Assessing the Sufficiency of Eligibility Criteria in Constructing an Externally Valid Population

**Version: 0.1**

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# List of abbreviations

ACE Angiotensin Converting Enzyme

ATE Average Treatment Effect

BP Blood Pressure

CI Confidence Interval

EBM Evidence Based Medicine

eGFR Estimated Glomerular Filtration Rate

LLT Lipid Lowering Therapy

OHDSI Observational Health Data Sciences and Informatics

OMOP Observational Medical Outcomes Partnership

OR Odds Ratio

RCT Randomized Controlled Trial

ULN Upper Limit of Normal

# Abstract

Evidence-Based Medicine (EBM) requires medical practitioners to consider empirical and experimental evidence when treating their patients (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996). EBM encourages clinicians to seek the most reputable evidence according to a hierarchy of study quality, wherein randomized controlled trials (RCTs) are regarded as least biased. This practice is driven by the assumption that the average treatment effect (ATE) reported in the RCT will replicate in the target population. Presumably, the eligibility criteria that constructed the trial is sufficient to identify a population for which the treatment population is fully replicable, but how the ATE varies as a function of eligibility criteria is still unknown. To address this question, this research undertakes two studies, which we call Study 1 and Study 2. In Study 1, we use the OHDSI CohortMethod package to calculate the unadjusted and adjusted ATE of observational cohorts constructed according to the criteria put forth by two publications, Hartley, et al. (Hartley, 2015) and PROVE-IT (Cannon et al., 2004), under an increasing number of the published eligibility criteria. We will then compare these observational estimates to the published effect estimate. Study 2 will investigate if and how observational cohorts subject to all eligibility criteria differ from the published trial data. In this study, we will compare the published *Baseline Demographics* (*Table 1)* data from three Landmark clinical trials, ACCOMPLISH (Jamerson et al., 2008), RENAAL (Brenner et al., 2001), and PROVE-IT (Cannon et al., 2004) to the same estimates from observational cohorts constructed according to (i) the indication of the intervention alone, and (ii) the indication subject to all eligibility criteria put forth by the trial.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| **Version** | **Date** | **Author** | **Action** |
| 0.1 | 16 Jan 2018 | AJ Averitt | Uploading Version 0.1 |

# Milestones

|  |  |
| --- | --- |
| **Milestone** | **Planned / Estimated Date** |
| Start of analysis |  |
| End of analysis |  |
| Posting of results |  |
| Submission of manuscript |  |

# Rationale and Background

Causal inference -- the process of drawing a conclusion about the impact of an exposure on an outcome -- is foundational to biomedicine. The current gold-standard approach for causal inference is randomized experimentation, wherein the allocation potentially biasing features would be equal between the arms, thereby insuring high internal validity (Rothman, Greenland, & Lash, 2008). Associations that result from randomized experimentation, if found significant by the inference procedure, are recognized as *causal knowledge*. In biomedicine, causal knowledge generated from RCTs is later applied in the treatment of patients; a practice known as evidence based medicine (EBM) (Sackett et al., 1996).

According to EBM practice, clinicians apply knowledge garnered from the RCT to the treatment of their patients under the belief that the average treatment effect (ATE) of intervention will show similar results in their treated population (Steckler & McLeroy, 2008). However, the populations that generated the RCT’s ATE often fail to resemble real-world target populations. RCT populations are often constructed to ensure high *interval validity.* Factors that support high internal validity, such as the curated trial population, presence of the control group, and randomized treatment allocation, often impede the external validity of scientific knowledge (Calder, Phillips, & Tybout, 1983; Dekkers, Elm, Algra, Romijn, & Vandenbroucke, 2010).

The mismatch between expectation and reality of RCT treatment effects is the most notable repercussion of poor external validity, and is a popular point of blame for the endemic underuse of treatments that are shown to have clinical benefit in trials (Rothwell, 2005). This emphasis of internal validity at the expense of external validity impedes the ability of clinical research to translate into practice in a number of ways. The gap between scientific knowledge and clinical practice that is attributable to poor external validity may be due to the experimental setting; the selection of trial participants; or discrepancies between the trial protocol and clinical use (Singer, Ryff, & Health, 2001; Steckler & McLeroy, 2008). But perhaps most important of these influences are the discriminative eligibility criteria that often result in trial coordinators choosing only a highly exclusive subpopulation of recruited participants that are often homogenous and ensure maximal internal validity (Umscheid, Margolis, & Grossman, 2011). Presumably, the eligibility criteria of an RCT should be sufficient to identify a population for which the RCT ATE will replicate; but how the real-world ATE varies as a function of eligibility criteria is still unknown.

## Research Questions

**Primary hypotheses**

**Study 1**

We hypothesize that each addition of an operationalized inclusion and exclusion criteria from an RCT protocol will increase distributional similarity between the observational and experimental cohorts, and will bring the ATE from an observational cohort closer to the reported ATE of published RCT outcomes. To test this hypothesis, we will assess whether the ATE with all criteria is significantly different than the ATE with no criteria and the RCT ATE, at a level of significance of 5%.

**Study 2**

We hypothesize that the observational cohort will sufficiently differ from the experimental cohorts to impede generalizability. To test this hypothesis, we will compare observational data to the experimental data put forth in the Baseline Demographics table of the trial, using appropriate statistical tests. Significance will be assessed at a level of 5%.

## Objectives

**Primary objective**

Assess the unadjusted and adjusted disproportionality estimates from cohorts that are constructed according to an increasing number of eligibility criteria that define a clinical trial population. We then will compare these estimates that which is reported from the RCT. To explore the sources of residual bias from these estimates, we will compare the “Table 1” RCT data to the same estimates from observational cohorts.

# Research methods

## Study Design

### Overview

This research seeks to explore the utility of eligibility criteria in defining an externally valid population. Causal estimates from RCTs, which we accept to be the least biased source of causal knowledge, can be compared to estimate of the same metric that are generated from observational cohorts, and thus, may provide a methodology to assess the validity of causal claims to specific populations. We hypothesize that each addition of an operationalized inclusion and exclusion criteria from an RCT protocol will increase distributional similarity between the observational and experimental cohorts, and will bring the ATE from an observational cohort closer to the reported ATE of published RCT outcomes. To address this question, this research undertakes two studies, which we call Study 1 and Study 2.

#### Study 1

Study 1 will seek to calculate ATEs from observational populations that are constructed according RCT protocols, under an increasing number of reported eligibility criteria. The study herein, seeks to replicate the ATE from two trials; the Hartley, et al. paper (NCT01189890), which investigated the occurrence of hypoglycemia associated with sitagliptin compared to glimepiride in elderly patients (65-80 years of age) with Type 2 Diabetes Mellitus (T2DM) and inadequate glycemic control (Hartley, 2015), and PROVE-IT (Cannon et al., 2004), which investigated the effect high-dose lipid-lowering therapy versus moderate dose lipid lowering therapy on a composite end endpoint of death and cardiovascular events.

In Study 1, the provided scripts will identify a baseline cohort of patients, meeting the indication, age requirements, and an exposure to either the treatment or comparator drug is identified from an OMOP-CDM. This baseline cohort will be queried multiple times; each query being subject to the addition of new eligibility criteria of the target RCT (See 7.1.2 and Appendices). With each incremental criterion, the unadjusted odds ratio (OR) and adjusted OR of the outcome, as determined by the CohortMethod package, is calculated and compared to the OR that was calculated for this endpoint at the RCT’s close. The CohortMethod is a consolidated R package, developed by the OHDSI community, that allows researchers to perform cohort studies with Common Data Model (CDM v5) formatted observational datasets. CohortMethod permits population-level estimations through single new-user cohort methods with propensity scores, among other methods of estimations (Schuemie, Suchard, & Ryan, 2016). These results will be output to an excel file which will be zipped and sent to the study coordinator.

#### Study 2

To investigate the potential sources of the residual bias to the effect estimate, observational cohorts that were curated according to eligibility criteria were compared to RCTs. Observational cohorts were created using OHDSI’s ATLAS tools. The trial indication identified a core set of patients to which inclusion and exclusion criteria of RCT’s were applied to appropriately narrow the cohort. The cohorts constructed both according to (i) the *Indication Only* and (ii) the *Indication + Eligibility Criteria* are compared to the RCT’s participant features that are reported in the baseline features table (Table 1). This data source is often is the most granular representation of trial participants available, and is sufficient to characterize discrepancies in the observational cohort that may be responsible for not replicable effect estimates.

In Study 2, we will construct cohorts from three Landmark clinical trials (i) ACCOMPLISH (Jamerson et al., 2008), which investigated at angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers on hypertension; (ii) RENAAL (Brenner et al., 2001), which investigated Losartan vs Placebo in combination with conventional anti-hypertensive therapies on diabetic nephropathy; and (iii) PROVE-IT (Cannon et al., 2004) which investigated the effect high-dose lipid-lowering therapy versus moderate dose lipid lowering therapy on a composite end endpoint of death and cardiovascular events.

A consolidated R script will identify two cohorts for each trial, and create and populate SQL tables with eligible patient IDs and cohort entry dates. The first, is a cohort comprised of individuals that meet the indication only of the trial; and the second is a cohort that meets both the indication of the trial and the eligibility criteria put forth in published materials. These cohorts will then be repeatedly queried to collect the metrics put forth in the trial’s Baseline Demographics table. These results will be output to an excel file which will be zipped and sent to the study coordinator.

### Study Populations

#### Study 1 Populations

To capture the incremental effect of the eligibility criteria on the ATE, study populations defined by an increasing number of eligibility criteria will be created both trials of Study 1. All subjects in the database that meet the following criteria will be included

##### **Sitagliptin vs Glimepiride on Hypoglycemia (NCT01189890)**

|  |  |
| --- | --- |
| **Study Population** | **Criteria** |
| 01: Index (Baseline) Population | Exposure to sitagliptin or glimepiride (prescription written)  Aged 65-80  At least 1 occurrence of Type 2 Diabetes Mellitus  Exactly 0 occurrences of sitagliptin (inpatient administration)  Exactly 0 occurrences of glimepiride (inpatient administration) |
| 02 | Study Pop. 01 + No Triglycerides ≥ 600mg/dL in the 365 prior to index |
| 03 | Study Pop. 02 + No Hypertension in the 365 days prior to index |
| 04 | Study Pop. 03 + No History of HIV |
| 05 | Study Pop. 04 + No History of Type 1 Diabetes Mellitus |
| 06 | Study Pop. 05 + No Surgical Procedures in the 28 days prior to index |
| 07 | Study Pop. 06 + No Cardiovascular Disease in the 365 days prior to index |
| 08 | Study Pop. 07 + No Liver Disease in the 365 days prior to index |
| 09 | Study Pop. 08 + No Peripheral Vascular Disease in the 365 days prior to index |
| 10 | Study Pop. 09 + No Insulin or GLP-1 use in the 365 days prior to index |
| 11 | Study Pop. 10 + No PPAR-γ use in the 112 days prior to index |
| 12 | Study Pop. 11 + No History of DPP-4 use |
| 13 | Study Pop. 12 + No History of Malignancy |
| 14 | Study Pop. 13 + No History of Hematologic Disease |
| 15 | Study Pop. 14 + No History of Renal Impairment |
| 16 | Study Pop. 15 + No History of eGFR ≤ 35 mg/g |
| 17 | Study Pop. 16 + No History of Substance Abuse |

##### **High vs moderate dose LLT on death and cardiovascular events (PROVE-IT)**

|  |  |
| --- | --- |
| **Study Population** | **Criteria** |
| 01: Index (Baseline) Population | Exposure to 80mg atorvastatin or 40mg pravastatin (prescription written)  Age ≥18  At least one occurrence of Acute Coronary Syndrome  Exactly 0 occurrences of Atorvastatin (inpatient administration)  Exactly 0 occurrences of Pravastatin (inpatient administration) |
| 02 | Study Pop. 01 + No Long Term LLT or Total Cholesterol < 200mg |
| 03 | Study Pop. 02 + No Statin of ≥80mg per day |
| 04 | Study Pop. 03 + No LLT with Fibric Acid |
| 05 | Study Pop. 04 + No LLT with Niacin |
| 06 | Study Pop. 05 + No CYP450 |
| 07 | Study Pop. 06 + No Percutaneous Coronary Intervention |
| 08 | Study Pop. 07 + No Coronary Artery Bypass Surgery |
| 09 | Study Pop. 08 + No Obstructive Hepatobilliary Disease |
| 10 | Study Pop. 09 + No Hepatic Disease |
| 11 | Study Pop. 10 + No Creatinine Kinases > 3x ULN |
| 12 | Study Pop. 11 + No Creatinine > 20mg |

#### Study 2 Populations

##### **ACE inhibitors and calcium channel blockers on hypertension (ACCOMPLISH**

|  |  |
| --- | --- |
| **Indication Only** | **Indication + Eligibility Criteria** |
| At least 1 occurrence of Hypertension | At least 1 occurrence of Hypertension |
| Aged ≥ 55 |
| At least 1 exposure to Antihypertensive Drugs or a Systolic Blood Pressure measurement ≥ 160 |
| At least one of the following for those ≥ 60 or at least two of the following for those 55-60: *Myocardial Infarction; Unstable Angina;, Coronary Revascularization; Stroke; Peripheral Arterial Occlusive Disease; Diabetes Mellitus; Left Ventricular Hypertrophy; Serum Creatinine >1.7 (male) or >1.5 (female); Albumin Creatinine Ratio >300 and exposure to at least 1 ACE Inhibitor or Aldosterone Receptor Blocker/ Albumin Creatinine Ratio >200 and exposure to exactly 0 ACE Inhibitor or Aldosterone Receptor Blocker* |
| No Angina Pectoris in 90 days before index |
| No History of Heart Failure |
| No Myocardial Infarction in 30 days before index |
| No ACS 30 days before index |
| No Coronary Revascularization in 30 days before index |
| No Stroke in 90 days before index |
| No Ischemic Cerebrovascular Episodes in 90 days before index |

##### **Losartan vs Placebo in combination with conventional anti-hypertensive therapies on diabetic nephropathy (RENAAL**

|  |  |
| --- | --- |
| **Indication Only** | **Indication + Eligibility Criteria** |
| At least 1 occurrence of Type II Diabetes Mellitus | At least 1 occurrence of Type II Diabetes Mellitus |
| At least one occurrence of Nephropathy | Age between 31 and 70 |
| At least one occurrence of Nephropathy |
| At least one hypertensive or normotensive measurement |
| No exposure to insulin in the 180 days before to index |
| No history of ketoacidosis |
| No history of HbA1c<12 |
| No positive pregnancy test in 300 days before to index |
| No Type I Diabetes |
| No Non-Diabetic Renal Disease |
| No Myocardial Infarction in 30 days before index |
| No CABG in 30 days before index |
| No Cerebrovascular Event in 180 days before index |
| No Percutaneous transluminal coronary angioplasty in 30 days before index |
| No Transient Ischemic Attack in the 365 days before index |
| No history of heart failure |
| No history of renal artery stenosis |
| No history of Primary Aldosteronism |
| No history of Phaeochromocytoma |

##### **High vs moderate dose LLT on death and cardiovascular events (PROVE-IT)**

|  |  |
| --- | --- |
| **Indication Only** | **Indication + Eligibility Criteria** |
| At least one occurrence of Acute Coronary Syndrome | At least one occurrence of Acute Coronary Syndrome |
| Age ≥ 18 |
| No Long Term LLT or Total Cholesterol < 200mg in 180 days before index |
| No Statin of ≥80mg per day in 30 days before index |
| No LLT with Fibric Acid in 30 days before index |
| No LLT with Niacin in 30 days before index |
| No CYP450 in 30 days before index |
| No Percutaneous Coronary Intervention in 180 days before index |
| No Coronary Artery Bypass Surgery in 60 days before index |
| No Obstructive Hepatobilliary Disease in 365 days before index |
| No history of Hepatic Disease |
| No history Creatinine Kinases > 3x ULN |
| No Creatinine > 20mg in 30 days before index |

### Analyses

#### Study 1

#### Unadjusted

For both trials in Study 1, unadjusted disproportionality estimates (odds ratio), and the associated 95% confidence interval, will be calculated from the pure count combinations of persons who meet the exposure and outcome criteria at each increasing eligibility criteria

#### Adjusted

Similarly for both trials in Study 1, with each increasing number of eligibility criteria, an adjusted disproportionality analysis will be conducted using the CohortMethod package. Adjustment will be made through use of matching of propensity scores. The propensity model will be fitted using a large-scaled regularized logistic regression; and the regularization hyperparameter will be selected by optimizing the likelihood in a 10-fold cross-validation.

The propensity scores will be matched within stratified quantiles, using a caliper of 0.2. A logistic regression, referred to as the *outcome model*, will regress the presence of the outcome conditioned on the matched sets, using only the treatment variable as the predictor. The outcome model’s coefficient of treatment and related 95% confidence interval, when exponentiated, supplies the odds ratio and CI of outcome of the intervention versus the comparator.

This adjusted estimate and unadjusted estimates for each trial will both be sequentially plotted over the number of increasing eligibility criteria, and exported as raw numbers in an excel table.

#### Study 2

Analysis of Study 2 data will be conducted after collection of data from participating institutions. At present, the authors intend to address (i) a per site assessment of the statistical difference between the observational population and the trial population and (ii) a group-wide assessment of the statistical difference between the observational populations, in aggregate, and the trial population.

## Variables

For a complete description of exposure, outcome, and eligibility criteria, please refer to Section 7.1.2 Study Populations and Section 11 Appendices.

A description of the cohort construction under increasing eligibility criteria for trials in Study 1 can be found in Sections 7.1.2.1.1 and 7.1.2.1.2. A description of the separation of *Indication Only* vs *Indication + Eligibility Criteria* for Study 2 can be found in Sections 7.1.2.2.1-3.

*Complete* definitions of cohorts (subject to all eligibility criteria) can be found in Section 11 Appendices.

### Potential Confounders

In the adjusted analysis, variables which fall into the following categories will be included as covariates of adjustment for potential confounders. Note that most covariates are assessed on or in the 365 days prior to index date.

* Demographics (age in 5-year increments, gender, race, ethnicity, year of index date, month of index date)
* Condition occurrence (one or more variables per diagnosis code)
* Condition era (one or more variables per diagnosis code)
* Condition group (one or more variables per MedDRA group or SNOMED groups)
* Drug exposure (one or more variables per drug code)
* Drug era (one or more variables per RxNorm ingredient)
* Drug group (one or more variables per ATC group)
* Procedure occurrence (one or more variables per procedure code)
* Observations (one or more variables per observation concept ID)
* Measurements (one or more variables per measurement concept ID, including variables for within / above / below normal range)
* Risk scores (including Charleston, DCSI, CHADS2, CHADS2VASc

Covariates with less than 100 non-zero values are discarded. All covariates were used in both the propensity model and the outcome model.

## Data Sources

The analyses will be performed across a network of observational healthcare databases. All databases have been transformed into the OMOP Common Data Model, version 4 or OMOP Common Data Model, version 5. The complete specification for OMOP Common Data Model, version 4 is available at: <http://omop.org/cdm>. The complete specification for OMOP Common Data Model, version 5 is available at: <https://github.com/OHDSI/CommonDataModel>. The following databases will be included in this analysis:

***NewYork-Presbyterian Hospital, Columbia University***

Columbia University Department of Biomedical Informatics DBMI serves as the central coordinating center for the Observational Health Data Sciences and Informatics (OHDSI) collaborative and thus provides faculty and students with privileged access to the OHDSI community.

## Sample Size and Study Power

Power calculations have been performed.

## Quality Control

The propensity scores will be evaluated by the following steps

* Inspection of the fitted propensity score model for large coefficients, which is indicative of model-misspecification, and a post-hoc review of difficult-to-explain predictors.
* Inspection of the propensity score distribution.
* Evaluation of covariate balance after matching using the standardized difference in means between treatment and comparator cohort before and after matching. Standardized differences greater than 0.2 will be reported and investigated.

We will investigate the outcome model by

* A post-hoc inspection of the fitted outcome model for large coefficients and difficult-to-explain predictors.

The error distribution estimated using the negative controls will be used to estimate residual bias after adjustments. The CohortMethod package itself, as well as other OHDSI packages on which CohortMethod depends, use unit tests for validation

## Strengths and Limitations of the Research Methods

**Strengths**

Because the ATE from the comparator trial is effectively adjusted due to baseline randomization, the observational estimates necessarily need to be adjusted as well. Making this necessary adjustment through use of the CohortMethod package is a strength of this research. The propensity score matching and full outcome models allow for balance on a large number of potential confounders, and provide the best possible adjustment given the information provided by the RCT.

The use of cohort studies to calculate the incremental ATE allow direct estimation of incidence rates following exposure of interest, and the new-user design can capture early events following treatment exposures while avoiding confounding from previous treatment effects. New use allows for a clear exposure index date.

**Limitations**

There are inherent limitations when translating the RCT eligibility criteria into operationalized OMOP CDM concepts. Furthermore, In the original RCT, hypoglycemia was a patient-reported outcome, wherein subjects would report the incidence of symptomatic hypoglycemia. As such, restricting this study to clinically observed instances of hypoglycemia may capture a small incidence of the outcome than was seen in the trial.

Additionally, there may be residual bias due to unmeasured confounders or a misspecified model.

# Protection of Human Subjects

The study is using only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

# Plans for Disseminating and Communicating Study Results

The study results will be posted on the OHDSI website after completion of the study. At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

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# Appendices

## Sitagliptin vs Glimepiride on Hypoglycemia (NCT01189890)

**Initial Event Cohort**

People having any of the following:

* a drug exposure of Sitagliptin20
  + drug type is any of: Prescription written
  + with age between 65 and 85 (inclusive)
* a drug exposure of Glimepiride6
  + drug type is any of: Prescription written
  + with age between 65 and 85 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having all of the following criteria:

* at least 1 occurrences of a condition occurrence of Type 2 Diabetes Mellitus24

starting between all days Before and 0 days Before event index date

* and exactly 0 occurrences of a drug exposure of Sitagliptin20
  + drug type is any of: Inpatient administration

starting between all days Before and 0 days Before event index date

* and exactly 0 occurrences of a drug exposure of Glimepiride6
  + drug type is any of: Inpatient administration

starting between all days Before and 0 days Before event index date

* And having all of the following criteria:
  + at least 1/exactly 0 occurrences of a drug exposure of Sitagliptin20

starting between all days Before and 0 days After event index date

* + and least 1/exactly 0 occurrences of a drug exposure of Glimepiride6

starting between all days Before and 0 days After event index date

Limit cohort of initial events to: **earliest event per person.**

**Inclusion Criteria**

Inclusion Criteria #1: No Criteria

Having all of the following criteria:

Inclusion Criteria #2: No Triglycerides>600

Having all of the following criteria:

* exactly 0 occurrences of a measurement of Triglycerides22
  + with value as number > 600

starting between 365 days Before and 1 days Before event index date

Inclusion Criteria #3: No Hypertension

Having all of the following criteria:

* exactly 0 occurrences of a measurement of BP Diastolic1
  + with value as number > 90

starting between 365 days Before and 1 days Before event index date

* and exactly 0 occurrences of a measurement of BP Systolic2
  + with value as number > 140

starting between 365 days Before and 1 days Before event index date

Inclusion Criteria #4: No HIV

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of HIV10

starting between all days Before and 1 days Before event index date

Inclusion Criteria #5: At Most 3x T1DM

Having all of the following criteria:

* at most 3 occurrences of a condition occurrence of Type 1 Diabetes Mellitus23

starting between all days Before and 1 days Before event index date

Inclusion Criteria #6: No Surgical Procedures

Having all of the following criteria:

* exactly 0 occurrences of a procedure of Surgical Procedure21

starting between 28 days Before and 1 days Before event index date

Inclusion Criteria #7: No CV Disease

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Cardiovascular Disease3

starting between 365 days Before and 1 days Before event index date

Inclusion Criteria #8: No Liver Disease

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Liver Disease14

starting between 365 days Before and 1 days Before event index date

Inclusion Criteria #9: No PVD

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of PVD18

starting between 365 days Before and 1 days Before event index date

Inclusion Criteria #10: No Insulin/GLP-1

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of Insulin, GLP-113

starting between 56 days Before and 1 days Before event index date

Inclusion Criteria #11: No PPAR-gamma

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of PPAR-gamma17

starting between 112 days Before and 1 days Before event index date

Inclusion Criteria #12: No DPP-4

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of DPP-44

starting between all days Before and 1 days Before event index date

Inclusion Criteria #13: No Malignancy/Certain Cancers

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of malignancy/"certain" cancers15

starting between all days Before and 1 days Before event index date

Inclusion Criteria #14: No Hematologic Disease

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Hematologic Disease8

starting between all days Before and 1 days Before event index date

Inclusion Criteria #15: No Renal Impairment

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Renal Impairment19

starting between all days Before and 1 days Before event index date

Inclusion Criteria #16: No GFR<=35

Having all of the following criteria:

* exactly 0 occurrences of a measurement of eGFR5
  + with value as number <= 35

starting between all days Before and 1 days Before event index date

Inclusion Criteria #17: No History of Substance Abuse

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of History of Drug Use9

starting between all days Before and 1 days Before event index date

Limit qualifying cohort to: **earliest event per person.**

Appendix 11.1: Concept Set Definitions

1. BP Diastolic

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3012888 | BP diastolic | Measurement | LOINC | NO | YES | NO |

2. BP Systolic

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3004249 | BP systolic | Measurement | LOINC | NO | YES | NO |

3. Cardiovascular Disease

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4215140 | Acute coronary syndrome | Condition | SNOMED | NO | YES | NO |
| 316139 | Heart failure | Condition | SNOMED | NO | YES | NO |
| 374384 | Cerebral ischemia | Condition | SNOMED | NO | YES | NO |
| 375557 | Cerebral embolism | Condition | SNOMED | NO | YES | NO |
| 372924 | Cerebral artery occlusion | Condition | SNOMED | NO | YES | NO |
| 373503 | Transient cerebral ischemia | Condition | SNOMED | NO | YES | NO |
| 40479625 | Atherosclerosis of artery | Condition | SNOMED | NO | YES | NO |

4. DPP-4

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21600783 | Dipeptidyl peptidase 4 (DPP-4) inhibitors | Drug | ATC | NO | YES | NO |

5. eGFR

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3049187 | eGFR with normals for non-black | Measurement | LOINC | NO | YES | NO |
| 3053283 | eGFR with normals for black | Measurement | LOINC | NO | YES | NO |

6. Glimepiride

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 1597756 | glimepiride | Drug | RxNorm | NO | YES | NO |

7. Glucose

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40776614 | Glucose | Bld-Ser-Plas | Measurement | LOINC | NO | YES | NO |

8. Hematologic Disease

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 443723 | Disorder of cellular component of blood | Condition | SNOMED | NO | YES | NO |
| 4280354 | Nutritional anemia | Condition | SNOMED | YES | YES | NO |

9. History of Drug Use

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 36903635 | Substance-related disorders | Condition | MedDRA | NO | YES | NO |
| 35809374 | Tobacco withdrawal symptoms | Condition | MedDRA | YES | YES | NO |
| 36919133 | Tobacco abuse | Condition | MedDRA | YES | YES | NO |
| 4209423 | Nicotine dependence | Condition | SNOMED | YES | YES | NO |
| 36919130 | Nicotine dependence | Condition | MedDRA | YES | YES | NO |
| 434697 | Maternal tobacco abuse | Condition | SNOMED | YES | YES | NO |

10. HIV

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 439727 | Human immunodeficiency virus infection | Condition | SNOMED | NO | YES | NO |

11. Hypoglycemia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 24609 | Hypoglycemia | Condition | SNOMED | NO | YES | NO |

12. Inpatient

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 38000180 | Inpatient administration | Type Concept | Drug Type | NO | YES | NO |

13. Insulin, GLP-1

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21600713 | INSULINS AND ANALOGUES | Drug | ATC | NO | YES | NO |
| 40219409 | GLP-1 Receptor Agonist | Drug | NDFRT | NO | YES | NO |

14. Liver Disease

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 194984 | Disease of liver | Condition | SNOMED | NO | YES | NO |

15. malignancy/"certain" cancers

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4300118 | Squamous cell carcinoma | Condition | SNOMED | YES | YES | NO |
| 4179980 | Malignant basal cell neoplasm of skin | Condition | SNOMED | YES | YES | NO |
| 443392 | Malignant neoplastic disease | Condition | SNOMED | NO | YES | NO |

16. Outpatient

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 38000177 | Prescription written | Type Concept | Drug Type | NO | YES | NO |

17. PPAR-gamma

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4354720 | PPAR gamma | Drug | NDFRT | NO | YES | NO |

18. PVD

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 321052 | Peripheral vascular disease | Condition | SNOMED | NO | YES | NO |

19. Renal Impairment

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 46271022 | Chronic kidney disease | Condition | SNOMED | NO | YES | NO |

20. Sitagliptin

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 1580747 | sitagliptin | Drug | RxNorm | NO | YES | NO |

21. Surgical Procedure

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4301351 | Surgical procedure | Procedure | SNOMED | NO | YES | NO |

22. Triglycerides

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3022192 | Triglyceride [Mass/volume] in Serum or Plasma | Measurement | LOINC | NO | YES | NO |

23. Type 1 Diabetes Mellitus

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 201254 | Type 1 diabetes mellitus | Condition | SNOMED | NO | YES | NO |

24. Type 2 Diabetes Mellitus

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 201826 | Type 2 diabetes mellitus |  |  |  |  |  |

## High vs moderate dose LLT on death and cardiovascular events (PROVE-IT)

**Initial Event Cohort**

People having any of the following: 

* a drug exposure of Atorvastatin 80mg2
  + drug type is any of: Prescription written
  + with age >= 18
* a drug exposure of Pravastatin 40mg 13
  + drug type is any of: Prescription written
  + with age >= 18

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having all of the following criteria:

* at least 1 occurrences of a condition occurrence of Acute Coronary Syndrome1

starting between all days Before and 0 days Before event index date

* and exactly 0 occurrences of a drug exposure of Atorvastatin 80mg2
  + drug type is any of: Inpatient administration

starting between all days Before and 0 days Before event index date

* and exactly 0 occurrences of a drug exposure of Pravastatin 40mg 13
  + drug type is any of: Inpatient administration

starting between all days Before and 0 days Before event index date

* And having all of the following criteria:
  + at least 1/exactly 0  occurrences of a drug exposure of Pravastatin 40mg 13

starting between all days Before and 0 days After event index date

* + and at least 1/exactly 0 occurrences of a drug exposure of Atorvastatin 80mg2

starting between all days Before and 0 days After event index date

Limit cohort of initial events to: **earliest event per person.**

**Inclusion Criteria**

Inclusion Criteria #1: No Criteria

Having all of the following criteria:

Inclusion Criteria #2: No Long Term LLT: Total Chol LTE 240mg OR Long Term LLT: Total Chol LTE 200mg

Having any of the following criteria:

* Having all of the following criteria:
  + exactly 0 occurrences of a drug exposure of Lipid Lowering Therapy 9

starting between 365 days Before and 0 days Before event index date

* + and exactly 0 occurrences of a measurement of Total Cholesterol 15
    - with value as number > 240

starting between 180 days Before and 0 days Before event index date

* Or having all of the following criteria:
  + at least 1 occurrences of a drug exposure of Lipid Lowering Therapy 9

starting between 365 days Before and 0 days Before event index date

* + and exactly 0 occurrences of a measurement of Total Cholesterol 15
    - with value as number > 200

starting between 180 days Before and 0 days Before event index date

Inclusion Criteria #3: No Statin of 80mg per day (or more?)

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of Statin14
  + with effective drug dose >= 80

starting between all days Before and 30 days Before event index date and ending between 30 days Before and 0 days Before event index date

Inclusion Criteria #4: No Lipid Lowering Therapy with Fibric Acid

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of Lipid Lowering Agent with Fibric Acid Derivatives7

starting between all days Before and 30 days Before event index date and ending between 30 days Before and 0 days Before event index date

Inclusion Criteria #5: No Lipid Lowering Therapy with Niacin

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of Lipid Lowering Agents with Niacin8

starting between all days Before and 30 days Before event index date and ending between 30 days Before and 0 days Before event index date

Inclusion Criteria #6: No CYP450 3A4

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of Inhibitors of CYP450 3A4 6

starting between all days Before and 30 days Before event index date and ending between 30 days Before and 0 days Before event index date

Inclusion Criteria #7: No Percutaneous Coronary Intervention

Having all of the following criteria:

* exactly 0 occurrences of a procedure of Percutaneous Coronary Intervention 12

starting between 180 days Before and 0 days Before event index date

Inclusion Criteria #8: No Coronary Artery Bypass Surgery

Having all of the following criteria:

* exactly 0 occurrences of a procedure of Bypass Surgery 3

starting between 60 days Before and 0 days Before event index date

Inclusion Criteria #9: No Obstructive Hepatobiliary Disease

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Obstructive Heptaobiliary Disease 11

starting between 365 days Before and 0 days Before event index date

Inclusion Criteria #10: No Hepatic Disease

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Liver Disease10

starting between all days Before and 0 days Before event index date

Inclusion Criteria #11: No Creatine Kinase Level GT 3x Normal

Having any of the following criteria:

* Having all of the following criteria:
  + exactly 0 occurrences of a measurement of Creatine Kinase4
    - with value as number > 354
    - gender is any of: FEMALE

starting between all days Before and 0 days Before event index date

* Or having all of the following criteria:
  + exactly 0 occurrences of a measurement of Creatine Kinase4
    - with value as number > 318
    - gender is any of: MALE

starting between all days Before and 0 days Before event index date

Inclusion Criteria #12: No Creatinine GT 20mg

Having all of the following criteria:

* exactly 0 occurrences of a measurement of Creatinine5
  + with value as number > 2

starting between 30 days Before and 0 days Before event index date

Limit qualifying cohort to: **earliest event per person.**

Appendix 11.2: Concept Set Definitions

1. Acute Coronary Syndrome

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4329847 | Myocardial infarction | Condition | SNOMED | NO | YES | NO |
| 35205182 | Angina unstable | Condition | MedDRA | NO | YES | NO |
| 44820858 | Acute myocardial infarction of anterolateral wall, subsequent episode of care | Condition | ICD9CM | YES | YES | NO |
| 44820859 | Acute myocardial infarction of inferolateral wall, subsequent episode of care | Condition | ICD9CM | YES | YES | NO |
| 44820860 | Acute myocardial infarction of inferoposterior wall, subsequent episode of care | Condition | ICD9CM | YES | YES | NO |
| 44819697 | Acute myocardial infarction of other anterior wall, subsequent episode of care | Condition | ICD9CM | YES | YES | NO |
| 44832374 | Acute myocardial infarction of other inferior wall, subsequent episode of care | Condition | ICD9CM | YES | YES | NO |
| 44834721 | Acute myocardial infarction of other lateral wall, subsequent episode of care | Condition | ICD9CM | YES | YES | NO |
| 44832376 | Acute myocardial infarction of other specified sites, subsequent episode of care | Condition | ICD9CM | YES | YES | NO |
| 44820861 | Acute myocardial infarction of unspecified site, subsequent episode of care | Condition | ICD9CM | YES | YES | NO |
| 314666 | Old myocardial infarction | Condition | SNOMED | YES | YES | NO |

2. Atorvastatin 80mg

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 1545959 | atorvastatin 80 MG Oral Tablet | Drug | RxNorm | NO | YES | NO |

3. Bypass Surgery

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 37522318 | Coronary artery bypass | Procedure | MedDRA | NO | YES | NO |

4. Creatine Kinase

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3007220 | Creatine kinase [Enzymatic activity/volume] in Serum or Plasma | Measurement | LOINC | NO | YES | NO |

5. Creatinine

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3016723 | Creatinine serum/plasma | Measurement | LOINC | NO | YES | NO |

6. Inhibitors of CYP450 3A4

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21601919 | Imidazole and triazole derivatives | Drug | ATC | NO | YES | NO |

7. Lipid Lowering Agent with Fibric Acid Derivatives

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21601864 | Fibrates | Drug | ATC | NO | YES | NO |

8. Lipid Lowering Agents with Niacin

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 1517824 | Niacin | Drug | RxNorm | NO | YES | NO |

9. Lipid Lowering Therapy

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21601853 | LIPID MODIFYING AGENTS | Drug | ATC | NO | YES | NO |

10. Liver Disease

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 194984 | Disease of liver | Condition | SNOMED | NO | NO | NO |

11. Obstructive Heptaobiliary Disease

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 35902850 | Obstructive bile duct disorders (excl neoplasms) | Condition | MedDRA | NO | YES | NO |

12. Percutaneous Coronary Intervention

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4216130 | Percutaneous coronary intervention | Procedure | SNOMED | NO | YES | NO |

13. Pravastatin 40mg

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 40175400 | Pravastatin Sodium 40 MG Oral Tablet | Drug | RxNorm | NO | YES | NO |

14. Statin

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21601855 | HMG CoA reductase inhibitors | Drug | ATC | NO | YES | NO |

15. Total Cholesterol

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3027114 | Cholesterol [Mass/volume] in Serum or Plasma |  |  |  |  |  |

## ACE inhibitors and calcium channel blockers on hypertension (ACCOMPLISH)

**Initial Event Cohort**

People having any of the following: 

* a condition occurrence of hypertension11
  + with age >= 60 OR with age 55-60 (see Inclusion Criteria #2 below\_

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

**Inclusion Criteria**

Inclusion Criteria #1: Systolic Blood Pressure OR Antihypertensive

Having any of the following criteria:

* at least 1 occurrences of a drug exposure of Antihypertensive Drugs6

starting between all days Before and 0 days Before event index date

* or at least 1 occurrences of a measurement of systolic blood pressure23
  + with value as number >= 160

starting between all days Before and 0 days Before event index date

Inclusion Criteria #2: At Least 1: (MI, UA, Revasc), Stroke, PAOD, Diabetes, LVH, Renal Events

Having at least 1 of the following criteria (if >50) or Having at least 2 of the following (if 55-60 at time of event)

* at least 1 occurrences of a condition occurrence of Myocardial Infarction16

starting between all days Before and 0 days Before event index date

* or at least 1 occurrences of a condition occurrence of Unstable Angina27

starting between all days Before and 0 days Before event index date

* or at least 1 occurrences of a condition occurrence of Coronary Revascularization8

starting between all days Before and 0 days Before event index date

* or at least 1 occurrences of a condition occurrence of stroke22

starting between all days Before and 0 days Before event index date

* or at least 1 occurrences of a procedure of Peripheral Arterial Occlusive Disease PROC18

starting between all days Before and 0 days Before event index date

* or at least 1 occurrences of a condition occurrence of Diabetes Mellitus9

starting between all days Before and 0 days Before event index date

* or at least 1 occurrences of a condition occurrence of Left Ventricular Hypertrophy 14

starting between all days Before and 0 days Before event index date

* Or having at least 1 of the following criteria:
  + at least 1 occurrences of a measurement of Serum Creatinine20
    - with value as number > 1.7
    - gender is any of: Male

starting between all days Before and 0 days Before event index date

* + or at least 1 occurrences of a measurement of Serum Creatinine21
    - with value as number > 1.5
    - gender is any of: Female

starting between all days Before and 0 days Before event index date

* + Or having any of the following criteria:
    - Having all of the following criteria:
      * at least 1 occurrences of a drug exposure of ACE Inhibitor or Aldosterone Receptor Blocker1

starting between all days Before and 0 days Before event index date

* + - * and at least 1 occurrences of a measurement of Albumin Creatinine Ratio3
        + with value as number > 300

starting between all days Before and 0 days Before event index date

* + - * And having all of the following criteria:
        + exactly 0 occurrences of a drug exposure of ACE Inhibitor or Aldosterone Receptor Blocker1

starting between all days Before and 0 days Before event index date

* + - * + and at least 1 occurrences of a measurement of Albumin Creatinine Ratio3

with value as number > 200

starting between all days Before and 0 days Before event index date

Inclusion Criteria #3: No Angina Pectoris

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Angina Pectoris4

starting between 90 days Before and 0 days Before event index date

Inclusion Criteria #4: No Heart Failure

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Heart Failure10

starting between 0 days Before and 0 days Before event index date

Inclusion Criteria #5: No MI 30 days before

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Myocardial Infarction16

starting between 30 days Before and 0 days Before event index date

Inclusion Criteria #6: No ACS 30 days before

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of ACS2

starting between 30 days Before and 0 days Before event index date

Inclusion Criteria #7: No Coronary Revascularization 30 days before

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Coronary Revascularization8

starting between 30 days Before and 0 days Before event index date

Inclusion Criteria #8: No Stroke 90 days before

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of stroke22

starting between 90 days Before and 0 days Before event index date

Inclusion Criteria #9: No Isc Cerebrovascular Episodes 90 days before

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Ischemic Cerebrovascular Episodes13

starting between 90 days Before and 0 days Before event index date

Limit qualifying cohort to: **earliest event per person.**

Appendix 11.3: Concept Set Definitions

1. ACE Inhibitor or Aldosterone Receptor Blocker

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21601783 | ACE INHIBITORS, PLAIN | Drug | ATC | NO | YES | NO |
| 21601533 | Aldosterone antagonists | Drug | ATC | NO | YES | NO |

2. ACS

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4215140 | Acute coronary syndrome | Condition | SNOMED | NO | YES | NO |

3. Albumin Creatinine Ratio

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3001802 | Microalbumin/Creatinine [Mass Ratio] in Urine | Measurement | LOINC | NO | YES | NO |

4. Angina Pectoris

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 321318 | Angina pectoris | Condition | SNOMED | NO | YES | NO |

5. Antidiabetic Drugs

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21600744 | BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS | Drug | ATC | NO | YES | NO |
| 21600713 | INSULINS AND ANALOGUES | Drug | ATC | NO | YES | NO |
| 4336036 | ORAL HYPOGLYCEMIC AGENTS,ORAL | Drug | VA Class | NO | YES | NO |

6. Antihypertensive Drugs

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21600381 | ANTIHYPERTENSIVES | Drug | ATC | NO | YES | NO |

7. Cardiovascular Disease\_ACCOMPLISH

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 134057 | Disorder of cardiovascular system | Condition | SNOMED | NO | YES | NO |

8. Coronary Revascularization

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 37522318 | Coronary artery bypass | Procedure | MedDRA | NO | YES | NO |

9. Diabetes Mellitus

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 35502089 | Glucose metabolism disorders (incl diabetes mellitus) | Condition | MedDRA | NO | YES | NO |

10. Heart Failure

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 316139 | Heart failure | Condition | SNOMED | NO | YES | NO |

11. hypertension

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 316866 | Hypertensive disorder | Condition | SNOMED | NO | YES | NO |

12. Insulin

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21600713 | INSULINS AND ANALOGUES | Drug | ATC | NO | YES | NO |

13. Ischemic Cerebrovascular Episodes

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 373503 | Transient cerebral ischemia | Condition | SNOMED | NO | YES | NO |
| 36718067 | Transient ischaemic attack | Condition | MedDRA | NO | YES | NO |

14. Left Ventricular Hypertrophy

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4231591 | Right ventricular hypertrophy | Condition | SNOMED | YES | YES | NO |
| 35205348 | Ventricular hypertrophy | Condition | MedDRA | NO | YES | NO |

15. Microalbuminuria

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3024561 | Albumin serum/plasma | Measurement | LOINC | NO | YES | NO |

16. Myocardial Infarction

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4329847 | Myocardial infarction | Condition | SNOMED | NO | YES | NO |
| 35205189 | Myocardial infarction | Condition | MedDRA | NO | YES | NO |

17. Overnight Fasting Blood Glucose

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3037110 | Fasting glucose [Mass/volume] in Serum or Plasma | Measurement | LOINC | NO | YES | NO |

18. Peripheral Arterial Occlusive Disease PROC

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 2002187 | Aorta-iliac-femoral bypass | Procedure | ICD9Proc | NO | YES | NO |
| 37522314 | Carotid endarterectomy | Procedure | MedDRA | NO | YES | NO |
| 37522318 | Coronary artery bypass | Procedure | MedDRA | NO | YES | NO |
| 37520683 | Leg amputation | Procedure | MedDRA | NO | YES | NO |

19. Renal Disease

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 37019308 | Renal disorder | Condition | MedDRA | NO | YES | NO |

20. Serum Creatinine

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3016723 | Creatinine serum/plasma | Measurement | LOINC | NO | YES | NO |

21. Serum Creatinine

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3016723 | Creatinine serum/plasma | Measurement | LOINC | NO | YES | NO |

22. stroke

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 500003201 | OMOP Stroke 1 | Condition | Cohort | NO | YES | NO |

23. systolic blood pressure

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3004249 | BP systolic | Measurement | LOINC | NO | YES | NO |
| 3018586 | Systolic blood pressure--sitting | Measurement | LOINC | NO | YES | NO |
| 3035856 | Systolic blood pressure--standing | Measurement | LOINC | NO | YES | NO |
| 3009395 | Systolic blood pressure--supine | Measurement | LOINC | NO | YES | NO |

24. Target Organ Damage

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4349444 | Hypertrophy, Left Ventricular | Drug | NDFRT | NO | YES | NO |
| 75650 | Proteinuria | Condition | SNOMED | NO | YES | NO |
| 37019318 | Renal failure | Condition | MedDRA | NO | YES | NO |
| 376103 | Retinopathy | Condition | SNOMED | NO | YES | NO |
| 443605 | Vascular dementia | Condition | SNOMED | NO | YES | NO |

25. Target Organ Damage

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4349444 | Hypertrophy, Left Ventricular | Drug | NDFRT | NO | YES | NO |
| 75650 | Proteinuria | Condition | SNOMED | NO | YES | NO |
| 37019318 | Renal failure | Condition | MedDRA | NO | YES | NO |
| 376103 | Retinopathy | Condition | SNOMED | NO | YES | NO |
| 443605 | Vascular dementia | Condition | SNOMED | NO | YES | NO |

26. Type 2 Diabetes Mellitus

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 201826 | Type 2 diabetes mellitus | Condition | SNOMED | NO | YES | NO |

27. Unstable Angina

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 35205182 | Angina unstable | Condition | MedDRA | NO | YES | NO |

## Losartan vs Placebo in combination with conventional anti-hypertensive therapies on diabetic nephropathy (RENAAL)

**Initial Event Cohort**

People having any of the following: 

* a condition occurrence of Type 2 Diabetes Mellitus34
  + with age between 31 and 70 (inclusive)

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

**Inclusion Criteria**

Inclusion Criteria #1: Nephropathy

Having all of the following criteria:

* at least 1 occurrences of a condition occurrence of Nephropathy16

starting between all days Before and 0 days Before event index date

Inclusion Criteria #2: Hypertensive or Normotensive

Having any of the following criteria:

* at least 1 occurrences of a condition occurrence of hypertension9

starting between all days Before and 0 days Before event index date

* or at least 1 occurrences of a measurement of Systolic BP sitting29
  + with value as number >= 110

starting between all days Before and 0 days Before event index date

Inclusion Criteria #3: Insulin

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of Insulin 10

starting between 180 days Before and 0 days Before event index date

Inclusion Criteria #4: Ketoacidosis

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Ketoacidosis12

starting between all days Before and 0 days Before event index date

Inclusion Criteria #5: HbA1c

Having all of the following criteria:

* at least 1 occurrences of a measurement of HbA1c4
  + with value as number < 12

starting between all days Before and 0 days Before event index date

Inclusion Criteria #6: Pregnancy

Having all of the following criteria:

* exactly 0 occurrences of a measurement of pregnancy test21
  + with value as number > 25

starting between 300 days Before and 0 days Before event index date

Inclusion Criteria #7: Type I Diabetes

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Type 1 Diabetes Melliuts32

starting between all days Before and 0 days Before event index date

Inclusion Criteria #8: Non Diabetic Renal Disease

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Non-Diabetic Renal Disease19

starting between all days Before and 0 days Before event index date

Inclusion Criteria #9: Myocardial Infarction

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Myocardial Infarction14

starting between 30 days Before and 0 days Before event index date

Inclusion Criteria #10: CABG

Having all of the following criteria:

* exactly 0 occurrences of a procedure of CABG1

starting between 30 days Before and 0 days Before event index date

Inclusion Criteria #11: Cerebrovascular Event

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Cerebrovascular Accident3

starting between 180 days Before and 0 days Before event index date

Inclusion Criteria #12: PTCA

Having all of the following criteria:

* exactly 0 occurrences of a procedure of PTCA23

starting between 30 days Before and 0 days Before event index date

Inclusion Criteria #13: TIA

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Transient Ischemic Attack31

starting between 365 days Before and 0 days Before event index date

Inclusion Criteria #14: Heart Failure

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Heart Failure7

starting between all days Before and 0 days Before event index date

Inclusion Criteria #15: Renal Artery Stenosis

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Renal Artery Stenosis (Broad)25

starting between all days Before and 0 days Before event index date

Inclusion Criteria #16: Primary Aldosteronism

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of Primary Aldosteronism22

starting between all days Before and 0 days Before event index date

Inclusion Criteria #17: Phaeochromocytoma

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of phaeochromocytoma20

starting between all days Before and 0 days Before event index date

Limit qualifying cohort to: **earliest event per person.**

Appendix 11.4: Concept Set Definitions

1. CABG

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 37522318 | Coronary artery bypass | Procedure | MedDRA | NO | YES | NO |

2. CABG

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 37522318 | Coronary artery bypass | Procedure | MedDRA | NO | YES | NO |

3. Cerebrovascular Accident

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 36703451 | Central nervous system haemorrhages and cerebrovascular accidents | Condition | MedDRA | NO | YES | NO |

4. HbA1c

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3004410 | Hemoglobin A1c (Glycated) | Measurement | LOINC | NO | YES | NO |

5. HbA1c

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3004410 | Hemoglobin A1c (Glycated) | Measurement | LOINC | NO | YES | NO |

6. HbA1c

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3004410 | Hemoglobin A1c (Glycated) | Measurement | LOINC | NO | YES | NO |

7. Heart Failure

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 316139 | Heart failure | Condition | SNOMED | NO | YES | NO |

8. Heart Failure

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 316139 | Heart failure | Condition | SNOMED | NO | YES | NO |

9. hypertension

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 316866 | Hypertensive disorder | Condition | SNOMED | NO | YES | NO |

10. Insulin

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21600713 | INSULINS AND ANALOGUES | Drug | ATC | NO | YES | NO |

11. Insulin

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 21600713 | INSULINS AND ANALOGUES | Drug | ATC | NO | YES | NO |

12. Ketoacidosis

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4209145 | Ketoacidosis | Condition | SNOMED | NO | YES | NO |

13. Ketoacidosis

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4209145 | Ketoacidosis | Condition | SNOMED | NO | YES | NO |

14. Myocardial Infarction

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4329847 | Myocardial infarction | Condition | SNOMED | NO | YES | NO |
| 35205189 | Myocardial infarction | Condition | MedDRA | NO | YES | NO |

15. Myocardial Infarction

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4329847 | Myocardial infarction | Condition | SNOMED | NO | YES | NO |
| 35205189 | Myocardial infarction | Condition | MedDRA | NO | YES | NO |

16. Nephropathy

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 37019299 | Nephropathy | Condition | MedDRA | NO | YES | NO |

17. Nephropathy

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 37019299 | Nephropathy | Condition | MedDRA | NO | YES | NO |

18. Nephropathy

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 37019299 | Nephropathy | Condition | MedDRA | NO | YES | NO |

19. Non-Diabetic Renal Disease

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 37019308 | Renal disorder | Condition | MedDRA | NO | YES | NO |
| 443731 | Renal disorder due to type 2 diabetes mellitus | Condition | SNOMED | YES | YES | NO |
| 193782 | End stage renal disease | Condition | SNOMED | YES | YES | NO |
| 46271022 | Chronic kidney disease | Condition | SNOMED | YES | YES | NO |

20. phaeochromocytoma

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4118993 | Pheochromocytoma | Condition | SNOMED | NO | YES | NO |

21. pregnancy test

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 44786908 | HEDIS 2014 Value Set - Pregnancy Tests | Measurement | LOINC | NO | YES | NO |

22. Primary Aldosteronism

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 35506454 | Primary hyperaldosteronism | Condition | MedDRA | NO | YES | NO |

23. PTCA

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4006788 | Percutaneous transluminal coronary angioplasty | Procedure | SNOMED | NO | YES | NO |
| 2000064 | Percutaneous transluminal coronary angioplasty [PTCA] | Procedure | ICD9Proc | NO | YES | NO |

24. PTCA

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4006788 | Percutaneous transluminal coronary angioplasty | Procedure | SNOMED | NO | YES | NO |
| 2000064 | Percutaneous transluminal coronary angioplasty [PTCA] | Procedure | ICD9Proc | NO | YES | NO |

25. Renal Artery Stenosis (Broad)

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 37003676 | Renal vascular and ischaemic conditions | Condition | MedDRA | NO | YES | NO |

26. Renal Artery Stenosis (Broad)

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 37003676 | Renal vascular and ischaemic conditions | Condition | MedDRA | NO | YES | NO |

27. Renal Artery Stenosis (Broad)

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 37003676 | Renal vascular and ischaemic conditions | Condition | MedDRA | NO | YES | NO |

28. Renal Artery Stenosis (Broad)

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 37003676 | Renal vascular and ischaemic conditions | Condition | MedDRA | NO | YES | NO |

29. Systolic BP sitting

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3018586 | Systolic blood pressure--sitting | Measurement | LOINC | NO | YES | NO |

30. Systolic BP sitting

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3018586 | Systolic blood pressure--sitting | Measurement | LOINC | NO | YES | NO |

31. Transient Ischemic Attack

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 373503 | Transient cerebral ischemia | Condition | SNOMED | NO | YES | NO |

32. Type 1 Diabetes Melliuts

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 201254 | Type 1 diabetes mellitus | Condition | SNOMED | NO | NO | NO |

33. Type 1 Diabetes Melliuts

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 201254 | Type 1 diabetes mellitus | Condition | SNOMED | NO | NO | NO |

34. Type 2 Diabetes Mellitus

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 201826 | Type 2 diabetes mellitus | Condition | SNOMED | NO | YES | NO |

35. Unnamed Concept Set

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |