=** 3,192	**n=** 4,628	**n=** 58,332	**n=** 9,150	**n=** 12,364	**n=** 42,972
Primary endpoints							
MACE	1.18 (0.93-1.51)	0.94 (0.59-1.48)	0.95 (0.68-1.33)	0.94 (0.80-1.10)	1.03 (0.80-1.32)	1.05 (0.81-1.37)	0.97 (0.82-1.15)
Ischemic heart disease	1.22¥ (0.72-2.08)	1.25 (0.64-2.44)	1.20 (0.62-2.35)	1.21 (0.87-1.70)	1.60¥ (0.98-2.62)	1.31 (0.83-2.08)	1.12 (0.80-1.58)
Cardiac arrhythmia	1.31 (0.81-2.10)	0.93 (0.54-1.60)	0.68 (0.39-1.18)	0.84 (0.59-1.19)	0.79 (0.53-1.17)	1.23 (0.81-1.87)	0.79 (0.57-1.10)
Cerebro-vascular disorders	1.52 (0.91-2.55)	0.53 (0.20-1.43)	0.76¥ (0.37-1.55)	1.16¥ (0.80-1.70)	1.02 (0.58-1.79)	1.08 (0.70-1.69)	0.98¥ (0.68-1.42)
Secondary endpoints							
Glaucoma	0.60 (0.30-1.24)	0.29** (0.09-0.94)	NA	0.89 (0.47-1.70)	1.05 (0.37-2.97)	0.64 (0.29-1.42)	0.52 (0.27-1.02)
BOO/urinary retention/BPH	0.95 (0.64-1.41)	1.81 (0.66-4.95)	1.58 (0.71-3.49)	0.86¥ (0.62-1.20)	1.08 (0.62-1.86)	0.85 (0.60-1.20)	0.79 (0.59-1.07)
Diabetes	1.02 (0.70-1.50)	1.60 (0.80-3.19)	1.78 (0.82-3.89)	0.87 (0.64-1.17)	0.76 (0.47-1.25)	1.18 (0.81-1.72)	0.98 (0.72-1.32)
Bronchospasm	NA	NA	0.32** (0.10-0.98)	0.48 (0.20-1.14)	NA	0.79 (0.24-2.56)	0.92 (0.34-2.46)
Mortality	1.56*¥ (1.16-2.08)	3.04* (1.79-5.17)	0.88 (0.57-1.37)	0.75**¥ (0.62-0.90)	1.47* (1.16-1.86)	0.91¥ (0.69-1.21)	0.93¥ (0.75-1.14)

* 95% confidence interval for the hazard ratio is above 1 (significantly increased risk)

** 95% confidence interval for the hazard ratio is below 1 (significantly decreased risk)

¥ Cochran's Q p below 0.05

NA = not available (less than 5 events in QVA149 and/or the comparator)

MACE= Major Adverse Cardiovascular Event

Similar inconsistencies in database-specific findings were noted in some comparisons for the endpoint of cerebrovascular events. Specifically, in the comparison of QVA149 vs. the free LABA/ICS combination, the covariate-adjusted event rate was significantly decreased on

QVA149 in SIDIAP but not in IPCI, where the estimated hazard ratio was not significantly different from the null value (Figure 15-37 in the Full Report). The IPCI and SIDIAP estimates differed significantly from each other in this comparison based on Cochran's Q test (p = 0.01), while estimates from the other databases were not available due to <5 events per comparison group (Figure 15-37 in the Full Report). In the comparison of QVA149 vs. the fixed LABA+ICS combination (Figure 15-38 in the Full Report) , the rate of cerebrovascular events was significantly increased on QVA149 in IPCI, but not in THIN, AUH or SIDIAP, with a significant treatment-by-database interaction (Cochran's Q p=0.007), indicating that individual databases were not estimating the same treatment effect parameter. There was no estimate from HSD in this comparison due to <5 events per comparator.

A marginally significant hazard ratio above 1 was also noted in the comparison of QVA149 vs. LAMA for the endpoint of ischemic heart disease in AUH (Figure 15-27 in the full report) and in the comparison of QVA149 vs. free LABA/LAMA combination without ICS for the endpoint of cerebrovascular events in IPCI (Figure 15-35 in the Full Report), while a significantly reduced risk on QVA149 was noted for the endpoint of cardiac arrhythmia in the comparison with fixed LABA+ICS combination in SIDIAP (Figure 15-31 in the Full Report). However, treatment-by-database intercations were not statistically significant in these comparisons (i.e., variability of database-specific findings was consistent with random error). The pooled estimates of the hazard ratios in these comparisons were not significantly different from the null value.

Secondary endpoints

In the analysis of secondary endpoints glaucoma, bladder outflow obstruction / urinary retention, diabetes mellitus, and parodoxical bronchospasm, no statistically significant increase in event rates was observed on QVA149 relative to any of the comparators in the pooled analysis or in any of the database-specific analyses. Reduced risk on QVA149 was noted for glaucoma in the comparison with free LABA/LAMA/ICS and for bronchospasm in the comparison with free LABA/ICS (Table 1-1).

In the analysis of mortality, individual databases showed conflicting results with opposite direction of association in several comparisons (Table 1-2). In the database-pooled analysis, mortality rate in the QVA149 cohort was significantly higher than that in the other LABA LAMA combination cohorts, including free LABA/LAMA without ICS (anchor), free LABA/LAMA with ICS, and fixed LABA+LAMA with or without ICS (Table 1-2). However, these findings were primarily driven by one database (UK THIN). In contrast, the mortality rate on QVA149 was significantly reduced relative to the fixed LABA+ICS combination (the largest comparator cohort) in the database-pooled analysis (Table 1-2). Mortality rates did not differ significantly between the comparisons groups in the database-pooled analysis when QVA149 was compared with free LABA/ICS (no LAMA), with LABA monotherapy, or with LAMA therapy (with or without ICS, no LABA) (Table 1-2).

The largest mortality hazard ratio in the database-pooled analysis was observed for the comparison of QVA149 versus free LABA/LAMA/ICS combination (Table 1-2), but this estimate included data from three databases with <5 events per comparison cohort and therefore could be strongly influenced by sparse-data bias. In the comparison of QVA149 versus the anchor cohort (LABA/LAMA without ICS), the pooled estimate of the HR was also

significantly above 1, although evidence of treatment-by-database interaction was present in this comparison. In particular, estimated HRs from THIN and IPCI were pointing in the opposite direction and had non-overlapping CIs (Table 1-2).

Treatment-by-database interaction was also present in the comparison of QVA149 with LAMA therapy, where the mortality HR estimate from THIN indicated significantly increased risk on QVA149, while that from SIDIAP indicated significantly decreased risk on QVA149 (Table 1-2). In this comparison, the database-specific HR estimates from THIN had non-overlapping CIs with HR estimates from Aarhus and SIDIAP, indicating that the estimates were statistically incompatible with each other (i.e., contradictory or internally inconsistent), as confirmed by a highly significant Cochran's Q test (p=0.002).

Clear evidence of treatment-by-database interaction in mortality analysis was also present in the comparison of QVA149 with the fixed LABA+ICS combination (Cochran's Q p=0.005), where the risk was significantly reduced on QVA149 in Aarhus and SIDIAP, as well as in the pooled analysis. In contrast, in IPCI and THIN the mortality HR was not significantly different from the null value (Table 1-2). In this comparison, the HR estimates from THIN and SIDIAP, which were pointing in the opposite directions, also had non-overlapping CIs (i.e., were statistically incompatible with each other). Evidence of treatment-by-database interaction was also present in the comparison of QVA149 with LABA (Table 1-2).

Table 1-2 Covariate-adjusted (IPTW) hazard ratios (95% CIs) for the secondary endpoint of all-cause mortality: database-specific and pooled estimates (QVA149 versus each comparator)

	Free LABA LAMA (no ICS) (anchor) **n**= 9,619	**Free LAMA LABA ICS** **n**= 3,192	**Free LABA/ICS (no LAMA)** **n**= 4,628	**Fixed LABA + ICS (+/- LAMA)** **n**= 58,332	**Fixed LABA + LAMA (+/- ICS)** **n**= 9,150	**LABA (no LAMA, no ICS)** **n**= 12,364	**LAMA (+/- ICS, no LABA)** **n**= 42,972
THIN (UK)	2.64* (1.56-4.47)	NA	0.87 (0.33-2.31)	1.32 (0.87-1.98)	1.77* (1.28-2.46)	1.43 (0.89-2.30)	1.77* (1.19-2.61)
IPCI (Netherlands)	0.73 (0.37-1.44)	1.88 (0.60-5.87)	0.54 (0.21-1.41)	0.75 (0.37-1.52)	1.35 (0.62-2.92)	0.55 (0.28-1.07)	0.89 (0.48-1.67)
AARHUS (Denmark)	1.32 (0.74-2.35)	NA	1.40 (0.50-3.97)	0.72** (0.57-0.92)	1.37 (0.95-1.97)	1.12 (0.68-1.82)	0.83 (0.62-1.13)
HSD (Italy)	NA	NA	NA	NA	NA	NA	NA
SIDIAP (Spain)	1.40 (0.82-2.39)	2.39 (0.93-6.14)	0.98 (0.55-1.74)	0.52** (0.39-0.70)	1.05 (0.48-2.29)	0.61 (0.35-1.06)	0.64** (0.46-0.91)
Pooled	1.56* (1.16-2.08)	3.04* (1.79-5.17)	0.88 (0.57-1.37)	0.75** (0.62-0.90)	1.47* (1.16-1.86)	0.91 (0.69-1.21)	0.93 (0.75-1.14)

Cochran's Q P-value	0.030	0.748	0.602	0.005	0.549	0.041	0.002

NA = not applicable (less than 5 events in QVA149 and/or the comparator)
* 95% confidence interval for the hazard ratio is above 1 (significantly increased risk)
** 95% confidence interval for the hazard ratio is below 1 (significantly decreased risk)

Discussion

In this observational cohort study, the rates of all primary and secondary endpoints, except for the secondary endpoint of all-cause mortality, were not significantly elevated on QVA149 relative to any of the seven comparator cohorts in the pooled analysis. For the endpoints ischemic heart disease and cerebrovascular events, statistically significant treatment-by-database interaction with reversal of the direction of association across databases (from higher risk on QVA149 vs. comparator to lower risk on QVA149 vs. the same comparator) was noted in some comparisons. In the analysis of all-cause mortality, individual databases likewise showed conflicting results with opposite directions of association in several comparisons.

Interpretation of these findings as causal effects is problematic due to lack of internal consistency of observed associations. For example, in the comparison of QVA149 with LAMA, all-cause mortality was significantly increased on QVA149 in THIN but it was significantly decreased on QVA149 in SIDIAP. It is very unlikely that magnitude and direction of true biological effect of QVA149 relative to LAMA would vary so dramatically between these countries. Region-specific channelling biases are a more likely explanation for these findings. While QVA149 was the first fixed LABA+LAMA combination in the Netherlands, Spain, Denmark, and Italy, Anoro® was the first drug in this class to appear on the market in the UK, which could contribute to country-specific differences in drug channeling mechanisms, although the exact nature of the resulting bias mechanism is unclear. From our data however it appears that the QVA149 treated patients had more severe COPD compared to the other exposure cohorts in THIN as well as in the other databases (Table 15-3). Prevalence of COPD exacerbations in the one year prior to cohort entry in THIN was also higher in the QVA149 cohort than in the comparison cohorts (Table 15-4).

Channeling bias in this type of analysis would likely operate at least in part through changes in pulmonary function and COPD severity over time. In particualr, progressive deterioration of pulmonary function resulting in increased mortality hazard is also likely to trigger modification of bronchodilation therapy, including initiation or discontinuation of QVA149 or other drugs. This mechanism would produce a non-causal association of overall mortality with those drugs which tend to be used in severe COPD patients with significant / life-threatening comorbidities. Unfortunately, this type of confounding by changes in pulmonary function over time could not be controlled in the present analysis due to lack of relevant time-dependent measures of COPD severity.

Indeed, the baseline (pre-index) assessment of COPD severity in this study had very limited accuracy, with large fractions of patients lacking spirometry data or assessed based on spirometry measurements as much as 5 years old. These assessments, however imperfect, indicated that the QVA149 cohort likely had the largest proportion of patients with severe and very severe COPD.

Lack of detailed data on the cause of death, especially in THIN, is another limitation of this study. It can be noted however that in those comparisons where all-cause mortality was increased on QVA149, the risk of major cardiovascular events was not elevated on QVA149 (Tables 1-1 and 1-2).

Other limitations of this analysis included short exposure follow-up time especially in the free combination exposure cohorts, jeopardizing the potential to identify AEs resulting from long term exposure. It must also be acknowledged that the free LABA/LAMA combination cohorts (with or without ICS) might consist at least in part of patient switching from LABA to LAMA or vice versa and not necessarily represent combined use in all patients.

Conclusion

In this observational cohort study, the rates of all primary and secondary endpoints, except for the secondary endpoint of all-cause mortality, were not significantly elevated on QVA149 relative to any of the seven comparator cohorts in the pooled analysis. However, individual databases showed conflicting results with opposite directions of association for several endpoints, including ischemic heart disease, cerebrovascualt events and all-cause mortality. Interpretation of the these findings as causal effects is problematic due to lack of internal consistency of observed associations, inability to control time-dependent confounding, and other potential sources of bias. Given lack of internal consistency of database-specific results and considering other limitations of the study, overall study findings must be interpreted with caution.

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2 List of abbreviations

ACE	Angiotensin-Converting Enzyme
ACS	Acute Coronary Syndrome
ADM	Administrative
AF	Atrial Fibrillation
AFL	Atrial Flutter
(A)MI	(Acute) Myocardial Infarction
AP	Angina Pectoris
ATC	Anatomical Therapeutic Chemical Classification system
AV	Atrioventricular
Blad obstr	Bladder obstruction
BNF	British National Formulary
BOO	Bladder Outflow Obstruction
BPH	Benign Prostatic Hyperplasia
CAT	COPD Assessment Test
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CUI	Concept Unique Identifier
CV	Cardiovascular
DK	Denmark
ECG	Electrocardiogram
EHR	Electronic Health Record
EMA	European Medicines Agency
ES	Spain
ESC	European Society of Cardiology
ESH	European Society of Hypertension
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practice
HF	Heart Failure
Hosp	Hospitalization
HSD	Health Search Database
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

HSD	Health Search Database
HR	Hazard Ratio
IPCI	Integrated Primary Care Information
IR	Incidence Rate
IQ	Interquartile
IT	Italy
LABA	Long Acting β_2-adrenergic Agonist
LAMA	Long Acting Muscarinic Antagonist
LQTS	Long QT Syndrome
LRTI	Low Respiratory Tract Infection
LTRA	Leukotriene Receptor Antagonist
LUTS	Lower Urinary Tract Symptoms
MACE	Major Cardiovascular Endpoint
MI	Myocardial infarction
MR	Medical Record
NHS	National Health Service (in United Kingdom)
NL	The Netherlands
NOS	Not otherwise specified
NSAID	Non-steroidal 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
Premat Dep	Premature depolarization
PSUR	Periodic Safety Update Report
PSVT	Paroxysmal Supraventricular Tachycardia
RCT	Randomized Controlled Trial
RMP	Risk Management Plan
RRE	Remote Research Environment
SABA	Short Acting β2-adrenergic 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
TdP	Torsade de Pointes

TIA	Transient Ischemic Attack
TG	Triglycerides
THIN	The Health Improvement Network
UK	United Kingdom
UMLS	Unified Medical Language System
UR	Urinary retention
Vent fibr	Ventricular fibrillation
Vent tach	Ventricular tachycardia
VT	Ventricular Tachycardia
WHO	World Health Organization

3 Investigators

Project lead

Principal investigators (PI)

Sub-investigators

[redacted]

4 Other responsible parties

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 November 2013	01 November 2013	Not applicable
End of data collection* for interim report 1	Q1 2015	25 February 2015	Not applicable
Registration in the EU PAS register	After PRAC/CHMP approval of protocol	28 October 2014	Not applicable
Interim report 1	Q2 2015	01 April 2015	Not applicable
End of data collection* for interim report 2	Q2 2016	7 April 2016	Not applicable
Interim report 2	Q2 2016	10 June 2016	Not applicable
End of data collection* for interim report 3	Q2 2017	16 March 2017	Not applicable
Interim report 3	Q2 2017	31 May 2017	Not applicable
End of data collection* for final study report	Q2 – Q3 2018	30 June 2018	Not applicable
Final report of study results	Q4 2018	3 December 2018	Not applicable

*Date from which the analytical dataset is completely available (ENCePP 2015).

6 Rationale and background

According to GOLD (Global Initiative of Lung Disease), chronic obstructive pulmonary 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 (GOLD, 2017). Exacerbations and co-morbidities contribute to the overall severity in individual patients.

Bronchodilators are the mainstay of symptomatic management of COPD and include β_2 adrenergic agonists, muscarinic antagonists, methylxanthines and phosphodiesterase – 4 inhibitors which reduce both bronchoconstriction and airway inflammation. These medications are used alone or in combination.

Indacaterol/glycopyrronium bromide (QVA149, registered as Ultibro® Breezhaler® and related products) is a once-daily, inhaled fixed-dose combination (FDC) of indacaterol maleate (QAB149, registered as Onbrez® Breezhaler® and related products) and glycopyrronium bromide (NVA237, registered as Seebri® Breezhaler® and related products) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). QVA149 was approved by the European Commission on September 19th 2013 and was first launched in the Netherlands in November, 2013.

The QVA149 mechanism of action (MOA) involves a two-way approach to enable enhanced bronchodilation through separate molecular pathways. Indacaterol, a long-acting β2-adrenergic agonist (LABA), acts through the adenylate cyclase pathway to increase intracellular concentrations of cyclic 3',5'-AMP and trigger smooth muscle relaxation in the airways.

Glycopyrronium bromide, a long-acting muscarinic antagonist (LAMA), acts through the parasympathetic neural pathway to block the acetylcholinergic effects of bronchoconstriction. The combined effects of the two components in QVA149 work in parallel to achieve bronchodilation.

Combining a LABA with a LAMA as concurrent therapy has been shown to significantly improve bronchodilation in COPD patients compared to the respective monotherapies (van Noord et al., 2010). Data from RCTs have shown that this leads to improvement in dyspnea, health status/quality of life and lower risk of COPD exacerbations compared to monotherapy. (Bateman et al., 2013, Donohue et al., 2013, Wedzicha et al., 2013).

QVA149 has demonstrated an acceptable safety profile in clinical trials (Vogelmeier, 2013, Welte, 2013), in the context of the QVA149 marketing authorization application; nevertheless, the MAH (i.e., Novartis) proactively proposed to conduct a post- authorization safety study (PASS) in the post-marketing setting. The proposal to conduct this PASS was endorsed by the Pharmacovigilance Risk Assessment Committee (PRAC) to assess risk management plan (RMP) specified safety outcomes in association with QVA149.

7 Research question and objectives

The purpose of this PASS is to assess the risk of various RMP-specified endpoints in a broader, real-world COPD population.

7.1 Main objective

To assess the incidence rates and relative risks (expressed as Hazard Ratios [HRs]) of various adverse events among patients with a diagnosis of COPD initiating inhaled QVA149 compared to patients with a diagnosis of COPD initiating comparator medications:

(1) a free combination of LABA and LAMA without inhaled corticosteroids (ICS) (anchor),

(2) a free combination of LABA/LAMA with ICS,

(3) a free combination of LABA/ICS (no LAMA),

(4) a fixed combination of LABA+ICS (with or without LAMA),

(5) a fixed combination of LABA+LAMA other than QVA149 (with or without ICS),

(6) LABA monotherapy (no LAMA, no ICS),

(7) LAMA with or without ICS (no LABA).

Free combination of LABA/LAMA without ICS was considered the main comparator (anchor) per protocol. The primary safety endpoints of interest included:

- Major adverse cardiovascular events (MACE) including myocardial infarction (MI) and stroke, and hospitalizations due to acute coronary syndrome (ACS) and/or heart failure (HF)
- Ischemic heart disease including MI and angina pectoris

- Cardiac arrhythmias (atrial fibrillation/flutter, ventricular arrhythmia (= ventricular tachycardia, ventricular fibrillation and torsade de pointes (TDP))
- Cerebrovascular events (ischemic and hemorrhagic stroke and transient ischemic attack (TIA)

7.2 Secondary objective

The secondary safety endpoints of interest include:

- (Narrow-angle) glaucoma
- Bladder outflow obstruction (BOO)/urinary retention (UR)/incident benign prostatic hyperplasia (BPH)
- Diabetes mellitus (DM)
- (paradoxical) Bronchospasm
- All-cause mortality

8 Amendments and updates to the protocol

Number	Date	Section of study protocol	Amendment or update	Reason
1	02 June 2014	4. Abstract	Abstract was updated to reflect changes in the body of the protocol	Based on PRAC comments
2	02 June 2014	6. Milestones	Date of final report of study results amended	Based on PRAC comments
3	02 June 2014	8.1 Primary objectives	Primary Objectives clarified	Based on PRAC comments
4	02 June 2014	8.2 Secondary objectives	Secondary objectives clarified	Based on PRAC comments
5	02 June 2014	9.2.1 Study population and study cohorts	Limitations of databases in relation to chosen methodology clarified	Based on PRAC comments
6	02 June 2014	Study period	Launch dates for Spain and Italy updated	Based on PRAC comments
7	02 June 2014	9.2.4 Follow-up	Death added as end of follow-up	Based on PRAC comments
8	02 June 2014	9.3.1 Endpoints of interest	Endpoints of interest + how these will be assessed have been updated and clarified	Based on PRAC comments
9	02 June 2014	9.3.5. Demography, lifestyle factors and comorbidity	Updated now including glaucoma and urinary retention/BPH	Based on PRAC comments
10	02 June 2014	9.5 Study size	Updated: - now including sample size assuming a 1:10 and 1:20 ratio for QVA149 vs. comparator medications - Individual database estimates have been corrected - Corrective measures in case identified users of QVA149 is lower than expected have been added	Based on PRAC comments
11	02 June 2014	9.7.1 Yearly analysis for study reports	Threshold of RR of >3 has been clarified	Based on PRAC comments
12	02 June 2014	9.7.2 Analysis	Updated now including analysis in strictly naive users + considering the complete follow-up where reference is anchor therapy	Based on PRAC comments
13	02 June 2014	9.9 Limitation of research methods	Have been updated including corrective measures in case of heterogeneity between Spanish and other databases	Based on PRAC comments

9 Research methods

9.1 Study design

Multinational, multi-database cohort study with secondary use of data from five electronic healthcare records (EHR) databases from five European countries, namely The Netherlands (NL; Integrated Primary Care Information [IPCI] Project), Italy (IT; Health Search Database [HSD]), United Kingdom (UK; The Health Improvement Network [THIN]), Denmark (DK; Aarhus University Prescription Database) and Spain (ES; System d'Informació per al Desenvolupament de la Investigació en Atenció Primària [SIDIAP]). For information about these databases, see Section 9.5 Data sources and measurement. Eligible study patients from these databases were followed up over time (see Sections 9.3.1 and 9.3.2).

For this final analysis, a cohort of COPD patients was identified. From this cohort, a new-user cohort of QVA149 treated patients was selected; comparator cohorts were also assembled, namely, new users of QVA149 vs. new users of comparator medications: (1) a free combination of LABA, and LAMA without ICS (anchor), (2) a free combination of LABA/LAMA with ICS, (3) a free combination of LABA/ICS (no LAMA), (4) a fixed combination of LABA+ICS (with or without LAMA), (5) a fixed combination of LABA+LAMA other than QVA149 (with or without ICS), (6) LABA monotherapy (no LAMA, no ICS), (7) LAMA with or without ICS (no LABA).

Patients in all cohorts were followed from the first prescription until the end of treatment episode (i.e., treatment stop date +30 days), switching or add-on therapy, end of study, disenrollment from the database or death, whichever came first. End of treatment was defined as the discontinuation of use of the respective cohort treatment. For the calculation of incidence rates for the endpoints of interest, follow-up time is censored upon occurrence of the endpoint. As multiple endpoints are studied, different follow-up times will be used per patient and per endpoint.

9.2 Setting

The study is based on data derived from five [redacted] electronic health care databases. This final report presents the results from [redacted] (also described as the study period in this report). For more detailed information on the individual databases, see Section 9.5 Data sources and measurement.

During the study, the progress of identification of QVA149 within all databases was closely monitored. The launch dates of QVA149 in the countries of the databases are shown below:

Table 9-1 Launch dates for QVA149 in the five participating countries

[redacted]

Country	Actual launch date
[redacted]	[redacted]

9.3 Subjects

9.3.1 In- and exclusion criteria

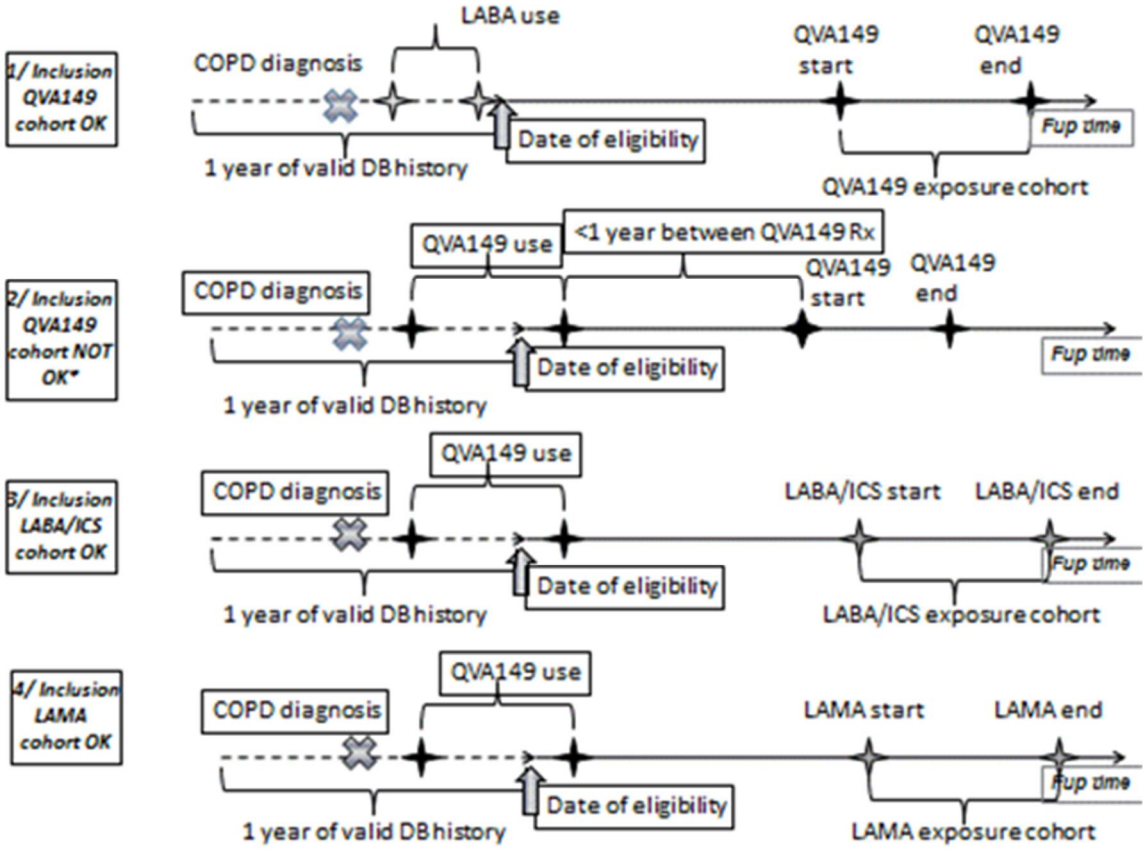
Inclusion criteria

All patients fulfilling the criteria for COPD diagnosis (Annex 2.4 – COPD definition), who are 40 years or older, with at least one year of database history, and a first time prescription/dispensing for QVA149, or comparator medications after 1 of November 2013 will be included in the study.

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 6 months of the first prescription/dispensing of any of the medications of interest or 3) who received the study medication of interest (QVA149 or comparator medications) in the one year prior to the index date (= time of first prescription) of the respective study cohorts will be excluded (see Figure 9-1). Patients thus need to be treatment-naïve to the exposure of interest for a minimum of one year. 4) use of one of the other cohort treatments which is ongoing for more than 30 days.

Figure 9-1 In- or exclusion in/from the study based on previous exposure of study medications



* In the second example, inclusion into the QVA149 would be OK if time window between date of eligibility and QVA149 start would be more than 1 year

9.3.2 Follow-up

For the primary analysis, patients initiating QVA149 or comparator medications were followed from the time of first prescription (index date) until the earliest of (i) end of treatment episode +30 days, (ii) end of study or disenrollment from the database, (iii) study endpoint of interest or (iv) death. If a patient switched from one exposure category to another exposure category, the grace period of 30 days following a treatment episode was not applied (see below).

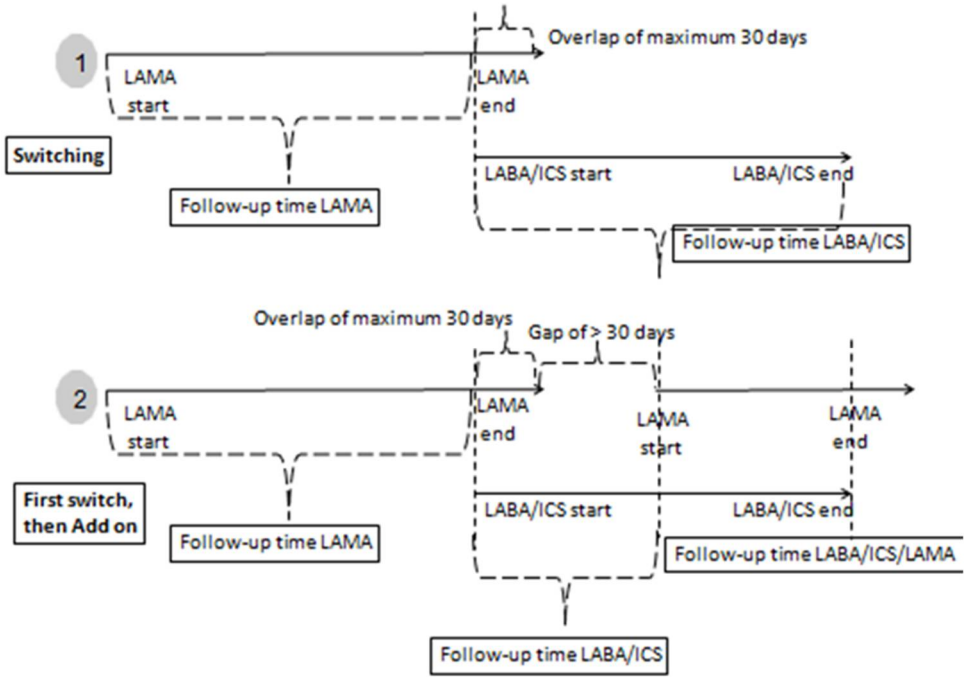
End of treatment was defined as the discontinuation of use of QVA149, or comparator medications for the respective treatment cohorts. This implies that follow-up, for the respective cohorts, ended when a patient discontinued, switched treatment, or initiated another comparator medication as add-on therapy.

Entering a combination cohort is illustrated in Figure 9-2: For patient 1, assume that there is no prescription preceding the time period showed. Because the overlap of the LAMA exposure and the LABA/ICS exposure is less than (or equal to) 30 days, this patient will not enter the LAMA/LABA/ICS cohort, but will enter the LABA/ICS cohort at start date of these prescriptions. If the overlap would have been longer than 30 days, the patient would have

contributed to the LAMA cohort, to the LAMA/LABA/ICS cohort, and finally to the LABA/ICS cohort.

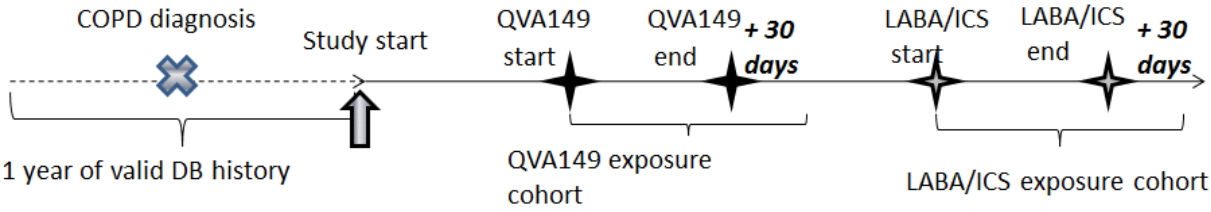
Patient 2 starts with the same exposure episodes of LAMA and (partly overlapping) LABA/ICS. Then a next LAMA episode is started. Because the ongoing LABA/ICS episode continues for more than 30 days, the patient enters the LAMA/LABA/ICS cohort.

Figure 9-2 Switching and add-on therapy



Upon discontinuation of 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



This implies that, if a patient switched from QVA149 to another comparator medication, this patient could be included in the comparator cohort; inclusion in a comparator cohort was only acceptable in cases where the patient was not exposed to that specific comparator treatment during the year prior to index date.

If add-on therapy was initiated (Figure 9-2), follow-up in the initial exposure cohort was discontinued; at this point in time the patient was included and followed up in one of the

combination-treatment exposure cohorts (free combination of LAMA/LABA, free combination of LABA/ICS, free combination of LAMA/LABA/ICS, fixed dose combination of LABA+ICS (with or without LAMA). Definitions of the end of the treatment episodes are further clarified in Section 9.4.2 - 'Exposure'.

9.4 Variables

9.4.1 Endpoints of interest

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

Primary endpoints

- Major adverse cardiovascular events which includes any event of myocardial infarction, stroke, or hospitalizations due to acute coronary syndrome and/or heart failure.
- Ischemic heart disease including any event of myocardial infarction or angina pectoris
- Cardiac arrhythmias (atrial fibrillation/flutter, ventricular arrhythmia (= ventricular tachycardia, ventricular fibrillation and torsade de pointes (TDP))
- Cerebrovascular events (any event of ischemic or hemorrhagic stroke or transient ischemic attack)

Secondary endpoints

- (Narrow-angle) glaucoma
- Bladder obstruction/urinary retention/incident benign prostatic hyperplasia (BPH)
- Diabetes mellitus
- (paradoxical) Bronchospasm
- All-cause mortality

As each endpoint was studied separately, patients who experienced more than one event during the study were included in the analysis of each endpoint. In case of combined endpoints (i.e. major cardiovascular events, ischemic heart disease, cardiac arrhythmia, cerebrovascular events, bladder obstruction/urinary retention/incident BPH) patients were censored upon the first event of interest. E.g. a patient diagnosed with myocardial infarction and later diagnosed with stroke, was censored at the date of the diagnosis of myocardial infarction for the analysis of Major adverse cardiovascular events as endpoint, however was studied separately for the analysis of cerebrovascular events.

The definitions of these endpoints are described under Annex 2.2 – Event definition.

Prior to analysis, all study patient events were identified in the database via 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').

In IPCI, HSD and SIDIAP, a validation of endpoints was done either through manual validation of the electronic medical files or hospital admissions linkage (SIDIAP only) was conducted. In IPCI (The Netherlands), because of lack of granularity in the ICPC coding, a free text search on potential endpoints was conducted in addition for the final report. In SIDIAP, linked hospital admissions was reviewed first, and a compatible hospital admission within ±2 months before/after the event date was considered confirmatory. In SIDIAP, only those with no linked confirmatory hospital admission were further validated. In all databases doing manual validation (IPCI, HSD and SIDIAP), free text and other disease codes were reviewed in a time window of 3 months before/after the date of the endpoint that needed to be validated. These windows hold for the validation of the endpoints, for the validation of COPD the complete medical history of the patient was considered except for SIDIAP where review is only allowed in max 3 months around a disease code.

Newly diagnosed diabetes mellitus as endpoint was not validated but was assessed based on a new disease code of diabetes mellitus in combination with a prescription of an antidiabetic drug or a HbA1c measurement >= 6.5% in the 6 months before or 1 year after the date of diagnosis. (Eastwood, 2016).

For the analysis, definite, probable and possible endpoints were combined into one category and considered as events of interest.

Because of the large cohort size, COPD was validated in a sample of 1,000 potential COPD patients from the QVA149 cohort and 1,000 COPD patients from the free LABA/LAMA combination (without ICS). Patients which were not confirmed as having COPD still remained in exposure cohorts as validation of COPD was only done in a subset of patients.

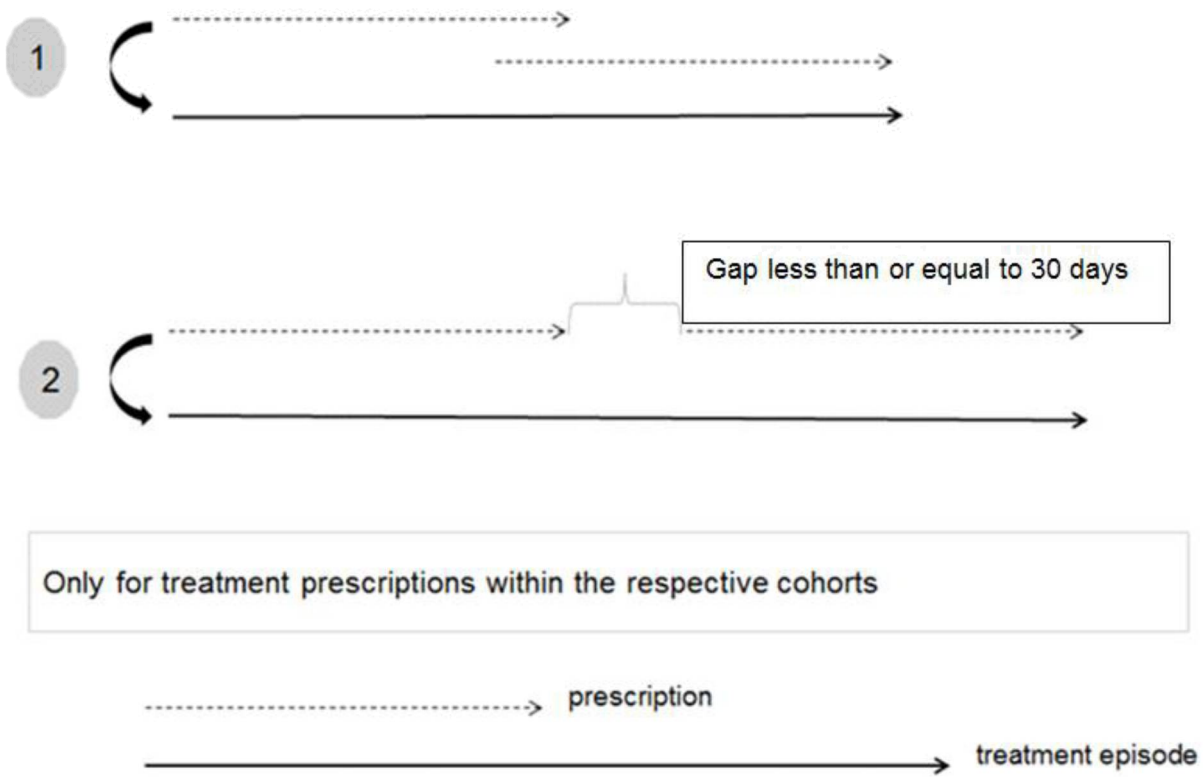
9.4.2 Exposure

Patients prescribed QVA149 and comparator medications were identified in the database by an automated search on the respective anatomical therapeutic chemical classification system (ATC) codes or Multilex codes of the prescription records in the respective databases (see Annex 2.3 – 'Exposure definition – respiratory medication use' and Annex 2.5 – 'Concomitant medication use').

From these medication prescriptions, episodes of medication exposure were created. In a first step the end dates of each prescription were calculated based on the amount of medication prescribed and the actual dosing of the individual patient. For Aarhus and SIDIAP, where information on dosing is not available, and for IPCI in case of missing dose, the total amount (per prescription) was divided by the recommended dosing according to the Summary of Product Characteristics (SmPC) of the respective medication. This duration of use was then added to the start date of the prescription resulting in an end date for each prescription.

From the individual prescriptions, episodes of use were created taking into account potential overlap and gaps (Figure 9-4). If a subsequent prescription of the same medication class overlapped the previous prescription, the two prescriptions were combined into one episode in which the episode end date was the end date of the second prescription ((1) in Figure 9-4). 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 9-4).

Figure 9-4 Creation of treatment episode for inhaled COPD therapies



Patients were classified as "exposed" to study medication (QVA149 or comparator medications) for the duration of the first treatment episode plus 30 days. This 30 days grace period was chosen as patients are considered not to be 100% compliant, especially in the case of chronic therapy. In a sensitivity analysis, as part of the final study report, the analysis was repeated where the first treatment episode was extended with a window of 60 days.

In the main analysis, patients who discontinued treatment and later restarted were only considered for their first episode of continuous use (+30 days) (Figure 9-5). The patient was 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. 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.

Figure 9-5 Identification of period of follow-up

9.4.3 COPD severity

COPD severity was determined where possible, as COPD severity is an important confounder and/or effect modifier in the association between the use of QVA149 or comparator medication and the risk of CV and/or cerebrovascular endpoints or mortality.

Severity of COPD was determined by spirometry, according to GOLD guidelines(GOLD, 2017), using the measurement closest before the index date with a maximum of 5 years.

Based on spirometry data, COPD severity was categorized into mild, moderate, severe and very severe addording to GOLD guidelines:

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.

Based on suggestions/recommendations from the Scientific Advisory Committee (SAC), which were given during review of previous interim reports (and applicable to the PASS QVA149), COPD severity based on spirometry data was also assessed in all patients with FEV_1 measurements, irrespective of availability or value of the FEV_1/FVC ratio.

In addition, COPD severity based on proxy data was also assessed according to published algorithms (Curkendall et al., 2006, Eisner et al., 2005, Soriano et al., 2001).

The COPD severity assessed closest to the index date (for all cohorts) was considered.

1. Mild: Patients initially diagnosed with COPD
2. Moderate: Patients on regular treatment (defined as at least 2 prescriptions of the same medication 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 onwards.
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.

In patients with missing spirometry data, COPD severity was imputed. For further details on COPD severity, see Annex 2.4 – 'COPD definition'.

9.4.4 Concomitant medication use

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

Concomitant use of respiratory medications

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 – respiratory medication use' and Annex 2.5 – 'Concomitant medication use'). Concomitant use of respiratory products was assessed at and in the one year prior to index date of the respective exposure cohorts. The following types of bronchodilating and anti-inflammatory agents were considered respiratory products:

- Single ingredient short acting muscarinic antagonists (SAMAs)
- Single ingredient short acting β_2-adrenergic agonists (SABAs)
- ICS
- Xanthines
- Fixed-combination therapy (LABA + ICS, anticholinergic agents + SABA)
- Oral β_2-adrenergic agonists
- Leukotriene receptor antagonists (LTRAs)
- Systemic corticosteroids (oral, intravenous or intramuscular administration)
- Single ingredient LABA
- Single ingredient LAMA
- Oral phosphodiesterase 4 (PDE-4) inhibitors

Other concomitant medication use

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

- Central nervous system medications (excluding medications with anticholinergic effects)

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

- Anticholinergic medications

Use of medications with anticholinergic effects (antipsychotic medications, tricyclic and tetracyclic antidepressant agents, disopyramide, antispasmodics, antiparkinsonian agents, cholinesterase inhibitors, atropine, H1-antihistamines, and anticholinergics for treatment of overactive bladder in patients with bladder outlet obstruction).

- Medications affecting cerebrovascular and cardiovascular disease

Use of systemic corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulant therapy (vit K antagonists and others), lipid lowering medications, platelet aggregation inhibitors, nitrates, anti-arrhythmics, cardiac glycosides, anti-diabetic medications and anti-hypertensive medications.

9.4.5 Demography, lifestyle factors and comorbidity

The following information was retrieved from the databases (where available):

- Age and gender (at time of index date)
- Smoking status (if available); patients will be classified as “current smoker”, “past smoker”, “never- smoker” or “smoking status missing” at the time of the index date
- Duration of COPD (from date of first-recorded diagnosis of COPD until index date)
- COPD severity at index date ,using most recent spirometry up to max. five years prior to index date
- COPD severity at index date based via proxy
- Number of COPD exacerbations requiring hospitalization or need of oral corticosteroids in the year prior to the index date. Hospitalization was assessed either via linkage with the hospital admission database (Aarhus). For IPCI, hospitalization for COPD exacerbation was identified by linking COPD (exacerbation) with hospital referral or hospital discharge letters.
- Number of courses of antibiotics for the treatment of lower respiratory tract infections and/or COPD exacerbations in the one year prior to the index date.
- The number of GP (outpatient) office visits (excluding telephone requests for repeat prescriptions only) and home visits, in the year prior to the index date
- Underlying comorbidity or “history of” at time of index date, namely:
  - Asthma
  - CV disease (hypertension, angina pectoris, MI, cardiac arrhythmia, HF)
  - Cerebrovascular disease (history of stroke and/or TIA at time of index date)
  - Metabolic disorders including diabetes mellitus, and dyslipidemia
  - Lung cancer
  - Other malignancies (excluding lung cancer and basocellular/spinocellular epithelioma)
  - Glaucoma
  - Bladder obstruction/urinary retention/incident BPH
  - Chronic kidney disease

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

definition'). For comorbidities such as coronary arrtery disease (angina pectoris and/or myocardial infarction), cardiac arrhythmia, heart failure, cerebrovascular disease patients, the date of diagnosis was taken into account to categorize whether patients were recently diagnosed (within one year of the index date) or diagnosed more than 1 year prior to the index date. This is described in more detail in the SAP.

9.5 Data sources and measurement

For this study, we used databases that comprise routine health care data 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 medications, strength and indication, plus their recognized reputation in the area of medication utilization and safety research. Multiple countries were included to provide international data and to guarantee sufficient exposure to QVA149. All participating databases are part of the EU-ADR Alliance, a stable collaboration framework for conducting drug safety studies in a federated manner, especially when the participation of several electronic healthcare record databases is required.

All databases used in this study comply with European Union (EU) guidelines on the use of medical data for medical research and have been validated for pharmaco-epidemiologic research (Cazzola et al., 2011, Ehrenstein et al., 2010, Garcia-Gil Mdel et al., 2011, Lewis et al., 2007, Vlug et al., 1999).

The databases that provide data 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 4 to 15.0 years. The databases are representative of the country-specific populations in terms of age and gender. These databases are primary care databases (except for the Aarhus database from DK, which is a prescription database with linkage to the hospital and out-patient registry) and the available data are complete as they originate from the general practitioner's (GP's) electronic primary care records.

The primary care databases represent 3.0-13.0% of the country-specific total population. As of 2016-2017, the total number of active persons in the source population encompassing all five databases was more than 16 million.

Table 9-2 Overview of databases

Database characteristics	IPCI	THIN	Aarhus	HSD	SIDIAP
Country	Netherlands	United Kingdom	Denmark	Italy	Spain
Type of database	MR	MR	ADM	MR	MR
Number of patients, *millions*	2.5	3.8	1.4	1.6	7.2
Mean follow-up in the database (years)	4.0	7.3	15.0	12.0	8.7
Date in	Yes	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes	Yes

Database characteristics	IPCI	THIN	Aarhus	HSD	SIDIAP
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 (March)
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 medications	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 (through linkage)
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 (through linkage)
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; ICD= International classification of disease, ICPC = International Classification of Primary Care; MR = Medical Records; Rx = Prescription

Data-cuts used for the final analysis are based on new-user exposure to QVA149 or defined comparators and availability of database updates, and are as follows: IPCI (01 November 2013 to 31 December 2016), THIN (01 November 2013 to 26 September 2017), Aarhus (01 November 2013 to 31 December 2016), HSD (01 November 2013 to 31 December 2017) and SIDIAP (01 November 2013 to 31 December 2016).

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

9.6 Bias

As we used data from databases from multiple countries, region-specific channelling biases might occur which might not adequately controlled for if this channeling in prescribing is guided by patient characteristics or country specific differences which are not part of the data which are collected for this study.

Lack of detailed data on the cause of death, especially in THIN, is another limitation of this study.

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. However, validation studies have shown that coding is reliable in the databases being used, and that these databases are suitable for pharmacoepidemiological research (Cazzola et al., 2011, Ehrenstein et al., 2010, Garcia-Gil Mdel et al., 2011, Lewis et al., 2007, Vlug et al., 1999). 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 prescription database (with linkage to the hospital and out-patient registry) (Aarhus), information on important covariates such as smoking status, spirometry results, and oxygen might be missing or reported in an inconsistent manner. This 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 QVA149 or comparator product and the risk of CV and/or cerebrovascular endpoints or mortality. For this reason, COPD severity was determined using spirometry data (if available) or via proxy, i.e., according to published algorithms (Curkendall et al., 2006, Eisner et al., 2005, Soriano et al., 2001). COPD severity was adjusted for in the final analysis. Unfortunately, our analysis did not account for changes in pulmonary function over time due to lack of relevant time-dependent measures of COPD severity. This might be a concern in case progressive deterioration of pulmonary function is not only associated with an increased of any of the endpoints (especially mortality) but is also likely to trigger modification of bronchodilation therapy, including initiation or discontinuation of QVA149 or other drugs. More information on the assessment of COPD severity is described under Annex 2.4 – 'COPD definition'. The potential for confounding is further discussed under Section 11.2 – Limitations.

In this study, we investigate the safety of QVA149 in relation to other drugs used for the treatment of COPD. For this study, we use real life data and choice of COPD controller therapy might be influenced by numerous factors such as COPD severity, underlying comorbidities and GP/specialist preference. Since any of these factors may be related to the outome as a plausible comorbidity, this might result in confounding by indication. For that reason, we tried to optimally control for confounding in our analysis but of course can not exclude that residual confounding might remain.

9.7 Study size

Sample size estimates were calculated assuming an HR 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 QVA149 being new to the market, we assumed a 1:4 ratio of QVA149 vs. comparator medications.

Sample size calculation was based on a log-rank test, which is asymptotically equivalent to the score test from the Cox model (Lu and Tsiatis 2008). Desired power was 80% and a 2-sided test with a significance level of 0.05 was specified. Based on information from the literature on the duration of LAMA treatment episodes, censoring was set after a median of 180 days (Dong Yaa-Hui 2012, Jara et al 2012, Singh et al 2011), assuming most censoring will be caused by the end of treatment period. Patients will be followed-up for the complete duration of their treatment episode (thus even beyond 180 days if the treatment episode lasts longer). To allow detecting an increased risk, if the risk is higher by at least a factor of two (HR=2), for an event with a background incidence rate of 10 per 1,000 person-years, and assuming a 1:4 ratio of numbers of QVA149 vs. comparator groups (single-constituent LAMA, free combination of LAMA/LABA, LABA/ICS, or LAMA/LABA/ICS, fixed dose combination of LABA+ICS with or without LAMA and fixed combination of LAMA+LABA other than QVA149), the group of QVA149 users should consist of at least 2,079 persons (at least 8,316 users in the comparator groups) (Lakatos, 1988, Cantor, 1997).

9.8 Data transformation

Data were extracted, validated and cleaned locally. All databases use different coding schemes (e.g. ICD9-CM (HSD) and ICD-10 (Aarhus, SIDIAP), ICPC (IPCI), READ (THIN)) and their content comes from different data sources (e.g., GP 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 considered for free text search of the events. Validation of events and comorbidities identified by free text search was conducted at the end of the study for the final analysis.

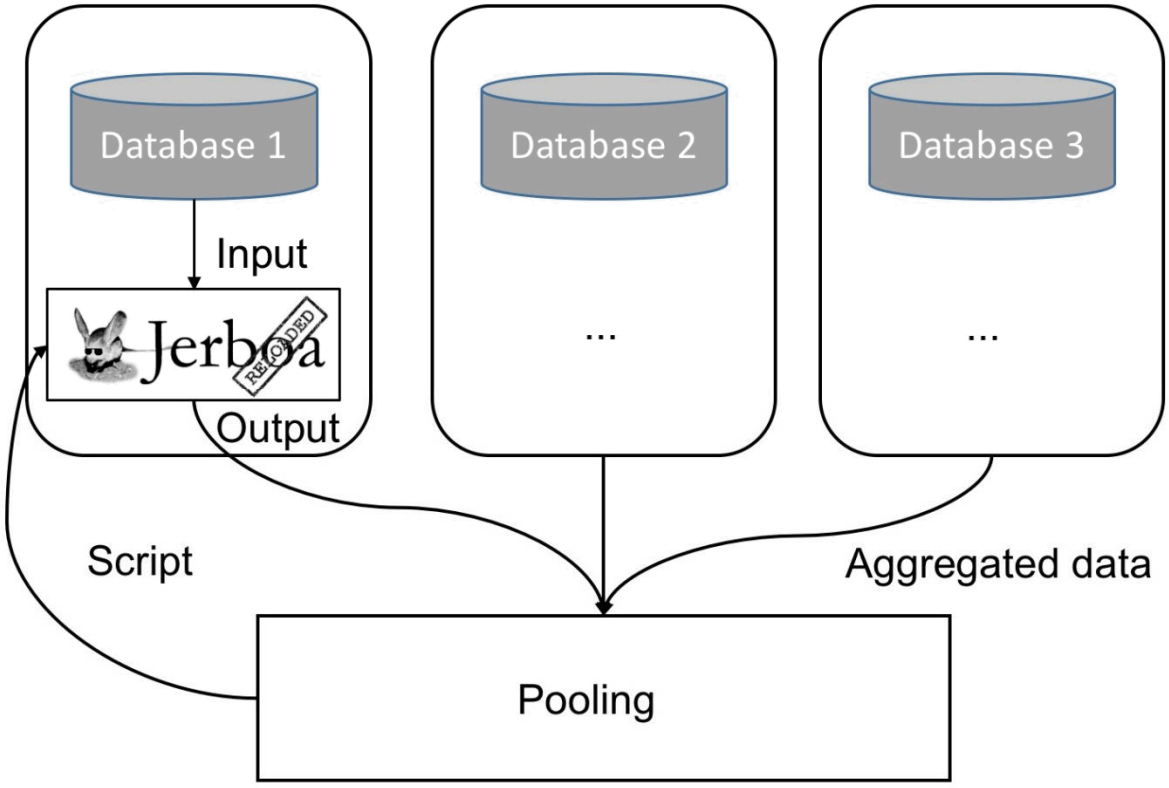
2) Definition of data extraction algorithm

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, medication, 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 output files (see Figure 9-6). 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 (http://synapse-pi.com/new_web/wp-content/uploads/2013/12/EU-ADR-alliance1.pdf) that combines health care data of 30 million individuals in Europe to detect adverse drug events. It has been used in many other EU funded projects and EMA tender protocols.

Figure 9-6 Model for data sharing and elaboration



Source: http://synapse-pi.com/new_web/wp-content/uploads/2013/12/EU-ADR-alliance1.pdf

4) Benchmarking of disease prevalence rates

For each comorbidity of interest, database specific prevalence rates were benchmarked using Jerboa. The observed prevalence rates were compared with prevalence rates estimated from previous database studies and literature. Outliers were identified and further investigated in an iterative manner.

9.9 Statistical methods

9.9.1 Main summary measures

In this final report, the following descriptive data are presented:

- Number of patients in the defined exposure cohorts (QVA149 and comparator cohorts)
- 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 8 exposure cohorts
- Incidence rates for all outcomes of interest across the 8 cohorts.
- Hazard rates comparing QVA to each comparator, using different methods

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 QVA149 or any of the other exposure cohorts were described using contingency tables for categorical variables and mean, standard deviation (SD), median, with IQR and range for continuous variables in each database. Because of large numbers, testing of differences between cohorts will result in several significant P-values, even in case of small differences. Therefore differences were not tested, but standardized differences between QVA149 and each of the other cohorts were provided.

9.9.2.2 Incidence rates of different endpoints and Kaplan-Meier curves

IRs with 95% CIs for all endpoints in all cohorts were calculated. To calculate the IRs of the endpoints of interest, the number of patients with the endpoint of interest was divided by the summed follow-up time of all patients in the cohort, censored at the event. The 95% CIs were calculated using the negative binomial distribution.

For the primary and secondary outcomes Kaplan-Meier curves were plotted by treatment cohort.

9.9.2.3 Hazard ratios of different endpoints

The relative risks (expressed as HRs with 95% CIs) were estimated for new users of QVA149 versus comparator users. For each comparator a separate modelwas fitted, so seven separate models. Follow-up time in the analyses was restricted to 365 days, as in the QVA149 cohort only 10% of the patients had a follow-up longer than 365 days, based on data from the last interim report. Analyses in a database or in the pooled data were done only if there were at least 5 events in both treatment cohorts (QVA149 and comparator).

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 and COPD severity assessed by spirometry.

Because the number of confounders is high relative to the expected numbers of events for several endpoints, inverse probability of treatment weighting (IPTW) analysis was conducted using weights determined by a propensity score model. First, logistic regression models were fitted for outcome QVA149 treatment versus each comparator treatment. In these seven propensity score models covariables as described in the SAP were included. In case of convergence problems when fitting a propensity score model, one or more covariables were excluded.

Because objective was to estimate the average tretment effect (ATE), for each patient, the stabilized weight was calculated (IPTW-ATE stabilized, defined as $w_{ate,stab}$ = Pr(Z=1)(Z/e)+ Pr(Z=0) [(1-Z)/(1-e)] with Z=1 for QVA user and Z=0 for the comparator treatment respectively, and e denotes the estimated propensity score (Austin 2016).

Plots with absolute standardized differences with and without weighting were provided to check the balancing of covariates after weighting (Austin 2014).

A Cox model was fitted comparing QVA149 with each comparator, while weighting by these IPTWs. Confidence intervals for the hazard ratios were computed based on the robust variance estimator (Lin 1994). This IPTW modeling process (fitting of propensity score model and Cox model) was executed on each imputed dataset and these results were combined.

Cox models in the data pooled over databases were all stratified by database, so using database-specific baseline hazard functions.

For the IPTW analysis in the pooled data, no separate propensity score models were fitted, but the weights estimated by database were used.

The covariates which were used to calculate the propensity scores are described inTable 9-3 . The comorbidity variables were refined to comprise severity and/or timing.

Table 9-3 Covariables in propensity score models

	Variable	Description	Definition
1	Age	Age at start of treatment (years)	
2	Gender	Gender of patient	
3	Smoking status	Smoking status at start treatment	
4	FEV1 severity	COPD severity based on spirometry	
5	CatHospCOPD	Number of hospitalizations for COPD	For all these variables, the number in the year prior to index date is determined. Categories are 0, 1, 2, 3 or more, used as continuous variable
6	CatH02ABCOPD	Number of systemic steroid episodes with indication COPD	
7	CatJ01LRTI	Number of antibiotic courses for treatment of LRTI or COPD exacerbations	
8	CatContPrac	Number of GP visits at practice	
9	CatContHome	Number of GP visits at home	
10	COPDdur	Duration of COPD	

	Variable	Description	Definition
11	RecentCAD	Recent Coronary Artery Disease	Categorical: 0 = No, if no event of MI, HOSPACS or UNSTABLEAP and no first event of AP in the year before index date 1 = Mild, if an event of UNSTABLEAP or a first event of AP, but no MI or HOSPACS in the year before index date 2 = Serious, if an event of MI or HOSPACS in the year before index date
12	PastCAD	Past Coronary Artery Disease	Categorical: 0 = No, if no event of MI, HOSPACS, UNSTABLEAP or AP more than one year before index date 1 = Mild, if an event of UNSTABLEAP or AP, but no MI or HOSPACS more than one year before index date 2 = Serious, if an event of MI or HOSPACS more than one year before index date
13	HistTimeAFIFLUT	History of atrial fibrilation, including timing	Categorical: 0 = No, if no event of AFIFLUT 1 = Recent, if first event of AFIFLUT in the year before index date. 2 = Past, if an event of AFIFLUT more than a year before index date.
14	RecentRecCardArr	Recent event of cardiac arrhythmia	Event of VENTTACH, VENTFIBR or TORSPOINT in the year before index date (binary)
15	PastRecCardArr	Past event of cardiac arrhythmia	Event of VENTTACH, VENTFIBR or TORSPOINT more than a year before index date (binary)

	Variable	Description	Definition
16	RecentHF2	Recent Heart Failure	Categorical: 0 = No, if no event of HOSPHF and no first event of HF in the year before index date 1 = Mild, if a first event of HF, but no HOSPHF in the year before index date 2 = Serious, if an event of HOSPHF in the year before index date
17	PastHF2	Past Heart Failure	Categorical: 0 = No, if no event of HOSPHF or HF more than one year before index date 1 = Mild, if an event of HF but no HOSPHF more than one year before index date 2 = Serious, if an event of HOSPHF more than one year before index date
18	RecentCerebro	Recent cerebrovasculair event	Categorical: 0 = No, if no event of STROKE or TIA in the year before index date 1 = Mild, if an event of TIA, but no STROKE in the year before index date 2 = Serious, if an event of STROKE in the year before index date
19	PastCerebro	Past cerebrovasculair event	Categorical: 0 = No, if no event of STROKE or TIA more than one year before index date 1 = Mild, if an event of TIA but no STROKE more than one year before index date 2 = Serious, if an event of STROKE more than one year before index date
20	HistAHT	History of arterial hypertension	Event of AHT in total history (binary)
21	HistCancer	History of cancer	Event of CANCER in total history (binary)
22	HistLungcancer	History of lungcancer	Event of LUNGCANCER in total history (binary)
23	HistAsthma	History of asthma	Event of ASTHMA in total history (binary)

	Variable	Description	Definition
24	CKD	Chronic kidney disease stage	Categories: No CKD Stage 1 or 2 or Stage unknown Stage 3 Stage 4 or 5
25	HistHEPAR	History of liver disease	Event of HEPAR in total history (binary)
26	HistGlaucoma	History of glaucoma	Event of NARGLAUC or OTHGLAUC in total history (binary)
27	HistURINRETENTION	History of urinary retention or bladder outflow obstruction	Event of URINRETENTION in total history (binary)
28	UseCNSmed	Use of Central Nervous System medications in pre-index year	N02A, N05C, N05B, N03A, N06AB
29	UseAntiChol	Anticholinergic drugs in pre-index year	N05A, N06AA, N06AX, C01BA03, A03A, N04A, N07A, A03BA01, R06A G04BD01, G04BD02, G04BD03, G04BD04, G04BD05, G04BD06, G04BD07, G04BD08, G04BD09, G04BD10, G04BD11, G04BD13
30	UseH02ABOther	Systemic corticosteroids in pre-index year	H02AB
31	UseNSAIDS	NSAIDs in pre-index year	M01A
32	UseAntiThromAg	Anti-thrombotic agents in pre-index year	B01A
33	UseLipidLow	Lipid lowering medications in pre-index year	C10A, C10B
34	Use PlatAggInh	Platelet aggregation inhibitors in pre-index year	B01AC
35	UseNitrates	Nitrates in pre-index year	C01DA
36	UseAntiArrh	Anti-arrhythmics in pre-index year	C01B
37	UseCardGlyc	Cardiac glycosides in pre-index year	C01AA, C01AB, C01AC, C01AX
38	UseAntiDiab	Anti-diabetic medications in pre-index year	A10
39	UseAntiHyp	Anti-hypertensive medications in pre-index year	C03, C07, C08, C09
40	UseRespMed	LAMA, LABA, ICS, LABAICS, LABALAMA, systemic corticosteroids for COPD exacerbations in pre-index year	R03BB04, R03BB05, R03BB06, R03BB07, R03AC11, R03AC12, R03AC13, R03AC14, R03AC18, R03AC19, R03BA, R03AK, R03AL03, R03AL04, R03AL05, R03AL06, R03AL07, H02AB with indication COPD

	Variable	Description	Definition
41	CalendarYear	Year of start cohort medication	Categories: 2013-2014 2015 2016-2017

9.9.2.4 Stratified analysis

Using the IPTW model (Cox regression, weighting by $w_{ate,stab}$), it was investigated whether there were important effect modifiers in the comparison of QVA149 to the comparator. As effect modifiers, the following were considered:

- Gender
- Age class, using two levels: age below 70 year and age 70 years or older
- COPD severity by spirometry, using three levels: mild, moderate, (very) severe
- ICS use in period 90 days before until 90 days after the index date: Yes, No. Stratified analysis by ICS use could not be performed for comparators with ICS use by definition. For comparators with "no ICS use" by definition, there still might have been ICS use before cohort and during the first 30 days.
- Probable or definite COPD
- Medical history of cardiovascular or cerebrovascular events. These events include: atrial fibrillation/flutter, angina pectoris and unstable angina pectoris, heart failure and hospitalisation for heart failure, stroke, TIA, ventricular tachycardia, ventricular fibrillation, TDP/LongQT, atrioventricular block, myocardial infarction, hospitalisation for ACS
- Calendar year of cohort entry (treatment initiation), categories 2013-2014, 2015, 2016-2017

Checking of these effect modifiers was done by including the potential modifier and the interaction 'treatment * modifier' to the IPTW model. If the P-value of the interaction term was below 0.10 in three of more of the imputed datasets, the IPTW model was fitted in the different strata of the modifier.

Because stratified models in each database separately were hampered by too few events within several cohorts within some of the strata, stratified analysis was only done in the pooled data.

9.9.2.5 Meta-analysis

Meta-analysis was done to combine IPTW results of the databases which provided a HR for a specific endpoint and comparator (at least 5 events in both QVA149 and comparator cohort during the first year of cohort time).

Forest plots of HRs were presented. Fixed and random meta-analysis estimates, Q statistic and I2 were calculated.

9.9.3 Missing values

Smoking status and COPD severity by spirometry have 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.

Because it can be questioned whether the charateristics smoking status and COPD severity assessed by spirometry will be "missing at random" extra sets with imputed data were created using some 'extreme' imputations:

- For all missings for smoking status impute 'Never smoker', imputation for COPD severity remains the same (5 imputations).
- For all missings for COPD severity impute 'Mild', imputation for smoking status remains the same (5 imputations).
- For all missings for COPD severity impute 'Very severe', imputation for smoking status remains the same (5 imputations).

9.9.4 Sensitivity analyses

9.9.4.1 Sensitivity analysis 1

In the main analyses, patient's follow-up time was censored at start of other treatment. In a sensitivity analysis, the IPTW-model was fitted now using each patient's follow-up time not censored at start of other treatment.

This analysis accounts for events caused by the cohort treatment but occurring shortly after stopping. Limitation of this analysis is that follow-up time and events might be counted twice, in case the time in 'new treatment'is included in the corresponding cohort.

9.9.4.2 Sensitivity analysis 2

In the main analyses, to the follow-up time a wash-out period of 30 days was added. 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 to account for the fact that patients might not be compliant all of the time.

9.9.4.3 Sensitivity analysis 3

In all cohorts, patients were one year naïve for the cohort treatment. The IPTW model was fitted also including only patients which are one year naïve not only for the cohort treatment but also for all other treatments defining a cohort. As single ICS use is not defining a cohort, patients only using ICS in the past are included in these naïve cohorts.

9.9.4.4 Sensitivity analysis 4

To analyze the complete follow-up of each patient from start of first treatment onwards, a dataset was constructed with data of each patient covering the time from start of first prescription of QVA149 or any of the comparator drugs until the endpoint of interest, end of

study, disenrollment from the database or death, whichever came first. All subsequent episodes with or without treatment were taken into account. Six binary time-varying variables were used, indicating the use of QVA149, LABA, LAMA, fixed LABA/ICS, fixed LABA/LAMA (excl. QVA149) and ICS. Episodes of use of these treatment may overlap. This model also contained the interaction LABA*LAMA. From this model the contrast between QVA and the combined use of LABA and LAMA and between QVA and fixed LABA/LAMA was estimated. The model also contained age at cohort entry and sex as covariates.

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 (SAP) (16 July 2018).

Differences with regard to the analysis as described in the most recent version of the protocol (version date 2 June 2014) are the following:

- For all patients COPD severity was assessed by proxy and, if possible, by spirometry. The latter was used in analysis. If missing, COPD severity assessed by spirometry was imputed.
- Differences in baseline characteristics were not tested, but standardized differences were provided
- In all models, follow-up was restricted to 365 days as the exposure time for the treatments appeared to be short.
- As the number of events was small relative to the number of covariates, models which were fitted were changed into the following:
    - Crude model
    - Model adjusted for age, gender, smoking status and COPD severity
    - Model weighted by inverse probability treatment weights (main model)
- The comorbidity variables were refined to comprise severity and/or timing
- For missing values, multiple imputation was done. In addition sensitivity analyses were done imputing specific values for all missings
- To avoid small strata because of few events, the strata for age were changed into <70 and >= 70 years or older and the COPD severity categories severe and very severe were combined into one stratum
- As since the protocol of 2 June 2014, other fixed LABA+LAMA than QVA149 were introduced onto the market, the other fixed LABA+LAMA was added as an additional exposure category changing the number of comparator cohorts from 6 to 7.

9.10 Quality control

The study was conducted according to the guidelines for Good Pharmaco-epidemiology Practice (GPP) and according to the ENCePP code of conduct (EMA 2013, ISPE 2008). All programs were programmed according to agreed coding standards and were validated by double

programming with second programmer involvement. Only validated software (SAS version 9.2, SAS Institute Inc., Cary, NC) was used for statistical analyses.

10 Results

Across all databases, more than 13 million patients qualified for potential study cohort selection during the study period. These patients had at least one year of medical history and were still active in the databases during the study period (1 November 2013 – 31 December 2017). There are differences between databases in study period depending on the database cut-off dates with most recent data being available for THIN (UK). The number of patients by database is shown in Table 10-1.

Table 10-1 Number of patients during study period

	THIN (UK) *	IPCI (NL)	Aarhus [DK]**	HSD [IT]***	SIDIAP [ES]
Study period	1 Nov 2013 to 26 September 2017	1 Nov 2013 to 31 December 2016	1 Nov 2013 to 31 December 2016	1 Nov 2013 to 31 December 2017	1 Nov 2013 to 31 December 2016
Number of patients who qualified for potential cohort selection	3,142,959	1,972,532	1,384,944	1,202,146	6,109,192
Launch date of QVA149 in the countries of the respective databases	01 December 2014	01 November 2013	25 November 2013	10 March 2014	15 April 2014

* = based on the THIN mid-year count in 2016. Mid year count of 2016 lower than mid year count of the previous report as THIN lost some practices that changed to another software system; **=based on subset of patients in the database for whom lung function data are available (i.e., FEV1) and optimal linkage to hospital & out-patient registers exist; ***=based on active patients in the database

10.1 Participants

Flow charts with the number of patients by database and exposure cohort are presented in Annex 2.1 - Figure 15-1 Flowcharts. Among the exposed patients, participants were excluded if they were not naive users or still used/initiated a product from one of the other exposure cohorts on the same day.

The number of patients by cohort and database are presented in Table10-2. In each exposure cohort with the exception of fixed combination LABA+LAMA (excl. QVA149), the proportion of patients from SIDIAP was the largest.

In total, 9,798 new users of QVA149 were identified, 1,346 (13.7%) in THIN (UK), 699 (7.1%) in IPCI (NL), 1,807 (18.4%) in Aarhus (DK), 385 (3.9%) in HSD (IT) and 5,561 (56.8%) in

SIDIAP (ES). The anchor cohort (free combination of LABA/LAMA, no ICS) consisted of 9,619 patients who were mainly identified in THIN (2,586 (26.9%)) and SIDIAP (4,219 (43.9%)). With regard to the other exposure cohorts, the newly exposed fixed combination cohort of LABA+ICS (with or without LAMA) was the largest (58,332 patients), followed by the cohort of new users of LAMA (42,972 patients), LABA (12,364 patients), fixed combination of LABA+LAMA (with or without ICS) (excl. QVA149) (9,150 patients) free combination of LABA and ICS, no LAMA (4,628 patients), and finally the smallest cohort, free combination of LABA/LAMA/ICS (3,192 patients).

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

Database	QVA149 (N=9,798)		LAMA/LABA (free comb., anchor) (N=9,619)		LAMA/LABA/ICS (free comb.) (N=3,192)		LABA/ICS (free) (N=4,628)		LABA+ICS (w/wo LAMA) (N=58,332)		LABA+LAMA[#] (N=9,150)		LABA (N=12,364)		LAMA (N=42,972)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
THIN (UK)	1,346	13.74%	2,586	26.88%	394	12.34%	583	12.60%	21,315	36.54%	4,921	53.78%	3,006	24.31%	18,598	43.28%
IPCI (NL)	699	7.13%	1,148	11.93%	496	15.54%	597	12.90%	7,001	12.00%	1,081	11.81%	1,526	12.34%	5,006	11.65%
Aarhus (DK)	1,807	18.44%	671	6.98%	242	7.58%	273	5.90%	3,481	5.97%	1,758	19.21%	1,078	8.72%	2,095	4.88%
HSD (IT)	385	3.93%	995	10.34%	335	10.49%	437	9.44%	5,897	10.11%	426	4.66%	875	7.08%	3,595	8.37%
SIDIAP (SP)	5,561	56.76%	4,219	43.86%	1,725	54.04%	2,738	59.16%	20,638	35.38%	964	10.54%	5,879	47.55%	13,678	31.83%

[#]= fixed combination other than QVA149

The size of the naïve analysis population is described below (by exposure cohort and database) in Table 10-3. By design, all exposure cohorts dropped in size, but especially for QVA149 the reduction from total to naïve cohort was more than 70%.

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

Database	QVA149 (N=2,633)		LAMA/LABA (free comb., anchor) (N=5,081)		LAMA/LABA/ICS (free comb.) (N=1,796)		LABA/ICS (free) (N=2,749)		LABA+ICS (w/wo LAMA) (N=29,519)		LABA+LAMA# (N=2,556)		LABA (N=7,875)		LAMA (N=31,466)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
THIN (UK)	226	8.58%	1,305	25.68%	241	13.42%	376	13.68%	9,148	30.99%	1,432	56.03%	1,855	23.56%	14,584	46.35%
IPCI (NL)	271	10.29%	603	11.87%	277	15.42%	330	12.00%	4,052	13.73%	336	13.15%	833	10.58%	3,680	11.70%
Aarhus (DK)	533	20.24%	350	6.89%	123	6.85%	133	4.84%	1,477	5.00%	476	18.62%	658	8.36%	1,357	4.31%
HSD (IT)	71	2.70%	468	9.21%	171	9.52%	233	8.48%	3,408	11.55%	82	3.21%	475	6.03%	2,314	7.35%
SIDIAP (SP)	1,532	58.18%	2,355	46.35%	984	54.79%	1,677	61.00%	11,434	38.73%	230	9.00%	4,054	51.48%	9,531	30.29%

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 median duration of patient follow-up by exposure cohort is presented in Table 10-4, by database and for the pooled data. The median duration of the pooled QVA149 cohort was 120 days and ranged between 92-136 days across the different databases. Median duration of patient follow-up in the pooled comparator exposure cohorts was shortest for the LAMA/LABA/ICS (free comb.) cohort (50 days) and longest for the fixed combination of LABA+LAMA (113 days).

Table 10-4 Median duration of follow-up (in days) by exposure cohort and database

Database	QVA149	LAMA/LABA (free comb., anchor)	LAMA/LABA/ICS (free comb.)	LABA/ICS (free)	LABA+ICS (w/wo LAMA)	LABA+LAMA[#]	LABA	LAMA
	(N=9,798)	(N=9,619)	(N=3,192)	(N=4,628)	(N=58,332)	(N=9,150)	(N=12,364)	(N=42,972)
	Median (min-max)	**Median (min-max)**	**Median (min-max)**	**Median (min-max)**	**Median (min-max)**	**Median (min-max)**	**Median (min-max)**	**Median (min-max)**
THIN (UK)	134 (1-950)	77 (1-1,376)	60 (4-1014)	73 (1-1,232)	129 (1-1,421)	118 (1-1,070)	81 (1-1,397)	90 (1-1,424)
IPCI (NL)	115 (1-1,047)	61 (1-1,106)	60 (1-909)	68 (1-727)	90 (1-1,146)	104 (1-682)	67 (1-1,124)	90 (1-1,146)
Aarhus (DK)	136 (1-1,111)	63 (1-1,014)	59.5 (8-999)	60 (2-1,063)	90 (2-1,133)	120 (1-835)	81 (1-1,144)	65 (1-1,087)
HSD (IT)	119 (1-809)	60 (1-1,313)	21 (3-668)	21 (1-456)	60 (1-1,389)	114 (3-682)	60 (1-1,065)	67 (1-1,388)
SIDIAP (SP)	92 (2-975)	60 (1-1,156)	50 (2-882)	60 (6-699)	60 (1-1,156)	90 (29-640)	60 (14-1,095)	60 (11-1,126)
Pooled	120 (1-1,111)	60 (1-1,376)	50 (1-1014)	60 (1-1,232)	90 (1-1,421)	113 (1-1,070)	60 (1-1,397)	73 (1-1.424)

[#]= fixed combination other than QVA149

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 10-5. For more detailed information of baseline characteristics in study cohorts, both pooled and by database, see Annex 2.1 - Table 15-1.

Mean age at the index date was comparable between exposure cohorts, namely 71.1 years for QVA149 compared to 71.3 years for the anchor (free combination LABA and LAMA) and 69.8-72.3 years for the other exposure cohorts. With regard to database specific characteristics, the mean age was the highest for HSD (72.2-75.0 over exposure cohorts) and SIDIAP (70.0-73.5). (Annex 2.1 - Table 15-1).

The pooled proportion of males in QVA149 was 69.9%, whereas it was between 56.6-68.1% in the other exposure cohorts. The proportion of males was the lowest for the fixed LABA+LAMA cohort (56.6%) and the fixed LABA+ICS cohort (57.3%). Gender distribution showed variations across the different data sources within HSD (IT) and SIDIAP (ES), both representing Southern European populations, the majority prescribed these products were males (Annex 2.1 - Table 15-1).

Proportions of smoking categories are described using as denominator all patients for whom smoking status is known. The proportion of current, past and non-smokers were comparable between the QVA149 exposure cohort and the anchor with nearly 90% of all patients being a current or past smoker. Similar findings were observed in the other exposure cohorts except for the free LABA+ICS cohort where 26.2% of patients were non-smokers and the fixed LABA+LAMA cohort where the proportion of non-smokers was only 5.6%. Differences in smoking status between databases were observed with the highest proportion of never-smokers in HSD (IT) (range over exposure cohorts 13.4-27.1%) and SIDIAP (ES) (range 17.3-32.6%), compared to the Northern European population (range 2.9-14.9%). The proportion of missing smoking status was the lowest for THIN (UK) (0.0-0.1%) and highest for Aarhus (DK) (range 20.8-36.6%) (Annex 2.1 - Table 15-2).

In preparation of the analysis, smoking status was imputed if missing. Results of imputation are described in (Annex 2.1 - Table 15-2) and displayed in Figure 15-6 Distribution of Smoking status – Imputed data.

Table 10-5 Baseline characteristics of exposure cohorts, pooled

	QVA N(%) 9,798	Free LABA+LAMA without ICS N(%) 9,619	Std Dif	Free LABA+LAMA with ICS N(%) 3,192	Std Dif	Free LABA+ICS N(%) 4,628	Std Dif	Fixed LABA ICS N(%) 58,332	Std Dif
Gender			-0.0571		-0.0386		-0.2188		-0.2633
Male	6,845 (69.9%)	6,465 (67.2%)		2,173 (68.1%)		2,752 (59.5%)		33,425 (57.3%)	
Age at cohort entry, mean (SD) (years)	71.1 (10.3)	71.3 (10.2)	-0.021	72.3 (10.1)	-0.120	71.8 (11.4)	-0.065	70.1 (11.5)	0.093
Smoking status			0.104		0.1641		0.3157		0.141
Current smoker	3,089 (33.8%)	3,279 (35.9%)		804 (26.8%)		1,128 (25.8%)		19,980 (36.3%)	
Past smoker	4,785 (52.4%)	4,814 (52.7%)		1,674 (55.7%)		2,099 (48.0%)		25,405 (46.1%)	
Never smoker	1,265 (13.8%)	1,041 (11.4%)		527 (17.5%)		1,144 (26.2%)		9,695 (17.6%)	
Unknown	659 (6.7%)	485 (5.0%)		187 (5.9%)		257 (5.6%)		3,252 (5.6%)	

	QVA N(%) 9,798	Fixed LABA LAMA N(%) 9,150	Std Dif	LABA N(%) 12,364	Std Dif	LAMA N(%) 42,972	Std Dif
Gender			-0.2772		-0.157		-0.19
Male	6,845 (69.9%)	5,181 (56.6%)		7,722 (62.5%)		26,154 (60.9%)	
Age at cohort entry, mean (SD) (years)	71.1 (10.3)	70.2 (10.1)	0.081	69.8 (11.0)	0.115	69.9 (10.9)	0.113
Smoking status			0.2817		0.1272		0.1949
Current smoker	3,089 (33.8%)	3,373 (38.9%)		4,439 (38.0%)		17,206 (41.8%)	
Past smoker	4,785 (52.4%)	4,804 (55.5%)		5,430 (46.4%)		18,841 (45.8%)	
Never smoker	1,265 (13.8%)	485 (5.6%)		1,824 (15.6%)		5,095 (12.4%)	
Unknown	659 (6.7%)	488 (5.3%)		671 (5.4%)		1,830 (4.3%)	

SD = standard deviation

Std Dif= Standardized difference

Std Dif of >0.5 or <-0.5 considered to be clinically meaningful

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.

10.2.2 COPD characteristics by exposure cohort pooled and by database

The COPD characteristics are presented in Table 10-6 and in more details [pooled and by database] in Annex 2.1 - Table 15-3 to Table 15-4 and Annex 2.1 - Figure 15-7).

The median duration of COPD was 3.8 years for the QVA149 cohort and comparable to the median duration of COPD of the anchor (4.2 years). The median duration of COPD was the highest for the LAMA/LABA/ICS combination (triple therapy)(6.1 years) and ranged between 1.9-4.9 years for the other exposure cohorts. The median duration was the highest for HSD for all exposure cohorts (6.5-8 years).

According to protocol, COPD was validated in 1,000 patients of the QVA149 cohort and 1,000 patients from the free LABA/LAMA (without ICS) exposure cohort for those database where validation was feasible (IPCI, HSD and SIDIAP). The result of this validation is provided in Annex 2.1 - Table 15-8. The positive predictive value (PPV) of COPD was high for SIDIAP (Spain) namely 88.1% and 99.3% for IPCI (The Netherlands). The PPV for COPD was much lower in HSD (Italy) namely 79.0% primarily because free text was often missing in HSD and patients only had a combination of a COPD disease code combined with use of respiratory drugs whereas details on symptoms and spirometry was lacking. Patients not confirmed as having COPD remained in the exposure cohort as COPD validation was only done in a subset of patients.

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. The median time (database pooled) from most recent spirometry to index date ranged between 75 (fixed LABA+LAMA) and 334 (free LABA+ICS) days with a median of 243 days for the QVA149 exposure cohort. Differences were observed between databases with shortest median time to spirometry for Aarhus (range 7-288 days), THIN (range 33-153 days) and IPCI (51-287 days). Median time to spirometry ranged between 135-582 days for HSD and 309.5-382 days for SIDIAP.

FEV_1 (as percentage of predicted) was available for a subset of patients in THIN (UK) (76.1-89.8%), IPCI (NL) (41.5-61.8%), Aarhus (DK) (38.1-70.5%), HSD (IT) (22.7-38.7%) and SIDIAP (ES) (58.5-74%). The pooled median FEV_1 percentage of predicted was 56% for QVA149, 61% for the anchor and ranged between 56-67.9% for the other exposure cohorts. FEV_1 percentage of predicted was the lowest for Aarhus and SIDIAP, across exposure cohorts.

For those patients where COPD severity was assessed by spirometry, the proportion of patients with severe and very severe COPD was the highest for the pooled QVA149 cohort (31.9% severe COPD – 4.3% very severe COPD), 24.0% (severe COPD) and 2.6% (very severe COPD) for the pooled anchor and ranged between 14.2-31.5% (severe COPD) and 1.4-5.0% (very severe COPD) for the other pooled exposure cohorts. The proportion of patients with moderate COPD was 52.5% for the pooled QVA149 cohort, 59.1% for the anchor and ranged between 52.6-60.5% for the other pooled exposure cohorts.

The proportion of patients with mild COPD was the lowest for the QVA149 exposure cohort (11.4%) and the free LABA/LAMA/ICS combination (10.9%).

When investigating differences in COPD severity across databases, in Aarhus, the proportion of patients with severe and very severe COPD was the highest across exposure cohorts.

Furthermore, as part of the analysis, COPD severity by spirometry was imputed if missing. (Annex 2.1 - Figure 15-7).

In addition, COPD severity was also assessed via previously published algorithms. In general, COPD severity by proxy, compared to COPD severity as assessed by spirometry, resulted in a higher proportion of patients with moderate COPD across all exposure cohorts and databases.

The proportion of patients with at least one hospitalization for COPD exacerbations in the year prior to index date was less than 11% in all exposure cohorts.

The database-pooled proportion of patients with at least one hospitalization for COPD exacerbations in the year prior to index date was 10.4% for QVA149, 6.2% for the anchor and between 3.4-9.2% for the other exposure cohorts. The proportion of patients with at least one COPD exacerbation requiring hospitalization was the highest for Aarhus across exposure cohorts (range 7.7-17.5%).

The proportion of patients requiring systemic corticosteroids for the treatment of COPD exacerbations in the year prior to index date was 10.8% for QVA149, 11.5% for the free LABA/LAMA (no ICS) and ranged from 8.2% (LABA) to 17.1% (free LAMA/LABA/ICS combination) for the other exposure cohorts with the lowest proportions in HSD (IT) and SIDIAP (ES) for all exposure cohorts. The proportion of patients using systemic corticosteroids for reason of COPD exacerbation and LRTI was the highest for IPCI (NL) (18.5-46.2%) and the lowest for HSD (IT) (4.4-8.4%) and SIDIAP (ES) (3.8-8.0%) (Annex 2.1 - Table 15-3 to Table 15-4). As differences between were suspected between databases with regard to the indication of use, use of systemic corticosteroids ,whether or not for COPD exacerbation in the year prior to index date was also investigated. In QVA149, 36.8% had used systemic corticosteroids in the year prior to index date, whereas this proportion was 34.9% for the anchor and ranged between 27.5% (LABA) to 52.5% for the free combination of LABA/LAMA/ICS. Use of systemic corticosteroids was more comparable between databases with the lowest use in SIDIAP (range 21.5-46.9%).(Annex 2.1 - Table 15-3 to Table 15-4)

The proportion of patients treated with antibiotics for COPD exacerbation/lower respiratory tract infection (LRTI) was 20.0% for both the QVA149 cohort and the free LABA/LAMA (no ICS) cohort and ranged from 17.3% (LAMA) to 24.1% (free LAMA/LABA/ICS combination) for the other exposure cohorts. With regard to differences by database, the proportion of patients using antibiotics for reason of COPD exacerbation and LRTI was the highest for IPCI (28.5-43.4% respectively) and the lowest for HSD (12.3-18.3%) and SIDIAP (15.1-20.2%) (Annex 2.1 - Table 15-3 to Table 15-4).

Table 10-6 COPD characteristics of exposure cohorts, pooled

POOLED		QVA149	Free LABA+LAMA without ICS	Std Dif	Free LABA+LAMA with ICS	Std Dif
Duration of COPD (yrs)	N	9,798	9,619	-0.069	3,192	-0.375
	Mean (SD)	5.5 (5.7)	5.6 (5.4)		7.1 (5.7)	
	Median (IQR)	3.8 (0.8-8.7)	4.2 (1.2-8.6)		6.1 (2.7-10.2)	
	Min-Max	0.0-49.9	0.0-49.7		0.0-44.9	
Days from spirometry to index date	N	6,419	6,705	0.090	2,099	-0.150
	Mean (SD)	395.3 (433.5)	359.7 (417.1)		433.4 (430.8)	
	Median (IQR)	243.0 (42.0-604.0)	211.0 (35.0-529.0)		313.0 (92.0-621.0)	
FEV1 percentage	N	6,419	6,705	-0.221	2,099	0.013
	Mean (SD)	57.4 (18.2)	61.4 (17.9)		57.2 (18.0)	
	Median (IQR)	56.0 (44.0-69.0)	61.0 (49.0-72.8)		56.0 (44.0-69.1)	
	Min-Max	18.3-184.0	19.6-204.7		18.3-128.6	
		9,798 (100.0%)	9,619 (100.0%)		3,192 (100.0%)	
COPD severity assessed by spirometry				0.1639		-0.0022
	Mild	730 (11.4%)	958 (14.3%)		229 (10.9%)	
	Moderate	3,370 (52.5%)	3,961 (59.1%)		1,104 (52.6%)	
	Severe	2,045 (31.9%)	1,611 (24.0%)		662 (31.5%)	
	Very severe	274 (4.3%)	175 (2.6%)		104 (5.0%)	
	Unknown	3,379 (34.5%)	2,914 (30.3%)		1,093 (34.2%)	
COPD severity assessed by proxy				-0.0701		-0.3578
	Mild	1,498 (15.3%)	864 (9.0%)		58 (1.8%)	
	Moderate	6,907 (70.5%)	7,664 (79.7%)		2,553 (80.0%)	
	Severe	1,297 (13.2%)	957 (10.0%)		510 (16.0%)	
	Very severe	96 (1.0%)	134 (1.4%)		71 (2.2%)	
Number of hospitalizations for COPD exacerbation				0.1563		0.0412
	None	8,776 (89.6%)	9,024 (93.8%)		2,899 (90.8%)	
	1	781 (8.0%)	507 (5.3%)		219 (6.9%)	
	2	169 (1.7%)	66 (0.7%)		41 (1.3%)	
	3 or more	72 (0.7%)	22 (0.2%)		33 (1.0%)	

POOLED		QVA149	Free LABA+ICS	Std Dif	Fixed LABA ICS	Std Dif
Duration of COPD (yrs)	N	9,798	4,628	-0.161	58,332	0.061
	Mean (SD)	5.5 (5.7)	6.3 (5.9)		5.2 (5.6)	
	Median (IQR)	3.8 (0.8-8.7)	4.9 (1.5-9.4)		3.7 (0.4-8.3)	
	Min-Max	0.0-49.9	0.0-49.9		0.0-49.8	
Days from spirometry to index date	N	6419	2788	-0.199	35145	0.101
	Mean (SD)	395.3 (433.5)	457.4 (437.9)		383.7 (449.1)	
	Median (IQR)	243.0 (42.0-604.0)	334.0 (104.0-683.0)		214.0 (19.0-597.5)	
FEV1 percentage	N	6,419	2,788	-0.490	35,145	-0.388
	Mean (SD)	57.4 (18.2)	66.6 (19.2)		64.8 (19.9)	
	Median (IQR)	56.0 (44.0-69.0)	65.6 (53.0-79.0)		64.0 (50.2-78.0)	
	Min-Max	18.3-184.0	21.6-130.7		15.2-379.8	
	Total	9,798 (100.0%)	4,628 (100.0%)		58332 (100.0%)	
COPD severity assessed by spirometry				0.0662		0.0321
	Mild	730 (11.4%)	669 (24.0%)		7,719 (22.0%)	
	Moderate	3,370 (52.5%)	1,566 (56.2%)		18977 (54.0%)	
	Severe	2,045 (31.9%)	509 (18.3%)		7,599 (21.6%)	
	Very severe	274 (4.3%)	44 (1.6%)		850 (2.4%)	
	Unknown	3,379 (34.5%)	1,840 (39.8%)		23187 (39.8%)	
COPD severity assessed by proxy				-0.0701		-0.3578
	Mild	1,498 (15.3%)	864 (9.0%)		58 (1.8%)	
	Moderate	6,907 (70.5%)	7,664 (79.7%)		2,553 (80.0%)	
	Severe	1,297 (13.2%)	957 (10.0%)		510 (16.0%)	
	Very severe	96 (1.0%)	134 (1.4%)		71 (2.2%)	
Number of hospitalizations for COPD exacerbation				0.1563		0.0412
	None	8,776 (89.6%)	9,024 (93.8%)		2,899 (90.8%)	
	1	781 (8.0%)	507 (5.3%)		219 (6.9%)	
	2	169 (1.7%)	66 (0.7%)		41 (1.3%)	

POOLED		QVA149	Free LABA+ICS	Std Dif	Fixed LABA ICS	Std Dif
	3 or more	72 (0.7%)	22 (0.2%)		33 (1.0%)	
POOLED		QVA149	Fixed LABA LAMA	Std Dif	LABA	Std Dif
Duration of COPD (yrs)	N	9,798	9,150	0.048	12,364	0.209
	Mean (SD)	5.5 (5.7)	5.3 (5.8)		4.5 (5.3)	
	Median (IQR)	3.8 (0.8-8.7)	3.6 (0.5-8.4)		2.7 (0.1-7.4)	
	Min-Max	0.0-49.9	0.0-49.8		0.0-49.1	
Days from spirometry to index date	N	6,419	6,669	0.422	7,956	0.187
	Mean (SD)	395.3 (433.5)	292.8 (416.6)		350.8 (436.8)	
	Median (IQR)	243.0 (42.0-604.0)	75.0 (1.0-434.0)		165.5 (13.0-546.0)	
FEV1 percentage	N	6,419	6,669	-0.185	7,956	-0.566
	Mean (SD)	57.4 (18.2)	60.9 (19.5)		67.8 (18.6)	
	Median (IQR)	56.0 (44.0-69.0)	60.1 (47.0-73.4)		67.9 (55.6-79.0)	
	Min-Max	18.3-184.0	17.5-405.4		18.3-379.8	
COPD severity assessed by spirometry				0.2083		0.1843
	Mild	730 (11.4%)	1,034 (15.5%)		1,908 (24.0%)	
	Moderate	3,370 (52.5%)	3,666 (55.0%)		4,812 (60.5%)	
	Severe	2,045 (31.9%)	1,732 (26.0%)		1,126 (14.2%)	
	Very severe	274 (4.3%)	237 (3.6%)		110 (1.4%)	
	Unknown	3,379 (34.5%)	2,481 (27.1%)		4,408 (35.7%)	
COPD severity assessed by proxy				-0.0146		0.4076
	Mild	1,498 (15.3%)	1,427 (15.6%)		3,681 (29.8%)	
	Moderate	6,907 (70.5%)	6,330 (69.2%)		7,899 (63.9%)	
	Severe	1,297 (13.2%)	1,239 (13.5%)		713 (5.8%)	
	Very severe	96 (1.0%)	154 (1.7%)		71 (0.6%)	
Number of hospitalizations for COPD exacerbation				0.06		0.2779
	None	8,776 (89.6%)	8,357 (91.3%)		11,937 (96.6%)	

POOLED		QVA149	Free LABA+ICS	Std Dif	Fixed LABA ICS	Std Dif
	1	781 (8.0%)	609 (6.7%)		356 (2.9%)	
	2	169 (1.7%)	119 (1.3%)		44 (0.4%)	
	3 or more	72 (0.7%)	65 (0.7%)		27 (0.2%)	

POOLED		QVA149	LAMA	Std Dif
Duration of COPD (yrs)	N	9,798	42,972	0.357
	Mean (SD)	5.5 (5.7)	4.0 (5.2)	
	Median (IQR)	3.8 (0.8-8.7)	1.9 (0.0-6.6)	
	Min-Max	0.0-49.9	0.0-49.9	
Days from spirometry to index date	N	6,419	27,579	0.407
	Mean (SD)	395.3 (433.5)	292.1 (414.2)	
	Median (IQR)	243.0 (42.0-604.0)	78.0 (4.0-431.0)	
FEV1 percentage	N	6,419	27,579	-0.503
	Mean (SD)	57.4 (18.2)	66.8 (18.8)	
	Median (IQR)	56.0 (44.0-69.0)	66.2 (54.0-78.0)	
	Min-Max	18.3-184.0	18.4-347.5	
COPD severity assessed by spirometry				0.1581
	Mild	730 (11.4%)	6,126 (22.2%)	
	Moderate	3,370 (52.5%)	16430 (59.6%)	
	Severe	2,045 (31.9%)	4,592 (16.7%)	
	Very severe	274 (4.3%)	431 (1.6%)	
	Unknown	3,379 (34.5%)	15393 (35.8%)	
COPD severity assessed by proxy				0.4865
	Mild	1,498 (15.3%)	15320 (35.7%)	
	Moderate	6,907 (70.5%)	24394 (56.8%)	
	Severe	1,297 (13.2%)	2,833 (6.6%)	
	Very severe	96 (1.0%)	425 (1.0%)	
Number of hospitalizations for COPD exacerbation				0.2487

POOLED		QVA149	LAMA	Std Dif
	None	8,776 (89.6%)	41227 (95.9%)	
	1	781 (8.0%)	1,504 (3.5%)	
	2	169 (1.7%)	171 (0.4%)	
	3 or more	72 (0.7%)	70 (0.2%)	

SD = standard deviation

Std Dif= Standardized difference

Std Dif of >0.5 or <-0.5 considered to be clinically meaningful

10.2.3 Co-morbidities across exposure cohorts pooled and by database

Comorbidities by exposure cohort are presented in Table 10-7 and by database in Annex 2.1-Table 15-5 Co-morbidities. General differences between databases are discussed under section 10.2.3.7.

10.2.3.1 Cardiovascular and cerebrovascular comorbidity

The proportion of patients with cardiovascular and cerebrovascular co-morbidities was high in all exposure cohorts, namely 61.7% for the pooled QVA149 exposure cohort, 62.5% for the pooled free LAMA/LABA (no ICS) cohort and ranged from 57.5% (LABA+LAMA fixed combination) to 65.2% (free LAMA/LABA/ICS combination) for the other exposure cohorts.

- Arterial hypertension was the most prevalent CV disease amongst all database-pooled exposure cohorts (range 45.5%-56.8%), with lowest proportion for the LABA+LAMA fixed combination and highest proportion for the free LABA/ICS exposure cohort.
- A history of angina pectoris was reported in 10.1% of QVA149 patients, 9.6% of free LAMA/LABA without ICS patients and ranged between 7.2% (free LABA/ICS combination) to 15.3% (fixed LABA+LAMA) for the other exposure cohorts.
- Baseline prevalence of MI historywas comparable across exposure cohorts namely 7.5% for the QVA149 exposure cohort, 7.2% for the anchor and between 5.8% (free LABA/ICS combination) to 8.4% (fixed LABA+LAMA) for the other exposure cohorts.
- A history of heart failure was frequently reported namely 9.0% for the database pooled QVA149 cohort, 8.4% for the anchor and between 6.8% (LABA) to 10.4% (free LAMA/LABA/ICS combination).
- The proportion of patients with a history of cardiac arrhythmia was the highest for the database- pooled QVA149 cohort (17.1%), 14.7% in the anchor cohort and between 13.4-17.0% for the other exposure cohorts. Atrial flutter/fibrillation was the most frequently reported type of cardiac arrhythmia. The prevalence of major cardiac arrhythmia (ventricular fibrillation, ventricular tachycardia and Torsade de Pointes/LongQT syndrome) was < = 2% in all exposure cohorts.
- The prevalence of any history of cerebrovascular comorbidity was comparable across database-pooled exposure cohorts namely 9.1% for QVA149, 9.5% for the anchor and between 9.0-10.0% for the other exposure cohorts.

10.2.3.2 Diabetes mellitus and hyperlipidemia

Almost 1 patient in 5 had a history of diabetes mellitus namely 19.5% for the QVA149 exposure cohort, 18.9% for the anchor and between 16.5% (LAMA+LABA fixed combination) and 21.4% (LABA/ICS free combination) for the other exposure cohorts.

Similar proportions for hyperlipidemia were observed namely 20.8% for the QVA149 exposure cohort, 22.3% for the anchor and between 20.9% (LABA) to 23.1% (LAMA) for the other exposure cohorts.

10.2.3.3 Cancer

The proportion of patients with lung cancer ranged between 1.4% (LABA database-pooled exposure cohort) to 3.0% with the highest proportion in the QVA149 database-pooled exposure

cohort and 2.2% in the anchor cohort. For cancer (excluding lung cancer and excluding superficial skin cancer) the proportion ranged from 13.5% to 16.6% with again highest proportion for the QVA149 database-pooled exposure cohort and 16.0% in the anchor cohort.

10.2.3.4 Asthma

The proportion of patients with a history of asthma was 11.9% for the database-pooled QVA149 cohort, 14.3% for the anchor and ranged between 13.4%-26.5% for the other exposure cohorts. The proportions were the highest in those exposure cohorts containing treatment with ICS namely 26.5% for the LABA/ICS free combination, 24.9% for the fixed LABA+ICS combination and 23.7% for the LAMA/LABA/ICS free combination.

10.2.3.5 Urinary retention/bladder outflow obstruction and benign prostatic hyperplasia

The proportion of these urological conditions was assessed in all patients and thus not limited to males only. The proportion of patients with a history of urinary retention/bladder outflow obstruction ranged from 2.3 to 2.9%. The proportion of patients with BPH ranged from 10.1% (LAMA+LABA fixed) to 20.4% (LAMA/LABA/ICS free combination).

10.2.3.6 Chronic kidney disease

Chronic kidney disease was assessed either via disease code or via creatinine clearance. Across database-pooled exposure cohorts, proportions of patients with chronic kidney disease (CKD) stage 4 ranged between 1.8 to 2.5%, proportions of patients with CKD stage 5 ranged between 0.4% to 0.6%, CKD stage 3 ranged between 19.7 to 27.3% and of CKD stage 2 ranged between 46.9 to 50.0%.

10.2.3.7 Differences in comorbidities between databases

Comorbidities by exposure cohort and by database are described in Annex 2.1- Table 15-5 Co-morbidities.

Differences in comorbidities between databases were observed with the lowest prevalence of arterial hypertension, diabetes mellitus and hyperlipidemia in Aarhus (DK). A history of ischemic heart disease (i.e., unstable angina pectoris, angina pectoris and myocardial infarction) was more frequently reported in THIN (UK), IPCI (NL) and Aarhus (DK). The prevalence of angina pectoris (for THIN, IPCI and Aarhus over the different exposure cohorts) ranged between 12.8-25.9% and the prevalence of myocardial infarction ranged between 5.7-11.6%. These prevalences were much lower in HSD (IT) and SIDIAP (ES) namely range for angina pectoris 2.2-4.2% and range of myocardial infarction 3.4-6.6%.

Up to 10.4% of patients were diagnosed with heart failure at cohort inception, with the highest proportions for IPCI (The Netherlands) (9.6-15.4%) and Aarhus (Denmark) (10.6-14.8%).

The proportion of hepatic impairment was the highest for THIN (UK) (3.4-5.4%) and HSD (Italy)(6.4-8.1%) compared to the other databases (range 0.6-3.3%).

The proportion of patients with a medical history of asthma was the highest in THIN (UK) across all exposure cohorts (range 23.4-63.6%) with the highest proportions in free ICS

containing regimens (61.4% free LABA plus ICS, 63.6% free LABA plus LAMA plus ICS combinations) and lowest for HSD (Italy) and SIDIAP (Spain) (range 4.9-19.0%).

The proportion of patients with lung cancer was the highest for IPCI (The Netherlands) and Aarhus (Denmark) in all exposure cohorts with the highest prevalence in the QVA149 exposure cohort (5.4 and 4.5% respectively).

Differences in the prevalence of BPH (both sexes combined) were observed across databases, with highest prevalences in HSD (Italy) (13.6-22.9%) and SIDIAP (Spain) (20.6-28.7%), both of which have a male preponderance of COPD patients. In the other databases, the prevalence of BPH ranged between 5.7-11.3%.

Table 10-7 Comorbidities of exposure cohorts pooled

POOLED	QVA N(%) 9,798	Free LABA+LAMA without ICS N(%) 9,619	Std Dif	Free LABA+LAMA with ICS N(%) 3,192	Std Dif
Cardiovascular comorbidities	6,047 (61.7%)	6,010 (62.5%)	-0.0157	2,081 (65.2%)	-0.0723
- Arterial hypertension	5,138 (52.4%)	5,143 (53.5%)	-0.0206	1,773 (55.6%)	-0.0623
- Unstable angina pectoris	225 (2.3%)	180 (1.9%)	0.0298	53 (1.7%)	0.0457
- Angina pectoris	988 (10.1%)	925 (9.6%)	0.0157	270 (8.5%)	0.056
- Myocardial infarction	732 (7.5%)	689 (7.2%)	0.0118	214 (6.7%)	0.0299
- Heart failure	883 (9.0%)	810 (8.4%)	0.021	333 (10.4%)	-0.0479
Cardiac arrhythmia	1,678 (17.1%)	1,410 (14.7%)	0.0675	543 (17.0%)	0.003
- Atrial fibrillation/flutter	1,332 (13.6%)	1,061(11.0%)	0.0781	390 (12.2%)	0.0411
- Torsade de Pointes/Long QT	1 (0.0%)	5 (0.1%)	-0.0237	1 (0.0%)	-0.0147
- Ventricular fibrillation	14 (0.1%)	9 (0.1%)	0.0144	9 (0.3%)	-0.0302
- Ventricular tachycardia	23 (0.2%)	28 (0.3%)	-0.011	8 (0.3%)	-0.0032
- AV block	166 (1.7%)	166 (1.7%)	-0.0024	70 (2.2%)	-0.0361
- Sick Sinus	41 (0.4%)	28 (0.3%)	0.0214	7 (0.2%)	0.0353
- Supraventricular tachycardia	159 (1.6%)	111 (1.2%)	0.0401	53 (1.7%)	-0.003
- Premature depolarization	140 (1.4%)	164 (1.7%)	-0.0222	71 (2.2%)	-0.0594

POOLED	QVA N(%) 9,798	Free LABA+ICS N(%) 4,628	Std Dif	Fixed LABA ICS N(%) 58,332	Std Dif
Cardiovascular comorbidities	6,047 (61.7%)	2,958 (63.9%)	-0.0455	34,854 (59.8%)	0.0403
- Arterial hypertension	5,138 (52.4%)	2,627 (56.8%)	-0.0869	29,844 (51.2%)	0.0256
- Unstable angina pectoris	225 (2.3%)	73 (1.6%)	0.0522	1,221 (2.1%)	0.0139
- Angina pectoris	988 (10.1%)	335 (7.2%)	0.1013	5,930 (10.2%)	-0.0027
- Myocardial infarction	732 (7.5%)	266 (5.8%)	0.0694	4,104 (7.0%)	0.0168
- Heart failure	883 (9.0%)	402 (8.7%)	0.0115	4,932 (8.5%)	0.0197
Cardiac arrhythmia	1,678 (17.1%)	746 (16.1%)	0.027	8,210 (14.1%)	0.0842
- Atrial fibrillation/flutter	1,332 (13.6%)	559 (12.1%)	0.0453	6,345 (10.9%)	0.083
- Torsade de Pointes/Long QT	1 (0.0%)	0 (0.0%)	0.0143	24 (0.0%)	-0.0193
- Ventricular fibrillation	14 (0.1%)	3 (0.1%)	0.0242	89 (0.2%)	-0.0025
- Ventricular tachycardia	23 (0.2%)	11 (0.2%)	-0.0006	135 (0.2%)	0.0007
- AV block	166 (1.7%)	84 (1.8%)	-0.0092	720 (1.2%)	0.0383
- Sick Sinus	41 (0.4%)	11 (0.2%)	0.0316	181 (0.3%)	0.018
- Supraventricular tachycardia	159 (1.6%)	59 (1.3%)	0.0291	768 (1.3%)	0.0254
- Premature depolarization	140 (1.4%)	96 (2.1%)	-0.0492	843 (1.5%)	-0.0014

POOLED	QVA N(%) 9,798	Fixed LABA LAMA N(%) 9,150	Std Dif	LABA N(%) 12,364	Std Dif
Cardiovascular comorbidities	6,047 (61.7%)	5,264 (57.5%)	0.0854	7,340 (59.4%)	0.0481
- Arterial hypertension	5,138 (52.4%)	4,164 (45.5%)	0.139	6,431 (52.0%)	0.0085
- Unstable angina pectoris	225 (2.3%)	271 (3.0%)	-0.0416	223 (1.8%)	0.0348
- Angina pectoris	988 (10.1%)	1,396 (15.3%)	-0.156	1,103 (8.9%)	0.0397
- Myocardial infarction	732 (7.5%)	768 (8.4%)	-0.0341	774 (6.3%)	0.0479
- Heart failure	883 (9.0%)	891 (9.7%)	-0.0249	834 (6.8%)	0.0842
Cardiac arrhythmia	1,678 (17.1%)	1,371 (15.0%)	0.0584	1,659 (13.4%)	0.1032
- Atrial fibrillation/flutter	1,332 (13.6%)	1,102(12.0%)	0.0464	1,255 (10.2%)	0.1066
- Torsade de Pointes/Long QT	1 (0.0%)	2 (0.0%)	-0.0092	5 (0.0%)	-0.019
- Ventricular fibrillation	14 (0.1%)	14 (0.2%)	-0.0026	19 (0.2%)	-0.0028
- Ventricular tachycardia	23 (0.2%)	30 (0.3%)	-0.0176	24 (0.2%)	0.0088
- AV block	166 (1.7%)	94 (1.0%)	0.0576	191 (1.5%)	0.0118
- Sick Sinus	41 (0.4%)	37 (0.4%)	0.0022	34 (0.3%)	0.0244
- Supraventricular tachycardia	159 (1.6%)	163 (1.8%)	-0.0123	144 (1.2%)	0.0391
- Premature depolarization	140 (1.4%)	112 (1.2%)	0.0179	174 (1.4%)	0.0018

POOLED	QVA N(%) 9,798	LAMA N(%) 42,972	Std Dif
Cardiovascular comorbidities	6,047 (61.7%)	25774 (60.0%)	0.0356
- Arterial hypertension	5,138 (52.4%)	21816 (50.8%)	0.0334
- Unstable angina pectoris	225 (2.3%)	917 (2.1%)	0.011
- Angina pectoris	988 (10.1%)	4,792 (11.2%)	-0.0347
- Myocardial infarction	732 (7.5%)	3,355 (7.8%)	-0.0127
- Heart failure	883 (9.0%)	3,482 (8.1%)	0.0325
Cardiac arrhythmia	1,678 (17.1%)	6,210 (14.5%)	0.0734
- Atrial fibrillation/flutter	1,332 (13.6%)	4,765 (11.1%)	0.0762
- Torsade de Pointes/Long QT	1 (0.0%)	12 (0.0%)	-0.0128
- Ventricular fibrillation	14 (0.1%)	66 (0.2%)	-0.0028
- Ventricular tachycardia	23 (0.2%)	117 (0.3%)	-0.0075
- AV block	166 (1.7%)	536 (1.3%)	0.0371
- Sick Sinus	41 (0.4%)	112 (0.3%)	0.0271
- Supraventricular tachycardia	159 (1.6%)	548 (1.3%)	0.0291
- Premature depolarization	140 (1.4%)	719 (1.7%)	-0.0198

POOLED	QVA N(%) 9,798	Free LABA+LAMA without ICS N(%) 9,619	Std Dif	Free LABA+LAMA with ICS N(%) 3,192	Std Dif
Cerebrovascular comorbidities	890 (9.1%)	911 (9.5%)	-0.0134	292 (9.2%)	-0.0022
- Stroke	643 (6.6%)	648 (6.7%)	-0.007	185 (5.8%)	0.0318
- TIA	344 (3.5%)	404 (4.2%)	-0.0358	129 (4.0%)	-0.0278
Diabetes mellitus (validated)	1,914 (19.5%)	1,822 (18.9%)	0.015	642 (20.1%)	-0.0145
Hyperlipidemia	2,035 (20.8%)	2,143 (22.3%)	-0.0367	706 (22.1%)	-0.0329
Hepatic injury	200 (2.0%)	293 (3.1%)	-0.0638	64 (2.0%)	0.0026
Lung cancer	295 (3.0%)	215 (2.2%)	0.0485	85 (2.7%)	0.021
Cancer (excluding lung cancer)	1,627 (16.6%)	1,539 (16.0%)	0.0164	512 (16.0%)	0.0153
Asthma	1,167 (11.9%)	1,373 (14.3%)	-0.0701	756 (23.7%)	-0.3115
BPH	1,808 (18.5%)	1,662 (17.3%)	0.0307	652 (20.4%)	-0.0499
Bladder obstruction/urinary retention	228 (2.3%)	250 (2.6%)	-0.0175	91 (2.9%)	-0.033
No CKD	2,704 (27.6%)	2,225 (23.1%)		767 (24.0%)	
Stage unknown	142 (1.5%)	127 (1.3%)		48 (1.5%)	
Stage 1	24 (0.2%)	55 (0.6%)		20 (0.6%)	
Stage 2	4,782 (48.8%)	4,647 (48.3%)		1,596 (50.0%)	
Stage 3	1,928 (19.7%)	2,317 (24.1%)		680 (21.3%)	
Stage 4	177 (1.8%)	205 (2.1%)		61 (1.9%)	
Stage 5	41 (0.4%)	43 (0.5%)		20 (0.6%)	

POOLED	QVA N(%) 9,798	Free LABA+ICS N(%) 4,628	Std Dif	Fixed LABA ICS N(%) 58,332	Std Dif
Cerebrovascular comorbidities	890 (9.1%)	414 (9.0%)	0.0048	5,554 (9.5%)	-0.0151
- Stroke	643 (6.6%)	286 (6.2%)	0.0157	4,097 (7.0%)	-0.0183
- TIA	344 (3.5%)	166 (3.6%)	-0.0041	2,388 (4.1%)	-0.0305
Diabetes mellitus (validated)	1,914 (19.5%)	990 (21.4%)	-0.046	10,431 (17.9%)	0.0424
Hyperlipidemia	2,035 (20.8%)	1,009 (21.8%)	-0.0252	13,153 (22.6%)	-0.0432
Hepatic injury	200 (2.0%)	102 (2.2%)	-0.0113	1,945 (3.3%)	-0.08
Lung cancer	295 (3.0%)	72 (1.6%)	0.0975	956 (1.6%)	0.0911
Cancer (excluding lung cancer)	1,627 (16.6%)	729 (15.8%)	0.0232	7,873 (13.5%)	0.087
Asthma	1,167 (11.9%)	1,226 (26.5%)	-0.3766	14,517 (24.9%)	-0.3397
BPH	1,808 (18.5%)	883 (19.1%)	-0.0161	7,328 (12.6%)	0.1633
Bladder obstruction/urinary retention	228 (2.3%)	108 (2.3%)	-0.0004	1,376 (2.4%)	-0.0021
Chronic kidney disease			0.1082		0.1476
No CKD	2,704 (27.6%)	1,099 (23.8%)		13,914 (23.9%)	
Stage unknown	142 (1.5%)	69 (1.5%)		820 (1.4%)	
Stage 1	24 (0.2%)	22 (0.5%)		390 (0.7%)	
Stage 2	4,782 (48.8%)	2,276 (49.2%)		27,369 (46.9%)	
Stage 3	1,928 (19.7%)	1,043 (22.5%)		14,065 (24.1%)	
Stage 4	177 (1.8%)	97 (2.1%)		1,423 (2.4%)	
Stage 5	41 (0.4%)	22 (0.5%)		351 (0.6%)	

POOLED	QVA N(%) 9,798	Fixed LABA LAMA N(%) 9,150	Std Dif	LABA N(%) 12,364	Std Dif
Cerebrovascular comorbidities	890 (9.1%)	913 (10.0%)	-0.0305	1,116 (9.0%)	0.002
- Stroke	643 (6.6%)	653 (7.1%)	-0.0227	768 (6.2%)	0.0144
- TIA	344 (3.5%)	410 (4.5%)	-0.0495	503 (4.1%)	-0.0292
Diabetes mellitus (validated)	1,914 (19.5%)	1,508 (16.5%)	0.0795	2,255 (18.2%)	0.0331
Hyperlipidemia	2,035 (20.8%)	2,032 (22.2%)	-0.035	2,585 (20.9%)	-0.0034
Hepatic injury	200 (2.0%)	357 (3.9%)	-0.1097	336 (2.7%)	-0.0444
Lung cancer	295 (3.0%)	262 (2.9%)	0.0087	172 (1.4%)	0.1106
Cancer (excluding lung cancer)	1,627 (16.6%)	1,319 (14.4%)	0.0605	1,742 (14.1%)	0.0698
Asthma	1,167 (11.9%)	1,880 (20.6%)	-0.2358	1,655 (13.4%)	-0.0444
BPH	1,808 (18.5%)	921 (10.1%)	0.2416	1,822 (14.7%)	0.1
Bladder obstruction/urinary retention	228 (2.3%)	261 (2.9%)	-0.0331	280 (2.3%)	0.0042
Chronic kidney disease			0.2343		0.0732
No CKD	2,704 (27.6%)	1,806 (19.7%)		3,152 (25.5%)	
Stage unknown	142 (1.5%)	101 (1.1%)		170 (1.4%)	
Stage 1	24 (0.2%)	40 (0.4%)		61 (0.5%)	
Stage 2	4,782 (48.8%)	4,451 (48.6%)		6,012 (48.6%)	
Stage 3	1,928 (19.7%)	2,498 (27.3%)		2,677 (21.7%)	
Stage 4	177 (1.8%)	211 (2.3%)		236 (1.9%)	
Stage 5	41 (0.4%)	43 (0.5%)		56 (0.5%)	

POOLED	QVA N(%) 9,798	LAMA N(%) 42,972	Std Dif
Cerebrovascular comorbidities	890 (9.1%)	4,047 (9.4%)	-0.0115
- Stroke	643 (6.6%)	3,010 (7.0%)	-0.0176
- TIA	344 (3.5%)	1,794 (4.2%)	-0.0345
Diabetes mellitus (validated)	1,914 (19.5%)	7,469 (17.4%)	0.0555
Hyperlipidemia	2,035 (20.8%)	9,942 (23.1%)	-0.0572
Hepatic injury	200 (2.0%)	1,516 (3.5%)	-0.0904
Lung cancer	295 (3.0%)	625 (1.5%)	0.1055
Cancer (excluding lung cancer)	1,627 (16.6%)	5,801 (13.5%)	0.0869
Asthma	1,167 (11.9%)	7,540 (17.6%)	-0.1595
BPH	1,808 (18.5%)	5,550 (12.9%)	0.1527
Bladder obstruction/urinary retention	228 (2.3%)	1,029 (2.4%)	-0.0045
Chronic kidney disease			0.1764
No CKD	2,704 (27.6%)	9,574 (22.3%)	
Stage unknown	142 (1.5%)	531 (1.2%)	
Stage 1	24 (0.2%)	217 (0.5%)	
Stage 2	4,782 (48.8%)	20,431 (47.5%)	
Stage 3	1,928 (19.7%)	10,901 (25.4%)	
Stage 4	177 (1.8%)	1,073 (2.5%)	
Stage 5	41 (0.4%)	245 (0.6%)	

Std Dif= Standardized difference

Std Dif of >0.5 or <-0.5 considered to be clinically meaningful

10.2.4 Use of other respiratory medications by exposure cohort

Use of other respiratory medications during the year prior to the index date and including the index date is presented in Table 10-8 and in Annex 2.1 - Table 15-6 for use of respiratory drugs in the different databases (by exposure cohort).

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

With respect to the use of single-ingredient short-acting bronchodilators (SAMA or SABA), the most frequently prescribed respiratory medication across all pooled exposure cohorts was SABA (48.6-69.8%) with lowest use in the LABA exposure cohort and highest use in the LAMA+LABA fixed combination. Use of SAMA ranged from 8.3-37%, with lowest use in the LAMA+LABA fixed combination and highest use in the LABA/ICS free combination. Use of SABA+SAMA fixed combinations ranged from 1.4% to 5.8% with lowest use in the LABA exposure cohort and highest use in the LAMA/LABA/ICS free combination.

The use of ICS (as monocomponent in one device) in the year prior the index date ranged from 12.5% to 26.3% (excluding those exposure cohorts where single ingredient ICS use at index date was present by definition) with lowest use in the cohort of new users of LABA and highest use in the LABA+ICS fixed combination.

Large differences in proportion of LABA and LAMA use (excluding those exposure cohorts where single ingredient LABA or LAMA was present by definition) were observed with lowest proportion in the LAMA cohort (5.4%) and highest use in the QVA149 cohort (28.1%). Use of LAMA ranged from 18.3% to 54.1%; with high use in the QVA149 cohort (52.2%) and the cohort of fixed combination of LABA+LAMA (other than QVA149) (54.1%).

Previous use of fixed-combination LABA+ICS ranged from 19.2% to 33.5% (excluding the LABA+ICS cohort where use at index date was present by definition) with highest use for the pooled QVA149 exposure cohort (33.5%) and the LAMA+LABA fixed cohort (32.3%). Previous use of fixed LABA+ICS combination was the lowest for the free combination of LABA and ICS.

Across pooled exposure cohorts, use of systemic corticosteroids in the year prior to the index date ranged from 27.5-52.5%. Systemic corticosteroids use for COPD exacerbation ranged from 8.1- to 17.1% with the highest prevalence in the cohort of patients with triple combination therapy (LAMA/LABA/ICS) and lowest use in LABA (8.1%) in monotherapy.

Previous use of xanthines ranged from 1.2 to 4.4% across pooled exposure cohorts with highest use in patients on triple therapy (LAMA/LABA/ICS). Use of LTRA ranged from 0.9 to 4.5% across all pooled exposure cohorts, with highest use in the LAMA/LABA/ICS cohorts. Finally, proportions of patients prescribed oral β_2-adrenergic agonists and oral PDE-4 inhibitors were low across all exposure cohorts and databases (<3%).

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 THIN (UK), where at least 83.7% of patients had used a SABA (range 83.7-94.7%) whereas the cohort-specific proportions for SAMA use in the UK ranged from 3.2-14.0%. Use of SAMA was almost non-existing in Denmark (Aarhus), whereas

in SIDIAP (Spain) the proportion of patients using SAMA (ranging from 31.9-53.5% across exposure cohorts) was similar to that of SABA (35.6-59.1%). In HSD (Italy) use of short-acting agents was lower than for the other databases namely between 4.3-13.7% for SAMA and 10.9-29.6% 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 2.0 to 8.3% in IPCI and Aarhus and ranged between 10.5-31.9% in HSD (Italy)

Use of systemic corticosteroids for the treatment of COPD in the year prior to the index date was higher in THIN (UK) (range 10.2-24.1%), IPCI (The Netherlands) (range 18.6-46.2%) and Aarhus (Denmark) (range 10.4-23.6%) compared to HSD (Italy) (range 4.3-8.4%) and SIDIAP (Spain) (range 3.7-7.9%).

Table 10-8 Use of other respiratory medications by exposure cohort, pooled

POOLED	QVA N(%)	Free LABA+LAMA without ICS N(%)	Std Dif	Free LABA+LAMA with ICS N(%)	Std Dif
Total	9,798 (100.0%)	9,619 (100.0%)		3,192 (100.0%)	
Single-ingredient short-acting muscarinic agents	2,024 (20.7%)	1,641 (17.1%)	0.0921	888 (27.8%)	-0.1677
Single-ingredient short-acting ß2 agonists	5,192 (53.0%)	5,223 (54.3%)	-0.0262	1,917 (60.1%)	-0.1429
LABA	2,756 (28.1%)	9,619 (100.0%)	-2.2605	3,192 (100.0%)	-2.2605
LAMA	5,113 (52.2%)	9,619 (100.0%)	-1.3537	3,192 (100.0%)	-1.3537
Inhaled corticosteroids (ICS)	2,542 (25.9%)	1,424 (14.8%)	0.2792	3,192 (100.0%)	-2.3892
Xanthines	214 (2.2%)	221 (2.3%)	-0.0077	140 (4.4%)	-0.1238
Fixed combination therapy LABA+ICS	3,282 (33.5%)	2,668 (27.7%)	0.1252	780 (24.4%)	0.2007
Fixed combination therapy LABA+LAMA	168 (1.7%)	63 (0.7%)	0.098	11 (0.3%)	0.136
QVA	9,798 (100.0%)	161 (1.7%)	10.8387	59 (1.9%)	10.3039
Fixed combination therapy other	0 (0.0%)	0 (0.0%)		0 (0.0%)	
Fixed combination therapy SABA+SAMA	234 (2.4%)	212 (2.2%)	0.0123	184 (5.8%)	-0.1713
Oral ß2-agonists	45 (0.5%)	33 (0.3%)	0.0184	12 (0.4%)	0.0129
Leukotriene receptor antagonists (LTRA)	205 (2.1%)	127 (1.3%)	0.0596	145 (4.5%)	-0.1371
Systemic corticosteroids	3,601 (36.8%)	3,355 (34.9%)	0.0391	1,676 (52.5%)	-0.3209
Systemic corticosteroids with indication COPD	1,062 (10.8%)	1,106 (11.5%)	-0.0209	546 (17.1%)	-0.1815
Oral phosphodiesterase-4 (PDE-4) inhibitors	129 (1.3%)	39 (0.4%)	0.0987	52 (1.6%)	-0.0259

POOLED	QVA N(%)	Free LABA+ICS N(%)	Std Dif	Fixed LABA ICS N(%)	Std Dif
Total	9,798 (100.0%)	4,628 (100.0%)		58,332 (100.0%)	
Single-ingredient short-acting muscarinic agents	2,024 (20.7%)	1,711 (37.0%)	-0.3662	10,269 (17.6%)	0.0777
Single-ingredient short-acting ß2 agonists	5,192 (53.0%)	2,517 (54.4%)	-0.028	33,769 (57.9%)	-0.0987
LABA	2,756 (28.1%)	4,628 (100.0%)	-2.2605	7,549 (12.9%)	0.3828
LAMA	5,113 (52.2%)	845 (18.3%)	0.7597	24,977 (42.8%)	0.1884
Inhaled corticosteroids (ICS)	2,542 (25.9%)	4,628 (100.0%)	-2.3892	15,332 (26.3%)	-0.0077
Xanthines	214 (2.2%)	108 (2.3%)	-0.0101	1,030 (1.8%)	0.0301
Fixed combination therapy LABA+ICS	3,282 (33.5%)	890 (19.2%)	0.3281	58,332 (100.0%)	-1.9926
Fixed combination therapy LABA+LAMA	168 (1.7%)	18 (0.4%)	0.1302	633 (1.1%)	0.0536
QVA	9,798 (100.0%)	50 (1.1%)	13.5307	686 (1.2%)	12.9638
Fixed combination therapy other	0 (0.0%)	0 (0.0%)		0 (0.0%)	
Fixed combination therapy SABA+SAMA	234 (2.4%)	198 (4.3%)	-0.1054	1,410 (2.4%)	-0.0019
Oral ß2-agonists	45 (0.5%)	19 (0.4%)	0.0074	176 (0.3%)	0.0256
Leukotriene receptor antagonists (LTRA)	205 (2.1%)	177 (3.8%)	-0.1024	1,227 (2.1%)	-0.0008
Systemic corticosteroids	3,601 (36.8%)	1,941 (41.9%)	-0.1063	22,672 (38.9%)	-0.0436
Systemic corticosteroids with indication COPD	1,062 (10.8%)	498 (10.8%)	0.0025	7,063 (12.1%)	-0.0398
Oral phosphodiesterase-4 (PDE-4) inhibitors	129 (1.3%)	22 (0.5%)	0.0894	88 (0.2%)	0.1369

POOLED	QVA N(%)	Fixed LABA LAMA N(%)	Std Dif	LABA N(%)	Std Dif
Total	9,798 (100.0%)	9,150 (100.0%)		12,364 (100.0%)	
Single-ingredient short-acting muscarinic agents	2,024 (20.7%)	757 (8.3%)	0.3576	2,726 (22.1%)	-0.0339
Single-ingredient short-acting ß2 agonists	5,192 (53.0%)	6,387 (69.8%)	-0.3506	6,010 (48.6%)	0.0877
LABA	2,756 (28.1%)	1,429 (15.6%)	0.3062	12364 (100.0%)	-2.2605
LAMA	5,113 (52.2%)	4,948 (54.1%)	-0.0379	2,676 (21.6%)	0.6671
Inhaled corticosteroids (ICS)	2,542 (25.9%)	1,578 (17.3%)	0.2126	1,548 (12.5%)	0.3456
Xanthines	214 (2.2%)	185 (2.0%)	0.0113	151 (1.2%)	0.0745
Fixed combination therapy LABA+ICS	3,282 (33.5%)	2,955 (32.3%)	0.0256	2,517 (20.4%)	0.2995
Fixed combination therapy LABA+LAMA	168 (1.7%)	9,150 (100.0%)	-10.7066	70 (0.6%)	0.1083
QVA	9,798 (100.0%)	497 (5.4%)	5.9006	121 (1.0%)	14.2249
Fixed combination therapy other	0 (0.0%)	0 (0.0%)		0 (0.0%)	
Fixed combination therapy SABA+SAMA	234 (2.4%)	233 (2.6%)	-0.0102	178 (1.4%)	0.0693
Oral ß2-agonists	45 (0.5%)	31 (0.3%)	0.0191	38 (0.3%)	0.0246
Leukotriene receptor antagonists (LTRA)	205 (2.1%)	155 (1.7%)	0.0292	116 (0.9%)	0.0946
Systemic corticosteroids	3,601 (36.8%)	3,759 (41.1%)	-0.0889	3,394 (27.5%)	0.2002
Systemic corticosteroids with indication COPD	1,062 (10.8%)	1,444 (15.8%)	-0.1459	1,000 (8.1%)	0.0941
Oral phosphodiesterase-4 (PDE-4) inhibitors	129 (1.3%)	44 (0.5%)	0.0886	13 (0.1%)	0.1446

POOLED	QVA N(%)	LAMA	Std Dif
Total	9,798 (100.0%)	42,972 (100.0%)	
Single-ingredient short-acting muscarinic agents	2,024 (20.7%)	6,617 (15.4%)	0.1371
Single-ingredient short-acting ß2 agonists	5,192 (53.0%)	23,395 (54.4%)	-0.0291
LABA	2,756 (28.1%)	2,298 (5.4%)	0.6408
LAMA	5,113 (52.2%)	42,972 (100.0%)	-1.3537
Inhaled corticosteroids (ICS)	2,542 (25.9%)	7,183 (16.7%)	0.2267
Xanthines	214 (2.2%)	582 (1.4%)	0.063
Fixed combination therapy LABA+ICS	3,282 (33.5%)	9,106 (21.2%)	0.2788
Fixed combination therapy LABA+LAMA	168 (1.7%)	147 (0.3%)	0.1364
QVA	9,798 (100.0%)	250 (0.6%)	18.487
Fixed combination therapy other	0 (0.0%)	0 (0.0%)	
Fixed combination therapy SABA+SAMA	234 (2.4%)	731 (1.7%)	0.0486
Oral ß2-agonists	45 (0.5%)	103 (0.2%)	0.0372
Leukotriene receptor antagonists (LTRA)	205 (2.1%)	634 (1.5%)	0.0466
Systemic corticosteroids	3,601 (36.8%)	12,874 (30.0%)	0.1445
Systemic corticosteroids with indication COPD	1,062 (10.8%)	3,830 (8.9%)	0.0646
Oral phosphodiesterase-4 (PDE-4) inhibitors	129 (1.3%)	31 (0.1%)	0.1503

Std Dif= Standardized difference
Std Dif of >0.5 or <-0.5 considered to be clinically meaningful

10.2.5 Use of concomitant medication other than respiratory medications

Use of concomitant medications (other than respiratory medications), which were assessed on the index date and during the year prior to the index date, is presented in Annex 2.1 - Table 15-7.

In line with the most frequently observed comorbidities, namely arterial hypertension, hyperlipidemia and diabetes mellitus, the proportion of patients using antihypertensive medication was high (range 61.9-69.8%), followed by lipid-lowering medications (range 42.5-47.6%), antithrombotic agents (platelet aggregation inhibitors or oral anticoagulants) (range 37.6-44.9%) and anti-diabetic medications (range 14.5-20.3%), across all pooled exposure cohorts.

Previous use of opioids ranged between 22.3-33.8%, of hypnotics ranged between 8.3-10.2%, of anxiolytics between 10.7-22.5%, of SSRI between 13.7-15.6% and of tricyclic and tetracyclic antidepressants between 10.9-16.6%. Previous use of antipsychotics ranged between 5.2-6.5%.

Country-specific differences were observed in relation to the use of hypnotics and anxiolytics across cohorts; use of these medications in Aarhus (Denmark) ranged from 0.3 to 1.2% and from 0.3 to 0.6%, respectively, whereas higher use was observed in the other databases (range 3.9-16.3%, range 7.9-30.2%, respectively), with the highest use in THIN (UK) and SIDIAP (Spain). Use of antidepressants was the highest in THIN and Aarhus and use of opioids was the highest in THIN (UK) (37.5-43.5%) and Aarhus (Denmark) (range 26.0-33.0%).

In the pooled dataset as well as in the individual databases, use of H1 antihistamines was the highest in ICS containing regimens. (pooled dataset 18.6% for free LABA+ICS combination)

In THIN, use of opioids (43.5%), hypnotics and sedatives (10.5%), SSRI (19.2%), antidepressants (other than SSRI) 21.8%, antithrombotic agents (41.2%), lipid lowering drugs (50.5%), nitrates (13.9%) and antihypertensive drugs (62.3%) was higher in QVA149 than in the other exposure cohorts. In the other databases, highest use in QVA149 was reported for antipsychotic drugs (4.7%) and antidepressants (11.9%) for IPCI; anxiolytics (14.0%) and platelet aggregation inhibitors (47.8%) for HSD.

10.3 Outcome data

According to the protocol, validation of endpoints as identified for the final 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 15-8 . Data are provided for the validation of COPD (sample of COPD patients) and the outcomes of interest.

With regard to the outcomes of interest, huge ranges in positive predictive value (PPV) between outcomes and databases were observed mainly because of low number for certain outcomes.

With regard to the validated outcomes which are part of the primary endpoints (atrial fibrillation/flutter, angina pectoris, hospitalization for heart failure, hospitalization for acute coronary syndrome, LongQTc, myocardial infarction, stroke, TIA, Torsade de Pointes, unstable AP, ventricular fibrillation and ventricular tachycardia), in IPCI, the range of PPV varied between 50% (LongQTc) and 100% (ventricular fibrillation and ventricular tachycardia). In

HSD (Italy), the PPV ranged between 26.4% (stroke) and 100% (LongQTc, Torsade de Pointes, unstable angina pectoris, and ventricular tachycardia). In SIDIAP, the PPV ranged between 75.7% (stroke) and 100% (LongQTc ventricular fibrillation).

With regard to the validated outcomes which are part of the secondary endpoints (benign prostatic hyperplasia (BPH), bronchospasm, narrow angle glaucoma, other glaucoma, bladder outflow obstruction/urinary retention), in IPCI, the range of PPV varied between 9.7% (bronchospasm) and 89.1% (bladder outflow obstruction/urinary retention). In HSD (Italy), the PPV ranged between 7.3% (bronchospasm) and 100% (bladder outflow obstruction/urinary retention). In SIDIAP, the PPV ranged between 28.2% (bronchospasm) and 85.6% (bladder outflow obstruction/urinary retention).

10.3.1 Frequencies of primary endpoints in the pooled dataset

Frequencies of patients having a new diagnosis of an event of interest during cohort time, by database and exposure cohort, are presented in Annex 2.1- Table 15-9. The proportions do not account for differences between the cohorts in the length of follow-up time.

Database-pooled frequencies and corresponding proportions of patients having a new primary endpoint, by exposure cohort, are described below and presented in Table 10-9. Patients can contribute to multiple end-points and some endpoints, such as major adverse cardiovascular events, consist of multiple events. For this description, the proportion of the endpoints within the cohorts for the main analysis (= cohort time restricted to 1 year) are described.

The proportion of patients with major adverse cardiovascular events was 2.8% for the QVA149 cohort, 1.2% for the anchor (LAMA/LABA free combination) and ranged between 1.3% (free LABA/LAMA/ICS and free LABA/ICS) - 2.2% (fixed LABA+LAMA) for the other exposure cohorts.

The proportion of patients with ischemic heart disease during cohort time was 0.7% for the QVA149 cohort, 0.4% for the anchor and ranged between 0.3% (free LABA/ICS, LABA) and 0.5% (fixed LABA+LAMA, fixed LABA+ICS) for the other exposure cohorts.

The proportion of patients with events of cardiac arrhythmia during follow-up was 0.8% for the QVA149 cohort, 0.6% for the anchor and ranged between 0.5% (LABA)-0.9% (fixed LABA+LAMA cohort) for the other exposure cohorts.

Cerebrovascular events during follow-up were reported in 0.5% of QVA149 cohort, 0.3% of the anchor and in 0.4% (free LABA/LAMA/ICS, free LABA/ICS, LABA) - 0.6% (fixed LABA+LAMA cohort) of the other exposure cohorts.

10.3.2 Frequencies of secondary endpoints in the pooled dataset

Database-pooled frequencies and corresponding proportions of patients having a new secondary endpoint, by exposure cohort, are presented in Table 10-10.

10.3.3 Cause specific death

Cause-specific death was assessed for those databases where cause of death is captured, namely IPCI (The Netherlands), Aarhus (Denmark) and THIN. Cause-specific death was categorized

as cardiovascular death, respiratory death (including lung cancer), cardiovascular and respiratory death, cerebrovascular death, cancer death, death due to other causes or cause of death unknown.

Cause-specific death by exposure cohort is provided in Annex 2.1- Table 15-10. The proportion of cause of death is not described in the text below if the number of patients with a specific cause of death is below 6.

In THIN, the proportion of patients for whom cause of death was unknown was high, and ranged from 95-100% across cohorts. This finding is attributed to patient de-registration from the general practice by a central National Health Service (NHS) system, as soon as notification of death is received. Cause of death is documented in the death certificate but this is not routinely available in the THIN database. As the number of patients with known cause of death is low in THIN, cause of death is not described in detail.

In IPCI, the proportion of patients for whom cause of death was missing was lower but still ranged between 13 and 33.3%. In IPCI, patients mainly died because of respiratory death (range 30.0 (free LABA/LAMA combination without ICS)-66.7% (free LABA+ICS) of patients with known cause of death). Cardiovascular death was reported in 30% for the anchor (LABA/LAMA free combination without ICS) and was up to 16.3% for the other exposure cohorts. Cardiovascular and respiratory related death was reported in 10.6% of the fixed LABA+ICS cohort and 12.1% in LAMA.

In Aarhus, the proportion of patients for whom cause of death was missing ranged between 6.3-85.3%). In Aarhus, patients mainly died because of respiratory death (range 12.5-53.3%) and cardiovascular death (range 18.1-24.3%). In the QVA149 exposure cohort, 24.3% were cardiovascular and 36.5% were respiratory deaths whereas the proportion of respiratory deaths was 53.3% for the anchor (LABA/LAMA free combination).

As the number of deceased study patients is small in many of the IPCI, Aarhus and THIN exposure cohorts and also because the proportion of patients where cause of death is lacking, it is difficult to draw conclusions on differences in cause of death across exposure cohorts.

Table 10-9 Number of patients with event of primary outcome of interest, by exposure cohort, pooled

Endpoint	Time Period	QVA149	Free LABA+LAMA without ICS	Free LABA+LAMA with ICS	Free LABA+ICS	Fixed LABA+ICS	Fixed LABA+LAMA	LABA	LAMA
		9,798	9,619	3,192	4,628	58,332	9,150	12,364	42,972
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
MACE	Total FU	528 (5.4%)	512 (5.3%)	188 (5.9%)	238 (5.1%)	2,746 (4.7%)	312 (3.4%)	534 (4.3%)	1,932 (4.5%)
	Cohort Time	292 (3.0%)	126 (1.3%)	44 (1.4%)	61 (1.3%)	1,125 (1.9%)	206 (2.3%)	151 (1.2%)	644 (1.5%)
	CT 1 yr	272 (2.8%)	119 (1.2%)	42 (1.3%)	59 (1.3%)	1,024 (1.8%)	197 (2.2%)	146 (1.2%)	593 (1.4%)
	CT ext 60	287 (2.9%)	121 (1.3%)	45 (1.4%)	65 (1.4%)	1,164 (2.0%)	209 (2.3%)	162 (1.3%)	648 (1.5%)
	Unr drugs	284 (2.9%)	125 (1.3%)	44 (1.4%)	65 (1.4%)	1,037 (1.8%)	205 (2.2%)	184 (1.5%)	709 (1.6%)
Ischemic heart disease	Total FU	143 (1.5%)	179 (1.9%)	71 (2.2%)	67 (1.4%)	976 (1.7%)	110 (1.2%)	204 (1.6%)	817 (1.9%)
	Cohort Time	76 (0.8%)	46 (0.5%)	14 (0.4%)	16 (0.3%)	345 (0.6%)	56 (0.6%)	41 (0.3%)	240 (0.6%)
	CT 1 yr	67 (0.7%)	40 (0.4%)	13 (0.4%)	14 (0.3%)	301 (0.5%)	50 (0.5%)	41 (0.3%)	210 (0.5%)
	CT ext 60	72 (0.7%)	40 (0.4%)	13 (0.4%)	14 (0.3%)	344 (0.6%)	54 (0.6%)	49 (0.4%)	231 (0.5%)
	Unr drugs	69 (0.7%)	44 (0.5%)	13 (0.4%)	16 (0.3%)	307 (0.5%)	56 (0.6%)	53 (0.4%)	256 (0.6%)
Cardiac arrhythmia	Total FU	203 (2.1%)	281 (2.9%)	106 (3.3%)	136 (2.9%)	1,462 (2.5%)	145 (1.6%)	291 (2.4%)	1,060 (2.5%)
	Cohort Time	91 (0.9%)	57 (0.6%)	23 (0.7%)	29 (0.6%)	554 (0.9%)	88 (1.0%)	58 (0.5%)	334 (0.8%)
	CT 1 yr	80 (0.8%)	54 (0.6%)	21 (0.7%)	28 (0.6%)	490 (0.8%)	79 (0.9%)	56 (0.5%)	300 (0.7%)
	CT ext 60	87 (0.9%)	58 (0.6%)	21 (0.7%)	33 (0.7%)	555 (1%)	84 (0.9%)	70 (0.6%)	341 (0.8%)
	Unr drugs	93 (0.9%)	60 (0.6%)	21 (0.7%)	31 (0.7%)	492 (0.8%)	89 (1.0%)	71 (0.6%)	354 (0.8%)
Cerebrovascu-lar disorders	Total FU	142 (1.4%)	192 (2%)	62 (1.9%)	85 (1.8%)	1,072 (1.8%)	101 (1.1%)	235 (1.9%)	857 (2.0%)
	Cohort Time	60 (0.6%)	27 (0.3%)	14 (0.4%)	17 (0.4%)	334 (0.6%)	58 (0.6%)	54 (0.4%)	228 (0.5%)
	CT 1 yr	53 (0.5%)	25 (0.3%)	14 (0.4%)	17 (0.4%)	269 (0.5%)	51 (0.6%)	48 (0.4%)	199 (0.5%)
	CT ext 60	61 (0.6%)	26 (0.3%)	15 (0.5%)	19 (0.4%)	329 (0.6%)	54 (0.6%)	58 (0.5%)	219 (0.5%)
	Unr drugs	54 (0.6%)	26 (0.3%)	16 (0.5%)	17 (0.4%)	273 (0.5%)	52 (0.6%)	55 (0.4%)	239 (0.6%)

Total FU= means total follow-up from start of cohort entry until the end of the studyperiod, leaving the database or death, whatever came first, CT= cohort time, Unr drugs= Cohort time not censored at start other drugs, MACE= Major adverse cardiovascular event, MACE consists of MI, stroke, hospitalization because of acute coronary syndrome or hospitalization because of heart failure; Ischemic heart disease includes myocardial infarction and angina pectoris; Cardiac arrhythmia consist of newly diagnosed atrial fibrillation/flutter, ventricular tachycardia, ventricular fibrillation and Torsade de Pointes; Cerebrovascular events consist of ischemic and hemorrhagic stroke or transient ischemic attacks.

Table 10-10 Number of patients with event of secondary outcome of interest, by exposure cohort, pooled

Endpoint	Time period	QVA149	Free LABA+LAMA without ICS	Free LABA+LAMA with ICS	Free LABA+ICS	Fixed LABA+ICS	Fixed LABA+LAMA	LABA	LAMA
		9,798	9,619	3,192	4,628	58,332	9,150	12,364	42,972
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Glaucoma*	Total FU	50 (0.5%)	68 (0.7%)	22 (0.7%)	33 (0.7%)	358 (0.6%)	18 (0.2%)	77 (0.6%)	260 (0.6%)
	Cohort Time	19 (0.2%)	15 (0.2%)	6 (0.2%)	1 (0.0%)	92 (0.2%)	10 (0.1%)	17 (0.1%)	74 (0.2%)
	CT 1 yr	15 (0.2%)	15 (0.2%)	6 (0.2%)	1 (0.0%)	77 (0.1%)	9 (0.1%)	17 (0.1%)	67 (0.2%)
	CT ext 60	18 (0.2%)	16 (0.2%)	7 (0.2%)	1 (0.0%)	90 (0.2%)	10 (0.1%)	18 (0.1%)	78 (0.2%)
	Unr drugs	15 (0.2%)	16 (0.2%)	6 (0.2%)	1 (0.0%)	77 (0.1%)	11 (0.1%)	18 (0.1%)	79 (0.2%)
Urology events*	Total FU	215 (2.2%)	284 (3.0%)	92 (2.9%)	132 (2.9%)	1,211 (2.1%)	73 (0.8%)	308 (2.5%)	944 (2.2%)
	Cohort Time	94 (1.0%)	58 (0.6%)	17 (0.5%)	15 (0.3%)	381 (0.7%)	44 (0.5%)	76 (0.6%)	267 (0.6%)
	CT 1 yr	80 (0.8%)	51 (0.5%)	16 (0.5%)	15 (0.3%)	344 (0.6%)	39 (0.4%)	73 (0.6%)	244 (0.6%)
	CT ext 60	91 (0.9%)	54 (0.6%)	16 (0.5%)	15 (0.3%)	391 (0.7%)	40 (0.4%)	80 (0.6%)	273 (0.6%)
	Unr drugs	84 (0.9%)	53 (0.6%)	17 (0.5%)	18 (0.4%)	347 (0.6%)	42 (0.5%)	87 (0.7%)	299 (0.7%)
Diabetes mellitus	Total FU	152 (1.6%)	198 (2.1%)	67 (2.1%)	82 (1.8%)	1,128 (1.9%)	94 (1%)	212 (1.7%)	764 (1.8%)
	Cohort Time	82 (0.8%)	58 (0.6%)	12 (0.4%)	14 (0.3%)	443 (0.8%)	65 (0.7%)	58 (0.5%)	256 (0.6%)
	CT 1 yr	76 (0.8%)	52 (0.5%)	12 (0.4%)	13 (0.3%)	386 (0.7%)	59 (0.6%)	54 (0.4%)	234 (0.5%)
	CT ext 60	79 (0.8%)	54 (0.6%)	12 (0.4%)	16 (0.3%)	429 (0.7%)	61 (0.7%)	59 (0.5%)	252 (0.6%)
	Unr drugs	81 (0.8%)	56 (0.6%)	14 (0.4%)	15 (0.3%)	389 (0.7%)	60 (0.7%)	62 (0.5%)	270 (0.6%)
(paradoxical)Bron-chospasm	Total FU	23 (0.2%)	26 (0.3%)	24 (0.8%)	39 (0.8%)	308 (0.5%)	10 (0.1%)	41 (0.3%)	133 (0.3%)
	Cohort Time	6 (0.1%)	3 (0.0%)	2 (0.1%)	6 (0.1%)	52 (0.1%)	4 (0.0%)	6 (0.0%)	15 (0.0%)
	CT 1 yr	6 (0.1%)	3 (0.0%)	2 (0.1%)	6 (0.1%)	51 (0.1%)	4 (0.0%)	6 (0.0%)	14 (0.0%)
	CT ext 60	8 (0.1%)	3 (0.0%)	2 (0.1%)	6 (0.1%)	63 (0.1%)	6 (0.1%)	6 (0.0%)	18 (0.0%)
	Unr drugs	7 (0.1%)	4 (0.0%)	2 (0.1%)	7 (0.2%)	51 (0.1%)	5 (0.1%)	9 (0.1%)	22 (0.1%)
Mortality	Total FU	840 (8.6%)	864 (9.0%)	331 (10.4%)	402 (8.7%)	5,140 (8.8%)	484 (5.3%)	861 (7.0%)	3238 (7.5%)
	Cohort Time	312 (3.2%)	96 (1.0%)	20 (0.6%)	46 (1.0%)	1,588 (2.7%)	232 (2.5%)	159 (1.3%)	687 (1.6%)
	CT 1 yr	251 (2.6%)	88 (0.9%)	18 (0.6%)	46 (1.0%)	1,330 (2.3%)	209 (2.3%)	149 (1.2%)	612 (1.4%)
	CT ext 60	301 (3.1%)	95 (1.0%)	20 (0.6%)	60 (1.3%)	1,644 (2.8%)	243 (2.7%)	178 (1.4%)	745 (1.7%)
	Unr drugs	265 (2.7%)	96 (1.0%)	19 (0.6%)	49 (1.1%)	1349 (2.3%)	229 (2.5%)	197 (1.6%)	805 (1.9%)

Total FU= means total follow-up from start of cohort entry until the end of the study period, leaving the database or death, whatever came first, CT= cohort time, Unr drugs= Cohort time not censored at start other drugs, Urology events consisting of bladder outflow obstruction/urinary retention/BPH, glaucoma consisting of narrow angle glaucoma and other glaucoma

10.4 Main results

10.4.1 Incidence rates across exposure cohorts

Database-pooled, crude incidence rates (with 95% CIs) for the main events of interest are presented in Table 10-11 and Figure 10-1 and Figure 10-2.

Primary outcomes

The unadjusted incidence rate of major adverse cardiovascular events was 58.8/1,000 PY for the QVA149 cohort, 40.7 for the anchor (free LABA and LAMA combination without ICS) and ranged between 38.6/1,000PY (LAMA)-65.2/1,000 PY (LABA/ICS free combination) for the other exposure cohorts. Amongst major adverse cardiovascular events, mainly hospitalization for heart failure was reported. Incidence rate of hospitalization for heart failure was 40.6/1,000 PY for QVA149, 22.8/1,000 PY for the anchor and ranged between 20.6/1,000 PY (LAMA)-38.2/1,000 PY (LABA/ICS free combination) for the other exposure cohorts.

The incidence rate of ischemic heart disease was 15.1/1,000 PY for the QVA149 cohort, 14.8/1,000 PY for the anchor and ranged between 10.7/1,000 PY (LABA)-19.4/1,000 PY (free LAMA/LABA/ICS combination) for the other exposure cohorts.

The incidence of cardiac arrhythmia was 18/1,000 PY for the QVA149 cohort, 18.3/1,000 PY for the anchor and ranged between 15.1/1,000 PY (LABA)-31.8/1,000 PY (free LABA/LAMA/ICS combination) for the other exposure cohorts. For cardiac arrhythmia mainly atrial flutter/fibrillation was reported. The incidence rate of this event was 19.7/1,000 PY for QVA149, 20.3/1,000 PY for the anchor and ranged between 16.8/1,000 PY (LABA)-35.3/1,000 PY (free LABA/ICS combination) for the other exposure cohorts.

The incidence rate of cerebrovascular events was 11.9/1,000 PY for the QVA149 cohort, 8.7/1,000 PY for the anchor and ranged between 12.7/1,000 PY (LABA+ICS fixed combination)-19.3/1,000 PY (free LAMA/LABA/ICS combination) across the other exposure cohorts.

With regard to database specific incidence rates of the primary outcomes, these were the highest in Aarhus for major adverse cardiovascular events (range 116-203/1,000 PY) and ischemic heart disease (range 18.9-74.6/1,000 PY) whereas the incidence rates of major adverse cardiovascular events (range 0-24.4/1,000 PY) and ischemic heart disease (range 18.9-74.6/1,000 PY) was the lowest in HSD.

Secondary outcomes

The unadjusted incidence rate of mortality was 61.4/1,000 PY for the QVA cohort, 30.7/1,000 PY for the anchor and ranged between 27.5/1,000 PY (free LAMA/LABA/ICS combination)-60.0/1,000 PY (fixed LABA+ICS combination) across the other exposure cohorts.

The incidence rate of diabetes mellitus was 19.9/1,000 PY for the QVA149 cohort, 22.6/1,000 PY for the anchor and ranged between 17.9/1,000 PY (fixed LABA+LAMA combination)-20.1/1,000 PY (fixed LABA+ICS).

The incidence rate of BOO/urinary retention/BPH was 18.6/1,000 PY for the QVA149 cohort, 18.7/1,000 PY for the anchor and ranged between 10.3/1,000 PY (fixed LAMA+LABA)-23.5/1,000 PY (free LAMA/LABA/ICS) across the other exposure cohorts.

The incidence rates of (narrow angle) glaucoma and paradoxical bronchospasm were low across all treatments.

With regard to database specific incidence rates of the secondary outcomes, these were the lowest in Aarhus for glaucoma (range 0-4.8/1,000 PY), BOO/urinary retention/BPH (range 0-14.4/1,000 PY) and diabetes mellitus (range 0-13.5/1,000 PY). The incidence of mortality was the lowest in HSD (range 9.1-48.7/1,000 PY) and SIDIAP (range 14.3-51.1/1,000 PY).

Table 10-11 Crude incidence rates for outcomes of interest, by exposure cohort, pooled

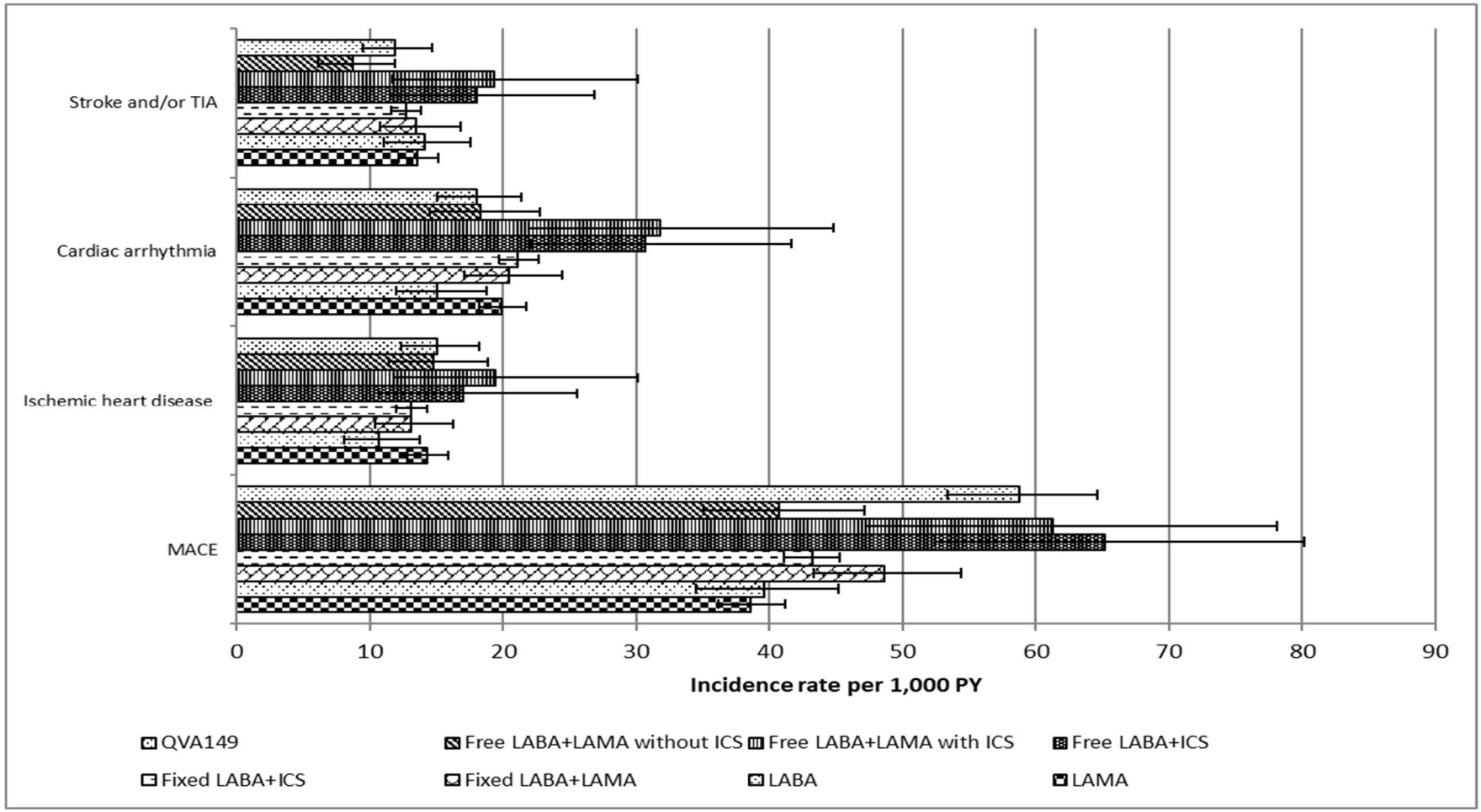
	QVA149				Free LABA+LAMA without ICS				Free LABA+LAMA with ICS			
Endpoint	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
MACE	292	4,964	58.8	[53.4,64.6]	126	3,093	40.7	[35.1,47.1]	44	718	61.3	[47.2,78.1]
Ischemic heart disease	76	5,045	15.1	[12.4,18.2]	46	3,106	14.8	[11.4,18.9]	14	722	19.4	[11.8,30.1]
Cardiac arrhythmia	91	5,042	18.0	[15.1,21.4]	57	3,112	18.3	[14.5,22.8]	23	722	31.8	[21.9,44.8]
Cerebrovascular disorders	60	5,059	11.9	[9.5,14.7]	27	3,116	8.7	[6.1,11.9]	14	724	19.3	[11.7,30.1]
Glaucoma	19	5,078	3.7	[2.5, 5.5]	15	3,123	4.8	[3.0, 7.4]	6	725	8.3	[3.6,16.3]
Bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia	94	5,046	18.6	[15.6,22.1]	58	3,105	18.7	[14.9,23.2]	17	722	23.5	[15.1,35.1]
Diabetes mellitus	82	4,117	19.9	[16.5,23.9]	58	2,564	22.6	[18.0,28.1]	12	601	20.0	[11.6,32.2]
Bronchospasm	6	5,082	1.2	[0.5, 2.3]	3	3,127	1.0	[0.3, 2.5]	2	725	2.8	[0.5, 8.7]
Mortality	312	5,084	61.4	[55.9,67.2]	96	3,127	30.7	[25.8,36.3]	20	727	27.5	[18.3,39.7]

	Free LABA+ICS				Fixed LABA ICS				Fixed LABA LAMA			
Endpoint	Events	PY	IR	95% CI	Events	PY	IR	95% CI	Events	PY	IR	95% CI
MACE	61	935	65.2	[52.4,80.1]	1,125	26,065	43.2	[41.1,45.3]	206	4,241	48.6	[43.3,54.4]
Ischemic heart disease	16	943	17.0	[10.7,25.6]	345	26,287	13.1	[12.0,14.3]	56	4,284	13.1	[10.4,16.3]
Cardiac arrhythmia	29	943	30.7	[22.1,41.7]	554	26,212	21.1	[19.7,22.7]	88	4,283	20.5	[17.1,24.5]
Cerebrovascular disorders	17	945	18.0	[11.5,26.9]	334	26,303	12.7	[11.6,13.9]	58	4,291	13.5	[10.8,16.8]
Glaucoma	1	948	1.1	[0.1, 5.0]	92	26,406	3.5	[2.9, 4.1]	10	4,305	2.3	[1.3, 3.9]
Bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia	15	946	15.9	[9.8,24.3]	381	26,287	14.5	[13.3,15.8]	44	4,290	10.3	[7.9,13.2]
Diabetes mellitus	14	751	18.6	[11.3,29.0]	443	22,012	20.1	[18.6,21.8]	65	3,624	17.9	[14.5,22.0]
Bronchospasm	6	946	6.3	[2.8,12.5]	52	26,442	2.0	[1.5, 2.5]	4	4,309	0.9	[0.3, 2.1]
Mortality	46	948	48.5	[37.6,61.6]	1,588	26,455	60.0	[57.6,62.5]	232	4,310	53.8	[48.3,59.8]

	LABA				LAMA			
Endpoint	Events	PY	IR	95% CI	Events	PY	IR	95% CI
MACE	151	3,812	39.6	[34.5,45.2]	644	16,665	38.6	[36.2,41.2]
Ischemic heart disease	41	3,836	10.7	[8.1,13.8]	240	16,757	14.3	[12.8,15.9]
Cardiac arrhythmia	58	3,830	15.1	[12.0,18.8]	334	16,748	19.9	[18.2,21.8]
Cerebrovascular disorders	54	3,834	14.1	[11.1,17.6]	228	16,767	13.6	[12.2,15.2]
Glaucoma	17	3,846	4.4	[2.8, 6.6]	74	16,831	4.4	[3.6, 5.3]
Bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia	76	3,827	19.9	[16.3,24.0]	267	16,761	15.9	[14.4,17.6]
Diabetes mellitus	58	3,168	18.3	[14.6,22.7]	256	14,027	18.3	[16.4,20.2]
Bronchospasm	6	3,850	1.6	[0.7, 3.1]	15	16,859	0.9	[0.5, 1.4]
Mortality	159	3,851	41.3	[36.1,47.0]	687	16,863	40.7	[38.3,43.3]

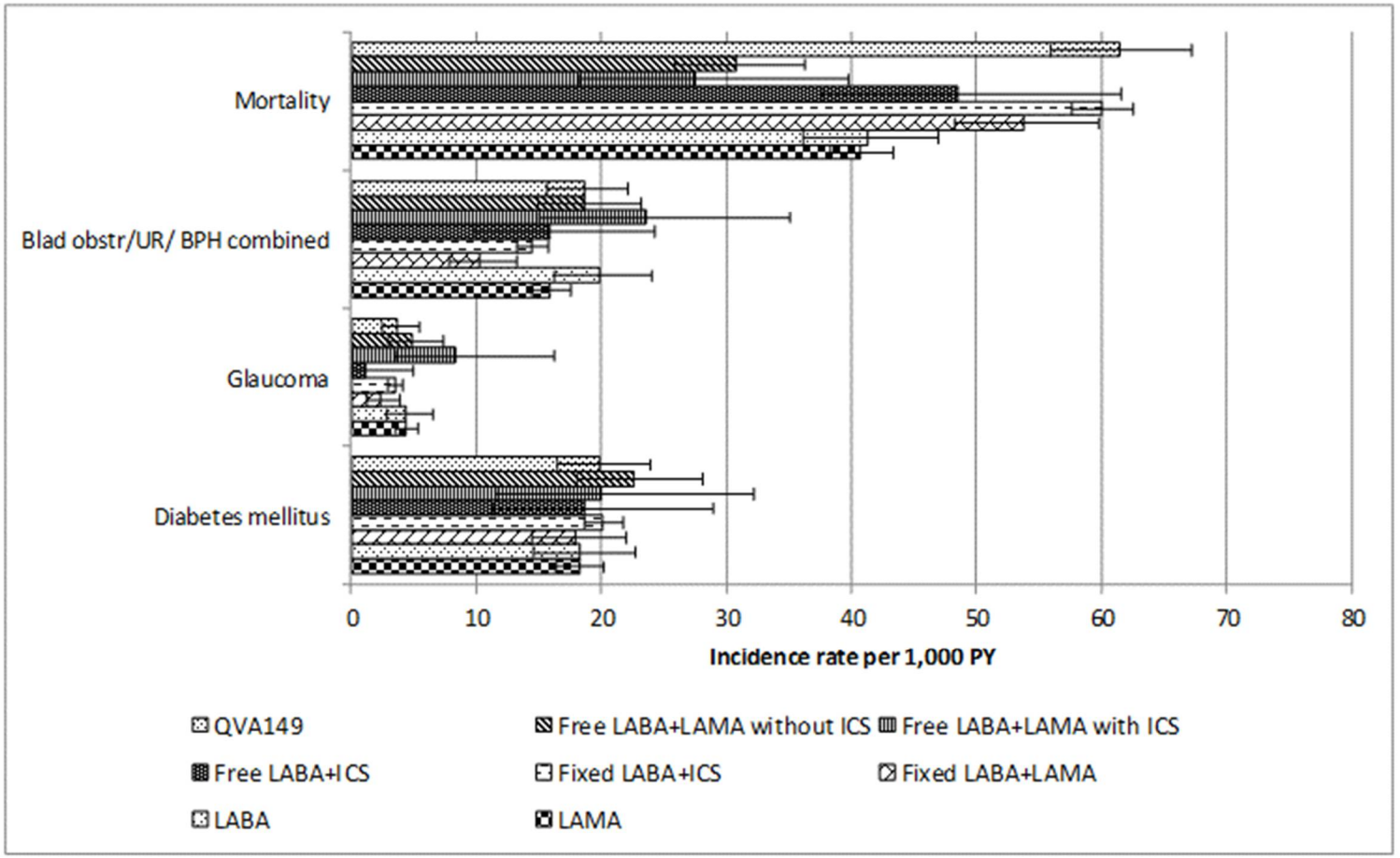
MACE= Major adverse cardiovascular event, MACE consists of MI, stroke, hospitalization because of acute coronary syndrome or hospitalization because of heart failure; Ischemic heart disease includes myocardial infarction and angina pectoris; Cardiac arrhythmia consist of newly diagnosed atrial fibrillation/flutter, ventricular tachycardia,ventricular fibrillation and Torsade de Pointes; Cerebrovascular events consist of ischemic and hemorrhagic stroke or transient ischemic attacks

Figure 10-1 Crude incidence rates of primary outcomes



I—I = 95% Confidence interval, MACE= Major adverse cardiovascular event which consists of MI, stroke, hospitalization because of acute coronary syndrome or hospitalization because of heart failure; Ischemic heart disease includes myocardial infarction and angina pectoris; Cardiac arrhythmia consist of newly diagnosed atrial fibrillation/flutter, ventricular tachycardia,ventricular fibrillation and Torsade de Pointes; Stroke consist of ischemic and hemorrhagic stroke, TIA= Transient Ischemic attack

Figure 10-2 Crude incidence rates of secondary outcomes



I—I = 95% Confidence interval, Blad obstr= bladder obstruction, UR= urinary retention. BPH=incident benign prostatic hyperplasia

10.4.2 Kaplan Meier Curves

Kaplan Meier curves by treatment cohort for mortality in the pooled dataset and by database are presented in Annex 2.1 - Figure 15-8 – Figure 15-13. Note that in these figures, the x-axis (follow-time) is restricted to 365 days, as is done in the analyses. The y-axis starts at .90, indicating 90% survivors. The colored areas indicate the 95% confidence bands of the survival curves. Reported at each figure is the p-value of the logrank test, testing the crude difference between the eight survival curves.

10.4.3 Hazard ratios comparing QVA149 vs. LABA/LAMA free combination without ICS for primary outcomes

The HRs of QVA149 in comparison to the LABA/LAMA free combination without ICS for the primary outcomes in the database-pooled data are described in Table 10-12. For this report, both crude HR, HR adjusted for a priori confounders (age, gender, smoking status and COPD severity) and HR from IPTW analysis are described. The HRs of the a priori confounders in the adjusted model are provided in Annex 2.1.

The IPTW analysis was considered as the main model.

10.4.3.1 Hazard ratios for major adverse cardiovascular events (MACE)

The crude HR of major adverse cardiovascular events (myocardial infarction, stroke, and hospitalizations because of acute coronary syndrome and/or heart failure) in QVA149 users in comparison to LABA/LAMA free combination was 1.18 (95% CI 0.94-1.47). Upon adjustment for a priori confounders, this HR was 1.19 (95% CI 0.94-1.49). The HR from the IPTW analysis was similar: 1.18 (95% CI 0.93-1.51) (Table 10-12).

Database specific HRs are described in Annex 2.1. When exploring results from the IPTW analysis by database, in none of the databases, the HR of major adverse cardiovascular events for QVA149 in comparison to LABA/LAMA free combination was statistically significant. In THIN (UK), the HR was the highest, namely with a HR of 1.33 (95% CI 0.63-2.80). The HR was the lowest in Aarhus (DK), with a HR of 1.03 (95% CI 0.68-1.56). In HSD (IT), no HR for major adverse cardiovascular events could be estimated because of few MAJOR ADVERSE CARDIOVASCULAR events (<5) in the respective exposure cohorts.

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 15-14).

10.4.3.2 Hazard ratios for ischemic heart disease

The crude HR of ischemic heart disease (myocardial infarction and (unstable) angina pectoris) in QVA149 users in comparison to LABA/LAMA free combination (no ICS) was 1.09 (95% CI 0.71-1.66). Upon adjustment for a priori confounders, this HR was 1.09 (95% CI 0.72-1.67). The HR from the IPTW analysis was 1.22 (95% CI 0.72-2.08) (Table 10-12).

Database specific HRs are described in Annex 2.1. When exploring results from the IPTW analysis by database, in none of the databases the HR of ischemic heart disease for QVA149 in comparison to LABA/LAMA free combination was statistically significant. In THIN (UK), the

HR was the highest, namely with a HR of 2.23 (95% CI 0.96-5.20). The HR was the lowest in SIDIAP (ES), with a HR of 0.60 (95% CI 0.27-1.34). In IPCI (NL), Aarhus (DK) and HSD (IT), no HR for ischemic heart disease could be estimated because of few events (<5) in the respective exposure cohorts. 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 15-21).

10.4.3.3 Hazard ratios for cardiac arrhythmia

The crude HR of cardiac arrhythmia (atrial fibrillation/flutter, ventricular tachycardia,ventricular fibrillation and Torsade de Pointes) in QVA149 users in comparison to LABA/LAMA free combination was 0.95 (95% CI 0.66-1.37). Upon adjustment for a priori confounders, this HR was 0.96 (95% CI 0.67-1.39). The HR from the IPTW analysis was 1.31 (95% CI 0.81-2.10) (Table 10-12).

Database specific HRs are described in Annex 2.1. When exploring results from the IPTW analysis by database, in none of the databases, the HR of cardiac arrhythmia for QVA149 in comparison to LABA/LAMA free combination was statistically significant. In THIN (UK), the HR was the highest, namely with a HR of 3.31 (95% CI 0.97-11.20). The HR was the lowest in SIDIAP (ES), with a HR of 1.04 (95% CI 0.61-1.78). In HSD (IT), no HR for cardiac arrhythmia could be estimated because of few events (<5) in the respective exposure cohorts.

The meta-analysis of the IPTW results provided lower estimates (HR 1.25, 95% CI 0.84-1.88) as the pooled IPTW analysis, both for the fixed- and random-effect model. In the pooled analysis, the database by-treatment interaction was statistically significant (p=0.3773) (Annex 2.1 - Figure 15-28).

10.4.3.4 Hazard ratios for cerebrovascular endpoint

The crude HR of cerebrovascular endpoint (stroke or TIA) in QVA149 users in comparison to LABA/LAMA free combination was 1.59 (95% CI 0.96-2.63). Upon adjustment for a priori confounders, this HR was 1.62 (95% CI 0.97-2.69). The HR from the IPTW analysis was 1.52 (95% CI 0.91-2.55) (Table 10-12).

Database specific HRs are described in Annex 2.1. When exploring results from the IPTW analysis by database, in IPCI (NL), the HR of cerebrovascular disorders for QVA149 in comparison to LABA/LAMA free combination (no ICS) was marginally significant (HR 2.96 (95% CI 1.02-8.60). However, treatment-by-database interaction was not statistically significant in this comparisons (i.e., variability of database-specific findings was consistent with random error). The pooled estimates of the hazard ratios in this comparison were not significantly different from the null value (Figure 15-35). The HR was the lowest in THIN (UK), with a HR of 0.69 (95% CI 0.23-2.08). In Aarhus and HSD, no HR for cerebrovascular endpoints could be estimated because of few events (<5) in the respective exposure cohorts.

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 15-35).

10.4.4 Hazard ratios comparing QVA149 vs. LABA/LAMA free combination without ICS for secondary outcomes

The HRs of QVA149 in comparison to the LABA/LAMA free combination without ICS for the secondary outcomes are described in Table 10-12.The IPTW analysis was considered as the main model.

10.4.4.1 Hazard ratios for glaucoma

The crude HR of glaucoma (narrow angle glaucoma and other glaucoma) in QVA149 users in comparison to LABA/LAMA free combination was 0.69 (95% CI 0.33-1.45). Upon adjustment for a priori confounders, this HR was 0.69 (95% CI 0.33-1.46). The HR from the IPTW analysis was 0.60 (95% CI 0.30-1.24) (Table 10-12).

Database specific HRs are described in Annex 2.1. In THIN, IPCI, Aarhus and HSD, no HR for glaucoma could be estimated because of few glaucoma events (<5) in the respective exposure cohorts.

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).

10.4.4.2 Hazard ratios for bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia

The crude HR of urological outcomes (bladder outflow obstruction, urinary retention or incident BPH) in QVA149 users in comparison to LABA/LAMA free combination was 0.99 (95% CI 0.68-1.42). Upon adjustment for a priori confounders, this HR was 1.00 (95% CI 0.69-1.44). The HR from the IPTW analysis was 0.95 (95% CI 0.64-1.41) (Table 10-12).

Database specific HRs are described in Annex 2.1. When exploring results from the IPTW analysis by database, in none of the databases, the HR of urological outcomes for QVA149 in comparison to LABA/LAMA free combination was statistically significant. In IPCI (NL), the HR was the highest, namely with a HR of 2.66 (95% CI 0.87-8.15). The HR was the lowest in THIN (UK), with a HR of 0.72 (95% CI 0.25-2.06). In Aarhus and HSD, no HR for urological conditions could be estimated because of few events (<5) in the respective exposure cohorts.

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 15-49).

10.4.4.3 Hazard ratios for diabetes mellitus

The crude HR of diabetes mellitus in QVA149 users in comparison to LABA/LAMA free combination was 1.1 (95% CI 0.76-1.59). Upon adjustment for a priori confounders, this HR was 1.10 (95% CI 0.76-1.59). The HR from the IPTW analysis was 1.02 (95% CI 0.70-1.50) (Table 10-12).

Database specific HRs are described in Annex 2.1. When exploring results from the IPTW analysis by database, in none of the databases, the HR of diabetes mellitus for QVA149 in comparison to LABA/LAMA free combination was statistically significant. In THIN, the HR was lower, namely with a HR of 0.67 (95% CI 0.25-1.79) than the HR for SIDIAP (HR 1.03;

95% CI 0.64-1.66). In IPCI, Aarhus and HSD, no HR for diabetes mellitus could be estimated because of few events (<5) in the respective exposure cohorts.

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 15-56).

10.4.4.4 Hazard ratios for mortality

The crude HR of mortality in QVA149 users in comparison to LABA/LAMA free combination was 1.76 (95% CI 1.36-2.28) in the database-pooled data. Upon adjustment for a priori confounders, this HR was 1.71 (95% CI 1.32-2.22). The HR from the pooled IPTW analysis was 1.56 (95% CI 1.16-2.08) (Table 10-12).

Database specific HRs are described in Annex 2.1. When exploring results from the IPTW analysis by database, a significant association was observed in THIN (UK) only (HR 2.64; 95% CI 1.56-4.47). In Aarhus (DK) and SIDIAP (ES), the HR was 1.32 (95% CI 0.74-2.35) and 1.40 (95% CI 0.82-2.39). In IPCI, the HR was 0.73 (95% CI 0.37-1.44). In HSD, no HR for mortality could be estimated because of few events (<5) in the respective exposure cohorts. There was heterogeneity between databases which was confirmed by the Cochran's Q statistic with a p value 0.03 implying that pooled and meta-analytical results need to be interpreted with caution.

The meta-analysis of the IPTW results provided similar estimates as the pooled IPTW analysis, both for the fixed- and random-effect model but the hazard ratio in the random effects meta-analysis was no longer statistically significant (Annex 2.1 - Figure 15-63).

10.4.4.5 Hazard ratios for (paradoxical) bronchospasm

As the number of paradoxical bronchospasms (<=0.1% of events per exposure cohort) was very low in all of the databases, it was not possible to estimate the association between use of QVA149 and risk of paradoxical bronchospasm relative to the free LABA/LAMA (no ICS)

10.4.5 Hazard ratios for QVA149 vs. other exposure cohorts for the primary outcomes

Use of QVA149 vs. LABA/LAMA free combination (anchor) and risk of the primary outcomes of interest was considered to be the main comparison in this protocol. However, as endpoints were assessed in all exposure categories, the HR for QVA149 vs. the other exposure cohorts could also be investigated. HR are described below with focus on other fixed combinations namely fixed LABA+LAMA and fixed LABA+ICS.

10.4.5.1 Hazard ratios for major adverse cardiovascular events (MACE) for QVA149 vs. other exposure cohorts

The crude HR of MACE in QVA149 users in comparison to the LABA/ICS fixed combination (with or without LAMA) was 0.87 (95% CI 0.76-1.00). Upon adjustment for a priori confounders, this HR was 0.85 (95% CI 0.73-0.97). The HR from the IPTW analysis was 0.94 (95% CI 0.80-1.10) (Table 10-13). 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 15-17).

The crude HR of MACE (myocardial infarction, stroke, and hospitalizations because of acute coronary syndrome and/or heart failure) in QVA149 users in comparison to the LABA/LAMA fixed combination was 1.01 (95% CI 0.83-1.24). Upon adjustment for a priori confounders, this HR was 0.99 (95% CI 0.81-1.21). The HR from the IPTW analysis was 1.03 (95% CI 0.80-1.32) (Table 10-14). 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 15-18).

For none of the other exposure categories as comparator, an association between QVA149 use and risk of MACE in the IPTW analysis nor in the fixed- and random-effect model could be observed (Annex 2.1 – Figure 15-17).

10.4.5.2 Hazard ratios for ischemic heart disease for QVA149 vs. other exposure cohorts

The crude HR of ischemic heart disease (myocardial infarction and (unstable) angina pectoris) (IHD) in QVA149 users in comparison to the LABA/ICS fixed combination (with or without LAMA) was 1.10 (95% CI 0.83-1.47). Upon adjustment for a priori confounders, this HR was 1.07 (95% CI 0.81-1.43). The HR from the IPTW analysis was 1.21 (95% CI 0.87-1.70) (Table 10-13). 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 15-24).

The crude HR of ischemic heart disease (myocardial infarction and (unstable) angina pectoris) in QVA149 users in comparison to the LABA/LAMA fixed combination was 1.64 (95% CI 1.09-2.46). Upon adjustment for a priori confounders, this HR was 1.64 (95% CI 1.09-2.46). The HR from the IPTW analysis was 1.60 (95% CI 0.98-2.62) (Table 10-14). The association remained significant in the fixed effect model (HR 1.71, 95% CI 1.10-2.64) but shifted towards the null in the random effect model (HR 1.31, 95% CI 0.46-3.76) (Annex 2.1 - Figure 15-25).

Database specific difference in HRs of the IPTW analysis were observed with an increased risk of ischemic heart disease on QVA149 vs. fixed LABA+LAMA in Aarhus (DK) (HR 2.73, 95% CI 1.39-5.34) and marginally in THIN (UK) (HR 1.94, 95% CI 1.00-3.76), but a decreased risk in SIDIAP (ES) (HR 0.31, 95% CI 0.10-0.97). The THIN, Aarhus and SIDIAP estimates differed significantly from each other in this comparison based on Cochran's Q test (p= 0.005) while estimates for HSD (IT) and IPCI (NL), could not be estimated because of few events (<5) in the respective exposure cohorts. In the pooled analysis, the database by-treatment was statistically significant (p=0.0217) (Annex 2.1 –Figure 15-25).

For none of the other exposure categories as comparator, an association between QVA149 use and risk of ischemic heart disease in the IPTW analysis nor in the fixed- and random-effect model could be observed. When investigating associations individually, per database, a marginally significant hazard ratio above 1 was noted in the comparison of QVA149 vs. LAMA for the endpoint of ischemic heart disease in AUH (HR 2.00 (95% CI 1.05-3.79) (Annex 2.1 - Figure 15-27). However, treatment-by-database interaction was not statistically significant in this comparison (i.e., variability of database-specific findings was consistent with random error).

10.4.5.3 Hazard ratios for cardiac arrhythmia for QVA149 vs. other exposure cohorts

The crude HR of cardiac arrhythmia (atrial fibrillation/flutter, ventricular tachycardia,ventricular fibrillation and Torsade de Pointes) in QVA149 users in comparison to the LABA/ICS fixed combination was 0.73 (95% CI 0.57-0.93). Upon adjustment for a priori confounders, this HR was 0.72 (95% CI 0.56-0.92). The HR from the IPTW analysis was 0.84 (95% CI 0.59-1.19) (Table 10-13). When investigating associations per database, a significant hazard ratio below 1 was noted in SIDIAP (HR 0.63 (95% CI 0.43-0.94)). However, treatment-by-database interaction were not statistically significant in these comparisons (i.e., variability of database-specific findings was consistent with random error) (Figure 15-31).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 15-31).

The crude HR of cardiac arrhythmia (atrial fibrillation/flutter, ventricular tachycardia,ventricular fibrillation and Torsade de Pointes) in QVA149 users in comparison to the LABA/LAMA fixed combination was 0.81 (95% CI 0.57-1.15). Upon adjustment for a priori confounders, this HR was 0.79 (95% CI 0.56-1.12). The HR from the IPTW analysis was 0.79 (95% CI 0.53-1.17) (Table 10-14). 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 15-32).

For none of the other exposure categories as comparator, an association between QVA149 use and risk of cardiac arrhythmia in the IPTW analysis nor in the fixed- and random-effect model could be observed (Annex 2.1).

10.4.5.4 Hazard ratios for cerebrovascular endpoint for QVA149 vs. other exposure cohorts

The crude HR of cerebrovascular endpoints (stroke or TIA) in QVA149 users in comparison to the LABA/ICS fixed combination (with or without LAMA) was 1.08 (95% CI 0.79-1.49). Upon adjustment for a priori confounders, this HR was 1.06 (95% CI 0.77-1.46). The HR from the IPTW analysis was 1.16 (95% CI 0.80-1.70) (Table 10-13) 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). Database specific difference in HRs of the IPTW analysis were observed with a statistically significant HRin IPCI (HR 2.57, 95% CI 1.14-5.77) but not in Aarhus (HR 1.70, 95% CI 0.87-3.31). THIN (HR 0.46, 95% CI 0.19-1.14) , or SIDIAP(HR 0.63, 95% CI 0.33-1.20) with a significant treatment-by-database interaction (Cochran's Q test p=0.007), indicating that individual databases were not estimating the same treatment effect parameter. There was no estimate from HSD in this comparison due to < 5 events per comparator.

The crude HR of cerebrovascular endpoints (stroke or TIA) in QVA149 users in comparison to the LABA/LAMA fixed combination was 1.24 (95% CI 0.81-1.89). Upon adjustment for a priori confounders, this HR was 1.22 (95% CI 0.80-1.87). The HR from the IPTW analysis was 1.02 (95% CI 0.58-1.79) (Table 10-14) (Annex 2.1 - Figure 15-39). In the pooled analysis, the database by-treatment was statistically significant (p<0.001).

For none of the other exposure categories as comparator, an association between QVA149 use and risk of cerebrovascular endpoints in the IPTW analysis nor in the fixed- and random-effect model could be observed (Annex 2.1). When investigating associations per database, in the comparison of QVA149 vs. the free LABA/ICS combination, the covariate-adjusted event rate was significantly decreased on QVA149 in SIDIAP but not in IPCI, where the estimated hazard ratio was not significantly different from the null value. The IPCI and SIDIAP estimates differed significantly from each other in this comparison based on Cochran's Q test ($p = 0.01$), while estimates from the other databases were not available due to <5 events per comparison group (Annex 2.1 - Figure 15-37).

10.4.6 Hazard ratios for QVA149 vs. other exposure cohorts for the secondary outcomes

Use of QVA149 vs. LABA/LAMA free combination (anchor) and risk of the secondary outcomes of interest was considered to be the main comparison in this protocol. However, as endpoints were assessed in all exposure categories, the HR for QVA149 vs. the other exposure cohorts could also be investigated.

10.4.6.1 Hazard ratios for glaucoma for QVA149 vs. other exposure cohorts

The crude HR of glaucoma (narrow angle glaucoma or other glaucoma) in QVA149 users in comparison to the LABA/ICS fixed combination (with or without LAMA) was 0.85 (95% CI 0.47-1.51). Upon adjustment for a priori confounders, this HR was 0.88 (95% CI 0.49-1.58). The HR from the IPTW analysis was 0.89 (95% CI 0.47-1.70) (Table 10-13). 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 15-45).

The crude HR of glaucoma (narrow angle glaucoma or other glaucoma) in QVA149 users in comparison to the LABA/LAMA fixed combination was 0.93 (95% CI 0.34-2.54). Upon adjustment for a priori confounders, this HR was 0.92 (95% CI 0.34-2.53). The HR from the IPTW analysis was 1.05 (95% CI 0.37-2.97). (Table 10-14). (Annex 2.1 - Figure 15-46). Reduced risk on QVA149 was noted for glaucoma in the comparison with free LABA/LAMA/ICS in the pooled analysis (Figure 15-43).

For none of the other exposure categories as comparator, an association between QVA149 use and risk of glaucoma in the IPTW analysis nor in the fixed- and random-effect model could be observed (Annex 2.1). Numbers however were very low, both in the QVA149 as in the other exposure cohorts.

10.4.6.2 Hazard ratios for bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia as endpoint for QVA149 vs. other exposure cohorts

The crude HR of urological outcomes (bladder outflow obstruction, urinary retention or incident BPH) in QVA149 users in comparison to the LABA/ICS fixed combination (with or without LAMA) was 0.94 (95% CI 0.73-1.22). Upon adjustment for a priori confounders, this HR was 0.83 (95% CI 0.64-1.07). The HR from the IPTW analysis was 0.86 (95% CI 0.62-1.20) (Table

10-13). 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 15-52).

The crude HR of urological outcomes (bladder outflow obstruction, urinary retention or incident BPH) in QVA149 users in comparison to the LABA/LAMA fixed combination was 1.18 (95% CI 0.75-1.86). Upon adjustment for a priori confounders, this HR was 1.13 (95% CI 0.72-1.78). The HR from the IPTW analysis was 1.08 (95% CI 0.62-1.86) (Table 10-14). 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 15-53).

For none of the other exposure categories as comparator, an association between QVA149 use and risk of a urological outcome in the IPTW analysis nor in the fixed- and random-effect model could be observed (Annex 2.1).

10.4.6.3 Hazard ratios for diabetes mellitus as endpoint for QVA149 vs. other exposure cohorts

The crude HR of diabetes mellitus in QVA149 users in comparison to the LABA/ICS fixed combination (with or without LAMA) was 0.91 (95% CI 0.70-1.18). Upon adjustment for a priori confounders, this HR was 0.85 (95% CI 0.66-1.11). The HR from the IPTW analysis was 0.87 (95% CI 0.64-1.17) (Table 10-13). 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 15-59).

The crude HR of diabetes mellitus in QVA149 users in comparison to the LABA/LAMA fixed combination was 0.80 (95% CI 0.53-1.21). Upon adjustment for a priori confounders, this HR was 0.80 (95% CI 0.53-1.21). The HR from the IPTW analysis was 0.76 (95% CI 0.47-1.25). (Table 10-14). 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 15-60).

For none of the other exposure categories as comparator, an association between QVA149 use and risk of diabetes mellitus in the IPTW analysis nor in the fixed- and random-effect model could be observed (Annex 2.1).

10.4.6.4 Hazard ratios for bronchospasm as endpoint for QVA149 vs. other exposure cohorts

A reduced risk for QVA149 was noted for bronchospasm in the comparison with free LABA/ICS in the pooled analysis (HR 0.32, 95% CI 0.10-0.98) (Annex 2.1 - Table 15-13).

10.4.6.5 Hazard ratios for mortality as endpoint for QVA149 vs. other exposure cohorts

In the analysis of mortality endpoint, individual databases showed conflicting results with opposite direction of association in several comparisons (Annex 2.1 – Figure 15-63 - Figure 15-69). In the database-pooled analysis, mortality rate in the QVA149 cohort was significantly higher than that in the other LABA LAMA coombination cohorts, including free LABA/LAMA with ICS, and fixed LABA+LAMMA with or without ICS. However, these findings were primarily driven by one database (UK THIN) for the comparison with fixed LABA+LAMA. In

contrast, the mortality rate on QVA149 was significanly reduced relative to the fixed LABA+ICS combination (the largest comparator cohort) in the database-pooled analysis (Annex 2.1 -Table 15-13) and Annex 2.1 - Figure 15-66). Mortality rates did not differ significantly between the comparisons groups when QVA149 was compared with free LABA/ICS (no LAMA), with LABA monotherapy, or with LAMA therapy (with or without ICS, no LABA) (Annex 2.1 -Table 15-13) (Annex 2.1 - Figure 15-65; Figure 15-68 ; Figure 15-69).

The largest mortality hazard ratio in the database-pooled analysis was observed for the comparison of QVA149 versus free LABA/LAMA/ICS combination, but this estimate included data from three databases with <5 events per comparison cohort and therefore could be strongly influenced by sparse-data bias, which generally results in highly unstable point estimates and invalid CIs. (Annex 2.1 - Figure 15-64) .

In the comparison of QVA149 with LAMA therapy, the mortality HR estimate from THIN indicated significantly increased risk on QVA149, while that from SIDIAP indicated significantly decreased risk on QVA149 (Annex 2.1 - Figure 15-69). In this comparison, the database-specific HR estimates from THIN had non-overlapping CIs with HR estimates from Aarhus and SIDIAP, indicating that the estimates were statistically incompatible with each other (i.e., contradictory or internally inconsistent), as confirmed by a highly significant Cochran's Q test (p=0.002).

Clear evidence of treatment-by-database interaction in mortality analysis was also present in the comparison of QVA149 with the fixed LABA+ICS combination (Cochran's Q p=0.005), where the risk was significantly reduced on QVA149 in Aarhus and SIDIAP, as well as in the pooled analysis (Annex 2.1 – Figure 15-66). In contrast, in IPCI and THIN the mortality HR was not significantly different from the null value. In this comparison, the HR estimates from THIN and SIDIAP which were pointing in the opposite directions also had non-overlapping CIs (i.e., were statistically incompatible with each other). Evidence of treatment-by-database interaction was also present in the comparison of QVA149 with LABA. (Annex 2.1 - Figure 15-68).

Table 10-12 Hazard ratios for primary and secondary events – QVA149 compared to LABA/LAMA free combination, pooled data

	Crude			adjusted for a priori confounders			IPTW analysis		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
MACE	1.18	[0.94,1.47]	0.1588	1.19	[0.94,1.49]	0.1421	1.18	[0.93,1.51]	0.1796
Ischemic heart disease	1.09	[0.71,1.66]	0.6928	1.09	[0.72,1.67]	0.6823	1.22	[0.72,2.08]	0.4534
Cardiac arrhythmia	0.95	[0.66,1.37]	0.7846	0.96	[0.67,1.39]	0.8459	1.31	[0.81,2.10]	0.2655
Cerebrovascular disorders	1.59	[0.96,2.63]	0.074	1.62	[0.97,2.69]	0.0628	1.52	[0.91,2.55]	0.1125
Glaucoma	0.69	[0.33,1.45]	0.3274	0.69	[0.33,1.46]	0.3352	0.60	[0.30,1.24]	0.1673
Urological outcomes	0.99	[0.68,1.42]	0.9416	1.00	[0.69,1.44]	0.9942	0.95	[0.64,1.41]	0.8097
Diabetes mellitus	1.10	[0.76,1.59]	0.6268	1.10	[0.76,1.59]	0.6166	1.02	[0.70,1.50]	0.9028
Mortality	1.76	[1.36,2.28]	<.0001	1.71	[1.32,2.22]	<.0001	1.56	[1.16,2.08]	0.003

Urological outcomes consist of bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia
MACE= Major adverse cardiovascular event

Table 10-13 Hazard ratios for primary and secondary events – QVA149 compared to LABA+ICS fixed combination

	Crude			adjusted for a priori confounders			IPTW analysis		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
MACE	0.87	[0.76,1.00]	0.0534	0.85	[0.73,0.97]	0.0201	0.94	[0.80,1.10]	0.4256
Ischemic heart disease	1.10	[0.83,1.47]	0.5003	1.07	[0.81,1.43]	0.6284	1.21	[0.87,1.70]	0.2604
Cardiac arrhythmia	0.73	[0.57,0.93]	0.0118	0.72	[0.56,0.92]	0.0091	0.84	[0.59,1.19]	0.3209
Cerebrovascular disorders	1.08	[0.79,1.49]	0.6197	1.06	[0.77,1.46]	0.7117	1.16	[0.80,1.70]	0.4365
Glaucoma	0.85	[0.47,1.51]	0.5744	0.88	[0.49,1.58]	0.6716	0.89	[0.47,1.70]	0.7273
Urological outcomes	0.94	[0.73,1.22]	0.6530	0.83	[0.64,1.07]	0.1506	0.86	[0.62,1.20]	0.3736
Diabetes mellitus	0.91	[0.70,1.18]	0.4770	0.85	[0.66,1.11]	0.2337	0.87	[0.64,1.17]	0.3518
Mortality	0.81	[0.70,0.94]	0.0055	0.79	[0.69,0.92]	0.0018	0.75	[0.62,0.90]	0.0021

Urological outcomes consist of bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia
MACE= Major adverse cardiovascular event

Table 10-14 Hazard ratios for primary and secondary events – QVA149 compared to LABA+LAMA fixed combination

	Crude			adjusted for a priori confounders			IPTW analysis		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
MACE	1.01	[0.83,1.24]	0.9158	0.99	[0.81,1.21]	0.9102	1.03	[0.80,1.32]	0.8385
Ischemic heart disease	1.64	[1.09,2.46]	0.0166	1.64	[1.09,2.46]	0.0171	1.60	[0.98,2.62]	0.0621
Cardiac arrhythmia	0.81	[0.57,1.15]	0.2437	0.79	[0.56,1.12]	0.1913	0.79	[0.53,1.17]	0.2400
Cerebrovascular disorders	1.24	[0.81,1.89]	0.3296	1.22	[0.80,1.87]	0.3542	1.02	[0.58,1.79]	0.9523
Glaucoma	0.93	[0.34,2.54]	0.8817	0.92	[0.34,2.53]	0.8745	1.05	[0.37,2.97]	0.9230
Urological outcomes	1.18	[0.75,1.86]	0.4649	1.13	[0.72,1.78]	0.5913	1.08	[0.62,1.86]	0.7899
Diabetes mellitus	0.80	[0.53,1.21]	0.80	0.80	[0.53,1.21]	0.2948	0.76	[0.47,1.25]	0.2781
Mortality	1.41	[1.15,1.73]	0.0010	1.35	[1.10,1.66]	0.0043	1.47	[1.16,1.86]	0.0014

Urological outcomes consist of bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia
MACE= Major adverse cardiovascular event

10.5 Stratified analysis

Stratified analysis was only conducted in the pooled dataset because of low numbers. Stratified models were only fitted in case P interaction < 0.10 in at least 3 imputed sets. Because stratified anlayses involved a large number of comparisons performed at 10% alpha without multiplicity adjustment, significant covariate-by-treatment interactions occuring due to type I error should be expected, and overall results must be interpreted with caution. The table with the results of the stratified analysis is provided in Annex 2.1 - Table 15-22.

As expected, many significant -covariate-by-treatment interactions emerged from this analysis. In several cases, variation in stratum-specific HRs was large, with some stratum-specific HRs indicating a significantly increased or significantly decreased risk of respective outcomes on QVA149 vs. comparators. Specifically, significantly increased risk ($p<0.05$) on QVA149 vs. comparator was noted for the following endpoints:

- IHD in the comparison with LABA/LAMA no ICS or fixed LABA+ICS in patients <70 year old but not in ≥ 70 year olds (Table 15-22)

- IHD in the comparison with fixed LABA+ICS or LAMA in definte COPD but not in probable COPD (Table 15-22)

- Bladder obstruction / urinary retention in the comparison with free LABA/LAMA/ICS in definite COPD but not in probable COPD and in patients with no history of cardiovascular or cerebrovascular disease, but not in patients with such history (Table 15-22)

- Mortality in the comparison with free LABA/LAMA no ICS in mild or moderate COPD but not in severe COPD and in the comparison with free LABA/LAMA/ICS in moderate or severe COPD but not in mild COPD (Table 15-22)

On the other hand, significantly decreased risk ($p<0.05$) on QVA149 vs. comparator was noted in many comparisons, including analyses of the following endpoints:

- MACE in the comparison with free LABA/LAMA/ICS in females but not in males, and in the comparison with fixed LABA+ICS in probable COPD but not in definite COPD (Table 15-22)

- Cardiac arrythmia in the comparisons with free LABA/LAMA/ICS, free LABA/ICS or LAMA in patients with history of cardiovascular or cerebrovascular disease, but not in patients without such history (Table 15-22)

- Cardiac arrythmia in the comparison with LAMA in patients using ICS at cohort start but not in patients who were not using ICS at cohort start (Table 15-22)

- Cerebrovascular events in the comparison with free LABA/LAMA/ICS in patients ≥70 years old but not in those <70 years old (Table 15-22)

- Glaucoma in the comparison with free LABA/LAMA/ICS in patients with definite COPD but not in those with probable COPD (Table 15-22)

- Bladder obstruction / urinary retension in the comparison with fixed LABA+ICS in patients ≥70 years old but not in those <70 years old (Table 15-22)

- Diabetes in the comparison with fixed LABA+LAMA in patients without history of cardiovascular or cerebrovascular disease, but not in patients with such history (Table 15-22)

- Mortality in the comparison with LAMA in patients with ICS at cohort start but not in patients without ICS at cohort start, and in patients with probable COPD but not in patients with definite COPD (Table 15-22).

Because biological mechanisms of these treatment-by-covariate interactions are not clear and statistical type I error is expected to occur with high frequency in such exploratory analyses involving multiple comparisons without mutliplicity adjustment, these findings must be interpreted with caution.

10.6 Sensitivity analysis

10.6.1 Sensitivity analysis 1 - No censoring at start of other drug

In the main analyses, patient's follow-up time was censored at start of other treatment. In a sensitivity analysis, the IPTW-model was fitted now using each patient's follow-up time not censored at start of other treatment. Results of this sensitivity analysis (pooled dataset) are described in (Annex 2.1 - Table 15-14). No important changes in the HRs for the outcomes of interest could be observed.

10.6.2 Sensitivity analysis 2 - Wash-out period of 60 days

In the main analyses, to the exposed cohort time a wash-out period of 30 days was added. 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. Results of this sensitivity analysis (pooled dataset) are described in (Annex 2.1 - Table 15-14). No important changes in the HRs for the outcomes of interest could be observed

10.6.3 Sensitivity analysis 3 - Analysis in complete naïve patients

In Sensitivity 3 which was restricted to treatment-naive patients, noteworthy changes in the point estimates of HR included a decrease in the HR for the endpoint of cardiac arrhythmia in the comparison of QVA149 vs. other fixed LABA+LAMA combinations from 0.79 (95% CI: 0.53, 1.17) in the main analysis to 0.49 (95% CI: 0.25, 0.98) in naive patients, with the latter estimate becoming marginally significant at the conventional level of significance (Annex 2.1 - Table 15-14) . On the other hand, for the mortality endpoint, in the comparison of QVA149 vs. free LABA/LAMA combination (no ICS), the point estimate of HR increased from 1.56 (95% CI: 1.16, 2.08) in the main analysis to 2.49 (95% CI: 0.95, 6.49) in naive patients, although the latter estimate was highly imprecise and no longer statistically significant (due to fewer patients and fewer events in Sensitivity Analysis 3) (Annex 2.1 - Table 15-14).

In the comparison of QVA149 vs. free LABA/LAMA combination with ICS, the mortality HR increased from 3.04 (95% CI: 1.79, 5.17) in the main analyses to 5.63 (95% CI: 2.15, 14.8) in the naive patients, but both estimates were based on <5 events per comparator in 3 out of 5 databases and therefore must be interpreted with caution due to sparse-data bias. The bias would be more severe in the naive patients due to sample size reduction relative to the main analysis. In the comparison of QVA149 vs. fixed LABA+LAMA combination in Sensitivity Analysis 3,

the mortality HR estimate was 1.47 as in the main analysis, but precision of this estimate was substantially reduced, with 95% CIs changing from (1.16, 1.86) in the main analysis to (0.91, 2.36) in the naive patients, with the latter HR estimate no longer being statistically significant.

10.6.4 Sensitivity analysis 4 - Analysis of total follow-up time

No association between QVA149 use vs. free combination LABA/LAMA and risk of outcomes of interest were observed except for an increased risk of mortality (HR 1.28, 95% 1.07-1.53) which was lower than the HR for mortality comparing QVA149 with the anchor in the main analysis (Annex 2.1 - Table 15-15). In contrast, in the comparison of QVA149 vs. fixed LABA+LAMA combination, the mortality HR estimate decreased from 1.47 (95% CI: 1.16, 1.86) in the main analysis, to 0.91 (95% CI: 0.78, 1.08) in Sensitivity Analysis 4, which was no longer statistically significant (Annex 2.1 - Table 15-15).

Use of QVA149 in comparison to fixed LABA/LAMA combination - was associated with a reduced risk of paradoxical bronchospasms but numbers were low (HR 0.41, 95% CI 0.17-0.99) (Annex 2.1 - Table 15-15).

10.7 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

Primary endpoints

No statistically significant increase in the rates of any of the primary safety endpoints was seen on QVA149 relative to any of the comparators in the pooled analysis. However, for some endpoints, individual databases showed conflicting results with opposite directions of association and statistically significant treatment-by-database interactions (Cochran's Q test). (Annex 2.1 - Figure 15-14 - Figure 15-69). Specifically, for the endpoint of ischemic heart disease in the comparison of QVA149 vs. fixed LABA+LAMA, the covariate-adjusted event rate was significantly increased on QVA149 in AUH and (marginally) in THIN, but it was significantly decreased on QVA149 in SIDIAP (Cochran's Q p=0.005) (Annex 2.1 - Figure 15-25).

Similar inconsistencies in database-specific findings were noted in some comparisons for the endpoint of cerebrovascular events. Specifically, in the comparison of QVA149 vs. the free LABA/ICS combination, the covariate-adjusted event rate was significantly decreased on QVA149 in SIDIAP but not in IPCI, where the estimated hazard ratio was not significantly different from the null value (Figure 15-37). The IPCI and SIDIAP estimates differed significantly from each other in this comparison based on Cochran's Q test (p = 0.01), while estimates from the other databases were not available due to <5 events per comparison group (Figure 15-37). In the comparison of QVA149 vs. the fixed LABA+ICS combination (Figure

15-38), the rate of cerebrovascular events was significantly increased on QVA149 in IPCI, but not in THIN, AUH or SIDIAP, with a significant treatment-by-database interaction (Cochran's Q p=0.007), indicating that individual databases were not estimating the same treatment effect parameter. There was no estimate from HSD in this comparison due to <5 events per comparator.

A marginally significant hazard ratio above 1 was also noted in the comparison of QVA149 vs. LAMA for the endpoint of ischemic heart disease in AUH (Figure 15-27 in the full report) and in the comparison of QVA149 vs. free LABA/LAMA combination without ICS for the endpoint of cerebrovascular events in IPCI (Figure 15-35 in the Full Report), while a significantly reduced risk on QVA149 was noted for the endpoint of cardiac arrhythmia in the comparison with fixed LABA+ICS combination in SIDIAP (Figure 15-31 in the Full Report). However, treatment-by-database intercations were not statistically significant in these comparisons (i.e., variability of database-specific findings was consistent with random error). The pooled estimates of the hazard ratios in these comparisons were not significantly different from the null value.

Secondary endpoints

In the analysis of secondary endpoints glaucoma, bladder outflow obstruction / urinary retention, diabetes mellitus, and parodoxical bronchospasm, no statistically significant increase in event rates was observed on QVA149 relative to any of the comparators in the pooled analysis or in any of the database-specific analyses. Reduced risk on QVA149 was noted for glaucoma in the comparison with free LABA/LAMA/ICS and for bronchospasm in the comparison with free LABA/ICS (Table 15-13).

In the analysis of mortality, individual databases showed conflicting results with opposite direction of association in several comparisons (Annex 2.1 – Figure 15-63 - Figure 15-69). In the database-pooled analysis, mortality rate in the QVA149 cohort was significantly higher than that in the other LABA LAMA combination cohorts, including free LABA/LAMA without ICS (anchor), free LABA/LAMA with ICS, and fixed LABA+LAMA with or without ICS (Annex 2.1 – Figure 15-63 - Figure 15-69). However, these findings were primarily driven by one database (UK THIN). In contrast, the mortality rate on QVA149 was significanly reduced relative to the fixed LABA+ICS combination (the largest comparator cohort) in the database-pooled analysis (Figure 15-66). Mortality rates did not differ significantly between the comparisons groups when QVA149 was compared with free LABA/ICS (no LAMA), with LABA monotherapy, or with LAMA therapy (with or without ICS, no LABA) (Annex 2.1 – Figure 15-63 - Figure 15-69).

The largest mortality hazard ratio in the database-pooled analysis was observed for the comparison of QVA149 versus free LABA/LAMA/ICS combination(Annex 2.1 - Figure 15-64). But this estimate included data from three databases with <5 events per comparison cohort and therefore could be strongly influenced by sparse-data bias. In the comparison of QVA149 versus the anchor cohort (LABA/LAMA without ICS), the pooled estimate of the HR was also significantly above 1, although evidence of treatment-by-database interaction was present in this comparison. In particular, estimated HRs from THIN and IPCI were pointing in the opposite direction and had non-overlapping CIs (Annex 2.1 - Figure 15-63) . Furthermore, in the comparison of QVA149 with LAMA therapy, the mortality HR estimate from THIN indicated significantly increased risk on QVA149, while that from SIDIAP indicated significantly

decreased risk on QVA149 (Annex 2.1 – Figure 15-69). In this comparison, the database-specific HR estimates from THIN had non-overlapping CIs with HR estimates from Aarhus and SIDIAP, indicating that the estimates were statistically incompatible with each other (i.e., contradictory or internally inconsistent), as confirmed by a highly significant Cochran's Q test (p=0.002).

Clear evidence of treatment-by-database interaction in mortality analysis was also present in the comparison of QVA149 with the fixed LABA+ICS combination (Cochran's Q p=0.005), where the risk was significantly reduced on QVA149 in Aarhus and SIDIAP, as well as in the pooled analysis. (Annex 2.1 –Figure 15-66). In contrast, in IPCI and THIN the mortality HR was not significantly different from the null value. In this comparison, the HR estimates from THIN and SIDIAP, which were pointing in the opposite directions, also had non-overlapping CIs (i.e., were statistically incompatible with each other). Evidence of treatment-by-database interaction was also present in the comparison of QVA149 with LABA.

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 9,798 new users of QVA149 was identified. Although the number of patients within the exposure cohorts of interest was large, the duration of follow-up was 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. Especially the median duration of follow-up was low for free combination exposure cohorts (i.e. median duration is only 60 days for the anchor vs. 120 days for QVA149). With regard to the creation of these exposure categories, patients were considered to be on combined therapy in case of at least 30 days of overlap of the individual drug categories. This exposure however might have been misclassified in case a physician decides to switch from one drug into another which could explain the short duration of free combination therapy.

Information on the dose and duration of a prescription is not captured in Aarhus and SIDIAP, hence necessitating duration estimation based on number of prescribed/dispensed doses, which might lead to misclassification of exposure time. In addition, exposure data for SIDIAP is based on dispensing data. For chronic therapy, patients attend GP visits for the first prescription; subsequent medication (of the same drug) is dispensed by the pharmacy without need of further prescriptions (the so-called"electronic dispensation"). Also, the exact date (day/month/year) of pharmacy dispensing is unknown in SIDIAP, as dates are available as month/year only. This has the potential to introduce bias not only with regard to patient assignment to certain exposure cohorts but as well might introduce measurement error of exposure time.

In contrast to the Aarhus and SIDIAP databases, the other databases only capture information on prescription and not on dispensing hence potentially leading to misclassification due to primary non-adherence. In addition, it is unknown whether or not the patient actually inhaled the prescribed product. However, as adherence to medications 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 used in this study (Lareau and Yawn, 2010).

11.2.2 Limitations with regard to COPD, comorbidity and endpoint identification

To make optimal use of collected data on FEV_1 percentage of predicted, COPD severity was assessed in all patients with FEV_1 data, even in patients without COPD according to GOLD or in case data on FVC was missing. When this was applied to our data, the proportion of patients with information on COPD severity based on spirometry data in the exposure groups ranged between 76.1-89.8% for THIN, 41.5-61.8% for IPCI, 38.1-70.5% for Aarhus, 22.7-38.7% for HSD and 58.5-74% SIDIAP. When spirometry was unavailable, COPD severity was assessed via proxy according to published literature (i.e., based on COPD severity scores using data from GP or healthcare databases) (Curkendall et al., 2006, Eisner et al., 2005, Soriano et al., 2001). In general, COPD severity appeared to be less severe when assessed by proxy than when assessed by spirometry.

As part of the final analysis, in IPCI, HSD and SIDIAP, a sample (1,000 for the QVA149 exposure cohort and 1,000 for the free LABA/LAMA w/o ICS combination) was validated by medically trained personnel according to a predefined algorithm. The positive predictive value (PPV) of COPD was high for SIDIAP (Spain) namely 88.1% and 99.3% for IPCI (The Netherlands). The PPV for COPD was much lower in HSD (Italy) namely 79.0% primarily because free text was often missing in HSD and patients only had a combination of a COPD disease code + use of respiratory drugs.

Co-morbidity was assessed via disease-specific codes. If disease coding was inconsistent or differential, this could have resulted in diagnostic bias with potential of over- and underreporting of comorbidities. Indeed, there is a potential of underreporting of underlying comorbidity if GPs only record disease symptoms and do not code the corresponding disease. Previous validation studies for these databases have shown that coding is reliable and that these databases are suitable for pharmaco-epidemiologic research (Cazzola et al., 2011, Ehrenstein et al., 2010, Garcia-Gil Mdel et al., 2011, Lewis et al., 2007, Vlug et al., 1999). 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. For this reason, for those databases where free-text is available (i.e., IPCI, HSD and SIDIAP), COPD diagnosis as well as all endpoints were manually validated. Differences in PPV between primary and secondary outcomes and between databases were observed. PPV was mainly low in case of few numbers and in case of use of aspecific disease codes such as “bronchospasm” as disease code for paradoxical bronchospasm. Unfortunately, there is no disease specific code for paradoxical bronchospasm – which is bronchospasm occurring within 1 hour of administration of COPD inhaler therapy. For that reason, potential cases were selected based on a search on disease codes of bronchospasm but upon free text validation few events remained.

In HSD, the PPV was low for not only paradoxical bronchospasm but also for BPH, hospitalization for heart failure and stroke. As BPH is a chronic condition, BPH was only considered an endpoint if the patient was newly diagnosed with BPH. Patients originally

identified as having BPH as outcome thus dropped because the condition was prevalent and not incident. With regard to the low PPV of stroke, in HSD a disease code of "paresis" was used for the initial search on patients with stroke. However, paresis is an aspecific term which might be present in various neurological conditions explaining the low PPV however, HSD always includes paresis amongst it's disease codes for searches on stroke to reduce the risk of false negatives. Finally, as HSD is not linked to hospital data and hospitalization is not well documented in the database. Events related to hospitalization such as hospitalization for COPD exacerbation, hospitalization for heart failure and hospitalization for acute coronary syndrome are underrepresented in HSD. For that reason, HSD conducted a search on "heart failure" and not on "hospitalization for heart failure". Although the PPV was low for certain outcomes not only in HSD but also in IPCI and SIDIAP it is unlikely that this would introduce a differential bias as validation was done, blinded to exposure.

For certain outcomes such as bronchospasms, namely bronchospasm occurring within 1 hour of administration of any of the study medications (also called paradoxical bronchospasms) numbers were very low implying that the association between use of QVA149 and risk of this outcome could not be assessed. Also the number of outcomes for narrow angle glaucoma was low, a diagnosis which is not easy to make in the primary care setting. Misclassification between "narrow angle glaucoma" and "other glaucoma" is likely however, the incidence rate of other glaucoma was low as well.

COPD exacerbations were defined as use of systemic steroids or use of antibiotics for reason of COPD. The indication of use of medicinal products is not available in all databases. Only IPCI captures the indication of use within the prescription files, however, even for IPCI, 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 rather than diagnostic codes, has occurred.

In contrast to Aarhus, the other databases are primary care database and comorbidities and outcomes requiring secondary and/or tertiary care such as hospitalization for ACS and HF, ischemic heart disease, stroke/TIA, severe cardiac arrhythmia and COPD exacerbations resulting in hospitalization might be underreported. [Coloma, 2011 #66] In primary care databases, the incidence and prevalence of comorbidities depend on physician diagnosis (and coding) and might be underestimated. In contrast, Aarhus retrieves information on disease codes from hospital data (ambulatory care or hospitalized patients). This implies that comorbidities, which do not necessarily require secondary or tertiary care (i.e., arterial hypertension, diabetes mellitus), might be underreported. In Aarhus, incidence rates of glaucoma and bladder outflow obstruction/urinary retention/BPH, diseases not necessarily requiring secondary care were indeed lower than in the other databases. (data not shown) SIDIAP has the advantage to be able to link to hospital data, rendering the potential of misclassification of hospitalization less likely compared to THIN, IPCI and HSD.

Differences in underlying co-morbidities were observed between databases. For instance, in HSD and especially SIDIAP the proportion of patients with a history of angina pectoris and MI was relatively low compared to the other databases. It is unknown whether or not this is due to real differences in risk of ischemic heart diseases as reported for Mediterranean countries or due to differences in coding and hence potential misclassification (de Lorgeril et al., 2002). Also the proportion of patients with BPH was higher in Italy and Spain compared to the other databases. Italy and Spain apply a system where the GP has an important role in the screening for BPH and prostate cancer. Also the prevalence of BPH in Italy and Spain is in line with literature (Bonfill et al., 2015, Carbone et al., 2016, Chicharro-Molero et al., 1998). In addition the asthma prevalence rates were higher in THIN (UK) and IPCI (NL) with the highest prevalences in ICS containing exposure cohorts: It is likely that patients with ACOS (asthma and COPD overlap syndrome) are treated with a combination of a long-acting bronchodilator (LABA or LAMA) with ICS (Montuschi et al., 2014). However, it is also well-known that GPs are often unable to make a differential diagnosis between asthma and COPD (Price and Brusselle, 2013). Finally, as a patient fulfilled criteria of asthma based on at least one record within the patient's medical history, we might have overestimated the proportion of COPD and/or asthma in those patients where COPD and/or asthma is no longer confirmed during patient's follow-up. This will inevitably introduce diagnostic bias into studies using data from primary care. The country specific differences in the prevalence of asthma might be explained by differences in coding practices but we also now from literature that the asthma prevalence in the total adult population is more than 10% in the UK and the Netherlands and between 1-5% in Italy and Spain(ERS, 2018).

Patients with a medical history of cardiovascular and cerebrovascular (CCV) events were not excluded from this study because many COPD patients have underlying cardiovascular and cerebrovascular comorbidity and the aim was to select a group of patients which were representative of patients with COPD under real life. These patients were also 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 the study, however, there is the potential of misclassification of outcomes, as for these patients it is much more difficult to assess whether a disease code refers to a new CCV event or whether the disease code refers to an event which happened in the patient's history. To overcome the issue of misclassification, all databases received clear instructions emphasizing that only new CCV events during follow-up should be considered. In addition in IPCI, HSD and SIDIAP, all endpoints, including cardiovascular and cerebrovascular endpoints were validated according to a predefined validation protocol.

Based on the review of the second QVA149 PASS interim report, the EMA/PRAC suggested to present results on the cause of mortality in all treatment groups to investigate patterns of cause of death in the QVA149 group. The cause of death could only be investigated in IPCI (through medical file review) and for THIN through specific disease codes linking to primary or secondary cause of death. For Aarhus, information on death was captured as Aarhus is able to link to the database with death certificates however, only for a subset of deceased study patients due to a lag time in data availability of 1-2 years. In IPCI, Aarhus and especially THIN, there is a large proportion of patients who died with missing information on cause of death. This is because the GP often does not know the cause of death or the patient is de-registered

from the practice by a central NHS system once notification of death is received. Cause of death is documented in the death certificate but this is not routinely available in the THIN database.

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, an inverse probability of treatment weighting (IPTW) analysis was done using weights determined by a propensity score model to control for confounding.

A sensitivity analysis was conducted considering treatment naïve patients only (naïve of all exposure cohort drugs within the one year prior to treatment start – use of other respiratory drugs in the one year prior was permitted). This analysis was important to control for the potential of COPD treatment step up where patients only initiate treatment with QVA149 (or other fixed LABA+LAMA) when other COPD treatment strategies have failed. This treatment pattern could introduce potential bias where patients first have to survive other treatment options before they are introduced to QVA149 (Suissa, 2018). However when considering the results of the analysis in naïve patients only, the association between use of QVA149 and mortality, in comparison to free LABA/LAMA (wo ICS) further increased. However the association was not significant with wide 95% CI. According to COPD guidelines, patients should first initiate treatment with LAMA (or LABA as an alternative) and if not doing well, COPD treatment step-up should be considered. If patients initiate treatment with fixed combination of LABA+LAMA as first COPD treatment, it is logical to assume that these patients have moderate or severe COPD at time of COPD diagnosis. The free combination of LABA/LAMA is the main comparator however it is likely to assume that an important proportion of these patients are on monotherapy instead of dual therapy as only 30 days of overlap between LABA and LAMA therapy is requested. This implies that we compare patients with different COPD severity which – despite our adjusted analysis – are not able to control for (GOLD, 2017).

Because QVA149 was launched only recently in comparison to other comparators, especially in THIN and SIDIAP, QVA149 exposure episodes may generally lay later in calendar time than the other exposure categories. This may introduce ascertainment bias where available follow-up time after end of cohort time (= end exposure) is shorter for QVA149 compared to the other exposure categories. To control for this, stratified analysis by calendar time was conducted (strata from treatment initiation in 2013-2015 and 2016-2017) but this analysis was jeopardized because of low number of outcomes and for instance for mortality, no conclusion could be drawn.

Median cohort time was short, especially for the free combinations of the different exposure categories where it is unknown whether this reflects true combined therapy or switching from one treatment to another. This short follow-up time might jeopardize the chance to develop any of the outcomes of interest. This bias was controlled for by increasing the wash-out period from 30 to 60 days with negligible effects on the risk estimates.

To conclude, although we tried to control for confounding both in the design of the study as well as in the analysis, there is the potential of residual confounding and bias mainly explained by the following: First follow-up exposure time was short, especially for the free combinations which jeopardizes the potential to investigate occurrence of long term effects such as diabetes mellitus, BPH and glaucoma. In our selection of comparators we might have introduced differences in underlying COPD severity and although we used spirometry data, this information was not available in all patients and if available not necessarily actual; Indeed differences in time from spirometry to index date were observed not only between exposure cohorts but also between databases with the largest timespam for HSD and SIDIAP. The outcomes of interest were first selected based on a disease code specific search and subsequently validated not only to investigate whether the patient developed the outcome but also to check whether it was a new event or a disease code referring to what happened in the past. Endpoint validation was only possible for IPCI, HSD and SIDIAP and the quality of validation depended on the availability of data such as hospital discharge letters or automatic linkage to hospital data. Also certain endpoints such as narrow angle glaucoma and paradoxical bronchospasms were difficult to capture in primary care databases. Because of the nature of the design we controlled for COPD severity, lifestyle factors, underlying comorbidity and use of concomitant medication prior to cohort entry however no analysis was conducted to controf for time varying conditions during treatment follow-up. Because of our choice of comparators, we might have introduced COPD severity bias as on the one hand QVA149 as fixed combination of LABA/LAMA is compared to monotherapy (LABA, LAMA) but also to triple therapy (LABA/LAMA/ICS free combination). Finally, related to this, treatment initiation with QVA149 might not only mean a COPD treatment step-up (in patients switching LABA or LAMA monotherapy to QVA149) but might also introduce a treatment step-down in patients switching from LAMA + LABA/ICS fixed dose combination to QVA149 as combined use of QVA149 with fixed LABA+ICS was exc luded from the protocol.

11.3 Interpretation

This final report presents the cardio- and cerebrovascular outcomes as well as the secondary outcomes namely diabetes mellitus, (narrow-angle) glaucoma; bladder outflow obstruction/urinary retention/incident BPH, (paradoxical) bronchospasm and all cause mortality both in patients newly using QVA149 and in patients initiating any of the comparator medications.

In the past, articles have been published on the association between use of LABA and/or LAMA and risk of cardiovascular events and/or mortality with conflicting results (Dong Yaa-Hui, 2012, Michele et al., 2010, Singh et al., 2011, Verhamme et al., 2013, Wise et al., 2013). In our data, we do not see an association between QVA149 vs. free LABA/LAMA (with or without ICS) with MACE nor with cardiac arrhythmia. This implies that, if there is an association with mortality, it is unlikely that this would be mortality related to cardiovascular or cerebrovascular causes. Also, if the association is real, it is difficult to explain why this association was only observed in THIN and not in the other databases. It is true however that the QVA149 population in THIN has (1) the highest prevalence of history of COPD exacerbations (12.5% of QVA149 patients had a history of hospitalization for COPD exacerbation in the year prior to cohort entry vs. 4.5-8.3% of the other exposure cohorts), and (2) a high prevalence of patients with severe

to very severe COPD (29.1%) . It thus seems that channeling bias, especially in the UK, is an issue where QVA149 is prescribed to patients with more severe conditions and thus at higher risk of mortality (Petri and Urquhart, 1991). Still, we could not find data in literature supporting that QVA149 prescribing practices are different in the UK compared to the other participating countries.

Not only channeling bias might explain the association between use of QVA149 and mortality. The recent IMPACT trial by Lipson et al. in more than 10,000 patients with COPD, compared the combination of fluticasone furoate (an inhaled glucocorticoid), umeclidinium (a LAMA), and vilanterol (a LABA) (triple therapy) with LABA+ICS (fluticasone furoate–vilanterol) and LAMA+LABA (umeclidinium–vilanterol) and reported a higher risk of mortality for patients on fixed LABA+LAMA compared to patients on LABA+ICS or triple therapy (Lipson et al., 2018). These results were then discussed in an editorial highlighting to the fact that the IMPACT trial did not exclude patients with asthma. In addition more than 70% of patients were using ICS and nearly 40% of patients were using triple therapy (in free combination) at time of enrollment. This implied that, for the patients assigned to the LAMA+LABA combination, many of whom were actually stepping down in their treatment, inhaled glucocorticoids were abruptly withdrawn at the time of randomization which could lead to COPD exacerbations and mortality (Suissa and Drazen, 2018). However, if this mechanism operated in the present study, its role is not entirely clear because use of free ICS concommitantly with QVA149 was allowed by definition of the QVA149 cohort (in contrast to IMPACT, where it was prohibited). Furthermore, mortality on QVA149 was significantly reduced relative to the fixed LABA+ICS combination in the pooled analysis and in database-specific analysis including Aarhus and SIDIAP. This is again in contrast to IMPACT where mortality on LABA+LAMA combinations was increased relative to LABA+ICS. The hypothesis of mortality resulting from ICS step-down also cannot explain higher mortality on QVA149 relative to the free LABA/LAMA no ICS (anchor) where use of ICS was absent by cohort definition.

To complete the review of relevant data, Level 1 evidence on mortality in patients treated with LABA+LAMA combinations was analyzed. In the following paragraphs, we summarize findings from published RCTs, with respect to all-cause mortality in patients treated with LABA+LAMA combinations versus LABA monotherapy, LAMA monotherapy, or LABA+ICS combination. The focus here is on meta-analyses of RCTs, which provide most precise and most reliable effect estimates. However, recent trials not yet included in published meta-analyses are also included in this review. Because this review examines LABA+LAMA combinations jointly as a class, it can only provide Level 1 evidence at the class effect level. In contrast, intra-class effects (e.g., of QVA149 vs. other fixed LABA+LAMA combinations) cannot be investigated based on published RCT data due to lack of relevant studies. Key findings with respect to class-level investigation of published RCT data are summarized below in Table 11-1.

Table 11-1 Published RCT data on mortality in patients treated with LABA+LAMA combinations vs. comparator treatments

Comparison	Trial(s)	Risk ratio (95% CI)	Reference
LABA+LAMA vs. LABA	Meta-analysis	0.99 (0.61, 1.66)	Oba et al 2016
	Meta-analysis	0.87 (0.38, 1.98)	Rogliani et al 2017

LABA+LAMA vs. LAMA	Meta-analysis	0.87 (0.64, 1.16)	Oba et al 2016
	Meta-analysis	0.85 (0.61, 1.17)	Rodrigo et al 2017*
	DYNAGITO	0.88 (0.68, 1.15)	Calverley et al 2018
LABA+LAMA vs. LABA+ICS	Meta-analysis	1.01 (0.61, 1.67)	Horita et al 2017
	Meta-analysis	1.04 (0.62, 1.72)	Rodrigo et al 2017
	FLAME	1.00 (0.57, 1.76)	Wedzicha et al 2016
	IMPACT	1.64 (1.07, 2.05)	Lipson et al 2018

Risk ratio > 1 indicates higher risk on LABA+LAMA combination versus the comparator treatment. The increased risk is statistically significant at 5% alpha if the 95% confidence interval for the risk ratio excludes 1

LABA+LAMA combinations vs. LABA monotherapy

There was no evidence of increased risk of mortality on LABA+LAMA combinations vs. LABA monotherapy in RCTs comparing these treatment modalities (Oba et al 2016, Rogliani et al 2017) (Table 11-1). The point estimates of the risk ratio were below the null value in both meta-analyses, although the precision of estimation was somewhat limited.

LABA+LAMA combinations vs. LAMA monotherapy

There was no evidence of increased mortality on LABA+LAMA combination relative to LAMA monotherapy in published meta-analyses (Table 11-1). These findings were also confirmed in the recently published DYNAGITO trial, which was not included in the two meta-analyses and thus can be viewed as providing independent confirmatory evidence (Table 11-1). Considering the meta-analyses and DYNAGITO findings, any large or modest increase in mortality on LABA+LAMA vs. LAMA therapy can be ruled out based on location of the upper 95% confidence limits in these comparisons.

LABA+LAMA combinations vs. LABA+ICS treatment

There was no increased risk of mortality on LABA+LAMA vs. LABA+ICS in the two meta-analyses (Table 11-1). Most events in both meta-analyses were contributed by the FLAME trial of QVA149 vs. a fixed combination of salmeterol plus fluticasone, which is also presented separately in Table 11-1. In contrast, in the recently published IMPACT trial which is not included in the meta-analyses, all-cause mortality was increased on LABA+LAMA combination relative to LABA+ICS (Table 11-1), with an absolute risk increase of 0.7% over 1-year follow-up period. However, as was noted in two editorials accompanying the original publication (Petite 2018, Wedzicha et al 2018), IMPACT allowed co-existing asthma with COPD but required abrupt discontinuation of ICS at baseline in the LABA-LAMA group. Such abrupt discontinuation of ICS in asthma patients would not be appropriate in clinical practice and was likely responsible for increased mortality in the LABA+LAMA group relative to LABA+ICS or triple therapy (LABA+LAMA+ICS) (Petite 2018, Wedzicha et al 2018). This is in contrast to the FLAME trial, where patients with asthma were excluded by design (Wedzicha et al 2018).

Other literature. Two recent randomized controlled trials, both with a duration of 12 weeks, studied the efficacy and safety of QVA149 (indacatorol/glycopyrronium 27.5/15.6 ug twice daily) compared to any of its mono-components or placebo and concluded that the safety profile was comparable across treatment groups with a superiority of QVA149 with regard to

improvement of FEV_1 (Mahler et al., 2015). Still it should be noted that these were relatively small trials, which excluded patients with asthma and studied the dose of QVA149 at half of the dose which is currently registered in Europe.

A meta-analysis on the safety of QVA149 and its mono-components and tiotropium versus placebo, including data from 11,404 patients from 14 randomized controlled trials, reported no higher hazard ratio of mortality (HR 0.93, 95% CI 0.34-2.54) and MACE (including hospitalization for heart failure and acute coronary syndrome) (HR 1.04, 95% CI 0.45–2.42) for the QVA149 treatment arms compared to placebo although the estimates had low precision due to small event counts (Wedzicha et al., 2014). In this meta-analysis, no direct comparison was made between QVA149 and any of its mono-components.

In summary, review of Level 1 evidence from published RCTs and their meta-analyses did not reveal increased risk of mortality on LABA+LAMA combinations as a class relative to LABA or LAMA monotherapy. Effect estimates in the LABA+LAMA vs. LAMA comparison were fairly precise, ruling out any large or modest increase in mortality rate on LABA+LAMA combinations relative to LAMA monotherapy. Evidence regarding mortality on LABA+LAMA vs. ICS-containing regimens (LABA+ICS or LABA+LAMA+ICS) is controversial. The FLAME trial of QVA149 and meta-analyses conducted prior to publication of the IMPACT trial did not reveal evidence of increased mortality on LABA+LAMA in COPD patients without asthma. In the IMPACT trial of non-QVA149 fixed LABA+LAMA, which included patients with co-existing asthma / COPD, overall mortality was increased (estimated 1-year risk difference 0.7%) in the LABA+LAMA arm relative to the ICS containing regimens, likely due to abrupt discontinuation of ICS required by the trial per protocol (Wedzicha et al 2018, Petite 2018).

Discontinuation of ICS at initiation of LABA+LAMA therapy could also potentially influence the observed findings with respect to mortality in the QVA149 PASS, although the exact role of this mechanism is not clear because free ICS was allowed by definition of the QVA149 cohort (in contrast to IMPACT) and mortality on QVA149 was in fact significantly reduced relative to the fixed LABA+ICS cohort in the pooled analysis, although with evidence of treatment-by-database interaction, suggesting that observed drug-event associations likely represent incompletely understood regional differences in drug channeling mechanisms rather than true causal effects.

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 QVA149 or any of the other exposure cohorts in various European regions, generalizability may not be appropriate for results for which differences between the databases have been observed.

12 Other information

12.1 Report of the meeting with the Scientific Advisory Committee (SAC) and discussion

On the 18 October 2018 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. In particular it was asked to clarify the meaning of "naïve patients" as naïve means no use of any of the 8 exposure categories in the year prior to the index date but might still mean use of other respiratory drugs (i.e. ICS, xanthines, LTRA, SABA, SAMA, systemic B2 agonists).

In addition, they made the following observations. For this study, the anchor consists of the free LABA+LAMA combination however median duration in this exposure is short, and shorter than QVA149. This short median duration of free LABA+LAMA combination might be a concern to study safety outcomes especially if rare. The fixed LABA+LAMA combination might be a better comparator, as the free LABA/LAMA combination might consist of patient switching from LABA to LAMA or vice versa and not necessarily represents combined use.

COPD severity is addressed by spirometry but also with information such as previous use of hospitalisations for COPD exacerbation, use of antibiotics for COPD exacerbation and/or lower respiratory tract infection and use of systemic corticosteroids for reason of COPD exacerbation. However, as the indication of use might not always be coded in the database and as there might be differences in coding between databases, the SAC also suggested to consider use of systemic corticosteroids whether or not coded for COPD exacerbation.

The SAC also made the observation that the prevalence of asthma is high especially in THIN (UK) and IPCI (the Netherlands). This high prevalence of asthma probably not only relates to misclassification between asthma and COPD but probably also represents patients with both asthma and COPD (ACO) as the prevalence of asthma is highest in the ICS containing regimens. One might speculate that the increased mortality in THIN of QVA149 versus free or fixed LABA/LAMA is due to respiratory mortality, since there are no major differences in cardiovascular outcomes; and that this increased respiratory mortality in THIN might occur especially in misclassified asthmatics (misdiagnosed as COPD) or patients with ACO (asthma COPD overlap), in whom prior ICS (triple therapy or ICS+LABA) was stopped.

Multiple sensitivity analyses were done but the SAC would like to seen an explanation in the report why these analysis were done. Also, the tables with sensitivity analyses should also include the results of the main analysis to make a more easily comparison. With regard to the analyses in naïve patients, the SAC commented that there appears in many instances an increase in the naïve population. This appears to be a systematic directional change despite small numbers.

The SAC also commented that (in the draft report), heterogeneity between data sources was rarely discussed or explained. Also, where there are systematic differences for results between data sources, a pooled estimate may be inappropriate (regardless of fixed or random effects models).

With regard to the interpretation section of the report, the SAC suggested to include explanatory hypothesis (causal and non-causal explanations) for any result. Also articles are cited which did not necessarily study the safety of QVA149 but other fixed LABA+LAMA combinations – this should be explained.

Despite the obvious efforts in designing and executing a large and complex study in an intelligent and thoughtful way, the SAC is left with the uncertainty about what the study can tell us about the safety of this drug in real life.

13 Conclusion

In this observational cohort study, the rates of all primary and secondary endpoints, except for the secondary endpoint of all-cause mortality, were not significantly elevated on QVA149 relative to any of the seven comparator cohorts in the pooled analysis. However, individual databases showed conflicting results with opposite directions of association for several endpoints, including ischemic heart disease, cerebrovascular events and all-cause mortality. Interpretation of these findings as causal effects is problematic due to lack of internal consistency of observed associations, inability to control for time-dependent confounding, and other potential sources of bias. Given lack of internal consistency of database-specific results and considering other limitations of the study, overall study findings must be interpreted with caution.

14 References

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15 Appendices

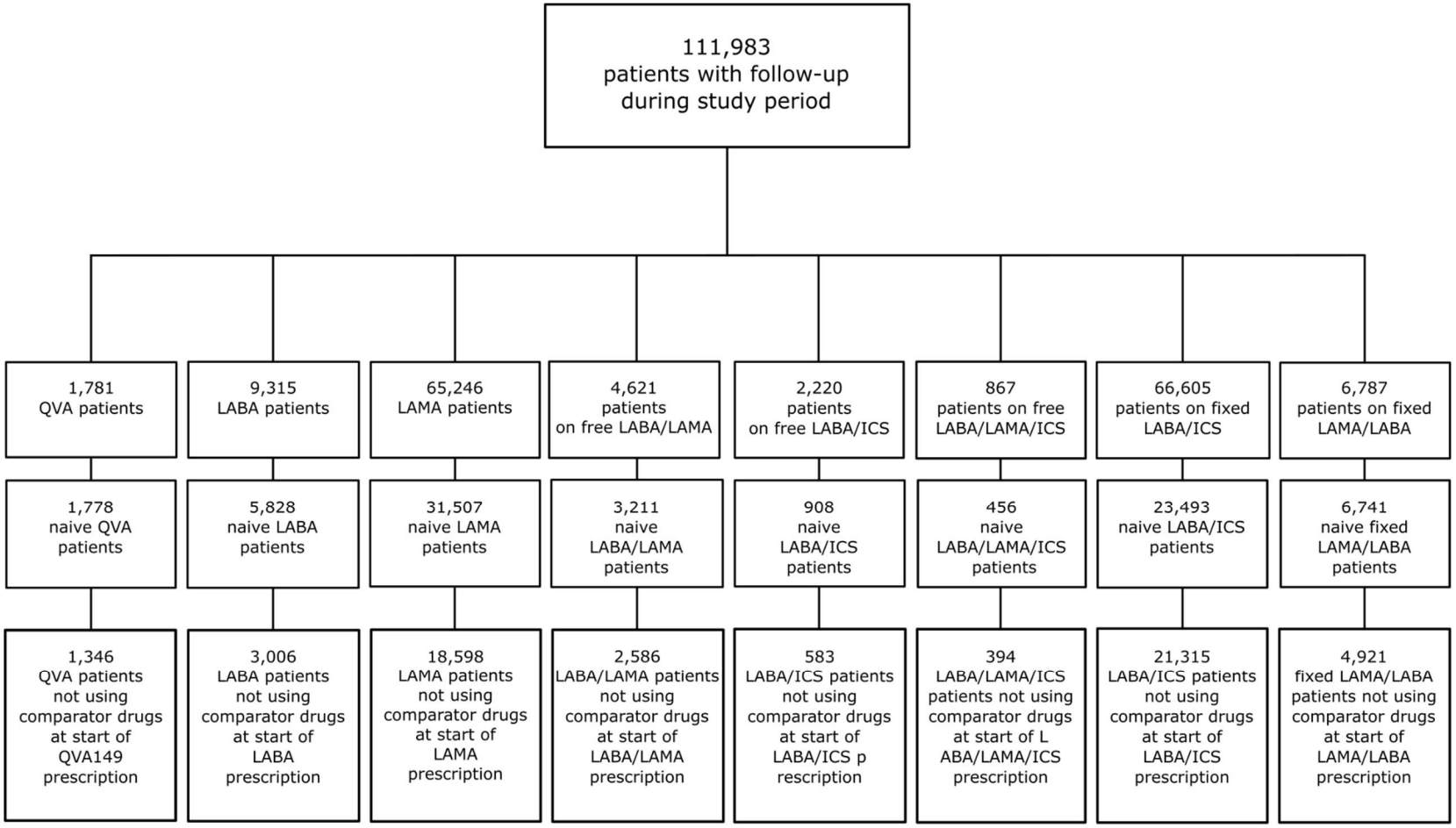
Annex 1 – List of stand-alone documents

There are no stand-alone documents.

Annex 2 – Additional information

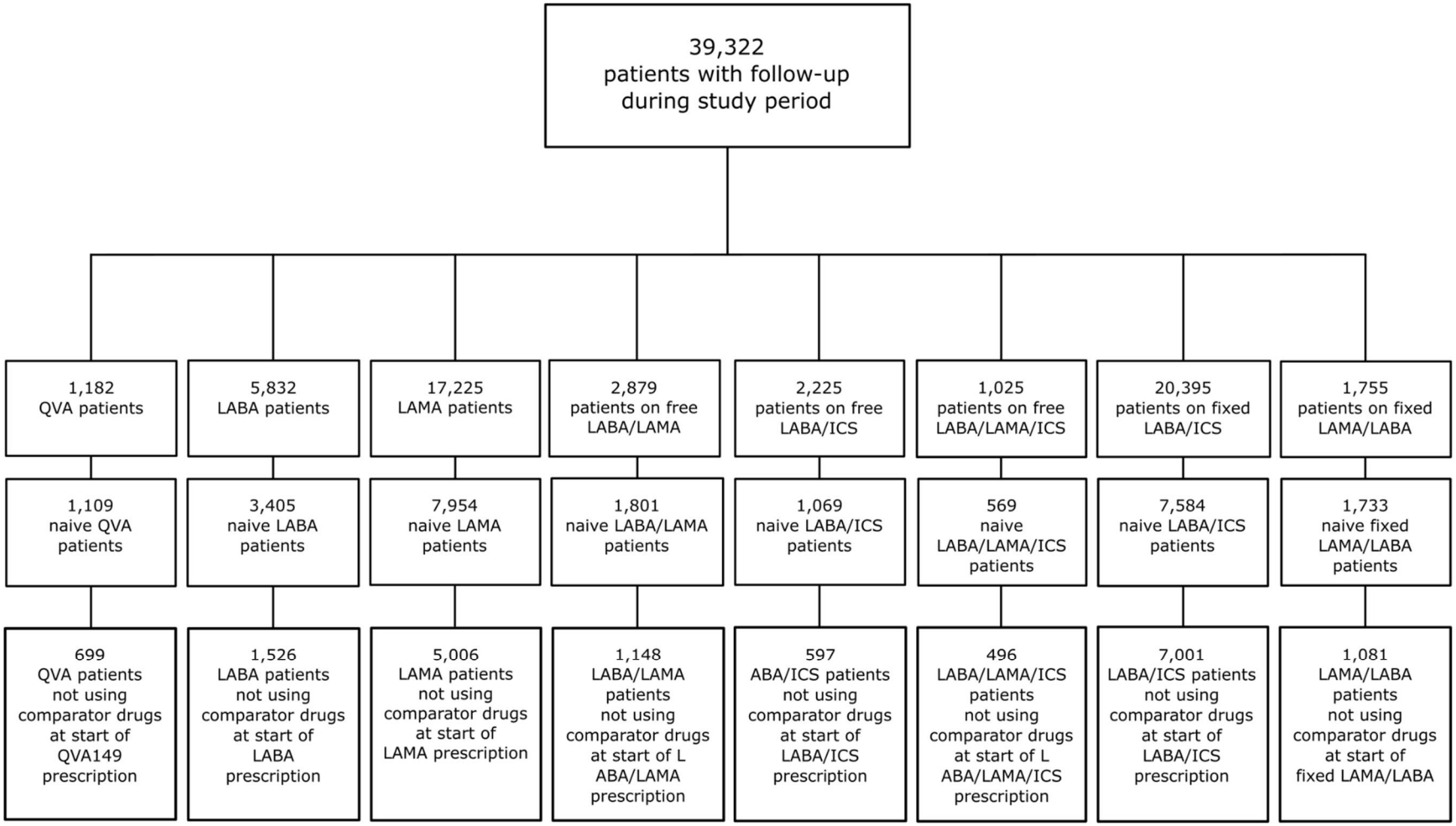
Annex 2.1 - Results tables and figures

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



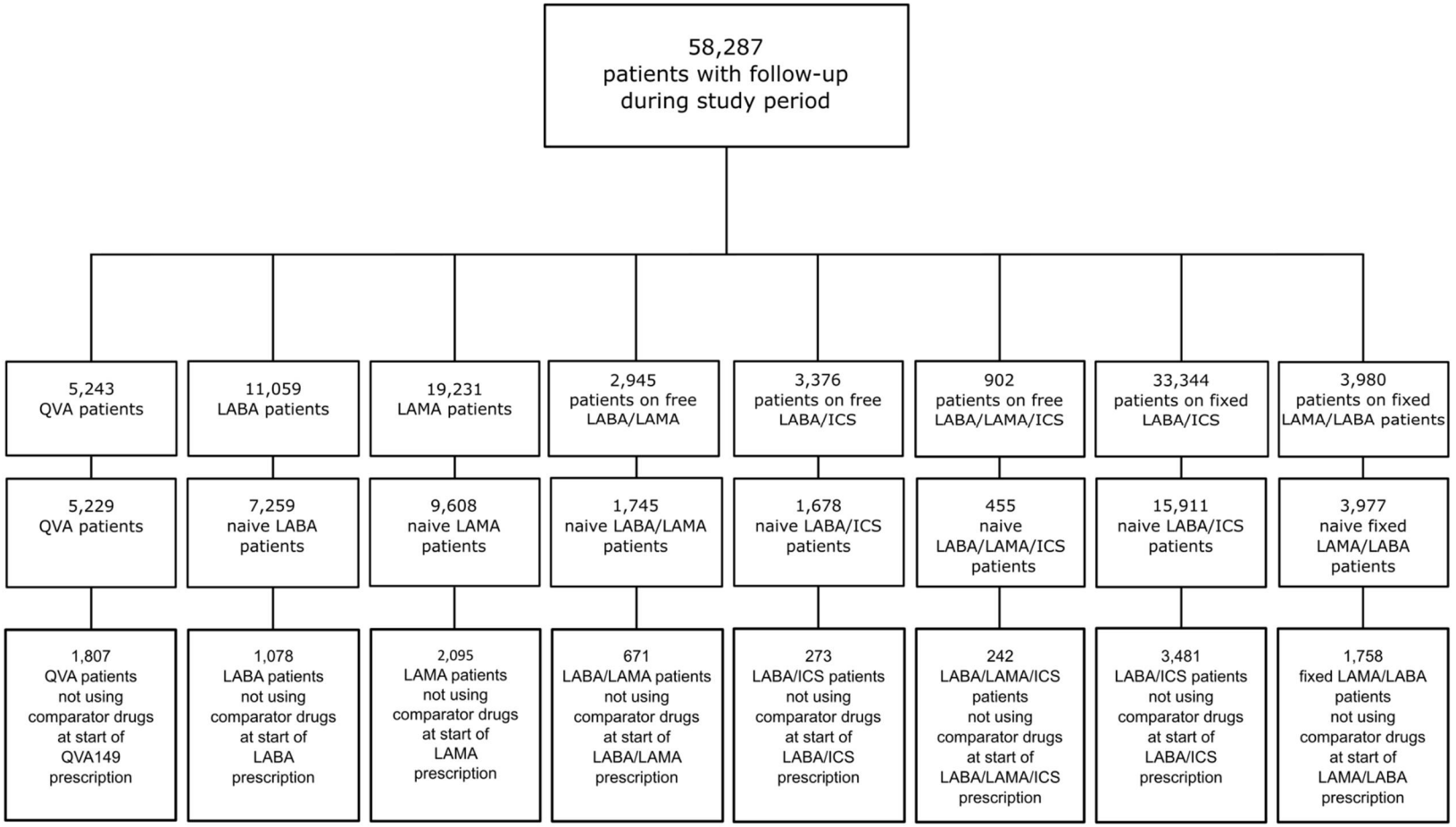
Naïve means no use of that respective drug class in the past. The total number of patients represent patients with a COPD disease code and active follow-up during the study period.

Figure 15-2 Flowchart for IPCI (NL) patient selection



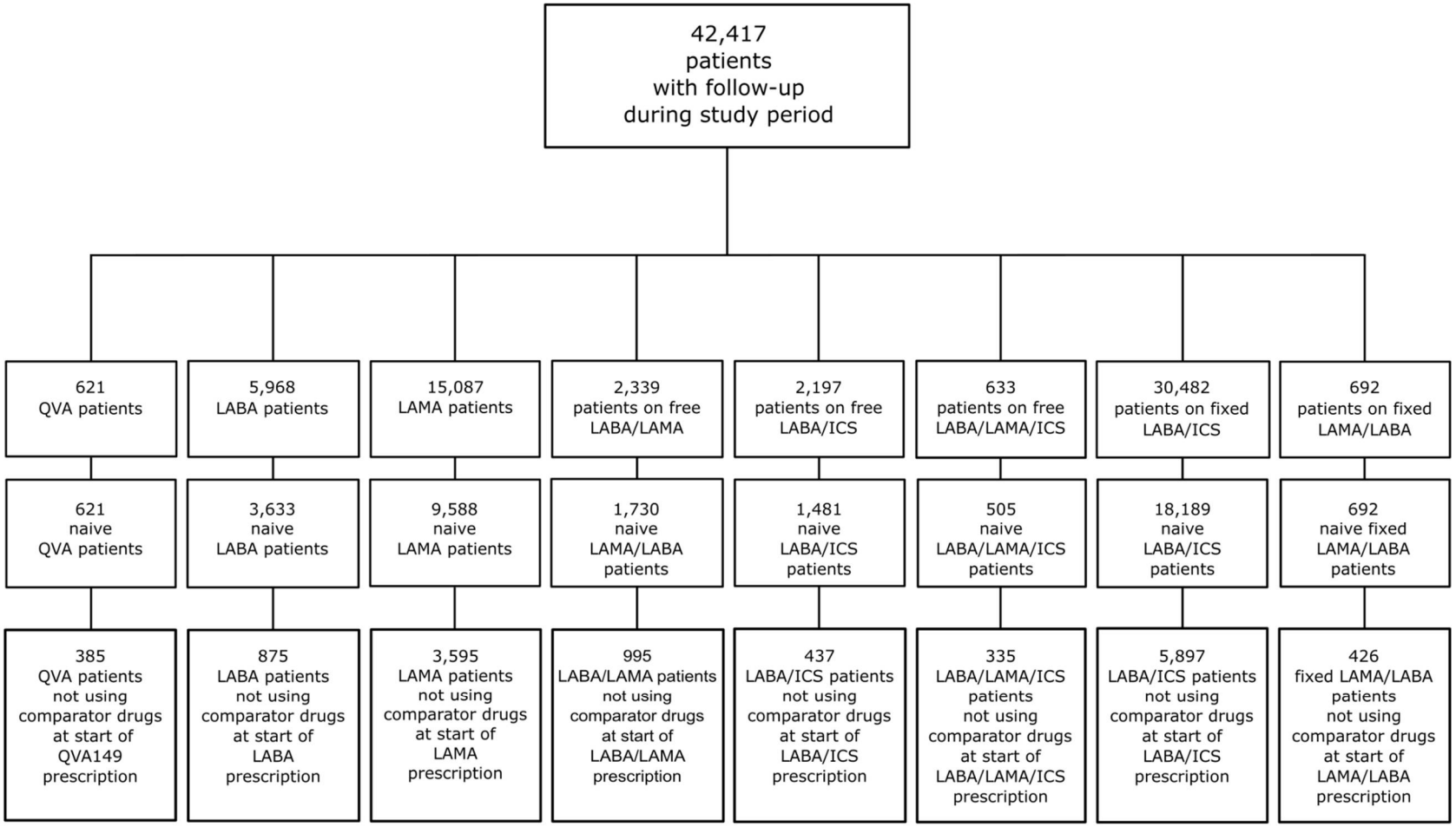
Naïve means no use of that respective drug class in the past. The total number of patients represent patients with a COPD disease code and active follow-up during the study period

Figure 15-3 Flowchart for Aarhus (DK) patient selection



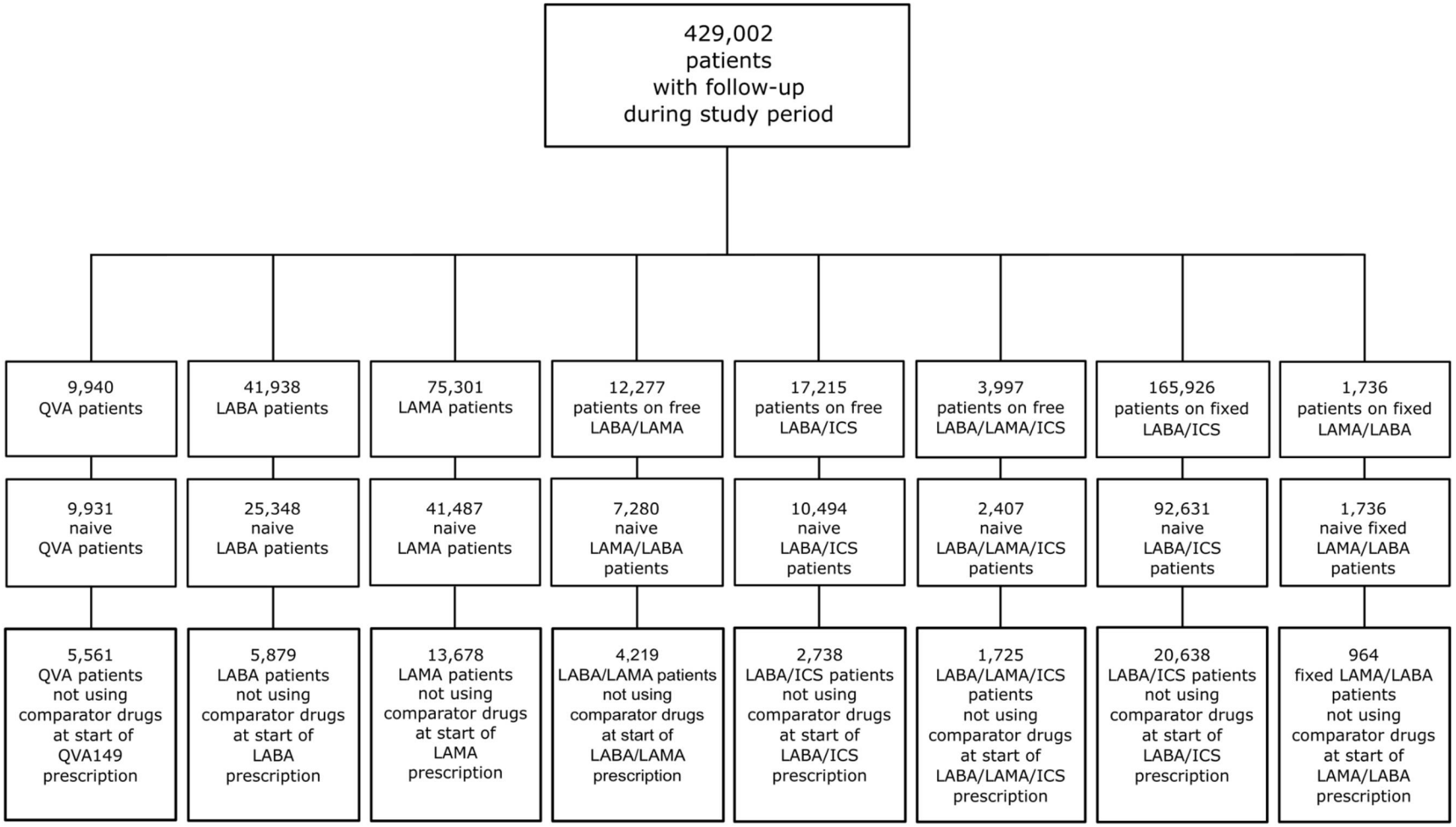
Naïve means no use of that respective drug class in the past. The total number of patients represent patients with a COPD disease code and active follow-up during the study period

Figure 15-4 Flowchart for HSD (IT) patient selection



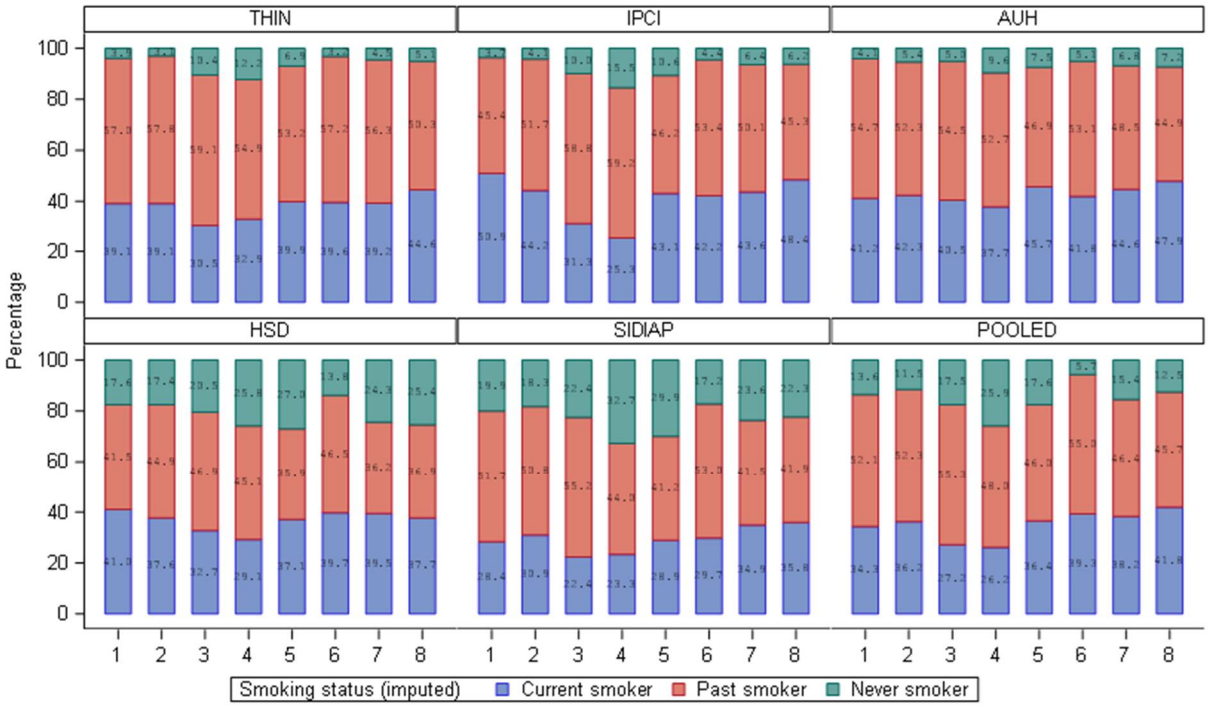
Naïve means no use of that respective drug class in the past. The total number of patients represent patients with a COPD disease code and active follow-up during the study period

Figure 15-5 Flowchart for SIDIAP (SP) patient selection



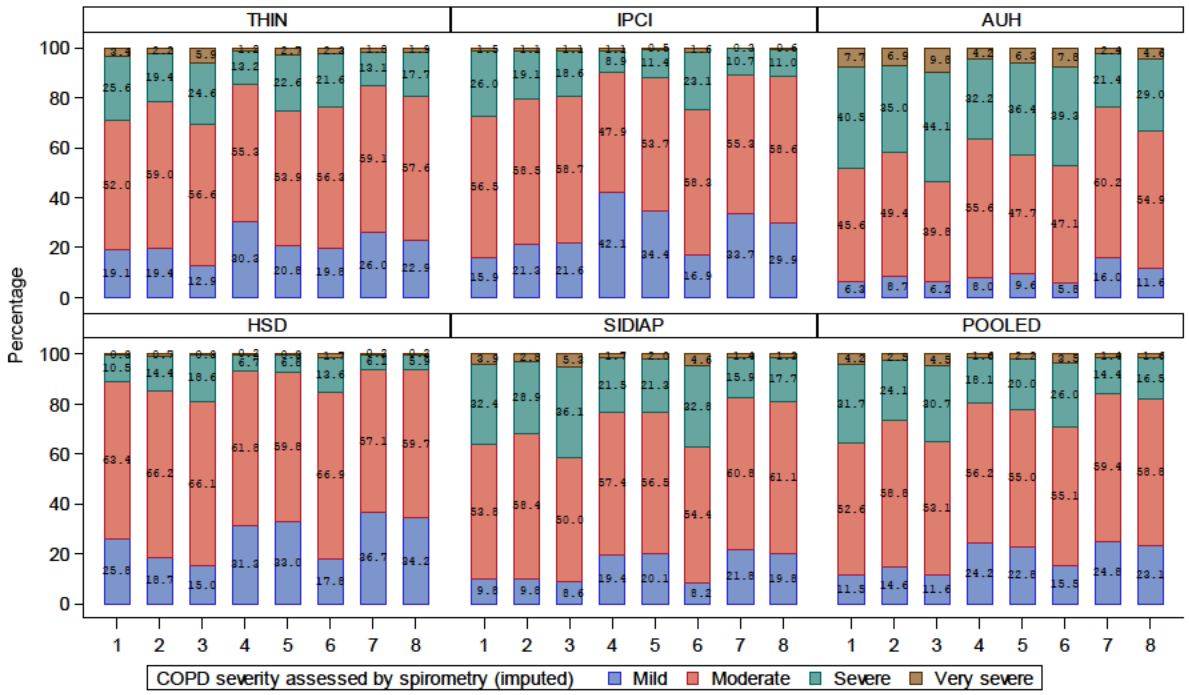
Naïve means no use of that respective drug class in the past. The total number of patients represent patients with a COPD disease code and active follow-up during the study period.

Figure 15-6 Distribution of Smoking status – Imputed data



1=QVA149, 2= free LABA+LAMA without ICS, 3= free LABA+LAMA with ICS, 4= free LABA+ICS, 5= fixed LABA+ICS, 6= fixed LABA+LAMA, 7= LABA, 8= LAMA

Figure 15-7 Distribution of COPD severity – imputed data



1=QVA149, 2= free LABA+LAMA without ICS, 3= free LABA+LAMA with ICS, 4= free LABA+ICS, 5= fixed LABA+ICS, 6= fixed LABA+LAMA, 7= LABA, 8= LAMA

Figure 15-8 KM curves – mortality (Pooled dataset)

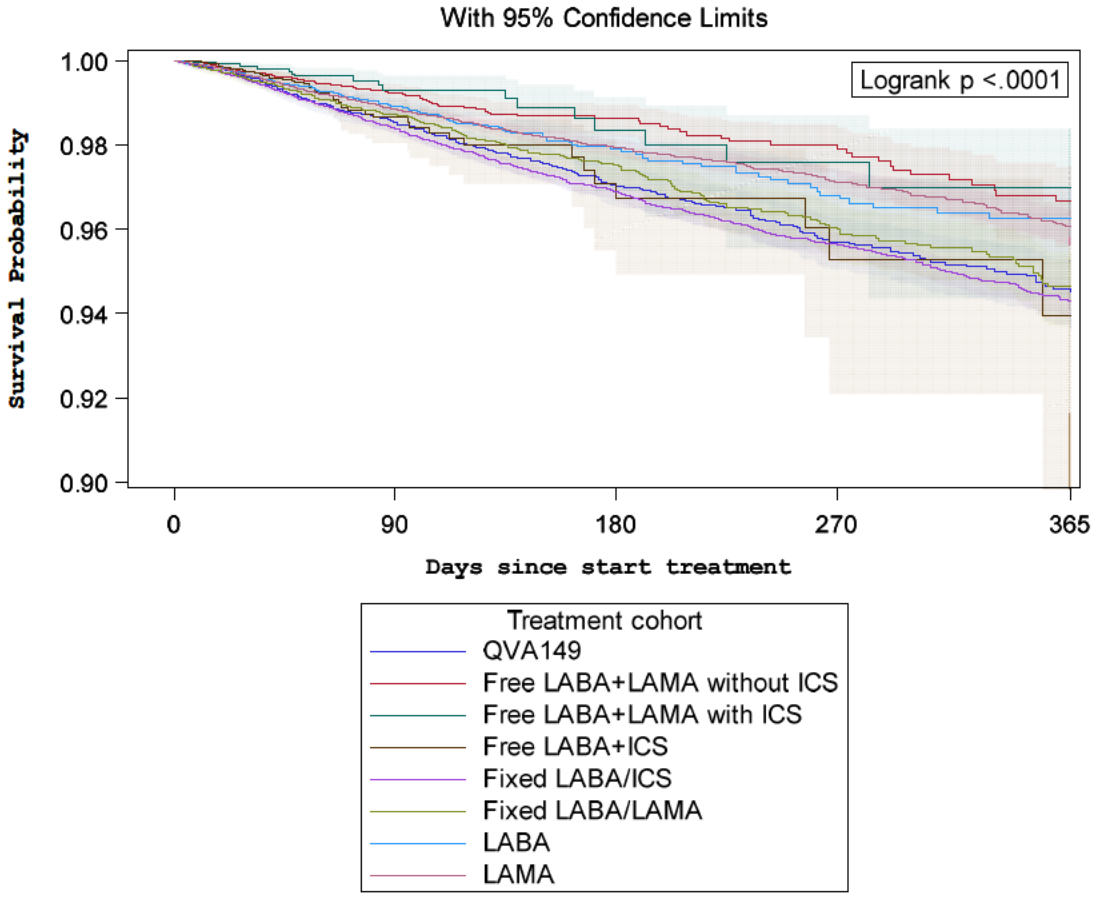


Figure 15-9 KM curves – mortality (THIN)

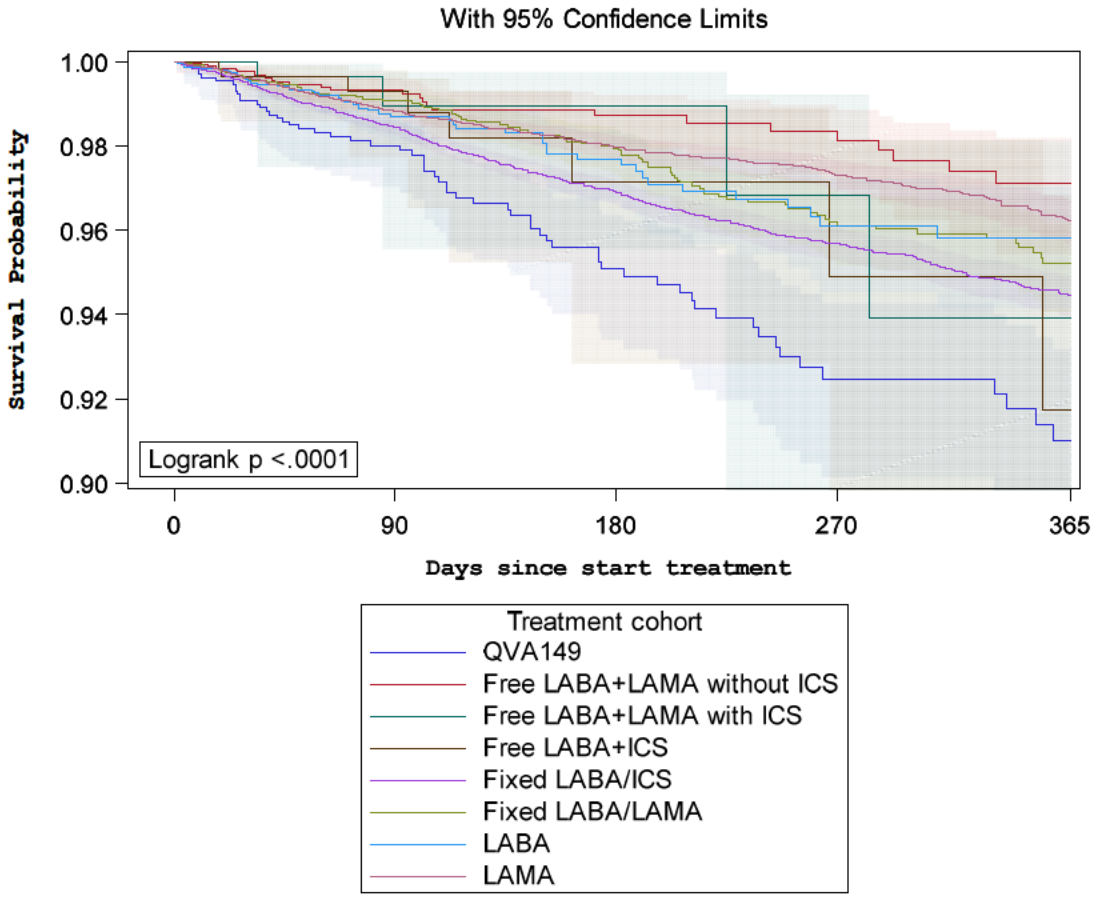


Figure 15-10 KM curves – mortality (IPCI)

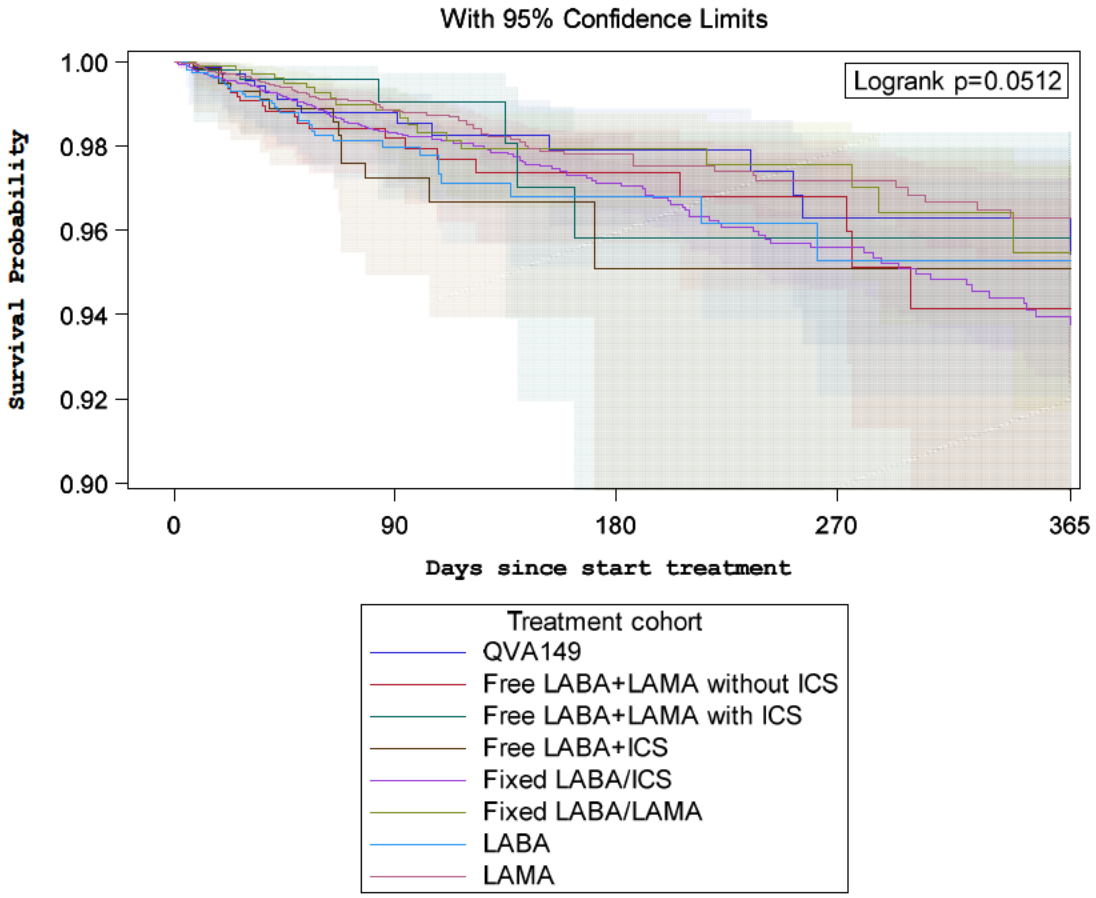


Figure 15-11 KM curves – mortality (Aarhus)

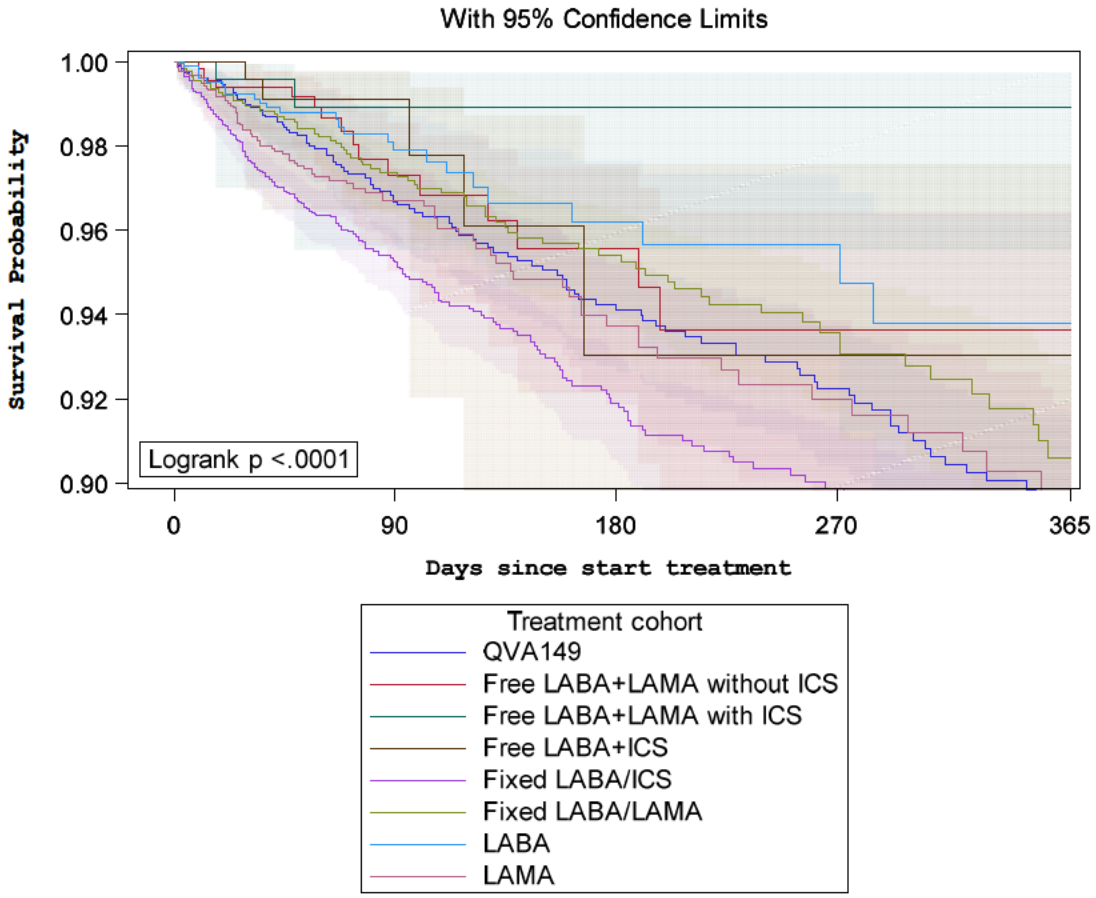


Figure 15-12 KM curves – mortality (HSD)

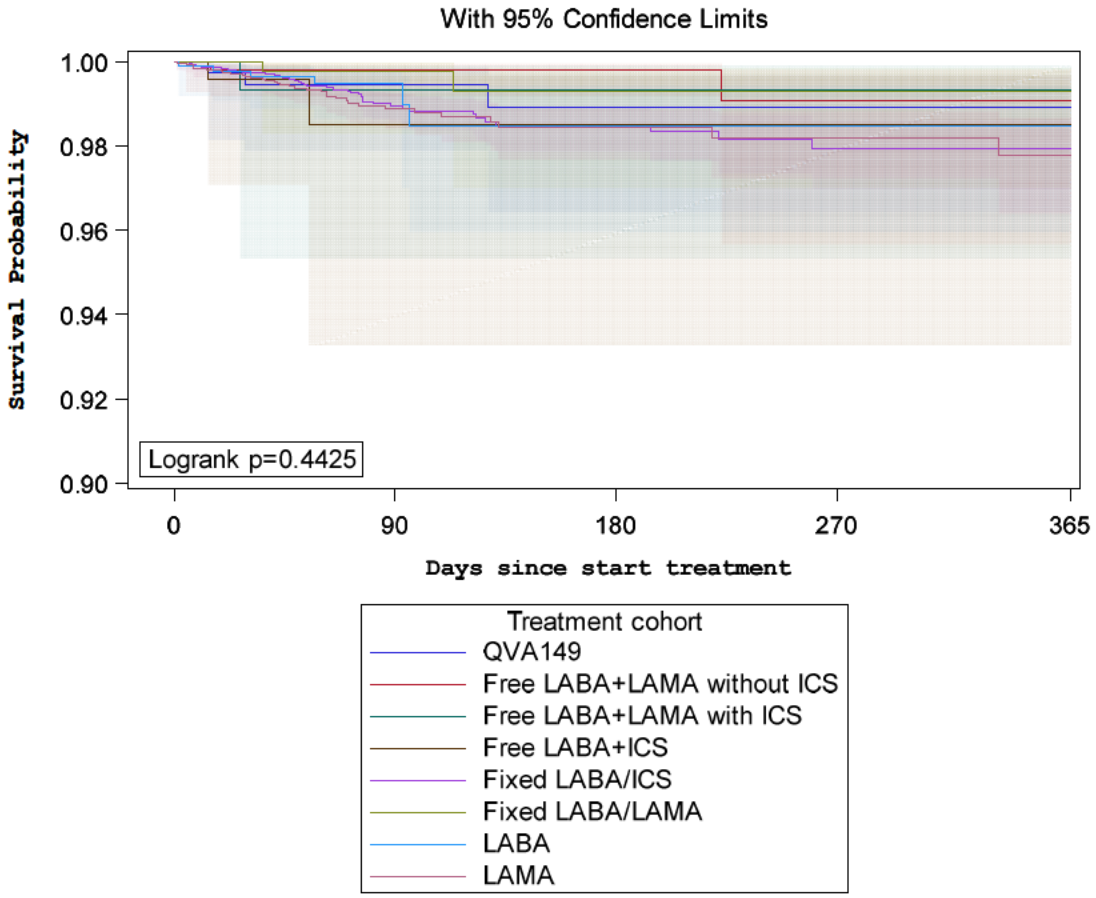


Figure 15-13 KM curves – mortality (SIDIAP)

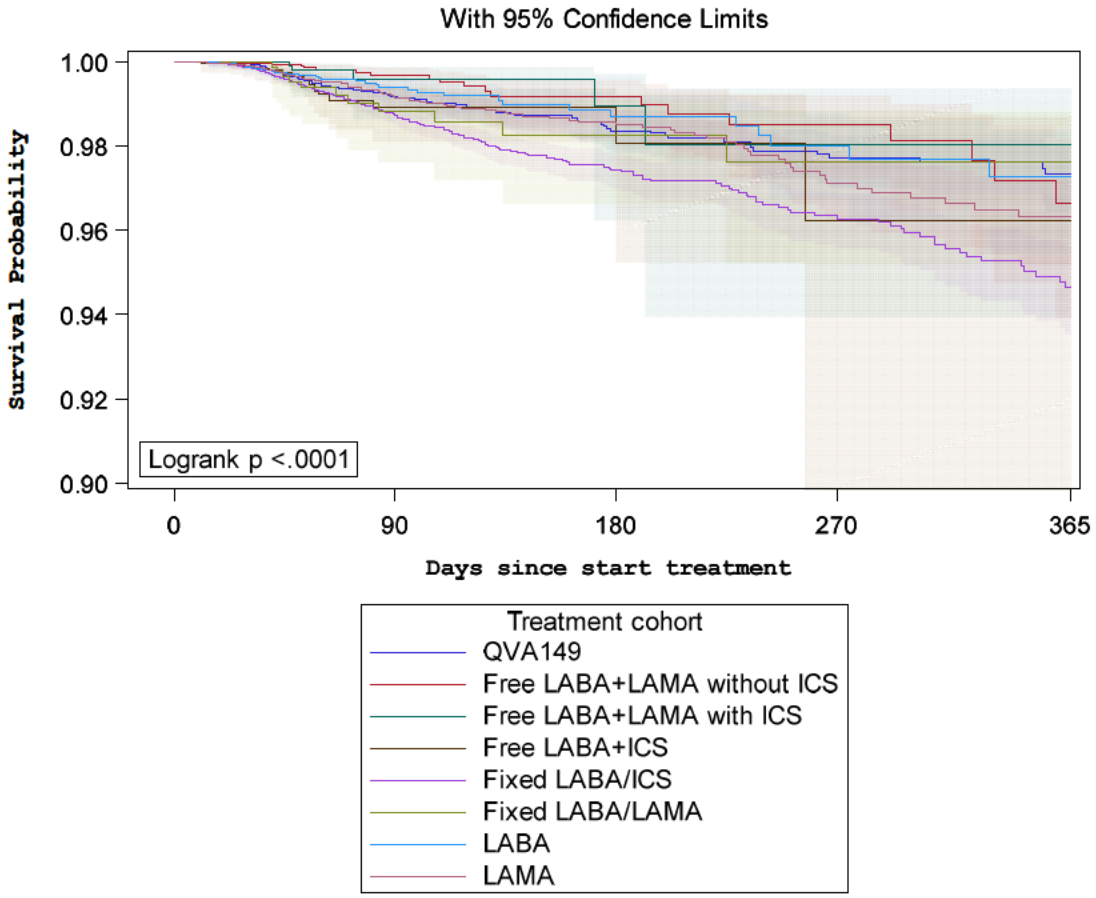
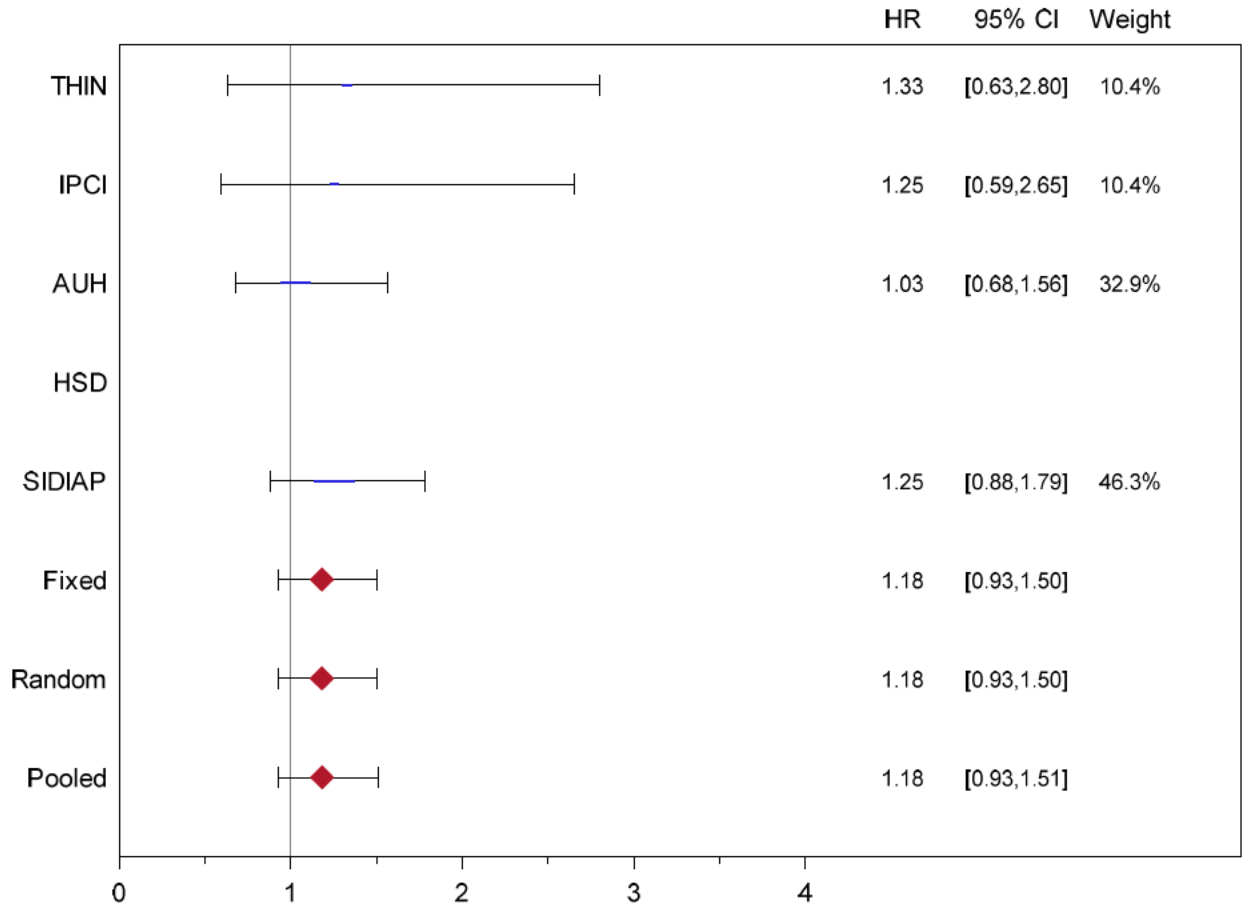
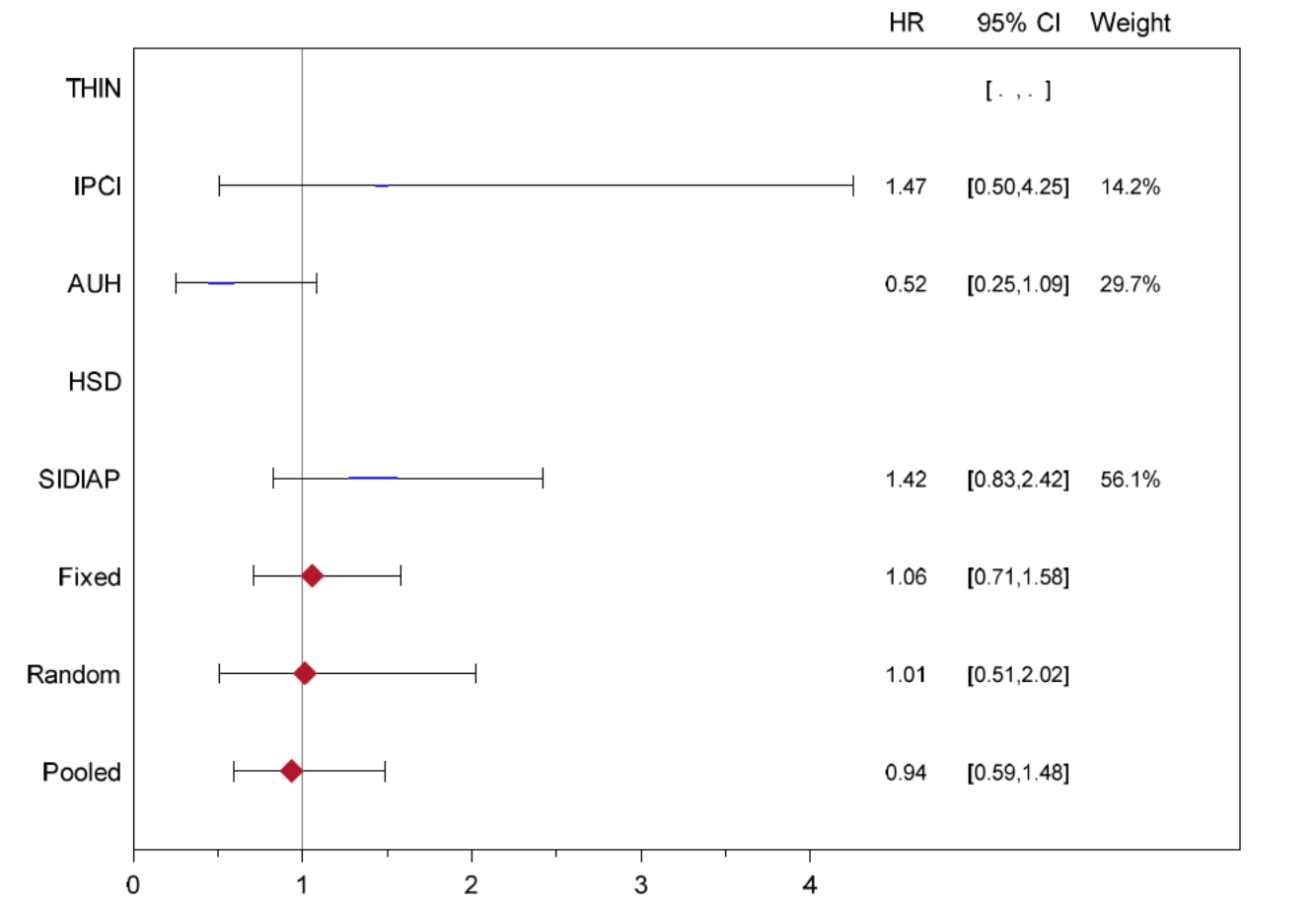


Figure 15-14 Forest plot results Model IPTW QVA149 versus free LABA/LAMA without ICS – Total analysis population – MACE as endpoint



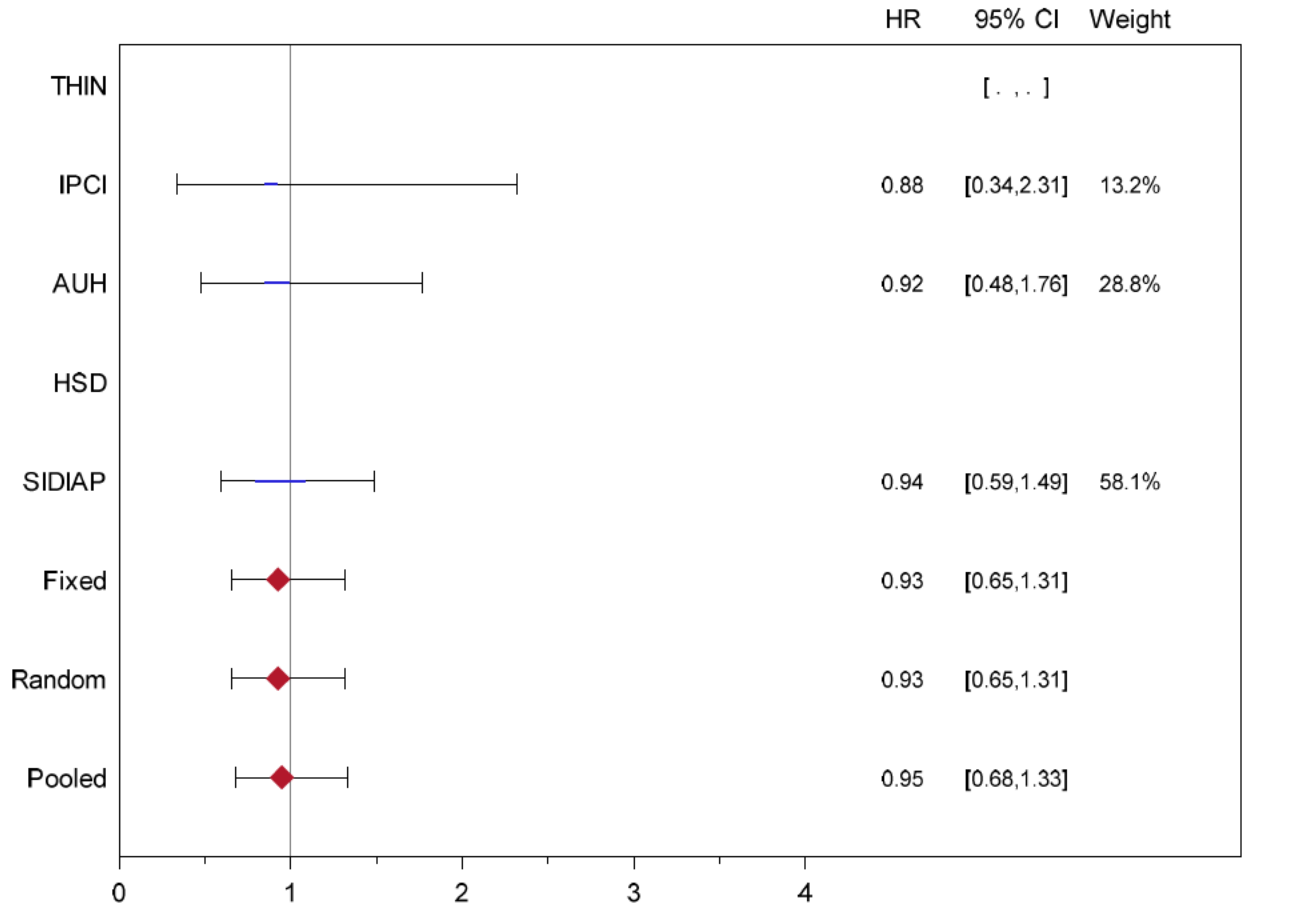
Cochran's Q = 0.651908, P = 0.884453, I-square = 0% . In pooled analysis: P interaction = 0.9522.

Figure 15-15 Forest plot results Model IPTW QVA149 versus free LABA/LAMA with ICS – Total analysis population – MACE as endpoint



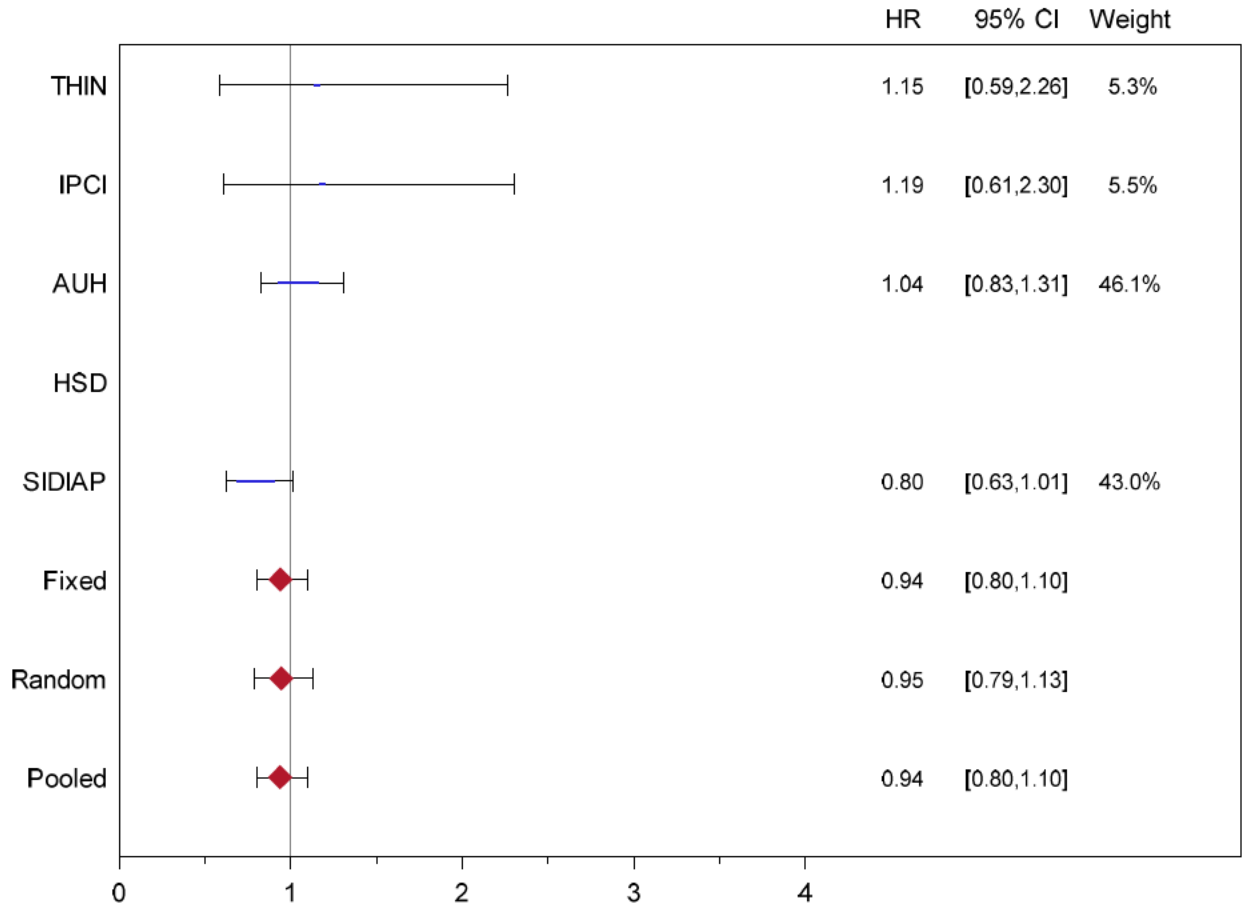
Cochran's Q = 5.05942, P = 0.079682, I-square = 60% . In pooled analysis: P interaction = 0.1721

Figure 15-16 Forest plot results Model IPTW QVA149 versus Free LABA+ICS – Total analysis population – MACE as endpoint



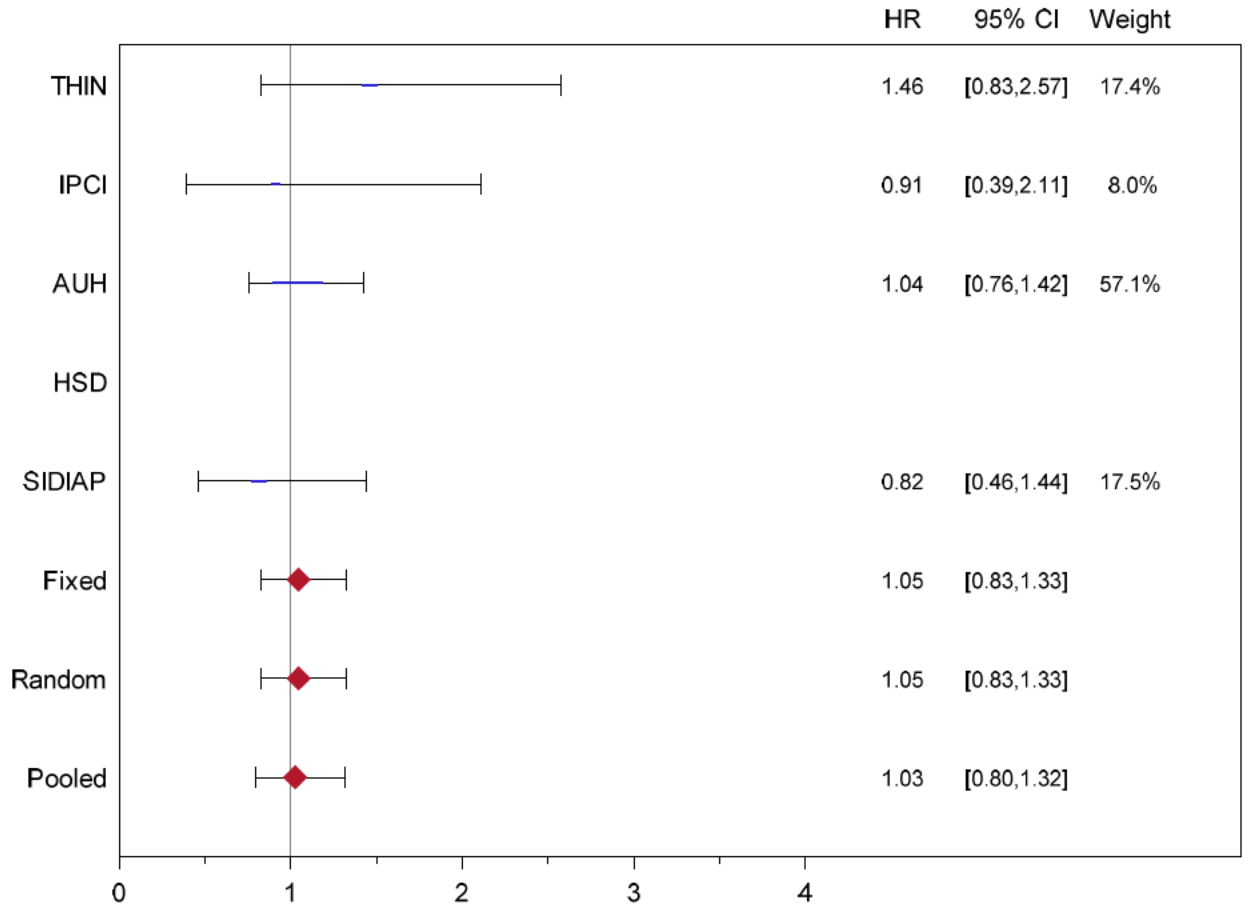
Cochran's Q = 0.013202, P = 0.993421, I-square = 0% . In pooled analysis: P interaction = <.0001

Figure 15-17 Forest plot results Model IPTW QVA149 versus Fixed LABA/ICS – Total analysis population – MACE as endpoint



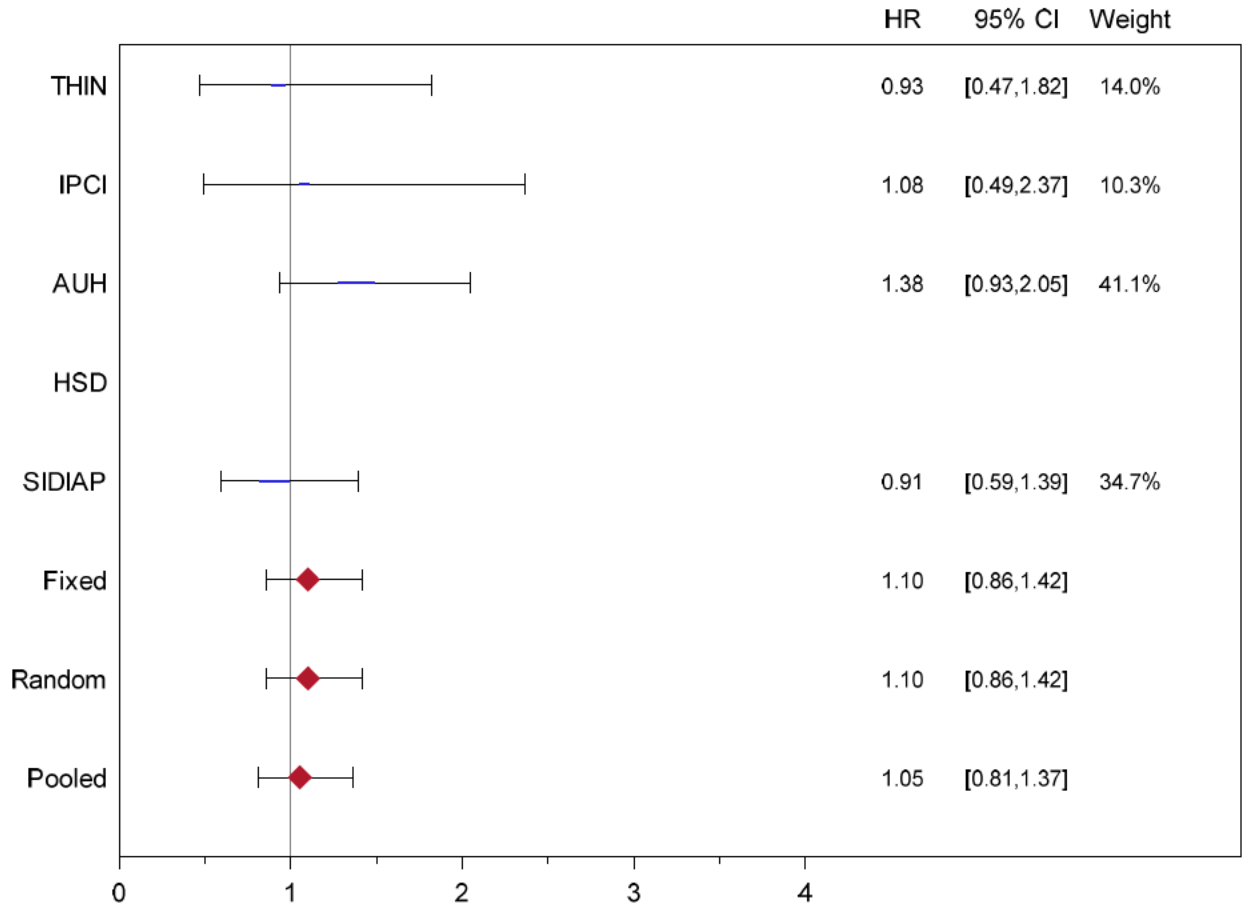
Cochran's Q = 3.494053, P = 0.321534, I-square = 14% . In pooled analysis: P interaction = 0.4648

Figure 15-18 Forest plot results Model IPTW QVA149 versus Fixed LABA/LAMA – Total analysis population – MACE as endpoint



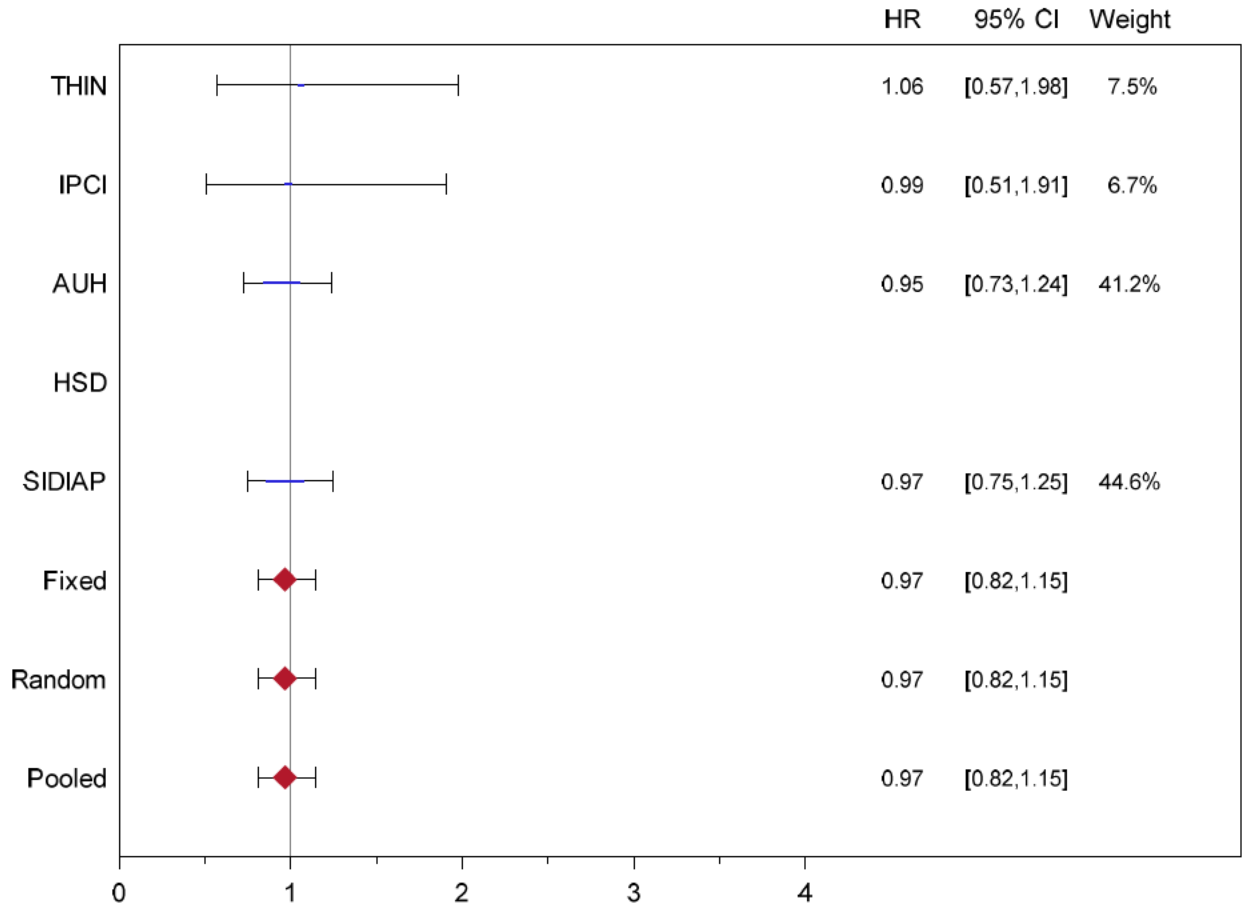
Cochran's Q = 2.135792, P = 0.544706, I-square = 0% . In pooled analysis: P interaction = 0.6979

Figure 15-19 Forest plot results Model IPTW QVA149 versus LABA – Total analysis population – MACE as endpoint



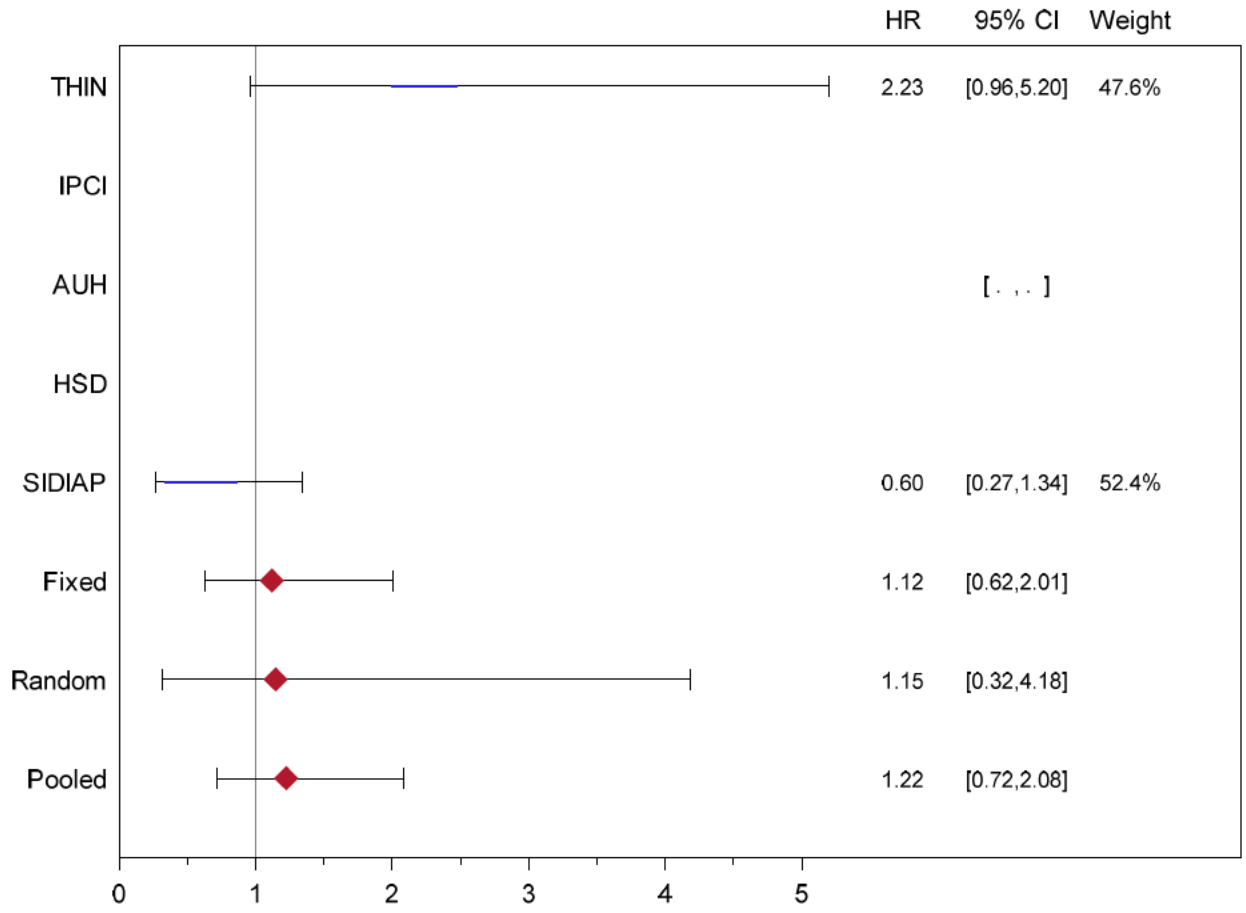
Cochran's Q = 2.330185, P = 0.506763, I-square = 0% . In pooled analysis: P interaction = 0.5921

Figure 15-20 Forest plot results Model IPTW QVA149 versus LAMA – Total analysis population – MACE as endpoint



Cochran's Q = 0.108644, P = 0.99078, I-square = 0% . In pooled analysis: P interaction = 0.9

Figure 15-21 Forest plot results Model IPTW QVA149 versus free LABA/LAMA without ICS – Total analysis population – ischemic heart disease as endpoint



Cochran's Q = 4.894018, P = 0.02695, I-square = 80% . In pooled analysis: P interaction = 0.2751

Figure 15-22 Forest plot results Model IPTW QVA149 versus free LABA/LAMA with ICS – Total analysis population – ischemic heart disease as endpoint

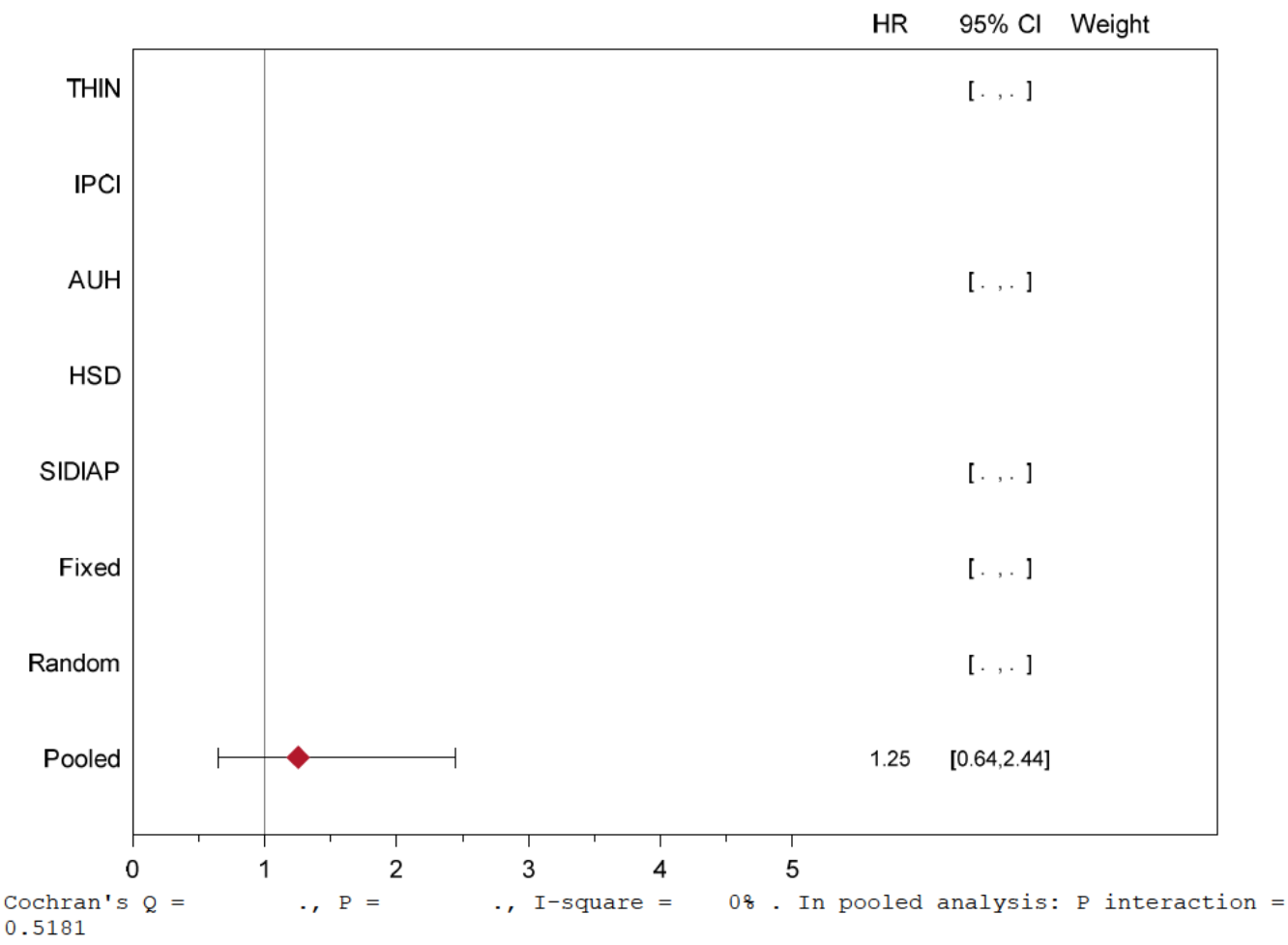


Figure 15-23 Forest plot results Model IPTW QVA149 versus Free LABA+ICS – Total analysis population – ischemic heart disease as endpoint

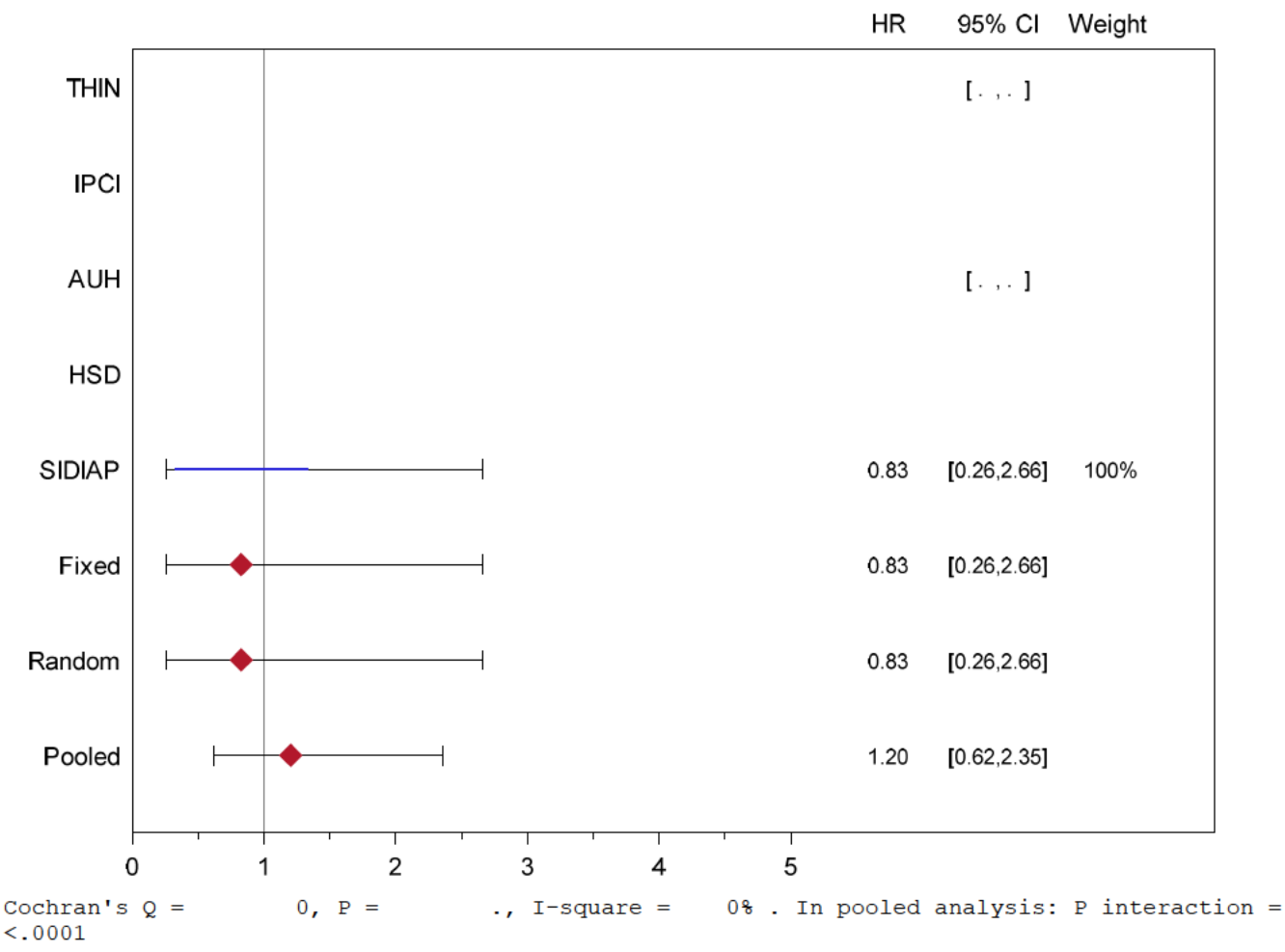
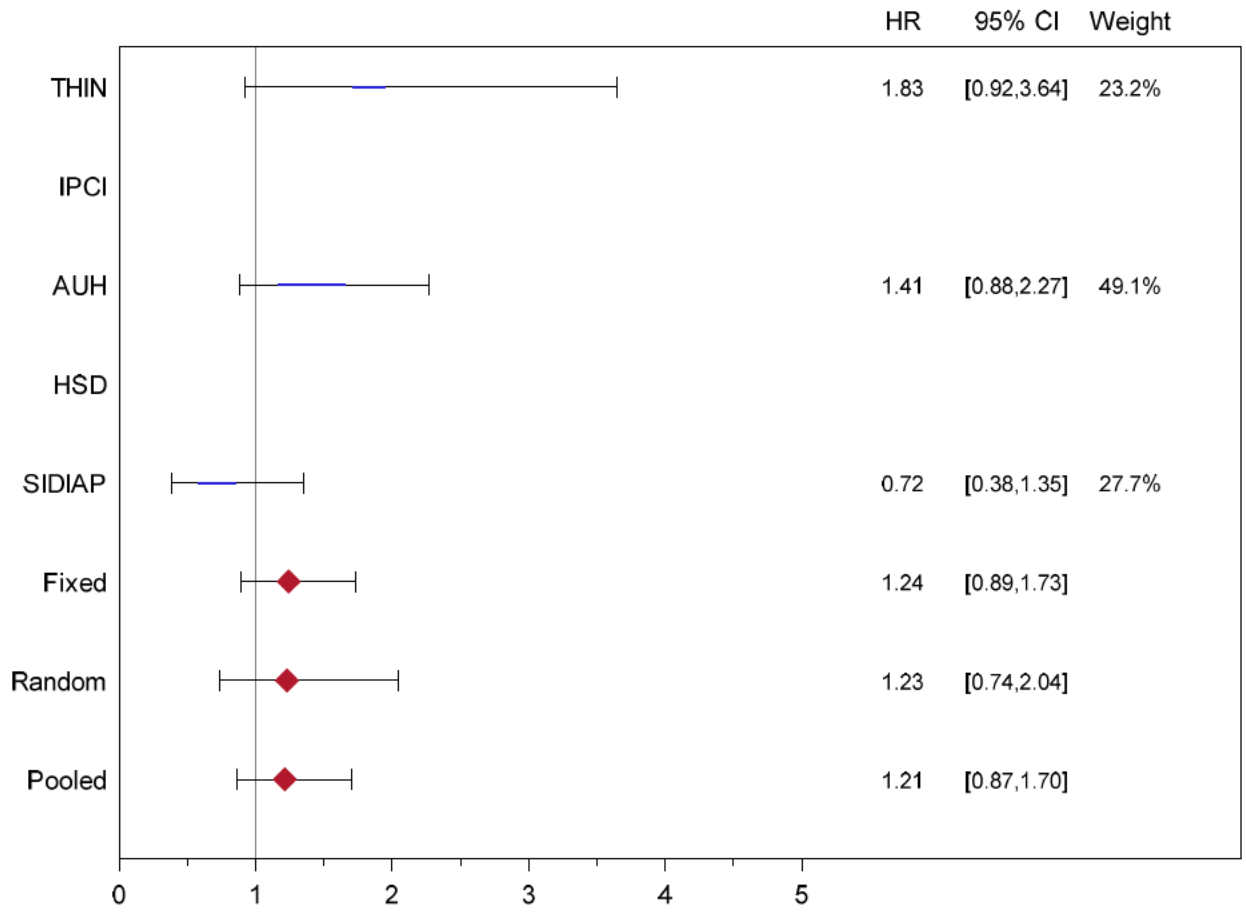
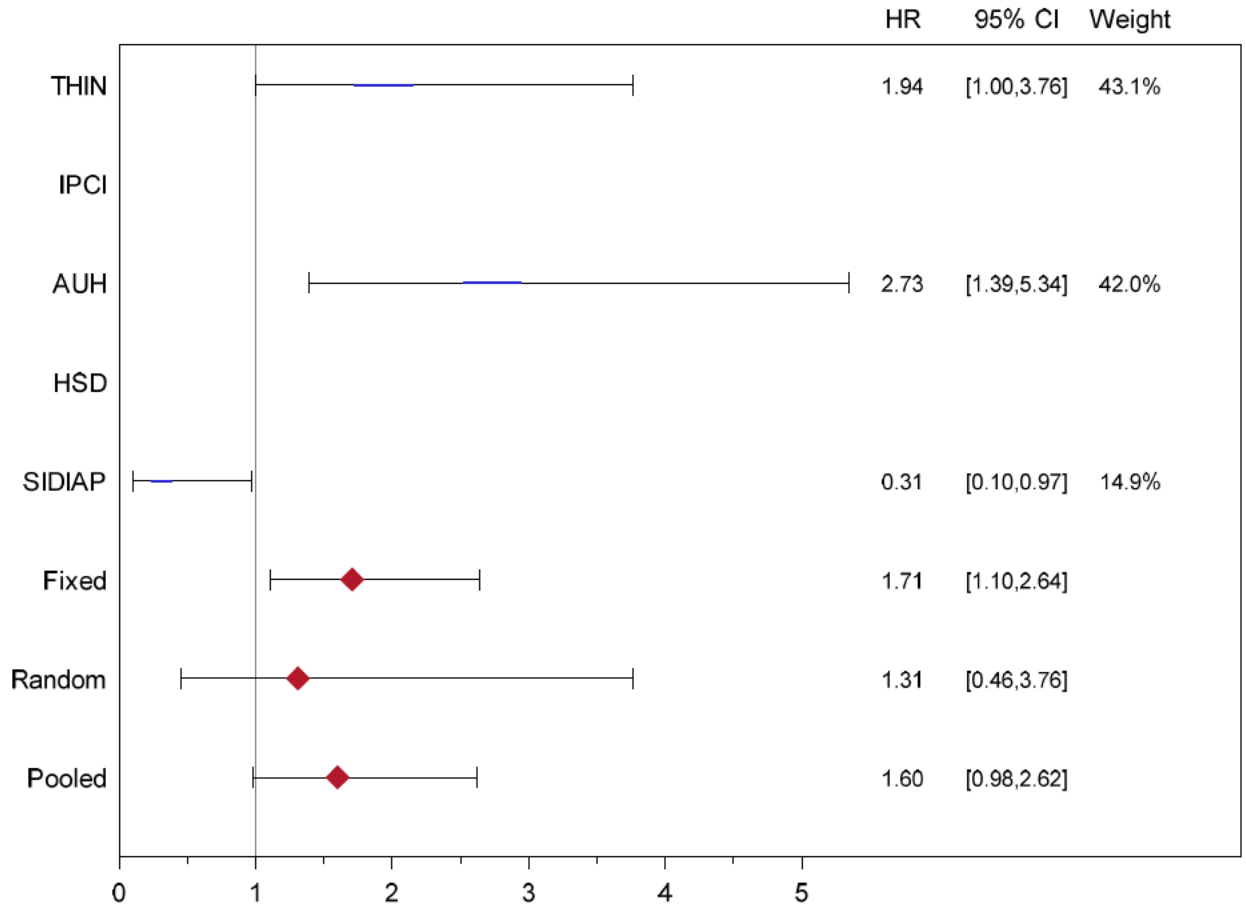


Figure 15-24 Forest plot results Model IPTW QVA149 versus Fixed LABA/ICS – Total analysis population – ischemic heart disease as endpoint



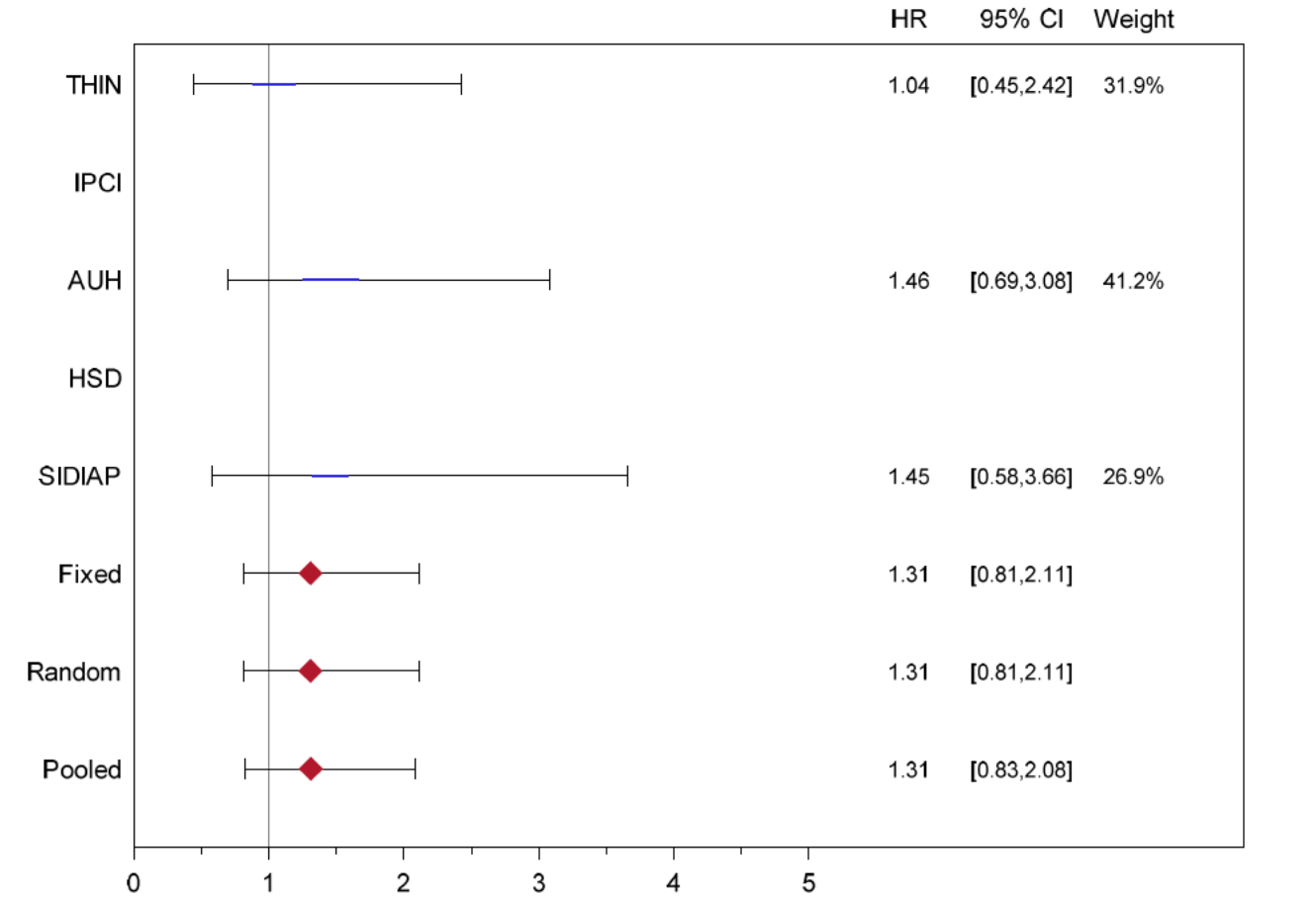
Cochran's Q = 4.383128, P = 0.111742, I-square = 54% . In pooled analysis: P interaction = 0.2985

Figure 15-25 Forest plot results Model IPTW QVA149 versus Fixed LABA/LAMA – Total analysis population – ischemic heart disease as endpoint



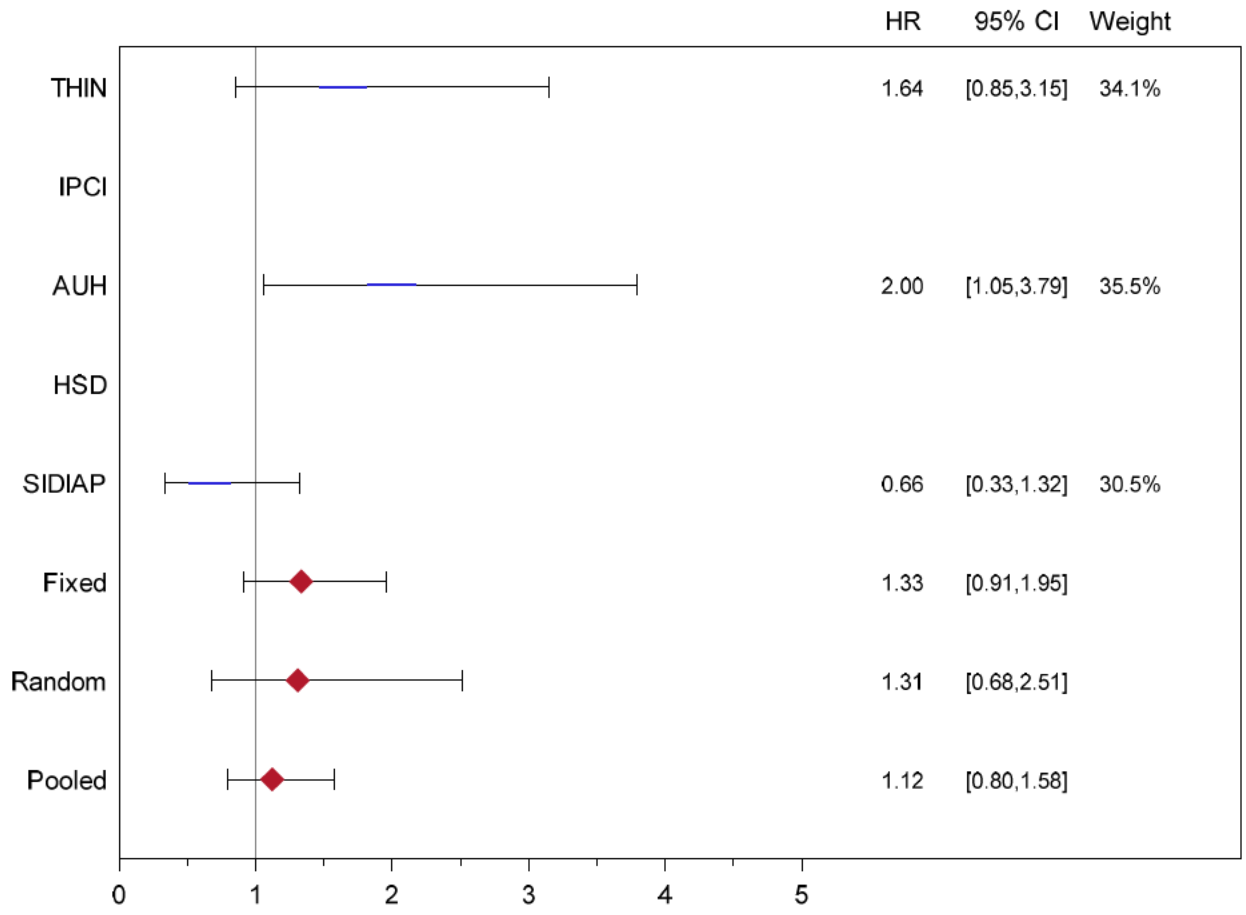
Cochran's Q = 10.65128, P = 0.004865, I-square = 81% . In pooled analysis: P interaction = 0.0217

Figure 15-26 Forest plot results Model IPTW QVA149 versus LABA – Total analysis population – ischemic heart disease as endpoint



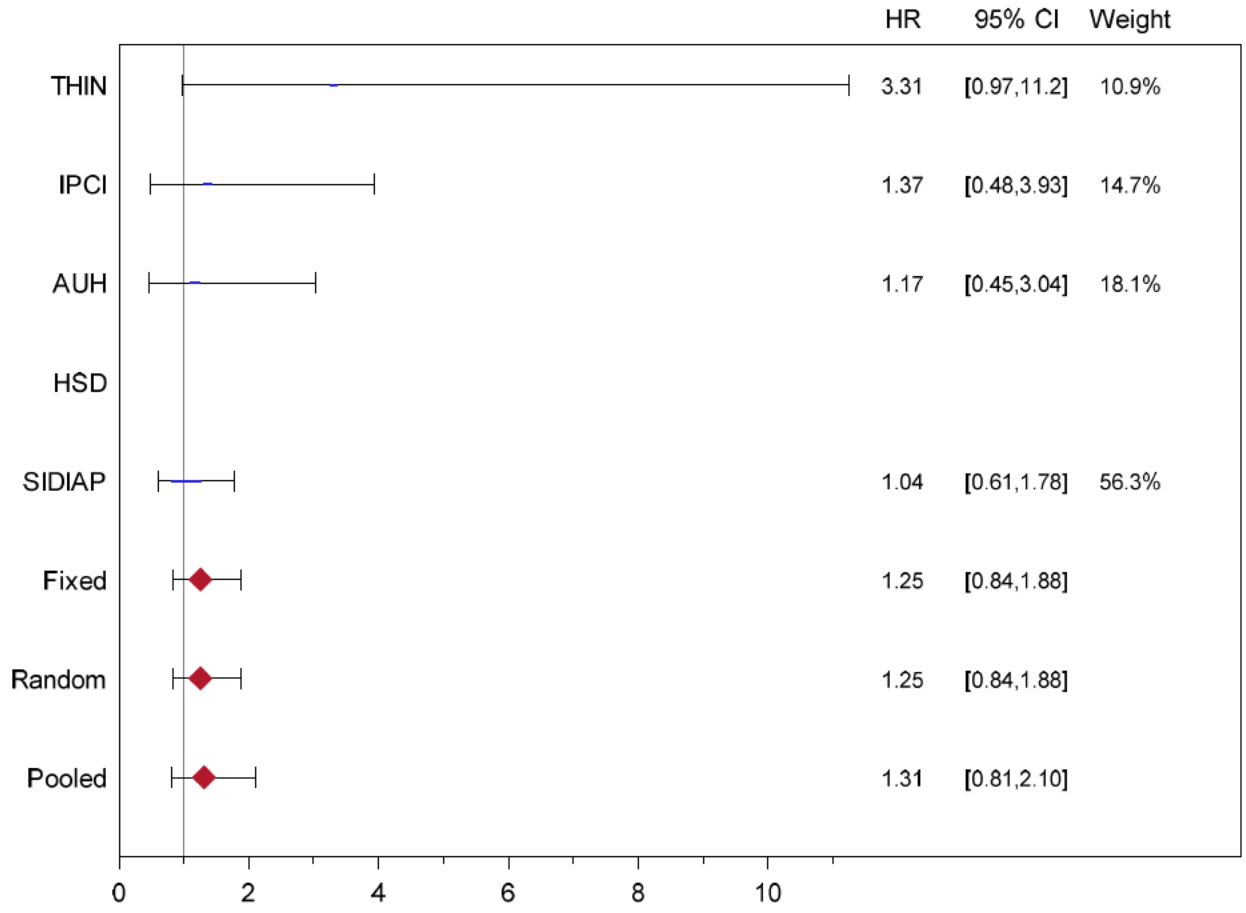
Cochran's Q = 0.420366, P = 0.810436, I-square = 0% . In pooled analysis: P interaction = 0.9426

Figure 15-27 Forest plot results Model IPTW QVA149 versus LAMA – Total analysis population – ischemic heart disease as endpoint



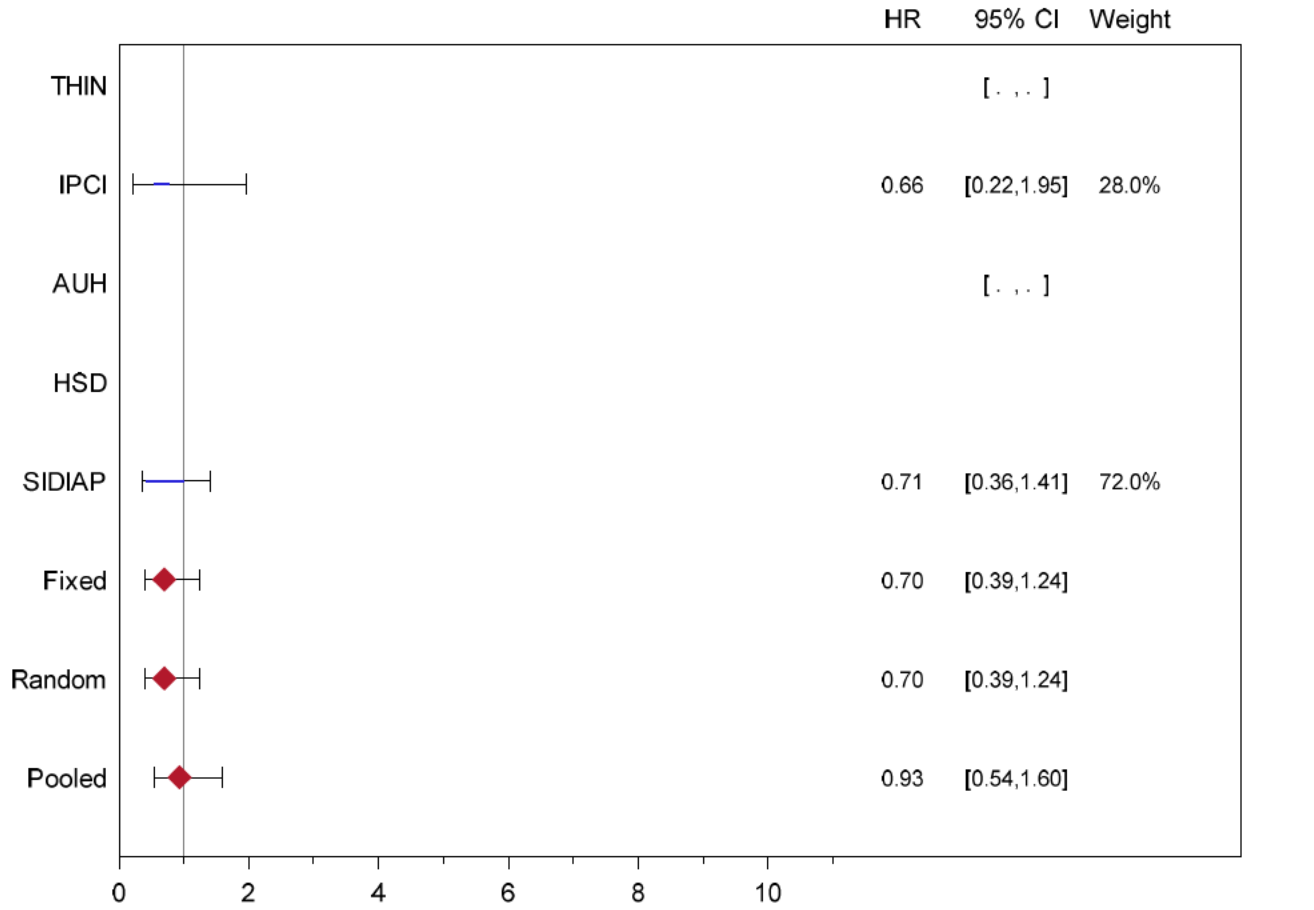
Cochran's Q = 5.838523, P = 0.053974, I-square = 66% . In pooled analysis: P interaction = 0.0844

Figure 15-28 Forest plot results Model IPTW QVA149 versus free LABA/LAMA without ICS – Total analysis population – cardiac arrhythmia as endpoint



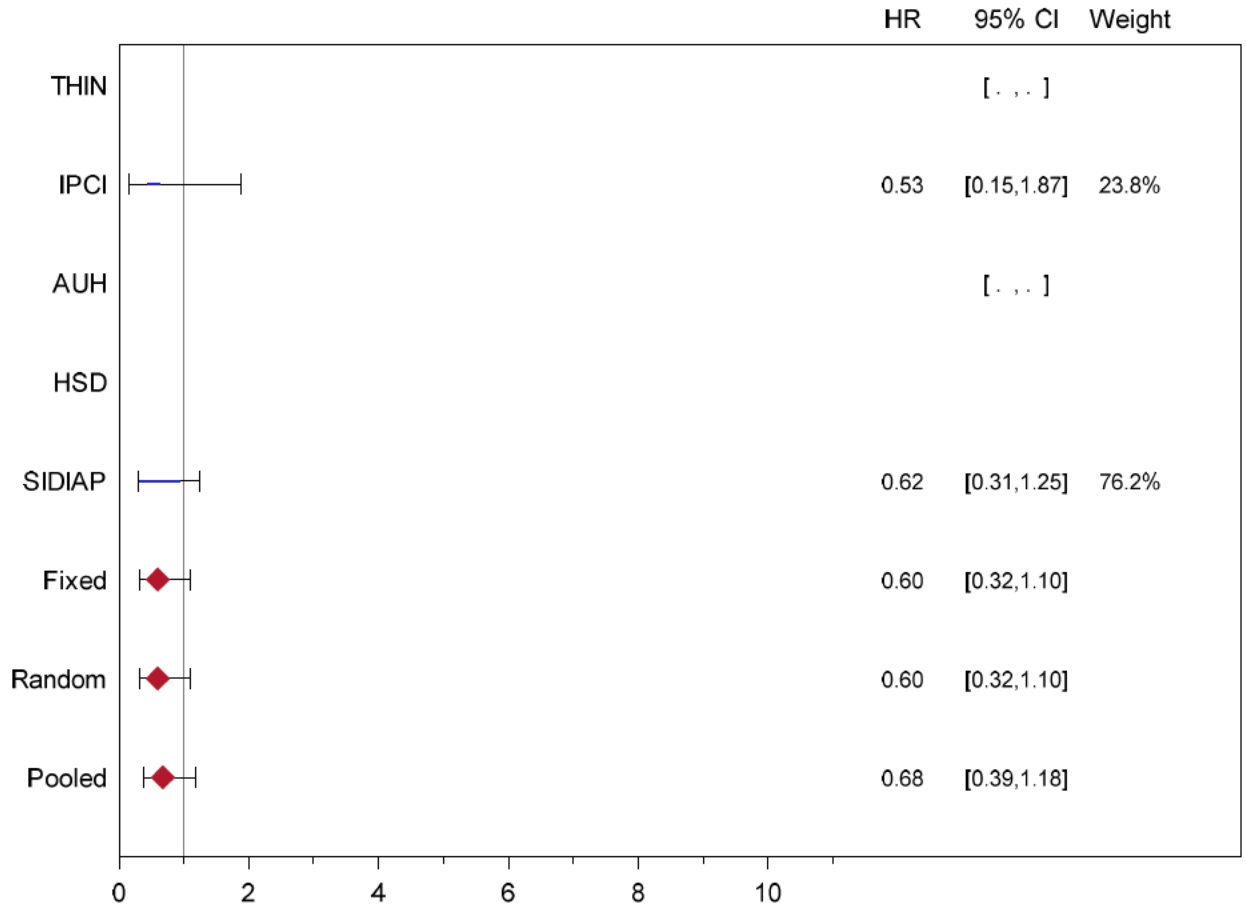
Cochran's Q = 2.934754, P = 0.401795, I-square = 0% . In pooled analysis: P interaction = 0.3773

Figure 15-29 Forest plot results Model IPTW QVA149 versus free LABA/LAMA with ICS – Total analysis population – cardiac arrhythmia as endpoint



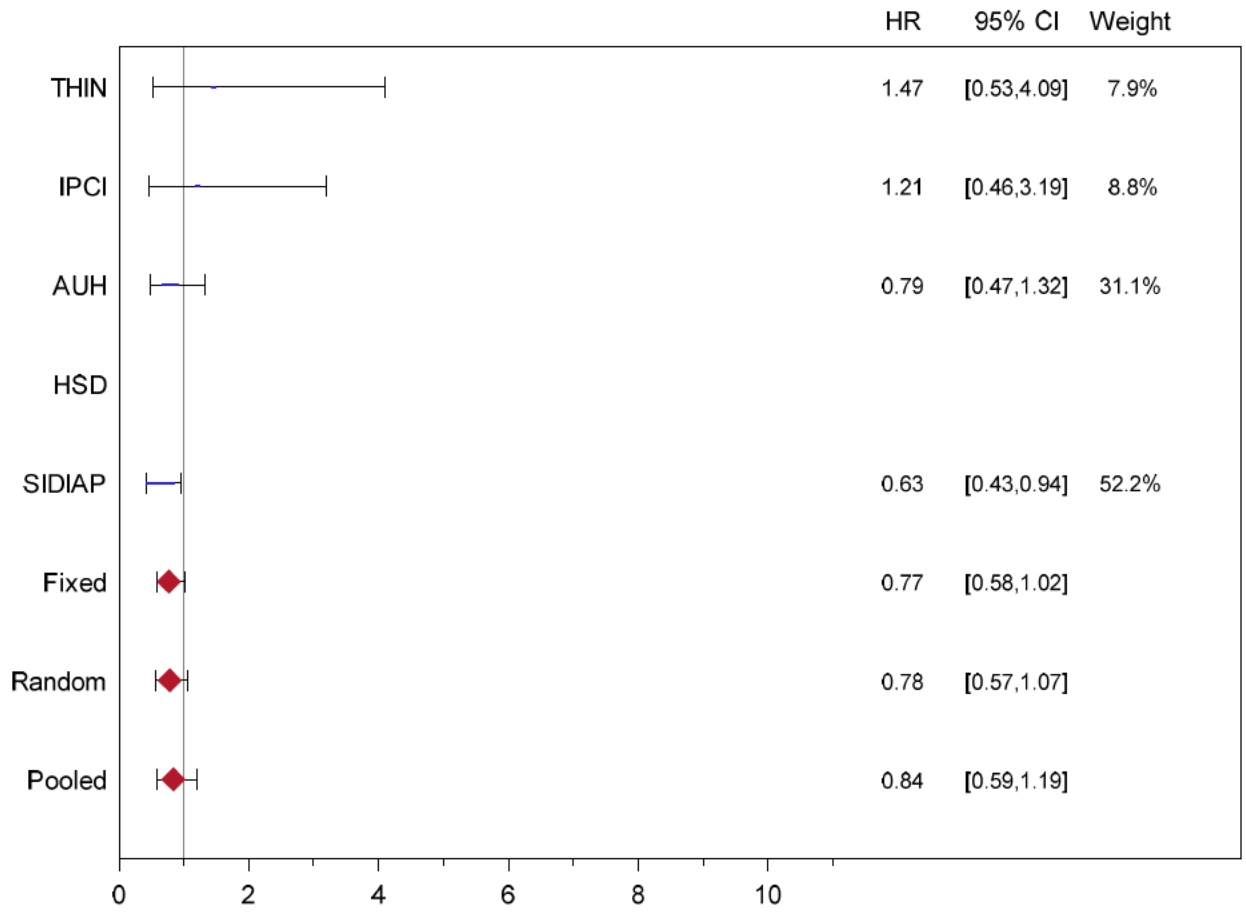
Cochran's Q = 0.016995, P = 0.896277, I-square = 0% . In pooled analysis: P interaction = <.0001

Figure 15-30 Forest plot results Model IPTW QVA149 versus Free LABA+ICS – Total analysis population – cardiac arrhythmia as endpoint



Cochran's Q = 0.040669, P = 0.840178, I-square = 0% . In pooled analysis: P interaction = 0.8230

Figure 15-31 Forest plot results Model IPTW QVA149 versus Fixed LABA/ICS – Total analysis population – cardiac arrhythmia as endpoint



Cochran's Q = 3.275434, P = 0.351076, I-square = 8% . In pooled analysis: P interaction = 0.4859

Figure 15-32 Forest plot results Model IPTW QVA149 versus Fixed LABA/LAMA – Total analysis population – cardiac arrhythmia as endpoint

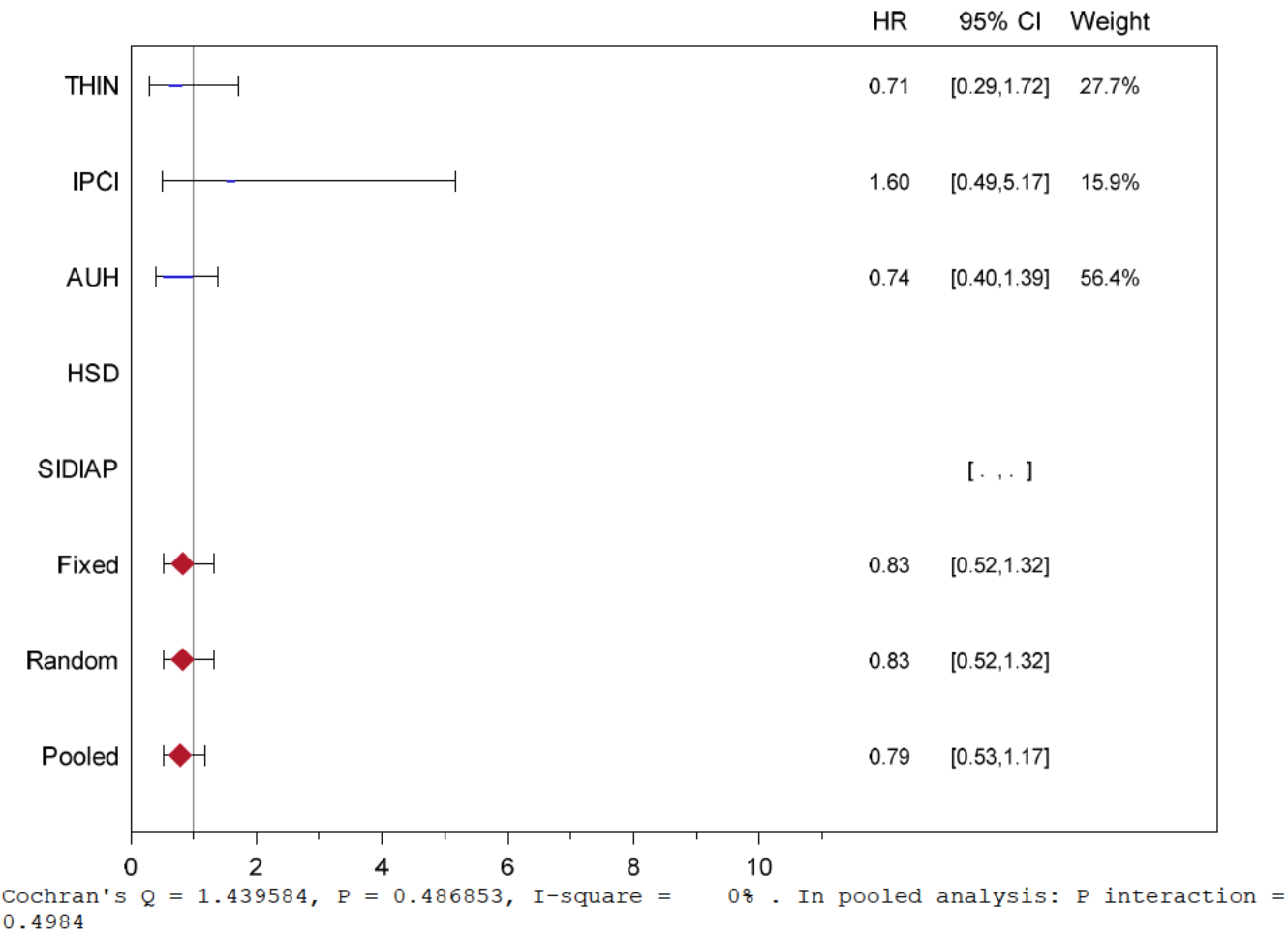
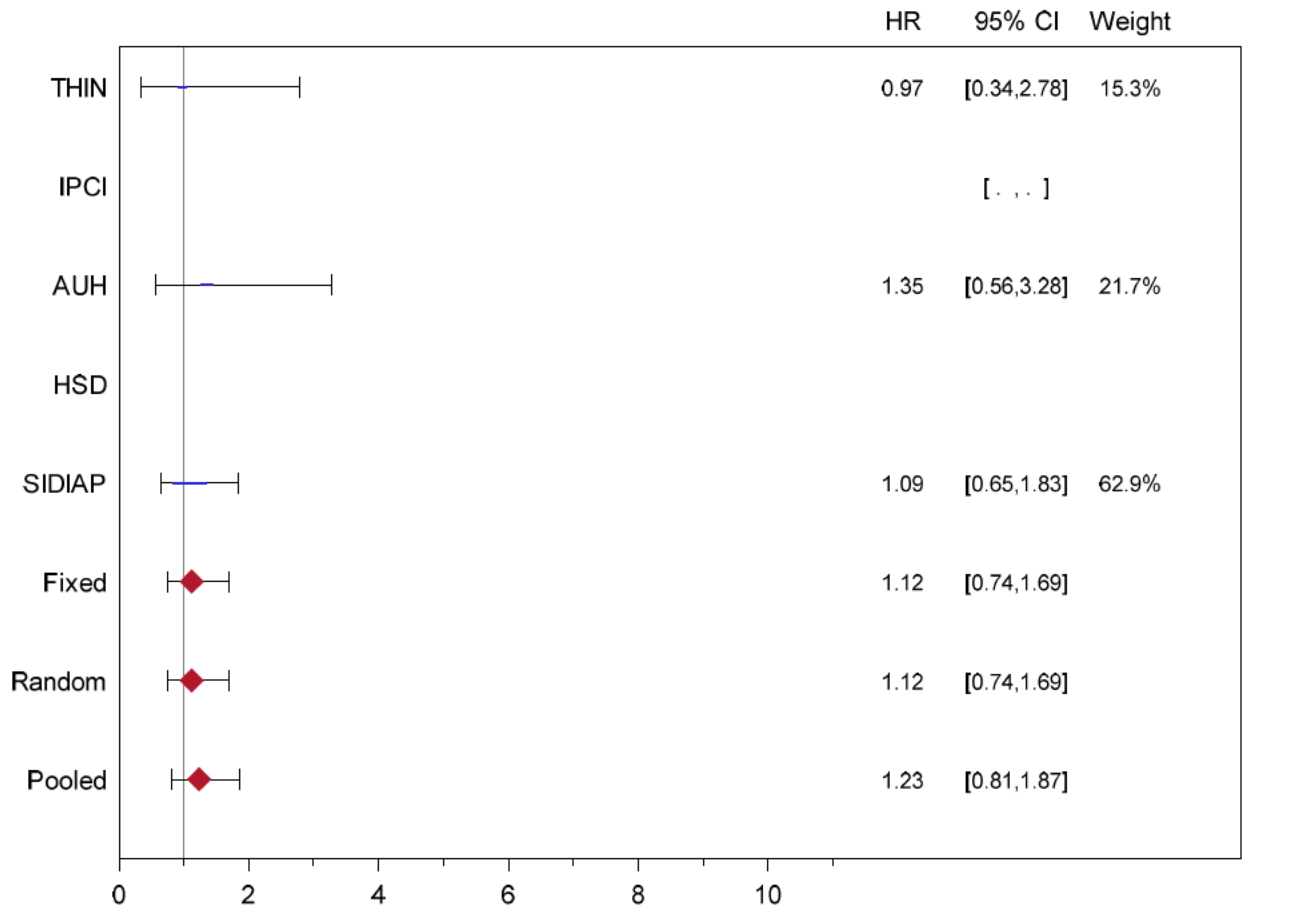
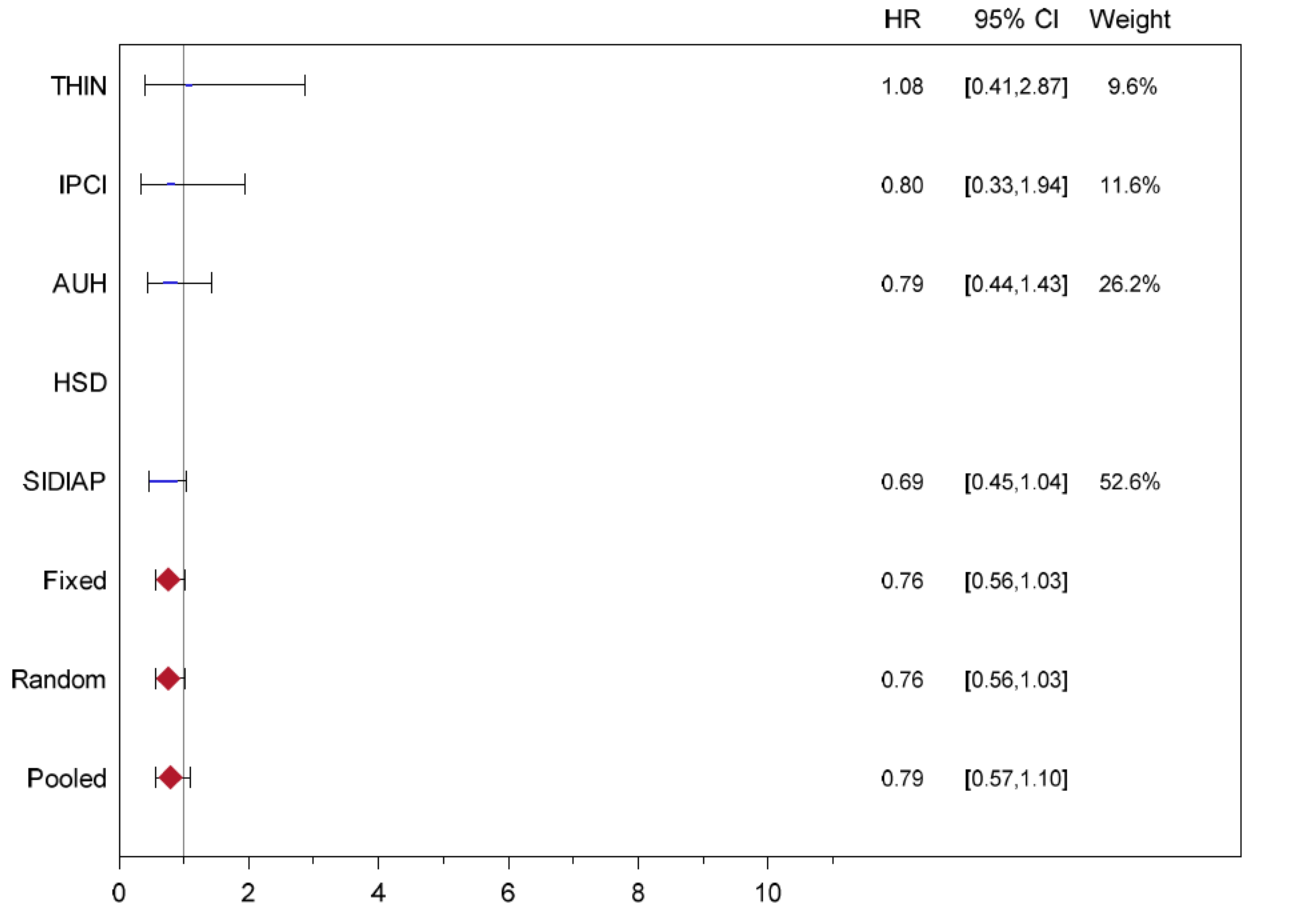


Figure 15-33 Forest plot results Model IPTW QVA149 versus LABA – Total analysis population – cardiac arrhythmia as endpoint



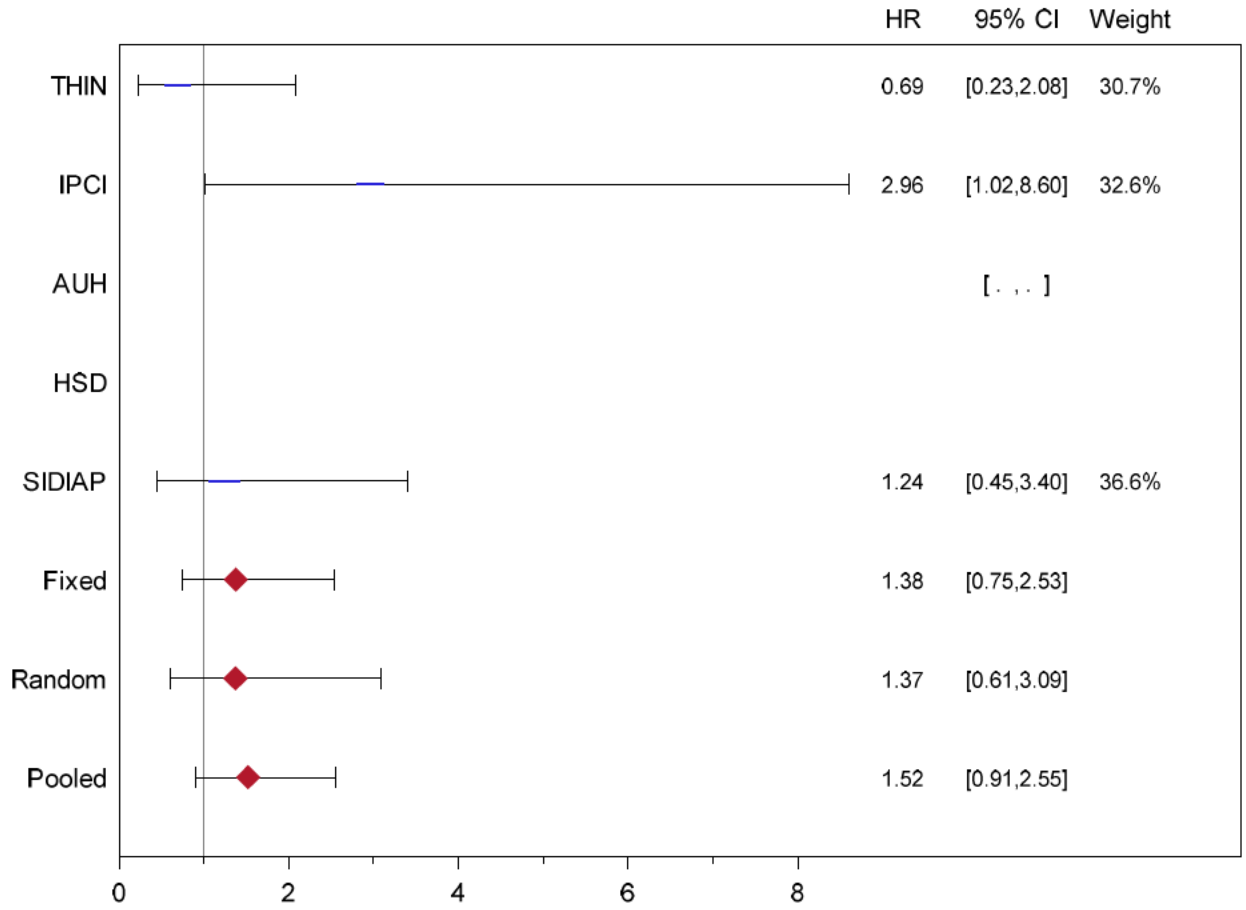
Cochran's Q = 0.259472, P = 0.878327, I-square = 0% . In pooled analysis: P interaction = 0.7670

Figure 15-34 Forest plot results Model IPTW QVA149 versus LAMA – Total analysis population – cardiac arrhythmia as endpoint



Cochran's Q = 0.763885, P = 0.858084, I-square = 0% . In pooled analysis: P interaction = 0.8895

Figure 15-35 Forest plot results Model IPTW QVA149 versus free LABA/LAMA without ICS – Total analysis population – cerebrovascular events as endpoint



Cochran's Q = 3.523583, P = 0.171737, I-square = 43% . In pooled analysis: P interaction = 0.4161

Figure 15-36 Forest plot results Model IPTW QVA149 versus free LABA/LAMA with ICS – Total analysis population – cerebrovascular events as endpoint

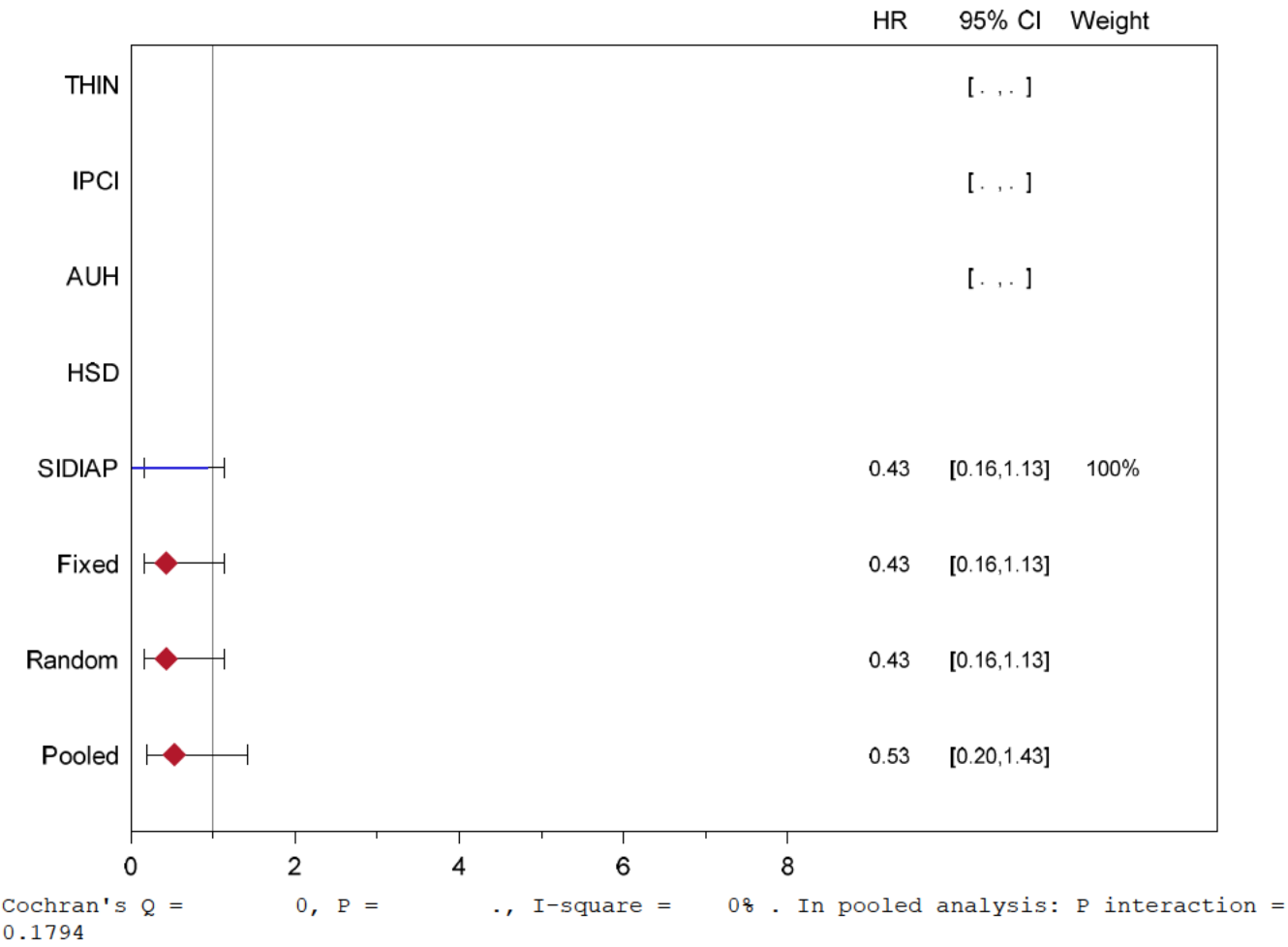
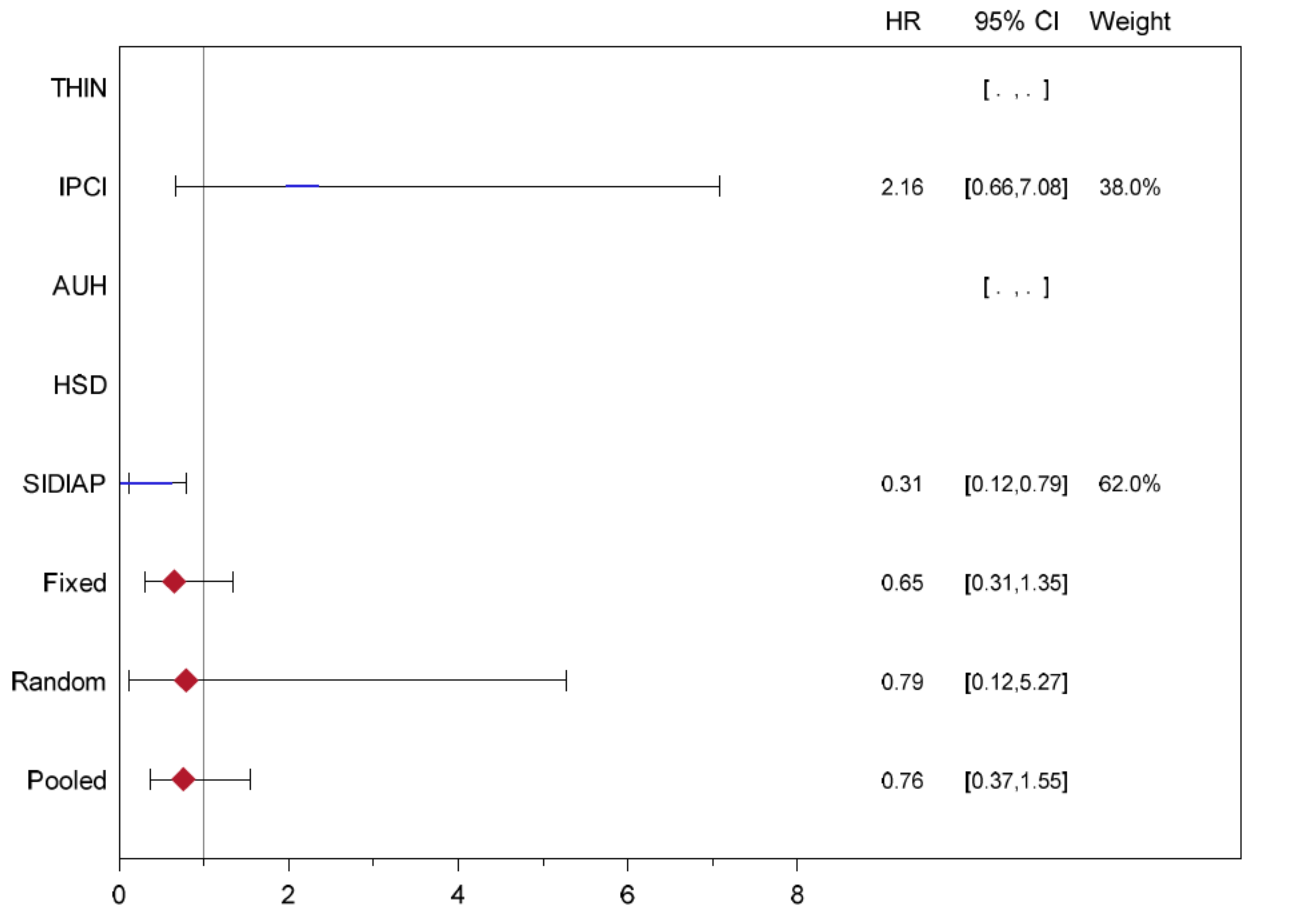
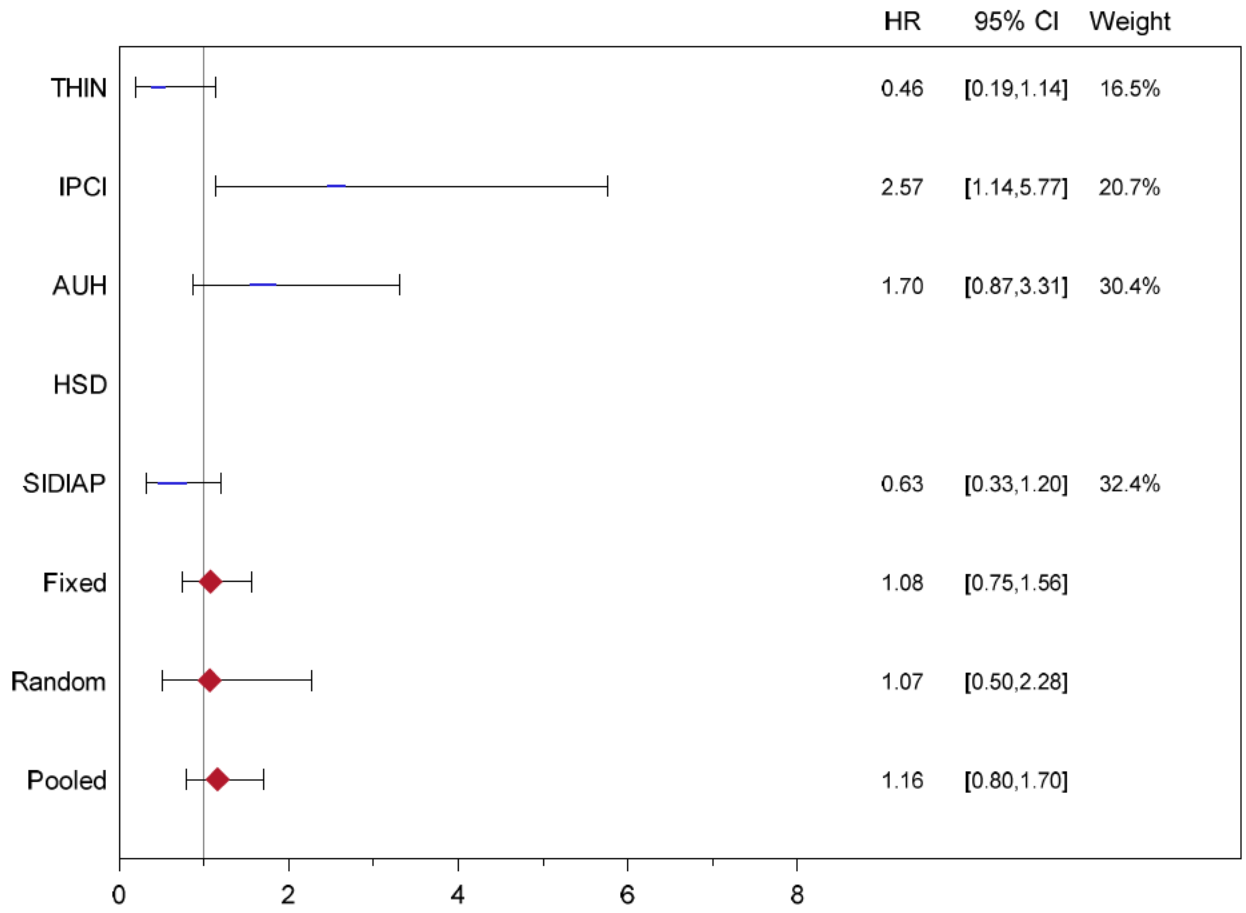


Figure 15-37 Forest plot results Model IPTW QVA149 versus Free LABA+ICS – Total analysis population – cerebrovascular events as endpoint



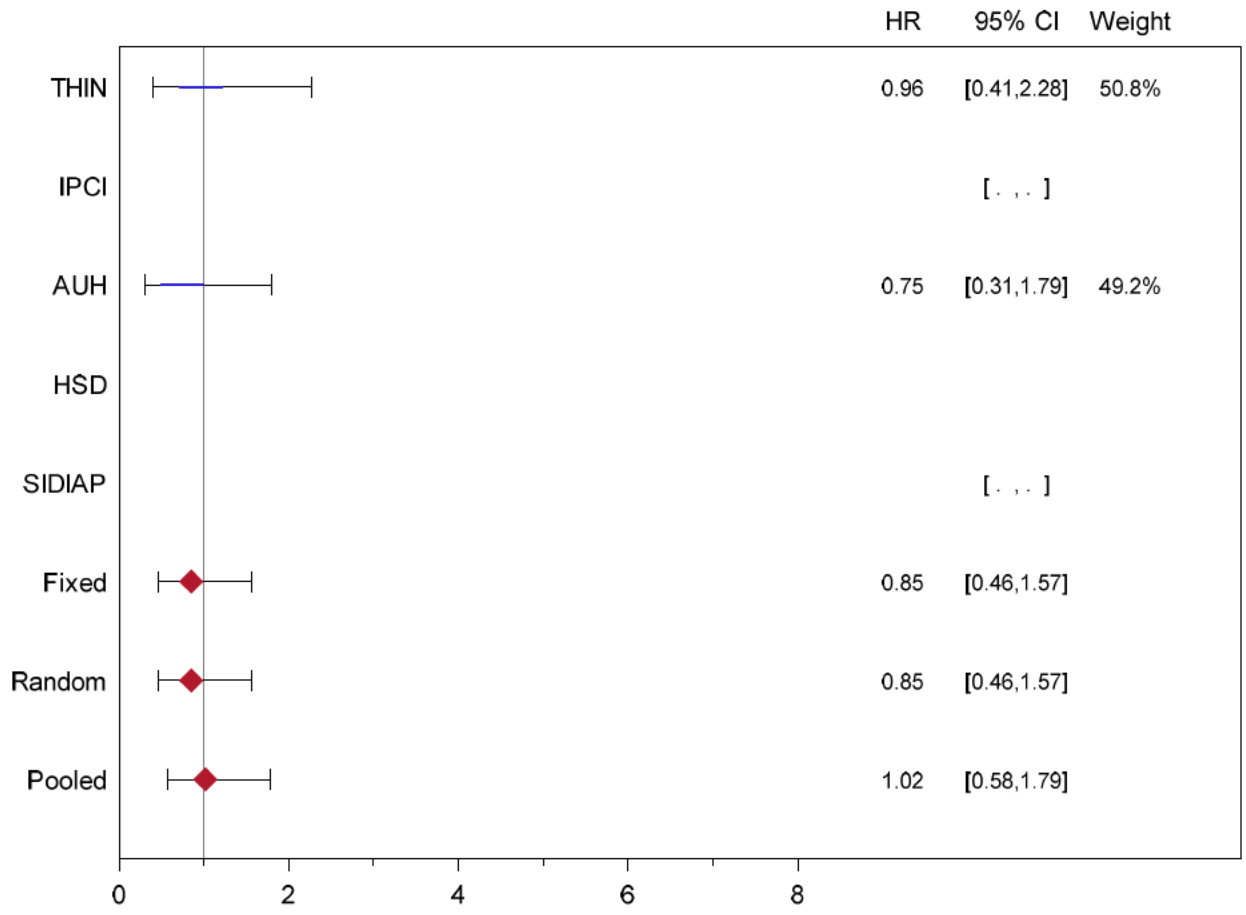
Cochran's Q = 6.342047, P = 0.011791, I-square = 84% . In pooled analysis: P interaction = <.0001

Figure 15-38 Forest plot results Model IPTW QVA149 versus Fixed LABA/ICS – Total analysis population – cerebrovascular events as endpoint



Cochran's Q = 12.20471, P = 0.006714, I-square = 75% . In pooled analysis: P interaction = 0.0045

Figure 15-39 Forest plot results Model IPTW QVA149 versus Fixed LABA/LAMA – Total analysis population – cerebrovascular events as endpoint



Cochran's Q = 0.165833, P = 0.683842, I-square = 0% . In pooled analysis: P interaction = <.0001

Figure 15-40 Forest plot results Model IPTW QVA149 versus LABA – Total analysis population – cerebrovascular events as endpoint

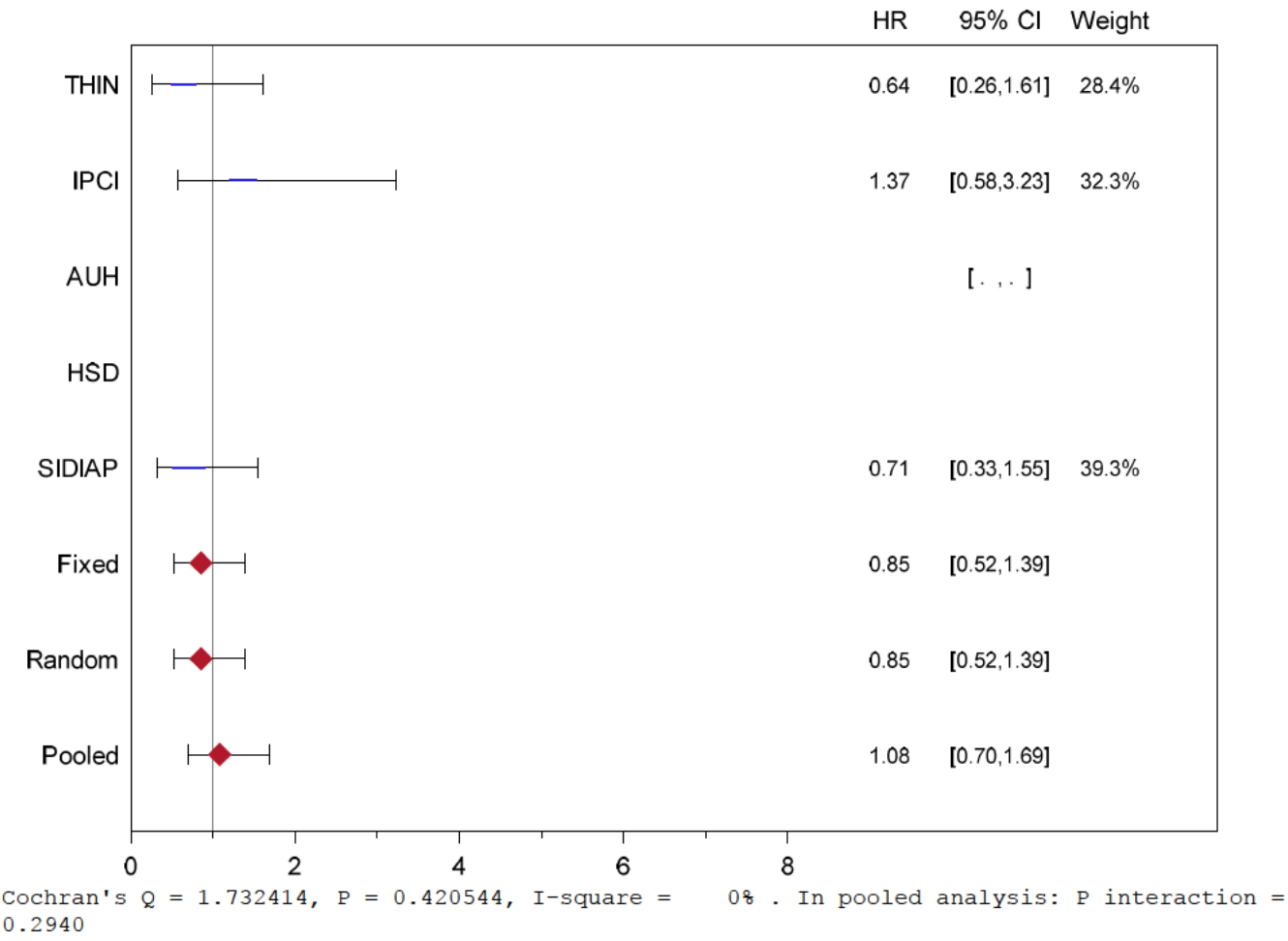
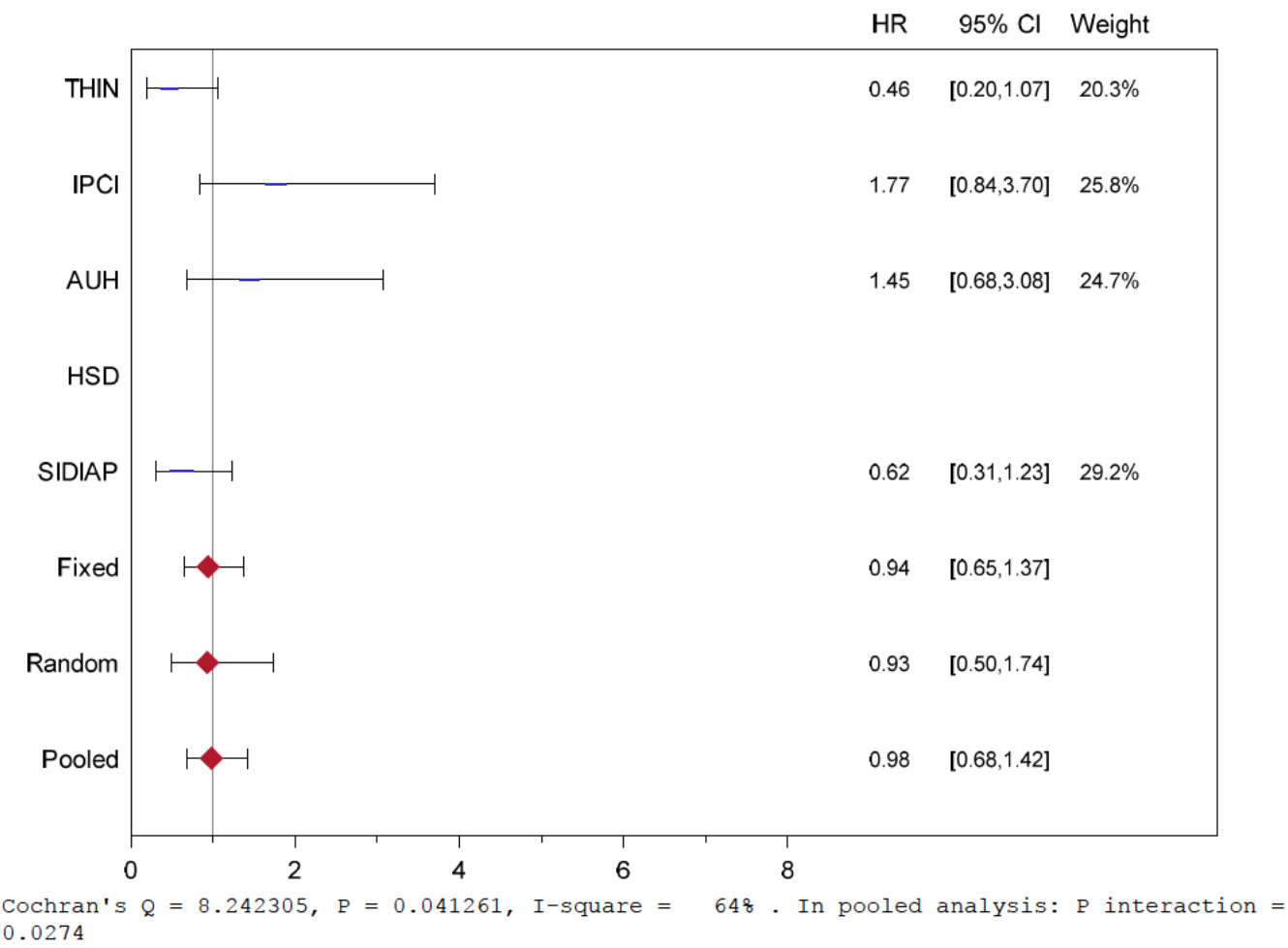


Figure 15-41 Forest plot results Model IPTW QVA149 versus LAMA – Total analysis population – cerebrovascular events as endpoint



Cochran's Q = 8.242305, P = 0.041261, I-square = 64% . In pooled analysis: P interaction = 0.0274

Figure 15-42 Forest plot results Model IPTW QVA149 versus free LABA/LAMA without ICS – Total analysis population – glaucoma as endpoint

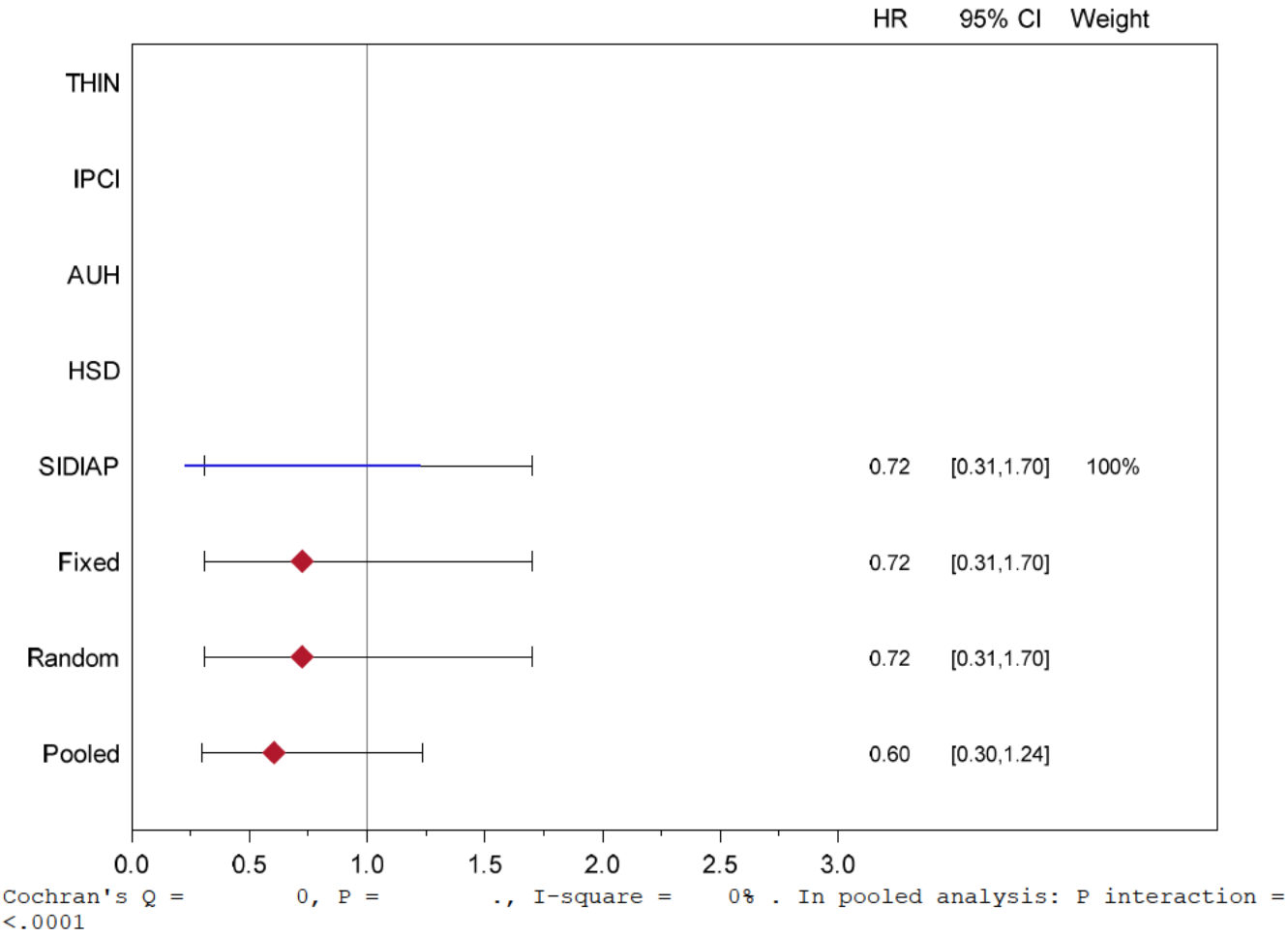


Figure 15-43 Forest plot results Model IPTW QVA149 versus free LABA/LAMA with ICS – Total analysis population – glaucoma as endpoint

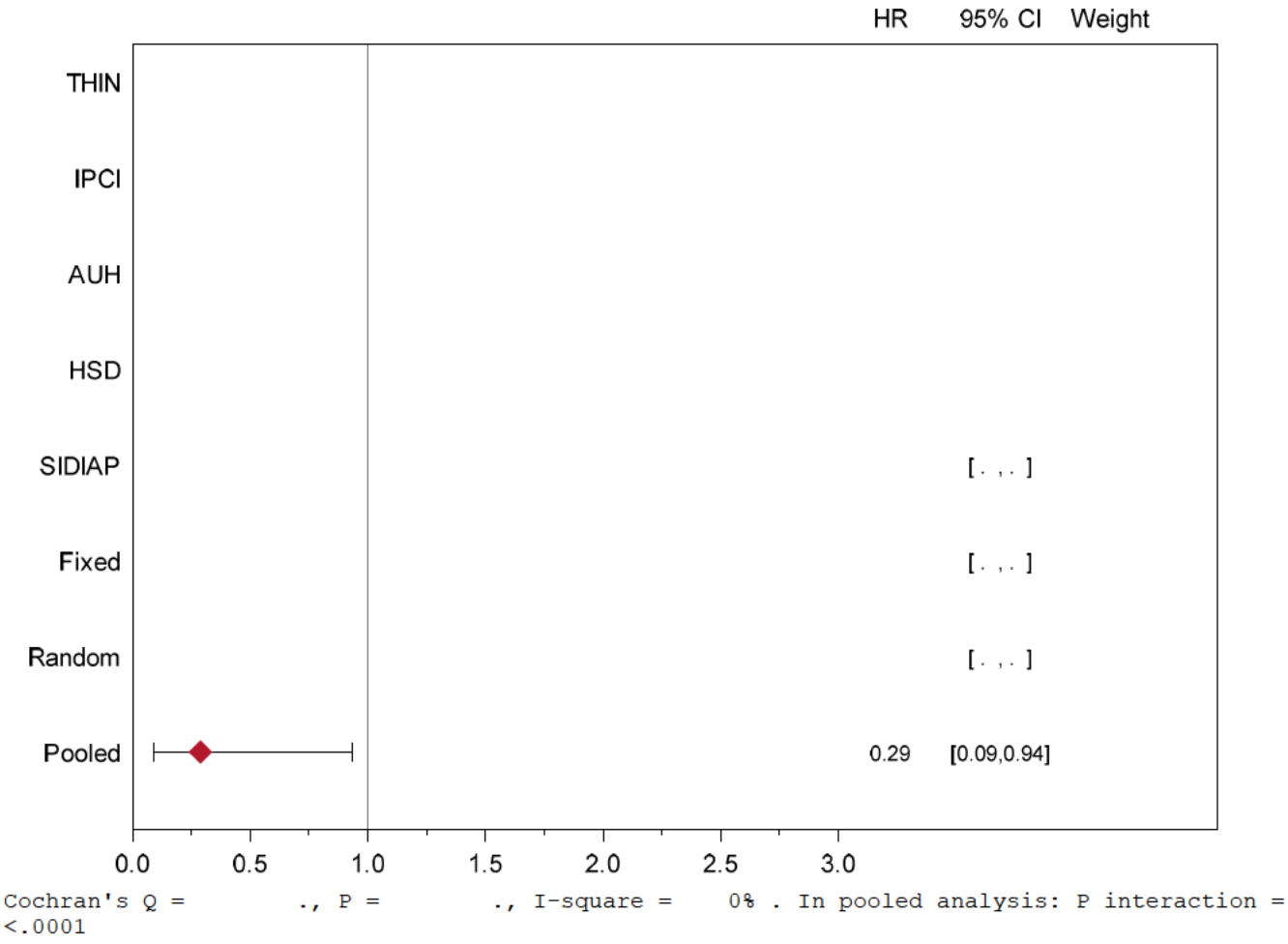
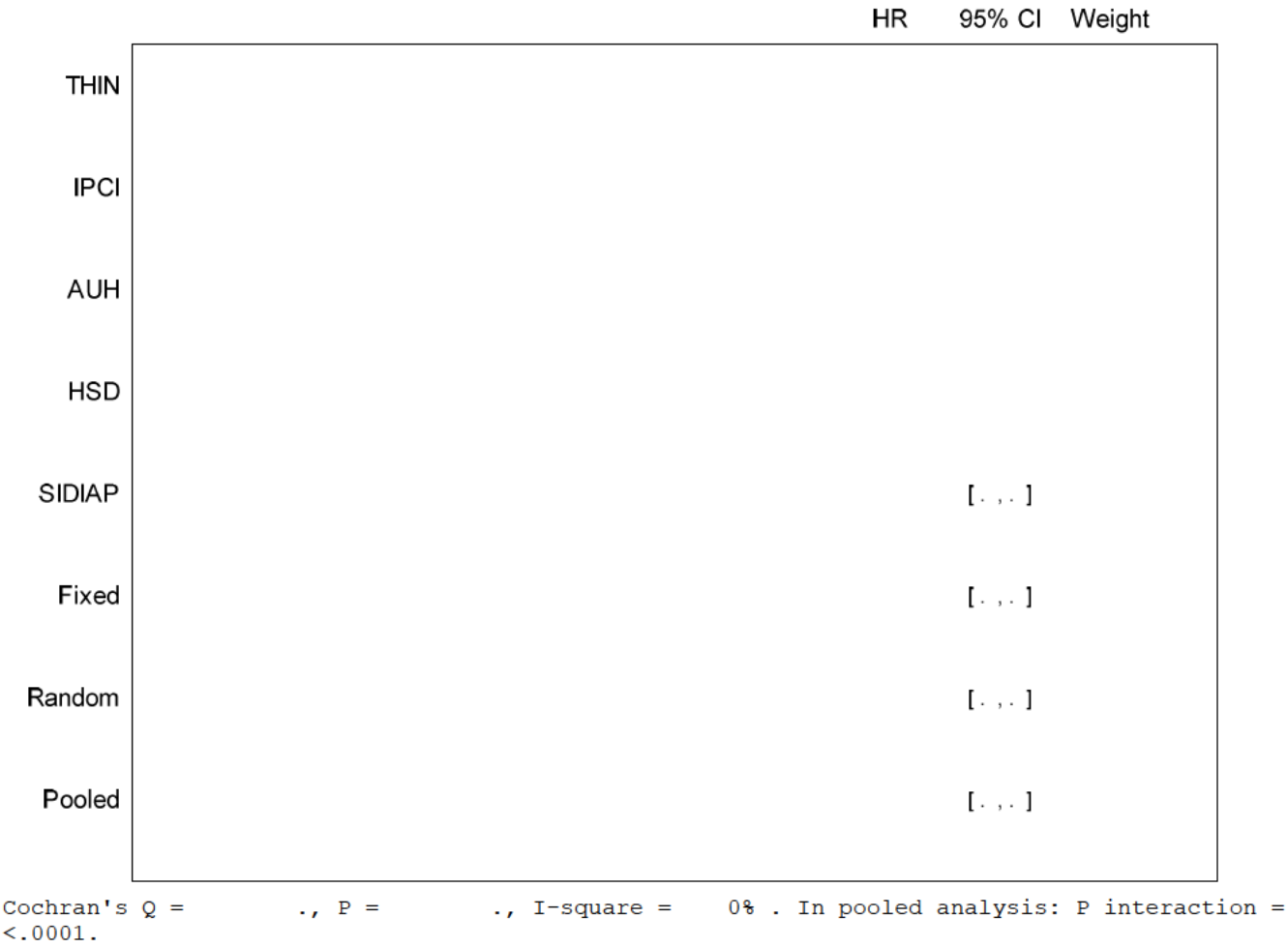


Figure 15-44 Forest plot results Model IPTW QVA149 versus Free LABA+ICS – Total analysis population – glaucoma as endpoint



Cochran's Q = ., P = ., I-square = 0% . In pooled analysis: P interaction = <.0001.

Figure 15-45 Forest plot results Model IPTW QVA149 versus Fixed LABA/ICS – Total analysis population – glaucoma as endpoint

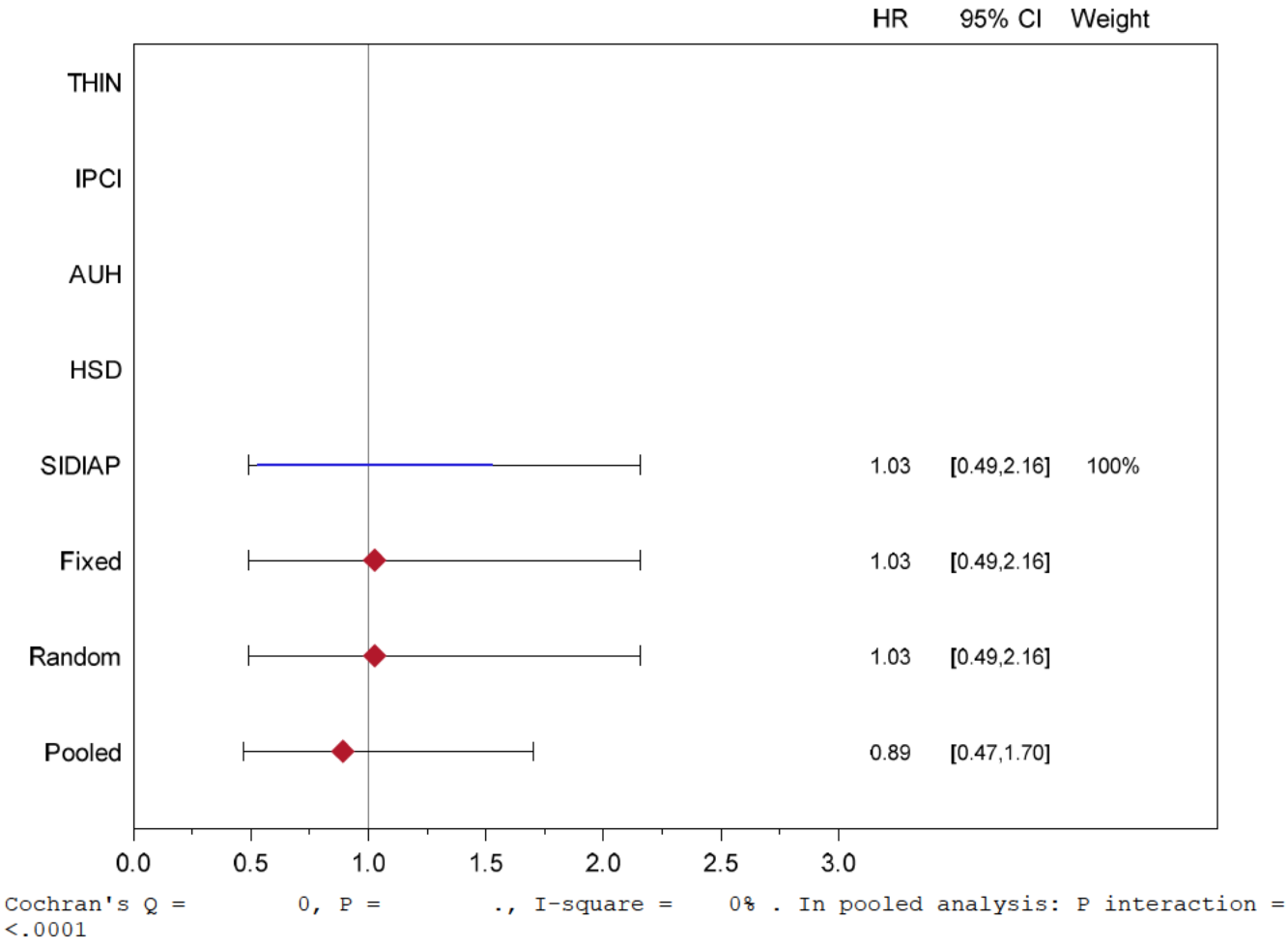


Figure 15-46 Forest plot results Model IPTW QVA149 versus Fixed LABA/LAMA – Total analysis population – glaucoma as endpoint

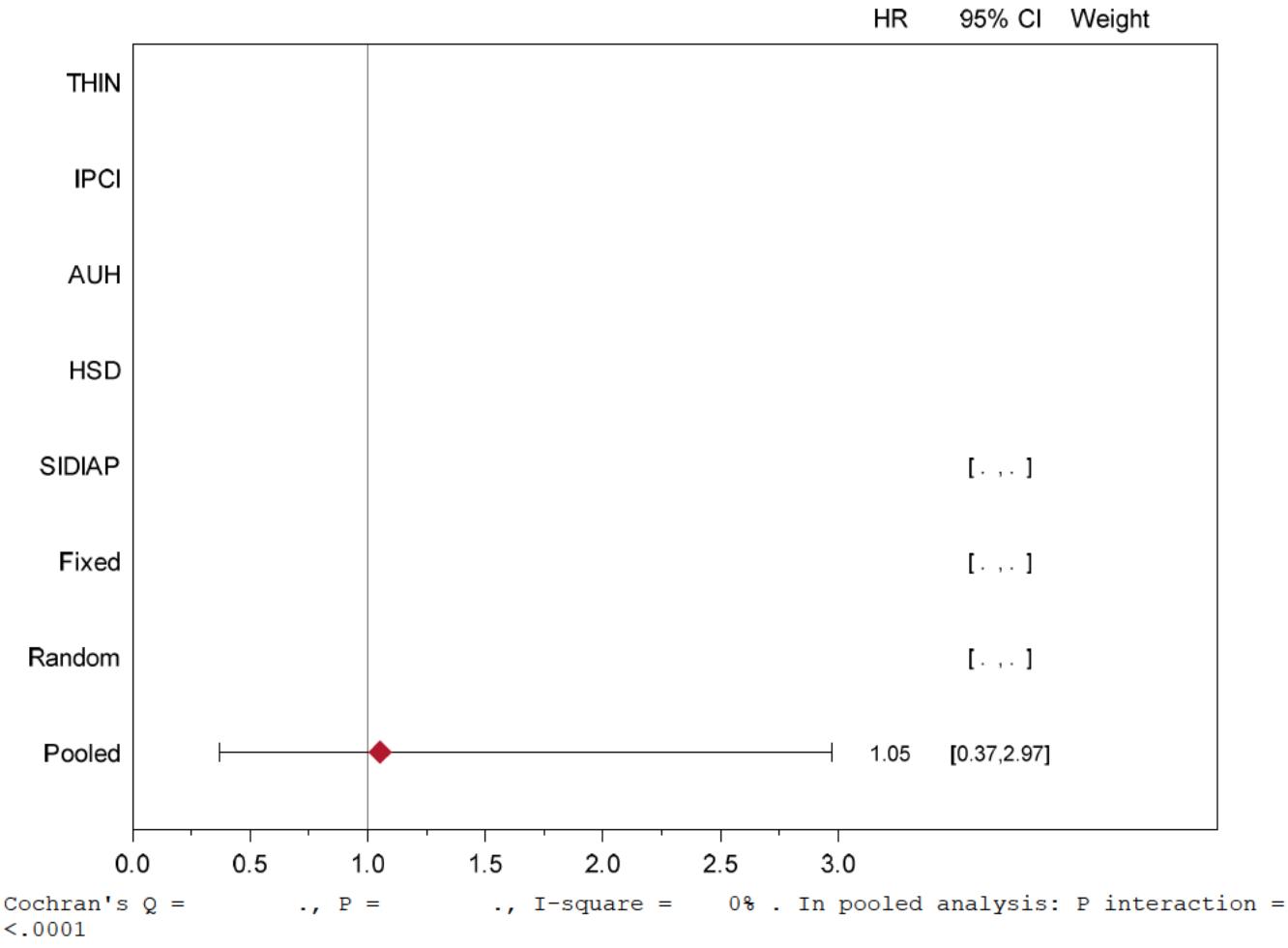


Figure 15-47 Forest plot results Model IPTW QVA149 versus LABA – Total analysis population – glaucoma as endpoint

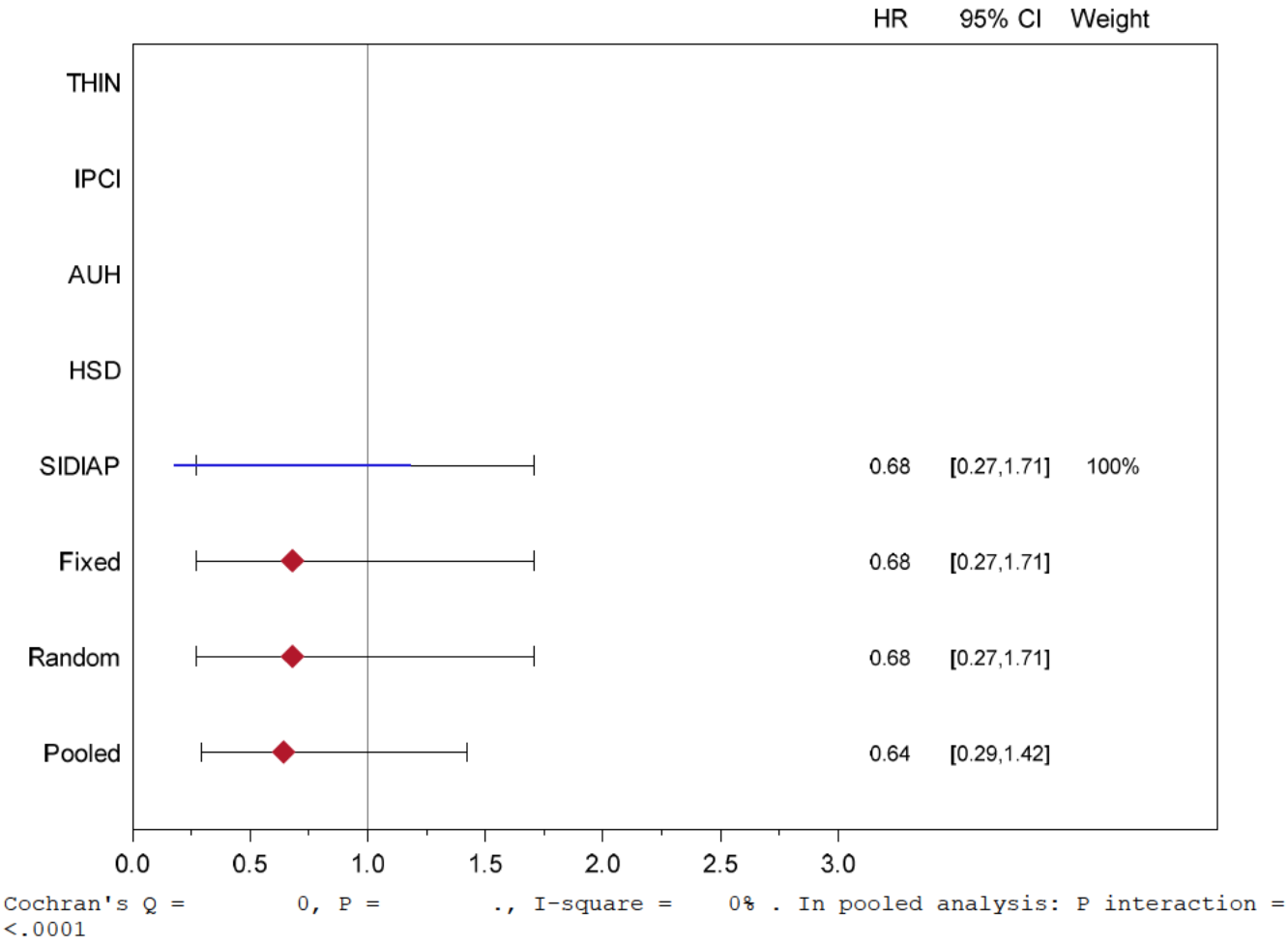
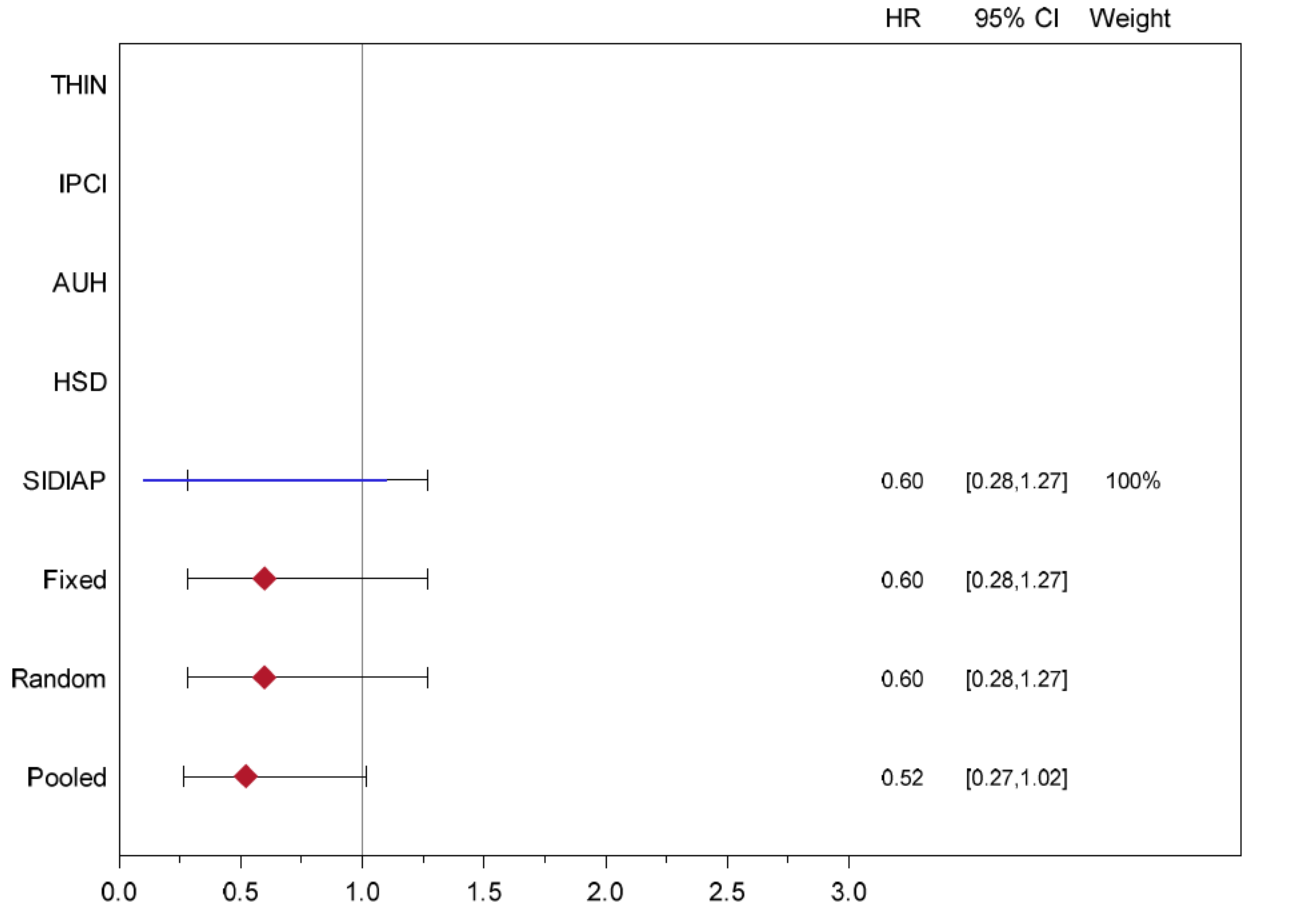
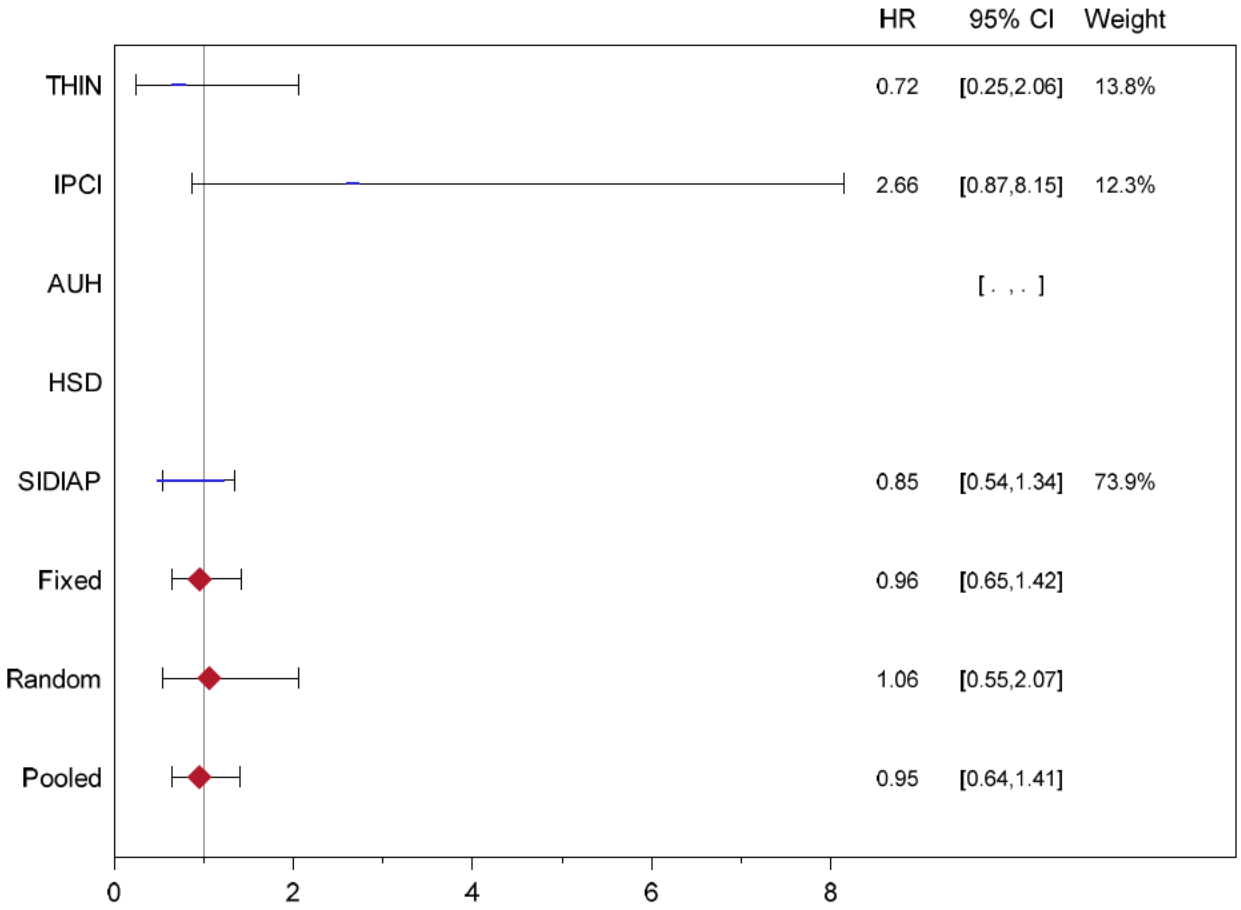


Figure 15-48 Forest plot results Model IPTW QVA149 versus LAMA – Total analysis population – glaucoma as endpoint



Cochran's Q = 0, P = ., I-square = 0% . In pooled analysis: P interaction = <.0001

Figure 15-49 Forest plot results Model IPTW QVA149 versus free LABA/LAMA without ICS – Total analysis population – Bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia as endpoint



Cochran's Q = 3.764696, P = 0.152232, I-square = 47% . In pooled analysis: P interaction = 0.3497

Figure 15-50 Forest plot results Model IPTW QVA149 versus free LABA/LAMA with ICS – Total analysis population – Bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia as endpoint

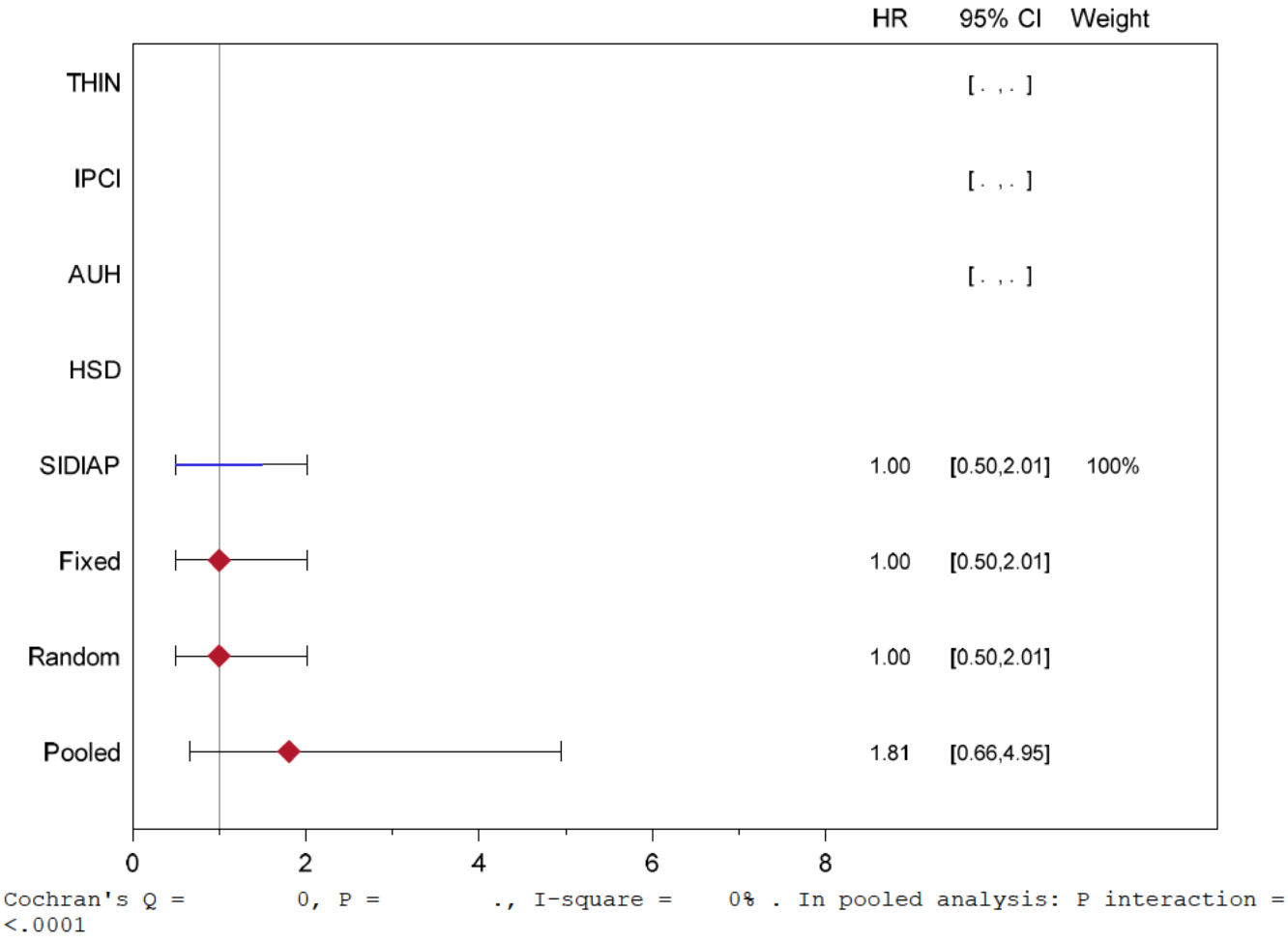


Figure 15-51 Forest plot results Model IPTW QVA149 versus Free LABA+ICS – Total analysis population – Bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia as endpoint

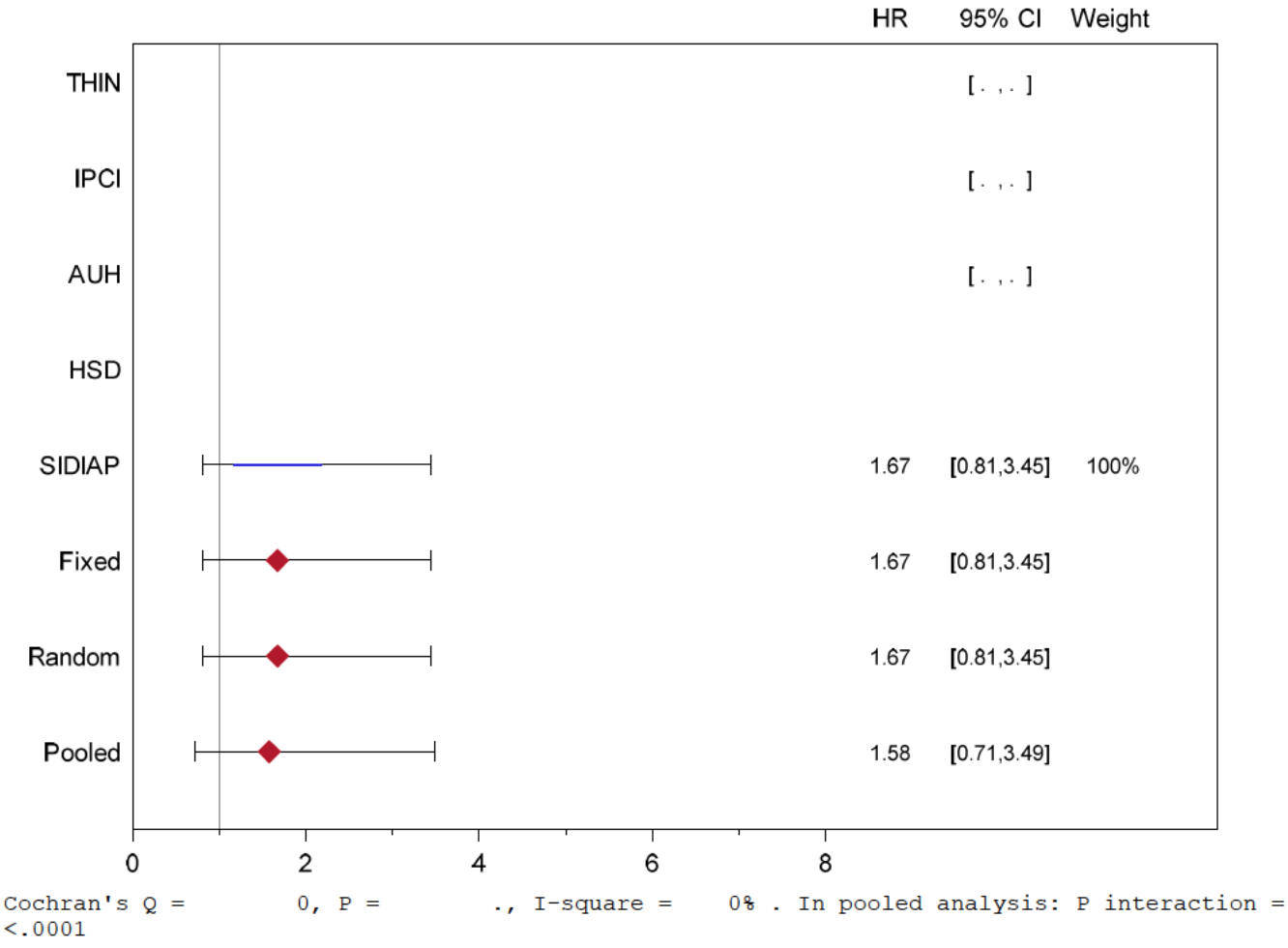
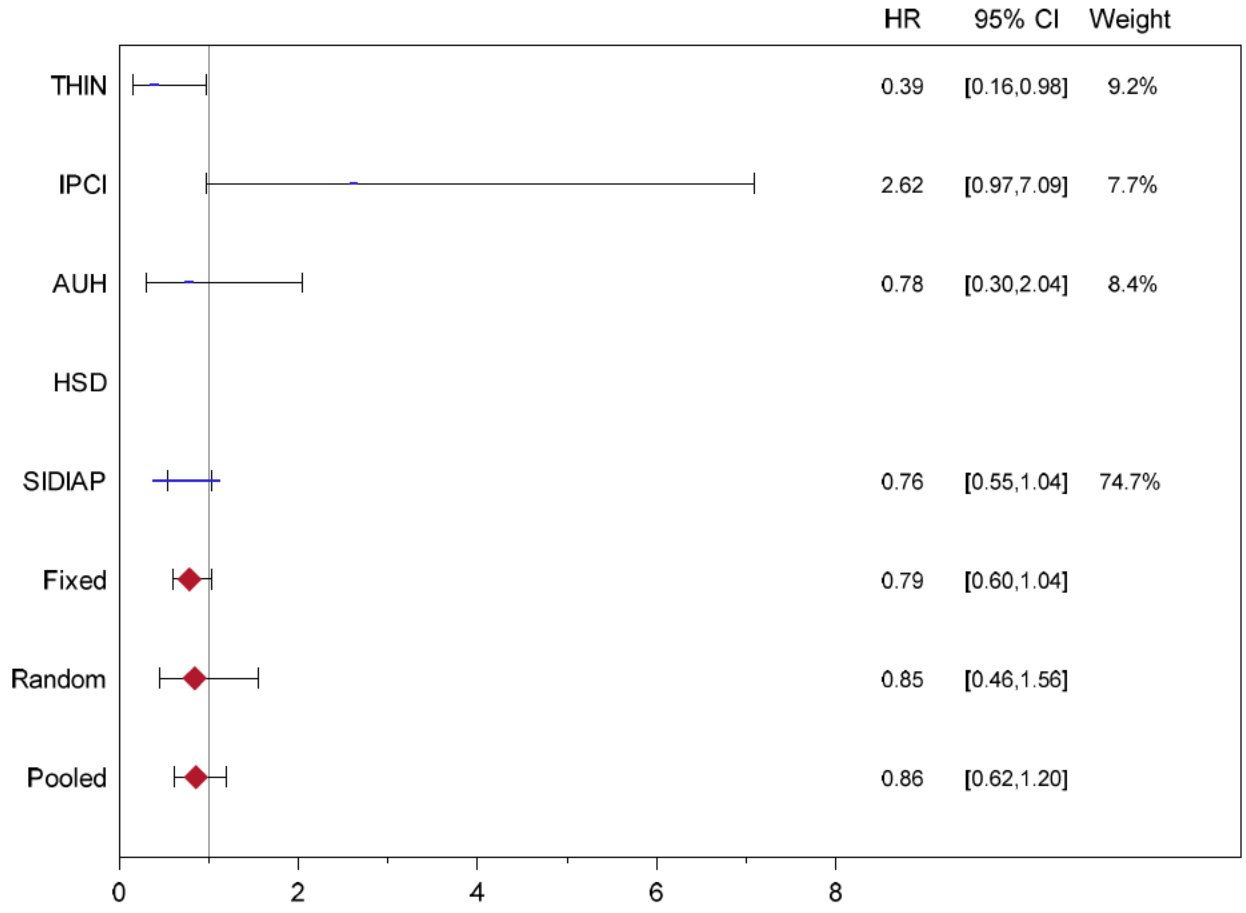
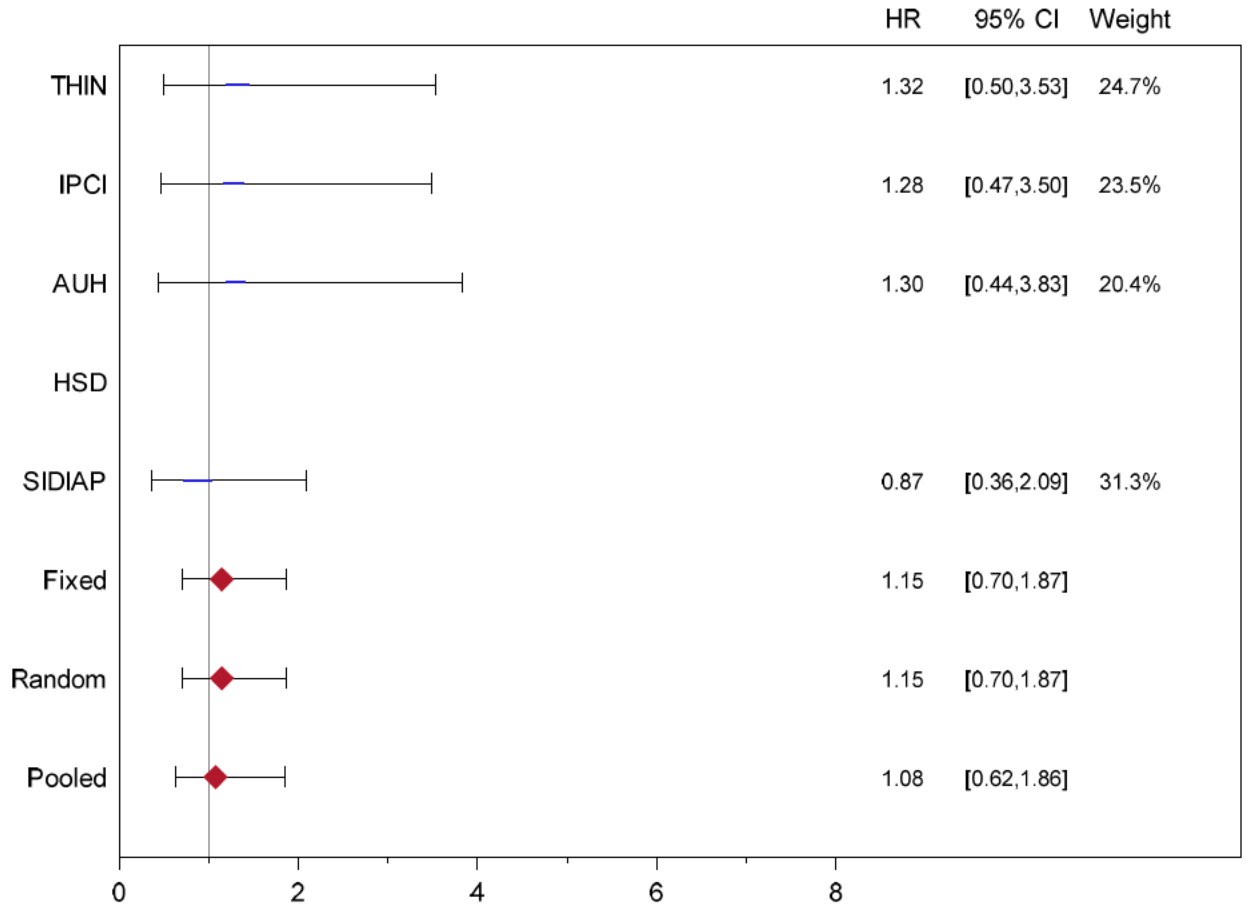


Figure 15-52 Forest plot results Model IPTW QVA149 versus Fixed LABA/ICS – Total analysis population – Bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia as endpoint



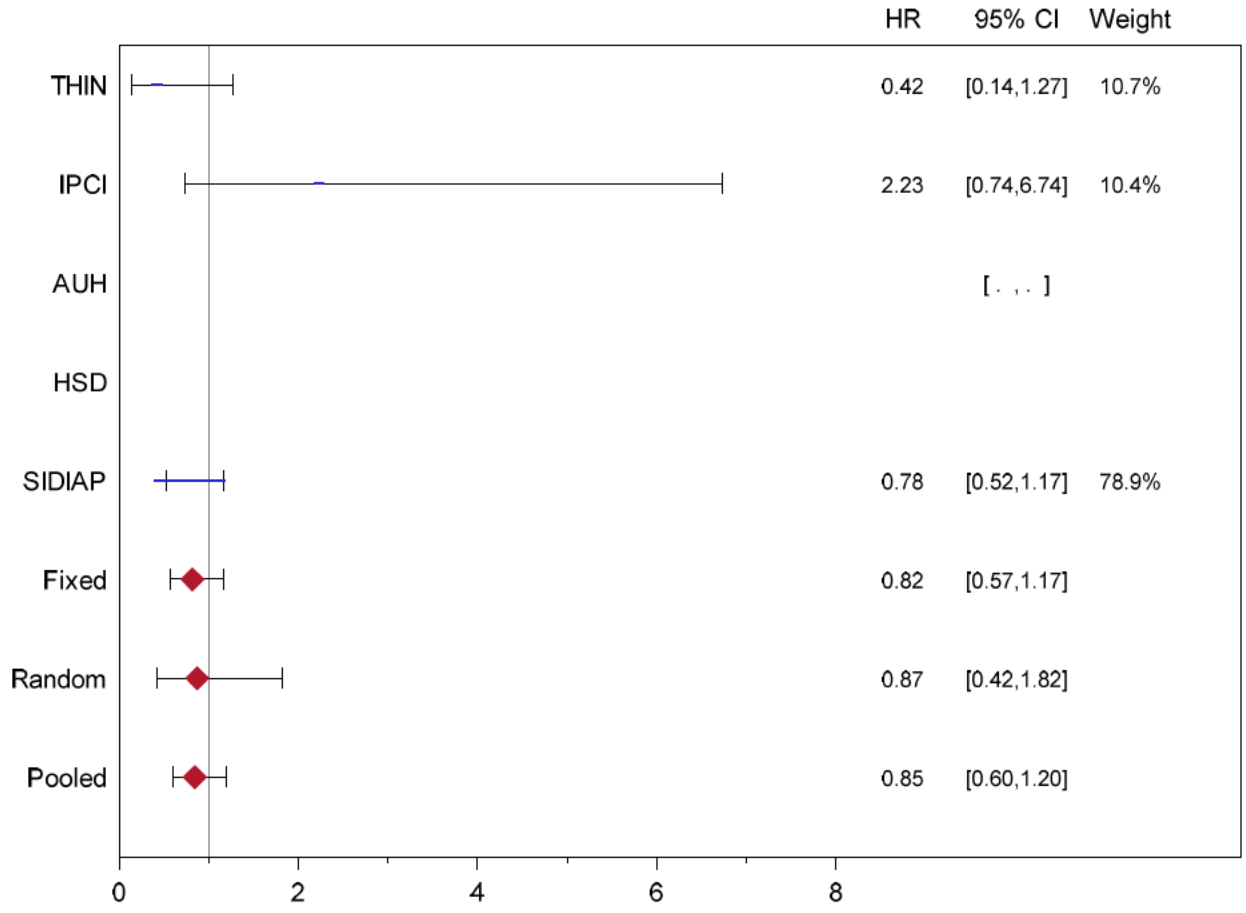
Cochran's Q = 7.914816, P = 0.047805, I-square = 62% . In pooled analysis: P interaction = 0.0624

Figure 15-53 Forest plot results Model IPTW QVA149 versus Fixed LABA/LAMA – Total analysis population – Bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia as endpoint



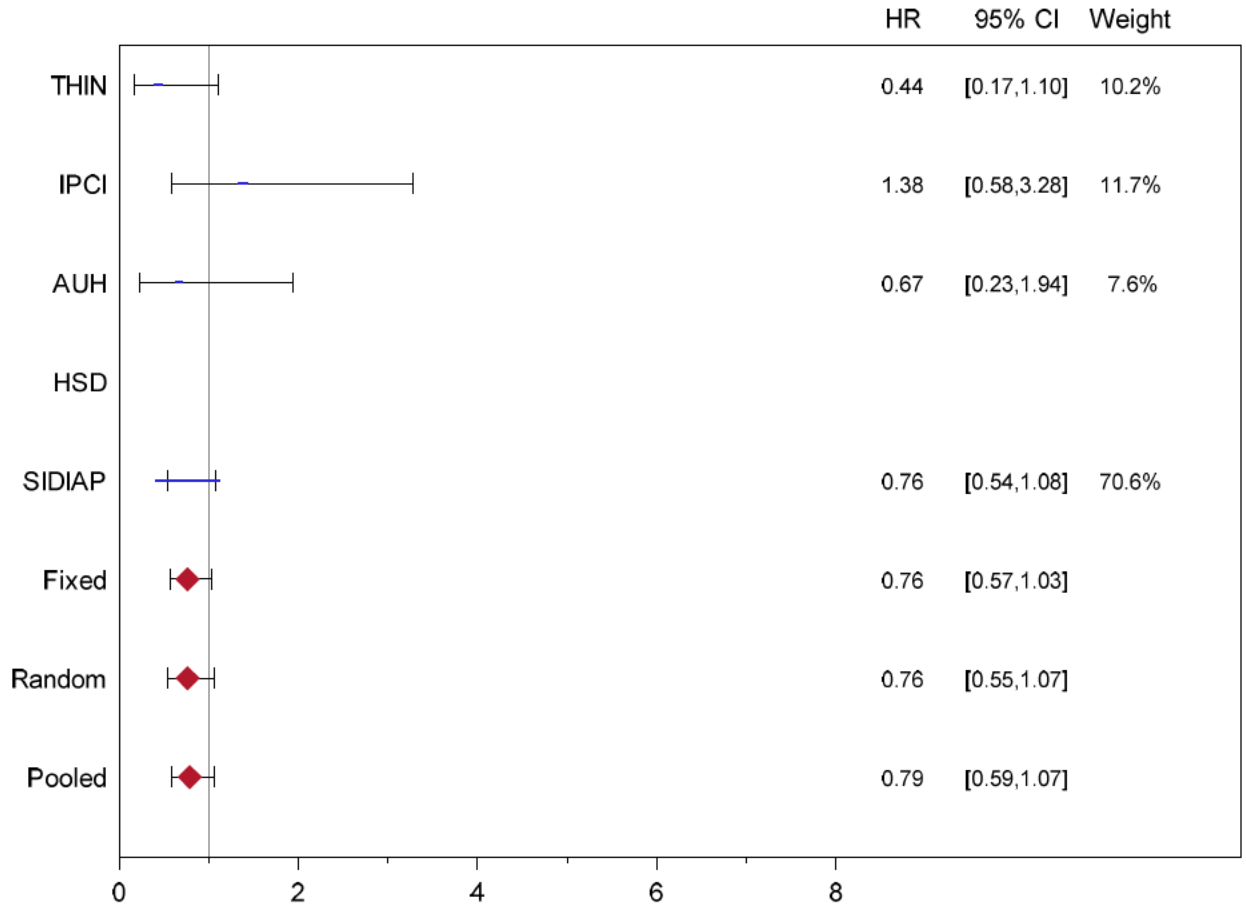
Cochran's Q = 0.553322, P = 0.90703, I-square = 0% . In pooled analysis: P interaction = 0.9064

Figure 15-54 Forest plot results Model IPTW QVA149 versus LABA – Total analysis population – Bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia as endpoint



Cochran's Q = 4.570139, P = 0.101767, I-square = 56% . In pooled analysis: P interaction = 0.1037

Figure 15-55 Forest plot results Model IPTW QVA149 versus LAMA – Total analysis population – Bladder outflow obstruction, urinary retention or incident benign prostatic hyperplasia as endpoint



Cochran's Q = 3.282083, P = 0.350144, I-square = 9% . In pooled analysis: P interaction = 0.4692

Figure 15-56 Forest plot results Model IPTW QVA149 versus free LABA/LAMA without ICS – Total analysis population – Diabetes mellitus as endpoint