Supplementary material

# Cohort Definitions

## Treatment cohorts

### First-line new user ACE inhibitors

#### Initial Event Cohort

People having any of the following:

* a drug exposure of [LEGEND HTN] ACE inhibitors (see 2 below)
  + for the first time in the person's history

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

For people matching the Primary Events, include:

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of Hypertension drugs (see 4 below) where event starts between all days Before and 1 days Before index start date
* and at least 1 occurrences of a condition occurrence of Hypertensive disorder (see 1 below) where event starts between 365 days Before and 0 days After index start date
* and exactly 1 distinct occurrences of a drug era of [Hypertension drugs (see 4 below) where event starts between 0 days Before and 7 days After index start date

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

Limit qualifying cohort to: earliest event per person.

#### End Date Strategy

##### Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of [LEGEND HTN] ACE inhibitors2

* allowing 30 days between exposures
* adding 0 days after exposure end
* using days supply and exposure end date for exposure duration.

##### Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

#### Concept Set Definitions

Hypertensive disorder

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

ACE inhibitors

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 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 |

First-line hypertension drugs

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 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 |
| 1307863 | Verapamil | Drug | RxNorm | NO | YES | NO |
| 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 |
| 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 |
| 1331235 | quinapril | Drug | RxNorm | NO | YES | NO |
| 1332418 | Amlodipine | 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 |
| 1353776 | Felodipine | 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 |
| 1395058 | Chlorthalidone | Drug | RxNorm | NO | YES | NO |
| 40226742 | olmesartan | Drug | RxNorm | NO | YES | NO |
| 40235485 | azilsartan | Drug | RxNorm | NO | YES | NO |

Hypertension drugs

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 40235485 | azilsartan | Drug | RxNorm | NO | YES | NO |
| 40226742 | olmesartan | Drug | RxNorm | NO | YES | NO |
| 1398937 | Clonidine | Drug | RxNorm | NO | YES | NO |
| 1395058 | Chlorthalidone | Drug | RxNorm | NO | YES | NO |
| 1386957 | Labetalol | Drug | RxNorm | NO | YES | NO |
| 1373928 | Hydralazine | Drug | RxNorm | NO | YES | NO |
| 1373225 | Perindopril | Drug | RxNorm | NO | YES | NO |
| 1367500 | Losartan | Drug | RxNorm | NO | YES | NO |
| 1363749 | Fosinopril | Drug | RxNorm | NO | YES | NO |
| 1363053 | Doxazosin | Drug | RxNorm | NO | YES | NO |
| 1353776 | Felodipine | Drug | RxNorm | NO | YES | NO |
| 1353766 | Propranolol | Drug | RxNorm | NO | YES | NO |
| 1351557 | candesartan | Drug | RxNorm | NO | YES | NO |
| 1350489 | Prazosin | Drug | RxNorm | NO | YES | NO |
| 1347384 | irbesartan | Drug | RxNorm | NO | YES | NO |
| 1346823 | carvedilol | Drug | RxNorm | NO | YES | NO |
| 1346686 | eprosartan | Drug | RxNorm | NO | YES | NO |
| 1345858 | Pindolol | Drug | RxNorm | NO | YES | NO |
| 1344965 | Guanfacine | Drug | RxNorm | NO | YES | NO |
| 1342439 | trandolapril | Drug | RxNorm | NO | YES | NO |
| 1341927 | Enalapril | Drug | RxNorm | NO | YES | NO |
| 1341238 | Terazosin | Drug | RxNorm | NO | YES | NO |
| 1340128 | Captopril | Drug | RxNorm | NO | YES | NO |
| 1338005 | Bisoprolol | Drug | RxNorm | NO | YES | NO |
| 1335471 | benazepril | Drug | RxNorm | NO | YES | NO |
| 1334456 | Ramipril | Drug | RxNorm | NO | YES | NO |
| 1332418 | Amlodipine | Drug | RxNorm | NO | YES | NO |
| 1331235 | quinapril | Drug | RxNorm | NO | YES | NO |
| 1328165 | Diltiazem | Drug | RxNorm | NO | YES | NO |
| 1327978 | Penbutolol | Drug | RxNorm | NO | YES | NO |
| 1326012 | Isradipine | Drug | RxNorm | NO | YES | NO |
| 1322081 | Betaxolol | Drug | RxNorm | NO | YES | NO |
| 1319998 | Acebutolol | Drug | RxNorm | NO | YES | NO |
| 1319880 | Nisoldipine | Drug | RxNorm | NO | YES | NO |
| 1318853 | Nifedipine | Drug | RxNorm | NO | YES | NO |
| 1318137 | Nicardipine | Drug | RxNorm | NO | YES | NO |
| 1317967 | aliskiren | Drug | RxNorm | NO | YES | NO |
| 1317640 | telmisartan | Drug | RxNorm | NO | YES | NO |
| 1314577 | nebivolol | Drug | RxNorm | NO | YES | NO |
| 1314002 | Atenolol | Drug | RxNorm | NO | YES | NO |
| 1313200 | Nadolol | Drug | RxNorm | NO | YES | NO |
| 1310756 | moexipril | Drug | RxNorm | NO | YES | NO |
| 1309799 | eplerenone | Drug | RxNorm | NO | YES | NO |
| 1309068 | Minoxidil | Drug | RxNorm | NO | YES | NO |
| 1308842 | valsartan | Drug | RxNorm | NO | YES | NO |
| 1308216 | Lisinopril | Drug | RxNorm | NO | YES | NO |
| 1307863 | Verapamil | Drug | RxNorm | NO | YES | NO |
| 1307046 | Metoprolol | Drug | RxNorm | NO | YES | NO |
| 1305447 | Methyldopa | Drug | RxNorm | NO | YES | NO |
| 991382 | Amiloride | Drug | RxNorm | NO | YES | NO |
| 978555 | Indapamide | Drug | RxNorm | NO | YES | NO |
| 974166 | Hydrochlorothiazide | Drug | RxNorm | NO | YES | NO |
| 970250 | Spironolactone | Drug | RxNorm | NO | YES | NO |
| 956874 | Furosemide | Drug | RxNorm | NO | YES | NO |
| 942350 | torsemide | Drug | RxNorm | NO | YES | NO |
| 932745 | Bumetanide | Drug | RxNorm | NO | YES | NO |
| 907013 | Metolazone | Drug | RxNorm | NO | YES | NO |
| 904542 | Triamterene | Drug | RxNorm | NO | YES | NO |

### First-line new user beta blockers

#### Initial Event Cohort

People having any of the following:

* a drug exposure of Beta blockers(see 2 below)
  + for the first time in the person's history

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

For people matching the Primary Events, include:

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of Hypertension drugs (see 4 below) where event starts between all days Before and 1 days Before index start date
* and at least 1 occurrences of a condition occurrence of Hypertensive disorder (see 1 below) where event starts between 365 days Before and 0 days After index start date
* and exactly 1 distinct occurrences of a drug era of Hypertension drugs (see 4 below) where event starts between 0 days Before and 7 days After index start date

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

Limit qualifying cohort to: earliest event per person.

#### End Date Strategy

##### Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of Beta blockers (see 2 below)

* allowing 30 days between exposures
* adding 0 days after exposure end

##### Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

#### Concept Set Definitions

Hypertensive disorder

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

Beta blockers

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 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 |

First-line hypertension drugs

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 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 |
| 1307863 | Verapamil | Drug | RxNorm | NO | YES | NO |
| 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 |
| 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 |
| 1331235 | quinapril | Drug | RxNorm | NO | YES | NO |
| 1332418 | Amlodipine | 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 |
| 1353776 | Felodipine | 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 |
| 1395058 | Chlorthalidone | Drug | RxNorm | NO | YES | NO |
| 40226742 | olmesartan | Drug | RxNorm | NO | YES | NO |
| 40235485 | azilsartan | Drug | RxNorm | NO | YES | NO |

Hypertension drugs

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 904542 | Triamterene | Drug | RxNorm | NO | YES | NO |
| 907013 | Metolazone | 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 |
| 974166 | Hydrochlorothiazide | Drug | RxNorm | NO | YES | NO |
| 978555 | Indapamide | Drug | RxNorm | NO | YES | NO |
| 991382 | Amiloride | Drug | RxNorm | NO | YES | NO |
| 1305447 | Methyldopa | Drug | RxNorm | NO | YES | NO |
| 1307046 | Metoprolol | Drug | RxNorm | NO | YES | NO |
| 1307863 | Verapamil | Drug | RxNorm | NO | YES | NO |
| 1308216 | Lisinopril | Drug | RxNorm | NO | YES | NO |
| 1308842 | valsartan | Drug | RxNorm | NO | YES | NO |
| 1309068 | Minoxidil | Drug | RxNorm | NO | YES | NO |
| 1309799 | eplerenone | Drug | RxNorm | NO | YES | NO |
| 1310756 | moexipril | 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 |
| 1317640 | telmisartan | Drug | RxNorm | NO | YES | NO |
| 1317967 | aliskiren | 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 |
| 1319998 | Acebutolol | Drug | RxNorm | NO | YES | NO |
| 1322081 | Betaxolol | Drug | RxNorm | NO | YES | NO |
| 1326012 | Isradipine | Drug | RxNorm | NO | YES | NO |
| 1327978 | Penbutolol | Drug | RxNorm | NO | YES | NO |
| 1328165 | Diltiazem | Drug | RxNorm | NO | YES | NO |
| 1331235 | quinapril | Drug | RxNorm | NO | YES | NO |
| 1332418 | Amlodipine | Drug | RxNorm | NO | YES | NO |
| 1334456 | Ramipril | Drug | RxNorm | NO | YES | NO |
| 1335471 | benazepril | Drug | RxNorm | NO | YES | NO |
| 1338005 | Bisoprolol | Drug | RxNorm | NO | YES | NO |
| 1340128 | Captopril | Drug | RxNorm | NO | YES | NO |
| 1341238 | Terazosin | Drug | RxNorm | NO | YES | NO |
| 1341927 | Enalapril | Drug | RxNorm | NO | YES | NO |
| 1342439 | trandolapril | Drug | RxNorm | NO | YES | NO |
| 1344965 | Guanfacine | Drug | RxNorm | NO | YES | NO |
| 1345858 | Pindolol | Drug | RxNorm | NO | YES | NO |
| 1346686 | eprosartan | Drug | RxNorm | NO | YES | NO |
| 1346823 | carvedilol | Drug | RxNorm | NO | YES | NO |
| 1347384 | irbesartan | Drug | RxNorm | NO | YES | NO |
| 1350489 | Prazosin | Drug | RxNorm | NO | YES | NO |
| 1351557 | candesartan | Drug | RxNorm | NO | YES | NO |
| 1353766 | Propranolol | Drug | RxNorm | NO | YES | NO |
| 1353776 | Felodipine | Drug | RxNorm | NO | YES | NO |
| 1363053 | Doxazosin | 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 |
| 1373928 | Hydralazine | Drug | RxNorm | NO | YES | NO |
| 1386957 | Labetalol | Drug | RxNorm | NO | YES | NO |
| 1395058 | Chlorthalidone | Drug | RxNorm | NO | YES | NO |
| 1398937 | Clonidine | Drug | RxNorm | NO | YES | NO |
| 40226742 | olmesartan | Drug | RxNorm | NO | YES | NO |
| 40235485 | azilsartan | Drug | RxNorm | NO | YES | NO |

## Outcome cohorts

### Hospitalization with heart failure

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

#### Initial Event Cohort

People having any of the following:

* a visit occurrence of Inpatient or ER visit (see 1 below)

having one of the following:

* + at least 1 occurrences of a condition occurrence of Heart Failure(see 2 below) where event starts between 0 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

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

Limit qualifying cohort to: all events per person.

#### End Date Strategy

##### Date Offset Exit Criteria

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

##### Cohort Collapse Strategy:

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

#### Concept Set Definitions

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 |

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 |

### Acute Myocardial Infarction

#### Initial Event Cohort

People having any of the following:

* a condition occurrence of [LEGEND HTN] Acute myocardial Infarction (see 2 below)

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

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit (see 1 below) where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

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

Limit qualifying cohort to: all events per person.

#### End Date Strategy

##### Date Offset Exit Criteria

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

##### Cohort Collapse Strategy:

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

#### Concept Set Definitions

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 |

Acute myocardial Infarction

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 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 |

### Stroke (ischemic or hemorrhagic) events

Stroke (ischemic or hemorrhagic) condition record during an inpatient or ER visit; successive records with > 180 day gap are considered independent episodes

#### Initial Event Cohort

People having any of the following:

* a condition occurrence of Stroke ischemic or hemorrhagic (see 2 below)

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

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit (see 1 below)

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

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

Limit qualifying cohort to: all events per person.

#### End Date Strategy

##### Date Offset Exit Criteria

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

##### Cohort Collapse Strategy:

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

#### Concept Set Definitions

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 |

Stroke (ischemic or hemorrhagic)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 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 |
| 376713 | Cerebral hemorrhage | Condition | SNOMED | NO | NO | NO |
| 432923 | Subarachnoid hemorrhage | Condition | SNOMED | NO | NO | NO |
| 439847 | Intracranial hemorrhage | Condition | SNOMED | NO | NO | NO |
| 441874 | Cerebral thrombosis | Condition | SNOMED | NO | NO | NO |
| 443454 | Cerebral infarction | Condition | SNOMED | NO | YES | NO |

### Abnormal weight gain events

Abnormal weight gain record of any type; successive records with > 90 day gap are considered independent episodes

#### Initial Event Cohort

People having any of the following:

* an observation of [LEGEND HTN] Abnormal weight gain (see 1 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.

Limit qualifying cohort to: all events per person.

#### End Date Strategy

##### Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

##### Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

#### Concept Set Definitions

Abnormal weight gain

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 439141 | Abnormal weight gain | Observation | SNOMED | NO | YES | NO |

### Angioedema events

Angioedema condition record during an inpatient or ER visit; successive records with >7 day gap are considered independent episodes

#### Initial Event Cohort

People having any of the following:

* a condition occurrence of [LEGEND HTN] Angioedema (see 2 below)

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

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit (see 1 below)

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

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

Limit qualifying cohort to: all events per person.

#### End Date Strategy

##### Date Offset Exit Criteria

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

##### Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 30 days.

#### Concept Set Definitions

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 |

Angioedema

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 432791 | Angioedema | Condition | SNOMED | NO | YES | NO |

### Cough events

Cough condition record of any type; successive records with > 90 day gap are considered independent episodes

#### Initial Event Cohort

People having any of the following:

* a condition occurrence of [LEGEND HTN] Cough (see 1 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.

Limit qualifying cohort to: all events per person.

#### End Date Strategy

##### Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

##### Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

Concept Set Definitions

Cough

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 254761 | Cough | Condition | SNOMED | NO | YES | NO |

### Hyperkalemia events

Condition record for hyperkalemia or potassium measurements > 5.6 mmol/L; successive records with >90 day gap are considered independent episodes

#### Initial Event Cohort

People having any of the following:

* a condition occurrence of [LEGEND HTN] Hyperkalemia (see 1 below)
* a measurement of [LEGEND HTN] Potassium measurement (see 2 below)
  + with value as number > 5.6
  + unit is any of: millimole per liter

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

Limit qualifying cohort to: all events per person.

#### End Date Strategy

##### Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

##### Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

#### Concept Set Definitions

Hyperkalemia

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 434610 | Hyperkalemia | Condition | SNOMED | NO | YES | NO |

Potassium measurement

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 4245152 | Potassium measurement | Measurement | SNOMED | NO | YES | NO |
| 4276440 | Potassium level - finding | Condition | SNOMED | NO | YES | NO |
| 40789893 | Potassium | Bld-Ser-Plas | Measurement | LOINC | NO | YES | NO |

### Hypokalemia events

Hypokalemia condition record of any type; successive records with > 90 day gap are considered independent episodes

#### Initial Event Cohort

People having any of the following:

* a condition occurrence of Hypokalemia (see 1 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.

Limit qualifying cohort to: all events per person.

#### End Date Strategy

##### Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

##### Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

#### Concept Set Definitions

Hypokalemia

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 437833 | Hypokalemia | Condition | SNOMED | NO | YES | NO |
| 45769152 | Bartter syndrome | Condition | SNOMED | YES | YES | NO |

### Hypotension events

Hypotension condition record of any type; successive records with > 90 day gap are considered independent episodes

#### Initial Event Cohort

People having any of the following:

* a condition occurrence of [LEGEND HTN] Hypotension (see 1 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.

Limit qualifying cohort to: all events per person.

#### End Date Strategy

##### Date Offset Exit Criteria

This cohort definition end date will be the index event's start date plus 1 days

##### Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

#### Concept Set Definitions

Hypotension

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 313232 | Hemodialysis-associated hypotension | Observation | SNOMED | YES | YES | NO |
| 314432 | Maternal hypotension syndrome | Condition | SNOMED | YES | YES | NO |
| 317002 | Low blood pressure | Condition | SNOMED | NO | YES | NO |

# Results

## CCAE

### Covariate balance

A picture containing boat, table, photo, water

Description automatically generated

Figure S1: Standardized mean difference of the covariates before and after PS-stratification in all risk strata. Here we present only the analysis where we stratify in quarters of predicted acute myocardial infarction risk and assess heterogeneity of treatment effect with respect to the same outcome.

### Propensity scores

A close up of a map

Description automatically generated

Figure S2: Distribution of propensity scores in all risk strata. Here we present only the analysis where we stratify in quarters of predicted acute myocardial infarction risk and assess heterogeneity of treatment effect with respect to the same outcome.

### Prediction

#### Discrimination

A close up of a map

Description automatically generated

Figure S3: ROC curve of the model predicting acute myocardial infarction based on the propensity score-matched sub-population.

A close up of a map

Description automatically generated

Figure S4: ROC curve of the model predicting acute myocardial infarction based on the entire population.

A close up of a map

Description automatically generated

Figure S5: ROC curve of the model predicting acute myocardial infarction based on the treatment arm.

A close up of a map

Description automatically generated

Figure S6: ROC curve of the model predicting acute myocardial infarction based on the comparator arm.

#### Calibration

A close up of a map

Description automatically generated

Figure S7: Calibration plot of the model predicting acute myocardial infarction based on the propensity score-matched sub-population.

A close up of a map

Description automatically generated

Figure S8: Calibration plot of the model predicting acute myocardial infarction based on the entire population.

A close up of a map

Description automatically generated

Figure S9: Calibration plot of the model predicting acute myocardial infarction based on the treatment arm.

A close up of a map

Description automatically generated

Figure S10: Calibration plot of the model predicting acute myocardial infarction based on the comparator arm.

## MDCD

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | ACE inhibitors |  |  | Beta blockers |  |  |
| Outcome | Risk quarter | Patients | Person years | Events | Patients | Person years | Events |
| Acute myocardial infarction | 1 | 14,347 | 19,972 | 15 | 13,858 | 17,056 | 20 |
|  | 2 | 18,412 | 26,737 | 99 | 9,793 | 14,180 | 53 |
|  | 3 | 18,893 | 31,231 | 226 | 9,312 | 15,041 | 174 |
|  | 4 | 15,168 | 27,383 | 561 | 13,036 | 22,158 | 587 |
| Heart failure (hosp) | 1 | 18,004 | 25,006 | 87 | 16,028 | 20,042 | 120 |
|  | 2 | 18,190 | 27,253 | 208 | 9,108 | 13,527 | 138 |
|  | 3 | 17,386 | 29,261 | 453 | 8,618 | 14,219 | 340 |
|  | 4 | 11,775 | 21,440 | 970 | 9,928 | 17,197 | 1,155 |
| Stroke (ischemic or hemorrhagic) | 1 | 17,963 | 24,939 | 59 | 15,996 | 19,991 | 46 |
|  | 2 | 18,063 | 27,086 | 180 | 9,045 | 13,411 | 104 |
|  | 3 | 17,129 | 28,846 | 356 | 8,582 | 14,155 | 208 |
|  | 4 | 11,917 | 21,627 | 536 | 10,891 | 18,601 | 573 |

Table S1: Number of patients, person years and events within quarters of predicted risk for acute myocardial infarction for the 3 main outcomes of the study (acute myocardial infarction, hospitalization with heart failure or haemorrhagic stroke) in MDCD.

A picture containing table

Description automatically generated

Figure S11: Overview of heterogeneity of ACE-inhibitors treatment within strata of predicted risk of acute myocardial infarction in MDCD. The graph contains the acute myocardial infarction outcome rates in quarters of predicted risk (top), the hazard ratios (middle) and the absolute risk differences (bottom).

A close up of a map

Description automatically generated

Figure S12: Hazard ratios for the main and safety outcomes, estimated by fitting cox regression models within quarters of predicted risk for acute myocardial infarctio in MDCD. The four risk quarters (Q1-Q4) are defined using the internally developed model for acute myocardial infarction.

A close up of a map

Description automatically generated

Figure S13: Absolute risk reduction for the main and safety outcomes, estimated as the difference in Kaplan-Meier estimates within quarters of predicted risk acute myocardial infarction in MDCD. The four risk quarters (Q1-Q4) are defined using the internally developed model for acute myocardial infarction.

## MDCR

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | ACE inhibitors |  |  | Beta blockers |  |  |
| Outcome | Risk quarter | Patients | Person years | Events | Patients | Person years | Events |
| Acute myocardial infarction | 1 | 27,853 | 57,541 | 231 | 15,057 | 32,627 | 142 |
|  | 2 | 27,596 | 56,910 | 387 | 15,134 | 32,861 | 238 |
|  | 3 | 25,893 | 53,202 | 560 | 17,017 | 35,187 | 404 |
|  | 4 | 20,319 | 38,710 | 828 | 22,590 | 42,073 | 903 |
| Heart failure (hosp) | 1 | 27,530 | 56,886 | 364 | 14,847 | 32,183 | 317 |
|  | 2 | 27,486 | 56,644 | 582 | 15,183 | 32,622 | 482 |
|  | 3 | 25,482 | 52,475 | 965 | 16,500 | 34,234 | 865 |
|  | 4 | 19,704 | 37,842 | 1,578 | 20,746 | 39,414 | 2,109 |
| Stroke (ischemic or hemorrhagic) | 1 | 27,291 | 56,413 | 375 | 14,734 | 31,988 | 229 |
|  | 2 | 27,054 | 55,846 | 490 | 15,011 | 32,220 | 371 |
|  | 3 | 24,763 | 50,976 | 752 | 16,209 | 33,763 | 629 |
|  | 4 | 18,666 | 35,775 | 979 | 20,905 | 39,444 | 1,094 |

Table S2: Number of patients, person years and events within quarters of predicted risk for hospitalization with heart failure for the 3 main outcomes of the study (acute myocardial infarction, hospitalization with heart failure and ischemic or hemorrhagic stroke) in MDCR.

A close up of a map

Description automatically generated

Figure S14: Overview of heterogeneity of ACE-inhibitors treatment within strata of predicted risk of acute myocardial infarction in MDCR. The graph contains the acute myocardial infarction outcome rates in quarters of predicted risk (top), the hazard ratios that remain quite constant, showing no difference in relative effect with increasing risk (middle) and the absolute risk differences that remain constant close to 0 with increasing risk (bottom).

A close up of a map

Description automatically generated

Figure S15: Hazard ratios for the main and safety outcomes, estimated by fitting cox regression models within quarters of predicted risk for acute myocardial infarction in MDCR. The strata are defined using the internally developed model for acute myocardial infarction.

A close up of a map

Description automatically generated

Figure S16: Absolute risk reduction for the main and safety outcomes, estimated as the difference in Kaplan-Meier estimates within quarters of predicted risk for hospitalization with heart failure in MDCR. The four risk quarters (Q1-Q4) are defined using the internally developed model for acute myocardial infarction.