

RESEARCH PROTOCOL:

Association of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) on coronavirus disease (COVID-19) incidence and complications

Version 1.2

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1. List of Abbreviations

| | |
|----------|--|
| ACE | Angiotensin converting enzyme |
| ARB | Angiotensin II receptor blocker |
| ARDS | Acute respiratory distress syndrome |
| ATC | Anatomical Therapeutic Chemical Classification System |
| CCB | Calcium channel blocker |
| CDM | Common data model |
| COVID-19 | Coronavirus disease 2019 |
| dCCB | Dihydropyridine calcium channel blockers |
| ECMO | Extracorporeal membrane oxygenation |
| MACE | Major acute cardiovascular event |
| OMOP | Observational Medical Outcomes Partnership |
| OHDSI | Observational Health Data Science and Informatics |
| RAS | Renin-angiotensin system |
| RxNorm | US-specific terminology in medicine that contains all medications available on the US market |
| SNOMED | Systematized Nomenclature of Medicine |
| THZ | Thiazide or thiazide-like diuretic |

2. Responsible Parties

2.1. Investigators and Authors

| Investigator/Author | Institution/Affiliation |
|---------------------|---|
| Marc A. Suchard* | Department of Biostatistics, UCLA Fielding School of Public Health, University of California, Los Angeles |
| Daniel R. Morales | Division of Population Health and Genomics, University of Dundee |
| Seng Chan You | Department of Biomedical Informatics, Ajou University |
| George Hripcsak | Department of Biomedical Informatics, Columbia University |
| Mitchell M. Conover | Observational Health Data Analytics, Janssen Research and Development |
| Patrick B. Ryan | Observational Health Data Analytics, Janssen Research and Development |
| Nicole Pratt | Quality Use of Medicines and Pharmacy Research Centre, University of South Australia |

* Principal investigator

2.2 Sponsor

This study was undertaken Observational Health Data Science and Informatics (OHDSI), an open collaboration. **MAS** receives grant funding from the US National Institutes of Health and contracts from Janssen Research and Development. **DM** has received funding from the Wellcome Trust, the UK National Institute for Health Research, the Chief Scientist Office, Health Data Research-UK, and Tenovus Scotland for research unrelated to this work. **SCY** receives grant funding from the Korean Ministry of Health & Welfare and from the Korean Ministry of Trade, Industry & Energy. **GH** receives grant funding from the US National Institutes of Health and contracts from Janssen Research and Development. **PBR** and **MC** are employees of Janssen Research and Development **PBR** is a shareholder in Johnson & Johnson. **PN** receives grant funding from the Australian National Health and Medical Research Council.

3. Abstract

This study will evaluate the effect of ACE inhibitor or ARB exposure on the risk of contracting COVID-19 infection and the risk of experiencing respiratory failure, pneumonia, acute kidney injury, and death in hypertensive patients following contracting COVID-19 infection. The analysis will be undertaken across a federated multi-national network of electronic health records and administrative claims from primary care and secondary care that have been mapped to the Observational Medical Outcomes Partnership Common Data Model in collaboration with the Observational Health Data Sciences and Informatics (OHDSI) and European Health Data and Evidence Network (EHDEN) initiatives. These data reflect the clinical experience of patients from six European countries (Belgium, Netherlands, Germany, France, Spain, and Estonia) the United Kingdom, the United States of America, South Korea, and Japan as data becomes available. We will use a prevalent user cohort design to estimate the relative risk of each outcome using an on-treatment analysis of monotherapy only and monotherapy or combo-therapy comparisons. In the analysis of respiratory failure, pneumonia, acute kidney injury, and death, we will conduct separate analyses assessing prevalent use of antihypertensives at the time of any diagnosis with COVID-19 or at the time of an inpatient admission with COVID-19 diagnosis. Data driven approaches will be used to identify potential covariates for inclusion in matched or stratified propensity score models identified using regularized logistic regression. Large-scale propensity score matching and stratification

strategies that allow balancing on a large number of baseline potential confounders will be used in addition to negative control outcomes to allow for evaluating residual bias in the study design as a whole as a diagnostic step.

4. Amendments and Updates

| Ver. | Date | Section of study protocol | Amendment or update | Reason |
|------|---------|--|--|--|
| 1.1 | 4/16/20 | Section 7, hypothesis 1, analysis Section 7, hypothesis 2, analysis | Add dCCB+THZ comparator cohorts | Improve power in smaller data sources |
| 1.1 | 4/16/20 | Section 9 | Additional details on justification of prevalent-user design | Clarify advantages and limitations |
| 1.1 | 4/16/20 | Section 15 | Minor typographical corrections | Improve readability |
| 1.2 | 5/15/20 | Section 16 | Add first-line antihypertensives licensed only in Europe | Include drugs not listed in ACC guidelines |

| Key Dates and Milestones | Planned / Estimated Date |
|-------------------------------------|---------------------------|
| Registration in the EU PAS Register | May 14, 2020 (EUPAS35296) |
| Start of analysis | April 7, 2020 |
| End of analysis | |
| Presentation of results | |

5. Rationale and Background

Since January 2020, a growing number of infections caused by coronavirus SARS-Cov2, COVID-19 has resulted in unprecedented pressure on healthcare systems worldwide, and a great number of casualties on a global scale. With an approximate 4% mortality based on data from China where the outbreak originated, there is a paucity of data on an international level surrounding the factors associated with disease severity or morbidity/mortality.^{1,2}

Recent studies have reported increased mortality and complications, including acute respiratory distress syndrome (ARDS), among SARS-CoV-2 infected patients who have hypertension.²⁻⁵ We will provide a brief summary of the existing evidence here; however, a more detailed review of the relevant gray and peer-reviewed literature is available in Appendix 1. There is speculation that the difference in outcomes in patients with hypertension may be mediated by the medications they are using^{3,6-11}, with several plausible mechanisms of action being hypothesized. In particular, several publications have raised the question of possible harmful and potentially helpful effects of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) on SARS-CoV-2 infection and subsequent complications from the infection.^{3,12-15}

Many have suggested that ACE inhibitors and ARBs increase the expression and/or activity of ACE-2 receptor in human cells, which may put patients at greater risk of COVID-19 infection and/or more severe disease outcomes since SARS-CoV-2 binds to ACE2 to enter the cell (see 1.3).^{9,10,16} However, there is limited data to suggest that ACE inhibitors and ARBs upregulate ACE-2 receptors. It has also been suggested that chronic ARB use may reduce the likelihood of COVID-19 infection and disease outcomes by inhibiting the angiotensin T1 receptor, which upregulates ACE-2.⁶⁻⁸ The current understanding of the mechanism through which COVID-19 leads to acute lung injury (which is described in more detail in Appendix 1) is that excessive angiotensin stimulates the angiotensin I receptor which increases pulmonary vascular permeability. While only limited evidence is available from animal models⁸, two mechanisms have been proposed^{7,17} for how ARBs disrupt this mechanism of lung injury: 1) ARBs prevent the angiotensin I receptor from being stimulated by the excess angiotensin, 2) ARBs upregulate

ACE-2 and reduce angiotensin production by ACE and increase production of the vasodilating angiotensin-(1-7) peptide. Furthermore, it has been asserted that ARBs may be the best opportunity to disrupt the mechanism of lung injury caused by SARS-CoV-2 infection without also disrupting ACE-2's regulation of critical processes.¹⁷

A small study of 78 COVID-19 hospitalized patients with hypertension compared the proportion of patients with severe disease according to baseline antihypertensive medicine use.¹⁸ In that study, of the 10 patients treated with ARBs, 30% had severe COVID-19 disease while of the 26 patients treated with CCBs 69% had severe disease. Only two patients were treated with ACE inhibitors. However, there is still no direct clinical evidence indicating a causal relationship between ACE inhibitors or ARBs with COVID-19 infection or disease outcomes.

These claims have produced substantial concerns for both people with hypertension and physicians who prescribe these medicines to an increasing number of hypertensive patients infected with SARS-CoV-2.

A chief concern arising from the paucity of data is that the current speculation may lead to improper or uninformed initiation or discontinuation of these medications. Recent communications from clinical and academic societies have urged patients to continue their antihypertensive treatments until evidence becomes available.¹²⁻¹⁵ However, a recent web posting by the Centre for Evidence-Based Medicine advised patients with mild hypertension (and marginal benefit from antihypertensive therapy) to consider discontinuing use of ACE inhibitors and ARBs.¹³ As voiced by multiple scientists and academic societies, there is an urgent need for population-level studies assessing the causal relationship between ACE inhibitors / ARBs and SARS-CoV-2 infection / disease course.^{3,7,9,11-15,19}

This protocol outlines a study in the Observational Health Data Science and Informatics (OHDSI) community^{4,20} with federated access to international data assets mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).²¹ This infrastructure provides a unique opportunity to address this question across a number of populations and contribute valuable insights that will inform the key clinical and policy decisions of the risk of antihypertensive treatment during the current SARS-Cov2, COVID-19 pandemic.

6. Study Objectives

Objective 1: To estimate the association of prevalent use of a) angiotensin converting enzyme (ACE) inhibitors and b) angiotensin II receptor blockers (ARB) on the risk of contracting COVID-19 infection in hypertensive patients.

Objective 2: To estimate the association of prevalent use of a) angiotensin converting enzyme (ACE) inhibitors and b) angiotensin II receptor blockers (ARB) on the risk of respiratory failure, pneumonia, acute kidney injury, and death in hypertensive patients diagnosed with COVID-19. As a secondary objective focused on potential benefits, estimate the association among prevalent users and differences in the risk of major acute cardiovascular events (MACE), including acute myocardial infarction, congestive heart failure, stroke or sudden cardiovascular death.

7. Research Methods

Data Sources

This study is a multi-national, observational prevalent user cohort study evaluating the association between ACE inhibitor or ARB exposure on the risk of contracting COVID-19 infection and the risk of experiencing adverse outcomes following contracting COVID-19 infection.

A South Korean national claims database and a U.S. (New York City) health system database have already begun accumulating COVID-19 patients and have tested the operability of our analysis package at their sites (**Table 1**). As data become available, we will include additional databases that have already been formatted to the OMOP CDM, which reflect the clinical experience of patients from six European countries (Belgium [general practice EHR], Netherlands [general practice EHR], Germany [general practice EHR, hospital EHR], France [general practice EHR, outpatient specialist EHR], Spain [general practice EHR, outpatient specialist EHR], and Estonia [EHR, claims, and registry data] the United Kingdom [general practice EHR, hospital EHR], the United States of America (general practice EHR, outpatient

specialist EHR, hospital EHR, insurance claims], South Korea [EHR, claims, and registry data], and Japan [insurance claims].

The study will be conducted using data from real world data sources that have been mapped to the OMOP Common Data Model in collaboration with the Observational Health Data Sciences and Informatics (OHDSI) and European Health Data and Evidence Network (EHDEN) initiatives. The OMOP Common Data Model (<https://github.com/OHDSI/CommonDataModel/wiki>) includes a standard representation of health care experiences (such as information related to drug utilization and condition occurrence), as well as common vocabularies for coding clinical concepts and enables consistent application of analyses across multiple disparate data sources.²¹

Table 1. Data sources formatted to the OMOP CDM that currently include COVID-19 patients.

| Data source | Source population | Sample size | Data type | Longitudinal history |
|--|---|--------------|--|---|
| South Korea: Health Insurance and Review Assessment (HIRA) | All citizens in South Korea | ≈ 50 million | Administrative fee-for-service claims data collected for healthcare reimbursement, including healthcare services such as treatments, pharmaceuticals, procedures, and diagnoses. | 5-years of available look-back (data older than 5-years is deleted from the database) |
| Columbia University Irving Medical Center | Patients of the Columbia University Irving Medical Center | ≈ 6 million | General practice electronic health records, outpatient specialist electronic health records, inpatient hospital electronic health records, hospital billing/summary | 1989 (1978 for diagnoses) |

Hypothesis 1

Patient Cohort

To test hypothesis 1, the cohort will consist of adult patients aged 18 years and over who receive at least one eligible prescription for an exposure drug between 1st November 2019 and 31st January 2020 (with index date set as the last prescription in this window) and are observable in each database for at least one year prior to the index date. Patients are required to have a history of hypertension at any point prior to or including the index date and to be

prescribed antihypertensive treatment recommended for first line or initial pharmacological treatment of hypertension at the index date as either monotherapy in one analysis or in combination with other hypertensive treatments that do overlap with the comparison cohort in a second analysis. Cohort exit will be the earliest of: the occurrence of an outcome event; the end of exposure; death; loss or deregistration from the database; or date of last data collection.

Exposures

The exposures of interest are defined by classes of antihypertensive medication commonly prescribed first line for the treatment of hypertension, with the primary (target) exposure of interest being ACE inhibitor and ARB class of medicines. Details of these exposures may be found in Appendix 2. Other classes of antihypertensive medicines to define active comparators will include dihydropyridine calcium channel blockers (dCCB) and thiazide or thiazide-like diuretics (THZ). Specification of these medicines are based on any drug containing the RxNorm ingredients of interest for class and follow previous antihypertensive drug classification use in comparative effectiveness research.²²

Antihypertensive exposure will first be defined as: a patient issued or dispensed at least one eligible prescription between 1st November 2019 and 31st January 2020 (with index date set as the last prescription in this window). For the analysis restricting to patients on monotherapy, we will require the absence of any other of the primary or secondary medication class treatments for hypertension prescribed between –180 days and 0 days prior to the index date. For this latter definition, qualifying medication classes are: ACE inhibitors, ARBs, any CCB, beta blockers, any diuretic, and alpha-blockers. In the second analysis including non-monotherapy users, this latter restriction does not apply. Continuous drug exposures will be defined from the start of follow-up by grouping sequential prescriptions that have fewer than 30 days gap between prescriptions. End of exposure will be defined as the end of the last prescription's drug supply.

Controls or Comparators

An active comparator control population will be created consisting of patients prescribed either dCCBs or THZs as monotherapy to minimize confounding by indication. Absence of treatment by multiple hypertension classes will follow the definition as above. However, residual

differences may still remain as suggested by difference in clinical practice around the choice of first-line antihypertensive treatment class, which will be addressed by applying statistical methods for confounding adjustment.

Outcomes

The primary outcomes of interest to test hypothesis 1 will be an incident COVID-19 infection diagnosis using both a broad and narrow definition, hospitalization with pneumonia, and hospitalization with pneumonia or ARDS or acute kidney injury or resulting in death. Details of these outcomes may be found in the Appendix. Up to 76 negative control outcome experiments will be performed examining the risk of residual confounding. The negative controls derive from a process similar to that outlined in Voss et al. and have been fully described previously.^{22,23}

Covariates

Data driven approaches will be used to identify potential covariates for inclusion in matched or stratified propensity score models identified using regularized logistic regression. These will include: gender, age group (5-year groups), index month, conditions (SNOMED concepts and descendants) any time prior to index, conditions in the 180 days prior to index, conditions in the 30 days prior to index, drugs (ATC classes and RxNorm ingredients) any time prior to index, drugs in the 180 days prior to index, drugs in the 30 days prior to index, procedures any time prior to index, procedures in the 180 days prior to index, procedures in the 30 days prior to index, devices any time prior to index, devices in the 180 days prior to index, devices in the 30 days prior to index, measurements any time prior to index, measurement in the 180 days prior to index, measurements in the 30 days prior to index, measurement values in the last 180 days, CHADS2Vasc, Diabetes Comorbidity Severity Index, and Charlson index.

Analysis

We will estimate the relative risk of each outcome using an on-treatment analysis for the following class exposure comparisons in patients with hypertension were (*) denotes the target class and “ACE” indicates here “ACE inhibitor” for brevity:

Mono-therapy only comparisons

1. ACE* vs dCCB
2. ACE* vs THZ
3. ACE* vs dCCB or THZ
4. ARB* vs dCCB
5. ARB* vs THZ
6. ARB* vs dCCB or THZ
7. ACE* vs ARB
8. ACE or ARB* vs dCCB
9. ACE or ARB* vs THZ
10. ACE or ARB* vs dCCB or THZ

Mono or combo-therapy comparisons

11. ACE +/- not-dCCB * vs dCCB +/- not-ACE
12. ACE +/- not-THZ * vs THZ +/- not-ACE
13. ACE +/- not-dCCB nor-THZ * vs dCCB or THZ +/- not-ACE
14. ARB +/- not-dCCB * vs dCCB +/- not-ARB
15. ARB +/- not-THZ * vs THZ +/- not-ARB
16. ARB +/- not-dCCB * nor-THZ * vs dCCB or THZ +/- not-ARB
17. ACE +/- not-ARB * vs ARB +/- not-ACE
18. ACE or ARB +/- not-dCCB * vs dCCB +/- not-ACE nor-ARB
19. ACE or ARB +/- not-THZ * vs THZ +/- not-ACE nor-ARB
20. ACE or ARB +/- not-dCCB nor-THZ * vs dCCB or THZ +/- not-ACE nor-ARB

We will describe patient characteristics (prevalence) for each cohort comparison and data source. To adjust for measured confounding, propensity score models for each class pair and data source will be created using a data-driven process using regularized logistic regression when target and comparator cohorts contain at least 500 patients within each data source. This process allows the data to decide which combinations of baseline patient characteristics, including demographics and previous conditions, drug exposures, procedures, and health-

service-use behaviors are most predictive of treatment assignment. For cohorts with fewer than 500 patients, we will build propensity score models using gender and age categorized in 5-year groups, and index month examining for any heterogeneity.

Patients will be stratified by propensity score or 1:1 matched to ensure sufficient balance is achieved if all after-adjustment baseline characteristics return absolute standardized mean differences of less than 0.1. We will make the choice for matching or stratification based on sufficient exposure cohort size. Cox proportional hazards models will be used to estimate hazard ratios (HRs) between target and comparator treatment cohorts for the risk of each outcome in each data source. We will aggregate HRs across data sources to produce meta-analytic estimates using a random-effects meta-analysis.

For each effect estimate, we will evaluate associations using negative control outcome experiments. We will use the empirical null distributions to calibrate each HR estimate, its 95% CI, and the p value to reject the null hypothesis of no differential effect. A HR will be considered significantly different from the null value when its calibrated 95% CI does not include this value (and corresponds to a calibrated p of less than 0.05 without correcting for multiple testing).

The following additional calculations will be performed: power calculations estimating minimum detectable relative risk; preference score (a transformation of propensity score that adjusts for prevalence differences between populations) distributions to evaluate empirical equipoise and population generalizability; patient characteristics to evaluate cohort balance before and after propensity score adjustment; negative-control calibration plots to assess residual bias; and Kaplan-Meier plots to examine HR proportionality assumptions.

If sufficient numbers of patients are available, a sensitivity analysis will be performed restricted to recent initiators of ACE inhibitors or ARBs and their active comparators. Recent initiators will be defined if the first ever ACE inhibitor, ARB or comparator prescription is recorded between – 60 days and 0 days prior to index.

Hypothesis 2

Patient Cohort

We will identify adult patients aged 18 years or over who have an incident diagnosis of COVID-19 occurring after 1st December 2019 and assign the date of diagnosis as the index date.

Patients will be required to be registered or observable in each database for at least 180 days prior to index date, have a history of hypertension at any point prior to the index date and be a prevalent user of antihypertensive treatment recommended for first line treatment of hypertension as monotherapy at the index date. The end of follow-up will be the earliest occurrence of either: the outcome event, discharge, date of last data collection, end of follow-up (30 days) or death. We will also complete additional analyses where we select the earliest observed date of hospitalization with COVID-19 as the index date.

Exposures

The exposures of interest are defined by classes of antihypertensive medication commonly prescribed first line for the treatment of hypertension, with the primary (target) exposures of interest being ACE inhibitors and ARBs. Details of these exposures may be found in the Appendix. Other classes of antihypertensive medicines which will be used to define active comparators will include dCCB and THZ. Specification of these medicines are based on any drug containing the RxNorm ingredients of interest for class and follow previous antihypertensive drug classification use in comparative effectiveness research.²²

Antihypertensive exposure will first be defined as: a patient issued or dispensed at least one eligible prescription between –60 days and -1 days prior to index date *or* when patients have prescriptions at any time before the index date with a continuous period of drug exposure extending to at least 30 days prior to the index date. Patients with monotherapy will then be identified by the absence of any other of the primary or secondary medication class treatments for hypertension prescribed between –180 days and –1 day prior to the index date. We also plan to conduct analyses where do not require the index treatment to be monotherapy and this restriction is not applied. For this latter definition, qualifying medication classes are: ACE inhibitors, ARBs, any CCB, beta blockers, any diuretic, and alpha-blockers. Continuous drug exposures will be defined by grouping sequential prescriptions that have fewer than 30 days

gap between prescriptions. End of exposure will be defined as the end of the last prescription's drug supply.

Outcomes

The primary outcomes of interest for hypothesis 2 will be the occurrence of a composite intensive respiratory intervention, consisting of mechanical ventilation, tracheostomy, extracorporeal membrane oxygenation (ECMO) or death. Details of these outcomes may be found in the Appendix. A secondary outcome aimed at informing benefit-risk will examine major acute cardiovascular events (MACE) including acute myocardial infarction, congestive heart failure, stroke or sudden cardiovascular death. Seventy-six negative control outcome experiments will be performed examining the risk of residual confounding. Details of these outcomes are contained in the Appendix and all cardiac-related and negative control outcomes definitions were previously used.²²

Covariates

Data driven approaches will be used to identify potential covariates for inclusion in matched or stratified propensity score models identified using regularized logistic regression. These will include: gender, age group (5-year groups), index month, conditions (SNOMED concepts and descendants) any time prior to index, conditions in the 180 days prior to index, conditions in the 30 days prior to index, drugs (ATC classes and RxNorm ingredients) any time prior to index, drugs in the 180 days prior to index, drugs in the 30 days prior to index, procedures any time prior to index, procedures in the 180 days prior to index, procedures in the 30 days prior to index, devices any time prior to index, devices in the 180 days prior to index, devices in the 30 days prior to index, measurements any time prior to index, measurement in the 180 days prior to index, measurements in the 30 days prior to index, measurement values in the last 180 days, CHADS2Vasc, Diabetes Comorbidity Severity Index, and Charlson index.

Analysis

We will estimate the relative risk of each outcome for the following class exposure comparisons in patients with hypertension were (*) denotes the target class and "ACE" indicates here "ACE inhibitor" for brevity:

Mono-therapy only comparisons anchored on a hospital admission with COVID-19 diagnosis

1. ACE* vs dCCB
2. ACE* vs THZ
3. ACE* vs dCCB or THZ
4. ARB* vs dCCB
5. ARB* vs THZ
6. ARB* vs dCCB or THZ
7. ACE* vs ARB
8. ACE or ARB* vs dCCB
9. ACE or ARB* vs THZ
10. ACE or ARB* vs dCCB or THZ

Mono-therapy only comparisons anchored on any COVID-19 diagnosis

11. ACE* vs dCCB
12. ACE* vs THZ
13. ACE* vs dCCB or THZ
14. ARB* vs dCCB
15. ARB* vs THZ
16. ARB* vs dCCB or THZ
17. ACE* vs ARB
18. ACE or ARB* vs dCCB
19. ACE or ARB* vs THZ
20. ACE or ARB* vs dCCB or THZ

Mono or combo-therapy comparisons anchored on a hospital admission with a COVID-19 diagnosis

21. ACE +/- not-dCCB * vs dCCB +/- not-ACE
22. ACE +/- not-THZ * vs THZ +/- not-ACE
23. ACE +/- not-dCCB nor-THZ * vs dCCB or THZ +/- not-ACE
24. ARB +/- not-dCCB * vs dCCB +/- not-ARB
25. ARB +/- not-THZ * vs THZ +/- not-ARB
26. ARB +/- not-dCCB nor-THZ * vs dCCB or THZ +/- not-ACE
27. ACE +/- not-ARB * vs ARB +/- not-ACE
28. ACE or ARB +/- not-dCCB * vs dCCB +/- not-ACE nor-ARB
29. ACE or ARB +/- not-THZ * vs THZ +/- not-ACE nor-ARB
30. ACE or ARB +/- not-dCCB nor-THZ * vs dCCB or THZ +/- not-ACE nor-ARB

Mono or combo-therapy comparisons anchored on any COVID-19 diagnosis

31. ACE +/- not-dCCB * vs dCCB +/- not-ACE
32. ACE +/- not-THZ * vs THZ +/- not-ACE
33. ACE +/- not-dCCB nor-THZ * vs dCCB or THZ +/- not-ACE
34. ARB +/- not-dCCB * vs dCCB +/- not-ARB

- 35. ARB +/- not-THZ * vs THZ +/- not-ARB
- 36. ARB +/- not-dCCB nor-THZ * vs dCCB or THZ +/- not-ACE
- 37. ACE +/- not-ARB * vs ARB +/- not-ACE
- 38. ACE or ARB +/- not-dCCB * vs dCCB +/- not-ACE nor-ARB
- 39. ACE or ARB +/- not-THZ * vs THZ +/- not-ACE nor-ARB
- 40. ACE or ARB +/- not-dCCB nor-THZ * vs dCCB or THZ +/- not-ACE nor-ARB

We will describe the patient characteristics (prevalence) for each cohort comparison and data source. To adjust for measured confounding, propensity score models for each class pair and data source will be created using a data-driven process using regularized logistic regression when target and comparator cohorts contain at least 500 patients within each data source. This process allows the data to decide which combinations of baseline patient characteristics, including demographics and previous conditions, drug exposures, procedures, and health-service-use behaviors are most predictive of treatment assignment. For cohorts with fewer than 500 patients, we will build propensity score models using gender, age categorized in 5-year groups, index year, and index month, examining for any effect estimate heterogeneity.

Patients will be stratified by propensity score or 1:1 matched to ensure sufficient balance is achieved if all after-adjustment baseline characteristics return absolute standardized mean differences of less than 0.1. We will make the choice for matching or stratification based on sufficient exposure cohort size. Logistic regression models will be used to estimate odds ratios (ORs) between target and comparator treatment cohorts for the risk of each outcome in each data source within 30 days of the index date. We will aggregate ORs across data sources to produce meta-analytic estimates using a random-effects meta-analysis. As a sensitivity analysis we will additionally adjust for age category and gender in outcome models.

For each effect estimate, we will evaluate the associations using negative control outcome experiments. We will use the empirical null distributions to calibrate each OR estimate, its 95% CI, and the p value to reject the null hypothesis of no differential effect. An OR will be considered significantly different from the null value when its calibrated 95% CI does not

include this value (and corresponds to a calibrated p of less than 0.05 without correcting for multiple testing).

The following additional calculations will be performed: power calculations estimating minimum detectable relative risk; preference score (a transformation of propensity score that adjusts for prevalence differences between populations) distributions to evaluate empirical equipoise and population generalizability; patient characteristics to evaluate cohort balance before and after propensity score adjustment; and negative control calibration plots to assess residual bias; and Kaplan-Meier plots to examine HR proportionality assumptions for Cox regression models when used.

If sufficient numbers of patients are available a sensitivity analysis will be performed restricted to recent initiators of ACE inhibitors or ARBs. Recent initiators of ACE inhibitor or ARB therapy will be defined if the first ever ACE inhibitor or ARB prescription is recorded between –60 days and –1 day prior to index.

8. Sample Size and Study Power

See previous section.

9. Strengths and Limitations

Comparative cohort studies allow direct estimation of relative incident event rates between subjects with the exposures of interest and controls while accounting for observed confounding in these rates when populations are balanced. This protocol employs large-scale propensity score matching and stratification strategies that allow balancing on a large number of baseline potential confounders and have been shown to also balance on important unobserved confounders, like baseline blood pressure in studies of anti-hypertensive treatments. Further, the use of negative control outcomes allows for evaluating the study design as a whole in terms of residual bias as a diagnostic step to help ensure casual validity of estimates.

In the interest of generating actionable evidence that can address urgent public health need and support decision making, we have incorporated several study-design features that allow us

to run this analysis as immediately as possible. We acknowledge, however, that there are also limitations to this analysis which need to be understood in order to properly interpret the results. To date, longitudinal healthcare data to study patients with COVID-19 is still accumulating, and there are only small amounts of data available in limited contexts and these data are held by independent data partners who cannot pool patient-level data across sites.

Ideally, a comparative cohort analysis estimating the effect of antihypertensive drugs on the incidence of COVID-19 (hypothesis 1) would be undertaken using a new user cohort design.³⁸ In a new user cohort design, all patients are aligned at the point of their drug initiation (which is referred to as the index date) and the variables included as confounders for adjustment in models include only those that preceded initiation of the drug. The new user design has advantages in reducing the risk of bias when time-varying hazards of the outcome exist. The new user design also reduces bias when depletion of susceptibles may occur, whereby people experiencing an event are more likely to do so shortly after drug initiation and those subjects with prevalent exposure are therefore at lower risk of experience the outcome of interest over time. A new user design, however, would require a larger number of patients than a prevalent user design and a long history of longitudinal data (capturing both inpatient and outpatient care) that is not available for all study sites. During the COVID-19 pandemic, there may be a smaller pool of new users as fewer patients may initiate ACE inhibitors and ARBs for routine hypertension management as social distancing and healthcare is prioritised on managing COVID-19. Additionally, COVID-19 is a new illness and did not exist in the population prior to the start of our observation period. Therefore, concerns over time-varying hazards and depletion of susceptibles are less likely to be relevant in this context. The potential biological mechanism relating to ACE2 expression may also not be as relevant at the point of ACE inhibitor or ARB initiation as changes to protein expression in response to exposure can take time to occur. Similar arguments hold for evaluating the effect of antihypertensive use on outcomes of COVID-19 infection and severity of disease.

Due to these issues, we have elected for a prevalent user design.³⁹ To address hypothesis 1 under this design, we define the index date and align patients on a specific point in calendar time (a prescription between 1st November 2019 and 31st January 2020) at which point they

became “at-risk” for COVID-19. For the analysis addressing hypothesis 2, we define the index date as the day patients are clinically recognized as having COVID-19. Of chief concern is that mediators on the causal pathway between exposure (to antihypertensive medications) and the outcome (H1: COVID-19 infection, H2: COVID-19 outcomes) may be included in the adjustment since true exposure begins before the “at-risk” study period. One possible mediator is duration of prior anti-hypertensive treatment. While prior treatment duration is difficult to ascertain in a prevalent user design, prior treatment remains highly correlated with many baseline features that our large-scale propensity model considers when balancing patients and can provide some protection against this design bias.

The prevalent user design was originally developed to address the challenge of having limited available data when comparing new-to-market drugs with established drugs.²⁴ In the original publication describing the prevalent user design, the authors highlight multiple sources of bias that are likely to arise in that context. Here, we use the prevalent user design to address the problem of not having sufficient data on a new illness (COVID-19), which affects all of our comparators equally. Thus, we assert that multiple forms of bias that arise in the new-to-market vs. traditional comparison (e.g. substantially longer duration of prior exposure among users of the established drug compared to users of the new-to-market drug, or unidirectional switching from the established drug to the new-to-market drug) are less likely to produce meaningful bias in our analysis.

Misclassification of study variables is unavoidable in observational analyses of secondary health data. It is possible that we misclassify our exposures by failing to observe medication use when a patient is actually taking it or, more commonly, seeing medication prescriptions in the data that the patient is not actually taking. However, we do not expect misclassification will be strongly differential with respect to the treatments being compared or with respect to outcome status. Thus, bias due to exposure misclassification will most likely be toward the null (i.e. increase the likelihood of a type II error).

Outcome misclassification is also an important concern, particularly in the analysis of hypothesis 1, since the COVID-19 outcome will be under diagnosed due to limited availability of

testing resources and the fact that many infected patients may remain asymptomatic or not require observed healthcare utilization. It is important to note that the extent of underdiagnosis will likely vary by site due to differences in national testing strategies. Furthermore, classification of the outcome could also vary with respect to calendar time, since underdiagnosis could become more or less frequent over the course of the pandemic. To address this inherent limitation, we have included a hospitalization-based COVID-19 outcome which will be well-classified in these data to provide additional context. We do not expect outcome misclassification to be differential with respect to these exposure groups. Thus, bias due to outcome misclassification will also most likely be toward the null.

10. Protection of Human Subjects

The study uses 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.

11. Management and Reporting of Adverse Events and Adverse Reactions

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

12. Plans for Disseminating and Communicating Study Results

This study protocol will be registered at the EU PAS Register and 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. The results will also be presented at the OHDSI in-person events.

13. List of Tables and Figures

Table 1. Data sources formatted to the OMOP CDM that currently include COVID-19 patients.

Table S1. Findings produced by real-world analyses of COVID-19 patients that assessed baseline hypertension

Figure S1. Hypothetical mechanism through which SARS-CoV-2 enters cells (blue= ACE-2 receptor, red: virus receptor binding sub-unit).¹³

Table S2. Overview of National Treatment Guidelines for hypertension for general populations and among specific sub-populations.

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15. Appendix 1: Review of Peer-Reviewed and Grey Literature

A spreadsheet containing information abstracted from publications and grey literature included in this literature review is linked below:

[Appendix 1. Literature Review Publications](#)

15.1 Overview

Since January 2020 there has been a growing number of infections caused by coronavirus SARS-Cov2. COVID-19 (the illness caused by SARS-Cov2) has resulted in an unprecedented pressure on healthcare systems worldwide, and a great number of casualties on a global scale. With an approximate 4% mortality based on data from China where the outbreak originated, there is a paucity of data on an international level surrounding the factors associated with disease severity or morbidity/mortality.^{1,2} The available data appears to indicate an association between hypertension and COVID-19 infections and disease outcomes. These findings, in combination with cellular studies indicating that coronaviruses enter cells using the angiotensin-converting-enzyme (ACE)-2 receptor, has generated substantial interest in studying COVID-19 incidence and disease outcomes among patients using antihypertensive drugs that act on the renin angiotensin system (RAS), namely ACE inhibitors and ARBs. For the scope of this literature review, we sought to assess the existing peer-reviewed and grey literature what is known biologically about this potential association, and what (if any) data exists to support or refute it.

Guan et al. have assembled one of the largest SARS-CoV-2 cohorts currently available for study, with 1099 patients with laboratory-confirmed Covid-19 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China.²⁻⁵ They observed elevated rates of pre-existing hypertension among the patients with more severe disease courses (23.7%) compared to those with non-severe disease courses (13.4%). They also observed more baseline

hypertension in patients who had the composite outcome of ICU-admission, use of mechanical ventilation, or death (35.8%) compared to those who did not (13.7%). In a different cohort of 191 SARS-CoV-2 infected patients drawn from two hospitals in China, Zhou et al. estimated the odds ratio (OR) for the univariate association between baseline hypertension and in-hospital death to be 3.05 (95% CI: 1.57, 5.92).^{6,7} Several relevant associations were observed in a separate study comprising 201 patients with confirmed COVID-19 pneumonia, who either had risk factors for acute respiratory distress syndrome (ARDS), or who progressed from ARDS to death.^{5,7-10} In total, 27.4% of these patients had a history of hypertension compared to only 13.7% of without. In an unadjusted Cox model predicting ARDS, the hazard ratio estimate for hypertension was 1.82 (95% CI: 1.13, 2.95). In a similar model predicting death among patients with ARDS, the hazard ratio for hypertension was 1.70 (95% CI: 0.92, 3.14). While interesting, these results are potentially spurious and statistically non-significant in the case of death among ARDS patients. In a single-center study of 138 patients with pneumonia caused by SARS-CoV-2 infection, Wang et al. found that the baseline rate of hypertension was 31.2% among cases admitted to the hospital and 58% among those admitted to the ICU.¹¹⁻¹⁵ However, they reported comparable baseline blood-pressure measurements for these patients.

However, none of these studies adjust for confounders or provide information about use of antihypertensive medications. It is possible that the higher prevalence of hypertension in patients with adverse outcomes following COVID-19 hospitalization reflects the increased age of those experiencing these outcomes (**Table S1**). It is important to note that conflicting evidence has been presented by a smaller study by Huang et al. which abstracted EMR data and self-/family-reported outcomes from 41 SARS-CoV-2 hospital patients.^{5,16} They found no difference in the rate of baseline hypertension among those who were admitted to the ICU (15%) compared to those who were not (14%). Another interesting perspective is provided by a 12-year retrospective follow-up study of 25 patients who previously recovered from SARS-CoV infections during the outbreak in 2002-2003.^{5,16-19} The authors documented long-term metabolic disruptions, most notably an increase in phosphatidylinositol and lysophosphatidylinositol.¹⁶⁻¹⁹ Collectively, the available population-level evidence provides little

clarity regarding the relationship between hypertension, antihypertensive medications, and SARS-CoV-2 infections and outcomes.

Table S1. Findings produced by real-world analyses of COVID-19 patients that assessed baseline hypertension

| Ref | Baseline HTN in SARS-Cov-2 | Age (median IQR) | Outcome | Baseline HTN (%) | Age (median IQR) | Outcome | Baseline (%) | Age (median IQR) |
|--------------|----------------------------|------------------|---|------------------|------------------------------------|--|------------------|--------------------------------|
| Huang et al. | 15% | 49 (41, 58) | ICU | 15% | 49 (41, 61) | No ICU | 14% | 49 (41, 57.5) |
| Guan et al. | 15% | 47 (35, 58) | (1) Severe Disease (2) ICU / ventilation / death | 23.70% 35.80% | 52 (40, 65) 63 (53, 71) | Non-severe No ICU / ventilation / death | 13.40% 13.70% | 45 (34, 57) 46 (35, 57) |
| Wang et al. | 31.20% | 56 (42, 68) | ICU | 58.30% | 66 (57, 78) | No ICU | 21.60% | 51 (37, 62) |
| Wu et al. | 19.40% | 51 (43, 60) | (1) ARDS (2) With ARD who died | 27.40% 36.40% | 58.5 (50, 69) 68.5 (59.3, 75.0) | No ARDS With ARDS did not die | 13.70% 17.50% | 48 (40, 54) 50 (40.3, 56.8) |
| Zhou et al. | 30% | 56 (46, 67) | Death | 48% | 69 (63-76) | Alive | 23% | 52 (45-58) |

15.2 Association Between COVID-19 Infection and Prevalent Hypertension

As noted above, there have been several epidemiologic studies recently published that observed elevated mortality and complications such as ARDS among SARS-CoV-2 infected patients who have hypertension.²⁻⁵ Similar observations were made among patients infected in the SARS-CoV outbreak in 2002-2003.^{5,7,8,16-21} However, these associations provide only indirect evidence of the relationship between hypertension and SARS-CoV-2 morbidity and mortality since they are crude contrasts that are not adjusted for confounding. It may be the case that the association between SARS-CoV-2 and ARDS and mortality are related to more advanced age and increased comorbidity burden, which are present among hypertensive patients.

Furthermore, these studies have not reported information about medication use among infected patients, leading to speculation that worse outcomes in hypertension patients may actually be mediated by the medications they are using.^{4,226-9} In particular, there has been wide speculation about possible helpful and harmful effects of ACEs and ARBs on SARS-CoV-2 infection and subsequent complications and hypothesize several plausible mechanisms of action.^{5,16-19} These claims led to substantial uncertainty for both people with hypertension and physicians who are treating an increasing number of hypertensive patients infected with SARS-CoV-2, and medicine regulatory agencies who monitor their safety. A small study of 78 COVID-19 hospitalized patients with hypertension compared the proportion of patients with severe

disease according to baseline antihypertensive medicine use (Liu et al 2020). In that study, of the 10 patients treated with ARBs 30% had severe disease while of the 26 patients treated with CCBs 69% had severe disease. Only two patients were treated with ACE inhibitors.

There is still no direct clinical evidence indicating a causal relationship between ACE inhibitors or ARBs with SARS-CoV-2 infection or disease outcomes. In absence of these data, a chief concern is that the current speculation may lead to improper or uninformed initiations or discontinuations of these medications resulting in unintended health consequences. Recent communications from clinical and academic societies have urged patients to continue their antihypertensive treatments until evidence becomes available.¹⁶⁻¹⁹ However, a recent web posting by the Centre for Evidence-Based Medicine advised patients with mild hypertension (and marginal benefit from antihypertensive therapy) to consider discontinuing use of ACE inhibitors and ARBs.¹⁶ As voiced by multiple scientists and academic societies, there is an urgent need for population-level studies assessing the causal relationship between ACE inhibitors / ARBs and SARS-CoV-2 infection / disease course.^{5,7,8,16-20,22}

15.3 Evidence of an ACE-2 Mediated Pathway for Coronavirus Entry into Host Cells

Despite limited population-level evidence, there is a rich body of literature describing how coronaviruses (and SARS-CoV-2 specifically) interact with RAS ACE-2 receptor, which is thought to be the primary mechanism through which SARS-CoV-2 enters human and animal cells.¹¹⁻¹⁵ This process, which has been studied by Walls et al. and summarized by Aronson & Ferner is as follows.^{15,16} Coronaviruses contain a sub-unit which binds to the ACE-2 receptor enzyme on the cell surface while a second sub-unit binds to the cell membrane. It is believed that to enter a human cell, two separate actions must take place which are facilitated by TMPRSS2, a host transmembrane serine protease. First the spiked glycoproteins of the coronavirus are activated by TMPRSS2 which cleaves the ACE-2 receptor. Second, TMPRSS2 activates a conformational change in the spiked glycoprotein which fuses the virus to the membrane and allows it to enter the cell (**Figure S1**). A similar mechanism has been well-documented for SARS-CoV, which caused the 2002-2003 outbreak.^{12,14,23-25} In fact, molecular structural models based on the known genetic sequence of SARS-CoV-2 indicate that the SARS-CoV-2 receptor binding sub-unit has even greater affinity for ACE-2 compared to SARS-CoV.^{20,26} This hypothesized mechanism of

cell entry is further supported by the fact that SARS-CoV has been observed in organs where ACE-2 receptors are found, which includes the lung alveolar epithelial cell, gastrointestinal system, heart, and kidneys.^{8,25} Damage to lung alveolar epithelial cells has been asserted as a mechanism through which SARS-CoV-2 causes lung injury and respiratory distress.

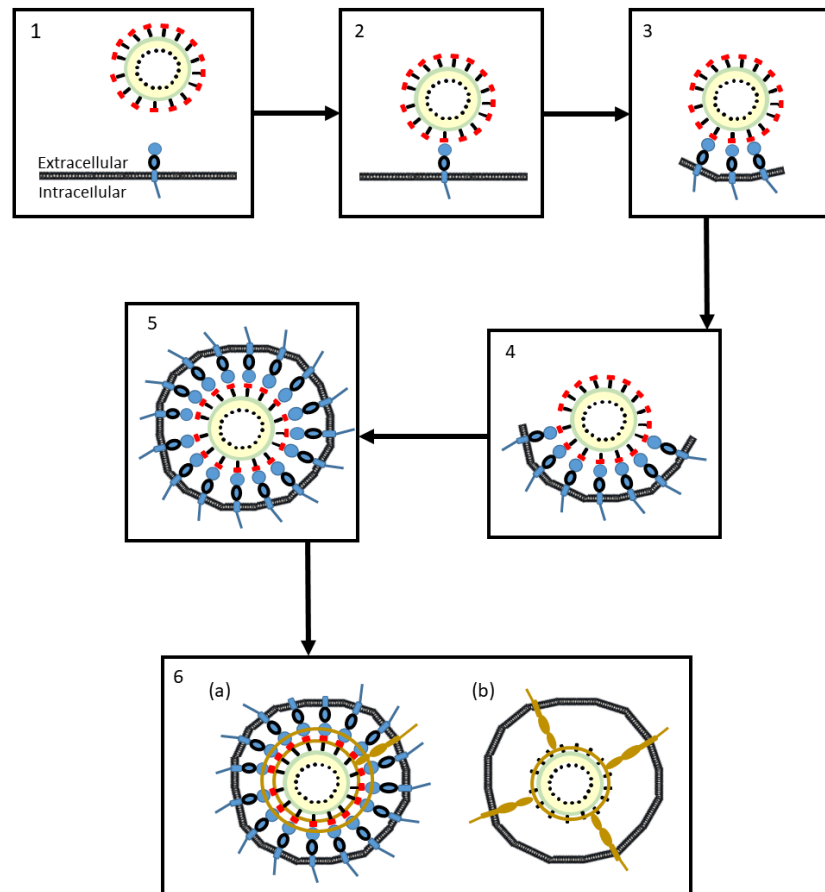


Figure S1. Hypothetical mechanism through which SARS-CoV-2 enters cells (blue= ACE-2 receptor, red: virus receptor binding sub-unit).¹⁶

In addition to the strong evidence for an ACE-2-mediated mechanism of cell entry, there are other findings that indicate an important interaction between use of ACE inhibitors / ARBs and the incidence / disease course of SARS-CoV-2 infection. It has been demonstrated in both humans and animals that use of ACEs and ARBs increase the expression of ACE-2 receptors in multiple organs.^{5,16,27-30} In the only study conducted in humans (N=617), Furuhashi et al. observed increased urinary concentration of ACE-2 after treatment with the ARB olmesartan; however, they did not observe changes after treatment with any other antihypertensive

treatments they tested (including other ARBs, ACE inhibitors, and calcium-channel blockers).²⁷ Experiments conducted on rats have demonstrated increased ACE-2 expression after different ARB treatments.²⁸⁻³⁰ These studies observed increased ACE-2 expression and activity in the kidneys after treatment with losartan²⁹ and in the myocardium after treatment with losartan or olmesartan (3-fold increase)^{28,30}. Additionally, Ferrario et al. also showed that the ACE inhibitor lisinopril produces a five-fold increase in ACE-2 expression.³⁰

While compelling, the evidence for the relationship between ACE-2 expression and treatment with ACE inhibitors / ARBs is still limited.⁵ There is only one human study available and it only observed a meaningful change in ACE-2 expression for patients treated with olmesartan, while other ARBs and ACE inhibitors tested showed no significant effect.²⁷ Furthermore, while multiple rat studies have documented changes in ACE-2 expression and activity after treatment with various ARBs, only one reported change in ACE-2 expression after treatment with an ACE inhibitor. As noted by Patel & Verma, there is still no evidence showing that ARBs or ACE inhibitors affect ACE-2 expression or activity in serum or pulmonary tissue, which would be especially relevant to the question of how these medications may interact with SARS-CoV-2.⁵

15.4 Hypothesized Mechanisms of Action

In the recent literature, various potential mechanisms of action have been hypothesized for how ACE inhibitors and ARBs may affect the risk of SARS-CoV-2 infections as well as the risk of complications of the disease. Some also describe mechanisms of protective effects of treatment with ACE inhibitors and ARBs, while others describe mechanisms limited to harmful effects. These mechanisms are only hypotheses and vary in the level of detail provided. However, we have summarized them below.

While many have suggested that ACE inhibitors and ARBs increase the expression and/or activity of ACE-2 receptor in human cells, which may put patients at greater risk of SARS-CoV-2 infection and/or more severe COVID-19 disease since SARS-CoV-2 binds to ACE2 to enter the cell (see 1.3)^{7,31,32}, it has also been suggested that chronic ARB use may reduce the likelihood of severe COVID-19 disease outcomes by inhibiting the angiotensin T1 receptor, which upregulates ACE-2.⁸⁻¹⁰ The hypothesized mechanism for typical lung injury in infected patients

with SARS-CoV-2 is as follows.^{10,16} The virus binds and downregulates the ACE-2 receptor in lung alveolar epithelial cells, causing ACE enzymes to increase production of angiotensin. Since the ACE-2 receptors are bound to the virus sub-unit, they are unavailable to convert excess angiotensin to angiotensin-(1-7), which is a vasodilator. The excessive angiotensin then stimulates the angiotensin I receptor which increases pulmonary vascular permeability, increasing the risk of lung injury. While only limited evidence is available from animal models¹⁰, two mechanisms have been proposed^{8,33} for how ARBs disrupt this mechanism of lung injury: 1) ARBs prevent the angiotensin I receptor from being stimulated by the excess angiotensin, 2) ARBs upregulate ACE-2 and reduce angiotensin production by ACE and increase production of the vasodilating angiotensin-(1-7) peptide. It has been asserted that ARBs may be the best opportunity to disrupt the mechanism of lung injury caused by SARS-CoV-2 infection without also disrupting ACE-2's regulation of critical processes.³³

The existing evidence is insufficient to determine whether a protective or harmful effect indeed exists. This study aims to estimate the effect by comparing prevalent ACE inhibitor and ARB use with other classes of antihypertensives in real world data sources.

15.5 Overview of ACE / ARB Medications and their Use

Around the world, hypertension is common as is treatment with antihypertensive medications. In South Korea, an analysis of a nationally-representative health survey estimated the prevalence of hypertension among people 30 years or older to be 29.1% (men: 35.0%, women: 22.9%) in the year 2016.³⁴ Furthermore, they found that only 40% of patients receiving antihypertensive treatments were receiving monotherapy, while 42% were prescribed two antihypertensive classes and 18% were prescribed three or more. Among monotherapy patients, 43.3% used ARBs, 42.9% used calcium channel blockers, 7.3% used beta blockers, 4.3% use thiazide-like diuretics, and only 1.9% used ACE inhibitors. A similar analysis, conducted in the United States using 2015-2016 data, estimated a nearly identical national prevalence of hypertension as Korea (29.0%) but identified less heterogeneity with respect to sex (men: 30.2%, women: 27.7%).³⁵ A different analysis, which analyzed nationally representative U.S. survey data from 2014, reported that in the United States, 29% of antihypertensive patients use ACE inhibitors, 24% use thiazide-like diuretics, 22% use ARBs, 21% use calcium channel

blockers, and 19% use beta-blockers.³⁶ They also report minimal variation in treatment selection with respect to patient characteristics.

ACE inhibitors and ARBs inhibit different parts of the RAS, which is a complex cascade of interactions between peptides, enzymes, and cell surface receptors that regulates blood pressure. A more detailed overview of the RAS is provided by Aronson & Ferner, but we will briefly summarize it here.¹⁶ ACE inhibitors block the action of the ACE-1 enzyme, which serves three purposes: 1) converting angiotensin I to angiotensin II, 2) converting the angiotensin-(1-9) peptide to the angiotensin-(1-7) peptide, and 3) degrading bradykinin in order to synthesize nitric oxide which can stimulate vasoconstriction using a separate pathway. Inhibiting the ACE-1 enzyme reduces the activation of ACE-1 and ACE-2 receptors by angiotensin II and angiotensin-(1-7) peptides. Through this mechanism, ACE inhibitors reduce vasoconstriction and produce a decrease in blood pressure. ARBs do not prevent the creation of angiotensin II and angiotensin-(1-7) peptides, but they prevent them from interacting with the ACE-1 receptor, which also reduces vasoconstriction and decreases blood pressure. It is important to note that there are ACE-independent pathways that do not require ACE-1 or ACE-2 enzymes to synthesize angiotensin II from angiotensin I or from angiotensinogen. It is important to note that neither ACE inhibitors or ARBS directly act upon the ACE-2 enzyme.⁸ As pointed out by Aronson & Ferner, inhibitors of ACE-2 have been developed but none have been marketed.³⁷

ACE inhibitors and ARBs are both indicated for the treatment of hypertension, heart failure, ischemic heart disease, and chronic kidney disease. However, use of both medication classes concurrently is not recommended.³⁸ Importantly, patients with these health conditions are often considered at higher risk of poor health outcomes when contracting respiratory infections compared to the general population. ACE inhibitors and ARBs are most frequently used to treat hypertension; however, CCBs are a common alternative antihypertensive therapy as are thiazide and thiazide-like diuretics. All treatment guidelines reviewed for the management of high blood pressure (which encompassed guidelines for the United Kingdom, the United States, South Korea, Australia, and the European Union) recommend ACE inhibitors or ARBs as a first-line antihypertensive treatment option among some patients (**Table S2** – *Note: this table is not exhaustive and does not consider all clinical scenarios but is intended to highlight systematic*

international differences in hypertension treatment).³⁸⁻⁴⁰ However, some guidelines recommend alternate first-line therapies in certain patients based on demographics (e.g. age/race) and comorbidity (e.g. diabetes, CKD). For example, the NICE guidelines specify that ACE inhibitors and ARBs are first-line therapies for patients less than age 55 and patients with comorbid type 2 diabetes, while CCBs are recommended as first line treatment for patients aged 55 or older and also patients who are of African/African-Caribbean family origin.³⁹

Table S2. Overview of National Treatment Guidelines for hypertension for general populations and among specific sub-populations.

| Antihypertensive | United Kingdom³⁹ | United States³⁸ | South Korea⁴¹ | Australia^{42,43} | European Union⁴⁴ |
|--------------------------|------------------------------------|-----------------------------------|---------------------------------|----------------------------------|------------------------------------|
| Thiazide diuretics | Secondary | Primary * | Primary | Primary | Primary |
| ACE inhibitors | Primary \$ * % | Primary \$ % | Primary * % | Primary % | Primary * % |
| ARB | Primary \$ * % | Primary \$ % | Primary * % | Primary % | Primary * % |
| Beta blockers | Secondary @ % | Secondary @ % | Secondary @ % | Secondary @ % | Secondary @ % |
| Calcium channel blockers | Primary * # | Primary # | Primary * # | Primary # | Primary * |

* This drug class is considered to be the first choice for hypertension treatment in the absence of specific indications in this country.

\$ This drug is considered best initial treatment in diabetic populations or those with CKD.

Relatively contra-indicated in patients with heart failure, although some individual medications in the class can still be used.

@ This drug is considered first line in patients with prior AMI.

% This drug class is indicated in heart failure.

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16. Appendix 2: Target, Comparator, and Outcome Cohort Definitions

16.1 Exposure Cohort Definitions

This section documents the exposure cohort definitions for hypotheses 1 and 2. Under hypothesis 1, we consider prevalent ACE inhibitor, ARB, dCCB and THZ users with and without monotherapy inclusion. Below is the complete specification for ACE inhibitor (monotherapy) users and ACE inhibitor (including non-monotherapy) users. The remaining exposure cohorts are similarly defined with appropriate changes to drug ingredient specifications.

[Hypothesis 1] Prevalent users of ACE inhibitor (monotherapy), with hypertension

Initial Event Cohort

People having any of the following:

- a drug exposure of [LEGEND] ACE inhibitors¹
 - occurrence start is between 2019-11-01 and 2020-01-31 (inclusive)

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

Inclusion Rules

Inclusion Criteria #1: Age \geq 18 years old

Having all of the following criteria:

- with the following event criteria:
 - with age \geq 18

Inclusion Criteria #2: has \geq 180d of prior observation

Having all of the following criteria:

- at least 1 occurrence of an observation period
 - where event starts between all days Before and 180 days Before index start date and event ends between 0 days Before and all days After index start date

Inclusion Criteria #3: Hypertension diagnosis anytime before (and including) start-date

Having all of the following criteria:

- at least 1 occurrence of a condition occurrence of [LEGEND]Hypertension⁸
 - where event starts between all days Before and 0 days Before index start date

Inclusion Criteria #4: No exposure to other antihypertensives in the 180 days before start date

This inclusion criteria varies depending on which T/C drug is being assessed (since that one will not be excluded)

Having all of the following criteria:

- at most 0 occurrence of a drug exposure of [LEGEND] Angiotensin receptor blockers (ARBs)²
 - where event starts between 180 days Before and 0 days Before index start date
- and at most 0 occurrence of a drug exposure of [LEGEND] Dihydropyridine calcium channel blockers (dCCB)⁴
 - where event starts between 180 days Before and 0 days Before index start date
- and exactly 0 occurrence of a drug exposure of [LEGEND] Non-dihydropyridine Calcium channel blockers (ndCCB)⁵
 - where event starts between 180 days Before and 0 days Before index start date
- and exactly 0 occurrence of a drug exposure of [LEGEND] beta-blockers³
 - where event starts between 180 days Before and 0 days Before index start date
- and exactly 0 occurrence of a drug exposure of [LEGEND] Thiazide or thiazide-like diuretics⁷

- where event starts between 180 days Before and 0 days Before index start date
- and exactly 0 occurrence of a drug exposure of [LEGEND] Diuretics⁵
- where event starts between 180 days Before and 0 days Before index start date

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] ACE inhibitors¹

- 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.

1. [LEGEND] 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 |
| 1342001 | Enalaprilat | 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 |
| 19040051 | spirapril | Drug | RxNorm | NO | YES | NO |
| 19050216 | Cilazapril | Drug | RxNorm | NO | YES | NO |
| 19102107 | zofenopril | Drug | RxNorm | NO | YES | NO |
| 19122327 | imidapril | Drug | RxNorm | NO | YES | NO |
| 45775374 | moexiprilat | Drug | RxNorm | NO | YES | NO |
| 45775375 | quinaprilat | Drug | RxNorm | NO | YES | NO |
| 45775527 | ramiprilat | Drug | RxNorm | NO | YES | NO |
| 45775529 | trandolaprilat | Drug | RxNorm | NO | YES | NO |
| 45775539 | fosinoprilat | Drug | RxNorm | NO | YES | NO |
| 45775544 | perindoprilat | Drug | RxNorm | NO | YES | NO |

2. [LEGEND] Angiotensin receptor blockers (ARBs)

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|--------------|--------|------------|----------|-------------|--------|
| 1308842 | valsartan | Drug | RxNorm | NO | YES | NO |
| 1317640 | telmisartan | Drug | RxNorm | NO | YES | NO |

| | | | | | | |
|----------|-------------|------|--------|----|-----|----|
| 1346686 | eprosartan | Drug | RxNorm | NO | YES | NO |
| 1347384 | irbesartan | Drug | RxNorm | NO | YES | NO |
| 1351557 | candesartan | Drug | RxNorm | NO | YES | NO |
| 1367500 | Losartan | Drug | RxNorm | NO | YES | NO |
| 40226742 | olmesartan | Drug | RxNorm | NO | YES | NO |
| 40235485 | azilsartan | Drug | RxNorm | NO | YES | NO |

3. [LEGEND] beta-blockers

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|--------------|--------|------------|----------|-------------|--------|
| 902427 | Timolol | Drug | RxNorm | NO | YES | NO |
| 905531 | Metipranolol | Drug | RxNorm | NO | YES | NO |
| 932815 | Levobunolol | Drug | RxNorm | NO | YES | NO |
| 950370 | Carteolol | Drug | RxNorm | NO | YES | NO |
| 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 |
| 1370109 | Sotalol | Drug | RxNorm | NO | YES | NO |
| 1386957 | Labetalol | Drug | RxNorm | NO | YES | NO |
| 19018489 | Bupranolol | Drug | RxNorm | NO | YES | NO |
| 19018640 | bopindolol | Drug | RxNorm | NO | YES | NO |
| 19024904 | Oxprenolol | Drug | RxNorm | NO | YES | NO |
| 19049145 | Celiprolol | Drug | RxNorm | NO | YES | NO |
| 19063575 | esmolol | Drug | RxNorm | NO | YES | NO |
| 19081284 | Alprenolol | Drug | RxNorm | NO | YES | NO |
| 19100435 | talinolol | Drug | RxNorm | NO | YES | NO |
| 19100451 | tertatolol | Drug | RxNorm | NO | YES | NO |

4. [LEGEND] Dihydropyridine calcium channel blockers (dCCB)

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|--------------|--------|------------|----------|-------------|--------|
| 1318137 | Nicardipine | Drug | RxNorm | NO | YES | NO |
| 1318853 | Nifedipine | Drug | RxNorm | NO | YES | NO |
| 1319133 | Nimodipine | Drug | RxNorm | NO | YES | NO |
| 1319880 | Nisoldipine | Drug | RxNorm | NO | YES | NO |
| 1326012 | Isradipine | Drug | RxNorm | NO | YES | NO |
| 1332418 | Amlodipine | Drug | RxNorm | NO | YES | NO |

| | | | | | | |
|----------|---------------|------|--------|----|-----|----|
| 1353776 | Felodipine | Drug | RxNorm | NO | YES | NO |
| 19004539 | lacidipine | Drug | RxNorm | NO | YES | NO |
| 19015802 | Iercanidipine | Drug | RxNorm | NO | YES | NO |
| 19020061 | Nitrendipine | Drug | RxNorm | NO | YES | NO |
| 19071995 | manidipine | Drug | RxNorm | NO | YES | NO |
| 19089969 | clevidipine | Drug | RxNorm | NO | YES | NO |
| 19102106 | mepirodipine | Drug | RxNorm | NO | YES | NO |
| 19113063 | nilvadipine | Drug | RxNorm | NO | YES | NO |

5. [LEGEND] Diuretics

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|----------------|--------|------------|----------|-------------|--------|
| 904542 | Triamterene | Drug | RxNorm | NO | YES | NO |
| 932745 | Bumetanide | Drug | RxNorm | NO | YES | NO |
| 942350 | torseamide | Drug | RxNorm | NO | YES | NO |
| 956874 | Furosemide | Drug | RxNorm | NO | YES | NO |
| 970250 | Spironolactone | Drug | RxNorm | NO | YES | NO |
| 991382 | Amiloride | Drug | RxNorm | NO | YES | NO |
| 1309799 | eplerenone | Drug | RxNorm | NO | YES | NO |

6. [LEGEND] Non-dihydropyridine Calcium channel blockers (ndCCB)

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|--------------|--------|------------|----------|-------------|--------|
| 1307863 | Verapamil | Drug | RxNorm | NO | YES | NO |
| 1328165 | Diltiazem | Drug | RxNorm | NO | YES | NO |
| 19057715 | Gallopamil | Drug | RxNorm | NO | YES | NO |

7. [LEGEND] Thiazide or thiazide-like diuretics

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|---------------------|--------|------------|----------|-------------|--------|
| 907013 | Metolazone | Drug | RxNorm | NO | YES | NO |
| 974166 | Hydrochlorothiazide | Drug | RxNorm | NO | YES | NO |
| 978555 | Indapamide | Drug | RxNorm | NO | YES | NO |
| 1316354 | Bendroflumethiazide | Drug | RxNorm | NO | YES | NO |
| 1395058 | Chlorthalidone | Drug | RxNorm | NO | YES | NO |
| 19010493 | Xipamide | Drug | RxNorm | NO | YES | NO |

8. [LEGEND] Hypertension

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

[Hypothesis 1] Prevalent users of ACE inhibitors (including non-monotherapy), with hypertension

Initial Event Cohort

People having any of the following:

- a drug exposure of [LEGEND] ACE inhibitors¹
 - occurrence start is between 2019-11-01 and 2020-01-31 (inclusive)

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

Inclusion Rules

Inclusion Criteria #1: Age \geq 18 years old

Having all of the following criteria:

- with the following event criteria:
 - with age \geq 18

Inclusion Criteria #2: has \geq 180d of prior observation

Having all of the following criteria:

- at least 1 occurrence of an observation period
where event starts between all days Before and 180 days Before index start date and event ends between 0 days Before and all days After index start date

Inclusion Criteria #3: Hypertension diagnosis anytime before (and including) start-date

Having all of the following criteria:

- at least 1 occurrence of a condition occurrence of [LEGEND]Hypertension²
where event starts between all days Before and 0 days Before index start date

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] ACE inhibitors¹

- 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.

1. [LEGEND] 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 |
| 1342001 | Enalaprilat | 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 |
| 19040051 | spirapril | Drug | RxNorm | NO | YES | NO |

| | | | | | | |
|----------|----------------|------|--------|----|-----|----|
| 19050216 | Cilazapril | Drug | RxNorm | NO | YES | NO |
| 19102107 | zofenopril | Drug | RxNorm | NO | YES | NO |
| 19122327 | imidapril | Drug | RxNorm | NO | YES | NO |
| 45775374 | moexiprilat | Drug | RxNorm | NO | YES | NO |
| 45775375 | quinaprilat | Drug | RxNorm | NO | YES | NO |
| 45775527 | ramiprilat | Drug | RxNorm | NO | YES | NO |
| 45775529 | trandolaprilat | Drug | RxNorm | NO | YES | NO |
| 45775539 | fosinoprilat | Drug | RxNorm | NO | YES | NO |
| 45775544 | perindoprilat | Drug | RxNorm | NO | YES | NO |

2. [LEGEND]Hypertension

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

For hypothesis 2, we consider prevalent ACE inhibitor, ARB, dCCB and THZ users with and without monotherapy inclusion and with and without hospitalization at COVID-19 diagnosis. Below is the complete specification for ACE inhibitor (monotherapy) users without hospitalization and ACE (monotherapy) users with hospitalization. The remaining exposure cohorts are similarly defined with appropriate changes to drug ingredient specifications.

[Hypothesis 2] Prevalent users of ACE inhibitors (monotherapy) with COVID-19, history of hypertension

Initial Event Cohort

People having any of the following:

- a condition occurrence of COVID-19 (including asymptomatic)¹
- a condition occurrence of Any Condition
 - Condition Source Concept is COVID-19 source codes²
- a measurement of COVID-19 specific testing (pre-coordinated Measurements) - Positive⁴
- a measurement of COVID-19 specific testing (pre-coordinated Measurements excluded)³
 - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present
- an observation of COVID-19 specific testing (pre-coordinated Measurements excluded)³
 - value as concept is any of: Present, Detected, Detected, Positive, Positive, Present
- an observation of Any Observation

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

Inclusion Rules

Inclusion Criteria #1: age >=18

Having all of the following criteria:

- with the following event criteria:
 - with age >= 18

Inclusion Criteria #2: has >=180d of prior observation

Having all of the following criteria:

- at least 1 occurrence of an observation period

where event starts between all days Before and 180 days Before index start date and event ends between 0 days Before and all days After index end date

Inclusion Criteria #3: Has T/C drug era overlapping day -30 or a drug exposure in the last 60 days
Having any of the following criteria:

- at least 1 occurrence of a drug era of [LEGEND] ACE inhibitors⁵
where event starts between all days Before and 1 days Before index start date and event ends between 30 days Before and all days After index start date
- or at least 1 occurrence of a drug exposure of [LEGEND] ACE inhibitors⁵
where event starts between 60 days Before and 1 days Before index start date

Inclusion Criteria #4: Hypertension diagnosis anytime before start-date

Having all of the following criteria:

- at least 1 occurrence of a condition occurrence of [LEGEND] Hypertension¹⁰
where event starts between all days Before and 1 days Before index start date

Inclusion Criteria #5: No exposure to any other antihypertensives within 180 days before start-date

This inclusion criteria varies depending on which T/C drug is being assessed (since that one will not be excluded)

Having all of the following criteria:

- exactly 0 occurrence of a drug exposure of [LEGEND] Angiotensin receptor blockers (ARBs)⁶
where event starts between 180 days Before and 1 days Before index start date
- and exactly 0 occurrence of a drug exposure of [LEGEND] Dihydropyridine calcium channel blockers (dCCB)⁸
where event starts between 180 days Before and 1 days Before index start date
- and exactly 0 occurrence of a drug exposure of [LEGEND] Non-dihydropyridine Calcium channel blockers (ndCCB)¹¹
where event starts between 180 days Before and 1 days Before index start date
- and exactly 0 occurrence of a drug exposure of [LEGEND] beta-blockers⁷
where event starts between 180 days Before and 1 days Before index start date
- and exactly 0 occurrence of a drug exposure of [LEGEND] Thiazide or thiazide-like diuretics¹²
where event starts between 180 days Before and 1 days Before index start date
- and exactly 0 occurrence of a drug exposure of [LEGEND] Diuretics⁹
where event starts between 180 days Before and 1 days Before index start date

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

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

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

1. COVID-19 (including asymptomatic)

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|---|-----------|------------|----------|-------------|--------|
| 37311061 | Disease caused by severe acute respiratory syndrome coronavirus 2 | Condition | SNOMED | NO | YES | NO |

2. COVID-19 source codes

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|--|-------------|------------|----------|-------------|--------|
| 586414 | Novel coronavirus infection | Condition | KCD7 | NO | NO | NO |
| 586415 | Provisional assignment of new diseases or emergency use | Condition | KCD7 | NO | NO | NO |
| 710155 | COVID-19 pneumonia (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710156 | COVID-19 pneumonia (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710157 | Suspected case of COVID-19 (machine translation) | Condition | ICD10CN | YES | NO | NO |
| 710158 | COVID-19 (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710159 | Confirmed COVID-19, excluding pneumonia (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710160 | Emergency use of U07.1 Disease caused by severe acute respiratory syndrome coronavirus 2 | Observation | ICD10CN | NO | NO | NO |
| 42501115 | Emergency use of U07.1 Disease caused by severe acute respiratory syndrome coronavirus 2 | Condition | KCD7 | NO | NO | NO |
| 45542411 | Contact with and (suspected) exposure to other viral communicable diseases | Observation | ICD10CM | YES | NO | NO |
| 45600471 | Other coronavirus as the cause of diseases classified elsewhere | Condition | ICD10CM | NO | NO | NO |
| 45756093 | Emergency use of U07.1 Disease caused by severe acute respiratory syndrome coronavirus 2 | Condition | ICD10 | NO | NO | NO |

3. COVID-19 specific testing (pre-coordinated Measurements excluded)

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|--|-------------|----------------|----------|-------------|--------|
| 756055 | Measurement of severe acute respiratory syndrome coronavirus 2 | Measurement | OMOP Extension | NO | YES | NO |
| 37310281 | 2019 novel coronavirus not detected | Measurement | SNOMED | YES | YES | NO |
| 37310282 | 2019 novel coronavirus detected | Measurement | SNOMED | YES | YES | NO |

4. COVID-19 specific testing (pre-coordinated Measurements) - Positive

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|---------------------------------|-------------|------------|----------|-------------|--------|
| 37310282 | 2019 novel coronavirus detected | Measurement | SNOMED | NO | YES | NO |

5. [LEGEND] 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 |

| | | | | | | |
|----------|----------------|------|--------|----|-----|----|
| 1342001 | Enalaprilat | 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 |
| 19040051 | spirapril | Drug | RxNorm | NO | YES | NO |
| 19050216 | Cilazapril | Drug | RxNorm | NO | YES | NO |
| 19102107 | zofenopril | Drug | RxNorm | NO | YES | NO |
| 19122327 | imidapril | Drug | RxNorm | NO | YES | NO |
| 45775374 | moexiprilat | Drug | RxNorm | NO | YES | NO |
| 45775375 | quinaprilat | Drug | RxNorm | NO | YES | NO |
| 45775527 | ramiprilat | Drug | RxNorm | NO | YES | NO |
| 45775529 | trandolaprilat | Drug | RxNorm | NO | YES | NO |
| 45775539 | fosinoprilat | Drug | RxNorm | NO | YES | NO |
| 45775544 | perindoprilat | Drug | RxNorm | NO | YES | NO |

6. [LEGEND] Angiotensin receptor blockers (ARBs)

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

7. [LEGEND] beta-blockers

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|--------------|--------|------------|----------|-------------|--------|
| 902427 | Timolol | Drug | RxNorm | NO | YES | NO |
| 905531 | Metipranolol | Drug | RxNorm | NO | YES | NO |
| 932815 | Levobunolol | Drug | RxNorm | NO | YES | NO |
| 950370 | Carteolol | Drug | RxNorm | NO | YES | NO |
| 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 |
| 1370109 | Sotalol | Drug | RxNorm | NO | YES | NO |
| 1386957 | Labetalol | Drug | RxNorm | NO | YES | NO |
| 19018489 | Bupranolol | Drug | RxNorm | NO | YES | NO |
| 19018640 | bopindolol | Drug | RxNorm | NO | YES | NO |
| 19024904 | Oxprenolol | Drug | RxNorm | NO | YES | NO |
| 19049145 | Celiprolol | Drug | RxNorm | NO | YES | NO |
| 19063575 | esmolol | Drug | RxNorm | NO | YES | NO |
| 19081284 | Alprenolol | Drug | RxNorm | NO | YES | NO |
| 19100435 | talinolol | Drug | RxNorm | NO | YES | NO |
| 19100451 | tertatolol | Drug | RxNorm | NO | YES | NO |

8. [LEGEND] Dihydropyridine calcium channel blockers (dCCB)

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|---------------|--------|------------|----------|-------------|--------|
| 1318137 | Nicardipine | Drug | RxNorm | NO | YES | NO |
| 1318853 | Nifedipine | Drug | RxNorm | NO | YES | NO |
| 1319133 | Nimodipine | Drug | RxNorm | NO | YES | NO |
| 1319880 | Nisoldipine | Drug | RxNorm | NO | YES | NO |
| 1326012 | Isradipine | Drug | RxNorm | NO | YES | NO |
| 1332418 | Amlodipine | Drug | RxNorm | NO | YES | NO |
| 1353776 | Felodipine | Drug | RxNorm | NO | YES | NO |
| 19004539 | lacidipine | Drug | RxNorm | NO | YES | NO |
| 19015802 | lercanidipine | Drug | RxNorm | NO | YES | NO |
| 19020061 | Nitrendipine | Drug | RxNorm | NO | YES | NO |
| 19071995 | manidipine | Drug | RxNorm | NO | YES | NO |
| 19089969 | clevidipine | Drug | RxNorm | NO | YES | NO |
| 19102106 | mepirodipine | Drug | RxNorm | NO | YES | NO |
| 19113063 | nilvadipine | Drug | RxNorm | NO | YES | NO |

9. [LEGEND] Diuretics

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|----------------|--------|------------|----------|-------------|--------|
| 904542 | Triamterene | Drug | RxNorm | NO | YES | NO |
| 932745 | Bumetanide | Drug | RxNorm | NO | YES | NO |
| 942350 | torsemide | Drug | RxNorm | NO | YES | NO |
| 956874 | Furosemide | Drug | RxNorm | NO | YES | NO |
| 970250 | Spironolactone | Drug | RxNorm | NO | YES | NO |
| 991382 | Amiloride | Drug | RxNorm | NO | YES | NO |
| 1309799 | eplerenone | Drug | RxNorm | NO | YES | NO |

10. [LEGEND] Hypertension

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

11. [LEGEND] Non-dihydropyridine Calcium channel blockers (ndCCB)

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|--------------|--------|------------|----------|-------------|--------|
| 1307863 | Verapamil | Drug | RxNorm | NO | YES | NO |
| 1328165 | Diltiazem | Drug | RxNorm | NO | YES | NO |
| 19057715 | Gallopamil | Drug | RxNorm | NO | YES | NO |

12. [LEGEND] Thiazide or thiazide-like diuretics

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|---------------------|--------|------------|----------|-------------|--------|
| 907013 | Metolazone | Drug | RxNorm | NO | YES | NO |
| 974166 | Hydrochlorothiazide | Drug | RxNorm | NO | YES | NO |
| 978555 | Indapamide | Drug | RxNorm | NO | YES | NO |
| 1316354 | Bendroflumethiazide | Drug | RxNorm | NO | YES | NO |
| 1395058 | Chlorthalidone | Drug | RxNorm | NO | YES | NO |
| 19010493 | Xipamide | Drug | RxNorm | NO | YES | NO |

[Hypothesis 2] Prevalent users of ACE inhibitors (monotherapy), hospitalized with COVID-19, history of hypertension

Initial Event Cohort

People having any of the following:

- a visit occurrence of [OHDSI Covid19 v1] Inpatient Visit¹³
 - occurrence start is after 2019-12-01

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 occurrence of a condition occurrence of COVID-19 (including asymptomatic)¹ where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a condition occurrence of Any Condition
 - Condition Source Concept is COVID-19 source codes² where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a measurement of COVID-19 specific testing (pre-coordinated Measurements) - Positive⁴ where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a measurement of COVID-19 specific testing (pre-coordinated Measurements excluded)³
 - value as concept is any of: Detected, Detected, Positive, Present, Present, Positive where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

- or at least 1 occurrence of an observation of COVID-19 specific testing (pre-coordinated Measurements excluded)³
 - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of an observation of Any Observation where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

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

Inclusion Rules

Inclusion Criteria #1: age >=18

Having all of the following criteria:

- with the following event criteria:
 - with age >= 18

Inclusion Criteria #2: has >=180d of prior observation

Having all of the following criteria:

- at least 1 occurrence of an observation period where event starts between all days Before and 180 days Before index start date and event ends between 0 days Before and all days After index end date

Inclusion Criteria #3: No hospitalization for COVID19 in the 6 months preceding admission

Having all of the following criteria:

- exactly 0 occurrences of a visit occurrence of [OHDSI Covid19 v1] Inpatient Visit¹³

Having any of the following criteria:

 - at least 1 occurrence of a condition occurrence of COVID-19 (including asymptomatic)¹ where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
 - or at least 1 occurrence of a condition occurrence of Any Condition
 - Condition Source Concept is COVID-19 source codes² where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
 - or at least 1 occurrence of an observation of Any Observation where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
 - or at least 1 occurrence of a measurement of COVID-19 specific testing (pre-coordinated Measurements) - Positive⁴ where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
 - or at least 1 occurrence of a measurement of COVID-19 specific testing (pre-coordinated Measurements excluded)³
 - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
 - or at least 1 occurrence of an observation of COVID-19 specific testing (pre-coordinated Measurements excluded)³

- value as concept is any of: Detected, Detected, Positive, Positive, Present, Present

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

where event starts between 180 days Before and 1 days Before index start date

Inclusion Criteria #4: Has T/C drug drug era overlapping day -30 or a drug exposure in the last 60 days

Having any of the following criteria:

- at least 1 occurrence of a drug era of [LEGEND] ACE inhibitors⁵
where event starts between all days Before and 1 days Before index start date and event ends between 30 days Before and all days After index start date
- or at least 1 occurrence of a drug exposure of [LEGEND] ACE inhibitors⁵
where event starts between 60 days Before and 1 days Before index start date

Inclusion Criteria #5: Hypertension diagnosis anytime before start-date.

Having all of the following criteria:

- at least 1 occurrence of a condition occurrence of [LEGEND] Hypertension¹⁰
where event starts between all days Before and 1 days Before index start date

Inclusion Criteria #6: No exposure to any other antihypertensives within 180 days before start-date

This inclusion criteria varies depending on which T/C drug is being assessed (since that one will not be excluded)

Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of [LEGEND] Angiotensin receptor blockers (ARBs)⁶
where event starts between 180 days Before and 1 days Before index start date
- and exactly 0 of a drug exposure of [LEGEND] Dihydropyridine calcium channel blockers (dCCB)⁸
where event starts between 180 days Before and 1 days Before index start date
- and exactly 0 occurrences of a drug exposure of [LEGEND] Non-dihydropyridine Calcium channel blockers (ndCCB)¹¹
where event starts between 180 days Before and 1 days Before index start date
- and exactly 0 occurrences of a drug exposure of [LEGEND] beta-blockers⁷
where event starts between 180 days Before and 1 days Before index start date
- and exactly 0 occurrences of a drug exposure of [LEGEND] Thiazide or thiazide-like diuretics¹²
where event starts between 180 days Before and 1 days Before index start date
- and exactly 0 occurrences of a drug exposure of [LEGEND] Diuretics⁹
where event starts between 180 days Before and 1 days Before index start date

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

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

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

1. COVID-19 (including asymptomatic)

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|---|-----------|------------|----------|-------------|--------|
| 37311061 | Disease caused by severe acute respiratory syndrome coronavirus 2 | Condition | SNOMED | NO | YES | NO |

2. COVID-19 source codes

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|--|-------------|------------|----------|-------------|--------|
| 586414 | Novel coronavirus infection | Condition | KCD7 | NO | NO | NO |
| 586415 | Provisional assignment of new diseases or emergency use | Condition | KCD7 | NO | NO | NO |
| 710155 | COVID-19 pneumonia (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710156 | COVID-19 pneumonia (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710157 | Suspected case of COVID-19 (machine translation) | Condition | ICD10CN | YES | NO | NO |
| 710158 | COVID-19 (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710159 | Confirmed COVID-19, excluding pneumonia (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710160 | Emergency use of U07.1 Disease caused by severe acute respiratory syndrome coronavirus 2 | Observation | ICD10CN | NO | NO | NO |
| 42501115 | Emergency use of U07.1 Disease caused by severe acute respiratory syndrome coronavirus 2 | Condition | KCD7 | NO | NO | NO |
| 45542411 | Contact with and (suspected) exposure to other viral communicable diseases | Observation | ICD10CM | YES | NO | NO |
| 45600471 | Other coronavirus as the cause of diseases classified elsewhere | Condition | ICD10CM | NO | NO | NO |
| 45756093 | Emergency use of U07.1 Disease caused by severe acute respiratory syndrome coronavirus 2 | Condition | ICD10 | NO | NO | NO |

3. COVID-19 specific testing (pre-coordinated Measurements excluded)

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|--|-------------|----------------|----------|-------------|--------|
| 756055 | Measurement of severe acute respiratory syndrome coronavirus 2 | Measurement | OMOP Extension | NO | YES | NO |
| 37310281 | 2019 novel coronavirus not detected | Measurement | SNOMED | YES | YES | NO |
| 37310282 | 2019 novel coronavirus detected | Measurement | SNOMED | YES | YES | NO |

4. COVID-19 specific testing (pre-coordinated Measurements) - Positive

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|---------------------------------|-------------|------------|----------|-------------|--------|
| 37310282 | 2019 novel coronavirus detected | Measurement | SNOMED | NO | YES | NO |

5. [LEGEND] 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 |
| 1342001 | Enalaprilat | 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 |
| 19040051 | spirapril | Drug | RxNorm | NO | YES | NO |
| 19050216 | Cilazapril | Drug | RxNorm | NO | YES | NO |
| 19102107 | zofenopril | Drug | RxNorm | NO | YES | NO |
| 19122327 | imidapril | Drug | RxNorm | NO | YES | NO |
| 45775374 | moexiprilat | Drug | RxNorm | NO | YES | NO |
| 45775375 | quinaprilat | Drug | RxNorm | NO | YES | NO |
| 45775527 | ramiprilat | Drug | RxNorm | NO | YES | NO |
| 45775529 | trandolaprilat | Drug | RxNorm | NO | YES | NO |
| 45775539 | fosinoprilat | Drug | RxNorm | NO | YES | NO |
| 45775544 | perindoprilat | Drug | RxNorm | NO | YES | NO |

6. [LEGEND] Angiotensin receptor blockers (ARBs)

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

7. [LEGEND] beta-blockers

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|--------------|--------|------------|----------|-------------|--------|
| 902427 | Timolol | Drug | RxNorm | NO | YES | NO |
| 905531 | Metipranolol | Drug | RxNorm | NO | YES | NO |
| 932815 | Levobunolol | Drug | RxNorm | NO | YES | NO |
| 950370 | Carteolol | Drug | RxNorm | NO | YES | NO |
| 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 |
| 1370109 | Sotalol | Drug | RxNorm | NO | YES | NO |
| 1386957 | Labetalol | Drug | RxNorm | NO | YES | NO |
| 19018489 | Bupranolol | Drug | RxNorm | NO | YES | NO |
| 19018640 | bopindolol | Drug | RxNorm | NO | YES | NO |
| 19024904 | Oxprenolol | Drug | RxNorm | NO | YES | NO |
| 19049145 | Celiprolol | Drug | RxNorm | NO | YES | NO |
| 19063575 | esmolol | Drug | RxNorm | NO | YES | NO |
| 19081284 | Alprenolol | Drug | RxNorm | NO | YES | NO |
| 19100435 | talinolol | Drug | RxNorm | NO | YES | NO |
| 19100451 | tertatolol | Drug | RxNorm | NO | YES | NO |

8. [LEGEND] Dihydropyridine calcium channel blockers (dCCB)

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|---------------|--------|------------|----------|-------------|--------|
| 1318137 | Nicardipine | Drug | RxNorm | NO | YES | NO |
| 1318853 | Nifedipine | Drug | RxNorm | NO | YES | NO |
| 1319133 | Nimodipine | Drug | RxNorm | NO | YES | NO |
| 1319880 | Nisoldipine | Drug | RxNorm | NO | YES | NO |
| 1326012 | Isradipine | Drug | RxNorm | NO | YES | NO |
| 1332418 | Amlodipine | Drug | RxNorm | NO | YES | NO |
| 1353776 | Felodipine | Drug | RxNorm | NO | YES | NO |
| 19004539 | lacidipine | Drug | RxNorm | NO | YES | NO |
| 19015802 | lercanidipine | Drug | RxNorm | NO | YES | NO |
| 19020061 | Nitrendipine | Drug | RxNorm | NO | YES | NO |
| 19071995 | manidipine | Drug | RxNorm | NO | YES | NO |
| 19089969 | clevidipine | Drug | RxNorm | NO | YES | NO |
| 19102106 | mepirodipine | Drug | RxNorm | NO | YES | NO |
| 19113063 | nilvadipine | Drug | RxNorm | NO | YES | NO |

9. [LEGEND] Diuretics

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|----------------|--------|------------|----------|-------------|--------|
| 904542 | Triamterene | Drug | RxNorm | NO | YES | NO |
| 932745 | Bumetanide | Drug | RxNorm | NO | YES | NO |
| 942350 | torsemide | Drug | RxNorm | NO | YES | NO |
| 956874 | Furosemide | Drug | RxNorm | NO | YES | NO |
| 970250 | Spironolactone | Drug | RxNorm | NO | YES | NO |
| 991382 | Amiloride | Drug | RxNorm | NO | YES | NO |
| 1309799 | eplerenone | Drug | RxNorm | NO | YES | NO |

10. [LEGEND] Hypertension

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

| | | | | | | |
|--------|-----------------------|-----------|--------|----|-----|----|
| 316866 | Hypertensive disorder | Condition | SNOMED | NO | YES | NO |
|--------|-----------------------|-----------|--------|----|-----|----|

11. [LEGEND] Non-dihydropyridine Calcium channel blockers (ndCCB)

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|--------------|--------|------------|----------|-------------|--------|
| 1307863 | Verapamil | Drug | RxNorm | NO | YES | NO |
| 1328165 | Diltiazem | Drug | RxNorm | NO | YES | NO |
| 19057715 | Gallopamil | Drug | RxNorm | NO | YES | NO |

12. [LEGEND] Thiazide or thiazide-like diuretics

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|---------------------|--------|------------|----------|-------------|--------|
| 907013 | Metolazone | Drug | RxNorm | NO | YES | NO |
| 974166 | Hydrochlorothiazide | Drug | RxNorm | NO | YES | NO |
| 978555 | Indapamide | Drug | RxNorm | NO | YES | NO |
| 1316354 | Bendroflumethiazide | Drug | RxNorm | NO | YES | NO |
| 1395058 | Chlorthalidone | Drug | RxNorm | NO | YES | NO |
| 19010493 | Xipamide | Drug | RxNorm | NO | YES | NO |

13. [OHDSI Covid19 v1] Inpatient 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 |

16.2 Outcome Cohort Definitions

This section documents the outcome cohort definitions for hypotheses 1 and 2. Under hypothesis 1, we consider a

- Broad definition of COVID-19 diagnosis
- Narrow definition of COVID-19 diagnosis
- Hospitalization with pneumonia, and
- Hospitalization with pneumonia or ARDS or acute kidney injury or resulting in death in 30 days.

Below are their complete specifications.

[COVID ID4 v1] Persons hospitalized with COVID-19, broad, no prior observation required

Initial Event Cohort

People having any of the following:

- a visit occurrence of [OHDSI Covid19 v1] Inpatient Visit¹³
 - occurrence start is after 2019-12-01

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 occurrence of a condition occurrence of COVID-19 (including asymptomatic)¹
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a condition occurrence of Any Condition
 - Condition Source Concept is COVID-19 source codes²
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a measurement of COVID-19 specific testing (pre-coordinated Measurements) - Positive⁴
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a measurement of COVID-19 specific testing (pre-coordinated Measurements excluded)³
 - value as concept is any of: Detected, Detected, Positive, Present, Present, Positive
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of an observation of COVID-19 specific testing (pre-coordinated Measurements excluded)³
 - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of an observation of Any Observation
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a condition occurrence of COVID-19 Suspected OR Suspected unspecific coronavirus infection - Source and Standard terminology⁵
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a condition occurrence of Any Condition
 - Condition Source Concept is COVID-19 Suspected OR Suspected unspecific coronavirus infection - Source and Standard terminology⁵
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- Or having all of the following criteria:
 - Having any of the following criteria:
 - at least 1 occurrence of a condition occurrence of [COVID19 v1] Fever (38.0°C or higher) pre-coordinated measurement and conditions⁸
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
 - or at least 1 occurrence of a measurement of [COVID19 v1] Fever (38.0°C or higher) pre-coordinated measurement and conditions⁸
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

- or at least 1 occurrence of a measurement of [COVID19 V1] Fever (38.0°C or higher) measurement and observation⁷
 - with value as number between 38 and 42 (inclusive)
 - unit is any of: degree Celsius

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a measurement of [COVID19 V1] Fever (38.0°C or higher) measurement and observation⁷
 - with value as number between 100.4 and 120 (inclusive)
 - unit is any of: degree Fahrenheit

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of an observation of [COVID19 V1] Fever (38.0°C or higher) measurement and observation⁷
 - with value as number between 38 and 42 (inclusive)
 - unit is any of: degree Celsius

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of an observation of [COVID19 V1] Fever (38.0°C or higher) measurement and observation⁷
 - with value as number between 100.4 and 120 (inclusive)
 - unit is any of: degree Fahrenheit

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- And having any of the following criteria:
 - at least 1 occurrence of a condition occurrence of [OHDSI Cov19] Cough¹²

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
 - or at least 1 occurrence of a condition occurrence of [COVID V1] Shortness of breath (dyspnea)⁶

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
 - or at least 1 occurrence of a condition occurrence of [COVID19 v1] Myalgia¹⁰

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
 - or at least 1 occurrence of a condition occurrence of [Covid19 V1] Malaise or Fatigue or (Malaise and Fatigue)⁹

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
 - or at least 1 occurrence of a condition occurrence of Any Condition
 - Condition Source Concept is [Covid19 V1] Malaise or Fatigue or (Malaise and Fatigue)⁹

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
 - or at least 1 occurrence of a condition occurrence of [COVID19 v1] Pneumonia¹¹

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

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

Inclusion Rules

Inclusion Criteria #1: age ≥ 18

Having all of the following criteria:

- with the following event criteria:
 - with age ≥ 18

Inclusion Criteria #2: does not have hospitalization for COVID19 in the 6 months preceding admission

Having all of the following criteria:

- exactly 0 occurrences of a visit occurrence of [OHDSI Covid19 v1] Inpatient Visit¹³

Having any of the following criteria:

- at least 1 occurrence of a condition occurrence of COVID-19 (including asymptomatic)¹
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a condition occurrence of Any Condition
 - Condition Source Concept is COVID-19 source codes²
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of an observation of Any Observation
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a measurement of COVID-19 specific testing (pre-coordinated Measurements) - Positive⁴
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a measurement of COVID-19 specific testing (pre-coordinated Measurements excluded)³
 - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of an observation of COVID-19 specific testing (pre-coordinated Measurements excluded)³
 - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a condition occurrence of COVID-19 Suspected OR Suspected unspecific coronavirus infection - Source and Standard terminology⁵
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a condition occurrence of Any Condition
 - Condition Source Concept is COVID-19 Suspected OR Suspected unspecific coronavirus infection - Source and Standard terminology⁵
where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date
- Or having all of the following criteria:
 - Having any of the following criteria:

- at least 1 occurrence of a condition occurrence of [COVID19 v1]
Fever (38.0°C or higher) pre-coordinated measurement and conditions⁸
where event
starts between 21 days Before and all days After index start date and event
starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a measurement of [COVID19 v1]
Fever (38.0°C or higher) pre-coordinated measurement and conditions⁸
where event
starts between 21 days Before and all days After index start date and event
starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a measurement of [COVID19 V1]
Fever (38.0°C or higher) measurement and observation⁷
 - with value as number between 38 and 42 (inclusive)
 - unit is any of: degree Celsius
where event
starts between 21 days Before and all days After index start date and event
starts between all days Before and 0 days After index end date
- or at least 1 occurrence of a measurement of [COVID19 V1]
Fever (38.0°C or higher) measurement and observation⁷
 - with value as
number between 100.4 and 120 (inclusive)
 - unit is any of: degree Fahrenheit
where event
starts between 21 days Before and all days After index start date and event
starts between all days Before and 0 days After index end date
- or at least 1 occurrence of an observation of [COVID19 V1]
Fever (38.0°C or higher) measurement and observation⁷
 - with value as number between 38 and 42 (inclusive)
 - unit is any of: degree Celsius
where event
starts between 21 days Before and all days After index start date and event
starts between all days Before and 0 days After index end date
- or at least 1 occurrence of an observation of [COVID19 V1]
Fever (38.0°C or higher) measurement and observation⁷
 - with value as
number between 100.4 and 120 (inclusive)
 - unit is any of: degree Fahrenheit
where event
starts between 21 days Before and all days After index start date and event
starts between all days Before and 0 days After index end date

- And having all of the following criteria:
 - at least 1 occurrence of a condition occurrence of [OHDSI Cov19] Cough¹²
 where event
 starts between 21 days Before and all days After index start date and event
 ends between all days Before and 0 days After index start date
 - and at least 1 occurrence of a condition occurrence of [COVID V1] Shortness of breath (dyspnea)⁶
 where event
 starts between 21 days Before and all days After index start date and event
 starts between all days Before and 0 days After index end date
 - and at least 1 occurrence of a condition occurrence of [COVID19 v1] Myalgia¹⁰
 where event
 starts between 21 days Before and all days After index start date and event
 starts between all days Before and 0 days After index end date
 - and at least 1 occurrence of a condition occurrence of [Covid19 V1] Malaise or Fatigue or (Malaise and Fatigue)⁹
 where event
 starts between 21 days Before and all days After index start date and event
 starts between all days Before and 0 days After index end date
 - and at least 1 occurrence of a condition occurrence of Any Condition
 - Condition Source Concept is [Covid19 V1] Malaise or Fatigue or (Malaise and Fatigue)⁹
 where event
 starts between 21 days Before and all days After index start date and event
 starts between all days Before and 0 days After index end date
 - and at least 1 occurrence of a condition occurrence of [COVID19 v1] Pneumonia¹¹
 where event
 starts between 21 days Before and all days After index start date and event
 starts between all days Before and 0 days After index end date

where event starts between 180 days Before and 1 days Before index start date

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 0 days.

1. COVID-19 (including asymptomatic)

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mappe d |
|------------|---|-----------|------------|-----------|-------------|---------|
| 37311061 | Disease caused by severe acute respiratory syndrome coronavirus 2 | Condition | SNOMED | NO | YES | NO |

2. COVID-19 source codes

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mappe d |
|------------|--|-------------|------------|-----------|-------------|---------|
| 586414 | Novel coronavirus infection | Condition | KCD7 | NO | NO | NO |
| 586415 | Provisional assignment of new diseases or emergency use | Condition | KCD7 | NO | NO | NO |
| 710155 | COVID-19 pneumonia (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710156 | COVID-19 pneumonia (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710157 | Suspected case of COVID-19 (machine translation) | Condition | ICD10CN | YES | NO | NO |
| 710158 | COVID-19 (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710159 | Confirmed COVID-19, excluding pneumonia (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710160 | Emergency use of U07.1 Disease caused by severe acute respiratory syndrome coronavirus 2 | Observation | ICD10CN | NO | NO | NO |
| 42501115 | Emergency use of U07.1 Disease caused by severe acute respiratory syndrome coronavirus 2 | Condition | KCD7 | NO | NO | NO |
| 45542411 | Contact with and (suspected) exposure to other viral communicable diseases | Observation | ICD10CM | YES | NO | NO |
| 45600471 | Other coronavirus as the cause of diseases classified elsewhere | Condition | ICD10CM | NO | NO | NO |
| 45756093 | Emergency use of U07.1 Disease caused by severe acute respiratory syndrome coronavirus 2 | Condition | ICD10 | NO | NO | NO |

3. COVID-19 specific testing (pre-coordinated Measurements excluded)

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mappe d |
|------------|--|-------------|----------------|-----------|-------------|---------|
| 756055 | Measurement of severe acute respiratory syndrome coronavirus 2 | Measurement | OMOP Extension | NO | YES | NO |
| 37310281 | 2019 novel coronavirus not detected | Measurement | SNOMED | YES | YES | NO |
| 37310282 | 2019 novel coronavirus detected | Measurement | SNOMED | YES | YES | NO |

4. COVID-19 specific testing (pre-coordinated Measurements) - Positive

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mappe d |
|------------|---------------------------------|-------------|------------|-----------|-------------|---------|
| 37310282 | 2019 novel coronavirus detected | Measurement | SNOMED | NO | YES | NO |

5. COVID-19 Suspected OR Suspected unspecific coronavirus infection - Source and Standard terminology

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mappe d |
|------------|--|-----------|------------|-----------|-------------|---------|
| 710157 | Suspected case of COVID-19 (machine translation) | Condition | ICD10CN | NO | NO | NO |
| 45763724 | Suspected coronavirus infection | Condition | SNOMED | NO | NO | NO |

6. [COVID V1] Shortness of breath (dyspnea)

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mappe d |
|------------|--|-----------|------------|-----------|-------------|---------|
| 312437 | Dyspnea | Condition | SNOMED | NO | YES | NO |
| 4191650 | Acute respiratory distress | Condition | SNOMED | NO | YES | NO |
| 4222908 | Borg Breathlessness Score: 0 none at all | Condition | SNOMED | YES | YES | NO |

7. [COVID19 V1] Fever (38.0°C or higher) measurement and observation

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mappe d |
|------------|-------------------------------------|-------------|------------|-----------|-------------|---------|
| 3004750 | Body temperature 10 hour | Measurement | LOINC | NO | YES | NO |
| 3006322 | Oral temperature | Measurement | LOINC | NO | YES | NO |
| 3006749 | Body temperature 24 hour | Measurement | LOINC | NO | YES | NO |
| 3007846 | Body temperature 12 hour | Measurement | LOINC | NO | YES | NO |
| 3008557 | Body temperature 10 hour maximum | Measurement | LOINC | NO | YES | NO |
| 3009553 | Body temperature at First encounter | Measurement | LOINC | NO | YES | NO |
| 3011783 | Body temperature 1 hour maximum | Measurement | LOINC | NO | YES | NO |
| 3015039 | Body temperature 8 hour maximum | Measurement | LOINC | NO | YES | NO |
| 3016117 | Body temperature 12 hour maximum | Measurement | LOINC | NO | YES | NO |
| 3016715 | Body temperature 24 hour maximum | Measurement | LOINC | NO | YES | NO |
| 3017614 | Body temperature 1 hour | Measurement | LOINC | NO | YES | NO |
| 3018145 | Body temperature 8 hour | Measurement | LOINC | NO | YES | NO |
| 3020891 | Body temperature | Measurement | LOINC | NO | YES | NO |
| 3022060 | Rectal temperature | Measurement | LOINC | NO | YES | NO |
| 3025085 | Axillary temperature | Measurement | LOINC | NO | YES | NO |
| 3025163 | Tympanic membrane temperature | Measurement | LOINC | NO | YES | NO |
| 3025704 | Body temperature - Urinary bladder | Measurement | LOINC | NO | YES | NO |
| 3025926 | Body temperature - Core | Measurement | LOINC | NO | YES | NO |
| 4038778 | O/E -skin temperature abnormal | Measurement | SNOMED | YES | YES | NO |

| | | | | | | |
|----------|--|-------------|--------|-----|-----|----|
| 4039791 | O/E - rectal temperature | Measurement | SNOMED | NO | YES | NO |
| 4039792 | O/E - core temperature | Measurement | SNOMED | YES | YES | NO |
| 4039793 | O/E - level of fever | Measurement | SNOMED | NO | YES | NO |
| 4039794 | O/E - temperature normal | Measurement | SNOMED | YES | YES | NO |
| 4039795 | O/E - temperature elevated | Measurement | SNOMED | YES | YES | NO |
| 4039796 | O/E - hyperpyrexia - greater than 40.5 degrees Celsius | Measurement | SNOMED | YES | YES | NO |
| 4040104 | O/E - groin temperature | Measurement | SNOMED | YES | YES | NO |
| 4040106 | O/E - temperature low | Measurement | SNOMED | YES | YES | NO |
| 4040476 | O/E - axillary temperature | Measurement | SNOMED | YES | YES | NO |
| 4077057 | O/E - oral temperature | Measurement | SNOMED | NO | YES | NO |
| 4151775 | O/E - tympanic temperature | Measurement | SNOMED | NO | YES | NO |
| 4164378 | O/E - hyperpyrexia | Measurement | SNOMED | YES | YES | NO |
| 4174894 | Core body temperature | Observation | SNOMED | NO | YES | NO |
| 4189949 | Groin temperature | Observation | SNOMED | YES | YES | NO |
| 4212763 | Forehead temperature | Observation | SNOMED | NO | YES | NO |
| 4265708 | Temperature of skin | Observation | SNOMED | NO | YES | NO |
| 4267945 | Temperature of vagina | Observation | SNOMED | YES | YES | NO |
| 4329518 | Body temperature taken with digital thermometer | Observation | SNOMED | NO | YES | NO |
| 21490588 | Esophageal temperature | Measurement | LOINC | NO | YES | NO |
| 21490590 | Nasopharyngeal temperature | Measurement | LOINC | NO | YES | NO |
| 21490688 | Body surface temperature | Measurement | LOINC | NO | YES | NO |
| 21490870 | Bladder temperature via Foley | Measurement | LOINC | NO | YES | NO |
| 21490906 | Nasal temperature | Measurement | LOINC | NO | YES | NO |
| 21490907 | Ear temperature | Measurement | LOINC | NO | YES | NO |
| 44809208 | Maximum body temperature | Observation | SNOMED | NO | YES | NO |
| 45769775 | Temperature of neonate at birth | Observation | SNOMED | YES | YES | NO |

8. [COVID19 v1] Fever (38.0°C or higher) pre-coordinated measurement and conditions

| Concept Id | Concept Name | Domain | Vocabulary | Exclude | Descendants | Mapped |
|------------|-----------------------------|-----------|------------|---------|-------------|--------|
| 437663 | Fever | Condition | SNOMED | NO | YES | NO |
| 438963 | Tick-borne relapsing fever | Condition | SNOMED | YES | YES | NO |
| 440285 | Malignant hyperthermia | Condition | SNOMED | YES | YES | NO |
| 443908 | Louse-borne relapsing fever | Condition | SNOMED | YES | YES | NO |

| | | | | | | |
|----------|--|-------------|------------------|-----|-----|----|
| 444413 | Febrile convulsion | Condition | SNOMED | NO | YES | NO |
| 3197956 | Postoperative fever | Condition | Nebraska Lexicon | YES | YES | NO |
| 4039793 | O/E - level of fever | Measurement | SNOMED | YES | YES | NO |
| 4086668 | Postoperative fever | Condition | SNOMED | YES | YES | NO |
| 4087017 | Tertian fever | Condition | SNOMED | YES | YES | NO |
| 4087628 | Malignant tertian fever | Condition | SNOMED | YES | YES | NO |
| 4087629 | Quartan fever | Condition | SNOMED | YES | YES | NO |
| 4093997 | Malarial fever | Condition | SNOMED | YES | YES | NO |
| 4094000 | Reversed diurnal fever | Condition | SNOMED | YES | YES | NO |
| 4094003 | Postpartum fever | Condition | SNOMED | YES | YES | NO |
| 4099900 | Relapsing fever of the Caucasus | Condition | SNOMED | YES | YES | NO |
| 4141062 | Fever greater than 100.4 Fahrenheit | Measurement | SNOMED | NO | YES | NO |
| 4143214 | Maternal pyrexia in labor | Condition | SNOMED | YES | YES | NO |
| 4150518 | Relapsing fever of Asia AND/OR Africa | Condition | SNOMED | YES | YES | NO |
| 4152360 | O/E - fever | Measurement | SNOMED | NO | YES | NO |
| 4170869 | Dehydration fever in newborn | Condition | SNOMED | YES | YES | NO |
| 4184347 | Relapsing fever of Central AND/OR South Africa | Condition | SNOMED | YES | YES | NO |
| 4199309 | Pel Ebstein fever | Condition | SNOMED | YES | YES | NO |
| 4200980 | Relapsing fever of Iberian Peninsula AND/OR Northwest Africa | Condition | SNOMED | YES | YES | NO |
| 4226022 | Drug-induced hyperpyrexia | Condition | SNOMED | YES | YES | NO |
| 4229442 | Relapsing fever of Iran AND/OR Central Asia | Condition | SNOMED | YES | YES | NO |
| 4239624 | Relapsing fever of Southern U.S., Mexico, Central AND/OR South America | Condition | SNOMED | YES | YES | NO |
| 4243806 | Transitory fever of newborn | Condition | SNOMED | YES | YES | NO |
| 4300533 | Relapsing fever of Western North America | Condition | SNOMED | YES | YES | NO |
| 4308214 | Relapsing fever of Western United States | Condition | SNOMED | YES | YES | NO |
| 4318555 | Fever of the newborn | Condition | SNOMED | YES | YES | NO |
| 4326408 | Relapsing fever of Central AND/OR South America | Condition | SNOMED | YES | YES | NO |
| 4346179 | Bancroftian filarial fever | Condition | SNOMED | YES | YES | NO |
| 4347651 | Malayan filarial fever | Condition | SNOMED | YES | YES | NO |
| 37016869 | Infection caused by Borrelia miyamotoi | Condition | SNOMED | YES | YES | NO |
| 37017455 | Pyrexia of unknown origin co-occurrent with human immunodeficiency virus infection | Condition | SNOMED | YES | YES | NO |
| 37205085 | Familial mesial temporal lobe epilepsy with febrile seizures | Condition | SNOMED | YES | YES | NO |
| 37397178 | PFAPA syndrome | Condition | SNOMED | YES | YES | NO |
| 40493465 | Paraneoplastic fever | Condition | SNOMED | YES | YES | NO |
| 43530637 | Postprocedural fever | Condition | SNOMED | YES | YES | NO |
| 43530646 | Post vaccination fever | Condition | SNOMED | YES | YES | NO |
| 44782483 | Post tetanus vaccination fever | Condition | SNOMED | YES | YES | NO |

| | | | | | | |
|----------|--|-----------|--------|-----|-----|----|
| 44784427 | Post diphtheria, tetanus and pertussis vaccination fever | Condition | SNOMED | YES | YES | NO |
| 44784428 | Post diphtheria vaccination fever | Condition | SNOMED | YES | YES | NO |
| 44784429 | Post pertussis vaccination fever | Condition | SNOMED | YES | YES | NO |

9. [Covid19 V1] Malaise or Fatigue or (Malaise and Fatigue)

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mappe d |
|------------|-------------------------------------|-----------|------------|-----------|-------------|---------|
| 439926 | Malaise and fatigue | Condition | SNOMED | NO | YES | NO |
| 1572255 | Malaise and fatigue | Condition | ICD10CM | NO | YES | NO |
| 1572256 | Other malaise and fatigue | Condition | ICD10CM | NO | YES | NO |
| 4090207 | Senile asthenia | Condition | SNOMED | YES | YES | NO |
| 4092860 | Rapid fatigue of gait | Condition | SNOMED | YES | YES | NO |
| 4158491 | C/O - debility - malaise | Condition | SNOMED | YES | YES | NO |
| 4219363 | Congenital debility of fetus | Condition | SNOMED | YES | YES | NO |
| 4221911 | Fatigue associated with AIDS | Condition | SNOMED | YES | YES | NO |
| 4223659 | Fatigue | Condition | SNOMED | NO | YES | NO |
| 4225027 | Malaise associated with AIDS | Condition | SNOMED | YES | YES | NO |
| 4272240 | Malaise | Condition | SNOMED | NO | YES | NO |
| 37205051 | Fatigue due to chemotherapy | Condition | SNOMED | YES | YES | NO |
| 37205052 | Fatigue due to radiation therapy | Condition | SNOMED | YES | YES | NO |
| 37396808 | Cancer-related fatigue | Condition | SNOMED | YES | YES | NO |
| 40484614 | Postexertional fatigue | Condition | SNOMED | YES | YES | NO |
| 44782753 | Weakness as a late effect of stroke | Condition | SNOMED | YES | YES | NO |
| 44823445 | Other malaise and fatigue | Condition | ICD9CM | NO | YES | NO |
| 44829293 | Malaise and fatigue | Condition | ICD9CM | NO | YES | NO |
| 45772721 | Fatigue due to treatment | Condition | SNOMED | YES | YES | NO |

10. [COVID19 v1] Myalgia

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mappe d |
|------------|--|-----------|------------|-----------|-------------|---------|
| 195464 | Epidemic pleurodynia | Condition | SNOMED | YES | YES | NO |
| 258828 | Eosinophilia myalgia syndrome | Condition | SNOMED | YES | YES | NO |
| 442315 | Fibrositis | Condition | SNOMED | YES | YES | NO |
| 442752 | Muscle pain | Condition | SNOMED | NO | YES | NO |
| 442774 | Intermittent claudication | Condition | SNOMED | YES | YES | NO |
| 4298555 | Epidemic cervical myalgia | Condition | SNOMED | YES | YES | NO |
| 4316217 | Primary fibromyalgia syndrome | Condition | SNOMED | YES | YES | NO |
| 4347181 | Fibrositis and nodular fasciitis | Condition | SNOMED | YES | YES | NO |
| 36713056 | Myalgia caused by statin | Condition | SNOMED | YES | YES | NO |
| 37118025 | Myofascial pain syndrome | Condition | SNOMED | YES | YES | NO |
| 37312366 | RSIS - Repetitive strain injury syndrome | Condition | SNOMED | YES | YES | NO |
| 46284893 | Secondary fibromyalgia | Condition | SNOMED | YES | YES | NO |

11. [COVID19 v1] Pneumonia

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mapped |
|------------|---|-----------|------------|-----------|-------------|--------|
| 252552 | Ornithosis with pneumonia | Condition | SNOMED | YES | YES | NO |
| 255848 | Pneumonia | Condition | SNOMED | NO | YES | NO |
| 4001167 | Acute ulcerative gastroenteritis complicating pneumonia | Condition | SNOMED | YES | YES | NO |
| 4049965 | Fungal pneumonia | Condition | SNOMED | YES | YES | NO |
| 4050869 | Atypical pneumonia | Condition | SNOMED | NO | YES | NO |
| 36712839 | Idiopathic pneumonia syndrome | Condition | SNOMED | YES | YES | NO |
| 45770911 | Acute pneumonia due to coccidioidomycosis | Condition | SNOMED | YES | YES | NO |

12. [OHDSI Cov19] Cough

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mapped |
|------------|----------------|-----------|------------|-----------|-------------|--------|
| 254761 | Cough | Condition | SNOMED | NO | YES | NO |
| 4089228 | Sputum finding | Condition | SNOMED | NO | YES | NO |

13. [OHDSI Covid19 v1] Inpatient Visit

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mapped |
|------------|------------------------------------|--------|------------|-----------|-------------|--------|
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

[COVID ID30 V1] Episodes of COVID-19, narrow

Initial Event Cohort

People having any of the following:

- a condition occurrence of COVID-19 (including asymptomatic)¹
- a condition occurrence of Any Condition
 - Condition Source Concept is COVID-19 source codes²
- a measurement of COVID-19 specific testing (pre-coordinated Measurements) - Positive⁴
- a measurement of COVID-19 specific testing (pre-coordinated Measurements excluded)³
 - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present
- an observation of COVID-19 specific testing (pre-coordinated Measurements excluded)³
 - value as concept is any of: Present, Detected, Detected, Positive, Positive, Present
- an observation of Any Observation

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.

1. COVID-19 (including asymptomatic)

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendant s | Mappe d |
|------------|---|-----------|------------|-----------|--------------|---------|
| 37311061 | Disease caused by severe acute respiratory syndrome coronavirus 2 | Condition | SNOMED | NO | YES | NO |

2. COVID-19 source codes

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendant s | Mappe d |
|------------|--|-------------|------------|-----------|--------------|---------|
| 586414 | Novel coronavirus infection | Condition | KCD7 | NO | NO | NO |
| 586415 | Provisional assignment of new diseases or emergency use | Condition | KCD7 | NO | NO | NO |
| 710155 | COVID-19 pneumonia (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710156 | COVID-19 pneumonia (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710157 | Suspected case of COVID-19 (machine translation) | Condition | ICD10CN | YES | NO | NO |
| 710158 | COVID-19 (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710159 | Confirmed COVID-19, excluding pneumonia (machine translation) | Observation | ICD10CN | NO | NO | NO |
| 710160 | Emergency use of U07.1 Disease caused by severe acute respiratory syndrome coronavirus 2 | Observation | ICD10CN | NO | NO | NO |
| 42501115 | Emergency use of U07.1 Disease caused by severe acute respiratory syndrome coronavirus 2 | Condition | KCD7 | NO | NO | NO |
| 45542411 | Contact with and (suspected) exposure to other viral communicable diseases | Observation | ICD10CM | YES | NO | NO |
| 45600471 | Other coronavirus as the cause of diseases classified elsewhere | Condition | ICD10CM | NO | NO | NO |
| 45756093 | Emergency use of U07.1 Disease caused by severe acute respiratory syndrome coronavirus 2 | Condition | ICD10 | NO | NO | NO |

3. COVID-19 specific testing (pre-coordinated Measurements excluded)

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendant s | Mappe d |
|------------|--|-------------|----------------|-----------|--------------|---------|
| 756055 | Measurement of severe acute respiratory syndrome coronavirus 2 | Measurement | OMOP Extension | NO | YES | NO |
| 37310281 | 2019 novel coronavirus not detected | Measurement | SNOMED | YES | YES | NO |
| 37310282 | 2019 novel coronavirus detected | Measurement | SNOMED | YES | YES | NO |

4. COVID-19 specific testing (pre-coordinated Measurements) - Positive

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendant s | Mappe d |
|------------|---------------------------------|-------------|------------|-----------|--------------|---------|
| 37310282 | 2019 novel coronavirus detected | Measurement | SNOMED | NO | YES | NO |

[COVID ID25 V1] Hospitalizations with pneumonia

Initial Event Cohort

People having any of the following:

- a visit occurrence of Inpatient or Inpatient/ER visit¹

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 occurrence of a condition occurrence of [COVID19 v1] Pneumonia² 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

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

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

End Date Strategy

Date Offset Exit Criteria

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

Cohort Collapse Strategy:

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

1. Inpatient or Inpatient/ER visit

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mapped |
|------------|------------------------------------|--------|------------|-----------|-------------|--------|
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. [COVID19 v1] Pneumonia

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mapped |
|------------|---|-----------|------------|-----------|-------------|--------|
| 252552 | Ornithosis with pneumonia | Condition | SNOMED | YES | YES | NO |
| 255848 | Pneumonia | Condition | SNOMED | NO | YES | NO |
| 4001167 | Acute ulcerative gastroenteritis complicating pneumonia | Condition | SNOMED | YES | YES | NO |
| 4049965 | Fungal pneumonia | Condition | SNOMED | YES | YES | NO |
| 4050869 | Atypical pneumonia | Condition | SNOMED | NO | YES | NO |
| 36712839 | Idiopathic pneumonia syndrome | Condition | SNOMED | YES | YES | NO |
| 45770911 | Acute pneumonia due to coccidioidomycosis | Condition | SNOMED | YES | YES | NO |

[COVID ID26 V1] Hospitalizations with pneumonia or ARDS or sepsis or AKI

Initial Event Cohort

People having any of the following:

a visit occurrence of Inpatient or Inpatient/ER visit¹

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 any of the following criteria:

- at least 1 occurrence of a condition occurrence of [COVID19 v1] Pneumonia⁴
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
- or at least 1 occurrence of a condition occurrence of [Covid19 V1] Acute respiratory distress syndrome (ARDS) or Acute Respiratory Failure³
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
- or at least 1 occurrence of a condition occurrence of [COVID19 V1] Acute Kidney Injury²
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
- or at least 1 occurrence of a condition occurrence of [covid19 v1] Sepsis⁵
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

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

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

End Date Strategy

Date Offset Exit Criteria

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

Cohort Collapse Strategy:

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

1. Inpatient or Inpatient/ER visit

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendant s | Mappe d |
|------------|------------------------------------|--------|------------|-----------|--------------|---------|
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. [COVID19 V1] Acute Kidney Injury

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendant s | Mappe d |
|------------|---|------------|------------|-----------|--------------|---------|
| 432961 | Acute renal papillary necrosis with renal failure | Conditio n | SNOMED | YES | YES | NO |
| 435308 | Acute glomerulonephritis | Conditio n | SNOMED | YES | YES | NO |
| 4032295 | Hyperacute rejection of renal transplant | Conditio n | SNOMED | YES | NO | NO |

| | | | | | | |
|----------|---|-----------|--------|-----|-----|----|
| 4032296 | Acute rejection of renal transplant - grade II | Condition | SNOMED | YES | NO | NO |
| 4032298 | Acute-on-chronic rejection of renal transplant | Condition | SNOMED | YES | NO | NO |
| 4126131 | Very mild acute rejection of renal transplant | Condition | SNOMED | YES | NO | NO |
| 4127550 | Acute rejection of renal transplant - grade I | Condition | SNOMED | YES | NO | NO |
| 4127551 | Acute rejection of renal transplant - grade III | Condition | SNOMED | YES | NO | NO |
| 4128371 | Acute rejection of renal transplant | Condition | SNOMED | YES | NO | NO |
| 4242411 | Acute nephropathy | Condition | SNOMED | NO | YES | NO |
| 4280571 | Acute pyelonephritis | Condition | SNOMED | YES | YES | NO |
| 36716182 | Acute kidney injury due to circulatory failure | Condition | SNOMED | NO | NO | NO |
| 36716183 | Acute kidney injury due to hypovolemia | Condition | SNOMED | NO | NO | NO |
| 36716312 | Acute kidney injury due to sepsis | Condition | SNOMED | NO | NO | NO |
| 44809061 | Acute kidney injury stage 1 | Condition | SNOMED | NO | NO | NO |
| 44809062 | Acute kidney injury stage 2 | Condition | SNOMED | NO | NO | NO |
| 44809063 | Acute kidney injury stage 3 | Condition | SNOMED | NO | NO | NO |

3. [Covid19 V1] Acute respiratory distress syndrome (ARDS) or Acute Respiratory Failure

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|--|-----------|------------|----------|-------------|--------|
| 258866 | Respiratory distress syndrome in the newborn | Condition | SNOMED | YES | YES | NO |
| 319049 | Acute respiratory failure | Condition | SNOMED | NO | YES | NO |
| 4191650 | Acute respiratory distress | Condition | SNOMED | YES | YES | NO |
| 4195694 | Acute respiratory distress syndrome | Condition | SNOMED | NO | YES | NO |

4. [COVID19 v1] Pneumonia

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|---|-----------|------------|----------|-------------|--------|
| 252552 | Ornithosis with pneumonia | Condition | SNOMED | YES | YES | NO |
| 255848 | Pneumonia | Condition | SNOMED | NO | YES | NO |
| 4001167 | Acute ulcerative gastroenteritis complicating pneumonia | Condition | SNOMED | YES | YES | NO |
| 4049965 | Fungal pneumonia | Condition | SNOMED | YES | YES | NO |
| 4050869 | Atypical pneumonia | Condition | SNOMED | NO | YES | NO |
| 36712839 | Idiopathic pneumonia syndrome | Condition | SNOMED | YES | YES | NO |

| | | | | | | |
|-----------------------------|---|-----------|--------|-----|-----|----|
| 45770911 | Acute pneumonia due to coccidioidomycosis | Condition | SNOMED | YES | YES | NO |
| Showing 1 to 7 of 7 entries | | | | | | |
| Previous1Next | | | | | | |

5. [covid19 v1] Sepsis

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|---|-----------|------------|----------|-------------|--------|
| 132797 | Sepsis | Condition | SNOMED | NO | YES | NO |
| 196236 | Septic shock | Condition | SNOMED | NO | YES | NO |
| 434821 | Systemic inflammatory response syndrome | Condition | SNOMED | NO | YES | NO |
| 4029281 | Sepsis syndrome | Condition | SNOMED | NO | YES | NO |
| 4031168 | Sepsis-associated organ dysfunction | Condition | SNOMED | NO | YES | NO |
| 4046106 | Sepsis-associated encephalopathy | Condition | SNOMED | NO | YES | NO |
| 4066124 | Puerperal septicemia - delivered with postnatal complication | Condition | SNOMED | NO | YES | NO |
| 4085627 | Miscarriage with septic shock | Condition | SNOMED | NO | YES | NO |
| 4119941 | Sepsis-associated lung injury | Condition | SNOMED | NO | YES | NO |
| 4204036 | Postprocedural intra-abdominal sepsis | Condition | SNOMED | NO | YES | NO |
| 4205449 | Menosepsis | Condition | SNOMED | NO | YES | NO |
| 36716312 | Acute kidney injury due to sepsis | Condition | SNOMED | NO | YES | NO |
| 36716754 | Transient neonatal neutropenia due to neonatal bacterial sepsis | Condition | SNOMED | NO | YES | NO |
| 37395517 | Acute kidney injury due to acute tubular necrosis due to sepsis | Condition | SNOMED | NO | YES | NO |
| 40487101 | Clinical sepsis | Condition | SNOMED | NO | YES | NO |

Under hypothesis 2, we consider a

- Composite intensive respiratory intervention, consisting of mechanical ventilation, tracheostomy, ECMO or death, and
- Composite major acute cardiovascular events, consisting of acute myocardial infarction, congestive heart failure, stroke and sudden cardiovascular death.

Definitions for the latter cardiovascular outcomes come from previous work (LEGEND-HTN). Below is the complete specification of composite intensive respiratory interventions.

[COVID ID27 V1] Hospitalizations with pneumonia or ARDS or sepsis or AKI requiring intensive services or resulting in death in 30d

Initial Event Cohort

People having any of the following:

- a visit occurrence of Inpatient or Inpatient/ER visit¹

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 any of the following criteria:

- at least 1 occurrence of a condition occurrence of [COVID19 v1] Pneumonia⁶
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
- or at least 1 occurrence of a condition occurrence of [Covid19 V1] Acute respiratory distress syndrome (ARDS) or Acute Respiratory Failure³
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
- or at least 1 occurrence of a condition occurrence of [COVID19 V1] Acute Kidney Injury²
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
- or at least 1 occurrence of a condition occurrence of [covid19 v1] Sepsis⁷
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

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

Inclusion Rules

Inclusion Criteria #1: has mechanical ventilation or tracheostomy or ECMO or has death in 30d

Having any of the following criteria:

- at least 1 occurrence of a procedure of [covid19 v1] Mechanical ventilation⁵
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
- or at least 1 occurrence of a condition occurrence of [covid19 v1] Mechanical ventilation⁵
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
- or at least 1 occurrence of an observation of [covid19 v1] Mechanical ventilation⁵
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
- or at least 1 occurrence of a procedure of [COVID19 v1] tracheostomy⁸
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
- or at least 1 occurrence of a procedure of [Covid19 v1] Extracorporeal membrane oxygenation (ECMO) procedure⁴
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
- or at least 1 occurrence of a death occurrence from Any Death
where event starts between 0 days Before and 30 days After index start date

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 1 days

Cohort Collapse Strategy:

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

1. Inpatient or Inpatient/ER visit

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mapped |
|------------|------------------------------------|--------|------------|-----------|-------------|--------|
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. [COVID19 V1] Acute Kidney Injury

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mapped |
|------------|---|-----------|------------|-----------|-------------|--------|
| 432961 | Acute renal papillary necrosis with renal failure | Condition | SNOMED | YES | YES | NO |
| 435308 | Acute glomerulonephritis | Condition | SNOMED | YES | YES | NO |
| 4032295 | Hyperacute rejection of renal transplant | Condition | SNOMED | YES | NO | NO |
| 4032296 | Acute rejection of renal transplant - grade II | Condition | SNOMED | YES | NO | NO |
| 4032298 | Acute-on-chronic rejection of renal transplant | Condition | SNOMED | YES | NO | NO |
| 4126131 | Very mild acute rejection of renal transplant | Condition | SNOMED | YES | NO | NO |
| 4127550 | Acute rejection of renal transplant - grade I | Condition | SNOMED | YES | NO | NO |
| 4127551 | Acute rejection of renal transplant - grade III | Condition | SNOMED | YES | NO | NO |
| 4128371 | Acute rejection of renal transplant | Condition | SNOMED | YES | NO | NO |
| 4242411 | Acute nephropathy | Condition | SNOMED | NO | YES | NO |
| 4280571 | Acute pyelonephritis | Condition | SNOMED | YES | YES | NO |
| 36716182 | Acute kidney injury due to circulatory failure | Condition | SNOMED | NO | NO | NO |
| 36716183 | Acute kidney injury due to hypovolemia | Condition | SNOMED | NO | NO | NO |
| 36716312 | Acute kidney injury due to sepsis | Condition | SNOMED | NO | NO | NO |
| 44809061 | Acute kidney injury stage 1 | Condition | SNOMED | NO | NO | NO |
| 44809062 | Acute kidney injury stage 2 | Condition | SNOMED | NO | NO | NO |
| 44809063 | Acute kidney injury stage 3 | Condition | SNOMED | NO | NO | NO |

3. [Covid19 V1] Acute respiratory distress syndrome (ARDS) or Acute Respiratory Failure

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mapped |
|------------|--|-----------|------------|-----------|-------------|--------|
| 258866 | Respiratory distress syndrome in the newborn | Condition | SNOMED | YES | YES | NO |
| 319049 | Acute respiratory failure | Condition | SNOMED | NO | YES | NO |

| | | | | | | |
|---------|-------------------------------------|-----------|--------|-----|-----|----|
| 4191650 | Acute respiratory distress | Condition | SNOMED | YES | YES | NO |
| 4195694 | Acute respiratory distress syndrome | Condition | SNOMED | NO | YES | NO |

4. [Covid19 v1] Extracorporeal membrane oxygenation (ECMO) procedure

| Concept Id | Concept Name | Domain | Vocabulary | Exclude | Descendants | Mapped |
|------------|--|-----------|------------|---------|-------------|--------|
| 1531630 | Extracorporeal Oxygenation, Membrane, Peripheral Venovenous | Procedure | ICD10PCS | NO | NO | NO |
| 1531631 | Extracorporeal Oxygenation, Membrane, Peripheral Venovenous | Procedure | ICD10PCS | NO | NO | NO |
| 1531632 | Extracorporeal Oxygenation, Membrane, Central | Procedure | ICD10PCS | NO | NO | NO |
| 2002247 | Extracorporeal membrane oxygenation [ECMO] | Procedure | ICD9Proc | NO | YES | NO |
| 2787820 | Extracorporeal Supersaturated Oxygenation, Intermittent | Procedure | ICD10PCS | NO | NO | NO |
| 2787821 | Extracorporeal Hyperbaric Oxygenation, Continuous | Procedure | ICD10PCS | NO | NO | NO |
| 4052536 | Extracorporeal membrane oxygenation | Procedure | SNOMED | NO | YES | NO |
| 4338595 | Cardiac support using extracorporeal membrane oxygenation circuitry | Procedure | SNOMED | NO | NO | NO |
| 44515635 | Extracorporeal membrane oxygenation | Procedure | OPCS4 | NO | YES | NO |
| 44811012 | Fluoroscopy guided percutaneous insertion of cannula for extracorporeal membrane oxygenation | Procedure | SNOMED | NO | NO | NO |
| 46257586 | Extracorporeal Membrane Oxygenation or Extracorporeal Life Support Services and Procedures | Procedure | CPT4 | NO | YES | NO |

5. [covid19 v1] Mechanical ventilation

| Concept Id | Concept Name | Domain | Vocabulary | Exclude | Descendants | Mapped |
|------------|---|-----------|------------|---------|-------------|--------|
| 765576 | Orotracheal intubation using bougie device | Procedure | SNOMED | NO | YES | NO |
| 2108641 | Glossectomy; complete or total, with or without tracheostomy, without radical neck dissection | Procedure | CPT4 | YES | YES | NO |
| 2108642 | Glossectomy; complete or total, with or without tracheostomy, with unilateral radical neck dissection | Procedure | CPT4 | YES | YES | NO |
| 2745440 | Insertion of Endotracheal Airway into Trachea, Percutaneous Approach | Procedure | ICD10PCS | NO | YES | NO |
| 2745444 | Insertion of Endotracheal Airway into Trachea, Via Natural or Artificial Opening | Procedure | ICD10PCS | NO | YES | NO |
| 2745447 | Insertion of Endotracheal Airway into Trachea, Via Natural or Artificial Opening Endoscopic | Procedure | ICD10PCS | NO | YES | NO |
| 4006318 | Respiratory assist, manual | Procedure | SNOMED | YES | YES | NO |
| 4013354 | Insertion of endotracheal tube | Procedure | SNOMED | NO | YES | NO |
| 4021786 | Fear of disconnection from ventilator | Condition | SNOMED | YES | YES | NO |
| 4031379 | Artificial ventilation finding | Condition | SNOMED | YES | YES | NO |
| 4072633 | Weaning from mechanically assisted ventilation | Procedure | SNOMED | NO | YES | NO |

| | | | | | | |
|----------|---|-------------|--------|-----|-----|----|
| 4074663 | Diaphragmatic augmentation | Procedure | SNOMED | YES | YES | NO |
| 4080957 | Endotracheal respiratory assistance | Procedure | SNOMED | NO | YES | NO |
| 4107247 | Inhalation anesthesia, machine system, semi-closed, no rebreathing of primary agent | Procedure | SNOMED | YES | YES | NO |
| 4168966 | Endotracheal tube present | Observation | SNOMED | NO | YES | NO |
| 4219858 | Problem with patient ventilator | Observation | SNOMED | NO | YES | NO |
| 4230167 | Artificial respiration | Procedure | SNOMED | NO | YES | NO |
| 4232550 | Home visit for mechanical ventilation care | Observation | SNOMED | NO | YES | NO |
| 4232891 | Mechanical ventilation response | Observation | SNOMED | YES | YES | NO |
| 4235361 | Hyperventilation therapy for traumatic brain injury | Procedure | SNOMED | NO | YES | NO |
| 4237618 | Ventilator care | Observation | SNOMED | NO | YES | NO |
| 4251737 | Ventilator care management | Procedure | SNOMED | NO | YES | NO |
| 4254108 | Resuscitation with artificial respiration | Procedure | SNOMED | YES | YES | NO |
| 4254905 | Ventilator care education | Procedure | SNOMED | YES | YES | NO |
| 4259233 | Ventilator care assessment | Procedure | SNOMED | YES | YES | NO |
| 4332501 | Management of noninvasive mechanical ventilation | Procedure | SNOMED | NO | YES | NO |
| 4348300 | Expired air ventilation | Procedure | SNOMED | YES | YES | NO |
| 4353715 | Ventilator finding | Observation | SNOMED | YES | YES | NO |
| 37116689 | Insertion of endotracheal ventilation catheter | Procedure | SNOMED | NO | YES | NO |
| 37206832 | Mechanical insufflation exsufflation | Procedure | SNOMED | NO | YES | NO |
| 40481547 | Dependence on ventilator | Condition | SNOMED | NO | YES | NO |
| 40487536 | Intubation of respiratory tract | Procedure | SNOMED | NO | YES | NO |
| 44509482 | Other specified ventilation support | Procedure | OPCS4 | NO | YES | NO |
| 44791135 | Ventilatory support | Procedure | SNOMED | NO | YES | NO |
| 44808555 | Provision of mechanical ventilator | Procedure | SNOMED | YES | YES | NO |

6. [COVID19 v1] Pneumonia

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mappe d |
|------------|---|-----------|------------|-----------|-------------|---------|
| 252552 | Ornithosis with pneumonia | Condition | SNOMED | YES | YES | NO |
| 255848 | Pneumonia | Condition | SNOMED | NO | YES | NO |
| 4001167 | Acute ulcerative gastroenteritis complicating pneumonia | Condition | SNOMED | YES | YES | NO |
| 4049965 | Fungal pneumonia | Condition | SNOMED | YES | YES | NO |
| 4050869 | Atypical pneumonia | Condition | SNOMED | NO | YES | NO |
| 36712839 | Idiopathic pneumonia syndrome | Condition | SNOMED | YES | YES | NO |

| | | | | | | |
|--------------|---|-----------|--------|-----|-----|----|
| 4577091 1 | Acute pneumonia due to coccidioidomycosis | Condition | SNOMED | YES | YES | NO |
|--------------|---|-----------|--------|-----|-----|----|

7. [covid19 v1] Sepsis

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mappe d |
|--------------|---|-----------|------------|-----------|-------------|---------|
| 132797 | Sepsis | Condition | SNOMED | NO | YES | NO |
| 196236 | Septic shock | Condition | SNOMED | NO | YES | NO |
| 434821 | Systemic inflammatory response syndrome | Condition | SNOMED | NO | YES | NO |
| 4029281 | Sepsis syndrome | Condition | SNOMED | NO | YES | NO |
| 4031168 | Sepsis-associated organ dysfunction | Condition | SNOMED | NO | YES | NO |
| 4046106 | Sepsis-associated encephalopathy | Condition | SNOMED | NO | YES | NO |
| 4066124 | Puerperal septicemia - delivered with postnatal complication | Condition | SNOMED | NO | YES | NO |
| 4085627 | Miscarriage with septic shock | Condition | SNOMED | NO | YES | NO |
| 4119941 | Sepsis-associated lung injury | Condition | SNOMED | NO | YES | NO |
| 4204036 | Postprocedural intra-abdominal sepsis | Condition | SNOMED | NO | YES | NO |
| 4205449 | Menosepsis | Condition | SNOMED | NO | YES | NO |
| 3671631 2 | Acute kidney injury due to sepsis | Condition | SNOMED | NO | YES | NO |
| 3671675 4 | Transient neonatal neutropenia due to neonatal bacterial sepsis | Condition | SNOMED | NO | YES | NO |
| 3739551 7 | Acute kidney injury due to acute tubular necrosis due to sepsis | Condition | SNOMED | NO | YES | NO |
| 4048710 1 | Clinical sepsis | Condition | SNOMED | NO | YES | NO |

8. [COVID19 v1] tracheostomy

| Concept Id | Concept Name | Domain | Vocabulary | Exclude d | Descendants | Mappe d |
|------------|---|-----------|------------|-----------|-------------|---------|
| 2110486 | Transoral approach to skull base, brain stem or upper spinal cord for biopsy, decompression or excision of lesion; requiring splitting of tongue and/or mandible (including tracheostomy) | Procedure | CPT4 | YES | YES | NO |
| 2743216 | Removal of Tracheostomy Device from Trachea, Via Natural or Artificial Opening | Procedure | ICD10PCS | NO | YES | NO |
| 2794811 | Medical and Surgical @ Respiratory System @ Change @ Trachea @ External @ Tracheostomy Device | Procedure | ICD10PCS | NO | YES | NO |
| 2829384 | Medical and Surgical @ Respiratory System @ Revision @ Trachea @ Percutaneous Endoscopic @ Tracheostomy Device | Procedure | ICD10PCS | NO | YES | NO |
| 2829386 | Medical and Surgical @ Respiratory System @ Revision @ Trachea @ Via Natural or Artificial Opening @ Tracheostomy Device | Procedure | ICD10PCS | NO | YES | NO |
| 2831237 | Medical and Surgical @ Respiratory System @ Bypass @ Trachea @ Open @ Tracheostomy Device | Procedure | ICD10PCS | NO | YES | NO |
| 2836115 | Medical and Surgical @ Respiratory System @ Bypass @ Trachea @ Percutaneous @ Tracheostomy Device | Procedure | ICD10PCS | NO | YES | NO |

| | | | | | | |
|---------|---|-----------|----------|----|-----|----|
| 2862930 | Medical and Surgical @ Respiratory System @ Revision @ Trachea @ Open @ Tracheostomy Device | Procedure | ICD10PCS | NO | YES | NO |
| 2870619 | Medical and Surgical @ Respiratory System @ Revision @ Trachea @ Percutaneous @ Tracheostomy Device | Procedure | ICD10PCS | NO | YES | NO |
| 4195473 | Temporary tracheostomy | Procedure | SNOMED | NO | YES | NO |
| 4208093 | Tracheostomy, emergency procedure by transtracheal approach | Procedure | SNOMED | NO | YES | NO |
| 4311023 | Revision of stoma of trachea | Procedure | SNOMED | NO | YES | NO |
| 4337047 | Insertion of tracheostomy tube | Procedure | SNOMED | NO | YES | NO |

[LEGEND-HTN] Total cardiovascular disease events

Initial Event Cohort

People having any of the following:

- a condition occurrence of [LEGEND HTN] Acute myocardial Infarction²
- a condition occurrence of [LEGEND HTN] Sudden cardiac death⁶
- a condition occurrence of [LEGEND HTN] Ischemic stroke⁵
- a condition occurrence of [LEGEND HTN] intracranial bleed Hemorrhagic stroke⁴
- a condition occurrence of [LEGEND HTN] Heart Failure³

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 all of the following criteria:

- at least 1 occurrence of a visit occurrence of Inpatient or ER visit¹
where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

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

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

End Date Strategy

Date Offset Exit Criteria

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

Cohort Collapse Strategy:

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

1. Inpatient or ER visit

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

2. [LEGEND HTN] 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 |

3. [LEGEND HTN] 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 |

4. [LEGEND HTN] intracranial bleed Hemorrhagic stroke

| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
|------------|-------------------------|-----------|------------|----------|-------------|--------|
| 376713 | Cerebral hemorrhage | Condition | SNOMED | NO | NO | NO |
| 432923 | Subarachnoid hemorrhage | Condition | SNOMED | NO | NO | NO |
| 439847 | Intracranial hemorrhage | Condition | SNOMED | NO | NO | NO |

5. [LEGEND HTN] Ischemic stroke

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

6. [LEGEND HTN] Sudden cardiac death

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

17. Appendix 3: ENCePP Checklist for Study Protocols

We have filled out the ENCePP Checklist for Study Protocols (Revision 4) which was adopted by the ENCePP Steering Group on October 15, 2019. A link to the completed form is provided below:

[Appendix 3. ENCePP Checklist for Study Protocol](#)

