**RESEARCH PROTOCOL**

**Large-scale evidence generation and evaluation across a network of databases   
for hypertension stepped-care treatment   
(LEGEND-HTNStepCare)**

**Version: 0.0.1**

**1. Amendments and Updates**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Version** | **Date** | **Section of study protocol** | **Amendment or update** | **Reason** |
| 0.0.1 | 14 Apr 2024 | All | Update | Initial draft |
|  |  |  |  |  |

**2. List of Abbreviations**

|  |  |
| --- | --- |
| ACEi | Angiotensin-converting enzyme inhibitor |
| ARB | Angiotensin receptor blocker |
| BB | Beta blocker |
| CCB | Calcium channel blocker |
| CDM | Common data model |
| dCCB | Dihydropyridine calcium channel blocker |
| HTN | Hypertension |
| LEGEND | Large-scale Evidence Generation and Evaluation across a Network of Databases |
| MACE | Major adverse cardiovascular event |
| MDRR | Minimum detectable risk ratio |
| ndCCB | Non-dihydropyridine calcium channel blocker |
| OHDSI | Observational |
| OMOP | Observational Medical Outcomes Partnership |
| PS | Propensity score |
| RAS | Renin-angiotensin-system |
| RCT | Randomized controlled trial |
| THZ | Thiazide or thiazide-like diuretics |

**3. Responsible Parties**

**3.1 Investigators**

|  |  |
| --- | --- |
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**3.2 Disclosures**

**RK** is a founder of Evidence2Health and receives grant from the US National Institutes of Health. **HMK** receives grants from the US Food & Drug Administration, Medtronics and Janssen Research and Development, is co-founder of HugoHealth and chairs the Cardiac Scientific Advisory Board of UnitedHealth. **MAS** receives grant funding from the US National Institutes of Health, the US Department of Veterans Affairs and the US Food & Drug Administration and contracts from Janssen Research and Development and IQVIA. **YL** receives grant funding from the US National Institutes of Health.

**4. Abstract**

**Background and Significance:** Hypertension is a major cause of morbidity and mortality globally and is associated with an elevated risk of cardiovascular events. Recommended anti-hypertensive agents can be applied to patients as a single agent (monotherapy) or in combination. In the case of combination, initial combination strategy can be considered, or stepped care strategy using a monotherapy followed by adding other agents use can be considered.

Many patients are unable to reach their target blood pressure with a monotherapy, therefore, they often use two or more medications in combination. Recent European hypertension guidelines recommend initial combination treatment for general patients with hypertension; however, the US guidelines maintain a recommendation of stepped care for most patients with uncontrolled blood pressure. Our team has already generated large-scale evidence comparing the effectiveness of each monotherapy and initial combination therapy for hypertension. Now, we will explore how the choice of step therapy medication affects patients’ cardiovascular and safety outcomes.

**Study Aims:** To determine real-world comparative effectiveness and safety of stepped care strategy of hypertension using health information encompassing millions of patients with hypertension, with a focus on individual at comorbidity risk and other key subgroups for treatment heterogeneity.

**Study Description:** We will conduct large-scale, systematic, observational studies to make pairwise comparisons of all stepped care regimens at the drug-, class- and population subgroup-level within our proposed Large-Scale Evidence Generations Across a Network of Database for Hypertension Stepped Care (LEGEND-HTNStepCare) initiative. LEGEND-HTNStepCare will leverage the Observational Health Data Sciences and Informatics (OHDSI) Community that provides access to a standing global network of administrative claims and electronic health record (EHR) data sources. LEGEND-HTNStepCare will study:

* **Population**: Adult, hypertension patients who newly added a secondary antihypertensive agent for their uncontrolled blood pressure by monotherapy
* **Comparators:** 
  + RAS agents: Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril, Azilsartan, Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan
  + THZ: Chlorthalidone, Hydrochlorothiazide, Indapamide, Metolazone
  + CCB: Amlodipine, Felodipine, Isradipine, Nicardipine, Nifedipine, Nisoldipine, Diltiazem, Verapamil
  + BB: Atenolol, Acebutolol, Betaxolol, Bisoprolol, Carvedilol, Labetalol, Metoprolol, Nadolol, Nebivolol, Penbutolol, Pindolol, Propranolol
* **Outcomes:**
  + Primary: 3- and 4-point major adverse cardiovascular events
  + Secondary effectiveness: Acute myocardial infarction, hospitalization with heart failure, revascularization, stroke, sudden cardiac death
  + Secondary safety: Abdominal pain, Abnormal weight gain, Abnormal weight loss, Acute pancreatitis, Acute renal failure, All-cause mortality, Angioedema, Anaphylactic reaction, Anemia, Anxiety, Bone fracture, Bradycardia, Cardiac arrhythmia, Chest pain or angina, Chronic kidney disease, Cough, Diarrhea, Dementia, Depression, Diarrhea, End stage renal disease, Fall, Gastrointestinal bleeding, Genitourinary infection, Gout, Headache, Hepatic failure, Hyperkalemia, Hypokalemia, Hyponatremia, Hypomagnesemia, Hypotension, Impotence, Joint pain, Malignant neoplasm, Measured renal dysfunction, Nausea, Neutropenia or agranulocytosis, Peripheral edema, Photosensitivity, Rash, Rhabdomyolysis, Syncope, Transient ischemic attack, Thrombocytopenia, Type 2 diabetes, Unstable angina, Vasculitis, Venous thromboembolism, Vertigo, Vomiting

For each data source and comparison, LEGEND-HTNStepCare will employ a state-of-the-art design:

* **Design**: Observational: active-comparator, new-user cohort study

Our systematic framework will address residual confounding, publication bias and p-hacking using data-driven, large-scale propensity adjustment for measured confounding, a large set of negative control outcome experiments to address unmeasured and systematic bias, prespecification and full disclosure of hypotheses tested and their results. These approaches capitalize on mature OHDSI open source resources and a large body of clinical and quantitative research that the LEGEND-HTNStepCare investigators originated and continue to drive. Finally, LEGEND-HTNStepCare is dedicated to open science and transparency and will publicly share all our analytic code from reproducible cohort definitions through turn-key software, enabling other research groups to leverage our methods, data, and results in order to verify and extend our findings.

**5. Milestones**

|  |  |  |
| --- | --- | --- |
| Milestone | Planned date | Actual date |
| Protocol online release | April 25, 2024 |  |
| Protocol registration |  |  |
| Collecting data partners |  |  |
| Start of analysis |  |  |
| End of analysis |  |  |
| Results of presentation |  |  |

**6 Rationale and Background**

Over 100 million US adults have hypertension, a leading cause of mortality and morbidity, and 70% of them cannot achieve adequate blood pressure control with monotherapy alone.(1) Although recent clinical practice guidelines suggest initiating therapy with two drugs,(2-4) more than 50% of people currently treated for hypertension start with a single medication.(5, 6) For these patients, clinical guidelines propose adding a second antihypertensive drug for treatment escalation.(4, 7)

However, the guidelines provide little guidance on which specific agents to add for which patients. There are no large randomized controlled trials (RCT) to guide recommendations about the choice of the second drug.(4) RCTs comparing antihypertensive drugs are not only expensive and time-consuming, but also cannot possibly test all the relevant drug combinations recommended by the guidelines. Given the abundance of potential strategies, there is a critical need to generate real-world evidence to guide the choice of comparators in future RCTs and to support guideline recommendations.

Advances in observational research design using real-world data provides an opportunity to produce high-quality evidence through strategies that support causal inference, enhance generalizability, and minimize bias. While this evidence will not supersede RCT evidence, it can identify promising directions for trials and provide Level of Evidence B for guideline recommendations.(8) Such research can be purposeful, pre-specified, and have strategies to prevent publication bias, p-hacking, and findings due to chance. In our prior work, we have successfully demonstrated how these methods can be applied to evaluate the effectiveness and safety of first-line antihypertensive monotherapies.(9-13) This will be the first study that applies these massive real-world datasets and reproducible methods to comprehensively evaluate the effectiveness and safety of the second antihypertensive agents added to monotherapy as a hypertension stepped care.

**7 Study Objectives**

Our long-term goal is to produce real-world evidence to inform decisions about RCTs for hypertension treatment escalation and to provide the highest quality non-randomized evidence to support guideline recommendations. The approach is distinctive because of the breadth and depth of data, and the use of state-of-the-art observational research methods to produce high-quality evidence. The overall objective in this protocol is to determine the comparative effectiveness and safety of the stepped care strategy in real-world settings. The central hypothesis is that there is heterogeneity in the effectiveness and safety of the secondary antihypertensive agent, and the optimal choice depends on patient characteristics and the initial therapy. Our preliminary data demonstrate a large variation in prescription patterns of the second agents added to monotherapy,(6) providing ample opportunity to leverage practice variation to test our hypothesis. The following three specific aims are proposed:

1. To determine the comparative effectiveness of the stepped-care strategy on major cardiovascular outcomes (e.g., myocardial infarction, stroke, heart failure).

2. To determine the comparative risk of the second antihypertensive agents on potential drug-related adverse events (e.g., acute renal failure, angioedema, gastrointestinal bleeding, hyperkalemia).

3. To assess heterogeneity in effectiveness and safety of the stepped care strategy among key patient subgroups defined by age, sex, race, ethnicity, and comorbidity.

**8 Research Methods**

LEGEND-HTNStepCare will execute three systematic, large-scale observational studies of second line HTN agents to estimate the relative risks of cardiovascular effectiveness and safety outcomes.

1. The Class-vs-Class Study will provide all pairwise comparisons between the stepped care combination with four major antihypertensive agent classes to evaluate their comparative effects on cardiovascular risk (Objective 1) and patient-centered safety outcomes (Objective 2);
2. The Drug-vs-Drug Study will furnish head-to-head pairwise comparisons between individual agents within and across class in stepped care combination (both Objectives 1 and 2); and
3. The Heterogeneity Study will refine these comparisons for hypertension patients for important subgroups (Objective 3).

In contrast to a single comparison approach, LEGEND-HTNStepCare will provide a comprehensive view of the findings and their consistency across populations, drugs, and outcomes. We will model each study on our successful collaborative research evaluating the comparative effectiveness of antihypertensives monotherapy previously published in The Lancet. (13)

Table 8.1 list the four major classes of antihypertensive agents and those ingredients licensed in the U.S. within each class. We will examine all xxx class-wise comparisons and all xxx ingredient-wise comparisons.

**Table 8.1 HTN drug classes and individual agents within each class**

|  |  |  |
| --- | --- | --- |
| **Major class** | **Class** | **Ingredient** |
| RAS acting agent | ACEi | Benazepril |
| RAS acting agent | ACEi | Captopril |
| RAS acting agent | ACEi | Enalapril |
| RAS acting agent | ACEi | Fosinopril |
| RAS acting agent | ACEi | Lisinopril |
| RAS acting agent | ACEi | Moexipril |
| RAS acting agent | ACEi | Perindopril |
| RAS acting agent | ACEi | Quinapril |
| RAS acting agent | ACEi | Ramipril |
| RAS acting agent | ACEi | Trandolapril |
| RAS acting agent | ARB | Azilsartan |
| RAS acting agent | ARB | Candesartan |
| RAS acting agent | ARB | Eprosartan |
| RAS acting agent | ARB | Irbesartan |
| RAS acting agent | ARB | Losartan |
| RAS acting agent | ARB | Olmesartan |
| RAS acting agent | ARB | Telmisartan |
| RAS acting agent | ARB | Valsartan |
| BB | BB | Atenolol |
| BB | BB | Acebutolol |
| BB | BB | Betaxolol |
| BB | BB | Bisoprolol |
| BB | BB | Carvedilol |
| BB | BB | Labetalol |
| BB | BB | Metoprolol |
| BB | BB | Nadolol |
| BB | BB | Nebivolol |
| BB | BB | Penbutolol |
| BB | BB | Pindolol |
| BB | BB | Propranolol |
| CCB | dCCB | Amlodipine |
| CCB | dCCB | Felodipine |
| CCB | dCCB | Isradipine |
| CCB | dCCB | Nicardipine |
| CCB | dCCB | Nifedipine |
| CCB | dCCB | Nisoldipine |
| CCB | ndCCB | Diltiazem |
| CCB | ndCCB | Verapamil |
| Diuretics | THZ | Chlorthalidone |
| Diuretics | THZ | Hydrochlorothiazide |
| Diuretics | THZ | Indapamide |
| Diuretics | THZ | Metolazone |

For each comparison, we are interested in the relative risk of each of the cardiovascular and safety outcomes described in Section 8.5.

**8.1 Study Design**

For each study, we will employ an active comparator, new-user cohort design.(14) New-user cohort design is advocated as the primary design to be considered for comparative effectiveness and drug safety. By identifying patients who start a new treatment course and using therapy initiation as the start of follow-up, the new-user design models a randomized controlled trial (RCT) where treatment commences at the index study visit. Exploiting such an index date allows a clear separation of baseline patient characteristics that occur prior to index date and are usable as covariates in the analysis without concern of inadvertently introducing mediator variables that arise between exposure and outcome. Excluding prevalent users as those without a sufficient washout period prior to first exposure occurrence further reduces bias due to balancing mediators on the causal pathway, time-varying hazards, and depletion of susceptibles. Our systematic framework across studies further will address residual confounding, publication bias, and p-hacking using data-driven, large-scale propensity adjustment for measured confounding, a large set of negative control outcome experiments to address unmeasured and systematic bias, and full disclosure of hypotheses tested. Figure 8.1 illustrates our design for all studies that the following sections describe in more detail.

Figure 8. Schematic of the LEGEND-HTNStepCare new-user cohort design and follow-up strategies

A black and white diagram with black text

Description automatically generated

\*This includes 1) the first-line agent is prescribed simultaneously on the index date, 2) both components are prescribed as a fixed dose single pill combination on the index date, 3) a last prescription for the first-line drug remains, so it can be considered simultaneous use. Dx: diagnosis; Rx: prescription.

**8.2 Data Source**

We will execute LEGEND-HTNStepCare as a series of OHDSI network studies. All data partners within OHDSI are encouraged to participate voluntarily and can do so conveniently, because of the community’s shared Observational Medical Outcome Partnership (OMOP) common data model (CDM) and OHDSI tool-stack. Many OHDSI community data partners have already committed to participate and we will recruit further data partners through OHDSI’s standard recruitment process, which includes protocol publication on OHDSI’s GitHub, an announcement in OHDSI’s research forum, presentation at the weekly OHDSI all-hands-on meeting and direct requests to data holders.

In Table 8.2, we report a brief description and size of the population it represents and its patient capture process and start date. While the earliest patient capture begins in 2000 (VA), the vast majority come from the 2010s to today, providing a decade of HTN treatment coverage. US population include those publicly insured, enriched for older individuals (VA) and racially diverse (VA, Sentara). The US data sources may capture the same patients across multiple sources. Different views of the same patients are an advantage in capturing the diversity of real-world health events that patients experience. All data sources will receive institutional review board approval or exemption for their participation before executing LEGEND-HTNStepCare.

**Table 8.2 Committed LEGEND-HTNStepCare data sources and the populations they cover.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Data source** | **Population** | **Patients** | **History** | **Data capture process and short description** |
| Yale New Haven Health System (YNHHS) | Academic medical center patients | 2M | 2010- | General practice, specialists and inpatient hospital services from the YNHHS in Connecticut. |
| Sentara Healthcare | Patients in a non-profit integrated healthcare system, all age, racially diverse | 7M | 2010- | The largest integrated health system in Northern Virginia with 12 hospitals and 566 outpatient sites. Sentara Healthcare serves the Hampton Roads region of Virginia, an area with 1.7 million residents, of which 31% are African American and 8% are Hispanic. |
| Department of Veterans Affairs Healthcare System (VA) | Veterans, older, racially diverse | 12M | 2000- | National VA healthcare system, the largest integrated provider of medical services in the US, provided at 170 VA medical centers and 1,063 outpatient sites. |
| Optum Electronic Health Records (PanTher) | US general population, all ages | 93M | 2006 - | Clinical information, prescriptions, lab results, vital signs, body measurements, diagnoses and procedures derived from clinical notes using natural language processing |
| Columbia University Irving Medical Center (CIUMC) | Academic medical center patients, all ages, racially diverse | 6M | 1989 - | General practice, specialists and inpatient hospital services from the New York-Presbyterian hospital and affiliated academic physician practices in New York |

**8.3 Study Population**

We will include all subjects in a data source who meet inclusion criteria for the stepped care exposure cohorts. Broadly, these cohorts will consist of hypertension patients with any of ACEis, ARBs, THZs, and CCBs previous as a first line hypertension treatment. We describe specific definitions of exposure cohorts for each study in the following sections.

**8.4 Exposure Comparators**

**8.4.1 Class-vs-Class Study comparisons**

The Class-vs-Class Study will construct nine exposure cohorts for secondary use of any drug ingredient within the four major classes in Table 8.1. Cohort entry (index date) for each patient is their first observed exposure to any drug ingredient for secondary added drug classes (different to primary class). Consistent with an idealized target trial for hypertension therapy and cardiovascular risk, inclusion criteria for patients based on the index date will include:

* Hypertension diagnosis but no secondary HTN diagnosis before the index date;
* At least 1 year of observation time before the index date (to improve new-user sensitivity);
* At least one prescription of first antihypertensive agents before 30 days earlier than the index date;
* No single use of antihypertensives at the index date;
* No prior drug exposure to a comparator antihypertensive agent; and
* No other antihypertensive agents (other diuretics: loop diuretics/K+ sparing diuretics/aldosterone antagonists; direct renin inhibitor; alpha-1 blocker; central alpha-2 agonist and other centrally acting drugs; direct vasodilators).

We will construct and compare separately cohort patients either with

* At least 1 months use of first-line antihypertensive agents use before the index date.

In this case, a month of first-line antihypertensive agents is consistent with 2017 AHA/ACC guidelines. We purposefully do not automatically exclude or restrict to patients with first line beta-blockers, with a history of myocardial infarction, stroke or other major cardiovascular events, which will allow us to report relative effectiveness and safety for individuals with both low or moderate and high cardiovascular risk. Likewise, we do not automatically exclude or restrict to individuals with severe renal impairment. We will use cohort diagnostics, such as achieving covariate balance and clinical empirical equipoise between exposure cohorts (Section 9) and stakeholder input to guide the possible need to exclude other prior diagnoses, such as heart failure.

Of note, the inclusion criteria do not directly incorporate quantitative measures of blood pressure control, such as elevated blood pressure; such laboratory values are irregularly captured in even EHR data sources. The ACC/AHA guidelines advise escalating to add a second agent when average BP is more than 20/10 mmHg above their BP target. We will conduct sensitivity analyses involving available BP measurements to demonstrate their balance between exposure cohorts (described later in Section 9). In the unlikely event that balance is not met, we will consider an inclusion criterion of BP > 140/90 mmHg within 6 months before the index.

For each data source, we will then execute all 12 pairwise major class comparisons for which the data source yields ≥ 1,000 patients in each arm (Appendix A. 1. 1). Appendix A. 1. 2 reports the complete OHDSI ATLAS cohort description for new-users of thiazide or thiazide-like diuretics with the first line RAS acting agent. This description lists complete specification of cohort entry events, additional inclusion criteria, cohort exit events, and all associate standard OMOP CDM concept code sets used in the definition. ATLAS automatically translates these definitions into network-deployable SQL source code. In addition, we plan to perform 44 comparisons based on detailed classes (Appendix A. 1. 3). Significantly fewer numbers of patients strongly suggest data source-specific differences in prescribing practices that may introduce residual bias and sufficient sample sizes are required to construct effective propensity score models.

**8.4.2 Drug-vs-Drug Study comparisons**

The Drug-vs-Drug Study will construct 1,216 exposure cohorts for new-users of each drug ingredient in Table 8.1. We will apply the same cohort definition, inclusion criteria and patient count minimum as described in Section 8.4.1.

Theoretically, 206,048 combinations of first line antihypertensives and second add-on agents are possible. However, we want to take into account the fact that Class-vs-Class comparisons will be performed and clinical situation when stepped care is performed. Therefore, we will focus primary clinical interpretation and scientific publishing to the 6,832 comparisons where the first-line drug is the same and the second line drug is a different ingredient within the same class (Appendix 2. .1. 1).

Appendix A. 2. 2 reports the complete OHDSI ATLAS cohort description for new-users of hydrochlorothiazide added to their benazepril treatment. Again, we programmatically construct all new-user drug-level cohort and automatically translate into SQL.

**8.4.3 Heterogeneity Study comparisons**

The Heterogeneity Study will further stratify all class- and drug-level exposure cohorts in Section 8.4.1 and 8.4.2 by clinically important patient characteristics that modify cardiovascular risk of relative treatment heterogeneity to provide patient-focused treatment recommendations. These factors will include:

* Age (18 – 44 / 45 – 64 / ≥ 65 at the index date)
* Sex (women/men)
* Race (African American or black)
* Heart failure
* Type 2 diabetes mellitus
* Renal impairment

We will narrow down the patient population to major comorbidities suggested in the guideline, such as heart failure, type 2 diabetes mellitus, and renal impairment. Heart failure and type 2 diabetes mellitus will be defined according to the diagnosis. Renal impairment through diagnosis codes for chronic kidney disease and end-stage renal disease, dialysis procedures, and laboratory measurements of estimated glomerular filtration rate, serum creatinine and urine albumin.

Appendix A. 3 presents complete OHDSI ATLAS specifications for these subgroups, including all standard OMOP CDM concept codes defining heart failure, diabetes, and renal impairment.

**8.4.4 Validation**

We will validate exposure cohorts and aggregate drug utilization using comprehensive cohort characterization tools against data sources. Chief among these tools stands OHDSI’s CohortDiagnostics package (<https://github.com/OHDSI/CohortDiagnostics>). For any cohort and data source mapped to OMOP CDM, this package systematically generates incidence new-user rates (stratified by age, gender, and calendar year), cohort characteristics (all comorbidities, drug use, procedures, health utilization) and the actual codes found in the data triggering the various rules in the cohort definitions. This can allow researchers and stakeholders to understand the heterogeneity of source coding for exposures and health outcomes as well as the impact of various inclusion criteria on overall cohort counts (details described in Section 9).

**8.5 Outcomes**

We originally identified outcomes for LEGEND-HTNStepCare from clinical trial endpoints from clinical guidelines and systematic reviews. We augmented these with adverse events from US structured product labels of hypertension drugs. 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, clinical guidelines and systematic review of clinical trial of hypertension treatments informed our clinical definition of cardiovascular outcomes. We developed all exposure cohorts according to the definition itself through ATLAS. We did not perform source record verification or other validation methods.

Across all data sources and pairwise exposure cohorts, we will assess relative risks of 32 cardiovascular and patient-centered outcomes (Table 8.3). Primary outcomes of interest are:

* 3-point major adverse cardiovascular events (MACE), including acute myocardial infarction, stroke, and sudden cardiac death
* 4-point major adverse cardiovascular events (MACE), including acute myocardial infarction, stroke, heart failure hospitalization, and sudden cardiac death

Secondary effectiveness outcomes include:

* Individual MACE components

In data sources with laboratory measurements, secondary outcomes further include:

* Blood pressure control

We will also study secondary antihypertensive agent adverse events and safety concerns highlighted in the 2017 ACC/AHA guidelines and from RCTs, including SPRINT trial. We will employ the same level of systematic rigor in studying outcomes regardless of their primary or secondary label.

A majority of outcome definitions have been previously implemented and validated in our own work, based heavily on prior development by others (see references in Table 8.5). To assess across-source consistency and general clinical validity, we will characterize outcome incidence, stratified by age, sex and index year for each data source.

**Table 8.5 LEGEND-HTNStepCare study outcomes**

|  |  |  |
| --- | --- | --- |
| **Phenotype** | **Brief logical description** | **Prior development** |
| **Primary cardiovascular outcomes** | | |
| 4-point MACE | Condition record of acute myocardial infarction, hemorrhagic or ischemic stroke or sudden cardiac death during an inpatient or ER visit, and inpatient or ER visit (hospitalization) with heart failure condition record | (15-31) |
| 3-point MACE | Condition record of acute myocardial infarction, hemorrhagic or ischemic stroke or sudden cardiac death during an inpatient or ER visit | (15-27) |
| **Secondary effectiveness outcomes** | | |
| Acute myocardial infarction | Condition record of acute myocardial infarction during inpatient or ER visit | (15-20) |
| Hospitalization with heart failure | Inpatient or ER visit with heart failure condition record | (28-34) |
| Revascularization | Procedure record of percutaneous coronary intervention or coronary artery bypass grafting during an inpatient or ER visit | (35) |
| Stroke | Condition record of hemorrhagic or ischemic stroke during an inpatient or ER visit | (21-26) |
| Sudden cardiac death | Condition record of sudden cardiac death during an inpatient or ER visit | (18, 27) |
| Blood pressure control | First BP measurement with value < 130/80 mmHg |  |
| **Secondary safety outcomes** | | |
| Abdominal pain | Abdominal pain condition record of any type; successive records with > 90 day gap are considered independent episodes | (36-38) |
| Abnormal weight gain | Abnormal weight gain record of any type; successive records with > 90 days gap are considered independent episodes; note, weight measurements not used | (39) |
| Abnormal weight loss | Abnormal weight loss record of any type; successive records with > 90 day gap are considered independent episodes, note, weight mesurements not used | (40) |
| Acute pancreatitis | Condition record of acute pancreatitis during an inpatient or ER visit | (41-44) |
| Acute renal failure | Condition record of acute renal failure during an inpatient or ER visit | (45-53) |
| All-cause mortality | Death record of any type | (18, 29, 54) |
| Angioedema | Condition record of angioedema during an inpatient or ER visit | (55, 56) |
| Anaphylactic reaction | Anaphylactic reaction condition record during an inpatient or ER visit; successive records with > 7 days gap are considered independent episodes | (55, 57) |
| Anemia | The first condition record of anemia | (58-60) |
| Anxiety | The first condition record of anxiety, which is followed by another anxiety condition record or a drug used to treat anxiety | (61-64) |
| Bone fracture | Bone fracture condition record of any type; successive records with > 90 day gap are considered independent episodes |  |
| Bradycardia | The first condition record of bradycardia which is followed by another bradycardia condition record | (65, 66) |
| 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 | (27, 67-70) |
| Chest pain or angina | The first condition record of chest pain or angina | (71) |
| 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 | (48, 72-79) |
| Cough | Cough condition record of any type; | (80, 81) |
| Diarrhea | Diarrhea condition record of any type; successive records with > 30 day gap are considered independent episodes | (82-84) |
| Dementia | The first condition record of dementia | (21, 85-91) |
| 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 procedure | (62, 87) (91) (92) (93) (94) (95) |
| Diarrhea | Diarrhea condition record of any type; successive records with > 30 day gap are considered independent episodes | (82-84) |
| 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 | (44, 78, 96) |
| Fall | Condition record of any type of fall; successive records with < 180 day gap are considered independent episodes | (97-99) |
| Gastrointestinal bleeding | Condition record of gastrointestinal hemorrhage during an inpatient or ER visit | (100-104) |
| Genitourinary infection | Condition record of any type of genital or urinary tract infection during an outpatient or ER visit | (105) |
| Gout | The first condition record of gout | (106-109) |
| Headache | Headache condition record of any type; successive records with > 30 day gap are considered independent episodes | (110, 111) |
| Hepatic failure | The first condition record of hepatic failure, necrosis or coma | (112-119) |
| Hyperkalemia | Condition record for hyperkalemia or potassium measurement > 5.6 mmol/L; successive records with > 90 day gap are considered independent episode | (120-122) |
| Hypokalemia | Condition record for hypokalemia; successive records with > 90 day gap are considered independent episode | (123) |
| Hyponatremia | Condition record for hyponatremia of any type; | (124, 125) |
| Hypomagnesemia | Hypomagnesemia condition record of any type; successive records with > 90 day gap are considered independent episodes | (126, 127) |
| Hypotension | Hypotension condition record of any type; successive records with > 90 day gap are considered independent episodes | (128) |
| Impotence | The first condition record of impotence | (129-132) |
| Joint pain | Joint pain condition record of any type; successive records with > 90 days gap are considered independent episode |  |
| 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) | (92, 133-145) |
| Measured renal dysfunction | The first creatinine measurement with value > 3 mg/dL | (53) |
| Nausea | Nausea condition record of any type; successive records with > 30 day gap are considered independent episode | (36, 146, 147) |
| Neutropenia or agranulocytosis | The first condition record of neutropenia or agranulocytosis | (148, 149) |
| Peripheral edema | Edema condition record of any type; successive records with > 180 day gap are considered independent episode |  |
| Photosensitivity | Condition record of drug-induced photosensitivity during any type of visit |  |
| Rash | Rash condition record of any type; successive records with > 90 day gap are considered independent episodes | (150) |
| Rhabdomyolysis | Rhabdomyolysis condition record of muscle disorder condition record with creatinine measurement 5\*ULN during an inpatient or ER visit; successive records with > 90 day gap are considered independent episodes | (151, 152) |
| Syncope | Syncope condition record of any type; successive records with > 180 day gap are considered independent episodes | (128) |
| Transient ischemic attack | Transient ischemic attack condition record during an inpatient or ER visit; successive records with > 30 days gap are considered independent episodes | (26) |
| Thrombocytopenia | The first condition record of thrombocytopenia | (146, 153, 154) |
| Type 2 diabetes | 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 measurement s with value > 6.5% | (155-157) |
| Unstable angina | Inpatient or ER visits with preinfarction syndrome condition record; all qualifying inpatient visit occurring > 7 days apart are considered independent episodes | (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 thromboembolism | Venous thromboembolism condition record of any type; successive records with > 180 day gap are considered independent episodes | (162-165) |
| 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 | (36, 146, 147) |

**8.6 Analysis**

**8.6.1 Contemporary utilization of drug classes and individual agents**

For all cohorts in the three studies, we will describe overall utilization as well as temporal trends in the use of each drug class and agents within the class. Further, we will evaluate these trends in patient groups by age (18-44 / 45-64 / ≥65 years), gender, race, and geographic regions. These data will provide insight into the current patterns of use ad possible disparities. These data are critical to guide the real-world application of treatment decision pathways for the treatment of HTN patients.

Specifically, we will calculate and validate aggregate drug utilization using the OHDSI’s CohortDiagnostics package against data sources. The CohortDiganostics package works in two steps: 1) Generate the utilization results and diagnostics against a data source and 2) Explore the generated utilization and diagnostics in a user-friendly graphical interface R-Shiny app. Through the interface, one can explore patient profiles of a random sample of subjects in a cohort. These diagnostics provide a consistent methodology to evaluate cohort definition and phenotype algorithms across a variety of observational databases. This will enable researchers and stakeholders to become informed on the appropriateness of including specific data sources within analyses, exposing potential risks related to heterogeneity and variability in patient care delivery that, when not addressed in the design, could result in errors such as high correlated covariates in propensity score matching of a target and a comparator cohort. Thus, the added value of this approach is two-fold in terms of exposing data quality for a study question and ensuring face validity checks are performed on proposed covariates to be used for balancing propensity scores.

**8.6.2 Relative risk of cardiovascular and patient-centered outcomes**

We will execute a systematic process to estimate the relative risk of cardiovascular and patient-centered outcomes between new-users of second-line HTN agents. The process will adjust for measured confounding, control from further residual (unmeasured) bias and accommodate important design choices to best emulate the nearly impossible to execute, idealized RCT that our stakeholders envision across data source populations, comparators, outcomes, and subgroups.

To adjust for potential measured confounding and improve the balance between cohorts, we will build large-scale propensity score (PS) models for each pairwise comparison and data source using a consistent data-driven process through regularized regression. This process engineers a large set of predefined baseline patient characteristics, including age, gender, race, index month/year and other demographics and prior conditions, drug exposures, procedures, laboratory measurements and health service utilization behaviors, to provide the most accurate prediction of treatment and balance patient cohorts across many characteristics. Construction of condition, drug, procedures and observations include occurrences within 365, 180, and 30 days prior to index date and are aggregated at several SNOMED (condition) and ingredient/ATC class (drug) levels. Other demographic measures include comorbidity risk scores (Charlson, DCSI, CHADS2, CHAD2VASc). From prior work, feature counts have ranged in the 1,000s-10,000s, and these large-scale PS models have outperformed hdPS in simulation and real-world examples.

We will:

* Exclude patients who have experienced the outcome prior to their index date,
* Stratify and variable-ratio match patients by PS, and
* Use Cox proportional hazard models

to estimate hazard ratios (HRs) between alternative target and comparator treatments for the risk of each outcome in each data source. In addition, we will perform a sensitivity analysis that does not exclude individuals who previously experienced a glycemic control outcome before the index date. The regression will condition on the PS strata/matching-unit with treatment allocation as the sole explanatory variable and censor patients at the end of their time-at-risk (TAR) or data source observation period. We will prefer stratification over matching if both sufficiently balance patients (see Section 9), as the former optimizes patient inclusions and thus generalizability.

We will execute each comparison using three different TAR definitions, reflecting different and import causal contrasts:

* Intent-to-treat (TAR: index + 1 🡪 end of observation) captures both direct treatment effects and (long-term) behavioral/treatment changes that initial assignment triggers
* On-treatment-1 (TAR: index + 1 🡪 treatment discontinuation) is more patient-centered and captures direct treatment effect while allowing for escalation with additional HTN agents; and
* On-treatment-2 (TAR: index + 1 🡪 discontinuation or escalation with HTN agents) carries the least possible confounding with other concurrent HTN agents.

Our “on-treatment” is often called “per-protocol”. Systematically executing with multiple causal contrasts enables us to identify potential biases that missing prescription data, treatment escalation and behavioral changes introduce, while preserving the ease of intent-to-treat interpretation and power if the data demonstrate them as unbiased. Appendix A.3 reports the modified cohort exit rule for the on-treatment-2 TAR.

We will aggregate HR estimates across non-overlapping data sources to produce meta-analytic estimates using a random-effects meta-analysis. The classic meta-analysis assumes that per-data source likelihoods are approximately normally distributed. This assumption fails when outcomes are rare as we expect for some safety events. Here, our recent research shows that as the number of data sources increases, the non-normality effect increases to where coverage of 95% confidence intervals (CIs) can be as low as 5%. To counter this, we will also apply a Bayesian meta-analysis model that neither assumes normality nor requires patient-level data sharing by building on composite likelihood methods and enables us to introduce appropriate overlap weights between data sources.

Residual study bias from unmeasured and systematic sources often remains in observational studies even after controlling for measured confounding through PS-adjustment. For each comparison-outcome effect, we will conduct negative control (falsification) outcome experiments, where the null hypothesis of no effect is believed to be true, using approximately 100 controls. We identified these controls through a data-rich algorithm that identifies prevalent OMOP condition concept occurrences that lack evidence of association with exposures in published literature, drug-product labeling and spontaneous reports, and were then adjudicated by clinical review. We previously validated 60 of the controls in LEGEND-HTN. Appendix C lists these negative controls and their OMOP condition concept IDs.

Using the empirical null distributions from these experiments, we will calibrate each study effect HR estimate, its 95% CI and the *p*-value to reject the null hypothesis of no differential effect. We will declare an HR as significantly different from no effect when its calibrated p < 0.05 without correcting for multiple testing. Finally, blinded to all trial results, study investigators will evaluate study diagnostics for all comparisons to assess if they were likely to yield unbiased estimates (Section 9).

**8.6.3 Sensitivity analyses and missingness**

Because of the potential confounding effect of blood pressure at baseline between treatment choice and outcomes and to better understand the impact of limited blood pressure level measurements on effectiveness and safety estimation that arises in some EHR data, we will perform pre-specified sensitivity analyses for all studies within data sources that contain reliable blood pressure measurements. Within a study, for each exposure pair, we will first rebuild PS models where we additionally include baseline blood pressure as patient characteristics, stratify or matching patients under the new PS models that directly adjust for potential confounding by blood pressure and then estimate effectiveness and safety HRs.

A limitation of the Cox model is that no doubly robust procedure is believed to exist for estimating HRs, due to their non-collapsibility. Doubly robust procedures combine baseline patient characteristic-adjusted outcome and PS models to control for confounding and, in theory, remain unbiased when either (but not necessarily both) model is correctly specified. Doubly robust procedures do exist for hazard differences, and we will validate the appropriateness of our univariable Cox modelling by comparing estimate differences under an additive hazards model with and without doubly robust-adjustment. In practice, however, neither the outcome nor PS model is correctly specified, leading to systematic error in the observational setting.

Missing data of potential concern are patient demographics (gender, age, race) for out inclusion criteria. We will include only individuals whose baseline eligibility can be characterized that will most notably influence race subgroup assessments in the **Heterogeneity Study**. No further missing data can arise in our large-scale PS models because all features, except for demographics, simply indicate the presence or absence of health records in a given time-period. Finally, we limit the impact of missing data, such as prescription information, relating to exposure time-at-risk by entertaining multiple definitions. In all reports, we will clearly tabulate numbers of missing observations and patient attrition.

**9 Sample Size and Study Power**

Within each data source, we will execute all comparisons with ≥ 1,000 eligible patients per arm. Blinded to effect estimates, investigators and stakeholders will evaluate extensive study diagnostics for each comparison to assess reliability and generalizability, and only report risk estimates that pass. These diagnostics will include

1. Minimum detectable risk ratio (MDRR) as a typical proxy for power,
2. Preference score distributions to evaluate empirical equipoise 10 and population generalizability,
3. Extensive patient characteristics to evaluate cohort balance before and after PS-adjustment,
4. Negative control calibration plots to assess residual bias, and
5. Kaplan-Meier plots to examine hazard ratio proportionality assumptions.

We will define cohorts to stand in empirical equipoise if the majority of patients carry preference score between 0.3 and 0.7 and to achieve balance if all after-adjustment characteristics return absolute standardized mean differences < 0.1.

**10 Strength and Limitations**

**10.1 Strength**

The strengths of this study stem from the research question, the methodologies employed, and our commitment to open science:

* This study is poised to be the first to systematically address the critical clinical question: What are the relative benefits and risks of adding a second antihypertensive drug to monotherapy in patients with hypertension?
* We are employing massive, diverse real-world datasets and cutting-edge observational research methods to provide comprehensive estimates of effectiveness and safety for second antihypertensive drugs added to monotherapy. These tools have previously evaluated antihypertensive monotherapies, but have not been used to assess the addition of a second drug when monotherapy is insufficient for managing hypertension.
* Unlike typical observational research, this study will minimize residual bias by employing reproducible methods to mitigate observed confounding. We will enhance transparency by reporting diagnostics such as empirical equipoise and covariate balance, and by using a large set of control outcomes to detect and correct for any remaining systematic errors. This approach marks a significant advancement in observational research.
* We will assess antihypertensive medications at both class and individual drug levels, evaluating effectiveness and safety across patient subgroups defined by demographic and clinical characteristics. This comprehensive approach has not been adequately explored in previous studies.
* Our commitment to Open Science includes making all study artifacts—such as the study protocol, analytical code, and full results—publicly available. We will also provide real-time access to these materials for external analysis and interpretation, a practice that goes beyond the transparency typically seen in past studies.

**10.2 Limitations**

Some additional aspects merit consideration:

• Residual Confounding: Despite our sophisticated analytic approach and diagnostics, residual confounding remains a possibility. We anticipate that ongoing and future randomized controlled trials (RCTs) will shed further light on this issue. We will use two distinct methods to triangulate residual confounding: large-scale propensity score (PS) adjustment and the use of numerous negative controls. Our PS adjustment incorporates tens of thousands of baseline covariates for matching and stratification.

• Medication Adherence: Merely having a prescription does not guarantee medication consumption. We will conduct sensitivity analyses using pharmacy refill data to infer adherence, and perform on-treatment analysis to adjust for potential discrepancies in adherence across different drug classes.

• Dose Variability: We will conduct sensitivity analyses among patients maintaining consistent dosing throughout the on-treatment period to account for differences in dosing and potency.

• Medication Indication: Some patients, like those with congestive heart failure, might be prescribed antihypertensive medications for reasons other than lowering blood pressure. We will exclude such patients from the study cohort during sensitivity analyses.

• Informative Censoring: There is a risk that censoring at the end of the on-treatment periods could be informative. We will utilize extensive negative controls to detect and adjust for any potential bias introduced by this censoring.

• Overlap of Patients Across Databases: While our study is designed to minimize patient overlap across databases by adhering to federated analytic principles, we acknowledge that some overlap may occur. We will ensure that patient experiences are reported distinctly for each database.

**11 Protection of Human Subjects**

LEGEND-HTNStepCare does not involve human subject research. The project does, however, use human data collected during routine healthcare provision. Most often data are de-identified within data source. All data partners executing the LEGEND-HTNStepCare studies within their data sources will have received institutional review board (IRB) approval or waiver for participation in accordance with their institutional governance prior to execution (see Table 11.1). LEGEND-HTNStepCare executes across a federated and distributed data network, where analysis code is sent to participating data partners and only aggregate summary statistics are returned, with no sharing of patient-level data between organizations.

Table 11.1 IRB approval or waiver statement from partners.

|  |  |
| --- | --- |
| **Data source** | **Statement** |
| Yale New Haven Health System | Use of the YNHHS EHR data source was approved by the Yale University Institutional Review Board as an OHDSI network study (IRB number: ) |
| Sentara Healthcare | Use of the Sentara Healthcare EHR data source was approved by Sentara Health System Institutional Review Board (IRB number:) |
| Department of Veterans Affairs (VA) | Use of the VA-OMOP data source was reviewed by the Department of Veterans Affairs Central Institutional Review Board (IRB) and was determined to meet the criteria for exemption under Exemption Category 4(3) and approved the request for Waiver of HIPAA Authorization. |

**12 Management and Reporting of Adverse Events and Adverse Reactions**

LEGEND-HTNStepCare uses coded data that already exist in electronic databases. In these types of databases, it is not usually possible to link (i.e., identify a potential causal association between) a particular product and medical event for any specific individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual adverse event reports. The study results will be assessed for medically important findings.

**13 Plans for Disseminating and Communicating Study Results**

**13.1 Transparent and re-usable research tools**

We will publicly register this protocol and announce its availability for feedback from stakeholders, the OHDSI community and within clinical professional societies. This protocol will link to open-source code for all steps to generating diagnostics, effect estimates, figures, and tables. Such transparency is possible because we will construct our studies on top of the OHDSI tool stack of open-source software tools that are community developed and rigorously tested. We will publicly host LEGEND-HTNStepCare source code at (https://github.com/ohdsi-studies/LegendHtnStepCare), allowing public contribution and review, and free re-use for anyone’s future research.

**13.2 Continuous sharing of results**

LEGEND-HTNStepCare embodies a new approach to generating evidence from healthcare data that overcome weaknesses in the current process of answering and publishing (or not) one question at a time. Generating evidence for thousands of research and control questions using a systematic process enables us to not only evaluate that process and the coherence and consistency of the evidence, but also to avoid p-hacking and publication bias. We will store and openly communicate all these results as they become available using a user-friendly web-based app that serves up all descriptive statistics, study diagnostics and effect estimates for each cohort comparison and outcome. Open access to this app will through a public facing LEGEND-HTNStepCare webpage.

**13.3 Scientific meetings and publications**

We will deliver multiple presentations annually at scientific venues including the annual meetings of the American College of Cardiology, American Heart Association and American Medical Informatics Association. We will also prepare multiple scientific publications for clinical, informatics and statistical journals.

**13.4 General public**

We believe in sharing our findings that will guide clinical care with the general public. LEGEND-HTNStepCare will use social-media (Twitter, LinkedIn) to facilitate this. With dedicated support from the OHDSI communications specialist, we will deliver regular press releases at key project stages, distributed via the extensive media networks of Yale and UCLA.

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**Appendix**

**A Exposure Cohort Definitions**

OHDSI’s ATLAS, a demo available at https://atlas-demo.ohdsi.org, serves as an open-source tool tailored for researchers aiming to perform scientific analyses on standardized observational data, which is converted into the OMOP Common Data Model v5. With ATLAS, researchers have the capability to construct cohorts by delineating groups of individuals based on either exposure to a medication or diagnosis of a specific medical condition, utilizing healthcare data. The software offers a vocabulary search functionality for medical concepts, enabling the identification of individuals with particular conditions or drug exposures. Additionally, the software facilitates population effect level estimation analyses, which permit the comparison of two distinct cohorts and make use of R packages for leverage. We developed all exposure cohorts according to the definition itself through ATLAS.

**Second-line antihypertensive drug class new-users**

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

Index rule defining the patient index date:

* First exposure to any drug containing the RxNorm ingredient 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
* Age over 18 years old at index date
* A diagnose of hypertension on or preceding the index date
* Prior exposure to antihypertensive drugs (first line monotherapy) between any time prior and 30 days preceding the index date
* Concurrent first-line antihypertensive drug use on the index date
* No observed prescription for any other antihypertensive agents except target and comparator group
* 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 choice 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.

|  |  |  |
| --- | --- | --- |
| **Major class** | **Class** | **Ingredient (ConceptID)** |
| RAS agent | 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) |
| BB | BB | Acebutolol (1319998), Atenolol (1314002),  Betaxolol (1322081), Bisoprolol (1338005),  Carvedilol (1346823), Labetalol (1386957),  Metoprolol (1307046), Nadolol (1313200),  Nebivolol (1314577), Penbutolol (1327978),  Pindolol (1345858), Propranolol (1353766) |
| CCB | dCCB | Amlodipine (1332418), Felodipine (1353776),  Isradipine (1326012), Nicardipine (1318137),  Nifedipine (1318853), Nisoldipine (1319880) |
| ndCCB | Diltiazem (1328165), Verapamil (1307863) |
| Diuretics | THZ | Chlorthalidone (1395058), Hydrochlorothiazide (974166), Indapamide (978555), Metolazone (907013) |

**A.1 Class-vs-Class Exposure**

**A. 1. 1 Major class-vs-major class comparison**

|  |  |
| --- | --- |
| **Target** | **Comparator** |
| RAS agents + CCB | RAS agents + BB |
| RAS agents + CCB | RAS agents + THZ |
| RAS agents + BB | RAS agents + THZ |
| CCB + RAS agents | CCB + BB |
| CCB + RAS agents | CCB + THZ |
| CCB + BB | CCB +THZ |
| THZ + RAS agents | THZ + CCB |
| THZ + RAS agents | THZ + BB |
| THZ + CCB | THZ + BB |
| BB + RAS agents | BB + CCB |
| BB + RAS agents | BB + THZ |
| BB + CCB | BB + THZ |

**A. 1. 2 Example definition of “Add on thiazide or thiazide like diuretics after initial RAS acting agent therapy” (RAS agents + Thiazide)**

**Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of 'Thiazide and thiazide like diuretics' for the first time in the person's history, who are >= 18 years old.

Limit cohort entry events to the earliest event per person.

**Inclusion Criteria**

1. Previous hypertension

Entry events having at least 1 condition occurrence of 'Hypertension', starting anytime on or before cohort entry start date.

1. Previous RAS agent

Entry events having at least 1 drug exposure of 'RAS agents', starting anytime up to 30 days before cohort entry start date.

1. new Rx of RAS agents

Entry events with any of the following criteria:

* having at least 1 drug era of 'RAS agents', starting anytime on or before cohort entry start date and ending 1 days after cohort entry start date.
* having at least 1 drug exposure of 'RAS agents', starting anytime on or before cohort entry start date and ending 1 days after cohort entry start date.

1. No other comparators (CCB, BB)

Entry events with all of the following criteria:

* having at most 0 drug exposures of 'CCB', starting anytime on or before cohort entry start date.
* having at most 0 drug exposures of 'BB', starting anytime on or before cohort entry start date.

1. No other secondary antihypertensive agents

Entry events having at most 0 drug exposures of 'other secondary antihypertensive agents'.

**Cohort Exit**

The cohort end date will be based on a continuous exposure to 'Thiazide and thiazide like diuretics': allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

**Concept Set Definition**

1. Thiazide and thiazide like diuretics

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 907013 | metolazone | Drug | RxNorm | NO | YES | NO |
| 974166 | hydrochlorothiazide | Drug | RxNorm | NO | YES | NO |
| 978555 | indapamide | Drug | RxNorm | NO | YES | NO |
| 1395058 | chlorthalidone | Drug | RxNorm | NO | YES | NO |

1. Hypertension

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 316866 | Hypertensive disorder | Condition | SNOMED | NO | YES | NO |
| 320128 | Essential hypertension | Condition | SNOMED | NO | YES | NO |
| 321074 | Pre-existing hypertension complicating pregnancy, childbirth and puerperium | Condition | SNOMED | **YES** | YES | NO |
| 4118910 | Maternal hypertension | Condition | SNOMED | **YES** | YES | NO |

1. RAS agents

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1308216 | lisinopril | Drug | RxNorm | NO | YES | NO |
| 1308842 | valsartan | Drug | RxNorm | NO | YES | NO |
| 1310756 | moexipril | Drug | RxNorm | NO | YES | NO |
| 1317640 | telmisartan | Drug | RxNorm | NO | YES | NO |
| 1331235 | quinapril | Drug | RxNorm | NO | YES | NO |
| 1334456 | ramipril | Drug | RxNorm | NO | YES | NO |
| 1335471 | benazepril | Drug | RxNorm | NO | YES | NO |
| 1340128 | captopril | Drug | RxNorm | NO | YES | NO |
| 1341927 | enalapril | Drug | RxNorm | NO | YES | NO |
| 1342439 | trandolapril | Drug | RxNorm | NO | YES | NO |
| 1346686 | eprosartan | Drug | RxNorm | NO | YES | NO |
| 1347384 | irbesartan | Drug | RxNorm | NO | YES | NO |
| 1351557 | candesartan | Drug | RxNorm | NO | YES | NO |
| 1363749 | fosinopril | Drug | RxNorm | NO | YES | NO |
| 1367500 | losartan | Drug | RxNorm | NO | YES | NO |
| 1373225 | perindopril | Drug | RxNorm | NO | YES | NO |
| 40226742 | olmesartan | Drug | RxNorm | NO | YES | NO |
| 40235485 | azilsartan | Drug | RxNorm | NO | YES | NO |

1. CCB

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1307863 | verapamil | Drug | RxNorm | NO | YES | NO |
| 1318137 | nicardipine | Drug | RxNorm | NO | YES | NO |
| 1318853 | nifedipine | Drug | RxNorm | NO | YES | NO |
| 1319880 | nisoldipine | Drug | RxNorm | NO | YES | NO |
| 1326012 | isradipine | Drug | RxNorm | NO | YES | NO |
| 1328165 | diltiazem | Drug | RxNorm | NO | YES | NO |
| 1332418 | amlodipine | Drug | RxNorm | NO | YES | NO |
| 1353776 | felodipine | Drug | RxNorm | NO | YES | NO |

1. BB

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1307046 | metoprolol | Drug | RxNorm | NO | YES | NO |
| 1313200 | nadolol | Drug | RxNorm | NO | YES | NO |
| 1314002 | atenolol | Drug | RxNorm | NO | YES | NO |
| 1314577 | nebivolol | Drug | RxNorm | NO | YES | NO |
| 1319998 | acebutolol | Drug | RxNorm | NO | YES | NO |
| 1322081 | betaxolol | Drug | RxNorm | NO | YES | NO |
| 1327978 | penbutolol | Drug | RxNorm | NO | YES | NO |
| 1338005 | bisoprolol | Drug | RxNorm | NO | YES | NO |
| 1345858 | pindolol | Drug | RxNorm | NO | YES | NO |
| 1346823 | carvedilol | Drug | RxNorm | NO | YES | NO |
| 1353766 | propranolol | Drug | RxNorm | NO | YES | NO |
| 1386957 | labetalol | Drug | RxNorm | NO | YES | NO |

1. Other secondary antihypertensive agents

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 904542 | triamterene | Drug | RxNorm | NO | YES | NO |
| 932745 | bumetanide | Drug | RxNorm | NO | YES | NO |
| 942350 | torsemide | Drug | RxNorm | NO | YES | NO |
| 956874 | furosemide | Drug | RxNorm | NO | YES | NO |
| 970250 | spironolactone | Drug | RxNorm | NO | YES | NO |
| 991382 | amiloride | Drug | RxNorm | NO | YES | NO |
| 1305447 | methyldopa | Drug | RxNorm | NO | YES | NO |
| 1309068 | minoxidil | Drug | RxNorm | NO | YES | NO |
| 1309799 | eplerenone | Drug | RxNorm | NO | YES | NO |
| 1317967 | aliskiren | Drug | RxNorm | NO | YES | NO |
| 1341238 | terazosin | Drug | RxNorm | NO | YES | NO |
| 1344965 | guanfacine | Drug | RxNorm | NO | YES | NO |
| 1350489 | prazosin | Drug | RxNorm | NO | YES | NO |
| 1363053 | doxazosin | Drug | RxNorm | NO | YES | NO |
| 1373928 | hydralazine | Drug | RxNorm | NO | YES | NO |
| 1398937 | clonidine | Drug | RxNorm | NO | YES | NO |

**A. 1. 3 Class-vs-class comparison**

|  |  |
| --- | --- |
| **Target** | **Comparator** |
| ACEi+dCCB | ACEi+ndCCB |
| ACEi+dCCB | ACEi+BB |
| ACEi+dCCB | ACEi+THZ |
| ACEi+ndCCB | ACEi+BB |
| ACEi+ndCCB | ACEi+THZ |
| ACEi+BB | ACEi+THZ |
| ARB+dCCB | ARB+ndCCB |
| ARB+dCCB | ARB+BB |
| ARB+dCCB | ARB+THZ |
| ARB+ndCCB | ARB+BB |
| ARB+ndCCB | ARB+THZ |
| ARB+BB | ARB+THZ |
| THZ+ACEi | THZ+ARB |
| THZ +ACEi | THZ+dCCB |
| THZ +ACEi | THZ+ndCCB |
| THZ +ACEi | THZ+BB |
| THZ +ARB | THZ+dCCB |
| THZ +ARB | THZ+ndCCB |
| THZ +ARB | THZ+BB |
| THZ +dCCB | THZ +ndCCB |
| THZ +dCCB | THZ+BB |
| THZ +ndCCB | THZ+BB |
| dCCB+ACEi | dCCB+ARB |
| dCCB+ACEi | dCCB+BB |
| dCCB+ACEi | dCCB+THZ |
| dCCB+ARB | dCCB+BB |
| dCCB+ARB | dCCB+THZ |
| dCCB+BB | dCCB+THZ |
| ndCCB+ACEi | ndCCB+ARB |
| ndCCB+ACEi | ndCCB+BB |
| ndCCB+ACEi | ndCCB+THZ |
| ndCCB+ARB | ndCCB+BB |
| ndCCB+ARB | ndCCB+THZ |
| ndCCB+BB | ndCCB+THZ |
| BB+ACEi | BB+ARB |
| BB+ACEi | BB+dCCB |
| BB+ACEi | BB+ndCCB |
| BB+ACEi | BB+THZ |
| BB+ARB | BB+dCCB |
| BB+ARB | BB+ndCCB |
| BB+ARB | BB+THZ |
| BB+dCCB | BB+ndCCB |
| BB+dCCB | BB+THZ |
| BB+ndCCB | BB+THZ |

**A. 1. 4** **Example definition of “Add on dihydropyridine calcium channel blocker after initial angiotensin converting enzyme inhibitor therapy” (ACEi + dCCB)**

**Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of 'dCCB' for the first time in the person's history, who are >= 18 years old.

Limit cohort entry events to the earliest event per person.

**Inclusion Criteria**

1. Previous hypertension

Entry events having at least 1 condition occurrence of 'Hypertension', starting anytime on or before cohort entry start date.

1. Previous ACEi agent

Entry events having at least 1 drug exposure of ACEi, starting anytime up to 30 days before cohort entry start date.

1. New Rx of ACEi agents

Entry events with any of the following criteria:

* having at least 1 drug era of ‘ACEi’, starting anytime on or before cohort entry start date and ending 1 days after cohort entry start date.
* having at least 1 drug exposure of 'ACEi', starting anytime on or before cohort entry start date and ending 1 days after cohort entry start date.

1. No other comparators (ndCCB, BB, ARB)

Entry events with all of the following criteria:

* having at most 0 drug exposures of 'ndCCB', starting anytime on or before cohort entry start date.
* having at most 0 drug exposures of 'BB', starting anytime on or before cohort entry start date.
* having at most 0 drug exposures of 'ARB', starting anytime on or before cohort entry start date.

1. No other secondary antihypertensive agents

Entry events having at most 0 drug exposures of 'other secondary antihypertensive agents'.

**Cohort Exit**

The cohort end date will be based on a continuous exposure to ‘dCCB': allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

The person also exists the cohort when encountering any of the following events:

1. Drug exposures of ‘other comparators (ndCCB, BB, ARB)’

**Concept Set Definitions**

1. dCCB

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1318137 | nicardipine | Drug | RxNorm | NO | YES | NO |
| 1318853 | nifedipine | Drug | RxNorm | NO | YES | NO |
| 1319880 | nisoldipine | Drug | RxNorm | NO | YES | NO |
| 1326012 | isradipine | Drug | RxNorm | NO | YES | NO |
| 1332418 | amlodipine | Drug | RxNorm | NO | YES | NO |
| 1353776 | felodipine | Drug | RxNorm | NO | YES | NO |

1. Hypertension

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 316866 | Hypertensive disorder | Condition | SNOMED | NO | YES | NO |
| 320128 | Essential hypertension | Condition | SNOMED | NO | YES | NO |
| 321074 | Pre-existing hypertension complicating pregnancy, childbirth and puerperium | Condition | SNOMED | **YES** | YES | NO |
| 4118910 | Maternal hypertension | Condition | SNOMED | **YES** | YES | NO |

1. ACEi

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1308216 | lisinopril | Drug | RxNorm | NO | YES | NO |
| 1310756 | moexipril | Drug | RxNorm | NO | YES | NO |
| 1331235 | quinapril | Drug | RxNorm | NO | YES | NO |
| 1334456 | ramipril | Drug | RxNorm | NO | YES | NO |
| 1335471 | benazepril | Drug | RxNorm | NO | YES | NO |
| 1340128 | captopril | Drug | RxNorm | NO | YES | NO |
| 1341927 | enalapril | Drug | RxNorm | NO | YES | NO |
| 1342439 | trandolapril | Drug | RxNorm | NO | YES | NO |
| 1363749 | fosinopril | Drug | RxNorm | NO | YES | NO |
| 1373225 | perindopril | Drug | RxNorm | NO | YES | NO |

1. ndCCB

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1307863 | verapamil | Drug | RxNorm | NO | YES | NO |
| 1328165 | diltiazem | Drug | RxNorm | NO | YES | NO |

1. BB

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1307046 | metoprolol | Drug | RxNorm | NO | YES | NO |
| 1313200 | nadolol | Drug | RxNorm | NO | YES | NO |
| 1314002 | atenolol | Drug | RxNorm | NO | YES | NO |
| 1314577 | nebivolol | Drug | RxNorm | NO | YES | NO |
| 1319998 | acebutolol | Drug | RxNorm | NO | YES | NO |
| 1322081 | betaxolol | Drug | RxNorm | NO | YES | NO |
| 1327978 | penbutolol | Drug | RxNorm | NO | YES | NO |
| 1338005 | bisoprolol | Drug | RxNorm | NO | YES | NO |
| 1345858 | pindolol | Drug | RxNorm | NO | YES | NO |
| 1346823 | carvedilol | Drug | RxNorm | NO | YES | NO |
| 1353766 | propranolol | Drug | RxNorm | NO | YES | NO |
| 1386957 | labetalol | Drug | RxNorm | NO | YES | NO |

1. ARB

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1308842 | valsartan | Drug | RxNorm | NO | YES | NO |
| 1317640 | telmisartan | Drug | RxNorm | NO | YES | NO |
| 1346686 | eprosartan | Drug | RxNorm | NO | YES | NO |
| 1347384 | irbesartan | Drug | RxNorm | NO | YES | NO |
| 1351557 | candesartan | Drug | RxNorm | NO | YES | NO |
| 1367500 | losartan | Drug | RxNorm | NO | YES | NO |
| 40226742 | olmesartan | Drug | RxNorm | NO | YES | NO |
| 40235485 | azilsartan | Drug | RxNorm | NO | YES | NO |

**A. 2 Drug-vs-Drug Exposure**

There can be hundreds of thousands of combinations of drug levels in stepped care. However, comparisons between other classes will be made as described in the previous sections. Therefore, in the drug level comparison, we limit the scope to combinations in which the second drug is compared in situations where the first drug was already decided considering the clinical decision process.

**A. 2. 1 Drug level comparison within the same first and second class**

1. Same first drug ingredient and different second drug ingredient (n = 6,832)

e.g., benazepril + hydrochlorothiazide vs benazepril + chlorthalidone

|  |  |  |
| --- | --- | --- |
| **Target**  **(n of combination)** | **Comparator**  **(n of combination)** | **Number of combinations** |
| RAS agents + CCB | RAS agents + CCB | 504 |
| RAS agents + BB | RAS agents + BB | 1,188 |
| RAS agents + Thiazide | RAS agents + Thiazide | 108 |
| CCB + RAS agents | CCB + RAS agents | 1,224 |
| CCB + BB | CCB + BB | 528 |
| CCB + Thiazide | CCB + Thiazide | 48 |
| Thiazide + RAS agents | Thiazide + RAS agents | 612 |
| Thiazide + CCB | Thiazide + CCB | 112 |
| Thiazide + BB | Thiazide + BB | 264 |
| BB + RAS agents | BB + RAS agents | 1,836 |
| BB + CCB | BB + CCB | 336 |
| BB + Thiazide | BB + Thiazide | 72 |
| **Sum** | | 6,832 |

1. Different first drug ingredient and same second drug ingredient (n = 6,832)

e.g., benazepril + hydrochlorothiazide vs lisinopril + hydrochlorothiazide

1. Different first drug ingredient and different second drug ingredient (n = 70,848)

e.g., benazepril + hydrochlorothiazide vs lisinopril + chlorthalidone

**A. 2. 2 Example of “Add on Hydrochlorothiazide after initial benazepril therapy”**

**Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of 'Hydrochlorothiazide' for the first time in the person's history, who are >= 18 years old.

Limit cohort entry events to the earliest event per person.

**Inclusion Criteria**

1. Previous hypertension

Entry events having at least 1 condition occurrence of 'Hypertension', starting anytime on or before cohort entry start date.

1. Previous benazepril agent

Entry events having at least 1 drug exposure of 'Benazepril', starting anytime up to 30 days before cohort entry start date.

1. new Rx of ACEI agents

Entry events with any of the following criteria:

* having at least 1 drug era of 'Benazepril', starting anytime on or before cohort entry start date and ending 1 days after cohort entry start date.
* having at least 1 drug exposure of 'Benazepril', starting anytime on or before cohort entry start date and ending 1 days after cohort entry start date.

1. No other comparators (CCB, BB, ARB, ACEi except benazepril, THZ except HCTZ)

Entry events with all of the following criteria:

* having at most 0 drug exposures of 'CCB', starting anytime on or before cohort entry start date.
* having at most 0 drug exposures of 'BB', starting anytime on or before cohort entry start date.
* having at most 0 drug exposures of 'ARB', starting anytime on or before cohort entry start date.
* having at most 0 drug exposures of 'ACEi except benazepril', starting anytime on or before cohort entry start date.
* having at most 0 drug exposures of 'TZD except HCTZ', starting anytime on or before cohort entry start date.

1. No other secondary antihypertensive agents

Entry events having at most 0 drug exposures of 'other secondary antihypertensive agents'.

**Cohort Exit**

The cohort end date will be based on a continuous exposure to 'Hydrochlorothiazide': allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

The person also exists the cohort when encountering any of the following events:

1. Drug exposures of ‘other comparators (CCB, BB, ARB, ACEi except benazepril)’

**Concept Set Definitions**

1. Hydrochlorothiazide

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 974166 | hydrochlorothiazide | Drug | RxNorm | NO | YES | NO |

1. Hypertension

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 316866 | Hypertensive disorder | Condition | SNOMED | NO | YES | NO |
| 320128 | Essential hypertension | Condition | SNOMED | NO | YES | NO |
| 321074 | Pre-existing hypertension complicating pregnancy, childbirth and puerperium | Condition | SNOMED | **YES** | YES | NO |
| 4118910 | Maternal hypertension | Condition | SNOMED | **YES** | YES | NO |

1. Benazepril

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1335471 | benazepril | Drug | RxNorm | NO | YES | NO |

1. CCB

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1307863 | verapamil | Drug | RxNorm | NO | YES | NO |
| 1318137 | nicardipine | Drug | RxNorm | NO | YES | NO |
| 1318853 | nifedipine | Drug | RxNorm | NO | YES | NO |
| 1319880 | nisoldipine | Drug | RxNorm | NO | YES | NO |
| 1326012 | isradipine | Drug | RxNorm | NO | YES | NO |
| 1328165 | diltiazem | Drug | RxNorm | NO | YES | NO |
| 1332418 | amlodipine | Drug | RxNorm | NO | YES | NO |
| 1353776 | felodipine | Drug | RxNorm | NO | YES | NO |

1. BB

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1307046 | metoprolol | Drug | RxNorm | NO | YES | NO |
| 1313200 | nadolol | Drug | RxNorm | NO | YES | NO |
| 1314002 | atenolol | Drug | RxNorm | NO | YES | NO |
| 1314577 | nebivolol | Drug | RxNorm | NO | YES | NO |
| 1319998 | acebutolol | Drug | RxNorm | NO | YES | NO |
| 1322081 | betaxolol | Drug | RxNorm | NO | YES | NO |
| 1327978 | penbutolol | Drug | RxNorm | NO | YES | NO |
| 1338005 | bisoprolol | Drug | RxNorm | NO | YES | NO |
| 1345858 | pindolol | Drug | RxNorm | NO | YES | NO |
| 1346823 | carvedilol | Drug | RxNorm | NO | YES | NO |
| 1353766 | propranolol | Drug | RxNorm | NO | YES | NO |
| 1386957 | labetalol | Drug | RxNorm | NO | YES | NO |

1. ARB

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1308842 | valsartan | Drug | RxNorm | NO | YES | NO |
| 1317640 | telmisartan | Drug | RxNorm | NO | YES | NO |
| 1346686 | eprosartan | Drug | RxNorm | NO | YES | NO |
| 1347384 | irbesartan | Drug | RxNorm | NO | YES | NO |
| 1351557 | candesartan | Drug | RxNorm | NO | YES | NO |
| 1367500 | losartan | Drug | RxNorm | NO | YES | NO |
| 40226742 | olmesartan | Drug | RxNorm | NO | YES | NO |
| 40235485 | azilsartan | Drug | RxNorm | NO | YES | NO |

1. ACEi except benazepril

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1308216 | lisinopril | Drug | RxNorm | NO | YES | NO |
| 1310756 | moexipril | Drug | RxNorm | NO | YES | NO |
| 1331235 | quinapril | Drug | RxNorm | NO | YES | NO |
| 1334456 | ramipril | Drug | RxNorm | NO | YES | NO |
| 1335471 | benazepril | Drug | RxNorm | **YES** | YES | NO |
| 1340128 | captopril | Drug | RxNorm | NO | YES | NO |
| 1341927 | enalapril | Drug | RxNorm | NO | YES | NO |
| 1342439 | trandolapril | Drug | RxNorm | NO | YES | NO |
| 1363749 | fosinopril | Drug | RxNorm | NO | YES | NO |
| 1373225 | perindopril | Drug | RxNorm | NO | YES | NO |

1. THZ except HCTZ

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 907013 | metolazone | Drug | RxNorm | NO | YES | NO |
| 974166 | hydrochlorothiazide | Drug | RxNorm | **YES** | YES | NO |
| 978555 | indapamide | Drug | RxNorm | NO | YES | NO |
| 1395058 | chlorthalidone | Drug | RxNorm | NO | YES | NO |

**A. 3 Heterogeneity Study Inclusion Criteria**

**A. 3. 1 Lower age group**

Entry events with the following event criteria: who are < 45 years old.

**A. 3. 2 Middle age group**

Entry events with all of the following criteria:

1. with the following event criteria: who are ≥ 45 years old

2. with the following event criteria: who are < 65 years old

**A. 3. 3 Older age group**

Entry events with the following event criteria: who are ≥ 65 years old.

**A. 3. 4 Female stratum**

Entry events with the following event criteria: who are female.

**A. 3. 5 Male stratum**

Entry events with the following event criteria: who are male.

**A. 3. 6 Race stratum**

Entry events with the following event criteria: race is:   
“Black or African American”, “black”, “African American”, “African”, “Bahamian”, “Barbadian”, “Dominican”, “Dominica islander”, “Haitian”, “Jamaican”, “Trinidadian”, or “West Indian”.

**A. 3. 7 Heart failure**

Entry events having at least 1 condition occurrence of ‘Heart failure’, starting anytime on or before cohort entry start date.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Code** | **Concept Name** | **Domain** | **Excluded** | **Descendants** | **Mapped** |
| 316139 | 84114007 | Heart failure | Condition | NO | YES | NO |
| 315295 | 82523003 | Congestive rheumatic heart failure | Condition | YES | YES | NO |

**A. 3. 8. Type 2 Diabetes**

Entry events having at least 1 condition occurrence of ‘Type 2 diabetes mellitus’, starting anytime on or before cohort entry start date.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Code** | **Concept Name** | **Domain** | **Excluded** | **Descendants** | **Mapped** |
| 201826 | 44054006 | Type 2 diabetes mellitus | Condition | NO | YES | NO |

**A. 3. 9. Renal impairment**

Entry events having at least 1 condition occurrence of ‘Renal impairment’, starting anytime on or before cohort entry start date.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Code** | **Concept Name** | **Domain** | **Excluded** | **Descendants** | **Mapped** |
| 4030518 | 236423003 | Renal impairment | Condition | NO | YES | NO |

**B Outcome Cohort Definitions**

**B. 1 Example of “4 Point major adverse cardiovascular events (4P MACE)**

**Description:** Condition record of acute myocardial infarction, hemorrhagic or ischemic stroke or sudden cardiac death during an inpatient or ER visit, and inpatient or ER visit (hospitalization) with heart failure condition record

**Cohort Entry Events**

People may enter the cohort when observing any of the following:

1. condition occurrences of 'Acute myocardial Infarction'.
2. condition occurrences of 'Sudden cardiac death'.
3. condition occurrences of 'Ischemic stroke'.
4. condition occurrences of 'Intracranial bleed Hemorrhagic stroke'.
5. condition occurrences of 'Heart Failure '.

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit', starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

**Cohort Exit**

The cohort end date will be offset from index event's start date plus 7 days.

**Cohort Eras**

Remaining events will be combined into cohort eras if they are within 180 days of each other.

**Concept Set Definitions**

1. Acute myocardial infraction

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 314666 | Old myocardial infarction | Condition | SNOMED | YES | YES | NO |
| 4329847 | Myocardial infarction | Condition | SNOMED | NO | YES | NO |

1. Sudden cardiac death

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 321042 | Cardiac arrest | Condition | SNOMED | NO | YES | NO |
| 437894 | Ventricular fibrillation | Condition | SNOMED | YES | YES | NO |
| 442289 | Death in less than 24 hours from onset of symptoms | Observation | SNOMED | NO | YES | NO |
| 4048809 | Brainstem death | Condition | SNOMED | NO | YES | NO |
| 4132309 | Sudden death | Observation | SNOMED | NO | YES | NO |
| 4317150 | Sudden cardiac death | Condition | SNOMED | NO | YES | NO |

1. Ischemic stroke

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 372924 | Cerebral artery occlusion | Condition | SNOMED | NO | NO | NO |
| 375557 | Cerebral embolism | Condition | SNOMED | NO | NO | NO |
| 441874 | Cerebral thrombosis | Condition | SNOMED | NO | NO | NO |
| 443454 | Cerebral infarction | Condition | SNOMED | NO | YES | NO |

1. Intracranial bleed Hemorrhagic stroke

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 376713 | Cerebral hemorrhage | Condition | SNOMED | NO | NO | NO |
| 432923 | Subarachnoid hemorrhage | Condition | SNOMED | NO | NO | NO |
| 439847 | Intracranial hemorrhage | Condition | SNOMED | NO | NO | NO |
| 4148906 | Spontaneous subarachnoid hemorrhage | Condition | SNOMED | NO | NO | NO |
| 43530727 | Spontaneous cerebral hemorrhage | Condition | SNOMED | NO | NO | NO |

1. Heart failure

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 315295 | Congestive rheumatic heart failure | Condition | SNOMED | YES | YES | NO |
| 316139 | Heart failure | Condition | SNOMED | NO | YES | NO |

1. Inpatient or ER visit

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |

**B. 2 Example of “Acute myocardial infarction”**

**Description:** Condition record of acute myocardial infarction during inpatient or ER visit

**Cohort Entry Events**

People may enter the cohort when observing any of the following:

1. condition occurrences of 'Acute myocardial Infarction'.

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit', starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

**Cohort Exit**

The cohort end date will be offset from index event's start date plus 7 days.

**Cohort Eras**

Remaining events will be combined into cohort eras if they are within 180 days of each other.

**Concept Set Definitions**

1. Acute myocardial infraction

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 314666 | Old myocardial infarction | Condition | SNOMED | YES | YES | NO |
| 4329847 | Myocardial infarction | Condition | SNOMED | NO | YES | NO |

1. Inpatient or ER visit

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |

**B. 3 Example of “Cardiac arrhythmia”**

**Description:** 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

**Cohort Entry Events**

People may enter the cohort when observing any of the following:

1. condition occurrence of 'Cardiac arrhythmia' for the first time in the person's history.

Limit cohort entry events to the earliest event per person.

Restrict entry events to with any of the following criteria:

1. having at least 1 condition occurrence of 'Cardiac arrhythmia', starting 1 days after cohort entry start date.
2. having at least 2 drug exposures of 'Drugs used to treat cardiac arrhythmia', starting between 0 days before and all days after cohort entry start date.
3. having at least 1 procedure occurrence of 'Procedures to treat cardiac arrhythmia', starting between 0 days before and all days after cohort entry start date.

**Cohort Exit**

The person exits the cohort at the end of continuous observation.

**Cohort Eras**

Remaining events will be combined into cohort eras if they are within 0 days of each other.

**Concept Set Definitions**

1. Cardiac arrhythmia

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 315078 | Palpitations | Condition | SNOMED | NO | YES | NO |
| 444070 | Tachycardia | Condition | SNOMED | NO | YES | NO |
| 38001137 | Cardiac arrhythmia & conduction disorders w CC | Observation | DRG | NO | YES | NO |
| 38001138 | Cardiac arrhythmia & conduction disorders w/o CC/MCC | Observation | DRG | NO | YES | NO |
| 44784217 | Cardiac arrhythmia | Condition | SNOMED | NO | YES | NO |

1. Drugs used to treat cardiac arrhythmia

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1309204 | Adenosine | Drug | RxNorm | NO | YES | NO |
| 1310149 | Warfarin | Drug | RxNorm | NO | YES | NO |
| 21600248 | ANTIARRHYTHMICS, CLASS I AND III | Drug | ATC | NO | YES | NO |
| 40228152 | dabigatran etexilate | Drug | RxNorm | NO | YES | NO |
| 40241331 | rivaroxaban | Drug | RxNorm | NO | YES | NO |
| 43013024 | apixaban | Drug | RxNorm | NO | YES | NO |
| 45892847 | edoxaban | Drug | RxNorm | NO | YES | NO |

1. Procedures to treat cardiac arrhythmia

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 2107068 | Operative tissue ablation and reconstruction of atria, performed at the time of other cardiac procedure(s), extensive (eg, maze procedure), with cardiopulmonary bypass (List separately in addition to code for primary procedure) | Procedure | CPT4 | NO | YES | NO |
| 4051932 | Procedure for arrhythmia | Procedure | SNOMED | NO | YES | NO |
| 45890325 | Cardioversion, elective, electrical conversion of arrhythmia | Procedure | CPT4 | NO | YES | NO |
| 45890400 | Operative tissue ablation and reconstruction of atria, extensive (eg, maze procedure) | Procedure | CPT4 | NO | YES | NO |

**C Negative Control Concepts**

|  |  |
| --- | --- |
| **Name** | **OMOP Concept Id** |
| Abnormal cervical smear | 434165 |
| Abnormal pupil | 436409 |
| Abrasion and/or friction burn of trunk without infection | 199192 |
| Absence of breast | 4088290 |
| Absent kidney | 4092879 |
| Acid reflux | 44783954 |
| Acquired hallux valgus | 75911 |
| Acquired keratoderma | 137951 |
| Acquired trigger finger | 77965 |
| Acute conjunctivitis | 376707 |
| Amputated foot | 4103640 |
| Anal and rectal polyp | 73241 |
| Burn of forearm | 133655 |
| Calcaneal spur | 73560 |
| Cannabis abuse | 434327 |
| Cervical somatic dysfunction | 4213540 |
| Changes in skin texture | 140842 |
| Chondromalacia of patella | 81378 |
| Cocaine abuse | 432303 |
| Colostomy present | 4201390 |
| Complication due to Crohn's disease | 46269889 |
| Contact dermatitis | 134438 |
| Contusion of knee | 78619 |
| Crohn's disease | 201606 |
| Derangement of knee | 76786 |
| Difficulty sleeping | 4115402 |
| Disproportion of reconstructed breast | 45757370 |
| Effects of hunger | 433111 |
| Endometriosis | 433527 |
| Epidermoid cyst | 4170770 |
| Feces contents abnormal | 4092896 |
| Foreign body in orifice | 259995 |
| Ganglion cyst | 40481632 |
| Genetic predisposition | 4166231 |
| Hammer toe | 433577 |
| Hereditary thrombophilia | 4231770 |
| Herpes zoster without complication | 440329 |
| High risk sexual behavior | 4012570 |
| Homocystinuria | 4012934 |
| Human papilloma virus infection | 441788 |
| Ileostomy present | 4201717 |
| Impacted cerumen | 374375 |
| Impingement syndrome of shoulder region | 4344500 |
| Ingrowing nail | 139099 |
| Injury of knee | 444132 |
| Irregular periods | 196168 |
| Kwashiorkor | 432593 |
| Late effect of contusion | 434203 |
| Late effect of motor vehicle accident | 438329 |
| Leukorrhea | 195873 |
| Macular drusen | 4083487 |
| Melena | 4103703 |
| Nicotine dependence | 4209423 |
| Noise effects on inner ear | 377572 |
| Non-toxic multinodular goiter | 136368 |
| Nonspecific tuberculin test reaction | 40480893 |
| Onychomycosis due to dermatophyte | 140648 |
| Opioid abuse | 438130 |
| Passing flatus | 4091513 |
| Postviral fatigue syndrome | 4202045 |
| Presbyopia | 373478 |
| Problem related to lifestyle | 46286594 |
| Psychalgia | 439790 |
| Ptotic breast | 81634 |
| Regular astigmatism | 380706 |
| Senile hyperkeratosis | 141932 |
| Somatic dysfunction of lumbar region | 36713918 |
| Splinter of face, without major open wound | 443172 |
| Sprain of ankle | 81151 |
| Strain of rotator cuff capsule | 72748 |
| Tear film insufficiency | 378427 |
| Tobacco dependence syndrome | 437264 |
| Vaginitis and vulvovaginitis | 194083 |
| Verruca vulgaris | 140641 |
| Wrist joint pain | 4115367 |
| Wristdrop | 440193 |