

Appendix

for

Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes

by

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Contents

Data sources	2
CCAE	2
Optum	2
MDCR	3
MDCD	3
JMDC	3
NHIS/NSC	3
PanTher	3
IMSG	4
CUMC	4
Cohort definitions	4
First-line antihypertensive drug class new-users	4
Effectiveness and safety outcomes	5
Definition process	5
Example ATLAS instantiations	9
Acute myocardial infarction	10
Hospitalization for heart failure	11
Stroke	12
Negative control outcomes	13
Additional tables and figures	16
Individual drugs within classes	16
Patient characteristics	17
Propensity score (PS) models and balance	27
PS-stratification	29
PS-matching	30
Comparative cohorts and events	31
Under an on-treatment, PS-stratified design	31
Under an intent-to-treat, PS-stratified design	33
Under an on-treatment, PS-matched design	35
Under an intent-to-treat, PS-matched design	37

Systematic error control	39
Under an on-treatment, PS-stratified design	39
Under an intent-to-treat, PS-stratified design	44
Under an on-treatment, PS-matched design	49
Under an intent-to-treat, PS-matched design	53
Effectiveness estimates	57
Under an on-treatment, PS-stratified design	57
Under an intent-to-treat, PS-stratified design	60
Under an on-treatment, PS-matched design	63
Under an intent-to-treat, PS-matched design	66
Safety profiles	69
Under an on-treatment, PS-stratified design	69
Under an intent-to-treat, PS-stratified design	72
Under an on-treatment, PS-matched design	75
Under an intent-to-treat, PS-matched design	77
Blood pressure sensitivity analysis in PanTHER	81

Data sources

CCAE

IBM MarketScan Commercial Claims and Encounters Database (CCAE) is a US employer-based private-payer administrative claims database. The data include adjudicated health insurance claims (e.g. inpatient, outpatient, and outpatient pharmacy) as well as enrollment data from large employers and health plans who provide private healthcare coverage to employees, their spouses, and dependents. Additionally, it captures laboratory tests for a subset of the covered lives. This administrative claims database includes a variety of fee-for-service, preferred provider organizations, and capitated health plans.

Optum

Optum Clininformatics Extended DataMart (Optum) is an adjudicated US administrative health claims database for members of private health insurance, who are fully insured in commercial plans or in administrative services only (ASOs), Legacy Medicare Choice Lives (prior to January 2006), and Medicare Advantage (Medicare Advantage Prescription Drug coverage starting January 2006). The population is primarily representative of commercial claims patients (0-65 years old) with some Medicare (65+ years old) however ages are capped at 90 years. It includes data captured from administrative claims processed from inpatient and outpatient medical services and prescriptions as dispensed, as well as results for outpatient lab tests processed by large national lab vendors who participate in data exchange with Optum. This dataset also provides date of death (month and year only) for members with both medical and pharmacy coverage from the Social Security Death Master File (however after 2011 reporting frequency changed due to changes in reporting requirements) and location information for patients is at the US state level.

MDCR

IBM MarketScan Medicare Supplemental and Coordination of Benefits Database (MDCR) represents health services of retirees in the United States with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans. These data include adjudicated health insurance claims (e.g. inpatient, outpatient, and outpatient pharmacy). Additionally, it captures laboratory tests for a subset of the covered lives.

MDCD

IBM MarketScan Multi-State Medicaid Database (MDCD) contains adjudicated US health insurance claims for Medicaid enrollees from multiple states and includes hospital discharge diagnoses, outpatient diagnoses and procedures, and outpatient pharmacy claims as well as ethnicity and Medicare eligibility. Members maintain their same identifier even if they leave the system for a brief period; however the dataset lacks lab data.

JMDC

Japan Medical Data Center (JMDC) database consists of data from 60 society-managed health insurance plans covering workers aged 18 to 65 and their dependents (children younger than 18 years old and elderly people older than 65 years old). JMDC data includes membership status of the insured people and claims data provided by insurers under contract (e.g. patient-level demographic information, inpatient and outpatient data inclusive of diagnosis and procedures, and prescriptions as dispensed claims information). Claims data are derived from monthly claims issued by clinics, hospitals and community pharmacies; for claims only the month and year are provided however prescriptions, procedures, admission, discharge, and start of medical care as associated with a full date. All diagnoses are coded using ICD-10. All prescriptions refer to national Japanese drug codes, which have been linked to ATC. Procedures are encoded using local procedure codes, which the vendor has mapped to ICD-9 procedure codes. The annual health checkups report a standard battery of measurements (e.g. BMI), which are not coded but clearly described.

NHIS/NSC

Korea National Health Insurance Service / National Sample Cohort (NHIS/NSC) is the national administrative claims database covering the South Korea population. It contains a 2% population sample cohort from 2002 - 2013.

PanTher

Optum Pan-Therapeutic (PanTher) is an aggregated electronic health record repository from US health systems and contains Humedica's electronic health record data. The medical record data includes clinical information, inclusive of prescriptions as prescribed and administered, lab results, vital signs, body measurements, diagnoses, procedures, and information derived from clinical notes using natural language processing (NLP).

IMSG

IMS/Iqvia Disease Analyzer Germany (IMSG) contains electronic health records data from German practices. The data are collected from physician practices and medical centers for all ages. Mostly primary care physician data however some data from specialty practices (where practices are electronically connected to each other) and some lab data is included. Key attributes include demographics, prescriptions as prescribed at brand level, diagnosis, lab measurements, actions (e.g. referrals, sick notes).

CUMC

Columbia University Medical Center (CUMC) is an electronic health record consisting of over 5 million patients from the New York-Presbyterian hospital and affiliated academic physician practice in New York.

Cohort definitions

OHDSI's ATLAS (<https://www.ohdsi.org/web/atlas>) is an open source software tool for researchers to conduct scientific analyses on standardized observational data converted to the OMOP Common Data Model v5. Researchers can create cohorts by defining groups of people based on an exposure to a drug or diagnosis of a particular condition using healthcare claims data. ATLAS has vocabulary searching of medical concepts to identify people with specific conditions, drug exposures etc. Patient profiles can be viewed within a specific cohort allowing visualization of a particular subject's health care records. Population effect level estimation analyses allows for comparison of two different cohorts and leverages R packages.

First-line antihypertensive drug class new-users

We define a cohort of new-users of a first-line antihypertensive drug class in the following way.

Index rule defining the patient index date:

- First exposure to any drug containing the RxNorm ingredients of interest for class (see Supplementary Table 1).

Inclusion rules based on the index date:

- At least 365 days of observation time prior to the index date
- No prior exposure to antihypertensive drugs (first-line or non-first-line, 58 total ingredients) preceding the index date
- No concurrent antihypertensive ingredient exposure on the index date
- A diagnose of hypertension on or preceding the index date
- No diagnose of the outcome of interest preceding the index date

We begin the outcome risk window 1 day after treatment initiation and consider two design choices to define the window end. First, we end the outcome time-at-risk window at first cessation of continuous drug exposure, analogous to an on-treatment design and, second, we end the outcome time-at-risk window when the patient is no longer observable in the database, analogous to an intent-to-treat design. Continuous drug exposures are constructed from the available longitudinal data by considering sequential prescriptions that have fewer than 30 days gap between prescriptions.

A parameterized SQL translation for cohort generation in any OMOP CDM v5 database is available in: https://github.com/OHDSI/Legend/blob/master/inst/sql/sql_server/CreateExposureCohortsHypertension.sql.

Supplementary Table 1: RxNorm ingredient concept IDs to construct first-line antihypertensive drug classes. These classes are: thiazide or thiazide-like diuretics (THZ), angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), dihydropyridine calcium channel blockers (dCCB) or non-dihydropyridine calcium channel blockers (ndCCB). Second-line treatments include 28 additional ingredients.

Class	RxNorm concept IDs
THZ	Chlorthalidone (1395058); HCTZ (974166); Indapamide (978555); Metolazone (907013)
ACEi	Benazepril (1335471); Captopril (1340128); Enalapril (1341927); Fosinopril (1363749); Lisinopril (1308216); Moexipril (1310756); Perindopril (1373225); Quinapril (1331235); Ramipril (1334456); Trandolapril (1342439)
ARB	Azilsartan (40235485); Candesartan (1351557); Eprosartan (1346686); Irbesartan (1347384); Losartan (1367500); Olmesartan (40226742); Telmisartan (1317640); Valsartan (1308842)
dCCB	Amlodipine (1332418); Felodipine (1353776); Isradipine (1326012); Nicardipine (1318137); Nifedipine (1318853); Nisoldipine (1319880)
ndCCB	Diltiazem (1328165); Verapamil (1307863)
2nd-line	Acebutolol (1319998); Aliskiren (1317967); Amiloride (991382); Atenolol (1314002); Betaxolol (1322081); Bisoprolol (1338005); Bumetanide (932745); Carvedilol (1346823); Clonidine (1398937); Doxazosin (1363053); Eplerenone (1309799); Furosemide (956874); Guanfacine (1344965); Hydralazine (1373928); Labetalol (1386957); Methyldopa (1305447); Metoprolol (1307046); Minoxidil (1309068); Nadolol (1313200); Nebivolol (1314577); Penbutolol (1327978); Pindolol (1345858); Prazosin (1350489); Propranolol (1353766); Spironolactone (970250); Terazosin (1341238); Torsemide (942350); Triamterene (904542)

Effectiveness and safety outcomes

Definition process

We originally identified outcomes for LEGEND from clinical trial endpoints from clinical guidelines and systematic reviews. We augmented these with adverse events from US structured product

labels of hypertension drugs (<https://dailymed.nlm.nih.gov/dailymed/>). For each outcome, we developed an operational phenotype definition to determine if observational data could in fact support evaluation of the outcome. We used the same approach to design, implement, and evaluate all phenotypes. Specifically, we conducted a PubMed literature review to identify prior observational studies that used the phenotype as an outcome, looking especially for studies where source record verification or other approaches validated the outcome. In addition, we reviewed eMERGE PheKB phenotype entries (<https://phekb.org/phenotypes>). Clinical guidelines and systematic review of clinical trials of hypertension treatments informed our clinical definitions of cardiovascular outcomes [1–3]. Where possible, conceptsets originated with published codelists (e.g. ICD-9-CM and ICD-10). We augmented these with lexical search and semantic exploration of the OHDSI standardized vocabularies. A clinical adjudicator then reviewed the cohort definitions and associated conceptsets. We developed concept definitions using ATLAS, the OHDSI open-source platform (<https://github.com/OHDSI/atlas>). We initially executed these definitions across 7 databases (CCAE, MDCR, MDCC, Optum, Panther, JMDC, IMS Germany) to identify qualifying patients. Because the databases used in this study do not all consistently contain laboratory values, diagnosis records alone identified outcomes involving electrolyte imbalance (hypokalemia, hypomagnesemia, hyponatremia). To assess consistency across data sources as well as general clinical reasonableness, we utilized these cohorts to characterize outcome incidence, stratifying by age decile, gender, and index year. We did not perform source record verification or other validation methods.

Supplementary Table 2: Outcome phenotype definitions. We include 9 effectiveness and 46 safety outcomes of interest. The effectiveness outcomes come from [1] and antihypertensive randomized controlled trial. The safety outcomes are known antihypertensive drug side effects.

Phenotype	Logical description	Supporting references
Abdominal pain	Abdominal pain condition record of any type; successive records with > 90 day gap are considered independent episodes	[4] [5] [6]
Abnormal weight gain	Abnormal weight gain record of any type; successive records with > 90 day gap are considered independent episodes; note, weight measurements not used	[7]
Abnormal weight loss	Abnormal weight loss record of any type; successive records with > 90 day gap are considered independent episodes; note, weight measurements not used	[8]
Acute myocardial infarction	Acute myocardial infarction condition record during an inpatient or ER visit; successive records with > 180 day gap are considered independent episodes	[9] [10] [11] [12] [13] [14]
Acute pancreatitis	Acute pancreatitis condition record during an inpatient or ER visit; successive records with >30 day gap are considered independent episodes	[15] [16] [17] [18]
Acute renal failure	A diagnosis of acute renal failure in an inpatient or ER setting; must be at least 30d between inpatient/ER visits to be considered separate episodes	[19] [20] [21] [22] [23] [24] [25] [26]
All-cause mortality	Death record of any type	[12] [27] [28]

Anaphylactoid reaction	Anaphylactoid reaction condition record during an inpatient or ER visit; successive records with >7 day gap are considered independent episodes	[29] [30]
Anemia	The first condition record of anemia	[31] [32] [33]
Angioedema	Angioedema condition record during an inpatient or ER visit; successive records with >7 day gap are considered independent episodes	[29] [34]
Anxiety	The first condition record of anxiety, which is followed by another anxiety condition record or a drug used to treat anxiety	[35] [36] [37] [38]
Bradycardia	The first condition record of bradycardia, which is followed by another bradycardia condition record	[39] [40]
Cardiac arrhythmia	The first condition record of cardiac arrhythmia, which is followed by another cardiac arrhythmia condition record, at least two drug records for a drug used to treat arrhythmias, or a procedure to treat arrhythmias	[41] [42] [43] [44] [45] [46] [47]
Cardiovascular disease	A condition record of ischemic stroke, hemorrhagic stroke, heart failure, acute myocardial infarction or sudden cardiac death during an inpatient or ER visit; successive records with > 180 day gap are considered independent episodes	[9] [10] [11] [12] [13] [14] [41]
Cardiovascular related mortality	Death record with at least 1 cardiovascular-related condition record (myocardial infarction, ischemic stroke, intracranial hemorrhage, sudden cardiac death, hospitalization for heart failure) in 30 days prior to death	[12]
Chest pain or angina	The first condition record of chest pain or angina	[48]
Chronic kidney disease	The first condition record of chronic kidney disease, which is followed by either another chronic kidney disease condition record or a dialysis procedure or observation	[21] [49] [50] [51] [52] [53] [54] [55] [56]
Cough	Cough condition record of any type; successive records with > 90 day gap are considered independent episodes	[57] [58] [59]
Decreased libido	The first condition record of decreased libido	[60]
Dementia	The first condition record of dementia	[61] [62] [63] [64] [65] [66] [67] [68]
Depression	The first condition record of depression, which is followed by another depression condition record, at least two drugs used to treat depression without another indication, or two psychotherapy procedures	[36] [37] [67] [69] [70] [71] [72]
Diarrhea	Diarrhea condition record of any type; successive records with > 30 day gap are considered independent episodes	[73] [74] [75]
End stage renal disease	End stage renal disease (ESRD) is defined by at least one diagnosis in any setting, followed by at least one additional diagnosis or a dialysis-related procedure within 90 days	[18] [54] [76]
Fall	Fall condition record of any type; successive records with > 180 day gap are considered independent episodes	[77] [78] [79]

Gastrointestinal bleeding	Gastrointestinal hemorrhage condition record during an inpatient or ER visit; successive records with > 30 day gap are considered independent episodes	[4] [13] [80] [81] [82] [83] [84]
Gout	The first condition record of gout	[85] [86] [87] [88]
Headache	Headache condition record of any type; successive records with > 30 day gap are considered independent episodes	[89] [90]
Heart failure	The first condition record of heart failure, which is followed by at least 1 heart failure condition record in the following year	[10] [91] [92] [93] [94] [95] [96] [97] [98] [99] [100]
Hemorrhagic stroke	Intracranial, cerebral or subarachnoid hemorrhage condition record during an inpatient or ER visit; successive records with > 180 day gap are considered independent episodes	[101] [102] [103] [104] [105]
Hepatic failure	The first condition record of hepatic failure, necrosis, or coma	[19] [106] [107] [108] [109] [110] [111] [112] [113]
Hospitalizations for heart failure	Inpatient or ER visits with heart failure condition record; all qualifying inpatient visits occurring > 7 days apart are considered independent episodes	[93] [98] [99] [114] [115]
Hyperkalemia	Condition record for hyperkalemia or potassium measurements > 5.6 mmol/L; successive records with >90 day gap are considered independent episodes	[116] [117] [118]
Hypokalemia	Hypokalemia condition record of any type; successive records with > 90 day gap are considered independent episodes	[119]
Hypomagnesemia	Hypomagnesemia condition record of any type; successive records with > 90 day gap are considered independent episodes	[120] [121]
Hyponatremia	Hyponatremia condition record of any type; successive records with > 90 day gap are considered independent episodes	[122] [123]
Hypotension	Hypotension condition record of any type; successive records with > 90 day gap are considered independent episodes	[124]
Impotence	The first condition record of impotence	[125] [126] [127] [128]
Ischemic stroke	Ischemic stroke condition record during an inpatient or ER visit; successive records with > 180 day gap are considered independent episodes	[91] [12] [13] [101] [129]
Malignant neoplasm	First occurrence of malignant neoplasm, followed by at least one additional diagnosis of the same type (melanoma, bladder, brain, breast, colon and rectum, kidney, leukemia, liver, lung, lymphoma, multiple myeloma, ovary, pancreas, prostate, thyroid, uterus, myelodysplastic syndrome)	[130] [131] [132] [133] [134] [135] [136] [137] [138] [139] [140] [141] [142] [143] [144] [145]
Measured renal dysfunction	The first creatinine measurement with value > 3 mg/dL	[26]

Nausea	Nausea condition record of any type; successive records with > 30 day gap are considered independent episodes	[4] [146] [147]
Neutropenia or agranulocytosis	The first condition record of neutropenia or agranulocytosis	[148] [149]
Rash	Rash condition record of any type; successive records with > 90 day gap are considered independent episodes	[150]
Rhabdomyolysis	Rhabdomyolysis condition record or muscle disorder condition record with creatine measurement 5*ULN during an inpatient or ER visit; successive records with >90 day gap are considered independent episodes	[151] [152]
Stroke	Stroke (ischemic or hemorrhagic) condition record during an inpatient or ER visit; successive records with > 180 day gap are considered independent episodes	[91] [12] [13] [43] [101] [102] [103] [104] [105] [129]
Sudden cardiac death	Sudden cardiac death condition record during an inpatient or ER visit; successive records with > 180 day gap are considered independent episodes	[12] [41]
Syncope	Syncope condition record of any type; successive records with > 180 day gap are considered independent episodes	[124]
Thrombocytopenia	The first condition record of thrombocytopenia	[146] [153] [154]
Transient ischemic attack	Transient ischemic attack condition record during an inpatient or ER visit; successive records with > 30 day gap are considered independent episodes	[101] [129]
Type 2 diabetes mellitus	The first condition record of Type 2 Diabetes Mellitus, which is followed by another Type 2 Diabetes Mellitus condition record, at least 2 drugs used to treat Type 2 diabetes, or at least 2 HbA1c measurements with value > 6.5%	[67] [155] [156] [157]
Unstable angina	Inpatient or ER visits with preinfarction syndrome condition record; all qualifying inpatient visits occurring > 7 days apart are considered independent episodes	[48] [158] [159]
Vasculitis	The first condition record of vasculitis, which is followed by another vasculitis condition record or drug to treat vasculitis	[160] [161]
Venous thromboembolic events	Venous thromboembolism condition record of any type; successive records with > 180 day gap are considered independent episodes	[162] [163] [164] [165]
Vertigo	The first condition record of vertigo	[166]
Vomiting	Vomiting condition record of any type; successive records with > 30 day gap are considered independent episodes	[4] [146] [147]

Example ATLAS instantiations

We provide here OHDSI ATLAS cohort instantiations for the three primary effectiveness outcomes. The remaining six effectiveness and 46 safety outcomes are similarly instantiated and included in the Study Protocol. Parameterized SQL translations for cohort generation in any OMOP CDM v5

database are available in: https://github.com/OHDSI/Legend/tree/master/inst/sql/sql_server.

Acute myocardial infarction

Description: Acute myocardial infarction condition record during an inpatient or ER visit; successive records with > 180 day gap are considered independent episodes

Initial Event Cohort

People having any of the following:

- a condition occurrence of "Acute myocardial Infarction" concept (see 2 below)

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person**.

For people matching the Primary Events, include:

Having any of the following criteria:

- at least 1 occurrences of a visit occurrence of "Inpatient or ER visit" concept (see 1 below)

where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person**.

Limit qualifying cohort to: **all events per person**.

End Date Strategy

Date Offset Exit Criteria

This cohort definition end date will be the index event's start date plus 7 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 180 days.

Concept Set Definitions

1. Inpatient or ER visit

Concept							
ID	Name	Domain	Vocabulary	Excluded	Descendants	Mapped	
262	Emergency Room and Inpatient Visit	Visit	Visit	NO	YES	NO	
9203	Emergency Room Visit	Visit	Visit	NO	YES	NO	
9201	Inpatient Visit	Visit	Visit	NO	YES	NO	

2. Acute myocardial Infarction

Concept							
ID	Name	Domain	Vocabulary	Excluded	Descendants	Mapped	
4329847	Myocardial infarction	Condition	SNOMED	NO	YES	NO	
314666	Old myocardial infarction	Condition	SNOMED	YES	YES	NO	

Hospitalization for heart failure

Description: Inpatient or ER visits with heart failure condition record; all qualifying inpatient visits occurring > 7 days apart are considered independent episodes

Initial Event Cohort

People having any of the following:

- a visit occurrence of "Inpatient or ER visit" concept (see 1 below)

Having all of the following criteria:

- at least 1 occurrences of a condition occurrence of "Heart Failure" concept (see 2 below)

where event starts between 0 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person**.

Limit qualifying cohort to: **all events per person**.

End Date Strategy

Date Offset Exit Criteria

This cohort definition end date will be the index event's end date plus 0 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 7 days.

Concept Set Definitions

1. Inpatient or ER visit

Concept							
ID	Name	Domain	Vocabulary	Excluded	Descendants	Mapped	
262	Emergency Room and Inpatient Visit	Visit	Visit	NO	YES	NO	
9203	Emergency Room Visit	Visit	Visit	NO	YES	NO	
9201	Inpatient Visit	Visit	Visit	NO	YES	NO	

2. Heart Failure

Concept							
ID	Name	Domain	Vocabulary	Excluded	Descendants	Mapped	
315295	Congestive rheumatic heart failure	Condition	SNOMED	YES	YES	NO	
316139	Heart failure	Condition	SNOMED	NO	YES	NO	

Stroke

Description: Stroke (ischemic or hemorrhagic) events

Initial Event Cohort

People having any of the following:

- a condition occurrence of "Stroke (ischemic or hemorrhagic)" concept (see 2 below)

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person**.

For people matching the Primary Events, include:

Having any of the following criteria:

- at least 1 occurrences of a visit occurrence of "Inpatient or ER visit" concept (see 1 below)

where event starts between all days Before and 1 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person**.

Limit qualifying cohort to: **all events per person**.

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 7 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 180 days.

Concept Set Definitions

1. Inpatient or ER visit

Concept							
ID	Name	Domain	Vocabulary	Excluded	Descendants	Mapped	
262	Emergency Room and Inpatient Visit	Visit	Visit	NO	YES	NO	
9203	Emergency Room Visit	Visit	Visit	NO	YES	NO	
9201	Inpatient Visit	Visit	Visit	NO	YES	NO	

2. Stroke (ischemic or hemorrhagic)

Concept						
ID	Name	Domain	Vocabulary	Excluded	Descendants	Mapped
372924	Cerebral artery occlusion	Condition	SNOMED	NO	NO	NO
375557	Cerebral embolism	Condition	SNOMED	NO	NO	NO
376713	Cerebral hemorrhage	Condition	SNOMED	NO	NO	NO
443454	Cerebral infarction	Condition	SNOMED	NO	YES	NO
441874	Cerebral thrombosis	Condition	SNOMED	NO	NO	NO
439847	Intracranial hemorrhage	Condition	SNOMED	NO	NO	NO
432923	Subarachnoid hemorrhage	Condition	SNOMED	NO	NO	NO

Negative control outcomes

We selected negative controls using a process similar to that outlined in Voss et al. [167]. We first construct a list of all conditions that satisfy the following criteria with respect to all drug exposures in the LEGEND-HTN study:

- No Medline abstract where the MeSH terms suggests a drug-condition association [168],
- No mention of the drug-condition pair on a US product label in the “Adverse Drug Reactions” or “Postmarketing” section [169],
- No US spontaneous reports suggesting that the pair is in an adverse event relationship [170, 171],
- OMOP vocabulary does not suggest that the drug is indicated for the condition,
- Vocabulary conditional concepts are usable (i.e., not too broad, not suggestive of an adverse event relationship, no pregnancy related), and
- Exact condition concept itself is used in patient level data.

We optimize remaining condition concepts, such that parent concepts remove children as defined by the OMOP vocabulary and perform manual review to exclude any pairs that may still be in a causal relationship or too similar to the study outcome. This process led to a candidate list of 76 negative controls:

Supplementary Table 3: Negative control outcomes.

Condition
Abnormal cervical smear
Abnormal pupil
Abrasion and/or friction burn of trunk without infection
Absence of breast
Absent kidney
Acid reflux
Acquired hallux valgus
Acquired keratoderma
Acquired trigger finger
Acute conjunctivitis
Amputated foot
Anal and rectal polyp

Burn of forearm
Calcaneal spur
Cannabis abuse
Cervical somatic dysfunction
Changes in skin texture
Chondromalacia of patella
Cocaine abuse
Colostomy present
Complication due to Crohn's disease
Contact dermatitis
Contusion of knee
Crohn's disease
Derangement of knee
Difficulty sleeping
Disproportion of reconstructed breast
Effects of hunger
Endometriosis
Epidermoid cyst
Feces contents abnormal
Foreign body in orifice
Ganglion cyst
Genetic predisposition
Hammer toe
Hereditary thrombophilia
Herpes zoster without complication
High risk sexual behavior
Homocystinuria
Human papilloma virus infection
Ileostomy present
Impacted cerumen
Impingement syndrome of shoulder region
Ingrowing nail
Injury of knee
Irregular periods
Kwashiorkor
Late effect of contusion
Late effect of motor vehicle accident
Leukorrhea
Macular drusen
Melena
Nicotine dependence
Noise effects on inner ear
Non-toxic multinodular goiter
Nonspecific tuberculin test reaction

Onychomycosis due to dermatophyte

Opioid abuse

Passing flatus

Postviral fatigue syndrome

Presbyopia

Problem related to lifestyle

Psychalgia

Ptotic breast

Regular astigmatism

Senile hyperkeratosis

Somatic dysfunction of lumbar region

Splinter of face, without major open wound

Sprain of ankle

Strain of rotator cuff capsule

Tear film insufficiency

Tobacco dependence syndrome

Vaginitis and vulvovaginitis

Verruca vulgaris

Wrist joint pain

Wristdrop

Additional tables and figures

Individual drugs within classes

Supplementary Table 4: Distribution of individual drugs within first-line classes.

Drug	Meta-analysis (%)	CCAE	Optum	MDCR	MDCD	JMDC	NHIS	PanTher	IMSG	CUMC
THZ										
HCTZ	93.8	94.4	94.6	93.5	94.4	39.7	90.6	92.4	91.2	92.7
Chlortalidone	4.9	4.6	3.8	4.0	4.9	0.1	0.3	6.5	3.9	6.7
Indapamide	1.1	0.8	1.2	2.0	0.4	60.1	6.8	0.8	4.9	0.4
Metolazone	0.3	0.1	0.4	0.6	0.4	-	2.3	0.3	-	0.2
ACEi										
Lisinopril	80.1	83.5	79.8	73.7	91.0	10.8	3.0	88.6	6.9	63.0
Ramipril	8.3	5.1	6.7	7.2	1.0	-	25.4	2.7	81.4	12.0
Enalapril	5.1	4.3	5.1	6.9	4.8	55.3	47.1	4.3	10.4	15.4
Benazepril	3.2	4.0	3.5	6.2	2.0	0.7	0.1	2.3	0.2	1.1
Quinapril	1.7	1.6	2.7	2.0	0.6	0.8	0.5	1.2	0.1	5.3
Fosinopril	0.6	0.6	0.8	0.9	0.2	-	5.8	0.4	0.1	1.1
Captopril	0.4	0.2	0.5	1.8	0.3	12.7	3.5	0.2	1.0	1.9
Trandolapril	0.3	0.3	0.4	0.5	0.0	6.0	-	0.1	0.0	0.1
Perindopril	0.2	0.2	0.4	0.4	0.0	13.7	7.0	0.0	0.0	0.1
Moexipril	0.2	0.2	0.3	0.4	0.0	-	7.7	0.1	0.0	0.1
ARB										
Losartan	44.5	44.6	40.9	45.1	61.0	7.8	34.6	62.0	8.3	44.3
Valsartan	21.6	22.4	26.1	25.1	21.7	13.7	13.2	18.7	24.8	24.8
Olmesartan	14.9	17.9	17.9	13.5	9.5	18.2	14.1	9.8	8.6	12.1
Irbesartan	6.5	7.2	6.6	7.5	3.2	8.9	9.6	4.9	4.2	9.0
Telmisartan	5.8	5.0	5.2	5.0	3.9	18.9	15.1	2.8	8.6	5.4
Candesartan	5.2	2.1	2.7	3.3	0.6	19.6	9.8	1.5	44.5	4.1
Azilsartan	1.2	0.4	0.3	0.2	0.1	12.9	-	0.3	0.4	0.2
Eprosartan	0.3	0.3	0.3	0.3	-	-	3.6	0.0	0.8	0.1
dCCB										
Amlodipine	85.2	85.0	85.1	85.3	76.8	82.7	76.2	88.8	85.0	80.2
Nifedipine	11.8	12.6	11.6	9.1	22.2	12.4	14.2	9.2	12.8	18.3
Felodipine	1.6	1.2	2.1	3.0	0.5	0.0	6.6	1.2	1.9	0.6
Nisoldipine	0.6	0.7	0.8	1.6	0.3	0.0	0.7	0.3	0.2	0.2
Nicardipine	0.5	0.0	0.0	0.1	0.0	4.9	0.3	0.4	0.0	0.5
Isradipine	0.4	0.5	0.4	0.9	0.1	-	2.0	0.2	0.1	0.2
ndCCB										
Diltiazem	62.3	58.0	62.5	75.9	64.2	67.9	90.0	62.3	17.1	67.6
Verapamil	37.7	42.0	37.5	24.1	35.8	32.1	10.0	37.7	82.9	32.4

Patient characteristics

[Starting on next page given table size]

Supplementary Table 5a: Baseline patient characteristics for THZ (T) and ARB (C) new-users in the CCAE database. We report proportion of initiators satisfying selected baseline characteristics and the standardized difference of population proportions (StdDiff) before and after stratification. Less extreme StdDiff through stratification suggest improved balance between patient cohorts through propensity score adjustment.

Characteristic	Before stratification			After stratification		
	T (%)	C (%)	StdDiff	T (%)	C (%)	StdDiff
Age group						
00-04	0.0	0.0	0.00	0.0	0.0	0.00
05-09	0.0	0.0	0.00	0.0	0.0	0.00
10-14	0.1	0.0	0.02	0.1	0.0	0.02
15-19	0.6	0.3	0.04	0.5	0.4	0.01
20-24	1.6	0.9	0.06	1.3	1.2	0.01
25-29	3.5	2.0	0.09	2.8	2.7	0.00
30-34	6.6	4.4	0.10	5.6	5.4	0.01
35-39	9.8	7.5	0.08	8.8	8.6	0.01
40-44	13.4	11.9	0.04	12.7	12.6	0.00
45-49	16.3	16.4	0.00	16.2	16.4	0.00
50-54	17.7	19.3	-0.04	18.4	18.6	-0.01
55-59	16.2	19.3	-0.08	17.7	17.6	0.00
60-64	13.2	16.5	-0.09	14.7	15.2	-0.01
65-69	1.1	1.4	-0.03	1.3	1.2	0.00
70-74	0.0	0.0	0.01	0.0	0.0	0.01
75-79	0.0	0.0	0.01	0.0	0.0	0.00
80-84	0.0	0.0	0.00	0.0	0.0	0.00
85-89	0.0	0.0	0.00	0.0	0.0	0.00
Gender: female	60.7	40.3	0.42	52.4	52.7	-0.01
Medical history: General						
Acute respiratory disease	26.1	26.0	0.00	26.2	26.6	-0.01
Attention deficit hyperactivity disorder	1.1	1.1	0.00	1.1	1.1	0.00
Chronic liver disease	1.1	1.5	-0.04	1.3	1.3	0.00
Chronic obstructive lung disease	1.4	2.0	-0.04	1.7	1.8	0.00
Crohn's disease	0.3	0.3	0.00	0.3	0.3	0.00
Dementia	0.1	0.1	0.00	0.1	0.1	0.00
Depressive disorder	8.1	6.5	0.06	7.5	7.7	0.00
Diabetes mellitus	4.6	13.8	-0.32	7.8	9.0	-0.04
Gastroesophageal reflux disease	7.5	8.3	-0.03	8.0	8.2	-0.01
Gastrointestinal hemorrhage	1.6	2.0	-0.03	1.9	1.8	0.01
Human immunodeficiency virus infection	0.3	0.2	0.02	0.2	0.2	0.00
Hyperlipidemia	25.5	39.1	-0.29	31.3	32.0	-0.02
Hypertensive disorder	100.0	100.0	0.00	100.0	100.0	0.00
Lesion of liver	0.2	0.2	-0.01	0.2	0.2	0.00
Obesity	10.0	7.3	0.10	9.0	9.0	0.00
Osteoarthritis	10.7	12.2	-0.05	11.6	11.7	0.00
Pneumonia	1.4	1.5	0.00	1.5	1.5	0.00
Psoriasis	0.9	1.1	-0.02	1.0	1.0	-0.01
Renal impairment	0.5	1.2	-0.07	0.8	0.9	-0.01
Rheumatoid arthritis	0.8	0.9	-0.01	0.9	1.0	-0.01
Schizophrenia	0.1	0.1	0.00	0.1	0.1	0.00
Ulcerative colitis	0.2	0.3	-0.01	0.3	0.3	0.00
Urinary tract infectious disease	6.4	5.6	0.03	6.2	6.2	0.00
Viral hepatitis C	0.3	0.4	-0.01	0.4	0.3	0.00
Visual system disorder	14.9	16.6	-0.05	15.7	15.9	-0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	0.3	0.5	-0.04	0.4	0.4	0.00
Cerebrovascular disease	1.0	1.5	-0.04	1.3	1.3	0.00
Coronary arteriosclerosis	1.0	2.5	-0.11	1.6	1.7	-0.01
Heart disease	6.5	11.2	-0.17	8.6	8.8	0.00
Heart failure	0.3	0.5	-0.03	0.4	0.4	0.00
Ischemic heart disease	0.9	1.8	-0.08	1.3	1.4	-0.01
Peripheral vascular disease	3.3	4.5	-0.06	3.9	4.0	-0.01
Pulmonary embolism	0.2	0.2	0.00	0.2	0.2	0.00
Venous thrombosis	1.0	1.1	-0.01	1.0	1.1	-0.01
Medical history: Neoplasms						
Hematologic neoplasm	0.4	0.5	-0.01	0.5	0.5	0.00
Malignant lymphoma	0.2	0.2	-0.01	0.2	0.2	0.01
Malignant neoplasm of anorectum	0.1	0.1	-0.01	0.1	0.1	0.00
Malignant neoplastic disease	3.8	4.8	-0.05	4.4	4.3	0.00
Malignant tumor of breast	1.0	0.9	0.01	1.0	0.9	0.00
Malignant tumor of colon	0.2	0.2	-0.01	0.2	0.2	0.00
Malignant tumor of lung	0.1	0.1	0.00	0.1	0.1	0.00
Malignant tumor of urinary bladder	0.1	0.1	-0.02	0.1	0.1	0.00
Primary malignant neoplasm of prostate	0.3	0.6	-0.03	0.4	0.4	0.00
Medication use						
Antibacterials for systemic use	50.7	50.1	0.01	50.7	50.8	0.00
Antidepressants	19.1	17.2	0.05	18.5	18.7	0.00
Antiepileptics	6.0	5.9	0.00	6.1	6.3	-0.01
Antinflammatory and antirheumatic products	26.3	23.6	0.06	25.3	25.5	-0.01
Antineoplastic agents	1.5	1.5	0.00	1.6	1.5	0.00
Antipsoriatics	0.4	0.5	-0.01	0.4	0.5	-0.01
Antithrombotic agents	2.2	2.9	-0.04	2.6	2.7	-0.01
Beta blocking agents	0.4	0.5	-0.01	0.4	0.5	0.00
Calcium channel blockers	0.0	0.0	0.00	0.0	0.0	0.00
Diuretics	0.0	0.0	0.00	0.0	0.0	0.00
Drugs for acid related disorders	14.0	15.6	-0.05	14.9	15.1	0.00
Drugs for obstructive airway diseases	20.3	19.2	0.03	20.0	20.3	-0.01
Drugs used in diabetes	3.1	10.3	-0.29	5.3	6.4	-0.05
Immunosuppressants	1.5	1.7	-0.02	1.6	1.7	-0.01
Lipid modifying agents	13.6	23.8	-0.26	17.6	18.4	-0.02
Opioids	16.0	14.8	0.03	15.8	16.0	0.00
Psycholeptics	18.2	18.2	0.00	18.4	19.0	-0.01
Psychostimulants, agents used for adhd and nootropics	3.1	2.9	0.01	3.1	3.1	0.00

Supplementary Table 5b: Baseline patient characteristics for THZ (T) and dCCB (C) new-users in the CCAE database. We report proportion of initiators satisfying selected baseline characteristics and the standardized difference of population proportions (StdDiff) before and after stratification. Less extreme StdDiff through stratification suggest improved balance between patient cohorts through propensity score adjustment.

Characteristic	Before stratification			After stratification		
	T (%)	C (%)	StdDiff	T (%)	C (%)	StdDiff
Age group						
00-04	0.0	0.1	-0.04	0.0	0.0	-0.02
05-09	0.0	0.1	-0.05	0.0	0.1	-0.03
10-14	0.1	0.3	-0.06	0.1	0.2	-0.02
15-19	0.6	1.1	-0.06	0.7	0.9	-0.02
20-24	1.6	2.2	-0.05	1.7	1.9	-0.01
25-29	3.5	4.6	-0.06	3.5	4.2	-0.03
30-34	6.6	7.5	-0.04	6.5	7.1	-0.02
35-39	9.8	9.5	0.01	9.5	9.7	-0.01
40-44	13.4	11.5	0.06	12.7	12.5	0.00
45-49	16.3	14.3	0.06	15.7	15.2	0.01
50-54	17.7	16.5	0.03	17.5	17.1	0.01
55-59	16.2	16.3	0.00	16.7	16.0	0.02
60-64	13.2	14.6	-0.04	14.2	14.0	0.01
65-69	1.1	1.3	-0.02	1.2	1.2	0.00
70-74	0.0	0.0	0.01	0.0	0.0	0.01
75-79	0.0	0.0	0.00	0.0	0.0	0.00
80-84	0.0	0.0	0.00	0.0	0.0	0.00
Gender: female	60.7	47.7	0.26	53.8	56.2	-0.05
Medical history: General						
Acute respiratory disease	26.1	25.1	0.02	25.8	25.8	0.00
Attention deficit hyperactivity disorder	1.1	1.2	-0.01	1.1	1.1	0.00
Chronic liver disease	1.1	1.4	-0.03	1.2	1.2	0.00
Chronic obstructive lung disease	1.4	2.3	-0.06	1.9	1.8	0.01
Crohn's disease	0.3	0.4	-0.02	0.3	0.3	0.00
Dementia	0.1	0.2	-0.02	0.2	0.1	0.00
Depressive disorder	8.1	7.1	0.04	7.6	7.9	-0.01
Diabetes mellitus	4.6	6.8	-0.09	5.6	5.7	0.00
Gastroesophageal reflux disease	7.5	8.1	-0.02	7.9	8.0	0.00
Gastrointestinal hemorrhage	1.6	2.0	-0.03	1.8	1.8	0.00
Human immunodeficiency virus infection	0.3	0.4	-0.02	0.3	0.3	0.00
Hyperlipidemia	25.5	28.1	-0.06	27.5	26.7	0.02
Hypertension disorder	100.0	100.0	0.00	100.0	100.0	0.00
Lesion of liver	0.2	0.5	-0.05	0.3	0.3	-0.01
Obesity	10.0	9.4	0.02	9.7	9.9	0.00
Osteoarthritis	10.7	11.2	-0.02	11.3	10.9	0.01
Pneumonia	1.4	2.1	-0.05	1.7	1.7	0.00
Psoriasis	0.9	0.9	0.00	0.9	0.9	0.00
Renal impairment	0.5	2.4	-0.16	1.1	1.4	-0.02
Rheumatoid arthritis	0.8	0.9	-0.01	0.9	0.9	0.00
Schizophrenia	0.1	0.1	-0.02	0.1	0.1	0.00
Ulcerative colitis	0.2	0.3	-0.02	0.3	0.3	0.00
Urinary tract infectious disease	6.4	7.1	-0.03	6.4	6.8	-0.02
Viral hepatitis C	0.3	0.5	-0.02	0.4	0.4	0.01
Visual system disorder	14.9	14.7	0.00	15.0	15.0	0.00
Medical history: Cardiovascular disease						
Atrial fibrillation	0.3	0.4	-0.03	0.3	0.3	0.00
Cerebrovascular disease	1.0	2.3	-0.10	1.6	1.6	0.00
Coronary arteriosclerosis	1.0	2.2	-0.10	1.5	1.5	0.00
Heart disease	6.5	11.6	-0.18	8.8	8.8	0.00
Heart failure	0.3	0.7	-0.06	0.5	0.5	0.00
Ischemic heart disease	0.9	2.2	-0.10	1.4	1.5	-0.01
Peripheral vascular disease	3.3	5.2	-0.10	4.1	4.1	0.00
Pulmonary embolism	0.2	0.4	-0.03	0.3	0.3	0.00
Venous thrombosis	1.0	1.3	-0.03	1.1	1.1	0.00
Medical history: Neoplasms						
Hematologic neoplasm	0.4	0.9	-0.06	0.6	0.7	-0.01
Malignant lymphoma	0.2	0.3	-0.03	0.2	0.3	0.00
Malignant neoplasm of anorectum	0.1	0.2	-0.02	0.1	0.1	0.00
Malignant neoplastic disease	3.8	5.1	-0.06	4.4	4.3	0.00
Malignant tumor of breast	1.0	0.8	0.02	0.9	0.9	0.00
Malignant tumor of colon	0.2	0.3	-0.03	0.2	0.3	0.00
Malignant tumor of lung	0.1	0.3	-0.04	0.1	0.2	0.00
Malignant tumor of urinary bladder	0.1	0.1	-0.02	0.1	0.1	0.00
Primary malignant neoplasm of prostate	0.3	0.6	-0.03	0.4	0.4	0.00
Medication use						
Antibacterials for systemic use	50.7	50.2	0.01	50.2	50.9	-0.01
Antidepressants	19.1	15.2	0.10	17.3	17.9	-0.02
Antiepileptics	6.0	6.4	-0.02	6.2	6.3	0.00
Antinflammatory and antirheumatic products	26.3	27.3	-0.02	26.5	27.1	-0.01
Antineoplastic agents	1.5	1.8	-0.02	1.6	1.6	0.00
Antipsoriatics	0.4	0.4	0.00	0.4	0.4	0.00
Antithrombotic agents	2.2	4.0	-0.10	3.0	3.0	0.00
Beta blocking agents	0.4	0.5	-0.01	0.4	0.5	0.00
Calcium channel blockers	0.0	0.0	-0.01	0.0	0.0	-0.01
Diuretics	0.0	0.0	0.00	0.0	0.0	0.00
Drugs for acid related disorders	14.0	14.6	-0.02	14.2	14.4	-0.01
Drugs for obstructive airway diseases	20.3	19.0	0.03	19.8	19.9	0.00
Drugs used in diabetes	3.1	4.0	-0.05	3.5	3.6	-0.01
Immunosuppressants	1.5	2.0	-0.04	1.6	1.7	-0.01
Lipid modifying agents	13.6	16.9	-0.09	15.7	15.1	0.01
Opioids	16.0	19.2	-0.08	16.9	17.8	-0.02
Psycholeptics	18.2	18.0	0.01	18.2	18.6	-0.01
Psychostimulants, agents used for adhd and nootropics	3.1	3.4	-0.02	3.2	3.3	-0.01

Supplementary Table 5c: Baseline patient characteristics for THZ (T) and ndCCB (C) new-users in the CCAE database. We report proportion of initiators satisfying selected base-line characteristics and the standardized difference of population proportions (StdDiff) before and after stratification. Less extreme StdDiff through stratification suggest improved balance between patient cohorts through propensity score adjustment.

Characteristic	Before stratification			After stratification		
	T (%)	C (%)	StdDiff	T (%)	C (%)	StdDiff
Age group						
05-09	0.0	0.0	-0.01	0.0	0.0	0.00
10-14	0.1	0.1	-0.01	0.1	0.1	-0.01
15-19	0.6	0.7	-0.02	0.6	0.6	0.00
20-24	1.6	1.6	0.00	1.6	1.5	0.01
25-29	3.5	3.0	0.03	3.5	3.5	0.00
30-34	6.6	5.3	0.05	6.4	6.8	-0.02
35-39	9.8	7.9	0.07	9.6	9.6	0.00
40-44	13.4	10.9	0.08	13.1	12.7	0.01
45-49	16.3	14.7	0.04	16.2	16.1	0.00
50-54	17.7	17.3	0.01	17.7	17.7	0.00
55-59	16.2	18.4	-0.06	16.3	16.3	0.00
60-64	13.2	18.1	-0.13	13.7	13.8	0.00
65-69	1.1	1.8	-0.06	1.1	1.3	-0.01
70-74	0.0	0.0	-0.02	0.0	0.0	0.00
75-79	0.0	0.0	0.00	0.0	0.0	0.01
80-84	0.0	0.0	-0.01	0.0	0.0	0.00
90-94	0.0	0.0	0.00	0.0	0.0	0.00
Gender: female	60.7	53.0	0.15	60.0	60.6	-0.01
Medical history: General						
Acute respiratory disease	26.1	30.1	-0.09	26.4	27.1	-0.02
Attention deficit hyperactivity disorder	1.1	1.0	0.01	1.1	1.0	0.00
Chronic liver disease	1.1	1.6	-0.04	1.1	1.2	-0.01
Chronic obstructive lung disease	1.4	5.2	-0.21	1.7	2.0	-0.02
Crohn's disease	0.3	0.5	-0.03	0.3	0.3	-0.01
Dementia	0.1	0.3	-0.03	0.1	0.1	0.00
Depressive disorder	8.1	9.9	-0.06	8.2	8.1	0.00
Diabetes mellitus	4.6	9.5	-0.19	5.1	5.4	-0.01
Gastroesophageal reflux disease	7.5	11.3	-0.13	7.8	7.9	0.00
Gastrointestinal hemorrhage	1.6	2.7	-0.08	1.7	1.7	0.00
Human immunodeficiency virus infection	0.3	0.2	0.01	0.3	0.2	0.01
Hyperlipidemia	25.5	33.9	-0.18	26.2	25.6	0.01
Hypertension disorder	100.0	100.0	0.00	100.0	100.0	0.00
Lesion of liver	0.2	0.4	-0.04	0.2	0.2	0.00
Obesity	10.0	8.3	0.06	9.7	9.8	0.00
Osteoarthritis	10.7	14.4	-0.11	11.0	11.1	0.00
Pneumonia	1.4	3.5	-0.13	1.6	1.7	-0.01
Psoriasis	0.9	0.9	0.00	0.9	0.9	0.00
Renal impairment	0.5	1.9	-0.12	0.6	0.8	-0.01
Rheumatoid arthritis	0.8	1.3	-0.05	0.9	0.8	0.01
Schizophrenia	0.1	0.1	-0.02	0.1	0.1	-0.01
Ulcerative colitis	0.2	0.4	-0.03	0.3	0.3	-0.01
Urinary tract infectious disease	6.4	7.6	-0.05	6.5	7.2	-0.03
Viral hepatitis C	0.3	0.5	-0.02	0.3	0.3	0.00
Visual system disorder	14.9	17.2	-0.06	15.1	14.7	0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	0.3	10.1	-0.46	0.4	2.1	-0.16
Cerebrovascular disease	1.0	3.6	-0.17	1.2	1.5	-0.02
Coronary arteriosclerosis	1.0	5.4	-0.25	1.3	1.5	-0.02
Heart disease	6.5	30.1	-0.64	7.9	9.7	-0.06
Heart failure	0.3	1.5	-0.12	0.4	0.5	-0.01
Ischemic heart disease	0.9	5.1	-0.25	1.2	1.4	-0.02
Peripheral vascular disease	3.3	7.2	-0.18	3.6	3.9	-0.02
Pulmonary embolism	0.2	0.7	-0.08	0.2	0.3	-0.01
Venous thrombosis	1.0	1.8	-0.07	1.0	1.1	-0.01
Medical history: Neoplasms						
Hematologic neoplasm	0.4	0.9	-0.06	0.5	0.5	-0.01
Malignant lymphoma	0.2	0.3	-0.03	0.2	0.2	-0.01
Malignant neoplasm of anorectum	0.1	0.2	-0.03	0.1	0.1	-0.01
Malignant neoplastic disease	3.8	5.8	-0.09	3.9	4.2	-0.01
Malignant tumor of breast	1.0	1.0	-0.01	1.0	1.1	-0.01
Malignant tumor of colon	0.2	0.3	-0.03	0.2	0.2	-0.01
Malignant tumor of lung	0.1	0.5	-0.08	0.1	0.2	-0.02
Malignant tumor of urinary bladder	0.1	0.1	-0.02	0.1	0.1	0.00
Primary malignant neoplasm of prostate	0.3	0.5	-0.03	0.4	0.3	0.01
Medication use						
Antibacterial agents for systemic use	50.7	52.8	-0.04	50.8	51.6	-0.02
Antidepressants	19.1	22.9	-0.09	19.4	19.5	0.00
Antiepileptics	6.0	11.3	-0.19	6.4	6.9	-0.02
Antinflammatory and antirheumatic products	26.3	27.4	-0.03	26.4	26.5	0.00
Antineoplastic agents	1.5	1.9	-0.03	1.5	1.7	-0.02
Antipsoritacs	0.4	0.4	-0.01	0.4	0.4	0.01
Antithrombotic agents	2.2	9.5	-0.31	2.5	3.4	-0.05
Beta blocking agents	0.4	1.1	-0.08	0.4	0.6	-0.02
Calcium channel blockers	0.0	0.1	-0.03	0.0	0.0	-0.02
Diuretics	0.0	0.0	0.00	0.0	0.0	0.00
Drugs for acid related disorders	14.0	19.6	-0.15	14.5	14.4	0.00
Drugs for obstructive airway diseases	20.3	23.6	-0.08	20.5	20.6	0.00
Drugs used in diabetes	3.1	5.5	-0.12	3.4	3.5	-0.01
Immunosuppressants	1.5	2.1	-0.05	1.5	1.8	-0.02
Lipid modifying agents	13.6	18.9	-0.14	14.1	13.7	0.01
Opioids	16.0	21.7	-0.14	16.4	17.8	-0.04
Psycholeptics	18.2	25.5	-0.18	18.8	19.1	-0.01
Psychostimulants, agents used for adhd and nootropics	3.1	6.1	-0.14	3.4	3.6	-0.01

Supplementary Table 5d: Baseline patient characteristics for ACEi (T) and ARB (C) new-users in the CCAE database. We report proportion of initiators satisfying selected baseline characteristics and the standardized difference of population proportions (StdDiff) before and after stratification. Less extreme StdDiff through stratification suggest improved balance between patient cohorts through propensity score adjustment.

Characteristic	Before stratification			After stratification		
	T (%)	C (%)	StdDiff	T (%)	C (%)	StdDiff
Age group						
00-04	0.0	0.0	0.01	0.0	0.0	0.01
05-09	0.0	0.0	0.02	0.0	0.0	0.02
10-14	0.2	0.0	0.04	0.1	0.1	0.02
15-19	0.7	0.3	0.06	0.6	0.6	0.01
20-24	1.4	0.9	0.04	1.3	1.3	0.00
25-29	2.6	2.0	0.04	2.4	2.3	0.01
30-34	5.0	4.4	0.03	4.9	4.7	0.01
35-39	8.1	7.5	0.02	8.0	7.9	0.00
40-44	12.1	11.9	0.00	12.0	12.0	0.00
45-49	16.1	16.4	-0.01	16.1	16.1	0.00
50-54	18.7	19.3	-0.02	18.9	18.8	0.00
55-59	18.3	19.3	-0.02	18.6	18.7	0.00
60-64	15.5	16.5	-0.03	15.7	16.1	-0.01
65-69	1.3	1.4	-0.01	1.3	1.4	0.00
70-74	0.0	0.0	0.00	0.0	0.0	0.00
75-79	0.0	0.0	0.00	0.0	0.0	0.00
80-84	0.0	0.0	0.00	0.0	0.0	0.00
85-89	0.0	0.0	0.00	0.0	0.0	0.00
Gender: female	38.4	40.3	-0.04	38.7	39.2	-0.01
Medical history: General						
Acute respiratory disease	24.5	26.0	-0.03	24.9	25.0	0.00
Attention deficit hyperactivity disorder	1.2	1.1	0.01	1.1	1.2	-0.01
Chronic liver disease	1.5	1.5	0.00	1.5	1.5	0.00
Chronic obstructive lung disease	1.8	2.0	-0.02	1.8	1.9	0.00
Crohn's disease	0.3	0.3	0.00	0.3	0.3	0.00
Dementia	0.1	0.1	0.00	0.1	0.1	0.00
Depressive disorder	7.4	6.5	0.04	7.2	7.5	-0.01
Diabetes mellitus	18.3	13.8	0.12	17.4	17.5	0.00
Gastroesophageal reflux disease	7.8	8.3	-0.02	7.9	7.9	0.00
Gastrointestinal hemorrhage	1.7	2.0	-0.02	1.8	1.8	0.00
Human immunodeficiency virus infection	0.2	0.2	0.01	0.2	0.2	0.00
Hyperlipidemia	36.1	39.1	-0.06	36.8	37.1	-0.01
Hypertensive disorder	100.0	100.0	0.00	100.0	100.0	0.00
Lesion of liver	0.2	0.2	0.00	0.2	0.2	0.00
Obesity	8.5	7.3	0.04	8.3	8.2	0.00
Osteoarthritis	11.3	12.2	-0.03	11.5	11.6	0.00
Pneumonia	1.5	1.5	0.00	1.5	1.5	0.00
Psoriasis	1.0	1.1	-0.01	1.0	1.0	0.00
Renal impairment	1.1	1.2	-0.01	1.1	1.1	0.00
Rheumatoid arthritis	0.8	0.9	-0.01	0.8	0.8	0.00
Schizophrenia	0.1	0.1	0.01	0.1	0.1	0.00
Ulcerative colitis	0.3	0.3	0.00	0.3	0.3	0.00
Urinary tract infectious disease	5.1	5.6	-0.02	5.2	5.3	-0.01
Viral hepatitis C	0.4	0.4	0.00	0.4	0.4	0.01
Visual system disorder	15.5	16.6	-0.03	15.8	15.8	0.00
Medical history: Cardiovascular disease						
Atrial fibrillation	0.4	0.5	-0.01	0.4	0.4	0.00
Cerebrovascular disease	1.7	1.5	0.02	1.7	1.6	0.00
Coronary arteriosclerosis	2.2	2.5	-0.02	2.3	2.3	0.00
Heart disease	9.0	11.2	-0.08	9.5	9.7	-0.01
Heart failure	0.5	0.5	-0.01	0.5	0.5	0.00
Ischemic heart disease	1.7	1.8	-0.01	1.8	1.8	0.00
Peripheral vascular disease	4.1	4.5	-0.02	4.2	4.3	0.00
Pulmonary embolism	0.2	0.2	0.00	0.2	0.2	0.00
Venous thrombosis	1.0	1.1	0.00	1.0	1.0	0.00
Medical history: Neoplasms						
Hematologic neoplasm	0.5	0.5	0.00	0.5	0.6	-0.01
Malignant lymphoma	0.2	0.2	0.00	0.2	0.2	0.00
Malignant neoplasm of anorectum	0.1	0.1	0.00	0.1	0.1	0.00
Malignant neoplastic disease	4.2	4.8	-0.03	4.3	4.4	0.00
Malignant tumor of breast	0.7	0.9	-0.02	0.7	0.8	-0.01
Malignant tumor of colon	0.2	0.2	0.00	0.2	0.2	0.00
Malignant tumor of lung	0.1	0.1	0.00	0.1	0.1	0.00
Malignant tumor of urinary bladder	0.1	0.1	0.00	0.1	0.1	0.00
Primary malignant neoplasm of prostate	0.5	0.6	0.00	0.5	0.5	0.00
Medication use						
Antibacterials for systemic use	48.8	50.1	-0.03	49.0	49.6	-0.01
Antidepressants	17.7	17.2	0.01	17.6	17.9	-0.01
Antiepileptics	6.2	5.9	0.01	6.1	6.3	-0.01
Antinflammatory and antirheumatic products	24.0	23.6	0.01	24.0	24.2	0.00
Antineoplastic agents	1.4	1.5	-0.01	1.4	1.5	0.00
Antipsoriatics	0.4	0.5	-0.02	0.4	0.4	-0.01
Antithrombotic agents	3.3	2.9	0.02	3.2	3.3	0.00
Beta blocking agents	0.5	0.5	0.00	0.5	0.5	0.00
Calcium channel blockers	0.0	0.0	0.01	0.0	0.0	0.00
Diuretics	0.0	0.0	0.00	0.0	0.0	0.00
Drugs for acid related disorders	14.1	15.6	-0.04	14.4	14.6	0.00
Drugs for obstructive airway diseases	18.1	19.2	-0.03	18.4	18.5	0.00
Drugs used in diabetes	15.6	10.3	0.16	14.5	14.6	0.00
Immunosuppressants	1.5	1.7	-0.02	1.5	1.6	-0.01
Lipid modifying agents	24.6	23.8	0.02	24.5	24.9	-0.01
Opioids	15.2	14.8	0.01	15.1	15.4	-0.01
Psycholeptics	17.6	18.2	-0.02	17.6	18.3	-0.02
Psychostimulants, agents used for adhd and nootropics	2.9	2.9	0.00	2.9	3.0	-0.01

Supplementary Table 5e: Baseline patient characteristics for ACEi (T) and dCCB (C) new-users in the CCAE database. We report proportion of initiators satisfying selected baseline characteristics and the standardized difference of population proportions (StdDiff) before and after stratification. Less extreme StdDiff through stratification suggest improved balance between patient cohorts through propensity score adjustment.

Characteristic	Before stratification			After stratification		
	T (%)	C (%)	StdDiff	T (%)	C (%)	StdDiff
Age group						
00-04	0.0	0.1	-0.03	0.0	0.0	-0.01
05-09	0.0	0.1	-0.04	0.0	0.1	-0.01
10-14	0.2	0.3	-0.04	0.2	0.2	-0.01
15-19	0.7	1.1	-0.04	0.8	0.9	-0.01
20-24	1.4	2.2	-0.06	1.4	1.7	-0.02
25-29	2.6	4.6	-0.11	2.7	3.2	-0.03
30-34	5.0	7.5	-0.10	5.1	5.8	-0.03
35-39	8.1	9.5	-0.05	8.2	8.5	-0.01
40-44	12.1	11.5	0.02	12.0	11.5	0.02
45-49	16.1	14.3	0.05	15.9	15.2	0.02
50-54	18.7	16.5	0.06	18.5	17.9	0.02
55-59	18.3	16.3	0.06	18.2	18.0	0.00
60-64	15.5	14.6	0.02	15.6	15.7	0.00
65-69	1.3	1.3	0.00	1.4	1.4	0.00
70-74	0.0	0.0	0.00	0.0	0.0	0.00
75-79	0.0	0.0	0.00	0.0	0.0	0.00
80-84	0.0	0.0	0.00	0.0	0.0	0.00
Gender: female	38.4	47.7	-0.19	39.6	41.3	-0.03
Medical history: General						
Acute respiratory disease	24.5	25.1	-0.01	24.7	25.1	-0.01
Attention deficit hyperactivity disorder	1.2	1.2	0.00	1.2	1.1	0.00
Chronic liver disease	1.5	1.4	0.00	1.5	1.3	0.01
Chronic obstructive lung disease	1.8	2.3	-0.04	2.0	2.0	0.00
Crohn's disease	0.3	0.4	-0.02	0.3	0.3	0.00
Dementia	0.1	0.2	-0.02	0.1	0.2	-0.01
Depressive disorder	7.4	7.1	0.01	7.3	7.7	-0.02
Diabetes mellitus	18.3	6.8	0.35	15.7	15.2	0.01
Gastroesophageal reflux disease	7.8	8.1	-0.01	8.0	7.9	0.00
Gastrointestinal hemorrhage	1.7	2.0	-0.02	1.8	1.8	0.00
Human immunodeficiency virus infection	0.2	0.4	-0.02	0.3	0.3	0.00
Hyperlipidemia	36.1	28.1	0.17	34.9	33.8	0.02
Hypertension disorder	100.0	100.0	0.00	100.0	100.0	0.00
Lesion of liver	0.2	0.5	-0.04	0.3	0.3	-0.01
Obesity	8.5	9.4	-0.03	8.6	8.7	0.00
Osteoarthritis	11.3	11.2	0.00	11.5	11.5	0.00
Pneumonia	1.5	2.1	-0.04	1.6	1.7	0.00
Psoriasis	1.0	0.9	0.01	1.0	1.0	0.00
Renal impairment	1.1	2.4	-0.10	1.3	1.5	-0.02
Rheumatoid arthritis	0.8	0.9	-0.02	0.8	0.8	0.00
Schizophrenia	0.1	0.1	-0.01	0.1	0.1	-0.01
Ulcerative colitis	0.3	0.3	-0.01	0.3	0.3	0.00
Urinary tract infectious disease	5.1	7.1	-0.08	5.4	5.8	-0.02
Viral hepatitis C	0.4	0.5	-0.01	0.4	0.4	0.01
Visual system disorder	15.5	14.7	0.02	15.5	15.3	0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	0.4	0.4	0.00	0.4	0.4	0.00
Cerebrovascular disease	1.7	2.3	-0.04	2.0	2.0	0.00
Coronary arteriosclerosis	2.2	2.2	0.00	2.4	2.3	0.00
Heart disease	9.0	11.6	-0.08	9.9	9.9	0.00
Heart failure	0.5	0.7	-0.03	0.5	0.6	0.00
Ischemic heart disease	1.7	2.2	-0.03	1.9	1.9	0.00
Peripheral vascular disease	4.1	5.2	-0.05	4.4	4.6	-0.01
Pulmonary embolism	0.2	0.4	-0.03	0.3	0.3	0.00
Venous thrombosis	1.0	1.3	-0.02	1.1	1.1	0.00
Medical history: Neoplasms						
Hematologic neoplasm	0.5	0.9	-0.05	0.6	0.6	-0.01
Malignant lymphoma	0.2	0.3	-0.03	0.2	0.2	0.00
Malignant neoplasm of anorectum	0.1	0.2	-0.02	0.1	0.1	0.01
Malignant neoplastic disease	4.2	5.1	-0.04	4.5	4.6	-0.01
Malignant tumor of breast	0.7	0.8	-0.01	0.7	0.8	0.00
Malignant tumor of colon	0.2	0.3	-0.02	0.3	0.2	0.00
Malignant tumor of lung	0.1	0.3	-0.04	0.1	0.2	-0.01
Malignant tumor of urinary bladder	0.1	0.1	-0.01	0.1	0.1	0.01
Primary malignant neoplasm of prostate	0.5	0.6	0.00	0.5	0.5	0.00
Medication use						
Antibacterial agents for systemic use	48.8	50.2	-0.03	48.8	49.8	-0.02
Antidepressants	17.7	15.2	0.07	17.1	17.9	-0.02
Antiepileptics	6.2	6.4	-0.01	6.3	6.4	0.00
Antinflammatory and antirheumatic products	24.0	27.3	-0.07	24.4	25.3	-0.02
Antineoplastic agents	1.4	1.8	-0.03	1.5	1.5	0.00
Antipsoriatcs	0.4	0.4	0.00	0.4	0.4	0.00
Antithrombotic agents	3.3	4.0	-0.04	3.6	3.6	0.00
Beta blocking agents	0.5	0.5	0.00	0.5	0.5	0.00
Calcium channel blockers	0.0	0.0	-0.01	0.0	0.0	0.00
Diuretics	0.0	0.0	0.00	0.0	0.0	0.00
Drugs for acid related disorders	14.1	14.6	-0.01	14.3	14.5	-0.01
Drugs for obstructive airway diseases	18.1	19.0	-0.02	18.4	18.5	0.00
Drugs used in diabetes	15.6	4.0	0.40	12.9	12.6	0.01
Immunosuppressants	1.5	2.0	-0.04	1.6	1.7	0.00
Lipid modifying agents	24.6	16.9	0.19	23.4	22.6	0.02
Opioids	15.2	19.2	-0.10	15.8	16.8	-0.03
Psycholeptics	17.6	18.0	-0.01	17.8	18.2	-0.01
Psychostimulants, agents used for adhd and nootropics	2.9	3.4	-0.03	3.0	3.1	-0.01

Supplementary Table 5f: Baseline patient characteristics for ACEi (T) and ndCCB (C) new-users in the CCAE database. We report proportion of initiators satisfying selected base-line characteristics and the standardized difference of population proportions (StdDiff) before and after stratification. Less extreme StdDiff through stratification suggest improved balance between patient cohorts through propensity score adjustment.

Characteristic	Before stratification			After stratification		
	T (%)	C (%)	StdDiff	T (%)	C (%)	StdDiff
Age group						
05-09	0.0	0.0	0.01	0.0	0.0	0.02
10-14	0.2	0.1	0.02	0.2	0.1	0.02
15-19	0.7	0.7	0.00	0.7	0.7	0.00
20-24	1.4	1.6	-0.02	1.4	1.4	0.00
25-29	2.6	3.0	-0.03	2.6	2.3	0.02
30-34	5.0	5.3	-0.01	5.0	5.0	0.00
35-39	8.1	7.9	0.01	8.1	7.8	0.01
40-44	12.1	10.9	0.04	12.0	11.3	0.02
45-49	16.1	14.7	0.04	16.0	16.2	0.00
50-54	18.7	17.3	0.04	18.6	19.0	-0.01
55-59	18.3	18.4	0.00	18.4	18.2	0.00
60-64	15.5	18.1	-0.07	15.6	16.7	-0.03
65-69	1.3	1.8	-0.04	1.3	1.3	0.00
70-74	0.0	0.0	-0.02	0.0	0.0	0.00
75-79	0.0	0.0	0.00	0.0	0.0	0.00
80-84	0.0	0.0	-0.01	0.0	0.0	0.00
90-94	0.0	0.0	-0.01	0.0	0.0	0.00
Gender: female	38.4	53.0	-0.30	39.0	38.3	0.01
Medical history: General						
Acute respiratory disease	24.5	30.1	-0.12	24.7	25.2	-0.01
Attention deficit hyperactivity disorder	1.2	1.0	0.02	1.1	1.0	0.01
Chronic liver disease	1.5	1.6	-0.01	1.5	1.6	-0.01
Chronic obstructive lung disease	1.8	5.2	-0.19	1.9	2.1	-0.02
Crohn's disease	0.3	0.5	-0.03	0.3	0.3	0.00
Dementia	0.1	0.3	-0.04	0.1	0.1	-0.01
Depressive disorder	7.4	9.9	-0.09	7.5	7.5	0.00
Diabetes mellitus	18.3	9.5	0.26	17.9	18.4	-0.02
Gastroesophageal reflux disease	7.8	11.3	-0.12	7.8	8.0	0.00
Gastrointestinal hemorrhage	1.7	2.7	-0.07	1.8	1.9	-0.01
Human immunodeficiency virus infection	0.2	0.2	0.00	0.2	0.2	0.01
Hyperlipidemia	36.1	33.9	0.05	35.9	36.4	-0.01
Hypertension disorder	100.0	100.0	0.00	100.0	100.0	0.00
Lesion of liver	0.2	0.4	-0.03	0.2	0.2	0.00
Obesity	8.5	8.3	0.01	8.4	8.8	-0.01
Osteoarthritis	11.3	14.4	-0.09	11.4	11.4	0.00
Pneumonia	1.5	3.5	-0.13	1.5	1.7	-0.02
Psoriasis	1.0	0.9	0.01	1.0	1.0	0.00
Renal impairment	1.1	1.9	-0.07	1.1	1.6	-0.04
Rheumatoid arthritis	0.8	1.3	-0.05	0.8	0.8	0.00
Schizophrenia	0.1	0.1	-0.02	0.1	0.1	0.00
Ulcerative colitis	0.3	0.4	-0.02	0.3	0.3	0.00
Urinary tract infectious disease	5.1	7.6	-0.10	5.2	5.7	-0.02
Viral hepatitis C	0.4	0.5	-0.01	0.4	0.5	-0.01
Visual system disorder	15.5	17.2	-0.04	15.6	15.3	0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	0.4	10.1	-0.44	0.5	2.0	-0.13
Cerebrovascular disease	1.7	3.6	-0.12	1.8	1.9	-0.01
Coronary arteriosclerosis	2.2	5.4	-0.16	2.4	2.5	-0.01
Heart disease	9.0	30.1	-0.55	9.5	11.4	-0.06
Heart failure	0.5	1.5	-0.10	0.5	0.6	-0.01
Ischemic heart disease	1.7	5.1	-0.19	1.8	1.9	-0.01
Peripheral vascular disease	4.1	7.2	-0.13	4.2	4.7	-0.02
Pulmonary embolism	0.2	0.7	-0.07	0.2	0.3	-0.02
Venous thrombosis	1.0	1.8	-0.06	1.1	1.2	-0.01
Medical history: Neoplasms						
Hematologic neoplasm	0.5	0.9	-0.05	0.5	0.5	0.00
Malignant lymphoma	0.2	0.3	-0.03	0.2	0.2	-0.01
Malignant neoplasm of anorectum	0.1	0.2	-0.02	0.1	0.1	0.00
Malignant neoplastic disease	4.2	5.8	-0.07	4.3	4.3	0.00
Malignant tumor of breast	0.7	1.0	-0.04	0.7	0.7	0.00
Malignant tumor of colon	0.2	0.3	-0.02	0.2	0.2	0.01
Malignant tumor of lung	0.1	0.5	-0.08	0.1	0.1	-0.01
Malignant tumor of urinary bladder	0.1	0.1	-0.01	0.1	0.1	0.01
Primary malignant neoplasm of prostate	0.5	0.5	0.00	0.5	0.5	0.00
Medication use						
Antibacterial agents for systemic use	48.8	52.8	-0.08	48.9	49.5	-0.01
Antidepressants	17.7	22.9	-0.13	17.9	17.9	0.00
Antiepileptics	6.2	11.3	-0.18	6.3	6.8	-0.02
Antinflammatory and antirheumatic products	24.0	27.4	-0.08	24.1	24.2	0.00
Antineoplastic agents	1.4	1.9	-0.04	1.4	1.4	0.00
Antipsoriatcs	0.4	0.4	-0.01	0.4	0.5	-0.02
Antithrombotic agents	3.3	9.5	-0.26	3.4	4.3	-0.04
Beta blocking agents	0.5	1.1	-0.07	0.5	0.7	-0.02
Calcium channel blockers	0.0	0.1	-0.02	0.0	0.0	-0.02
Diuretics	0.0	0.0	0.00	0.0	0.0	0.01
Drugs for acid related disorders	14.1	19.6	-0.15	14.3	14.2	0.00
Drugs for obstructive airway diseases	18.1	23.6	-0.14	18.2	18.5	-0.01
Drugs used in diabetes	15.6	5.5	0.33	15.1	15.5	-0.01
Immunosuppressants	1.5	2.1	-0.05	1.5	1.5	0.00
Lipid modifying agents	24.6	18.9	0.14	24.4	24.2	0.00
Opioids	15.2	21.7	-0.17	15.4	15.5	0.00
Psycholeptics	17.6	25.5	-0.20	17.8	18.2	-0.01
Psychostimulants, agents used for adhd and nootropics	2.9	6.1	-0.16	3.0	3.3	-0.02

Supplementary Table 5g: Baseline patient characteristics for ARB (T) and dCCB (C) new-users in the CCAE database. We report proportion of initiators satisfying selected baseline characteristics and the standardized difference of population proportions (StdDiff) before and after stratification. Less extreme StdDiff through stratification suggest improved balance between patient cohorts through propensity score adjustment.

Characteristic	Before stratification			After stratification		
	T (%)	C (%)	StdDiff	T (%)	C (%)	StdDiff
Age group						
00-04	0.0	0.1	-0.04	0.0	0.0	-0.02
05-09	0.0	0.1	-0.05	0.0	0.1	-0.04
10-14	0.0	0.3	-0.07	0.1	0.2	-0.02
15-19	0.3	1.1	-0.10	0.6	0.7	-0.01
20-24	0.9	2.2	-0.10	1.2	1.6	-0.03
25-29	2.0	4.6	-0.15	2.5	3.3	-0.04
30-34	4.4	7.5	-0.13	4.9	5.9	-0.04
35-39	7.5	9.5	-0.07	7.9	8.5	-0.02
40-44	11.9	11.5	0.01	11.9	11.5	0.01
45-49	16.4	14.3	0.06	15.8	15.2	0.02
50-54	19.3	16.5	0.07	18.6	17.8	0.02
55-59	19.3	16.3	0.08	18.5	17.9	0.01
60-64	16.5	14.6	0.05	16.4	15.8	0.02
65-69	1.4	1.3	0.01	1.4	1.5	0.00
70-74	0.0	0.0	0.00	0.0	0.0	0.00
75-79	0.0	0.0	0.00	0.0	0.0	0.00
80-84	0.0	0.0	0.00	0.0	0.0	0.00
Gender: female	40.3	47.7	-0.15	42.3	44.2	-0.04
Medical history: General						
Acute respiratory disease	26.0	25.1	0.02	26.0	25.6	0.01
Attention deficit hyperactivity disorder	1.1	1.2	0.00	1.2	1.1	0.01
Chronic liver disease	1.5	1.4	0.01	1.5	1.4	0.01
Chronic obstructive lung disease	2.0	2.3	-0.02	2.5	2.1	0.02
Crohn's disease	0.3	0.4	-0.01	0.3	0.3	0.00
Dementia	0.1	0.2	-0.02	0.1	0.2	0.00
Depressive disorder	6.5	7.1	-0.02	7.0	7.0	0.00
Diabetes mellitus	13.8	6.8	0.23	10.4	9.9	0.02
Gastroesophageal reflux disease	8.3	8.1	0.01	8.7	8.4	0.01
Gastrointestinal hemorrhage	2.0	2.0	0.00	2.1	2.0	0.00
Human immunodeficiency virus infection	0.2	0.4	-0.04	0.3	0.3	0.00
Hyperlipidemia	39.1	28.1	0.23	35.1	33.9	0.02
Hypertension disorder	100.0	100.0	0.00	100.0	100.0	0.00
Lesion of liver	0.2	0.5	-0.04	0.3	0.4	0.00
Obesity	7.3	9.4	-0.08	8.4	8.3	0.00
Osteoarthritis	12.2	11.2	0.03	12.4	11.9	0.01
Pneumonia	1.5	2.1	-0.04	1.9	1.8	0.01
Psoriasis	1.1	0.9	0.02	1.0	1.0	0.00
Renal impairment	1.2	2.4	-0.09	1.8	1.8	0.00
Rheumatoid arthritis	0.9	0.9	0.00	1.0	0.9	0.01
Schizophrenia	0.1	0.1	-0.02	0.1	0.1	0.00
Ulcerative colitis	0.3	0.3	0.00	0.3	0.3	0.00
Urinary tract infectious disease	5.6	7.1	-0.06	6.0	6.5	-0.02
Viral hepatitis C	0.4	0.5	-0.02	0.4	0.4	0.00
Visual system disorder	16.6	14.7	0.05	16.0	15.7	0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	0.5	0.4	0.01	0.5	0.5	0.01
Cerebrovascular disease	1.5	2.3	-0.06	2.2	1.9	0.02
Coronary arteriosclerosis	2.5	2.2	0.02	2.7	2.4	0.02
Heart disease	11.2	11.6	-0.01	12.2	11.8	0.01
Heart failure	0.5	0.7	-0.02	0.7	0.7	0.00
Ischemic heart disease	1.8	2.2	-0.03	2.3	2.1	0.02
Peripheral vascular disease	4.5	5.2	-0.03	5.1	4.9	0.01
Pulmonary embolism	0.2	0.4	-0.03	0.3	0.3	0.00
Venous thrombosis	1.1	1.3	-0.02	1.2	1.2	0.00
Medical history: Neoplasms						
Hematologic neoplasm	0.5	0.9	-0.05	0.7	0.7	0.00
Malignant lymphoma	0.2	0.3	-0.02	0.3	0.3	0.00
Malignant neoplasm of anorectum	0.1	0.2	-0.02	0.2	0.1	0.01
Malignant neoplastic disease	4.8	5.1	-0.01	5.0	5.0	0.00
Malignant tumor of breast	0.9	0.8	0.01	0.9	0.8	0.01
Malignant tumor of colon	0.2	0.3	-0.02	0.3	0.3	0.00
Malignant tumor of lung	0.1	0.3	-0.04	0.2	0.2	0.00
Malignant tumor of urinary bladder	0.1	0.1	0.00	0.1	0.1	0.00
Primary malignant neoplasm of prostate	0.6	0.6	0.00	0.5	0.6	0.00
Medication use						
Antibacterials for systemic use	50.1	50.2	0.00	50.0	50.3	-0.01
Antidepressants	17.2	15.2	0.06	16.4	16.7	-0.01
Antiepileptics	5.9	6.4	-0.02	6.5	6.2	0.01
Antinflammatory and antirheumatic products	23.6	27.3	-0.09	25.0	25.4	-0.01
Antineoplastic agents	1.5	1.8	-0.02	1.7	1.7	0.01
Antipsoriatics	0.5	0.4	0.01	0.5	0.5	0.00
Antithrombotic agents	2.9	4.0	-0.06	4.0	3.4	0.03
Beta blocking agents	0.5	0.5	0.00	0.5	0.5	0.00
Calcium channel blockers	0.0	0.0	-0.01	0.0	0.0	0.00
Diuretics	0.0	0.0	0.00	0.0	0.0	0.00
Drugs for acid related disorders	15.6	14.6	0.03	15.3	15.4	0.00
Drugs for obstructive airway diseases	19.2	19.0	0.00	19.5	19.2	0.01
Drugs used in diabetes	10.3	4.0	0.24	7.2	6.6	0.02
Immunosuppressants	1.7	2.0	-0.02	1.9	1.8	0.01
Lipid modifying agents	23.8	16.9	0.17	21.4	20.4	0.02
Opioids	14.8	19.2	-0.12	16.5	17.2	-0.02
Psycholeptics	18.2	18.0	0.01	18.8	18.2	0.02
Psychostimulants, agents used for adhd and nootropics	2.9	3.4	-0.03	3.2	3.2	0.00

Supplementary Table 5h: Baseline patient characteristics for ARB (T) and ndCCB (C) new-users in the CCAE database. We report proportion of initiators satisfying selected base-line characteristics and the standardized difference of population proportions (StdDiff) before and after stratification. Less extreme StdDiff through stratification suggest improved balance between patient cohorts through propensity score adjustment.

Characteristic	Before stratification			After stratification		
	T (%)	C (%)	StdDiff	T (%)	C (%)	StdDiff
Age group						
05-09	0.0	0.0	-0.02	0.0	0.0	-0.01
10-14	0.0	0.1	-0.03	0.0	0.1	-0.02
15-19	0.3	0.7	-0.05	0.4	0.4	0.00
20-24	0.9	1.6	-0.06	1.0	1.0	0.00
25-29	2.0	3.0	-0.07	2.1	2.0	0.00
30-34	4.4	5.3	-0.04	4.5	4.5	0.00
35-39	7.5	7.9	-0.02	7.6	7.6	0.00
40-44	11.9	10.9	0.03	11.8	11.6	0.01
45-49	16.4	14.7	0.04	16.2	16.4	0.00
50-54	19.3	17.3	0.05	19.1	19.0	0.00
55-59	19.3	18.4	0.02	19.2	18.8	0.01
60-64	16.5	18.1	-0.04	16.7	17.3	-0.02
65-69	1.4	1.8	-0.03	1.5	1.5	0.00
70-74	0.0	0.0	-0.02	0.0	0.0	-0.01
75-79	0.0	0.0	0.00	0.0	0.0	0.00
80-84	0.0	0.0	-0.01	0.0	0.0	0.00
Gender: female	40.3	53.0	-0.26	42.2	40.8	0.03
Medical history: General						
Acute respiratory disease	26.0	30.1	-0.09	26.4	27.0	-0.01
Attention deficit hyperactivity disorder	1.1	1.0	0.01	1.1	0.9	0.02
Chronic liver disease	1.5	1.6	-0.01	1.5	1.6	0.00
Chronic obstructive lung disease	2.0	5.2	-0.18	2.3	2.6	-0.02
Crohn's disease	0.3	0.5	-0.03	0.3	0.4	-0.02
Dementia	0.1	0.3	-0.04	0.1	0.1	0.00
Depressive disorder	6.5	9.9	-0.12	6.8	6.9	0.00
Diabetes mellitus	13.8	9.5	0.13	13.2	13.6	-0.01
Gastroesophageal reflux disease	8.3	11.3	-0.10	8.6	9.1	-0.02
Gastrointestinal hemorrhage	2.0	2.7	-0.05	2.1	2.2	-0.01
Human immunodeficiency virus infection	0.2	0.2	-0.01	0.2	0.2	-0.01
Hyperlipidemia	39.1	33.9	0.11	38.3	38.7	-0.01
Hypertensive disorder	100.0	100.0	0.00	100.0	100.0	0.00
Lesion of liver	0.2	0.4	-0.03	0.2	0.2	0.00
Obesity	7.3	8.3	-0.04	7.3	8.0	-0.02
Osteoarthritis	12.2	14.4	-0.06	12.4	12.7	-0.01
Pneumonia	1.5	3.5	-0.13	1.7	1.9	-0.02
Psoriasis	1.1	0.9	0.02	1.1	1.1	-0.01
Renal impairment	1.2	1.9	-0.06	1.2	1.6	-0.03
Rheumatoid arthritis	0.9	1.3	-0.04	1.0	0.9	0.00
Schizophrenia	0.1	0.1	-0.03	0.1	0.1	-0.01
Ulcerative colitis	0.3	0.4	-0.02	0.3	0.3	0.00
Urinary tract infectious disease	5.6	7.6	-0.08	5.8	6.0	-0.01
Viral hepatitis C	0.4	0.5	-0.01	0.4	0.4	-0.01
Visual system disorder	16.6	17.2	-0.02	16.6	16.0	0.02
Medical history: Cardiovascular disease						
Atrial fibrillation	0.5	10.1	-0.44	0.9	2.4	-0.13
Cerebrovascular disease	1.5	3.6	-0.14	1.7	1.8	0.00
Coronary arteriosclerosis	2.5	5.4	-0.15	2.8	3.1	-0.02
Heart disease	11.2	30.1	-0.48	12.8	14.7	-0.05
Heart failure	0.5	1.5	-0.10	0.6	0.7	-0.02
Ischemic heart disease	1.8	5.1	-0.18	2.2	2.4	-0.02
Peripheral vascular disease	4.5	7.2	-0.11	4.8	5.1	-0.01
Pulmonary embolism	0.2	0.7	-0.08	0.2	0.3	-0.01
Venous thrombosis	1.1	1.8	-0.06	1.1	1.2	0.00
Medical history: Neoplasms						
Hematologic neoplasm	0.5	0.9	-0.04	0.6	0.6	0.00
Malignant lymphoma	0.2	0.3	-0.02	0.2	0.3	-0.01
Malignant neoplasm of anorectum	0.1	0.2	-0.02	0.1	0.1	0.00
Malignant neoplastic disease	4.8	5.8	-0.05	4.8	5.0	-0.01
Malignant tumor of breast	0.9	1.0	-0.02	0.9	1.0	0.00
Malignant tumor of colon	0.2	0.3	-0.02	0.2	0.2	0.00
Malignant tumor of lung	0.1	0.5	-0.08	0.1	0.2	-0.02
Malignant tumor of urinary bladder	0.1	0.1	-0.01	0.1	0.1	0.00
Primary malignant neoplasm of prostate	0.6	0.5	0.00	0.5	0.6	-0.01
Medication use						
Antibacterials for systemic use	50.1	52.8	-0.05	50.4	50.6	-0.01
Antidepressants	17.2	22.9	-0.14	17.9	18.3	-0.01
Antiepileptics	5.9	11.3	-0.19	6.5	7.0	-0.02
Antiinflammatory and antirheumatic products	23.6	27.4	-0.09	24.0	23.9	0.00
Antineoplastic agents	1.5	1.9	-0.03	1.6	1.6	0.00
Antipsoriatics	0.5	0.4	0.01	0.5	0.5	0.00
Antithrombotic agents	2.9	9.5	-0.28	3.4	4.2	-0.05
Beta blocking agents	0.5	1.1	-0.06	0.5	0.6	-0.01
Calcium channel blockers	0.0	0.1	-0.03	0.0	0.0	-0.02
Diuretics	0.0	0.0	0.00	0.0	0.0	0.01
Drugs for acid related disorders	15.6	19.6	-0.10	16.1	16.4	-0.01
Drugs for obstructive airway diseases	19.2	23.6	-0.11	19.6	20.2	-0.01
Drugs used in diabetes	10.3	5.5	0.18	9.7	9.7	0.00
Immunosuppressants	1.7	2.1	-0.03	1.7	1.7	0.00
Lipid modifying agents	23.8	18.9	0.12	23.0	22.6	0.01
Opioids	14.8	21.7	-0.18	15.5	15.6	0.00
Psycholeptics	18.2	25.5	-0.18	19.1	19.1	0.00
Psychostimulants, agents used for adhd and nootropics	2.9	6.1	-0.15	3.3	3.5	-0.01

Supplementary Table 5i: Baseline patient characteristics for dCCB (T) and ndCCB (C) new-users in the CCAE database. We report proportion of initiators satisfying selected base-line characteristics and the standardized difference of population proportions (StdDiff) before and after stratification. Less extreme StdDiff through stratification suggest improved balance between patient cohorts through propensity score adjustment.

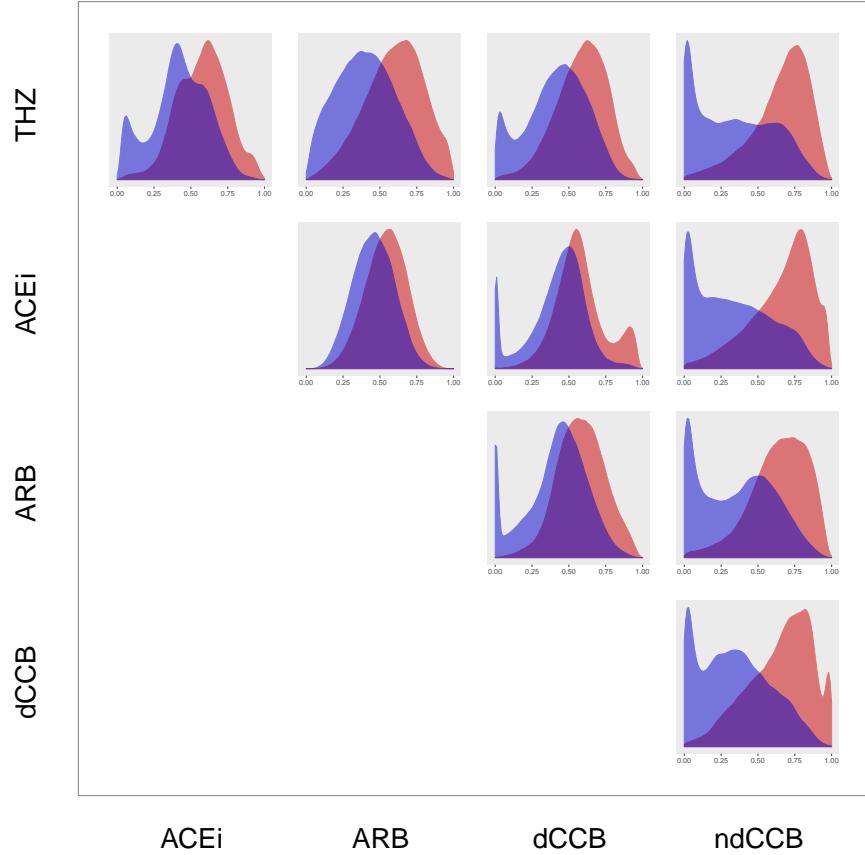
Characteristic	Before stratification			After stratification		
	T (%)	C (%)	StdDiff	T (%)	C (%)	StdDiff
Age group						
00-04	0.1	0.0	0.1	0.0	0.0	0.04
05-09	0.1	0.0	0.04	0.1	0.0	0.03
10-14	0.3	0.1	0.05	0.3	0.1	0.03
15-19	1.1	0.7	0.04	1.1	0.8	0.03
20-24	2.2	1.6	0.04	2.1	2.1	0.00
25-29	4.6	3.0	0.08	4.4	3.8	0.03
30-34	7.5	5.3	0.09	7.1	7.1	0.00
35-39	9.5	7.9	0.06	9.2	9.1	0.00
40-44	11.5	10.9	0.02	11.4	11.4	0.00
45-49	14.3	14.7	-0.01	14.4	14.7	-0.01
50-54	16.5	17.3	-0.02	16.7	16.8	0.00
55-59	16.3	18.4	-0.06	16.5	16.7	0.00
60-64	14.6	18.1	-0.09	15.1	16.0	-0.02
65-69	1.3	1.8	-0.04	1.4	1.3	0.01
70-74	0.0	0.0	-0.02	0.0	0.0	0.00
75-79	0.0	0.0	0.00	0.0	0.0	0.00
80-84	0.0	0.0	-0.01	0.0	0.0	0.00
Gender: female	47.7	53.0	-0.11	48.7	46.4	0.05
Medical history: General						
Acute respiratory disease	25.1	30.1	-0.11	25.8	25.7	0.00
Attention deficit hyperactivity disorder	1.2	1.0	0.02	1.1	1.0	0.02
Chronic liver disease	1.4	1.6	-0.01	1.4	1.5	0.00
Chronic obstructive lung disease	2.3	5.2	-0.15	2.7	2.8	-0.01
Crohn's disease	0.4	0.5	-0.02	0.4	0.4	0.00
Dementia	0.2	0.3	-0.02	0.2	0.2	0.01
Depressive disorder	7.1	9.9	-0.10	7.4	7.2	0.01
Diabetes mellitus	6.8	9.5	-0.10	7.2	7.2	0.00
Gastroesophageal reflux disease	8.1	11.3	-0.11	8.5	8.9	-0.01
Gastrointestinal hemorrhage	2.0	2.7	-0.05	2.1	2.2	-0.01
Human immunodeficiency virus infection	0.4	0.2	0.03	0.3	0.3	0.00
Hyperlipidemia	28.1	33.9	-0.12	28.7	29.6	-0.02
Hypertension disorder	100.0	100.0	0.00	100.0	100.0	0.00
Lesion of liver	0.5	0.4	0.01	0.5	0.4	0.01
Obesity	9.4	8.3	0.04	9.1	9.1	0.00
Osteoarthritis	11.2	14.4	-0.09	11.6	12.1	-0.02
Pneumonia	2.1	3.5	-0.09	2.2	2.3	-0.01
Psoriasis	0.9	0.9	0.00	0.9	1.0	-0.01
Renal impairment	2.4	1.9	0.04	2.3	2.9	-0.03
Rheumatoid arthritis	0.9	1.3	-0.04	1.0	1.0	0.00
Schizophrenia	0.1	0.1	-0.01	0.1	0.1	0.00
Ulcerative colitis	0.3	0.4	-0.02	0.3	0.3	0.00
Urinary tract infectious disease	7.1	7.6	-0.02	7.2	7.3	-0.01
Viral hepatitis C	0.5	0.5	0.00	0.5	0.5	0.00
Visual system disorder	14.7	17.2	-0.07	15.0	15.0	0.00
Medical history: Cardiovascular disease						
Atrial fibrillation	0.4	10.1	-0.44	0.7	2.5	-0.14
Cerebrovascular disease	2.3	3.6	-0.08	2.5	3.0	-0.03
Coronary arteriosclerosis	2.2	5.4	-0.17	2.7	2.8	0.00
Heart disease	11.6	30.1	-0.47	13.2	14.9	-0.05
Heart failure	0.7	1.5	-0.07	0.8	0.9	-0.02
Ischemic heart disease	2.2	5.1	-0.16	2.6	2.8	-0.01
Peripheral vascular disease	5.2	7.2	-0.08	5.4	6.4	-0.04
Pulmonary embolism	0.4	0.7	-0.05	0.4	0.5	-0.01
Venous thrombosis	1.3	1.8	-0.04	1.3	1.3	0.00
Medical history: Neoplasms						
Hematologic neoplasm	0.9	0.9	0.00	0.9	0.8	0.01
Malignant lymphoma	0.3	0.3	0.00	0.3	0.3	0.00
Malignant neoplasm of anorectum	0.2	0.2	-0.01	0.2	0.2	-0.01
Malignant neoplastic disease	5.1	5.8	-0.03	5.1	5.1	0.00
Malignant tumor of breast	0.8	1.0	-0.03	0.8	0.7	0.01
Malignant tumor of colon	0.3	0.3	0.00	0.3	0.4	-0.01
Malignant tumor of lung	0.3	0.5	-0.04	0.3	0.3	0.00
Malignant tumor of urinary bladder	0.1	0.1	0.00	0.1	0.1	0.00
Primary malignant neoplasm of prostate	0.6	0.5	0.00	0.5	0.5	0.01
Medication use						
Antibacterials for systemic use	50.2	52.8	-0.05	50.4	50.0	0.01
Antidepressants	15.2	22.9	-0.20	16.2	16.1	0.00
Antiepileptics	6.4	11.3	-0.17	6.9	7.3	-0.02
Antinflammatory and antirheumatic products	27.3	27.4	0.00	27.2	25.7	0.03
Antineoplastic agents	1.8	1.9	-0.01	1.8	1.9	-0.01
Antipsoriatics	0.4	0.4	0.00	0.4	0.4	0.00
Antithrombotic agents	4.0	9.5	-0.22	4.3	5.4	-0.05
Beta blocking agents	0.5	1.1	-0.06	0.5	0.6	-0.01
Calcium channel blockers	0.0	0.1	-0.02	0.0	0.1	-0.03
Diuretics	0.0	0.0	0.00	0.0	0.0	0.01
Drugs for acid related disorders	14.6	19.6	-0.13	15.3	15.2	0.00
Drugs for obstructive airway diseases	19.0	23.6	-0.11	19.5	19.4	0.00
Drugs used in diabetes	4.0	5.5	-0.07	4.3	4.2	0.00
Immunosuppressants	2.0	2.1	-0.01	2.0	2.0	0.00
Lipid modifying agents	16.9	18.9	-0.05	17.1	18.2	-0.03
Opioids	19.2	21.7	-0.06	19.4	19.0	0.01
Psycholeptics	18.0	25.5	-0.18	18.9	19.2	-0.01
Psychostimulants, agents used for adhd and nootropics	3.4	6.1	-0.13	3.7	3.7	0.00

Propensity score (PS) models and balance

To build large-scale PS models, we systematically engineered and extracted a large, consistent set of baseline patient characteristics that included:

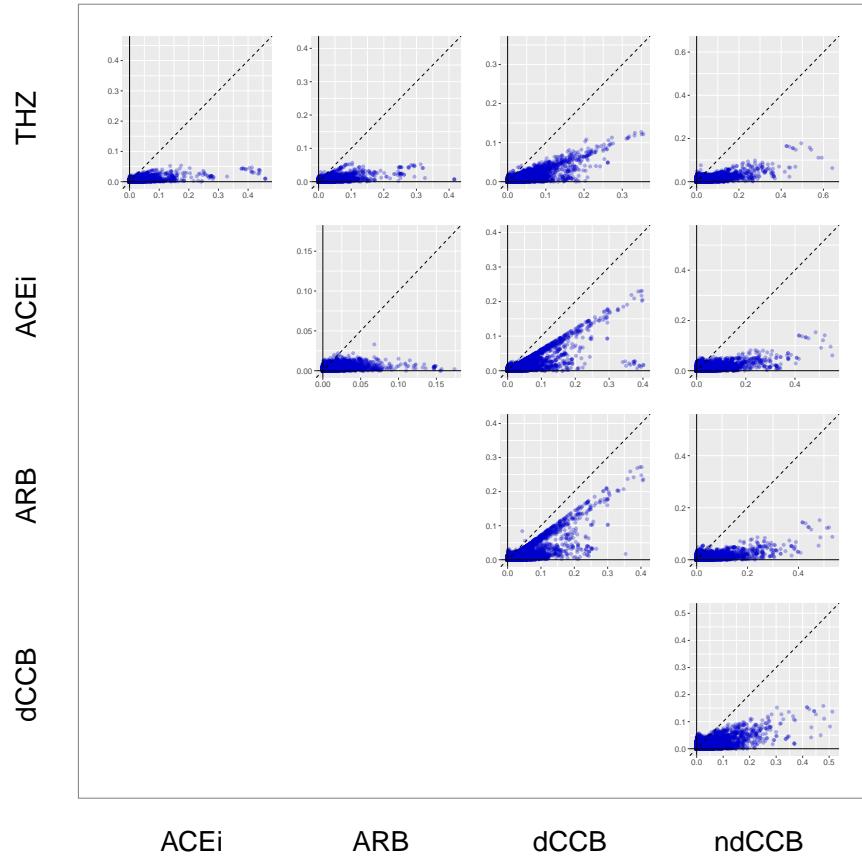
- Demographics (age in 5-year bands, gender, index year, index month)
- Conditions (condition occurrence in lookback window)
 - in 365 days prior to index date
 - in 30 days prior to index date
- Condition aggregation
 - SMOMED
- Drugs (drug occurrence in lookback window)
 - in 365 days prior to index date
 - in 30 days prior to index date
- Drug aggregation
 - Ingredient
 - ATC class
- Procedures (occurrence in look-back window)
 - in 365 days prior to index date
 - in 30 days prior to index date
- Observations (occurrence in look-back window)
 - in 365 days prior to index date
 - in 30 days prior to index date
- Measurements (including laboratories)
 - Within normal
 - Above normal range
 - Below normal range
- Comorbidity or risk scores (including Charlson, DCSI, CHADS2, CHADS2VASc)

We exclude all covariates that occur in fewer than 0.1% of patients within the target and comparator cohorts prior to model fitting for computational efficiency.



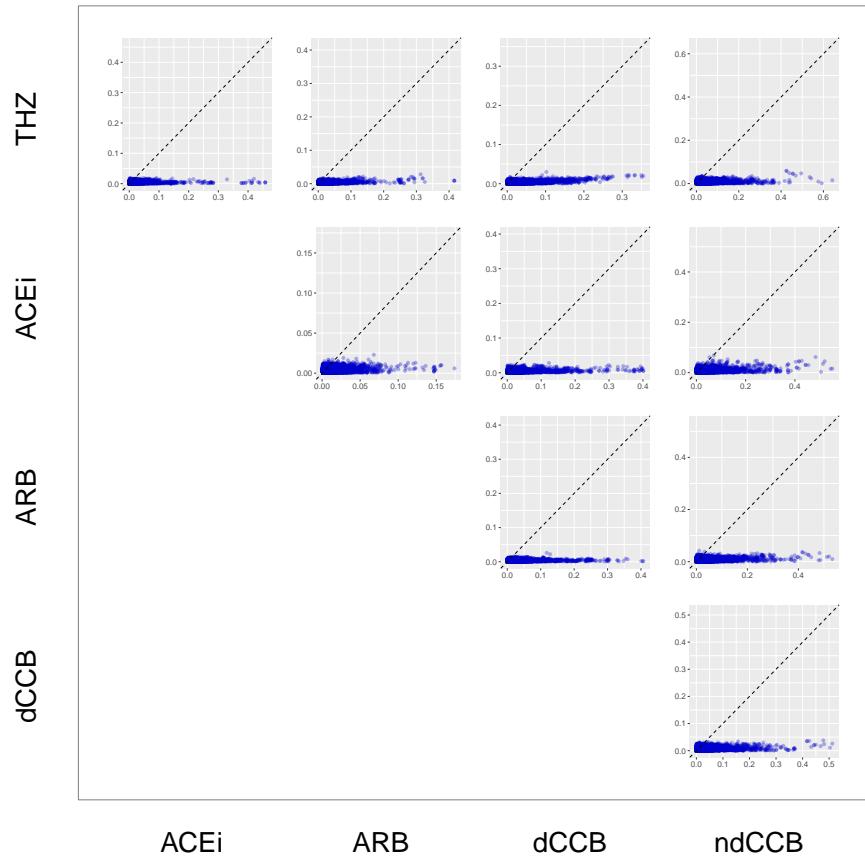
Supplementary Figure 1: Preference score distributions comparing THZ, ACEi, ARB, dCCB and ndCCB new-users in CCAE. The preference score is a transformation of the propensity score that adjusts for prevalence differences between populations. For each class pair, we fit a large-scale propensity score model using >40,000 baseline patient characteristics. A higher overlap between score distributions indicates that patients in the target (left, red) and comparator (bottom, blue) populations are more similar in terms of their predicted probability of receiving one treatment over the other. We define clinical empirical equipoise when a majority of patients in both populations carry preference scores between 0.3 and 0.7. We achieve equipoise in all comparisons.

PS-stratification



Supplementary Figure 2: Patient characteristic balance for THZ, ACEi, ARB, dCCB or ndCCB new-users before and after large-scale PS-stratification. Each dot represents the standardized difference of means for a single covariate before (x-axis) and after (y-axis) stratification. Interested readers should visit the LEGEND-HTN results website (<http://data.ohdsi.org/LegendBasicViewer/>) where they can interactively hover the mouse arrow over individual dots for more covariate details.

PS-matching



Supplementary Figure 3: Patient characteristic balance for THZ, ACEi, ARB, dCCB or ndCCB new-users before and after large-scale PS-matching. Each dot represents the standardized difference of means for a single covariate before (x-axis) and after (y-axis) stratification. Interested readers should visit the LEGEND-HTN results website (<http://data.ohdsi.org/LegendBasicViewer/>) where they can interactively hover the mouse arrow over individual dots for more covariate details.

Comparative cohorts and events

Under an on-treatment, PS-stratified design

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Supplementary Table 6: Patient cohort sizes and primary effectiveness events for THZ, ACEi, ARB, dCCB and ndCCB new-user comparisons under an on-treatment, PS-stratified design. We report total number of stratified patients evaluated in each pair-wise comparison, their total follow-up time (in years), number of incident primary efficacy events, and computed event incidence rate (IR) per 1,000 patient years (PY) in patient cohorts. We also report for each comparison a minimum detectable relative risk (MDRR). Note that the IR does not account for any stratification or propensity score adjustment.

Target (T)	Comp. (C)	Patients			PYs			Events			IR		
		T	C	T	C	T	C	T	C	T	C	MDRR	
THZ	ACEi	819,076	2,240,983	496,513	1,437,207	1,325	5,966	2,67	4,15	1,08			
THZ	ARB	819,033	661,227	496,385	478,782	1,325	1,699	2,67	3,55	1,11			
THZ	dCCB	819,080	716,583	496,513	425,004	1,325	2,003	2,67	4,71	1,10			
THZ	ndCCB	808,499	135,712	484,401	87,618	1,276	736	2,63	8,40	1,19			
ACEi	ARB	2,240,845	661,190	1,436,835	478,781	5,960	1,699	4,15	3,55	1,08			
ACEi	dCCB	2,240,991	716,560	1,437,222	425,008	5,967	2,003	4,15	4,71	1,08			
ACEi	ndCCB	2,229,462	135,712	1,424,315	87,618	5,876	736	4,13	8,40	1,16			
Acute myocardial infarction	dCCB	714,532	764,774	545,202	470,604	1,769	2,047	3,24	4,35	1,10			
Acute myocardial infarction	ndCCB	642,542	135,712	457,668	87,618	1,640	736	3,58	8,40	1,16			
dCCB	ndCCB	682,067	135,712	390,349	87,618	1,900	736	4,87	8,40	1,16			
THZ	ACEi	817,106	2,237,088	495,211	1,434,943	1,957	8,172	3,95	5,69	1,06			
THZ	ARB	817,064	659,692	495,086	477,658	1,956	2,468	3,95	5,17	1,09			
THZ	dCCB	817,110	713,145	495,211	422,774	1,957	3,398	3,95	8,04	1,08			
THZ	ndCCB	806,648	133,463	483,348	85,598	1,841	1,890	3,81	22,08	1,14			
ACEi	ARB	2,236,971	659,655	1,434,619	477,657	8,165	2,468	5,69	5,17	1,07			
ACEi	dCCB	2,237,096	713,122	1,434,958	422,778	8,172	3,398	5,69	8,04	1,06			
ACEi	ndCCB	2,225,746	133,463	1,422,513	85,598	7,967	1,890	5,60	22,08	1,13			
ACEi	dCCB	712,912	761,218	543,676	468,192	2,784	3,547	5,12	7,58	1,07			
ACEi	ndCCB	641,034	133,463	456,578	85,598	2,364	1,890	5,18	22,08	1,12			
ACEi	ndCCB	678,742	133,463	388,299	85,598	3,243	1,890	8,35	22,08	1,11			
THZ	ACEi	815,144	2,222,271	493,386	1,423,784	1,720	6,781	3,49	4,76	1,07			
THZ	ARB	815,102	657,776	493,252	475,434	1,718	1,991	3,48	4,19	1,10			
THZ	dCCB	815,148	706,597	493,386	417,219	1,720	2,775	3,49	6,65	1,09			
THZ	ndCCB	804,768	134,472	481,621	86,501	1,622	819	3,37	9,47	1,18			
ACEi	ARB	2,222,135	657,740	1,423,405	475,434	6,775	1,991	4,76	4,19	1,07			
ACEi	dCCB	2,222,279	706,575	1,423,799	417,223	6,782	2,775	4,76	6,65	1,07			
ACEi	ndCCB	2,211,115	134,472	1,411,389	86,501	6,609	819	4,68	9,47	1,15			
ACEi	dCCB	710,701	754,216	541,224	462,297	2,186	2,909	4,04	6,29	1,08			
ACEi	ndCCB	639,498	134,472	454,987	86,501	1,833	819	4,03	9,47	1,15			
dCCB	ndCCB	672,644	134,472	383,208	86,501	2,491	819	6,50	9,47	1,14			

Under an intent-to-treat, PS-stratified design

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Supplementary Table 7: Patient cohort sizes and primary effectiveness events for THZ, ACEi, ARB, dCCB and ndCCB new-user comparisons under an intent-to-treatment, PS-stratified design. We report total number of stratified patients evaluated in each pair-wise comparison, their total follow-up time (in years), number of incident primary efficacy events, and computed event incidence rate (IR) per 1,000 patient years (PY) in patient cohorts. We also report for each comparison a minimum detectable relative risk (MDRR). Note that the IR does not account for any stratification or propensity score adjustment.

Target (T)	Comp. (C)	Patients			PYs			Events			IR		
		T	C	T	C	T	C	T	C	T	C	MDRR	
THZ	ACEi	822,775	2,248,845	2,719,319	6,806,120	8,837	28,825	3.25	4.24	1.03			
THZ	ARB	822,728	665,388	2,718,905	2,060,909	8,835	8,160	3.25	3.96	1.04			
THZ	dCCB	822,779	723,548	2,719,319	2,098,342	8,837	10,554	3.25	5.03	1.04			
THZ	ndCCB	810,281	137,249	2,645,132	466,561	8,516	3,511	3.22	7.53	1.08			
ACEi	ARB	2,248,702	665,349	6,804,645	2,060,908	28,801	8,160	4.23	3.96	1.04			
ACEi	dCCB	2,248,853	723,517	6,806,205	2,098,370	28,826	10,555	4.24	5.03	1.03			
ACEi	ndCCB	2,233,738	137,249	6,724,310	466,561	28,314	3,511	4.21	7.53	1.07			
ACEi	dCCB	718,755	775,127	2,208,880	2,222,373	8,348	10,675	3.78	4.80	1.04			
ARB	ndCCB	644,160	137,249	1,969,746	466,561	7,871	3,511	4.00	7.53	1.07			
ARB	ndCCB	683,716	137,249	1,883,748	466,561	9,718	3,511	5.16	7.53	1.07			
THZ	ACEi	820,749	2,244,813	2,700,044	6,761,760	15,783	47,084	5.85	6.96	1.03			
THZ	ARB	820,706	663,800	2,699,652	2,046,074	15,771	13,725	5.84	6.71	1.03			
THZ	dCCB	820,753	720,035	2,700,044	2,072,283	15,783	19,900	5.85	9.60	1.03			
THZ	ndCCB	808,422	134,959	2,628,075	450,655	15,098	8,521	5.74	18.91	1.05			
ACEi	ARB	2,244,693	663,761	6,760,494	2,046,072	47,043	13,725	6.96	6.71	1.03			
ACEi	dCCB	2,244,821	720,003	6,761,837	2,072,312	47,086	19,901	6.96	9.60	1.03			
ACEi	ndCCB	2,230,016	134,959	6,683,516	450,655	46,000	8,521	6.88	18.91	1.05			
ACEi	dCCB	717,080	771,447	2,192,882	2,195,482	14,411	20,322	6.57	9.26	1.03			
ARB	ndCCB	642,642	134,959	1,956,030	450,655	13,191	8,521	6.74	18.91	1.05			
ARB	ndCCB	680,374	134,959	1,859,883	450,655	18,427	8,521	9.91	18.91	1.05			
THZ	ACEi	818,791	2,229,962	2,702,543	6,753,792	11,140	32,713	4.12	4.84	1.03			
THZ	ARB	818,745	661,881	2,702,131	2,049,813	11,129	9,477	4.12	4.62	1.04			
THZ	dCCB	818,795	713,311	2,702,544	2,065,818	11,140	14,293	4.12	6.92	1.04			
THZ	ndCCB	806,545	135,998	2,631,079	461,752	10,454	4,150	3.97	8.99	1.07			
ACEi	ARB	2,229,820	661,843	6,752,315	2,049,812	32,686	9,477	4.84	4.62	1.03			
ACEi	dCCB	2,229,970	713,279	6,753,856	2,065,851	32,716	14,295	4.84	6.92	1.03			
ACEi	ndCCB	2,215,339	135,998	6,675,681	461,752	31,763	4,150	4.76	8.99	1.07			
ARB	dCCB	714,869	764,165	2,196,599	2,187,975	9,872	14,645	4.49	6.69	1.04			
ARB	ndCCB	641,103	135,998	1,961,762	461,752	8,746	4,150	4.46	8.99	1.07			
dCCB	ndCCB	674,232	135,998	1,858,163	461,752	12,254	4,150	6.59	8.99	1.06			

Under an on-treatment, PS-matched design

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Supplementary Table 8: Patient cohort sizes and primary effectiveness events for THZ, ACEi, ARB, dCCB and ndCCB new-user comparisons under an on-treatment, PS-matched design. We report total number of stratified patients evaluated in each pair-wise comparison, their total follow-up time (in years), number of incident primary efficacy events, and computed event incidence rate (IR) per 1,000 patient years (PY) in patient cohorts. We also report for each comparison a minimum detectable relative risk (MDRR). Note that the IR does not account for any stratification or propensity score adjustment.

Target (T)	Comp. (C)	Patients			PYs			Events			IR		
		T	C	T	C	T	C	T	C	T	C	MDRR	
THZ	ACEi	748,214	2,240,609	456,864	1,436,952	1,242	5,965	2,72	4,15	1,08			
THZ	ARB	442,166	660,848	269,069	478,470	845	1,698	3,14	3,55	1,12			
THZ	dCCB	488,243	716,077	276,313	424,868	938	2,001	3,39	4,71	1,11			
THZ	ndCCB	104,153	135,312	60,574	87,402	294	733	4,85	8,39	1,19			
ACEi	ARB	647,096	661,158	427,379	478,767	1,746	1,699	4,09	3,55	1,10			
ACEi	dCCB	625,970	715,602	377,862	424,783	1,908	2,001	5,05	4,71	1,09			
ACEi	ndCCB	123,154	135,603	80,737	87,568	560	734	6,94	8,38	1,17			
ACEi	imfarctial	498,301	737,277	365,943	466,433	1,267	2,043	3,46	4,38	1,10			
ACEi	ndCCB	105,652	135,143	72,696	87,277	389	729	5,35	8,35	1,18			
dCCB	ndCCB	111,015	135,442	71,258	87,403	449	734	6,30	8,40	1,18			
THZ	ACEi	746,259	2,236,675	455,585	1,434,664	1,769	8,164	3,88	5,69	1,07			
THZ	ARB	440,971	659,323	268,418	477,357	1,167	2,464	4,35	5,16	1,10			
THZ	dCCB	486,605	712,640	275,246	422,638	1,415	3,395	5,14	8,03	1,09			
THZ	ndCCB	103,242	132,925	60,147	85,342	568	1,864	9,44	21,84	1,12			
ACEi	ARB	645,510	659,622	426,381	477,643	2,445	2,468	5,73	5,17	1,08			
ACEi	dCCB	623,015	712,105	375,827	422,547	3,089	3,398	8,22	8,04	1,07			
ACEi	ndCCB	121,586	133,341	79,716	85,526	1,247	1,885	15,64	22,04	1,11			
ACEi	dCCB	496,889	733,446	364,746	463,984	2,035	3,525	5,58	7,60	1,08			
ACEi	ndCCB	104,775	132,948	72,118	85,309	819	1,862	11,36	21,83	1,12			
dCCB	ndCCB	109,959	133,219	70,508	85,415	948	1,875	13,45	21,95	1,11			
THZ	ACEi	744,356	2,221,770	453,756	1,423,418	1,571	6,772	3,46	4,76	1,07			
THZ	ARB	439,762	657,439	267,290	475,169	1,007	1,989	3,77	4,19	1,11			
THZ	dCCB	484,706	706,031	273,686	417,064	1,245	2,774	4,55	6,65	1,09			
THZ	ndCCB	103,220	134,069	59,983	86,284	379	815	6,32	9,45	1,18			
ACEi	ARB	643,915	657,707	425,177	475,419	1,917	1,991	4,51	4,19	1,09			
ACEi	dCCB	616,861	705,626	371,519	417,002	2,451	2,772	6,60	6,65	1,08			
ACEi	ndCCB	122,118	134,365	80,080	86,447	654	819	8,17	9,47	1,16			
ARB	dCCB	494,754	726,710	362,540	458,142	1,634	2,883	4,51	6,29	1,09			
ARB	ndCCB	104,896	133,895	72,115	86,157	484	814	6,71	9,45	1,17			
dCCB	ndCCB	109,925	134,210	70,412	86,289	533	816	7,57	9,46	1,17			

Under an intent-to-treat, PS-matched design

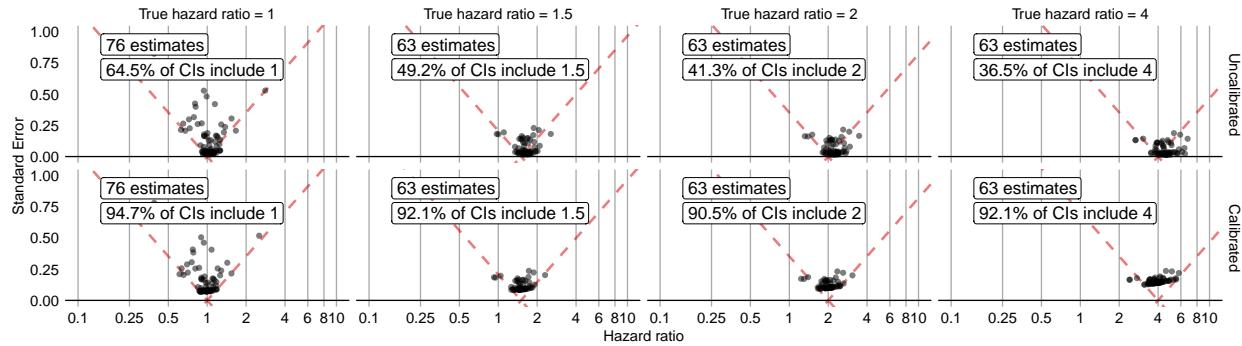
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Supplementary Table 9: Patient cohort sizes and primary effectiveness events for THZ, ACEi, ARB, dCCB and ndCCB new-user comparisons under an intent-to-treatment, PS-matched design. We report total number of stratified patients evaluated in each pair-wise comparison, their total follow-up time (in years), number of incident primary efficacy events, and computed event incidence rate (IR) per 1,000 patient years (PY) in patient cohorts. We also report for each comparison a minimum detectable relative risk (MDRR). Note that the IR does not account for any stratification or propensity score adjustment.

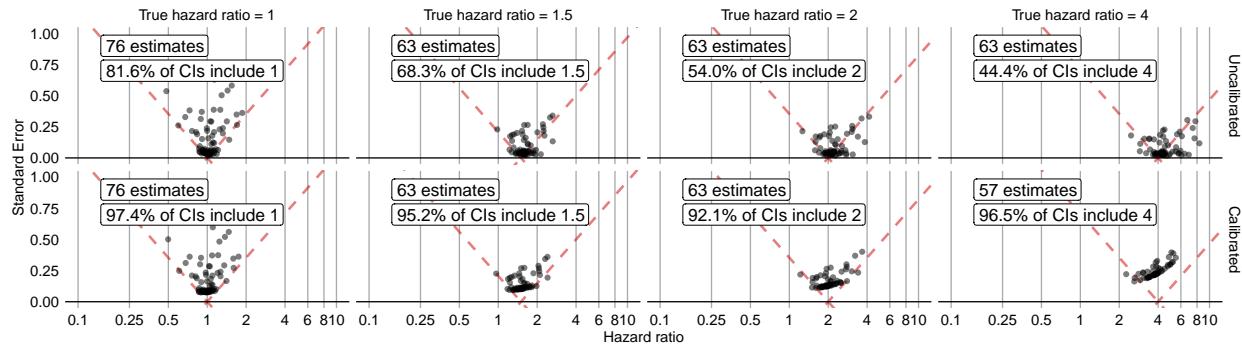
Target (T)	Comp. (C)	Patients			PYs			Events			IR		
		T	C	T	C	T	C	T	C	T	C	MDRR	
THZ	ACEi	751,086	2,248,479	2,457,470	6,805,125	8,152	28,810	3,32	4,23	1.03			
THZ	ARB	444,561	665,026	1,418,466	2,060,080	5,433	8,155	3,83	3,96	1.05			
THZ	dCCB	490,965	722,986	1,486,171	2,097,078	6,149	10,547	4,14	5,03	1.05			
THZ	ndCCB	104,659	136,813	382,770	465,654	2,205	3,491	5,76	7,50	1.08			
ACEi	ARB	650,900	665,316	1,976,316	2,060,859	8,256	8,160	4,18	3,96	1.04			
ACEi	dCCB	629,384	722,381	1,805,916	2,095,644	9,040	10,552	5,01	5,04	1.04			
ACEi	ndCCB	123,987	137,140	442,693	466,372	2,883	3,505	6,51	7,52	1.07			
ARB	dCCB	501,807	746,789	1,488,889	2,160,801	5,907	10,638	3,97	4,92	1.05			
ARB	ndCCB	106,193	136,676	387,300	465,382	2,235	3,493	5,77	7,51	1.08			
dCCB	ndCCB	111,630	136,975	397,046	465,860	2,681	3,501	6,75	7,52	1.07			
THZ	ACEi	749,091	2,244,409	2,440,182	6,760,743	14,229	47,040	5,83	6,96	1.03			
THZ	ARB	443,337	663,444	1,408,045	2,045,266	9,406	13,711	6,68	6,70	1.04			
THZ	dCCB	489,282	719,479	1,472,047	2,071,063	11,064	19,891	7,52	9,60	1.03			
THZ	ndCCB	103,742	134,375	375,011	449,487	4,732	8,441	12,62	18,78	1.05			
ACEi	ARB	649,263	663,727	1,960,772	2,046,024	13,959	13,723	7,12	6,71	1.03			
ACEi	dCCB	626,359	718,811	1,783,329	2,069,554	16,774	19,892	9,41	9,61	1.03			
ACEi	ndCCB	122,395	134,835	429,733	450,431	6,739	8,506	15,68	18,88	1.05			
ACEi	dCCB	500,336	742,843	1,476,157	2,133,558	10,635	20,216	7,20	9,48	1.03			
ARB	ndCCB	105,304	134,440	379,144	449,625	4,853	8,445	12,80	18,78	1.05			
dCCB	ndCCB	110,556	134,711	387,686	450,046	5,887	8,485	15,18	18,85	1.05			
THZ	ACEi	747,186	2,229,464	2,442,180	6,752,188	10,022	32,688	4,10	4,84	1.03			
THZ	ARB	442,119	661,556	1,409,897	2,049,085	6,413	9,466	4,55	4,62	1.05			
THZ	dCCB	487,388	712,710	1,472,909	2,064,513	7,550	14,281	5,13	6,92	1.04			
THZ	ndCCB	103,721	135,554	378,954	460,836	2,715	4,130	7,16	8,96	1.07			
ACEi	ARB	647,667	661,809	1,966,499	2,049,762	9,460	9,477	4,81	4,62	1.04			
ACEi	dCCB	620,155	712,157	1,778,545	2,063,167	11,358	14,287	6,39	6,92	1.04			
ACEi	ndCCB	122,936	135,891	438,688	461,556	3,560	4,147	8,12	8,98	1.07			
ARB	dCCB	498,189	735,865	1,477,026	2,126,274	7,327	14,531	4,96	6,83	1.04			
ARB	ndCCB	105,433	135,419	384,387	460,574	2,600	4,124	6,76	8,95	1.07			
dCCB	ndCCB	110,513	135,732	393,372	461,050	3,300	4,137	8,39	8,97	1.07			

Systematic error control

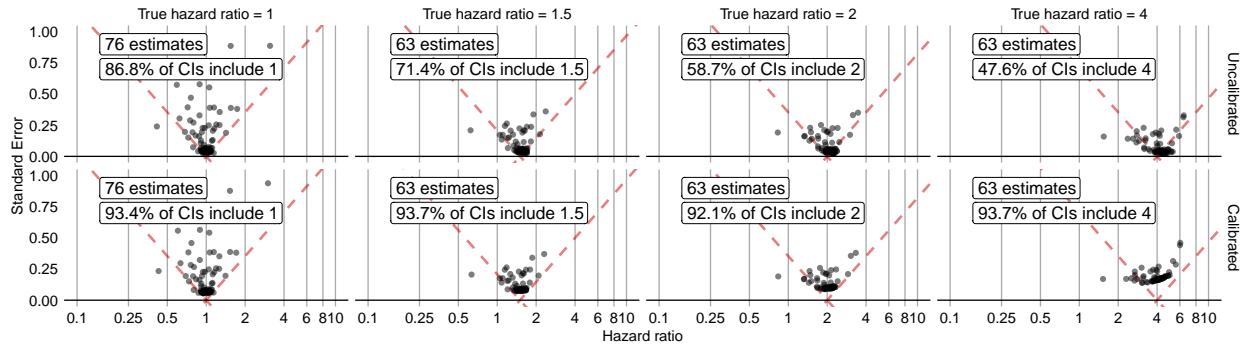
Under an on-treatment, PS-stratified design



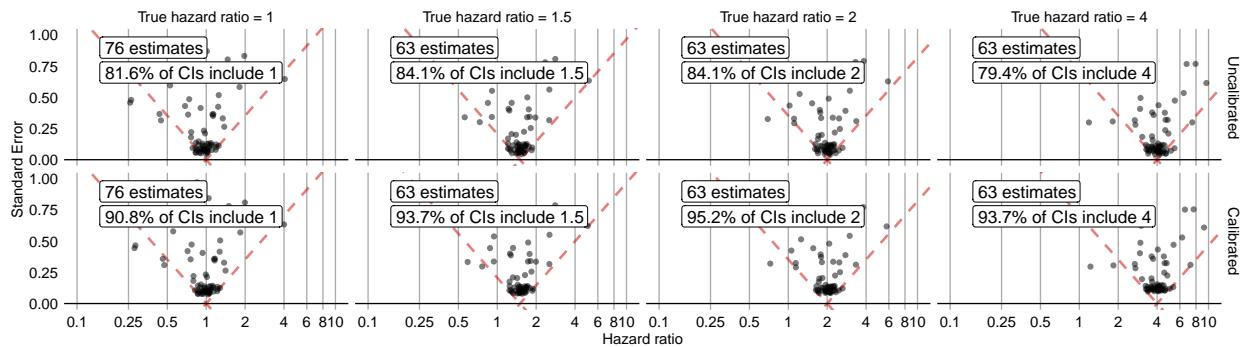
Supplementary Figure 4a: Systematic error control of effect estimation comparing THZ and ACEi new-users in the CCAE database under an on-treatment, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration. The left plots with hazard ratios = 1 present negative controls, while plots with hazard ratios > 1 present synthetic positive controls.



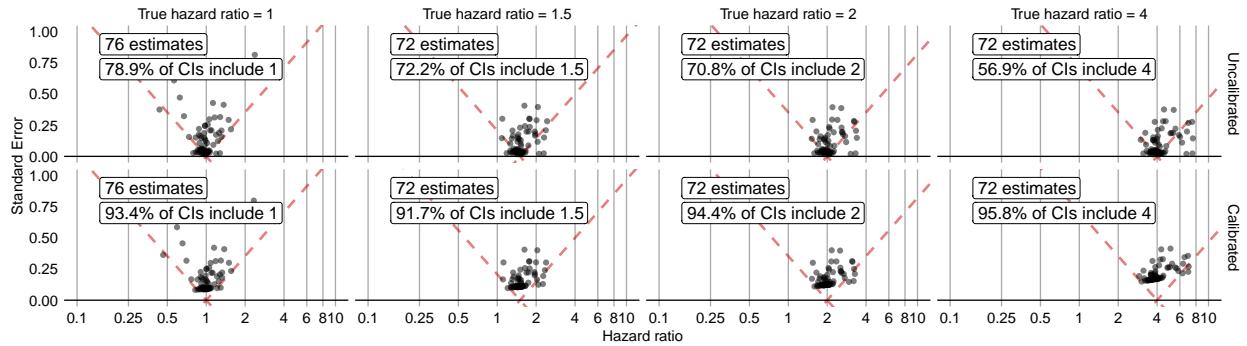
Supplementary Figure 4b: Systematic error control of effect estimation comparing THZ and ARB new-users in the CCAE database under an on-treatment, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration. The left plots with hazard ratios = 1 present negative controls, while plots with hazard ratios > 1 present synthetic positive controls.



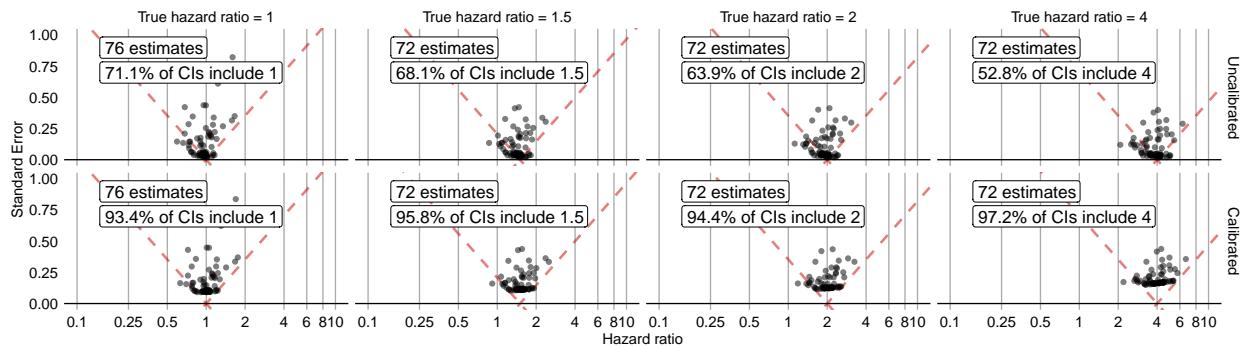
Supplementary Figure 4c: Systematic error control of effect estimation comparing THZ and dCCB new-users in the CCAE database under an on-treatment, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration. The left plots with hazard ratios = 1 present negative controls, while plots with hazard ratios > 1 present synthetic positive controls.



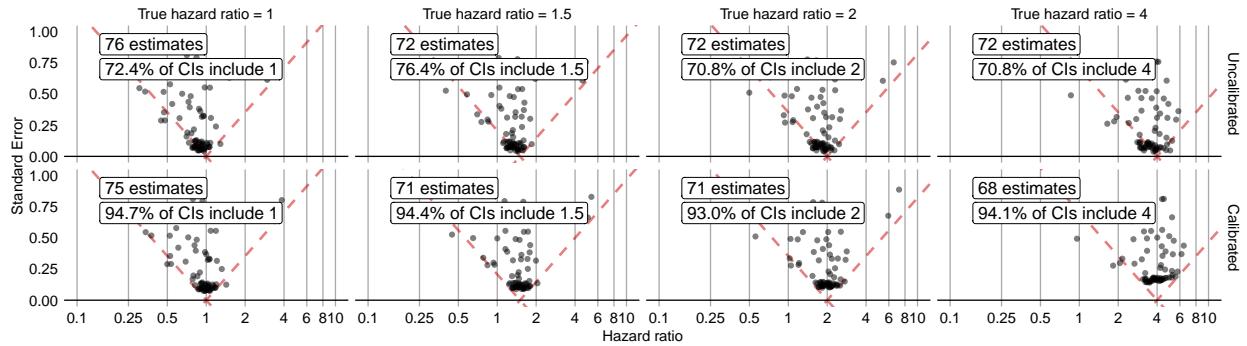
Supplementary Figure 4d: Systematic error control of effect estimation comparing THZ and ndCCB new-users in the CCAE database under an on-treatment, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration. The left plots with hazard ratios = 1 present negative controls, while plots with hazard ratios > 1 present synthetic positive controls.



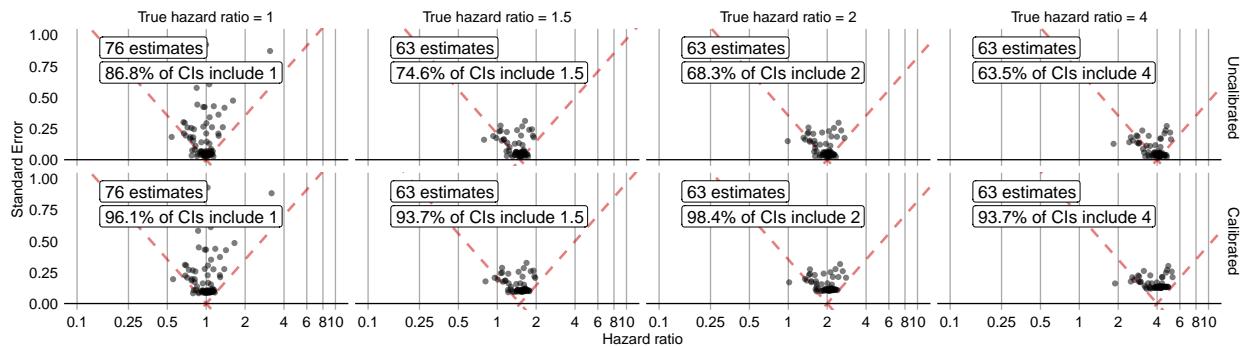
Supplementary Figure 4e: Systematic error control of effect estimation comparing ACEi and ARB new-users in the CCAE database under an on-treatment, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration. The left plots with hazard ratios = 1 present negative controls, while plots with hazard ratios > 1 present synthetic positive controls.



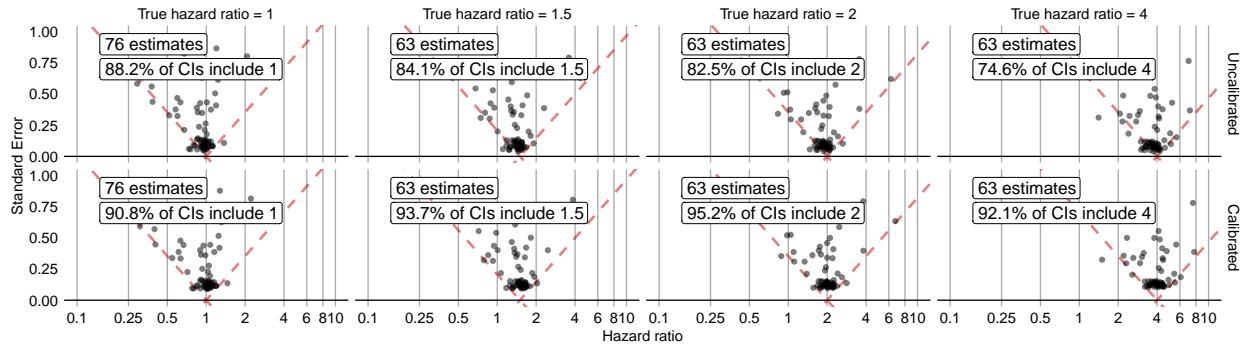
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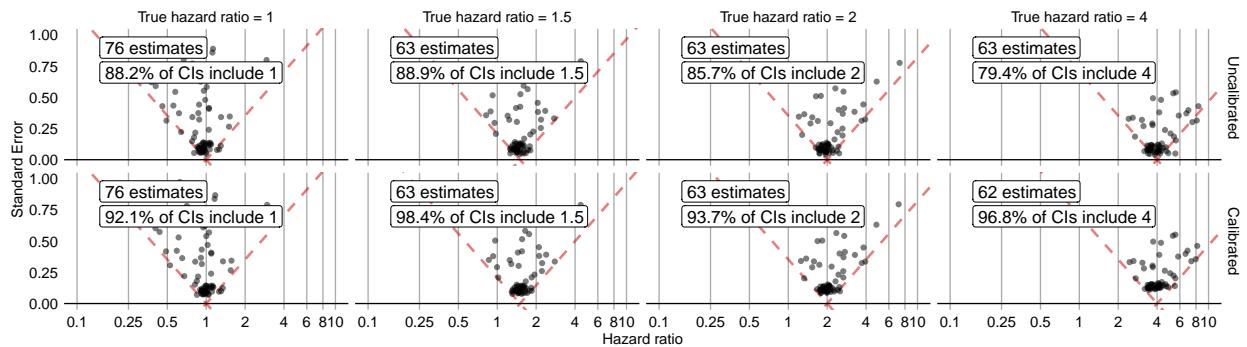
Supplementary Figure 4g: Systematic error control of effect estimation comparing ACEi and ndCCB new-users in the CCAE database under an on-treatment, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration. The left plots with hazard ratios = 1 present negative controls, while plots with hazard ratios > 1 present synthetic positive controls.



Supplementary Figure 4h: Systematic error control of effect estimation comparing ARB and dCCB new-users in the CCAE database under an on-treatment, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration. The left plots with hazard ratios = 1 present negative controls, while plots with hazard ratios > 1 present synthetic positive controls.

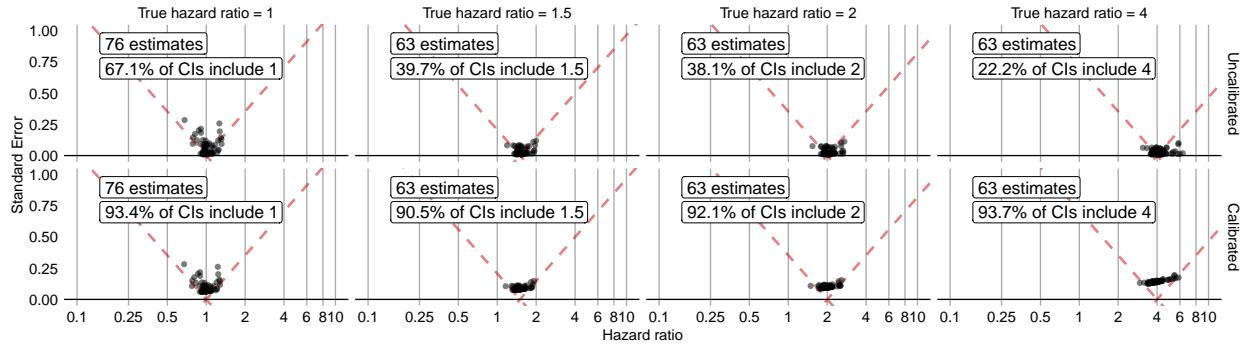


Supplementary Figure 4i: Systematic error control of effect estimation comparing ARB and ndCCB new-users in the CCAE database under an on-treatment, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration. The left plots with hazard ratios = 1 present negative controls, while plots with hazard ratios > 1 present synthetic positive controls.

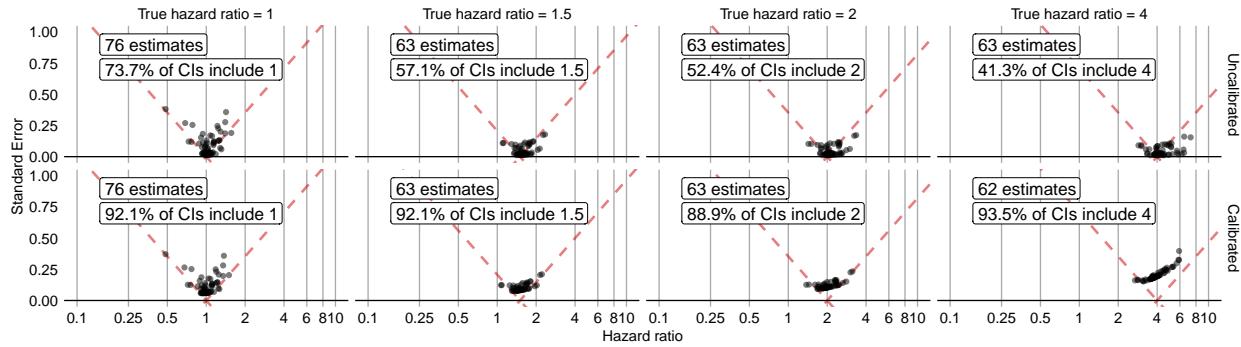


Supplementary Figure 4j: Systematic error control of effect estimation comparing dCCB and ndCCB new-users in the CCAE database under an on-treatment, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration. The left plots with hazard ratios = 1 present negative controls, while plots with hazard ratios > 1 present synthetic positive controls.

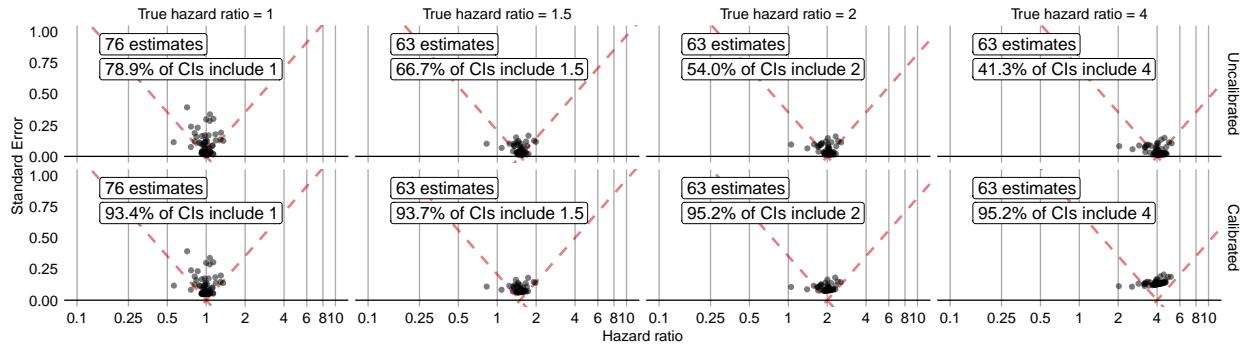
Under an intent-to-treat, PS-stratified design



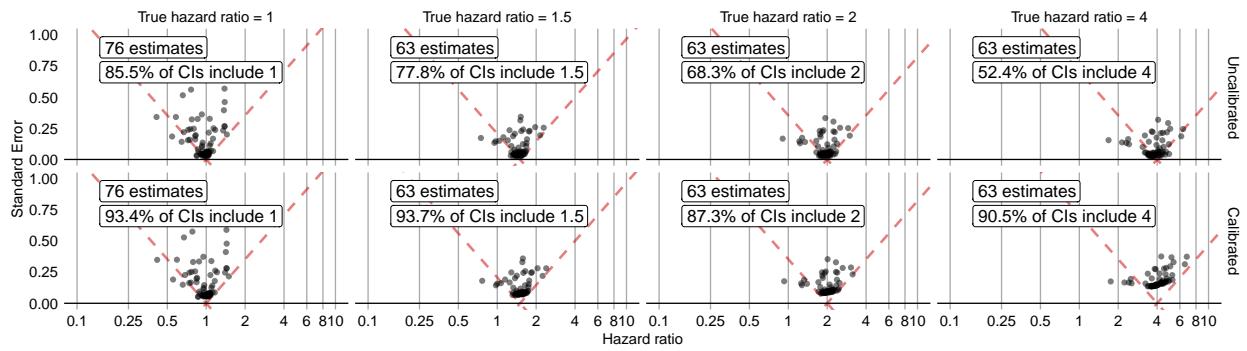
Supplementary Figure 5a: Systematic error control of effect estimation comparing THZ and ACEi new-users in the CCAE database under an intent-to-treat, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



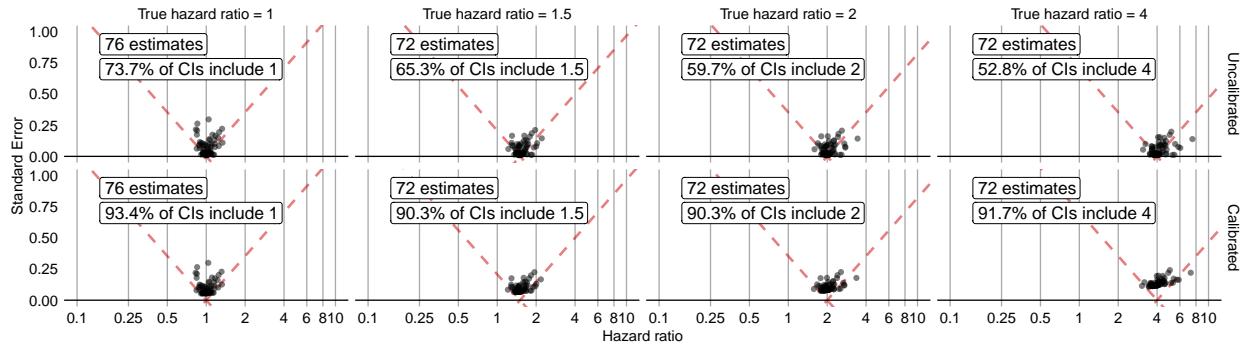
Supplementary Figure 5b: Systematic error control of effect estimation comparing THZ and ARB new-users in the CCAE database under an intent-to-treat, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



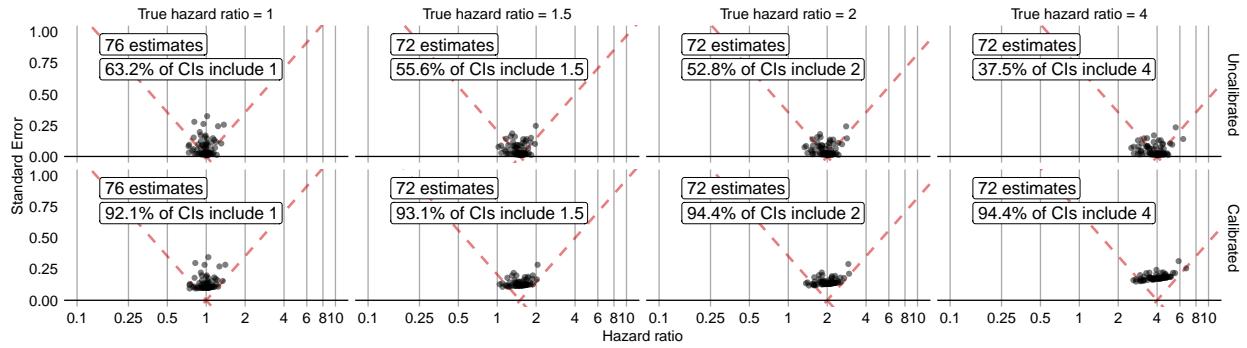
Supplementary Figure 5c: Systematic error control of effect estimation comparing THZ and dCCB new-users in the CCAE database under an intent-to-treat, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



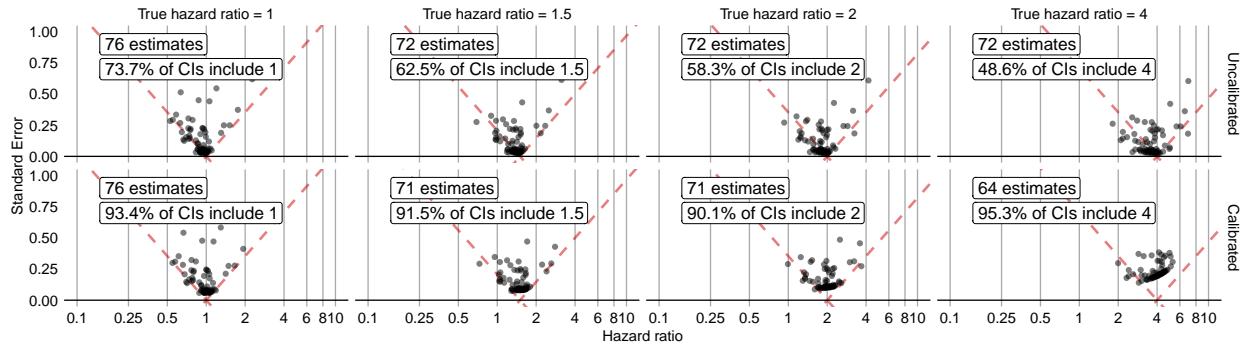
Supplementary Figure 5d: Systematic error control of effect estimation comparing THZ and ndCCB new-users in the CCAE database under an intent-to-treat, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



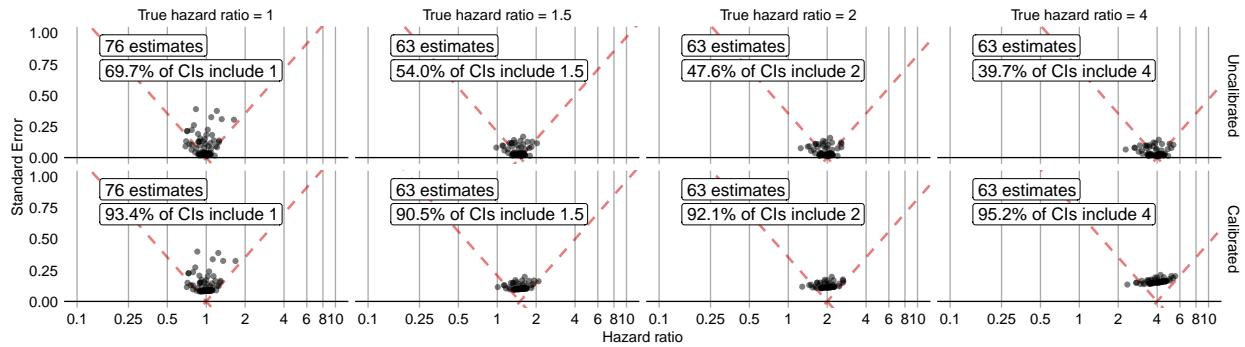
Supplementary Figure 5e: Systematic error control of effect estimation comparing ACEi and ARB new-users in the CCAE database under an intent-to-treat, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



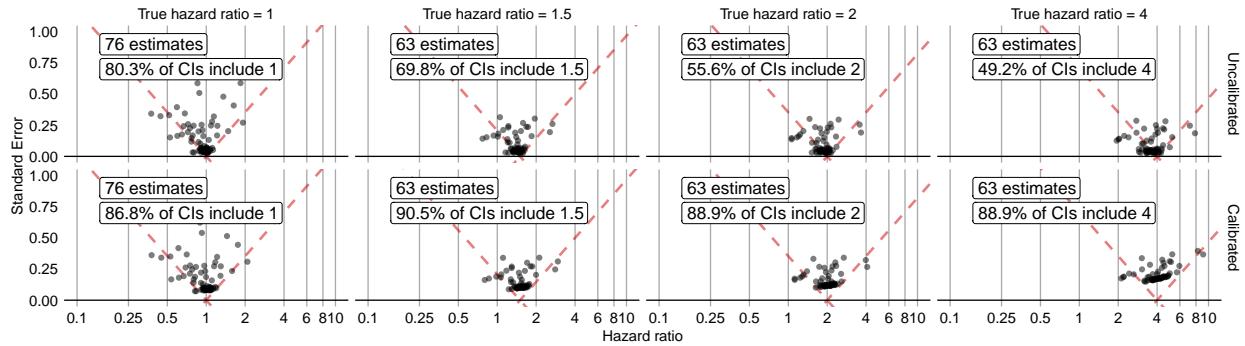
Supplementary Figure 5f: Systematic error control of effect estimation comparing ACEi and dCCB new-users in the CCAE database under an intent-to-treat, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



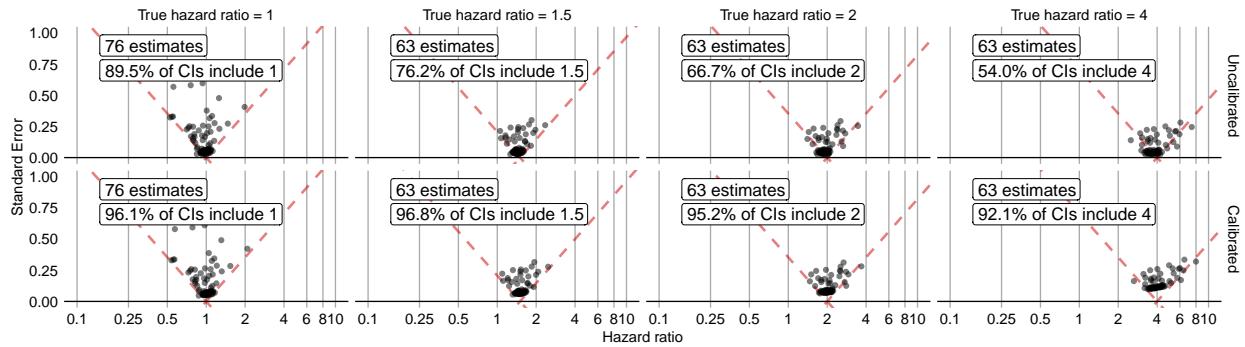
Supplementary Figure 5g: Systematic error control of effect estimation comparing ACEi and ndCCB new-users in the CCAE database under an intent-to-treat, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



Supplementary Figure 5h: Systematic error control of effect estimation comparing ARB and dCCB new-users in the CCAE database under an intent-to-treat, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.

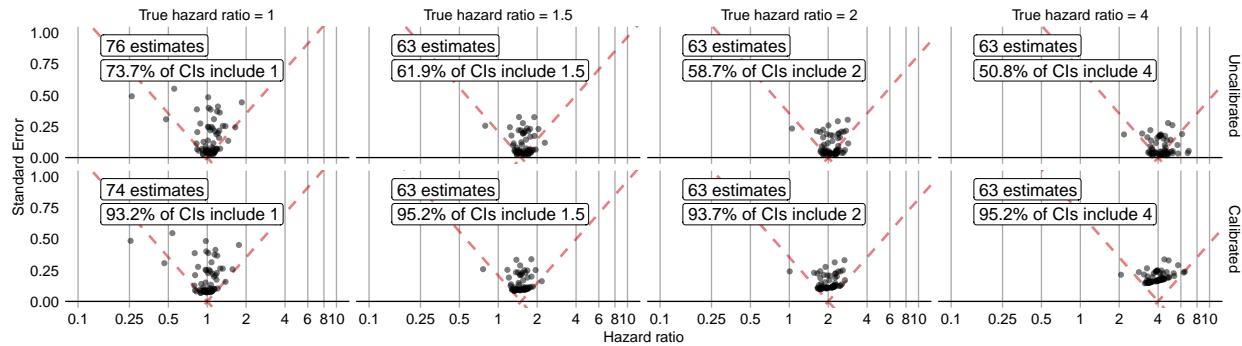


Supplementary Figure 5i: Systematic error control of effect estimation comparing ARB and ndCCB new-users in the CCAE database under an intent-to-treat, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.

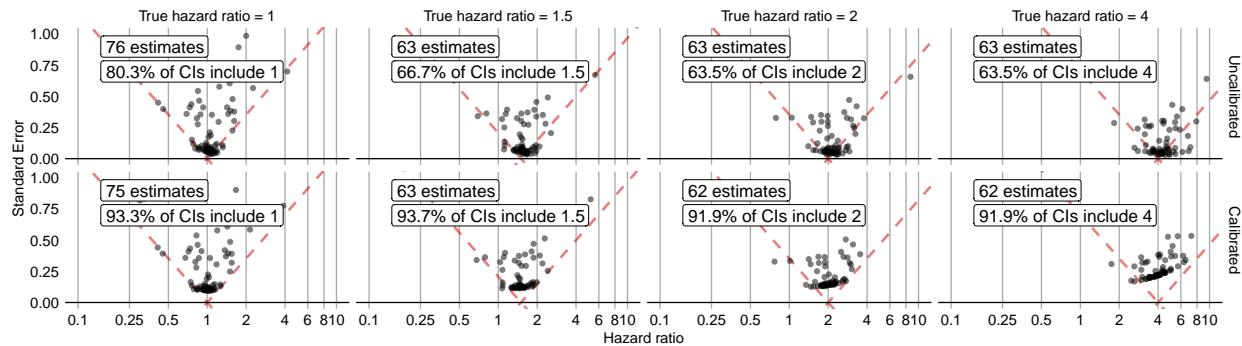


Supplementary Figure 5j: Systematic error control of effect estimation comparing dCCB and ndCCB new-users in the CCAE database under an intent-to-treat, PS-stratified design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.

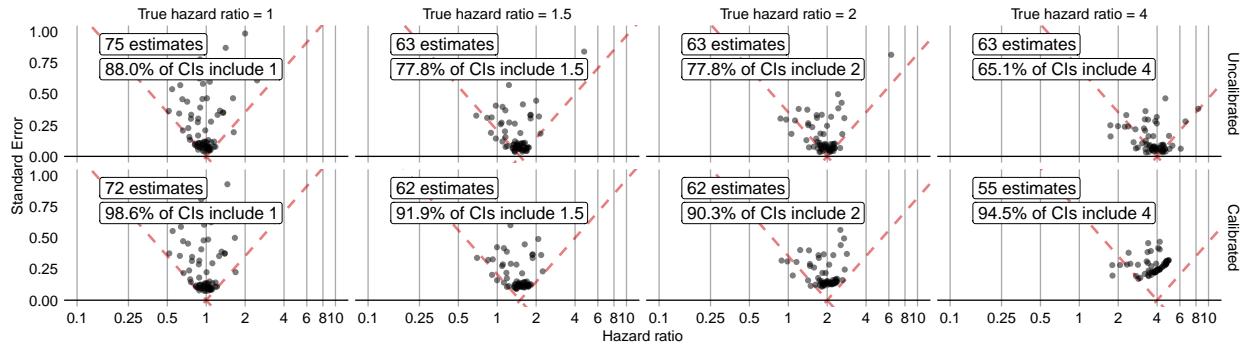
Under an on-treatment, PS-matched design



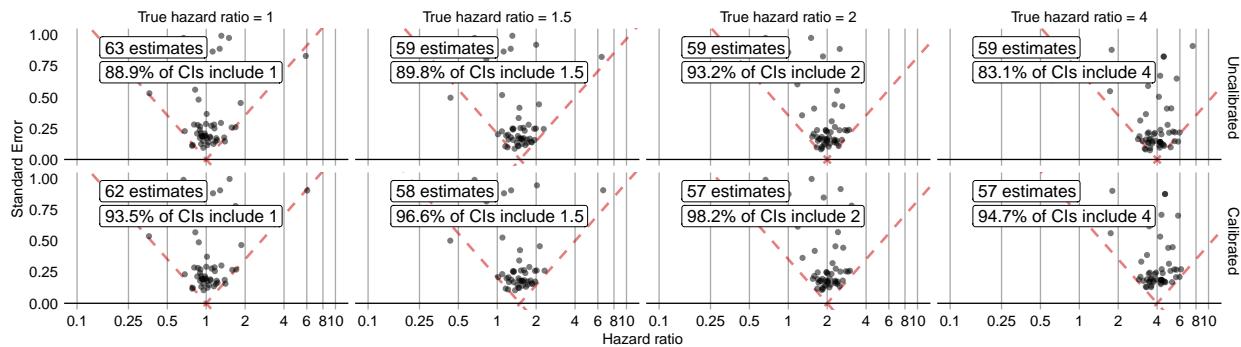
Supplementary Figure 6a: Systematic error control of effect estimation comparing THZ and ACEi new-users in the CCAE database under an on-treatment, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



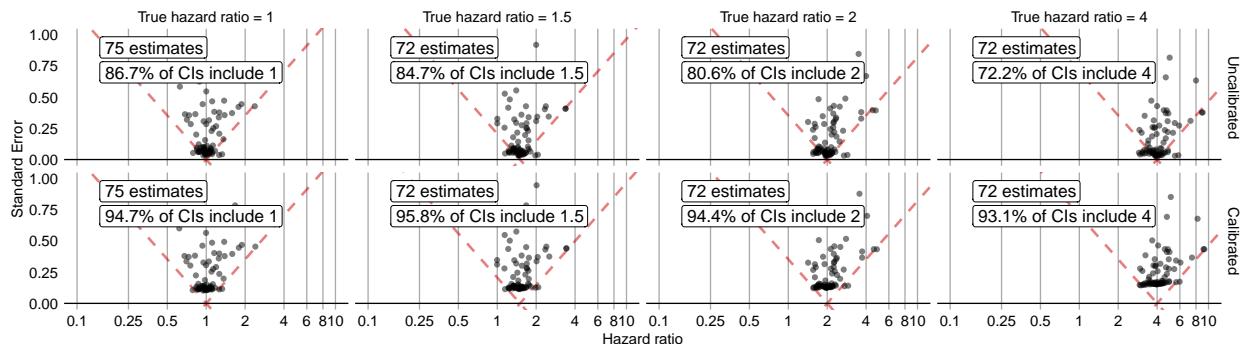
Supplementary Figure 6b: Systematic error control of effect estimation comparing THZ and ARB new-users in the CCAE database under an on-treatment, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



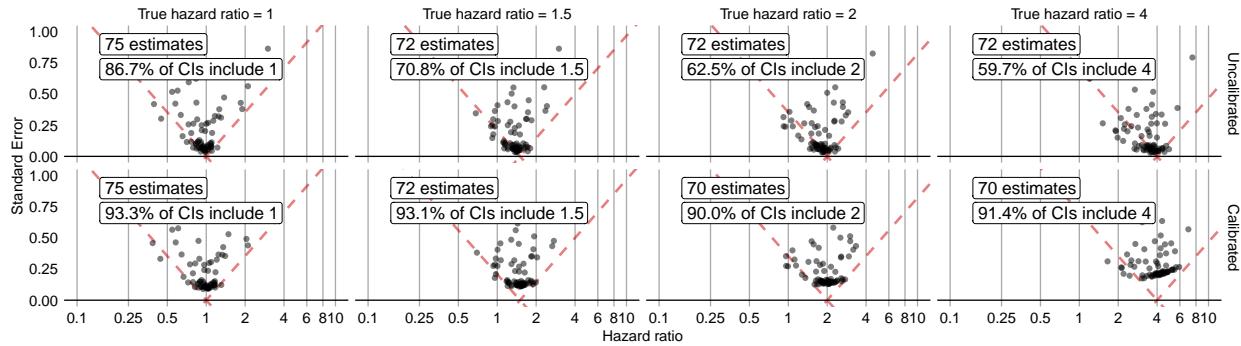
Supplementary Figure 6c: Systematic error control of effect estimation comparing THZ and dCCB new-users in the CCAE database under an on-treatment, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



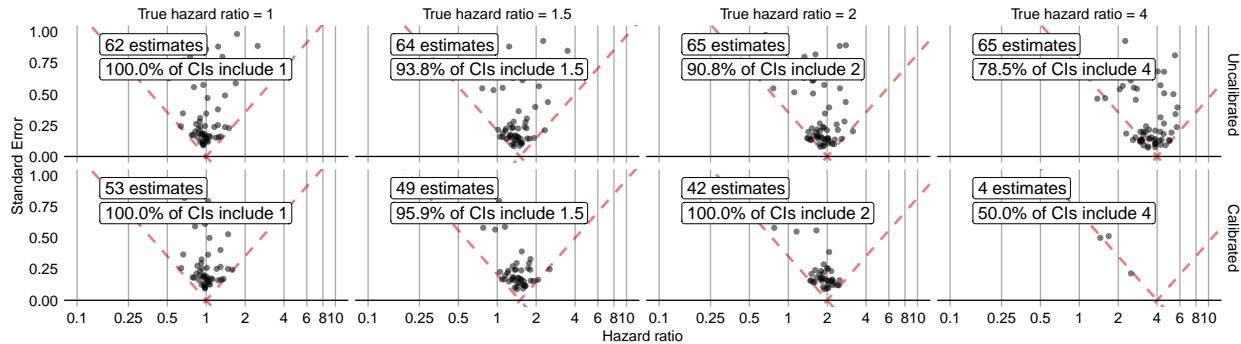
Supplementary Figure 6d: Systematic error control of effect estimation comparing THZ and ndCCB new-users in the CCAE database under an on-treatment, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



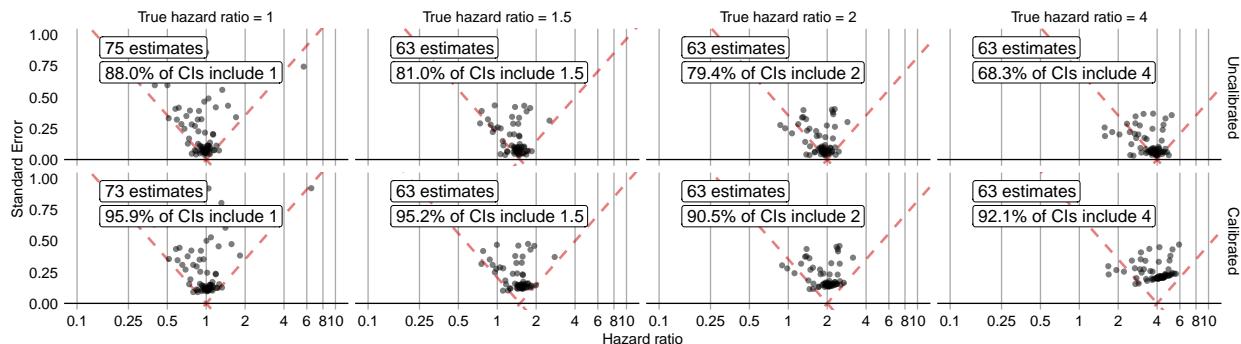
Supplementary Figure 6e: Systematic error control of effect estimation comparing ACEi and ARB new-users in the CCAE database under an on-treatment, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



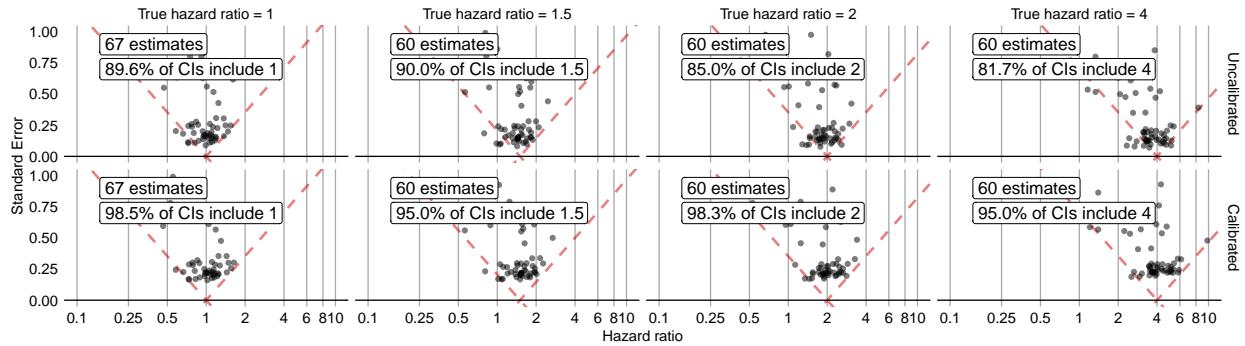
Supplementary Figure 6f: Systematic error control of effect estimation comparing ACEi and dCCB new-users in the CCAE database under an on-treatment, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



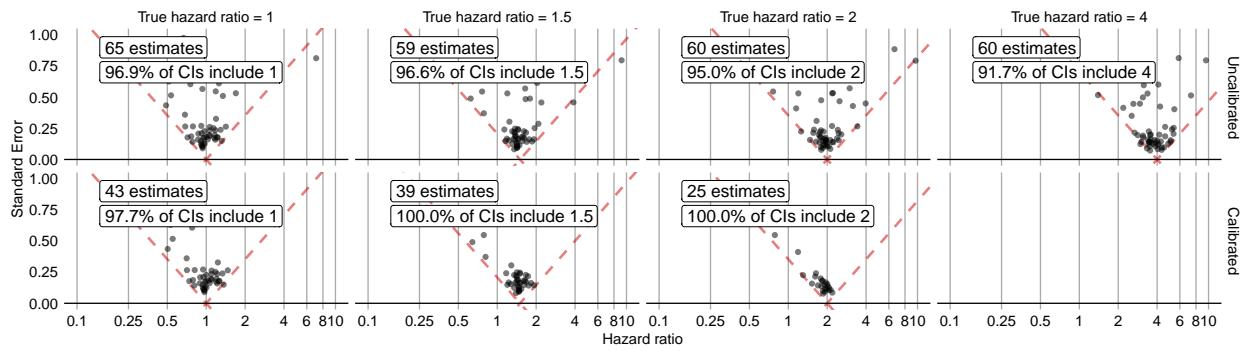
Supplementary Figure 6g: Systematic error control of effect estimation comparing ACEi and ndCCB new-users in the CCAE database under an on-treatment, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



Supplementary Figure 6h: Systematic error control of effect estimation comparing ARB and dCCB new-users in the CCAE database under an on-treatment, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.

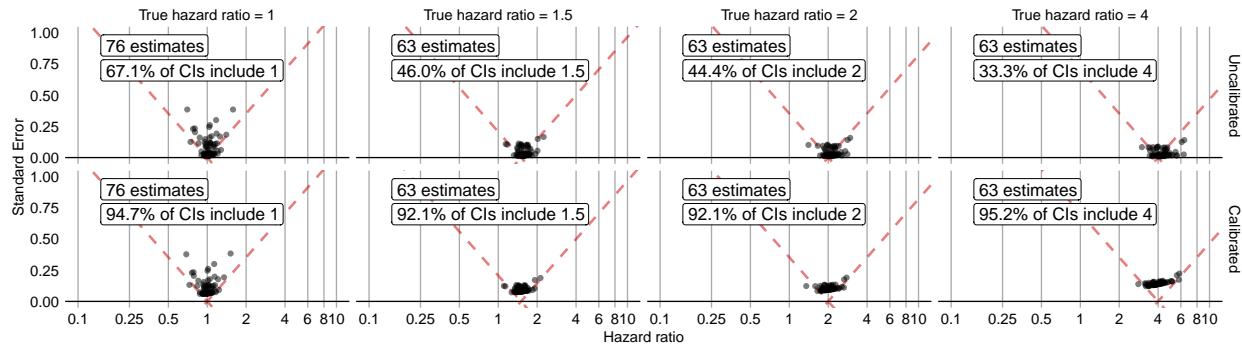


Supplementary Figure 6i: Systematic error control of effect estimation comparing ARB and ndCCB new-users in the CCAE database under an on-treatment, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.

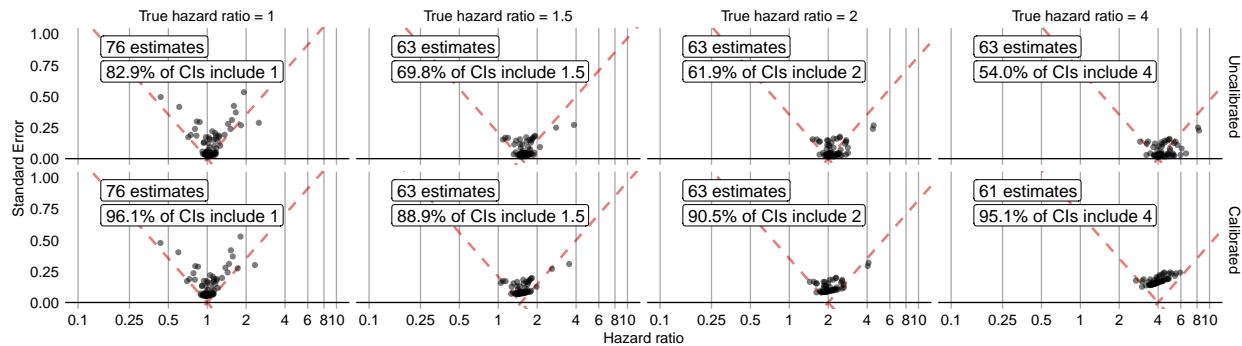


Supplementary Figure 6j: Systematic error control of effect estimation comparing dCCB and ndCCB new-users in the CCAE database under an on-treatment, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.

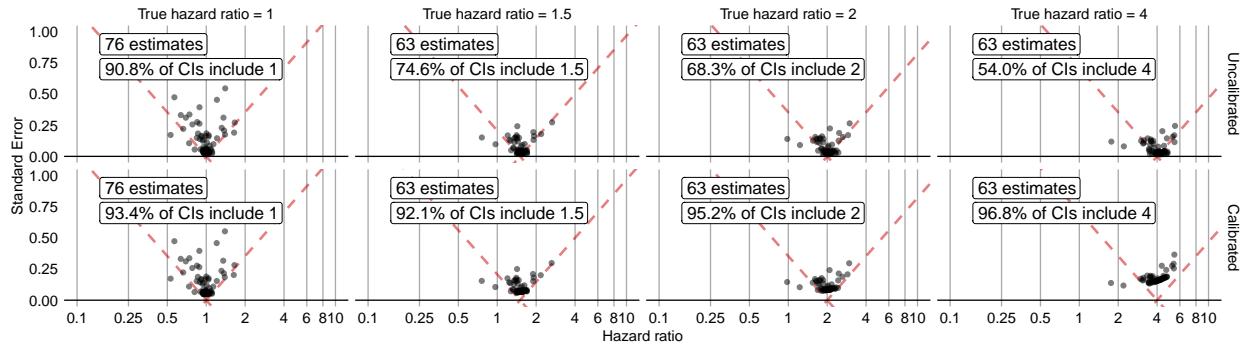
Under an intent-to-treat, PS-matched design



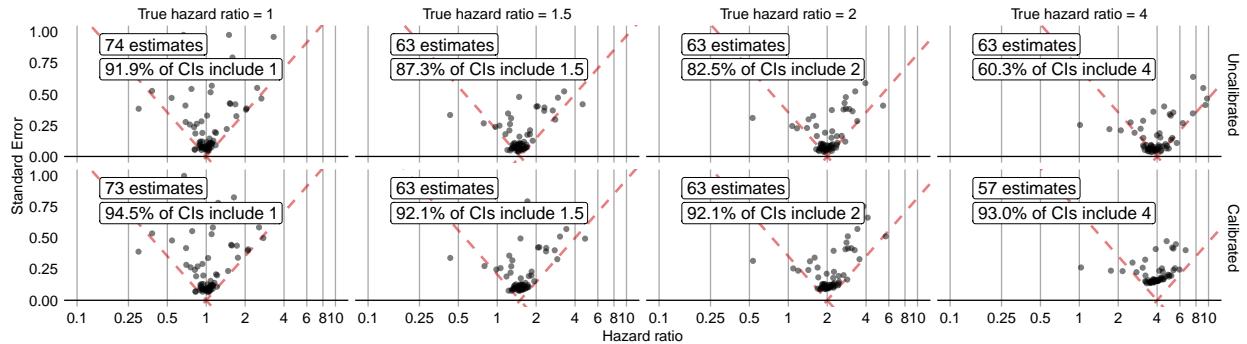
Supplementary Figure 7a: Systematic error control of effect estimation comparing THZ and ACEi new-users in the CCAE database under an intent-to-treat, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



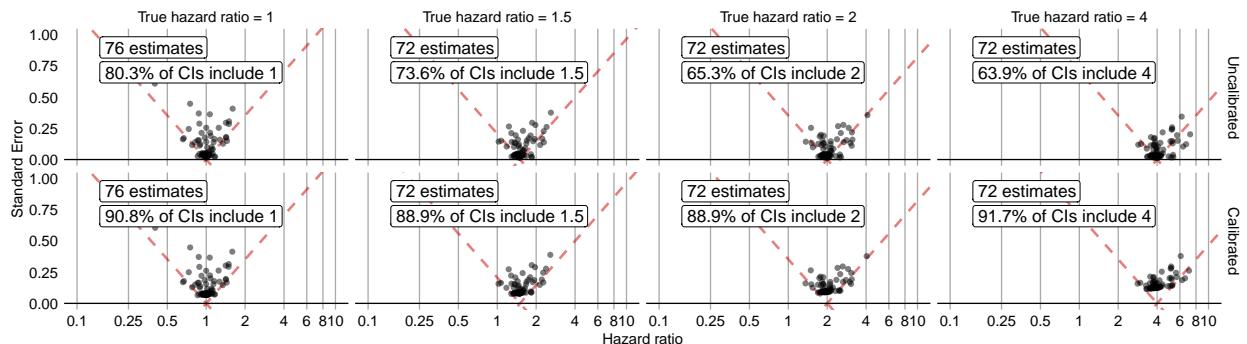
Supplementary Figure 7b: Systematic error control of effect estimation comparing THZ and ARB new-users in the CCAE database under an intent-to-treat, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



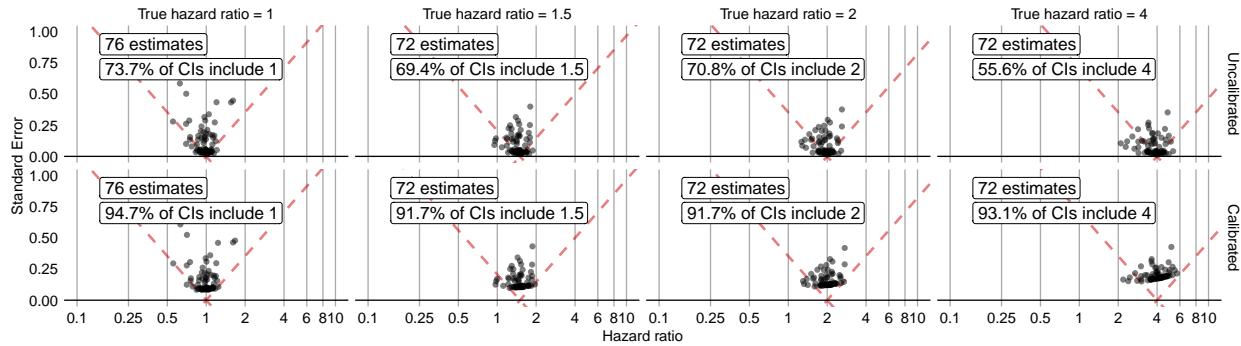
Supplementary Figure 7c: Systematic error control of effect estimation comparing THZ and dCCB new-users in the CCAE database under an intent-to-treat, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



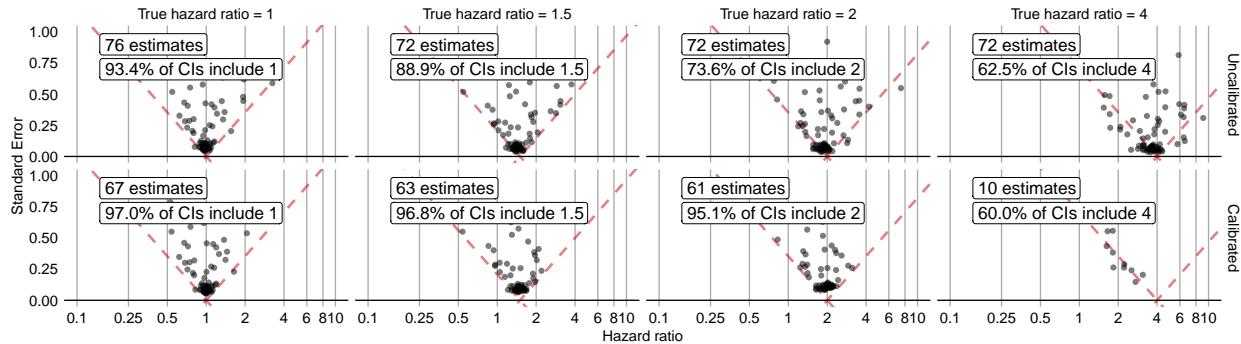
Supplementary Figure 7d: Systematic error control of effect estimation comparing THZ and ndCCB new-users in the CCAE database under an intent-to-treat, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



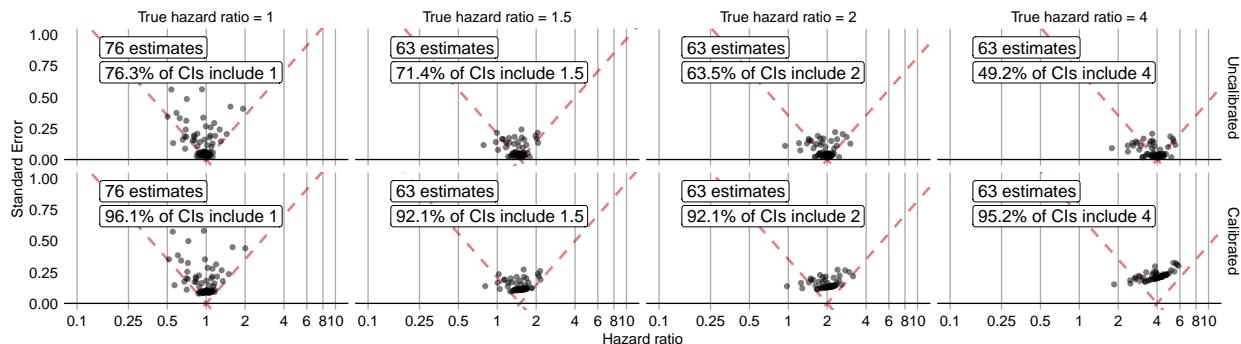
Supplementary Figure 7e: Systematic error control of effect estimation comparing ACEi and ARB new-users in the CCAE database under an intent-to-treat, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



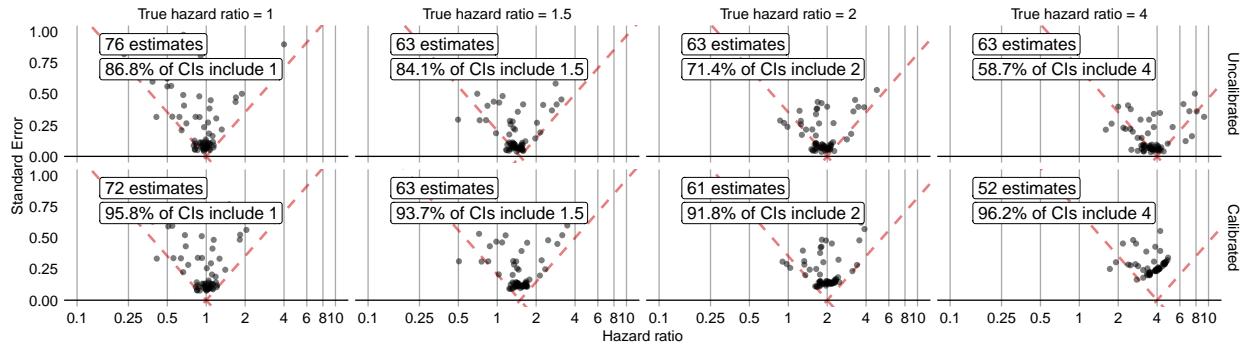
Supplementary Figure 7f: Systematic error control of effect estimation comparing ACEi and dCCB new-users in the CCAE database under an intent-to-treat, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



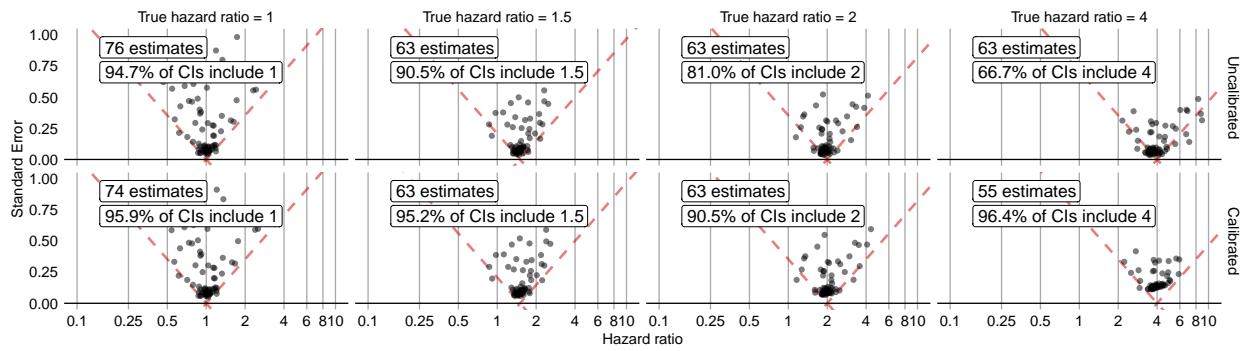
Supplementary Figure 7g: Systematic error control of effect estimation comparing ACEi and ndCCB new-users in the CCAE database under an intent-to-treat, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



Supplementary Figure 7h: Systematic error control of effect estimation comparing ARB and dCCB new-users in the CCAE database under an intent-to-treat, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



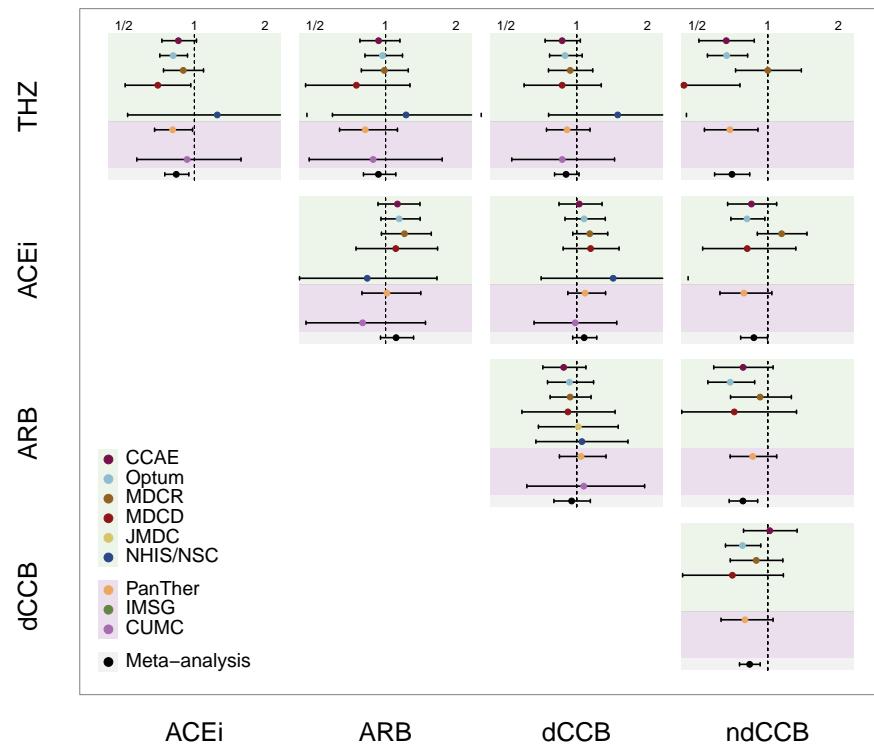
Supplementary Figure 7i: Systematic error control of effect estimation comparing ARB and ndCCB new-users in the CCAE database under an intent-to-treat, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.



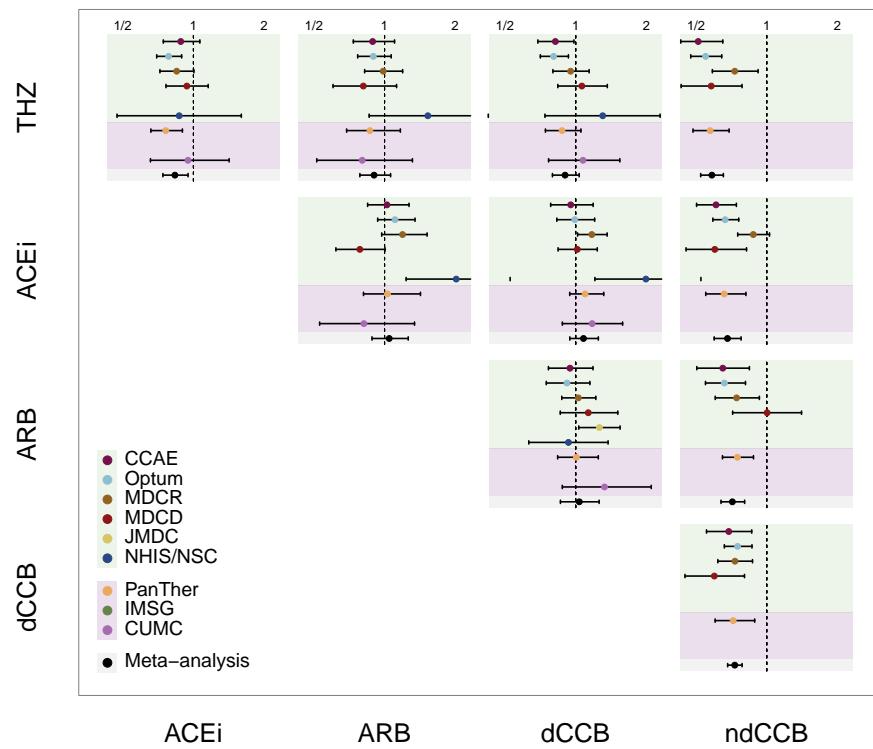
Supplementary Figure 7j: Systematic error control of effect estimation comparing dCCB and ndCCB new-users in the CCAE database under an intent-to-treat, PS-matched design. The top plots HRs and their corresponding standard errors before calibration for each negative and synthetic positive control. The bottom plots the same estimates after calibration.

Effectiveness estimates

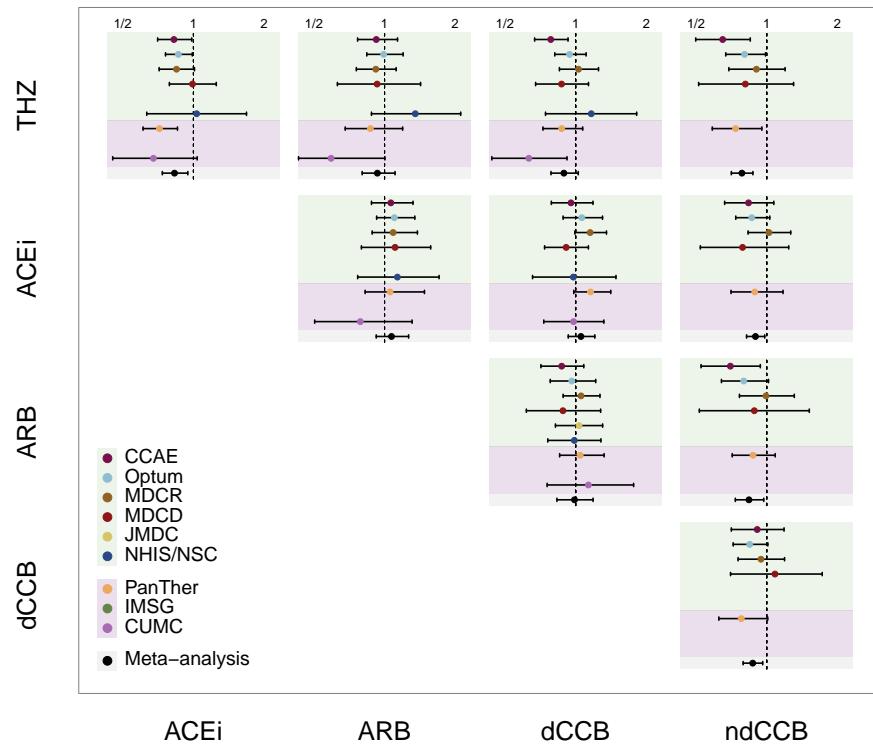
Under an on-treatment, PS-stratified design



Supplementary Figure 8a: Acute myocardial infarction risk by data source under an on-treatment, PS-stratified design. Points report HR estimates and lines mark their 95% CIs. Colors identify databases; the top block are insurance claims databases, the middle block are EHRs and black highlights a meta-analysis across all other sources. Not all databases contain sufficient new-users for study inclusion.

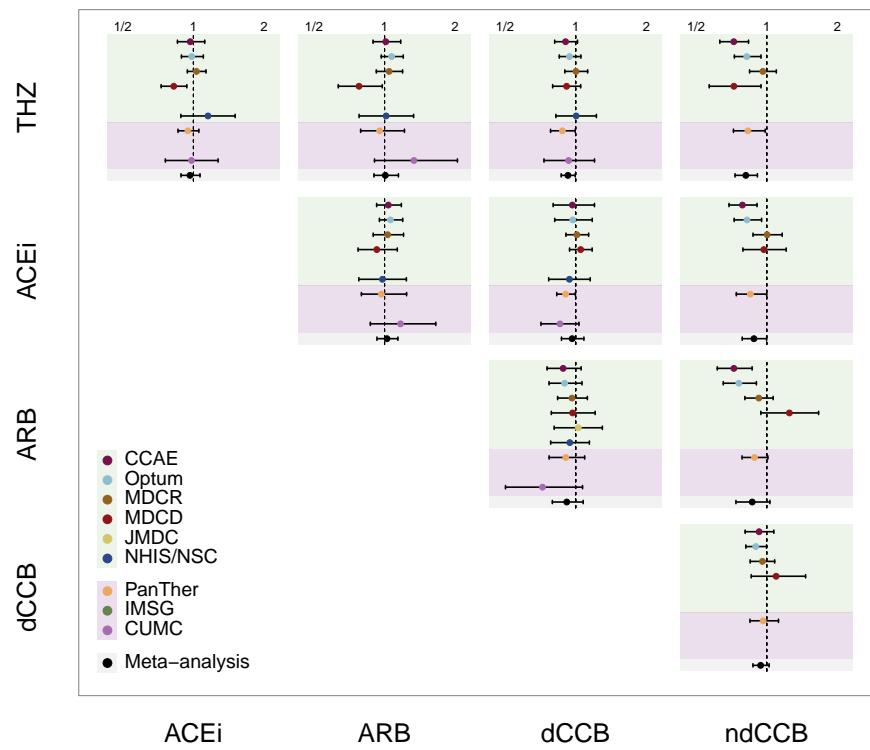


Supplementary Figure 8b: Hospitalization with heart failure risk by data source under an on-treatment, PS-stratified design. Points report HR estimates and lines mark their 95% CIs. Colors identify databases; the top block are insurance claims databases, the middle block are EHRs and black highlights a meta-analysis across all other sources. Not all databases contain sufficient new-users for study inclusion.

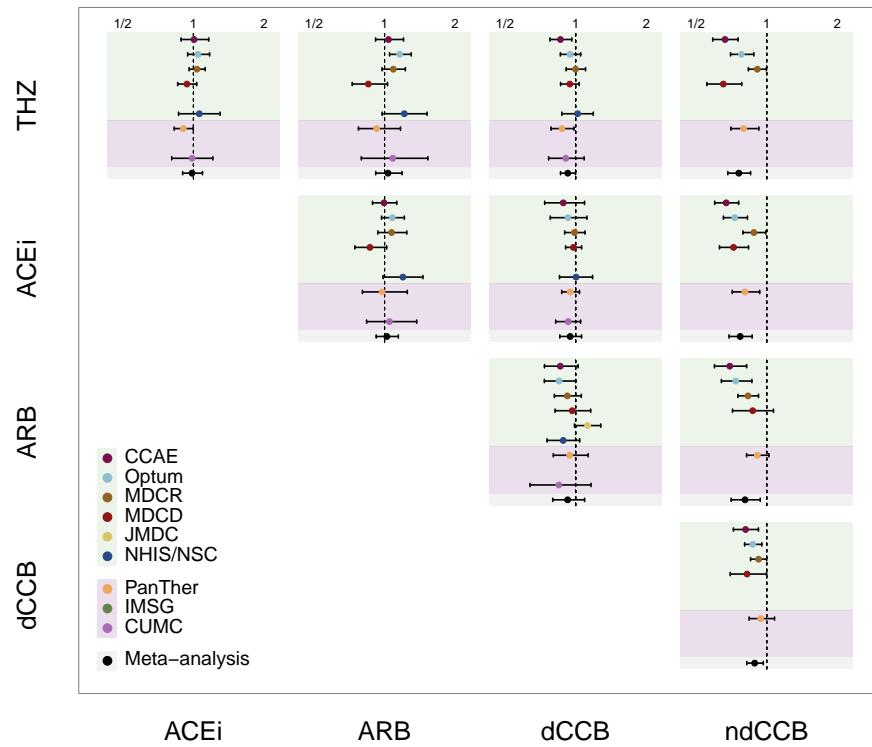


Supplementary Figure 8c: Stroke risk by data source under an on-treatment, PS-stratified design. Points report HR estimates and lines mark their 95% CIs. Colors identify databases; the top block are insurance claims databases, the middle block are EHRs and black highlights a meta-analysis across all other sources. Not all databases contain sufficient new-users for study inclusion.

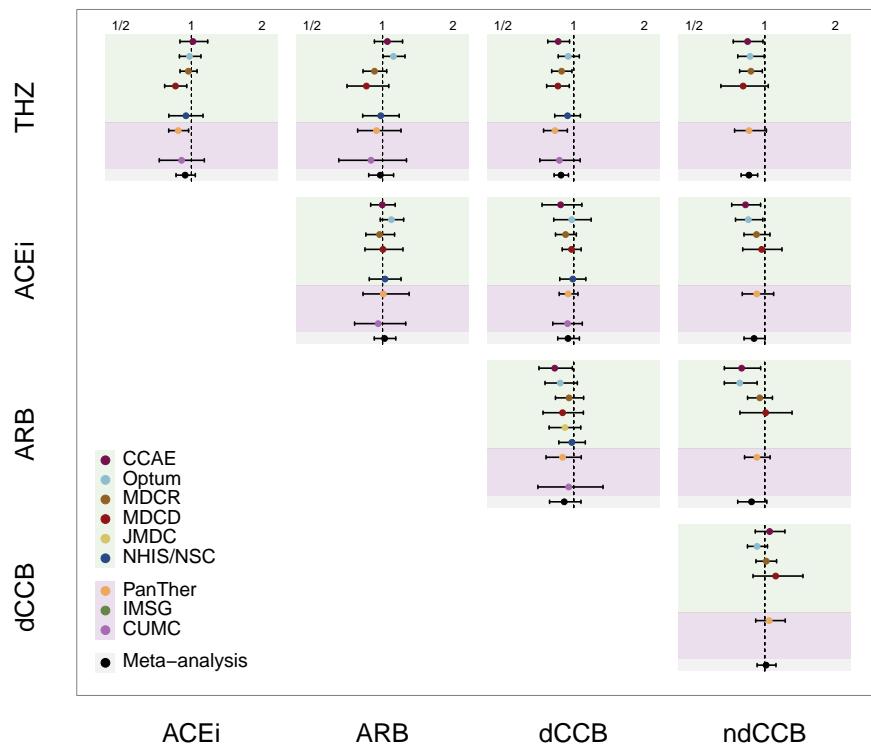
Under an intent-to-treat, PS-stratified design



Supplementary Figure 9a: Acute myocardial infarction risk by data source under an intent-to-treat, PS-stratified design. Points report HR estimates and lines mark their 95% CIs. Colors identify databases; the top block are insurance claims databases, the middle block are EHRs and black highlights a meta-analysis across all other sources. Not all databases contain sufficient new-users for study inclusion.

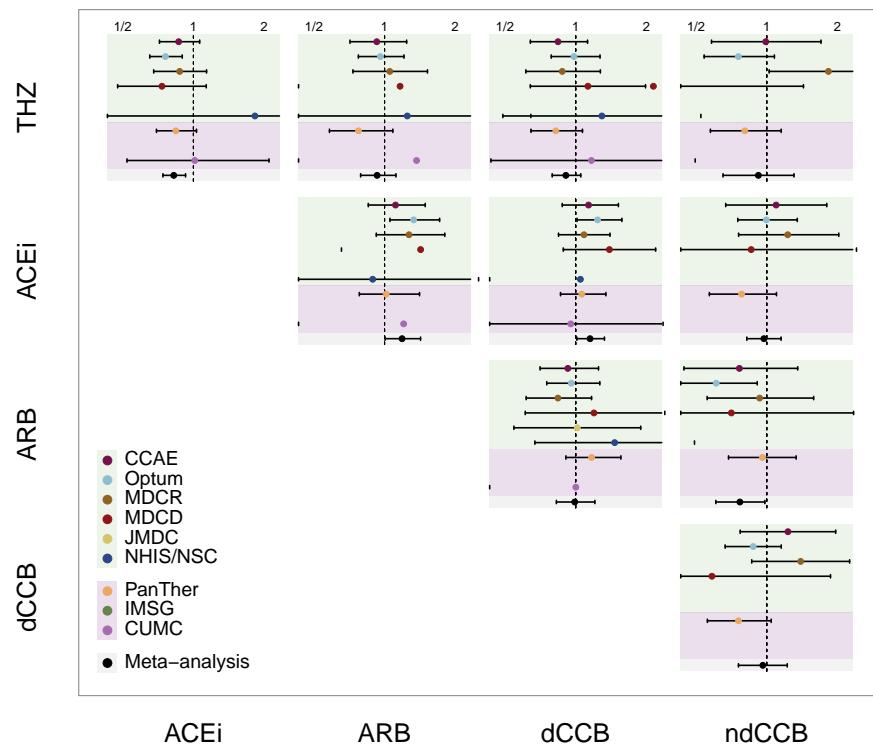


Supplementary Figure 9b: Hospitalization with heart failure risk by data source under an intent-to-treat, PS-stratified design. Points report HR estimates and lines mark their 95% CIs. Colors identify databases; the top block are insurance claims databases, the middle block are EHRs and black highlights a meta-analysis across all other sources. Not all databases contain sufficient new-users for study inclusion.

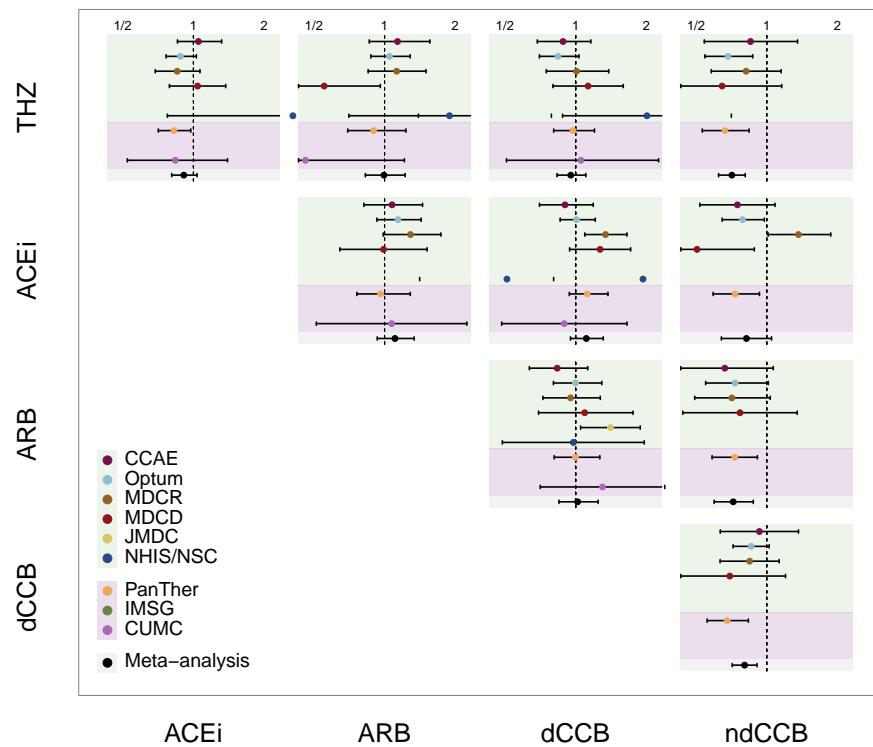


Supplementary Figure 9c: Stroke risk by data source under an intent-to-treat, PS-stratified design. Points report HR estimates and lines mark their 95% CIs. Colors identify databases; the top block are insurance claims databases, the middle block are EHRs and black highlights a meta-analysis across all other sources. Not all databases contain sufficient new-users for study inclusion.

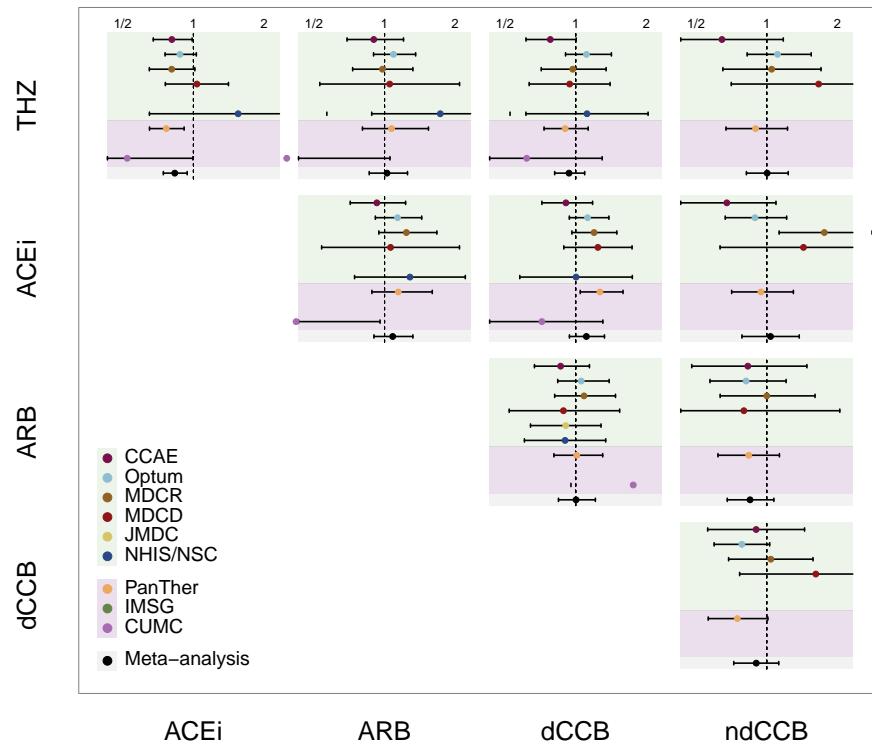
Under an on-treatment, PS-matched design



Supplementary Figure 10a: Acute myocardial infarction risk by data source under an on-treatment, PS-matched design. Points report HR estimates and lines mark their 95% CIs. Colors identify databases; the top block are insurance claims databases, the middle block are EHRs and black highlights a meta-analysis across all other sources. Not all databases contain sufficient new-users for study inclusion.

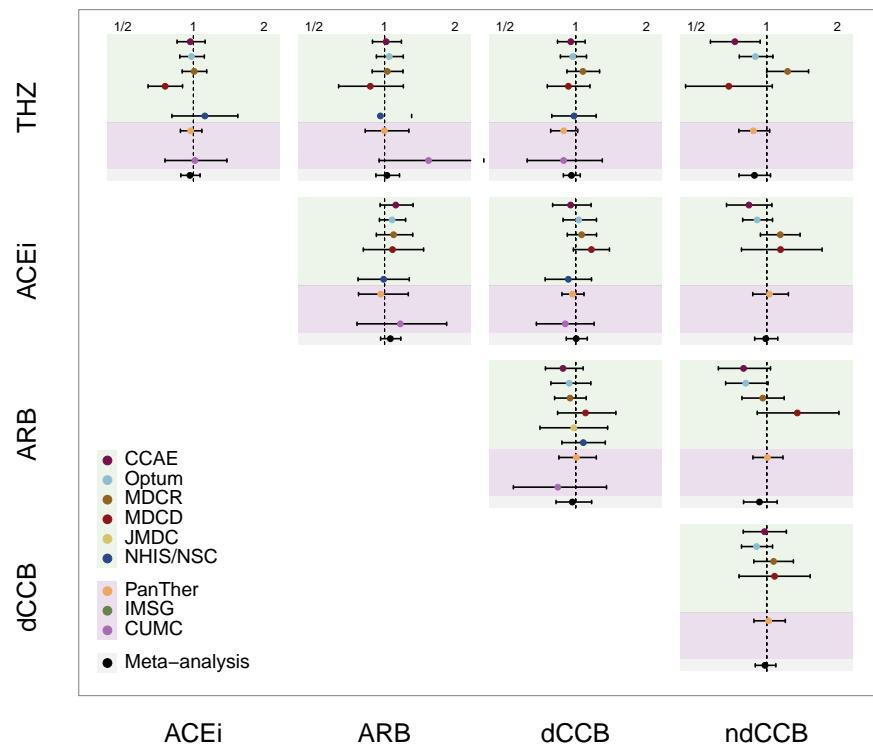


Supplementary Figure 10b: Hospitalization with heart failure risk by data source under an on-treatment, PS-matched design. Points report HR estimates and lines mark their 95% CIs. Colors identify databases; the top block are insurance claims databases, the middle block are EHRs and black highlights a meta-analysis across all other sources. Not all databases contain sufficient new-users for study inclusion.

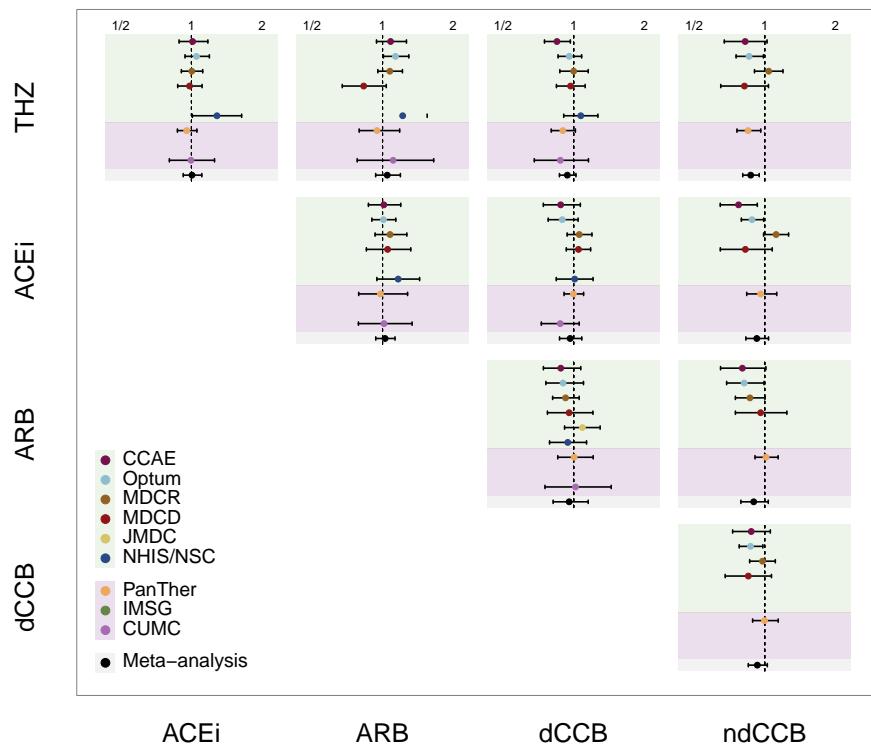


Supplementary Figure 10c: Stroke risk by data source under an on-treatment, PS-matched design. Points report HR estimates and lines mark their 95% CIs. Colors identify databases; the top block are insurance claims databases, the middle block are EHRs and black highlights a meta-analysis across all other sources. Not all databases contain sufficient new-users for study inclusion.

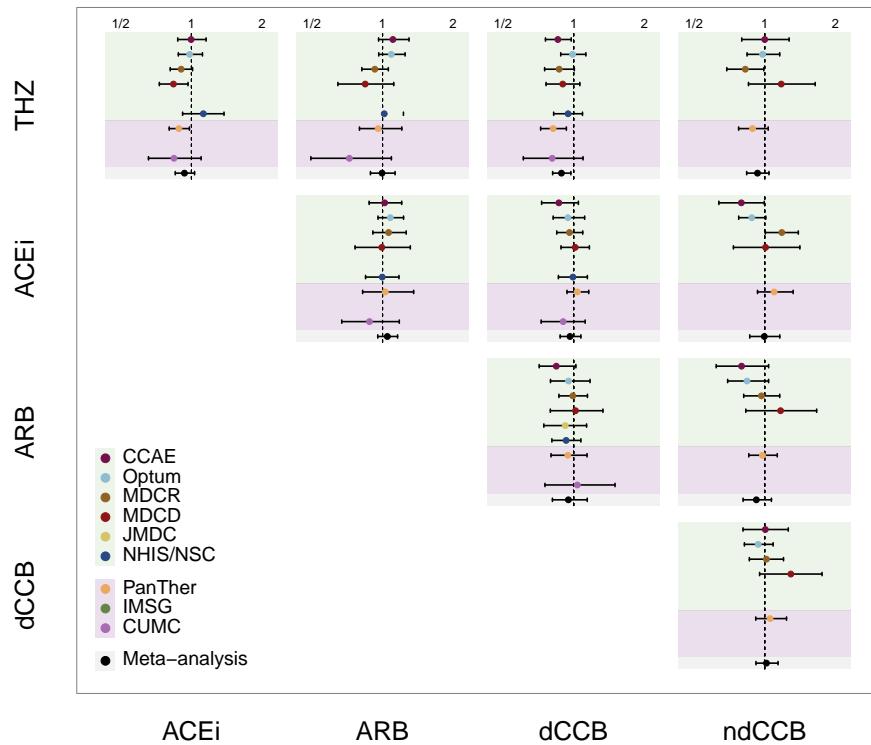
Under an intent-to-treat, PS-matched design



Supplementary Figure 11a: Acute myocardial infarction risk by data source under an intent-to-treat, PS-matched design. Points report HR estimates and lines mark their 95% CIs. Colors identify databases; the top block are insurance claims databases, the middle block are EHRs and black highlights a meta-analysis across all other sources. Not all databases contain sufficient new-users for study inclusion.



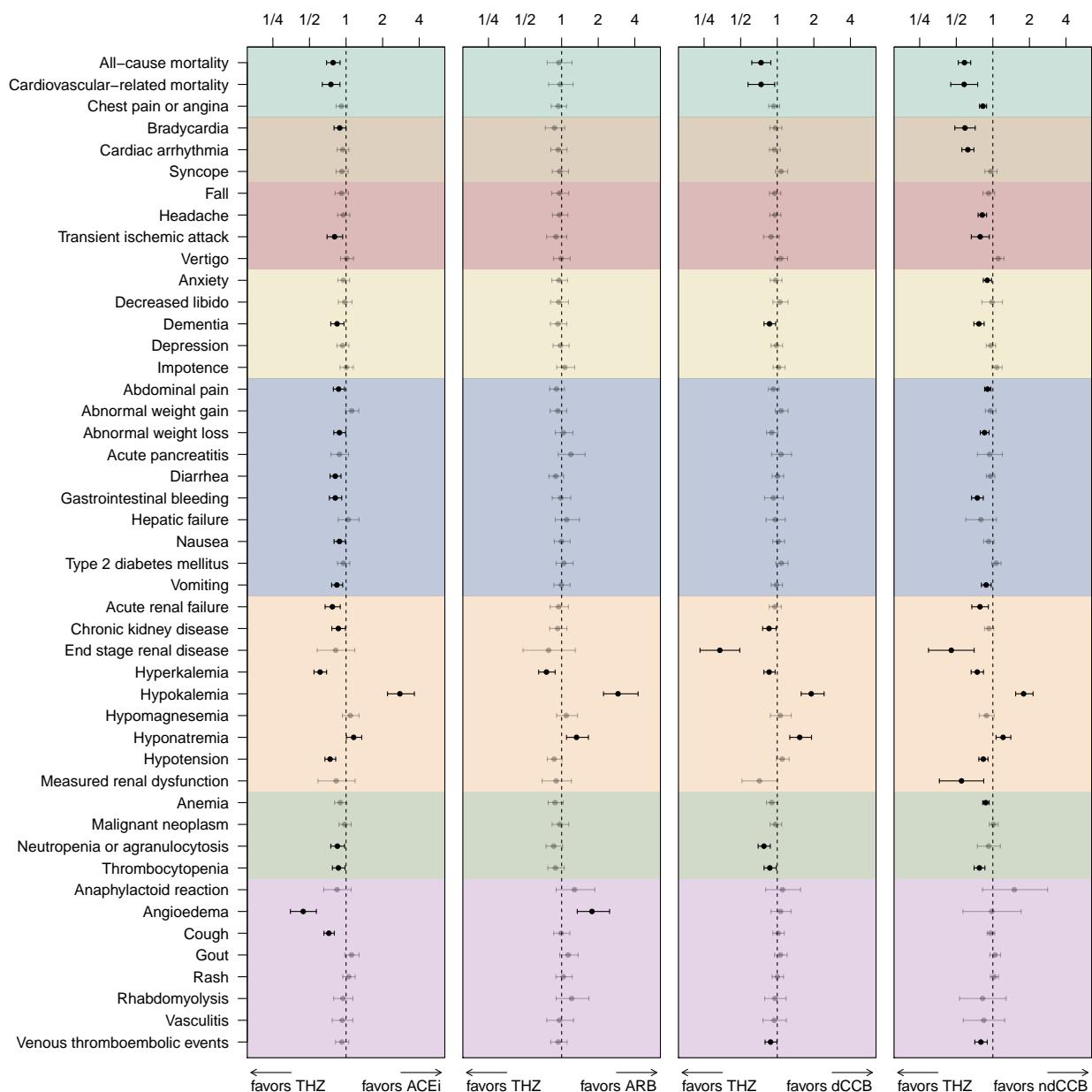
Supplementary Figure 11b: Hospitalization with heart failure risk by data source under an intent-to-treat, PS-matched design. Points report HR estimates and lines mark their 95% CIs. Colors identify databases; the top block are insurance claims databases, the middle block are EHRs and black highlights a meta-analysis across all other sources. Not all databases contain sufficient new-users for study inclusion.



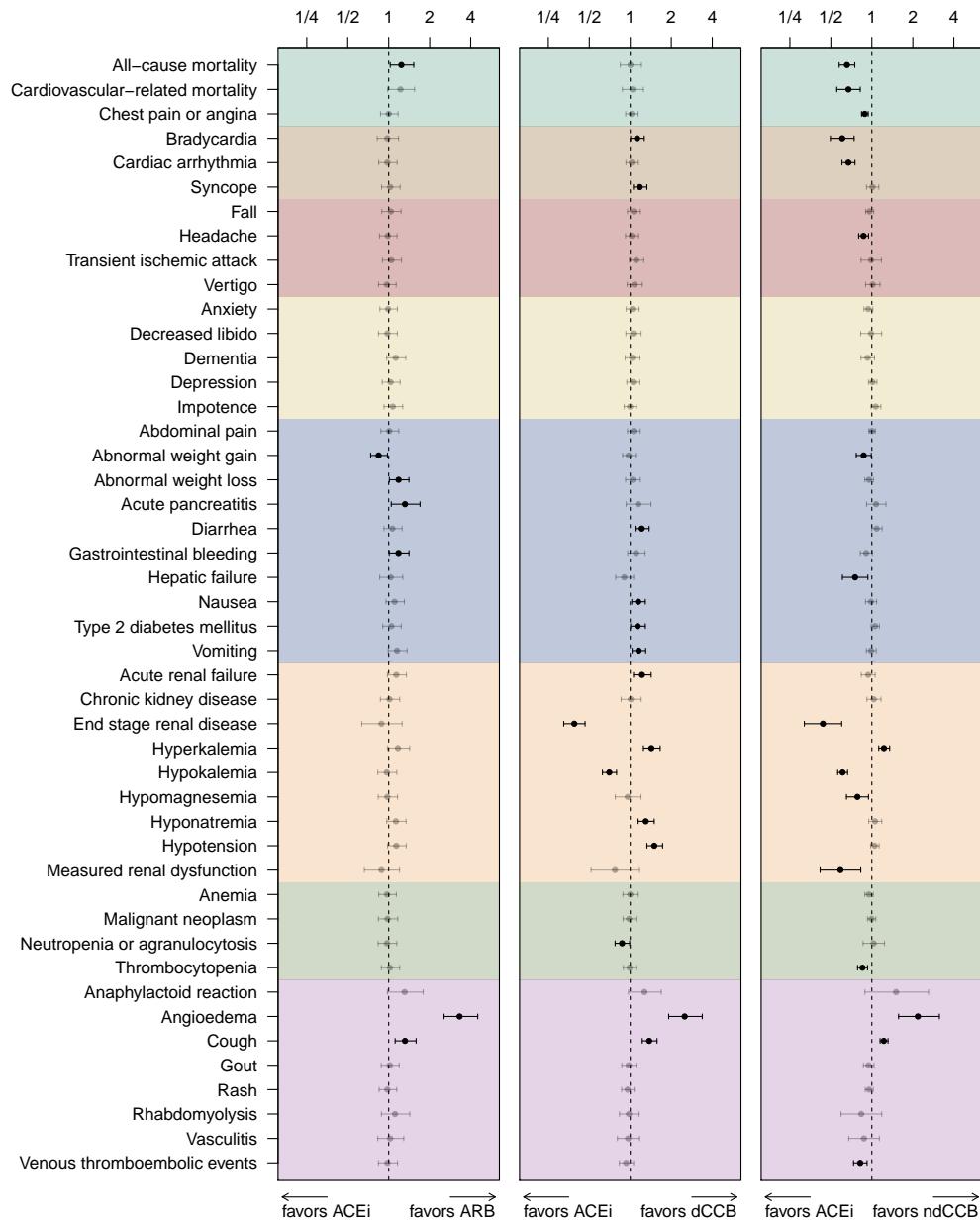
Supplementary Figure 11c: Stroke risk by data source under an intent-to-treat, PS-matched design. Points report HR estimates and lines mark their 95% CIs. Colors identify databases; the top block are insurance claims databases, the middle block are EHRs and black highlights a meta-analysis across all other sources. Not all databases contain sufficient new-users for study inclusion.

Safety profiles

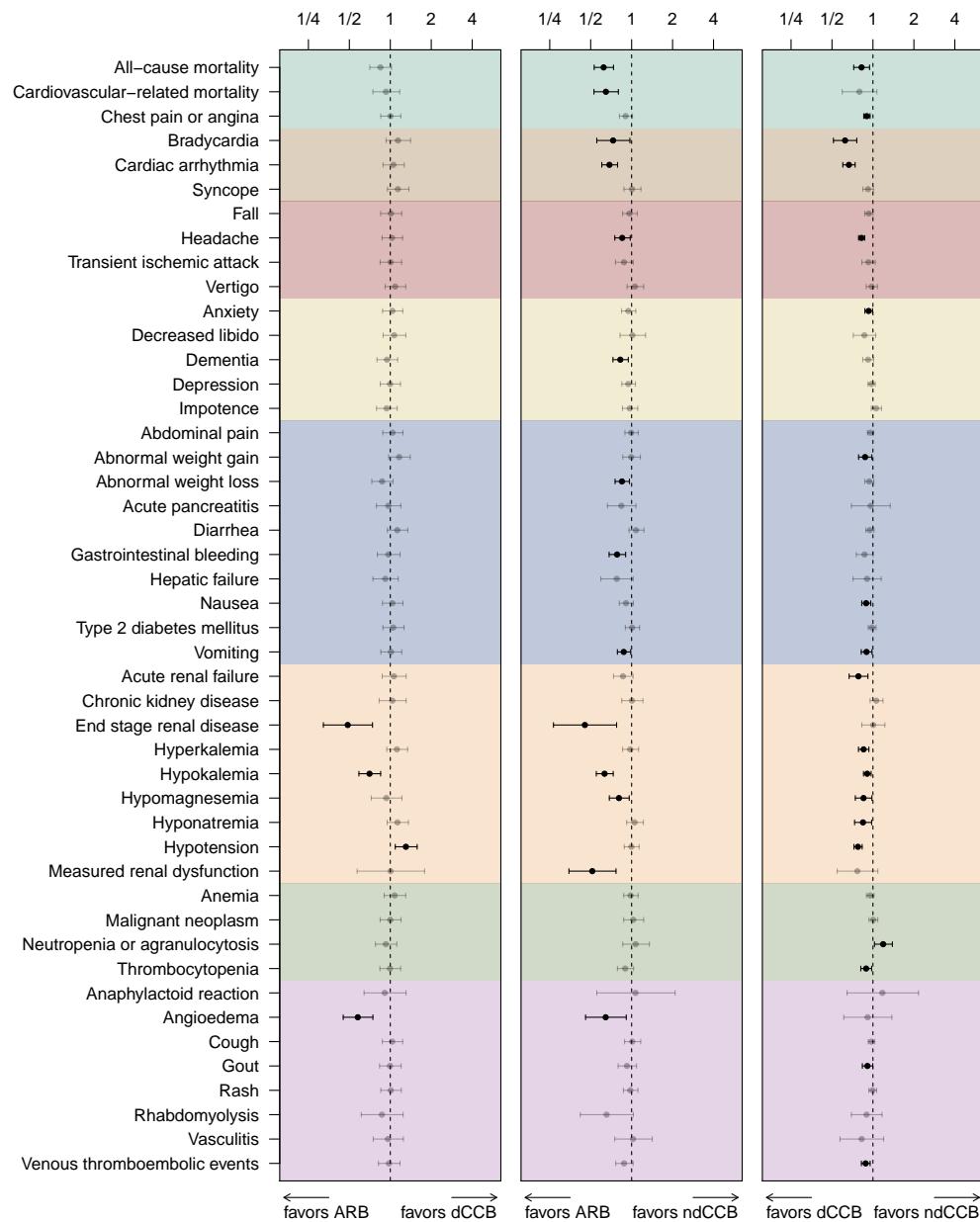
Under an on-treatment, PS-stratified design



Supplementary Figure 12a: Meta-analytic safety profiles comparing THZ to ACEi, ARB, dCCB and ndCCB new-users under an on-treatment, PS-stratified design. Points and lines identify HR estimates with their 95% CI, respectively. Outcomes in grey signify that the CI covers HR = 1 (null hypothesis of no differential risk).

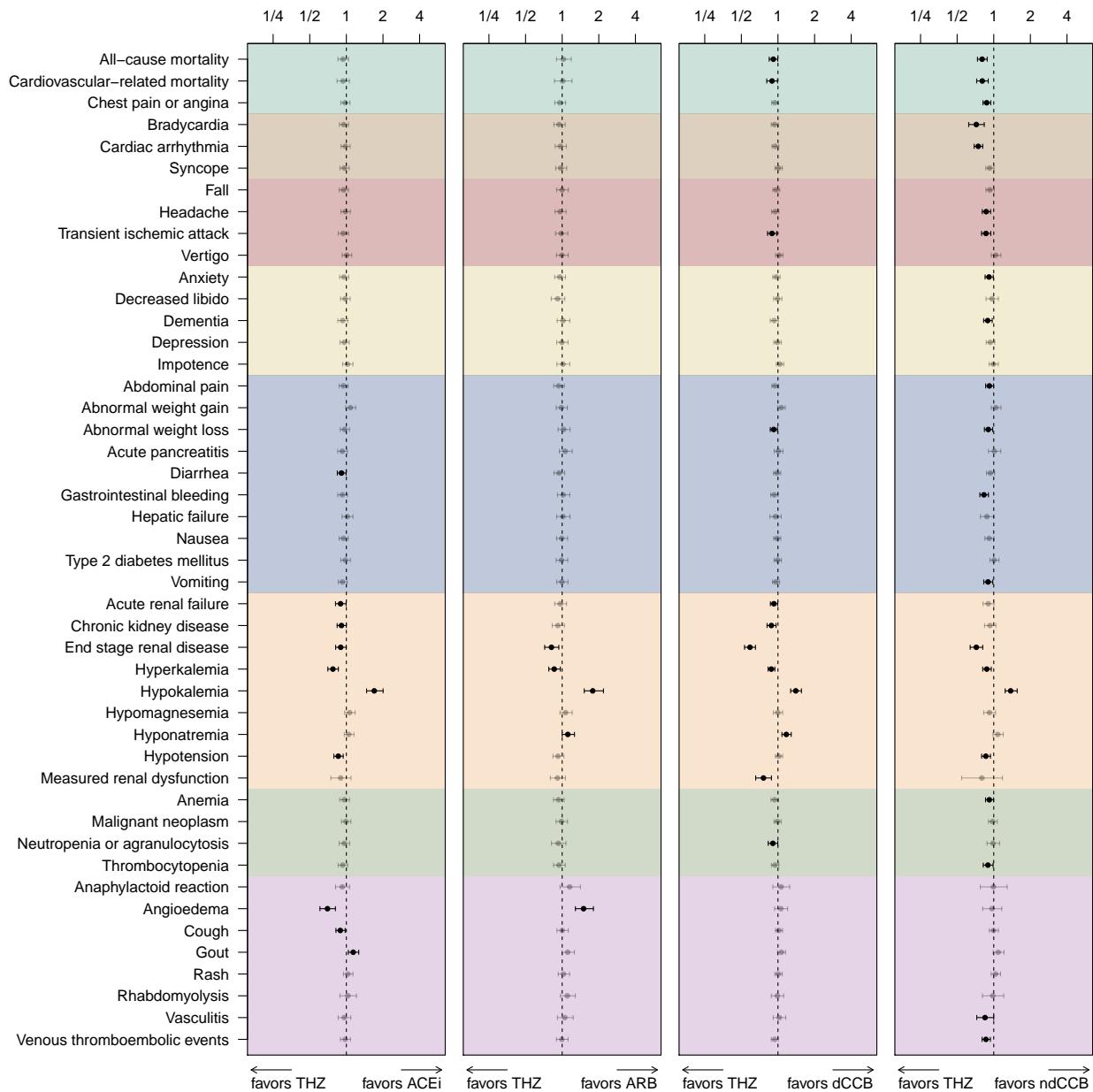


Supplementary Figure 12b: Meta-analytic safety profiles comparing ACEi to ARB, dCCB and ndCCB new-users under an on-treatment, PS-stratified design. Points and lines identify HR estimates with their 95% CI, respectively. Outcomes in grey signify that the CI covers HR = 1 (null hypothesis of no differential risk).

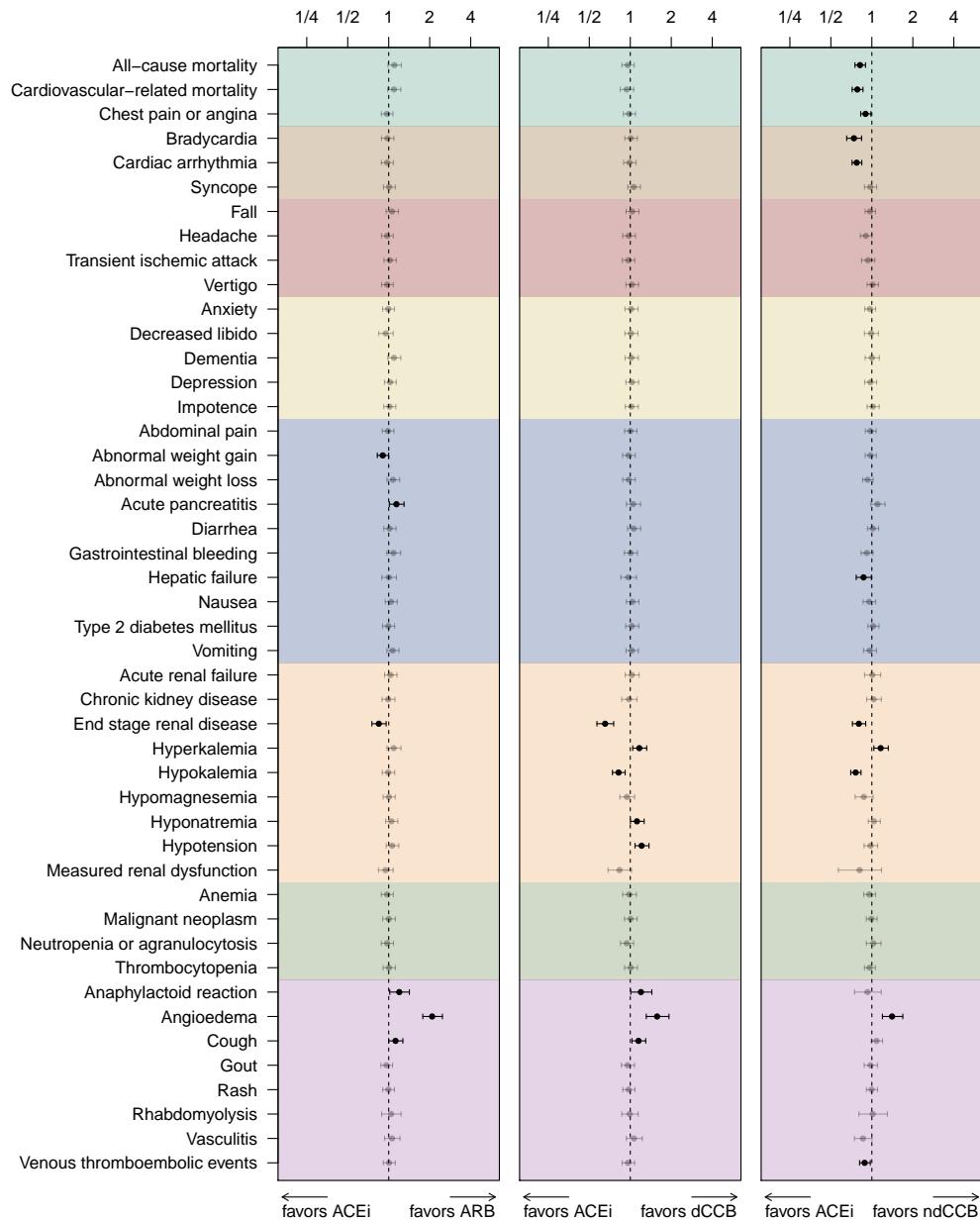


Supplementary Figure 12c: Meta-analytic safety profiles comparing ARB, dCCB and ndCCB new-users under an on-treatment, PS-stratified design. Points and lines identify HR estimates with their 95% CI, respectively. Outcomes in grey signify that the CI covers $HR = 1$ (null hypothesis of no differential risk).

Under an intent-to-treat, PS-stratified design



Supplementary Figure 13a: Meta-analytic safety profiles comparing THZ to ACEi, ARB, dCCB and ndCCB new-users under an intent-to-treat, PS-stratified design. Points and lines identify HR estimates with their 95% CI, respectively. Outcomes in grey signify that the CI covers HR = 1 (null hypothesis of no differential risk).

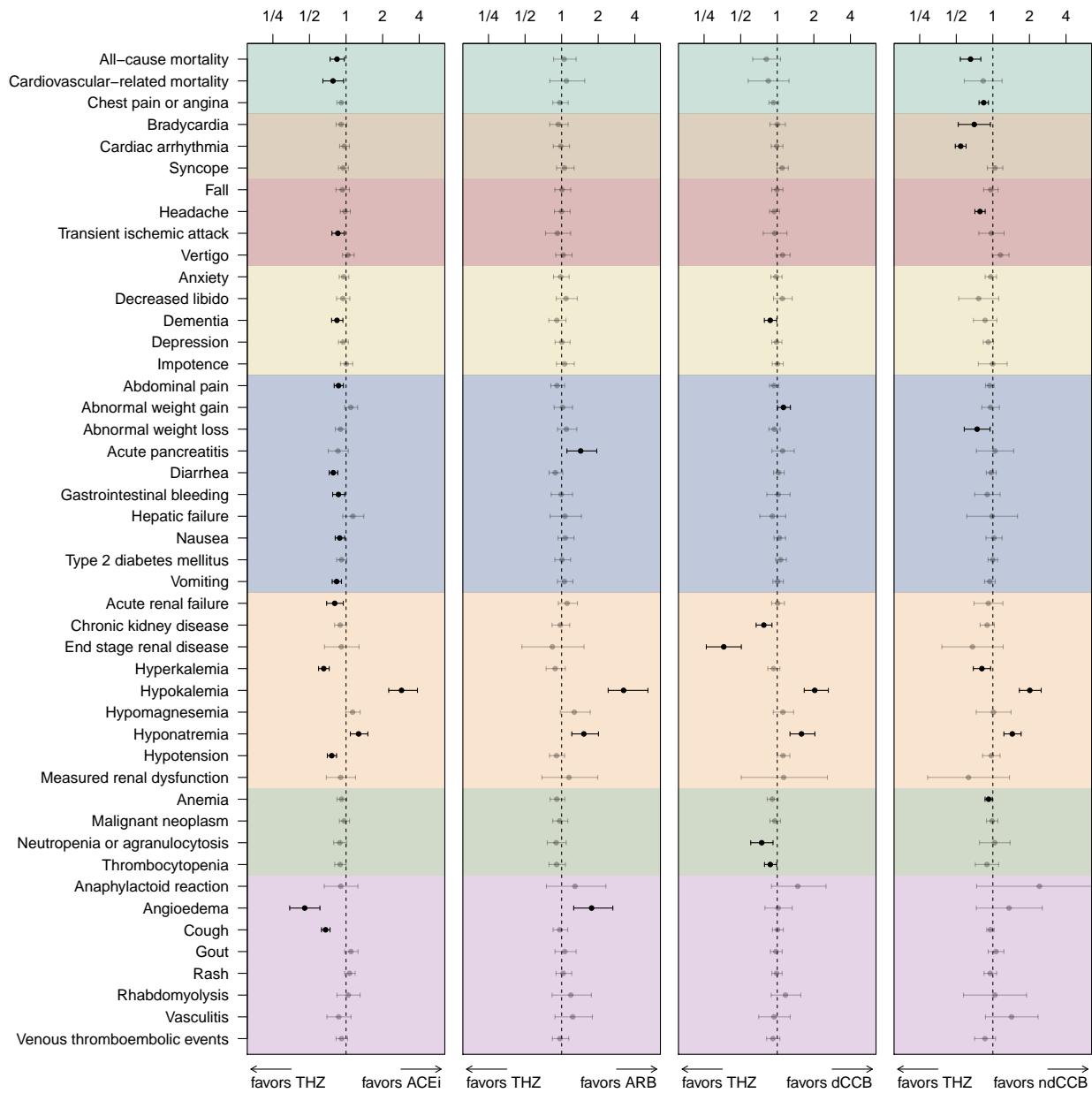


Supplementary Figure 13b: Meta-analytic safety profiles comparing ACEi to ARB, dCCB and ndCCB new-users under an intent-to-treat, PS-stratified design. Points and lines identify HR estimates with their 95% CI, respectively. Outcomes in grey signify that the CI covers HR = 1 (null hypothesis of no differential risk).

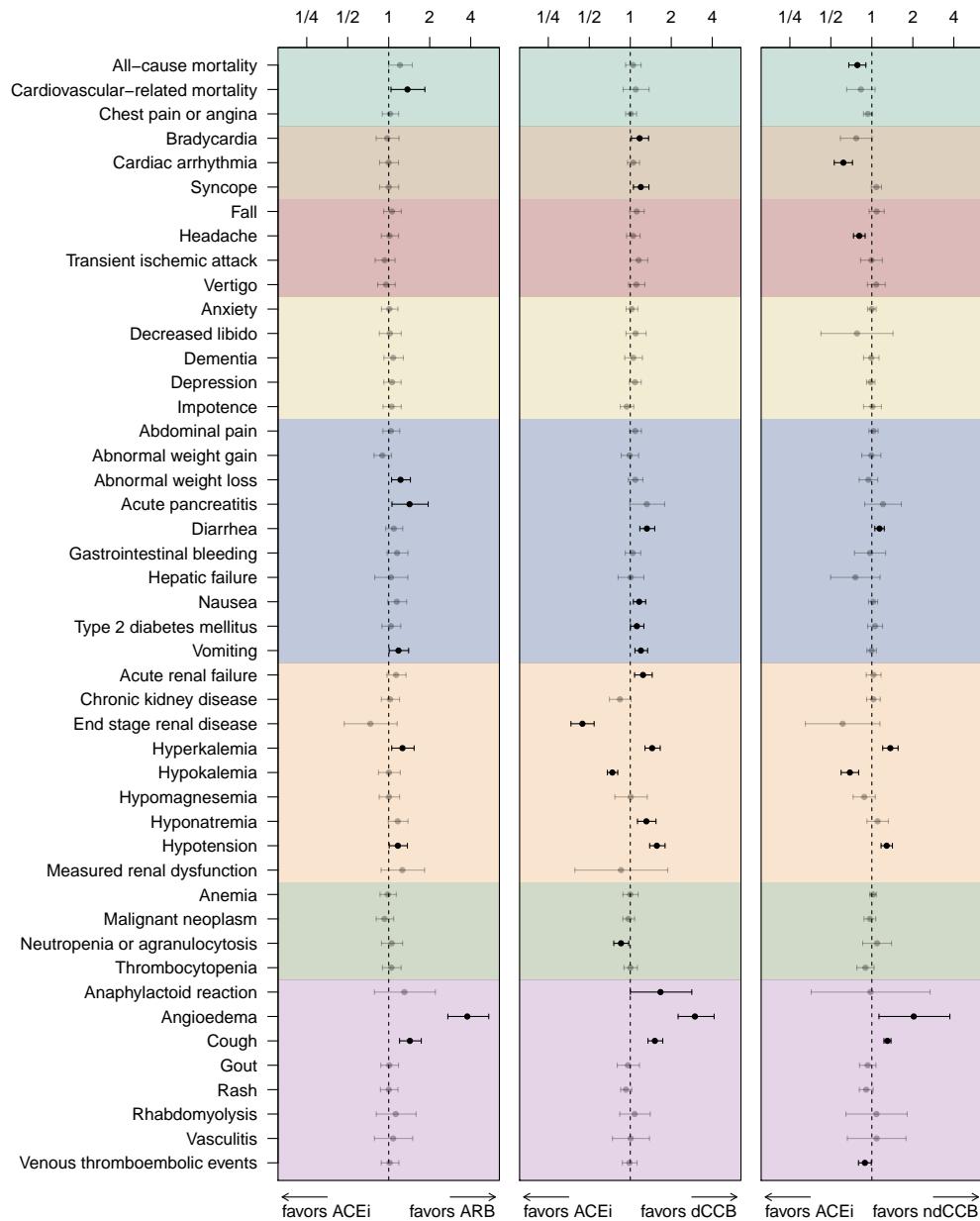


Supplementary Figure 13c: Meta-analytic safety profiles comparing ARB, dCCB and ndCCB new-users under an intent-to-treat, PS-stratified design. Points and lines identify HR estimates with their 95% CI, respectively. Outcomes in grey signify that the CI covers HR = 1 (null hypothesis of no differential risk).

Under an on-treatment, PS-matched design

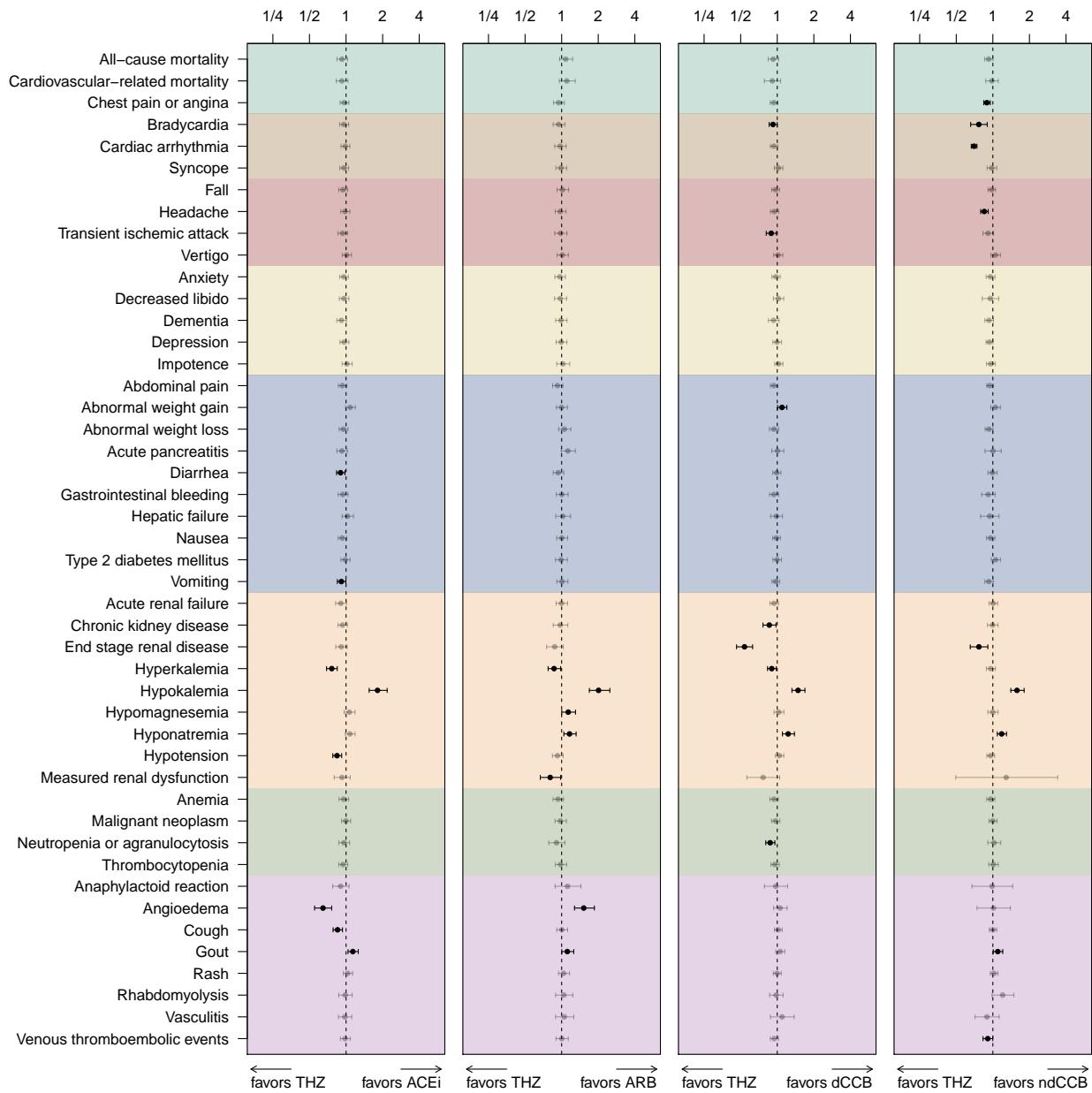


Supplementary Figure 14a: Meta-analytic safety profiles comparing THZ to ACEi, ARB, dCCB and ndCCB new-users under an on-treatment, PS-matched design. Points and lines identify HR estimates with their 95% CI, respectively. Outcomes in grey signify that the CI covers $HR = 1$ (null hypothesis of no differential risk).

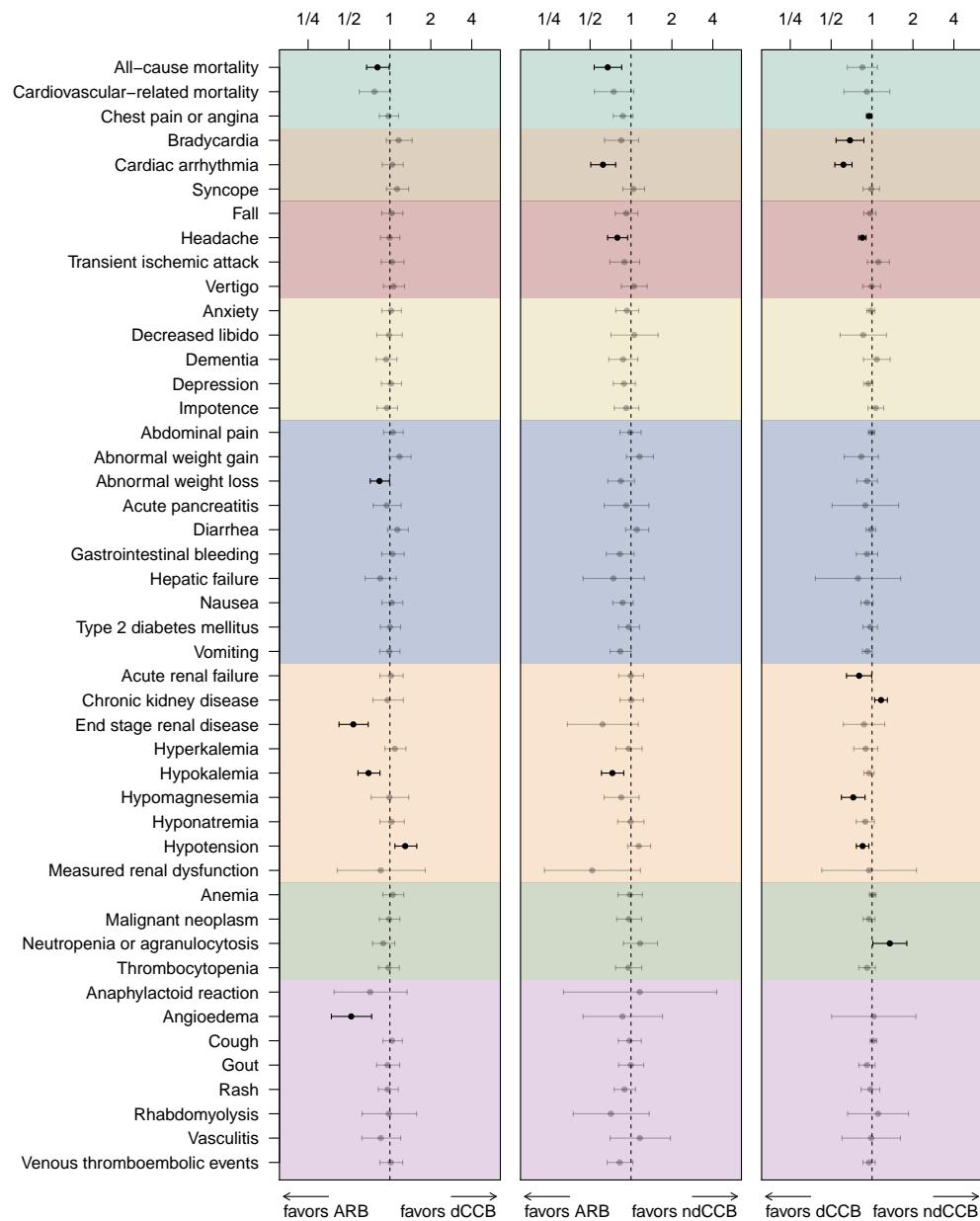


Supplementary Figure 14b: Meta-analytic safety profiles comparing ACEi to ARB, dCCB and ndCCB new-users under an on-treatment, PS-matched design. Points and lines identify HR estimates with their 95% CI, respectively. Outcomes in grey signify that the CI covers HR = 1 (null hypothesis of no differential risk).

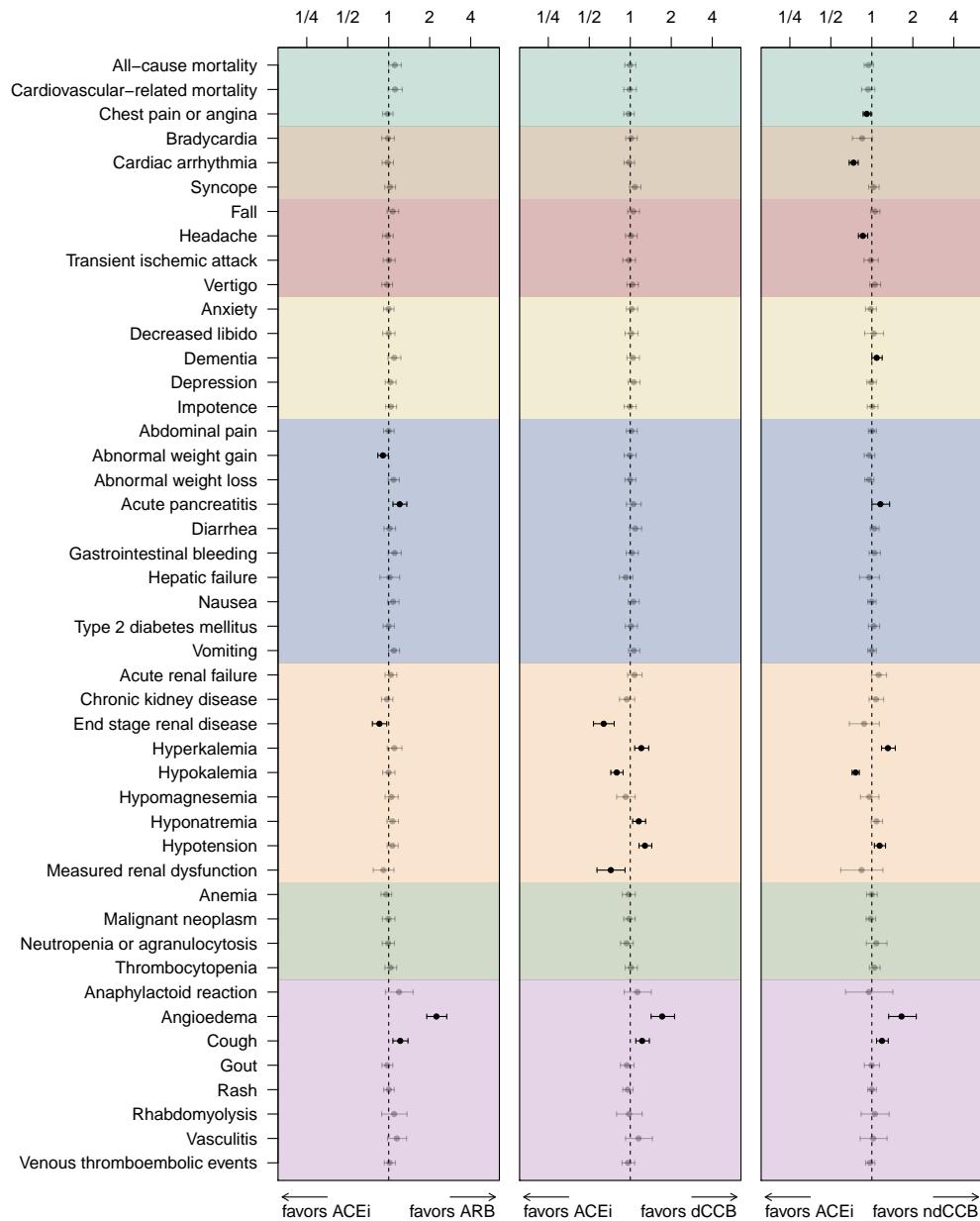
Under an intent-to-treat, PS-matched design



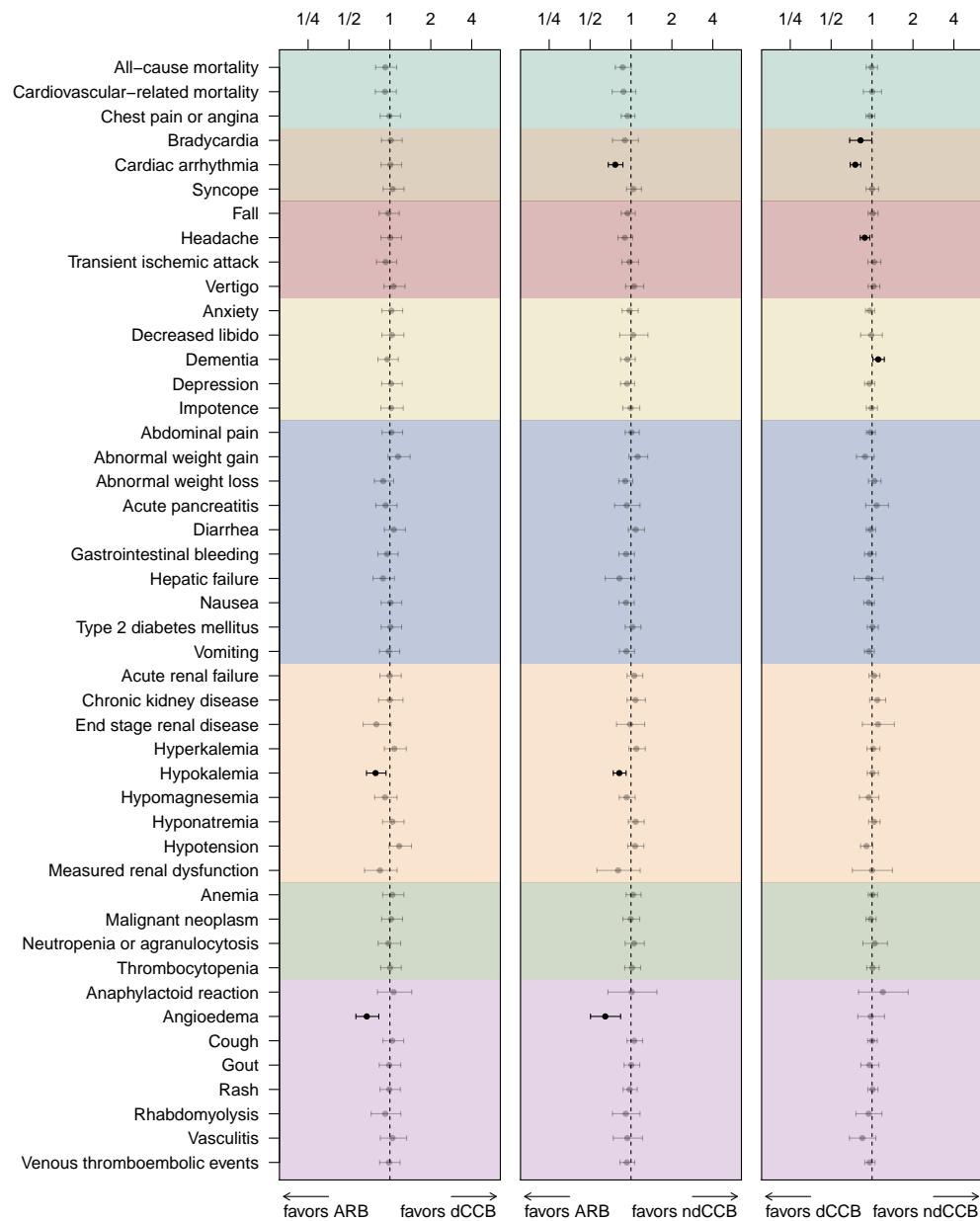
Supplementary Figure 15a: Meta-analytic safety profiles comparing THZ to ACEi, ARB, dCCB and ndCCB new-users under an intent-to-treat, PS-matched design. Points and lines identify HR estimates with their 95% CI, respectively. Outcomes in grey signify that the CI covers HR = 1 (null hypothesis of no differential risk).



Supplementary Figure 14c: Meta-analytic safety profiles comparing ARB, dCCB and ndCCB new-users under an on-treatment, PS-matched design. Points and lines identify HR estimates with their 95% CI, respectively. Outcomes in grey signify that the CI covers HR = 1 (null hypothesis of no differential risk).

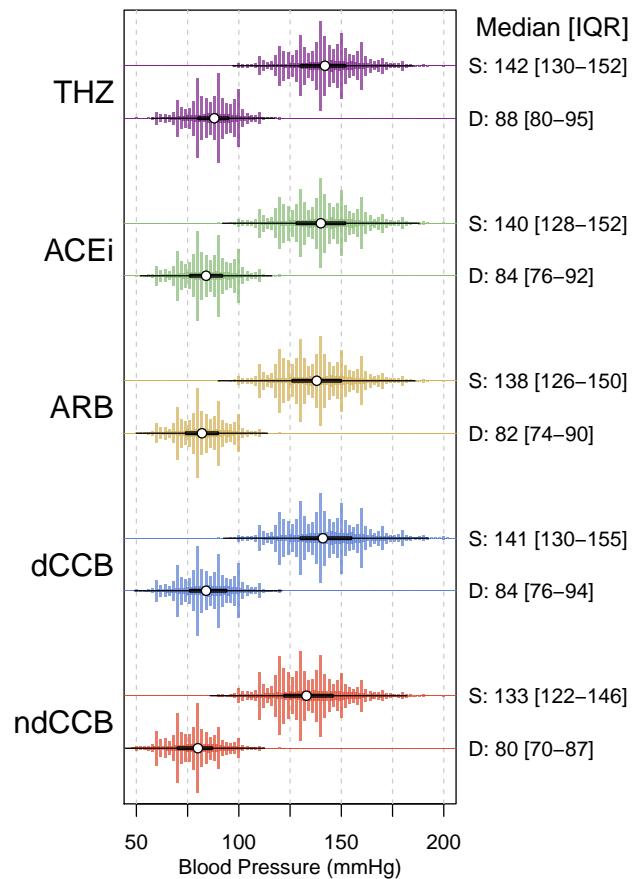


Supplementary Figure 15b: Meta-analytic safety profiles comparing ACEi to ARB, dCCB and ndCCB new-users under an intent-to-treat, PS-matched design. Points and lines identify HR estimates with their 95% CI, respectively. Outcomes in grey signify that the CI covers $HR = 1$ (null hypothesis of no differential risk).

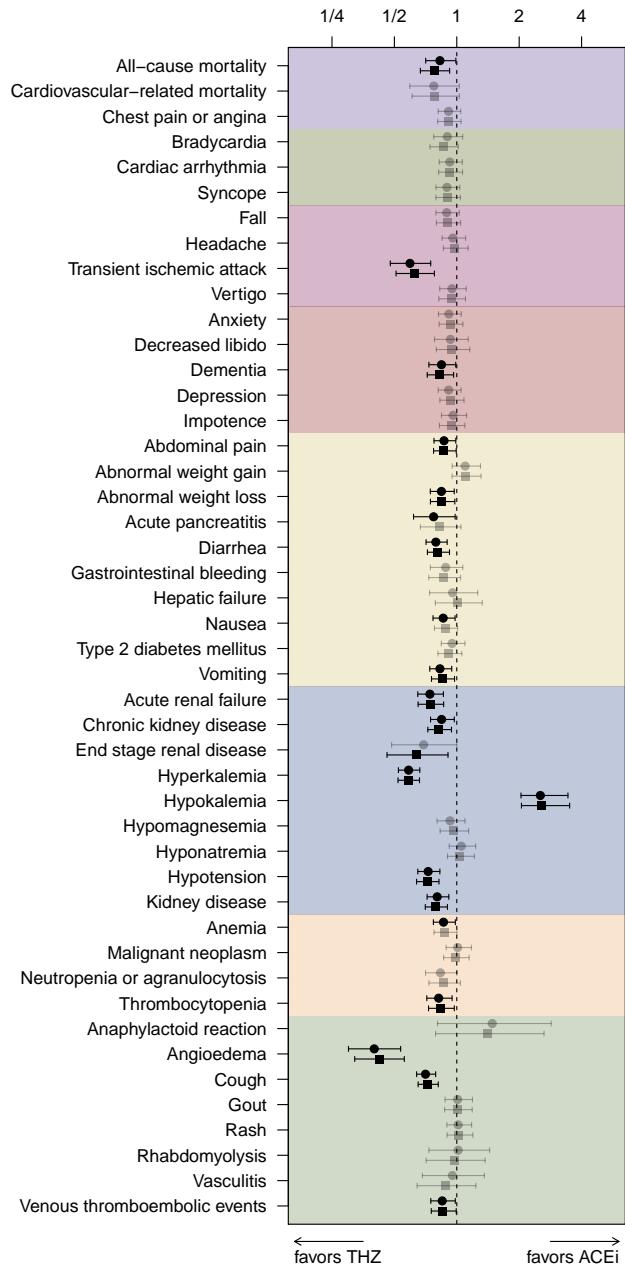


Supplementary Figure 15c: Meta-analytic safety profiles comparing ARB, dCCB and ndCCB new-users under an intent-to-treat, PS-matched design. Points and lines identify HR estimates with their 95% CI, respectively. Outcomes in grey signify that the CI covers $HR = 1$ (null hypothesis of no differential risk).

Blood pressure sensitivity analysis in PanTher



Supplementary Figure 16: Base-line systolic (S) and diastolic (D) blood pressure measurements across THZ, ACEi, ARB, dCCB and ndCCB new-users in PanTher. We report drug-class median and interquartile range (IQR) values.



Supplementary Figure 17: Blood pressure (BP) sensitivity analysis of safety outcomes comparing THZ and ACEi new-users in PanTher. “Original” HR estimates (points) use large-scale propensity score stratification without BP measurement inclusion. “BP-adjusted” HR estimates (squares) use large-scale propensity score stratification including baseline BP measurements. Lines show their 95% CIs.

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