Study Synopsis: Natural History of Coagulopathy in COVID-19

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The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I.

COVID-19 Coagulopathy Project Study Synopsis

Table of Contents

History of Modifications

Version	Date	Modification	Author
1.0	10/22/20	Original FDA Cleared Version	Sentinel Operations Center
2.0	06/04/21	Modification to indicate that attached outcome code lists are draft.	Sentinel Operations Center

1 Specific Aims

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen that causes coronavirus disease 2019 (COVID-19), has become a global pandemic.[1, 2] Case series of hospitalized patients have indicated that up to half may develop arterial or venous thrombotic complications.[3-11] However, these series included small samples, evaluated mainly hospitalized patients, and did not examine the factors associated with these events. As a result, there are major knowledge gaps on the incidence, determinants, and consequences of arterial and venous thrombotic complications with COVID-19. Studies that evaluate the epidemiology of these events using real-world data are needed to provide accurate evidence on their frequency and mechanisms, which can inform the development of interventions to reduce the risk of these adverse outcomes.

To address key knowledge gaps on the epidemiology of arterial and venous thrombotic events with COVID-19, this project first seeks to identify health plan members diagnosed with COVID-19 within the Sentinel System.[12] We will then ascertain the development of arterial and venous thrombotic events separately, given their potentially different pathogenic mechanisms. In Aim 1, we will determine the incidence of arterial and venous thrombotic complications (evaluated separately) and their consequences (i.e., death within 90 days of the event) in the COVID-19 cohort. We will examine the risk of events stratified by demographic characteristics, severity of infection, setting of diagnosis (ambulatory and hospital; nursing home, if data available), and use of anticoagulant or anti-platelet drugs prior to COVID-19 diagnosis. Understanding the frequency and consequences of thrombotic events with COVID-19 will help to inform strategies for thromboprophylaxis in these patients.

Since the risk factors for arterial and venous thrombotic complications in COVID-19 patients are unknown, Aim 2 will evaluate the determinants of these events (separately) in the COVID-19 cohort from Aim 1. We hypothesize that patient characteristics that promote stasis of circulation (i.e., obesity, heart failure, polycythemia, older age, alcohol abuse, and atrial fibrillation), vascular endothelial injury (i.e., diabetes, hypertension, vascular disease, and current tobacco use), and hypercoagulability (i.e., cancer, pregnancy, select medications/transfusions, inherited thrombophilia, antiphospholipid antibody syndrome, and history of myocardial infarction [MI], stroke, or venous thromboembolism) will be risk factors for thromboembolism in COVID-19. Elucidation of the determinants of arterial and venous thrombotic events in COVID-19 will help identify the subgroups at highest risk for these events and can inform development of interventions (e.g., thromboprophylaxis) to reduce their risk after COVID-19 diagnosis.[13]

Finally, a major question in the field is whether the thrombotic events observed with COVID-19 are unique to this respiratory viral infection. Few studies evaluating these complications with COVID-19 have included a comparator group to determine whether rates of events are higher with COVID-19 than with other respiratory viruses.[8, 14, 15] To address this important knowledge gap, in Aim 3 we will determine the relative risk of thrombotic complications among persons with COVID-19 compared to those with influenza virus infection. This comparative analysis will provide important biological insights into whether rates of thrombotic complications are higher with COVID-19 compared to infection with another major respiratory virus. If thrombotic event rates are indeed higher in COVID-19, clinicians might consider thromboprophylaxis in high-risk ambulatory patients and increased thromboprophylaxis intensity in hospitalized patients. Our Specific Aims and hypotheses are:

Aim 1: Determine the 90-day incidence of arterial and venous thrombotic complications (evaluated separately) with COVID-19 and subsequent risk of death within 90 days of the event.

Hypothesis: Events will occur within 90 days and may result in death.

Aim 2: Evaluate patient characteristics present prior to COVID-19 diagnosis as risk factors for arterial and venous thrombotic events (evaluated separately).

Hypothesis: Characteristics that promote stasis of circulation (i.e., obesity, heart failure, polycythemia, older age, alcohol abuse, and atrial fibrillation), endothelial injury (i.e., diabetes, hypertension, vascular disease, and tobacco use), and hypercoagulability (i.e., cancer, pregnancy, select medications/transfusions, MI/stroke/venous thromboembolism history, inherited thrombophilia, and antiphospholipid antibody syndrome) will be risk factors for thromboembolism.

Aim 3: Compare the 90-day risk of arterial and venous thrombotic events (evaluated separately) between health plan members diagnosed with COVID-19 and those diagnosed with influenza.

Hypothesis: Risk of arterial and venous thrombotic events will be higher with COVID-19 than influenza.

The completion of these aims will address important gaps on the epidemiology of thrombotic complications in COVID-19. Our aims will inform the need for routine monitoring of COVID-19 patients for thrombotic complications and identify the subgroups at high risk for these events after diagnosis; interventions could then be developed and tested in such groups to reduce this risk. These analyses will inform future comparative effectiveness and safety studies of drugs to reduce the risk of thrombotic events in COVID-19.

2 Research Strategy

2.1 Significance

SARS-CoV-2 infection causes COVID-19 and is an evolving pandemic. In December 2019, cases of pneumonia of unknown etiology emerged in Wuhan, China and spread rapidly to other regions of the country.[1, 2] Deep sequencing analysis from lower respiratory tract specimens identified the pathogen as a novel coronavirus called SARS-CoV-2.[16] The World Health Organization designated the disease caused by the infection as COVID-19 and declared the outbreak a global pandemic on March 11, 2020. As of October 15, 2020, >38 million cases of COVID-19 have been reported in 213 countries, including the US, resulting in >1 million deaths worldwide.[17]

Coagulopathy and thrombotic events are increasingly reported with COVID-19. Although the majority of patients with COVID-19 present with fever, myalgias, dry cough, and fatigue, and recover with no sequelae,[2, 18-27] case series have highlighted abnormalities in coagulation in these patients.[28] Importantly, the spike protein of SARS-CoV-2 can bind to angiotensin converting enzyme 2 receptors on the cells of the vascular endothelium, as well as epithelial cells in the lungs, heart, gastrointestinal tract, and liver/biliary tree.[29, 30] Infection of vascular endothelial cells can induce cytopathic injury and dysfunction, which can precipitate vasoconstriction, inflammation, and platelet aggregation. Abnormal coagulation parameters in COVID-19 may include prolonged prothrombin time, thrombocytopenia, elevated D-dimer levels (a degradation product of cross-linked fibrin), and decreased fibrinogen levels.

Case series (**Table 1**) have indicated that up to 50% of hospitalized patients may develop arterial thrombosis (e.g., MI or stroke) or venous thromboembolism (e.g., acute deep venous thrombosis [DVT] or pulmonary embolism [PE]), which could lead to death.[3-11] However, existing studies have important limitations. They included small sample sizes (resulting in a lack of precision in the incidence of this event with COVID-19), evaluated hospital-based cohorts (it is unknown whether thrombotic events may also occur in less sick patients), and rarely included

a comparator group (limiting ability to determine if the risk of thromboembolism is higher with COVID-19 versus other groups). Consequently, there are major knowledge gaps on the incidence, determinants, and consequences of arterial and venous thrombotic events with COVID-19. Studies that evaluate the epidemiology of these complications using real-world data are needed to provide evidence on their frequency and mechanisms, which will inform the development of interventions to reduce the risk of these outcomes.

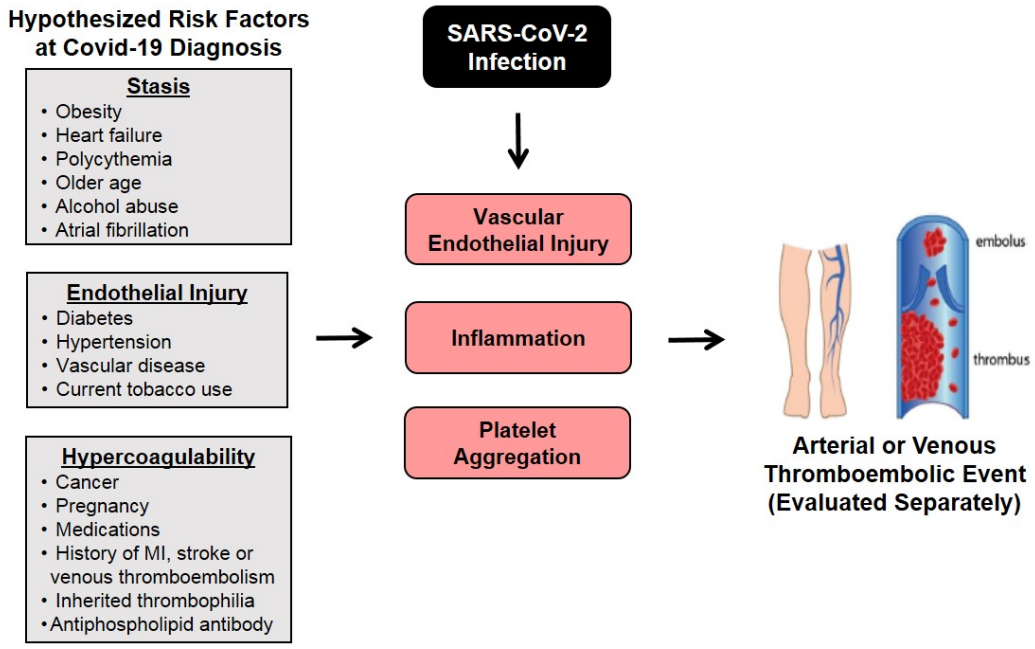
Table 1. Published case series reporting incidence of thrombotic events with COVID-19.

Reference	Setting	No. COVID-19 Patients	% Administered DVT Prophylaxis at Admission	Outcome Evaluated	Incidence of Events
Klok	Netherlands	184 in ICU	100%	Arterial/ venous clot	31 (16.8%)
Lodigiani	Italy	48 in ICU	100%	VTE events	8 (16.7%)
Ziehr	US	66 in ICU (all on ventilator)	Not Reported	VTE events	11 (16.7%)
Llitjos	France	26 in ICU	100%	DVT	13 (50.0%)
Cui	China	81 in ICU	0%	VTE events	20 (24.7%)
Poissy	France	107 in ICU	Not Reported	PE	22 (20.6%)
Goyal	US	393 hospitalized	Not Reported	VTE events	13 (3.3%)
Cattaneo	Italy	388 hospitalized	100% (enoxaparin 40 mg QD)	DVT	0 (0.0%)
Al-Samkari	US	400 hospitalized	97.3%	VTE Arterial thrombosis	19 (4.8%) 11 (2.8%)

Abbreviations: DVT=deep venous thrombosis; ICU=intensive care unit; PE=pulmonary embolism; VTE=venous thromboembolic events

Host risk factors for thrombotic events in COVID-19 have been incompletely examined and remain unknown. Certain host factors (**Figure 1**) might heighten the risk of arterial or venous thrombotic events by promoting Virchow's triad of stasis of circulation (i.e., obesity, heart failure, polycythemia, older age, alcohol abuse, and atrial fibrillation), vascular endothelial injury (i.e., diabetes mellitus, hypertension, vascular disease, and current tobacco use), and hypercoagulability (i.e., cancer, pregnancy, select drugs/transfusions, MI/stroke/DVT/PE history, inherited thrombophilia, and antiphospholipid antibody syndrome).[31-33] However, existing studies have not evaluated factors associated with the development of arterial or venous thrombotic events. Consequently, the risk factors for these complications in COVID-19 remain unclear. Understanding the determinants of these events in COVID-19 are crucial to reducing their risk, which could ultimately help to reduce morbidity and mortality.

Figure 1. Hypothesized risk factors for arterial or venous thrombotic events among COVID-19 patients.



Existing studies evaluating rates of thrombotic complications with COVID-19 have lacked comparator groups. Without controlled studies comparing rates of arterial/venous thrombotic events between patients with COVID-19 and those with other respiratory viral infections, the field cannot determine if rates of such complications are higher with COVID-19. This information is critically important to determine whether patients with COVID-19 should be monitored more closely for coagulopathy and thrombotic events compared to those with other respiratory viral infections. Influenza virus infection is an appropriate comparator to COVID-19 for evaluation of arterial and venous thrombotic events because it is a common respiratory virus that may precipitate hospitalization when severe and has been associated with increased risk of both acute MI[34] and ischemic stroke.[35] One recent cohort study from two New York City academic hospitals observed a higher rate of ischemic stroke among adults who presented to the hospital with COVID-19 than with influenza (odds ratio, 7.6; 95% confidence interval [CI], 2.3-25.2).[15] However, this study only evaluated ischemic stroke as an outcome, accounted for few potential confounders (i.e., age, sex, race), and had limited generalizability. Consequently, the relative risk of arterial and venous thrombotic complications among patients with COVID-19 compared to those with influenza virus infection remains unknown. If thrombotic event rates are indeed higher in COVID-19 patients, then clinicians will need to monitor these patients more closely for the development of such complications and potentially consider thromboprophylaxis (e.g., aspirin) in high-risk ambulatory patients and increased intensity of thromboprophylaxis in hospitalized patients.

Data from the Sentinel System can address important questions on COVID-19 epidemiology. Data Partners within the Sentinel System, particularly the integrated health systems that record data from both electronic health records and claims, offer a unique opportunity to study the natural history of COVID-19.[12] The laboratory data collected by these systems can identify health plan members who tested positive for COVID-19, minimizing the likelihood of misclassification, and permit evaluation of coagulation-related laboratory results. Data from integrated health systems allow inclusion of those with mild COVID-19, who do not

require hospitalization, as well as hospitalized members. Longitudinal records from all care settings (e.g., outpatient, hospital) allow determination of relevant comorbidities and medications dispensed to COVID-19 members prior to and after diagnosis. Importantly, Sentinel has conducted validations of many of these variables, reducing the potential for misclassification bias. Finally, Sentinel includes a diverse population of members from different regions in the US. Thus, Sentinel represents an ideal setting in which to evaluate the epidemiology of COVID-19 complications such as arterial and venous thrombotic events.

Summary of significance: The study results would have important significance for COVID-19 patients:

Biological significance:

- Gain insights into the factors associated with the development of thrombotic events in COVID-19.
- Determine if the risk of thrombotic events is higher with COVID-19 than with influenza virus infection.

Clinical significance:

- Determination of the risk factors for arterial and venous thrombotic complications in COVID-19 could suggest interventions to reduce the risk of these events after diagnosis.
- Identifying the factors associated with thrombotic events in COVID-19 will help identify the subgroups at highest risk, who should be closely monitored for these complications after diagnosis.

Public health significance:

- Modifying the risk factors for thrombotic complications in COVID-19 could help to prevent their development and prolong survival.

3 Approach

Our scientific approach was informed by medical literature review, discussions among Workgroup members, and input from stakeholders on the Reagan-Udall Foundation for the FDA Parallel Analysis Workgroup (see **Appendix 1**).

3.1 Proposed Sentinel System Data Sources

To answer Aims 1-3, at present, our priority data sources include Sentinel's integrated health systems, which record data from both electronic health records and claims. The data from these systems collect information on demographics, outpatient and hospital encounters, diagnoses, laboratory results, pharmacy dispensing records, and death date. Sentinel Data Partners that are integrated health systems represent ideal data sources in which to answer our aims because they can: 1) provide potentially large samples of health plan members with COVID-19 from different regions of the US; 2) record laboratory results, permitting identification of laboratory-confirmed COVID-19 and coagulation laboratory results; 3) collect data on dispensed medications, allowing determination of drugs dispensed prior to and after COVID-19 diagnosis that might affect the risk of arterial thrombosis and venous thromboembolism; and 4) record outpatient and hospital diagnoses of arterial and venous thrombotic events, allowing ascertainment of the COVID-19-related complications of interest. We will work with Sentinel's Data Partners to determine which are interested in collaborating on this project and which could enable short lag times in data ascertainment. Despite our focus on integrated health system data, we will explore the feasibility and added value of including data from electronic health record-only and claims-only Data Partners as well.

3.2 Study Design

All three aims will be addressed using a retrospective cohort design. A cohort design is ideal because it allows direct calculation of the incidence rates of arterial and venous thrombotic events in subgroups of health plan members and is effective at elucidating the temporal relationship between exposures and outcomes. A case-control study design, in which subjects are selected based on the presence or absence of a disease, would not allow us to directly measure and compare the incidences of thrombotic complications, since we would set the overall frequency of these events with this study design. While a nested case-control study could be conducted, data have already been collected on all health plan members, so there would be no gains in efficiency with this design.

3.3 Study Patients

3.3.1 Aims 1 and 2

For Aims 1 and 2, health plan members with COVID-19 will be included if they had: 1) a COVID-19 International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) outpatient or hospital discharge diagnosis (in any position) OR a positive SARS-CoV-2 nucleic acid test recorded between April 1, 2020 (the date that the COVID-19 ICD-10-CM diagnosis first became available to use) and 90 days before the study end date (to be determined by logistical considerations), and 2) ≥365 days of continuous enrollment in their respective plan (both medical and pharmacy coverage) at the time of diagnosis.

Although the first case of COVID-19 in the United States was diagnosed on January 10,2020,[36] SARS-CoV-2 testing was limited prior to April 2020. We therefore propose to begin inclusion of COVID-19 health plan members from participating Sentinel Data Partners on April 1, 2020. Preliminary analysis of the COVID-19 U07.1 ICD-10-CM diagnosis code in either the ambulatory or hospital setting has yielded a positive predictive value of >85% (personal communication, J. Brown). Our rational for focusing on nucleic acid tests, in which viral RNA from a respiratory tract specimen is reverse-transcribed into DNA and then amplified through polymerase chain reaction (PCR), is because these tests are currently the most widely used for the detection of SARS-CoV-2 and have high sensitivity and specificity.[37-39] Antigen tests, which probe for nucleocapsid or spike proteins of SARS-CoV-2 from a respiratory tract specimen via lateral flow or enzyme-linked immunosorbent assay tests, currently have a false-negative rate of 20-30%, and false-positive rate of approximately 3% and so may lead to major misclassification of COVID-19 status.[37-39] Serological tests, which assess host response proteins such as immunoglobulin M, immunoglobulin G, or interleukins, are used to determine previous viral exposure in the population or to assess immune status among individuals and so are not appropriate to identify newly diagnosed persons with COVID-19. Within electronic health record systems, we will use Logical Observation Identifiers Names and Codes (LOINC; **Appendix 2**) indicating the presence of SARS-CoV-2 by nucleic acid testing to identify health plan members with COVID-19. We are currently evaluating the capture of SARS-CoV-2 nucleic acid tests across participating Data Partners to determine the feasibility of such analyses. All eligible health plan members will be selected for study inclusion.

For Aims 1 and 2, the index date will be either the date of first COVID-19 ICD-10-CM diagnosis or the date of specimen collection for the first positive SARS-COV-2 diagnostic test (if specimen collection date is not available, test order date will be used; else test result date will be used). Members who have no ICD-10-CM diagnosis but only an initial diagnostic test results that is pending at the time of creation of the dataset or is inconclusive will be excluded. The 365 days prior to the index date will be the baseline period, during which baseline variables will be collected. Of note, since persons who have a prior arterial or venous thrombotic event are at increased risk for subsequent events,[40] prior diagnosis of arterial thrombosis or venous

thromboembolism will not constitute an exclusion criterion. Follow-up will continue until a study endpoint (defined in **Section 3.4.**), disenrollment from medical or pharmacy coverage, death, or 90 days after the index date, whichever occurs first. Due to continued uncertainty regarding how long coagulation may be altered after SARS-CoV-2 infection, we will evaluate thrombotic complications over 90 days to ensure adequate capture of events.[41]

3.3.2 Aim 3

This aim will compare rates of thrombotic complications between health plan members diagnosed with COVID-19 and those diagnosed with influenza virus infection. We chose influenza virus infection as the comparator group for this aim because influenza is another common respiratory virus that may precipitate hospitalization when severe and is also associated with an increased risk of acute MI[34] and ischemic stroke.[35]

Health plan members with COVID-19 will be eligible for inclusion if they had: 1) a COVID-19 International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) outpatient or hospital discharge diagnosis (in any position) OR a positive SARS-CoV-2 nucleic acid test recorded between April 1, 2020 (the date that the COVID-19 ICD-10-CM diagnosis first became available to use) and 90 days before the study end date (to be determined by logistical considerations), and 2) ≥365 days of continuous enrollment in their respective plan (both medical and pharmacy coverage) at the time of diagnosis.

Health plan members with influenza A or B virus infection will be eligible for inclusion if they had: 1) an influenza A or B ICD-10-CM outpatient or hospital discharge diagnosis (in any position) OR a positive influenza A or B nucleic acid test recorded between October 1, 2018 and April 30, 2019, and 2) ≥365 days of continuous enrollment in their health plan (both medical and pharmacy coverage) at time of diagnosis. To ensure that members with influenza A or B virus infection do not have occult COVID-19, we will include health plan members who were diagnosed with influenza during a time period when SARS-CoV-2 infection was not present in the US (i.e., influenza season from October 1, 2018 - April 30, 2019).[42]

Within electronic health records, we will use LOINCs indicating the presence of SARS-CoV-2 and influenza by nucleic acid testing to identify health plan members with COVID-19 and influenza, respectively. We are currently evaluating the capture of SARS-CoV-2 and influenza nucleic acid tests across participating Data Partners to determine the feasibility of such analyses. All eligible health plan members identified with COVID-19 and influenza will be selected for study inclusion.

For this aim, the index date will be the date of first COVID-19 or influenza ICD-10 or nucleic acid diagnosis. For analyses based on a positive nucleic acid test, the index date will be the date of specimen collection for the first positive SARS-COV-2 or influenza A or B nucleic acid test (if specimen collection date is not available, test order date will be used; else test result date will be used). Members who have initial diagnostic test results that are pending at the time of creation of the dataset or inconclusive will be excluded.

Health plan members who are identified as coinfected with any other laboratory-confirmed respiratory virus (e.g., parainfluenza, adenovirus, respiratory syncytial virus, rhinovirus, human metapneumovirus) based on an ICD-10-CM diagnosis or positive nucleic acid test will be excluded, since we wish to determine the risk of arterial and venous thromboembolic events in individuals infected with only SARS-CoV-2 or only influenza. The 365 days prior to the index date will be the baseline period. Follow-up will continue until a study endpoint (defined in **Section 3.4.**), disenrollment from medical or pharmacy coverage, death, or 90 days after the index date, whichever occurs first.

3.4 Main Study Outcomes

For all three aims, we will separately evaluate two primary outcomes: 1) hospital ICD-10-CM discharge diagnosis (primary or secondary position) of an arterial thrombosis event (i.e., acute MI or acute ischemic or embolic stroke), and 2) hospital ICD-10-CM discharge diagnosis (primary or secondary position) of a venous thromboembolism event (i.e., acute DVT or PE). To minimize the potential for outcome misclassification, we will ascertain ICD-10-CM diagnoses for these outcomes that have been mapped to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic coding-based algorithms for arterial thrombosis events (i.e., acute MI and ischemic/embolic stroke)[43-47] and venous thromboembolism events (i.e., DVT, PE)[43, 48] which were previously validated compared to medical record review within Sentinel data (**Table 2**). ICD-10-CM diagnoses for these conditions are in draft status and are included in **Appendix 3**. The Workgroup will consider evaluating the positive predictive value of the ICD-10-CM algorithms for arterial and venous thrombotic events (separately) via chart review in limited samples.

Table 2. Conditions evaluated as primary arterial and venous thrombotic events

Arterial Thrombosis	Venous Thromboembolism
Acute myocardial infarction	Acute deep venous thrombosis
Acute ischemic or embolic stroke	Acute pulmonary embolism

For Aims 1 and 3, we will evaluate five secondary endpoints. First, we will expand the primary arterial and venous thrombotic endpoints to include acute MI, ischemic/embolic stroke, DVT, and PE ambulatory, Emergency Department, or hospital discharge (primary or secondary position) ICD-10-CM diagnoses. Second, since the diagnoses listed in **Table 2** may not encompass the full range of arterial or venous thrombotic events, we will expand the primary arterial thrombosis endpoint to also include an ambulatory, Emergency Department, or hospital discharge ICD-10-CM diagnosis (primary or secondary position) of angina, transient ischemic attack, peripheral arterial disease, or amputation and expand the primary venous thromboembolism endpoint to also include an ambulatory, Emergency Department or hospital discharge ICD-10-CM diagnosis (primary or secondary position) of venous thrombosis of devices, implants, or grafts. Third, since providers may not have performed diagnostic testing to confirm a diagnosis of an arterial thrombosis or venous thromboembolism (e.g., because of COVID-19 precautions limiting patient contact or transport, or due to proning of patients for mechanical ventilation, making confirmatory testing challenging) but may have instead empirically initiated thrombolytic therapy or anticoagulant treatment, respectively, as a secondary endpoint, we will classify health plan members as having an arterial or venous thrombotic event if they meet the algorithm for the primary outcome or are dispensed thrombolytic therapy and/or therapeutic anticoagulation therapy during follow-up. Evaluation of this secondary endpoint will be reliant on the study team's ability to distinguish therapeutic anticoagulation therapy from prophylactic anticoagulation during the baseline and follow-up periods. This will be explored during study implementation. Evaluation of this outcome will also require exclusion of members who were dispensed thrombolytic therapy or therapeutic anticoagulation treatment during the baseline period to be able to ascertain new initiation of these medications during follow-up. Fourth, since major bleeding may also be a significant complication of COVID-19 coagulopathy, we will also evaluate the first major bleeding event after start of follow-up, defined as first hospital discharge (primary or secondary position) or Emergency Department ICD-10-CM diagnosis for intracranial (i.e., intracerebral, subdural, or subarachnoid), upper or lower gastrointestinal tract, or retroperitoneal bleeding, as previously described.[49] Finally, we will also evaluate all-cause mortality. In-hospital death is captured by Sentinel Data Partners either via electronic health records or claims. During the implementation

phase of the project, we will identify approaches to maximize ascertainment of out of hospital deaths.

3.5 Data Collection

3.5.1 Demographic Characteristics (Aims 1-3)

We will collect baseline data on age, sex, race, ethnicity, geographic area (i.e., 5-digit zip code), and site of diagnosis (i.e., ambulatory, hospital, and nursing home [if available]).

3.5.2 Baseline Comorbidities (Aims 1-3)

During the baseline period, we will determine diagnoses of alcohol abuse, antiphospholipid antibody syndrome, asthma, atrial fibrillation, cancer (excluding non-melanoma skin cancers), chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, HIV infection, hypertension, inherited (primary) thrombophilia, neurological disease, obesity, pregnancy, rheumatologic disease, stroke (embolic or ischemic), tobacco use (current), vascular disease (i.e., cardiovascular, cerebrovascular, and/or peripheral arterial), and venous thromboembolism (i.e., deep venous thrombosis, pulmonary embolism, and/or thrombosis due to cardiac/vascular prosthetic device, implant, or graft). Diagnosis code lists for these conditions have been developed as part of the Sentinel COVID-19 Natural History Master Protocol.[50] Body weight (kg) and height (m) will be collected from dates closest to the index date during the baseline period. We will determine the severity of infection (COVID-19 or influenza) at diagnosis based on the operational severity definition that has been specified within the Sentinel COVID-19 Natural History Master Protocol.[50] We will also classify baseline presence of frailty using a validated claims-based frailty index.[51] We will evaluate baseline healthcare utilization by determining the number of ambulatory encounters, Emergency Department visits, and hospitalizations during the baseline period.

3.5.3 Laboratory Data (Aims 1-3)

On or within +/-7 days around the index date, we will aim to collect: hemoglobin, platelet count, international normalized ratio (INR), prothrombin time, partial thromboplastin time, D-dimer, fibrinogen, ferritin, erythrocyte sedimentation rate, C-reactive protein, and procalcitonin. If multiple results for a test were recorded within this period, we will collect the result closest to the index date. The rationale for selecting a window of +/-7 days around the index date was because members diagnosed with COVID-19 in the ambulatory setting may have had laboratory testing performed prior to or several days after testing for SARS-CoV-2. At any time throughout the baseline period or during follow-up, we will aim to identify results for: ABO blood type, factor V Leiden, factor VIII, antithrombin, von Willebrand factor, prothrombin gene mutation, protein C, protein S, and antiphospholipid antibody (e.g., lupus anticoagulant, anticardiolipin, anti-B2 glycoprotein 1).

3.5.4 Medications (Aims 1-3)

We will determine exposure to drugs prior to COVID-19 diagnosis that may affect arterial or venous thrombotic event risk, including anticoagulants, anti-platelet drugs, and statins. In addition, some drugs enhance venous thromboembolism risk, including oral chemotherapeutic agents (e.g., lenalidomide), oral contraceptives, tamoxifen (selective estrogen modulator), and estrogen and testosterone replacement therapy.[52] We have developed an initial list of medications of interest in each drug class of interest. We will evaluate drug exposure by determining dispensed fills or administrations (via National Drug Codes [NDC] and Healthcare Common Procedure Coding System [HCPCS]) within 183 days prior to the index date. Exposure windows will end 3 days prior to the index date in order to minimize the potential for protopathic bias.[53] Thus, individuals initiated on any of the medications of interest <3 days prior to COVID-19 diagnosis will not be classified as exposed to these products. During the implementation of the study, we will determine how best to operationalize baseline medication

exposure (e.g., based on dispensed medication fills, building episodes that allow for stockpiling, or alternative approaches).

In addition, we will determine the days of exposure to an anticoagulant, anti-platelet drug, thrombolytic agent, or transfusion with blood products or immunoglobulins after the index date until a censoring event to enhance our understanding of use of these medications after COVID-19 diagnosis. During the implementation phase of this project, we will explore potential approaches to distinguishing between anticoagulant medication dispensed as therapy versus prophylaxis. For health plan members who are hospitalized, we determine the length of hospital stay as a proxy for immobility.

3.5.5 Hypothesized Risk Factors for Thrombotic Events (Aim 2)

Definitions for the hypothesized risk factors of interest associated with arterial and venous thrombotic events are presented in **Table 3**, according to the mechanisms by which they might precipitate such an event (i.e., stasis of circulation, endothelial injury, or hypercoagulability). These definitions were proposed in the Sentinel COVID-19 Natural History Master Protocol.[50] Given that Aim 2 seeks to evaluate patient characteristics present *prior to* COVID-19 diagnosis as risk factors for arterial and venous thrombotic events, these risk factors will be ascertained during the 365-day baseline period. Exposure to the medications of interest (listed in **Section 3.5.4.** above) will be ascertained between the period spanning 183 days prior and 3 days prior to the index date in order to examine the effect of medications taken in the ambulatory setting on rates of arterial and venous thrombotic events.

Table 3. Definitions for hypothesized risk factors for thrombotic events.

Category	Risk Factor	Definition
Stasis of Circulation	Obesity	Body mass index >30 kg/m^2
	Heart failure	ICD-10-CM diagnosis codes
	Polycythemia	Hemoglobin >16 gm/dL
	Older age	Will explore different age thresholds
	Alcohol abuse	ICD-10-CM diagnosis codes
	Atrial fibrillation	ICD-10-CM diagnosis codes
Endothelial Injury	Diabetes	ICD-10-CM diagnosis codes or registry
	Hypertension	ICD-10-CM diagnosis codes
	Vascular disease	ICD-10-CM diagnosis codes
	Current tobacco use	EHR data, ICD-10-CM diagnosis codes
Hypercoagulability	Cancer	ICD-10-CM diagnosis codes
	Pregnancy	ICD-10-CM diagnosis codes
	Drugs/Transfusions	NDC, HCPCS codes
	Stroke/VTE	ICD-10-CM diagnosis codes
	Thrombophilia	ICD-10-CM diagnosis codes
	Antiphospholipid Ab	ICD-10-CM diagnosis codes

Abbreviations: Ab=antibody; EHR=electronic health records; HCPCS=Healthcare Common Procedure Coding System; ICD-10-CM=International Classification of Diseases, Tenth Revision, Clinical Modification; NDC=National Drug Code; VTE=venous thromboembolic events

3.6 Statistical Analysis

3.6.1 Descriptive Statistics

For Aims 1 and 2, we will describe the characteristics of the overall cohort of health plan members with COVID-19. For Aim 3, we will compare the characteristics of members who were diagnosed with COVID-19 to those who were diagnosed with influenza virus infection. Group

differences will be assessed by using standardized mean differences for continuous variables and standardized difference in proportion for categorical variables, using a threshold of ≥0.10 to suggest meaningful imbalance.

3.6.2 Incidence and Consequences of Thrombotic Events with COVID-19 (Aim 1 Primary Analysis)

To address Aim 1, we will calculate the absolute risk and unadjusted incidence rates of arterial and venous thrombotic events over 90 days in the COVID-19 cohort. Results will be determined overall and stratified by age groups (proposed grouping: <20; 20-44; 45-54; 55-64; 65-74; 75-84; ≥85 years, which were age groups evaluated by the US Centers for Disease Control and Prevention for evaluation of rates of severe COVID-19[54]), sex, race/ethnicity, severity of infection at diagnosis, setting of diagnosis (i.e., ambulatory, hospital, nursing home), history of vascular disease or venous thromboembolism (further stratified by use of anticoagulant therapy), and anticoagulant or anti-platelet drug exposure within 183 days prior to COVID-19 diagnosis.

We will explore determining the absolute risk and unadjusted incidence rates of arterial and venous thrombotic events over 90 days stratified by exposure to certain medications during follow-up, including anticoagulants, anti-platelet agents, and medications used to control cytokine response (e.g., tofacitinib, baricitinib). We will first explore use of these medications during follow-up to determine if we should limit ascertainment of the medications during some time period.

Among health plan members identified as having a thrombotic complication, we will determine the absolute risk and rate of death within 90 days, stratified by arterial thrombosis or venous thromboembolism events.

3.6.3 Relative Risk (RR) of Thrombotic Events Associated with Hypothesized Risk Factors (Aim 2 Primary Analysis)

To answer the hypotheses of Aim 2, we will use modified Poisson regression[55] to calculate adjusted RRs with 95% CIs of the primary and secondary outcomes associated with the hypothesized risk factors of interest, controlling for potential confounders. Variables listed in **Section 3.5.** will be evaluated as potential confounders. Potential confounding factors will be retained in the model if their inclusion changes the unadjusted RR of arterial or venous thrombotic events by ≥15%.[56]

In exploratory analyses, we will evaluate select laboratory variables (i.e., D-dimer, fibrinogen, ferritin, erythrocyte sedimentation rate, C-reactive protein, procalcitonin, and ABO blood type, depending on their frequency of measurement) as risk factors for arterial or venous thrombotic events. These analyses are exploratory because these laboratory tests may not have been assessed frequently in clinical practice. Additionally, while our focus is on patient factors present prior to COVID-19 diagnosis, we will also explore whether COVID-19 severity at diagnosis is associated with an increased risk of arterial or venous thrombotic events.

3.6.4 RR of Thrombotic Events in Persons with COVID-19 Versus Influenza (Aim 3 Primary Analysis)

There may be differences in the prevalence of demographic characteristics, comorbidities, laboratory abnormalities, severity of infection, usage of medications, and healthcare utilization during the baseline period between the COVID-19 and influenza cohorts. Because of the many potential confounders relative to the number of arterial or venous thrombotic events in this analysis, we will develop propensity scores to control for confounding.[57, 58] We will estimate propensity scores for COVID-19 diagnosis by using logistic regression, incorporating all baseline

variables in **Section 3.5.** as independent variables and COVID-19 (versus influenza) status as the dependent variable. We will exclude health plan members from the COVID-19 cohort whose propensity score exceeds the maximum or minimum values in the comparator cohort and vice-versa (i.e., trim the tails). We propose to use propensity score stratification (rather than matching) in order to efficiently retain health plan members in the analysis because it may be difficult to identify propensity score matches, which would reduce sample size and, consequently, power to detect associations. While inverse probability of treatment weighting would be an appropriate alternative approach, the drawback is that for datasets from some Data Partners, weights might be extremely large, leading to challenges regarding how truncation of weights should be handled across these datasets (and how that might affect the proposed meta-analysis below). If there are too few events within some propensity score strata to perform stratification, then we will adjust for propensity score in analyses. Adjusting for propensity score might ultimately provide a more robust means to consistently analyze outcomes from Data Partners with low event numbers.

To address our hypothesis for Aim 3, we will again use modified Poisson regression[55] to calculate RRs with 95% CIs of the primary and secondary outcomes in health plan members diagnosed with COVID-19 compared to those diagnosed with influenza. We will stratify results by severity of infection at diagnosis, setting of diagnosis (i.e., ambulatory, hospital, nursing home), and prior history of arterial thrombosis or venous thromboembolism (further stratified by baseline anticoagulant use).

3.6.5 Sensitivity Analyses

For each aim, we will conduct sensitivity analyses in which we: 1) expand the COVID-19 cohort to include persons diagnosed with SARS-CoV-2 via ICD-10-CM code, positive SARS-CoV-2 nucleic acid test, or positive SARS-CoV-2 antigen testing; 2) restrict the COVID-19 cohort to only those confirmed to have a positive SARS-CoV-2 nucleic acid or antigen test; 3) condition analyses on geographic region (since this might affect COVID-19 exposure and selection into the cohort); 4) separately stratify by severity of infection at diagnosis and the setting of the diagnosis (i.e., ambulatory, hospital, nursing home); and 5) assess the effects of unmeasured confounders.[59]

In Aim 3, since health plan members who undergo laboratory testing for COVID-19 or influenza may be different from those diagnosed but not laboratory-confirmed, we will compare the characteristics of persons within each cohort who underwent laboratory confirmation of their infection compared to those who were diagnosed but not laboratory-confirmed in order to determine if there are any systematic differences in characteristics between these groups within the COVID-19 and influenza cohorts.

Additionally, because there is uncertainty regarding when the arterial and venous thrombotic events of interest may occur following SARS-CoV-2 infection, in Aim 1 we will explore conducting temporal scan analyses to determine if events are randomly distributed over time or if there are specific risk windows for each outcome following SARS-CoV-2 infection.[60] Freely available SaTScan software (www.satscan.org) will be used. Alternatively, we may re-run the Aim 1 analysis as specified, but with a 30- or 45-day window instead of 90 days.

We will also explore conducting a self-controlled analysis using an exposure-crossover design[61] for Aim 3 given concerns about the comparability of the COVID-19 and influenza cohorts. This design will evaluate whether rates of arterial and venous thrombotic events are different before and after COVID-19 or influenza diagnosis.

3.6.6 Meta-Analyses

Since each Data Partner will conduct the above analyses separately, we will perform a meta-analysis across the databases. Once estimates from each of the databases have been determined, we will combine these estimates using random effects models to calculate pooled summary estimates of the incidence rates and RRs of the outcomes of interest.[62] This statistical technique weighs individual studies by variance (both within- and between-study variance) and yields a pooled point estimate and 95% CI. We will also evaluate the presence of heterogeneity across trials by using the I^2 statistic, which quantifies the percentage of variability that can be attributed to between-study differences.[63] If significant heterogeneity is found, we will still report a pooled estimate using a random effects approach (in addition to report separate estimates for each database). A larger between study variance will increase the standard error of the pooled effect.

3.6.7 Approach to Missing Data

Missing data can reduce power and bias results.[64, 65] We will determine the proportion of missing baseline data for each variable not identified by diagnosis codes (e.g., height and weight). If necessary, we will implement multiple imputation using chained equations, creating 10 imputed datasets using all variables in **Section 3.5.** and outcomes.[66] Results across datasets will be combined to arrive at CIs that account for within- and across-dataset variances.[67]

3.7 Potential Limitations and Approaches to Minimize Them

3.7.1 Selection Bias

There is the potential for selection bias in our analyses due to variations in COVID-19 testing over time and according to geographic region, demographics, and severity of infection. We will evaluate the potential for this bias through the sensitivity analyses planned (detailed in **Section C.6.5.**). Moreover, this study selects health plan members on the basis of an event - COVID-19 diagnosis - that could have been affected by some of the study's exposures of interest (e.g., diabetes, hypertension, vascular disease). By doing so, it risks creating or altering associations between exposures and outcomes, a form of bias known as collider stratification bias.[68] This will be addressed by acknowledging that relationships observed among persons diagnosed with COVID-19, while useful clinically, may not represent true causal relationships between the risk factor and outcome of interest.

3.7.2 Misclassification Bias

Misclassification of COVID-19 and influenza diagnoses will be minimized by classifying infection status via highly specific laboratory tests. Misclassification of arterial or venous thrombotic complications is possible, since the ICD-10-CM coding algorithms we will use to ascertain these events have not been validated compared to chart review. To minimize misclassification, we will evaluate arterial thrombosis events (i.e., acute MI and ischemic/embolic stroke)[43-47] and venous thromboembolism (i.e., DVT, PE)[43, 48] based on previously validated algorithms within Sentinel data. We will map the existing validated ICD-9-CM code-based algorithms for these events to ICD-10-CM diagnoses.

Due to the nature of the data, we may have incomplete ascertainment of out-of-hospital death and care provided within nursing homes. Certain laboratory tests or their results may also not be completely captured in these data (e.g., other respiratory viruses besides SARS-CoV-2 and influenza as well as some listed in **Section 3.5.3.**). We will work with the Data Partners to understand the availability of these specific laboratory data.

3.7.3 Unmeasured Confounding

To assess the effect of unmeasured confounding, particularly in Aims 2 and 3, we will conduct sensitivity analyses to determine the potential impact of unmeasured confounders on observed associations between exposures of interest and thrombotic complications.[59, 69]

3.7.4 Generalizability

The generalizability of this study will depend upon the sources of data available from Sentinel's Data Partners.

3.8 Summary and Future Directions

These aims will provide valuable data on the epidemiology of thrombotic events with COVID-19. The results will suggest interventions to decrease the risk of these events and inform future comparative effectiveness and safety studies, which could help reduce morbidity and mortality with COVID-19.

4 References Cited

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727-733.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
3. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145-147.
4. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;191:9-14.
5. Ziehr DR, Alladina J, Petri CR, et al. Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study. Am J Respir Crit Care Med 2020;201:1560-1564.
6. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost 2020;18:1743-1746.
7. Cui S, Chen S, Li X, et al. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 2020;18:1421-1424.
8. Poissy J, Goutay J, Caplan M, et al. Pulmonary embolism in patients with COVID-19 : Awareness of an increased prevalence. Circulation 2020;142:184-186.
9. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical Characteristics of Covid-19 in New York City. N Engl J Med 2020;382:2372-2374.
10. Cattaneo M, Bertinato EM, Birocchi S, et al. Pulmonary Embolism or Pulmonary Thrombosis in COVID-19? Is the Recommendation to Use High-Dose Heparin for Thromboprophylaxis Justified? Thromb Haemost 2020.
11. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID and Coagulation: Bleeding and Thrombotic Manifestations of SARS-CoV2 Infection. Blood 2020.
12. Platt R, Brown JS, Robb M, et al. The FDA Sentinel Initiative - An Evolving National Resource. N Engl J Med 2018;379:2091-2093.
13. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020;18:1023-1026.
14. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020;46:1089-1098.
15. Merkler AE, Parikh NS, Mir S, et al. Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza. JAMA Neurol 2020.

16. Chen L, Liu W, Zhang Q, et al. RNA based mNGS approach identifies a novel human coronavirus from two individual pneumonia cases in 2019 Wuhan outbreak. Emerg Microbes Infect 2020;9:313-319.
17. Johns Hopkins University Center for Systems Science and Engineering. COVID-19 Dashboard. Accessed at: https://coronavirus.jhu.edu/map.html. Accessed on October 15, 2020.
18. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-513.
19. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020.
20. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020.
21. 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.
22. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA 2020.
23. 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 2020;395:1054-1062.
24. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: Early experience and forecast furing an emergency response. N Engl J Med 2020:In Press.
25. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020;20:425-434.
26. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020.
27. Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 2020;368:m606.
28. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844-847.
29. Chen Y, Guo Y, Pan Y, et al. Structure analysis of the receptor binding of 2019-nCoV. Biochem Biophys Res Commun 2020.
30. Walls AC, Park YJ, Tortorici MA, et al. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell 2020.
31. Blann AD. How a damaged blood vessel wall contibutes to thrombosis and hypertenasion. Pathophysiol Haemost Thromb 2003;33:445-8.
32. Chung I, Lip GY. Virchow's triad revisited: blood constituents. Pathophysiol Haemost Thromb 2003;33:449-54.
33. Lowe GD. Virchow's triad revisited: abnormal flow. Pathophysiol Haemost Thromb 2003;33:455-7.
34. Kwong JC, Schwartz KL, Campitelli MA, et al. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. N Engl J Med 2018;378:345-353.
35. Boehme AK, Luna J, Kulick ER, et al. Influenza-like illness as a trigger for ischemic stroke. Ann Clin Transl Neurol 2018;5:456-463.

36. Team CCR, Jorden MA, Rudman SL, et al. Evidence for Limited Early Spread of COVID-19 Within the United States, January-February 2020. MMWR Morb Mortal Wkly Rep 2020;69:680-684.
37. Cheng MP, Papenburg J, Desjardins M, et al. Diagnostic Testing for Severe Acute Respiratory Syndrome-Related Coronavirus 2: A Narrative Review. Ann Intern Med 2020;172:726-734.
38. Sethuraman N, Jeremiah SS, Ryo A. Interpreting Diagnostic Tests for SARS-CoV-2. JAMA 2020.
39. Weissleder R, Lee H, Ko J, et al. COVID-19 diagnostics in context. Sci Transl Med 2020;12.
40. Lowe GD. Common risk factors for both arterial and venous thrombosis. Br J Haematol 2008;140:488-95.
41. Lewnard JA, Liu VX, Jackson ML, et al. Incidence, clinical outcomes, and transmission dynamics of severe coronavirus disease 2019 in California and Washington: prospective cohort study. BMJ 2020;369:m1923.
42. Xu X, Blanton L, Elal AIA, et al. Update: Influenza Activity in the United States During the 2018-19 Season and Composition of the 2019-20 Influenza Vaccine. MMWR Morb Mortal Wkly Rep 2019;68:544-551.
43. Ammann EM, Cuker A, Carnahan RM, et al. Chart validation of inpatient International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) administrative diagnosis codes for venous thromboembolism (VTE) among intravenous immune globulin (IGIV) users in the Sentinel Distributed Database. Medicine (Baltimore) 2018;97:e9960.
44. Ammann EM, Schweizer ML, Robinson JG, et al. Chart validation of inpatient ICD-9-CM administrative diagnosis codes for acute myocardial infarction (AMI) among intravenous immune globulin (IGIV) users in the Sentinel Distributed Database. Pharmacoepidemiol Drug Saf 2018;27:398-404.
45. Cutrona SL, Toh S, Iyer A, et al. Validation of acute myocardial infarction in the Food and Drug Administration's Mini-Sentinel program. Pharmacoepidemiol Drug Saf 2013;22:40-54.
46. Roumie CL, Mitchel E, Gideon PS, et al. Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data. Pharmacoepidemiol Drug Saf 2008;17:20-6.
47. Wahl PM, Rodgers K, Schneeweiss S, et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. Pharmacoepidemiol Drug Saf 2010;19:596-603.
48. Yih WK, Greene SK, Zichittella L, et al. Evaluation of the risk of venous thromboembolism after quadrivalent human papillomavirus vaccination among US females. Vaccine 2016;34:172-8.
49. Al-Ani F, Shariff S, Siqueira L, et al. Identifying venous thromboembolism and major bleeding in emergency room discharges using administrative data. Thromb Res 2015;136:1195-8.
50. United States Food and Drug Administration Sentinel Initiative. Master Protocol Development: COVID-19 Natural History. Accessed at: https://www.sentinelinitiative.org/sentinel/methods/master-protocol-development-covid-19-natural-history. Accessed on July 17, 2020.
51. Kim DH, Schneeweiss S, Glynn RJ, et al. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. J Gerontol A Biol Sci Med Sci 2018;73:980-987.
52. Kovacic APM, Caprnda M, Mrhar A, et al. Impact of drugs on venous thromboembolism risk in surgical patients. Eur J Clin Pharmacol 2019;75:751-767.

53. Horwitz RI, Feinstein AR. The problem of "protopathic bias" in case-control studies. Am J Med 1980;68:255-8.
54. Team CCR. Severe outcomes among patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep 2020;69:343-346.
55. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159:702-6.
56. Rothman KJ, Greenland S. Modern Epidemiology. Philadelphia: Lippincott Williams and Wilkins, 1998.
57. Perkins SM, Tu W, Underhill MG, et al. The use of propensity scores in pharmacoepidemiologic research. Pharmacoepidemiol Drug Saf 2000;9:93-101.
58. Braitman LE, Rosenbaum PR. Rare outcomes, common treatments: analytic strategies using propensity scores. Ann Intern Med 2002;137:693-5.
59. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics 1998;54:948-63.
60. Kulldorff M, Nagarwalla N. Spatial disease clusters: detection and inference. Stat Med 1995;14:799-810.
61. Redelmeier DA. The exposure-crossover design is a new method for studying sustained changes in recurrent events. J Clin Epidemiol 2013;66:955-63.
62. Serghiou S, Goodman SN. Random-Effects Meta-analysis: Summarizing Evidence With Caveats. JAMA 2019;321:301-302.
63. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
64. Patrician PA. Multiple imputation for missing data. Res Nurs Health 2002;25:76-84.
65. Sinharay S, Stern HS, Russell D. The use of multiple imputation for the analysis of missing data. Psychol Methods 2001;6:317-29.
66. Royston P. Multiple imputation of missing values: update. The STATA Journal 2005;5:188-201.
67. Freedman VA, Wolf DA. A case study on the use of multiple imputation. Demography 1995;32:459-70.
68. Griffith G, Morris TT, Tudball M, et al. Collider bias undermines our understanding of COVID-19 disease risk and severity. medRxiv 2020;Accessed at: https://www.medrxiv.org/content/10.1101/2020.05.04.20090506v3. Accessed on July 17, 2020.
69. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies. JAMA 2019;321:602-603.

5 Appendix

5.1 Appendix 1. Responses to Questions from the 6/24/2020 Reagan-Udall Foundation Evidence Accelerator Parallel Analysis Meeting

1) It seems that perhaps thrombotic complications occur in some patients despite routine pharmacologic thromboprophylaxis or even among patients on anticoagulation. Will this retrospective study be able to tease out these patients (on venous thromboembolism (VTE) prophylaxis versus on anticoagulation for other reasons)?

Response: This current project is not designed to examine the comparative effectiveness of in-hospital VTE prophylaxis or anticoagulant/anti-platelet therapies on arterial/venous thromboembolic complications. The aims of this current study are focused on the natural history of arterial and venous thromboembolic complications with coronavirus disease 2019 (COVID-19). However, future Sentinel studies are being planned to examine the comparative effectiveness of these medications on thrombotic complications in COVID-19.

2) To help answer questions around whether the incidence of thrombosis of COVID-19 is higher than expected, could we also look at similarly ill patients (i.e. COVID-19 acute respiratory distress syndrome [ARDS] versus non-COVID-19 ARDS) in ICU and incidence of thrombotic complications?

Response: The third aim of our proposal seeks to compare the incidence of arterial/venous thromboembolic events between hospitalized health plan members with COVID-19 diagnosis and hospitalized members with an influenza diagnosis during a time period prior to the COVID-19 era. This comparison allows us to examine rates of thrombotic outcomes in two groups of health plan members, each of whom has a respiratory viral infection, allowing comparability between the cohorts with regard to the etiology of their respiratory illness. As suggested by the respondent, we will conduct analyses whereby we stratify hospitalized persons according to the severity of their disease (e.g., ARDS status).

3) Your influenza comparator covers the period of Oct-Dec 2019. Brownstein's satellite data seems to suggest that the coronavirus outbreak in Wuhan may have hit earlier than October 2019: https://abcnews.go.com/amp/International/satellite-data-suggests-coronavirus-hit-china-earlier-researchers/story?id=71123270. Should we use another time period as a comparator?

Response: The third aim of our proposal seeks to compare the incidence of arterial/venous thromboembolic events after COVID-19 diagnosis with that after influenza diagnosis. We have now chosen to select a comparator cohort of health plan members hospitalized for influenza between October 1, 2018 and April 30, 2019 because data from the Centers for Disease Control and Prevention suggest that SARS-CoV-2 transmission likely began in late January 2020 on the West Coast (see Jorden MA, Rudman SL, et al. Evidence for Limited Early Spread of COVID-19 Within the US, January–February 2020. MMWR Morb Mortal Wkly Rep 2020;69:680–684. DOI: http://dx.doi.org/10.15585/mmwr.mm6922e1).[36] Thus, to eliminate the possibility that our comparator cohort of hospitalized influenza health plan members might have coinfection with SARS-CoV-2, we have limited the comparator cohort period of observation to before COVID-19's arrival in the US.

4) Will you collect data on antiphospholipid antibody/lupus anticoagulant status? Anecdotally a lot of acute strokes in young persons are arising persons who are antiphospholipid antibody-positive.

Response: We are indeed planning to collect data on history of antiphospholipid antibody/lupus anticoagulant for our analyses.

5) Are you collecting information on amputation, aspirin (as an antiplatelet besides the others) and thrombolytic agents.

Response: We appreciate these suggestions. We will be sure that our protocol includes the collection of data on amputations (to indicate possible limb ischemia from arterial thromboembolic events). We will also collect data on use of aspirin and other antiplatelet drugs as well as thrombolytic agents within 90 days prior to COVID-19 diagnosis.

6) I am wondering how soon you can get these data given the lag in Sentinel claims data?

Response: Sentinel has collaborations with a variety of Data Partners, some of whom have short time lags for acquisition of data for analysis. We will work with Sentinel's Data Partners to determine which are interested in collaborating on this project and will allow for short lag times.

7) Did you consider medications taken by the patient prior to hospitalization (current prescriptions)?

Response: We are planning to collect outpatient prescription fills of certain medications (e.g., anticoagulants, anti-platelet, medications that might affect coagulation) that were dispensed within 90 days prior to COVID-19 diagnosis.

8) A number of drugs have VTE listed as a known adverse effect, e.g. antipsychotics, tricyclic antidepressants, some NSAIDs (https://link.springer.com/article/10.1007/s00228-019-02636-x). Whether such medications taken prior to hospitalization increase the risk of VTE with COVID-19 is a major question. Will these medications be examined as risk factors for thrombotic complications in COVID-19?

Response: We agree that evaluating the use of drugs that have VTE as a known adverse effect will be important to examine as risk factors for venous thromboembolic complications in COVID-19. As part of our first aim, we will describe the use of such medications. However, the current project is not designed to examine the comparative safety of these drugs on venous thromboembolic complications in COVID-19. Future Sentinel studies are being planned to examine the comparative safety of these medications on thrombotic complications in COVID-19.

5.2 Appendix 2. Logical Observation Identifiers Names and Codes (LOINC) indicating SARS-CoV-2 presence on designated laboratory tests

LOINC Code	Description
94306-8	SARS-CoV-2 RNA panel – Unspecified specimen by NAA with probe detection
94307-6	SARS-CoV-2 N gene in Unspecified specimen by NAA using primer-probe set N1
94308-4	SARS-CoV-2 N gene in Unspecified specimen by NAA using primer-probe set N2
94309-2	SARS-CoV-2 RNA in Unspecified specimen by NAA with probe detection
94310-0	SARS-like coronavirus N gene in Unspecified specimen by NAA with probe detection
94311-8	SARS-CoV-2 N gene in Unspecified specimen by NAA using primer-probe set N1
94312-6	SARS-CoV-2 N gene in Unspecified specimen by NAA using primer-probe set N2
94313-4	SARS-like coronavirus N gene in Unspecified specimen by NAA with probe detection
94314-2	SARS-CoV-2 RdRp gene in Unspecified specimen by NAA with probe detection
94315-9	SARS-CoV-2 E gene in Unspecified specimen by NAA with probe detection
94316-7	SARS-CoV-2 N gene in Unspecified specimen by NAA with probe detection
94500-6	SARS-CoV-2 RNA in Respiratory specimen by NAA with probe detection
94502-2	SARS-related coronavirus RNA in Respiratory specimen by NAA with probe detection
94509-7	SARS-CoV-2 E gene in Unspecified specimen by NAA with probe detection
94510-5	SARS-CoV-2 N gene in Unspecified specimen by NAA with probe detection
94511-3	SARS-CoV-2 ORF1ab region in Unspecified specimen by NAA with probe detection
94531-1	SARS-CoV-2 RNA panel – Respiratory specimen by NAA with probe detection
94532-9	SARS-related coronavirus+MERS coronavirus RNA in Respiratory specimen by NAA with probe detection
94533-7	SARS-CoV-2 N gene in Respiratory specimen by NAA with probe detection
94534-5	SARS-CoV-2 RdRp gene in Respiratory specimen by NAA with probe detection
94559-2	SARS-CoV-2 ORF1ab region in Respiratory specimen by NAA with probe detection
94565-9	SARS-CoV-2 RNA in Nasopharynx by NAA with non-probe detection
94639-2	SARS-CoV-2 ORF1ab region in Unspecified specimen by NAA with probe detection
94640-0	SARS-CoV-2 S gene in Respiratory specimen by NAA with probe detection
94641-8	SARS-CoV-2 S gene in Unspecified specimen by NAA with probe detection
94642-6	SARS-CoV-2 S gene in Respiratory specimen by NAA with probe detection
94643-4	SARS-CoV-2 S gene in Unspecified specimen by NAA with probe detection
94644-2	SARS-CoV-2 ORF1ab region in Respiratory specimen by NAA with probe detection
94645-9	SARS-CoV-2 RdRp gene in Unspecified specimen by NAA with probe detection
94646-7	SARS-CoV-2 RdRp gene in Respiratory specimen by NAA with probe detection
94647-5	SARS-related coronavirus RNA in Unspecified specimen by NAA with probe detection
94660-8	SARS-CoV-2 RNA in Serum or Plasma by NAA with probe detection
94745-7	SARS-CoV-2 RNA
94746-5	SARS-CoV-2 RNA
94756-4	SARS-CoV-2 N gene
94757-2	SARS-CoV-2 N gene
94758-0	SARS-related coronavirus E gene
94759-8	SARS-CoV-2 RNA
94760-6	SARS-CoV-2 N gene
94765-5	SARS-related coronavirus E gene
94766-3	SARS-CoV-2 N gene
94767-1	SARS-CoV-2 S gene
94819-0	SARS-CoV-2 RNA

LOINC Code	Description
94845-5	SARS-CoV-2 RNA
95380-2	Influenza virus A + B & SARS-CoV-2 (COVID-19) & SARS-related CoV RNA panel – Resp specimen by NAA w/ probe detection
95406-5	SARS-CoV-2 RNA
95409-9	SARS-CoV-2 N gene
95422-2	Influenza virus A + B RNA and SARS-CoV-2 (COVID-19) N gene panel – Respiratory specimen by NAA with probe detection
95423-0	Influenza virus A + B and SARS-CoV-2 (COVID-19) identified in Respiratory specimen by NAA with probe detection
95425-5	SARS-CoV-2 (COVID-19) N gene in Saliva (oral fluid) by NAA with probe detection
95521-1	SARS-CoV-2 N gene
95522-9	SARS-CoV-2 N gene
95608-6	SARS-CoV-2 RNA

5.3 Appendix 3. International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnoses and descriptions for conditions representing arterial and venous thrombotic events[1]

Diagnosis	ICD-10-CM	Code Description
Pulmonary embolism	I26	Pulmonary embolism
Pulmonary embolism	I26.0	Pulmonary embolism with acute cor pulmonale
Pulmonary embolism	I26.01	Septic pulmonary embolism with acute cor pulmonale
Pulmonary embolism	I26.02	Saddle embolus of pulmonary artery with acute cor pulmonale
Pulmonary embolism	I26.92	Saddle embolus of pulmonary artery without acute cor pulmonale
Pulmonary embolism	I26.09	Other pulmonary embolism with acute cor pulmonale
Pulmonary embolism	I26.9	Pulmonary embolism without acute cor pulmonale
Pulmonary embolism	I26.90	Septic pulmonary embolism without acute cor pulmonale
Pulmonary embolism	I26.93	Single subsegmental pulmonary embolism without acute cor pulmonale
Pulmonary embolism	I26.99	Other pulmonary embolism without acute cor pulmonale
Pulmonary embolism	T80.0XXA	Air embolism following infusion, transfusion and therapeutic injection, initial encounter
Pulmonary embolism	T81.718A	Complication of other artery following a procedure, not elsewhere classified, initial encounter
Pulmonary embolism	T81.72XA	Complication of vein following a procedure, not elsewhere classified, initial encounter
Pulmonary embolism	T82.817A	Embolism due to cardiac prosthetic devices, implants and grafts, initial encounter
Pulmonary embolism	T82.818A	Embolism due to vascular prosthetic devices, implants and grafts, initial encounter
Deep venous thrombosis	I80.10	Phlebitis and thrombophlebitis of unspecified femoral vein
Deep venous thrombosis	I80.11	Phlebitis and thrombophlebitis of right femoral vein
Deep venous thrombosis	I80.12	Phlebitis and thrombophlebitis of left femoral vein
Deep venous thrombosis	I80.13	Phlebitis and thrombophlebitis of femoral vein, bilateral
Deep venous thrombosis	I80.201	Phlebitis and thrombophlebitis of unspecified deep vessels of right lower extremity
Deep venous thrombosis	I80.202	Phlebitis and thrombophlebitis of unspecified deep vessels of left lower extremity
Deep venous thrombosis	I80.203	Phlebitis and thrombophlebitis of unspecified deep vessels of lower extremities, bilateral
Deep venous thrombosis	I80.209	Phlebitis and thrombophlebitis of unspecified deep vessels of unspecified lower extremity
Deep venous thrombosis	I80.211	Phlebitis and thrombophlebitis of right iliac vein
Deep venous thrombosis	I80.212	Phlebitis and thrombophlebitis of left iliac vein
Deep venous thrombosis	I80.213	Phlebitis and thrombophlebitis of iliac vein, bilateral
Deep venous thrombosis	I80.219	Phlebitis and thrombophlebitis of unspecified iliac vein
Deep venous thrombosis	I80.221	Phlebitis and thrombophlebitis of right popliteal vein
Deep venous thrombosis	I80.222	Phlebitis and thrombophlebitis of left popliteal vein

[1] This ICD-10-CM list is a draft. A final code list will be made publicly available upon study completion.

Diagnosis	ICD-10-CM	Code Description
Deep venous thrombosis	I80.223	Phlebitis and thrombophlebitis of popliteal vein, bilateral
Deep venous thrombosis	I80.229	Phlebitis and thrombophlebitis of unspecified popliteal vein
Deep venous thrombosis	I80.231	Phlebitis and thrombophlebitis of right tibial vein
Deep venous thrombosis	I80.232	Phlebitis and thrombophlebitis of left tibial vein
Deep venous thrombosis	I80.233	Phlebitis and thrombophlebitis of tibial vein, bilateral
Deep venous thrombosis	I80.239	Phlebitis and thrombophlebitis of unspecified tibial vein
Deep venous thrombosis	I80.291	Phlebitis and thrombophlebitis of other deep vessels of right lower extremity
Deep venous thrombosis	I80.292	Phlebitis and thrombophlebitis of other deep vessels of left lower extremity
Deep venous thrombosis	I80.293	Phlebitis and thrombophlebitis of other deep vessels of lower extremity, bilateral
Deep venous thrombosis	I80.299	Phlebitis and thrombophlebitis of other deep vessels of unspecified lower extremity
Deep venous thrombosis	I80.3	Phlebitis and thrombophlebitis of lower extremities, unspecified
Deep venous thrombosis	I80.8	Phlebitis and thrombophlebitis of other sites
Deep venous thrombosis	I82.4	Acute embolism and thrombosis of deep veins of lower extremity
Deep venous thrombosis	I82.40	Acute embolism and thrombosis of unspecified deep veins of lower extremity
Deep venous thrombosis	I82.401	Acute embolism and thrombosis of unspecified deep veins of right lower extremity
Deep venous thrombosis	I82.402	Acute embolism and thrombosis of unspecified deep veins of left lower extremity
Deep venous thrombosis	I82.403	Acute embolism and thrombosis of unspecified deep veins of lower extremity, bilateral
Deep venous thrombosis	I82.409	Acute embolism and thrombosis of unspecified deep veins of unspecified lower extremity
Deep venous thrombosis	I82.41	Acute embolism and thrombosis of femoral vein
Deep venous thrombosis	I82.411	Acute embolism and thrombosis of right femoral vein
Deep venous thrombosis	I82.412	Acute embolism and thrombosis of left femoral vein
Deep venous thrombosis	I82.413	Acute embolism and thrombosis of femoral vein, bilateral
Deep venous thrombosis	I82.419	Acute embolism and thrombosis of unspecified femoral vein
Deep venous thrombosis	I82.42	Acute embolism and thrombosis of iliac vein
Deep venous thrombosis	I82.421	Acute embolism and thrombosis of right iliac vein
Deep venous thrombosis	I82.422	Acute embolism and thrombosis of left iliac vein
Deep venous thrombosis	I82.423	Acute embolism and thrombosis of iliac vein, bilateral
Deep venous thrombosis	I82.429	Acute embolism and thrombosis of unspecified iliac vein
Deep venous thrombosis	I82.43	Acute embolism and thrombosis of popliteal vein
Deep venous thrombosis	I82.431	Acute embolism and thrombosis of right popliteal vein
Deep venous thrombosis	I82.432	Acute embolism and thrombosis of left popliteal vein
Deep venous thrombosis	I82.433	Acute embolism and thrombosis of popliteal vein, bilateral
Deep venous thrombosis	I82.439	Acute embolism and thrombosis of unspecified popliteal vein
Deep venous thrombosis	I82.44	Acute embolism and thrombosis of tibial vein
Deep venous thrombosis	I82.441	Acute embolism and thrombosis of right tibial vein

Diagnosis	ICD-10-CM	Code Description
Deep venous thrombosis	I82.442	Acute embolism and thrombosis of left tibial vein
Deep venous thrombosis	I82.443	Acute embolism and thrombosis of tibial vein, bilateral
Deep venous thrombosis	I82.449	Acute embolism and thrombosis of unspecified tibial vein
Deep venous thrombosis	I82.45	Acute embolism and thrombosis of peroneal vein
Deep venous thrombosis	I82.451	Acute embolism and thrombosis of right peroneal vein
Deep venous thrombosis	I82.452	Acute embolism and thrombosis of left peroneal vein
Deep venous thrombosis	I82.453	Acute embolism and thrombosis of peroneal vein, bilateral
Deep venous thrombosis	I82.459	Acute embolism and thrombosis of unspecified peroneal vein
Deep venous thrombosis	I82.46	Acute embolism and thrombosis of calf muscular vein
Deep venous thrombosis	I82.461	Acute embolism and thrombosis of right calf muscular vein
Deep venous thrombosis	I82.462	Acute embolism and thrombosis of left calf muscular vein
Deep venous thrombosis	I82.463	Acute embolism and thrombosis of calf muscular vein, bilateral
Deep venous thrombosis	I82.469	Acute embolism and thrombosis of unspecified calf muscular vein
Deep venous thrombosis	I82.49	Acute embolism and thrombosis of other specified deep vein of lower extremity
Deep venous thrombosis	I82.491	Acute embolism and thrombosis of other specified deep vein of right lower extremity
Deep venous thrombosis	I82.492	Acute embolism and thrombosis of other specified deep vein of left lower extremity
Deep venous thrombosis	I82.493	Acute embolism and thrombosis of other specified deep vein of lower extremity, bilateral
Deep venous thrombosis	I82.499	Acute embolism and thrombosis of other specified deep vein of unspecified lower extremity
Deep venous thrombosis	I82.4Y	Acute embolism and thrombosis of unspecified deep veins of proximal lower extremity
Deep venous thrombosis	I82.4Y1	Acute embolism and thrombosis of unspecified deep veins of right proximal lower extremity
Deep venous thrombosis	I82.4Y2	Acute embolism and thrombosis of unspecified deep veins of left proximal lower extremity
Deep venous thrombosis	I82.4Y3	Acute embolism and thrombosis of unspecified deep veins of proximal lower extremity, bilateral
Deep venous thrombosis	I82.4Y9	Acute embolism and thrombosis of unspecified deep veins of unspecified proximal lower extremity
Deep venous thrombosis	I82.4Z	Acute embolism and thrombosis of unspecified deep veins of distal lower extremity
Deep venous thrombosis	I82.4Z1	Acute embolism and thrombosis of unspecified deep veins of right distal lower extremity
Deep venous thrombosis	I82.4Z2	Acute embolism and thrombosis of unspecified deep veins of left distal lower extremity
Deep venous thrombosis	I82.4Z3	Acute embolism and thrombosis of unspecified deep veins of distal lower extremity, bilateral
Deep venous thrombosis	I82.4Z9	Acute embolism and thrombosis of unspecified deep veins of unspecified distal lower extremity
Deep venous thrombosis	I82.A	Embolism and thrombosis of axillary vein

Diagnosis	ICD-10-CM	Code Description
Deep venous thrombosis	I82.A1	Acute embolism and thrombosis of axillary vein
Deep venous thrombosis	I82.A11	Acute embolism and thrombosis of right axillary vein
Deep venous thrombosis	I82.A12	Acute embolism and thrombosis of left axillary vein
Deep venous thrombosis	I82.A13	Acute embolism and thrombosis of axillary vein, bilateral
Deep venous thrombosis	I82.A19	Acute embolism and thrombosis of unspecified axillary vein
Myocardial infarction	I21.01	ST elevation (STEMI) myocardial infarction involving left main coronary artery
Myocardial infarction	I21.02	ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery
Myocardial infarction	I21.09	ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall
Myocardial infarction	I21.11	ST elevation (STEMI) myocardial infarction involving right coronary artery
Myocardial infarction	I21.19	ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall
Myocardial infarction	I21.21	ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery
Myocardial infarction	I21.29	ST elevation (STEMI) myocardial infarction involving other sites
Myocardial infarction	I21.3	ST elevation (STEMI) myocardial infarction of unspecified site
Myocardial infarction	I21.4	Non-ST elevation (NSTEMI) myocardial infarction
Myocardial infarction	I21.9	Acute myocardial infarction, unspecified
Myocardial infarction	I21.A1	Myocardial infarction type 2
Myocardial infarction	I21.A9	Other myocardial infarction type
Myocardial infarction	I22.0	Subsequent ST elevation (STEMI) myocardial infarction of anterior wall
Myocardial infarction	I22.1	Subsequent ST elevation (STEMI) myocardial infarction of inferior wall
Myocardial infarction	I22.2	Subsequent non-ST elevation (NSTEMI) myocardial infarction
Myocardial infarction	I22.8	Subsequent ST elevation (STEMI) myocardial infarction of other sites
Myocardial infarction	I22.9	Subsequent ST elevation (STEMI) myocardial infarction of unspecified site
Myocardial infarction	I21	Acute myocardial infarction
Myocardial infarction	I21.0	ST elevation (STEMI) myocardial infarction of anterior wall
Myocardial infarction	I21.1	ST elevation (STEMI) myocardial infarction of inferior wall
Myocardial infarction	I21.2	ST elevation (STEMI) myocardial infarction of other sites
Myocardial infarction	I21.A	Other type of myocardial infarction
Myocardial infarction	I22	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
Ischemic/Embolic Stroke	I63.00	Cerebral infarction due to thrombosis of unspecified precerebral artery
Ischemic/Embolic Stroke	I63.011	Cerebral infarction due to thrombosis of right vertebral artery
Ischemic/Embolic Stroke	I63.012	Cerebral infarction due to thrombosis of left vertebral artery

Diagnosis	ICD-10-CM	Code Description
Ischemic/Embolic Stroke	I63.013	Cerebral infarction due to thrombosis of bilateral vertebral arteries
Ischemic/Embolic Stroke	I63.019	Cerebral infarction due to thrombosis of unspecified vertebral artery
Ischemic/Embolic Stroke	I63.02	Cerebral infarction due to thrombosis of basilar artery
Ischemic/Embolic Stroke	I63.031	Cerebral infarction due to thrombosis of right carotid artery
Ischemic/Embolic Stroke	I63.032	Cerebral infarction due to thrombosis of left carotid artery
Ischemic/Embolic Stroke	I63.033	Cerebral infarction due to thrombosis of bilateral carotid arteries
Ischemic/Embolic Stroke	I63.039	Cerebral infarction due to thrombosis of unspecified carotid artery
Ischemic/Embolic Stroke	I63.09	Cerebral infarction due to thrombosis of other precerebral artery
Ischemic/Embolic Stroke	I63.10	Cerebral infarction due to embolism of unspecified precerebral artery
Ischemic/Embolic Stroke	I63.111	Cerebral infarction due to embolism of right vertebral artery
Ischemic/Embolic Stroke	I63.112	Cerebral infarction due to embolism of left vertebral artery
Ischemic/Embolic Stroke	I63.113	Cerebral infarction due to embolism of bilateral vertebral arteries
Ischemic/Embolic Stroke	I63.119	Cerebral infarction due to embolism of unspecified vertebral artery
Ischemic/Embolic Stroke	I63.12	Cerebral infarction due to embolism of basilar artery
Ischemic/Embolic Stroke	I63.131	Cerebral infarction due to embolism of right carotid artery
Ischemic/Embolic Stroke	I63.132	Cerebral infarction due to embolism of left carotid artery
Ischemic/Embolic Stroke	I63.133	Cerebral infarction due to embolism of bilateral carotid arteries
Ischemic/Embolic Stroke	I63.139	Cerebral infarction due to embolism of unspecified carotid artery
Ischemic/Embolic Stroke	I63.19	Cerebral infarction due to embolism of other precerebral artery
Ischemic/Embolic Stroke	I63.20	Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries
Ischemic/Embolic Stroke	I63.211	Cerebral infarction due to unspecified occlusion or stenosis of right vertebral arteries
Ischemic/Embolic Stroke	I63.212	Cerebral infarction due to unspecified occlusion or stenosis of left vertebral arteries
Ischemic/Embolic Stroke	I63.213	Cerebral infarction due to unspecified occlusion or stenosis of bilateral vertebral arteries
Ischemic/Embolic Stroke	I63.219	Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral arteries
Ischemic/Embolic Stroke	I63.22	Cerebral infarction due to unspecified occlusion or stenosis of basilar arteries
Ischemic/Embolic Stroke	I63.231	Cerebral infarction due to unspecified occlusion or stenosis of right carotid arteries
Ischemic/Embolic Stroke	I63.232	Cerebral infarction due to unspecified occlusion or stenosis of left carotid arteries

Diagnosis	ICD-10-CM	Code Description
Ischemic/Embolic Stroke	I63.233	Cerebral infarction due to unspecified occlusion or stenosis of bilateral carotid arteries
Ischemic/Embolic Stroke	I63.239	Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid arteries
Ischemic/Embolic Stroke	I63.29	Cerebral infarction due to unspecified occlusion or stenosis of other precerebral arteries
Ischemic/Embolic Stroke	I63.30	Cerebral infarction due to thrombosis of unspecified cerebral artery
Ischemic/Embolic Stroke	I63.311	Cerebral infarction due to thrombosis of right middle cerebral artery
Ischemic/Embolic Stroke	I63.312	Cerebral infarction due to thrombosis of left middle cerebral artery
Ischemic/Embolic Stroke	I63.313	Cerebral infarction due to thrombosis of bilateral middle cerebral arteries
Ischemic/Embolic Stroke	I63.319	Cerebral infarction due to thrombosis of unspecified middle cerebral artery
Ischemic/Embolic Stroke	I63.321	Cerebral infarction due to thrombosis of right anterior cerebral artery
Ischemic/Embolic Stroke	I63.322	Cerebral infarction due to thrombosis of left anterior cerebral artery
Ischemic/Embolic Stroke	I63.323	Cerebral infarction due to thrombosis of bilateral anterior arteries
Ischemic/Embolic Stroke	I63.329	Cerebral infarction due to thrombosis of unspecified anterior cerebral artery
Ischemic/Embolic Stroke	I63.331	Cerebral infarction due to thrombosis of right posterior cerebral artery
Ischemic/Embolic Stroke	I63.332	Cerebral infarction due to thrombosis of left posterior cerebral artery
Ischemic/Embolic Stroke	I63.333	Cerebral infarction to thrombosis of bilateral posterior arteries
Ischemic/Embolic Stroke	I63.339	Cerebral infarction due to thrombosis of unspecified posterior cerebral artery
Ischemic/Embolic Stroke	I63.341	Cerebral infarction due to thrombosis of right cerebellar artery
Ischemic/Embolic Stroke	I63.342	Cerebral infarction due to thrombosis of left cerebellar artery
Ischemic/Embolic Stroke	I63.343	Cerebral infarction to thrombosis of bilateral cerebellar arteries
Ischemic/Embolic Stroke	I63.349	Cerebral infarction due to thrombosis of unspecified cerebellar artery
Ischemic/Embolic Stroke	I63.39	Cerebral infarction due to thrombosis of other cerebral artery
Ischemic/Embolic Stroke	I63.40	Cerebral infarction due to embolism of unspecified cerebral artery
Ischemic/Embolic Stroke	I63.411	Cerebral infarction due to embolism of right middle cerebral artery

Diagnosis	ICD-10-CM	Code Description
Ischemic/Embolic Stroke	I63.412	Cerebral infarction due to embolism of left middle cerebral artery
Ischemic/Embolic Stroke	I63.413	Cerebral infarction due to embolism of bilateral middle cerebral arteries
Ischemic/Embolic Stroke	I63.419	Cerebral infarction due to embolism of unspecified middle cerebral artery
Ischemic/Embolic Stroke	I63.421	Cerebral infarction due to embolism of right anterior cerebral artery
Ischemic/Embolic Stroke	I63.422	Cerebral infarction due to embolism of left anterior cerebral artery
Ischemic/Embolic Stroke	I63.423	Cerebral infarction due to embolism of bilateral anterior cerebral arteries
Ischemic/Embolic Stroke	I63.429	Cerebral infarction due to embolism of unspecified anterior cerebral artery
Ischemic/Embolic Stroke	I63.431	Cerebral infarction due to embolism of right posterior cerebral artery
Ischemic/Embolic Stroke	I63.432	Cerebral infarction due to embolism of left posterior cerebral artery
Ischemic/Embolic Stroke	I63.433	Cerebral infarction due to embolism of bilateral posterior cerebral arteries
Ischemic/Embolic Stroke	I63.439	Cerebral infarction due to embolism of unspecified posterior cerebral artery
Ischemic/Embolic Stroke	I63.441	Cerebral infarction due to embolism of right cerebellar artery
Ischemic/Embolic Stroke	I63.442	Cerebral infarction due to embolism of left cerebellar artery
Ischemic/Embolic Stroke	I63.443	Cerebral infarction due to embolism of bilateral cerebellar arteries
Ischemic/Embolic Stroke	I63.449	Cerebral infarction due to embolism of unspecified cerebellar artery
Ischemic/Embolic Stroke	I63.49	Cerebral infarction due to embolism of other cerebral artery
Ischemic/Embolic Stroke	I63.50	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery
Ischemic/Embolic Stroke	I63.511	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
Ischemic/Embolic Stroke	I63.512	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery
Ischemic/Embolic Stroke	I63.513	Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle arteries
Ischemic/Embolic Stroke	I63.519	Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery
Ischemic/Embolic Stroke	I63.521	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery
Ischemic/Embolic Stroke	I63.522	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery
Ischemic/Embolic Stroke	I63.523	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior arteries

Diagnosis	ICD-10-CM	Code Description
Ischemic/Embolic Stroke	I63.529	Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery
Ischemic/Embolic Stroke	I63.531	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery
Ischemic/Embolic Stroke	I63.532	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery
Ischemic/Embolic Stroke	I63.533	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior arteries
Ischemic/Embolic Stroke	I63.539	Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery
Ischemic/Embolic Stroke	I63.541	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery
Ischemic/Embolic Stroke	I63.542	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery
Ischemic/Embolic Stroke	I63.543	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries
Ischemic/Embolic Stroke	I63.549	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery
Ischemic/Embolic Stroke	I63.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery
Ischemic/Embolic Stroke	I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
Ischemic/Embolic Stroke	I63.8	Other cerebral infarction
Ischemic/Embolic Stroke	I63.9	Cerebral infarction, unspecified
Ischemic/Embolic Stroke	I67.89	Other cerebrovascular disease
Ischemic/Embolic Stroke	I63	Cerebral infarction
Ischemic/Embolic Stroke	I63.0	Cerebral infarction due to thrombosis of precerebral arteries
Ischemic/Embolic Stroke	I63.01	Cerebral infarction due to thrombosis of vertebral artery
Ischemic/Embolic Stroke	I63.03	Cerebral infarction due to thrombosis of carotid artery
Ischemic/Embolic Stroke	I63.1	Cerebral infarction due to embolism of precerebral arteries
Ischemic/Embolic Stroke	I63.11	Cerebral infarction due to embolism of vertebral artery
Ischemic/Embolic Stroke	I63.13	Cerebral infarction due to embolism of carotid artery
Ischemic/Embolic Stroke	I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
Ischemic/Embolic Stroke	I63.21	Cerebral infarction due to unspecified occlusion or stenosis of vertebral arteries
Ischemic/Embolic Stroke	I63.23	Cerebral infarction due to unspecified occlusion or stenosis of carotid arteries
Ischemic/Embolic Stroke	I63.3	Cerebral infarction due to thrombosis of cerebral arteries
Ischemic/Embolic Stroke	I63.31	Cerebral infarction due to thrombosis of middle cerebral artery
Ischemic/Embolic Stroke	I63.32	Cerebral infarction due to thrombosis of anterior cerebral artery
Ischemic/Embolic Stroke	I63.33	Cerebral infarction due to thrombosis of posterior cerebral artery
Ischemic/Embolic Stroke	I63.34	Cerebral infarction due to thrombosis of cerebellar artery
Ischemic/Embolic Stroke	I63.4	Cerebral infarction due to embolism of cerebral arteries

Diagnosis	ICD-10-CM	Code Description
Ischemic/Embolic Stroke	I63.41	Cerebral infarction due to embolism of middle cerebral artery
Ischemic/Embolic Stroke	I63.42	Cerebral infarction due to embolism of anterior cerebral artery
Ischemic/Embolic Stroke	I63.43	Cerebral infarction due to embolism of posterior cerebral artery
Ischemic/Embolic Stroke	I63.44	Cerebral infarction due to embolism of cerebellar artery
Ischemic/Embolic Stroke	I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
Ischemic/Embolic Stroke	I63.51	Cerebral infarction due to unspecified occlusion or stenosis of middle cerebral artery
Ischemic/Embolic Stroke	I63.52	Cerebral infarction due to unspecified occlusion or stenosis of anterior cerebral artery
Ischemic/Embolic Stroke	I63.53	Cerebral infarction due to unspecified occlusion or stenosis of posterior cerebral artery
Ischemic/Embolic Stroke	I63.54	Cerebral infarction due to unspecified occlusion or stenosis of cerebellar artery