RESEARCH PROTOCOL:

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

Version 1.0

Table of Contents

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** is a Wellcome Trust Clinical Research Development Fellow and has received funding support from 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

Number	Date	Section of study protocol	Amendment or update	Reason
None				

Key Dates and Milestones	Planned / Estimated Date
Registration in the EU PAS Register	
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 models[8], 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 are 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 between1st 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. ARB* vs dCCB
4. ARB* vs THZ
5. ACE* vs ARB
6. ACE or ARB* vs dCCB
7. ACE or ARB* vs THZ

Mono or combo-therapy comparisons

8. ACE +/- not-dCCB * vs dCCB +/- not-ACE
9. ACE +/- not-THZ * vs THZ +/- not-ACE
10. ARB +/- not-dCCB * vs dCCB +/- not-ARB
11. ARB +/- not-THZ * vs THZ +/- not-ARB
12. ACE +/- not-ARB * vs ARB +/- not-ACE
13. ACE or ARB +/- not-dCCB * vs dCCB +/- not-ACE nor-ARB
14. ACE or ARB +/- not-THZ * vs 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. ARB* vs dCCB
4. ARB* vs THZ
5. ACE* vs ARB
6. ACE or ARB* vs dCCB
7. ACE or ARB* vs THZ

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

8. ACE* vs dCCB
9. ACE* vs THZ
10. ARB* vs dCCB
11. ARB* vs THZ
12. ACE* vs ARB
13. ACE or ARB* vs dCCB
14. ACE or ARB* vs THZ

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

15. ACE +/- not-dCCB * vs dCCB +/- not-ACE
16. ACE +/- not-THZ * vs THZ +/- not-ACE
17. ARB +/- not-dCCB * vs dCCB +/- not-ARB
18. ARB +/- not-THZ * vs THZ +/- not-ARB
19. ACE +/- not-ARB * vs ARB +/- not-ACE
20. ACE or ARB +/- not-dCCB * vs dCCB +/- not-ACE nor-ARB
21. ACE or ARB +/- not-THZ * vs THZ +/- not-ACE nor-ARB

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

22. ACE +/- not-dCCB * vs dCCB +/- not-ACE
23. ACE +/- not-THZ * vs THZ +/- not-ACE
24. ARB +/- not-dCCB * vs dCCB +/- not-ARB
25. ARB +/- not-THZ * vs THZ +/- not-ARB
26. ACE +/- not-ARB * vs ARB +/- not-ACE
27. ACE or ARB +/- not-dCCB * vs dCCB +/- not-ACE nor-ARB
28. ACE or ARB +/- not-THZ * vs 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 following exposures of interest and control for observed confounding in these rate estimates by contrasting balanced populations of subjects. 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 the urgent public health need, 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 samples available in limited contexts and these samples 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 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 in adjustment models include only those that preceded initiation of the drug. 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. Similar arguments hold for evaluating the effect of antihypertensive use on outcomes of COVID-19 infection and severity of disease.

To help overcome data limitations and increase sample size, 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.

14. References

1. *Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)* Geneva, Switzerland: World Health Organization (WHO);2020.

2. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020.

3. Patel AB, Verma A. COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers: What Is the Evidence? *JAMA.* 2020.

4. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med.* 2020.

5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England).* 2020.

6. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol.* 2016;14(8):523-534.

7. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res.* 2020.

8. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med.* 2005;11(8):875-879.

9. Sommerstein R. Rapid Response - Re: Preventing a covid-19 pandemic: ACE inhibitors as a potential risk factor for fatal Covid-19. *BMJ.* 2020:E-published ahead of print.

10. Diaz JH. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. *J Travel Med.* 2020.

11. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. *New England Journal of Medicine.* 2020.

12. Precisazioni AIFA su Malattia da coronavirus Covid-19 ed utilizzo di ACE-Inibitori e Sartani [AIFA specifications on Covid-19 coronavirus disease and use of ACE-Inhibitors and ARBs]. 2020; https://www.aifa.gov.it/web/guest/-/precisazioni-aifa-su-malattia-da-coronavirus-covid-19-ed-utilizzo-di-ace-inibitori-e-sartani. Accessed March 24, 2020.

13. Aronson JK, Ferner RE. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers in COVID-19. *Oxford COVID-19 Evidence Service* 2020; https://www.cebm.net/angiotensin-converting-enzyme-ace-inhibitors-and-angiotensin-receptor-blockers-in-covid-19/. Accessed March 24, 2020, 2020.

14. Bozkurt B, Kovacs R, Harrington B. HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19. *ACC News Story* 2020; https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19. Accessed March 24, 2020.

15. de Simone G. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers. *Council on Hypertension* 2020; https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang. Accessed March 24, 2020.

16. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? *Journal of Hypertension.* 2020;Publish Ahead of Print.

17. Loroch V, Montijn R, Offringa A. Closing the door to corona: AT1R antagonists may be life-saving for acutely ill SARS-CoV-2-infected patients. 2020; https://www.closingthedoortocorona.org/. Accessed March 26, 2020.

18. Liu Y, Huang F, Xu J, et al. Anti-hypertensive Angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients. *medRxiv.* 2020.

19. Chen Y, Guo Y, Pan Y, Zhao ZJ. Structure analysis of the receptor binding of 2019-nCoV. *Biochem Biophys Res Commun.* 2020.

20. Hripcsak G, Duke JD, Shah NH, et al. Observational Health Data Sciences and Informatics (OHDSI): Opportunities for Observational Researchers. *Studies in health technology and informatics.* 2015;216:574-578.

21. Overhage JM, Ryan PB, Reich CG, Hartzema AG, Stang PE. Validation of a common data model for active safety surveillance research. *Journal of the American Medical Informatics Association : JAMIA.* 2012;19(1):54-60.

22. Suchard MA, Schuemie MJ, Krumholz HM, et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic,

multinational, large-scale analysis. *Lancet (London, England).* 2019;394(10211):1816-1826.

23. Voss EA, Boyce RD, Ryan PB, van der Lei J, Rijnbeek PR, Schuemie MJ. Accuracy of an automated knowledge base for identifying drug adverse reactions. *Journal of biomedical informatics.* 2017;66:72-81.

24. Suissa S, Moodie EE, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. *Pharmacoepidemiology and drug safety.* 2017;26(4):459-468.

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 a growing number of infections caused by coronavirus SARS-Cov2, COVID-19 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 limited available data appears to indicate some association between hypertension and COVID-2 infections and disease outcomes. These findings, in combination with cellular studies that indicate 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), including 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 comprised of 201 patients with confirmed COVID-19 pneumonia, who had risk factors for acute respiratory distress syndrome (ARDS), or who progressed from ARDS to death.[5,7-10] In total, 27.4% of ARDS patients had a history of hypertension compared to only 13.7% of non-ARDS patients. 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 confounding 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	23.70%	52 (40, 65)	Non-severe	13.40%	45 (34, 57)
			(2) ICU / ventilation / death	35.80%	63 (53, 71)	No ICU / ventilation / death	13.70%	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	27.40%	58.5 (50, 69)	No ARDS	13.70%	48 (40, 54)
			(2) With ARD who died	36.40%	68.5 (59.3, 75.0)	With ARDS did not die	17.50%	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 acute respiratory distress syndrome (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. 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.

However, 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 this data, a chief concern is that the current speculation may lead to improper or uninformed initiations or discontinuations of these medications. 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 RAAS 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 ACE-2 receptor enzyme on the cell surface while a second sub-unit binds to the cell membrane. It is believed that to enter the 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 entry into 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 structure 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.

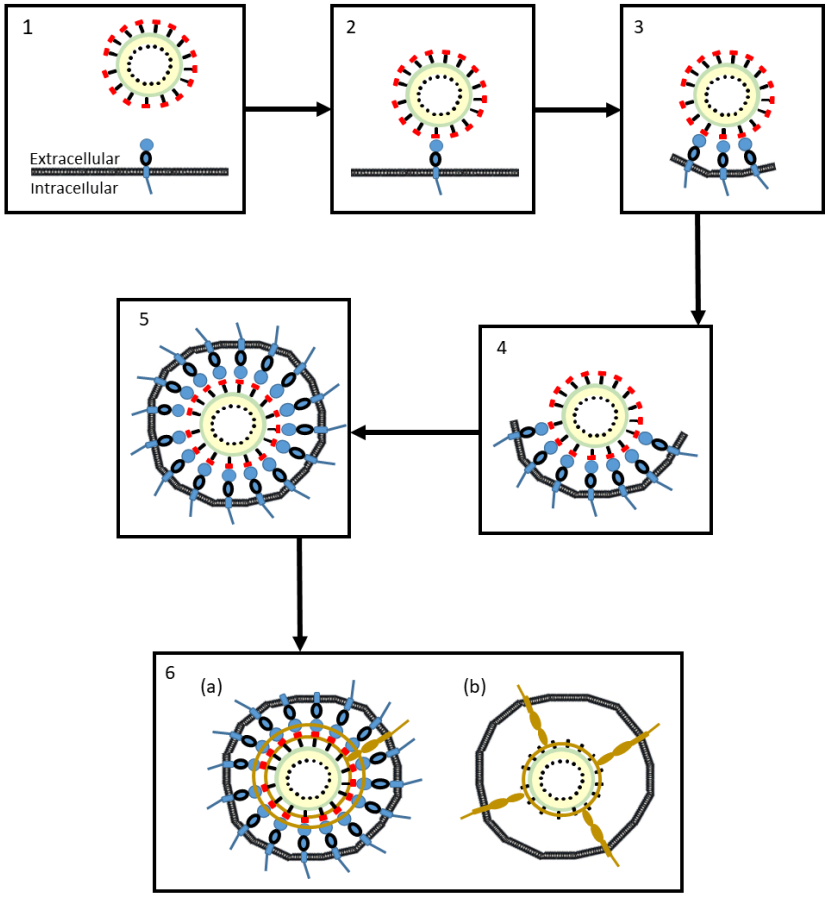

Figure S1. Hypothetical mechanism through which SARS-CoV-2 enters cells (blue= ACE-2 receptor, red: virus receptor binding sub-unit).[16]

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 of the other antihypertensive

treatments they tested (including other ARBs, ACE inhibitors, and calcium-channel blockers).[27] Experiments conducted on rats have demonstrated increases in ACE-2 expression after different ARB treatments.[28-30] These studies observed increased ACE-2 expression and activity in the kidneys after treatment with losartan[29] 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 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 describe mechanisms of protective effects of treatment with ACE inhibitors and ARBs, while others describe mechanisms of harmful effects. These mechanisms are only hypotheses and vary in the level of detail provided. However, we have described them below.

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] However, 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,

which patients infected 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 models[10], 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 was 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. 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 for patients 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 Kingdom[39]	United States[38]	South Korea[41]	Australia[42,43]	European Union[44]
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.

15.6 References

1. *Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)* Geneva, Switzerland: World Health Organization (WHO);2020.

2. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020.

3. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med.* 2020.

4. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England).* 2020.

5. Patel AB, Verma A. COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers: What Is the Evidence? *JAMA.* 2020.

6. Wu Q, Zhou L, Sun X, et al. Altered Lipid Metabolism in Recovered SARS Patients Twelve Years after Infection. *Sci Rep.* 2017;7(1):9110.

7. Sommerstein R. Rapid Response - Re: Preventing a covid-19 pandemic: ACE inhibitors as a potential risk factor for fatal Covid-19. *BMJ.* 2020:E-published ahead of print.

8. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res.* 2020.

9. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol.* 2016;14(8):523-534.

10. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med.* 2005;11(8):875-879.

11. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet (London, England).* 2020;395(10224):565-574.

12. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020.

13. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *J Virol.* 2020;94(7).

14. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 2020;579(7798):270-273.

15. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell.* 2020.

16. Aronson JK, Ferner RE. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers in COVID-19. *Oxford COVID-19 Evidence Service* 2020; https://www.cebm.net/angiotensin-converting-enzyme-ace-inhibitors-and-angiotensin-receptor-blockers-in-covid-19/. Accessed March 24, 2020, 2020.

17. Bozkurt B, Kovacs R, Harrington B. HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19. *ACC News Story* 2020; https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19. Accessed March 24, 2020.

18. Precisazioni AIFA su Malattia da coronavirus Covid-19 ed utilizzo di ACE-Inibitori e Sartani [AIFA specifications on Covid-19 coronavirus disease and use of ACE-Inhibitors and ARBs]. 2020; https://www.aifa.gov.it/web/guest/-/precisazioni-aifa-su-malattia-da-coronavirus-covid-19-ed-utilizzo-di-ace-inibitori-e-sartani. Accessed March 24, 2020.

19. de Simone G. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers. *Council on Hypertension* 2020; https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang. Accessed March 24, 2020.

20. Chen Y, Guo Y, Pan Y, Zhao ZJ. Structure analysis of the receptor binding of 2019-nCoV. *Biochem Biophys Res Commun.* 2020.

21. Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. *Int J Infect Dis.* 2016;49:129-133.

22. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. *New England Journal of Medicine.* 2020.

23. Ge XY, Li JL, Yang XL, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature.* 2013;503(7477):535-538.

24. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature.* 2003;426(6965):450-454.

25. Turner AJ, Hiscox JA, Hooper NM. ACE2: from vasopeptidase to SARS virus receptor. *Trends Pharmacol Sci.* 2004;25(6):291-294.

26. Brielle ES, Schneidman-Duhovny D, Linial M. The SARS-CoV-2 exerts a distinctive strategy for interacting with the ACE2 human receptor. *bioRxiv.* 2020.

27. Furuhashi M, Moniwa N, Mita T, et al. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. *American journal of hypertension.* 2015;28(1):15-21.

28. Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB, Ferrario CM. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. *Hypertension (Dallas, Tex : 1979).* 2004;43(5):970-976.

29. Klimas J, Olvedy M, Ochodnicka-Mackovicova K, et al. Perinatally administered losartan augments renal ACE2 expression but not cardiac or renal Mas receptor in spontaneously hypertensive rats. *J Cell Mol Med.* 2015;19(8):1965-1974.

30. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation.* 2005;111(20):2605-2610.

31. Diaz JH. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. *J Travel Med.* 2020.

32. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? *Journal of Hypertension.* 2020;Publish Ahead of Print.

33. Loroch V, Montijn R, Offringa A. Closing the door to corona: AT1R antagonists may be life-saving for acutely ill SARS-CoV-2-infected patients. 2020; https://www.closingthedoortocorona.org/. Accessed March 26, 2020.

34. Kim HC, Cho MC. Korea hypertension fact sheet 2018. *Clinical hypertension.* 2018;24:13.

35. Fryar CD, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Hypertension Prevalence and Control Among Adults: United States, 2015-2016. *NCHS data brief.* 2017(289):1-8.

36. Shah SJ, Stafford RS. Current Trends of Hypertension Treatment in the United States. *American journal of hypertension.* 2017;30(10):1008-1014.

37. Mores A, Matziari M, Beau F, Cuniasse P, Yiotakis A, Dive V. Development of potent and selective phosphinic peptide inhibitors of angiotensin-converting enzyme 2. *Journal of medicinal chemistry.* 2008;51(7):2216-2226.

38. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension (Dallas, Tex : 1979).* 2018;71(6):1269-1324.

39. Hypertension in adults: diagnosis and management (NICE guideline NG136). 2019; https://www.nice.org.uk/guidance/NG136/resources. Accessed March 28, 2020.

40. Wright JM, Musini VM, Gill R. First-line drugs for hypertension. *Cochrane Database of Systematic Reviews.* 2018(4).

41. Lee HY, Shin J, Kim GH, et al. 2018 Korean Society of Hypertension Guidelines for the management of hypertension: part II-diagnosis and treatment of hypertension. *Clinical hypertension.* 2019;25:20.

42. Harrap SB, Lung T, Chalmers J. New Blood Pressure Guidelines Pose Difficult Choices for Australian Physicians. *Circulation research.* 2019;124(7):975-977.

43. Gabb GM, Mangoni AA, Anderson CS, et al. Guideline for the diagnosis and management of hypertension in adults - 2016. *The Medical journal of Australia.* 2016;205(2):85-89.

44. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *European heart journal.* 2018;39(33):3021-3104.

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 inhibitors[1]
    - 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 >= 18 years old
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 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]Hypertension[8]
  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)[6]
  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-blockers[3]
  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 diuretics[7]

where event starts between 180 days Before and 0 days Before index start date
- and exactly 0 occurrence of a drug exposure of [LEGEND] Diuretics[5]
  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 inhibitors[1]
- 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
1342439	trandolapril	Drug	RxNorm	NO	YES	NO
1363749	Fosinopril	Drug	RxNorm	NO	YES	NO
1373225	Perindopril	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
1307046	Metoprolol	Drug	RxNorm	NO	YES	NO

1313200	Nadolol	Drug	RxNorm	NO	YES	NO
1314002	Atenolol	Drug	RxNorm	NO	YES	NO
1314577	nebivolol	Drug	RxNorm	NO	YES	NO
1319998	Acebutolol	Drug	RxNorm	NO	YES	NO
1322081	Betaxolol	Drug	RxNorm	NO	YES	NO
1327978	Penbutolol	Drug	RxNorm	NO	YES	NO
1338005	Bisoprolol	Drug	RxNorm	NO	YES	NO
1345858	Pindolol	Drug	RxNorm	NO	YES	NO
1346823	carvedilol	Drug	RxNorm	NO	YES	NO
1353766	Propranolol	Drug	RxNorm	NO	YES	NO
1386957	Labetalol	Drug	RxNorm	NO	YES	NO

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
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

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	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

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

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

1395058	Chlorthalidone	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 inhibitors[1]
    - 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 >= 18 years old
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 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]Hypertension[2]
  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 inhibitors[1]

- 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
1342439	trandolapril	Drug	RxNorm	NO	YES	NO
1363749	Fosinopril	Drug	RxNorm	NO	YES	NO
1373225	Perindopril	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 codes[2]
- a measurement of COVID-19 specific testing (pre-coordinated Measurements) - Positive[4]
- 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 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 inhibitors[5]
  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 inhibitors[5]
  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] Hypertension[10]
  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-blockers[7]
  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 diuretics[12]
  where event starts between 180 days Before and 1 days Before index start date
- and exactly 0 occurrence of a drug exposure of [LEGEND] Diuretics[9]
  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
1342439	trandolapril	Drug	RxNorm	NO	YES	NO
1363749	Fosinopril	Drug	RxNorm	NO	YES	NO
1373225	Perindopril	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
1307046	Metoprolol	Drug	RxNorm	NO	YES	NO
1313200	Nadolol	Drug	RxNorm	NO	YES	NO
1314002	Atenolol	Drug	RxNorm	NO	YES	NO
1314577	nebivolol	Drug	RxNorm	NO	YES	NO
1319998	Acebutolol	Drug	RxNorm	NO	YES	NO
1322081	Betaxolol	Drug	RxNorm	NO	YES	NO
1327978	Penbutolol	Drug	RxNorm	NO	YES	NO
1338005	Bisoprolol	Drug	RxNorm	NO	YES	NO
1345858	Pindolol	Drug	RxNorm	NO	YES	NO
1346823	carvedilol	Drug	RxNorm	NO	YES	NO
1353766	Propranolol	Drug	RxNorm	NO	YES	NO
1386957	Labetalol	Drug	RxNorm	NO	YES	NO

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
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

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
1328165	Diltiazem	Drug	RxNorm	NO	YES	NO
1307863	Verapamil	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
1395058	Chlorthalidone	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 Visit[13]
    - 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 codes[2]

  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) - Positive[4]
  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 Visit[13]
  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 codes[2]

    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) - Positive[4]
  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 inhibitors[5]
  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 inhibitors[5]
  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] Hypertension[10]
  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-blockers[7]
  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 diuretics[12]
  where event starts between 180 days Before and 1 days Before index start date
- and exactly 0 occurrences of a drug exposure of [LEGEND] Diuretics[9]
  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
1342439	trandolapril	Drug	RxNorm	NO	YES	NO
1363749	Fosinopril	Drug	RxNorm	NO	YES	NO
1373225	Perindopril	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
1307046	Metoprolol	Drug	RxNorm	NO	YES	NO
1313200	Nadolol	Drug	RxNorm	NO	YES	NO
1314002	Atenolol	Drug	RxNorm	NO	YES	NO
1314577	nebivolol	Drug	RxNorm	NO	YES	NO
1319998	Acebutolol	Drug	RxNorm	NO	YES	NO
1322081	Betaxolol	Drug	RxNorm	NO	YES	NO
1327978	Penbutolol	Drug	RxNorm	NO	YES	NO
1338005	Bisoprolol	Drug	RxNorm	NO	YES	NO
1345858	Pindolol	Drug	RxNorm	NO	YES	NO
1346823	carvedilol	Drug	RxNorm	NO	YES	NO
1353766	Propranolol	Drug	RxNorm	NO	YES	NO
1386957	Labetalol	Drug	RxNorm	NO	YES	NO

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
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

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
1328165	Diltiazem	Drug	RxNorm	NO	YES	NO
1307863	Verapamil	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
1395058	Chlorthalidone	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 Visit[13]
    - 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 codes[2]

  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) - Positive[4]
  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 terminology[5]
  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 terminology[5]

  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 conditions[8]
      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 conditions[8]
      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 observation[7]
      - 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 observation[7]
      - 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 observation[7]
      - 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 observation[7]
      - 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] Cough[12]

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] Myalgia[10]
  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] Pneumonia[11]
  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 Visit[13]
  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 codes[2]

    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) - Positive[4]
    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 terminology[5]
  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 terminology[5]

  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 conditions[8]
          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 conditions[8]
          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 observation[7]
            - 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 observation[7]

        - 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 observation[7]
        - 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 observation[7]
        - 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] Cough[12]
      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] Myalgia[10]
      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] Pneumonia[11]

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

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

12. [OHDSI Cov19] Cough

Concept Id	Concept Name	Domain	Vocabulary	Excluded	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	Excluded	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 codes[2]
- a measurement of COVID-19 specific testing (pre-coordinated Measurements) - Positive[4]
- 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	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

[COVID ID25 V1] Hospitalizations with pneumonia

Initial Event Cohort

People having any of the following:

- a visit occurrence of Inpatient or Inpatient/ER visit[1]

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] Pneumonia[2]
  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	Excluded	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	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

[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 visit[1]
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] Pneumonia[4]
  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 Failure[3]
  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 Injury[2]

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] Sepsis[5]
  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	Excluded	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	Excluded	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	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 visit[1]

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] Pneumonia[6]
  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 Failure[3]

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 Injury[2] 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] Sepsis[7] 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 ventilation[5] 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 ventilation[5] 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 ventilation[5] 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] tracheostomy[8] 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) procedure[4] 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	Excluded	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	Excluded	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	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] Extracorporeal membrane oxygenation (ECMO) procedure

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
1531630	Extracorporeal Oxygenation, Membrane, Peripheral Veno-venous	Procedure	ICD10PCS	NO	NO	NO
1531631	Extracorporeal Oxygenation, Membrane, Peripheral Veno-arterial	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	Excluded	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	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

7. [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

8. [COVID19 v1] tracheostomy

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
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 Infarction[2]
- a condition occurrence of [LEGEND HTN] Sudden cardiac death[6]
- a condition occurrence of [LEGEND HTN] Ischemic stroke[5]
- a condition occurrence of [LEGEND HTN] intracranial bleed Hemorrhagic stroke[4]
- a condition occurrence of [LEGEND HTN] Heart Failure [3]

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 visit[1]
  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