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Thromboembolic Event Case Algorithms
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List of Acronyms

ADE	Adverse drug event
AID	Acute ischemic stroke
AMI	Acute myocardial infarction
BEST	Biologics Effectiveness and Safety Sentinel Initiative
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CI	Confidence interval
CK-MB	Creatine kinase-muscle/brain
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
CT	Computed tomography
DVT	Deep vein thrombosis
ECG	Electrocardiogram
FDA	Food and Drug Administration
GEMs	General Equivalence Mappings
HCPCS	Healthcare Common Procedure Coding System
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
ICD-10-CA	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IVIG	Intravenous immune globulin
LOINC	Logical Observation Identifiers Names and Codes
MRI	Magnetic resonance imagine
NDC	National Drug Code
NPV	Negative predictive value
PE	Pulmonary embolism
PICO	Population, intervention, comparator, outcome
PPV	Positive predictive value
TEE	Thromboembolic event
TIA	Transient ischemic attack
ULN	Upper limit of normal
URL	Upper reference limit
VTE	Venous thromboembolism
WNL	Within normal limits.

Defining Thromboembolic Events Using Administrative Claims Data: A Series of Case Algorithms

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A Summary

The Biologics Effectiveness and Safety (BEST) Sentinel Initiative conducted a literature review to identify validated methods for using administrative claims data to ascertain potential cases of five categories of thromboembolic events: pulmonary embolism, deep vein thrombosis, acute myocardial infarction, stroke and arterial embolism and thrombosis. Insights were drawn primarily from studies that defined outcomes using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding system to identify potential cases in the United States. However, findings from international studies using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), the International Statistical Classification of Diseases and Related Problems, Tenth Revision, Canada (ICD-10-CA), and the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) were also leveraged to inform the overall approach.

The results of this literature review were used as the basis for developing preliminary drafts of administrative claims-based outcome definitions (or algorithms) for each outcome of interest. Where ICD-10-CM codes had not previously been reported in the literature, codes were mapped from ICD-9-CM to ICD-10-CM via forward–backward mapping, using General Equivalence Mappings (GEMs) for reference.[i] Algorithm codes were also informed by international sources. Draft algorithms were subject to review by BEST Sentinel Initiative clinical subject matter experts, resulting in further refinements.

The literature review methodology, findings, and subsequent refinements are presented herein, along with the algorithms developed for each outcome of interest. These algorithms were tested using the IBM® MarketScan® Research Databases to assess the feasibility of their use by generating descriptive statistics on the frequency of occurrence of these outcomes. Data for commercially insured and Medicare patients were accessed via the Treatment Pathways 4.0 analytic platform. The results of this testing are also reported below.

B Background

Among other responsibilities, the U.S. Food and Drug Administration (FDA) is mandated to protect the public health by ensuring the safety and efficacy of drugs, biologics, and medical devices.[ii] In support of this mandate, the FDA Center for Biologics Evaluation and Research (CBER) has a mission to conduct policy and regulatory reviews of biologics and related products, including blood products, vaccines, allergenics, tissues, and cellular and gene therapies. CBER assesses the risks and benefits of new biologic products, as well as previously approved products that have been proposed for new indications.

[i] Additional information about GEMs and the methodology for forward and backward mapping can be found at CMS.gov. ICD-10-CM/PCS Frequently Asked Questions. Last Modified July 11, 2018. https://www.cms.gov/Medicare/Coding/ICD10/Frequently-Asked-Questions.html
[ii] U.S. Food and Drug Administration. What We Do. https://www.fda.gov/aboutfda/whatwedo/

The CBER assessment process emphasizes the pursuit of the maximum safety and public benefit while minimizing risks to the public for each biologic product. The BEST Sentinel Initiative is a program initiated by CBER with the objective of assessing the safety and effectiveness of biologic products using large datasets of administrative claims and clinical data.

The objective of this project was to assess the state of knowledge regarding validated methods of using administrative claims databases to identify various thromboembolic events (TEEs). These methods could draw on a variety of coding standards, including the International Classification of Diseases (ICD) coding system, the Healthcare Common Procedure Coding System (HCPCS), Current Procedural Terminology (CPT®), Logical Observation Identifiers Names and Codes (LOINC), and National Drug Codes (NDCs).

The overarching TEE disease category includes a number of disease entities. In general, TEEs result from a blood clot — or *thrombus* — forming in a vein or artery, which can lead to a range of adverse consequences ranging from congestion and irritation to tissue damage and necrosis. In certain situations, the thrombus can dislodge from its site of origin and travel to another part of the body, in which case it is called an *embolism*. TEEs have been studied extensively as a potential adverse drug event (ADE) for biologics, including immunoglobulins.[1-3]

Researchers sought to advance understanding of how TEEs can be reliably and validly identified using administrative claims data. Several TEEs are considered herein, including:

1. Acute pulmonary embolism (PE): refers to an arterial blockage in the lung that results from embolism of a substance, usually a blood clot, (venous thromboembolism (VTE)), from elsewhere in the body.[iii]
2. Acute deep vein thrombosis (DVT): refers to a blockage of a vein, usually occurring in the extremities.
3. Acute myocardial infarction (AMI): blockage (usually in a coronary artery) resulting in reduced blood flow to the heart and subsequent tissue death (infarction).
4. Cerebrovascular accident (Stroke): reduced blood flow to the brain, which can result in tissue death (infarction). The blockage can result from ischemia, a thrombosis (formation of a clot), an embolism (a clot that formed elsewhere in the body), and hemorrhage (bleeding). Although the focus was on stroke resulting from thrombosis or embolism, hemorrhagic stroke (or intracerebral hemorrhage) was also considered.
5. Arterial thrombosis and embolism: an arterial blockage that occurs at a specific body site, including in the aorta and extremities, or results from a thrombus or other substance dislodging from elsewhere in the body.

A comprehensive literature review of methods to identify potential TEEs using administrative claims data was conducted, leveraging findings from U.S. and international studies to inform the development of code-based outcome definitions (hereafter referred to as *algorithms*) for each TEE of interest. These draft algorithms — and their associated rules and assumptions — were then subject to review by clinical subject matter experts and testing in an administrative claims dataset (IBM MarketScan Research Databases) using a cloud-based analytic tool, the IBM MarketScan Treatment Pathways platform.[iv] **Sections C** and **D** summarize the literature review methodology and findings, respectively. **Section E** provides clinical case definitions for each TEE of interest, which could be of value in further assessing the performance of the proposed algorithms via chart review validation studies. **Sections F** and **G** present the TEE algorithms and their associated assumptions and decisions, respectively. **Section H** presents the results of the initial characterization of the algorithms in a claims database, including an assessment of the impact of the transition to ICD-10-CM on the proportion of individuals reported to experience a TEE. **Section I** provides discussion and concluding thoughts.

[iii] Although the blockage often is in an artery, PE is classified as a venous thromboembolism because the blockage forms in a vein.
[iv] IBM MarketScan Research. Insight for Better Healthcare. https://marketscan.truvenhealth.com/marketscanportal/Portal.aspx

C Methodology

A literature review search strategy was formulated in consultation with experts from FDA CBER, covering outcomes related to thromboembolic events, venous thromboembolism, arterial thrombosis, atherothrombosis, arterial embolism, pulmonary embolism, myocardial infarction, deep vein thrombosis, and stroke.

The review process involved conducting systematic searches of existing publications available in the FDA Sentinel databases.[v] These searches were followed by a structured review of the academic literature, using PubMed, Medline, and Google Scholar. A snowballing technique was applied, wherein references listed in relevant publications were also searched.

The search strategy was complemented by a review of clinical guidelines and targeted searches of potentially relevant organizations (such as the U.S. Armed Forces Health Surveillance Branch, the Agency for Healthcare Research and Quality, and Health Canada's *Canada Vigilance Program*).

Articles retrieved from execution of the search strategy were subject to title and abstract screening by a single reviewer, and retained abstracts were moved to full text review. A Microsoft® Excel spreadsheet was developed to record data extracted from relevant studies. The data elements are summarized in **Figure 1.**

A relevance ranking was assigned based on the judgement of the reviewer and the available information on study location ("Group/Country"), the algorithm specifications ("Algorithm/Criteria"), and measures of validation and diagnostic accuracy (such as positive predictive value [PPV] and negative predictive value [NPV]).

Title	Author	Year	Group/Country	Summary	Relevance	Disease Definition	Algorithm/Criteria	Validity	Comments

Figure 1. Data elements recorded in extraction spreadsheet.

D Results

Following the two-stage review process, 55 articles were retained for data extraction. The intent was to obtain a representative sample of the literature and not to conduct a full systematic review, although findings from several previously published systematic reviews assessing the validity and accuracy of diagnostic codes for PE,[4] DVT,[4] AMI,[5] and stroke[6-8] informed algorithm development. This section presents the results of the literature review, summarizing TEE-specific results in the subsections below.

D1 Pulmonary Embolism

[v] U.S. Food and Drug Administration. Science & Research (Biologics). Content current as of March 28, 2019. https://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/default.htm
Sentinel. Publications and Presentations. https://www.sentinelinitiative.org/communications/publications

The code-based definition for PE was consistent across studies and geographic areas. In a study of venous thromboembolism ascertained from the Sentinel Distributed Database, Ammann and colleagues[9] used the following ICD-9-CM codes[vi]:

- 415.11: iatrogenic pulmonary embolism and infarction
- 415.12: septic pulmonary embolism
- 415.13: saddle embolus of pulmonary artery
- 415.19: other pulmonary embolism and infarction

Study authors reported a wide range of PPV performance associated with this algorithm, ranging from 20% (95% confidence interval [CI] 3–56%) for position-unspecified diagnoses to 90% (95% CI 68–99%) for principal position diagnoses. A *principal diagnosis* is the condition primarily responsible for hospital admission, whereas a *secondary diagnosis* is a "condition also present on admission, that developed during the hospital stay, or that influenced the care of the patient or length of stay" (p. 3).[9] A position-unspecified code, meanwhile, would represent cases in which this position is not reported. The PPV for all potential cases (regardless of coded diagnosis position) was 68% (95% CI 49–83%). This approach of using ICD-9-CM 415.1x codes to identify cases of potential PE is consistent with the methodology of previous U.S. studies, which report a broad range of performance on measures of validity and diagnostic accuracy.[10-24]

Although U.S. studies using the ICD-10-CM version were not found, studies from other countries provided a useful reference. A Canadian study used ICD-9-CM codes 415.0 and 415.1x and ICD-10-CA codes I26.0 and I26.9 (which translate directly to ICD-10-CM) to identify potential cases of PE in inpatient and outpatient settings.[25] Study authors reported a sensitivity of 74.8% (95% CI 67–82), a specificity of 91.9% (95% CI 89–94), an NPV of 93.4% (95% CI 91–95), and a PPV of 70.5% (63–78) for these codes when including codes in any diagnostic position; the PPV increased to 83.8% (95% CI 76–90%) when only codes in the principal diagnostic position were assessed. The use of I26.0 and I26.9 was found in another Canadian study, which assessed the validity of codes using emergency department data.[26] In that study, which did not specify the diagnosis position(s) used in the analyses of a 1,453-patient cohort, authors reported a sensitivity of 91.1% (95% CI 89–93%), a specificity of 99.9% (95% CI 99.9–99.9%), an NPV of 99.9% (95% CI 99.9–99.9%), and a PPV of 82.3% (95% CI 80–84%). A third Canadian study using ICD-10-CM I26, which also did not report on diagnosis position(s), reported a PPV of 56% (95% CI 42–68%).[27]

The use of ICD-10 code I26 to identify possible cases of PE was also observed in a French study, in which a PPV of 99.0% (95% CI 94–99.9%) was associated with a principal position I26 code.[28] The same approach was reported in a Danish study, which reported a PPV of 95% (95% CI 84–99%) for first-time PE when assessing codes in the primary diagnostic position.[29]

D2 Deep Vein Thrombosis

Many of the studies that examined the performance of PE codes also assessed codes for DVT, grouping them under the umbrella of VTE. However, the application of DVT codes was less consistent across studies.

In a recent chart validation study using the Sentinel Distributed Database, Ammann and colleagues[9] used the following ICD-9-CM codes to identify potential cases of DVT:[vii]

[vi] Review authors noted that ICD-9-CM code 415.0 (Acute cor pulmonale) was included in some definitions but was excluded in most literature studies reviewed. On the basis of clinical consultation, the decision was made to exclude this code because the condition is not specific to pulmonary embolism and can be associated with other diagnoses, including acute respiratory distress syndrome or other disorders.

[vii] ICD-9-CM codes 451.8x (phlebitis and thrombophlebitis of other sites) and 453.8x (acute venous embolism and thrombosis of other specified veins) were excluded from the DVT code list developed by Ammann and colleagues. Because the BEST-IBM team

- 451.11: phlebitis and thrombophlebitis of femoral vein (deep) (superficial)
- 451.19: phlebitis and thrombophlebitis of deep veins of lower extremities, other
- 451.2: phlebitis and thrombophlebitis of lower extremities, unspecified
- 451.9: phlebitis and thrombophlebitis of unspecified site
- 453.1: thrombophlebitis migrans
- 453.2: other venous embolism and thrombosis of inferior vena cava
- 453.40: acute venous embolism and thrombosis of unspecified deep vessels of lower extremity
- 453.41: acute venous embolism and thrombosis of deep vessels of proximal lower extremity
- 453.42: acute venous embolism and thrombosis of deep vessels of distal lower extremity
- 453.9: other venous embolism and thrombosis of unspecified site

Study authors reported a PPV of 54% (95% CI 34–72%) for all potential cases, although this ranged from 29% (95% CI 10–56%) for position-unspecified diagnoses to 90% (55–100%) for principal position diagnoses. On a code-specific basis, the PPV values for phlebitis and thrombophlebitis codes (451.xx) were generally lower than those for acute venous embolism and thrombosis codes.

Although the definition for DVT used by Ammann and colleagues[9] is consistent with that of previous studies,[10,21,22,30,31] the choice of ICD-9-CM codes to identify DVT has varied across studies. For example, some studies used only ICD-9-CM 451.xx and 453.8 to identify potential cases.[18,19] Wiley and colleagues used only 451.xx codes and required two or more prescriptions for anticoagulants for a positive identification.[11] A previous CBER study protocol[20] used the same algorithm but added ICD-9-CM codes 325.xx (phlebitis and thrombophlebitis of intracranial venous sinuses) and 437.6 (nonpyogenic thrombosis of intracranial venous sinus), although the BEST Initiative did not view these as appropriate for inclusion. Another study used 451 and 453 codes but added the placement of a vena cava filter to their definition, reporting a PPV of 47%.[24] Other studies added codes associated with DVT during pregnancy or puerperium.[14,17,32-34]

Similar to PE, U.S. validation studies that included ICD-10-CM coding for DVT were not found. However, use of ICD-10 coding in other countries varied across studies and was generally associated with low performance on measures of validation and diagnostic accuracy. A Canadian study combined ICD-9-CM codes (451.x and 453.x) with ICD-10-CA codes I80.1 (phlebitis and thrombophlebitis of femoral vein), I80.2 (phlebitis and thrombophlebitis of other deep vessels of lower extremities), I80.3 (phlebitis and thrombophlebitis of lower extremities, unspecified), I80.8 (phlebitis and thrombophlebitis of other sites), I80.9 (phlebitis and thrombophlebitis of unspecified site), I82.8 (embolism and thrombosis of other specified veins), I82.9 (embolism and thrombosis of unspecified vein), and pregnancy-related codes (O22.3, O87).[25] These codes were associated with a sensitivity of 75.2% (95% CI 66–83), a specificity of 95.8% (95% CI 94–97%), an NPV of 95.3% (95% CI 93–97%), and a PPV of 77.5% (68–85%). Another Canadian study used ICD-10-CM codes I80.1, I80.2, I80.3, and I82.4x (acute embolism and thrombosis of deep veins of lower extremities), reporting a PPV of 42% (95% CI 29–57%).[27] A Danish study reported a PPV of 86% (95% CI 74–93%) associated with the use of ICD-10 codes I80.1, I80.2, and I80.3.[29]

D3 Acute Myocardial Infarction

The use of ICD-9-CM codes to identify potential cases of AMI was found to be consistent across studies. As reported in a Mini-Sentinel AMI validation study, 410.x0 (unspecified episode of care) and 410.x1 (initial episode of care) are used to identify potential AMI cases, whereas 410.x2 codes (subsequent episode of care) are excluded.[35,36] Cutrona and colleagues[35] based this approach on a review of prior U.S. and international studies[37-40] and limited their definition to codes in the principal diagnostic position. They also excluded codes for chronic events, such as ICD-9-CM codes 412 (old myocardial infarction) and 414 (chronic ischemic heart disease). Codes related to acute ischemic heart disease (such as

sought to identify cases regardless of diagnostic coding position, 453.8x codes were included in the algorithm presented herein. The 451.8x codes were excluded along with other phlebitis and thrombophlebitis codes (ICD-9-CM code 451.xx).

intermediate coronary syndrome and angina) were also excluded. Authors reported an overall PPV of 86% (95% CI 79–91%), which ranged from 76.3% to 94.3% across the participating data providers. This algorithm has been adopted in subsequent Mini-Sentinel studies.[20,41]

One study[42] — reporting a PPV of 87% (95% CI 51–88%) — included the following ICD-9-CM codes in its myocardial infarction algorithm: 410 (myocardial infarction), 411 (other acute and subacute forms of ischemic heart disease), 412 (old myocardial infarction), 413 (angina pectoris), 414 (ischemic heart disease), 429.2 (cardiovascular disease, unspecified), and v45.81 (presence of aortocoronary bypass graft). However, out of concern that inclusion of these other groups would result in the improper inclusion of many non-AMI cases, codes other than 410.x0 and 410.x1 were not included in the algorithm presented in this report.

Although U.S. studies reporting the use of ICD-10-CM codes for AMI were not found, international studies used the ICD-10 I21 codes (which correspond to the ICD-10-CM I21.xx codes). A Danish validation study using I21 (acute myocardial infarction) codes reported a PPV of 97% (95% CI 91–99),[29] whereas another Danish study using I21 codes reported a worst-case PPV of 74.0% (95% CI 67–81%) and best-case PPV of 100% (95% CI 100–100) associated with principal position hospital discharge codes.[43]

In a Canadian study, ICD-10 I21 codes (I21.0, I21.1, I21.2, I21.3, I21.4) were used to identify cases of AMI, and the study authors suggested that ICD-10 codes were better able to distinguish between ST-elevation and non-ST-elevation AMIs than were ICD-9-CM codes.[44] Another Canadian study used the same codes (I21.0–I21.3) to identify AMI associated with ST elevation and found that 94% of cases were correctly classified.[45]

Because some ICD-10 I21 codes do not translate directly to ICD-10-CM, BEST Initiative authors chose to conduct forward–backward mapping to translate the well-accepted and validated ICD-9-CM algorithm to ICD-10-CM. This was informed by a recent U.S. study by Panozzo and colleagues,[46] who used GEMs to translate ICD-9-CM algorithms for AMI to ICD-10-CM, via simple-forward, simple-backward, and forward–backward mapping. ICD-10-CM codes included I21.0x, I21.1x, I21.2x, I21.3, I21.4, I21.9, I22.0, I22.1, I22.2, I22.8, and I22.9, which are very similar to those selected by Panozzo and colleagues.

D4 Stroke

The use of ICD-9-CM codes to identify potential cases of stroke was consistent across studies identified from the literature. A recent chart validation study using the Sentinel Distributed Database used the following codes to identify potential cases of inpatient acute ischemic stroke:[47]

- 433.x1: occlusion and stenosis of precerebral arteries with mention of infarction
- 434.xx: occlusion of cerebral arteries
- 436: acute, but ill-defined, cerebrovascular disease

Study authors reported a low overall PPV of 27% (95% CI 19–35%), which ranged from 6% (95% CI 2–15%) for position-unspecified diagnoses to 60% (95% CI 32–84%) for principal-position diagnoses. However, authors noted that PPVs associated with codes 433.x1 and 434.x1 (occlusion with cerebral infarction) were higher than those for codes 434.x0 (occlusion without cerebral infarction) and 436. The exclusion of 434.x0 and 436 increased the principal-position PPV to 69%.

Although the PPV reported by Ammann and colleagues[47] was meaningfully lower than PPVs reported in earlier studies, it is consistent with the general use of codes, which have previously been associated with PPVs of 73–94%.[6,8,40,48-53] For example, a U.S. validation study using ICD-9-CM codes 433.x1, 434.x1, and 436 reported a sensitivity of 58.6% (95% CI 52–65%), a specificity of 99.8% (95% CI 99.7–99.9%), and a PPV of 91.1% (95% CI 87–96%).[54] Ammann and colleagues concluded that the poorer performance of the algorithm in their study may have been due to the particular characteristics of their study population and that their findings may not be generalizable to the broader population.[47]

While U.S. validation studies using ICD-10-CM were not found, international studies using ICD-10 were identified. A French validation study used primary position ICD-10 codes I61 (intracerebral hemorrhage), I63 (cerebral infarction), I64 (stroke, not specified as hemorrhage or infarction), and G46 (vascular syndromes of brain in cerebrovascular diseases), excluding codes for transient ischemic attacks (TIA) and subarachnoid hemorrhage.[55] Among hospitalized patients, the algorithm was associated with a sensitivity of 77.1% (95% CI 74–80%) and a PPV of 69.2% (95% CI 66–72%). Meanwhile, in a Canadian study, Hall and colleagues identified cases of stroke and TIA using the following ICD-10-CA codes: I60 (subarachnoid hemorrhage, excluding I60.8), I61 (intracerebral hemorrhage), H34.1 and I63 (ischemic, excluding I63.6), I64 (unable to determine stroke), and H34.0 and G45 (TIA, excluding G45.4).[56] These authors reported a sensitivity for stroke and TIA (combined) of 82.2% (95% CI 81–83%) and a PPV of 68.8% (95% CI 67–70%) in an inpatient setting.

Through discussion with clinical stakeholders, it was decided that further subcategorization of stroke codes would be worthwhile. Codes were therefore organized according to the following four categories: cerebral infarction and thrombosis, occlusion without mention of infarction, TIA, and hemorrhagic stroke. This approach expands the analytical flexibility of the stroke algorithm, allowing users to tailor the modules to suit their research question.

Noting that the relevant ICD-10 and ICD-10-CA codes did not translate directly to ICD-10-CM, the BEST Initiative chose to map ICD-9-CM codes to ICD-10-CM via forward–backward mapping; this approach was also informed by the general categories included in prior international studies. This exercise resulted in the inclusion of I61.x (nontraumatic intracerebral hemorrhage), I62.xx (other and unspecified nontraumatic intracerebral hemorrhage), I63.xxx (cerebral infarction), I65 (occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction), I66 (occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction), I67.6 (nonpyogenic thrombosis of intracranial venous system), G45.x (transient cerebral ischemic attacks and related syndromes), and G46.x (vascular syndromes of brain in cerebrovascular diseases). The mapping for ischemic stroke categories resulted in a list of diagnostic codes similar to that developed in a mapping effort by Panozzo and colleagues.[46]

D5 Arterial Embolism and Thrombosis

The “Arterial Embolism and Thrombosis” category was not originally included in the literature review search strategy and was largely developed on the basis of clinical expertise. Following the formal literature review and during the review of the preliminary draft algorithms, CBER clinicians recommended that this new outcome category be created to include ICD-10-CM I74 codes (arterial embolism and thrombosis).

The proposed codes included I74.0x (embolism and thrombosis of abdominal aorta), I74.1x (embolism and thrombosis of other and unspecified parts of aorta), I74.2 (embolism and thrombosis of arteries of the upper extremities), I74.3 (embolism and thrombosis of arteries of the lower extremities),I74.4 (embolism and thrombosis of arteries of extremities, unspecified), I74.5 (embolism and thrombosis of iliac artery), I74.8 (embolism and thrombosis of other arteries), and I74.9 (embolism and thrombosis of unspecified artery). It was noted that these codes matched exactly with those used in a French study to define “peripheral arterial thrombosis.”[28] In this study, the authors reported a PPV of 83% (95% CI 74–89%) associated with this definition. The proposed ICD-10-CM codes were then mapped to the corresponding ICD-9-CM codes via simple-backward mapping and quality-checked via simple-forward mapping.

E Case Definitions

A chart review validation study for the proposed algorithms was outside the scope of this review. However, the BEST Initiative did make note of commonly used case definitions for each outcome of interest. These case definitions are provided in the sections below and may be of value if the decision is made to proceed with a chart review validation study in the future.

E1 Pulmonary Embolism

The definition proposed for PE is based on the one used in the Worchester Venous Thromboembolism Study[14] and applied in a recent FDA CDER chart validation study.[9,viii]

- **Definite PE:** Confirmed by pulmonary angiography, spiral computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, or pathology.
- **Probable PE:** If the above tests not performed or were indeterminate, but ventilation-perfusion scan findings were of high probability.
- **Possible PE:** If all of the above tests were not performed or were indeterminate and two of the following criteria were satisfied: medical record indicates physician-diagnosed acute PE, signs or symptoms of acute PE were documented and the patient underwent therapy with anticoagulants, or an inferior vena cava filter was placed.
- **No PE or status unknown:** Based on the judgment of the physician adjudicator, potential cases not meeting diagnostic criteria for confirmation as a definite, probable, or possible PE were classified as no acute PE or as having an unknown status due to incomplete documentation or ambiguity.

E2 Deep Vein Thrombosis

As with PE, the DVT case definition was developed for the Worchester Venous Thromboembolism Study[14] and applied in a recent FDA CDER chart validation study:[9,ix]

- **Definite DVT:** Confirmed by conventional venography, compression/duplex ultrasound, CT scan/CT angiography, or pathology.
- **Probable DVT:** If the above tests not performed or were indeterminate, but impedance plethysmography, radionucleotide venography, or radiolabeled fibrinogen scan test results were reported as positive.
- **Possible DVT:** If all of the above tests were not performed or were indeterminate and two of the following criteria were satisfied: medical record indicates physician-diagnosed acute DVT, signs or symptoms of acute DVT were documented and the patient underwent therapy with anticoagulants, or an inferior vena cava filter was placed.
- **No DVT or status unknown:** Based on the judgment of the physician adjudicator, potential cases not meeting diagnostic criteria for confirmation as a definite, probable, or possible DVT were classified as no acute DVT or as having an unknown status due to incomplete documentation or ambiguity.

E3 Acute Myocardial Infarction

The case definition for AMI is adapted from the third universal definition developed jointly by the European Society of Cardiology, the American College of Cardiology, the American Heart Association, and the World Heart Federation.[57] This definition was also proposed in a recent CBER study protocol[20] and is summarized in **Table 1**.[x]

[viii] Criteria are adapted from Ammann et al., 2018, p. 2 (verbatim with exception of substituting *PE* for *VTE*).
[ix] Criteria are adapted from Ammann et al., 2018, p. 2 (verbatim with exception of substituting *DVT* for *VTE*).
[x] Copied verbatim from Chrischilles et al., 2015, pp. 20-21.

Table 1A. Case definition for AMI (cardiac pain present).

ECG Pattern/Symptoms	Abnormal	Equivocal	Incomplete	Normal
Evolving, diagnostic ECG: Evolving Q wave and evolving ST-T abnormalities	Definite MI	Definite MI	Definite MI	Definite MI
Positive ECG: Equivocal Q wave evolution with ST-T depression/inversion; or evolving ST-T elevation alone; or new left bundle branch bloc	Definite MI	Definite MI	Probable MI	No MI
Nonspecific ECG: evolution of minor ST-T depression/inversion or minor Q-wave evolution alone and not classified above	Definite MI	Probable MI	No MI	No MI
ECG negative for ischemia: Normal ECG, other ECG, or ECG absent	Definite MI	No MI	No MI	No MI

Table 1B. Case definition for AMI (cardiac pain absent).

ECG Pattern/Symptoms	Abnormal	Equivocal	Incomplete	Normal
Evolving, diagnostic ECG: Evolving Q wave and evolving ST-T abnormalities	Definite MI	Definite MI	Definite MI	Probable MI
Positive ECG: Equivocal Q wave evolution with ST-T depression/inversion; or evolving ST-T elevation alone; or new left bundle branch block	Definite MI	Probable MI	No MI	No MI
Nonspecific ECG: evolution of minor ST-T depression/inversion or minor Q-wave evolution alone and not classified above	Probable MI	No MI	No MI	No MI
ECG negative for ischemia: Normal ECG, ECG absent or unreadable	No MI	No MI	No MI	No MI

Table 1C. Cardiac enzyme interpretation for AMI diagnosis.

Cardiac enzyme	Abnormal	Equivocal	Normal
CK-MB (highest value)	>99th percentile URL	>ULN and <99th percentile URL	WNL
Troponin (highest value)	>99th percentile URL	>ULN and <99th percentile URL	WNL
CK (no MB available-consider highest value)	N/A	>99th percentile URL	WNL

Abbreviations: AMI, acute myocardial infarction; CK-MB, creatine kinase-muscle/brain; ECG, electrocardiogram; N/A, not applicable; ULN, upper limit of normal; URL, upper reference limit; WNL, within normal limits.

E4 Stroke

For the case definition of stroke, the BEST Initiative focused on acute ischemic stroke (AIS), wherein the event occurs because of the reduced flow of blood to the brain; this incorporates strokes due to thrombi (thrombotic stroke) and emboli (embolic stroke). The criteria were drawn from those developed jointly by the American Heart Association and the American Stroke Association and were adapted and applied in a recent CDER publication.[47,xi]

[xi] Criteria were copied verbatim from Ammann et al., 2017, p. 3.

- **Definite:** To qualify as a definite AIS, a potential case was required to have documentation of an acute focal ischemic infarction of the central nervous system based on imaging, for example, CT or MRI, or surgical or pathological findings.
- **Probable:** A case was counted as a *probable* AIS if there was rapid onset of neurologic deficit documented but CT/MRI was unavailable or done too early. The deficit must not have been secondary to brain hemorrhage, trauma, tumor, infection, or another identifiable mimic, and must have lasted more than 24 hours (unless death supervened).
- **Possible:** If neither imaging evidence nor clinical signs and symptoms consistent with AIS were documented in the chart, a physician diagnosis of AIS recorded in the chart was counted as a possible event.
- **No AIS or AIS status unknown:** Cases that fit none of the criteria above were classified as *no AIS* or *status unknown/insufficient information* based on the completeness of the patient's medical chart.

E5 Arterial Embolism and Thrombosis

This category was developed post hoc, so specific case definitions were not extracted during the literature review. However, a subsequent review of relevant articles found that information on criteria to adjudicate potential cases of arterial embolism and thrombosis was limited. It may be that a reliable definition for the adjudication of possible arterial embolism and thrombosis cases (definite, probable, possible, none) is not yet available.

A French study that used the same code-based definition as that summarized in **Section H5** and outlined in detail in **Appendix** A5 provided the following description of their chart review process:

> *To be categorized as a true positive case, thrombosis had to be proven by an imaging technique (ultrasonography, Doppler, computed tomography, magnetic resonance imaging or arteriography). In case of true positive, we also assessed whether the detail of the ICD-10 code was compatible with the location of the thrombosis among peripheral arterial and venous thrombosis and whether there were signs of acute cor pulmonale among pulmonary embolism cases*. (p.109)[28]

F Thromboembolic Event Algorithms

The results of the literature review were leveraged to identify examples of high-quality, administrative claims-based case definitions, prioritizing where possible those that had been developed for use in the United States and those that had been subject to chart review validation studies.

Where appropriate, algorithms were mapped from ICD-9-CM to ICD-10-CM via forward–backward mapping using the Centers for Medicare & Medicaid Services (CMS) GEMs for reference.[58-61] Draft algorithms were then subject to review by clinical subject matter experts from IBM Watson Health, FDA CBER, and Acumen.

The code-based algorithms for each TEE of interest are summarized at a high level in **Table 2** and specified in detail in **Appendix A**.[xii] In all cases, the presence of one of the codes listed in the algorithm definitions was considered to indicate a potential case, regardless of healthcare setting or coding position. The authors recognize that both healthcare setting and diagnostic coding position are likely to influence

[xii] Table 2 is intended to be illustrative of the code groups included for each outcome but does not necessarily imply that all subsidiary codes have been included. Readers are encouraged to refer to the full algorithms in **Appendix A** for details.

measures of validity and diagnostic accuracy but viewed such restrictions as dependent on specific research questions and more appropriate for application at the study planning stage.

Table 2. Summary of TEE algorithms.

TEE Outcome	ICD-9-CM	ICD-10-CM
Pulmonary embolism	415.1x	I26.0x; I26.9x
Deep vein thrombosis		
Lower body	453.2; 453.3; 453.4x; 453.6	I82.4xx; I82.8xx
Other (upper body, other, unspecified)	453.0; 453.8x; 453.9	I81; I82.0; I82.2xx; I82.6xx; I82.890; I82.90; I82.Axx; I82.Bxx; I82.Cxx
Acute myocardial infarction	410.x0; 410.x1	I21.xx; I22.x
Stroke		
Thrombosis and infarction	433.x1; 434.x1	I63.xxx
Occlusion without mention of infarction	433.x0; 434.x0; 437.6	I65.xx; I66.xx; I67.6
Transient ischemic attack	435.x	G45.x; G46.x
Hemorrhagic stroke	432.1; 432.9	I61.x; I62.0x; I62.9
Arterial embolism and thrombosis (any code)	444.xx	I74.xx

To generate estimates of the frequency of use for each code, authors ran code-specific queries for 2014–2017 among a large MarketScan Research Databases patient cohort. Annual counts of individual diagnostic codes are provided in **Appendix B**.

Codes relating to outcomes during pregnancy or due to chronic conditions were excluded, as were those associated with follow-up visits. Similarly, because the emphasis was on acute outcomes that could be associated with an exposure to a biologic, codes related to chronic conditions were excluded. This differs from some previous studies that grouped chronic and acute codes together. The following codes were excluded: chronic pulmonary embolism (ICD-9-CM code 416.2; ICD-10-CM code I27.82), chronic venous embolism and thrombosis (ICD-9-CM code 453.xx; ICD-10-CM codes I82.2xx, I82.5xx, I82.7xx, I82.891, I82.91), and chronic heart diseases (ICD-9-CM code 414).

A list of excluded codes for each TEE of interest is provided in **Appendix C**, along with the annual counts for each. The intent of these lists is not to provide an exhaustive catalog of codes that were left out; rather, the intention is to call attention to the specific types of codes that were related to the outcomes of interest but were ultimately excluded, as well as the commonality of their use. Reasons for exclusion are provided in **Section G** and **Appendix A**.

G Assumptions and Decisions

The algorithms included in **Appendix A** were reviewed internally and with CBER experts and partners. General decisions and assumptions are listed below, and outcome-specific assumptions and decisions are included in the subsections. Note that some of these assumptions may be adjusted as a result of study research questions that remain to be developed.

- Although the outcome-specific algorithms for the various TEE categories are intended for independent application, the code-based definitions could also be combined to query cases of "any" TEE.
- In all cases, a single code, regardless of healthcare setting or coding position, was viewed to represent the occurrence of a TEE. Recognizing that this can affect measures of validity and diagnostic accuracy, it was decided that exclusion based on these dimensions could improperly exclude cases and was best made at the study planning stage (depending on the regulatory question to be addressed).
- For all categories, it is recommended that authors consider the application of a minimum enrollment requirement. For example, the characterization summarized in **Section H** required that individuals be enrolled in an insurance program for a full calendar year to be included in a particular year's cohort (e.g., an individual must have been enrolled for all of 2014 to be included in the "2014" study cohort). However, the application of such an eligibility criterion may depend on the particular research question.

G1 Pulmonary Embolism

The assumptions and decisions relevant to PE are listed below:

- The BEST Initiative sought to develop an algorithm that was specific to acute PE (whether first-time or recurrent), aiming to exclude chronic cases for which there would be less reliability in associating exposure to a biologic with the PE outcome. This is due to the intended use of the algorithm for surveillance of biologic safety.
    - Although chronic PE is quite rare, use of PE codes may not reliably distinguish between acute and chronic cases. As such, future users of the algorithm may want to consider some sort of washout period, wherein individuals who had received a diagnosis code for PE in a certain period of time *prior* to the exposure of interest would be excluded from consideration for an acute event. However, the appropriateness of such a washout period may depend on the study research question and priorities and could be decided at the study planning stage.
- The inclusion of ICD codes for iatrogenic (415.11) and septic (415.12, I26.01, I26.90) PE was discussed. It was decided that these would be included for the time being, although their inclusion may depend on the specific study research question.
- It was decided that procedural (CPT, HCPCS), laboratory (LOINC), and prescription (NDC) coding languages would not be included in the algorithm.
    - Few published studies used non-ICD coding to define PE.
    - One potential procedural code for prothrombin time (CPT 85610) was excluded. This test is fairly accessible and inexpensive and is obtained fairly often. It was decided that this inclusion could bias results because testing is only needed to monitor therapy with some anticoagulants (e.g., warfarin) and does not apply equally across all individuals on anticoagulants. As such, this test may no longer increase PPV, as new anticoagulants continue to be introduced into the clinic. The approach of incorporating this CPT code for prothrombin time was reported in a 1994 publication[13] and is less relevant to current practice.
    - One study tested the impact of including oral anticoagulant prescriptions filled in the 183 days prior to index hospitalization.[9] It is expected that inclusion/exclusion of anticoagulants will depend on the regulatory question to be addressed.
- ICD-9-CM code 415.0 (acute cor pulmonale) was excluded because it is not specific to PE. This exclusion is in line with the approach of a previous Sentinel study.[9]
- Codes for PE related to pregnancy were excluded.

G2 Deep Vein Thrombosis

The assumptions and decisions for DVT are listed below:

- As with PE, the BEST Initiative sought to develop a case-based definition for DVT that excluded cases of chronic DVT. Codes for “chronic” DVT have been excluded because of the likelihood that this diagnosis reflects chronic venous disease (sequelae of DVT), but the possibility that chronic cases are misreported as acute events remains.
    - Depending on the study research question and priorities, future users of the algorithm may want to consider a washout period wherein individuals would be excluded from consideration for an acute event if they had received a diagnosis code for DVT in a certain period of time before the exposure of interest.
- Codes were categorized by location of DVT to enable conducting analyses of lower-body DVTs only. Because DVTs occurring at sites other than the lower extremities are more likely to be associated with an underlying hypercoagulable disease state (e.g., myeloproliferative neoplasm, lupus anticoagulant, paroxysmal nocturnal hemoglobinuria) or an implanted medical device, this subset of the population may be at higher risk of DVT than those with lower body DVT. On the basis of clinical consultation, the renal vein was selected as the boundary between "Lower Body" and “Other” DVTs, with veins above this added to the "Other" category (along with codes for "Other" and "Unspecified" DVTs).
    - Although the inferior vena cava spans the renal vein, it was categorized as "Lower Body" on the basis of the clinical opinion that a thrombus would be more likely to originate from the lower body.
    - Because DVTs of the iliac vein tend to be among the most clinically meaningful, these can be isolated for subgroup analysis if desired.
- It was decided that codes for DVT of the upper extremities and embolism and thrombosis in superficial veins would be included.
    - A Mini-Sentinel study protocol[20] previously proposed excluding upper extremity DVTs, “as central venous catheters present a potential source of time-varying confounding.” Researchers sought instead to address this issue by enabling the exclusion of any non-lower-body DVTs (classified in the “Other DVT” category).
    - It could be argued that thrombosis and embolism of superficial veins should not be categorized as *deep* vein thrombosis. However, these codes were included in an effort to be as inclusive as possible. These codes could be removed depending on the specific regulatory question and the level of specificity being sought.
- It was decided that procedural (CPT, HCPCS), laboratory (LOINC), and prescription (NDC) codes would not be included in the algorithm, consistent with approaches noted in the literature.
- Codes for phlebitis and thrombophlebitis were excluded because the clinical opinion was that these were more closely associated with local tissue irritation than with systemic issues (e.g., clots, obstructions) associated with embolic and thrombotic events.
- DVT codes related to pregnancy were excluded.

G3 Acute Myocardial Infarction

The assumptions and decisions for AMI are listed below:

- The following ICD-10-CM codes were originally included in the AMI algorithm: I22 (subsequent ST-elevation and non-ST-elevation myocardial infarction) and I24.0 (acute coronary thrombosis not resulting in myocardial infarction).
    - These codes were included to assess the extent to which they were present in the study population. The codes translate to ICD-9-CM codes that include old MI, chronic heart disease, and unspecified cardiovascular disease.

    - Following testing, I24.0 was removed because it is unlikely to code for AMI and was not associated with a high code count (N=4,881 between 2015 and 2017).
- It was decided that procedural (CPT, HCPCS), laboratory (LOINC), and prescription (NDC) codes would not be included in the algorithm. This decision is consistent with approaches noted in the literature.
- Where specified, subsequent episodes of care (i.e., follow-up visits) were excluded to avoid improperly classifying a follow-up visit as an AMI, which could lead to a spurious association if that visit was in close proximity to a particular biologic exposure being assessed. As informed by prior studies, “unspecified” episodes of care (e.g., 410.x0) have been included, although there is the potential that these codes include subsequent episodes of care.
    - The impact of including these codes could be tested via sensitivity analysis.
- The following ICD-9-CM codes have been excluded: 411.1 (intermediate coronary syndrome), 411.8 (other acute and subacute forms of ischemic heart disease), 413.0 (angina decubitus), 413.1 (Prinzmetal angina), and 413.9 (other and unspecified angina pectoris).
    - Similarly, the following ICD-10-CM codes have been excluded: I20.0 (unstable angina), I20.1 (angina pectoris with documented spasm), I20.8 (other forms of angina pectoris), I20.9 (angina pectoris, unspecified), I24.0 (acute coronary thrombosis not resulting in myocardial infarction), and I24.8 (other forms of acute ischemic heart disease).
    - These were also excluded from previous studies,[29,35,36,43,44] at least in part because of concerns about the availability and reliability of information for such cases.[20] However, it was noted that codes for angina could be used as for a supplementary analysis where a potential risk is detected among the AMI codes.

G4 Stroke

The assumptions and decisions for stroke are listed below:

- To allow outcomes to be tailored to specific questions under investigation, stroke codes have been separated into the following categories: cerebral infarction/thrombosis, occlusion without mention of infarction, TIA, and hemorrhagic stroke. The first three categories could be applied together or in a stepwise fashion if a signal was detected for cerebral infarction/thrombosis. Hemorrhagic stroke (intracerebral hemorrhage) is separated because the mechanism of action (bleeding as opposed to clotting) is meaningfully different from other stroke-related categories included.
- The proper categorization of nonpyogenic thrombosis of intracranial venous sinus/system (437.6/I67.6) was discussed among clinicians. It was decided that these codes would be best categorized within the “occlusion without mention of infarction" category, because they likely refer to blockages that are insufficient to cause infarction.
- Researchers discussed whether to include TIA as a stroke outcome category. Recognizing that TIA events were excluded from a previous Sentinel study protocol because of concerns surrounding the adequacy of information available for chart review,[20] it was decided that TIAs would be included as a separate category given their position on the spectrum of cerebrovascular events.
- The proper inclusion of G46.x codes was discussed among clinicians. It was decided that the TIA category would be most appropriate because these codes are associated with conditions that are insufficient to categorize as occlusion or infarction events. This approach is also consistent with the categorization of similar syndromes (435.x, G45.x).
- It was decided that procedural (CPT, HCPCS), laboratory (LOINC), and prescription (NDC) codes would not be included in the algorithm. This decision is consistent with approaches noted in the literature.

G5 Arterial Embolism and Thrombosis

The assumptions and decisions for arterial embolism and thrombosis are listed below:

- It was decided that procedural (CPT, HCPCS), laboratory (LOINC), and prescription (NDC) coding languages would not be included in the algorithm. This decision is consistent with approaches noted in the literature.
- It was decided that codes related to embolism/thrombosis due to prosthetic devices, implants, and grafts would be excluded because the patient population is likely to have other risks of thrombosis. Including these codes could therefore confound the product exposure–embolism outcome association.

H Algorithm Characterization

Seeking to both test the feasibility of algorithm use and describe the epidemiology of thromboembolic events in the United States, the BEST Initiative used the IBM MarketScan Research Databases (Commercial and Medicare Supplemental), accessed via the Treatment Pathways platform, to generate descriptive analyses of the ICD codes for each outcome of interest, assessing the frequency of diagnoses by age, gender and year as well as the impact of the transition to ICD-10-CM on the identification of TEEs in U.S. administrative claims databases. The Treatment Pathways platform supports customizable analyses of data stored on IBM Watson Health servers. The BEST Initiative used the 100% Treatment Pathways sample of data from January 1, 2011 through December 31, 2017. The analyses relied on the code lists presented in **Appendix A**.

Age- and gender-specific data on enrollment and TEE case counts were extracted from the MarketScan Research Databases. In addition to the code-specified queries described in **Section F** (and summarized in **Appendix B**), the authors executed queries that aggregated all ICD-9-CM codes, all ICD-10-CM codes, and all codes (ICD-9-CM and ICD-10-CM) for each outcome of interest. Analyses were organized by outcome and are presented in the subsections below.[xiii]

The figures presented below have been drawn from a large patient dataset in the study period of January 1, 2014–December 31, 2017. For all analyses, authors only queried ICD-9-CM for January 1, 2014–September 30, 2015 and only queried ICD-10-CM codes for October 1, 2015–December 31, 2017. This is because October 1, 2015, is the date that the United States transitioned from ICD-9-CM to ICD-10-CM, and the authors sought to exclude codes that were reported in error from the analysis.

Individuals had to be continuously enrolled in any enrollment category to be included in the analysis for a particular year. For example, patients had to be continuously enrolled from January 1 to December 31, 2014, in order to be included in the 2014 dataset. From 2014–2017, there were 41,172,696 unique individuals that were enrolled for at least one calendar year. Age was calculated at the end of each calendar year (i.e., age in 2014 was calculated as of December 31, 2014). Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under one year old), this population group has been left out of the charts depicting the proportions of individuals with a TEE by age.

It is important to note that counts of individual patients who had a diagnosis code related to the TEEs of interest were reviewed, rather than counts of TEE cases. As such, counts relate to the first diagnosed TEE of interest for an individual during a given surveillance period (e.g., January 1–December 31, 2014), and individuals could only be counted once per surveillance period. As a result, the counts aggregating numerous codes (presented below) will differ from counts from code-specific queries (**Appendix B**). However, because as each TEE of interest was queried separately as an independent outcome,

[xiii] Given that the same analyses are being reported for each TEE of interest, the same reporting structure and style has been used for each subsection.

individuals could be counted in multiple TEE categories. A patient could, for example, be included in the results for both PE and DVT.

H1 Pulmonary Embolism

Table 3 provides a summary of aggregate counts for ICD-9-CM and ICD-10-CM codes, suggesting that PE occurs in approximately 2.26–2.41 individuals per 1,000 included in Research Databases per year.

Table 3. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in PE algorithm (January 1, 2014–December 31, 2017).

Code	Calendar Year			
	2014	2015*	2016	2017
ICD-9-CM	64,970	43,957		
ICD-10-CM		25,209	50,096	44,781
ICD-9-CM OR ICD-10-CM	64,970	53,373	50,096	44,781
MarketScan Research Databases enrollment	28,407,959	22,117,235	21,616,367	19,802,253
Proportion of patients with PE per 1,000 enrolled population	2.29	2.41	2.32	2.26

* In 2015, queries combining ICD-9-CM and ICD-10-CM codes returned lower patient counts than individual queries did. This is because of cases in which both ICD-9-CM and ICD-10-CM codes were reported for the same individual, in the January–September and October–December timeframe, respectively. This overlap is the result of the transition from ICD-9-CM to ICD-10-CM in 2015 and resulted in 15,793 duplications (i.e., individuals that were counted in both the ICD-9-CM and ICD-10-CM query).

The BEST Initiative sought to assess whether the 2015 transition to ICD-10-CM and any associated changes in coding practices resulted in notable shifts in the frequency of PE reporting. **Figure 2** illustrates the proportion of the enrolled population with a diagnosis related to PE and suggests that the transition did not result in a substantial change to the proportion of individuals receiving a PE diagnosis.

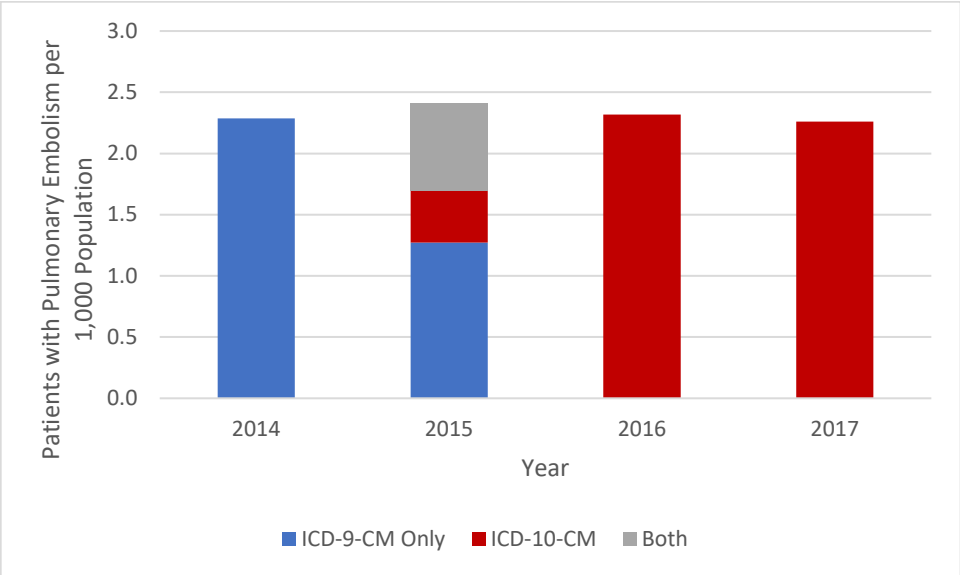

Figure 2. Proportion of patients with pulmonary embolism per 1,000 enrolled, by year (2014–2017).

Note: In 2015, a patient could receive both an ICD-9-CM and an ICD-10-CM diagnosis, in the January–September and October–December timeframe, respectively.

Figure 3 presents counts of patients with PE, defined by ICD-9-CM codes listed in **Appendix A1** and stratified by age category. Counts were calculated using a combined cohort of 33,216,843 patients who were continuously enrolled for at least one calendar year in 2014–2015. There were 95,629 individuals with at least one ICD-9-CM code for PE between January 1, 2014, and September 30, 2015, with an average age (calculated at the first event) of 58 years.

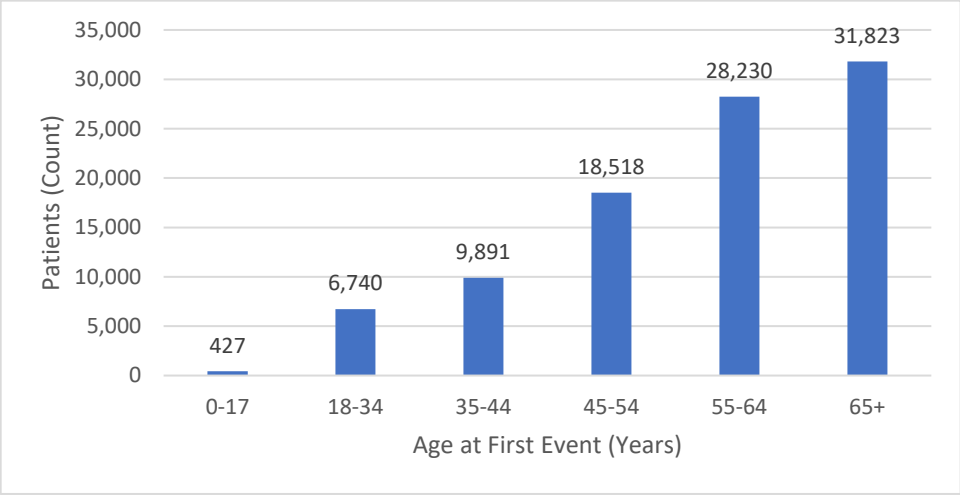

Figure 3. Patients with at least one diagnosis for pulmonary embolism defined by ICD-9-CM codes, January 1, 2014–September 30, 2015, stratified by age.

Figure 4 presents counts of patients with PE, defined by ICD-10-CM codes listed in **Appendix A1** and stratified by age category. Counts were drawn from a cohort of 30,319,401 patients who were enrolled for at least one calendar years between 2015 and 2017. Among 99,386 individuals with at least one ICD-10-CM code for PE between October 1, 2015 and December 31, 2017, the average age at first event was 59 years.

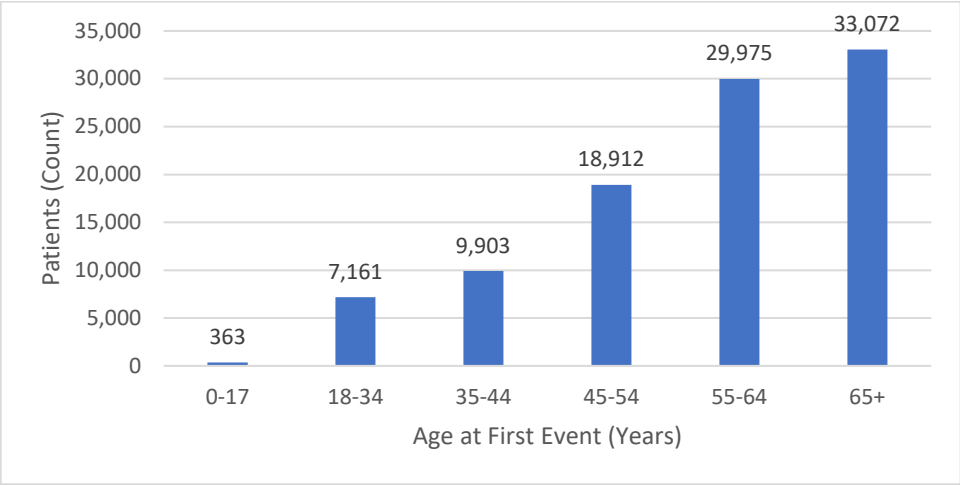

Figure 4. Patients with at least one diagnosis for pulmonary embolism defined by ICD-10-CM codes, October 1, 2015–December 31, 2017, stratified by age.

Figure 5 presents counts of patients with either an ICD-9-CM or ICD-10-CM code for PE among a cohort of 41,172,696 individuals who were continuously enrolled for at least one calendar year between 2014 and 2017. Among 167,945 individuals who received at least one diagnosis code for PE between January

1, 2014, and December 31, 2017, the average age at first diagnosis was 58 years and absolute patient counts were highest in the 65+ years age category.

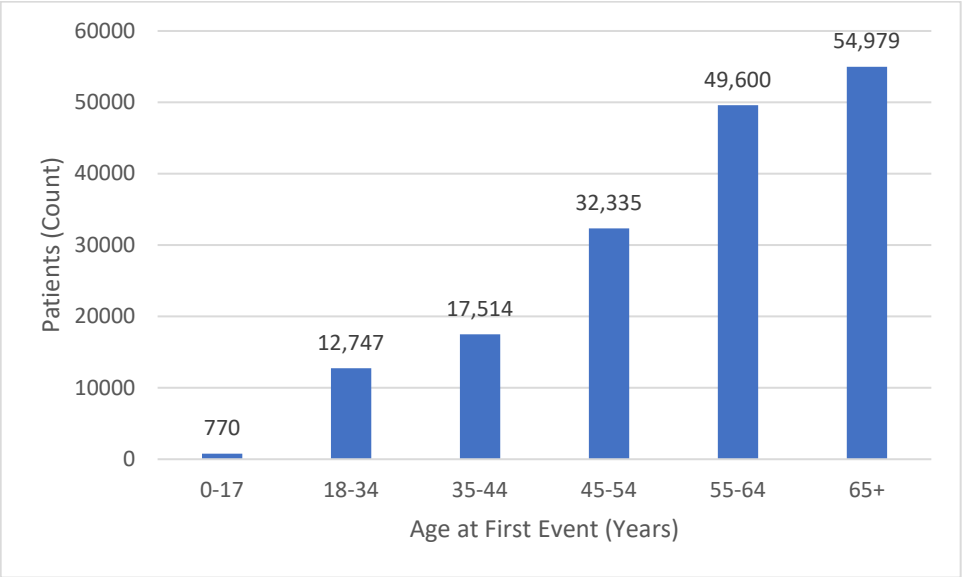

Figure 5. Patients with at least one diagnosis for pulmonary embolism defined by ICD-9-CM or ICD-10-CM codes, January 1, 2014–December 31, 2017, stratified by age.

The proportions of patients experiencing PE were calculated by age and gender. To do this, age- and gender-specific counts of individuals experiencing PE were extracted alongside the size of the enrolled population, using these figures to calculate proportions of individuals with PE. Patients 85 years and older were grouped together to account for the smaller enrolled population sizes that tend to be available for these cohorts. The 41-million-patient cohort was used for this analysis and individuals were not required to be enrolled for the full four-year period to be included in this analysis. **Figure 6** summarizes the proportion of the population with at least one ICD-9-CM or ICD-10-CM code for PE (per 1,000 population with continuous enrollment in the MarketScan Research Databases) between January 1, 2014, and December 31, 2017, by age and gender. Results suggest that the proportion of patients experiencing PE increases with age and is similar between genders (although slightly higher in middle-aged males).

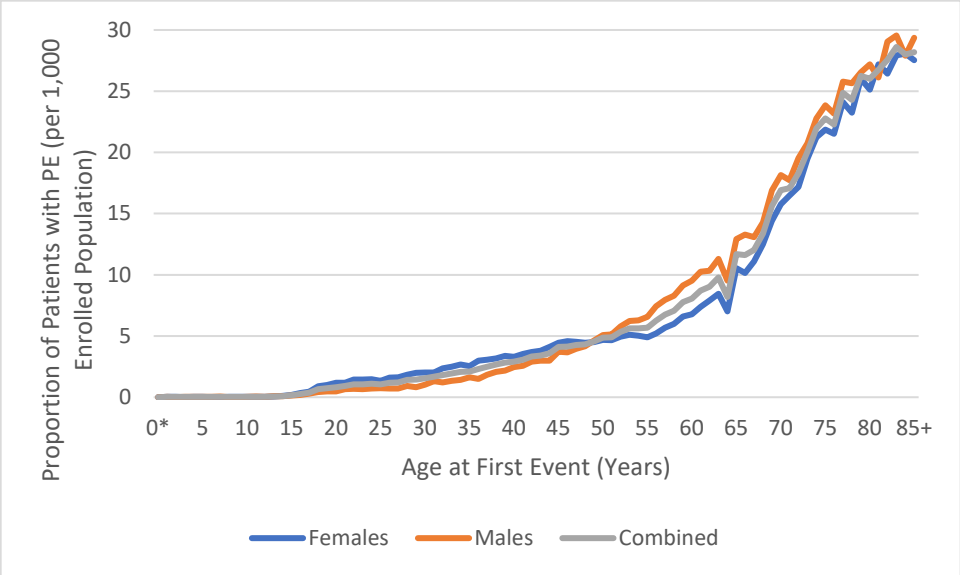

Figure 6. Proportion of patients with at least one diagnosis for pulmonary embolism (ICD-9-CM or ICD-10-CM) per 1,000 population, by gender (January 1, 2014–December 31, 2017).*

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 year old experiencing PE has been excluded from the chart and marked as zero.

Abbreviation: PE, pulmonary embolism.

The BEST Initiative also sought to assess whether there was notable variation in the proportion of patients with PE across the years being queried. **Figure 7** presents the annual proportions of patients with PE for ages 1–85+ years. Results suggest that proportions were fairly consistent across years, although they may have varied more among the elderly; this may be due to smaller population sizes. Note that the proportions presented in **Figure 7** are substantially lower than those in **Figure 6**, where PE encounters were queried for the entire 2014–2017 period instead of for a single year.

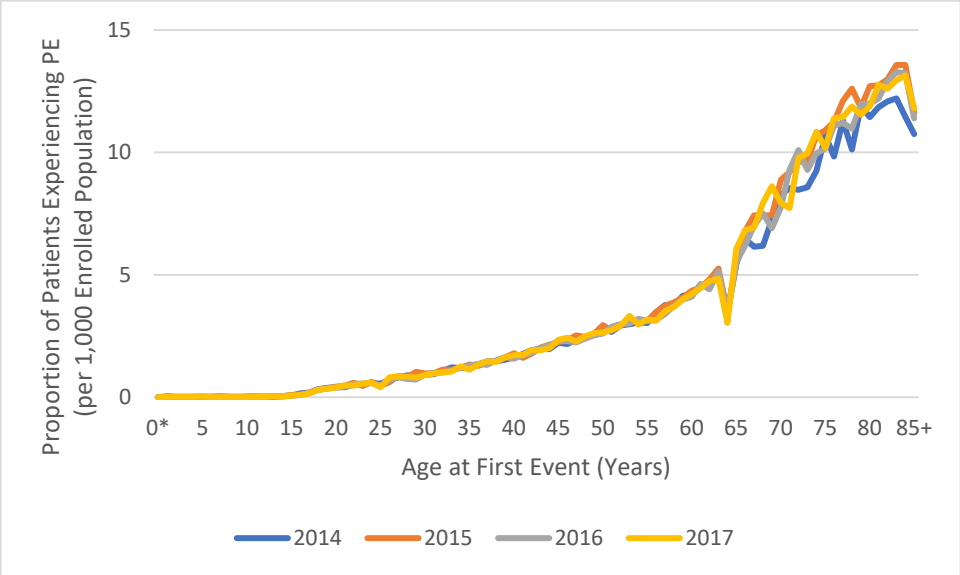

Figure 7. Proportion of patients with at least one diagnosis for pulmonary embolism (ICD-9-CM or ICD-10-CM) per 1,000 population, by calendar year (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 year old experiencing PE has been excluded from the chart and marked as zero.

Abbreviation: PE, pulmonary embolism.

Analyses were also conducted to test whether there was a temporal association in the occurrence or reporting of PE according to the time of the year. To test this, enrollment and PE encounter data for January 1–June 30 and July 1–December 31 were queried for each year. As presented in **Table 4** and **Figure 8**, there did not appear to be a substantial difference in the proportion of patients experiencing PE between the first and second halves of the year.

Table 4. ***Counts and proportions of patients experiencing pulmonary embolism*, defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2017).***

Description	Calendar Year			
	2014	**2015**	**2016**	**2017**
January–June patient count	46,888	38,806	36,451	32,442
July–December patient count	48,368	38,843	34,112	31,668
January–June enrollment	31,110,014	24,094,695	23,531,649	21,656,153
July–December enrollment	30,867,380	23,759,879	23,759,879	21,105,240
January–June proportion (per 1,000 enrolled)	**1.51**	**1.61**	**1.55**	**1.50**
July–December proportion (per 1,000 enrolled)	**1.57**	**1.63**	**1.44**	**1.50**

* The sum of the proportions presented here will exceed those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they are counted only once when the query spans the full year.

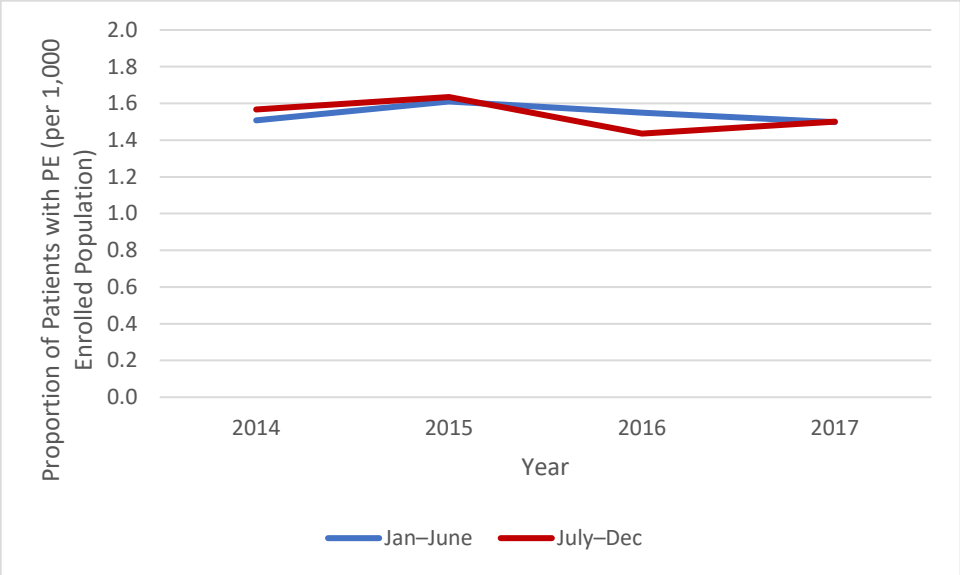

Figure 8. Proportion of patients with at least one diagnosis for PE (ICD-9-CM or ICD-10-CM), stratified by time of year (2014–2017).

Abbreviation: PE, pulmonary embolism.

H2 Deep Vein Thrombosis

As a result of the subcategorization of this outcome, three different analyses were run for DVT: "Lower Body DVT", "Other DVT", and "Any DVT" (combining the two categories). The tables and charts presented in this subsection refer to the "Any DVT" analyses, whereas analyses for the other two categories are included in **Appendix D1**.

Table 5 provides a summary of aggregate counts for ICD-9-CM and/or ICD-10-CM codes, suggesting that DVT occurs in approximately 4.36–4.96 individuals per 1,000 included in the MarketScan data per year.

Table 5. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in the deep vein thrombosis algorithm (January 1, 2014–December 31, 2017).

Code	Calendar Year			
	2014	2015*	2016	2017
ICD-9-CM	134,716	89,364		
ICD-10-CM		43,349	98,623	86,245
ICD-9-CM OR ICD-10-CM	134,716	109,688	98,623	86,245
MarketScan Research Databases enrollment	28,407,959	22,117,235	21,616,367	19,802,253
Proportion of patients with deep vein thrombosis per 1,000 enrolled population	4.74	4.96	4.56	4.36

* In 2015, queries combining ICD-9-CM and ICD-10-CM codes returned lower patient counts than when codes were queried individually. This is because of cases in which both ICD-9-CM and ICD-10-CM codes were reported for the same individual, in the January–September and October–December timeframe, respectively.

The BEST Initiative sought to assess whether the 2015 transition to ICD-10-CM and any associated changes in coding practices resulted in notable shifts in the frequency of DVT reporting. **Figure 9**

illustrates the proportion of the enrolled population with a diagnosis related to DVT and suggests that the transition did not result in a substantial change to the proportion of individuals receiving a DVT diagnosis.

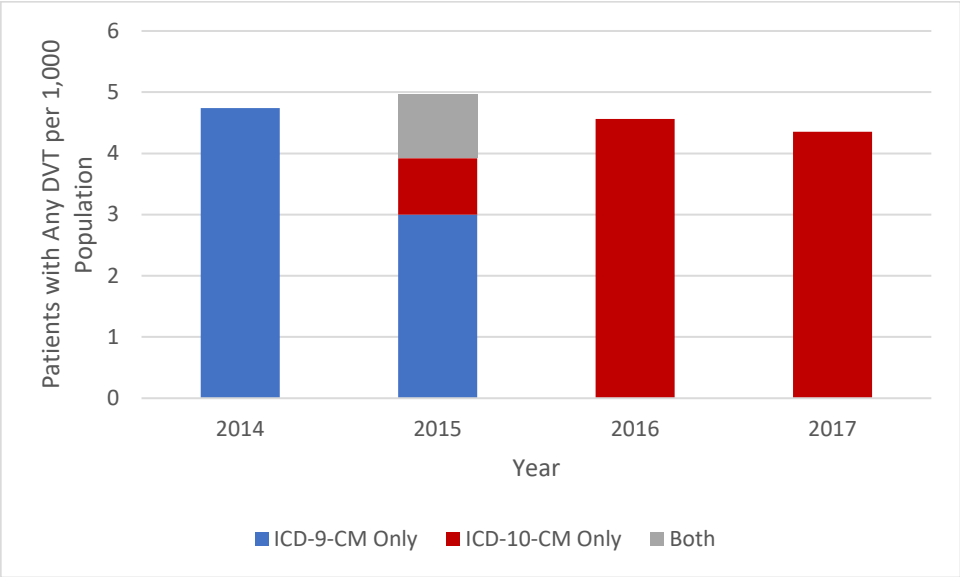

Figure 9. Proportion of patients with DVT per 1,000 enrolled, by year (2014–2017).

Abbreviation: DVT, deep vein thrombosis.

Note: In 2015, a patient could receive both an ICD-9-CM and an ICD-10-CM diagnosis, in the January–September and October–December timeframe, respectively.

Figure 10 presents counts of patients with DVT, defined by ICD-9-CM codes listed in **Appendix A2** and stratified by age category. Counts were calculated using a combined cohort of 33,216,843 patients who were continuously enrolled for at least one calendar year in 2014–2015. There were 203,982 individuals with at least one ICD-9-CM code for DVT between January 1, 2014 and September 30, 2015, with an average age (calculated at the first event) of 58 years.

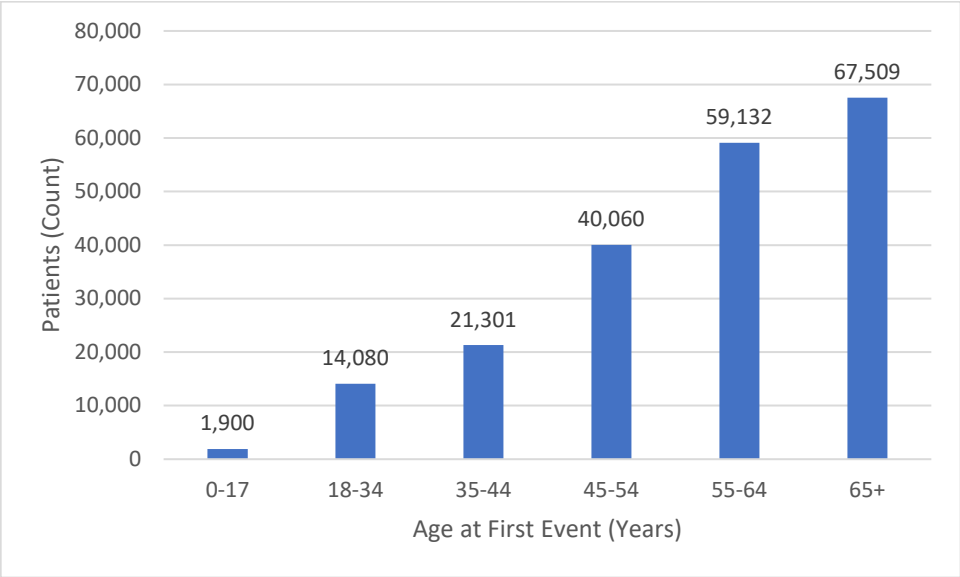

Figure 10. Patients with at least one diagnosis for deep vein thrombosis defined by ICD-9-CM codes, January 1, 2014–September 30, 2015, stratified by age.

Figure 11 presents counts of patients with DVT, defined by ICD-10-CM codes listed in **Appendix A2** and stratified by age category. Counts were drawn from a cohort of 30,319,401 patients that were enrolled for at least one calendar year between 2015 and 2017. Among 201,741 individuals with at least one ICD-10-CM code for DVT between October 1, 2015, and December 31, 2017, the average age at first event was 58 years.

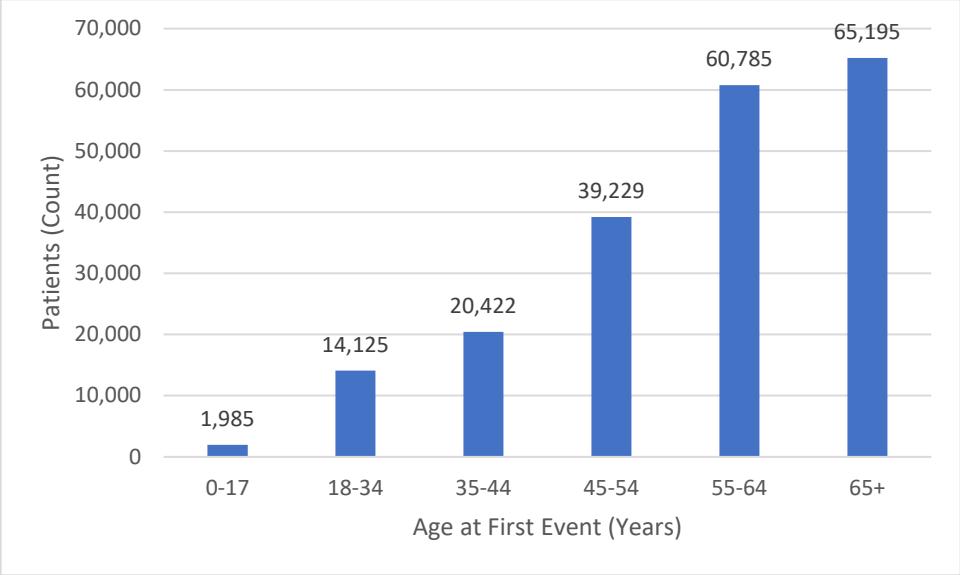

Figure 11. Patients with at least one diagnosis for deep vein thrombosis defined by ICD-10-CM codes, October 1, 2015–December 31, 2017, stratified by age.

Figure 12 presents counts of patients with either an ICD-9-CM or ICD-10-CM code for DVT among a cohort of 41,172,696 individuals who were continuously enrolled for at least one calendar year between 2014 and 2017. Among 361,267 individuals who received at least one diagnosis code for DVT between January 1, 2014, and December 31, 2017, the average age at first diagnosis was 58 years and absolute patient counts were highest in the 65+ years age category.

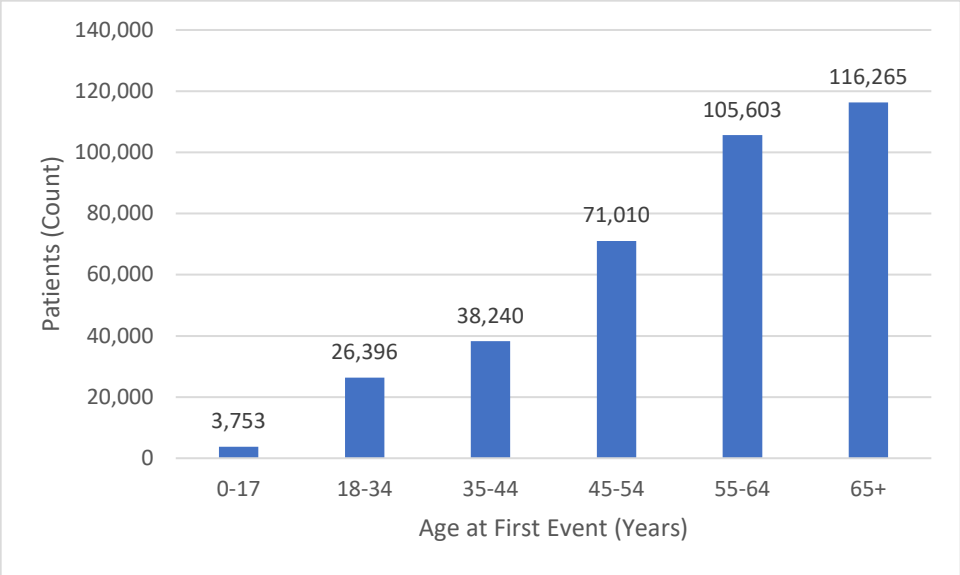

Figure 12. Patients with at least one diagnosis for deep vein thrombosis defined by ICD-9-CM or ICD-10-CM codes, January 1, 2014–December 31, 2017, stratified by age.

Figure 13 summarizes the proportion of the population with at least one ICD-9-CM or ICD-10-CM code for DVT (per 1,000 population enrolled in the MarketScan Research Databases) between January 1, 2014 and December 31, 2017, by age and gender. Results suggest that the proportion of patients experiencing DVT increases with age and is similar between genders (although, as with PE, the proportion may be slightly higher in middle-aged males).

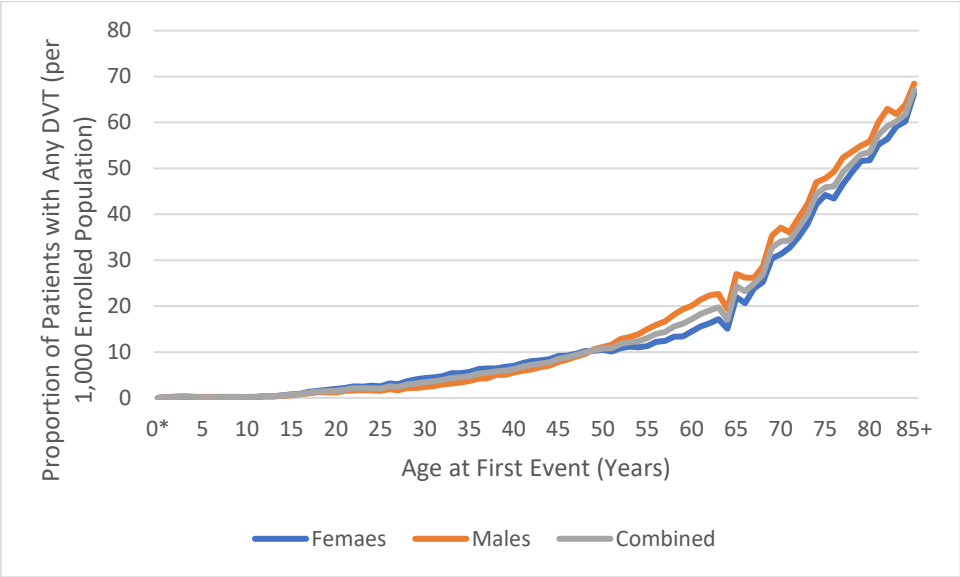

Figure 13. Proportion of patients with at least one diagnosis for deep vein thrombosis (ICD-9-CM or ICD-10-CM) per 1,000 population, by gender (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 year old experiencing DVT has been excluded from the chart and marked as zero.

Abbreviation: DVT, deep vein thrombosis.

Figure 14 presents the annual proportions of patients with DVT for ages 1–85+ years. Results suggest that proportions were fairly consistent across years.

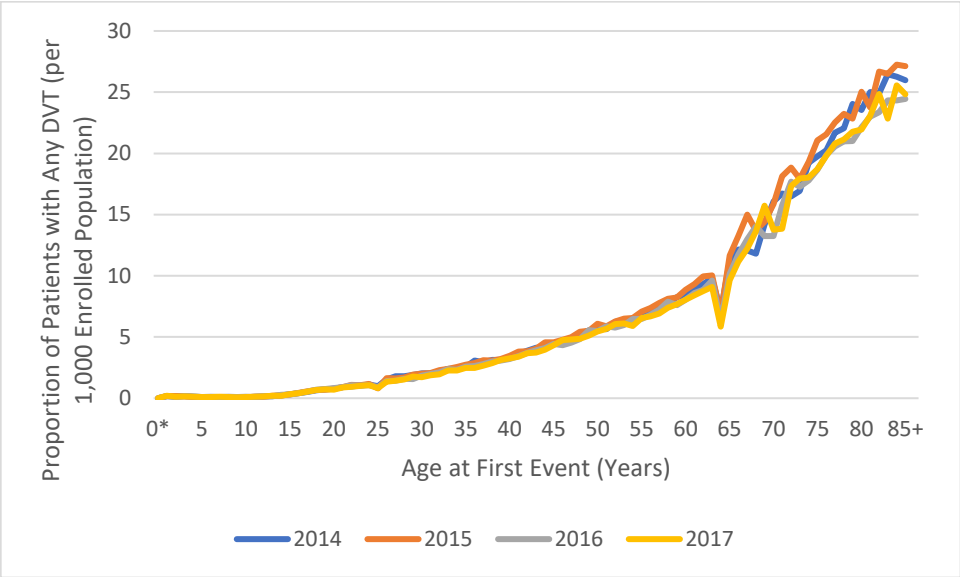

Figure 14. Proportion of patients with at least one diagnosis for deep vein thrombosis (ICD-9-CM or ICD-10-CM) per 1,000 population, by calendar year (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 year old experiencing DVT has been excluded from the chart and marked as zero.

Abbreviation: DVT, deep vein thrombosis.

Table 6 and **Figure 15** present the results of analyses to test whether the occurrence or reporting of DVT varied according to the time of the year, by querying data for January 1–June 30 and July 1–December 31. The results did not indicate that there was a notable difference in the frequency of DVT occurrence between the first and second halves of the calendar year.

Table 6. ***Counts and proportions of patients experiencing DVT*, defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2017).***

Description	Calendar Year			
	2014	**2015**	**2016**	**2017**
January–June patient count	91,318	75,318	67,218	58,536
July–December patient count	94,415	86,618	61,851	57,472
January–June enrollment	31,110,014	24,094,695	23,531,649	21,656,153
July–December enrollment	30,867,380	23,759,879	23,759,879	21,105,240
January–June proportion (per 1,000 enrolled)	**2.94**	**3.13**	**2.86**	**2.70**
July–December proportion (per 1,000 enrolled)	**3.06**	**3.65**	**2.60**	**2.72**

* The sum of the proportions presented here will exceed those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they would only be counted once when the query spans the full year.

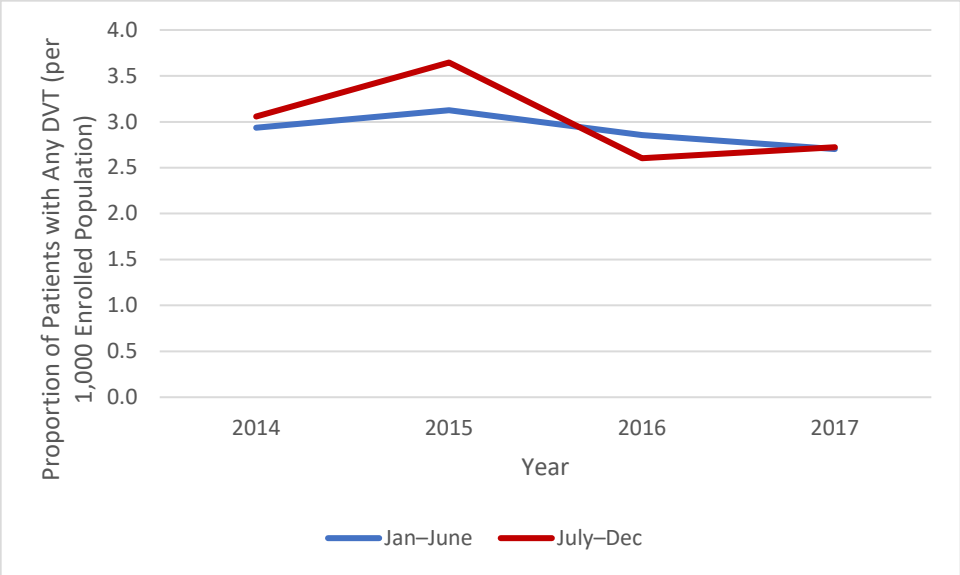

Figure 15. Proportion of patients with at least one diagnosis for deep vein thrombosis (ICD-9-CM or ICD-10-CM), stratified by time of year (2014–2017).

Abbreviation: DVT, deep vein thrombosis.

H3 Acute Myocardial Infarction

Table 7 provides a summary of aggregate counts for ICD-9-CM and/or ICD-10-CM codes, suggesting that AMI occurs in approximately 2.83–3.16 individuals per 1,000 included in the MarketScan data per year.

Table 7. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in AMI algorithm (January 1, 2014–December 31, 2017).

Code	Calendar Year			
	2014	2015*	2016	2017
ICD-9-CM	80,411	49,765		
ICD-10-CM		23,883	68,253	61,559
ICD-9-CM OR ICD-10-CM	80,411	67,375	68,253	61,559
MarketScan Research Databases enrollment	28,407,959	22,117,235	21,616,367	19,802,253
Proportion of patients with AMI per 1,000 enrolled	2.83	3.05	3.16	3.11

* In 2015, queries combining ICD-9-CM and ICD-10-CM codes returned lower patient counts than when codes were queried individually. This is because of cases where both ICD-9-CM and ICD-10-CM codes were reported for the same individual, in the January–September and October–December timeframe, respectively. This overlap is the result of the transition from ICD-9-CM to ICD-10-CM in 2015 and resulted in 6,273 duplications (i.e. individuals that were counted in both the ICD-9-CM and ICD-10-CM query).

Abbreviations: AMI, acute myocardial infarction.

The BEST Initiative sought to assess whether the 2015 transition to ICD-10-CM and any associated changes in coding practices resulted in notable shifts in the frequency of reporting AMI. **Figure 16** illustrates the proportion of the enrolled population with a diagnosis related to AMI and suggests that the transition did not result in a substantial change to the proportion of individuals receiving an AMI diagnosis.

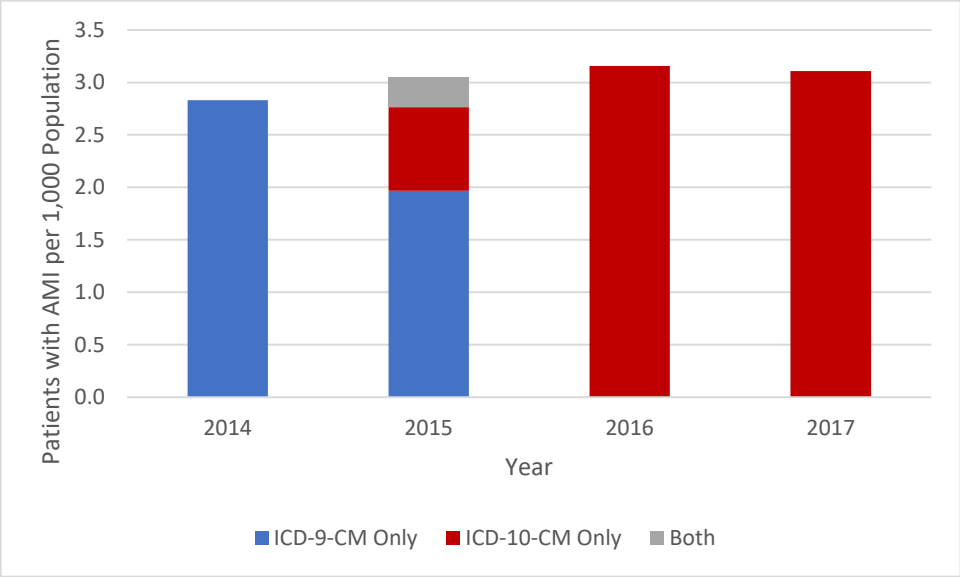

Figure 16. Proportion of patients with AMI per 1,000 enrolled, by year (2014–2017).

Abbreviation: AMI, acute myocardial infarction.

Note: In 2015, a patient could receive both an ICD-9-CM and an ICD-10-CM diagnosis, in the January–September and October–December timeframe, respectively.

Figure 17 presents counts of patients with AMI, defined by ICD-9-CM codes listed in **Appendix A3** and stratified by age category. Counts were calculated using a combined cohort of 33,216,843 patients who were continuously enrolled for at least one calendar year in 2014–2015. There were 131,840 individuals with at least one ICD-9-CM code for AMI between January 1, 2014, and September 30, 2015, with an average age (calculated at the first event) of 64 years.

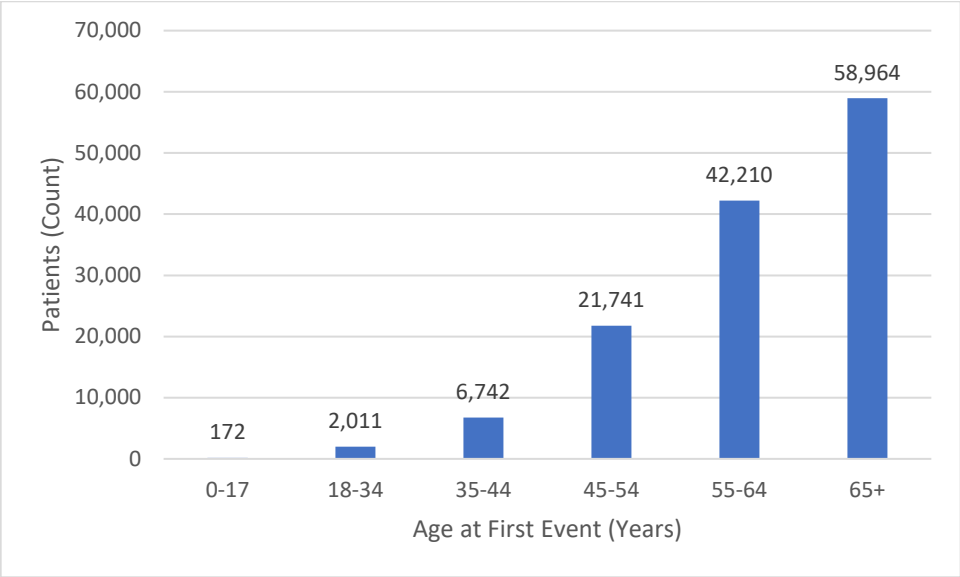

Figure 17. Patients with at least one diagnosis for acute myocardial infarction defined by ICD-9-CM codes, January 1, 2014–September 30, 2015, stratified by age.

Figure 18 presents counts of patients with AMI, defined by ICD-10-CM codes listed in **Appendix A3** and stratified by age category. Counts were drawn from a cohort of 30,319,401 patients who were enrolled for at least one calendar year between 2015 and 2017. Among 155,135 individuals with at least one ICD-10-CM code for DVT between October 1, 2015, and December 31, 2017, the average age at first event was 65 years.

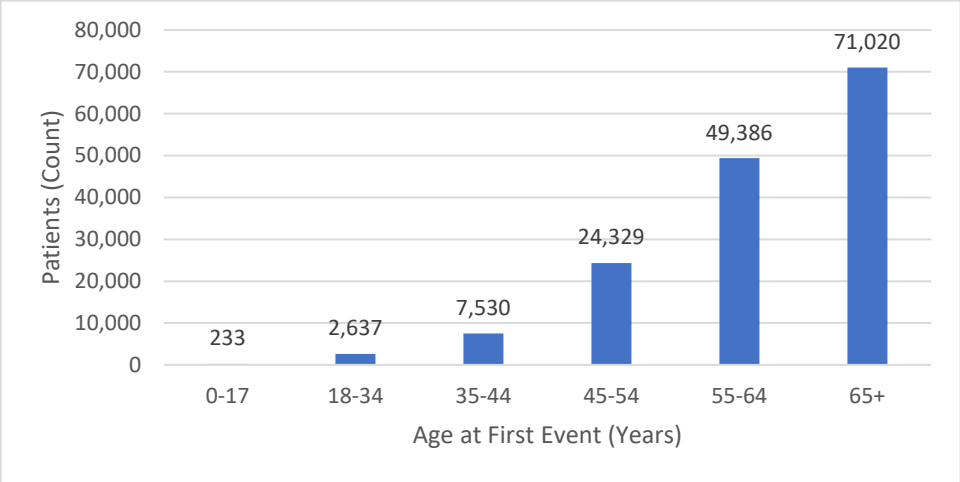

Figure 18. Patients with at least one diagnosis for acute myocardial infarction defined by ICD-10-CM codes, October 1, 2015–December 31, 2017, stratified by age.

Figure 19 presents counts of patients with either an ICD-9-CM or ICD-10-CM code for AMI among a cohort of 41,172,696 individuals who were continuously enrolled for at least one calendar year between 2014 and 2017. Among 268,777 individuals who received at least one diagnosis code for AMI between January 1, 2014, and December 31, 2017, the average age at first diagnosis was 64 years and absolute patient counts were highest in 65+ years age category.

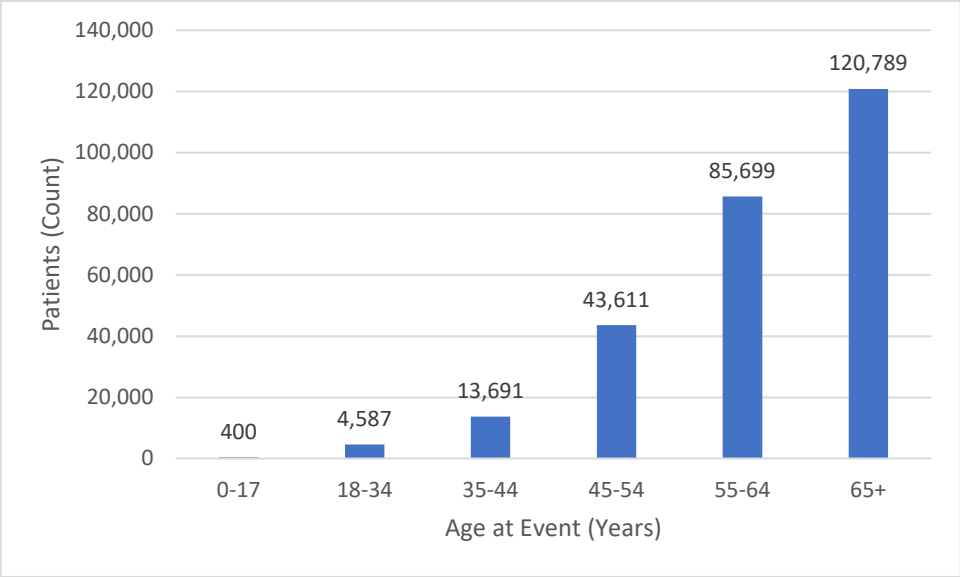

Figure 19. Patients with at least one diagnosis for acute myocardial infarction defined by ICD-9-CM or ICD-10-CM codes, January 1, 2014–December 31, 2017, stratified by age.

Figure 20 summarizes the proportion of the population with at least one ICD-9-CM or ICD-10-CM code for AMI (per 1,000 population enrolled in the MarketScan Research Databases) between January 1,

2014, and December 31, 2017, by age and gender. Results suggest that the proportion of patients experiencing AMI increases with age starting at 40 years old, and that a higher proportion of men than women experience AMI.

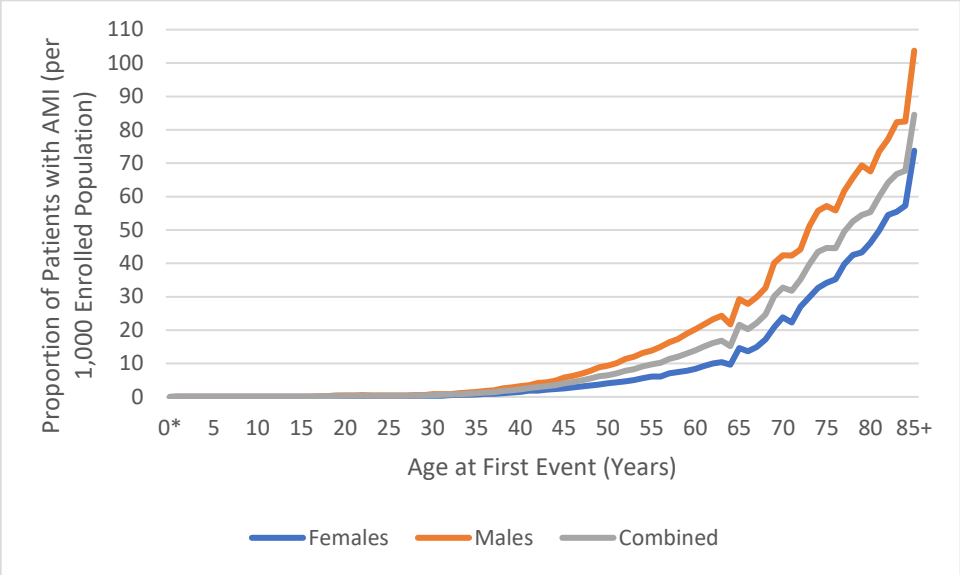

Figure 20. Proportion of patients with at least one diagnosis for AMI (ICD-9-CM or ICD-10-CM) per 1,000 population, by gender (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 year old experiencing AMI has been excluded from the chart and marked as zero.

Abbreviation: AMI, acute myocardial infarction.

Figure 21 presents the annual proportions of patients with AMI for ages 1–85+ years. Results suggest that proportions were fairly consistent across years.

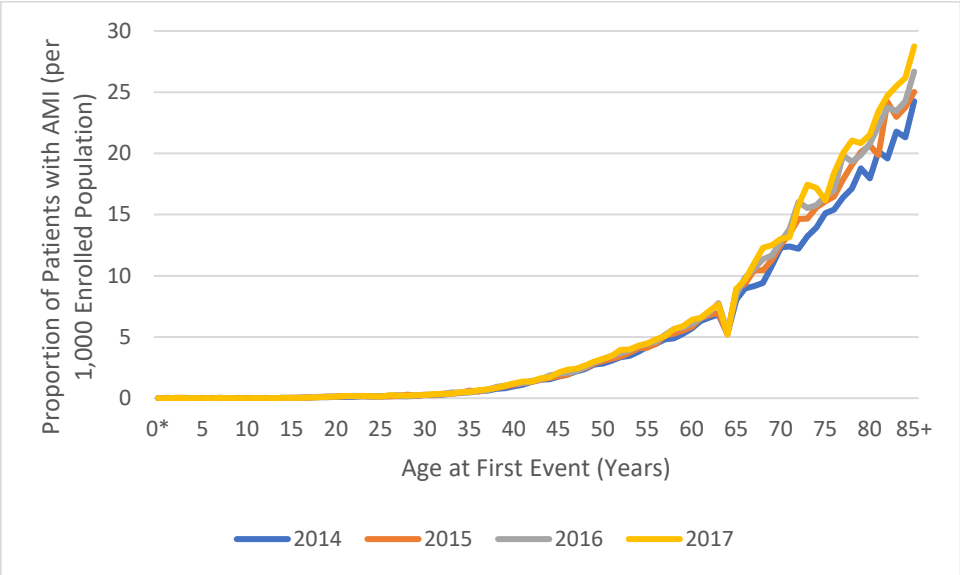

Figure 21. Proportion of patients with at least one diagnosis for AMI (ICD-9-CM or ICD-10-CM) per 1,000 population, by calendar year (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 year old experiencing AMI has been excluded from the chart and marked as zero.

Table 8 and **Figure 22** present the results of analyses to test whether the occurrence or reporting of AMI varied according to the time of the year, by querying data for January 1–June 30 and July 1–December 31. Results did not indicate a notable difference in the frequency of AMI reporting between the first and second halves of the calendar year.

Table 8. ***Counts and proportions of patients experiencing acute myocardial infarction*, defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2017).***

Description	Calendar Year			
	2014	**2015**	**2016**	**2017**
January–June patient count	47,663	39,862	41,763	38,358
July–December patient count	49,010	40,862	41,288	37,253
January–June enrollment	31,110,014	24,094,695	23,531,649	21,656,153
July–December enrollment	30,867,380	23,759,879	23,759,879	21,105,240
January–June proportion (per 1,000 enrolled)	**1.53**	**1.65**	**1.77**	**1.77**
July–December proportion (per 1,000 enrolled)	**1.59**	**1.72**	**1.74**	**1.77**

* The sum of the proportions presented here will exceed those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they would be counted only once when the query spans the full year.

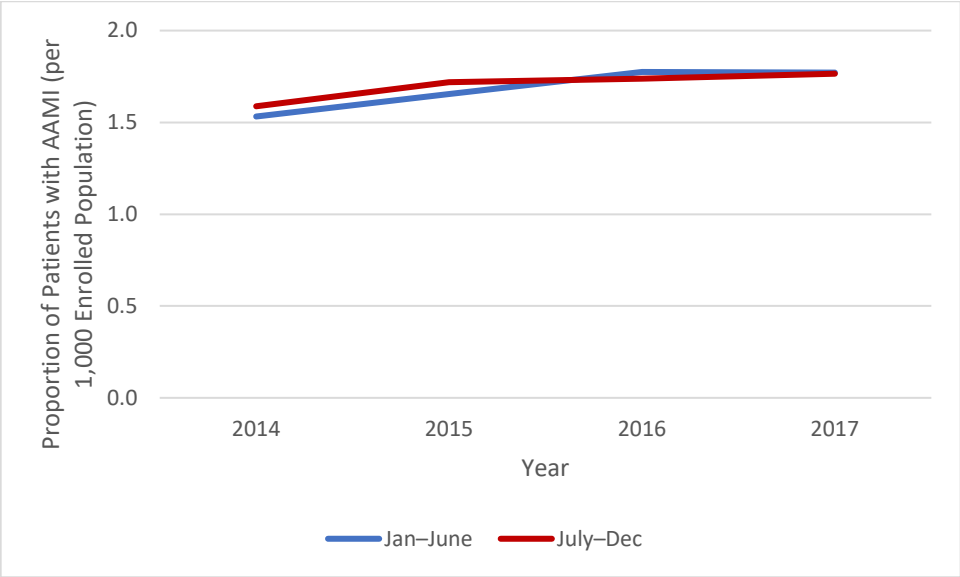

Figure 22. Proportion of patients with at least one diagnosis for acute myocardial infarction (ICD-9-CM or ICD-10-CM), stratified by time of year (2014–2017).

Abbreviation: AMI, acute myocardial infarction.

H4 Stroke

As with DVT, the subcategorization of stroke outcomes resulted in five different analyses being run for stroke:

1. Stroke with thrombosis or infarction
2. Occlusion without mention of infarction
3. Transient ischemic attack
4. Hemorrhagic stroke
5. Non-hemorrhagic stroke (combining categories 1–3)

The tables and charts in this section refer to the combined, non-hemorrhagic stroke category, whereas analyses for the other categories are presented in **Appendix D2**. Note that this combined category includes a spectrum of stroke-related outcomes, and the decision was made to include TIAs as part of this spectrum. Hemorrhagic stroke was excluded from the combined category because its mechanism of onset (bleeding as opposed to clotting) is contrary to those of the other categories.

Table 9 provides a summary of aggregate counts for ICD-9-CM and/or ICD-10-CM codes, suggesting that non-hemorrhagic stroke occurs in approximately 14.21–15.32 individuals per 1,000 included in the MarketScan data per year.

Table 9. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM non-hemorrhagic stroke diagnosis codes (January 1, 2014–December 31, 2017).

Code	Calendar Year			
	2014	**2015***	**2016**	**2017**
ICD-9-CM	410,584	268,131		
ICD-10-CM		122,299	324,428	281,308
ICD-9-CM OR ICD-10-CM	410,584	338,778	324,428	281,308
MarketScan Research Databases Enrollment	28,407,959	22,117,235	21,616,367	19,802,253
Proportion of Patients with Non-Hemorrhagic Stroke per 1,000 Enrolled	14.45	15.32	15.01	14.21

* In 2015, queries combining ICD-9-CM and ICD-10-CM codes returned lower patient counts than did individual queries. This is because of cases in which both ICD-9-CM and ICD-10-CM codes were reported for the same individual, in the January–October and October–December time frames, respectively.

The BEST Initiative sought to assess whether the 2015 transition to ICD-10-CM and any associated changes in coding practices resulted in notable shifts in the frequency of reporting for stroke. **Figure 23** illustrates the proportion of the enrolled population with a diagnosis related to non-hemorrhagic stroke and suggests that the transition did not result in a substantial change to the proportion of individuals receiving a diagnosis.

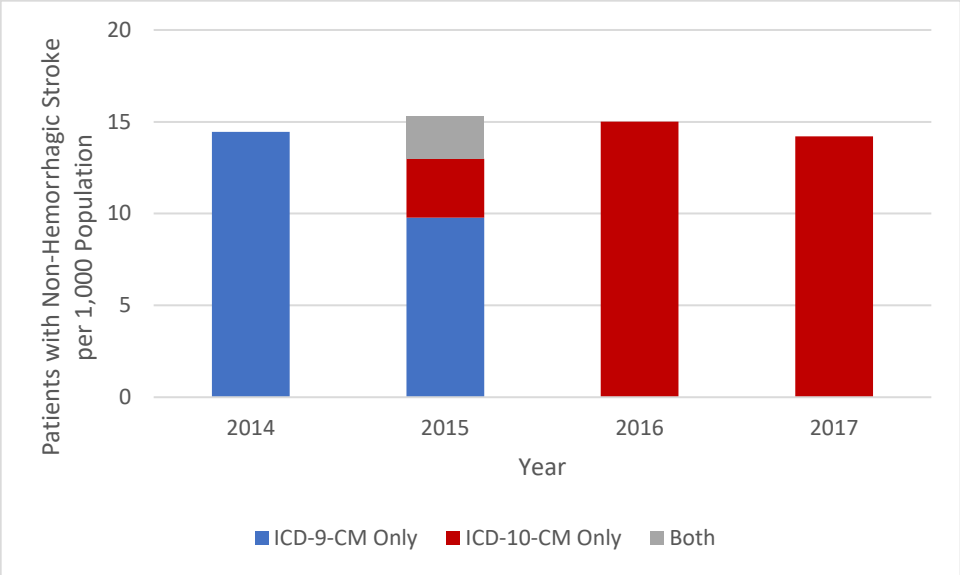

Figure 23. Proportion of patients with non-hemorrhagic stroke per 1,000 enrolled, by year (2014–2017).

Note: In 2015, a patient could receive both an ICD-9-CM and an ICD-10-CM diagnosis, in the January–September and October–December timeframe, respectively.

Figure 24 presents counts of patients with non-hemorrhagic stroke, defined by ICD-9-CM codes listed in **Appendix A4** and stratified by age category. Counts were calculated using a combined cohort of 33,216,843 patients who were continuously enrolled for at least one calendar year in 2014–2015. There were 609,126 individuals with at least one ICD-9-CM code for non-hemorrhagic stroke between January 1, 2014, and September 30, 2015, with an average age (calculated at the first event) of 65 years.

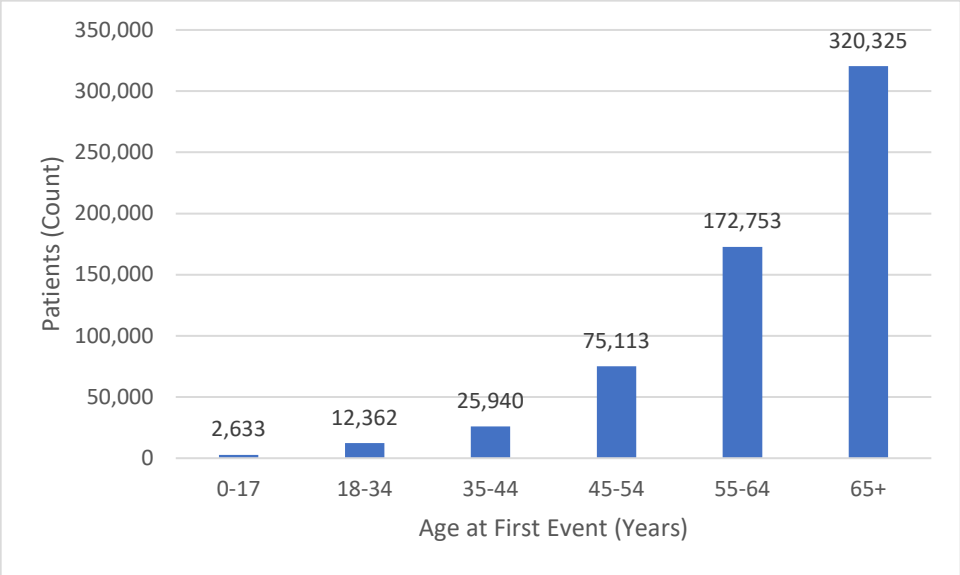

Figure 24. Patients with at least one diagnosis for non-hemorrhagic stroke defined by ICD-9-CM codes, January 1, 2014–September 30, 2015, by age.

Figure 25 presents counts of patients with non-hemorrhagic stroke, defined by ICD-10-CM codes listed in **Appendix A4** and stratified by age category. Counts were drawn a cohort of 30,319,401 patients who

were enrolled for at least one calendar years between 2015 and 2017. Among 608,993 individuals with at least one ICD-10-CM code for non-hemorrhagic stroke between October 1, 2015, and December 31, 2017, the average age at first event was 65 years.

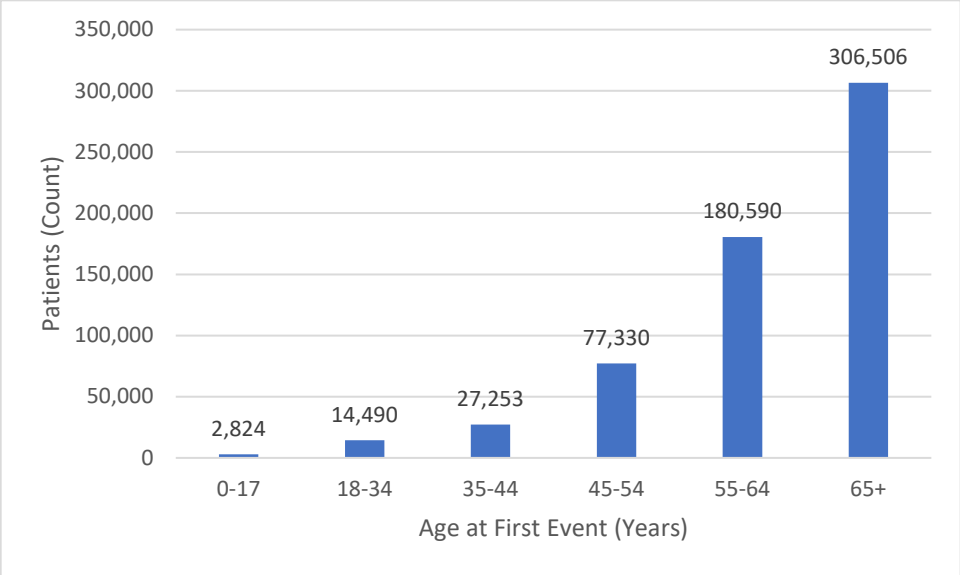

Figure 25. Patients with at least one diagnosis for non-hemorrhagic stroke defined by ICD-10-CM codes, October 1, 2015–December 31, 2017, by age.

Figure 26 presents counts of patients with either an ICD-9-CM or ICD-10-CM code for non-hemorrhagic stroke among a cohort of 41,172,696 individuals who were continuously enrolled for at least one calendar year between 2014 and 2017. Among 1,031,257 individuals who received at least one diagnosis code for non-hemorrhagic stroke between January 1, 2014, and December 31, 2017, the average age at first diagnosis was 64 years and absolute patient counts were highest in the 65+ years category.

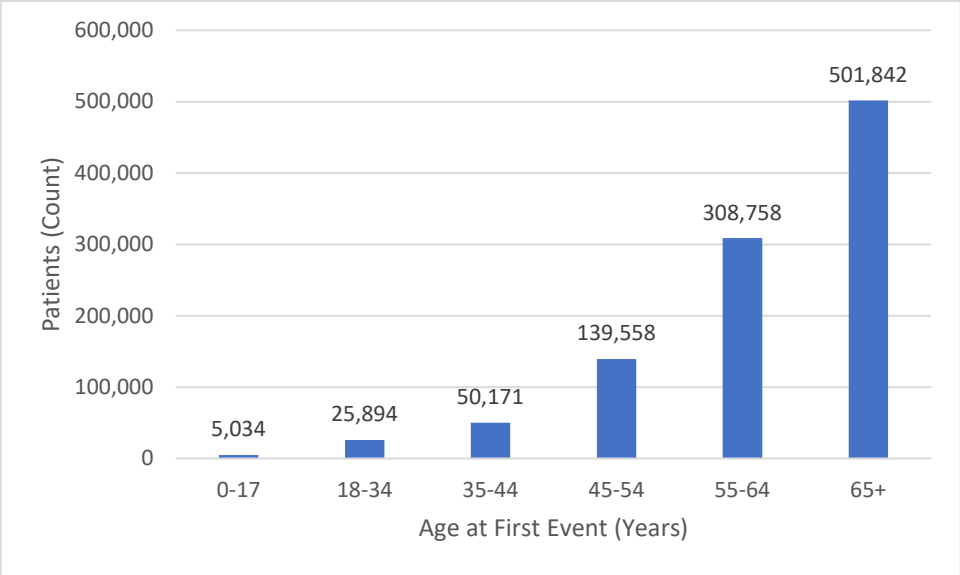

Figure 26. Patients with at least one diagnosis for non-hemorrhagic stroke defined by ICD-9-CM or ICD-10-CM codes, January 1, 2014–December 31, 2017, stratified by age.

Figure 27 summarizes the proportion of the population with at least one ICD-9-CM or ICD-10-CM code for non-hemorrhagic stroke (per 1,000 population in theMarketScan Research Databases) between January 1, 2014, and December 31, 2017, by age and gender. Results suggest that the proportion of patients experiencing non-hemorrhagic stroke increases with age from around 30 years old and is similar between genders until later in life, when it is more common among men.

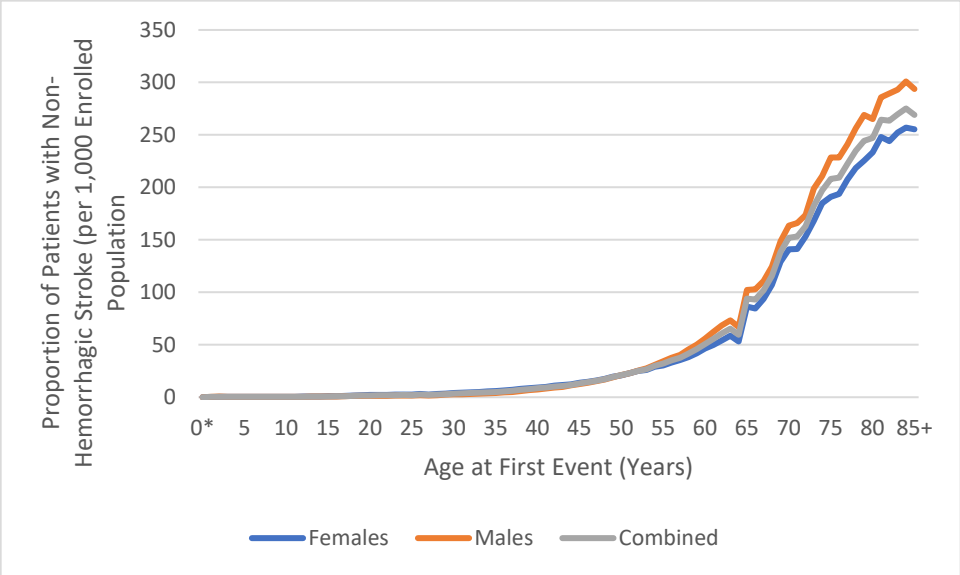

Figure 27. Proportion of patients with at least one diagnosis for non-hemorrhagic stroke (ICD-9-CM or ICD-10-CM) per 1,000 population, by gender (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 year old experiencing non-hemorrhagic stroke has been excluded from the chart and marked as zero.

Figure 28 presents the annual proportions of patients with non-hemorrhagic stroke for ages 1–85+ years. Results suggest that proportions were fairly consistent across years.

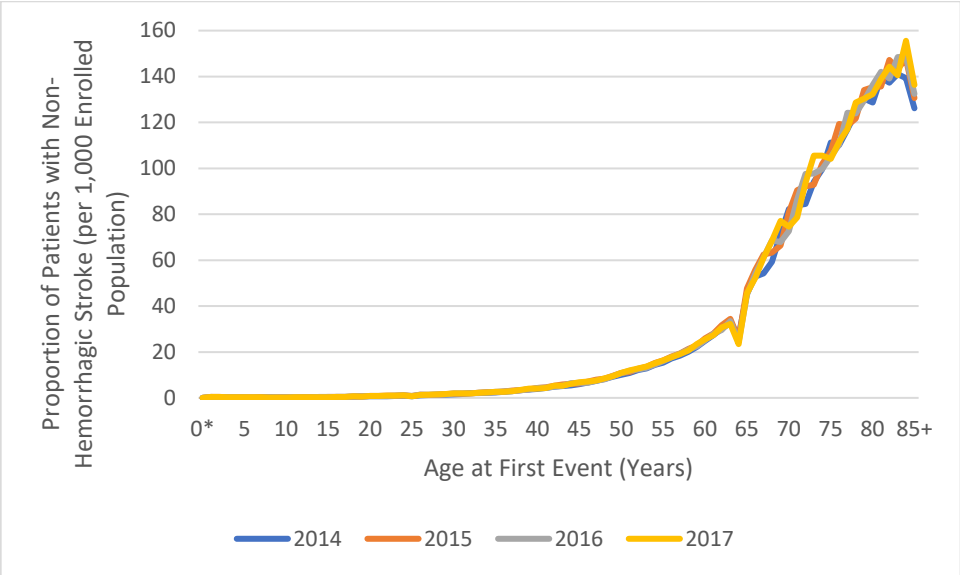

Figure 28. Proportion of patients with at least one diagnosis for non-hemorrhagic stroke (ICD-9-CM or ICD-10-CM) per 1,000 population, by calendar year (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 year old experiencing non-hemorrhagic stroke has been excluded from the chart and marked as zero.

Table 10 and **Figure 29** present the results of analyses that tested whether the occurrence or reporting of non-hemorrhagic stroke varied according to the time of the year, by querying data for January 1–June 30 and July 1–December 31. The results did not suggest that there was a notable difference in the frequency of reporting between the first and second halves of the calendar year.

Table 10. ***Counts and proportions of patients experiencing non-hemorrhagic stroke*, defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2017).***

Description	Calendar Year			
	2014	**2015**	**2016**	**2017**
January–June patient count	252,818	212,169	208,293	180,767
July–December patient count	260,755	214,679	196,305	179,053
January–June enrollment	31,110,014	24,094,695	23,531,649	21,656,153
July–December enrollment	30,867,380	23,759,879	23,759,879	21,105,240
January–June proportion (per 1,000 enrolled)	**8.13**	**8.81**	**8.85**	**8.35**
July–December proportion (per 1,000 enrolled)	**8.45**	**9.04**	**8.26**	**8.48**

* The sum of the proportions presented here will exceed those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they would only be counted once when the query spans the full year.

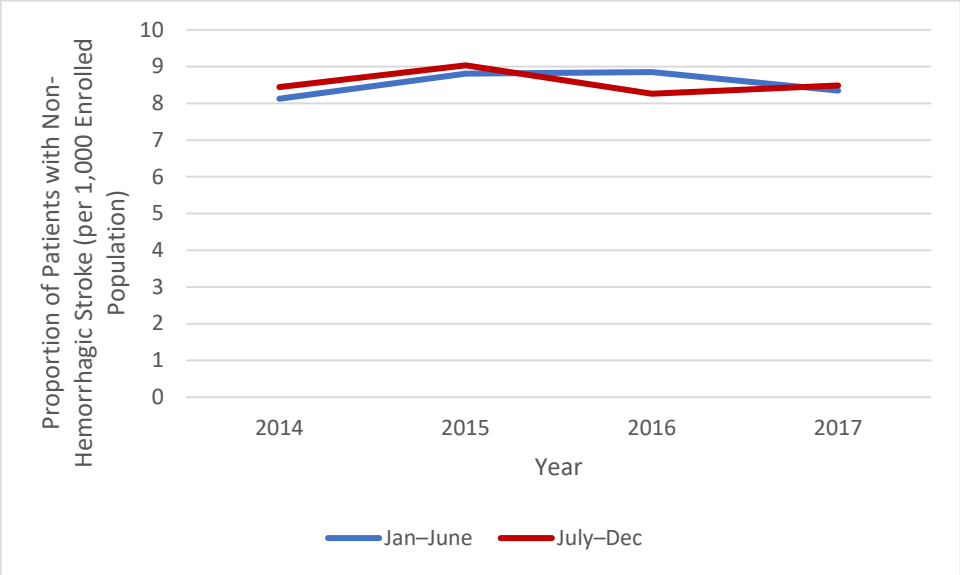

Figure 29. Proportion of patients with at least one diagnosis for non-hemorrhagic stroke (ICD-9-CM or ICD-10-CM), stratified by time of year (2014–2017).

H5 Arterial Embolism and Thrombosis

Table 11 provides a summary of aggregate counts for ICD-9-CM and/or ICD-10-CM codes, suggesting that arterial embolism and thrombosis occurs in approximately 0.71–0.77 individuals per 1,000 included in the MarketScan data per year.

Table 11. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in arterial embolism and thrombosis algorithm (January 1, 2014–December 31, 2017).

Code	Calendar Year			
	2014	2015*	2016	2017
ICD-9-CM	20,574	12,864		
ICD-10-CM		5,677	16,265	13,973
ICD-9-CM OR ICD-10-CM	2,574	17,075	16,265	13,973
MarketScan Research Databases enrollment	28,407,959	22,117,235	21,616,367	19,802,253
Proportion of patients with arterial embolism or thrombosis per 1,000 enrolled	0.72	0.77	0.75	0.71

* In 2015, queries combining ICD-9-CM and ICD-10-CM codes returned lower patient counts than when codes were queried individually. This is because of cases where both ICD-9-CM and ICD-10-CM codes were reported for the same individual, in the January–September and October–December time frames, respectively. This overlap is due to the transition from ICD-9-CM to ICD-10-CM in 2015 and resulted in 1,466 duplications (i.e., individuals who were counted in both the ICD-9-CM and ICD-10-CM queries).

The BEST Initiative sought to assess whether the 2015 transition to ICD-10-CM and any associated changes in coding practices resulted in notable shifts in the frequency of reporting for arterial embolism and thrombosis. **Figure 30** illustrates the proportion of the enrolled population with a diagnosis related to arterial embolism or thrombosis and suggests that the transition did not result in a substantial change to the proportion of individuals receiving a diagnosis.

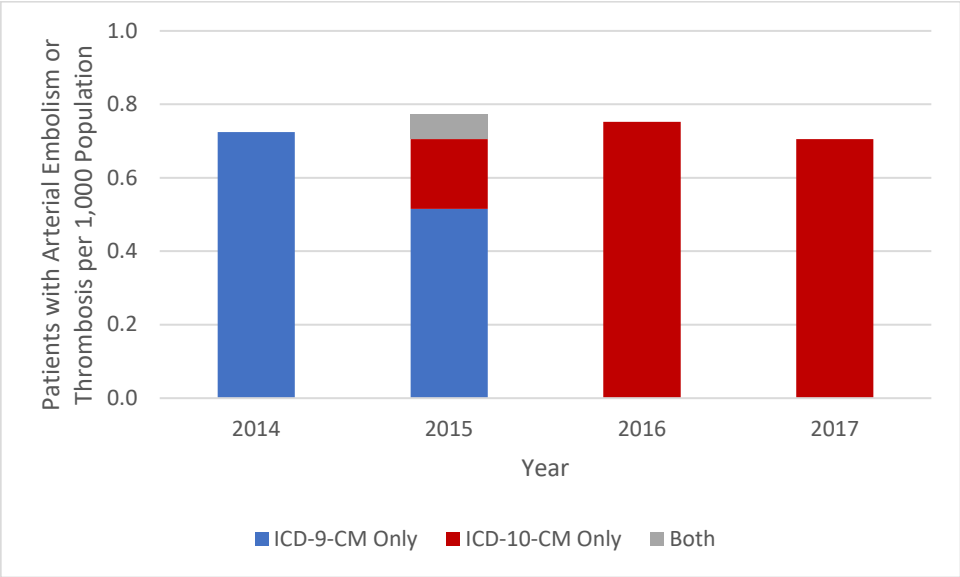

Figure 30. Proportion of patients with arterial embolism or thrombosis per 1,000 enrolled, by year (2014–2017).

Note: In 2015, a patient could receive both an ICD-9-CM and an ICD-10-CM diagnosis, in the January–September and October–December timeframe, respectively.

Figure 31 presents counts of patients with arterial embolism or thrombosis, defined by ICD-9-CM codes listed in **Appendix A5** and stratified by age category. Counts were calculated using a combined cohort of 33,216,843 patients who were continuously enrolled for at least one calendar year in 2014–2015. There were 32,930 individuals with at least one ICD-9-CM code for arterial embolism or thrombosis between January 1, 2014, and September 30, 2015, with an average age (calculated at the first event) of 63 years.

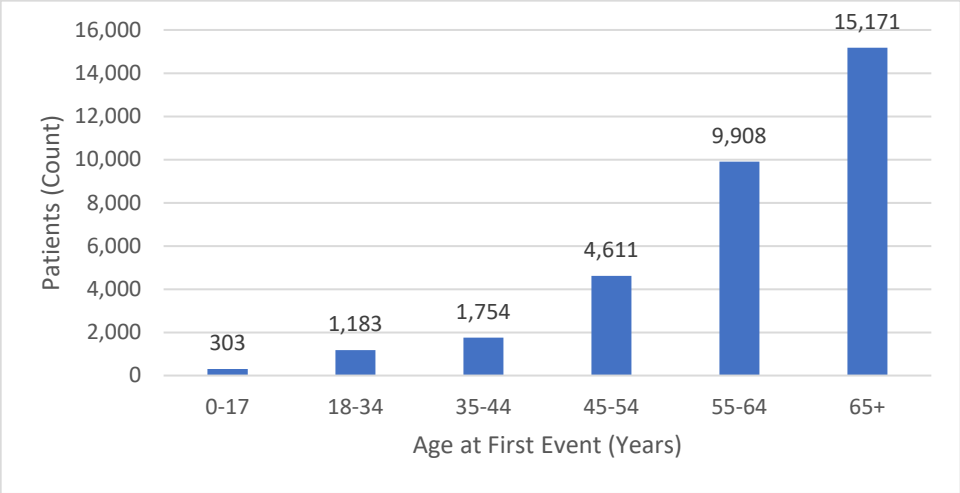

Figure 31. Patients with at least one diagnosis for arterial embolism or thrombosis defined by ICD-9-CM codes, January 1, 2014–September 30, 2015, stratified by age.

Figure 32 presents counts of patients with arterial embolism or thrombosis, defined by ICD-10-CM codes listed in **Appendix A5** and stratified by age category. Counts were drawn a cohort of 30,319,401 patients who were enrolled for at least one calendar years between 2015 and 2017. Among 35,046 individuals with at least one ICD-10-CM code for arterial embolism or thrombosis between October 1, 2015, and December 31, 2017, the average age at first event was 63 years.

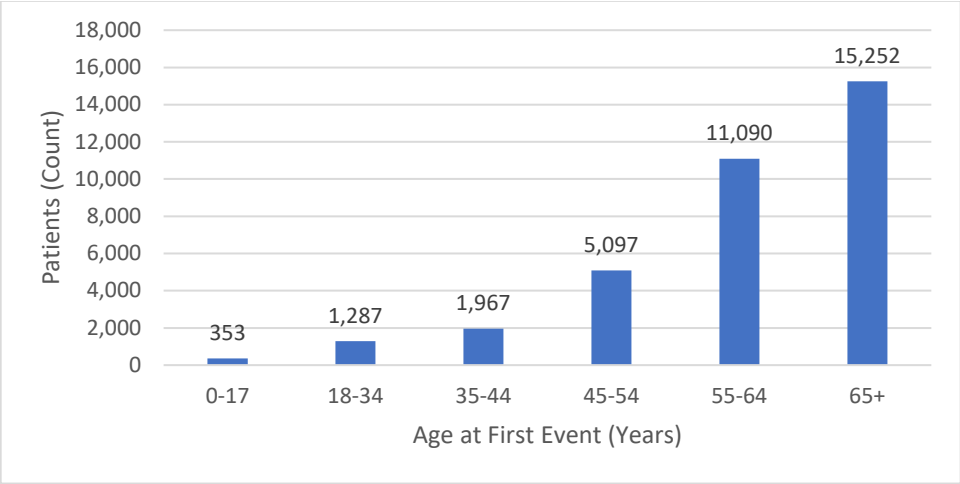

Figure 32. Patients with at least one diagnosis for arterial embolism or thrombosis defined by ICD-10-CM codes, October 1, 2015–December 31, 2017, stratified by age.

Figure 33 presents counts of patients with either an ICD-9-CM or ICD-10-CM code for arterial embolism or thrombosis among a cohort of 41,172,696 individuals who were continuously enrolled for at least one calendar year between 2014 and 2017. Among 64,046 individuals who received at least one diagnosis code for arterial embolism or thrombosis between January 1, 2014, and December 31, 2017, the average

age at first diagnosis was 63 years and absolute patient counts were highest in the 65+ years age category.

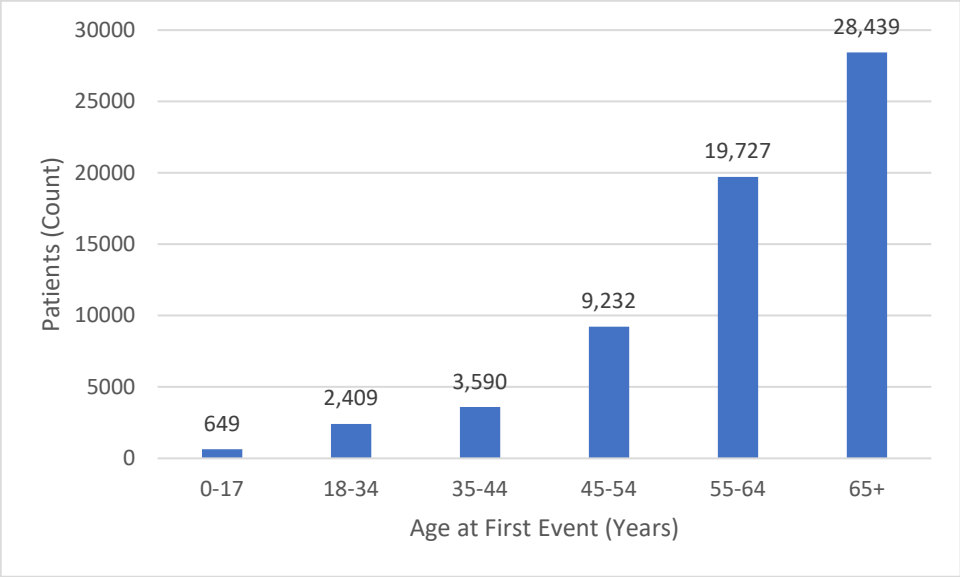

Figure 33. Patients with at least one diagnosis for arterial embolism or thrombosis defined by ICD-9-CM or ICD-10-CM codes, January 1, 2014–December 31, 2017, stratified by age.

Figure 34 summarizes the proportion of the population with at least one ICD-9-CM or ICD-10-CM code for arterial embolism or thrombosis (per 1,000 population in the MarketScan Research Databases) between January 1, 2014, and December 31, 2017, by age and gender. Results suggest that the proportion of patients experiencing arterial embolism or thrombosis increases with age and is highest among older men.

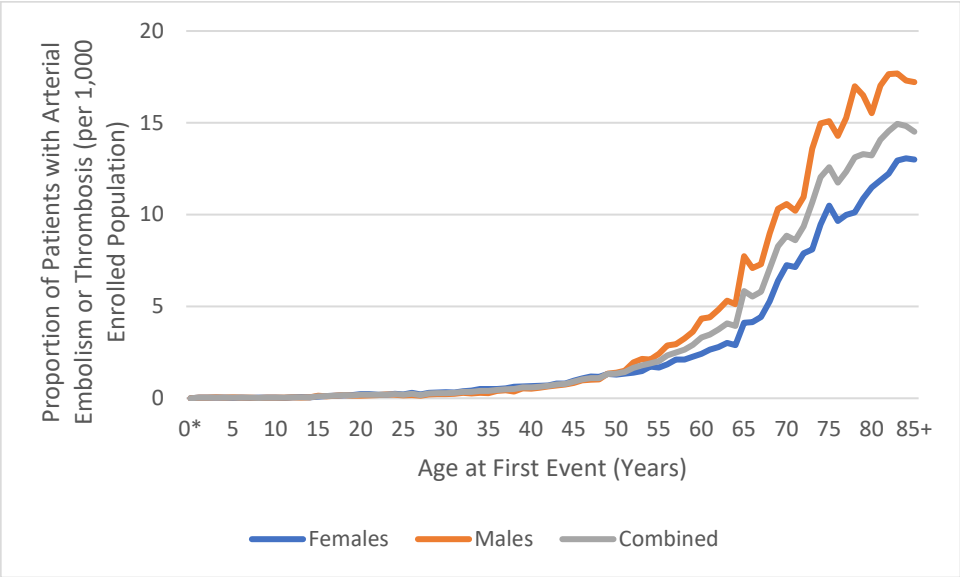

Figure 34. Proportion of patients with at least one diagnosis for arterial embolism or thrombosis (ICD-9-CM or ICD-10-CM) per 1,000 population, by gender (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 year old experiencing non-hemorrhagic stroke has been excluded from the chart and marked as zero.

Figure 35 presents the annual proportions of patients with arterial embolism or thrombosis for ages 1–85+ years. Results suggest that proportions were fairly consistent across years.

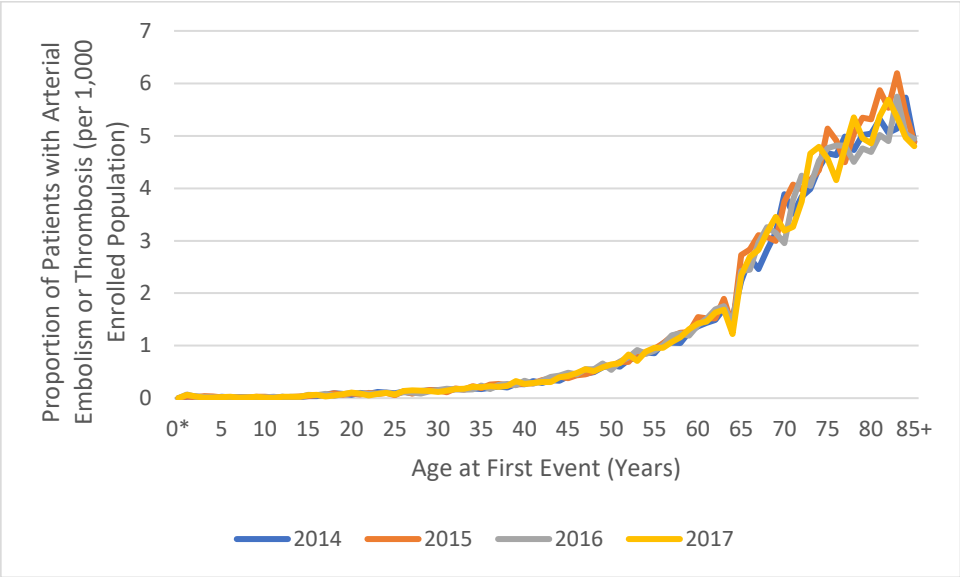

Figure 35. Proportion of patients with at least one diagnosis for arterial embolism or thrombosis (ICD-9-CM or ICD-10-CM) per 1,000 population, by calendar year (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 year old experiencing non-hemorrhagic stroke has been excluded from the chart and marked as zero.

Table 12 and **Figure 36** present the results of analyses that tested whether the occurrence or reporting of arterial embolism and thrombosis varied according to the time of the year, by querying data for January 1–June 30 and July 1–December 31. Results did not suggest that there was a notable difference in the frequency of arterial embolism or thrombosis between the first and second half of the calendar year.

Table 12. ***Counts and proportions of patients experiencing arterial embolism or thrombosis*, defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2017).***

Description	Calendar Year			
	2014	**2015**	**2016**	**2017**
January–June patient count	12,487	10,193	9,987	8,598
July–December patient count	12,499	10,340	9,271	8,377
January–June enrollment	31,110,014	24,094,695	23,531,649	21,656,153
July–December enrollment	30,867,380	23,759,879	23,759,879	21,105,240
January–June proportion (per 1,000 enrolled)	**0.40**	**0.42**	**0.42**	**0.40**
July–December proportion (per 1,000 enrolled)	**0.40**	**0.44**	**0.39**	**0.40**

* The sum of the proportions presented here will exceed those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they would only be counted once when the query spans the full year.

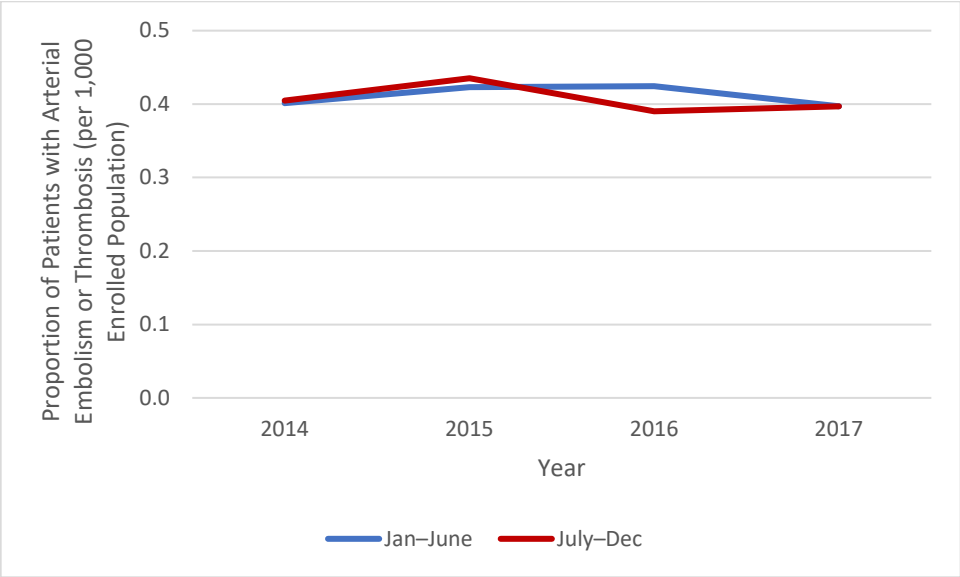

Figure 36. Proportion of patients with at least one diagnosis for arterial embolism or thrombosis (ICD-9-CM or ICD-10-CM), stratified by time of year (2014–2017).

I Discussion and Conclusion

The objective of this review was to identify and describe validated methods of identifying TEEs of interest using administrative claims data. A comprehensive literature review found numerous U.S. studies using ICD-9-CM codes as well as international studies that used ICD-10 modifications. Insights from these studies were leveraged to develop algorithms combining ICD-9-CM and ICD-10-CM codes.

A wide PPV range has been associated with ICD codes for PE, with one systematic review reporting a range of 24–92%.[4] Performance is likely to depend on factors such as the population of interest, healthcare setting, and diagnostic position of the codes being considered. However, the high degree of consistency in the codes selected for inclusion in algorithms to identify PE would suggest that they can be applied with a fairly high degree of reliability.

The selection of DVT codes — and restrictions on other dimensions such as diagnostic code position and healthcare setting — varied across published studies. A systematic review reported that a PPV of 31–97% was associated with code-based definitions for DVT, noting that the best performance was associated with combining codes for phlebitis and thrombophlebitis and for embolism and thrombosis.[4] In the development of the acute DVT algorithm presented in this report, the BEST Initiative chose to exclude codes for thrombophlebitis and phlebitis, viewing these more as local irritations than the systemic outcomes associated with thrombotic events. Instead, the approach drew on that of White and colleagues, who reported a PPV for any acute venous embolism of 94% (95% CI 90–97%) associated with thrombosis codes in the primary diagnostic position.[23] However, the wide range of validation and diagnostic accuracy performance associated with code-based definitions for DVT suggests that results arising from the use of this algorithm should be interpreted with caution, especially in the absence of a standalone chart validation study. This is particularly true given the additional subcategorization of DVT (lower body vs. other) proposed here to expand analytical flexibility.

A systematic review of 30 validation studies assessing the use of administrative data to identify myocardial infarction events reported strong performance in measures of validity and diagnostic

accuracy.[5] More than half of studies using hospital data were associated with a sensitivity of at least 86%, and PPV was at least 93% in 15 of 29 studies that reported the measure. Where reported, specificity and NPV ranged from 89–99% and 75–99%, respectively. Taking this in conjunction with a fairly consistent inclusion of codes in AMI algorithms across studies, it seems likely that the code-based definition for AMI can be applied with a reasonable degree of confidence.

Excepting the poor validation measure performance reported by Ammann and colleagues,[47] code-based definitions for stroke are generally associated with adequate measures of validity and diagnostic accuracy. A systematic review of 35 articles on the performance of administrative claims-based algorithms to identify cerebrovascular accidents or TIA reported that algorithms to identify stroke and intracranial bleeds were associated with PPVs of at least 80%, whereas TIA algorithms were associated with PPVs of at least 70%.[6] Another systematic review of 77 articles assessing the validity of ICD codes for identifying cases of stroke reported that, in most cases, the PPV for ischemic stroke exceeded 82%.[7] However, given the subcategorization and mapping that took place for the stroke algorithm presented in this report, findings resulting from its application should be interpreted with caution in the absence of further validation.

The “Arterial Embolism and Thrombosis” category was developed on the basis of clinical expertise but was found to match exactly the ICD-10 codes used in a French study to define “peripheral arterial thrombosis.”[28] The algorithm was associated with a PPV of 83% (95% CI 73.9–89.1%), although the context-dependence of measures of diagnostic accuracy suggests that additional validation efforts would be of value.

Draft algorithms were subject to review and revision by clinical subject matter experts, with the final iterations tested in the IBM MarketScan Research Databases (Commercial and Medicare Supplemental), accessed via the Treatment Pathways online analytic platform. Descriptive statistics relating to age- and gender-specific counts and proportions of patients experiencing TEEs, as well as variation over time, were generated.

Of the five TEEs queried, arterial embolism and thrombosis was found to be the least common (occurring in 0.71–0.77 individuals per 1,000 enrolled per year); this was followed by PE (2.26–2.41 individuals per 1,000 per year), AMI (2.83–3.16 individuals per 1,000 per year), DVT (4.36–4.96 individuals per 1,000 per year), and non-hemorrhagic stroke (14.21–15.32 individuals per 1,000 per year). The frequency of reporting for the stroke category may have been related to the spectrum of outcomes included. On the basis of visual inspection of charts (no tests of statistical significance were conducted), proportions of individuals experiencing TEEs were found to be higher in men, particularly for arterial embolism and thrombosis, AMI, and stroke.

Variation of in the frequency of individuals experiencing TEEs according to age was assessed via visual inspection of charts. The general trend was similar across outcomes, with a very low frequency observed among young populations and proportions increasing with age from approximately 40 years. The average age associated with a TEE diagnosis was 58 years for DVT, 58 years for PE, 63 years for arterial embolism and thrombosis, 64 years for AMI, and 64 years for non-hemorrhagic stroke. The proportion of adults receiving a TEE diagnosis tended to decrease at 65 years before continuing to increase, though this is believed to be an artefact associated with a transition from commercial insurance to Medicare.

The Best Initiative sought to assess whether there were notable variations in the proportion of individuals experiencing TEEs over time. Visual inspection of annual proportions between 2014 and 2017 showed no indication that the 2015 transition to ICD-10-CM meaningfully affected the frequency of reporting for the five main TEE outcomes. However, the frequency of reporting for “Other DVT” and “Hemorrhagic Stroke” seemed to decrease and increase, respectively, following the transition (**Appendix D**).

Seasonal variations in the frequency of TEEs have been reported previously, and these studies suggest that PE and DVT are more common in the winter.[62-64] AMI also appears to be more common in the winter and less common in the spring,[65-67] whereas stroke appears to be more common in the fall.[68] These

variations likely depend on the geographic area of study but present an important source of time-varying confounding and warrant further study to elucidate potential associations. The BEST Initiative assessed whether there was a notable difference in the frequency of reporting of TEEs between the first half (January 1–June 30) and second half (July 1–December 31) of the year but did not detect a reliable pattern for any of the outcomes of interest. A supplementary, post-hoc analysis (presented in **Appendix D**) was conducted to assess whether there was a notable difference in the proportion of enrolled patients experiencing each of the five key outcomes of interest between the Spring/Summer (April–September) and Fall/Winter (January–March and October–December) seasons. While there was some suggestion that non-hemorrhagic stroke may have been more commonly reported in the Spring/Summer period, it is not clear whether this difference was significant. No other outcomes demonstrated notable differences between seasons. It is possible that a longer time horizon, more granular queries (i.e. by month), more geographically specific testing, and/or assessment of cases (instead of individuals experiencing an event) would be required to detect a potential temporal association in the epidemiology of TEEs.

At a high level, findings from these descriptive analyses of the selected codes and algorithms are generally consistent with those of previously published studies. Pulmonary embolism and DVT have been found to increase in frequency from about 45 years of age, particularly among males, and — although exact data are limited — the incidence rate among the general population seems to be about 1–2 cases per 1,000.[14,69-72] The descriptive analyses detected a slightly higher proportion of individuals experiencing PE and DVT among older men. Cutrona and colleagues[36] reported an average age of 69.5 years and 53% male population in their AMI stroke cohort, whereas a Canadian study reported an age-standardized AMI incidence rate of 1.7–2.4 per 1,000.[73] A study by the American Heart Association reported that the frequency of stroke increased dramatically among those 60 years and older and was higher among men.[74] In a French study of arterial thrombosis, authors reported a mean age of 65.8 years among 100 randomly sampled cases, with a disproportionately high representation of men.[28]

This project had several limitations that should be considered when interpreting findings. First, the wide range of performance on measures of validity and diagnostic accuracy, reported for several outcomes of interest, shows the degree to which performance depends on contextual factors such as population characteristics, healthcare settings, and the specifics of the algorithm and case definition. It should not be assumed that the measures of validation and diagnostic accuracy reported are directly transferrable to the algorithms proposed, and future chart validation studies will be of value. Second, despite a small number of studies suggesting that the inclusion of procedural or prescription codes could improve algorithm performance, review authors chose to limit algorithms to diagnostic codes, reflecting the more common approach observed in the literature. Third, the descriptive analyses of algorithm-identified TEE cases in MarketScan Treatment Pathways did not include uninsured or publicly insured individuals, and may not be representative of the entire U.S. population; additional studies would be required to confirm any patterns observed. Finally, all trends reported were qualitative and based on visual inspection of charts; quantitative analyses should be conducted to explore potential associations.

J Acknowledgements

Development of the TEE algorithms and review report benefitted from significant engagement with the FDA CBER team and its partners. We thank them for their contributions and feedback. Additional feedback on the proposed algorithm and draft report was provided by IBM Watson Health, Acumen, and Epi Excellence LLC. MarketScan is a registered trademark of IBM Corporation in the United States, other countries or both.

K References

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Appendix A. Complete Thromboembolic Event Algorithms

Full administrative claims code-based algorithms for the five thromboembolic outcomes of interest are presented in the subsections below. It should be noted that the algorithms may be subject to minor refinements as a result of specific research questions that arise in the future. The list includes codes that were effective as of March 2, 2020.

Specific codes that were related to the outcomes of interest but excluded from the algorithms are not reported here but are listed in **Appendix C**.

A1. Pulmonary Embolism

The pulmonary embolism (PE) algorithm is presented in **Table A.1.1** and can be summarized as follows:

1. **INCLUDE: ANY** of the codes listed below, regardless of healthcare setting or coding position (only one code required).
2. **EXCLUDE:** Codes related to outcome during pregnancy.

Table A.1.1. PE algorithm.

Code	Description	Code Category	Code Type
415.11	Iatrogenic pulmonary embolism and infarction	DX	09
415.12	Septic pulmonary embolism	DX	09
415.13	Saddle embolus of pulmonary artery	DX	09
415.19	Other pulmonary embolism and infarction	DX	09
I26.01	Septic pulmonary embolism with acute cor pulmonale	DX	10
I26.02	Saddle embolus of pulmonary artery with acute cor pulmonale	DX	10
I26.09	Other pulmonary embolism with acute cor pulmonale	DX	10
I26.90	Septic pulmonary embolism without acute cor pulmonale	DX	10
I26.92	Saddle embolus of pulmonary artery without acute cor pulmonale	DX	10
I26.93	Single subsegmental pulmonary embolism without acute cor pulmonale	DX	10
I26.94	Multiple subsegmental pulmonary emboli without acute cor pulmonale	DX	10
I26.99	Other pulmonary embolism without acute cor pulmonale	DX	10

Abbreviation: DX, ICD-CM diagnosis; PE, pulmonary embolism.

A2. Deep Vein Thrombosis

The deep vein thrombosis (DVT) algorithm is presented in **Table A.2.1** and can be summarized as follows:

1. **INCLUDE: ANY** of the codes listed below, regardless of healthcare setting or coding position (only one code required)
2. **EXCLUDE:** Codes related to phlebitis and thrombophlebitis, chronic embolism and thrombosis, and embolism and thrombosis during pregnancy

DVT codes were also categorized by location, to enable subset analyses of lower body DVTs, depending on the regulatory question to be addressed. The renal vein was considered the anatomical dividing point between lower and upper veins, with veins above the renal vein added to the "other" category (along with codes for "other" and "unspecified" DVTs).[xiv]

Table A.2.1. DVT algorithm.

Code	Description	Code Category	Code Type
Lower Body			
453.2	Other venous embolism and thrombosis of inferior vena cava	DX	09
453.3	Other venous embolism and thrombosis of renal vein	DX	09
453.40	Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity	DX	09
453.41	Acute venous embolism and thrombosis of deep vessels of proximal lower extremity	DX	09
453.42	Acute venous embolism and thrombosis of deep vessels of distal lower extremity	DX	09
453.6	Venous embolism and thrombosis of superficial vessels of lower extremity	DX	09
I82.220	Acute embolism and thrombosis of inferior vena cava	DX	10
I82.3	Embolism and thrombosis of renal vein	DX	10
I82.401	Acute embolism and thrombosis of unspecified deep veins of right lower extremity	DX	10
I82.402	Acute embolism and thrombosis of unspecified deep veins of left lower extremity	DX	10
I82.403	Acute embolism and thrombosis of unspecified deep veins of lower extremity, bilateral	DX	10
I82.409	Acute embolism and thrombosis of unspecified deep veins of unspecified lower extremity	DX	10
I82.411	Acute embolism and thrombosis of right femoral vein	DX	10
I82.412	Acute embolism and thrombosis of left femoral vein	DX	10
I82.413	Acute embolism and thrombosis of femoral vein, bilateral	DX	10
I82.419	Acute embolism and thrombosis of unspecified femoral vein	DX	10
I82.421	Acute embolism and thrombosis of right iliac vein	DX	10
I82.422	Acute embolism and thrombosis of left iliac vein	DX	10
I82.423	Acute embolism and thrombosis of iliac vein, bilateral	DX	10
I82.429	Acute embolism and thrombosis of unspecified iliac vein	DX	10
I82.431	Acute embolism and thrombosis of right popliteal vein	DX	10
I82.432	Acute embolism and thrombosis of left popliteal vein	DX	10
I82.433	Acute embolism and thrombosis of popliteal vein, bilateral	DX	10
I82.439	Acute embolism and thrombosis of unspecified popliteal vein	DX	10

[xiv] Although the inferior vena cava spans the renal vein, it was categorized as "Lower Body" on the basis of the clinical opinion that clots would be more likely to originate from the lower body.

Code	Description	Code Category	Code Type
I82.441	Acute embolism and thrombosis of right tibial vein	DX	10
I82.442	Acute embolism and thrombosis of left tibial vein	DX	10
I82.443	Acute embolism and thrombosis of tibial vein, bilateral	DX	10
I82.449	Acute embolism and thrombosis of unspecified tibial vein	DX	10
I82.451	Acute embolism and thrombosis of right peroneal vein	DX	10
I83.452	Acute embolism and thrombosis of left peroneal vein	DX	10
I82.453	Acute embolism and thrombosis of peroneal vein, bilateral	DX	10
I82.459	Acute embolism and thrombosis of unspecified peroneal vein	DX	10
I82.461	Acute embolism and thrombosis of right calf muscular vein	DX	10
I82.462	Acute embolism and thrombosis of left calf muscular vein	DX	10
I82.463	Acute embolism and thrombosis of calf muscular vein, bilateral	DX	10
I82.469	Acute embolism and thrombosis of unspecified calf muscular vein	DX	10
I82.491	Acute embolism and thrombosis of other specified deep vein of right lower extremity	DX	10
I82.492	Acute embolism and thrombosis of other specified deep vein of left lower extremity	DX	10
I82.493	Acute embolism and thrombosis of other specified deep vein of lower extremity, bilateral	DX	10
I82.499	Acute embolism and thrombosis of other specified deep vein of unspecified lower extremity	DX	10
I82.4Y1	Acute embolism and thrombosis of unspecified deep veins of right proximal lower extremity	DX	10
I82.4Y2	Acute embolism and thrombosis of unspecified deep veins of left proximal lower extremity	DX	10
I82.4Y3	Acute embolism and thrombosis of unspecified deep veins of proximal lower extremity, bilateral	DX	10
I82.4Y9	Acute embolism and thrombosis of unspecified deep veins of unspecified proximal lower extremity	DX	10
I82.4Z1	Acute embolism and thrombosis of unspecified deep veins of right distal lower extremity	DX	10
I82.4Z2	Acute embolism and thrombosis of unspecified deep veins of left distal lower extremity	DX	10
I82.4Z3	Acute embolism and thrombosis of unspecified deep veins of distal lower extremity, bilateral	DX	10
I82.4Z9	Acute embolism and thrombosis of unspecified deep veins of unspecified distal lower extremity	DX	10
I82.811	Embolism and thrombosis of superficial veins of right lower extremities	DX	10
I82.812	Embolism and thrombosis of superficial veins of left lower extremities	DX	10
I82.813	Embolism and thrombosis of superficial veins of lower extremities, bilateral	DX	10
I82.819	Embolism and thrombosis of superficial veins of unspecified lower extremities	DX	10
Other (Upper Body, Other, Unspecified)			
453.0	Budd-Chiari syndrome	DX	09
453.81	Acute venous embolism and thrombosis of superficial veins of upper extremity	DX	09
453.82	Acute venous embolism and thrombosis of deep veins of upper extremity	DX	09

Code	Description	Code Category	Code Type
453.83	Acute venous embolism and thrombosis of upper extremity, unspecified	DX	09
453.84	Acute venous embolism and thrombosis of axillary veins	DX	09
453.85	Acute venous embolism and thrombosis of subclavian veins	DX	09
453.86	Acute venous embolism and thrombosis of internal jugular veins	DX	09
453.87	Acute venous embolism and thrombosis of other thoracic veins	DX	09
453.89	Acute venous embolism and thrombosis of other specified veins	DX	09
453.9	Other venous embolism and thrombosis of unspecified site	DX	09
I81	Portal vein thrombosis	DX	10
I82.0	Budd-Chiari syndrome	DX	10
I82.210	Acute embolism and thrombosis of superior vena cava	DX	10
I82.290	Acute embolism and thrombosis of other thoracic veins	DX	10
I82.601	Acute embolism and thrombosis of unspecified veins of right upper extremity	DX	10
I82.602	Acute embolism and thrombosis of unspecified veins of left upper extremity	DX	10
I82.603	Acute embolism and thrombosis of unspecified veins of upper extremity, bilateral	DX	10
I82.609	Acute embolism and thrombosis of unspecified veins of unspecified upper extremity	DX	10
I82.611	Acute embolism and thrombosis of superficial veins of right upper extremity	DX	10
I82.612	Acute embolism and thrombosis of superficial veins of left upper extremity	DX	10
I82.613	Acute embolism and thrombosis of superficial veins of upper extremity, bilateral	DX	10
I82.619	Acute embolism and thrombosis of superficial veins of unspecified upper extremity	DX	10
I82.621	Acute embolism and thrombosis of deep veins of right upper extremity	DX	10
I82.622	Acute embolism and thrombosis of deep veins of left upper extremity	DX	10
I82.623	Acute embolism and thrombosis of deep veins of upper extremity, bilateral	DX	10
I82.629	Acute embolism and thrombosis of deep veins of unspecified upper extremity	DX	10
I82.890	Acute embolism and thrombosis of other specified veins	DX	10
I82.90	Acute embolism and thrombosis of unspecified vein	DX	10
I82.A11	Acute embolism and thrombosis of right axillary vein	DX	10
I82.A12	Acute embolism and thrombosis of left axillary vein	DX	10
I82.A13	Acute embolism and thrombosis of axillary vein, bilateral	DX	10
I82.A19	Acute embolism and thrombosis of unspecified axillary vein	DX	10
I82.B11	Acute embolism and thrombosis of right subclavian vein	DX	10
I82.B12	Acute embolism and thrombosis of left subclavian vein	DX	10
I82.B13	Acute embolism and thrombosis of subclavian vein, bilateral	DX	10
I82.B19	Acute embolism and thrombosis of unspecified subclavian vein	DX	10
I82.C11	Acute embolism and thrombosis of right internal jugular vein	DX	10
I82.C12	Acute embolism and thrombosis of left internal jugular vein	DX	10
I82.C13	Acute embolism and thrombosis of internal jugular vein, bilateral	DX	10
I82.C19	Acute embolism and thrombosis of unspecified internal jugular vein	DX	10

Abbreviation: DVT, deep vein thrombosis; DX, ICD-CM diagnosis.

A3. Acute Myocardial Infarction

The algorithm for acute myocardial infarction is presented in **Table A.3.1** and can be summarized as follows:

1. **INCLUDE: ANY** of the codes listed below, regardless of healthcare setting or coding position (only one code required)
2. **EXCLUDE:** Codes related to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 411.1 (intermediate coronary syndrome), ICD-9-CM code 412 (old myocardial infarction), ICD-9-CM code 414 (chronic ischemic heart disease), and ICD-9-CM code 413 (angina) have been excluded, along with their Tenth Revision (ICD-10-CM) equivalents.

A.3.1. AMI algorithm.

Code	Description	Code Category	Code Type
410.00	Acute myocardial infarction of anterolateral wall, episode of care unspecified	DX	09
410.01	Acute myocardial infarction of anterolateral wall, initial episode of care	DX	09
410.10	Acute myocardial infarction of other anterior wall, episode of care unspecified	DX	09
410.11	Acute myocardial infarction of other anterior wall, initial episode of care	DX	09
410.20	Acute myocardial infarction of inferolateral wall, episode of care unspecified	DX	09
410.21	Acute myocardial infarction of inferolateral wall, initial episode of care	DX	09
410.30	Acute myocardial infarction of inferoposterior wall, initial episode of care	DX	09
410.31	Acute myocardial infarction of inferoposterior wall, episode of care unspecified	DX	09
410.40	Acute myocardial infarction of other inferior wall, episode of care unspecified	DX	09
410.41	Acute myocardial infarction of other inferior wall, initial episode of care	DX	09
410.50	Acute myocardial infarction of other lateral wall, episode of care unspecified	DX	09
410.51	Acute myocardial infarction of other lateral wall, initial episode of care	DX	09
410.60	True posterior wall infarction, episode of care unspecified	DX	09
410.61	True posterior wall infarction, initial episode of care	DX	09
410.70	Subendocardial infarction, episode of care unspecified	DX	09
410.71	Subendocardial infarction, initial episode of care	DX	09
410.80	Acute myocardial infarction of other specified sites, episode of care unspecified	DX	09
410.81	Acute myocardial infarction of other specified sites, initial episode of care	DX	09
410.90	Acute myocardial infarction of unspecified site, episode of care unspecified	DX	09
410.91	Acute myocardial infarction of unspecified site, initial episode of care	DX	09

Code	Description	Code Category	Code Type
I21.01	ST elevation myocardial infarction (STEMI) involving left main coronary artery	DX	10
I21.02	ST elevation myocardial infarction (STEMI) involving left anterior descending coronary artery	DX	10
I21.09	ST elevation myocardial infarction (STEMI) involving other coronary artery of anterior wall	DX	10
I21.11	ST elevation myocardial infarction (STEMI) involving right coronary artery	DX	10
I21.19	ST elevation myocardial infarction (STEMI) involving other coronary artery of inferior wall	DX	10
I21.21	ST elevation myocardial infarction (STEMI) involving left circumflex coronary artery	DX	10
I21.29	ST elevation myocardial infarction (STEMI) involving other sites	DX	10
I21.3	ST elevation myocardial infarction (STEMI) of unspecified site	DX	10
I21.4	Non-ST elevation myocardial infarction (NSTEMI)	DX	10
I21.9	Acute myocardial infarction, unspecified	DX	10
I21.A1	Myocardial infarction type 2	DX	10
I21.A9	Other myocardial infarction type	DX	10
I22.0	Subsequent ST elevation myocardial infarction (STEMI) of anterior wall	DX	10
I22.1	Subsequent ST elevation myocardial infarction (STEMI) of inferior wall	DX	10
I22.2	Subsequent non-ST elevation myocardial infarction (NSTEMI)	DX	10
I22.8	Subsequent ST elevation myocardial infarction (STEMI) of other sites	DX	10
I22.9	Subsequent ST elevation myocardial infarction (STEMI) of unspecified site	DX	10

Abbreviations: AMI, acute myocardial infarction; DX, ICD-CM diagnosis.

A4. Stroke

The algorithm for stroke is presented in **Table A.4.1** and can be summarized as follows:

1. **INCLUDE: ANY** of the codes listed below, regardless of healthcare setting or coding position (only one code required)
2. **EXCLUDE:** Codes related to leukoencephalopathy, encephalopathy, other cerebrovascular disease, nontraumatic extradural or subarachnoid hemorrhage, and intraoperative or postprocedural infarction

Stroke codes were divided into subcategories to allow for specific outcomes of interest to be studied. Codes have been organized into the following four subcategories: cerebral infarction/thrombosis, occlusion without mention of infarction, transient ischemic attacks, and hemorrhagic stroke. The first three categories are based on the clinical severity and meaningfulness of the outcome. Codes could be applied in a stepwise fashion, allowing for signal detection of the most clinically serious category (cerebral infarction/thrombosis) followed by less severe outcomes. Meanwhile, codes for hemorrhagic stroke (intracerebral hemorrhage) were separated as the pathologic mechanism different from the other categories (bleeding vs. clotting). This approach supports the inclusion of various categories of stroke-related outcomes via individual, stepwise, or combined analyses with sensitivity analyses undertaken as appropriate to the regulatory question.

A.4.1. Stroke algorithm.

Code	Description	Code Category	Code Type
Cerebral Infarction and Thrombosis			
433.01	Occlusion and stenosis of basilar artery with cerebral infarction	DX	09
433.11	Occlusion and stenosis of carotid artery with cerebral infarction	DX	09
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction	DX	09
433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction	DX	09
433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction	DX	09
433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction	DX	09
434.01	Cerebral thrombosis with cerebral infarction	DX	09
434.11	Cerebral embolism with cerebral infarction	DX	09
434.91	Cerebral artery occlusion, unspecified with cerebral infarction	DX	09
I63.00	Cerebral infarction due to thrombosis of unspecified precerebral artery	DX	10
I63.011	Cerebral infarction due to thrombosis of right vertebral artery	DX	10
I63.012	Cerebral infarction due to thrombosis of left vertebral artery	DX	10
I63.013	Cerebral infarction due to thrombosis of bilateral vertebral arteries	DX	10
I63.019	Cerebral infarction due to thrombosis of unspecified vertebral artery	DX	10
I63.02	Cerebral infarction due to thrombosis of basilar artery	DX	10
I63.031	Cerebral infarction due to thrombosis of right carotid artery	DX	10
I63.032	Cerebral infarction due to thrombosis of left carotid artery	DX	10
I63.033	Cerebral infarction due to thrombosis of bilateral carotid arteries	DX	10
I63.039	Cerebral infarction due to thrombosis of unspecified carotid artery	DX	10
I63.09	Cerebral infarction due to thrombosis of other precerebral artery	DX	10
I63.10	Cerebral infarction due to embolism of unspecified precerebral artery	DX	10
I63.111	Cerebral infarction due to embolism of right vertebral artery	DX	10
I63.112	Cerebral infarction due to embolism of left vertebral artery	DX	10
I63.113	Cerebral infarction due to embolism of bilateral vertebral arteries	DX	10
I63.119	Cerebral infarction due to embolism of unspecified vertebral artery	DX	10

Code	Description	Code Category	Code Type
I63.12	Cerebral infarction due to embolism of basilar artery	DX	10
I63.131	Cerebral infarction due to embolism of right carotid artery	DX	10
I63.132	Cerebral infarction due to embolism of right carotid artery	DX	10
I63.133	Cerebral infarction due to embolism of carotid artery	DX	10
I63.139	Cerebral infarction due to embolism of right carotid artery	DX	10
I63.19	Cerebral infarction due to embolism of other precerebral artery	DX	10
I63.20	Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries	DX	10
I63.211	Cerebral infarction due to unspecified occlusion or stenosis of right vertebral arteries	DX	10
I63.212	Cerebral infarction due to unspecified occlusion or stenosis of left vertebral arteries	DX	10
I63.213	Cerebral infarction due to unspecified occlusion or stenosis of bilateral vertebral arteries	DX	10
I63.219	Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral arteries	DX	10
I63.22	Cerebral infarction due to unspecified occlusion or stenosis of basilar arteries	DX	10
I63.231	Cerebral infarction due to unspecified occlusion or stenosis of right carotid arteries	DX	10
I63.232	Cerebral infarction due to unspecified occlusion or stenosis of left carotid arteries	DX	10
I63.233	Cerebral infarction due to unspecified occlusion or stenosis of bilateral carotid arteries	DX	10
I63.239	Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid arteries	DX	10
I63.29	Cerebral infarction due to unspecified occlusion or stenosis of other precerebral arteries	DX	10
I63.30	Cerebral infarction due to thrombosis of unspecified cerebral artery	DX	10
I63.311	Cerebral infarction due to thrombosis of right middle cerebral artery	DX	10
I63.312	Cerebral infarction due to thrombosis of left middle cerebral artery	DX	10
I63.313	Cerebral infarction due to thrombosis of bilateral middle cerebral arteries	DX	10
I63.319	Cerebral infarction due to thrombosis of unspecified middle cerebral artery	DX	10
I63.321	Cerebral infarction due to thrombosis of right anterior cerebral artery	DX	10
I63.322	Cerebral infarction due to thrombosis of left anterior cerebral artery	DX	10
I63.323	Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries	DX	10
I63.329	Cerebral infarction due to thrombosis of unspecified anterior cerebral artery	DX	10
I63.331	Cerebral infarction due to thrombosis of right posterior cerebral artery	DX	10
I63.332	Cerebral infarction due to thrombosis of left posterior cerebral artery	DX	10
I63.333	Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries	DX	10
I63.339	Cerebral infarction due to thrombosis of unspecified posterior cerebral artery	DX	10
I63.341	Cerebral infarction due to thrombosis of right cerebellar artery	DX	10
I63.342	Cerebral infarction due to thrombosis of left cerebellar artery	DX	10
I63.343	Cerebral infarction due to thrombosis of bilateral cerebellar arteries	DX	10

Code	Description	Code Category	Code Type
I63.349	Cerebral infarction due to thrombosis of unspecified cerebellar artery	DX	10
I63.39	Cerebral infarction due to thrombosis of other cerebral artery	DX	10
I63.40	Cerebral infarction due to embolism of unspecified cerebral artery	DX	10
I63.411	Cerebral infarction due to embolism of right middle cerebral artery	DX	10
I63.412	Cerebral infarction due to embolism of left middle cerebral artery	DX	10
I63.413	Cerebral infarction due to embolism of bilateral middle cerebral arteries	DX	10
I63.419	Cerebral infarction due to embolism of unspecified middle cerebral artery	DX	10
I63.421	Cerebral infarction due to embolism of right anterior cerebral artery	DX	10
I63.422	Cerebral infarction due to embolism of left anterior cerebral artery	DX	10
I63.423	Cerebral infarction due to embolism of bilateral anterior cerebral arteries	DX	10
I63.429	Cerebral infarction due to embolism of unspecified anterior cerebral artery	DX	10
I63.431	Cerebral infarction due to embolism of right posterior cerebral artery	DX	10
I63.432	Cerebral infarction due to embolism of left posterior cerebral artery	DX	10
I63.433	Cerebral infarction due to embolism of bilateral posterior cerebral arteries	DX	10
I63.439	Cerebral infarction due to embolism of unspecified posterior cerebral artery	DX	10
I63.441	Cerebral infarction due to embolism of right cerebellar artery	DX	10
I63.442	Cerebral infarction due to embolism of left cerebellar artery	DX	10
I63.443	Cerebral infarction due to embolism of bilateral cerebellar arteries	DX	10
I63.449	Cerebral infarction due to embolism of unspecified cerebellar artery	DX	10
I63.49	Cerebral infarction due to embolism of other cerebral artery	DX	10
I63.50	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery	DX	10
I63.511	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery	DX	10
I63.512	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery	DX	10
I63.513	Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle cerebral arteries	DX	10
I63.519	Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery	DX	10
I63.521	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery	DX	10
I63.522	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery	DX	10
I63.523	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior cerebral arteries	DX	10
I63.529	Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery	DX	10
I63.531	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery	DX	10
I63.532	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery	DX	10
I63.533	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior cerebral arteries	DX	10

Code	Description	Code Category	Code Type
I63.539	Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery	DX	10
I63.541	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery	DX	10
I63.542	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery	DX	10
I63.543	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries	DX	10
I63.549	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery	DX	10
I63.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery	DX	10
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic	DX	10
I63.81	Other cerebral infarction due to occlusion or stenosis of small artery	DX	10
I63.89	Other cerebral infarction	DX	10
I63.9	Cerebral infarction, unspecified	DX	10
Occlusion Without Mention of Infarction			
433.00	Occlusion and stenosis of basilar artery without mention of cerebral infarction	DX	09
433.10	Occlusion and stenosis of carotid artery without mention of cerebral infarction	DX	09
433.20	Occlusion and stenosis of vertebral artery without mention of cerebral infarction	DX	09
433.30	Occlusion and stenosis of multiple and bilateral precerebral arteries without mention of cerebral infarction	DX	09
433.80	Occlusion and stenosis of other specified precerebral artery without mention of cerebral infarction	DX	09
433.90	Occlusion and stenosis of unspecified precerebral artery without mention of cerebral infarction	DX	09
434.00	Cerebral thrombosis without mention of cerebral infarction	DX	09
434.10	Cerebral embolism without mention of cerebral infarction	DX	09
434.90	Cerebral artery occlusion, unspecified without mention of cerebral infarction	DX	09
437.6	Nonpyogenic thrombosis of intracranial venous sinus	DX	09
I65.01	Occlusion and stenosis of right vertebral artery	DX	10
I65.02	Occlusion and stenosis of left vertebral artery	DX	10
I65.03	Occlusion and stenosis of bilateral vertebral arteries	DX	10
I65.09	Occlusion and stenosis of unspecified vertebral artery	DX	10
I65.1	Occlusion and stenosis of basilar artery	DX	10
I65.21	Occlusion and stenosis of right carotid artery	DX	10
I65.22	Occlusion and stenosis of left carotid artery	DX	10
I65.23	Occlusion and stenosis of bilateral carotid arteries	DX	10
I65.29	Occlusion and stenosis of unspecified carotid artery	DX	10
I65.8	Occlusion and stenosis of other precerebral arteries	DX	10
I65.9	Occlusion and stenosis of unspecified precerebral artery	DX	10
I66.01	Occlusion and stenosis of right middle cerebral artery	DX	10
I66.02	Occlusion and stenosis of left middle cerebral artery	DX	10
I66.03	Occlusion and stenosis of bilateral middle cerebral arteries	DX	10
I66.09	Occlusion and stenosis of unspecified middle cerebral artery	DX	10
I66.11	Occlusion and stenosis of right anterior cerebral artery	DX	10
I66.12	Occlusion and stenosis of left anterior cerebral artery	DX	10

Code	Description	Code Category	Code Type
I66.13	Occlusion and stenosis of bilateral anterior cerebral arteries	DX	10
I66.19	Occlusion and stenosis of unspecified anterior cerebral artery	DX	10
I66.21	Occlusion and stenosis of right posterior cerebral artery	DX	10
I66.22	Occlusion and stenosis of left posterior cerebral artery	DX	10
I66.23	Occlusion and stenosis of bilateral posterior cerebral arteries	DX	10
I66.29	Occlusion and stenosis of unspecified posterior cerebral artery	DX	10
I66.3	Occlusion and stenosis of cerebellar arteries	DX	10
I66.8	Occlusion and stenosis of other cerebral arteries	DX	10
I67.6	Nonpyogenic thrombosis of intracranial venous system	DX	10
TIA			
435.0	Basilar artery syndrome	DX	09
435.1	Vertebral artery syndrome	DX	09
435.2	Subclavian steal syndrome	DX	09
435.3	Vertebrobasilar artery syndrome	DX	09
435.8	Other specified transient cerebral ischemias	DX	09
435.9	Unspecified transient cerebral ischemia	DX	09
G45.0	Vertebro-basilar artery syndrome	DX	10
G45.1	Carotid artery syndrome (hemispheric)	DX	10
G45.2	Multiple and bilateral precerebral artery syndromes	DX	10
G45.3	Amaurosis fugax	DX	10
G45.4	Transient global amnesia	DX	10
G45.8	Other transient cerebral ischemic attacks and related syndromes	DX	10
G45.9	Transient cerebral ischemic attack, unspecified	DX	10
G46.0	Middle cerebral artery syndrome	DX	10
G46.1	Anterior cerebral artery syndrome	DX	10
G46.2	Posterior cerebral artery syndrome	DX	10
G46.3	Brain stem stroke syndrome	DX	10
G46.4	Cerebellar stroke syndrome	DX	10
G46.5	Pure motor lacunar syndrome	DX	10
G46.6	Pure sensory lacunar syndrome	DX	10
G46.7	Other lacunar syndromes	DX	10
G46.8	Other vascular syndromes of brain in cerebrovascular diseases	DX	10
Hemorrhagic Stroke			
432.1	Subdural hemorrhage	DX	09
432.9	Unspecified intracranial hemorrhage	DX	09
I61.0	Nontraumatic intracerebral hemorrhage in hemisphere, subcortical	DX	10
I61.1	Nontraumatic intracerebral hemorrhage in hemisphere, cortical	DX	10
I61.2	Nontraumatic intracerebral hemorrhage in hemisphere, unspecified	DX	10
I61.3	Nontraumatic intracerebral hemorrhage in brain stem	DX	10
I61.4	Nontraumatic intracerebral hemorrhage in cerebellum	DX	10
I61.5	Nontraumatic intracerebral hemorrhage, intraventricular	DX	10
I61.6	Nontraumatic intracerebral hemorrhage, multiple localized	DX	10
I61.8	Other nontraumatic intracerebral hemorrhage	DX	10
I61.9	Nontraumatic intracerebral hemorrhage, unspecified	DX	10
I62.00	Nontraumatic subdural hemorrhage, unspecified	DX	10
I62.01	Nontraumatic acute subdural hemorrhage	DX	10
I62.02	Nontraumatic subacute subdural hemorrhage	DX	10
I62.9	Nontraumatic intracranial hemorrhage, unspecified	DX	10

Abbreviation: TIA, transient ischemic attack; DX, ICD-CM diagnosis.

A5. Arterial Embolism and Thrombosis

The algorithm for arterial embolism and thrombosis is presented in **Table A.5.1** and can be summarized as follows:

1. **INCLUDE: ANY** of the codes listed below, regardless of healthcare setting or coding position (only one code required)
2. **EXCLUDE:** Codes related to arterial embolism or thrombosis due to prosthetic devices, implants, and grafts[xv]

Table A.5.1. Arterial embolism and thrombosis algorithm.

Code	Description	Code Category	Code Type
444.01	Saddle embolus of abdominal aorta	DX	09
444.09	Other arterial embolism and thrombosis of abdominal aorta	DX	09
444.1	Embolism and thrombosis of thoracic aorta	DX	09
444.21	Arterial embolism and thrombosis of upper extremity	DX	09
444.22	Arterial embolism and thrombosis of lower extremity	DX	09
444.81	Embolism and thrombosis of iliac artery	DX	09
444.89	Embolism and thrombosis of other specified artery	DX	09
444.9	Embolism and thrombosis of unspecified artery	DX	09
I74.01	Saddle embolus of abdominal aorta	DX	10
I74.09	Other arterial embolism and thrombosis of abdominal aorta	DX	10
I74.10	Embolism and thrombosis of unspecified parts of aorta	DX	10
I74.11	Embolism and thrombosis of thoracic aorta	DX	10
I74.19	Embolism and thrombosis of other parts of aorta	DX	10
I74.2	Embolism and thrombosis of arteries of the upper extremities	DX	10
I74.3	Embolism and thrombosis of arteries of the lower extremities	DX	10
I74.4	Embolism and thrombosis of arteries of extremities, unspecified	DX	10
I74.5	Embolism and thrombosis of iliac artery	DX	10
I74.8	Embolism and thrombosis of other arteries	DX	10
I74.9	Embolism and thrombosis of unspecified artery	DX	10

Abbreviation: DX, ICD-CM diagnosis.

[xv] It was decided that these populations were likely to have other risks of thrombosis and may therefore confound the product–embolism exposure–outcome association.

Appendix B. Individual Code Counts for Proposed Algorithms

As an initial test of the proposed TEE algorithms, authors ran code-specific queries on a large patient dataset to assess the number of patients with each diagnosis code proposed for inclusion. This was done to identify what specific codes were likely to account for the majority of the results being returned. The most frequently reported codes for each TEE outcome of interest are highlighted for emphasis. An arbitrary threshold of ≥10% of total count was used to define a "frequently used'' code. It should be noted that a transition to a higher number of codes in ICD-10-CM could obscure "frequently used'' codes relative to ICD-9-CM, although this analysis is simply meant to inform a general overview of the most frequently used codes. Researchers used the IBM MarketScan Research Databases, accessed via the Treatment Pathways platform, querying the past four years of available data (January 1, 2014–December 31, 2017). In 2014, there were 28,407,959 patients enrolled for the entire year; 22,117235 in 2015; 21,616,367 in 2016; 19,802,253 in 2017; and 41,172,696 for at least one calendar year in 2014–2017. Results for each outcome of interest are presented in the sections below.

The transition from International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) to the Tenth Revision (ICD-10-CM) occurred October 1, 2015; no ICD-9-CM codes were queried after this date and no ICD-10-CM codes were queried before this date. The coding standard-specific subtotal rows were calculated by querying all of the codes for a particular coding standard together; the "Total (Count)" column was calculated by querying the individual code in a cohort of patients that were enrolled for at least one calendar year between 2014 and 2017.

Subtotal rows and Total columns may be smaller than the sum of individual cells because patients with multiple codes in a single year and with more than one of the same diagnosis codes in different years will only be counted once in these rows and columns. As a result, the sum of all "% of Total" cells in a single column may exceed 100%. However, the "Total" column could also be larger than the sum of individual years, as a result of situations where an individual is only enrolled for part of the year that they experience a TEE but is then continuously enrolled for a separate year. For example, an individual could be continuously enrolled for a few days, weeks, or months in 2016 and experience a TEE, then be continuously enrolled for all of 2017. This event would not be captured in the column for the 2016 (as the individual would be excluded from that cohort) but would be captured in the "Total" column.

B1. Pulmonary Embolism

Code-specific query results for pulmonary embolism (PE) are presented in **Table B.1.1**. It appears that codes for "Other" PE (ICD-9-CM code 415.9; ICD-10-CM code I26.99) are the most frequently reported codes.

Table B.1.1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in the pulmonary embolism algorithm (2014–2017).

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
ICD-9-CM											
415.11	Iatrogenic pulmonary embolism and infarction	8,375	12.9	4,983	9.34					12,862	7.7
415.12	Septic pulmonary embolism	784	1.2	497	0.9					1,379	0.8
415.13	Saddle embolus of pulmonary artery	1,330	2.0	960	1.8					2,358	1.4
415.19	Other pulmonary embolism and infarction	62,096	95.6	42,055	78.8					92,906	55.3
ICD-9-CM Subtotal		**64,970**	**100.**	**43,957**	**82.4**					**96,808**	**57.6**
ICD-10-CM											
I26.01	Septic pulmonary embolism with acute cor pulmonale			158	0.3	634	1.3	443	1.0	1,335	0.8
I26.02	Saddle embolus of pulmonary artery with acute cor pulmonale			250	0.5	924	1.8	980	2.2	2,183	1.3
I26.09	Other pulmonary embolism with acute cor pulmonale			1,666	3.1	4,554	9.1	3,869	8.6	10,412	6.2
I26.90	Septic pulmonary embolism without acute cor pulmonale			458	0.9	1,318	2.6	1,183	2.6	3,157	1.9
I26.92	Saddle embolus of pulmonary artery without acute cor pulmonale			647	1.2	2,100	4.2	2,047	4.6	4,776	2.8
I26.93	Single subsegmental pulmonary embolism without acute cor pulmonale			0	0.0	0	0.0	0	0.0	0	0.0
I26.94	Multiple subsegmental pulmonary emboli without acute cor pulmonale			0	0.0	0	0.0	0	0.0	0	0.0
I26.99	Other pulmonary embolism without acute cor pulmonale			24,148	45.2	48,155	96.1	42,980	96.0	96,531	57.5
ICD-10-CM Subtotal				**25,209**	**47.2**	**50,096**	**100.0**	**44,781**	**100.0**	**100,256**	**59.7**
Total		**64,970**	**100.0**	**53,373**	**100.0**	**50,096**	**100.0**	**44,781**	**100.0**	**167,945**	**100.0**

B2. Deep Vein Thrombosis

Code-specific query results for DVT are presented in **Table B.2.1**. The "% of Total" columns were calculated using the subcategory-specific totals (i.e., all Lower DVT codes were assessed in the context of the Lower DVT total).

For "Lower Body DVT," embolism and thrombosis of "unspecified" (ICD-9-CM code 453.40; ICD-10-CM codes I82.401, I82.402, I82.409) deep veins and deep vessels of the proximal and distal lower extremities (ICD-9-CM codes 453.41, 453.42) were the most frequently reported codes. It should be noted that the 453.41 and 453.42 codes convert to several I82.xxx codes, which likely did not meet the predetermined threshold of ≥10% of all codes because of a higher number of coding options.

For "Other" DVT codes — which include upper body, unspecified, and "other" codes — acute embolism and thrombosis of unspecified veins (ICD-9-CM 453.9; ICD-10-CM I82.90) were the most frequently reported.

Table B.2.1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in the DVT algorithm (2014–2017).

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
Lower Body											
ICD-9-CM											
453.2	Other venous embolism and thrombosis of inferior vena cava	1,515	1.4	887	1.0					2,495	0.9
453.3	Other venous embolism and thrombosis of renal vein	770	0.7	499	0.6					1,219	0.4
453.40	Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity	88,560	81.9	60,593	67.6					137,222	46.9
453.41	Acute venous embolism and thrombosis of deep vessels of proximal lower extremity	23,882	22.1	14,981	16.7					39,580	13.5
453.42	Acute venous embolism and thrombosis of deep vessels of distal lower extremity	21,168	19.6	12,892	14.4					34,577	11.8
453.6	Venous embolism and thrombosis of superficial vessels of lower extremity	11,715	10.8	7,092	7.9					19,635	6.7
ICD-9-CM Subtotal		**108,135**	**100.0**	**72,704**	**81.2**					**166,535**	**57.0**
ICD-10-CM											
I82.220	Acute embolism and thrombosis of inferior vena cava			287	0.3	929	1.1	842	1.2	2,190	0.7

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
I82.3	Embolism and thrombosis of renal vein			286	0.3	565	0.7	468	0.7	1,186	0.4
I82.401	Acute embolism and thrombosis of unspecified deep veins of right lower extremity			5,504	6.1	14,849	18.1	11,903	16.9	31,840	10.9
I82.402	Acute embolism and thrombosis of unspecified deep veins of left lower extremity			6,175	6.9	16,450	20.1	13,357	18.9	35,027	12.0
I82.403	Acute embolism and thrombosis of unspecified deep veins of lower extremity, bilateral			2,418	2.7	5,972	7.3	4,654	6.6	13,421	4.6
I82.409	Acute embolism and thrombosis of unspecified deep veins of unspecified lower extremity			19,603	21.9	41,328	50.5	31,345	44.4	81,768	28.0
I82.411	Acute embolism and thrombosis of right femoral vein			1,616	1.8	5,505	6.7	5,299	7.5	13,425	4.6
I82.412	Acute embolism and thrombosis of left femoral vein			1,925	2.1	6,631	8.1	6,366	9.0	15,814	5.4
I82.413	Acute embolism and thrombosis of femoral vein, bilateral			358	0.4	1,177	1.4	1,140	1.6	3,169	1.1
I82.419	Acute embolism and thrombosis of unspecified femoral vein			526	0.6	1,055	1.3	845	1.2	2,434	0.8
I82.421	Acute embolism and thrombosis of right iliac vein			251	0.3	861	1.1	802	1.1	2,098	0.7
I82.422	Acute embolism and thrombosis of left iliac vein			367	0.4	1,299	1.6	1,285	1.8	3,125	1.1
I82.423	Acute embolism and thrombosis of iliac vein, bilateral			81	0.1	310	0.4	328	0.5	801	0.3
I82.429	Acute embolism and thrombosis of unspecified iliac vein			172	0.2	442	0.5	317	0.4	954	0.3
I82.431	Acute embolism and thrombosis of right popliteal vein			1,459	1.6	5,119	6.2	4,985	7.1	12,311	4.2
I82.432	Acute embolism and thrombosis of left popliteal vein			1,687	1.9	6,231	7.6	6,107	8.7	14,851	5.1
I82.433	Acute embolism and thrombosis of popliteal vein, bilateral			191	0.2	653	0.8	614	0.9	1,749	0.6
I82.439	Acute embolism and thrombosis of unspecified popliteal vein			249	0.3	585	0.7	424	0.6	1,281	0.4
I82.441	Acute embolism and thrombosis of right tibial vein			795	0.9	2,821	3.4	2,697	3.8	6,865	2.3
I82.442	Acute embolism and thrombosis of left tibial vein			815	0.9	3,192	3.9	3,230	4.6	7,761	2.7
I82.443	Acute embolism and thrombosis of tibial vein, bilateral			118	0.1	377	0.5	351	0.5	988	0.3
I82.449	Acute embolism and thrombosis of unspecified tibial vein			203	0.2	437	0.5	289	0.4	937	0.3
I82.451	Acute embolism and thrombosis of right peroneal vein			0	0.0	0	0.0	0	0.0	0	0.0

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
I83.452	Acute embolism and thrombosis of left peroneal vein			0	0.0	0	0.0	0	0.0	0	0.0
I82.453	Acute embolism and thrombosis of peroneal vein, bilateral			0	0.0	0	0.0	0	0.0	0	0.0
I82.459	Acute embolism and thrombosis of unspecified peroneal vein			0	0.0	0	0.0	0	0.0	0	0.0
I82.461	Acute embolism and thrombosis of right calf muscular vein			0	0.0	0	0.0	0	0.0	0	0.0
I82.462	Acute embolism and thrombosis of left calf muscular vein			0	0.0	0	0.0	0	0.0	0	0.0
I82.463	Acute embolism and thrombosis of calf muscular vein, bilateral			0	0.0	0	0.0	0	0.0	0	0.0
I82.469	Acute embolism and thrombosis of unspecified calf muscular vein			0	0.0	0	0.0	0	0.0	0	0.0
I82.491	Acute embolism and thrombosis of other specified deep vein of right lower extremity			942	1.1	3,280	4.0	3,494	4.9	8,217	2.8
I82.492	Acute embolism and thrombosis of other specified deep vein of left lower extremity			1,039	1.2	3,937	4.8	4,085	5.8	9,620	3.3
I82.493	Acute embolism and thrombosis of other specified deep vein of lower extremity, bilateral			319	0.4	1,237	1.5	1,394	2.0	3,289	1.1
I82.499	Acute embolism and thrombosis of other specified deep vein of unspecified lower extremity			367	0.4	1,053	1.3	1,095	1.6	2,495	0.9
I82.4Y1	Acute embolism and thrombosis of unspecified deep veins of right proximal lower extremity			238	0.3	1,136	1.4	1,288	1.8	2,775	0.9
I82.4Y2	Acute embolism and thrombosis of unspecified deep veins of left proximal lower extremity			322	0.4	1,423	1.7	1,567	2.2	3,388	1.2
I82.4Y3	Acute embolism and thrombosis of unspecified deep veins of proximal lower extremity, bilateral			80	0.1	366	0.4	482	0.7	992	0.3
I82.4Y9	Acute embolism and thrombosis of unspecified deep veins of unspecified proximal lower extremity			632	0.7	1,552	1.9	1,608	2.3	3,406	1.2
I82.4Z1	Acute embolism and thrombosis of unspecified deep veins of right distal lower extremity			1,192	1.3	4,126	5.0	3,643	5.2	9,482	3.2
I82.4Z2	Acute embolism and thrombosis of unspecified deep veins of left distal lower extremity			1,452	1.6	4,973	6.1	4,424	6.3	11,416	3.9
I82.4Z3	Acute embolism and thrombosis of unspecified deep veins of distal lower extremity, bilateral			284	0.3	849	1.0	797	1.1	2,142	0.7
I82.4Z9	Acute embolism and thrombosis of unspecified deep veins of unspecified distal lower extremity			783	0.9	1,899	2.3	1,481	2.1	3,929	1.3
I82.811	Embolism and thrombosis of superficial veins of right lower extremities			1,022	1.1	3,530	4.3	3,373	4.8	8,438	2.9
I82.812	Embolism and thrombosis of superficial veins of left lower extremities			1,073	1.2	3,868	4.7	3,720	5.3	9,182	3.1

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
I82.813	Embolism and thrombosis of superficial veins of lower extremities, bilateral			196	0.2	612	0.7	599	0.8	1,541	0.5
I82.819	Embolism and thrombosis of superficial veins of unspecified lower extremities			314	0.4	772	0.9	569	0.8	1,717	0.6
ICD-10-CM				**36,493**	**40.7**	**81,913**	**100.0**	**70,587**	**100.0**	**166,429**	**56.9**
Lower Body DVT Total		**108,135**	**80.3**	**89,578**	**100.0**	**81,913**	**100.0**	**70,587**	**100.0**	**292,366**	**100.0**
Other (Upper Body, Other, Unspecified											
ICD-9-CM											
453.0	Budd-chiari syndrome	1,187	2.5	729	2.1					1,877	0.5
453.81	Acute venous embolism and thrombosis of superficial veins of upper extremity	6,011	12.6	3,621	10.3					10,440	2.9
453.82	Acute venous embolism and thrombosis of deep veins of upper extremity	5,174	10.8	3,362	9.6					8,962	2.5
453.83	Acute venous embolism and thrombosis of upper extremity, unspecified	2,155	4.5	1,203	3.4					3,578	1.0
453.84	Acute venous embolism and thrombosis of axillary veins	1,756	3.7	1,066	3.0					3,055	0.8
453.85	Acute venous embolism and thrombosis of subclavian veins	2,302	4.8	1,356	3.9					3,925	1.1
453.86	Acute venous embolism and thrombosis of internal jugular veins	1,668	3.5	995	2.8					2,876	0.8
453.87	Acute venous embolism and thrombosis of other thoracic veins	701	1.5	387	1.1					1,176	0.3
453.89	Acute venous embolism and thrombosis of other specified veins	8,125	17.0	4,853	13.8					13,298	3.7
453.9	Other venous embolism and thrombosis of unspecified site	29,282	61.2	16,952	48.2					44,522	12.3
ICD-9-CM Subtotal		**47,826**	**100.0**	**28,568**	**81.2**					**75,008**	**20.8**
ICD-10-CM											
I81	Portal vein thrombosis			1,341	3.8	3,206	12.9	3,074	13.7	7,349	5.9
I82.0	Budd-Chiari syndrome			406	1.2	905	3.7	749	3.3	1,952	1.6

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
I82.210	Acute embolism and thrombosis of superior vena cava			122	0.3	336	1.4	308	1.4	822	0.7
I82.290	Acute embolism and thrombosis of other thoracic veins			108	0.3	356	1.4	329	1.5	853	0.7
I82.601	Acute embolism and thrombosis of unspecified veins of right upper extremity			192	0.5	606	2.4	482	2.1	1,423	1.1
I82.602	Acute embolism and thrombosis of unspecified veins of left upper extremity			134	0.4	503	2.0	421	1.9	1,206	1.0
I82.603	Acute embolism and thrombosis of unspecified veins of upper extremity, bilateral			16	0.0	63	0.3	52	0.2	152	0.1
I82.609	Acute embolism and thrombosis of unspecified veins of unspecified upper extremity			136	0.4	343	1.4	321	1.4	813	0.6
I82.611	Acute embolism and thrombosis of superficial veins of right upper extremity			661	1.9	2,552	10.3	2,238	10.0	6,516	5.2
I82.612	Acute embolism and thrombosis of superficial veins of left upper extremity			637	1.8	2,423	9.8	2,312	10.3	6,165	4.9
I82.613	Acute embolism and thrombosis of superficial veins of upper extremity, bilateral			70	0.2	224	0.9	244	1.1	664	0.5
I82.619	Acute embolism and thrombosis of superficial veins of unspecified upper extremity			211	0.6	496	2.0	379	1.7	1,157	0.9
I82.621	Acute embolism and thrombosis of deep veins of right upper extremity			809	2.3	2,501	10.1	2,306	10.3	6,241	5.0
I82.622	Acute embolism and thrombosis of deep veins of left upper extremity			747	2.1	2,254	9.1	2,065	9.2	5,529	4.4
I82.623	Acute embolism and thrombosis of deep veins of upper extremity, bilateral			96	0.3	323	1.3	259	1.2	794	0.6
I82.629	Acute embolism and thrombosis of deep veins of unspecified upper extremity			550	1.6	1,201	4.8	947	4.2	2,807	2.2
I82.890	Acute embolism and thrombosis of other specified veins			1,084	3.1	3,056	12.3	2,741	12.2	7,090	5.7
I82.90	Acute embolism and thrombosis of unspecified vein			2,997	8.5	7,586	30.6	6,653	29.7	16,619	13.3
I82.A11	Acute embolism and thrombosis of right axillary vein			201	0.6	777	3.1	850	3.8	2,129	1.7
I82.A12	Acute embolism and thrombosis of left axillary vein			152	0.4	733	3.0	685	3.1	1,778	1.4
I82.A13	Acute embolism and thrombosis of axillary vein, bilateral			12	0.0	55	0.2	66	0.3	157	0.1
I82.A19	Acute embolism and thrombosis of unspecified axillary vein			51	0.1	169	0.7	110	0.5	342	0.3
I82.B11	Acute embolism and thrombosis of right subclavian vein			225	0.6	742	3.0	745	3.3	2,008	1.6
I82.B12	Acute embolism and thrombosis of left subclavian vein			224	0.6	865	3.5	734	3.3	2,075	1.7

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
I82.B13	Acute embolism and thrombosis of subclavian vein, bilateral			10	0.0	43	0.2	38	0.2	112	0.1
I82.B19	Acute embolism and thrombosis of unspecified subclavian vein			62	0.2	159	0.6	131	0.6	381	0.3
I82.C11	Acute embolism and thrombosis of right internal jugular vein			256	0.7	832	3.4	864	3.9	2,245	1.8
I82.C12	Acute embolism and thrombosis of left internal jugular vein			167	0.5	558	2.3	527	2.3	1,429	1.1
I82.C13	Acute embolism and thrombosis of internal jugular vein, bilateral			25	0.1	47	0.2	69	0.3	173	0.1
I82.C19	Acute embolism and thrombosis of unspecified internal jugular vein			89	0.3	273	1.1	225	1.0	637	0.5
ICD-10-CM Subtotal				**9,305**	**26.5**	**24,775**	**100.0**	**22,429**	**100.0**	**56,821**	**45.3**
Other DVT Total		**47,826**	**35.5**	**35,177**	**100.0**	**24,775**	**100.0**	**22,429**	**100.0**	**125,388**	**100.0**
Any DVT total		**134,716**	**100.0**	**109,688**	**100.0**	**98,623**	**100.0**	**86,245**	**100.0**	**361,267**	**100.0**

Abbreviation: DVT, deep vein thrombosis.

B3. Acute Myocardial Infarction

Code-specific query results for acute myocardial infarction (AMI) are presented in **Table B.3.1**. Codes for subendocardial infarction (ICD-9-CM codes 410.70, 410.71), AMI of unspecified site (ICD-9-CM code 410.90), ST-elevation myocardial infarction (STEMI) (ICD-10-CM code I21.3) and non-ST-elevation myocardial infarction (NSTEMI) myocardial infarction (ICD-10-CM I21.4) appear to be the most frequently reported codes.

Table B.3.1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in the AMI algorithm (2014–2017).

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
ICD-9-CM											
410.00	Acute myocardial infarction of anterolateral wall, episode of care unspecified	3,455	4.3	2,087	3.1					5,915	2.2
410.01	Acute myocardial infarction of anterolateral wall, initial episode of care	2,200	2.7	1,236	1.8					3,722	1.4
410.10	Acute myocardial infarction of other anterior wall, episode of care unspecified	4,913	6.1	3,435	5.1					8,729	3.2
410.11	Acute myocardial infarction of other anterior wall, initial episode of care	4,786	6.0	2,678	4.0					8,070	3.0
410.20	Acute myocardial infarction of inferolateral wall, episode of care unspecified	843	1.0	490	0.7					1,379	0.5
410.21	Acute myocardial infarction of inferolateral wall, initial episode of care	1,542	1.9	820	1.2					2,525	0.9
410.30	Acute myocardial infarction of inferoposterior wall, initial episode of care	410	0.5	254	0.4					680	0.3
410.31	Acute myocardial infarction of inferoposterior wall, episode of care unspecified	891	1.1	655	1.0					1,645	0.6
410.40	Acute myocardial infarction of other inferior wall, episode of care unspecified	6,388	7.9	3,828	5.7					10,578	3.9
410.41	Acute myocardial infarction of other inferior wall, initial episode of care	6,637	8.3	3,842	5.7					11,200	4.2
410.50	Acute myocardial infarction of other lateral wall, episode of care unspecified	683	0.8	404	0.6					1,178	0.4
410.51	Acute myocardial infarction of other lateral wall, initial episode of care	820	1.0	473	0.7					1,402	0.5
410.60	True posterior wall infarction, episode of care unspecified	185	0.2	140	0.2					347	0.1
410.61	True posterior wall infarction, initial episode of care	295	0.4	171	0.3					505	0.2
410.70	Subendocardial infarction, episode of care unspecified	22,229	27.6	15,746	23.4					40,127	14.9
410.71	Subendocardial infarction, initial episode of care	34,812	43.3	20,745	30.8					60,510	22.5

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
410.80	Acute myocardial infarction of other specified sites, episode of care unspecified	3,531	4.4	2,209	3.3					6,035	2.2
410.81	Acute myocardial infarction of other specified sites, initial episode of care	1,511	1.9	837	1.2					2,527	0.9
410.90	Acute myocardial infarction of unspecified site, episode of care unspecified	34,817	43.3	20,563	30.5					56,597	21.1
410.91	Acute myocardial infarction of unspecified site, initial episode of care	14,101	17.5	8,136	12.1					24,327	9.1
ICD-9-CM Subtotal		**80,411**	**100.0**	**49,765**	**73.9**					**133,075**	**49.5**
ICD-10-CM											
I21.01	ST elevation myocardial infarction (STEMI) involving left main coronary artery			196	0.3	488	0.7	437	0.7	1,244	0.5
I21.02	ST elevation myocardial infarction (STEMI) involving left anterior descending coronary artery			950	1.4	3,204	4.7	3,054	5.0	7,405	2.8
I21.09	ST elevation myocardial infarction (STEMI) involving other coronary artery of anterior wall			2,571	3.8	7,029	10.3	5,697	9.2	16,444	6.1
I21.11	ST elevation myocardial infarction (STEMI) involving right coronary artery			932	1.4	3,218	4.7	3,050	4.9	7,429	2.8
I21.19	ST elevation myocardial infarction (STEMI) involving other coronary artery of inferior wall			2,861	4.2	8,490	12.4	7,155	11.6	19,412	7.2
I21.21	ST elevation myocardial infarction (STEMI) involving left circumflex coronary artery			317	0.5	931	1.4	901	1.5	2,201	0.8
I21.29	ST elevation myocardial infarction (STEMI) involving other sites			1,411	2.1	4,046	5.9	3,297	5.3	9,557	3.6
I21.3	ST elevation myocardial infarction (STEMI) of unspecified site			8,387	12.4	24,326	35.6	19,893	32.3	55,770	20.7
I21.4	Non-ST elevation myocardial infarction (NSTEMI)			12,945	19.2	40,487	59.3	37,287	60.5	97,428	36.2
I21.9	Acute myocardial infarction, unspecified			0	0.0	0	0.0	1,413	2.3	1,478	0.5
I21.A1	Myocardial infarction type 2			0	0.0	0	0.0	1,059	1.7	1,059	0.0
I21.A9	Other myocardial infarction type			0	0.0	0	0.0	252	0.4	252	0.1
I22.0	Subsequent ST elevation myocardial infarction (STEMI) of anterior wall			134	0.2	461	0.7	350	0.6	989	0.4
I22.1	Subsequent ST elevation myocardial infarction (STEMI) of inferior wall			210	0.3	507	0.7	429	0.7	1,192	0.4
I22.2	Subsequent non-ST elevation myocardial infarction (NSTEMI)			501	0.7	1,247	1.8	990	1.6	3,091	1.2
I22.8	Subsequent ST elevation myocardial infarction (STEMI) of other sites			51	0.1	187	0.3	122	0.2	390	0.1
I22.9	Subsequent ST elevation myocardial infarction (STEMI) of unspecified site			216	0.3	560	0.8	401	0.7	1,314	0.5

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
I24.0	Acute coronary thrombosis not resulting in myocardial infarction*			903	1.3	2,276	3.3	1,589	2.6	4,881	1.8
ICD-10-CM Subtotal				**23,883**	**35.4**	**68,253**	**100.0**	**61,559**	**99.8**	**156,446**	**58.2**
Total		**80,411**	**100.0**	**67,375**	**100.0**	**68,253**	**61,669**	**100.0**	**268,777**	**100.0**	**100.0**

* ICD-10-CM code I24.0 (Acute coronary thrombosis not resulting in myocardial infarction) was excluded during testing because of the relatively low representation of the code and the fact that the encounter did not represent a myocardial infarction event. This exclusion is reflected in the descriptive analyses, but the code is included here to present the results of the original code-specific query testing.

B4. Stroke

Code-specific query results for stroke are presented in **Table B.4.1**. The "% of Total" columns were calculated using the subcategory-specific totals (e.g., all Cerebral Infarction and Thrombosis codes were assessed in the context of the Cerebral Infarction and Thrombosis total).

For the "Cerebral Infarction and Thrombosis" category, unspecified cerebral artery occlusion and infarction (ICD-9-CM code 434.91; ICD-10-CM codes I63.50, I63.9) appeared to be the most frequently reported codes.

For the "Occlusion Without Mention of Infarction" category, occlusion and stenosis of the carotid (ICD-9-CM code 433.10) and precerebral (ICD-9-CM code 433.30; ICD-10-CM code I65) arteries appeared to be the most frequently reported codes.

For the "TIA" category, unspecified transient cerebral ischemia (ICD-9-CM code 435.9; ICD-10-CM code G45.9) appeared to be the most frequently reported codes.

For the "Hemorrhagic Stroke" category, subdural (ICD-9-CM code 432.1; ICD-10-CM code I62.00) unspecified intracranial (ICD-9-CM code 432.9; ICD-0-CM code I62.9), and unspecified intracerebral hemorrhage (ICD-10-CM code I61.9) appeared to be the most frequently reported codes.

Table B.4.1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in the stroke algorithm (2014–2017).

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
Cerebral Infarction and Thrombosis											
ICD-9-CM											
433.01	Occlusion and stenosis of basilar artery with cerebral infarction	770	0.7	560	0.5					1,376	0.4
433.11	Occlusion and stenosis of carotid artery with cerebral infarction	9,943	8.5	6,153	5.9					16,036	4.5
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction	937	0.8	595	0.6					1,570	0.4
433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction	2,370	2.0	1,527	1.5					4,178	1.2
433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction	428	0.4	253	0.2					702	0.2
433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction	728	0.6	487	0.5					1,260	0.4
434.01	Cerebral thrombosis with cerebral infarction	10,060	8.6	5,908	5.7					15,784	4.5
434.11	Cerebral embolism with cerebral infarction	11,314	9.7	7,029	6.7					18,852	5.3
434.91	Cerebral artery occlusion, unspecified with cerebral infarction	104,240	88.9	73,319	70.2					170,402	48.3
ICD-9-CM Subtotal		**117,212**	**100.0**	**81,287**	**77.8**					**188,235**	**53.3**

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
ICD-10-CM											
I63.00	Cerebral infarction due to thrombosis of unspecified precerebral artery			322	0.3	1,263	1.2	1,163	1.3	2,694	0.8
I63.011	Cerebral infarction due to thrombosis of right vertebral artery			59	0.1	258	0.2	269	0.3	607	0.2
I63.012	Cerebral infarction due to thrombosis of left vertebral artery			63	0.1	227	0.2	216	0.2	526	0.1
I63.013	Cerebral infarction due to thrombosis of bilateral vertebral arteries			0	0.0	0	0.0	31	0.0	33	0.0
I63.019	Cerebral infarction due to thrombosis of unspecified vertebral artery			57	0.1	243	0.2	207	0.2	493	0.1
I63.02	Cerebral infarction due to thrombosis of basilar artery			89	0.1	333	0.3	328	0.4	826	0.2
I63.031	Cerebral infarction due to thrombosis of right carotid artery			199	0.2	351	0.3	477	0.5	1,272	0.4
I63.032	Cerebral infarction due to thrombosis of left carotid artery			208	0.2	554	0.5	439	0.5	1,209	0.3
I63.033	Cerebral infarction due to thrombosis of bilateral carotid arteries			0	0.0	0	0.0	30	0.0	35	0.0
I63.039	Cerebral infarction due to thrombosis of unspecified carotid artery			124	0.1	407	0.4	268	0.3	772	0.2
I63.09	Cerebral infarction due to thrombosis of other precerebral artery			85	0.1	320	0.3	279	0.3	711	0.2
I63.10	Cerebral infarction due to embolism of unspecified precerebral artery			272	0.3	930	0.9	905	1.0	2,166	0.6
I63.111	Cerebral infarction due to embolism of right vertebral artery			44	0.0	142	0.1	150	0.2	366	0.1
I63.112	Cerebral infarction due to embolism of left vertebral artery			38	0.0	123	0.1	104	0.1	273	0.1
I63.113	Cerebral infarction due to embolism of bilateral vertebral arteries			0	0.0	0	0.0	15	0.0	16	0.0
I63.119	Cerebral infarction due to embolism of unspecified vertebral artery			19	0.0	107	0.1	101	0.1	228	0.1
I63.12	Cerebral infarction due to embolism of basilar artery			78	0.1	251	0.2	244	0.3	634	0.2
I63.131	Cerebral infarction due to embolism of right carotid artery			141	0.1	458	0.4	398	0.4	1,047	0.3
I63.132	Cerebral infarction due to embolism of right carotid artery			153	0.1	476	0.5	335	0.4	1,027	0.3
I63.133	Cerebral infarction due to embolism of carotid artery			0	0.0	0	0.0	41	0.0	46	0.0
I63.139	Cerebral infarction due to embolism of right carotid artery			199	0.2	388	0.4	244	0.3	823	0.2
I63.19	Cerebral infarction due to embolism of other precerebral artery			64	0.1	153	0.1	122	0.1	377	0.1
I63.20	Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries			185	0.2	542	0.5	401	0.4	1,112	0.3
I63.211	Cerebral infarction due to unspecified occlusion or stenosis of right vertebral arteries			93	0.1	392	0.4	379	0.4	924	0.3

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
I63.212	Cerebral infarction due to unspecified occlusion or stenosis of left vertebral arteries			106	0.1	415	0.4	379	0.4	949	0.3
I63.213	Cerebral infarction due to unspecified occlusion or stenosis of bilateral vertebral arteries			0	0.0	0	0.0	39	0.0	43	0.0
I63.219	Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral arteries			90	0.1	333	0.3	265	0.3	714	0.2
I63.22	Cerebral infarction due to unspecified occlusion or stenosis of basilar arteries			182	0.2	612	0.6	524	0.6	1,394	0.4
I63.231	Cerebral infarction due to unspecified occlusion or stenosis of right carotid arteries			555	0.5	1,776	1.7	1,540	1.7	4,315	1.2
I63.232	Cerebral infarction due to unspecified occlusion or stenosis of left carotid arteries			545	0.5	1,699	1.6	1,005	1.1	3,623	1.0
I63.233	Cerebral infarction due to unspecified occlusion or stenosis of bilateral carotid arteries			0	0.0	1	0.0	422	0.5	452	0.1
I63.239	Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid arteries			529	0.5	1,305	1.2	779	0.8	2,589	0.7
I63.29	Cerebral infarction due to unspecified occlusion or stenosis of other precerebral arteries			77	0.1	280	0.3	244	0.3	633	0.2
I63.30	Cerebral infarction due to thrombosis of unspecified cerebral artery			1,463	1.4	3,444	3.3	2,369	2.6	6,953	2.0
I63.311	Cerebral infarction due to thrombosis of right middle cerebral artery			497	0.5	1,698	1.6	1,518	1.7	3,972	1.1
I63.312	Cerebral infarction due to thrombosis of left middle cerebral artery			522	0.5	1,802	1.7	1,549	1.7	4,144	1.2
I63.313	Cerebral infarction due to thrombosis of bilateral middle cerebral arteries			0	0.0	0	0.0	19	0.0	22	0.0
I63.319	Cerebral infarction due to thrombosis of unspecified middle cerebral artery			116	0.1	283	0.3	217	0.2	617	0.2
I63.321	Cerebral infarction due to thrombosis of right anterior cerebral artery			44	0.0	152	0.1	127	0.1	333	0.1
I63.322	Cerebral infarction due to thrombosis of left anterior cerebral artery			53	0.1	135	0.1	131	0.1	356	0.1
I63.323	Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries			0	0.0	0	0.0	10	0.0	11	0.0
I63.329	Cerebral infarction due to thrombosis of unspecified anterior cerebral artery			25	0.0	55	0.1	32	0.0	118	0.0
I63.331	Cerebral infarction due to thrombosis of right posterior cerebral artery			81	0.1	336	0.3	339	0.4	778	0.2
I63.332	Cerebral infarction due to thrombosis of left posterior cerebral artery			88	0.1	289	0.3	316	0.3	693	0.2
I63.333	Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries			0	0.0	0	0.0	17	0.0	17	0.0
I63.339	Cerebral infarction due to thrombosis of unspecified posterior cerebral artery			34	0.0	79	0.1	43	0.0	156	0.0
I63.341	Cerebral infarction due to thrombosis of right cerebellar artery			81	0.1	209	0.2	188	0.2	481	0.1

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
I63.342	Cerebral infarction due to thrombosis of left cerebellar artery			65	0.1	204	0.2	192	0.2	469	0.1
I63.343	Cerebral infarction due to thrombosis of bilateral cerebellar arteries			0	0.0	0	0.0	14	0.0	15	0.0
I63.349	Cerebral infarction due to thrombosis of unspecified cerebellar artery			54	0.1	157	0.1	95	0.1	293	0.1
I63.39	Cerebral infarction due to thrombosis of other cerebral artery			221	0.2	665	0.6	608	0.7	1,494	0.4
I63.40	Cerebral infarction due to embolism of unspecified cerebral artery			1,982	1.9	4,931	4.7	3,829	4.2	11,026	3.1
I63.411	Cerebral infarction due to embolism of right middle cerebral artery			565	0.5	2,142	2.0	2,282	2.5	5,539	1.6
I63.412	Cerebral infarction due to embolism of left middle cerebral artery			678	0.6	2,587	2.5	2,577	2.8	6,463	1.8
I63.413	Cerebral infarction due to embolism of bilateral middle cerebral arteries			0	0.0	1	0.0	94	0.1	117	0.0
I63.419	Cerebral infarction due to embolism of unspecified middle cerebral artery			124	0.1	440	0.4	309	0.3	951	0.3
I63.421	Cerebral infarction due to embolism of right anterior cerebral artery			52	0.0	210	0.2	200	0.2	504	0.1
I63.422	Cerebral infarction due to embolism of left anterior cerebral artery			66	0.1	208	0.2	185	0.2	483	0.1
I63.423	Cerebral infarction due to embolism of bilateral anterior cerebral arteries			0	0.0	0	0.0	38	0.0	41	0.0
I63.429	Cerebral infarction due to embolism of unspecified anterior cerebral artery			53	0.1	174	0.2	108	0.1	340	0.1
I63.431	Cerebral infarction due to embolism of right posterior cerebral artery			91	0.1	407	0.4	419	0.5	990	0.3
I63.432	Cerebral infarction due to embolism of left posterior cerebral artery			140	0.1	398	0.4	438	0.5	1,035	0.3
I63.433	Cerebral infarction due to embolism of bilateral posterior cerebral arteries			0	0.0	1	0.0	46	0.1	56	0.0
I63.439	Cerebral infarction due to embolism of unspecified posterior cerebral artery			58	0.1	191	0.2	153	0.2	431	0.1
I63.441	Cerebral infarction due to embolism of right cerebellar artery			111	0.1	369	0.4	325	0.4	890	0.3
I63.442	Cerebral infarction due to embolism of left cerebellar artery			78	0.1	308	0.3	223	0.2	684	0.2
I63.443	Cerebral infarction due to embolism of bilateral cerebellar arteries			0	0.0	0	0.0	67	0.1	75	0.0
I63.449	Cerebral infarction due to embolism of unspecified cerebellar artery			81	0.1	238	0.2	173	0.2	529	0.1
I63.49	Cerebral infarction due to embolism of other cerebral artery			282	0.3	932	0.9	811	0.9	2,163	0.6
I63.50	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery			9,970	9.5	17,504	16.6	10,217	11.1	36,710	10.4

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
I63.511	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery			741	0.7	2,557	2.4	2,539	2.8	6,676	1.9
I63.512	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery			846	0.8	2,924	2.8	2,731	3.0	7,359	2.1
I63.513	Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle cerebral arteries			0	0.0	0	0.0	54	0.1	62	0.0
I63.519	Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery			164	0.2	356	0.3	245	0.3	879	0.2
I63.521	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery			95	0.1	838	0.8	653	0.7	1,876	0.5
I63.522	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery			116	0.1	829	0.8	636	0.7	1,817	0.5
I63.523	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior cerebral arteries			0	0.0	0	0.0	69	0.1	86	0.0
I63.529	Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery			58	0.1	137	0.1	108	0.1	325	0.1
I63.531	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery			155	0.1	578	0.5	582	0.6	1,439	0.4
I63.532	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery			197	0.2	652	0.6	630	0.7	1,565	0.4
I63.533	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior cerebral arteries			0	0.0	1	0.0	23	0.0	31	0.0
I63.539	Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery			53	0.1	183	0.2	133	0.1	386	0.1
I63.541	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery			105	0.1	342	0.3	309	0.3	833	0.2
I63.542	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery			131	0.1	342	0.3	278	0.3	836	0.2
I63.543	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries			0	0.0	0	0.0	31	0.0	35	0.0
I63.549	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery			112	0.1	231	0.2	183	0.2	563	0.2
I63.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery			391	0.4	1,000	1.0	754	0.8	2,263	0.6
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic			91	0.1	285	0.3	267	0.3	652	0.2
I63.8	Other cerebral infarction [*note recent split to two categories]			3,171	3.0	13,481	12.8	13,826	15.0	32,832	9.3
I63.9	Cerebral infarction, unspecified			30,496	29.2	85,552	81.3	76,345	83.0	181,380	51.4
ICD-10-CM Subtotal				**41,683**	**39.9**	**105,224**	**100.0**	**91,934**	**100.0**	**215,006**	**60.9**
Total		**117,212**	**100.0**	**104,467**	**100.0**	**105,224**	**100.0**	**91,934**	**100.0**	**352,900**	**100.0**
Occlusion without mention of infarction											
ICD-9-CM											
433.00	Occlusion and stenosis of basilar artery without mention of cerebral infarction	3,223	1.2	1,856	0.9					5,103	0.8

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
433.10	Occlusion and stenosis of carotid artery without mention of cerebral infarction	227,610	84.4	144,712	66.9					336,372	50.8
433.20	Occlusion and stenosis of vertebral artery without mention of cerebral infarction	4,805	1.8	3,029	1.4					8,011	1.2
433.30	Occlusion and stenosis of multiple and bilateral precerebral arteries without mention of cerebral infarction	63,873	23.7	40,673	18.8					103,823	15.7
433.80	Occlusion and stenosis of other specified precerebral artery without mention of cerebral infarction	920	0.3	598	0.3					1,573	0.2
433.90	Occlusion and stenosis of unspecified precerebral artery without mention of cerebral infarction	1,660	0.6	873	0.4					2,591	0.4
434.00	Cerebral thrombosis without mention of cerebral infarction	3,115	1.2	1,689	0.8					4,804	0.7
434.10	Cerebral embolism without mention of cerebral infarction	2,162	0.8	1,200	0.6					3,432	0.5
434.90	Cerebral artery occlusion, unspecified without mention of cerebral infarction	8,893	3.3	5,070	2.3					14,437	2.2
437.6	Nonpyogenic thrombosis of intracranial venous sinus	447	0.2	257	0.1					710	0.1
ICD-9-CM Subtotal		**269,675**	**100.0**	**170,762**	**79.0**					**401,322**	**60.6**
ICD-10-CM											
I65*	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction			67,512	31.2	195,654	90.5	169,596	97.9	367,383	55.5
I66*	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction			2,139	1.0	6,643	3.1	5,850	3.4	15,413	2.3
I67.6	Nonpyogenic thrombosis of intracranial venous system			168	0.1	441	0.2	434	0.3	1,032	0.2
ICD-10-CM Subtotal				**69,147**	**32.0**	**199,916**	**92.4**	**173,295**	**100.0**	**376,516**	**56.9**
Total		**269,675**	**100.0**	**216,280**	**100.0**	**199,916**	**92.4**	**173,295**	**100.0**	**662,174**	**100.0**
TIA											
ICD-9-CM											
435.0	Basilar artery syndrome	2,631	2.3	1,844	2.0					4,546	1.3
435.1	Vertebral artery syndrome	2,623	2.3	1,720	1.8					4,327	1.3
435.2	Subclavian steal syndrome	1,943	1.7	1,264	1.3					3,095	0.9
435.3	Vertebrobasilar artery syndrome	3,853	3.4	3,033	3.2					6,951	2.0
435.8	Other specified transient cerebral ischemias	7,985	7.0	5,828	6.2					13,803	4.0
435.9	Unspecified transient cerebral ischemia	101,832	89.0	62,694	66.4					161,273	47.2
ICD-9-CM Subtotal		**114,422**	**100.0**	**71,789**	**76.0**					**181,774**	**53.2**
ICD-10-CM											
G45.0	Vertebro-basilar artery syndrome			2,474	2.6	9,303	10.0	8,791	11.2	19,818	5.8
G45.1	Carotid artery syndrome (hemispheric)			1,441	1.5	4,395	4.7	4,018	5.1	9,637	2.8
G45.2	Multiple and bilateral precerebral artery syndromes			110	0.1	339	0.4	313	0.4	757	0.2
G45.3	Amaurosis fugax			1,318	1.4	4,500	4.9	4,139	5.3	9,698	2.8

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
G45.4	Transient global amnesia			1,046	1.1	3,298	3.6	2,838	3.6	6,928	2.0
G45.8	Other transient cerebral ischemic attacks and related syndromes			3,711	3.9	11,776	12.7	10,243	13.0	25,406	7.4
G45.9	Transient cerebral ischemic attack, unspecified			22,699	24.0	68,076	73.5	55,926	71.1	140,523	41.2
G46.0	Middle cerebral artery syndrome			130	0.1	496	0.5	458	0.6	1,163	0.3
G46.1	Anterior cerebral artery syndrome			40	0.0	106	0.1	112	0.1	259	0.1
G46.2	Posterior cerebral artery syndrome			41	0.0	120	0.1	121	0.2	277	0.1
G46.3	Brain stem stroke syndrome			251	0.3	774	0.8	686	0.9	1,713	0.5
G46.4	Cerebellar stroke syndrome			654	0.7	1,833	2.0	1,590	2.0	4,113	1.2
G46.5	Pure motor lacunar syndrome			48	0.1	130	0.1	180	0.2	347	0.1
G46.6	Pure sensory lacunar syndrome			31	0.0	65	0.1	61	0.1	149	0.0
G46.7	Other lacunar syndromes			154	0.2	527	0.6	489	0.6	1,128	0.3
G46.8	Other vascular syndromes of brain in cerebrovascular diseases			116	0.1	330	0.4	205	0.3	666	0.2
ICD-10-CM Subtotal				**30,808**	**32.6**	**92,579**	**100.0**	**78,624**	**100.0**	**190,322**	**55.8**
Total		**114,422**	**100.0**	**94,400**	**100.0**	**92,579**	**100.0**	**78,624**	**100.0**	**341,360**	**100.0**
Hemorrhagic Stroke											
ICD-9-CM											
432.1	Subdural hemorrhage	10,716	63.6	6,804	42.0					18,310	25.3
432.9	Unspecified intracranial hemorrhage	8,192	48.7	4,951	30.5					14,687	20.3
ICD-9-CM Subtotal		**16,838**	**100.0**	**10,580**	**65.3**					**29,179**	**40.3**
ICD-10-CM											
I61.0	Nontraumatic intracerebral hemorrhage in hemisphere, subcortical			398	2.5	1,157	5.9	1,176	6.9	3,242	4.5
I61.1	Nontraumatic intracerebral hemorrhage in hemisphere, cortical			459	2.8	1,455	7.5	1,510	8.8	4,142	5.7
I61.2	Nontraumatic intracerebral hemorrhage in hemisphere, unspecified			253	1.6	637	3.3	528	3.1	1,703	2.4
I61.3	Nontraumatic intracerebral hemorrhage in brain stem			137	0.8	378	1.9	412	2.4	1,149	1.6
I61.4	Nontraumatic intracerebral hemorrhage in cerebellum			238	1.5	655	3.4	575	3.4	1,792	2.5
I61.5	Nontraumatic intracerebral hemorrhage, intraventricular			600	3.7	1,799	9.2	1,587	9.3	5,528	7.6
I61.6	Nontraumatic intracerebral hemorrhage, multiple localized			79	0.5	239	1.2	204	1.2	725	1.0
I61.8	Other nontraumatic intracerebral hemorrhage			700	4.3	2,198	11.3	2,278	13.3	6,494	9.0
I61.9	Nontraumatic intracerebral hemorrhage, unspecified			3,017	18.6	7,739	39.6	6,766	39.6	20,089	27.8
I62.00	Nontraumatic subdural hemorrhage, unspecified			2,783	17.2	7,336	37.6	6,395	37.5	18,044	24.9
I62.01	Nontraumatic acute subdural hemorrhage			606	3.7	1,768	9.1	1,449	8.5	4,711	6.5
I62.02	Nontraumatic subacute subdural hemorrhage			254	1.6	770	3.9	605	3.5	1,898	2.6
I62.03	Nontraumatic chronic subdural hemorrhage			470	2.9	1,260	6.5	1,198	7.0	3,281	4.5
I62.9	Nontraumatic intracranial hemorrhage, unspecified			2,471	15.2	6,504	33.3	5,366	31.4	17,288	23.9

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
ICD-10-CM Subtotal				**7,593**	**46.9**	**19,529**	**100.0**	**17,072**	**100.0**	**47,466**	**65.6**
Total		**16,838**	**100.0**	**16,207**	**100.0**	**19,529**	**100.0**	**17,072**	**100.0**	**72,348**	**100.0**

* Codes are non-billable; subsidiary codes were included in a single query.

B5. Arterial Embolism and Thrombosis

Code-specific query results for arterial thrombosis and embolism are presented in **Table B.5.1**. Codes for arterial embolism and thrombosis of the lower extremities (ICD-9-CM code 444.22; ICD-10-CM code I74.3) appear to be the most frequently reported codes.

Table B.5.1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in the arterial embolism and thrombosis algorithm (2014–2017).

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
ICD-9-CM											
444.01	Saddle embolus of abdominal aorta	104	0.5	66	0.4					174	0.3
444.09	Other arterial embolism and thrombosis of abdominal aorta	1,565	7.6	981	5.7					2,558	4.0
444.1	Embolism and thrombosis of thoracic aorta	605	2.9	386	2.3					1,018	1.6
444.21	Arterial embolism and thrombosis of upper extremity	2,172	10.6	1,258	7.4					3,500	5.5
444.22	Arterial embolism and thrombosis of lower extremity	11,237	54.6	7,142	41.8					18,442	28.8
444.81	Embolism and thrombosis of iliac artery	2,422	11.8	1,492	8.7					4,023	6.3
444.89	Embolism and thrombosis of other specified artery	1,504	7.3	932	5.5					2,513	3.9
444.9	Embolism and thrombosis of unspecified artery	4,172	20.3	2,524	14.8					6,775	10.6
ICD-9-CM Subtotal		**20,574**	**100.0**	**12,864**	**75.3**					**33,263**	**51.9**
ICD-10-CM											
I74.01	Saddle embolus of abdominal aorta			19	0.1	35	0.2	35	0.3	100	0.2
I74.09	Other arterial embolism and thrombosis of abdominal aorta			319	1.9	1,110	6.8	1,125	8.1	2,554	4.0
I74.10	Embolism and thrombosis of unspecified parts of aorta			107	0.6	333	2.0	401	2.9	887	1.4
I74.11	Embolism and thrombosis of thoracic aorta			86	0.5	215	1.3	174	1.2	508	0.8
I74.19	Embolism and thrombosis of other parts of aorta			20	0.1	97	0.6	76	0.5	217	0.3
I74.2	Embolism and thrombosis of arteries of the upper extremities			468	2.7	1,417	8.7	1,246	8.9	3,250	5.1
I74.3	Embolism and thrombosis of arteries of the lower extremities			2,242	13.1	6,713	41.3	5,796	41.5	14,918	23.3
I74.4	Embolism and thrombosis of arteries of extremities, unspecified			188	1.1	523	3.2	365	2.6	1,131	1.8
I74.5	Embolism and thrombosis of iliac artery			687	4.0	2,298	14.1	2,047	14.6	5,126	8.0
I74.8	Embolism and thrombosis of other arteries			513	3.0	1,732	10.6	1,437	10.3	3,925	6.1
I74.9	Embolism and thrombosis of unspecified artery			1,727	10.1	4,409	27.1	3,538	25.3	9,303	14.5
ICD-10-CM Subtotal				**5,677**	**33.2**	**16,265**	**100.0**	**13,973**	**100.0**	**35,231**	**55.0**
Total		**20,574**	**100.00**	**17,075**	**100.0**	**16,265**	**100.0**	**13,973**	**100.0**	**64,046**	**100.0**

Appendix C. Individual Code Counts for Excluded Codes

To test the impact of the exclusions proposed for each of the thromboembolic events (TEE) algorithms, authors ran code-specific queries on a large patient dataset to assess the number of patients with each diagnosis code proposed for exclusion. This was done in order to gain an understanding of how many patients will be excluded as a result of each code being omitted from the algorithm; however, it should be noted that patients with excluded codes may be included in the analysis if they *also* have a code from one of the algorithms detailed in **Appendix A**. Researchers used the MarketScan Research Databases, accessed via the Treatment Pathways platform, querying data for January 1, 2014–December 31, 2017. In 2014, there were 28,407,959 patients enrolled for the entire year; 22,117235 in 2015; 21,616,367 in 2016; 19,802,253 in 2017; and 41,172,696 for at least one calendar year in 2014–2017. Results for each outcome of interest are presented in the subsections below. The most frequently reported codes are highlighted for emphasis.

The transition from International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) to the Tenth Revision (ICD-10-CM) occurred October 1, 2015; no ICD-9-CM codes were queried after this date, and no ICD-10-CM codes were queried before this date. The coding standard-specific subtotal rows were calculated by querying the all codes for a particular coding standard together; the “Total (Count)” column was calculated by querying the individual code in a cohort of patients that were enrolled for at least one calendar year between 2014 and 2017.

Subtotal rows and Total columns may be smaller than the sum of individual cells, because patients with multiple codes in a single year and with more than one of the same diagnosis codes in different years will only be counted once in these rows and columns. As a result, the sum of all “% of Total” cells in a single column may exceed 100%. However, the “Total” column could also be larger than the sum of individual years, as a result of situations where an individual is only enrolled for part of the year that they experience a TEE but is then continuously enrolled for a separate year. For example, an individual could be continuously enrolled for a few days, weeks, or months in 2016 and experience a TEE, then be continuously enrolled for all of 2017. This event would not be captured in the column for the 2016 (as the individual would be excluded from that cohort) but would be captured in the “Total” column.

C1. Pulmonary Embolism

Code-specific query results for codes excluded from the PE algorithm are presented in **Table C.1.1**. Chronic pulmonary embolism appeared to be the most frequently reported code of those excluded.

Table C.1.1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes excluded from the pulmonary embolism algorithm (2014–2017).

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
ICD-9-CM											
415.0	Acute cor pulmonale	2,180	39.4	1,332	25.4					3,757	18.7
416.2	Chronic pulmonary embolism	3,422	61.9	2,233	42.5					5,551	27.7
ICD-10-CM											
I27.82	Chronic pulmonary embolism			2,313	44.0	5,787	100.0	5,170	100.0	12,122	60.4
Total		**5,530**	**100.0**	**5,251**	**100.0**	**5,787**	**100.0**	**5,170**	**100.0**	**20,056**	**100.0**

C2. Deep Vein Thrombosis

Code-specific query results for codes excluded from the DVT algorithm are presented in **Table C.2.1**. It appears that codes for phlebitis and thrombophlebitis (ICD-9-CM code 451; ICD-10-CM code I80) are the most frequently reported codes.

Table C.2.1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes excluded from the DVT algorithm (2014–2017).

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
ICD-9-CM											
451*	Phlebitis and thrombophlebitis	69,840	84.3	39,939	65.1					107,646	51.7
453.1	Thrombophlebitis migrans	366	0.4	188	0.3					569	0.3
453.50	Chronic venous embolism and thrombosis of unspecified deep vessels of lower extremity	6,183	7.5	4,168	6.8					10,024	4.8
453.51	Chronic venous embolism and thrombosis of deep vessels of proximal lower extremity	5,370	6.5	3,516	5.7					8,874	4.3
453.52	Chronic venous embolism and thrombosis of deep vessels of distal lower extremity	3,971	4.8	2,564	4.2					6,518	3.1
453.71	Chronic venous embolism and thrombosis of superficial veins of upper extremity	558	0.7	346	0.6					998	0.5
453.72	Chronic venous embolism and thrombosis of deep veins of upper extremity	1,043	1.3	590	1.0					1,665	0.8
453.73	Chronic venous embolism and thrombosis of upper extremity, unspecified	260	0.3	137	0.2					408	0.2
453.74	Chronic venous embolism and thrombosis of axillary veins	246	0.3	157	0.3					411	0.2
453.75	Chronic venous embolism and thrombosis of subclavian veins	428	0.5	251	0.4					704	0.3
453.76	Chronic venous embolism and thrombosis of internal jugular veins	424	0.5	263	0.4					724	0.3
453.77	Chronic venous embolism and thrombosis of other thoracic veins	192	0.2	100	0.2					315	0.2
453.79	Chronic venous embolism and thrombosis of other specified veins	874	1.1	538	0.9					1,440	0.7
ICD-9-CM Subtotal		**82,848**	**100.0**	**48,835**	**79.6**					**127,812**	**61.3**
ICD-10-CM											
I80*	Phlebitis and thrombophlebitis			14,085	23.0	38,707	85.6	30,715	85.3	80,680	38.7

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
I82.1	Thrombophlebitis migrans.			112	0.2	266	0.6	176	0.5	570	0.3
I82.211	Chronic embolism and thrombosis of superior vena cava			44	0.1	123	0.3	103	0.3	275	0.1
I82.221	Chronic embolism and thrombosis of inferior vena cava			98	0.2	279	0.6	244	0.7	618	0.3
I82.291	Chronic embolism and thrombosis of other thoracic veins			44	0.1	137	0.3	110	0.3	290	0.1
I82.519	Chronic embolism and thrombosis of unspecified femoral vein			75	0.1	237	0.5	224	0.6	503	0.2
I82.529	Chronic embolism and thrombosis of unspecified iliac vein			52	0.1	150	0.3	89	0.2	283	0.1
I82.539	Chronic embolism and thrombosis of unspecified popliteal vein			22	0.0	74	0.2	70	0.2	165	0.1
I82.5Y9	Chronic embolism and thrombosis of unspecified deep veins of unspecified proximal lower extremity			141	0.2	381	0.8	359	1.0	801	0.4
I82.711	Chronic embolism and thrombosis of superficial veins of right upper extremity			49	0.1	170	0.4	191	0.5	465	0.2
I82.712	Chronic embolism and thrombosis of superficial veins of left upper extremity			61	0.1	214	0.5	170	0.5	508	0.2
I82.713	Chronic embolism and thrombosis of superficial veins of upper extremity, bilateral			10	0.0	34	0.1	31	0.1	88	0.0
I82.719	Chronic embolism and thrombosis of superficial veins of unspecified upper extremity			19	0.0	35	0.1	31	0.1	87	0.0
I82.891	Chronic embolism and thrombosis of other specified veins			229	0.4	604	1.3	577	1.6	1,401	0.7
I82.91	Chronic embolism and thrombosis of unspecified vein			3,185	5.2	5,396	11.9	3,764	10.5	11,108	5.3
ICD-10-CM Subtotal				**17,847**	**29.1**	**45,224**	**100.0**	**36,003**	**100.0**	**94,626**	**45.4**
Total		**82,848**	**100.0**	**61,318**	**100.0**	**45,224**	**100.0**	**36,003**	**100.0**	**208,379**	**100.0**

Abbreviation: DVT, deep vein thrombosis.

C3. Acute Myocardial Infarction

Code-specific query results for codes excluded from the acute myocardial infarction (AMI) algorithm are presented in **Table C.3.1**. Excluded codes were categorized as those that should be excluded from the main analysis but had potential value for identifying a high-risk group for analysis and those that should be ignored altogether. The codes for old myocardial infarction (ICD-9-CM code 412; ICD-10-CM code I25.2) and chronic ischemic heart diseases (ICD-9-CM code 414) appeared to be the frequently reported codes.

Table C.3.1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes excluded from the AMI algorithm (2014–2017).

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
Exclude from main analysis (can analyze as high-risk group)											
ICD-9-CM											
412	Old myocardial infarction	115,851	12.8	76,940	12.0					177,362	14.1
414*	Chronic ischemic heart diseases	889,470	98.1	618,717	96.7					1,159,797	92.5
ICD-10-CM											
I25.2	Old myocardial infarction			34,993	5.5	101,349	99.2	88,373	99.1	192,370	15.3
Ignore											
ICD-9-CM											
410.02	Acute myocardial infarction of anterolateral wall, subsequent episode of care	631	0.1	406	0.1					1,048	0.1
410.12	Acute myocardial infarction of other anterior wall, subsequent episode of care	1,909	0.2	1,034	0.2					2,921	0.2
410.22	Acute myocardial infarction of inferolateral wall, subsequent episode of care	378	0.0	209	0.0					581	0.0
410.32	Acute myocardial infarction of inferoposterior wall, subsequent episode of care	250	0.0	152	0.0					388	0.0
410.42	Acute myocardial infarction of other inferior wall, subsequent episode of care	2,001	0.2	1,113	0.2					3,003	0.2
410.52	Acute myocardial infarction of other lateral wall, subsequent episode of care	209	0.0	112	0.0					308	0.0
410.62	True posterior wall infarction, subsequent episode of care	93	0.0	45	0.0					145	0.0
410.72	Subendocardial infarction, subsequent episode of care	5,266	0.6	3,584	0.6					9,264	0.7
410.82	Acute myocardial infarction of other specified sites, subsequent episode of care	387	0.0	243	0.0					650	0.1
410.92	Acute myocardial infarction of unspecified site, subsequent episode of care	4,613	0.5	2,784	0.4					7,554	0.6

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
ICD-9-CM Subtotal		**14,321**	**1.6**	**8,766**	**1.4**					**23,444**	**1.9**
ICD-10-CM											
I23*	Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28-day period)			416	0.1	1,246	1.2	1,222	1.4	3,124	0.2
Total		**906,539**	**100.0**	**639,759**	**100.0**	**102,163**	**100.0**	**89,177**	**100.0**	**1,253,986**	**100.0**

Abbreviation: AMI, acute myocardial infarction.

C4. Stroke

Code-specific query results for codes excluded from the arterial embolism and thrombosis algorithm are presented in **Table C.5.1**. The codes associated with embolism due to vascular prosthetic devices, implants, and grafts (ICD-10-CM code T82.818) and thrombosis due to vascular prosthetic devices, implants and grafts (ICD-10-CM code T82.868) appear to be the most frequently reported codes.

Table C.4.1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes excluded from the stroke algorithm (2014–2017).

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
ICD-9-CM											
046.3	Progressive multifocal leukoencephalopathy	139	0.1	76	0.1					212	0.0
348.39	Other encephalopathy	9,043	5.4	5,702	4.4					15,603	3.6
430	Subarachnoid hemorrhage	8,734	5.2	5,572	4.3					14,853	3.5
432.0	Nontraumatic extradural hemorrhage	788	0.5	478	0.4					1,374	0.3
436	Acute, but ill-defined, cerebrovascular disease	73,611	43.7	43,880	33.9					161,273	37.5
437.0	Cerebral atherosclerosis	15,696	9.3	10,253	7.9					26,199	6.1
437.1	Other generalized ischemic cerebrovascular disease	42,451	25.2	23,355	18.0					70,958	16.5
437.2	Hypertensive encephalopathy	2,589	1.5	1,705	1.3					4,565	1.1
437.3	Cerebral aneurysm, nonruptured	15,875	9.4	10,772	8.3					24,318	5.7
437.4	Cerebral arteritis	600	0.4	337	0.3					972	0.2
437.5	Moyamoya disease	554	0.3	425	0.3					795	0.2
437.9	Unspecified cerebrovascular disease	23,830	14.1	15,152	11.7					38,035	8.8
443.29	Dissection of other artery	956	0.6	678	0.5					1,676	0.4
997.02	Iatrogenic cerebrovascular infarction or hemorrhage	661	0.4	337	0.3					1,084	0.3
ICD-9-CM Subtotal		**168,504**	**100.0**	**105,455**	**81.4**					**264,192**	**61.4**
ICD-10-CM											
I60*	Nontraumatic subarachnoid hemorrhage			2,686	2.1	7,239	7.1	6,209	7.4	17,348	4.0
I62.1	Nontraumatic extradural hemorrhage			160	0.1	337	0.3	217	0.3	797	0.2
I67.0	Dissection of cerebral arteries, nonruptured			53	0.0	184	0.2	129	0.2	368	0.1
I67.1	Cerebral aneurysm, nonruptured			5,091	3.9	13,909	13.7	12,771	15.3	26,652	6.2
I67.2	Cerebral atherosclerosis			4,342	3.4	13,646	13.5	11,538	13.8	29,547	6.9
I67.3	Progressive vascular leukoencephalopathy			35	0.0	146	0.1	135	0.2	301	0.1
I67.4	Hypertensive encephalopathy			591	0.5	1,891	1.9	1,572	1.9	4,434	1.0
I67.5	Moyamoya disease			253	0.2	529	0.5	503	0.6	934	0.2

Code	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
I67.7	Cerebral arteritis, not elsewhere classified			158	0.1	419	0.4	351	0.4	907	0.2
I67.8*	Other specified cerebrovascular diseases			21,759	16.8	56,970	56.2	45,448	54.3	124,622	29.0
I67.9	Cerebrovascular disease, unspecified			6,195	4.8	17,580	17.3	14,051	16.8	35,987	8.4
I97.811	Intraoperative cerebrovascular infarction during other surgery			11	0.0	44	0.0	26	0.0	88	0.0
I97.821	Postprocedural cerebrovascular infarction following other surgery			63	0.0	157	0.2	133	0.2	430	0.1
ICD-10-CM Subtotal				**38,363**	**29.6**	**101,345**	**100.0**	**83,688**	**100.0**	**212,411**	**49.4**
Total		**168,504**	**100.0**	**129,603**	**100.0**	**101,345**	**100.0**	**83,688**	**100.0**	**430,226**	**100.0**

* Codes are non-billable; subsidiary codes were included in a single query.

C5. Arterial Embolism and Thrombosis

Code-specific query results for codes excluded from the arterial embolism and thrombosis algorithm are presented in **Table C.5.1**. The codes associated with embolism due to vascular prosthetic devices, implants, and grafts (ICD-10-CM code T82.818) and thrombosis due to vascular prosthetic devices, implants and grafts (ICD-10-CM code T82.868) appear to be the most frequently reported codes.

Table C.5.1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes* excluded from the arterial embolism and thrombosis algorithm (2014–2017).

Code*	Code Description	Calendar Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
ICD-10-CM											
T82.817	Embolism due to cardiac prosthetic devices, implants and grafts			24	1.3	76	1.3	34	0.6	146	1.1
T82.818	Embolism due to vascular prosthetic devices, implants and grafts			274	14.5	651	11.1	517	9.7	1,576	11.8
T82.867	Thrombosis due to cardiac prosthetic devices, implants and grafts			108	5.7	440	7.5	399	7.5	1,054	7.9
T82.868	Thrombosis due to vascular prosthetic devices, implants and grafts			1,485	78.4	4,705	80.4	4,356	81.8	10,760	80.3
T83.81	Embolism due to genitourinary prosthetic devices, implants and grafts			9	0.5	25	0.4	9	0.2	46	0.3
T83.86	Thrombosis due to genitourinary prosthetic devices, implants and grafts			27	1.4	63	1.1	27	0.5	128	1.0
T84.81	Embolism due to internal orthopedic prosthetic devices, implants and grafts			53	2.8	132	2.3	68	1.3	257	1.9
T84.86	Thrombosis due to internal orthopedic prosthetic devices, implants and grafts			7	0.4	39	0.7	36	0.7	88	0.7
T85.810	Embolism due to nervous system prosthetic devices, implants and grafts			0	0.0	0	0.0	1	0.0	1	0.0
T85.818	Embolism due to other internal prosthetic devices, implants and grafts			0	0.0	0	0.0	12	0.2	14	0.1
T85.860	Thrombosis due to nervous system prosthetic devices, implants and grafts			0	0.0	0	0.0	2	0.0	2	0.0
T85.868	Thrombosis due to other internal prosthetic devices, implants and grafts			0	0.0	2	0.0	92	1.7	101	0.8
Total				**1,895**	**100.0**	**5,849**	**100.0**	**5,328**	**100.0**	**13,399**	**100.0**

* All listed codes are non-billable; subsidiary codes for each group were included in a single query.

Appendix D. Supplementary Analyses

D1. Deep Vein Thrombosis

Table D.1.1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in "Lower DVT" algorithm (January 1, 2014–December 31, 2017).

Code	Calendar Year			
	2014	2015	2016	2017
ICD-9-CM	108,135	72,704		
ICD-10-CM		36,493	81,913	70,587
ICD-9-CM OR ICD-10-CM	108,135	89,578	81,913	70,587
MarketScan Research Databases enrollment	28,407,959	22,117,235	21,616,367	19,802,253
Proportion of patients with lower DVT per 1,000 enrolled population	3.81	4.05	3.79	3.56

Abbreviation: DVT, deep vein thrombosis.

Table D.1.2. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in "Other DVT" algorithm (January 1, 2014–December 31, 2017).

Code	Calendar Year			
	2014	2015	2016	2017
ICD-9-CM	47,826	28,568		
ICD-10-CM		9,305	24,775	22,429
ICD-9-CM OR ICD-10-CM	47,826	35,177	24,775	22,429
MarketScan Research Databases enrollment	28,407,959	22,117,235	21,616,367	19,802,253
Proportion of patients with lower DVT per 1,000 enrolled population	1.68	1.59	1.15	1.13

Abbreviation: DVT, deep vein thrombosis.

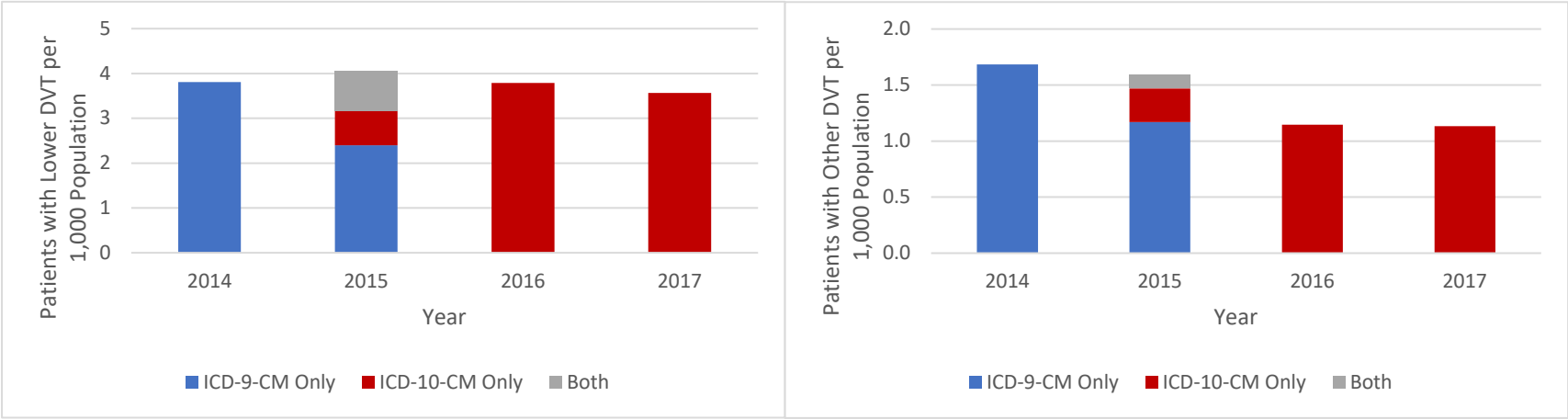

Figure D.1.1. Proportion of patients with Lower DVT (left) and Other DVT[a] (right) per 1,000 enrolled, by year (2014–2017).

Abbreviation: DVT, deep vein thrombosis.

Note: In 2015, a patient could receive both an ICD-9-CM and an ICD-10-CM diagnosis, in the January–September and October–December timeframe, respectively.

[a] Results suggest that transition to ICD-10-CM may have resulted in reduced reporting of "Other DVT"

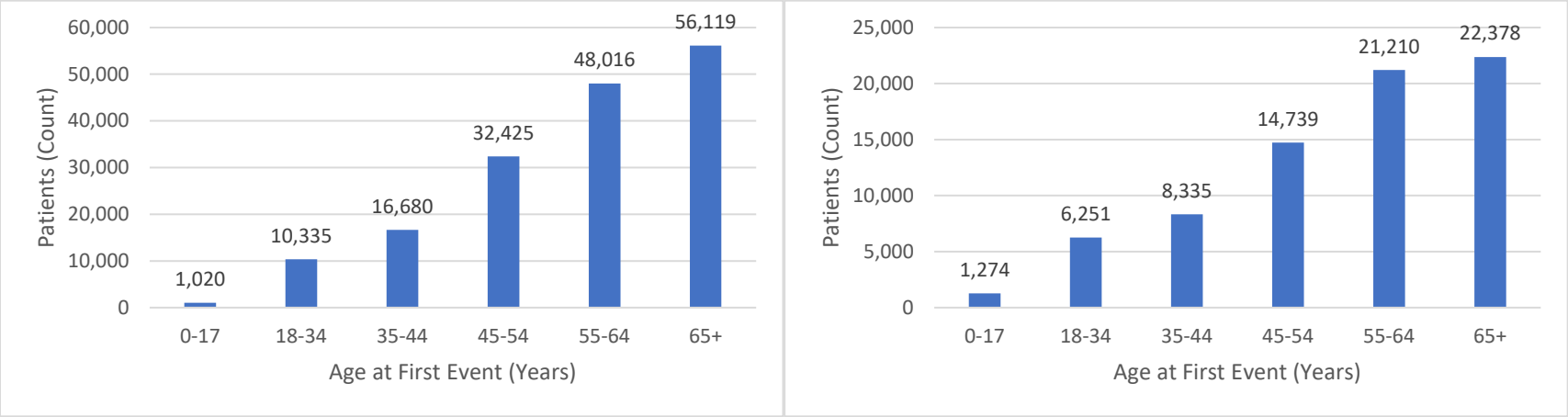

Figure D.1.2. Patients with at least one diagnosis for Lower DVT (left) and Other DVT (right) defined by ICD-9-CM codes, January 1, 2014–September 30, 2015, stratified by age.

Abbreviation: DVT, deep vein thrombosis.

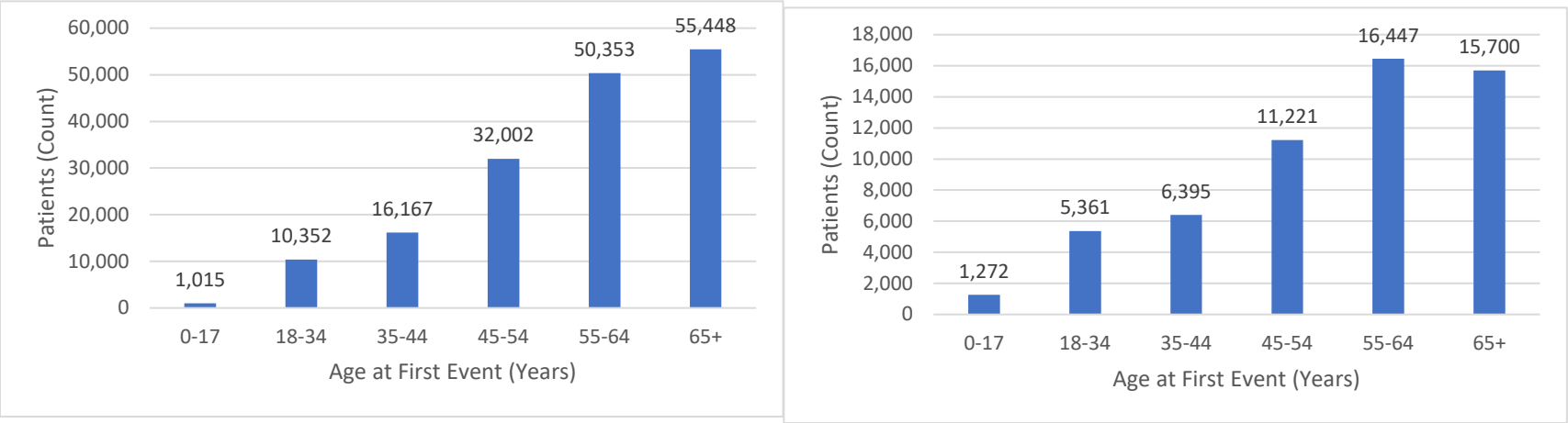

Figure D.1.3. Patients with at least one diagnosis for Lower DVT (left) and Other DVT (right) defined by ICD-10-CM codes, October 1, 2015–December 31, 2017, stratified by age.

Abbreviation: DVT, deep vein thrombosis.

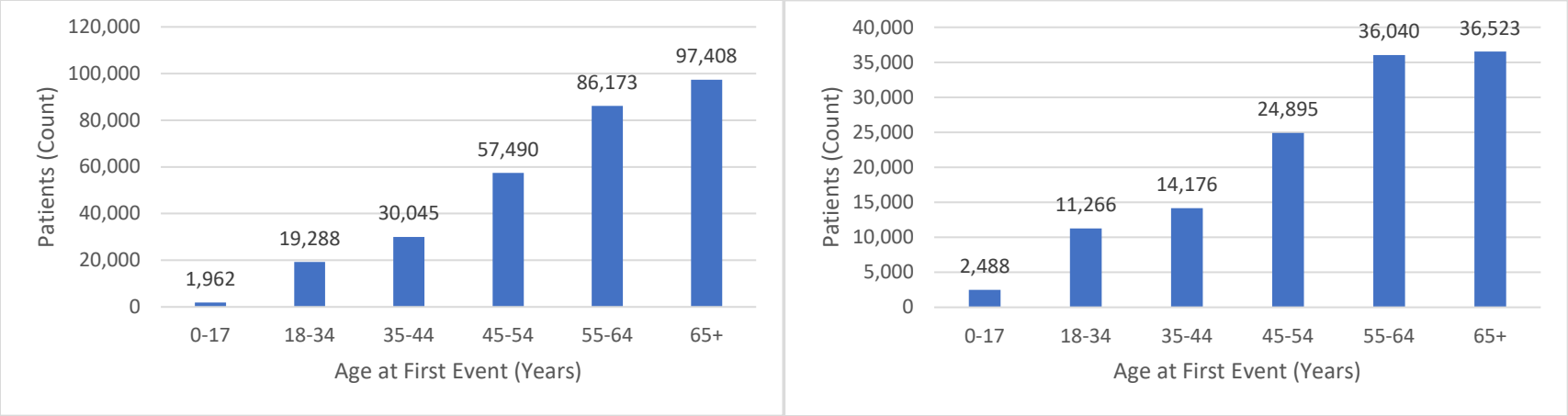

Figure D.1.4. Patients with at least one diagnosis for Lower DVT (left) and Other DVT (right) defined by ICD-9-CM or ICD-10-CM codes, January 1, 2014–December 31, 2017, stratified by age.

Abbreviation: DVT, deep vein thrombosis.

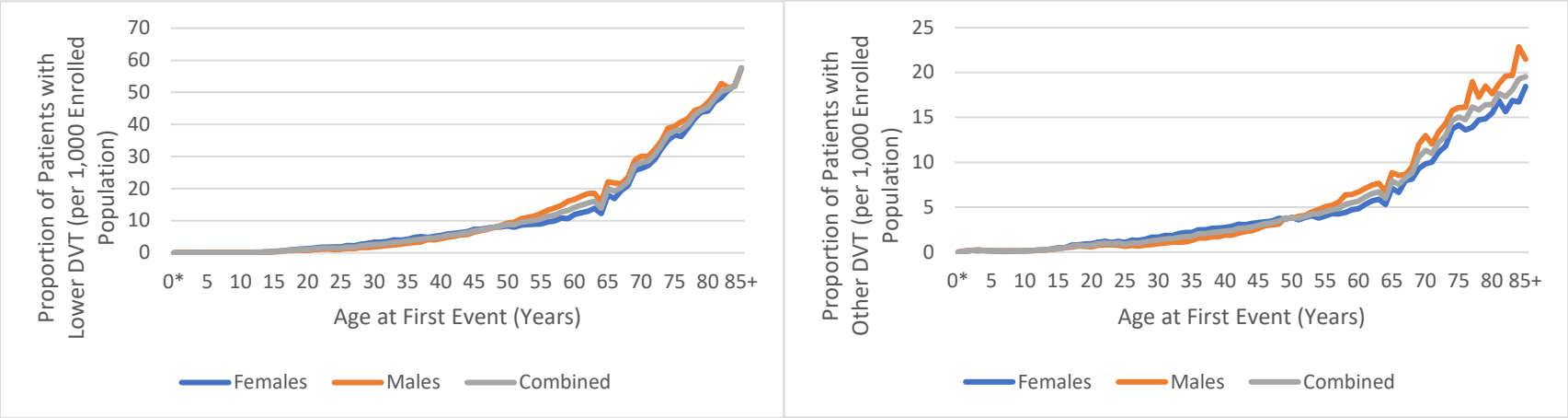

Figure D.1.5. Proportion of patients with at least one diagnosis (ICD-9-CM or ICD-10-CM) for Lower DVT (left) and Other DVT (right) per 1,000 population, by gender (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), proportion of those under 1 experiencing DVT has been excluded from the chart and marked as zero.

Abbreviation: DVT, deep vein thrombosis.

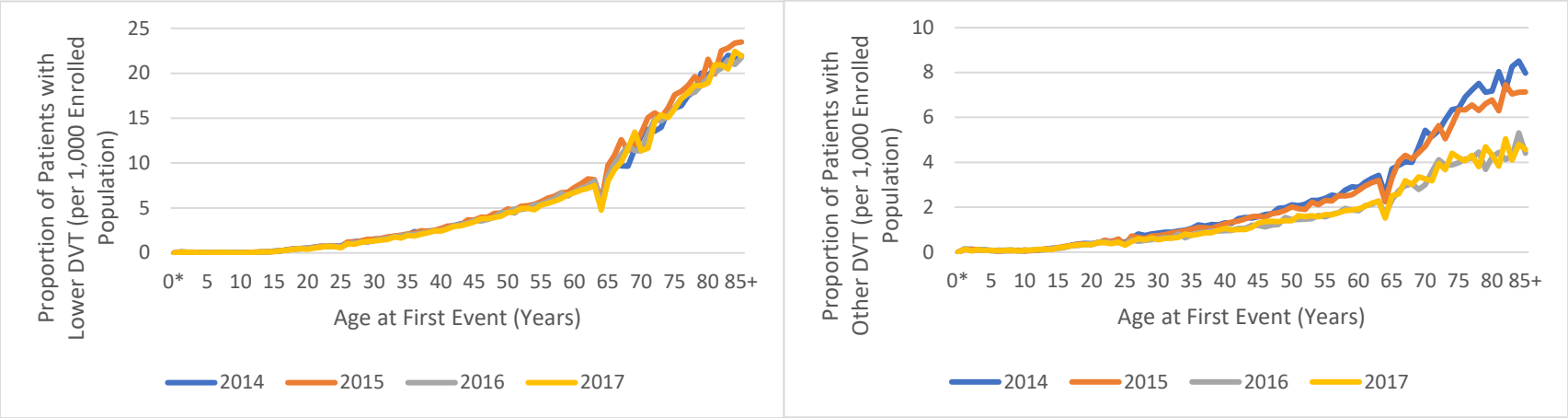

Figure D.1.6. Proportion of patients with at least one diagnosis (ICD-9-CM or ICD-10-CM) for Lower DVT (left) and Other DVT[a] (right) per 1,000 population, by calendar year (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), proportion of those under 1 experiencing DVT has been excluded from the chart and marked as zero.

Abbreviation: DVT, deep vein thrombosis.

[a] Results suggest that frequency of reporting for "Other DVT' decreased in years following transition to ICD-10-CM.

Table D.1.3 Counts and proportions of patients experiencing Lower DVT, defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2017).

Description	Calendar Year			
	2014	**2015**	**2016**	**2017**
January–June patient count	72,439	60,988	55,997	47,876
July–December patient count	75,728	61,142	50,842	46,732
January–June enrollment	31,110,014	24,094,695	23,531,649	21,656,153
July–December enrollment	30,867,380	23,759,879	23,759,879	21,105,240
January–June proportion (per 1,000 enrolled)	**2.33**	**2.53**	**2.38**	**2.21**
July–December proportion (per 1,000 enrolled)	**2.45**	**2.57**	**2.14**	**2.21**

Abbreviation: DVT, deep vein thrombosis.

Table D.1.4 Counts and proportions of patients experiencing Other DVT, defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2017).

Description	Calendar Year			
	2014	**2015**	**2016**	**2017**
January–June patient count	30,871	23,491	15,827	14,499
July–December patient count	30,779	36,305	15,087	14,390
January–June enrollment	31,110,014	24,094,695	23,531,649	21,656,153
July–December enrollment	30,867,380	23,759,879	23,759,879	21,105,240
January–June proportion (per 1,000 enrolled)	**0.99**	**0.97**	**0.67**	**0.67**
July–December proportion (per 1,000 enrolled)	**1.00**	**1.53**	**0.63**	**0.68**

Abbreviation: DVT, deep vein thrombosis.

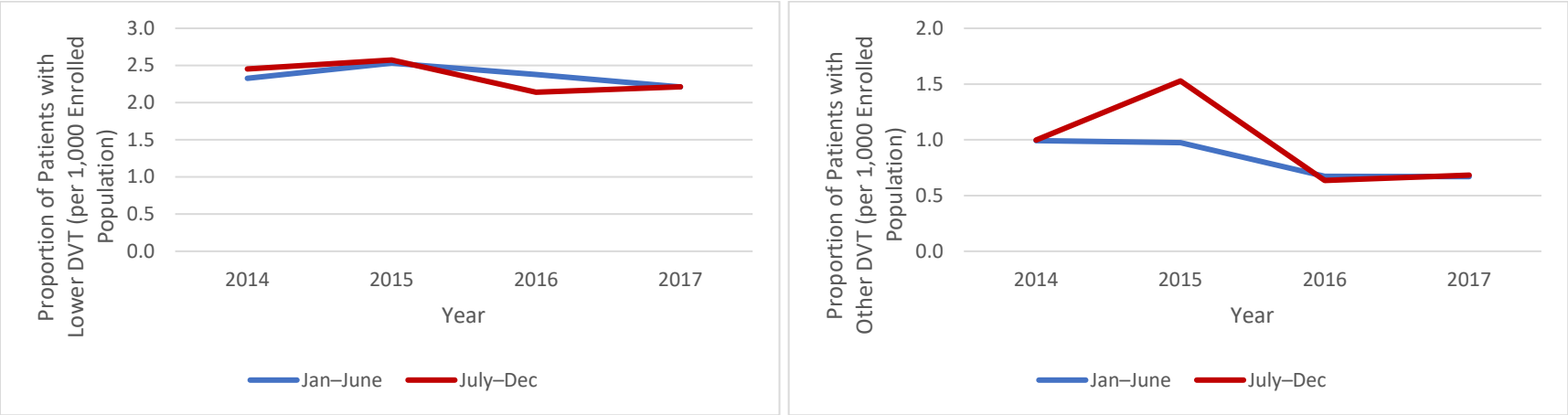

Figure D.1.7. Proportion of patients with at least one diagnosis (ICD-9-CM or ICD-10-CM) for Lower DVT (left) and Other DVT (right), stratified by time of year (2014–2017).

Abbreviation: DVT, deep vein thrombosis.

D2. Stroke

Table D.2.1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in "Thrombosis and Infarction" algorithm (January 1, 2014–December 31, 2017).

Code	Calendar Year			
	2014	2015	2016	2017
ICD-9-CM	117,212	81,287		
ICD-10-CM		41,683	105,224	91,934
ICD-9-CM OR ICD-10-CM	117,212	104,467	105,224	91,934
MarketScan Research Databases enrollment	28,407,959	22,117,235	21,616,367	19,802,253
Proportion of patients with infarction or thrombosis per 1,000 enrolled population	4.13	4.72	4.87	4.64

Table D.2.2. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in "Occlusion Without Mention of Infarction" algorithm (January 1, 2014–December 31, 2017).

Code	Calendar Year			
	2014	2015	2016	2017
ICD-9-CM	269,675	170,762		
ICD-10-CM		69,147	199,916	173,295
ICD-9-CM OR ICD-10-CM	269,675	216,280	199,916	173,295
MarketScan Research Databases enrollment	28,407,959	22,117,235	21,616,367	19,802,253
Proportion of patients with occlusion w/o mention of infarction per 1,000 enrolled population	9.49	9.78	9.25	8.75

Table D.2.3. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in "TIA" algorithm (January 1, 2014–December 31, 2017).

Code	Calendar Year			
	2014	2015	2016	2017
ICD-9-CM	114,422	71,789		
ICD-10-CM		30,808	92,578	78,624
ICD-9-CM OR ICD-10-CM	114,422	94,400	92,578	78,624
MarketScan Research Databases enrollment	28,407,959	22,117,235	21,616,367	19,802,253
Proportion of patients with TIA per 1,000 enrolled population	4.03	4.27	4.28	3.97

Abbreviation: TIA, transient ischemic attacks.

Table D.2.4. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in "Hemorrhagic Stroke" algorithm (January 1, 2014–December 31, 2017).

Code	Calendar Year			
	2014	2015	2016	2017
ICD-9-CM	16,838	10,580		
ICD-10-CM		7,593	19,529	17,072
ICD-9-CM OR ICD-10-CM	16,838	16,207	19,529	17,072
MarketScan Research Databases enrollment	28,407,959	22,117,235	21,616,367	19,802,253
Proportion of patients with hemorrhagic stroke per 1,000 enrolled population	0.59	0.73	0.90	0.86

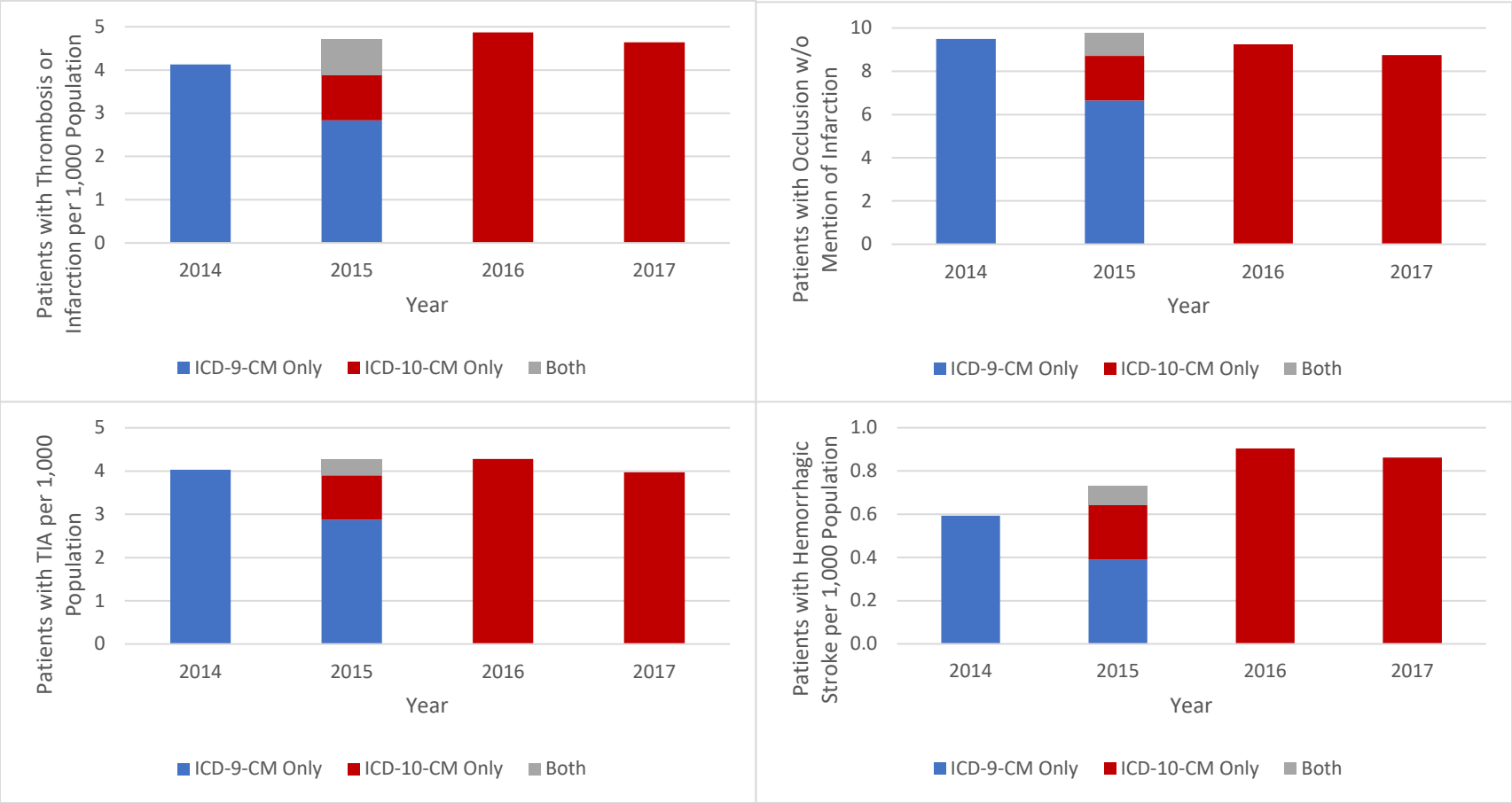

Figure D.2.1. Proportion of patients with stroke with thrombosis or infarction (top left), occlusion without mention of infarction (top right), TIA (bottom left) and hemorrhagic stroke[a] (bottom right) per 1,000 enrolled, by year (2014–2017).

Abbreviation: TIA, transient ischemic attacks.

Note: In 2015, a patient could receive both an ICD-9-CM and an ICD-10-CM diagnosis, in the January–September and October–December timeframe, respectively.

[a] Results suggest that the frequency of reporting for hemorrhagic stroke increased following the transition to ICD-10-CM.

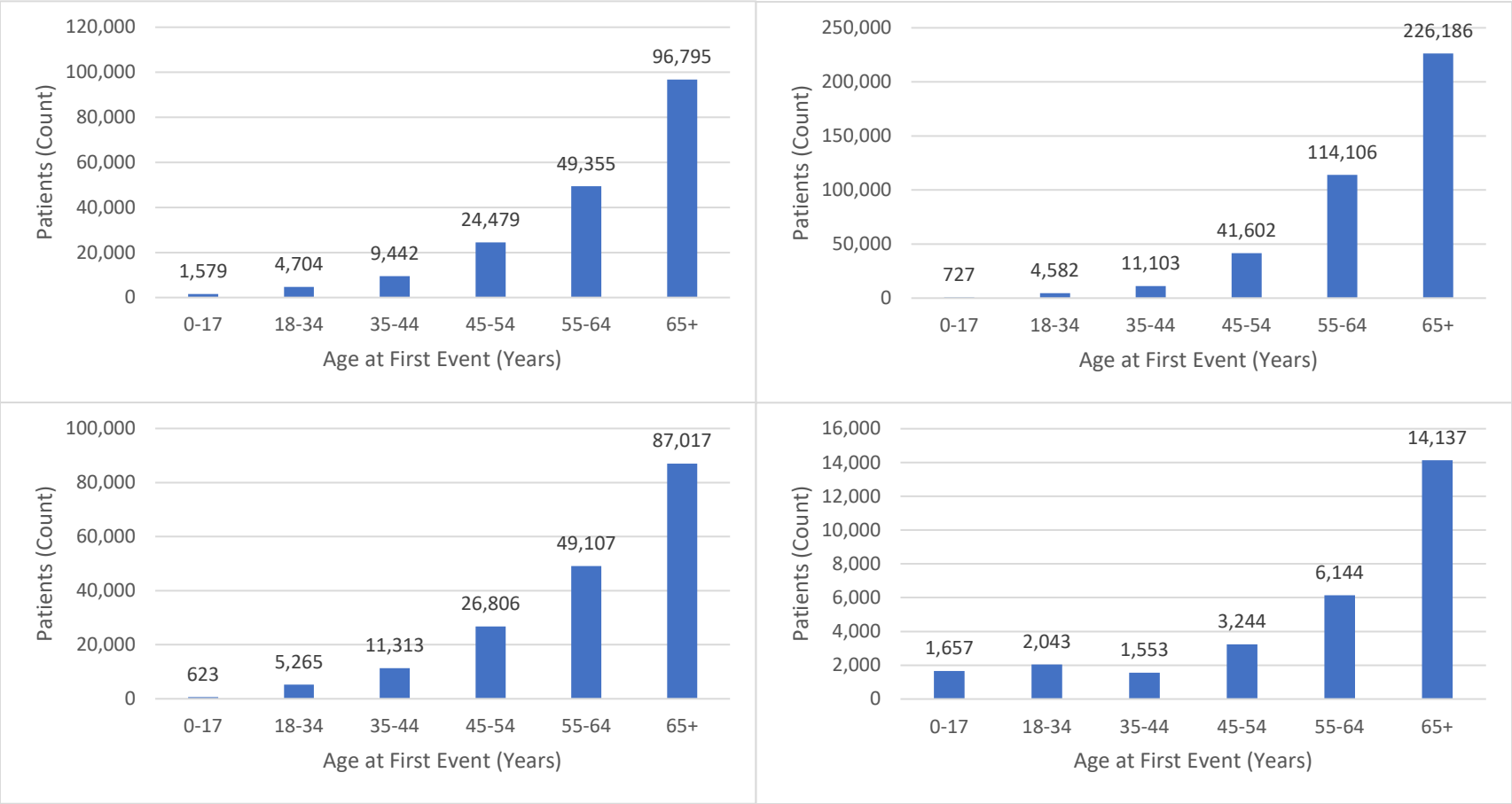

Figure D.2.2. Patients with at least one diagnosis for stroke with thrombosis or infarction (top left), occlusion without mention of infarction (top right), TIA (bottom left) and hemorrhagic stroke (bottom right) defined by ICD-9-CM codes, January 1, 2014–September 30, 2015, stratified by age.

Abbreviation: TIA, transient ischemic attacks.

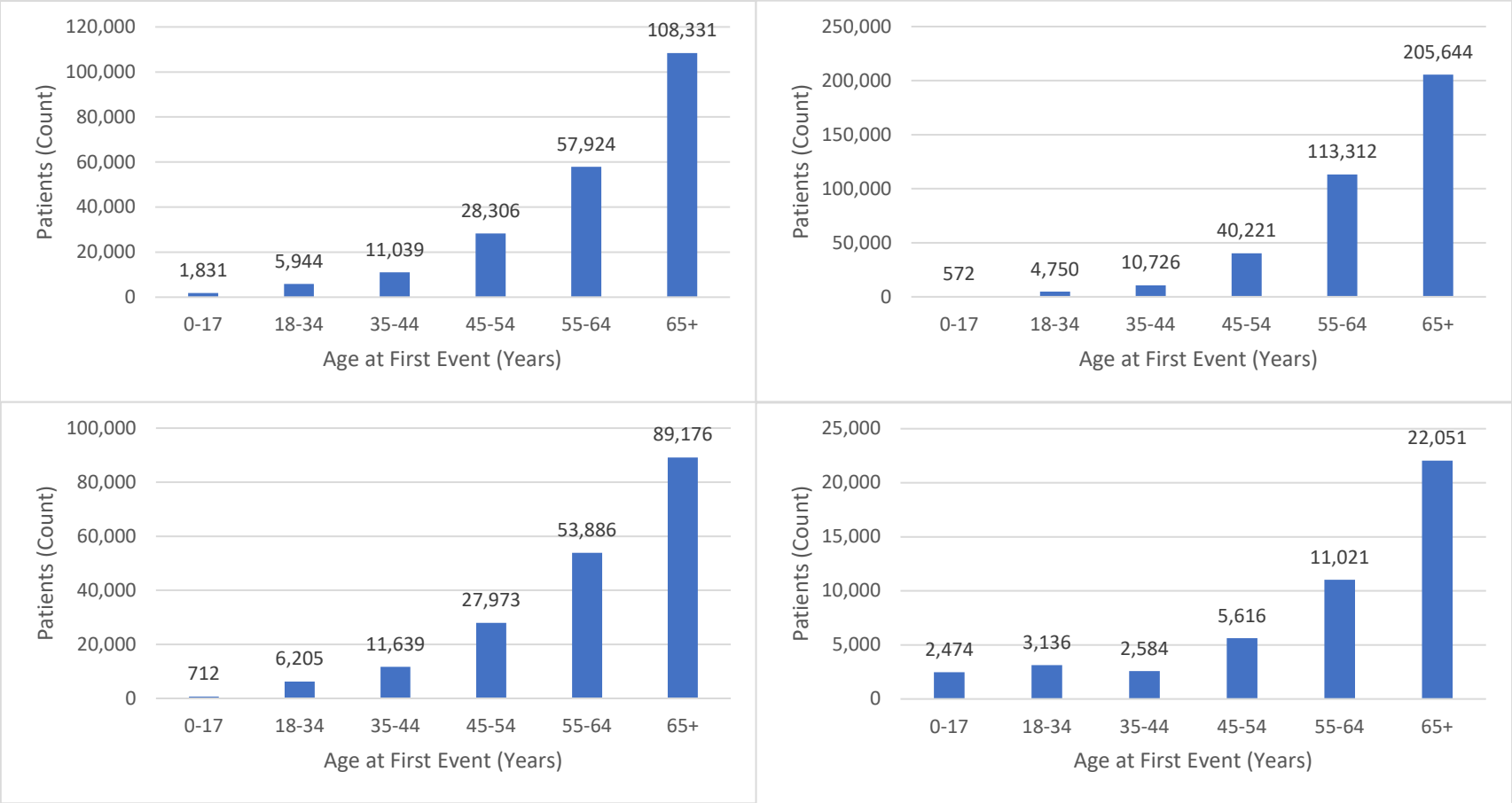

Figure D.2.3. Patients with at least one diagnosis for stroke with thrombosis or infarction (top left), occlusion without mention of infarction (top right), TIA (bottom left) and hemorrhagic stroke (bottom right) defined by ICD-10-CM codes, October 1, 2015–December 31, 2017, stratified by age.

Abbreviation: TIA, transient ischemic attacks.

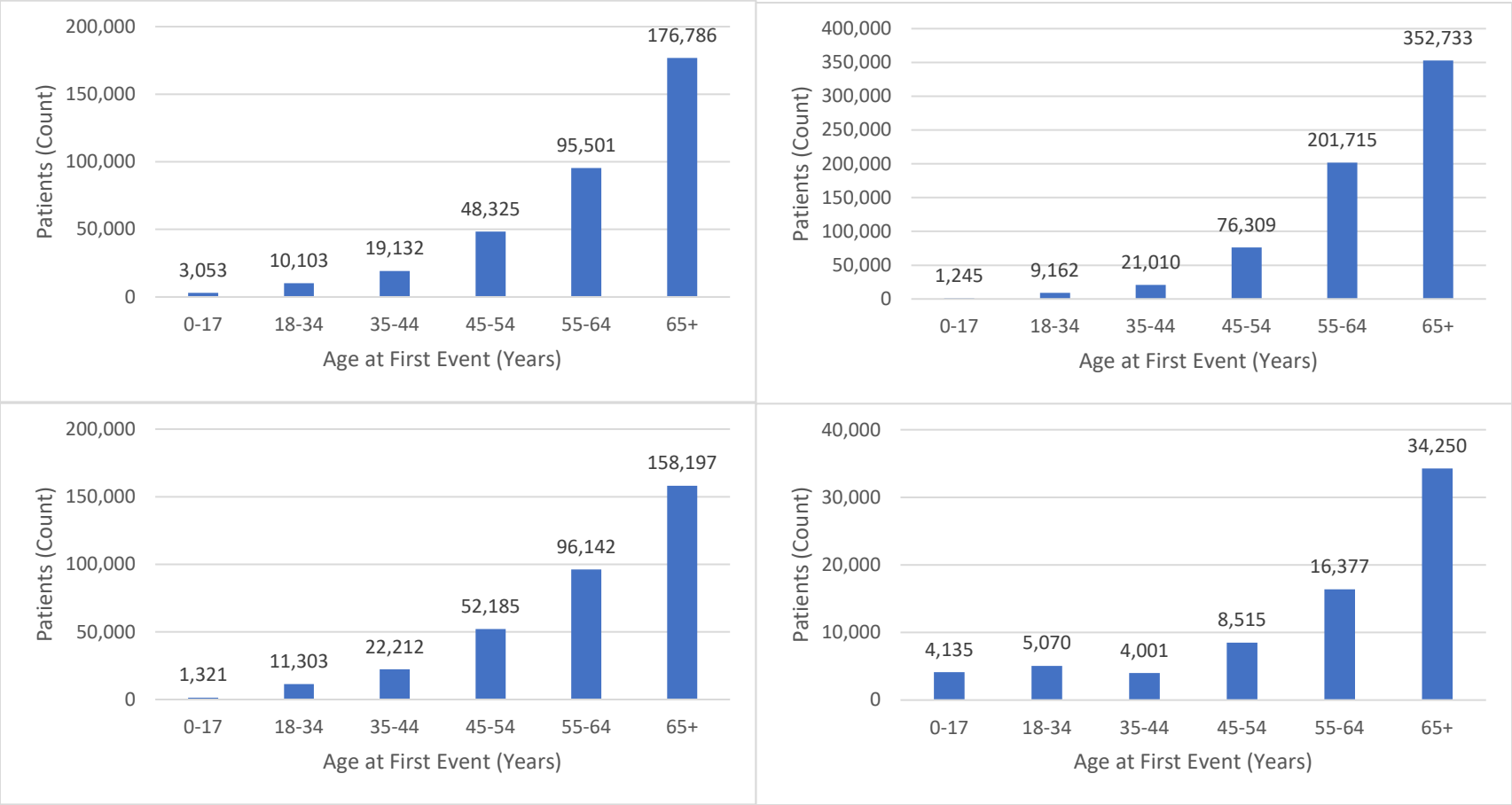

Figure D.2.4. Patients with at least one diagnosis for stroke with thrombosis or infarction (top left), occlusion without mention of infarction (top right), TIA (bottom left) and hemorrhagic stroke (bottom right) defined by ICD-9-CM or ICD-10-CM codes, January 1, 2014–December 31, 2017, stratified by age.

Abbreviation: TIA, transient ischemic attacks.

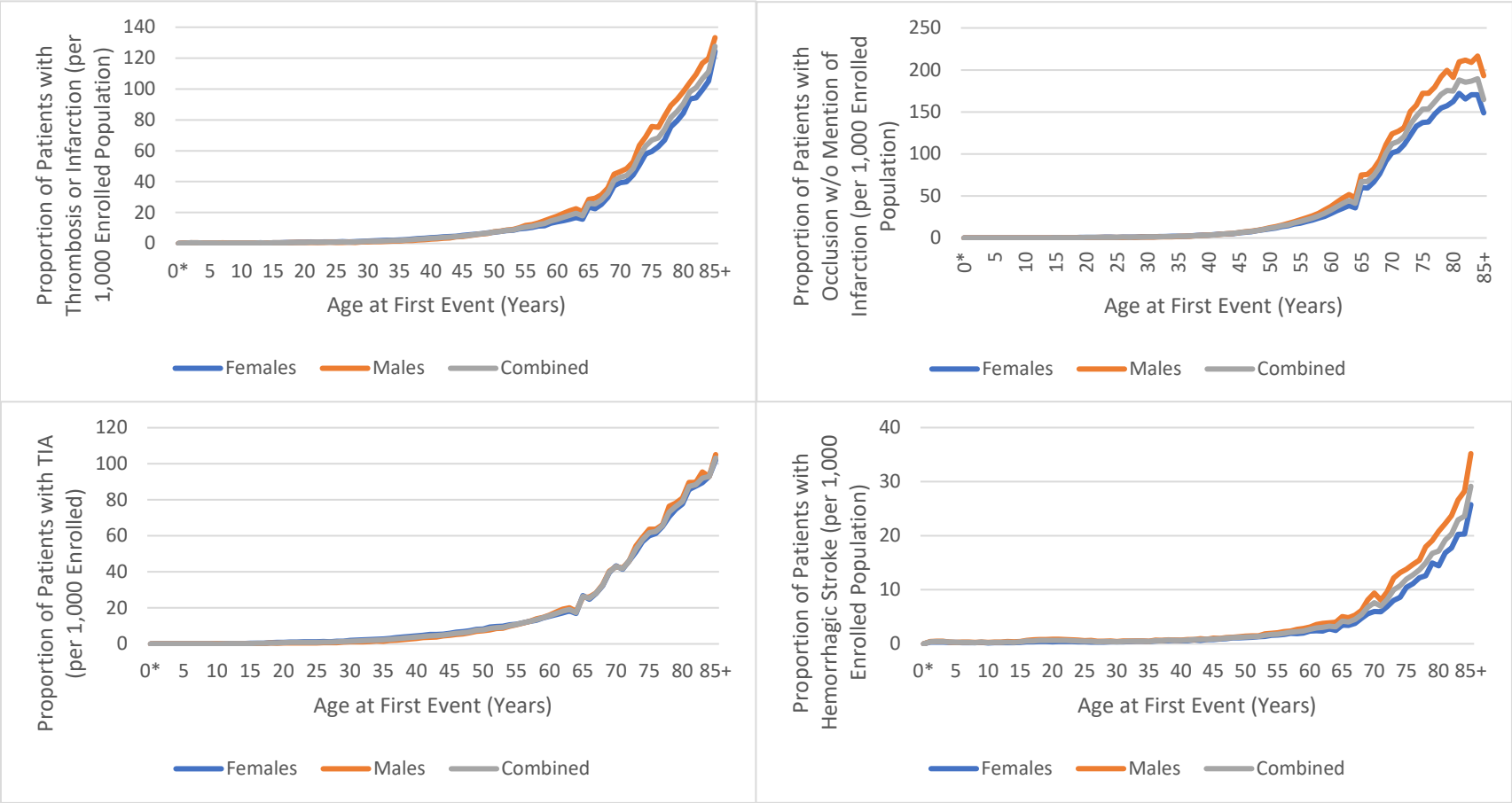

Figure D.2.5. Proportion of patients with at least one diagnosis (ICD-9-CM or ICD-10-CM) for stroke with thrombosis or infarction (top left), occlusion without mention of infarction (top right), TIA (bottom left) and hemorrhagic stroke (bottom right) per 1,000 population, by gender (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 experiencing stroke has been excluded from the chart and marked as zero.

Abbreviation: TIA, transient ischemic attacks.

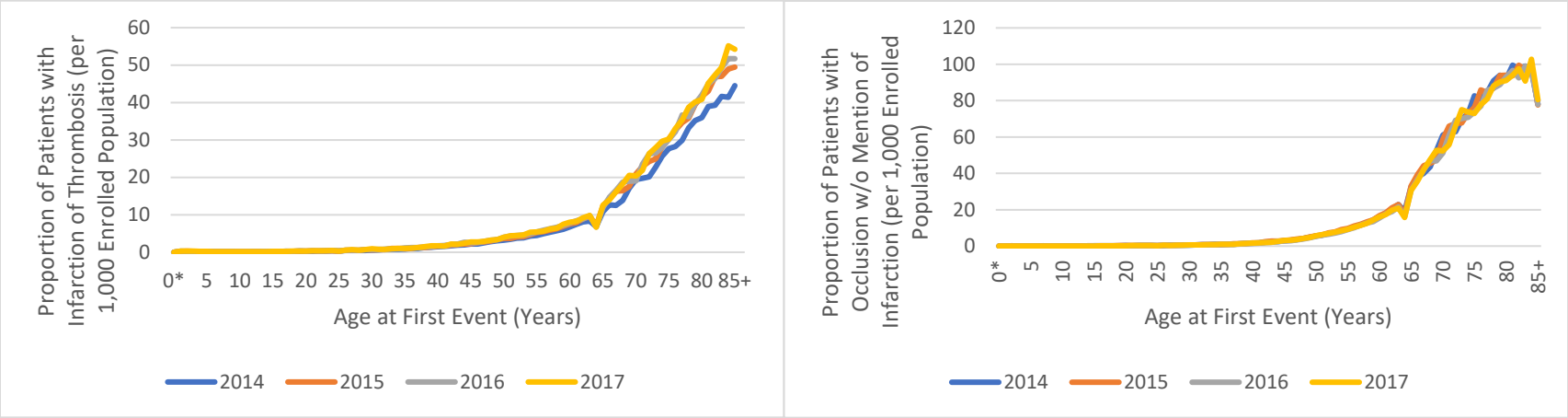

Figure D.2.6. Proportion of patients with at least one diagnosis (ICD-9-CM or ICD-10-CM) for stroke with thrombosis or infarction (top left), occlusion without mention of infarction (top right), TIA (bottom left) and hemorrhagic stroke (bottom right) per 1,000 population, by calendar year (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 experiencing stroke has been excluded from the chart and marked as zero.

Abbreviation: TIA, transient ischemic attacks.

Table D.2.5. Counts and proportions of patients experiencing stroke with infarction or thrombosis, defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2017).

Description	Calendar Year			
	2014	**2015**	**2016**	**2017**
January–June patient count	73,235	66,112	69,700	61,528
July–December patient count	77,973	69,366	67,815	61,231
January–June enrollment	31,110,014	24,094,695	23,531,649	21,656,153
July–December enrollment	30,867,380	23,759,879	23,759,879	21,105,240
January–June proportion (per 1,000 enrolled)	**2.35**	**2.74**	**2.96**	**2.84**
July–December proportion (per 1,000 enrolled)	**2.53**	**2.92**	**2.85**	**2.90**

Table D.2.6. Counts and proportions of patients experiencing stroke with occlusion without mention of infarction, defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2017).

Description	Calendar Year			
	2014	**2015**	**2016**	**2017**
January–June patient count	160,518	131,469	122,365	105,629
July–December patient count	163,327	129,646	114,805	104,980
January–June enrollment	31,110,014	24,094,695	23,531,649	21,656,153
July–December enrollment	30,867,380	23,759,879	23,759,879	21,105,240
January–June proportion (per 1,000 enrolled)	**5.16**	**5.46**	**5.20**	**4.88**
July–December proportion (per 1,000 enrolled)	**5.29**	**5.46**	**4.83**	**4.97**

Table D.2.7. Counts and proportions of patients experiencing TIA, defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2017).

Description	Calendar Year			
	2014	**2015**	**2016**	**2017**
January–June patient count	66,601	54,957	56,178	47,740
July–December patient count	68,573	56,219	50,866	45,941
January–June enrollment	31,110,014	24,094,695	23,531,649	21,656,153
July–December enrollment	30,867,380	23,759,879	23,759,879	21,105,240
January–June proportion (per 1,000 enrolled)	**2.14**	**2.28**	**2.39**	**2.20**
July–December proportion (per 1,000 enrolled)	**2.22**	**2.37**	**2.14**	**2.18**

Abbreviation: TIA, transient ischemic attacks.

Table D.2.8. Counts and proportions of patients experiencing hemorrhagic stroke, defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2017).

Description	Calendar Year			
	2014	**2015**	**2016**	**2017**
January–June patient count	10,174	8,776	12,604	11,004
July–December patient count	10,859	11,335	12,317	10,684
January–June enrollment	31,110,014	24,094,695	23,531,649	21,656,153
July–December enrollment	30,867,380	23,759,879	23,759,879	21,105,240
January–June proportion (per 1,000 enrolled)	**0.33**	**0.36**	**0.54**	**0.51**
July–December proportion (per 1,000 enrolled)	**0.35**	**0.48**	**0.52**	**0.51**

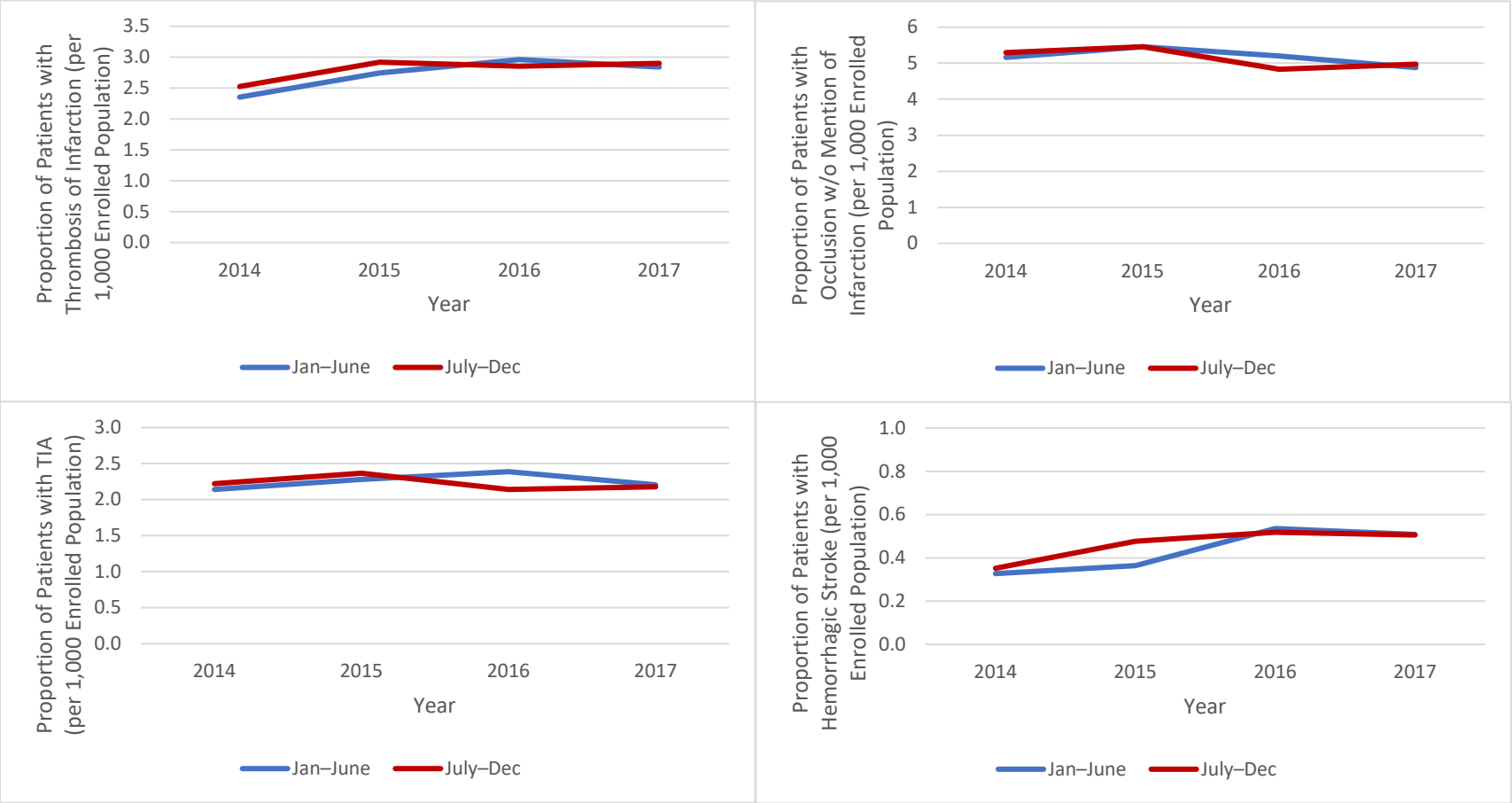

Figure D.2.7. Proportion of patients with at least one diagnosis (ICD-9-CM or ICD-10-CM) for stroke with thrombosis or infarction (top left), occlusion without mention of infarction (top right), TIA (bottom left) and hemorrhagic stroke (bottom right), stratified by time of year (2014–2017).

Abbreviation: TIA, transient ischemic attacks.

D3. Counts of Patients with TEEs by Season

Post-hoc analyses were conducted to test whether there was a seasonal association in the occurrence or reporting of the five main TEE categories, possibly as a result of an association with weather patterns or vaccination schedules. To test this, enrollment and TEE encounter data for Fall/Winter (January 1–March 31 and October 1–December 31) and Spring/Summer (April 1–September 30) were queried for each year. The proportion of patients receiving a diagnosis for non-hemorrhagic stroke appeared to be higher in the Spring/Summer period. It is not clear whether the difference between seasons (<1 person per 1,000 enrollees for each year queried) is clinically or statistically significant. No other outcomes demonstrated notably variation between seasons.

Table D.3.1. Counts and proportions of patients with at least one diagnosis code for pulmonary embolism* (defined by ICD-9-CM and ICD-10-CM codes), stratified by season (2014–2017).

Description	Calendar year			
	2014	2015	2016	2017
Fall/Winter Patient Count	56,429	45,253	42,676	37,678
Spring/Summer Patient Count	47,324	38,784	36,090	31,864
Fall/Winter Enrollment	36,459,990	27,751,531	27,071,490	24,695,788
Spring/Summer Enrollment	30,773,308	23,767,603	23,390,113	21,380,134
Fall/Winter	1.55	1.63	1.58	1.53
Spring/Summer	1.54	1.63	1.54	1.49

* The sum of the proportions presented here exceeds those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they would only be counted once when the query spans the full year.

Table D.3.2. Counts and proportions of patients with at least one diagnosis code for any DVT* (defined by ICD-9-CM and ICD-10-CM codes), stratified by season (2014–2017).

Description	Calendar year			
	2014	2015	2016	2017
Fall/Winter Patient Count	106,614	84,374	76,488	66,762
Spring/Summer Patient Count	93,863	76,079	67,089	58,312
Fall/Winter Enrollment	36,459,990	27,751,531	27,071,490	24,695,788
Spring/Summer Enrollment	30,773,308	23,767,603	23,390,113	21,380,134
Fall/Winter	2.92	3.04	2.83	2.70
Spring/Summer	3.05	3.20	2.87	2.73

* The sum of the proportions presented here exceeds those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they would only be counted once when the query spans the full year.

Table D.3.3. Counts and proportions of patients with at least one diagnosis code for AMI* (defined by ICD-9-CM and ICD-10-CM codes), stratified by season (2014–2017).

Description	Calendar year			
	2014	2015	2016	2017
Fall/Winter Patient Count	54,562	46,747	47,803	43,318
Spring/Summer Patient Count	47,689	38,840	41,601	37,481
Fall/Winter Enrollment	36,459,990	27,751,531	27,071,490	24,695,788
Spring/Summer Enrollment	30,773,308	23,767,603	23,390,113	21,380,134
Fall/Winter	1.50	1.68	1.77	1.75
Spring/Summer	1.55	1.63	1.78	1.75

* The sum of the proportions presented here exceeds those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they would only be counted once when the query spans the full year.

Table D.3.4. Counts and proportions of patients with at least one diagnosis code for non-hemorrhagic stroke* (defined by ICD-9-CM and ICD-10-CM codes), stratified by season (2014–2017).

Description	Calendar year			
	2014	2015	2016	2017
Fall/Winter Patient Count	271,457	227,163	221,376	193,859
Spring/Summer Patient Count	260,505	214,397	208,852	180,529
Fall/Winter Enrollment	36,459,990	27,751,531	27,071,490	24,695,788
Spring/Summer Enrollment	30,773,308	23,767,603	23,390,113	21,380,134
Fall/Winter	7.45	8.19	8.18	7.85
Spring/Summer	8.47	9.02	8.93	8.44

* The sum of the proportions presented here exceeds those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they would only be counted once when the query spans the full year.

Table D.3.5. Counts and proportions of patients with at least one diagnosis code for arterial embolism or thrombosis* (defined by ICD-9-CM and ICD-10-CM codes), stratified by season (2014–2017).

Description	Calendar year			
	2014	2015	2016	2017
Fall/Winter Patient Count	13,520	11,266	10,708	8,999
Spring/Summer Patient Count	12,589	10,172	9,889	8,741
Fall/Winter Enrollment	36,459,990	27,751,531	27,071,490	24,695,788
Spring/Summer Enrollment	30,773,308	23,767,603	23,390,113	21,380,134
Fall/Winter	0.37	0.41	0.40	0.36
Spring/Summer	0.41	0.43	0.42	0.41

* The sum of the proportions presented here exceeds those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they would only be counted once when the query spans the full year.

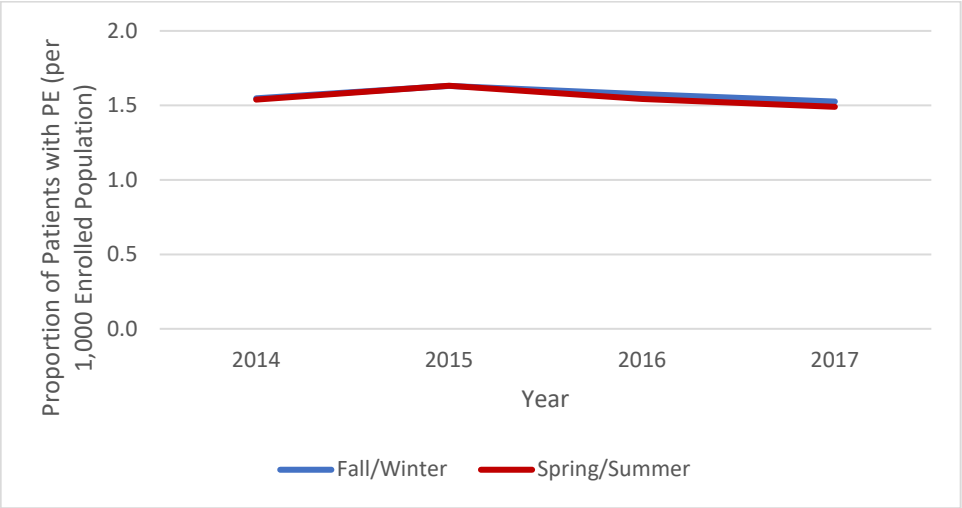

Figure B.3.1. Proportion of patients with at least one diagnosis code for pulmonary embolism (ICD-9-CM or ICD-10-CM), stratified by season (2014–2017).

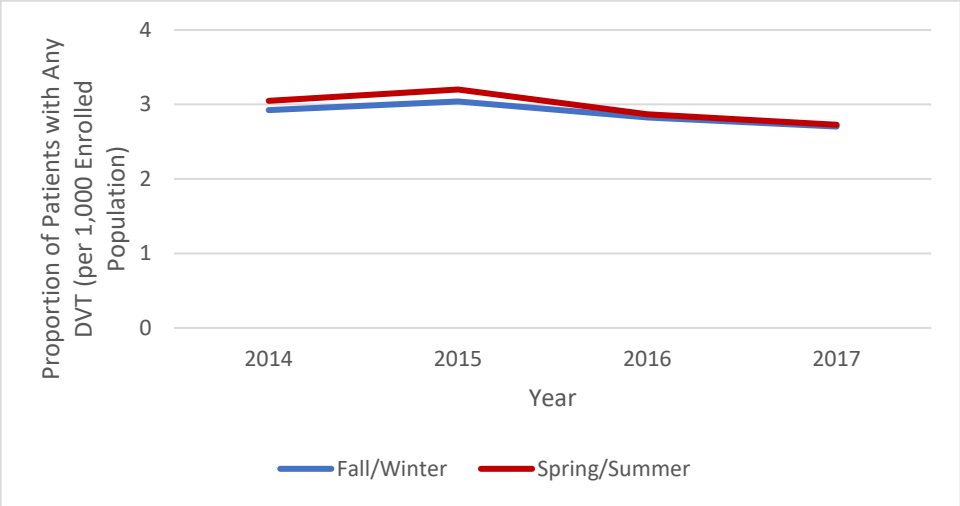

Figure B.3.2. Proportion of patients with at least one diagnosis code for any DVT (ICD-9-CM or ICD-10-CM), stratified by season (2014–2017).

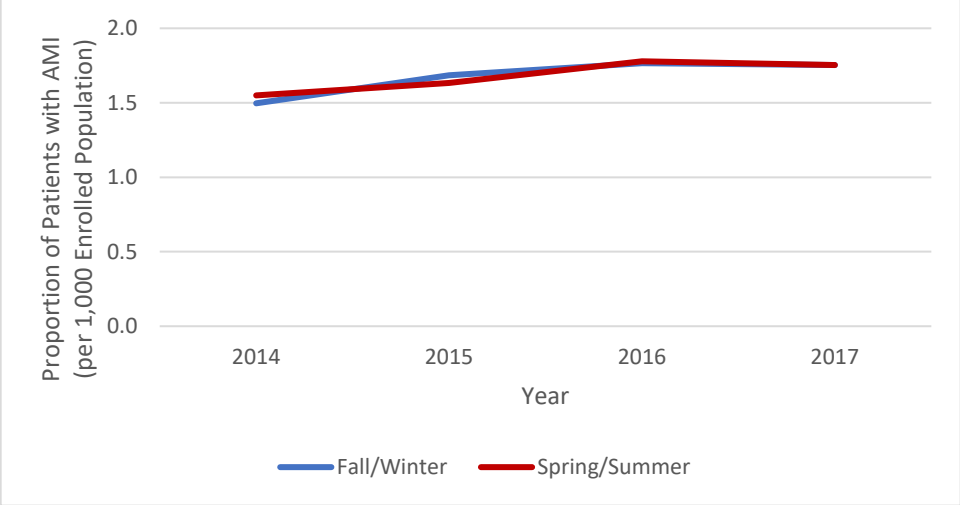

Figure B.3.3. Proportion of patients with at least one diagnosis code for AMI (ICD-9-CM or ICD-10-CM), stratified by season (2014–2017).

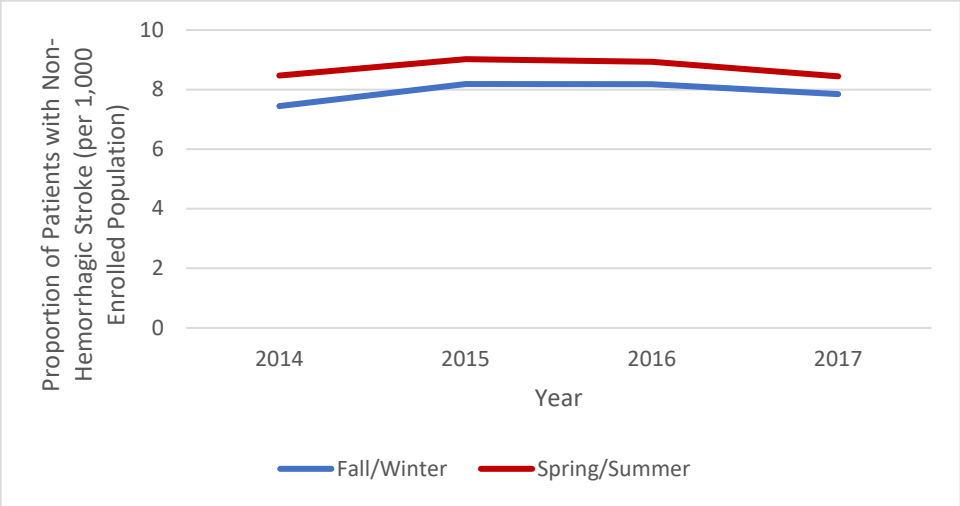

Figure B.3.4. Proportion of patients with at least one diagnosis code for non-hemorrhagic stroke (ICD-9-CM or ICD-10-CM), stratified by season (2014–2017).

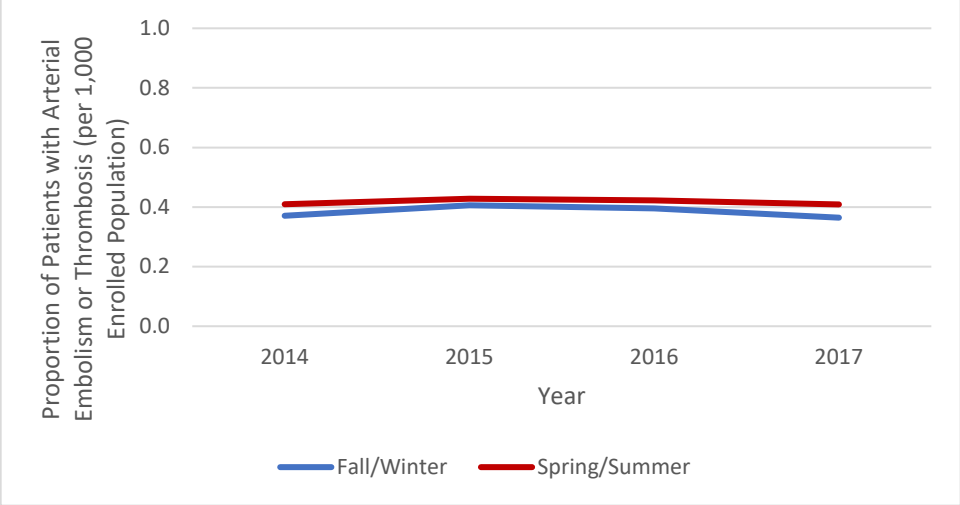

Figure B.3.5. Proportion of patients with at least one diagnosis code for arterial embolism or thrombosis (ICD-9-CM or ICD-10-CM), stratified by season (2014–2017).