NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Investigating the effect of the 13-valent pneumococcal conjugate vaccine on major adverse cardiovascular events among Medicare enrollees aged ≥65 years in the United States
Protocol number	B1851222
Protocol version identifier	1.0
Date	28 March 2025
EU Post Authorization Study (PAS) register number	EUPAS1000000520
Active substance	World Health Organization's Anatomical Therapeutic Chemical (ATC) code - J07AL02 13-valent pneumococcal conjugate vaccine
Medicinal product	Prevenar 13
Research question and objectives	Research question: Is prior receipt of PCV13 associated with reduced risk of major adverse cardiovascular events (MACE) outcomes in adults aged ≥65 years? The primary objective of this study is to: 1. Evaluate the effect of the 13-valent pneumococcal conjugate vaccine (PCV13) receipt on the risk of major adverse cardiovascular events (MACE) at 1 and 3 years of follow-up among adults aged ≥65 years The secondary objectives of this study are to: 1. Evaluate the effect of PCV13 receipt on the risk of myocardial infarction at 1 and 3 years of follow-up among adults aged ≥65 years 2. Evaluate the effect of PCV13 receipt on the risk of stroke at 1 and 3 years of follow-up among adults aged ≥65 years

	3. Evaluate the effect of PCV13 receipt on the risk of hospitalization due to heart failure at 1 and 3 years of follow-up among adults aged ≥65 years 4. Examine the degree to which community-acquired pneumonia (CAP) mediates the relationship between PCV13 receipt and MACE at 1 year of follow-up among adults aged >=65 years
Country(ies) of study	United States
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ACIP	Advisory Committee on Immunization Practices
ATC	Anatomical Therapeutic Chemical
CAD	Coronary artery disease
CAP	Community-acquired pneumonia
CCW	Chronic Conditions Warehouse
CDC	Centers for Disease Control and Prevention
CDE	Controlled Direct Effect
CI	Confidence intervals
CIF	Cumulative incidence function
CFR	Code of Federal Regulations
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic obstructive pulmonary disease
CPT	Current Procedural Terminology
DUA	Data Use Agreement
EC	Ethics Committee
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPIC	Etiology of Pneumonia in the Community
FDA	Food and Drug Administration
FFS	Fee-for-Service
GPP	Guidelines for Good Pharmacoepidemiologic Practice
HCPCS	Healthcare Common Procedure Coding System

HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth revision, Clinical Modification
ICD-9-PCS	International Classification of Diseases, Ninth Revision, Procedure Coding System
ICD-10-PCS	International Classification of Diseases, Tenth Revision, Procedure Coding System
IPCW	Inverse probability of censoring weighting
IPTW	Inverse probability of treatment weighting
IRB	Institutional Review Board
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LTCF	Long-term care facility
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MMWR	Morbidity and Mortality Weekly Report
NDC	National drug code
NIE	Natural Indirect Effect
PAD	Peripheral arterial disease
PASS	Post-authorization safety study
PCV	Pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
PS	Propensity score

SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SMD	Standardized mean difference
SNF	Skilled nursing facility
SQL	Structured Query Language
STEMI	ST elevation myocardial infarction
ssUAD	Serotype-specific urinary antigen detection
TIA	Transient ischemic attacks
US	United States
VRDC	Virtual Research Data Center

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4. ABSTRACT

Title	Investigating the effect of the 13-valent pneumococcal conjugate vaccine on major adverse cardiovascular events among Medicare enrollees aged ≥65 years in the United States Version 1.0 Protocol date: 28 March 2025 Author: Amanda Miles, MPH Affiliation: Pfizer Inc., 66 Hudson Blvd. East, New York, NY 10001, United States
Rationale and background	Adult patients with community-acquired pneumonia (CAP), particularly pneumococcal CAP, are at substantial risk of major cardiovascular events (MACE). There is evidence from observational studies that respiratory vaccines, influenza vaccination in particular, can reduce the risk of MACE in adults.[1, 2] However, data on the potential effects of 13-valent pneumococcal conjugate vaccine (PCV13) to reduce MACE in adults are limited.
Research question and objectives	Research question: Is prior receipt of PCV13 associated with reduced risk of major adverse cardiovascular events (MACE) outcomes in adults aged ≥65 years? The primary objective of this study is to: 1. Evaluate the effect of PCV13 receipt on the risk of major adverse cardiovascular events (MACE) at 1 and 3 years of follow-up among adults aged ≥65 years The secondary objectives of this study are to: 1. Evaluate the effect of PCV13 receipt on the risk of myocardial infarction at 1 and 3 years of follow-up among adults aged ≥65 years 2. Evaluate the effect of PCV13 receipt on the risk of stroke at 1 and 3 years of follow-up among adults aged ≥65 years 3. Evaluate the effect of PCV13 receipt on the risk of hospitalization due to heart failure at 1 and 3 years of follow-up among adults aged ≥65 years 4. Examine the degree to which CAP mediates the relationship between PCV13 receipt and MACE at 1 year of follow-up among adults aged >=65 years
Study Design	The study will be a retrospective cohort study using Medicare administrative claims data.

	The index date for the vaccinated cohort is defined as the first date of PCV13 vaccination. For the unvaccinated cohort, the index date is defined as the date of the first available healthcare claim that occurs after the eligibility date (September 14, 2014) and ensures a six-month continuous period following enrollment.
Population	The study cohort will be identified using administrative claims. The study population includes individuals aged ≥65 years of age and enrolled in Medicare Fee-for-Service (FFS) Parts A and B as of September 14, 2014. Individuals are required to have at least 6 months of prior continuous enrollment in Medicare FFS Parts A and B as of the index date to be included in the study. Individuals with evidence of PCV13 receipt prior to index, evidence of PPSV23 receipt in the 365 days prior to index, enrollment in Medicare Part C between September 14, 2014 and index, a high-risk condition for CAP in the 365d prior to index, iatrogenic immunosuppression in the 6 months prior to index, a pneumonia diagnosis code in the hospital setting in the 365d prior to index, or a MACE event in the hospital, skilled nursing facility (SNF), or long-term care facility (LTCF) setting in the 365d prior to index will be excluded. PCV13 vaccinated time segments are excluded if the individual had a pneumonia diagnosis code in the hospital setting or a MACE diagnosis code in the hospital, SNF, or LTCF setting in the 13 days after PCV13 vaccination. For PCV13 vaccinated individuals contributing unvaccinated and vaccinated time segments, inclusion/exclusion criteria and baseline characteristics will be assessed separately for each index date.
Variables	**Exposure** : PCV13 vaccination **Outcomes**: Any MACE, Myocardial infarction, Stroke, Stroke sensitivity, Heart Failure, Cataract surgery (Negative control outcome), lipoma (Negative control outcome), Follow-up time (descriptive) Covariates: Age, Sex, Race/ethnicity, Geographic region, Respiratory season of index, Year of index date, Month of index date, Outpatient heart failure, Coronary artery disease (CAD), Hypertension, Valvular heart disease, Unstable angina, Stable angina, Aortic aneurysm and dissection, Arrhythmia, Atrial fibrillation, Cardiomyopathy, Peripheral arterial disease (PAD), Pulmonary hypertension, Rheumatic heart disease, Congenital heart defects, High cholesterol, High triglycerides, Metabolic syndrome, Autoimmune disease, Transient ischemic attacks (TIA), Dementia, Chronic obstructive pulmonary disease (COPD), Connective tissue disease, Peptic ulcer disease, Chronic liver disease, Diabetes mellitus, Hemiplegia, Solid tumor, Chronic lung disease, Asthma, Alcoholism, Smoking, Obesity, Functional/mobility status, Physical/wellness visit, Number of hospitalizations in the prior 180d, Number of outpatient visits in the prior 180d, Nursing home stay, Skilled nursing facility (SNF) stay, Influenza vaccine, Type of index influenza vaccine administered, PPSV23 receipt, Respiratory failure, Influenza infection, Outpatient pneumonia, Telehealth visits, Flu test in the prior 365 days, Number of labs ordered in the prior 365 days, Number of lipid lab tests ordered in the prior 365 days, Echocardiogram, Electrocardiogram

Data source	The Medicare administrative claims database includes individuals ≥65 years of age and individuals with a qualifying disability who are enrolled in a Medicare fee-for-service plan. The database includes enrollment information for these individuals as well as adjudicated claims for inpatient care, ambulatory care, and outpatient prescriptions.
Study size	Treatment-to-control group allocation ratio (2:3) and the hazard rate for the control group (0.0507) were estimated based on a feasibility analysis using the Medicare fee-for-service claims database. We assumed a hazard ratio of 0.85 for the PCV13 vaccinated compared to the unvaccinated group and used a two-sided test with a significance level of 5%. To account for different follow-up durations, we calculated required sample sizes for average follow-up durations of 0.75, 1, 2.75, and 3 years. The sample sizes were calculated to achieve 80% power in each scenario. Assuming an average follow-up duration of 3 years, the study will require a minimum sample size of 9,600 adults. Assuming an average follow-up duration of 0.75 years, the study will require a minimum sample size of 36,485 adults. A feasibility analysis using the Medicare fee-for-service claims database estimated approximately 25 million adults are eligible for inclusion in the study during the years of interest.
Data analysis	Separate analyses will be conducted with 0 to 1 year and 0 to 3 years of follow-up. A cause-specific Cox proportional hazards model with time-varying covariates will be used for the primary analysis. The cause-specific cox model will be used to estimate hazard ratios (HRs) for each MACE outcome, comparing PCV13 vaccinated with PCV13 unvaccinated Medicare enrollees. The weighted cumulative incidence function (CIF) will also be presented, describing and accounting for competing risk events. The analysis will utilize Inverse Probability of Treatment Weighting (IPTW) to adjust for baseline differences between the vaccinated and unvaccinated cohorts. Covariates with residual imbalance after weighting will be included in the final models for further adjustment to control for potential confounders. The primary analysis models will also adjust for influenza vaccination status during follow-up as a time-varying covariate. The study will also include a mediation analysis, which is considered a secondary analysis. The mediation analysis will estimate the direct and indirect effects of PCV13 receipt on MACE, examining the extent to which the relationship between PCV13 and MACE within 1 year of follow-up is mediated by CAP. The mediation analysis will utilize the product method,[3] which uses a logistic weighted mediation model to assess the mediator and a Cox model weighted outcome model to derive the HR and confidence intervals (CI). The study will also include three sensitivity analyses. The first sensitivity analysis will incorporate the Fine-Gray model, which provides an alternative to the cause-specific Cox model and helps ensure the robustness of the findings when comparing different analytical approaches to competing risks. Second, the study will include a sensitivity analysis using an alternative definition of stroke. The primary analysis

	will include ischemic stroke only and the sensitivity analysis will include hemorrhagic and ischemic stroke. The third sensitivity analysis will modify the definition of CAP in the mediation analysis to only include CAP cases in the hospital setting.
Milestones	Completion of feasibility assessment : 24 July 2024 Registration, HMA-EMA Catalogues of RWD studies: 11 April 2025 Expected Start of data collection : 15 April 2025 Expected End of data collection : 01 September 2025 Expected Final study report : 01 April 2026

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Completion of feasibility assessment	24 July 2024
Registration in the HMA-EMA Catalogues of RWD studies	11 April 2025
Start of data collection	15 April 2025
End of data collection	01 September 2025
Final study report	01 April 2026

7. RATIONALE AND BACKGROUND

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality in older adults. A systematic review conducted in 2020 reported that in the United States (US), the estimated annual incidence of hospitalized CAP among adults aged ≥65 years ranges from 847 to 3500 per 100,000 persons.[4] In a prospective study of adults hospitalized with CAP conducted in Louisville, Kentucky during 2014 to 2016, 6.5% of patients died during hospitalization, and mortality increased to 30.6% at 1 year after hospitalization.[5] CAP can be caused by a wide range of viral, bacterial, and fungal pathogens, with *Streptococcus pneumoniae* typically reported as a leading bacterial cause. In the Etiology of Pneumonia in the Community (EPIC) study conducted by the US Centers for Disease Control and Prevention (CDC) at 5 hospitals during 2010–2012, *S. pneumoniae* was the most common bacteria identified and the third most common pathogen overall, behind rhinovirus and influenza virus.[6] A systematic literature review published in 2020 that included 146 studies evaluating CAP etiology in adults in developed countries found that *S. pneumoniae* remains the most common bacterial cause of CAP, despite some declines in incidence in recent years.[7] Detection of pneumococcal CAP is underestimated using traditional diagnostic methods such as sputum culture, as evidenced by the EPIC study, which found that use of serotype-specific urinary antigen detection (ssUAD) assay that detects the serotypes included in the 13-valent pneumococcal conjugate vaccine (PCV13) substantially increased detection of pneumococcal pneumonia.[8] The Louisville, Kentucky adult CAP study conducted ssUAD testing for 24 pneumococcal serotypes and found that 13% of patients had pneumococcal pneumonia.[9] They estimated that each year in the United States, more than 225,000 adults are hospitalized for pneumococcal CAP, and one quarter of these patients die within one year after hospitalization.[9]

Cardiovascular complications are common during and after CAP, with up to 30% of hospitalized CAP patients experiencing a major adverse cardiovascular event (MACE).[10] Cardiovascular complications during and after CAP are closely associated with poor outcomes including mortality.[10] Several pathophysiological mechanisms may contribute to the association between CAP and MACE outcomes, such as systemic inflammation resulting from pneumonia, or disruption of a previously stable plaque leading to an acute myocardial infarction.[10-12] Additionally, there is evidence that the pathogens causing pneumonia, including *S. pneumoniae* in particular, can directly damage the cardiovascular system.[10] Adult patients with pneumococcal CAP are at substantial risk for MACE.[13] MACE outcomes are also common in adults with invasive pneumococcal disease. In a cohort of Dutch adults aged ≥45 years, 4.2% experienced a cardiovascular event within one year after hospitalization for invasive pneumococcal disease, with acute coronary syndromes primarily occurring within 12 days of admission.[14] Evidence from in vitro and animal studies has implicated the pneumococcal toxin pneumolysin in cardiac injury.[15] In a non-human primate model of severe

pneumococcal pneumonia, examination of cardiac tissue showed that *S. pneumoniae* invaded the myocardium and induced cardiac injury with necroptosis and apoptosis, and cardiac scarring occurred after antibiotic treatment.[16] Studies in mouse models have determined that heart damage varies by pneumococcal strain.[17] Similarly, clinical studies have revealed that MACE in patients with invasive pneumococcal disease are serotype dependent.[18]

The 13-valent pneumococcal conjugate vaccine (PCV13) provides protection against invasive pneumococcal disease and vaccine-type pneumococcal CAP in older adults.[19] Additionally, PCV13 is associated with reduced incidence of all-cause CAP and lower respiratory infections in older adults.[20] There is evidence that respiratory vaccines, influenza vaccination in particular, can reduce the risk of MACE in adults.[2] Several observational studies have investigated whether the 23-valent pneumococcal polysaccharide vaccine (PPV23) provides protection against MACE outcomes such as myocardial infarction and stroke, with results varying by study and outcome.[21, 22] To date, no published data on the effectiveness of PCV13 on MACE outcomes are available, however a retrospective cohort study in Hong Kong adults aged ≥65 investigated whether sequential vaccination with PCV13 and 23-valent pneumococcal polysaccharide vaccine (PPSV23) would provide protection against cardiovascular diseases compared with a single pneumococcal vaccine.[23] Tong et al. found that older adults who received sequential dual vaccination had a lower risk of cardiovascular diseases [Hazard Ratio (95% confidence interval): 0.75 (0.71, 0.80)] compared with those who received a single pneumococcal vaccine.[23] Post-hoc analysis indicated that the decreased cardiovascular disease risk was mediated by a reduction in all-cause pneumonia.

This observational study was designed to evaluate the effect of PCV13 on MACE outcomes among adults aged ≥65 years in the United States using a large claims database from the Medicare health insurance program.

The biological mechanism behind the potential impact of PCV13 receipt on risk of MACE is through a reduction in all-cause pneumonia, which is an infection commonly associated with cardiovascular complications.[10-12] While the intention of the study is to investigate the hypothesis that PCV13 receipt reduces the risk of certain adverse events (e.g. MACE, myocardial infarction (MI), stroke, etc) through the prevention of pneumonia, it is possible that during this enquiry, the study may collect data which indicates an unanticipated safety signal.

This noninterventional study is designated as a post-authorization safety study (PASS) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

Research question:

Is prior receipt of PCV13 associated with reduced risk of major adverse cardiovascular events (MACE) outcomes in adults aged ≥65 years?

The primary objective of this study is to:

1. Evaluate the effect of PCV13 receipt on the risk of major adverse cardiovascular events (MACE) at 1 and 3 years of follow-up among adults aged ≥65 years

The secondary objectives of this study are to:

1. Evaluate the effect of PCV13 receipt on the risk of myocardial infarction at 1 and 3 years of follow-up among adults aged ≥65 years

2. Evaluate the effect of PCV13 receipt on the risk of stroke at 1 and 3 years of follow-up among adults aged ≥65 years

3. Evaluate the effect of PCV13 receipt on the risk of hospitalization due to heart failure at 1 and 3 years of follow-up among adults aged ≥65 years

4. Examine the degree to which CAP mediates the relationship between PCV13 receipt and MACE at 1 year of follow-up among adults aged >=65 years

9. RESEARCH METHODS

9.1. Study Design

This structured secondary data collection study will be a retrospective cohort study using Centers for Medicare and Medicaid Services (CMS) Medicare data to examine the effect of PCV13 receipt on the risk of MACE among adults aged ≥65 years in the United States. Individuals will be identified using Medicare Fee-for-Service (FFS) Parts A and B enrollment and claims data.

The analysis will be conducted at the time-segment level using a target trial emulation approach. In this time-segment design, individuals who receive a PCV13 vaccine during the study period can contribute up to two time segments during the follow-up period: a PCV13 unvaccinated time segment and a PCV13 vaccinated time segment. Each segment will be attributed to the appropriate vaccination exposure status cohort, resulting in the individual having two separate index dates included in the analysis. Inclusion/exclusion criteria and baseline characteristics will be assessed separately for these two index dates. For PCV13 unvaccinated patients, multiple eligible times may be identified within the study period, but only the first eligible time will be selected due to the large sample size of the unvaccinated cohort. Individuals who remain unvaccinated throughout the entire follow-up period can contribute a maximum of 1 time segment, which will be attributed to the unvaccinated cohort. All analyses will be conducted based on time-segment level data, which allows the exposure variable – PCV13 vaccination – to be treated as time-invariant within each segment.

The index date for the vaccinated cohort is defined as the date of first PCV13 vaccination. For the unvaccinated cohort, the index date is defined as the date of the first available healthcare claim that occurs after the eligibility date (September 14, 2014) and ensures a six-month period of continuous enrollment prior to the index date. Eligible vaccinated and unvaccinated index dates are 1) between September 14, 2014 and November 30, 2019 and 2) after the individual has at least 6 months of continuous enrollment in Medicare FFS Parts A and B. The 6 months of continuous enrollment prior to the index date for each time segment will be used as the baseline period. Baseline covariates, including demographics, preventative care behaviors, and comorbidities will be assessed during this period.

During PCV13 unvaccinated time segments, unvaccinated individuals will be followed from their unvaccinated index date until experiencing one of the following: 1) the outcome, 2) disenrollment, 3) death, 4) receipt of a PCV13 vaccine, 5) receipt of a PPSV23 vaccine, or 6) the end of the study period. During PCV13 vaccinated time segments, vaccinated individuals will be followed starting 14 days after their first PCV13 vaccination and until experiencing one of the following: 1) the outcome,

2) disenrollment, 3) death, 4) receipt of a second PCV13 vaccine, 5) receipt of a PPSV23 vaccine, or 6) the end of the study period.

Rationale: A retrospective cohort study design was selected because the PCV13 vaccine was recommended by the Advisory Committee on Immunization Practices (ACIP) for all adults age ≥65 years in the United States in 2014.[24] Data on PCV13 eligible individuals with 3 years of follow-up already exists in the Medicare database, which means that the data does not need to be collected prospectively. Additionally, a retrospective cohort was selected instead of a case control design because 1) major cardiovascular events are not considered a rare outcome and 2) a cohort design establishes the temporal relationship between the exposure and outcome. PCV13-vaccinated and PCV13-unvaccinated were selected as the comparison groups because is the comparison that would allow the study to evaluate the impact of PCV13 receipt on risk of MACE.

9.2. Setting

The study period is September 14, 2014 through December 31, 2019. However, Medicare data will be used going back to 1) September 14, 2013 to assess baseline characteristics and 2) January 1, 2010 to ascertain whether the individual received a PCV13 or PPSV23 vaccine prior to the study period.

The study population includes individuals aged ≥65 years and enrolled in Medicare Fee-for-Service (FFS) Parts A and B as of September 14, 2014. Individuals are required to have at least 6 months of prior continuous enrollment in Medicare FFS Parts A and B as of the index date to be included in the study. Individuals with evidence of PCV13 receipt prior to the index date, evidence of PPSV23 receipt in the 365 days prior to the index date, enrollment in Medicare Part C between September 14, 2014 and the index date, a high-risk condition for CAP in the 365 days prior to index, iatrogenic immunosuppression in the 6 months prior to index, a pneumonia diagnosis code in the hospital setting in the 365 days prior to index, a MACE event in the hospital, skilled nursing facility (SNF), or long-term care facility (LTCF) setting in the 365 days prior to index will be excluded. PCV13 vaccinated individuals with a pneumonia diagnosis code in the hospital setting or a MACE diagnosis code in the hospital, SNF, or LTCF setting in the 13 days following first PCV13 vaccination will also be excluded.

For PCV13 vaccinated individuals contributing unvaccinated and vaccinated time segments, inclusion and exclusion criteria will be assessed separately for each index date.

Inclusion criteria rationale:

- Individuals were required to be enrolled in Medicare FFS Parts A and B because that is the database being used for the study. Individuals were required to be enrolled as of September 14, 2014 so that the analysis would not misclassify an individual as unvaccinated if the individual received their PCV13 vaccine after the ACIP recommendation, but prior to enrolling in Medicare FFS (i.e. vaccination claims will only be included in the database if the vaccine was received while the individual was enrolled in Medicare FFS).
- The study includes adults age ≥65 years as of September 14, 2014 because that is the date that the CDC ACIP gave the age-based PCV13 recommendation for adults age ≥65 years. As such, these adults would have been eligible to receive the PCV13 vaccine (i.e. exposure of interest).
- Individuals were required to have at least 6 months of prior continuous enrollment in Medicare FFS prior to the index date to assess baseline characteristics.

Exclusion criteria rationale:

- Individuals with evidence of PCV13 vaccination prior to the index date were excluded because the individual would not be eligible to receive a PCV13 vaccine during the study period
- Individuals with evidence of PPSV23 vaccination in the 365 days prior to the index date were excluded because PPSV23 receipt within 365 days prior to PCV13 receipt could result in hyporesponsiveness to the PCV13 vaccine. In addition, the CDC ACIP PCV13 recommendation on September 14, 2014 recommends that individuals only receive a dose of PCV13 if the individual had not previously received a pneumococcal vaccine or if the individual received PPSV23 ≥1 year prior. This exclusion criterion was included to align with the CDC ACIP recommendations at the start of the study period.
- The CDC ACIP recommended PCV13 for adults age ≥19 years with a high-risk condition for pneumonia on October 12, 2012.[25] Individuals with ≥1 diagnosis code for a pneumonia high-risk condition in the 365 days prior or evidence of iatrogenic immunosuppression in the 6 months prior to index were excluded because these individuals were eligible to receive PCV13 prior to turning age 65 years and before being eligible to enroll in Medicare health insurance. Since records of vaccination prior to enrolling in Medicare are not available in the database, these individuals were excluded to reduce the risk of misclassifying PCV13 vaccination status.
- Individuals with a pneumonia diagnosis code in the hospital setting in the 365 days prior to the index date were excluded because recent history of severe pneumonia increases the risk of a future diagnosis of pneumonia. Pneumonia is the hypothesized mediator for the impact of PCV13 on risk of MACE. Excluding these individuals equalizes this risk for the PCV13 vaccinated and PCV13 unvaccinated cohorts.
- Individuals with a MACE diagnosis code in the hospital, SNF, and LTCF setting the 365 days prior to the index date were excluded because recent history of an acute MACE event increases the risk of a future MACE event. Excluding these individuals equalizes this risk for the PCV13 vaccinated and PCV13 unvaccinated cohorts.
- Individuals with Medicare Part C enrollment between September 14, 2014 and the index date were excluded because the individual would have been eligible to receive PCV13, but any vaccination records during enrollment in Medicare Part C would not be included in the individual's Medicare FFS records. As such, these individuals were excluded to reduce the risk of misclassifying PCV13 vaccination status.
- PCV13 vaccinated individuals with a pneumonia diagnosis code in the hospital setting or a MACE diagnosis code in the hospital, SNF, or LTCF setting in the 13 days after first PCV13 vaccination because the vaccine is not considered to be fully effective until 14 days following vaccination.

Exclusion criteria: Sample size impact

- Approximately 25 million individuals are estimated to be eligible for inclusion in the study. As such, these exclusion criteria do not substantially impact the ability to meet the minimum sample size required for this study. Please refer to **Section 9.5** for additional information on the minimum sample size required for this study.

9.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria as of the index date to have the respective time segment included in the study:

1. Enrolled in Medicare FFS Parts A and B as of September 14, 2014 (date of PCV13 ≥65 recommendation in the Morbidity and Mortality Weekly Report (MMWR)[24])
2. Aged ≥65 years as of September 14, 2014
3. Continuous enrollment in Medicare FFS Parts A and B for at least 6 months prior to the index date

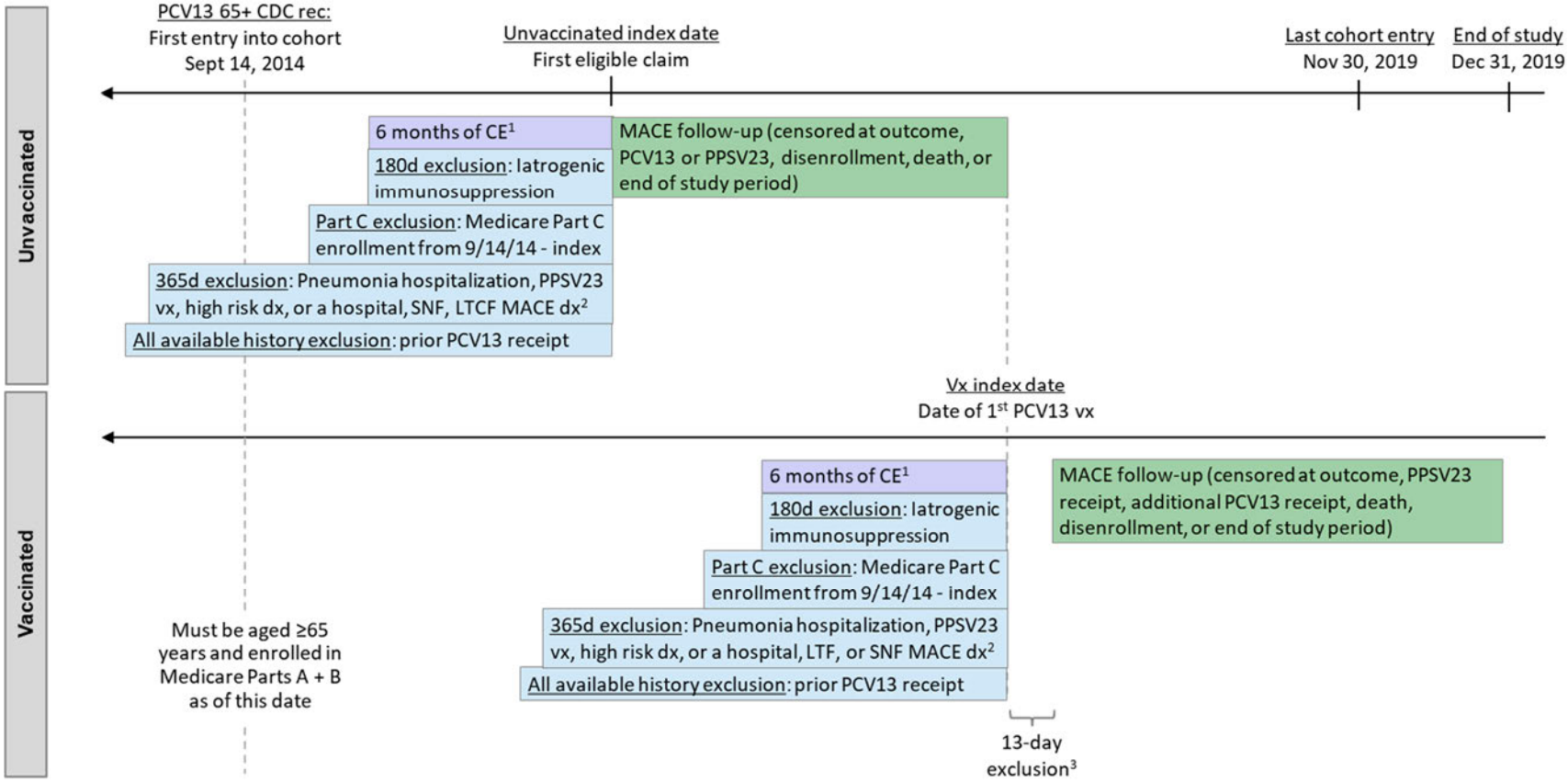
9.2.2. Exclusion Criteria

Patients meeting any of the following criteria as of the index date will not have the respective time segment included in the study:

1. Evidence of PCV13 vaccination prior to the index date
2. Evidence of PPSV23 vaccination in the 365 days prior to the index date[a]
3. ≥1 diagnosis code for a high-risk condition in the 365 days prior to the index date[a]
4. Evidence of iatrogenic immunosuppression in the 6 months prior to the index date
5. Pneumonia diagnosis code in the hospital setting in the 365 days prior to the index date[a]
6. MACE diagnosis code in the hospital, SNF, or LTCF setting in the 365 days prior to the index date[a]
7. Medicare Part C enrollment between September 14, 2014 and the index date
8. PCV13 vaccinated individuals with a pneumonia diagnosis code in the hospital setting or a MACE diagnosis code in the hospital, SNF, or LTCF setting in the 13 days after first PCV13 vaccination

a. For adults with ≥6 months, but less than 365 days of prior continuous enrollment, the exclusion criteria will be evaluated during the continuous enrollment period that the adult has available.

Figure 1. Illustrative Timeline



1. Continuous enrollment (CE)
2. Vaccination (vx); diagnosis (dx); skilled nursing facility (SNF); long-term care facility (LTCF)
3. Excludes vaccinated time segments where the adult had a pneumonia hospitalization or a hospital, SNF, LTCF MACE dx in the 13 days after PCV13 vaccination

9.3. Variables

9.3.1. Exposure

Table 1. Exposure Variable

Variable	Role	Operational definition	Measurement period
PCV13 vaccination	Exposure	One claim (Current procedural terminology® [CPT] or National Drug Codes [NDC]) for PCV13 vaccination. CPT and NDC codes for PCV13 vaccination are listed in Appendix Table 1.	Follow-up

9.3.2. Outcomes

Table 2. Outcome Variables

Variable	Role	Operational definition	Measurement period
Any MACE	Outcome	≥1 International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or International Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM) diagnosis code for myocardial infarction, stroke, or heart failure in the hospital, SNF, or LTCF setting. Analyses include first event only and the code must occur one of the following time periods: 1. ≥0 days after the unvaccinated index date and before the minimum date of censoring for the unvaccinated time segment 2. ≥14 days after the vaccinated index date and before the minim date of censoring for the vaccinated time segment.	Follow-up

		ICD-9-CM or ICD-10-CM codes are listed in Appendix Table 2.	
Myocardial infarction	Outcome	≥1 ICD-9-CM or ICD-10-CM diagnosis code for myocardial infarction in the hospital, SNF, or LTCF setting. Analyses include first event only and the code must occur one of the following time periods: 1. ≥0 days after the unvaccinated index date and before the minimum date of censoring for the unvaccinated time segment 2. ≥14 days after the vaccinated index date and before the minim date of censoring for the vaccinated time segment. ICD-9-CM or ICD-10-CM codes are listed in Appendix Table 2.	Follow-up
Stroke	Outcome	≥1 ICD-9-CM or ICD-10-CM diagnosis code for ischemic stroke in the hospital, SNF, or LTCF setting. Analyses include first event only and the code must occur one of the following time periods: 1. ≥0 days after the unvaccinated index date and before the minimum date of censoring for the unvaccinated time segment 2. ≥14 days after the vaccinated index date and before the minim date of censoring for the vaccinated time segment. ICD-9-CM or ICD-10-CM codes are listed in Appendix Table 2.	Follow-up
Stroke sensitivity	Outcome	≥1 ICD-9-CM or ICD-10-CM diagnosis code for ischemic or hemorrhagic stroke in the hospital, SNF, or LTCF setting.	Follow-up

		Analyses include first event only and the code must occur one of the following time periods: 1. ≥0 days after the unvaccinated index date and before the minimum date of censoring for the unvaccinated time segment 2. ≥14 days after the vaccinated index date and before the minim date of censoring for the vaccinated time segment. ICD-9-CM or ICD-10-CM codes are listed in Appendix Table 2.	
Heart failure	Outcome	≥1 ICD-9-CM or ICD-10-CM diagnosis code for heart failure in the SNF, or LTCF setting. Analyses include first event only and the code must occur one of the following time periods: 1. ≥0 days after the unvaccinated index date and before the minimum date of censoring for the unvaccinated time segment 2. ≥14 days after the vaccinated index date and before the minim date of censoring for the vaccinated time segment. ICD-9-CM or ICD-10-CM codes are listed in Appendix Table 2.	Follow-up
Cataract surgery	Negative control outcome	≥1 International Classification of Diseases, Ninth Revision, Procedure Coding System (ICD-9-PCS), International Classification of Diseases, Tenth Revision, Procedure Coding System (ICD-10-PCS), CPT, or Healthcare Common Procedure Coding System (HCPCS) code for cataract surgery in any setting.	Follow-up

		Analyses include first event only and the code must occur one of the following time periods: 1. ≥0 days after the unvaccinated index date and before the minimum date of censoring for the unvaccinated time segment 2. ≥14 days after the vaccinated index date and before the minim date of censoring for the vaccinated time segment.	
Lipoma	Negative control outcome	≥1 ICD-9-CM or ICD-10-CM diagnosis code for lipoma in any setting. Analyses include first event only and the code must occur one of the following time periods: 1. ≥0 days after the unvaccinated index date and before the minimum date of censoring for the unvaccinated time segment 2. ≥14 days after the vaccinated index date and before the minim date of censoring for the vaccinated time segment.	Follow-up
Follow-up time	Outcome descriptive	Unvaccinated follow-up time is measured from the unvaccinated index date through minimum date of censoring. Vaccinated follow-up time is measured from 14 days after first PCV13 vaccination through the minimum date of censoring. Mean, standard deviation (SD), median (Q1-Q3), minimum, and maximum, will also be summarized for the length of follow-up in each group.	Follow-up

9.3.3. Mediation

Table 3. Mediation Variables

Variable	Role	Operational definition	Measurement period
Community-acquired pneumonia (CAP)	Mediator	≥1 ICD-9-CM or ICD-10-CM diagnosis code for CAP in any setting, where there were no hospital admissions or ventilator use within the 30 days prior. CAP with be categorized as having 0 or ≥1 CAP event. Individuals will be classified as having ≥1 CAP event if there is at least one diagnosis code for CAP during one of the following time segments: 1. ≥0 days after the unvaccinated index date and before the minimum date of censoring for the unvaccinated time segment 2. ≥14 days after the vaccinated index date and before the minim date of censoring for the vaccinated time segment. ICD-9-CM and ICD-10-CM codes are listed in Annex 1.	Follow-up
Community-acquired pneumonia (CAP) sensitivity	Mediator	≥1 ICD-9-CM or ICD-10-CM diagnosis code for CAP in the hospital setting, where there were no hospitalizations or ventilator use in the 30 days prior the hospital admission associated with the CAP diagnosis. For individuals with multiple CAP diagnosis codes during the 1-year follow-up period, CAP will be classified as the highest level of care associated with a CAP diagnosis code. CAP with be categorized as having 0 or ≥1 CAP event. Individuals will be classified as having ≥1 CAP event if there is at least one diagnosis code for	Follow-up

		CAP during one of the following time segments: 3. ≥0 days after the unvaccinated index date and before the minimum date of censoring for the unvaccinated time segment 4. ≥14 days after the vaccinated index date and before the minimum date of censoring for the vaccinated time segment. ICD-9-CM and ICD-10-CM codes are listed in Annex 1.	

9.3.4. Censoring

Table 4. Censoring Variables

Variable	Role	Operational definition	Measurement period
Outcome under study	Censoring	See outcome table above. Table 2.	Follow-up
Disenrollment	Censoring	The month an individual disenrolls from the insurance plan, as indicated in the Master Beneficiary Summary File. Disenrollment date is calculated as the maximum date of enrollment.	Follow-up
Death	Censoring	Date of death reported in the database.	Follow-up
End of study period	Censoring	December 31, 2019	Follow-up
End of follow-up	Censoring	365 days after the index date for the 1-year analysis and 1095 days after the index date for the 3 year analysis.	Follow-up
PPSV23 receipt	Censoring	1 CPT or NDC code for PPSV23 vaccination during follow-up.	Follow-up
PCV13 receipt	Censoring	1 CPT or NDC code for PCV13 receipt during unvaccinated follow-up. 1 CPT or NDC code for receipt of a second PCV13 vaccine during vaccinated follow-up.	Follow-up

9.3.5. Covariates

Table 5. Covariates

Variable	Role	Operational definition	Measurement period
Age	Patient characteristics	The number of years between the index date and the patient birth year for each time segment. Age will be reported overall and in the following categories: 65-69 years, 70-74 years, 75-79 years, 80-84 years, and 85+ years. Continuous statistics including mean, standard deviation (SD), median (Q1-Q3), minimum, and maximum, will also be summarized.	Baseline
Sex	Patient characteristics	Sex will be reported as Male (1), Female (2), and Unknown (0)	Baseline
Race/ethnicity	Patient characteristics	Self-reported race will be reported as White (1), Black (2), Other (3), Asian (4), Hispanic (5), North American Native (6), and Unknown (0).	Baseline
Geographic region	Patient characteristics	US geographic region will be derived from the patient state and categorized into the following: Northeast – Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, Pennsylvania Midwest – Indiana, Illinois, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota South – Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, Texas	Baseline

		West – Arizona, Colorado, Idaho, New Mexico, Montana, Utah, Nevada, Wyoming, Alaska, California, Hawaii, Oregon, Washington Other/unknown – Puerto Rico/ unknown region	
Respiratory season of index	Patient characteristics	The respiratory season of the individual's index date for each time segment. August 2014 – July 2015 August 2015 – July 2016 August 2016 – July 2017 August 2017 – July 2018 August 2018 – July 2019 August 2019 – November 2019	Baseline
Year of index date	Patient characteristics	The year of the individual's index date for each time segment. 2014, 2015, 2016, 2017, 2018, 2019.	Baseline
Month of index date	Patient characteristics	The month of the individual's index date for each time segment. January, February, March, April, May, June, July, August, September, October, November, or December.	Baseline
Outpatient heart failure	Patient characteristics	Any code for heart failure in the outpatient setting in the 365 days prior to the index date.	Baseline
Coronary artery disease (CAD)	Patient characteristics	Any code (any setting) for coronary artery disease (CAD) in the 365 days prior to the index date.	Baseline
Hypertension	Patient characteristics	Any code (any setting) for hypertension in the 365 days prior to the index date.	Baseline
Valvular heart disease	Patient characteristics	Any code (any setting) for valvular heart disease in the 365 days prior to the index date.	Baseline
Unstable angina	Patient characteristics	Any code (any setting) for unstable angina in the 365 days prior to the index date.	Baseline

Stable angina	Patient characteristics	Any code (any setting) for stable angina in the 365 days prior to the index date.	Baseline
Aortic aneurysm and dissection	Patient characteristics	Any code (any setting) for aortic aneurysm and dissection in the 365 days prior to the index date.	Baseline
Arrhythmia	Patient characteristics	Any code (any setting) for arrhythmia in the 365 days prior to the index date.	Baseline
Atrial fibrillation	Patient characteristics	Any code (any setting) for atrial fibrillation in the 365 days prior to the index date.	Baseline
Cardiomyopathy	Patient characteristics	Any code (any setting) for cardiomyopathy in the 365 days prior to the index date.	Baseline
Peripheral arterial disease (PAD)	Patient characteristics	Any code (any setting) for peripheral arterial disease (PAD) in the 365 days prior to index	Baseline
Pulmonary hypertension	Patient characteristics	Any code (any setting) for pulmonary hypertension in the 365 days prior to the index date.	Baseline
Rheumatic heart disease	Patient characteristics	Any code (any setting) for rheumatic heart disease in the 365 days prior to the index date.	Baseline
Congenital heart defects	Patient characteristics	Any code (any setting) for congenital heart defects in the 365 days prior to the index date.	Baseline
High cholesterol	Patient characteristics	Any code (any setting) for high cholesterol in the 365 days prior to the index date.	Baseline
High triglycerides	Patient characteristics	Any code (any setting) for high triglycerides in the 365 days prior to the index date.	Baseline
Metabolic syndrome	Patient characteristics	Any code (any setting) for metabolic syndrome in the 365 days prior to the index date.	Baseline
Autoimmune disease	Patient characteristics	Any code (any setting) for autoimmune disease in the 365 days prior to index.	Baseline

Transient ischemic attacks (TIA)	Patient characteristics	Any code (any setting) for TIA in the 365 days prior to index.	Baseline
Dementia	Patient characteristics	Any code (any setting) for dementia in the 365 days prior to index.	Baseline
Chronic obstructive pulmonary disease (COPD)	Patient characteristics	Any code (any setting) for COPD in the 365 days prior to index.	Baseline
Connective tissue disease	Patient characteristics	Any code (any setting) for a connective tissue disease in the 365 days prior to index.	Baseline
Peptic ulcer disease	Patient characteristics	Any code (any setting) for peptic ulcer disease in the 365 days prior to index.	Baseline
Chronic liver disease	Patient characteristics	Any code (any setting) for chronic liver disease in the 365 days prior to index.	Baseline
Diabetes mellitus	Patient characteristics	Any code (any setting) for diabetes mellitus in the 365 days prior to index.	Baseline
Hemiplegia	Patient characteristics	Any code (any setting) for hemiplegia in the 365 days prior to index.	Baseline
Solid tumor	Patient characteristics	Any code (any setting) for solid tumor malignancy within the 365 days prior to index.	Baseline
Chronic lung disease	Patient characteristics	Any code (any setting) for chronic lung disease within the 365 days prior to index.	Baseline
Asthma	Patient characteristics	Any code (any setting) for asthma within the 365 days prior to index.	Baseline
Alcoholism	Patient characteristics	Any code (any setting) for alcoholism in the 365 days prior to index.	Baseline
Smoking	Patient characteristics	Any code (any setting) for smoking in the 365 days prior to index.	Baseline
Obesity	Patient characteristics	Any code (any setting) for obesity during the 365 days prior to index.	Baseline
Functional/mobility status	Patient characteristics	A procedure code indicating decreased functional status or mobility in the 365 days prior to index.	Baseline

Physical/wellness visit	Patient characteristics	A CPT or diagnosis code for a wellness visit in the 365 days prior to index.	Baseline
Number of hospitalizations in the prior 180d	Patient characteristics	Count of unique days with an acute hospital admission in the 180 days prior to index • Dichotomous, yes/no • Continuous statistics including mean, standard deviation (SD), median (Q1 Q3), minimum, and maximum	Baseline
Number of outpatient visits in the prior 180d	Patient characteristics	Count unique days with an outpatient visit in the 180 days prior to index • Dichotomous, yes/no • Continuous statistics including mean, standard deviation (SD), median (Q1 Q3), minimum, and maximum	Baseline
Nursing home stay	Patient characteristics	Any claim with care location of nursing home in the 365 days prior to index.	Baseline
Skilled nursing facility (SNF) stay	Patient characteristics	Any claim with care location of SNF in the 365 days prior to index.	Baseline
Influenza vaccine	Patient characteristics	Baseline influenza vaccination status: One claim (NDC or CPT) for influenza vaccine of any type in the 365d prior to index. Time-varying influenza vaccination status during follow-up: Patients will be identified and can transition between periods of influenza vaccine exposure and non-exposure throughout the study period. Individuals will be classified as vaccinated starting 15 days after their first claim for an influenza vaccine during each respiratory season and considered vaccinated until the end of that respiratory season.	Baseline and follow-up

		The 1-year mediation analysis will adjust for baseline influenza vaccination status only.	
Type of index influenza vaccine administered	Patient characteristics	Categories include: Enhanced, standard, and unknown influenza vaccine type	Baseline
PPSV23 receipt	Patient characteristics	One claim (NDC or CPT) for a PPSV23 vaccine between 1 year and 5 years prior to the index date.	Baseline
Respiratory failure	Patient characteristics	Any code (any setting) within the prior 365 days for respiratory failure. Prior respiratory failure will be included as a descriptive variable only.	Baseline
Influenza infection	Patient characteristics	≥1 ICD-9-CM or ICD-10-CM code for influenza in 365 days prior to index	Baseline
Outpatient pneumonia	Patient characteristics	≥1 ICD-9-CM or ICD-10-CM code for pneumonia in the outpatient setting in the 365 days prior to index.	Baseline
Telehealth visits	Patient characteristics	Count of unique days with telehealth visit in the 365 days prior to index. • Dichotomous, yes/no • Number categories: 0, 1, 2+ • Continuous statistics including mean, standard deviation (SD), median (Q1 Q3), minimum, and maximum	Baseline
Flu test in the prior 365 days		Influenza test ordered in the 365 days prior to index. • Dichotomous, yes/no	Baseline
Number of labs ordered in the prior 365 days	Patient characteristics	Count of unique days with any lab ordered in the 365 days prior to index • Dichotomous, yes/no • Number categories: 0, 1, 2+	Baseline

		• Continuous statistics including mean, standard deviation (SD), median (Q1 Q3), minimum, and maximum	
Number of lipid lab tests ordered in the prior 365 days	Patient characteristics	Count of unique days with a lipid lab ordered in the 365 days prior to index • Dichotomous, yes/no • Number categories: 0, 1, 2+ • Continuous statistics including mean, standard deviation (SD), median (Q1 Q3), minimum, and maximum	Baseline
Echocardiogram	Patient characteristics	Count of unique days with an echocardiogram procedure code in the 365 days prior to index. • Dichotomous, yes/no • Number categories: 0, 1, 2+ • Continuous statistics including mean, standard deviation (SD), median (Q1 Q3), minimum, and maximum	Baseline
Electrocardiogram	Patient characteristics	Count of unique days with an electrocardiogram procedure code in the 365 days prior to index. • Dichotomous, yes/no • Number categories: 0, 1, 2+ Continuous statistics including mean, standard deviation (SD), median (Q1 Q3), minimum, and maximum	Baseline

9.4. Data Sources

The Medicare administrative claims database includes individuals ≥65 years of age and individuals with a qualifying disability who are enrolled in a Medicare FFS plan in the United States. The database includes enrollment information for these individuals and adjudicated claims for inpatient

care, ambulatory care, and outpatient prescriptions. Medicare FFS Parts A, B, and D administrative claims data is currently available from 2010 through March 30, 2024 and Medicare Part C data is available from 2015 – 2021. Several studies and systematic reviews have demonstrated the validity of using administrative data in the United States to identify MACE events.[26-30]

9.5. Study Size

To determine the appropriate sample size for our study, we conducted a power analysis based on log-rank test. The analysis was designed to evaluate the effect of PCV13 vaccination on the risk of first event MACE, with the following key assumptions:

- Treatment-to-control group allocation ratio: Based on the feasibility study using data from September 14, 2014, to December 31, 2019, the proportion of the vaccinated group is 39.6%. Consequently, the treatment-to-control group allocation ratio was set to 2:3.
- Hazard ratio (HR): We assumed a hazard ratio of 0.85 for the vaccinated group compared to the unvaccinated group, indicating a 15% reduction in the risk of first event MACE associated with PCV13 vaccination. Another scenario with an HR of 0.8 is also provided.
- Hazard rate for control group: Based on the above feasibility study, the 5-year overall event probability was 21.2%. Consequently, we calculated the hazard rate for the control group to be 0.0507. This calculation was derived from the pre-assumed HR of 0.85, the overall 5-year survival probability, and the treatment-to-control group allocation ratio. For the scenario with HR=0.8, the corresponding hazard rate for the control group is 0.0518.
- Follow-up time: In this study, not all patients will complete the full duration of follow-up due to censoring events such as vaccination status switching or death. To account for this in the sample size calculation, we adjusted the calculation using shorter average follow-up periods. Specifically, we considered four follow-up durations: 1-year, 0.75 year, 3 years, and 2.75 years.
- Statistical power: 80%.
- Test was two-sided with significance level (α): 0.05, which corresponds to a 5% chance of a Type I error.

The required total sample sizes for each scenario were determined as follows to achieve a 80% power:

Table 6. Sample Size

Hazard Ratio	Control Group Hazard Rate	Follow-up time in years	Total N Required
0.85	0.0507	1	27,520
		0.75	36,485
		3	9,600
		2.25	12,585

0.80	0.0518	1	14,825
		0.75	19,655
		3	5,170
		2.25	6,775

These sample size calculations ensure that the study is adequately powered to detect a clinically meaningful difference in first event MACE risk between the vaccinated and unvaccinated cohorts for both the 1-year and 3-year survival analysis. The TWOSAMPLESURVIVAL statement from the SAS POWER procedure was utilized to conduct sample size calculation for comparing two survival curves using the log-rank test. This analysis was performed using SAS Studio 3.81 (Cary, NC).

9.6. Data Management

All Medicare claims structured data described are stored within the Chronic Conditions Warehouse (CCW) Virtual Research Data Center (VRDC). The VRDC is a secure research environment only accessible to approved users listed on Pfizer's Data Use Agreement (DUA) with CMS for the project "Understanding the impact of vaccine-preventable diseases and vaccine uptake in Medicare Fee for Service and Medicaid populations". Data are queried and analyzed using SAS, Structured Query Language (SQL), and R, with the latter two languages accessed through the Databricks Platform.

No patient level data will be removed from the VRDC, only aggregate patient counts will be exported. In addition, patient counts containing a value of 1 to 10 will be censored in accordance with CMS cell size suppression policies.

9.7. Data Analysis

The analyses will be conducted separately at 1 year and 3 years of follow-up.

Descriptive statistics will be used to summarize baseline characteristics by vaccination group before and after propensity score weighting. Categorical variables will be summarized using frequency counts and percentages. Continuous variables will be summarized using mean, standard deviation, median, 25th and 75th percentile, minimum, and maximum.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Balancing and Covariate Adjustment Methods

The analysis will utilize inverse probability of treatment weighting (IPTW) to adjust for differences in the baseline characteristics between the PCV13 vaccinated and PCV13 unvaccinated cohorts. IPTW creates a pseudo-population in which the distribution of measured baseline covariates is independent of treatment assignment, thereby mimicking randomization.

Propensity scores (PS) will be created using a logistic regression model and used to calculate the inverse probability of treatment weights. Standardized mean differences (SMD) will be used to assess covariate balance before and after weighting. An absolute standardized difference less than or equal to

0.1 will be considered as balanced. Stabilized weights will be used to limit the impact of outliers and truncation at the 1st and 99th percentiles may be considered. Covariates with residual imbalance after weighting will be included in the final models for further adjustment to control for potential confounders. Depending on the balance checks for censoring status within the IPTW-weighted population, IPTW may be combined with inverse probability of censoring weighting (IPCW) to address potential issues of informative censoring. IPCW adjusts for potential biases due to censoring, with weights calculated based on the probability of censoring at various time points.

Only baseline covariates will be adjusted for using IPTW. Time-varying influenza vaccination status will be adjusted for directly in the Cox proportional hazards models for the primary outcomes analysis. Individuals will be classified as vaccinated starting 15 days after their first claim for an influenza vaccine during each respiratory season and considered vaccinated until the end of that respiratory season. The Cox model will treat influenza vaccination as a time-varying variable using a counting process. Baseline covariates included in the PS models for IPTW and IPCW will be finalized based on their clinical and statistical importance and will be detailed in the SAP.

Primary Outcome Analysis

The weighted cumulative incidence function (CIF) will be estimated to describe and account for mortality as a competing risk of MACE. This approach provides a non-parametric estimate of the cumulative incidence function, accounting for the competing risk events. The crude weighted CIF will be presented with the log-rank test to compare the CIF curve between the PCV13 vaccinated and PCV13 unvaccinated cohorts.

A cause-specific Cox proportional hazards model with a time-varying covariate for influenza vaccination status and a time-segment approach to PCV13 vaccination status will be used for the primary analysis. The cause-specific cox model will be used to estimate hazard ratios (HRs) for the first event of each MACE outcome, comparing PCV13 vaccinated with PCV13 unvaccinated Medicare beneficiaries. The model accounts for the possibility of competing risks by focusing on the cause-specific hazard. A time segment approach will be used to account for changes in PCV13 exposure status during follow-up, allowing adults who receive PCV13 during the study period to contribute a PCV13 unvaccinated and a PCV13 vaccinated time segment to the study.

For the any MACE outcome model, individuals are censored after experiencing their first MACE event during a given time segment, irrespective of whether the MACE event is myocardial infarction, stroke, or heart failure. The remaining models examine each type of MACE separately and experiencing one type of MACE event (i.e., myocardial infarction) is not a censoring criterion for the other types of MACE outcomes (i.e., stroke or heart failure) during a given time segment.

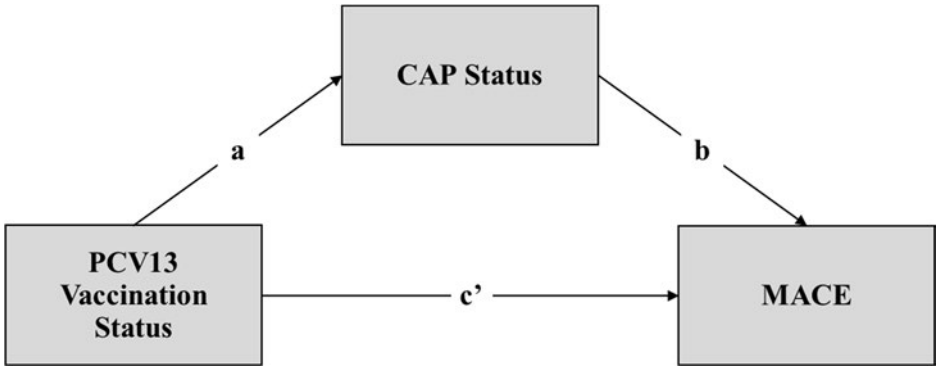
The HR for PCV13, with a 95% confidence interval, will be calculated over the follow-up period. If the proportional hazards assumption is violated—indicating the effect of PCV13 on the risk of MACE events changes over time—HRs will be estimated for specific follow-up periods (i.e., 0-1 years and 0-3 years).

Mediation Analysis

The study will also include a secondary analysis to examine mediation. The mediation analysis will estimate the direct and indirect effects of PCV13 receipt on MACE, examining the extent to which the relationship between PCV13 and MACE within 1 year of follow-up is mediated by CAP. Direct (c') and indirect effects (a*b) will be estimated. This analysis will employ the product method,[3] which

uses a logistic weighted mediation model to assess the mediator and a Cox model weighted outcome model to derive the HR and confidence intervals. Additionally, a counterfactual-based mediation analysis may be considered. This approach utilizes simulations to estimate the Controlled Direct Effect (CDE) and the Natural Indirect Effect (NIE), providing a comprehensive understanding of the mediation process. The mediation analysis will only adjust for influenza vaccination status during baseline. Further details on the mediation analysis will be provided in the SAP.

Figure 2. Diagram of the Mediation Model



Negative Control Outcomes

Residual confounding of our HRs due to inadequate control for health care seeking behavior and healthy vaccinee behaviors in our analyses will be explored. To examine residual confounding, the analysis will include at least two negative control outcomes. Potential negative control outcomes are outcomes that are not causally related to PCV13 receipt, but share the same sources of bias as MACE outcomes in our study population.

Sensitivity Analysis

The study will include three sensitivity analyses. The first sensitivity analysis will use the Fine-Gray model to assess the robustness of the HRs. The Fine-Gray model is a subdistribution hazards model, which evaluates of the effect of covariates on the CIF for each competing risk outcome separately. This model provides an alternative to the cause-specific Cox model and helps ensure the robustness of the findings against an alternative analytical approach for examining competing risks. Second, the study will incorporate a sensitivity analysis to examine an alternative definition of stroke. The primary analysis will include ischemic stroke only and the sensitivity analysis will include hemorrhagic and ischemic stroke. The stroke sensitivity definition will only be examined for the objective assessing the effect of PCV13 on the risk of stroke. The third sensitivity analysis will modify the definition of CAP in the mediation analysis to only include CAP cases with a diagnosis code in the hospital setting. A separate analysis of CAP cases in the outpatient or other non-hospital settings may be considered. Additional details will be provided in the SAP.

9.8. Quality Control

Upon initiation of analyses, edit, range, and logic checks will be performed on each data field by the project programmer to ensure the quality and completeness of the study database and all of the variables therein. Only observed data will be used in measuring study variables. It is anticipated that demographic information will be available for nearly all individuals in the study population. All other variables will be defined based on the presence of specific data (e.g., diagnosis, procedure, and drug codes) in the analytic file; the absence of such data will be assumed to indicate the absence of the characteristic/event captured by the variable.

Two analysts will program the study independently in accordance with the study protocol and SAP, accessing the data using the VRDC provided by the CCW. If any differences are detected in the results, the analysts will work together to align and address any issues leading to the discrepancy. In addition, analysts will censor all counts less than 11 prior to submission to the VRDC staff. Additional values may be censored to prevent back calculation. The VRDC team will review all submitted output. Once results have been released from the VRDC, the lead biostatisticians and epidemiologist will complete a final review.

Analytic programs are stored within the VRDC where analysis occurs. Once the analysis is complete, programs will be submitted for review to the VRDC team and exported. Programs will be saved within the Pfizer system.

9.9. Limitations of the Research Methods

There are several limitations associated with this study. First, the study population only includes individuals enrolled in Medicare FFS Parts A and B and as such, may not generalize to other populations, such as those with employer-sponsored health insurance, Medicare Advantage coverage, other government insurance, or the uninsured. Second, healthcare claims data are collected for billing purposes and may be subject to misclassification, misdiagnosis, and underreporting. As such, residual confounding due to missing or unmeasured information is possible, such as vaccination misclassification if an individual received a vaccine in a setting where an insurance claim was not files (i.e. paid out of pocket, etc). To assess the extent and direction of any unmeasured confounding, we will assess the effect of PCV13 on two negative control outcomes.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

The study databases will be de-identified prior to their release to study investigators, as set forth in the corresponding Data Use Agreement. The study databases have been evaluated and certified by an independent third party to be compliant with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 statistical de-identification standards and to satisfy the conditions set forth in Sections 164.514 (a)-(b)1ii of the HIPAA Privacy Rule regarding the determination and documentation of statistically de-identified data. Use of the study databases for health services research is therefore fully compliant with the HIPAA Privacy Rule and federal guidance on Public Welfare and the Protection of Human Subjects (45 Code of Federal Regulations [CFR] 46 §46.101) and IRB approval is not required.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiologic Practices (GPP), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (https://www.ispor.org/heor-resources/good-practices), and Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.[31, 32]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Formal communication of the results of this research will be done by study investigators through peer-reviewed publications. For all publications relating to the Study, Pfizer will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

16. ANNEX 1. LIST OF STANDALONE DOCUMENTS

Number	Document reference number	Date	Title
1	1.0	10-Sep-2024	Diagnosis Codes (ICD-10-CM) for Identifying All-cause Pneumonia

17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required.

18. ANNEX 3. ADDITIONAL INFORMATION

Appendix Table 1. NDC and CPT® Codes for Identifying PCV13 Vaccination

Code	Type	Description
50090194409	NDC	13-valent pneumococcal conjugate vaccine
54569661300	NDC	13-valent pneumococcal conjugate vaccine
50090194400	NDC	13-valent pneumococcal conjugate vaccine
00005197105	NDC	13-valent pneumococcal conjugate vaccine
00005197104	NDC	13-valent pneumococcal conjugate vaccine
00005197102	NDC	13-valent pneumococcal conjugate vaccine
00005197101	NDC	13-valent pneumococcal conjugate vaccine
90670	CPT	13-valent pneumococcal conjugate vaccine

Appendix Table 2. Diagnosis Codes for Identifying MACE

Code type	Code	Description
Myocardial Infarction		
ICD-10-CM	I21	Acute myocardial infarction
ICD-10-CM	I21.01	ST elevation (STEMI) myocardial infarction involving left main coronary artery
ICD-10-CM	I21.02	ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery
ICD-10-CM	I21.09	ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall
ICD-10-CM	I21.11	ST elevation (STEMI) myocardial infarction involving right coronary artery
ICD-10-CM	I21.19	ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall
ICD-10-CM	I21.21	ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery
ICD-10-CM	I21.29	ST elevation (STEMI) myocardial infarction involving other sites
ICD-10-CM	I21.3	ST elevation (STEMI) myocardial infarction of unspecified site
ICD-10-CM	I21.4	Non-ST elevation (NSTEMI) myocardial infarction
ICD-10-CM	I21.9	Acute myocardial infarction, unspecified
ICD-10-CM	I21.A1	Myocardial infarction type 2
ICD-10-CM	I21.A9	Other myocardial infarction type
ICD-10-CM	I21.B	Myocardial infarction with coronary microvascular dysfunction
ICD-10-CM	I22	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
ICD-10-CM	I22.0	Subsequent ST elevation (STEMI) myocardial infarction of anterior wall
ICD-10-CM	I22.1	Subsequent ST elevation (STEMI) myocardial infarction of inferior wall
ICD-10-CM	I22.2	Subsequent non-ST elevation (NSTEMI) myocardial infarction
ICD-10-CM	I22.8	Subsequent ST elevation (STEMI) myocardial infarction of other sites
ICD-10-CM	I22.9	Subsequent ST elevation (STEMI) myocardial infarction of unspecified site
ICD-9-CM	410.01	Acute myocardial infarction of anterolateral wall, initial episode of care
ICD-9-CM	410.11	Acute myocardial infarction of other anterior wall, initial episode of care
ICD-9-CM	410.21	Acute myocardial infarction of inferolateral wall, initial episode of care
ICD-9-CM	410.31	Acute myocardial infarction of inferoposterior wall, initial episode of care
ICD-9-CM	410.41	Acute myocardial infarction of other inferior wall, initial episode of care
ICD-9-CM	410.51	Acute myocardial infarction of other lateral wall, initial episode of care
ICD-9-CM	410.61	True posterior wall infarction, initial episode of care
ICD-9-CM	410.71	Subendocardial infarction, initial episode of care
ICD-9-CM	410.81	Acute myocardial infarction of other specified sites, initial episode of care
ICD-9-CM	410.91	Acute myocardial infarction of unspecified site, initial episode of care
Heart failure		
ICD-10-CM	I50	Heart failure
ICD-10-CM	I50.1	Left ventricular failure
ICD-10-CM	I50.2	Systolic (congestive) heart failure
ICD-10-CM	I50.20	Unspecified systolic (congestive) heart failure
ICD-10-CM	I50.21	Acute systolic (congestive) heart failure
ICD-10-CM	I50.22	Chronic systolic (congestive) heart failure
ICD-10-CM	I50.23	Acute on chronic systolic (congestive) heart failure
ICD-10-CM	I50.3	Diastolic (congestive) heart failure

ICD-10-CM	I50.30	Unspecified diastolic (congestive) heart failure
ICD-10-CM	I50.31	Acute diastolic (congestive) heart failure
ICD-10-CM	I50.32	Chronic diastolic (congestive) heart failure
ICD-10-CM	I50.33	Acute on chronic diastolic (congestive) heart failure
ICD-10-CM	I50.4	Combined systolic (congestive) and diastolic (congestive)
ICD-10-CM	I50.40	Unspecified combined systolic (congestive) and diastolic (congestive) heart failure
ICD-10-CM	I50.41	Acute combined systolic (congestive) and diastolic (congestive) heart failure
ICD-10-CM	I50.42	Chronic combined systolic (congestive) and diastolic (congestive) heart failure
ICD-10-CM	I50.43	Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure
ICD-10-CM	I50.8	Other heart failure
ICD-10-CM	I50.81	Right heart failure
ICD-10-CM	I50.810	Right heart failure, unspecified
ICD-10-CM	I50.811	Acute right heart failure
ICD-10-CM	I50.812	Chronic right heart failure
ICD-10-CM	I50.813	Acute on chronic right heart failure
ICD-10-CM	I50.814	Right heart failure due to left heart failure
ICD-10-CM	I50.82	Biventricular heart failure
ICD-10-CM	I50.83	High output heart failure
ICD-10-CM	I50.84	End stage heart failure
ICD-10-CM	I50.89	Other heart failure
ICD-10-CM	I50.9	Heart failure, unspecified
ICD-9-CM	428	Heart failure
ICD-9-CM	428.0	Congestive heart failure, unspecified
ICD-9-CM	428.1	Left heart failure
ICD-9-CM	428.2	Systolic heart failure, unspecified
ICD-9-CM	428.20	Systolic heart failure, unspecified
ICD-9-CM	428.21	Acute systolic heart failure
ICD-9-CM	428.22	Chronic systolic heart failure
ICD-9-CM	428.23	Acute on chronic systolic heart failure
ICD-9-CM	428.3	Diastolic heart failure
ICD-9-CM	428.30	Diastolic heart failure, unspecified
ICD-9-CM	428.31	Acute diastolic heart failure
ICD-9-CM	428.32	Chronic diastolic heart failure
ICD-9-CM	428.33	Acute on chronic diastolic heart failure
ICD-9-CM	428.4	Combined systolic and diastolic heart failure
ICD-9-CM	428.40	Combined systolic and diastolic heart failure, unspecified
ICD-9-CM	428.41	Acute combined systolic and diastolic heart failure
ICD-9-CM	428.42	Chronic combined systolic and diastolic heart failure
ICD-9-CM	428.43	Acute on chronic combined systolic and diastolic heart failure
ICD-9-CM	428.9	Heart failure, unspecified
Stroke: Primary definition		
ICD-10-CM	I63	Cerebral infarction
ICD-10-CM	I63.0	Cerebral infarction due to thrombosis of precerebral arteries
ICD-10-CM	I63.00	Cerebral infarction due to thrombosis of unspecified precerebral artery
ICD-10-CM	I63.01	Cerebral infarction due to thrombosis of vertebral artery
ICD-10-CM	I63.011	Cerebral infarction due to thrombosis of right vertebral artery

ICD-10-CM	I63.012	Cerebral infarction due to thrombosis of left vertebral artery
ICD-10-CM	I63.013	Cerebral infarction due to thrombosis of bilateral vertebral arteries
ICD-10-CM	I63.019	Cerebral infarction due to thrombosis of unspecified vertebral artery
ICD-10-CM	I63.02	Cerebral infarction due to thrombosis of basilar artery
ICD-10-CM	I63.03	Cerebral infarction due to thrombosis of carotid artery
ICD-10-CM	I63.031	Cerebral infarction due to thrombosis of right carotid artery
ICD-10-CM	I63.032	Cerebral infarction due to thrombosis of left carotid artery
ICD-10-CM	I63.033	Cerebral infarction due to thrombosis of bilateral carotid arteries
ICD-10-CM	I63.039	Cerebral infarction due to thrombosis of unspecified carotid artery
ICD-10-CM	I63.09	Cerebral infarction due to thrombosis of other precerebral artery
ICD-10-CM	I63.1	Cerebral infarction due to embolism of precerebral arteries
ICD-10-CM	I63.10	Cerebral infarction due to embolism of unspecified precerebral artery
ICD-10-CM	I63.11	Cerebral infarction due to embolism of vertebral artery
ICD-10-CM	I63.111	Cerebral infarction due to embolism of right vertebral artery
ICD-10-CM	I63.112	Cerebral infarction due to embolism of left vertebral artery
ICD-10-CM	I63.113	Cerebral infarction due to embolism of bilateral vertebral arteries
ICD-10-CM	I63.119	Cerebral infarction due to embolism of unspecified vertebral artery
ICD-10-CM	I63.12	Cerebral infarction due to embolism of basilar artery
ICD-10-CM	I63.13	Cerebral infarction due to embolism of carotid artery
ICD-10-CM	I63.131	Cerebral infarction due to embolism of right carotid artery
ICD-10-CM	I63.132	Cerebral infarction due to embolism of left carotid artery
ICD-10-CM	I63.133	Cerebral infarction due to embolism of bilateral carotid arteries
ICD-10-CM	I63.139	Cerebral infarction due to embolism of unspecified carotid artery
ICD-10-CM	I63.19	Cerebral infarction due to embolism of other precerebral artery
ICD-10-CM	I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
ICD-10-CM	I63.20	Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries
ICD-10-CM	I63.21	Cerebral infarction due to unspecified occlusion or stenosis of vertebral arteries
ICD-10-CM	I63.211	Cerebral infarction due to unspecified occlusion or stenosis of right vertebral artery
ICD-10-CM	I63.212	Cerebral infarction due to unspecified occlusion or stenosis of left vertebral artery
ICD-10-CM	I63.213	Cerebral infarction due to unspecified occlusion or stenosis of bilateral vertebral arteries
ICD-10-CM	I63.219	Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral artery
ICD-10-CM	I63.22	Cerebral infarction due to unspecified occlusion or stenosis of basilar artery
ICD-10-CM	I63.23	Cerebral infarction due to unspecified occlusion or stenosis of carotid arteries
ICD-10-CM	I63.231	Cerebral infarction due to unspecified occlusion or stenosis of right carotid arteries
ICD-10-CM	I63.232	Cerebral infarction due to unspecified occlusion or stenosis of left carotid arteries
ICD-10-CM	I63.233	Cerebral infarction due to unspecified occlusion or stenosis of bilateral carotid arteries
ICD-10-CM	I63.239	Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid artery
ICD-10-CM	I63.29	Cerebral infarction due to unspecified occlusion or stenosis of other precerebral arteries
ICD-10-CM	I63.3	Cerebral infarction due to thrombosis of cerebral arteries
ICD-10-CM	I63.30	Cerebral infarction due to thrombosis of unspecified cerebral artery

ICD-10-CM	I63.31	Cerebral infarction due to thrombosis of middle cerebral artery
ICD-10-CM	I63.311	Cerebral infarction due to thrombosis of right middle cerebral artery
ICD-10-CM	I63.312	Cerebral infarction due to thrombosis of left middle cerebral artery
ICD-10-CM	I63.313	Cerebral infarction due to thrombosis of bilateral middle cerebral arteries
ICD-10-CM	I63.319	Cerebral infarction due to thrombosis of unspecified middle cerebral artery
ICD-10-CM	I63.32	Cerebral infarction due to thrombosis of anterior cerebral artery
ICD-10-CM	I63.321	Cerebral infarction due to thrombosis of right anterior cerebral artery
ICD-10-CM	I63.322	Cerebral infarction due to thrombosis of left anterior cerebral artery
ICD-10-CM	I63.323	Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries
ICD-10-CM	I63.329	Cerebral infarction due to thrombosis of unspecified anterior cerebral artery
ICD-10-CM	I63.33	Cerebral infarction due to thrombosis of posterior cerebral artery
ICD-10-CM	I63.331	Cerebral infarction due to thrombosis of right posterior cerebral artery
ICD-10-CM	I63.332	Cerebral infarction due to thrombosis of left posterior cerebral artery
ICD-10-CM	I63.333	Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries
ICD-10-CM	I63.339	Cerebral infarction due to thrombosis of unspecified posterior cerebral artery
ICD-10-CM	I63.34	Cerebral infarction due to thrombosis of cerebellar artery
ICD-10-CM	I63.341	Cerebral infarction due to thrombosis of right cerebellar artery
ICD-10-CM	I63.342	Cerebral infarction due to thrombosis of left cerebellar artery
ICD-10-CM	I63.343	Cerebral infarction due to thrombosis of bilateral cerebellar arteries
ICD-10-CM	I63.349	Cerebral infarction due to thrombosis of unspecified cerebellar artery
ICD-10-CM	I63.39	Cerebral infarction due to thrombosis of other cerebral artery
ICD-10-CM	I63.4	Cerebral infarction due to embolism of cerebral arteries
ICD-10-CM	I63.40	Cerebral infarction due to embolism of unspecified cerebral artery
ICD-10-CM	I63.41	Cerebral infarction due to embolism of middle cerebral artery
ICD-10-CM	I63.411	Cerebral infarction due to embolism of right middle cerebral artery
ICD-10-CM	I63.412	Cerebral infarction due to embolism of left middle cerebral artery
ICD-10-CM	I63.413	Cerebral infarction due to embolism of bilateral middle cerebral arteries
ICD-10-CM	I63.419	Cerebral infarction due to embolism of unspecified middle cerebral artery
ICD-10-CM	I63.42	Cerebral infarction due to embolism of anterior cerebral artery
ICD-10-CM	I63.421	Cerebral infarction due to embolism of right anterior cerebral artery
ICD-10-CM	I63.422	Cerebral infarction due to embolism of left anterior cerebral artery
ICD-10-CM	I63.423	Cerebral infarction due to embolism of bilateral anterior cerebral arteries
ICD-10-CM	I63.429	Cerebral infarction due to embolism of unspecified anterior cerebral artery
ICD-10-CM	I63.43	Cerebral infarction due to embolism of posterior cerebral artery
ICD-10-CM	I63.431	Cerebral infarction due to embolism of right posterior cerebral artery
ICD-10-CM	I63.432	Cerebral infarction due to embolism of left posterior cerebral artery
ICD-10-CM	I63.433	Cerebral infarction due to embolism of bilateral posterior cerebral arteries
ICD-10-CM	I63.439	Cerebral infarction due to embolism of unspecified posterior cerebral artery
ICD-10-CM	I63.44	Cerebral infarction due to embolism of cerebellar artery
ICD-10-CM	I63.441	Cerebral infarction due to embolism of right cerebellar artery
ICD-10-CM	I63.442	Cerebral infarction due to embolism of left cerebellar artery
ICD-10-CM	I63.443	Cerebral infarction due to embolism of bilateral cerebellar arteries
ICD-10-CM	I63.449	Cerebral infarction due to embolism of unspecified cerebellar artery
ICD-10-CM	I63.49	Cerebral infarction due to embolism of other cerebral artery
ICD-10-CM	I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries

ICD-10-CM	I63.50	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery
ICD-10-CM	I63.51	Cerebral infarction due to unspecified occlusion or stenosis of middle cerebral artery
ICD-10-CM	I63.511	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
ICD-10-CM	I63.512	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery
ICD-10-CM	I63.513	Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle cerebral arteries
ICD-10-CM	I63.519	Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery
ICD-10-CM	I63.52	Cerebral infarction due to unspecified occlusion or stenosis of anterior cerebral artery
ICD-10-CM	I63.521	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery
ICD-10-CM	I63.522	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery
ICD-10-CM	I63.523	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior cerebral arteries
ICD-10-CM	I63.529	Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery
ICD-10-CM	I63.53	Cerebral infarction due to unspecified occlusion or stenosis of posterior cerebral artery
ICD-10-CM	I63.531	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery
ICD-10-CM	I63.532	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery
ICD-10-CM	I63.533	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior cerebral arteries
ICD-10-CM	I63.539	Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery
ICD-10-CM	I63.54	Cerebral infarction due to unspecified occlusion or stenosis of cerebellar artery
ICD-10-CM	I63.541	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery
ICD-10-CM	I63.542	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery
ICD-10-CM	I63.543	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries
ICD-10-CM	I63.549	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery
ICD-10-CM	I63.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery
ICD-10-CM	I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
ICD-10-CM	I63.8	Other cerebral infarction
ICD-10-CM	I63.81	Other cerebral infarction due to occlusion or stenosis of small artery
ICD-10-CM	I63.89	Other cerebral infarction
ICD-10-CM	I63.9	Cerebral infarction, unspecified
ICD-9-CM	433.01	Occlusion and stenosis of basilar artery with cerebral infarction
ICD-9-CM	433.11	Occlusion and stenosis of carotid artery with cerebral infarction
ICD-9-CM	433.21	Occlusion and stenosis of vertebral artery with cerebral infarction

ICD-9-CM	433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
ICD-9-CM	433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
ICD-9-CM	433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
ICD-9-CM	434.01	Cerebral thrombosis with cerebral infarction
ICD-9-CM	434.11	Cerebral embolism with cerebral infarction
ICD-9-CM	434.91	Cerebral artery occlusion, unspecified with cerebral infarction
Stroke: Sensitivity definition		
ICD-10-CM	I60	Nontraumatic subarachnoid hemorrhage
ICD-10-CM	I60.0	Nontraumatic subarachnoid hemorrhage from carotid siphon and bifurcation
ICD-10-CM	I60.00	Nontraumatic subarachnoid hemorrhage from unspecified carotid siphon and bifurcation
ICD-10-CM	I60.01	Nontraumatic subarachnoid hemorrhage from right carotid siphon and bifurcation
ICD-10-CM	I60.02	Nontraumatic subarachnoid hemorrhage from left carotid siphon and bifurcation
ICD-10-CM	I60.1	Nontraumatic subarachnoid hemorrhage from middle cerebral artery
ICD-10-CM	I60.10	Nontraumatic subarachnoid hemorrhage from unspecified middle cerebral artery
ICD-10-CM	I60.11	Nontraumatic subarachnoid hemorrhage from right middle cerebral artery
ICD-10-CM	I60.12	Nontraumatic subarachnoid hemorrhage from left middle cerebral artery
ICD-10-CM	I60.2	Nontraumatic subarachnoid hemorrhage from anterior communicating artery
ICD-10-CM	I60.3	Nontraumatic subarachnoid hemorrhage from posterior communicating artery
ICD-10-CM	I60.30	Nontraumatic subarachnoid hemorrhage from unspecified posterior communicating artery
ICD-10-CM	I60.31	Nontraumatic subarachnoid hemorrhage from right posterior communicating artery
ICD-10-CM	I60.32	Nontraumatic subarachnoid hemorrhage from left posterior communicating artery
ICD-10-CM	I60.4	Nontraumatic subarachnoid hemorrhage from basilar artery
ICD-10-CM	I60.5	Nontraumatic subarachnoid hemorrhage from vertebral artery
ICD-10-CM	I60.50	Nontraumatic subarachnoid hemorrhage from unspecified vertebral artery
ICD-10-CM	I60.51	Nontraumatic subarachnoid hemorrhage from right vertebral artery
ICD-10-CM	I60.52	Nontraumatic subarachnoid hemorrhage from left vertebral artery
ICD-10-CM	I60.6	Nontraumatic subarachnoid hemorrhage from other intracranial arteries
ICD-10-CM	I60.7	Nontraumatic subarachnoid hemorrhage from unspecified intracranial artery
ICD-10-CM	I60.8	Other nontraumatic subarachnoid hemorrhage
ICD-10-CM	I60.9	Nontraumatic subarachnoid hemorrhage, unspecified
ICD-10-CM	I61	Nontraumatic intracerebral hemorrhage
ICD-10-CM	I61.0	Nontraumatic intracerebral hemorrhage in hemisphere, subcortical
ICD-10-CM	I61.1	Nontraumatic intracerebral hemorrhage in hemisphere, cortical
ICD-10-CM	I61.2	Nontraumatic intracerebral hemorrhage in hemisphere, unspecified
ICD-10-CM	I61.3	Nontraumatic intracerebral hemorrhage in brain stem
ICD-10-CM	I61.4	Nontraumatic intracerebral hemorrhage in cerebellum
ICD-10-CM	I61.5	Nontraumatic intracerebral hemorrhage, intraventricular
ICD-10-CM	I61.6	Nontraumatic intracerebral hemorrhage, multiple localized
ICD-10-CM	I61.8	Other nontraumatic intracerebral hemorrhage
ICD-10-CM	I61.9	Nontraumatic intracerebral hemorrhage, unspecified
ICD-10-CM	I62	Other and unspecified nontraumatic intracranial hemorrhage
ICD-10-CM	I62.0	Nontraumatic subdural hemorrhage
ICD-10-CM	I62.00	Nontraumatic subdural hemorrhage, unspecified
ICD-10-CM	I62.01	Nontraumatic acute subdural hemorrhage

ICD-10-CM	I62.02	Nontraumatic subacute subdural hemorrhage
ICD-10-CM	I62.03	Nontraumatic chronic subdural hemorrhage
ICD-10-CM	I62.1	Nontraumatic extradural hemorrhage
ICD-10-CM	I62.9	Nontraumatic intracranial hemorrhage, unspecified
ICD-10-CM	I63	Cerebral infarction
ICD-10-CM	I63.0	Cerebral infarction due to thrombosis of precerebral arteries
ICD-10-CM	I63.00	Cerebral infarction due to thrombosis of unspecified precerebral artery
ICD-10-CM	I63.01	Cerebral infarction due to thrombosis of vertebral artery
ICD-10-CM	I63.011	Cerebral infarction due to thrombosis of right vertebral artery
ICD-10-CM	I63.012	Cerebral infarction due to thrombosis of left vertebral artery
ICD-10-CM	I63.013	Cerebral infarction due to thrombosis of bilateral vertebral arteries
ICD-10-CM	I63.019	Cerebral infarction due to thrombosis of unspecified vertebral artery
ICD-10-CM	I63.02	Cerebral infarction due to thrombosis of basilar artery
ICD-10-CM	I63.03	Cerebral infarction due to thrombosis of carotid artery
ICD-10-CM	I63.031	Cerebral infarction due to thrombosis of right carotid artery
ICD-10-CM	I63.032	Cerebral infarction due to thrombosis of left carotid artery
ICD-10-CM	I63.033	Cerebral infarction due to thrombosis of bilateral carotid arteries
ICD-10-CM	I63.039	Cerebral infarction due to thrombosis of unspecified carotid artery
ICD-10-CM	I63.09	Cerebral infarction due to thrombosis of other precerebral artery
ICD-10-CM	I63.1	Cerebral infarction due to embolism of precerebral arteries
ICD-10-CM	I63.10	Cerebral infarction due to embolism of unspecified precerebral artery
ICD-10-CM	I63.11	Cerebral infarction due to embolism of vertebral artery
ICD-10-CM	I63.111	Cerebral infarction due to embolism of right vertebral artery
ICD-10-CM	I63.112	Cerebral infarction due to embolism of left vertebral artery
ICD-10-CM	I63.113	Cerebral infarction due to embolism of bilateral vertebral arteries
ICD-10-CM	I63.119	Cerebral infarction due to embolism of unspecified vertebral artery
ICD-10-CM	I63.12	Cerebral infarction due to embolism of basilar artery
ICD-10-CM	I63.13	Cerebral infarction due to embolism of carotid artery
ICD-10-CM	I63.131	Cerebral infarction due to embolism of right carotid artery
ICD-10-CM	I63.132	Cerebral infarction due to embolism of left carotid artery
ICD-10-CM	I63.133	Cerebral infarction due to embolism of bilateral carotid arteries
ICD-10-CM	I63.139	Cerebral infarction due to embolism of unspecified carotid artery
ICD-10-CM	I63.19	Cerebral infarction due to embolism of other precerebral artery
ICD-10-CM	I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
ICD-10-CM	I63.20	Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries
ICD-10-CM	I63.21	Cerebral infarction due to unspecified occlusion or stenosis of vertebral arteries
ICD-10-CM	I63.211	Cerebral infarction due to unspecified occlusion or stenosis of right vertebral artery
ICD-10-CM	I63.212	Cerebral infarction due to unspecified occlusion or stenosis of left vertebral artery
ICD-10-CM	I63.213	Cerebral infarction due to unspecified occlusion or stenosis of bilateral vertebral arteries
ICD-10-CM	I63.219	Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral artery
ICD-10-CM	I63.22	Cerebral infarction due to unspecified occlusion or stenosis of basilar artery
ICD-10-CM	I63.23	Cerebral infarction due to unspecified occlusion or stenosis of carotid arteries
ICD-10-CM	I63.231	Cerebral infarction due to unspecified occlusion or stenosis of right carotid arteries
ICD-10-CM	I63.232	Cerebral infarction due to unspecified occlusion or stenosis of left carotid arteries

ICD-10-CM	I63.233	Cerebral infarction due to unspecified occlusion or stenosis of bilateral carotid arteries
ICD-10-CM	I63.239	Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid artery
ICD-10-CM	I63.29	Cerebral infarction due to unspecified occlusion or stenosis of other precerebral arteries
ICD-10-CM	I63.3	Cerebral infarction due to thrombosis of cerebral arteries
ICD-10-CM	I63.30	Cerebral infarction due to thrombosis of unspecified cerebral artery
ICD-10-CM	I63.31	Cerebral infarction due to thrombosis of middle cerebral artery
ICD-10-CM	I63.311	Cerebral infarction due to thrombosis of right middle cerebral artery
ICD-10-CM	I63.312	Cerebral infarction due to thrombosis of left middle cerebral artery
ICD-10-CM	I63.313	Cerebral infarction due to thrombosis of bilateral middle cerebral arteries
ICD-10-CM	I63.319	Cerebral infarction due to thrombosis of unspecified middle cerebral artery
ICD-10-CM	I63.32	Cerebral infarction due to thrombosis of anterior cerebral artery
ICD-10-CM	I63.321	Cerebral infarction due to thrombosis of right anterior cerebral artery
ICD-10-CM	I63.322	Cerebral infarction due to thrombosis of left anterior cerebral artery
ICD-10-CM	I63.323	Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries
ICD-10-CM	I63.329	Cerebral infarction due to thrombosis of unspecified anterior cerebral artery
ICD-10-CM	I63.33	Cerebral infarction due to thrombosis of posterior cerebral artery
ICD-10-CM	I63.331	Cerebral infarction due to thrombosis of right posterior cerebral artery
ICD-10-CM	I63.332	Cerebral infarction due to thrombosis of left posterior cerebral artery
ICD-10-CM	I63.333	Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries
ICD-10-CM	I63.339	Cerebral infarction due to thrombosis of unspecified posterior cerebral artery
ICD-10-CM	I63.34	Cerebral infarction due to thrombosis of cerebellar artery
ICD-10-CM	I63.341	Cerebral infarction due to thrombosis of right cerebellar artery
ICD-10-CM	I63.342	Cerebral infarction due to thrombosis of left cerebellar artery
ICD-10-CM	I63.343	Cerebral infarction due to thrombosis of bilateral cerebellar arteries
ICD-10-CM	I63.349	Cerebral infarction due to thrombosis of unspecified cerebellar artery
ICD-10-CM	I63.39	Cerebral infarction due to thrombosis of other cerebral artery
ICD-10-CM	I63.4	Cerebral infarction due to embolism of cerebral arteries
ICD-10-CM	I63.40	Cerebral infarction due to embolism of unspecified cerebral artery
ICD-10-CM	I63.41	Cerebral infarction due to embolism of middle cerebral artery
ICD-10-CM	I63.411	Cerebral infarction due to embolism of right middle cerebral artery
ICD-10-CM	I63.412	Cerebral infarction due to embolism of left middle cerebral artery
ICD-10-CM	I63.413	Cerebral infarction due to embolism of bilateral middle cerebral arteries
ICD-10-CM	I63.419	Cerebral infarction due to embolism of unspecified middle cerebral artery
ICD-10-CM	I63.42	Cerebral infarction due to embolism of anterior cerebral artery
ICD-10-CM	I63.421	Cerebral infarction due to embolism of right anterior cerebral artery
ICD-10-CM	I63.422	Cerebral infarction due to embolism of left anterior cerebral artery
ICD-10-CM	I63.423	Cerebral infarction due to embolism of bilateral anterior cerebral arteries
ICD-10-CM	I63.429	Cerebral infarction due to embolism of unspecified anterior cerebral artery
ICD-10-CM	I63.43	Cerebral infarction due to embolism of posterior cerebral artery
ICD-10-CM	I63.431	Cerebral infarction due to embolism of right posterior cerebral artery
ICD-10-CM	I63.432	Cerebral infarction due to embolism of left posterior cerebral artery
ICD-10-CM	I63.433	Cerebral infarction due to embolism of bilateral posterior cerebral arteries
ICD-10-CM	I63.439	Cerebral infarction due to embolism of unspecified posterior cerebral artery
ICD-10-CM	I63.44	Cerebral infarction due to embolism of cerebellar artery

ICD-10-CM	I63.441	Cerebral infarction due to embolism of right cerebellar artery
ICD-10-CM	I63.442	Cerebral infarction due to embolism of left cerebellar artery
ICD-10-CM	I63.443	Cerebral infarction due to embolism of bilateral cerebellar arteries
ICD-10-CM	I63.449	Cerebral infarction due to embolism of unspecified cerebellar artery
ICD-10-CM	I63.49	Cerebral infarction due to embolism of other cerebral artery
ICD-10-CM	I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
ICD-10-CM	I63.50	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery
ICD-10-CM	I63.51	Cerebral infarction due to unspecified occlusion or stenosis of middle cerebral artery
ICD-10-CM	I63.511	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
ICD-10-CM	I63.512	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery
ICD-10-CM	I63.513	Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle cerebral arteries
ICD-10-CM	I63.519	Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery
ICD-10-CM	I63.52	Cerebral infarction due to unspecified occlusion or stenosis of anterior cerebral artery
ICD-10-CM	I63.521	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery
ICD-10-CM	I63.522	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery
ICD-10-CM	I63.523	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior cerebral arteries
ICD-10-CM	I63.529	Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery
ICD-10-CM	I63.53	Cerebral infarction due to unspecified occlusion or stenosis of posterior cerebral artery
ICD-10-CM	I63.531	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery
ICD-10-CM	I63.532	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery
ICD-10-CM	I63.533	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior cerebral arteries
ICD-10-CM	I63.539	Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery
ICD-10-CM	I63.54	Cerebral infarction due to unspecified occlusion or stenosis of cerebellar artery
ICD-10-CM	I63.541	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery
ICD-10-CM	I63.542	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery
ICD-10-CM	I63.543	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries
ICD-10-CM	I63.549	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery
ICD-10-CM	I63.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery
ICD-10-CM	I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
ICD-10-CM	I63.8	Other cerebral infarction
ICD-10-CM	I63.81	Other cerebral infarction due to occlusion or stenosis of small artery
ICD-10-CM	I63.89	Other cerebral infarction

ICD-10-CM	I63.9	Cerebral infarction, unspecified
ICD-9-CM	430	Subarachnoid hemorrhage
ICD-9-CM	431	Intracerebral hemorrhage
ICD-9-CM	432	Other and unspecified intracranial hemorrhage
ICD-9-CM	432.0	Nontraumatic extradural hemorrhage
ICD-9-CM	432.1	Subdural hemorrhage
ICD-9-CM	432.9	Unspecified intracranial hemorrhage
ICD-9-CM	433.01	Occlusion and stenosis of basilar artery with cerebral infarction
ICD-9-CM	433.11	Occlusion and stenosis of carotid artery with cerebral infarction
ICD-9-CM	433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
ICD-9-CM	433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
ICD-9-CM	433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
ICD-9-CM	433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
ICD-9-CM	434.01	Cerebral thrombosis with cerebral infarction
ICD-9-CM	434.11	Cerebral embolism with cerebral infarction
ICD-9-CM	434.91	Cerebral artery occlusion, unspecified with cerebral infarction

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