SENTINEL PRODUCT ASSESSMENT

EVALUATION OF THE RISK OF THROMBOEMBOLIC EVENTS AFTER IMMUNOGLOBULIN ADMINISTRATION, 2006-2012

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July 13, 2017

The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. BloodSCAN is the Sentinel component for safety surveillance of blood products and blood components. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) contract number HHSF223201400030I. This project was funded by the FDA through HHS Mini-Sentinel contract number HHSF223200910006I.

Sentinel Product Assessment
Evaluation of the Risk of Thromboembolic Events after Immunoglobulin Administration

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I. EXECUTIVE SUMMARY

Background: Since 2013, the U.S. Food and Drug administration (FDA) has required that intravenous immune globulin (IGIV) products carry a boxed warning concerning the risk of thromboembolic events (TEEs). This determination was based on numerous case reports, a study that reported on same-day IGIV-associated TEEs recorded in a large database of administrative/claims data, and laboratory evaluations of the thrombogenicity of IGIV products. However, questions remain concerning the magnitude of this risk and the extent to which it may vary based on factors such as a patient's indication for IGIV, baseline risk of TEE, dose received, and brand or product type.

Objectives: We assessed whether there is a transient increase in TEE risk following IGIV administration. In secondary and exploratory analyses, we evaluated possible subgroup differences, estimated the absolute risk of TEE attributable to IGIV, and conducted supplementary cohort studies.

Methods: Members of 13 participating Data Partners who initiated IGIV use in 2006-2012 were eligible for study inclusion. A self-controlled risk-interval (SCRI) design was used to assess whether the risk of arterial and venous TEEs was elevated following IGIV treatment. In a SCRI analysis, the relative risk (RR) is estimated using only patients who experienced a risk window (RW) or control window (CW) event, and is based on a comparison of the outcome incidence rates in the RW and CW. The pre-specified RWs were days 0-2 following IGIV for arterial TEEs (acute myocardial infarction or ischemic stroke) and days 0-13 days for venous TEEs (deep vein thrombosis, pulmonary embolism or cerebral venous thrombosis). For both the arterial and venous TEE risk assessments, the control window was days 14-27 after IGIV. An additional eligibility restriction for the venous TEE risk assessment was that only IGIV treatments administered in an outpatient setting were considered, due to concerns about time-varying risk of venous TEE in hospitalized patients.

Potential RW and CW cases were identified from the Data Partners' administrative data records. Medical charts for these patients were requested and reviewed by physician-adjudicators to confirm IGIV exposure, TEE outcome, and the time interval between the two. As specified in our study protocol, the primary analysis included only definite chart-confirmed cases where the recency of IGIV exposure could also be verified in the patient's chart(s). To guard against the potential for bias if the availability of complete chart information was differential by RW/CW status, we also performed a sensitivity analysis where we included all confirmed TEE cases (definite, probable and possible) and relied on IGIV treatment dates recorded in the administrative data if this information was unavailable in the chart.

Based on the relative frequency of chart-confirmed RW and CW events, the RR of TEE due to IGIV exposure was estimated. Because this estimate is informed only by within-person event rate comparisons, it is not confounded by any time-constant, between-person differences in TEE risk. The increase in absolute risk caused by IGIV was estimated by considering the total number of chart-confirmed RW events, the underlying denominator of eligible IGIV treatments, and the proportion of TEEs attributable to IGIV per the RR estimate.

Tests for interaction by product, dose, and IGIV indication were pre-specified as secondary analyses; additional tests were performed as exploratory analyses. Effect modification on the ln(RR) scale was assessed by adding interaction terms to the SCRI regression models.

Results: The primary SCRI analyses identified an excess risk of arterial TEE within days 0-2 following outpatient and inpatient IGIV treatments and no significant increase in venous TEE risk within days 0-13 following outpatient IGIV treatments.

Arterial TEE risk assessment

- Eligible cohort: 19,008 IGIV new users who received a total of 93,370 IGIV treatments (outpatient and inpatient).
- RR estimates
  - 4.69 (95% CI: 1.87, 11.90) based on per-protocol analysis of definite TEE cases with chart-confirmed IGIV exposure.
  - 3.72 (95% CI: 1.75, 7.84) in the sensitivity analysis that included all confirmed cases and incorporated both chart and administrative data on IGIV exposure.
- Attributable absolute risk
  - 8.86 (95% CI: 3.25, 14.6) per 10,000 patients or 1.80 (95% CI: 0.66, 2.97) per 10,000 treatment episodes for the per-protocol analysis
  - 9.45 (95% CI: 3.64, 15.6) per 10,000 patients or 1.92 (95% CI: 0.74, 3.18) per 10,000 treatment episodes in the sensitivity analysis.

Venous TEE risk assessment

- Eligible cohort: 13,888 patients who received 86,400 eligible outpatient IGIV treatments.
- RR estimates
  - 1.07 (95% CI: 0.34, 3.48) for the per-protocol analysis based on per-protocol analysis of definite TEE cases with chart-confirmed IGIV exposure.
  - 1.04 (95% CI: 0.47, 2.34) in the sensitivity analysis.
- Attributable absolute risk
  - 0.97 (95% CI: -14.2, 14.4) per 10,000 patients or 0.16 (95% CI: -2.29, 2.31) per 10,000 treatment episodes for the per-protocol analysis.
  - 0.81 (95% CI: -13.6, 15.2) per 10,000 patients or 0.13 (95% CI: -2.18, 2.44) per 10,000 treatment episodes in the sensitivity analysis.

No statistically significant interaction by any product or patient characteristic was found. In an exploratory subgroup analysis that assessed whether the risk of IGIV-associated TEE changed over the course of the study period, it appeared that the RR for the arterial TEE endpoint was greater in 2011-2012 than in 2006-2010 (p = 0.006).

In the exploratory cohort analyses, there was inconsistent evidence for an increased risk of arterial TEE and/or venous TEE. However, in the course of chart-confirming potential cases for the SCRI analyses, we learned that the administrative data had important limitations. Often, the true temporal relationship between IGIV treatment and TEE onset was not represented accurately in the administrative data—particularly for IGIV treatments in the inpatient setting. These limitations may explain incongruities between our chart-confirmed SCRI results and our administrative data-only cohort study results.

Conclusions: We found evidence for a transient increase in the risk of arterial TEEs during days 0-2 following IGIV treatment. No statistically significant association between recent IGIV exposure in outpatient settings and venous TEE risk was found. Contrary to our initial hypothesis, we did not find evidence that the risk of IGIV-associated TEEs declined during the study period, as additional risk mitigation strategies were implemented by IGIV manufacturers. Continued pharmacovigilance efforts are warranted to monitor and limit the risk of IGIV-associated TEEs.

Limitations: The possibility of delayed venous TEE symptom onset and diagnosis means that an increase in venous TEE risk cannot be ruled out definitively by our self-controlled approach. In addition, our venous TEE risk assessment was limited to patients who received IGIV on an outpatient basis, which

means that our results may underestimate the risk for higher-risk hospitalized patients and therefore may not be generalizable to those populations.

Another study limitation was the high proportion of potential cases identified in the administrative data for which chart retrieval was not possible (30% and 38% of potential arterial and venous TEE cases, respectively). In sensitivity analyses we explored the potential impact of missing data on our results, and found that the risk estimates did not change substantially. The reasons that charts were unavailable for review did not give us reason to suspect that our analyzable sample was systematically different than the total set of potential cases identified in the administrative data.

Finally, SCRI analyses are subject to potential biases related to within-person time-varying confounding. A number of events in this study occurred in hospitalized patients who were experiencing severe acute illness prior to receiving IGIV. Although we found no evidence of effect modification by IGIV indication, we cannot rule out that some of the elevated risk of arterial TEE in the RW may have been related to acute illness rather than IGIV.

II. BACKGROUND

The Blood Safety Continuous Active Surveillance Network (BloodSCAN) is a component of the Sentinel System initiated by the Center for Biologics Evaluation and Research (CBER) as an active surveillance system that focuses on evaluating recipient safety of FDA-regulated blood components and plasma-derived products. As part of the BloodSCAN activities, this Workgroup conducted a retrospective protocol-based assessment of thromboembolic events (TEE) after non-specific immunoglobulin (IG) administration, and validated the algorithms used to identify the exposure and the outcome.

The 12 FDA-approved non-specific IG products that were included in this study are listed in **Table 1**. Hyper-immune globulin products were excluded from this study, since this group of products have very specific indications and are used by a relatively small population of patients. The majority of IG use is via the intravenous route (IV), though some products are available for intramuscular (IM) or subcutaneous (SC) administration. Formulations and manufacturing processes vary across products so it is important to distinguish among them.

Table 1. Immunoglobulin products with FDA approval

Product Name	Route	Approval Date	Product Description
Bivigam	IV	December 19, 2012	Liquid 10%
Carimune NF, Panglobulin, Sandoglobulin	IV	June 7, 1984	Lyophilized powder for reconstitution
Flebogamma; Flebogamma DIF	IV	December 15, 2003 July 27, 2010	Liquid 5% Liquid 10%
Gammagard S/D; Gammagard S/D Less IgA	IV	February 18, 1986	Lyophilized powder for reconstitution
Gammagard Liquid	IV or SC	April 27, 2005 (SC approved July 11, 2011)	Liquid 10%
GamaSTAN S/D	IM	January 11, 1944	2 mL and 10 mL vials
Hizentra	SC	March 4, 2010	Liquid 20%
Octagam	IV	May 21, 2004	Liquid 5%
Gamunex; Gamunex-C	IV or SC	August 27, 2003 (SC approved October 13, 2010)	Liquid 10%
Privigen	IV	July 26, 2007	Liquid 10%
Gammaplex	IV	September 17, 2009	Liquid 5%
Gammaked (Identical to Gamunex)	IV or SC	August 27, 2003	Liquid 10%

IG is a purified plasma fraction of polyclonal immunoglobulin G, and production of IG products involves pooling human plasma from thousands of donors.[1] IG is used to treat a wide variety of conditions, including primary and secondary immune deficiencies, autoimmune disorders, and inflammatory disorders (See **Appendix A**). While indication varies by product, many of the diagnoses in **Appendix A** are considered "off-label" for all the IG products. Depending on the indication for IG, some patients may have only one treatment episode, while others will have repeated episodes. Doses used vary by indication, with low dose IG for immune deficiencies and high doses to suppress inflammatory or immune-mediated processes.[2] At low doses, an IG treatment episode generally consists of an IG infusion given on a single day. For patients receiving high doses of IG, a treatment episode may consist of IG treatments given on multiple consecutive days (up to five). A treatment episode typically consists of IG administered on as few as one and as many as five consecutive days. In chronic users, treatment typically recurs every three to four weeks. Some users have only sporadic repeated treatment episodes.

A case series describing the association of TEE with IGIV exposure was first reported in the medical literature in 1986, and in 2002 the FDA began requiring manufacturers to include a warning about TEEs in IGIV product packaging.[3,4] By 2007, at least 55 cases of IGIV-linked TEEs had been described in publications,[5] and investigators' estimates of the frequency of TEEs among patients receiving IGIV range from one to 13%.[6,7-12] In 2010 an increase in TEEs reported following Octagam administration resulted in a voluntary recall in both the U.S. and the EU.[13,14] Subsequent investigation by FDA and Octapharma, the manufacturer of Octagam, discovered increased coagulation factor XIa (FXIa) in implicated lots.[15] Increased FXIa was also found in lots from other IG products by investigators at FDA.[16] Researchers at the Paul Ehrlich Institute (PEI) tested 19 lots from five different manufacturers and identified both kallikrein and FXIa as major contaminants in IGIVs.[17] In response to this issue, manufacturers of IG products "instituted validated risk mitigation strategies to address the risk of FXIa in immune globulin

products and to address the risk of harmful procoagulant activity in these products."[15,16,18-20] FDA convened a public workshop on May 17-18, 2011 to address procoagulant activity in IG products. Prior to and after this workshop the Agency conducted testing for procoagulant activity. In addition, it reviewed adverse event data from multiple sources including the FDA Adverse Event Reporting System (FAERS), European passive reporting databases, and a large healthcare claims database, the HealthCore Integrated Research Database (HIRD, a Sentinel Data Partner).[21] Although these reports are subject to limitations, they provided a clearer picture of the nature and frequency of these events after IG administration. In September 2013, FDA required, under the 2007 FDA Amendments Act (FDAAA), sponsors to add a boxed warning to the labeling for all human IG products (IV, SC and IM) to highlight the risk of thrombosis and suggestions for risk mitigation.[22]

Several proposed pathophysiological mechanisms provide biologic plausibility for an association between IG use and TEEs. As discussed above some IG products have been found to contain activated coagulation factors.[17,23] In addition, IG can increase blood viscosity beyond the normal upper limit of 1.9 centipoise (cp),[24] perhaps by triggering erythrocyte aggregation and platelet activation.[6,25] Even small changes in serum viscosity may affect capillary blood flow. Thus, a slight viscosity increase such as that caused by IG, although not higher than one cp, may be sufficient to precipitate a TEE in a predisposed individual.[24] Finally, a reversible increase in arterial vascular tone has also been reported to occur following IGIV infusion.[26,27]

The literature provides some indication about the likely window of elevated risk for TEEs after IG exposure. IG has been implicated in both arterial and venous TEEs, and the time of onset has been observed to differ for the two types of TEE, although this could be due to the differences in temporal patterns of symptom onset and diagnosis. The time of onset of thrombosis relative to IGIV administration was reported in a literature review that yielded 63 cases (51 arterial, 12 venous).[28] Forty-one percent occurred within four hours of the infusion, and 63% occurred within 24 hours. Only eight percent were reported more than one week after the IGIV infusion. In the review, 77% of arterial events occurred in the first 24 hours after the infusion, whereas 46% of venous events occurred within 24 hours. In a review of a larger series of case reports,[10] arterial thrombosis accounted for 66% of the 92 cases, of which nearly two-thirds were strokes and one quarter were acute myocardial infarctions (AMI). Deep vein thrombosis (DVT) or pulmonary embolism (PE) accounted for 24 of the 31 venous thromboembolic events with the remainder accounted for by superficial vein thrombosis (three events), central retinal vein occlusion (3), and transverse sinus vein thrombosis (1).

FDA assembled a case series of reports received in the FAERS between January 1, 2006 and December 31, 2010.[29] There were 209 unique TEEs reported. The average age was 54.1 years (median 58.6; range 82 days to 88 years). Arterial events accounted for 58% (n = 122), venous for 36% (n = 76), 2.9% (n = 6) of patients had both, and 2.4% (n = 5) were classified as type unspecified. Stroke and AMI accounted for the large majority of patients with arterial events (73% of 128 patients); DVT and PE accounted for the large majority of patients with venous events (74% of 82 patients). Five patients with arterial events (3.9%) had multiple-site events; this was also the case for ten patients with venous events (12.2%). For cases in which time of onset was known, arterial events occurred most commonly during infusion or in the first 24 hours after infusion (61.4%). In contrast, venous events occurred most commonly two or more days after infusion (74.6%), with 52.5% occurring more than five days after the infusion. The most common risk factors present among people with arterial events were male gender, hypertension, hyperlipidemia, and coronary disease. The most common risk factors among those with venous events were use of oral contraceptives, previous DVT, or in-dwelling catheter.

Estimates of TEE frequency from published case reports, case series, and the FAERS have well-known limitations, but complement existing FDA safety surveillance programs. Case series reports tend to be small and are often gathered from patients with a single common diagnosis or a single institution. Data from FAERS are subject to under reporting and incomplete information, and lack a denominator. The only two large retrospective cohort studies were conducted in collaboration between CBER and HealthCore Inc. to examine the association between IG and TEE and ascertain potential risk factors.[21,30] These investigations compared the effects of different IG products on same day or next day TEE and ascertained potential risk factors for TEE occurrence in a large administrative claims database, based on the recorded procedure and diagnosis codes and with no medical record confirmation of exposures or events. In the study by Daniel et al[29],[21] of 11,785 people exposed to IV, SC and IM IG products, 122 (one percent) had a TEE on the same day as an IG administration, and TEE incidences per 1,000 exposed people ranged from 6.1 to 20.5 across different products. The investigation by Daniel et al[2129] for the first time identified an elevated TE risk with Vivaglobin, a subcutaneous IG product. The study by Sridhar et al.,[30] with extended study interval, further confirmed an elevated risk with Vivaglobin, and also conducted laboratory assessment that demonstrated measurable FXIa activity in random lots of five IG products purchased in 2013: Gammaplex, Gammagard SD (lyophilized), Octagam, Gammagard Liquid, and Flebogamma, which suggest the need for further investigations and continuous monitoring of procoagulant activity of IG products.

This BloodSCAN protocol-based assessment provides the first large scale examination of the risk of TEE following IGIV with medical record confirmation. The Sentinel Distributed Database (SDD) used by BloodSCAN included, as of August 2015, healthcare records for 193 million patients from 2000-2015.[31] This assessment relied primarily on a self-controlled risk interval (SCRI) study design to estimate the short-term, transient risks of arterial and venous TEEs attributable to IGIV treatment. To better inform risk mitigation efforts, a number of pre-specified subgroup analyses were performed to identify patient groups that may be at particularly high risk of IGIV-associated TEE. Two exploratory cohort analyses were also performed to evaluate assumptions made by our SCRI design choices, and to provide additional contextual information.

III. OBJECTIVES

This Sentinel safety assessment evaluated the effect of immunoglobulin (IG) treatment on the risk of TEEs. Several aspects of the relationship were of interest to the FDA. These included: the relative and absolute magnitudes of TEE risk attributable to IG; the temporal relationship between IG exposure and the two TEE types (arterial and venous); and whether risk of arterial or venous TEE differs by IG dose, product/brand, indication for use, the patient's baseline TEE risk/risk factors, and the patient's past exposure to IG. Because IGIV is more commonly used than IGSC or IGIM, and most TEE adverse events reports have concerned IGIV, the primary exposure of interest was IGIV.

A. PRIMARY OBJECTIVES

1. With the use of a SCRI design, estimate the relative risk of chart-confirmed arterial TEE (stroke or AMI), comparing the risk vs. control intervals following IGIV administration among new users of IGIV.

2. With the use of a SCRI design, estimate the relative risk of chart-confirmed venous TEE (DVT or PE), comparing the risk vs. control intervals following outpatient IGIV administration among new users of IGIV.

B. SECONDARY OBJECTIVES

1. For each primary objective, explore whether the relative risk is modified by
    a. Product/brand
    b. Dose
    c. Type of indication (primary immunodeficiency, secondary immunodeficiency, inflammatory/other).
2. With the use of a SCRI design, estimate the relative risk of the composite outcome of any TEE (arterial or venous), comparing the risk vs. control intervals following IGIV administration among new users of any IGIV (inpatient or outpatient administration for arterial TEE; outpatient administration for venous TEE).
3. Quantify the positive predictive values of the arterial, venous, and composite TEE definitions.

C. EXPLORATORY OBJECTIVES BASED ON CHART CONFIRMED DATA

1. For each primary objective, explore whether the relative risk is modified by
    a. History of the outcome event (i.e. arterial or venous TEE)
    b. Baseline TEE risk (assessed using disease risk scores)
    c. Treatment episode number. A significant number of patients receive high doses of IG over multiple days. In this study, we operationally defined a *treatment episode* as a single IG treatment on one day or a series of two or more IG treatments occurring over multiple days, allowing for a gap of no more than two days.
    d. Days since treatment
    e. Infusion rate (may be incomplete or unobtainable)
    f. Recency of product: whether IGIV product was delivered (and presumably manufactured) in 2011/2012 after manufacturing changes were undertaken to remove FXIa from IG products and reduce the risk of TEE, as described in the introduction.

D. EXPLORATORY OBJECTIVES BASED ON ADMINISTRATIVE DATA

1. Describe the overall trajectory of TEE incidence (without medical record confirmation) among all eligible IG-exposed individuals for any route of administration, by time after IG exposure and re-exposure, to evaluate the choice of the risk and control window and examine differences by route of administration, comparing risk after receiving IG by IM or SC versus risk after IGIV.
2. Describe the overall trajectory of TEE incidence (without medical record confirmation) among all eligible individuals with indications for IG, including those untreated by IG, to provide an additional comparative framework that may be helpful in assessing what TEE risk would have been among the IG-treated individuals had they never been treated with IG.
3. Estimate the attributable risk – the number of TEEs per 1,000 new-users of IGIV and per 1,000 episodes of IGIV treatment.

IV. METHODS

A. DATA SOURCE AND STUDY POPULATION

This assessment included 13 Data Partners contributing data to the SDD that (a) participated in chart retrieval and (b) had patients meeting the preliminary eligibility criteria for the primary self-controlled analyses. The study population consisted of individuals of any age who were members of any of the participating Data Partners during the period, January 1, 2006 through December 31, 2012, prior to the 2013 addition of a boxed warning concerning thrombosis to IGIV products. Within this period, individuals were included in the primary analyses if they (a) were new users (defined below) of any IGIV product during the study period, (b) had a chart-confirmed arterial or venous TEE during a post-IGIV risk or control window, and (c) maintained health plan enrollment from the date of IGIV treatment initiation through the TEE date.

New users were defined as patients with an IGIV treatment record that was directly preceded by at least 183 days of health plan enrollment during which no IG use was observed. The requirement of at least 183 days of enrollment prior to IGIV initiation was selected to optimize the ability to identify prior IG use, prior TEE, and other disease risk factors while balancing the possibility of a large loss of case numbers with a stricter enrollment criterion.

Health plan members were eligible for inclusion in the exploratory objective D1 cohort analyses (see D.1. above) of TEE incidence following IG exposure (IV, SC, or IM) if they were new users of an IG product and had a recognized indication for IG use (defined in **Appendix A**) recorded during the 183 days prior to the new use date. Health plan members were eligible for the exploratory objective D2 cohort analyses (see D.2. above), in which patients who received IG were compared with those who did not, if they had a recognized indication for IG use and a 183-day enrollment period for the assessment of baseline covariates.

In summary: our primary analyses were restricted to new-users of IGIV during pre-defined risk intervals and comparison intervals. One set of exploratory analyses examined risk during all available post-IG follow-up in new users. Another set of exploratory analyses evaluated TEE risk in IG users and a comparison group of non-users with an indication for IG use.

B. STUDY DESIGN AND ANALYSIS PLAN

To address the primary and secondary objectives we employed a self-controlled design to compare the risk of TEE between a pre-specified post-treatment risk interval and control interval. We use the term “self-controlled” for this method because, instead of comparing outcomes across individuals who received different treatments (or no treatment), we are comparing outcomes across different time periods within the same treated individuals. We compared TEE rates immediately after IG treatment (the risk window, RW) and during a control window (CW) sufficiently remote from treatment to be assumed to represent the patient’s baseline risk in the absence of exposure to IG. A number of the risk factors for TEE that would be difficult to control for in a cohort analysis comparing individuals who received IG versus alternatives (or no treatment) are not problematic for a self-controlled design because these factors can be assumed to be stable within a person between the risk and control interval. The workgroup considered possible comparison groups suitable for a cohort design and performed some cohort analyses to address the “exploratory” objectives, but for our primary analyses these were deemed too vulnerable to confounding.

In the self-controlled analysis, the risk interval was day 0-2, i.e., the day(s) of IG exposure plus the two days after IG exposure, for arterial TEE, and day 0-13 days for venous TEE. Days 14-27 after exposure were designated as the control window for both the arterial and venous outcomes. Since IGIV treatment can be administered on multiple consecutive days, we used the following approach to define post-IGIV risk and control windows for multi-day treatment episodes: each day IGIV was received was considered as "day 0," "day 1" was designated as one day after treatment, "day 2" was designated as two days after treatment, etc. If IGIV was administered over three consecutive days, those three days on which IGIV was administered would be classified as "day 0," after which would come day 1 and day 2, for a total risk window duration of five days (see **Figure 1**, **Figure 2**, **Figure 3**, and **Figure 4**). In addition, gaps of one or two days between IGIV treatment records were allowed in order to account for minor interruptions in a multiple-day treatment episode (e.g., due to weekends).

Figure 1.Risk windows for arterial events, single dose

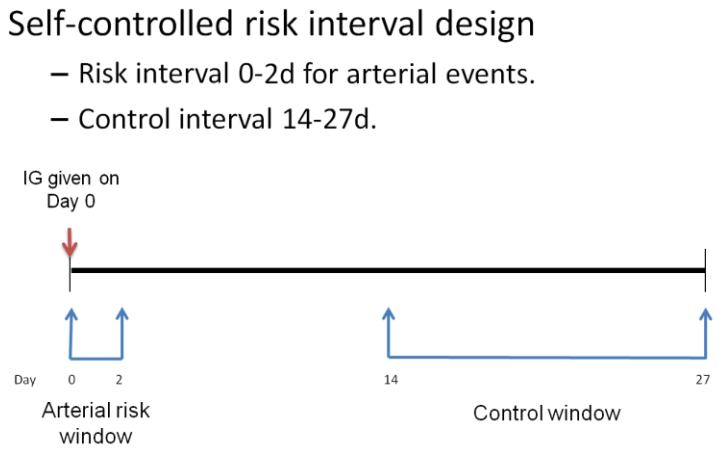


Figure 2. Risk windows for arterial events, multiple doses

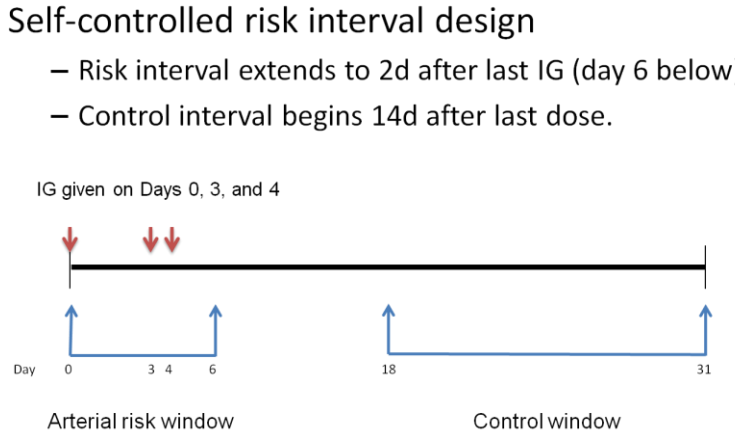


Figure 3. Risk windows for venous events, single dose

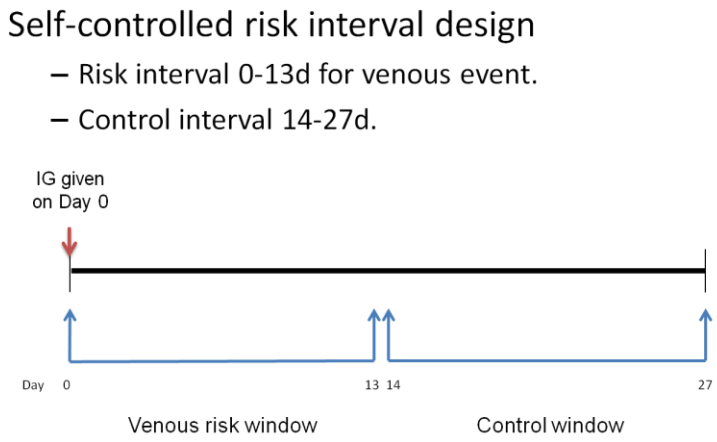
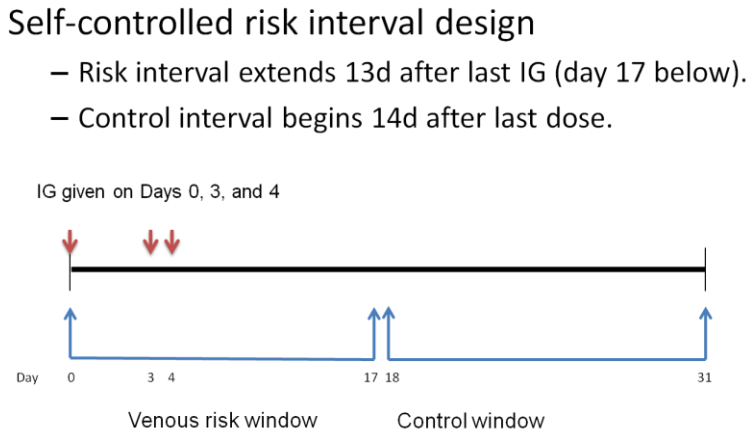


Figure 4. Risk windows for venous events, multiple doses



For the venous TEE endpoint, the self-controlled analyses included only risk or control window events that occurred following outpatient infusions of IGIV. Among hospitalized patients, the risk of venous TEE may increase substantially with prolonged immobility,[32] which would violate our study design's assumption that for a given patient the risk of a TEE is constant across the designated risk and control windows.

The choice of these risk and control windows was based on what is known about the temporal relationship between IG use and arterial and venous TEE incidence from prior literature and FAERS data,[28,29] as well as preliminary data obtained from modular programs run on the SDD.[33] Risk and control windows were defined relative to the proximate IGIV date, viz., the date of the IGIV treatment that occurred on or prior and proximal to the TEE date. To ensure that patients had observable risk and control periods, we required that each patient had health plan enrollment and no IGIV use for at least 20 days following the proximate IGIV date, with 7 observable days being the minimum length for the control period. (A caveat: if a patient was deceased upon discharge from a risk window TEE hospital encounter, that patient would still be included in the analysis.)

Stratifying by patient and conditioning on the fact that each case had exactly one event, stratified conditional Poisson regression was used to estimate the TEE incidence density or rate in the risk window relative to the control window (rate ratio or RR). Because our concern was focused on safety rather than

effectiveness, we pre-specified a one-sided null hypothesis: that the relative risk of TEE on a day during the defined risk interval directly after immunoglobulin exposure compared with a day in the unexposed control interval is not greater than 1.0. Due to data sparseness, exact tests were used for these hypothesis tests.[34]

The analysis methods are shown schematically in **Table 2** below. The exposure risk interval and control interval were specified a priori. Change in TEE risk in relation to time-since-IG-treatment was further explored in the analyses using automated data. These exploratory analyses evaluated (but did not inform) the choice of the risk and control intervals.

We conducted an exploratory analysis in which we stratified the episodes of IG treatment on calendar year of administration and compared relative risk estimates from the more recent time period (2011-2012) with those from 2006-2010. The more recent time period should encompass the period when some manufacturers modified their processes to decrease procoagulant activity. (However, even among brand identified IGIV, we could not necessarily differentiate whether or not a patient received product produced under the processes intended to reduce residual procoagulant activity.)

Table 2. Overview of analysis methods

IG Exposure	TEE Outcome	Analysis	Method	Notes
Any IGIV	Arterial TEE	Primary	SCRI using chart-confirmed data	Risk interval: 0-2 days Control interval: 14-27 days
Any IGIV administered in an outpatient setting	Venous TEE	Primary	SCRI using chart-confirmed data	Risk interval: 0-13 days Control interval: 14-27 days
Subgroups defined by IGIV product, dose, and indication	Arterial TEE	Secondary	SCRI using chart-confirmed data, subgroup analysis	Risk interval: 0-2 days Control interval: 14-27 days Also, days since treatment (day 0 versus the control period, day 1 versus the control period, and day 2 versus the control period)
Subgroups defined by IGIV product, dose, and indication	Venous TEE	Secondary	SCRI using chart-confirmed data, subgroup analysis	Risk interval: 0-13 days Control interval: 14-27 days Also, days since treatment (day 0 versus the control period, day 1 versus the control period, and day 2 versus the control period)
Arterial TEE endpoint: Any IGIV administration in an inpatient or	Any TEE (venous or	Secondary	SCRI using chart-confirmed data	Risk interval: 0-2 days (arterial); 0-13 days

IG Exposure	TEE Outcome	Analysis	Method	Notes
outpatient setting Venous TEE endpoint: Any IGIV administration in an outpatient setting	arterial)			(venous) Control interval: 14-27 days
Subgroups defined by history of outcome event, baseline arterial TEE risk, days since treatment, treatment episode number, infusion rate, and calendar year of treatment (especially 2006-2010 versus 2011-2012 to assess the possibility that newer manufacturer processes are producing safer IG products)	Arterial TEE	Exploratory	SCRI using chart-confirmed data, subgroup analysis	Risk interval: 0-2 days Control interval: 14-27 days Also, days since treatment (day 0 versus the control period, day 1 versus the control period, and day 2 versus the control period).
Subgroups defined by history of outcome event, baseline venous TEE risk, days since treatment, treatment episode number, infusion rate, and calendar year of treatment (especially 2006-2010 versus 2011-2012 to assess the possibility that newer manufacturer processes are producing safer IG products)	Venous TEE	Exploratory	SCRI using chart-confirmed data, subgroup analysis	Risk interval: 0-13 days Control interval: 14-27 days Also, days since treatment (day 0 versus the control period, day 1 versus the control period, and day 2 versus the control period)
Any route of IG (IV, SC, IM)	Arterial TEE, Venous TEE	Exploratory	Cohort analysis using electronic data using all eligible IG-exposed individuals (IV, IM, or SC), without chart confirmation	Explore varying risk intervals: Arterial – 0-1, 2-7, 8-30, 31-90, 91-180, 181-365, Venous – 0-1, 2-7, 8-30, 31-90, 91-180, 181-365 Explore heterogeneity of risk between subgroups, e.g., IV vs. SC, IM users
Any route of IG (IV, SC, IM)	Arterial TEE, Venous TEE	Exploratory	Cohort analysis using electronic data using individuals with IG indication with and without IG treatment, without chart confirmation	Explore calendar time trends Explore TEE incidence among exposed vs. unexposed individuals

C. IDENTIFICATION OF IMMUNOGLOBULIN NEW USERS

We identified health plan members of any age with administration of any IG product (IV, SC, or IM) using CPT, HCPCS and ICD-9-CM procedure codes and National Drug Codes (NDC) for non-specific IG (**Appendix B**). The study population consisted of new IGIV users who initiated treatment from January 1, 2006 through December 31, 2012. New IGIV users were defined as those with an IGIV treatment preceded by a period of 183 days of medical and pharmaceutical insurance coverage, during which no IG treatments were observed (see **Figure 5**). The first such IGIV treatment date was defined as the patient's new use date.

Patients were followed from the IGIV new use date until the first occurrence of an inpatient TEE diagnosis during a risk or control window following an eligible IGIV treatment episode, loss of enrollment, or the end of the study period (**Figure 6**). Arterial and venous TEEs were considered as separate, co-primary endpoints. For each patient and TEE class (arterial or venous), we identified the first such inpatient TEE diagnosis and the proximate IGIV treatment episode (i.e., the one that was prior to or coincident with that TEE hospitalization).

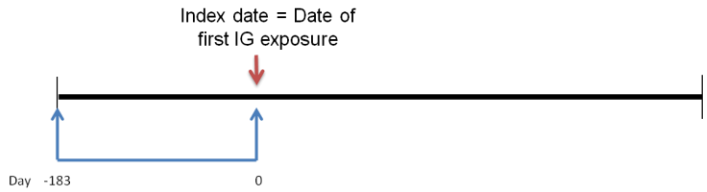
An IGIV treatment episode was considered ineligible for the self-controlled analyses if any of the following conditions were met:

a. The treatment episode included receipt of subcutaneous or intramuscular IG, or 2+ distinct IGIV brands.
b. The treatment episode was fewer than 20 days away from a prior or subsequent treatment episode, or from the end of the study period (**Figure 6**). (A SCRI design requires that the patient have an observable control window.)
c. A possible indication for IG use was not observed in the 183 days prior to the treatment episode.
d. An inpatient TEE diagnosis code meeting the endpoint definition was observed in the 30 days prior to the treatment episode.
e. Inpatient IGIV treatment episodes were not eligible for the venous TEE risk assessment.

For the arterial TEE endpoint, both outpatient and inpatient IGIV administrations were included as potentially eligible exposures of interest, and the endpoint definition consisted of an inpatient TEE diagnosis (principal, secondary, or position-unspecified). For the venous TEE endpoint, we restricted to outpatient IGIV exposures due to concerns about time-varying venous TEE risks due to prolonged immobility in hospitalized patients. In evaluating venous TEE risk, only outpatient IGIV administrations were included as eligible exposures, and the endpoint definition consisted of a primary or position-unspecified venous TEE diagnosis code (i.e., a diagnosis code that may represent the underlying reason for the patient's hospital admission).

Figure 5. New IG user definition

- Continuous plan enrollment for ≥ 183 days before the index date
- No administration of any IG product for ≥ 183 days before the index date

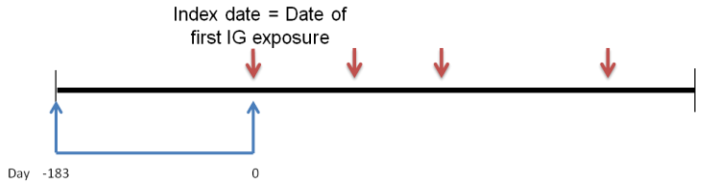


New user must have at least 183 days of enrollment and no IG use.

Figure 6. User contributing multiple episodes

Episodes are included if "new user" criteria are met and patient then has multiple treatment episodes.

- Episodes must be at least 20d apart
- Episodes in which the patient receives >1 product of interest are excluded



In this example, new user criteria is met and the user contributes 4 episodes.

D. SUBGROUP ANALYSES

Several pre-specified secondary and exploratory stratified analyses were conducted, with subgroups defined by IG product, IG dose, history of TEE, IG treatment episode number, and IG indication. Data on characteristics used to stratify patients in these analyses were obtained through available administrative data and (where possible) confirmed during chart review. For example, product type was captured by medical record review, product-specific HCPCS codes, and product-specific NDC codes.

E. IDENTIFICATION OF OUTCOMES OF INTEREST

The co-primary outcomes of interest were arterial and venous TEEs. The former included cases of AMI and acute ischemic stroke (AIS); the latter included cases of lower-extremity DVT, PE, and cerebral venous thrombosis (CVT). International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) discharge diagnosis codes from inpatient encounters were used to identify potential cases (see **Appendix C**).

Arterial thrombi are commonly attributable to atherosclerotic plaque rupture and platelet-mediated thrombosis (e.g., type 1 AMI, cerebral ischemia secondary to large-artery thrombosis). By contrast, venous thrombi develop in vessels with slower blood flow and lower shear stress, and stasis and

hypercoagulability rather than endothelial injury are the predominant causes of venous thrombi.[35,36] Due to these differences in pathophysiology, the development and propagation of venous TEEs often occurs over a longer period of time relative to an arterial TEE triggered by a plaque rupture.[37] Despite these differences, arterial and venous thrombi share some common risk factors, including coagulation cascade dysregulation and systemic inflammation. IG recipients are believed to be at an increased risk for thrombosis in both the arterial and venous circulation due to increased blood viscosity or the presence of other pro-thrombotic plasma constituents in IGIV products, which would contribute to blood stasis and hypercoagulability, respectively. The pre-specified risk window is slightly different for arterial and venous events, since in prior reports arterial events have been concentrated in the first 24 hours after treatment, whereas venous events have typically been observed two or more days after infusion.[28] The primary analyses examined arterial and venous TEE risks separately due to their differing pathophysiology and expected temporal relationship with IGIV exposure. A secondary outcome of interest was the composite outcome of any TEE (arterial or venous).

A well-validated algorithm for all types of TEE is not available, though an AMI algorithm has been validated in Sentinel.[38] During the pilot phase of Sentinel known as 'Mini-Sentinel,' the Mini-Sentinel Protocol Core reviewed and recommended algorithms for stroke, PE, and DVT. In addition, a Mini-Sentinel systematic review of administrative diagnosis codes for stroke documented algorithms with high positive predictive values.[39] The literature is not as extensive for venous TEE. The venous TEE codes included are based on the Mini-Sentinel Protocol Core recommended algorithm, which has been well-validated in hospital claims. The key source of information about this algorithm is a review of 3456 cases hospitalized between 2005 and 2007 in a large number of hospitals.[40] The PPV for any acute venous thrombosis for a venous TEE code in a secondary position was 75%. The venous TEE endpoint definition was also informed by preliminary data available from a vaccine safety study in the Sentinel database.[41] To capture the serious event of cerebral venous thrombosis, two codes (325.xx and 437.6) were added to the Sentinel algorithm but the PPV for these is based on limited data.[42] The 453.8x code series was removed from the algorithm because most codes refer to upper extremity and torso thrombosis, which may be related to a central venous catheter rather than a pro-thrombotic effect of the infused IG.

Within the Sentinel Common Data Model, diagnosis codes associated with inpatient encounters are categorized as principal, secondary, or "unable to classify" (i.e., position unspecified). These classifications reflect standard coding practices and the addition of a third category to accommodate heterogeneity across Sentinel Data Partners in how encounters and coding positions are defined. Under Uniform Hospital Discharge Data Set (UHDDS) guidelines used by U.S. hospitals and insurers,[43] inpatient diagnoses are coded as follows:

- *Principal diagnosis*: the condition established after study to be chiefly responsible for occasioning the admission of the patient to the hospital
- *Secondary diagnosis*: a condition also present on admission, that developed during the hospital stay, or that influenced the care of the patient or length of stay

In the SDD, there are also position-unspecified diagnoses that cannot be classified as principal or secondary. These diagnosis codes may represent diagnoses originating from non-facility claims associated with an inpatient stay, e.g., a physician services claim submitted separately from the facility claim. Codes of this type generally come from claims-based Data Partners.

For the ascertainment of potential venous TEEs following outpatient administrations of IGIV, we included primary or position-unspecified diagnosis codes from inpatient hospitalizations. In assessing arterial TEE risk, where we considered IGIV administrations occurring in both inpatient and outpatient

settings, all inpatient arterial TEE diagnoses (any position) were selected for chart review. The choice of a broader endpoint definition for the arterial TEE endpoint was due to the fact that under standard coding practices, events that develop during the course of a hospital stay would be listed as secondary diagnoses on hospital discharge and billing forms.[44]

All TEE algorithms for use in the assessment were validated as described in the validation protocol.[31] Definite cases (see section J) were included in the primary analyses. Outcomes were selected primarily based on likelihood that they could be validated using objective criteria. Transient ischemic attacks (TIA) and non-MI coronary syndromes (e.g. unstable angina, ICD-9-CM code 411) were considered but excluded due to subjective validation criteria. Also excluded were a number of less common types of thrombosis, particularly those that are likely related to comorbidities (e.g. portal vein thrombosis is typically related to severe liver disease). Outcomes less specific to thrombosis, such as abdominal ischemia, were excluded. Hemorrhagic stroke was considered because it can be a consequence of cerebral venous occlusion, but ultimately excluded because most hemorrhagic strokes are not related to a cerebral venous occlusion. Most of these outcomes are severe enough that medical attention should be sought if they occur. However, there may be a lag between onset and diagnosis for venous TEE, particularly DVT.

F. POTENTIAL CONFOUNDERS

Because the primary study design was self-controlled, the analysis was inherently adjusted for measured and unmeasured confounders that do not vary over relatively short periods of time, such as age, gender, race/ethnicity, and chronic disorders (though the severity of some of these might wax or wane).

A time-varying covariate that is of interest is the potential reduced risk of TEE due to IG anti-inflammatory effects. This would imply that the total effect of IG treatment on TEE risk may include a longer term benefit mediated by an anti-inflammatory causal pathway as well as a harm due to short-term risk of thrombosis. An anti-inflammatory benefit might tend to bias upwards our estimate of the short term relative risk of TEE after IG, if the beneficial pathway reduces risk during our designated control interval 3-4 weeks post-treatment. Exploratory analyses of the trajectory of TEE incidence over time since last dose were conducted to help evaluate the possibility of time-varying confounding by anti-inflammatory effects of IG. Another potential time-varying confounder was pregnancy, which may increase the risk of TEE. For this reason, an IGIV treatment episode was excluded if the individual was found to be pregnant or post-partum based on chart review.

The exploratory analyses were not self-controlled; they were cohort analyses implemented by Cox regression (described in more detail below in section H). They adjusted for measured TEE risk factors using a disease risk score summarizing the relation of TEE risk to the demographics, healthcare utilization, type of indication for IG use (as categorized in **Appendix A**), comorbidities, and treatments identified during the 183-day baseline period. **Appendix D** lists the variables that were used to measure TEE risk factors during the baseline period preceding the index date. The purpose of combining the TEE risk factors into a summary disease risk score was two-fold: 1) to stratify patients in the self-controlled analyses by level of risk in order to evaluate possible effect modification whereby IGIV may be more or less safe according to level of TEE risk, and 2) to adjust for potential confounders in the exploratory cohort analyses that compared exposed individuals versus unexposed individuals. Age on the index date and sex were determined from the SDD's demographic file. Calendar year was also included in disease risk score calculations to account for any changes in practice that may influence event risk or detection. As in the primary self-controlled analyses, pregnant and post-partum women were excluded from the

exploratory cohort analyses due to concerns about time-varying confounding, and because the accurate detection of venous TEEs in pregnant women is complicated by the existence of ICD-9-CM diagnosis codes that are specific to venous TEEs in pregnant women and have a low PPV according to prior research.[45] Codes used to define periods of pregnancy for the cohort analyses are listed in **Appendix D**

Conditions listed in **Appendix D** were identified by ICD-9-CM diagnosis codes recorded during an outpatient, inpatient, or emergency department visit from the SDD's diagnosis file. Prescription drugs listed in **Appendix D** were ascertained from SDD's outpatient pharmacy dispensing file using NDCs. Over-the-counter use (e.g. aspirin) as not captured unless prescribed and billed to insurance. Due to the sparseness of race data across Data Partners, race was not included as a covariate. **Appendix A** lists codes used to determine IG indication from the electronic data in the exploratory analyses.

In addition to stratification by quantile of disease risk score, history of TEE was of particular interest as an effect modifier because this is likely to be documented in patient's medication charts and is already used to guide TEE prevention recommendations for IG use. Secondary analyses of each primary outcome (arterial, venous) assessed whether history of that outcome event (arterial, venous) may be an effect modifier of the association. Similarly, type of indication (**Appendix A**), dose, product, treatment episode number, and time since last dose were identified as important clinically relevant factors that may modify the association.

G. FOLLOW-UP

1. Self-controlled analyses

The primary analyses included new users of IGIV who had a chart-confirmed TEE during a post-treatment risk interval or control interval. In analyses of arterial TEE, we included only the first arterial TEE during the four weeks following a treatment episode; in analyses of venous TEE, we included only the first venous TEE during the four weeks following a treatment episode. Ordinarily, a patient's control window was two weeks in length (days 14-27 following the proximate IG date). Several factors may have resulted in the truncation of a patient's control window: the end of the study period (December 31, 2012), disenrollment not attributable to death, another episode of IG treatment, or an expected subsequent IG treatment based on an established pattern of frequent IG treatments. If any of these events took place during days 21-27 following the proximate IG date, the control window was shortened to include only observable days. If a patient had fewer than seven observable control period days, the patient was excluded as uninformative.

2. Exploratory cohort analyses

For our exploratory objective D1 cohort analyses, we followed new IG users from their treatment initiation date until the earliest occurrence of the first outcome event of interest, death, disenrollment from the health plan, end of medical benefit, the study end date, or one year of patient follow-up. For our exploratory objective D2 cohort analyses, we followed individuals with an IG indication from the date that indication was recorded until the earliest occurrence of the first outcome event of interest, death, disenrollment from the health plan, end of medical benefit, or study end date. Cox proportional hazards regression was used to evaluate the relationship between IG exposure and TEE risk in both sets of analyses. In both analyses the timeline for defining risk sets was calendar time.

H. STATISTICAL ANALYSES

1. Self-controlled analyses

The primary and secondary objectives were addressed using a SCRI design that compared TEE incidence densities during a post-exposure risk interval (days 0-2 for arterial outcomes, days 0-13 for venous outcomes) and a two-week comparison interval (days 14-27 for both types of outcomes). Because the time at risk on day 0 only includes the period after exposure to IGIV, we treated day 0 as a half-day in our analyses.

The risk and control intervals are diagrammed below for analyses of arterial outcomes (**Figure 1** and **Figure 2**) and venous outcomes (**Figure 3** and **Figure 4**), after an episode of IGIV treatment that is delivered on a single day (**Figure 1** and **Figure 3**) or multiple days (**Figure 2** and above). The TEE incidence density or rate ratio (RR) for the risk window compared to the control window was estimated with stratified conditional Poisson regression.[46] With the SCRI method, inference about the RR is informed only by IG-treated individuals who had an outcome event during the risk or control interval.

2. Estimation of attributable absolute risk

The number of TEEs caused by IGIV per 10,000 patients and 10,000 treatment episodes was quantified using the RR estimates from the self-controlled analyses, the number of IGIV treatment episodes eligible for study inclusion, and the proportion of potential risk window cases that could be confirmed or ruled out by chart review.

$$Attributable\ incidence\ rate = \frac{E}{T * C} * \left[1 - \left(\frac{1}{RR}\right)\right] * 10{,}000$$

Where E = # of chart-confirmed cases in the risk window
T = # of courses of IGIV therapy from which risk window cases could have arisen
C = proportion of potential risk window cases that could be chart-reviewed and either confirmed or ruled out.
RR = relative risk estimate from self-controlled analysis (incidence density in risk window relative to incidence density in control window)

3. Exploratory cohort analyses

a. *Overview*. The exploratory cohort analyses included an assessment of TEE risk in a cohort of new IG users (exploratory objective D1) and in a cohort of patients with a recognized indication for IG, including both IG users and non-users (exploratory objective D2). In both sets of cohort analyses, Cox regression was used to assess the relationship between IG treatment, classified by recency of exposure of days, and the relative hazard of arterial and venous TEEs. The timeline used for grouping patients into risk sets was calendar time. To adjust for baseline TEE risk, all analyses were stratified by disease risk score decile and Data Partner.

b. *Objective D1 exploratory cohort analyses: TEE risk in new IG users, restricted to outpatient IG administrations.* These analyses included eligible new users of IM, SC, or IGIV with a recognized indication for IG use (defined in **Appendix A**) who initiated IG use in 2006-2012. Follow-up began on the date of the first IG treatment claim that was preceded by at least 183 days of treatment-free enrollment. In addition, patients were required to have a recorded diagnosis representing a potential IG indication during this 183-day lookback period. Follow-up ended at

the first occurrence of a principal inpatient TEE diagnosis, or at censoring due to disenrollment, the end of the study period, or reaching a full year of follow-up. Separate analyses were conducted for the arterial and venous TEE endpoints.

The primary explanatory variable of interest was recency of IG exposure in days, coded as a time-varying covariate and classified as follows: days 1-2 post-IG, days 3-13, days 14-27, days 28-90, days 91-180, or days 181+. Due to data sparseness, the latter three categories were combined into a single group (days 28+) and used as the reference exposure category.

Our primary interest in this analysis was the temporal relationship between IG treatment and TEE risk. At the time this study was conducted, specific treatment dates during a hospital stay were not available for inpatient IG treatment records in the SDD. For this reason, we censored patients during periods of hospitalization, removing them from the study cohort until they had been discharged and a subsequent outpatient IG treatment record was observed.

To examine patterns in the relative hazard of TEE across subgroups, separate models were fit for distinct subgroups of patients defined by route of administration (intramuscular, subcutaneous, intravenous or unspecified), indication category (autoimmune/inflammatory disorder, immune deficiency, or others) as determined from the administrative data, and baseline TEE risk (upper two DRS deciles at each Data Partner defined as high risk; all other patients as low risk).

c. *Objective D2 exploratory cohort analyses: TEE risk in patients with a recognized indication for IG use (both IG users and non-users).* Individuals with recognized IG indications were identified using the codes in **Appendix A**. Patient follow-up began after a possible indication and at least 183 days of health plan enrollment had been observed. Follow-up ended at the first occurrence of a principal or secondary inpatient TEE diagnosis, or at censoring due to disenrollment, the end of the study period, or reaching a full year of follow-up. Separate analyses were conducted for the arterial and venous TEE endpoints.

   IG exposure status during follow-up was coded as a time-varying covariate. Cox regression was used to evaluate the relative hazard of TEE across levels of IG exposure status (unexposed, days 0-60 post-IG, or days 61+ post-IG), with unexposed patients serving as the reference group. In subgroup analyses, we stratified patients by calendar year (2006-2010 or 2011-2012) to explore whether the IG-associated TEE risks were reduced during the 2011-2012 period, after IG products may have been modified as part of risk-mitigation efforts by industry.

d. *Use of chart review results to inform exploratory cohort study design choices*. The exposure and endpoint definitions used in the exploratory cohort analyses were informed by the results of chart review conducted for the primary self-controlled analyses. In the exploratory D1 cohort analyses, where we were primarily interested in TEE incidence across finely grained categories of IG recency, we included only outpatient IG treatment episodes, and our endpoint definition was restricted to principal-position discharge diagnosis codes for TEE. Chart review had shown that the temporal relationship between IG exposure and TEE onset could not be determined reliably from administrative data in hospitalized patients. (In the SDD, all procedure and diagnosis codes associated with a hospital encounter are typically assigned a single date: the date of the hospital admission.) In the exploratory D2 cohort analyses, where we were primarily interested in changes in risk across calendar time, all IG exposures were included, and the endpoint definition included both principal and secondary inpatient discharge diagnosis codes

for TEE, which would reflect both the patient's reason for admission and events that occurred during the hospital stay.

4. Disease risk score

Arterial and venous TEE disease risk score (DRS) covariate coefficients (betas) were obtained from a time-to-event analysis of predictors of TEE risk in a cohort of IG-untreated patients with a recognized indication for IG use (**Appendix A**). Cox regression was used to estimate the contribution of individual TEE risk factors (evaluated during a 183-day baseline period) to a patient's overall TEE risk. (See **Appendix D** for details.) The DRS was the linear predictor (xbeta) yielded by the fitted Cox model. Separate DRS models were fit for the arterial and venous TEE endpoints at each participating Data Partner.

A Cox linear predictor was calculated for each patient in the self-controlled and exploratory cohort analyses using the DRS coefficient weights obtained from each Data Partner. These linear predictors were averaged with inverse-variance weighting to obtain a single arterial TEE DRS and venous TEE DRS for each patient. The DRS were used in two ways: (a) to examine whether any of the IGIV effects that may be found in our primary self-controlled analyses are larger (or smaller) in patients who are at higher (or lower) levels of risk for TEE, and also (b) to adjust for potential confounders in our exploratory cohort analyses (which need such adjustment more than our primary self-controlled analyses).

I. THROMBOEMBOLIC EVENTS AND IMMUNOGLOBULIN EXPOSURE VALIDATION

1. Overview of chart review process

Possible post-IGIV risk and control window TEE cases identified in the SDD underwent medical record review. Charts were reviewed to confirm the event, obtain information about the onset of the event, confirm the exposure and dates of exposure, and obtain information about the details of exposure (dose, infusion rate, specific product, route of administration). Information on indication for IGIV use, history of prior events, and major cardiovascular and thrombotic risk factors were also collected. Nurses abstracted the information into computerized abstraction forms and recorded chart page numbers for key information. Academic physicians with appropriate clinical expertise (e.g., in cardiology, hematology or vascular neurology) reviewed the abstracted data and adjudicated the cases according to the criteria described below. Computerized adjudication forms were used, and consistency and completeness checks were programmed to alert abstractors and adjudicators to potential errors. In general, each case was reviewed by only one physician. Adjudicators could request a second opinion if they were unsure about a particular case. To the extent that the chart information on TEE outcome, IGIV exposure, and/or the timing interval was ambiguous, final adjudication decisions were made following discussion and case review by the study investigators.

For exposure verification, the dates and times of all exposures within a specific time window were recorded, including the date and time of the first exposure. The average infusion rate was calculated by using data on dose, time infusion began and ended, and patient weight. The indication for IGIV (e.g., motor nerve defect) was recorded for each patient as well as the specific brand of IGIV if available. The planned regimen including the planned dose, planned number of days per episode, and planned number of episodes, was recorded as well as any differences between the planned regimen and the administered regimen. For patients with a plan for multiple treatment episodes, the planned number of days between episodes was also collected. This allowed for the assignment of a shorter control window

if the planned start of the next treatment episode was within 27 days. The treatment episode number was also collected when multiple treatment episodes were documented. Other data collected on the exposure included location of administration (e.g., inpatient, outpatient infusion suite, home), patient demographics (e.g., age, race), and administration of other therapeutics such as anticoagulants or thrombolytics.

2. Adjudication criteria for study endpoints

The adjudication criteria for acute ischemic stroke (AIS) were based on the 2013 American Heart Association / American Stroke Association definition of ischemic stroke,[47] plus the addition of a "possible" AIS category for cases where chart information was incomplete. Potential cases were adjudicated as a definite, probable, or possible AIS, no AIS, or as status unknown / insufficient information, as described below.

- *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, e.g., computed tomography (CT) or magnetic resonance imaging (MRI), 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).[47]
- *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.

AMI adjudication criteria were adapted from the third universal definition of myocardial infarction developed under the auspices of the European Society of Cardiology, the American College of Cardiology Foundation, the American Heart Association, and the World Health Federation.[48] In addition to the third universal definition of definite and probable AMIs, we added the category of possible AMI to account for cases where parts of a patient's medical chart were unavailable or illegible. If a case could not be counted as a definite or probable AMI or ruled out based on the information available in the chart, a case was classified as a possible AMI if there was a documented physician diagnosis of AMI. The decision tree used to classify potential cases as definite, probable or possible AMIs, no AMI, or status unknown / insufficient information is provided in **Appendix E**.

PE and DVT validation criteria are described in **Table 3**.[49] DVTs of the upper extremities and torso were not included as study outcome events due to the likelihood of time-varying confounding by the presence of central venous catheters.

Potential cerebral venous thrombosis (CVT) cases were adjudicated similarly to AIS cases. Adjudication as a definite CVT case required confirmation by MRI, CT, catheter cerebral angiography, magnetic or computerized cerebral venography, or ultrasound. In the absence of imaging, cases with clinical signs and symptoms consistent with CVT were classified as probable cases.[50] If none of the above were available in the chart but a physician diagnosis was documented, the case was counted as a "possible" CVT. Based on the judgment of the physician adjudicator, potential cases not meeting diagnostic criteria

for confirmation as a definite, probable, or possible CVT were classified as no acute CVT or as having an unknown status due to incomplete documentation or ambiguity.

Table 3. Venous thromboembolism case validation criteria*

	Pulmonary Embolism	Deep Vein Thrombosis
Definite	Confirmed by pulmonary angiography, spiral CT scan, MRI scan, or pathology	Confirmed by conventional venography, compression/ duplex ultrasound, CT scan/CT angiography, or pathology
Probable	If above tests not performed or were indeterminate, but ventilation-perfusion scan findings were of high probability	If above tests not performed or were indeterminate, but impedance plethysomography, radionucleotide venography, or radiolabelled fibrinogen scan test results were reported as positive
Possible	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 IVC filter was placed.	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 IVC filter was placed.
No venous TEE or venous TEE status unknown	Based on the judgment of the physician adjudicator, potential cases not meeting diagnostic criteria for confirmation as a definite, probable, or possible venous TEE were classified as no acute venous TEE or as having an unknown status due to incomplete documentation or ambiguity.	

*A physician diagnosis that reports the criteria used for the diagnosis can qualify as a definite or probable DVT or PE.

For a small number of potential cases, the chart(s) received contained no recorded diagnosis of an acute TEE, no indication that an acute TEE was considered as part of a differential diagnosis, no diagnostic testing, and no symptoms suggestive of a possible TEE. These cases were flagged by the abstractors and not reviewed by the physician adjudicators due to resource constraints. For these cases, if the chart(s) received included the discharge summary for the index TEE hospital encounter, the potential case was considered to have been miscoded and classified as no TEE. Otherwise the case status was classified as unknown due to chart incompleteness. Whether the decision to categorize a potential case as “no TEE” or “unknown and/or insufficient information” was made by the adjudicator or abstractor had no bearing in our analyses.

V. RESULTS

A. IGIV TREATMENT EPISODES ELIGIBLE FOR STUDY INCLUSION

During the study period, we identified 19,008 new users of IGIV and 93,370 IGIV treatment episodes that were eligible for the arterial TEE risk assessment, and 13,888 new users of IGIV and 86,400 IGIV treatment episodes that were eligible for the venous TEE risk assessment (**Table 4**). Selected baseline descriptive statistics for these two IGIV new user cohorts are provided in **Table 5**.

Table 4. Identification of eligible IGIV new users and treatment episodes to define underlying patient cohort for self-controlled analyses

Inclusion criteria	Number of patients meeting criteria for inclusion	Number of IG claims or treatment episodes meeting criteria for inclusion
01. All IG users and IG claims from study period (2006-2012)	68,159	774,444
02. New IGIV users and their associated IG claims	23,203	178,233
03. New IGIV users and their associated IG treatment episodes	23,203	142,347
04. Exclude treatment episodes with IGSC, IGIM or multiple brands	23,134	133,461
05. Exclude treatment episodes with <21 days from prior or subsequent treatment episode, or from the end of study period	21,534	98,412
06. Restrict to treatment episodes where a possible IG indication was observed during the interval [Episode_start-183, Episode_start+1]	19,069	93,555
07.1A. Arterial TEE assessment: Restrict to treatment episodes not preceded by an arterial TEE diagnosis in 30 days prior	19,008	93,370
07.1V. Venous TEE assessment: Restrict to treatment episodes not preceded by a venous TEE diagnosis in 30 days prior	19,040	93,416
07.2V. Venous TEE assessment: Restrict to treatment episodes that included a non-inpatient IGIV treatment record	13,888	86,400

Table 5. Descriptive statistics for IGIV new users eligible for self-controlled arterial and venous TEE risk assessments

Covariate	Arterial TEE risk assessment new user cohort (outpatient and inpatient IGIV): 19,008 patients with 93,370 eligible treatment episodes. N (%)	Venous TEE risk assessment new user cohort (outpatient IGIV only): 13,888 patients with 86,400 eligible treatment episodes. N (%)
Age		
• 0-19 years	3,953 (21%)	1,986 (14%)
• 20-39 years	2,632 (14%)	1,975 (14%)
• 40-59 years	6,117 (32%)	4,951 (36%)
• 60-79 years	5,431 (29%)	4,369 (31%)
• 80+ years	875 (5%)	607 (4%)
Female sex	9,891 (52%)	7,409 (53%)
Eligible IGIV treatment episodes per patient		
• 1 treatment episode	9,953 (52%)	5,438 (39%)
• 2-6 treatment episodes	5,348 (28%)	4,821 (35%)
• 7+ treatment episodes	3,707 (20%)	3,629 (26%)
Potential indications for IG use*		
• Autoimmune/inflammatory condition	11,676 (61%)	9,235 (66%)
• Immune deficiency	6,465 (34%)	5,904 (43%)
• Infection	2,258 (12%)	1,775 (13%)
• Bone marrow or hematopoietic stem cell transplant	499 (3%)	286 (2%)
• Other indication	1,135 (6%)	996 (7%)
Cardiovascular risk factors*		
• Myocardial infarction	526 (3%)	396 (3%)
• Angina	2,098 (11%)	1,583 (11%)
• Atrial fibrillation or flutter	1,064 (6%)	808 (6%)
• Ischemic stroke	468 (2%)	370 (3%)
• Peripheral vascular disease	1,195 (6%)	886 (6%)
• Hypertension, uncomplicated	6,795 (36%)	5,270 (38%)
• Hypertension, complicated	1,450 (8%)	1,006 (7%)
• Diabetes	3,641 (19%)	2,750 (20%)
Factors associated with venous thromboembolism risk*		
• Venous thromboembolism	836 (4%)	657 (5%)
• Oral anticoagulant use	1,016 (5%)	774 (6%)
• Hospitalization	6,855 (36%)	5,352 (39%)
• Condition associated with immobility	5,869 (31%)	4,627 (33%)
• Cancer	5,717 (30%)	4,858 (35%)

* Potential indications, cardiovascular risk factors, and venous thromboembolism risk factors were assessed using diagnoses and procedures recorded in administrative data during the 183 days prior to the IGIV new use date. These indication indicator variables are not mutually exclusive, so indication percentages may sum to greater than 100%.

B. MEDICAL RECORD CONFIRMATION OF TEE OUTCOME AND IGIV EXPOSURE

1. Arterial TEE endpoint

For the arterial TEE endpoint, we identified 321 potential risk window (RW) or control window (CW) cases. Charts were requested for the TEE and IGIV encounters. In the event that these charts were unavailable, possibly informative charts for subsequent encounters were selected for retrieval based on diagnosis and procedure codes recorded in the administrative data. Potential arterial TEE cases were abstracted if a chart was received for the index TEE encounter or a subsequent second-choice TEE-related encounter. This criterion for successful chart retrieval was met for 224 potential cases (70%), of which 97 were confirmed as acute TEEs (92 eligible for the IGIV risk assessment and 5 ineligible), 112 were ruled out, and 15 had an unknown outcome status due to chart incompleteness or ambiguity (**Figure 7**). Reasons that charts were unavailable are detailed in **Appendix F**. In **Appendix G**, we present figures showing missing data rates and the disposition of potential arterial TEE cases, stratified by the IGIV-TEE time interval as it appeared in the SDD.

Of the confirmed arterial TEE cases, based on documentation of IGIV exposure in the medical chart(s) received, 16 occurred in the RW (days 0-2 after IGIV), 15 in the washout period (days 3-13), and 12 in the CW (days 14-27). Thirty-nine cases did not receive IGIV in the 30 days prior to TEE onset; for 1 case the interval between IGIV and TEE onset was indeterminate; and for 9 cases the proximate IGIV date could not be determined from the chart(s) received (**Figure 7**).

2. Venous TEE endpoint

For the venous TEE endpoint, we identified 121 potential risk or control window cases. Potential venous TEE cases were abstracted if a chart was received for the index TEE encounter. This criterion for successful chart retrieval was met for 75 potential cases (62%), of which 45 were confirmed as acute TEEs (37 eligible for the IGIV risk assessment and 8 ineligible), 17 were ruled out, and 13 had an unknown outcome status due to chart incompleteness or ambiguity (**Figure 8**).

Of the confirmed venous TEE cases, based on documentation of IGIV exposure in the medical chart(s) received, 9 occurred in the RW (days 0-13 after IGIV) and 7 in the CW (days 14-27). One case did not receive IGIV in the 30 days prior to TEE onset; for 6 cases the interval between IGIV and TEE onset was indeterminate; and for 14 cases the proximate IGIV date could not be determined from the chart(s) received (**Figure 8**). Reasons that charts were unavailable are detailed in **Appendix F**. In **Appendix G**, we present figures showing missing data rates and the disposition of potential venous TEE cases, stratified by the IGIV-TEE time interval as it appeared in the SDD.

3. Chart retrieval process

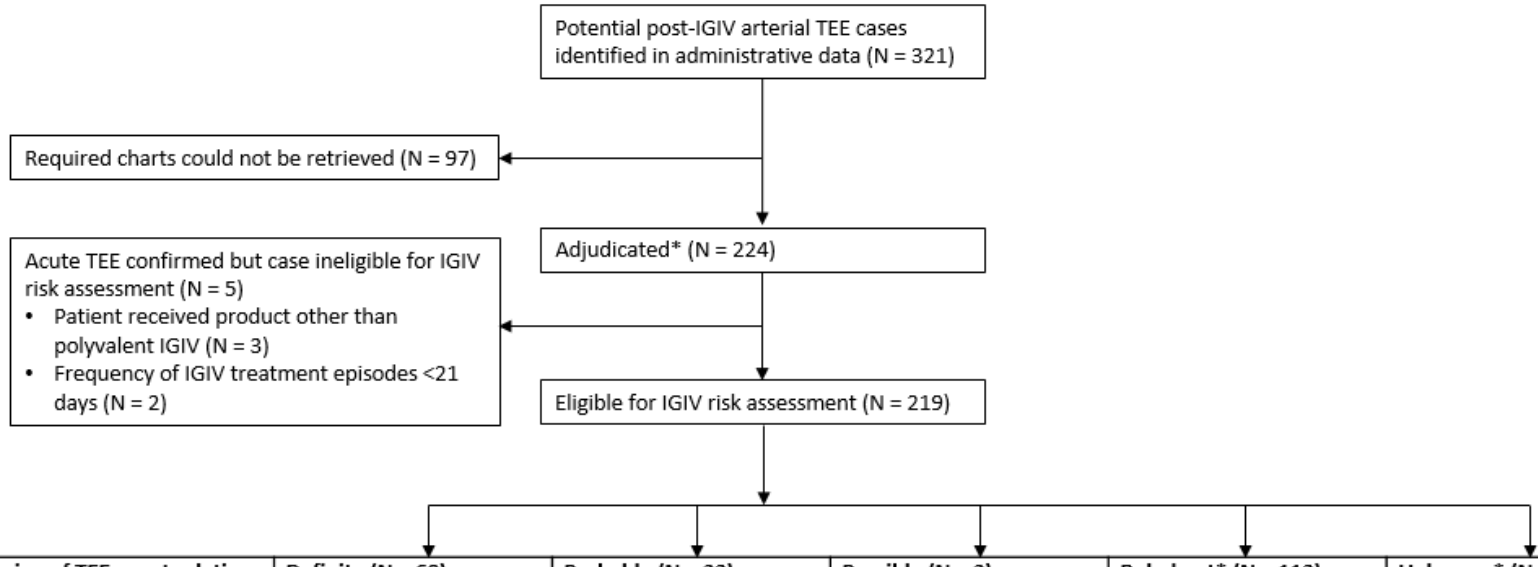
Required charts were unavailable for 30% of arterial TEE cases and 38% of venous TEE cases. This difference may be explained by the differing requirements for chart retrieval completeness for the two endpoints. For the arterial endpoint, cases were abstracted if a chart was received for the index TEE encounter or a subsequent second-choice TEE-related encounter. For the venous endpoint, the chart for

the index TEE was required. This decision was made due to the assumption that the chart from the index TEE encounter would be required to determine the onset date for venous TEEs.

Common reasons that index TEE encounter charts were unobtainable included difficulties in mapping records in the SDD to patient or provider identifiers (N=27), difficulties in identifying the chart corresponding to a requested patient encounter (N=32), and non-response or refusal by healthcare providers (N=64). A more detailed taxonomy of reasons that charts were unavailable is provided in **Appendix F**.

In prior Sentinel product assessments that included chart validation of outcome, charts have been unobtainable for 20-25% of potential cases. Possible reasons for the higher rate of missing data in our study include the following: a longer time lag between our initial identification of potential cases and chart retrieval, our requirement that the chart for the index TEE hospitalization be received for the venous TEE cases, and the fact that some patients in our sample were complex cases with extremely long charts that could not be retrieved and reviewed due to financial constraints.

Figure 7. Disposition of all potential post-IGIV arterial thromboembolic event (TEE) cases ascertained in the Sentinel Distributed Database (SDD)

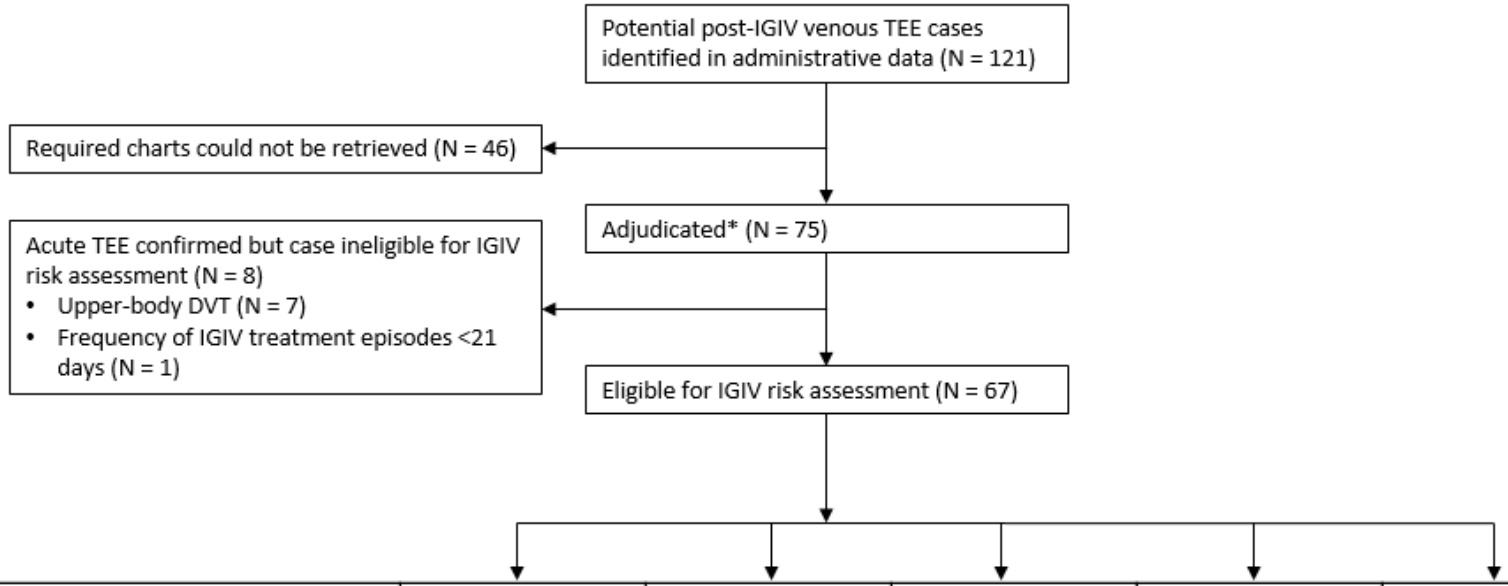


Timing of TEE onset relative to IGIV	Definite (N = 68)		Probable (N = 22)		Possible (N = 2)		Ruled out* (N = 112)		Unknown* (N = 15)	
	AMI = 41	AIS = 27	AMI = 20	AIS = 2	AMI = 1	AIS = 1	AMI = 22	AIS = 90	AMI = 12	AIS = 3
Risk window (days 0-2)	7	5	2	1	1		Uninformative for IGIV risk assessment			
Washout period (days 3-13)	7	6	2							
Control window (days 14-27)	7	4	1							
After control window										
Indeterminate		1								
No IGIV in 30 days prior	15	11	12	1						
Proximate IGIV date not documented in chart(s)**	5		3			1				

*In limited circumstances (see methods section), a potential case could be ruled out or classified as uninformative based on the judgment of the abstractor and was not physician-adjudicated. For the arterial TEE endpoint, this included 6 cases evaluated as insufficient information / acute TEE status unknown and 8 cases where an acute TEE was ruled out.

**For the cases where the proximate IGIV date was not found in the chart: based on the treatment dates recorded in the administrative data, 4 of the definite AMIs would be in the control window and 1 in the washout period, 2 of the probable AMIs would be in the control period and 1 in the washout period, and the 1 possible AIS would be in the washout period.

Figure 8. Disposition of all potential post-IGIV venous thromboembolic event (TEE) cases ascertained in the Sentinel Distributed Database (SDD)



Timing of TEE onset relative to IGIV	Definite (N = 35)	Probable (N = 0)	Possible (N = 2)	Ruled out (N = 17)	Unknown* (N = 13)
Risk window (days 0-13)	8		1	Uninformative for IGIV risk assessment	
Control window (days 14-27)	7				
After control window					
Indeterminate	6				
No IGIV in 30 days prior	1				
Proximate IGIV date not documented in chart(s)**	13		1		

*In limited circumstances (see methods section), a potential case could be ruled out or classified as uninformative based on the judgment of the abstractor and was not physician-adjudicated. For the venous TEE endpoint, this included four cases evaluated as insufficient information / acute TEE status unknown.
**For the cases where the proximate IGIV date was not found in the chart: based on the treatment dates recorded in the administrative data, 5 of the definite venous TEEs would be in the risk window, 7 in the control window, and 1 as having had no IGIV in 30 days prior to TEE onset; the possible venous TEE would be in the risk window.

C. PRIMARY SELF-CONTROLLED RISK INTERVAL ANALYSES

1. Chart documentation of IGIV exposure and per protocol and post hoc analyses

The co-primary analyses were SCRI assessments of the risk of arterial and venous TEE following IGIV. Per protocol, the primary analyses were restricted to cases adjudicated as definite acute TEEs for whom recency of IGIV exposure could also be chart confirmed. Chart documentation of whether and how recently a patient had received IGIV was more likely for potential risk window cases than control window cases, since confirming the latter more often required the successful retrieval of two separate charts rather than just one. For this reason, we also present the results of *post hoc* analyses wherein all confirmed acute TEE cases are included, and the IGIV exposure dates recorded in the administrative data are used if that information was unavailable in the charts received. All confirmed acute TEE cases (definite, probable and possible) were included in these *post hoc* analyses.

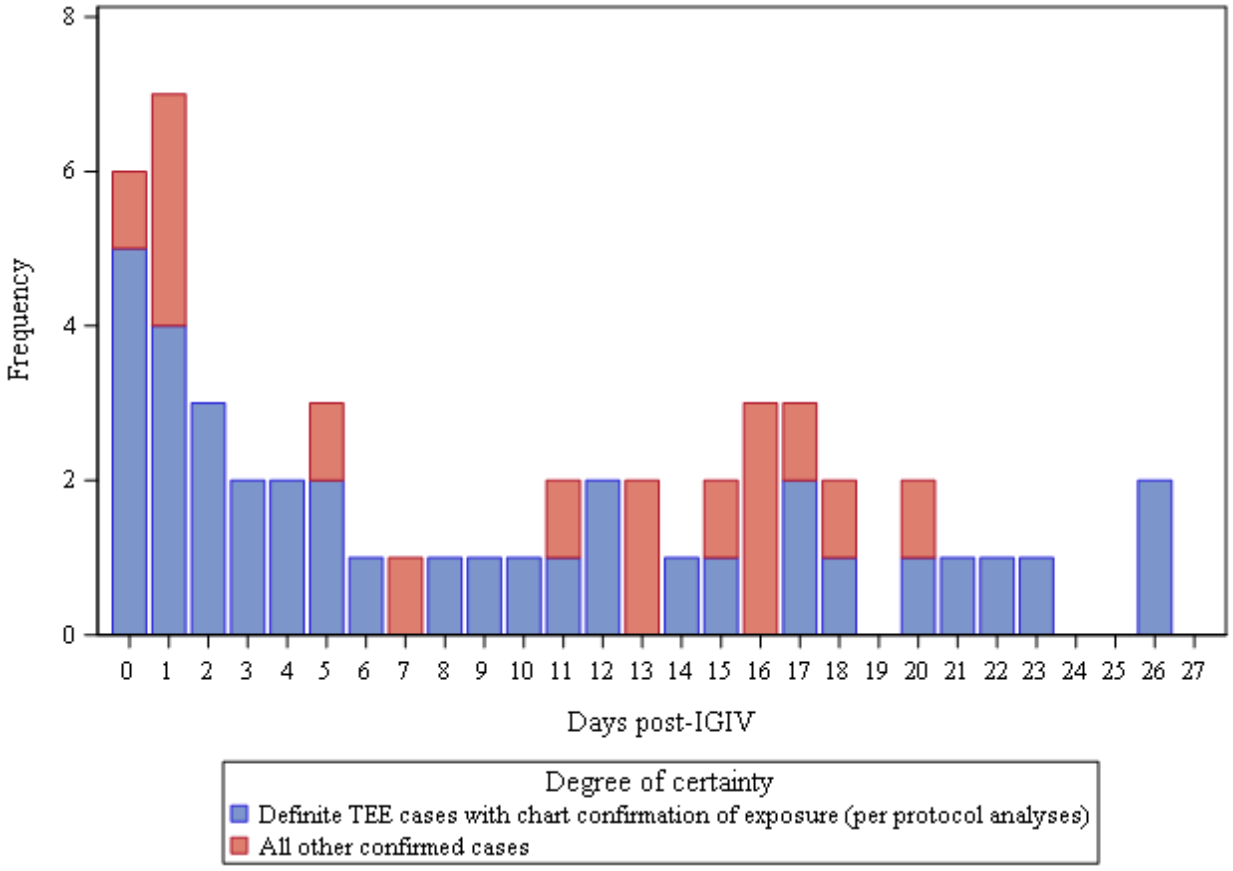
2. Calculating days at risk during risk and control windows

For the arterial TEE endpoint, the RW was days 0-2 following IGIV treatment. For the venous TEE endpoint, the RW was days 0-13. To account for the fact that the portion of day 0 prior to the IGIV infusion would not be in the risk window, it was counted as a half-day rather than a full day, as specified in the study protocol. The CW for both endpoints was days 14-27 post-IGIV. For patients who received a multi-day IGIV treatment, each additional infusion day was added to the length of the risk window. For patients who received IGIV at intervals <28 days, the CW was truncated to the number of control window days that could be observed between treatment cycles.

3. Arterial TEE main results

Twelve definite arterial TEEs were observed during the RW and 11 during the CW. The estimated TEE incidence density or rate ratio (RR) for the RW relative to the CW was 4.69 (95% CI: 1.87, 11.90; one-sided p-value <0.001). With the addition of cases adjudicated as probable or possible, as well as those where IGIV recency could be determined only from the administrative data, there were 16 RW cases and 18 CW cases (**Figure 7** and **Figure 9**). Based on this larger sample of confirmed cases, the arterial TEE RR estimate was 3.72 (95% CI: 1.75, 7.84; one-sided p-value <0.001).

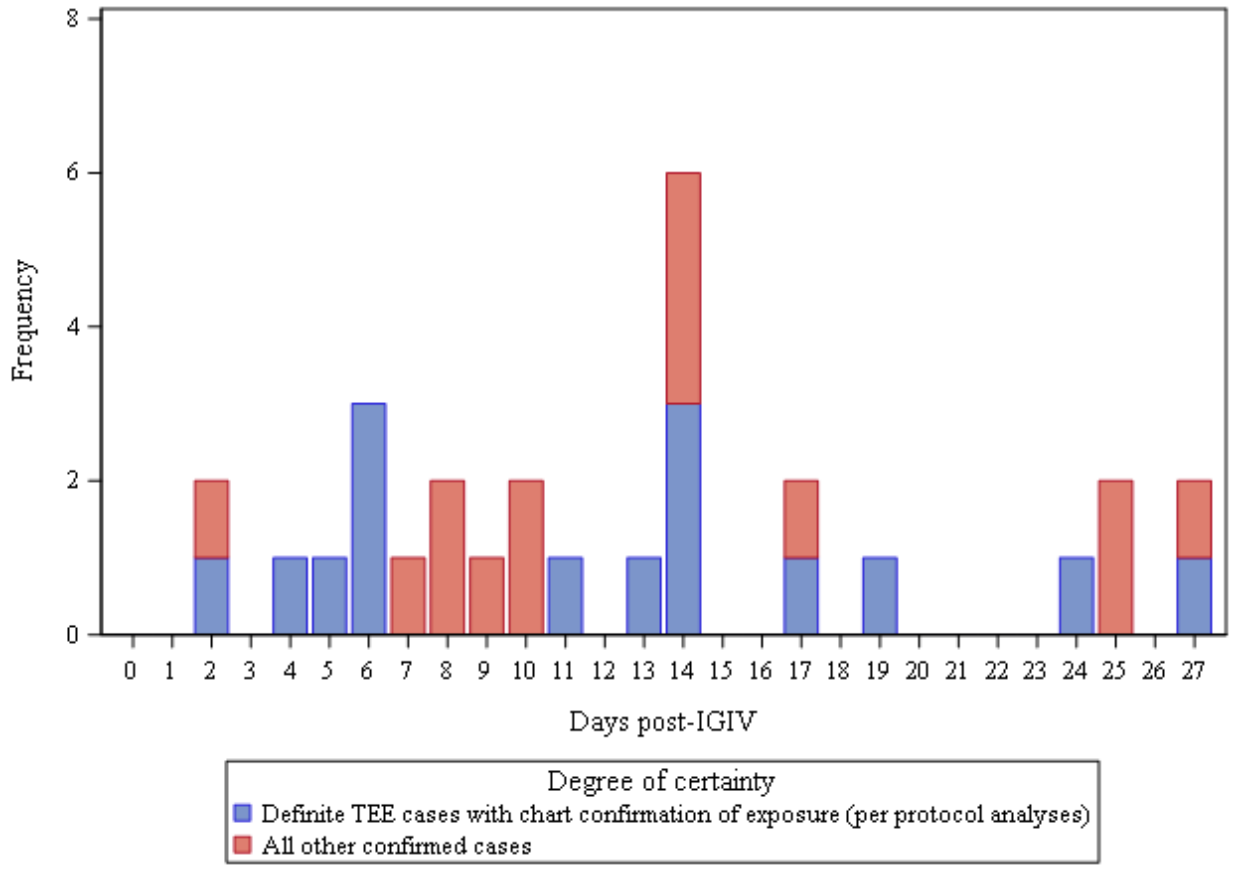
Figure 9. Frequency of arterial thromboembolic event (TEE) cases by recency of exposure to IGIV



4. Venous TEE main results

Eight definite venous TEEs were observed during the RW and 7 during the CW. The estimated RR for the RW relative to the CW was 1.07 (95% CI: 0.34, 3.48; one-sided p-value = 0.55). With the addition of cases adjudicated as probable or possible, as well as those where IGIV recency could be determined only from the administrative data, there were 15 RW cases and 14 CW cases (**Figure 8** and **Figure 10**). Based on this larger sample of confirmed cases, the venous TEE RR estimate was 1.04 (95% CI: 0.47, 2.34; one-sided p-value = 0.53).

Figure 10. Frequency of venous thromboembolic event (TEE) cases by recency of exposure to IGIV



D. SECONDARY COMPOSITE TEE ANALYSIS

Considered together as a composite endpoint, 20 definite arterial or venous TEEs were observed during the RW and 18 during the CW. The estimated RR for the RW relative to the CW was 2.67 (95% CI: 1.27, 5.66; one-sided p-value = 0.004). With the addition of cases adjudicated as probable or possible, as well as those where IGIV recency could be determined only from the administrative data, there were 31 RW cases and 32 CW cases. Based on this larger sample of confirmed cases, the composite TEE RR estimate was 2.05 (95% CI: 1.16, 3.62; one-sided p-value = 0.006).

E. SECONDARY SUBGROUP ANALYSES

We report on results of subgroup analyses for the 38 RW or CW patients included in the primary per protocol analyses. In conducting the subgroup analyses, we first tested for evidence of statistical interaction between RW/CW status and the subgroup classification. Patients with an unknown subgroup status were combined and included in the subgroup analyses as an unknown/unspecified category. Because of the large number of hypothesis tests performed, we report subgroup-specific effect estimates only in the event that the test for interaction reached nominal statistical significance ($p < 0.05$). We repeated these tests for interaction using the full *post hoc* sample of 63 confirmed cases with IGIV recency determined from the chart or administrative data.

1. IGIV brand

Chart information on IGIV brand was available for 13 of the 38 patients included in the per-protocol SCRI analyses. Of these, 11 patients also had a brand-specific billing code recorded in the administrative data. In all 11 cases, the brands identified in the chart and administrative data were concordant. Because the administrative billing codes appeared to be reliable, we used both sources of information to determine IGIV brand for a total of 25 patients; the other 13 cases were classified as brand unspecified. No evidence for interaction by IGIV brand was found for the arterial TEE (per protocol sample: p = 0.46; full sample: p = 0.10) or venous TEE (per protocol sample: p = 0.21; full sample: p = 0.23) endpoints.

2. Dose

Based on chart data, nine patients received high-dose IGIV (≥1 g / kg body weight), 15 received low-dose IGIV, and for 14 patients dose was not documented. No evidence for interaction by IGIV dose was found for the arterial TEE (per protocol sample: p = 0.86; full sample: p = 1.00) or venous TEE (per protocol sample: p = 0.43; full sample: p = 0.88) endpoints.

3. Indication

Eighteen patients had an inflammatory or autoimmune indication for IGIV use, 14 had an immune deficiency indication, five had another type of indication, and for one patient indication was unknown. No evidence for interaction by IGIV indication category was found for the arterial TEE (per protocol sample: p = 0.92; full sample: p = 0.85) or venous TEE (per protocol sample: p = 0.64; full sample: p = 1.00) endpoints.

F. EXPLORATORY SUBGROUP ANALYSES

1. History of the outcome event

Six of 23 definite arterial TEE cases had a prior AMI or ischemic stroke, and five of 15 venous TEE cases had a prior venous TEE. No evidence for interaction by history of a prior outcome event was found for the arterial TEE (per protocol sample: p = 0.63; full sample: p = 0.27) or venous TEE (per protocol sample: p = 1.00; full sample: p = 0.70) endpoints.

2. Baseline TEE risk

Each patient's baseline TEE risk, quantified as a disease risk score (DRS), was estimated based on the diagnoses, procedures, medication use, and healthcare utilization recorded in the administrative data during the 183 days prior to the proximate IGIV treatment episode. We used the 75th percentiles for the arterial and venous TEE DRS distributions for the new IGIV user cohort at the largest Data Partner as cut-points for categorizing patients as "high risk" or "low risk." Using this definition, 15 of 23 definite arterial TEE cases and eight of 15 venous TEE cases were high-risk patients. No evidence for interaction between recent IGIV exposure and baseline TEE risk was found for the arterial TEE (per protocol sample: p = 0.66; full sample: p = 0.48) or venous TEE (per protocol sample: p = 0.33; full sample: p = 0.48) endpoints.

3. Treatment episode number

Based on treatment records in the administrative data, for 15 patients (39%) the IGIV treatment episode that preceded their index acute TEE was their first IGIV treatment. No evidence for interaction by

treatment episode number (classified as first or subsequent) was found for the arterial TEE (per protocol sample: p = 0.68; full sample: p = 0.29) or venous TEE (per protocol sample: p = 0.55; full sample: p = 0.64) endpoints.

4. Days since IGIV treatment

For the arterial TEE endpoint, risk was highest during the day of an IGIV infusion (day 0 events = 6) and the following day (day 1 events = 7), and only slightly elevated on the second day after an infusion (day 2 events = 3) (**Figure 9**). For the venous TEE endpoint, the day on which the largest number of events occurred was day 14 post-IGIV; however, no clear temporal pattern in TEE incidence was observed during the 27 days following IGIV (**Figure 10**).

5. Infusion rate

IGIV infusion rate data were available only for 13 (34%) of the definite RW or CW TEE cases, and for 14 (22%) of the full sample of confirmed TEE cases. Due to the large amount of missing data we did not undertake formal hypothesis tests or RR estimation. Among the 13 arterial and venous TEE cases for whom these data were available, there was no indication that the maximum infusion rate was higher among RW cases (mean = 170 mL / hour) compared to CW cases (mean = 204 mL / hour).

6. Calendar year

The proximate IGIV episode occurred in 2011-12 for 17 definite RW or CW cases and in 2006-2010 for 21 cases. No evidence for interaction by calendar year category (2006-10 versus 2011-12) was found for the venous TEE endpoint (per protocol sample: p = 1.00; full sample: p = 0.26). For the arterial TEE endpoint, evidence for interaction was found in the full sample (p = 0.006) but not in the per protocol sample of definite TEE cases with chart confirmation of exposure (p = 0.20). Stratum-specific risk estimates are shown below in **Table 6**.

Table 6. Calendar year stratum-specific arterial TEE rate ratio estimates

Sample	Stratum	Relative arterial TEE rate in RW compared to CW
Definite TEE cases with chart-confirmed IGIV exposure recency	IGIV exposure 2006-10	2.10 (95% CI: 0.35, 9.27)
	IGIV exposure 2011-12	8.90 (95% CI: 2.42, 40.35)
All confirmed cases with IGIV recency based on chart or administrative data	IGIV exposure 2006-10	1.25 (95% CI: 0.30, 4.04)
	IGIV exposure 2011-12	12.13 (95% CI: 3.59, 52.48)

G. ABSOLUTE ATTRIBUTABLE RISK ESTIMATES

Attributable absolute risk estimates for recent IGIV exposure are provided in **Table 7**. These estimates account for the number of patients at risk (see **Table 5**), the proportion of confirmed RW events attributable to IGIV (based on self-controlled RR estimates), and the proportion of potential cases with missing data on outcome or exposure (see **Figure 7** and **Figure 8**). Results are presented both for the per-protocol analyses, where only definite TEE cases with chart-confirmed IGIV exposure are included, and for the expanded sample with all confirmed TEE cases. For the former, confirmed cases were classified as missing data if they were probable or possible TEEs, or if IGIV recency could not be chart confirmed. Bootstrapped confidence intervals, estimated from 1,000 replicate samples based on the

sample of informative RW and CW cases included in each analysis, were used for the attributable event rate estimates.

Table 7. Estimated absolute risk of arterial and venous TEE attributable to recent IGIV exposure

Outcome	Population at risk	Confirmed RW events	Proportion of cases where TEE status and IGIV recency known	Adjusted* RW event count	Rate ratio from SCRI analysis (95% CI)	Events attributable to IGIV (95% CI)	Attributable event rates (95% CI)
Arterial TEE (per-protocol analysis: definite cases with chart-confirmed IGIV exposure)	19,008 patients with 93,370 eligible treatment episodes	12	0.561	21.4	4.69 (1.87, 11.90)	16.8 (8.18, 27.7)	8.86 (3.25, 14.6) per 10,000 patients; 1.80 (0.66, 2.97) per 10,000 treatment episodes
Arterial TEE (sensitivity analysis: all confirmed cases)	19,008 patients with 93,370 eligible treatment episodes	16	0.651	24.57	3.72 (1.75, 7.84)	18.0 (6.93, 29.7)	9.45 (3.64, 15.6) per 10,000 patients; 1.92 (0.74, 3.18) per 10,000 treatment episodes
Venous TEE (per-protocol analysis: definite cases with chart-confirmed IGIV exposure)	13,888 patients with 86,400 eligible treatment episodes (outpatient only)	8	0.388	20.60	1.07 (0.34, 3.48)	1.35 (-19.8, 20.0)	0.97 (-14.2, 14.4) per 10,000 patients; 0.16 (-2.29, 2.31) per 10,000 treatment episodes
Venous TEE (sensitivity analysis: all confirmed cases)	13,888 patients with 86,400 eligible treatment episodes (outpatient only)	15	0.512	29.27	1.04 (0.47, 2.34)	1.13 (-18.8, 21.1)	0.81 (-13.6, 15.2) per 10,000 patients; 0.13 (-2.18, 2.44) per 10,000 treatment episodes

* Adjusted for missing data: risk window count / proportion of potential cases identified for whom acute TEE status would be determined.

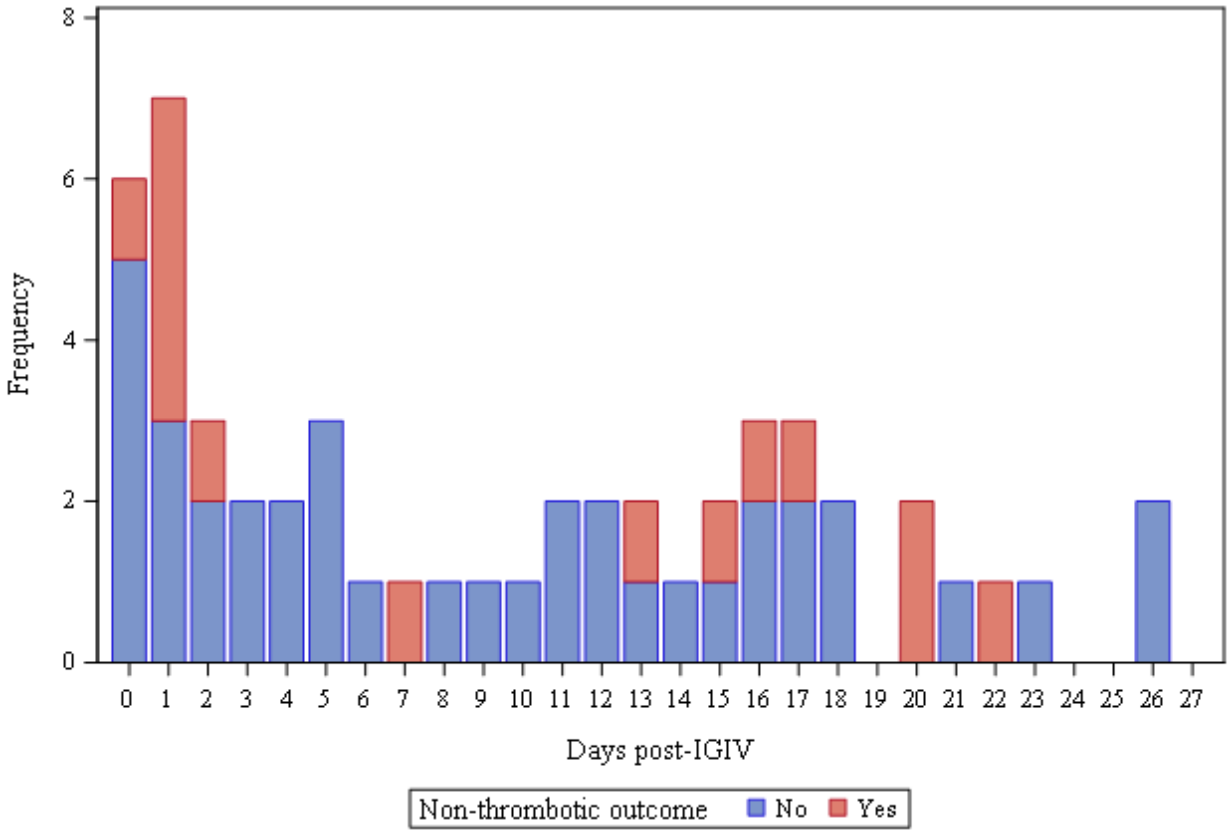
H. ADDITIONAL SENSITIVITY ANALYSES

1. Arterial TEE risk assessment excluding AMI cases with suspected non-thrombotic etiology

Adjudicator comments as to whether confirmed Acute Myocardial Infarctions (AMIs) were likely to have a non-thrombotic etiology were collected and used to sub-classify AMIs. In the full sample of 34 confirmed RW or CW arterial cases with IGIV recency determined from chart or administrative data, six RW cases and six CW cases were classified as type 2 AMIs attributable to demand ischemia. The majority

of these cases occurred in the setting of anemia, respiratory insufficiency, and/or septic shock. Since our initial study hypotheses were primarily concerned with the risk of thrombosis and thromboembolism associated with IGIV, as a sensitivity analysis we repeated our arterial TEE risk assessment after excluding these cases. After applying this exclusion, there were 10 RW cases and 12 CW cases, and the RR estimate was 3.76 (95% CI: 1.43, 9.59). **Figure 11** shows the confirmed arterial TEEs by IG recency and whether a non-thrombotic etiology was suspected.

Figure 11. Frequency of cases meeting arterial thromboembolic event (TEE) endpoint definition by recency of exposure to IGIV and whether a non-thrombotic etiology was suspected



2. Comparison of SCRI risk estimates with chart validation versus administrative data alone

Our arterial TEE risk estimates were considerably smaller in magnitude than we had initially expected based on the high number of apparent same-day events observed in the SDD (prior to chart validation). An unexpectedly high proportion of these possible arterial TEEs were ruled out as true risk-window events during chart review. The high rate of arterial TEE RW false positives was largely attributable to inpatient IGIV encounters. Some of these potential TEE cases were not confirmed as true events, and a significant number of confirmed events were not RW events. At the time of this study, within the SDD, the hospital admission date was generally the date assigned to all inpatient diagnosis and procedure records associated with a given hospital stay. Thus, the true temporal sequence of these diagnoses and procedures could not be determined without chart review. In **Appendix F**, we present figures showing the final disposition of all cases (e.g., confirmed as RW event, confirmed as CW event, ruled out, missing data) stratified by the time interval between IGIV and TEE, as it appeared in the SDD.

In **Table 8**, we compare our SCRI risk estimates with those that would have been obtained had we not performed chart reviews and assumed the following: that all possible TEE cases identified in the SDD were true acute TEE cases, that the SDD dates recorded for the IGIV treatments and TEE diagnoses reflected the exact dates of treatment and event onset, that IGIV treatment preceded TEE diagnosis in all cases where both were recorded on the same date. On both relative and absolute risk scales, the arterial TEE risk estimates were considerably exaggerated in the SCRI analyses that relied on administrative data alone. After restricting to outpatient IGIV records, the SDD-only SCRI estimate was much closer to our SCRI estimate based on chart-validated cases. The results did not differ greatly for the venous TEE analyses, which were restricted to outpatient IGIV treatments and were not subject to the temporality issues arising from inpatient IGIV records.

Table 8. Comparison of self-controlled risk interval (SCRI) IGIV risk estimates based on chart-confirmed data and administrative data alone

Endpoint	Scenario	RW/CW events	Rate ratio	Absolute risk
Arterial TEE	All chart-confirmed RW or CW cases	16/18	3.72 (95% CI: 1.75, 7.84)	9.45 (95% CI: 3.64, 15.6) per 10,000 patients
	All RW or CW as determined from SDD	190/66	16.1 (95% CI: 12.1, 21.7)	93.7 (95% CI: 85.1, 102.1) per 10,000 patients
	All arterial RW or CW as determined from SDD after restricting to outpatient IGIV encounters	17/43	2.21 (95% CI: 1.18, 3.96)	6.71 (95% CI: 1.62, 12.7) per 10,000 patients
Venous TEE	All chart-confirmed venous RW or CW cases (outpatient IGIV encounters only)	15/14	1.04 (95% CI: 0.47, 2.34)	0.81 (95% CI: -13.6, 15.2) per 10,000 patients
	All venous RW or CW as determined from SDD (outpatient IGIV encounters only)	63/57	1.15 (95% CI: 0.79, 1.67)	5.92 (95% CI: -8.36, 19.9) per 10,000 patients

I. EXPLORATORY COHORT ANALYSES

1. Objective D1 exploratory cohort analyses: TEE risk by time since outpatient IG treatment

For the objective D1 exploratory cohort analyses of arterial TEE risk, 18,984 eligible new IG users were identified. Cohort identification steps are shown in Table H 3; baseline cohort characteristics are described in Table H 4. Overall, no statistically significant association was observed between time-since-IG and arterial TEE risk (Table H 5). The majority of the person-time and the events were contributed by patients who received intravenous IG products. In subgroup analyses, non-significant increases in risk were observed during days 1-27 following IG treatment among IGIV users, among patients with a possible autoimmune/inflammatory condition recorded in the administrative data, and among high-risk patients. Inferences about other subgroups were limited by sparse data. See Table H 5 for full results.

For the objective D1 exploratory cohort analyses of venous TEE risk, 18,960 eligible new IG users were identified. Cohort identification steps are shown in Table H 3; baseline cohort characteristics are

described in Table H 4. An elevated risk of venous TEE was observed during days 1-2 following IG treatment (HR = 3.51, 95% CI: 1.67, 7.40, where the reference category was days 28+ post-IG); this risk declined as the time since IG treatment increased (Table H 6). Subgroup analyses revealed that this pattern was most pronounced among patients receiving IGIV products, those with a possible autoimmune/inflammatory condition observed in the administrative data, and—in relative terms—those with a lower baseline risk of venous TEE. A non-significant increase in venous TEE risk shortly after IG exposure was observed in high-risk patients. Inferences about other subgroups were limited by sparse data. See Table H 6 for full results.

2. Review of chart validation data relevant to days 1-2 venous TEE risk signal in objective D1 exploratory cohort analyses

As outlined in the study protocol, one of the motivations for the exploratory cohort analyses was to evaluate the appropriateness of the SCRI RW and CW choices. Because of the increased risk of venous TEEs during days 1-2 detected in the D1 exploratory cohort analyses, we sought to determine whether a similar pattern existed among the chart-confirmed cases included in the SCRI results. In the SCRI analyses, we identified 0 potential day 0 events, 8 potential day 1 events, and 4 potential day 2 events (see Figure G 4).

Charts were received for 4 of 8 potential day 1 venous TEE cases, all of which were coded as principal position diagnoses. In one case, the occurrence of a venous TEE was ruled out; for the other 3, the venous TEE was confirmed but was not a RW event.

- Case 1: The patient had acute shortness of breath on the day after IGIV. PE was considered as part of the differential diagnosis, but was ruled out.
- Case 2: The patient was hospitalized for DVT on the day after IGIV. However, in retrospect it was clear that the initial DVT symptoms started 4 days prior to admission (3 days prior to IGIV).
- Case 3: The patient had a clinic follow-up visit prior to a planned monthly IGIV infusion. The patient reported experiencing shortness of breath that had started in the morning treatment. Physician ordered a chest X-ray prior to the IGIV infusion that was planned for that day. After imaging was read, PE was diagnosed, and patient was admitted to the hospital on the following day. Unclear from chart whether IGIV was actually given following the chest x-ray, but clear that the event onset preceded any IGIV given that day.
- Case 4: As part of ongoing monitoring of the patient's chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), the patient received chest imaging during an outpatient visit. The patient was found to have an asymptomatic PE. The patient was then admitted to the hospital for PE, one day after receiving IGIV. Because the PE was an asymptomatic incidental finding, the IGIV-TEE interval was judged to be indeterminate.

Charts were also received for 3 of 4 potential day 2 venous TEE cases, all of which were position-unspecified diagnoses. One patient met the case definition, one had an upper-extremity DVT and did not meet the case definition, and one was ruled out.

- Case 5: Patient was hospitalized for PE 2 days following the IGIV record in the administrative data. Patient presented with acute shortness of breath and dizziness, and reported that the symptoms began the day prior to hospitalization (i.e., one day after IGIV). This case was excluded from the SCRI assessment, per protocol, because the patient was receiving IGIV every 14 days, and thus had no observable control window.

- Case 6: Patient was admitted for an upper extremity (left subclavian) DVT. Patient did not meet the case definition because upper extremity DVTs were excluded per protocol due to concern about time-varying confounding by central lines. (This patient had no central line but recently had a cardiac pacemaker placed.)
- Case 7: PE was considered as part of differential diagnosis but ruled out. Patient presented with worsening chest pain, coughing and wheezing. The patient was a complex case with a heart transplant, cardiomyopathy and recurrent pneumonia.

The chart validation results for these patients, who appeared to be day 1-2 venous TEE cases in the administrative data, provide an explanation for why a day 1-2 venous TEE risk signal was observed in the objective D1 exploratory cohort analysis but not in the chart-confirmed data obtained for the SCRI analyses.

3. Objective D2 exploratory cohort analyses: TEE risk in IG-exposed and unexposed patients by calendar year

In the objective D2 exploratory cohort analyses of arterial TEE risk, 2,033,045 patients with a potential IG indication were eligible for inclusion, of whom 11,861 initiated IG treatment during the one-year follow-up period (Table I 1). Baseline cohort characteristics are shown in Table I 2. Overall, the risk of arterial TEE was elevated during days 0-60 following IG exposure (HR = 1.60, 95% CI: 1.27, 2.02) relative to the untreated patients, and was non-significantly elevated compared to untreated patients during days 61+ post-IG (HR = 1.06, 95% CI: 0.76, 1.49). In subgroup analyses, we found that the risk of arterial TEE during days 0-60 post-IG treatment was higher during the 2011-12 calendar period (HR = 2.10, 95% CI: 1.51, 2.91) compared to 2006-10 (HR = 1.29, 95% CI: 0.92, 1.80). See Table I 3 for full results.

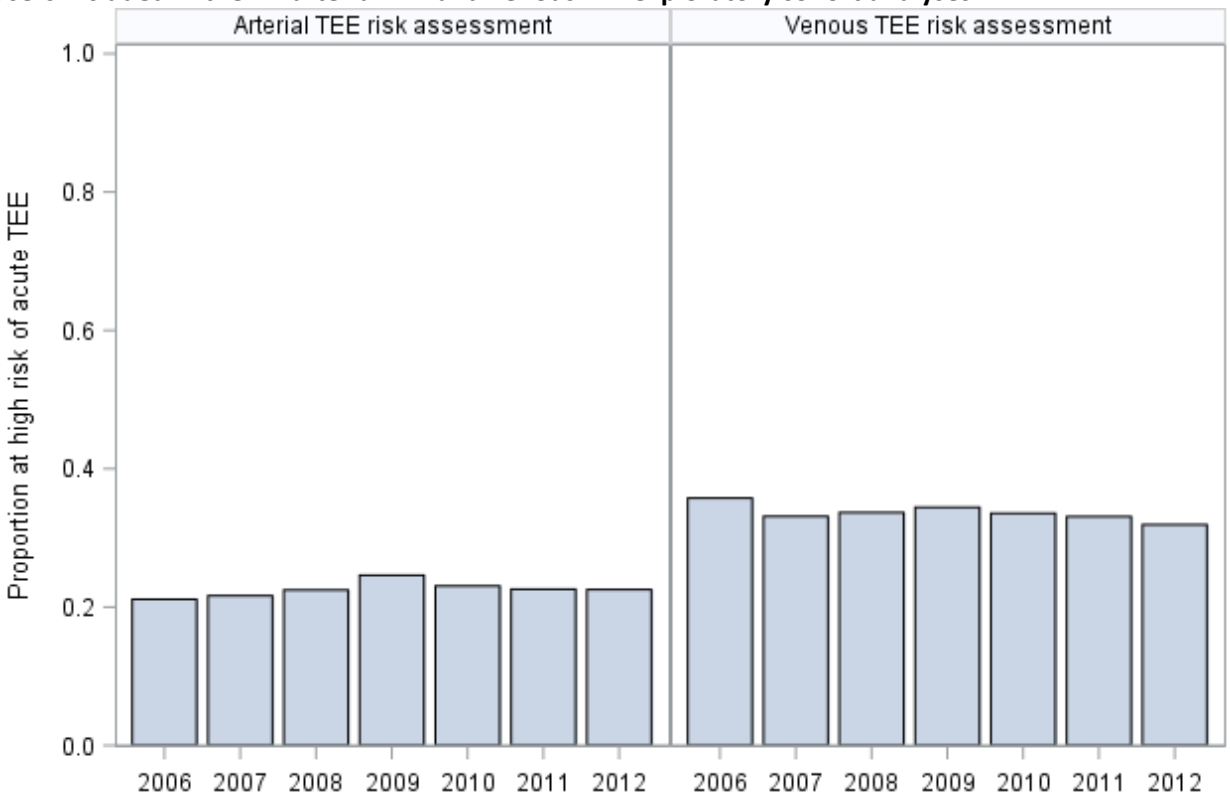
In the objective D2 exploratory cohort analyses of venous TEE risk, 2,040,588 patients with a potential IG indication were eligible for inclusion, of whom 11,840 initiated IG treatment during the one-year follow-up period (Table I 1). Baseline cohort characteristics are shown in Table I 2. Overall, the risk of venous TEE was not elevated during days 0-60 (HR = 1.05, 95% CI: 0.83, 1.32) or days 61+ (HR = 0.73, 95% CI: 0.52, 1.03) following IG exposure relative to untreated patients. In subgroup analyses, we found a trend toward an increased risk of venous TEE during days 0-60 post-IG during 2011-12 (HR = 1.41, 95% CI: 1.02, 1.96), but not during 2006-10 (HR = 0.83, 95% CI: 0.60, 1.16). See Table I 4 for full results.

Since the increase in IG-associated risk over the study period was contrary to our initial hypothesis that the risk might decrease in years that followed manufacturing changes, we evaluated the consistency of these findings across Data Partners. Figure I 1 shows forest plots of the natural log of the HR for days 0-60 post-IG at each Data Partner, with smaller Data Partners grouped together due to data sparseness. For both arterial and venous TEE risk, evidence of heterogeneity across Data Partners was found for the 2006-2010 period (arterial TEE: $p = 0.01$, $I^2 = 66\%$; venous TEE: $p = 0.055$, $I^2 = 54\%$), but not the 2011-2012 period (arterial TEE: $p = 0.58$, $I^2 = 0\%$; venous TEE: $p = 0.48$, $I^2 = 0\%$).

We also explored whether the baseline TEE risk among included IG users changed significantly during the study period. We classified IG users in the D2 exploratory users as “high risk” if—among all included patients with a potential IG indication at a Data Partner—they ranked in the top two DRS deciles based on their TEE risk factors at baseline. We then restricted to IG users and determined the proportion of person-time contributed by these high-risk individuals for each year of the study period. As shown in **Figure 12**, the proportion of the IG user cohort defined as high risk patients did not change greatly over the course of the study period. **Figure 12** also shows that, relative to the reference population of all

patients with potential IG indications, a higher proportion of IG users included in the D2 exploratory cohort analyses were at high risk of venous TEE than arterial TEE.

Figure 12. Proportion of person-time contributed by high-risk patients by calendar year among IG users included in the D2 arterial TEE and venous TEE exploratory cohort analyses



J. CHART VALIDATION STATISTICS

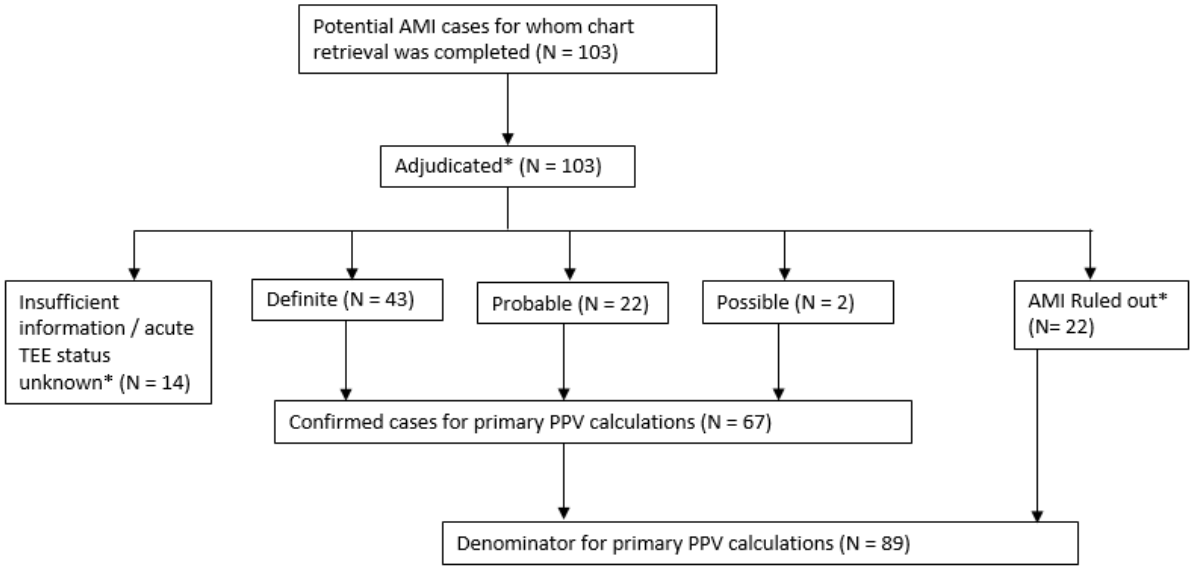
1. Eligible samples for positive predictive value (PPV) calculations for study endpoint definitions based on inpatient diagnoses recorded in the administrative data.

We report on the positive predictive values (PPVs) separately for each of the three main TEE types included as study endpoints: AMI, AIS, and venous thromboembolism (VTE, i.e., DVT and/or PE). Due to the rarity of CVT, no potential post-IGIV cases meeting eligibility criteria were identified in the administrative data, so we do not report on PPVs for CVT codes. The number of cases eligible for the PPV assessments differs slightly from the number eligible for the IGIV risk assessment. For the PPV reports, we include all potential cases where an acute TEE could be confirmed or ruled out, including some cases that were ineligible for the IGIV risk assessment (e.g., TEE cases that did not occur during a post-IGIV risk or control window). **Figure 13**, **Figure 14**, **Figure 15** illustrate which potential cases were available for the PPV calculations. Baseline characteristics for these patients by event type are provided in **Table 9**.

PPVs were calculated by dividing the number of confirmed cases by the number of cases for whom acute TEE status could be determined. In our PPV calculations, we counted definite, probable, and possible TEEs as confirmed cases and removed from the denominator those cases where there was

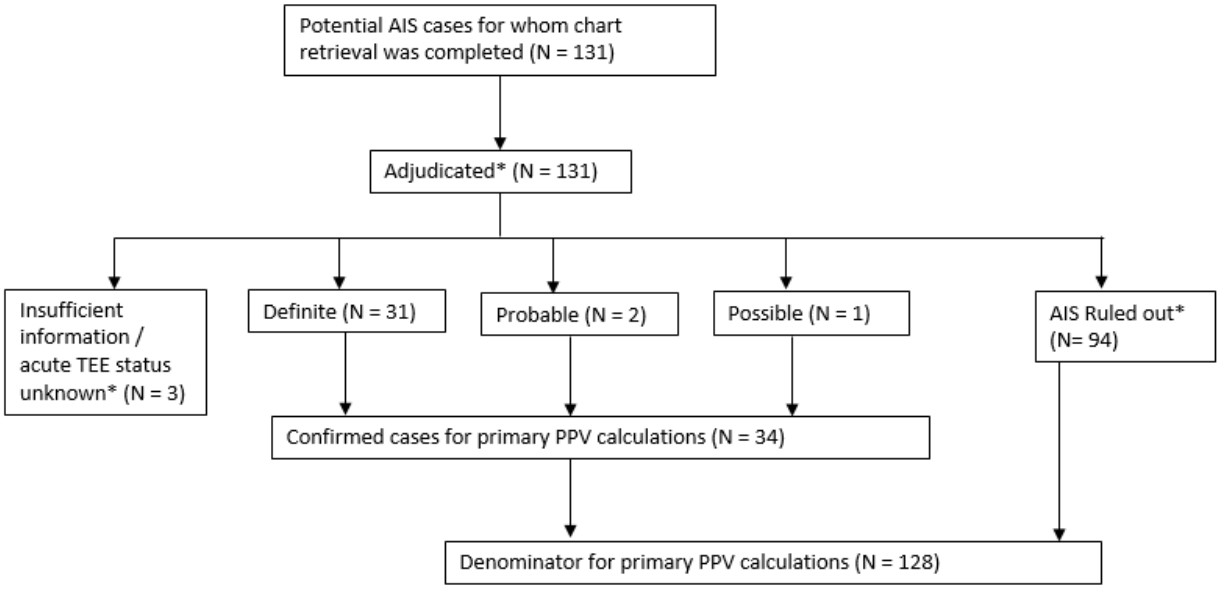
insufficient information to determine acute TEE status. Exact binomial 95% confidence intervals (Clopper-Pearson) were calculated for the PPV estimates to quantify their precision.

Figure 13. Potential acute myocardial infarction (AMI) cases eligible for positive predictive value (PPV) calculations



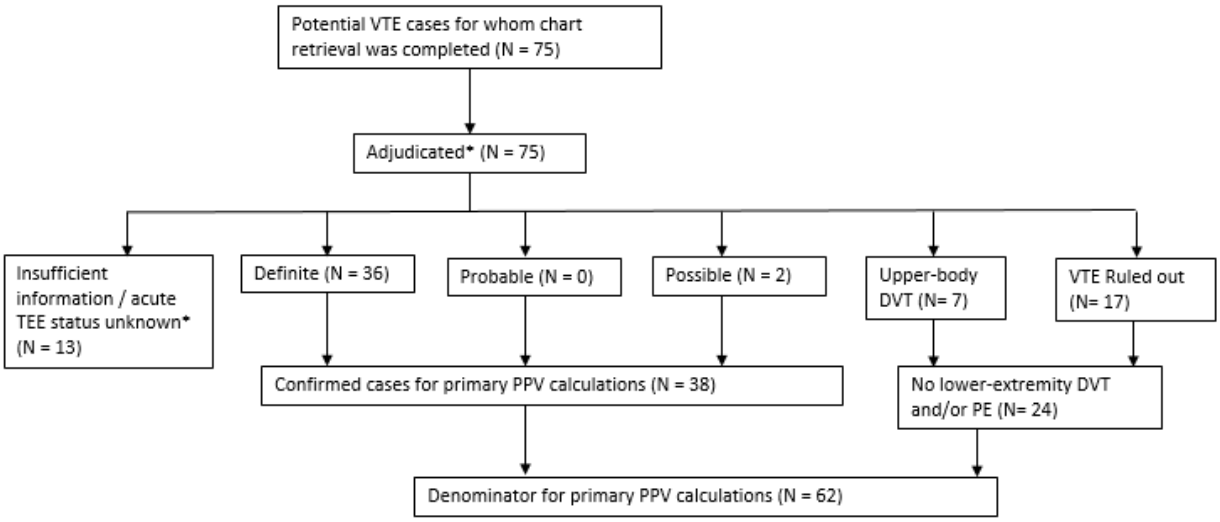
*In limited circumstances (see methods section), a potential case could be ruled out or classified as uninformative based on the judgment of the abstractor and was not physician-adjudicated. For AMI, this included three cases evaluated as insufficient information / acute TEE status unknown and five cases as no AMI.

Figure 14. Potential acute ischemic stroke (AIS) cases eligible for positive predictive value (PPV) calculations



*In limited circumstances (see methods section), a potential case could be ruled out or classified as uninformative based on the judgment of the abstractor and was not physician-adjudicated. For AIS, this included two cases evaluated as insufficient information / acute TEE status unknown and three cases as no AIS.

Figure 15. Potential acute venous thromboembolism (VTE) cases eligible for positive predictive value (PPV) calculations



*In limited circumstances (see methods section), a potential case could be ruled out or classified as uninformative based on the judgment of the abstractor and was not physician-adjudicated. For VTE, this included four cases evaluated as insufficient information / acute TEE status unknown.

Table 9. Baseline characteristics of potential acute myocardial infarction (AMI), ischemic stroke (AIS), and venous thromboembolism (VTE) cases identified from the Sentinel Distributed Database

	AMI (N = 103)†	AIS (N = 131)†	VTE (N = 75)
Demographics			
Age			
• 0-19 years	3%	11%	3%
• 20-39 years	6%	11%	12%
• 40-59 years	27%	30%	44%
• 60-79 years	50%	35%	33%
• 80+ years	15%	13%	8%
Female sex	48%	50%	44%
Possible indication for IGIV use*			
Autoimmune/inflammatory condition	66%	66%	69%
Immune deficiency	38%	26%	65%
Infection	16%	14%	25%
Bone marrow or hematopoietic stem cell transplant	8%	5%	15%
Other indication	25%	19%	31%
Major cardiovascular risk factors*			
Myocardial infarction	22%	10%	12%
Angina	39%	21%	19%
Atrial fibrillation or flutter	15%	15%	8%
Ischemic stroke	6%	15%	9%
Peripheral vascular disease	17%	9%	8%
Hypertension, uncomplicated	56%	53%	55%
Hypertension, complicated	19%	16%	13%
Diabetes mellitus	26%	31%	32%
Factors related to VTE risk*			
History of VTE	8%	5%	24%
Oral anticoagulant use	11%	13%	19%
Hospitalization	43%	47%	53%
Condition associated with impaired mobility	39%	38%	57%
Cancer	41%	28%	56%
Data Partner type			
Insurer/claims-based	81%	76%	96%
Integrated healthcare delivery system	19%	24%	4%

*Possible indications, cardiovascular risk factors, and venous thromboembolism risk factors were assessed using diagnoses and procedures recorded in administrative data during the 183 days prior to the proximate IGIV date. The indication indicator variables are not mutually exclusive, so indication percentages may sum to greater than 100%.

†Note on case counts: the number of potential arterial TEE cases for whom required charts could be retrieved was 224. The sum of potential AMI and AIS cases, considered separately, is 234. Ten patients had a hospital encounter with both AMI and AIS diagnoses recorded in the administrative data.

2. Estimated PPVs of study endpoint definitions for acute thromboembolic events (TEEs)

For AMI, outcome status could be determined for 89 potential cases, of which 67 were confirmed by physician adjudicators. The PPVs for the inpatient AMI diagnoses recorded in the administrative data were 75% overall (67/89, 95% CI: 65-84%), 93% (28/30, 95% CI: 78-99%) for principal-position diagnoses,

88% (29/33, 95% CI: 72-97%) for secondary diagnoses, and 38% (10/26, 95% CI: 20-59%) for position-unspecified diagnoses (**Table 10**). While data on suspected AMI etiology were not collected systematically during the adjudication process, the adjudicators noted that a substantial number of the confirmed AMIs (46%) were likely to be nonthrombotic. These cases were counted as confirmed events since they met criteria for AMI as defined in the study protocol. The majority of these nonthrombotic AMIs were attributable to demand ischemia in the setting of anemia, respiratory insufficiency, and/or septic shock. (Such conditions are more common in certain IGIV user subgroups than in the general population.) Nonthrombotic etiologies were suspected in 21%, 72%, and 40% of confirmed AMIs with primary, secondary, and unspecified coding positions, respectively.

Table 10. Positive predictive values (PPVs)* associated with inpatient administrative diagnosis codes for acute myocardial infarction (AMI) by position

	PPVs for all potential AMI cases (N = 89)	PPVs for principal position AMI diagnoses (N = 30)	PPVs for secondary AMI diagnoses (N = 33)	PPVs for position-unspecified AMI diagnoses (N = 26)
All AMI codes	75% (67/89, 95% CI: 65-84%)	93% (28/30, 95% CI: 78-99%)	88% (29/33, 95% CI: 72-97%)	38% (10/26, 95% CI: 20-59%)
By diagnosis code recorded in administrative data				
410.x0	33% (5/15, 95% CI: 12-62%)	100% (1/1, 95% CI: 3-100%)	33% (1/3, 95% CI: 1-91%)	27% (3/11, 95% CI: 6-61%)
410.x1	84% (62/74, 95% CI: 73-91%)	93% (27/29, 95% CI: 77-99%)	93% (28/30, 95% CI: 78-99%)	47% (7/15, 95% CI: 21-73%)
Data Partner type				
Insurer/claims-based	71% (49/69, 95% CI: 59-81%)	92% (22/24, 95% CI: 73-99%)	89% (17/19, 95% CI: 67-99%)	38% (10/26, 95% CI: 20-59%)
Integrated care delivery systems	90% (18/20, 95% CI: 68-99%)	100% (6/6, 95% CI: 54-100%)	86% (12/14, 95% CI: 57-98%)	--
By whether an acute AMI code was observed in prior 183 days				
No prior AMI	78% (54/69, 95% CI: 67-87%)	92% (23/25, 95% CI: 74-99%)	96% (22/23, 95% CI: 78-100%)	43% (9/21, 95% CI: 22-66%)
Prior AMI	65% (13/20, 95% CI: 41-85%)	100% (5/5, 95% CI: 48-100%)	70% (7/10, 95% CI: 35-93%)	20% (1/5, 95% CI: 1-72%)

*Statistics reported in this table reflect the PPV of administrative ICD-9-CM AMI diagnosis codes for a confirmed (definite, probable, or possible) acute AMI. Patients with a classification of insufficient information / acute TEE status unknown were removed from the denominator for the PPV calculations and not included in this table.

For AIS, outcome status could be determined for 128 potential cases, of which 34 were confirmed by physician adjudicators. The PPVs for the inpatient AIS diagnoses recorded in the administrative data were 27% overall (34/128, 95% CI: 19-35%), 60% (9/15, 95% CI: 32-84%) for principal-position diagnoses, 42% (21/50, 95% CI: 28-57%) for secondary diagnoses, and 6% (4/63, 95% CI: 2-15%) for position-unspecified diagnoses (**Table 11**). One patient was found to have a venous rather than arterial stroke and was counted as "no AIS" in these figures.

Table 11.Positive predictive values (PPVs)* associated with inpatient administrative diagnosis codes for acute ischemic stroke (AIS) by position

	PPVs for all potential AIS cases (N = 128)	PPVs for principal position AIS diagnoses (N = 15)	PPVs for secondary AIS diagnoses (N = 50)	PPVs for position-unspecified AIS diagnoses (N = 63)
All AIS codes	27% (34/128, 95% CI: 19-35%)	60% (9/15, 95% CI: 32-84%)	42% (21/50, 95% CI: 28-57%)	6% (4/63, 95% CI: 2-15%)
By diagnosis code recorded in administrative data				
433.x1	50% (3/6, 95% CI: 12-88%)	50% (1/2, 95% CI: 1-99%)	100% (1/1, 95% CI: 3-100%)	33% (1/3, 95% CI: 1-91%)
434.x0	0% (0/9, 95% CI: 0-34%)	0% (0/2, 95% CI: 0-84%)	--	0% (0/7, 95% CI: 0-41%)
434.x1	33% (31/95, 95% CI: 23-43%)	73% (8/11, 95% CI: 39-94%)	43% (20/47, 95% CI: 28-58%)	8% (3/37, 95% CI: 2-22%)
436	0% (0/18, 95% CI: 0-19%)	--	0% (0/2, 95% CI: 0-84%)	0% (0/16, 95% CI: 0-21%)
Data Partner type				
Insurer/claims-based	19% (19/98, 95% CI: 12-29%)	64% (7/11, 95% CI: 31-89%)	33% (8/24, 95% CI: 16-55%)	6% (4/63, 95% CI: 2-15%)
Integrated care delivery systems	50% (15/30, 95% CI: 31-69%)	50% (2/4, 95% CI: 7-93%)	50% (13/26, 95% CI: 30-70%)	--
By whether an AIS diagnosis code was observed in prior 183 days				
No prior AIS	28% (30/108, 95% CI: 20-37%)	64% (9/14, 95% CI: 35-87%)	41% (17/41, 95% CI: 26-58%)	8% (4/53, 95% CI: 2-18%)
Prior AIS	20% (4/20, 95% CI: 6-44%)	0% (0/1, 95% CI: 0-98%)	44% (4/9, 95% CI: 14-79%)	0% (0/10, 95% CI: 0-31%)
Possible autoimmune/inflammatory indication for IGIV use				
Autoimmune/ inflammatory indication	29% (25/85, 95% CI: 20-40%)	54% (7/13, 95% CI: 25-81%)	44% (15/34, 95% CI: 27-62%)	8% (3/38, 95% CI: 2-21%)
No autoimmune/ inflammatory indication	21% (9/43, 95% CI: 10-36%)	100% (2/2, 95% CI: 16-100%)	38% (6/16, 95% CI: 15-65%)	4% (1/25, 95% CI: 0-20%)

*Statistics reported in this table reflect the PPV of administrative ICD-9-CM AIS diagnosis codes for confirmed (definite, probable, or possible) acute AIS. Patients with a classification of insufficient information / acute TEE status unknown were removed from the denominator for the PPV calculations and not included in this table.

For VTE, acute TEE status could be determined for 62 potential cases, of which 38 were confirmed by physician adjudicators. The PPVs for the inpatient VTE diagnoses recorded in the administrative data were 61% overall (38/62, 95% CI: 48-73%), 90% (27/30, 95% CI: 73-98%) for principal-position diagnoses, 80% (4/5, 95% CI: 28-99%) for secondary diagnoses, and 26% (7/27, 95% CI: 11-46%) for position-unspecified diagnoses (**Table 12**). Seven cases had upper-torso DVTs, which are counted as non-cases in these estimates. Upper-torso DVTs were not included in our study endpoint definition because they are often attributable to central lines, a potential source of time-varying confounding. If these cases were counted as confirmed events, the overall PPV for the endpoint definition would be 72.5%.

Table 12. Positive predictive values (PPVs)* associated with inpatient administrative diagnosis codes for venous thromboembolism (VTE) by position

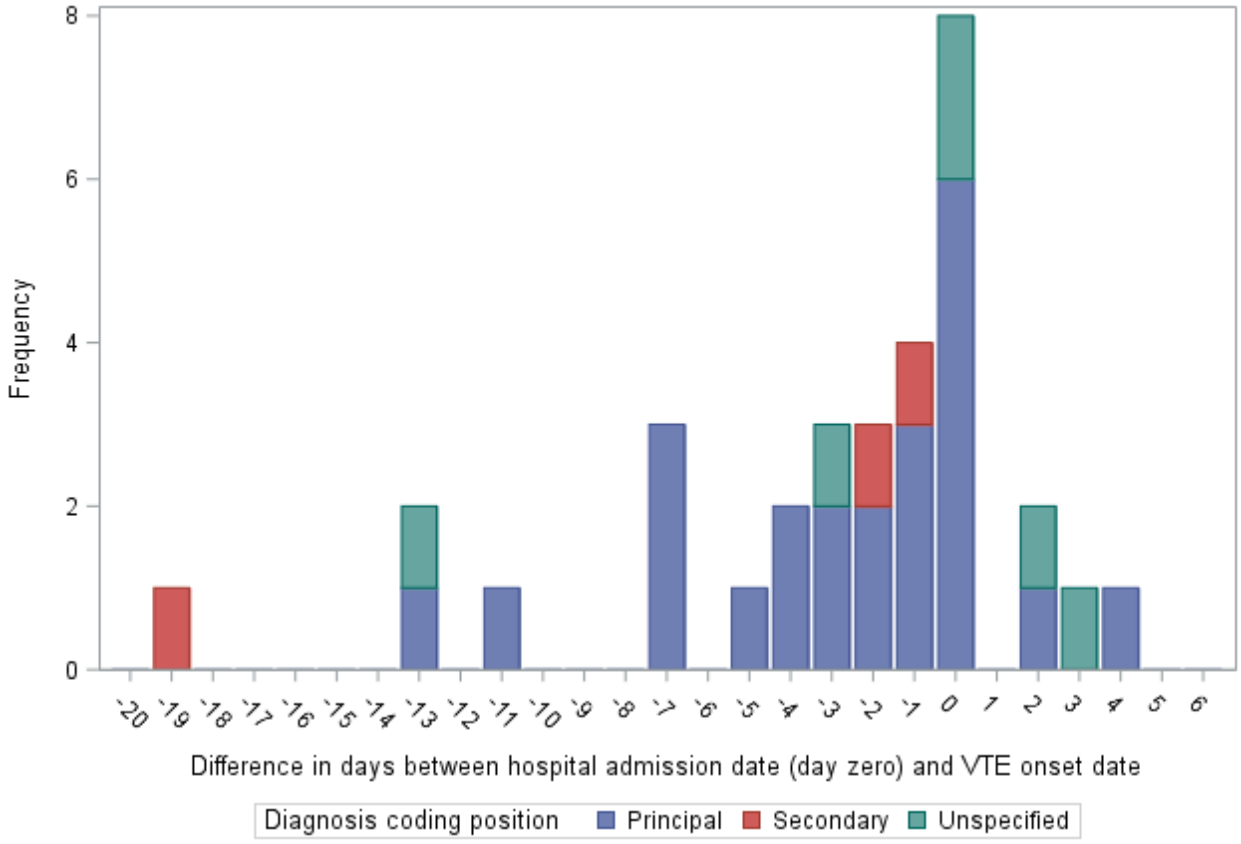
	PPVs for all potential VTE cases (N = 62)	PPVs for principal position VTE diagnoses (N = 30)	PPVs for secondary VTE diagnoses (N = 5)†	PPVs for position-unspecified VTE diagnoses (N = 27)†
All VTE codes	61% (38/62, 95% CI: 48-73%)	90% (27/30, 95% CI: 73-98%)	80% (4/5, 95% CI: 28-99%)	26% (7/27, 95% CI: 11-46%)
By diagnosis code recorded in administrative data				
Deep vein thrombosis codes	54% (15/28, 95% CI: 34-72%)	90% (9/10, 95% CI: 55-100%)	100% (1/1, 95% CI: 3-100%)	29% (5/17, 95% CI: 10-56%)
451.11	0% (0/1, 95% CI: 0-98%)	--	--	0% (0/1, 95% CI: 0-98%)
451.19	25% (1/4, 95% CI: 1-81%)	--	--	25% (1/4, 95% CI: 1-81%)
451.2	0% (0/1, 95% CI: 0-98%)	--	--	0% (0/1, 95% CI: 0-98%)
451.9	--	--	--	--
453.1	--	--	--	--
453.2	--	--	--	--
453.40	44% (4/9, 95% CI: 14-79%)	50% (1/2, 95% CI: 1-99%)	--	43% (3/7, 95% CI: 10-82%)
453.41	88% (7/8, 95% CI: 47-100%)	100% (5/5, 95% CI: 48-100%)	100% (1/1, 95% CI: 3-100%)	50% (1/2, 95% CI: 1-99%)
453.42	100% (3/3, 95% CI: 29-100%)	100% (3/3, 95% CI: 29-100%)	--	--
453.9	0% (0/2, 95% CI: 0-84%)	--	--	0% (0/2, 95% CI: 0-84%)
Pulmonary embolism codes	68% (23/34, 95% CI: 49-83%)	90% (18/20, 95% CI: 68-99%)	75% (3/4, 95% CI: 19-99%)	20% (2/10, 95% CI: 3-56%)
415.11	--	--	--	--
415.12	0% (0/1, 95% CI: 0-98%)	--	--	0% (0/1, 95% CI: 0-98%)
415.13	--	--	--	--
415.19	70% (23/33, 95% CI: 51-84%)	90% (18/20, 95% CI: 68-99%)	75% (3/4, 95% CI: 19-99%)	22% (2/9, 95% CI: 3-60%)
Data Partner type				
Insurer/claims-based	59% (35/59, 95% CI: 46-72%)	89% (24/27, 95% CI: 71-98%)	80% (4/5, 95% CI: 28-99%)	26% (7/27, 95% CI: 11-46%)
Integrated care delivery systems	100% (3/3, 95% CI: 29-100%)	100% (3/3, 95% CI: 29-100%)	--	--
By whether an acute VTE code was observed in prior 183 days				
No prior VTE	70% (35/50, 95% CI: 55-82%)	93% (26/28, 95% CI: 76-99%)	100% (3/3, 95% CI: 29-100%)	32% (6/19, 95% CI: 13-57%)
Prior VTE	25% (3/12, 95% CI: 5-57%)	50% (1/2, 95% CI: 1-99%)	50% (1/2, 95% CI: 1-99%)	13% (1/8, 95% CI: 0-53%)

*Statistics reported in this table reflect the PPV of administrative ICD-9-CM VTE diagnosis codes for a confirmed (definite, probable, or possible) acute VTE. Patients with a classification of insufficient information / acute TEE status unknown were removed from the denominator for the PPV calculations and not included in this table.

†Though the venous TEE endpoint definition included only principal or position-unspecified TEE diagnosis codes, data for the five potential cases with both secondary and position-unspecified diagnosis codes are reported separately as secondary diagnoses in this table. In the SDD, position-unspecified diagnoses may originate from physician/provider claims rather than institutional claims/records and may have lower PPVs than principal or secondary inpatient diagnoses.

For a significant number of VTE cases, VTE onset occurred prior to the day of hospital admission. **Figure 16** shows the difference in days between the VTE onset date (i.e., the first date on which clinical sign/symptoms consistent with VTE were reported) and the index hospital admission date for 32 of the 38 confirmed VTE cases. For the other six confirmed cases, the onset date was indeterminate.

Figure 16. Distribution of the difference in days* between acute venous thromboembolism (VTE) onset and the index hospital admission date among confirmed VTE cases



*A negative number indicates that VTE onset occurred prior to the hospital admission date (day 0). VTE onset is shown above for the 32 confirmed VTE cases for which the date of VTE onset could be determined; for six confirmed cases, the date of VTE onset was indeterminate.

VI. DISCUSSION

A. KEY FINDINGS

The primary self-controlled analyses identified an excess risk of arterial TEE within days 0-2 following IGIV treatment in any setting and no significant increase in venous TEE risk within days 0-13 following IGIV in the outpatient setting. Our arterial TEE risk assessment included cases drawn from an eligible population of 19,008 IGIV users who received 93,370 IGIV treatments. The ratio of the arterial TEE rates for the RW relative to the CW were 4.69 (95% CI: 1.87, 11.90) in the primary per-protocol analysis, and 3.72 (95% CI: 1.75, 7.84) in the sensitivity analysis that included all confirmed cases and incorporated both chart and administrative data on IGIV exposure. The arterial TEE absolute attributable risk estimates were 8.86 (95% CI: 3.25, 14.6) per 10,000 patients or 1.80 (95% CI: 0.66, 2.97) per 10,000 treatment episodes for the per-protocol analysis, and 9.45 (95% CI: 3.64, 15.6) per 10,000 patients or 1.92 (95% CI: 0.74, 3.18) per 10,000 treatment episodes in the sensitivity analysis with the expanded case sample.

The venous TEE self-controlled analyses included cases identified from an underlying population of 13,888 patients who received 86,400 eligible outpatient IGIV treatments. There was no indication that the risk of venous TEE was elevated during the RW compared to the CW (RR = 1.07, 95% CI: 0.34, 3.48, for the per-protocol analysis; 1.04, 95% CI: 0.47, 2.34, for the sensitivity analysis). The point estimates and confidence intervals for the absolute risk estimates were 0.97 (95% CI: -14.2, 14.4) per 10,000 patients or 0.16 (95% CI: -2.29, 2.31) per 10,000 treatment episodes for the per-protocol analysis, and 0.81 (95% CI: -13.6, 15.2) per 10,000 patients or 0.13 (95% CI: -2.18, 2.44) per 10,000 treatment episodes in the sensitivity analysis with the expanded case sample. The venous TEE results should be considered and interpreted with caution since this study excluded inpatient IGIV exposure which is likely to involve high-risk patients.

B. SECONDARY AND EXPLORATORY ANALYSES

We conducted a number of subgroup analyses in order to potentially identify individuals who may be predisposed to TEEs either due to characteristics of the treatment scenario (product/brand, dose, type of indication, infusion rate, treatment episode number, and recency of product) or indicators of patient baseline risk (history of the outcome event, disease risk score). We were unable to identify any predisposed subgroup; however, our statistical power to detect clinically meaningful subgroup differences was limited by the small number of confirmed cases. In exploratory subgroup analyses using chart-confirmed data we observed a significant interaction between IGIV exposure and calendar year period for the arterial TEE endpoint. We examined this further in exploratory cohort analyses, which were suggestive of a similar trend. We explored whether this time trend could be explained by an increase in baseline TEE risk among IG users during the study period, but we did not find meaningful differences in baseline TEE risk among IG users after stratifying by calendar year (**Figure 12**). In light of risk-mitigation efforts by industry, this finding was contrary to our initial hypotheses. Chance cannot be ruled out as a reasonable explanation: if a Bonferroni correction is used to account for total number of subgroup interaction tests is performed, the finding would not reach statistical significance (interaction in full sensitivity analysis sample: $p = 0.006$; threshold for global $\alpha = 0.05$ across all tests for interaction: $p = 0.0014$).

To evaluate the appropriateness of the RW and CW definitions we conducted several exploratory analyses. Our analysis of chart confirmed data revealed a pattern of arterial events most commonly on

days 0 and 1, with little evidence of increased risk during the washout period. Our examination of confirmed venous TEEs following outpatient exposures showed no temporal pattern over 27 days, except that the largest number of events was observed on day 14. The objective D1 exploratory cohort analyses using administrative data only also provided information concerning the relationship between time-since-IG and TEE risk. Because we learned through chart validation that the administrative data were unreliable for determining the days between IG and TEE onset when IG was administered during a hospital stay, we excluded inpatient exposures and person-time; therefore, these analyses provide information that is only relevant for outpatient IG administrations. Unexpectedly, we found no statistically significant association between time-since-IG and arterial TEE risk, and an elevated risk of venous TEE during days 1-2 following IG treatment. However, from our chart review data, we know that venous TEE symptom onset preceded hospital admission date for venous TEE by a median of 1.5 days (**Figure 16**). Moreover, of the venous TEE cases in the SCRI that appeared to be day 1-2 events in the administrative data, a meaningful proportion were rule-out diagnoses or were found not to be RW events because of the potential for a lag between when the venous TEE began and when it was diagnosed (see results section J.2). This was a very small set of observations (7 cases), limiting our ability to generalize to other cases observed in the SDD. Nevertheless, these examples of temporal imprecision and surveillance bias raise doubts about the venous TEE risk signal that we observed during the day 1-2 risk period in the cohort analyses. The discrepancy between our self-controlled and cohort analyses for the arterial TEE endpoint may be explainable by the restriction to patients receiving IG on an outpatient basis—a lower-risk group—in the exploratory cohort analyses, and by outcome misclassification. (The PPV associated with principal AIS diagnoses was only 60%).

C. COMPARISON WITH RESULTS FROM PRIOR STUDIES

Prior studies have provided varying estimates of the frequency of TEEs in those receiving IGIV, with reports of TEEs occurring in 0.5-15% of patients treated with IGIV.[7-12,21,24,30,51-54] However, without an untreated comparator group, how much of that risk is attributable to IGIV versus other risk factors cannot be determined. We report a significant but small attributable risk of arterial TEE in a large cohort of IGIV users using a self-controlled design that controls for sources of between-person confounding. This finding was consistent in both the per protocol analyses and sensitivity analyses that included all confirmed cases.

Compared to FAERS data on IGIV-associated TEE cases,[55] confirmed TEE cases in the present study were older (median ages of 58 versus 65 years). Seventy-one percent of our cases were arterial TEEs, as compared with approximately 60% in the FAERS case series. This difference may be attributable to the fact that we only included venous TEEs that occurred after outpatient use of IGIV. Additionally, the ratio of AMI to AIS cases differed in FAERS and the present study (33:60 in FAERS as compared with 41:27), when considering all cases irrespective of timing.

The lack of an association between IGIV use and venous TEE risk in our study was unexpected in light of prior administrative database studies which reported high rates of same-day IGIV-associated TEEs, the majority of them venous TEEs.[21,30] There are several possible explanations for the differences. First, in the present study, potential post-IGIV cases were chart confirmed, reducing some of the potential for artefactual associations attributable to limitations in the administrative data. Second, our choice of risk and control windows for venous events may have obscured a true association by under-stating the RW risk and over-stating the CW risk. Initial clot formation may precede venous TEE symptom onset and diagnosis by days or weeks.[37] For example, calf venous TEE is often asymptomatic, with symptoms not arising until the clot extends to proximal deep veins. It is conceivable that some of the 14 venous TEE

cases in the CW—six of which became symptomatic on day 14 following IGIV—may be attributable to IGIV. Third, the studied populations may have been different with respect to predisposing risk factors for IG-exposed persons studied including but not limited to the demographic characteristics, underlying health conditions, indications for use, dose, rate of administration, or presence of elevated FXIa activity, which needs further investigation. An important difference in the study populations was that our SCRI venous TEE risk assessment included only patients who received IGIV on an outpatient basis; this may have had the effect of excluding patients with a higher baseline risk of venous TEEs. Finally, during the course of this study we learned of the possibility that outpatient procedure records in the SDD could be reclassified as inpatient if a patient were hospitalized later that day. This may have limited our ability to detect same-day venous TEEs. However, we believe that the impact of this claims processing practice should be minor given the longer time interval between initial clot formation and symptom onset that would be expected for venous TEEs.

D. STRENGTHS

A major strength of the study was that exposure, outcomes, and the timing of each was chart confirmed. This was particularly important for ischemic stroke events where the PPV was lower than in the literature and for venous events where the insidious onset in some cases meant the onset date was an average of 1.5 days prior to the date in the administrative data. Had we relied on administrative data alone, we would have over-estimated the risks of IGIV-associated TEEs due to the inclusion of spurious same-day events (see **Table 8**). Other strengths were that this assessment drew from a large population-based sample of new IGIV users, and the underlying denominator data allowed for the estimation of attributable absolute risks. The possibility of between-person confounding was addressed through the use of a self-controlled study design.[56]

E. LIMITATIONS

There were also several limitations to the study. First, the rate of unavailable charts was higher than expected based on prior Sentinel product assessments.[57] We postulated that this could be due to the time lag between case identification and requesting of medical records, requirement for multiple components (both exposure and outcome validation), and the nature of the study population (healthier, younger patients may have shorter and easier to obtain records). Missing chart data affected power and was slightly more common for CW events. (For a more remote IGIV exposure, chart-confirming the last date of treatment was more likely to require the retrieval of two separate charts—rather than just the chart for the TEE outcome.) In order to correct for this potential source of bias, we conducted sensitivity analyses in which we relied on administrative data for IGIV exposure when chart data were unavailable. The resulting estimates were similar. Other than slightly higher rates of missing IGIV exposure data for CW cases, the reasons that charts were unavailable did not give us reason to suspect that our analyzable sample was systematically different than the total set of potential cases identified in the SDD. Typical reasons included an inability to link SDD records to patient or provider identifiers, or refusal by the provider (see **Appendix F**).

We expected that successful retrieval rates might be lower for charts from earlier in the study period (2006-2012); however, chart retrieval rates did not vary substantially across calendar year of admission. The low chart retrieval rates coupled with lower-than-expected rates of confirmed cases meant that we had less power than we initially estimated. There were very small numbers for certain subgroups, and our tests for interaction may have lacked power to detect clinically meaningful effect modification.

In addition to the impact on study power, missing chart data is problematic because of the possibility that these data were not missing at random. Missing data on IGIV exposure was slightly more common for CW events. (For a more remote IGIV exposure, chart confirming the last date of treatment was more likely to require the retrieval of two separate charts—rather than just the chart for the TEE outcome.) In order to correct for this potential source of bias, we conducted sensitivity analyses in which we relied on administrative data for IGIV exposure when chart data were unavailable. The resulting estimates were similar but somewhat closer to the null.

A second limitation is that our primary self-controlled analyses depend on an assumption that, for each patient, the underlying risk of TEE is constant over the RW and CW except for the effect of IGIV. It is possible that this may not be the case for patients who are acutely ill, hospitalized and/or in a perioperative period. The possibility of time-varying confounding is considerably greater for the venous TEE endpoint, and inpatient IGIV treatments were excluded from our venous TEE risk assessment.

It should be noted that our venous TEE risk assessment included only outpatient IGIV exposures. This study design decision was made to reduce the risk of time-varying confounding and maximize the internal validity of the study. However, the restriction had the effect of excluding a significant number of patients (see **Table 4**) who would be expected to have a higher baseline risk of venous TEE due to hospitalization or disease severity. While the remaining cohort of outpatient IGIV users did include a number of patients with a substantial burden of venous TEE risk factors (e.g., 39% had been hospitalized in the prior 6 months; see **Table 5**), our venous TEE results may not be generalizable to patients receiving IGIV in inpatient settings or who otherwise are at high risk for venous TEEs.

Finally, we included only AMI, AIS, DVT, PE and CVT in our endpoint definition, and thus may have understated the absolute risk of all TEEs. In the FAERS data approximately three-fourths of all TEEs were AMI, AIS, DVT or PE.[55]

F. APPLICATIONS TO SENTINEL

Practical lessons learned from the study were identification of IGIV exposures in administrative data, event timing in administrative data, TEE validation, TEE definitions and secondary discharge diagnosis codes, and the potential for use of Sentinel tools for similar analyses.

1. IGIV administrative data coding

We were able to identify IGIV exposures in administrative data using both procedure and NDC codes, with certain strengths and limitations. First, the majority of IGIV administrations in this project were identified with procedure codes (**Appendix B**); none of the project's Sentinel Data Partners utilized NDC codes exclusively for IGIV administration. NDC codes pertaining to IGIV allow for brand identification, while only some CPT and HCPCS codes for IGIV are brand-specific. Second, during medical record review we found that IGIV brand was often not recorded in the patient's medical charts, but when brand was recorded there was general concordance with administrative coding. Third, we observed different patterns of IGIV use in inpatient and outpatient settings. Finally, when medical records were requested for IGIV administrations identified by NDC codes, Sentinel claims-based Data Partners were unable to locate charts. This may be because pharmacy claims cannot be easily linked to medical charts at claims-based data partners. In contrast, integrated care delivery sites were generally able to retrieve medical charts closest to the dates of the IG administration as identified by NDC codes. In summary, careful review of the study question and the specificity of available codes in use (procedure codes or NDC codes) are important, particularly if comparisons across IGIV brands are of interest.

2. Timing of inpatient events

There were practical lessons about identification of the relative timing of *inpatient* IG exposures and TEE outcomes in the SDD. Notably, we found *inpatient* IGIV administration date is often imprecise in claims data. At many Sentinel Data Partners, IGIV administration date reflects the hospital admission date, and the specific date of *inpatient* IGIV administration during a hospital stay (unless the stay was only 1 day) is not available without medical record review. A similar limitation occurred with inpatient diagnoses, and in this project the inpatient diagnosis date was typically the hospital admission date. Due to these limitations, we observed a large number of "day 0" arterial TEEs in the administrative data (i.e., exposure and outcome were recorded on the same day). Medical record review found that a meaningful number of these cases were TEEs, but were not RW events (**Appendix F**). These lessons about exposure and outcome timing in the SDD confirmed the importance of medical chart review for the project.

3. TEE validation

Validating exposures and outcomes with medical records was not only crucial to the project, but it also provided several generally applicable lessons for TEE outcomes in Sentinel activities. For example, we found that algorithms for VTE and AMI performed particularly well (PPVs >80% for principal or secondary diagnosis codes). The findings for AMI were similar to those from a prior validation report of AMI within the SDD.[58] However, we generally observed low PPVs (<38%) for inpatient discharge diagnosis codes marked 'unable to classify.' The codes marked as 'unable to classify' are frequently from non-facility claims associated with an inpatient stay. PPVs were lower for AIS, and further work is needed to establish the generalizability of this finding beyond the population of IGIV users included in the present study.

During this project, we were also able to examine the PPVs of individual ICD-9-CM discharge diagnosis codes associated with AIS, AMI, and VTE. ICD-9-CM 410.x1 codes for AMI were associated with higher PPVs than 410.x0 codes. For AIS, we observed especially low PPVs for the ICD-9 codes 434.x0 (0%) and 436 (0%). Similarly, certain ICD-9 codes for VTE (451.11, 451.19, 451.2, 451.9, 453.1, 453.2, 453.9, 415.11) were either not observed in our project or had very low PPV (<25%). However, as we only examined TEE outcomes in patients exposed to IGIV, any algorithm refinements would need to be considered in the context of the specific medical product in question.

4. TEE endpoint definitions and secondary discharge diagnosis codes

To maximize the positive predictive value for acute TEE (as opposed to "history of" or "rule out" diagnoses), the workgroup initially considered excluding secondary diagnosis codes in TEE endpoint definitions. However, had we excluded secondary diagnosis codes from the endpoint definition when inpatient exposures were being evaluated, TEE ascertainment would have been incomplete for events beginning during the course of a hospital-stay that may have occurred due to inpatient exposures. Under UHDDS guidelines used by U.S. hospitals and insurers, an inpatient principal diagnosis is the "condition established after study to be chiefly responsible for occasioning the admission of the patient to the hospital." Under standard coding practices, serious medical conditions that develop during the course of a hospital stay would appear as secondary inpatient diagnoses. For this reason, ascertainment of acute TEEs following IGIV exposure in inpatient settings would have been incomplete without including secondary diagnosis codes in our endpoint algorithms. PPVs for secondary TEE diagnoses were moderately lower than for principal TEE diagnoses. To the extent that the Data Partners follow the UHDDS guidelines, Sentinel is able to capture the principal and secondary discharge diagnoses

consistent with the guidelines in the SCDM. The decision of whether to include secondary diagnoses in TEE endpoint definitions may depend on study-specific considerations, such as whether adverse events following inpatient exposures are of interest.figuew

5. Implications for Sentinel Routine Query Tools

Although this project's aims were accomplished with de novo code, it would currently be possible to utilize Sentinel routine tools to conduct certain aspects of the project. For example, algorithms utilized in the project for both the IGIV exposure and TEE outcome identification can be implemented using Sentinel tools. Additionally, there is now a Sentinel Self-Controlled Risk Interval (SCRI) tool which can implement a SCRI design analysis similar those employed in this project. However, any use of the Sentinel SCRI tool to examine the effect of IGIV treatment on the risk of TEEs would suffer from the severe limitations regarding timing of IGIV administration noted above. We found that medical record review to accurately identify timing of exposure and outcomes was crucial in this project. In addition, arterial and venous TEE disease risk scores were estimated in a cohort of IG-untreated patients with a recognized indication for IG use (**Appendix A**). Pooled DRS may be useful for a variety of purposes: (a) high-dimensional covariate adjustment at smaller Data Partners, (b) evaluating how patients' baseline event risk may modify the risk of adverse events, (c) characterizing differences in baseline event risk in medical product users across Data Partners and time periods, and (d) potentially providing another approach to reduce sharing of individual-level patient health information.

G. CONCLUSIONS

This study found evidence for a transient increase in the risk of arterial TEEs during days 0-2 following IGIV treatment (RR = 3.72, 95% CI: 1.75, 7.84; attributable risk = 9.45 (95% CI: 3.64, 15.6) per 10,000 patients, based on all confirmed cases). No statistically significant association between recent IGIV exposure and venous TEE risk following outpatient IGIV treatments was found. The possibility of delayed venous TEE symptom onset and diagnosis means that an increase in venous TEE risk cannot be ruled out definitively by our self-controlled approach. In addition, the venous TEE risk assessment excluded IGIV treatments in the inpatient setting, likely excluding patients with the highest baseline risk of venous TEEs. Contrary to our initial hypothesis, we did not find evidence that the risk of IGIV-associated TEEs declined during the study period, as additional risk mitigation strategies were implemented by IGIV manufacturers. Continued pharmacovigilance efforts are warranted to monitor and limit the risk of IGIV-associated TEEs.

VII. APPENDIX

A. APPENDIX A: DEFINITIONS OF INDICATIONS FOR IMMUNOGLOBULIN USE

Below is a table displaying administrative diagnosis and procedure codes associated with indicated conditions for intravenous, subcutaneous or intramuscular immunoglobulin use. **Table A 1** groups indicated conditions into the following categories: (1) inflammatory and/or autoimmune conditions, (2) immune deficiency, (3) treatment of acute infection, (4) pre- or post-exposure prophylaxis against infection, (5) hematopoietic stem cell or bone marrow transplantation, and (6) other. In order to be included in the primary self-controlled analyses, patients were required to have had an IG indication observed in the interval [proximate IG date 183 days, proximate IG date +1 day]. We attempted to confirm the route of administration and indication in each reviewed case for the objectives using chart confirmed data, though the ability to do this was dependent upon adequate documentation in the patient chart.

FDA-approved and other generally recognized indications for IG use[59] have a "Y" in the column "Recognized Indication." To be eligible for inclusion in the disease risk score cohorts and exploratory cohort analyses, we required that patients have at least one recognized indication for IG use recorded during the 183-day lookback period.

Table A 1 also includes the typical dose of IG administered for each indication, and its associated diagnosis code and description. The majority of literature on IG use in acute conditions, such as inflammatory disorders, reports administration of IGIV at a total dose of > 1 g/kg in a treatment episode, which often spans multiple days. In contrast, the labeled doses of IGIV for primary immune deficiency range from 200-800 mg/kg, typically at 3-4 week intervals. Similarly, the labeled IGIV dose for secondary immune deficiency in products labeled for that condition is 400 mg/kg every 3 to 4 weeks. IGIV is also administered in treatment episodes using doses lower than 1 g/kg for some preventive and chronic indications. Thus, 1g/kg was chosen as a convenient cutoff for categorizing dose into high, low, and unclassifiable (H, L, and U, respectively, in **Table A 1** below).

Table A 1. Indicated conditions for IG use: categorization and associated administrative diagnosis/procedure codes

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	0363	Waterhouse-Friderichsen syndrome, meningococcal	3. Active infection	N	U
DX09	042	Human immunodeficiency virus infection	2. Immune deficiency	Y	L
DX09	052	Chickenpox	3. Active infection	N	U
DX09	056	Rubella	3. Active infection	N	U
DX09	0664	West Nile fever	3. Active infection	N	H

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	0785	Cytomegaloviral disease	3. Active infection	N	L
DX09	07983	Parvovirus B19	3. Active infection	N	H
DX09	084	Malaria	3. Active infection	N	L
DX09	1361	Bechet's syndrome	1. Autoimmune/inflammatory condition	N	H
DX09	138	Late effects of acute poliomyelitis	6. Other	N	H
DX09	1640	Malignant neoplasm of thymus	6. Other	N	H
DX09	172	Malignant melanoma of skin	6. Other	N	H
DX09	176	Kaposi's sarcoma	6. Other	N	H
DX09	20190	Hodgkin's disease, unspecified type, extranodal and solid organ types	6. Other	N	H
DX09	20208	Nodular lymphoma involving lymph nodes of multiple sites	6. Other	N	H
DX09	20210	Mycosis fungoides, unspecified site, extranodal and solid organ sites	6. Other	N	H
DX09	20280	Other malignant lymphomas, unspecified site, extranodal and solid organ sites	6. Other	N	H
DX09	20281	Other malignant lymphomas involving lymph nodes of head, face, and neck	6. Other	N	H
DX09	20300	Multiple myeloma, without mention of having achieved remission, failed remission	2. Immune deficiency	Y	U
DX09	20400	Lymphoid leukemia, acute, without mention of having achieved remission	6. Other	Y	L
DX09	20401	Lymphoid leukemia, acute, in remission	6. Other	Y	L
DX09	20402	Lymphoid leukemia, acute, in relapse	2. Immune deficiency	Y	L
DX09	2041	Chronic lymphoid leukemia	2. Immune deficiency	Y	L
DX09	20480	Other lymphoid leukemia, without mention of having achieved remission, failed remission	2. Immune deficiency	Y	L
DX09	20490	Unspecified lymphoid leukemia, without mention of having achieved remission, failed remission	2. Immune deficiency	Y	L
DX09	20501	Myeloid leukemia, acute, in remission	6. Other	Y	L
DX09	20510	Myeloid leukemia, chronic, without mention of having achieved remission, failed remission	6. Other	Y	L

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	20820	Leukemia of unspecified cell type, subacute, without mention of having achieved remission	2. Immune deficiency	Y	L
DX09	20890	Unspecified leukemia, without mention of having achieved remission	2. Immune deficiency	Y	L
DX09	23871	Essential thrombocythemia	6. Other	N	U
DX09	23875	Myelodysplastic syndrome, unspecified	6. Other	Y	L
DX09	23877	Post-transplant lymphoproliferative disorder	6. Other	Y	L
DX09	23879	Other lymphatic and hematopoietic tissues	6. Other	N	U
DX09	24200	Toxic diffuse goiter without mention of thyrotoxic crisis or storm	1. Autoimmune/inflammatory condition	Y	H
DX09	2580	Polyglandular activity in multiple endocrine adenomatosis	1. Autoimmune/inflammatory condition	N	H
DX09	27502	Hemochromatosis due to repeated RBC transfusions	1. Autoimmune/inflammatory condition	N	H
DX09	27503	Other hemochromatosis	1. Autoimmune/inflammatory condition	N	H
DX09	27786	Peroxisomal disorders	6. Other	N	H
DX09	27787	Disorders of mitochondrial metabolism	6. Other	N	L
DX09	279	Disorders involving the immune mechanism	2. Immune deficiency	Y	L
DX09	2790	Deficiency of humoral immunity	2. Immune deficiency	Y	L
DX09	2791	Deficiency of cell-mediated immunity	2. Immune deficiency	Y	L
DX09	2792	Combined immunity deficiency	2. Immune deficiency	Y	L
DX09	2793	Unspecified immunity deficiency	2. Immune deficiency	Y	L
DX09	2794	Autoimmune disease, not elsewhere classified	1. Autoimmune/inflammatory condition	N	L
DX09	2795	Graft-versus-host disease	1. Autoimmune/inflammatory condition	Y	H
DX09	2830	Autoimmune hemolytic anemias	1. Autoimmune/inflammatory condition	Y	H
DX09	28311	Hemolytic-uremic syndrome	1. Autoimmune/inflammatory condition	N	H
DX09	28401	Constitutional red blood cell aplasia	1. Autoimmune/inflammatory condition	N	H
DX09	2849	Aplastic anemia, unspecified	1. Autoimmune/inflammatory condition	N	H
DX09	2864	von Willebrand's disease	1. Autoimmune/inflammatory condition	N	H
DX09	28652	Acquired hemophilia	1. Autoimmune/inflammatory condition	Y	H

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	28659	Other hemorrhagic disorder due to intrinsic circulating anticoagulants, antibodies, or inhibitors	1. Autoimmune/inflammatory condition	N	H
DX09	2870	Allergic purpura	1. Autoimmune/inflammatory condition	N	H
DX09	2873	Primary thrombocytopenia	1. Autoimmune/inflammatory condition	N	H
DX09	28730	Primary thrombocytopenia, unspecified	1. Autoimmune/inflammatory condition	N	H
DX09	28731	Immune thrombocytopenic purpura	1. Autoimmune/inflammatory condition	Y	H
DX09	28732	Evans' syndrome	1. Autoimmune/inflammatory condition	Y	H
DX09	2874	Secondary thrombocytopenia	1. Autoimmune/inflammatory condition	N	H
DX09	28741	Posttransfusion purpura	1. Autoimmune/inflammatory condition	Y	H
DX09	2875	Thrombocytopenia, unspecified	1. Autoimmune/inflammatory condition	N	H
DX09	2880	Neutropenia (excluding 288.09, see below)	6. Other	N	H
DX09	28809	Other neutropenia (agranulocytosis, immune, toxic)	1. Autoimmune/inflammatory condition	N	H
DX09	2881	Functional disorders of polymorphonuclear neutrophils	6. Other	N	H
DX09	2884	Hemophagocytic syndromes	1. Autoimmune/inflammatory condition	N	H
DX09	2891	Chronic lymphadenitis	1. Autoimmune/inflammatory condition	N	H
DX09	2893	Lymphadenitis, unspecified, except mesenteric	1. Autoimmune/inflammatory condition	N	H
DX09	28984	Heparin-induced thrombocytopenia (HIT)	1. Autoimmune/inflammatory condition	N	H
DX09	299	Pervasive developmental disorders	6. Other	N	L
DX09	32361	Infectious acute disseminated encephalomyelitis	1. Autoimmune/inflammatory condition	Y	H
DX09	32381	Other causes of encephalitis and encephalomyelitis	1. Autoimmune/inflammatory condition	Y	H
DX09	3310	Alzheimer's disease	1. Autoimmune/inflammatory condition	N	H
DX09	3332	Myoclonus	1. Autoimmune/inflammatory condition	N	H
DX09	33391	Stiff-man syndrome	1. Autoimmune/inflammatory condition	Y	H
DX09	33520	Amyotrophic lateral sclerosis	1. Autoimmune/inflammatory condition	N	H
DX09	340	Multiple sclerosis	1. Autoimmune/inflammatory condition	Y	H
DX09	3483	Encephalopathy, not classified elsewhere	1. Autoimmune/inflammatory condition	N	H
DX09	3535	Neuralgic amyotrophy	1. Autoimmune/inflammatory condition	N	H

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	3570	Acute infectious polyneuritis	1. Autoimmune/inflammatory condition	Y	H
DX09	3571	Polyneuropathy in collagen vascular disease	1. Autoimmune/inflammatory condition	Y	H
DX09	3572	Polyneuropathy in diabetes	1. Autoimmune/inflammatory condition	N	H
DX09	35781	Chronic inflammatory demyelinating polyneuritis	1. Autoimmune/inflammatory condition	Y	H
DX09	35782	Critical illness polyneuropathy	1. Autoimmune/inflammatory condition	N	H
DX09	3579	Unspecified inflammatory and toxic neuropathy	1. Autoimmune/inflammatory condition	N	H
DX09	3580	Myasthenia gravis	1. Autoimmune/inflammatory condition	Y	H
DX09	3583	Lambert-Eaton syndrome	1. Autoimmune/inflammatory condition	Y	H
DX09	35971	Inclusion body myositis	1. Autoimmune/inflammatory condition	N	H
DX09	3630	Focal chorioretinitis and focal retinochoroiditis	1. Autoimmune/inflammatory condition	Y	H
DX09	37612	Orbital myositis	1. Autoimmune/inflammatory condition	N	L
DX09	3773	Optic neuritis	1. Autoimmune/inflammatory condition	N	H
DX09	37855	External ophthalmoplegia	6. Other	N	L
DX09	37959	Other irregularities of eye movements (opsoclonus)	1. Autoimmune/inflammatory condition	Y	H
DX09	390	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	391	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	392	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	393	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	394	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	395	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	396	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	397	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	398	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	420	Acute pericarditis	1. Autoimmune/inflammatory condition	N	H
DX09	422	Acute myocarditis	1. Autoimmune/inflammatory condition	Y	H
DX09	423	Other diseases of pericardium	1. Autoimmune/inflammatory condition	N	H
DX09	42491	Endocarditis in diseases classified elsewhere	1. Autoimmune/inflammatory condition	Y	H

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	425	Cardiomyopathy	1. Autoimmune/inflammatory condition	N	H
DX09	428	Heart failure	1. Autoimmune/inflammatory condition	N	H
DX09	4460	Polyarteritis nodosa	1. Autoimmune/inflammatory condition	N	H
DX09	4461	Acute febrile mucocutaneous lymph node syndrome [MCLS]	1. Autoimmune/inflammatory condition	Y	H
DX09	4464	Wegener's granulomatosis	1. Autoimmune/inflammatory condition	N	H
DX09	52801	Mucositis (ulcerative) due to antineoplastic therapy	6. Other	N	L
DX09	555	Regional enteritis	1. Autoimmune/inflammatory condition	N	H
DX09	57142	Autoimmune hepatitis	1. Autoimmune/inflammatory condition	N	H
DX09	580	Acute glomerulonephritis	1. Autoimmune/inflammatory condition	N	H
DX09	581	Nephrotic syndrome	1. Autoimmune/inflammatory condition	Y	H
DX09	582	Chronic glomerulonephritis	1. Autoimmune/inflammatory condition	N	H
DX09	583	Nephritis and nephropathy, not specified as acute or chronic	1. Autoimmune/inflammatory condition	Y	H
DX09	6475	Rubella complicating pregnancy	3. Active infection	Y	L
DX09	6553	Suspected damage to fetus from viral disease in the mother	3. Active infection	Y	L
DX09	68601	Pyoderma gangrenosum	1. Autoimmune/inflammatory condition	N	H
DX09	691	Atopic dermatitis and related conditions	1. Autoimmune/inflammatory condition	N	H
DX09	6944	Pemphigus	1. Autoimmune/inflammatory condition	N	H
DX09	6945	Pemphigoid	1. Autoimmune/inflammatory condition	N	H
DX09	6946	Benign mucous membrane pemphigoid	1. Autoimmune/inflammatory condition	N	H
DX09	6948	Other specified bullous dematoses	1. Autoimmune/inflammatory condition	N	H
DX09	6951	Erythema multiforme	1. Autoimmune/inflammatory condition	Y	H
DX09	6954	Lupus erythematosus	1. Autoimmune/inflammatory condition	Y	H
DX09	696	Psoriasis and similar disorders	1. Autoimmune/inflammatory condition	N	H
DX09	7018	Other specified hypertrophic and atrophic conditions of the skin	1. Autoimmune/inflammatory condition	N	H
DX09	70409	Other alopecia	6. Other	N	L
DX09	708	Urticaria	1. Autoimmune/inflammatory condition	N	H

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	7100	Systemic lupus erythematosus	1. Autoimmune/inflammatory condition	Y	H
DX09	7101	Systemic sclerosis	1. Autoimmune/inflammatory condition	N	H
DX09	7102	Sicca syndrome	1. Autoimmune/inflammatory condition	N	H
DX09	7103	Dermatomyositis	1. Autoimmune/inflammatory condition	Y	H
DX09	7104	Polymyositis	1. Autoimmune/inflammatory condition	Y	H
DX09	7108	Other specified diffuse diseases of connective tissue	1. Autoimmune/inflammatory condition	N	H
DX09	7109	Unspecified diffuse connective tissue disease	1. Autoimmune/inflammatory condition	N	H
DX09	7112	Arthropathy in Behcet's syndrome	1. Autoimmune/inflammatory condition	N	H
DX09	7140	Rheumatoid arthritis	1. Autoimmune/inflammatory condition	N	H
DX09	7143	Juvenile chronic polyarthritis	1. Autoimmune/inflammatory condition	N	H
DX09	7281	Muscular calcification and ossification	6. Other	N	U
DX09	7287	Other fibromatoses of muscle, ligament, and fascia	6. Other	N	U
DX09	72886	Necrotizing fasciitis	3. Active infection	N	H
DX09	75739	Other anomalies of skin (Other)	1. Autoimmune/inflammatory condition	N	H
DX09	7761	Transient neonatal thrombocytopenia	1. Autoimmune/inflammatory condition	Y	H
DX09	78071	Chronic fatigue syndrome	6. Other	N	U
DX09	99591	Systemic inflammatory response syndrome due to infectious process without acute organ dysfunction	3. Active infection	N	L
DX09	99592	Systemic inflammatory response syndrome due to infectious process with acute organ dysfunction	3. Active infection	N	L
DX09	9968	Complications of transplanted organ	3. Active infection	Y	H
DX09	99685	Complications of transplanted organ (bone marrow)	5. Hematopoietic stem cell/bone marrow transplant	Y	U
DX09	9997	Rh incompatibility reaction, not elsewhere classified	1. Autoimmune/inflammatory condition	N	U
DX09	V014	Contact with or exposure to rubella	4. Pre/post exposure infection prophylaxis	Y	L
DX09	V0171	Contact with or exposure to varicella	4. Pre/post exposure infection prophylaxis	Y	L
DX09	V0179	Contact with or exposure to other viral disease	4. Pre/post exposure infection prophylaxis	N	L
DX09	V042	Need for prophylactic vaccination and inoculation against measles alone	4. Pre/post exposure infection prophylaxis	Y	L

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	V043	Need for prophylactic vaccination and inoculation against rubella alone	4. Pre/post exposure infection prophylaxis	Y	L
DX09	V0489	Contact with or exposure to other viral disease	4. Pre/post exposure infection prophylaxis	N	L
DX09	V053	Need for prophylactic vaccination and inoculation against viral hepatitis	4. Pre/post exposure infection prophylaxis	N	L
DX09	V072	Prophylactic immunotherapy	2. Immune deficiency	Y	L
DX09	V1585	Exposure to potentially hazardous body fluids	4. Pre/post exposure infection prophylaxis	Y	U
DX09	V4281	Organ or tissue replaced by transplant, bone barrow	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PX09	4100	Bone marrow transplant, not otherwise specified	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PX09	4102	Allogeneic bone marrow transplant with purging	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PX09	4103	Allogeneic bone marrow transplant without purging	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PX09	4105	Allogeneic hematopoietic stem cell transplant without purging	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PX09	4108	Allogeneic hematopoietic stem cell transplant	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PXC4	38240	Hematopoietic progenitor cell (HPC) transplantation, allogeneic	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PXC4	38242	Allogeneic lymphocyte infusion	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PXHC	S2065	Pancreas/kidney transplant	1. Autoimmune/inflammatory condition	Y	H
PXHC	S2150	Allogeneic bone marrow transplant	5. Hematopoietic stem cell/bone marrow transplant	Y	U

*Code type abbreviations: DX09 = ICD-9-CM diagnosis code, PXC4 = Current Procedural Terminology 4 (CPT-4) procedure code, PXHC = Healthcare Common Procedure Coding System (HCPCS) code

†Decimal points removed from code field

‡Dose abbreviations: H = high dose (≥1 g/kg), L = low dose (< 1 g/kg), U = unclassified

B. APPENDIX B: LIST OF IMMUNOGLOBULIN EXPOSURE CODES

Below is a table displaying the details for immunoglobulin exposure codes we considered for this study. **Table B 1** includes the code type, drug product, route of administration, and description associated with each code. We also considered and included NDC codes related to the ingredient "globulin, immune" as of August 2013, though they are not featured in the table.

Table B 1. MS IGIV-TEE codes for IG administration (excluding NDCs)

Code	Code Type	Drug Product	Route	Description
90281	CPT	Unspecified	Intramuscular	Immune globulin (IG), human, for intramuscular use
90283	CPT	Unspecified	Intravenous	Immune globulin (IGIV), human, for intravenous use
90284	CPT	Unspecified	Subcutaneous	Immune globulin (IGSC), human, for use in subcutaneous infusions, 100 mg, each
90399	CPT	Unspecified	Unspecified	Unlisted immune globulin
C9270	HCPCS	Gammaplex	Intravenous	Injection, immune globulin (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1459	HCPCS	Privigen	Intravenous	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1460	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 1 cc
J1470	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 2 cc
J1480	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 3 cc
J1490	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 4 cc
J1500	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 5 cc
J1510	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 6 cc
J1520	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 7 cc
J1530	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 8 cc
J1540	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 9 cc
J1550	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 10 cc
J1557	HCPCS	Gammaplex	Intravenous	Injection, immune globulin (Gammaplex), intravenous, non-

Code	Code Type	Drug Product	Route	Description
				lyophilized (e.g., liquid), 500 mg
J1559	HCPCS	Hizentra	Subcutaneous	Injection, immune globulin (Hizentra), 100 mg
J1560	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, over 10 cc
J1561	HCPCS	Gamunex/ Gamunex-C/ Gammaked	Intravenous	Injection, immune globulin (Gamunex/Gamunex-C/ Gammaked), non-lyophilized (e.g., liquid), 500 mg
J1562	HCPCS	Vivaglobin	Subcutaneous	Injection, immune globulin (Vivaglobin), 100 mg. [Code effective date: 20080101]
J1563	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, 1g
J1564	HCPCS	Unspecified	Intravenous	Injection, immune globulin, 10 mg
J1566	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, lyophilized (e.g., powder), 500 mg
J1567	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), 500 mg
J1568	HCPCS	Octagam	Intravenous	Injection, immune globulin (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	HCPCS	Gammagard Liquid	Intravenous	Injection, immune globulin (Gammagard Liquid), intravenous, non-lyophilized, (e.g., liquid), 500 mg
J1572	HCPCS	Flebogamma	Intravenous	Injection, immune globulin (Flebogamma), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1599	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg
P9014	HCPCS	Unspecified	Intramuscular	Globulin, gamma, 1 mL
Q4087	HCPCS	Octagam	Intravenous	Injection, immune globulin (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
Q4088	HCPCS	Gammagard Liquid	Intravenous	Injection, immune globulin (Gammagard Liquid), intravenous, non-lyophilized, (e.g., liquid), 500 mg

Code	Code Type	Drug Product	Route	Description
Q4091	HCPCS	Flebogamma	Intravenous	Injection, immune globulin (Flebogamma), intravenous, non-lyophilized, (e.g., liquid), 500 mg
Q4092	HCPCS	Gamunex	Intravenous	Injection, immune globulin (Gamunex), intravenous, non-lyophilized (e.g., liquid), 500 mg
Q4097	HCPCS	Privigen	Intravenous	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
Q9941	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, lyophilized, 1g
Q9942	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, lyophilized, 10 mg
Q9943	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, non-lyophilized, 1g
Q9944	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, non-lyophilized, 10 mg
S9545	HCPCS	Unspecified	Intravenous	Administration of immune globulin, intravenously, in the home setting, including all nursing care, equipment, and supplies; per diem
9914	ICD-9	Unspecified	Unspecified	Injection or infusion of immunoglobulin

C. APPENDIX C: DIAGNOSIS CODES FOR SERIOUS THROMBOEMBOLIC EVENTS

Below is a table displaying the details for the diagnosis codes for serious thromboembolic events we considered for this study. **Table C 1** includes the outcome class, outcome, and ICD-9 code.

Table C 1. MS IGIV-TEE diagnosis codes for serious thromboembolic events

Outcome Class	Outcome	ICD-9 Code	
Arterial	Ischemic Stroke (based on Protocol Core recommendation)	433.x1	Occlusion and stenosis of precerebral arteries with cerebral infarction
		434.xx	Occlusion of cerebral arteries
		436	Acute, but ill-defined, cerebrovascular disease
	Myocardial infarction (algorithm used in MS AMI chart validation protocol, except they restricted to primary position inpatient diagnoses)	410.x0	Acute myocardial infarction, episode of care unspecified
		410.x1	Acute myocardial infarction, initial episode of care
Venous	Pulmonary embolism	415.1x	Pulmonary embolism and infarction
	Deep vein thrombosis (based on Protocol Core recommendation for venous thromboembolism, plus cerebral venous thrombosis and minus the 453 code series for upper extremity thrombosis)	451.11	Phlebitis and thrombophlebitis of femoral vein
		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	Acute venous embolism and thrombosis of unspecified site
		325.xx	Phlebitis and thrombophlebitis of intracranial venous sinuses
		437.6	Nonpyogenic thrombosis of intracranial venous sinus

D. APPENDIX D: CODES USED TO SELECT THROMBOEMBOLIC EVENT RISK FACTORS

1. List of potential confounders

Below are tables displaying the details for the potential confounders (non-medication) we considered for this study.**Table D 1** includes covariates not defined by specific codes. **Table D 2** includes the look-back period, code type, and codes related to each potential confounder.

Table D 1. Demographic, calendar time, and medical utilization risk factors

Covariate	Time to define
Age (centered at age 45; linear and quadratic terms)	At baseline
Sex	At baseline
Calendar year (centered at 2009)	At baseline
Hospitalization	In last 183 days
Non-acute institutional stay (e.g., skilled nursing facility or rehabilitation facility stay)	In last 183 days
Emergency department visit	In last 183 days

Table D 2. Codes used to select TEE medical condition risk factors

Covariate	Lookback period for condition (days)	Code type*	Codes
Angina or chronic ischemic heart disease	183	DX09	413.x, 414.x
Atrial fibrillation or flutter	183	DX09	427.3x
Cardiac arrhythmia other than atrial fibrillation	183	DX09	426.10, 426.11, 426.13, 426.2, 426.3, 426.4, 426.50, 426.51, 426.52, 426.53, 426.6, 426.7, 426.8x, 427.0, 427.2, 427.60, 427.9, 785.0
Central venous catheter	183	PX09	38.97
		PXC4	36555-36558, 36560-36561, 36563, 36565-36566, 36568-36571, 36575-36576, 36578, 36580-36585, 36597-36598
Cerebrovascular hemorrhage	183	DX09	430.x, 431.x, 432.x
CHF or cardiomyopathy	183	DX09	402.01, 402.11, 402.91, 425.x, 428.x, 429.3
Chronic inflammatory condition	183	DX09	446.x, 555.x, 556.x, 581.x, 695.4, 701.0, 710.0, 710.1, 710.2, 710.3, 710.4, 710.8, 710.9, 711.2, 714.x, 725.x
Chronic renal disease	183	DX09	582.x, 583.x, 585.x, 586, 588.x, 792.5, V42.0, V45.1x, V56.0, V56.1, V56.2, V56.3x, V56.8

Covariate	Lookback period for condition (days)	Code type*	Codes
Coagulation defects	183	DX09	286.x, 287.x
Cognitive disorder	183 for dementia; 30 for delirium	DX09	290.3, 290.x, 291.0, 292.81, 293.0, 293.1, 294.1, 294.2x, 331.0, 331.1x, 331.2, 331.82
Complicated hypertension	183	DX09	402.x, 403.x, 404.x, 405.x
COPD	183	DX09	491.x, 492.x, 496.x
Coronary revascularization	183	DX09	996.03, V45.81, V45.82
		PX09	00.66, 36.0x, 36.1x, 36.2x, 37.22, 37.23, 88.5x
		PXC4	33510-33514, 33516-33523, 33525, 92973-92974, 92977, 92980-92982, 92984, 92987, 92995-92996
		PXHC	G0290, G0291, S2205, S2206, S2207, S2208, S2209
Diabetes without chronic complication	183	DX09	250.0x, 250.1x, 250.2x, 250.3x, 250.8x, 250.9x
Diabetes with chronic complication	183	DX09	250.4x, 250.5x, 250.6x, 250.7x, 357.2x, 362.0x, 366.41
High risk cancer	90	DX09	151.x, 157.x, 162.x, 179.x, 180.x, 181.x, 182.x, 183.x, 184.x, 186.x, 188.x, 196.x, 197.x, 198.x, 199.x, 201.x, 202.x, 203.x, 204.x, 205.x, 206.x, 207.x, 208.x, 273.0, 273.3
Hyperlipidemia	183	DX09	272.0, 272.1, 272.2, 272.3
Immobility condition	30 for burn injuries; 90 for fractures; 183 for all others	DX09	260.x, 261.x, 262.x, 263.x, 284.8x, 284.9, 288.0, 289.9, 332.0, 332.1, 334.1, 342.x, 343.x, 344.x, 707.x, 741.x, 783.0, 783.2x, 783.3x, 783.4x, 799.4, 800.x, 801.x, 802.x, 803.x, 804.x, 805.x, 806.x, 807.x, 808.x, 809.x, 820.x, 821.x, 822.x, 823.x, 824.x, 825.x, 826.x, 827.x, 828.x, 829.x, 851.x, 852.x, 853.x, 854.x, 861.x, 862.x, 863.x, 864.x, 865.x, 866.x, 867.x, 868.x, 869.x, 870.x, 890.x, 891.x, 892.x, 893.x, 894.x, 895.x, 896.x, 897.x, 925.x, 926.x, 927.x, 929.x, 948.1, 948.2, 948.3, 948.4, 948.5, 948.6, 948.7, 948.8, 948.9, 952.x, 978.x, V54.13, V54.14, V54.15, V54.16, V54.17, V54.23, V54.24, V54.25, V54.26, V54.27
		PX09	41.0x

Covariate	Lookback period for condition (days)	Code type*	Codes
		PXHC	A4310, A4311, A4312, A4313, A4314, A4315, A4316, A4320, A4321, A4322, A4326, A4327, A4328, A4331, A4332, A4333, A4334, A4338, A4340, A4344, A4346, A4347, A4348, A4349, A4354, A4355, A4357, A4358, B4027, B4028, B4034, B4035, B4036, B4083, B4086, B4087, B4088, B4100, B4102, B4103, B4104, B4149, B4150, B4152, B4153, B4154, B4155, B4157, B4158, B4159, B4160, B4161, B4162, B4164, B4168, B4172, B4176, B4178, B4180, B4185, B4189, B4193, B4197, B4199, B4216, B4220, B4222, B4224, B5000, B5100, B5200, B9000, B9002, B9004, B9006, B9998, B9999, E0100, E0105, E0130, E0135, E0140, E0141, E0143, E0144, E0147, E0148, E0149, E0153, E0154, E0155, E0156, E0157, E0158, E0159, E0163, E0165, E0167, E0168, E0170, E0171, E0172, E0175, E0240, E0241, E0242, E0243, E0244, E0245, E0246, E0247, E0248, E0250, E0251, E0255, E0256, E0260, E0261, E0265, E0266, E0270, E0271, E0272, E0273, E0274, E0275, E0276, E0277, E0280, E0290, E0291, E0292, E0293, E0294, E0295, E0296, E0297, E0301, E0302, E0303, E0304, E0305, E0310, E0315, E0316, E0325, E0326, E0370, E0371, E0372, E0373, E0424, E0425, E0430, E0431, E0433, E0434, E0435, E0439, E0440, E0441, E0442, E0443, E0444, E0621, E0625, E0627, E0628, E0629, E0630, E0635, E0636, E0637, E0638, E0639, E0640, E0641, E0642, E0700, E0705, E0710, E0791, E0950, E0951, E0952, E0955, E0956, E0957, E0958, E0959, E0960, E0961, E0966, E0967, E0968, E0969, E0970, E0971, E0973, E0974, E0978, E0980, E0981, E0982, E0983, E0984, E0985, E0986, E0988, E0990, E0992, E0994, E0995, E1002, E1003, E1004, E1005, E1006, E1007, E1008, E1009, E1010, E1011, E1014, E1015, E1016, E1017, E1018, E1020, E1028, E1029, E1030, E1031, E1035, E1038, E1039, E1050, E1060, E1070, E1083, E1084, E1085, E1086, E1087, E1088, E1089, E1090, E1092, E1093, E1100, E1110, E1129, E1130, E1140, E1150, E1160, E1161, E1170, E1171, E1172, E1180, E1190, E1195, E1200, E1220, E1221, E1222, E1223, E1224, E1225, E1226, E1227, E1228, E1230, E1231, E1232, E1233, E1234, E1235, E1236, E1237, E1238, E1239, E1240, E1250, E1260, E1270, E1280, E1285, E1290, E1295, E1296, E1297, E1298,

Covariate	Lookback period for condition (days)	Code type*	Codes
			E1390, E1391, E1392, E1405, E1406, E2201, E2202, E2203, E2204, E2205, E2206, E2207, E2208, E2209, E2210, E2211, E2212, E2213, E2214, E2215, E2216, E2217, E2218, E2219, E2220, E2221, E2222, E2223, E2224, E2225, E2226, E2300, E2301, E2310, E2311, E2312, E2313, E2321, E2322, E2323, E2324, E2325, E2326, E2327, E2328, E2329, E2330, E2331, E2340, E2341, E2342, E2343, E2351, E2358, E2359, E2360, E2361, E2362, E2363, E2364, E2365, E2366, E2367, E2368, E2369, E2370, E2371, E2372, E2373, E2374, E2375, E2376, E2377, E2378, E2381, E2382, E2383, E2384, E2385, E2386, E2387, E2388, E2389, E2390, E2391, E2392, E2393, E2394, E2395, E2396, E2397, E2399, E2402, E2601, E2602, E2603, E2604, E2605, E2606, E2607, E2608, E2609, E2610, E2611, E2612, E2613, E2614, E2615, E2616, E2617, E2618, E2619, E2620, E2621, G0270, G0271
Intermediate coronary syndrome or unstable angina	183	DX09	411.1, 411.8x
Ischemic stroke or central venous thrombosis	183	DX09	325.x, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.x, 436, 437.6
Low risk cancer or cancer treatment	90	DX09	140.x, 141.x, 142.x, 143.x, 144.x, 145.x, 146.x, 147.x, 148.x, 149.x, 150.x, 152.x, 153.x, 154.x, 155.x, 156.x, 158.x, 159.x, 160.x, 161.x, 163.x, 164.x, 165.x, 170.x, 171.x, 174.x, 175.x, 176.x, 185.x, 187.x, 189.x, 190.x, 191.x, 192.x, 193.x, 194.x, 195.x, 200.x, V58.0, V66.1, V67.1
		PX09	92.20, 92.21, 92.22, 92.23, 92.24, 92.25, 92.26, 92.27, 92.28, 92.29
		PXC4	77371-77373, 77401-77525, 77761-77799
		PXRE	0330, 0333
Moderate to severe liver disease	183	DX09	456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.8
Mood disorder	183	DX09	296.0x, 296.1x, 296.2, 296.3, 296.4x, 296.5x, 296.6x, 296.7, 296.80, 296.81, 296.82, 296.89, 300.4, 309.x, 311
Myocardial infarction	183	DX09	410.x, 411.0, 412

Covariate	Lookback period for condition (days)	Code type*	Codes
Venous thromboembolism not included in outcome definition	183	DX09	336.1, 362.3x, 449, 451.0, 451.8x, 452, 453.0, 453.3, 453.5x, 453.6x, 453.7x, 453.8x, 573.4, 593.81
Other cardiovascular disease	183	DX09	420.x, 421.x, 422.x, 423.x, 429.x, 440.x, 444.x, 445.x, 745.x, 746.x, 747.x, V45.00, V45.09, V53.3x
		PXC4	33924, 75573
Other infection	183 for HIV/AIDS; 60 for all others	DX09	001.x, 002.x, 003.0, 003.20, 003.21, 003.22, 003.23, 003.24, 003.29, 003.8, 003.9, 004.x, 005.x, 006.x, 007.x, 008.x, 009.x, 020.3, 020.4, 020.5, 021.1, 021.2, 022.1, 022.2, 026.1, 031.0, 032.84, 036.0, 036.1, 036.82, 039.1, 042.x, 046.2, 047.x, 049.0, 049.1, 049.8, 049.9, 052.0, 052.1, 053.0, 054.3, 054.72, 055.0, 055.1, 056.01, 056.71, 058.2, 062.x, 063.x, 064.x, 066.2, 072.1, 072.2, 073.0, 083.0, 091.81, 094.81, 098.82, 100.81, 112.4, 112.83, 114.0, 114.2, 114.4, 114.5, 115.01, 115.05, 115.11, 115.15, 115.91, 115.95, 130.0, 130.4, 136.3, 139.0, 320.x, 321.x, 322.x, 323.x, 341.2, 480.x, 481.x, 482.x, 483.x, 484.x, 485.x, 486.x, 487.x, 488.x, 513.0, 517.1, 590.x, 595.x, 597.x, 598.0, 599.0, 711.x, 730.x
Other ischemic cerebrovascular disease	183	DX09	362.34, 433.00, 433.10, 433.20, 433.30, 433.80, 433.90, 435.x, 437.0, 437.1, 437.9, 438.x, 781.4, 784.3, 997.0
		PX09	00.61, 00.63, 38.11, 38.11, 38.12, 38.12, 38.41, 38.42, 39.28
		PXC4	0075T, 0076T, 35301, 35390, 35501, 35601, 35901, 37215-37216
		PXHC	S2211
Other venous catheterization	183	PX09	38.93
Overweight condition	183	DX09	277.7, 278.0x
Peripheral venous thromboembolism per study definition, including pulmonary embolism	183	DX09	415.1x, 416.2, 451.11, 451.19, 451.2, 451.9, 453.1, 453.2, 453.40, 453.41, 453.42, 453.9
Peripheral vascular disease	183	DX09	440.x, 441.2, 441.4, 441.7, 441.9, 443.1, 443.2, 443.8, 443.9, 447.1, 557.1, 557.9, V43.4
		PX09	38.18, 39.25, 39.29, 84.10, 84.11, 84.12, 84.13,

Covariate	Lookback period for condition (days)	Code type*	Codes
			84.14, 84.15, 84.16, 84.17
		PXC4	27295, 27590-27592, 27598, 27880-27882, 27888-27889, 28800, 28805, 28810, 28820, 28825, 35351, 35355, 35361, 35363, 35371-35372, 35454, 35456, 35459, 35470, 35473-35474, 35482-35483, 35492-35493, 35495, 35521, 35533, 35541, 35546, 35548-35549, 35551, 35556, 35558, 35563, 35565-35566, 35570-35571, 35681-35683, 35879, 37207-37208, 37220-37235
Psychotic disorder	183	DX09	293.81, 293.82, 295.x, 297.x, 298.x
Pulmonary congestion or hypostasis	183	DX09	514.x
Sepsis and related	60 for sepsis; 183 for shock	DX09	003.1, 020.2, 022.3, 036.2, 038.x, 054.5, 449, 785.52, 785.5x, 790.7, 995.91, 995.92
Substance abuse	183	DX09	291.0, 291.1, 291.2, 291.3, 291.5, 291.8x, 291.9, 303.9x, 304.0x, 304.1x, 304.2x, 304.3x, 304.4x, 304.5x, 304.6x, 304.7x, 304.8x, 304.9x, 305.0x, 305.2x, 305.3x, 305.4x, 305.5x, 305.6, 305.7, 305.8x, 305.9x, 571.0, 571.1, 571.2, 571.3, V11.3, V65.42
Surgery	90	DX09	V67.0x
		PX09	00.7x, 00.8x, 03.4, 03.5x, 03.9x, 79.85, 79.86, 80.45, 80.46, 80.6, 80.85, 80.86, 80.95, 80.96, 81.40, 81.42, 81.43, 81.51, 81.52, 81.53, 81.54, 81.55, 84.16, 84.18
		PXC4	01214-01215, 01402, 20930-20938, 22010-22015, 22100-22116, 22206-22226, 22318-22328, 22532-22534, 22548-22585, 22590-22632, 22800-22819, 22830, 22840-22865, 27075-27079, 27130-27138, 27218, 27226-27228, 27253, 27258-27259, 27299, 27447, 27486-27487, 29861-29863, 43644-43645, 43800-43881, 49570-49575, 50010-50045, 50070, 50100-50135, 50205-50290, 50320-50340, 50370, 50382-50384, 50400-50540, 50593, 50600-50630, 50650-50660, 50700-50940, 51020-51040, 51080, 53000-53085, 53210-53275, 53400-53520, 53855, 56620-56740, 56800-56810, 57000-57335, 57530-57556, 57720, 58140-58146, 58150-58294, 58400-58540, 58600-58615, 58700-58720, 58750-58770, 58820-58825, 58920-58960, 58999, 61320-61321,

Covariate	Lookback period for condition (days)	Code type*	Codes
			61546, 61680-61692, 61697-61710, 62160-62165, 63001-63017, 63045-63051, 63055-63066, 63075-63091, 63101-63103, 63170-63200, 63250-63295, 63300-63308, 63650-63688
		PXHC	S2083, S2213
Tobacco use	183	DX09	305.1, 649.0x, 989.84, V15.82
		PXC1	83887, 99406, 99407
		PXC2	1034F, 1035F, 4000F, 4001F, 4004F
		PXHC	C9801, C9802, G0375, G0376, G0436, G0437, G8093, G8094, G8402, G8403, G8453, G8454, G8455, G8456, G8688, G9016, S4990, S4991, S4995, S9075, S9453
Uncomplicated hypertension	183	DX09	401.x
		PXC2	4050F
Valvular disease	183	DX09	093.2x, 394.x, 395.x, 396.x, 397.x, 424.x, 746.3, 746.4, 746.5, 746.6, V42.2, V43.3
Other venous thromboembolism risk indicators	30 for HIT or trans-fusion; 90 for secondary hyper-coag-ulable state or VTE risk NOS; 183 for others	DX09	238.4, 270.4, 282.6, 289.0, 289.6, 289.81, 289.82, 289.84, 454.x, V12.51, V58.2
		PXC2	3551F, 3552F, 4044F
		PXC4	85300-85306, 85380, 85400-85421, 86147
		PXHC	P9010, P9011, P9012, P9016, P9017, P9019, P9020, P9021, P9022, P9023, P9031, P9032, P9033, P9034, P9035, P9036, P9037, P9038, P9039, P9040, P9051, P9052, P9053, P9054, P9055, P9056, P9057, P9058, P9059, P9060
		PXRE	0380, 0381, 0382, 0383, 0384, 0385, 0386, 0387, 0389, 0391

*Code type abbreviations: DX09 = ICD-9-CM diagnosis code, PXC4 = Current Procedural Terminology 4 (CPT-4) procedure code, PXHC = Healthcare Common Procedure Coding System (HCPCS) code

2. List of medication covariates

Below is a table displaying the drug classes that served as covariates (medication) for disease risk score calculations. **Table D 3** includes the classes, subclass1, and subclass2 (if applicable) associated with the medications we considered via NDC codes, as well as HCPCS and CPT codes for cancer chemotherapy.

Table D 3. Classes and subclasses of medication covariates*

Class	Subclass
Cardiovascular	Oral anticoagulants
	Antiplatelet agents (including aspirin)
	Antihypertensives
	Lipid lowering agents
	Antiarrhythmic agents
	Anti-anginal agents
Hematologic growth factors	Hematopoietic agents
Antidiabetic agents	Oral antidiabetic agents
	Insulin
Pain medications	NSAIDs and Cox-2 Inhibitors Opiates
Central nervous system	SSRI/SNRI/Tertiary amine TCA
	Antipsychotics
Hormones, steroids, or related	Corticosteroids
	Sex steroids
Cancer treatments	Thalidomide analogues (infusion chemotherapy and radiation therapy assessed using procedure codes)

*Use defined as a prescription fill during the 183-day lookback period.

3. Pregnancy and the post-partum period

Below is a table displaying the codes drawn from the Sentinel Gardasil Study[41] to identify pregnancy and the post-partum period for excluding pregnant patients from the exploratory cohort analyses (pregnant patients were excluded based on chart review in the self-controlled analysis). **Table D 4** lists codes indicative of pregnancy or post-partum status and time frames from an encounter with that code during which an individual will be classified as pregnant or post-partum.

Table D 4. MS IGIV-TEE codes for identification of pregnancy and the post-partum period

Category*	ICD-9 Code	Description	Period considered pregnancy or post-partum relative to diagnosis date	First-in-X-days criterion
Stillborn	656.4	Intrauterine death affecting management of mother	–42–280	280
Stillborn	656.4	Intrauterine death affecting management of mother unspecified as to episode of care	–42–280	280
Stillborn	656.41	Intrauterine death affecting management of mother delivered	–42–280	280
Stillborn	656.43	Intrauterine death affecting management of mother antepartum	–42–280	280
Stillborn	768	Fetal death from asphyxia or anoxia before onset of labor or at unspecified time	–42–280	280
Stillborn	768.1	Fetal death from asphyxia or anoxia during labor	–42–280	280
Stillborn	V27.1	Mother with single stillborn	–42–280	280
Stillborn	V27.3	Mother with twins one liveborn and one stillborn	–42–280	280
Stillborn	V27.4	Mother with twins both stillborn	–42–280	280
Stillborn	V27.6	Mother with other multiple birth some liveborn	–42–280	280
Stillborn	V27.7	Mother with other multiple birth all stillborn	–42–280	280
Stillborn	V32*	Twin birth mate stillborn	–42–280	280
Stillborn	V35*	Other multiple birth (three or more) mates all stillborn	–42–280	280
Stillborn	V36*	Other multiple birth (three or more) mates liveborn and stillborn	–42–280	280

Category*	ICD-9 Code	Description	Period considered pregnancy or post-partum relative to diagnosis date	First-in-X-days criterion
Preterm	644.2*	Early onset of delivery delivered with or without antepartum condition	–42–258	280
Delivery	650*	Normal delivery	–42–280	280
Delivery	669.5*	Forceps or vacuum extractor delivery without mention of indication	–42–280	280
Delivery	669.6*	Breech extraction without mention of indication	–42–280	280
Delivery	669.7*	Cesarean delivery without mention of indication	–42–280	280
Delivery	V24*	Postpartum care and examination	–42–280	280
Delivery	V27.0	Mother with single liveborn	–42–280	280
Delivery	V27.2	Mother with twins both liveborn	–42–280	280
Delivery	V27.5	Mother with other multiple birth all liveborn	–42–280	280
Delivery	V27.9	Mother with unspecified outcome of delivery	–42–280	280
Delivery	V30*	Single liveborn	–42–280	280
Delivery	V31*	Twin birth mate liveborn	–42–280	280
Delivery	V33*	Twin birth unspecified whether mate liveborn or stillborn	–42–280	280
Delivery	V34*	Other multiple birth (three or more) mates all liveborn	–42–280	280
Delivery	V37*	Other multiple birth (three or more) unspecified whether mates liveborn or stillborn	–42–280	280
Delivery	V39*	Liveborn unspecified whether single twin or	–42–280	280

Category*	ICD-9 Code	Description	Period considered pregnancy or post-partum relative to diagnosis date	First-in-X-days criterion
		multiple		
SAB	632*	Missed abortion	0-105	280
SAB	634*	Spontaneous abortion	0-105	280
TAB	635*	Legally induced abortion	0-105	280
TAB	636*	Illegal abortion	0-105	280
TAB	637*	Unspecified abortion	0-105	280
TAB	640.01	Threatened abortion delivered	0-105	280
TAB	640.81	Other specified hemorrhage in early pregnancy delivered	0-105	280
TAB	640.91	Unspecified hemorrhage in early pregnancy delivered	0-105	280

*SAB = spontaneous abortion; TAB = therapeutic or elective abortion

E. APPENDIX E: DECISION TREE REFLECTING ADJUDICATION CRITERIA FOR POTENTIAL CASES OF ACUTE MYOCARDIAL INFARCTION (AMI)

STEP 1. Criteria for Definite Acute Myocardial Infarction (AMI) or sudden cardiac death

Check if present:

Evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia (e.g. symptoms such chest pain, shortness of breath). Any one of the following meets the definition for diagnosis of AMI:

- ☐ 1. Diagnostic cardiac biomarkers & EKG changes (**need BOTH A & B**)
  - ☐ A. Detection of rise and/or fall of cardiac biomarkers ([preferably cardiac troponin (cTn) but CK-MB or CK is acceptable if troponin is not available] with at least one value above the 99th percentile of the upper reference limit (URL)*
  - ☐ B. **AND** one or more of the following:
    - ☐ Ischemic symptoms
    - ☐ ECG changes indicative of new ischemia (new ST-T changes or new LBBB)
    - ☐ Development of pathological Q waves in ECG
    - ☐ Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality Identification of intracoronary thrombus by angiography or autopsy
- ☐ 2. Cardiac death with symptoms suggestive of myocardial ischemia and ischemic EKG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarkers would be increased.
- ☐ 3. Pathological findings postmortem of an acute AMI
- ☐ 4. PCI related AMI: elevations in cTn levels greater than 5x 99th percentile URL* in patients with normal baseline values (e.g. <99th percentile URL) or a rise in cTn values >20% if the baseline values were elevated or falling during the first 48 hours post-PCI. In addition, (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality.
- ☐ 5. Stent thrombosis AMI detected by coronary angiography or autopsy in the setting of myocardial ischemia with a rise/and or fall of cardiac biomarker values with at least one value above 99th percentile.
- ☐ 6. CABG related AMI: elevations in cardiac biomarkers greater than 10 x 99th percentile URL* in patients with normal baseline values (e.g. <99th percentile URL) during the first 72 hours post-CABG and one or more of the following:
  - ☐ New pathological Q waves
  - ☐ New LBBB
  - ☐ Angiographically documented new graft or native coronary artery occlusion
  - ☐ Imaging evidence of new loss of viable myocardium or a regional wall motion abnormality

*Note: if the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available then the URL for the myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the AMI decision limit for the particular laboratory should be used as the URL.

If the above criteria are met then check box below and form is finished, if not proceed to step 2.

☐ Definite AMI

STEP 2. If criteria above for definite AMI are not met, use the table below to determine probability of AMI based on symptoms, cardiac biomarkers, and ECG

	Cardiac Enzymes			
	Abnormal	**Equivocal**	**Incomplete**	**Normal**
ECG Pattern/Symptoms				
Cardiac pain present:				
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 block	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
Cardiac pain absent:				
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

Interpretation of Cardiac Enzymes			
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: electrocardiogram (ECG), within normal limits (WNL), upper reference limit (URL), upper limit of normal (ULN), creatine kinase (CK).

STEP 3. Adjudication decision

- ☐ Definite AMI
- ☐ Probable AMI
- ☐ Possible AMI (criteria for definite or probable AMI not met, but physician diagnosis of AAMI documented in chart)
- ☐ No AMI (ruled out)
- ☐ Insufficient information / unknown

If 'Probable', 'possible' or 'insufficient information / unknown', what data were needed but not available:

- ☐ Cardiac biomarkers
- ☐ ECGs
- ☐ Information on ischemic symptoms
- ☐ Other _____
- ☐ None
- ☐ If this information is obtained return for adjudication

F. APPENDIX F: REASONS CHARTS COULD NOT BE OBTAINED FOR REVIEW

Charts required for adjudication of acute TEE status were unavailable for 143 potential TEE cases (97 arterial and 46 venous). For the arterial endpoint, cases were abstracted if a chart was received for the index TEE encounter or a subsequent second-choice TEE-related encounter. For the venous endpoint, the chart for the index TEE was required. This decision was made due to resource limitations, and the assumption that the chart from the index TEE encounter would be required to determine the onset date for venous TEEs. **Table F 1** below describes the reasons that charts corresponding to the index TEE encounter could not be retrieved for these 143 cases.

Table F 1. Reasons that index TEE encounter charts were unobtainable for the 143 potential TEE cases that did not proceed to abstraction

Reason	Frequency
Unable to map patient and/or provider of requested encounter to identifiers needed for chart retrieval	28
Unable to identify patient and/or provider for chart corresponding to requested encounter	5
Could not establish contact with provider	16
Provider does not participate in research studies	1
Provider did not participate due to legal/compliance/HIPAA concerns	25
Provider did not participate (reason unspecified)	22
No record of patient at facility	18
Requested dates of service unavailable in chart corresponding to requested encounter	9
Chart not retrieved due to resource constraints	6
Chart not informative due to insufficient information	1
Chart processed after deadline for chart review	3
Other or unspecified	9

Table F 2 below provides information on the IGIV chart retrieval status for the 143 potential TEE cases that were not chart-reviewed. For 32 of these cases, the IGIV chart was received but not the TEE chart. Cases proceeded to abstraction based on whether the required TEE chart(s) were retrieved successfully.

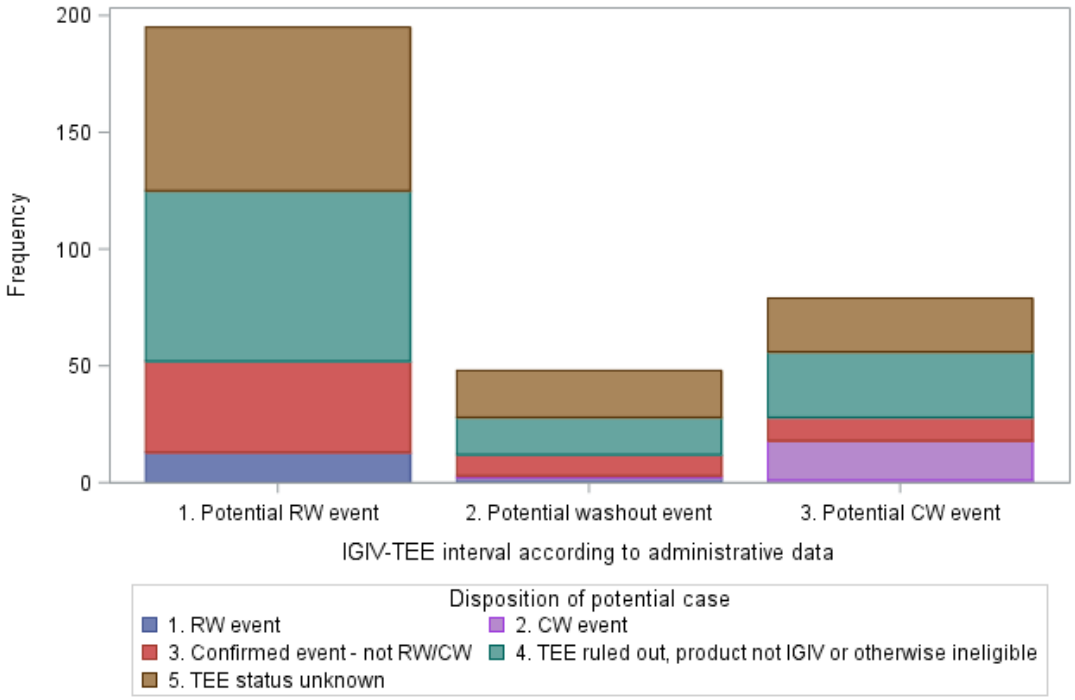
Table F 2. Proximate IGIV encounter chart retrieval status for the 143 potential TEE cases that did not proceed to abstraction

Reason	Frequency
Unable to map patient and/or provider of requested encounter to identifiers needed for chart retrieval	27
Unable to identify patient and/or provider for chart corresponding to requested encounter	3
Pharmacy dispensing record – no corresponding chart	4
Could not establish contact with provider	11
Provider does not participate in research studies	1
Provider did not participate due to legal/compliance/HIPAA concerns	20
Provider did not participate (reason unspecified)	13
No record of patient at facility	10
Requested dates of service unavailable in chart corresponding to requested encounter	10
Chart not retrieved due to resource constraints	6

Reason	Frequency
Chart not informative due to insufficient information	1
Chart processed after deadline for chart review	3
Incomplete case – IG chart available, TEE chart not obtained	32
Other or unspecified	2

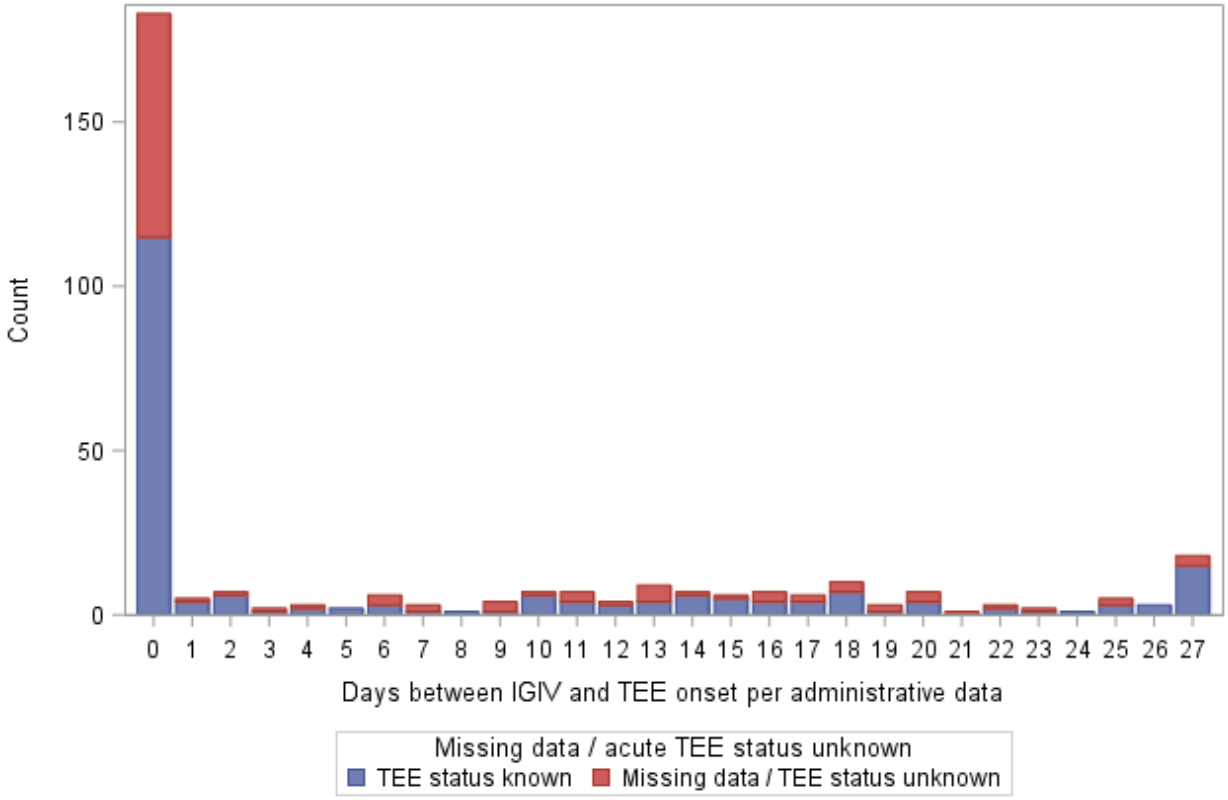
G. APPENDIX G: DISPOSITION OF ALL POTENTIAL POST-IGIV RISK WINDOW (RW) AND CONTROL WINDOW (CW) TEES, STRATIFIED BY RW/CW STATUS AS RECORDED IN THE SENTINEL DISTRIBUTED DATABASE (SDD)

Figure G 1. Disposition of all potential arterial TEE cases by the time interval between IGIV and TEE, as recorded in the SDD



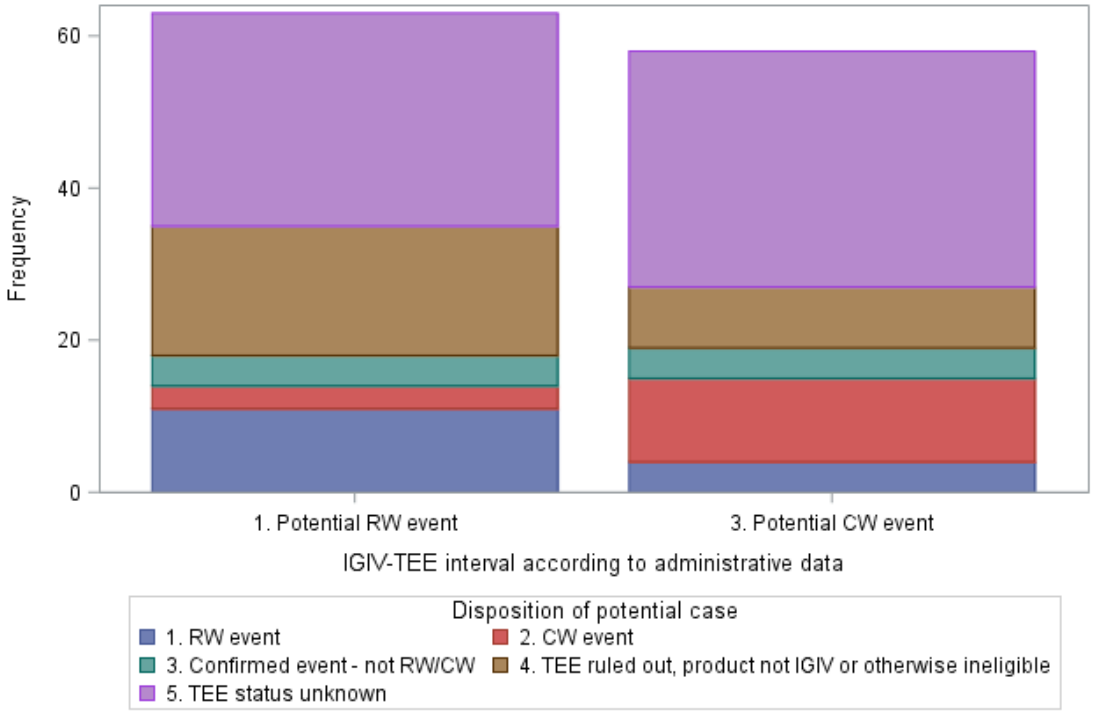
Note: Potential RW event: difference between TEE date and IGIV date, as recorded in the SDD, was 0-2 days; potential washout event: difference was 3 to 13 days; potential CW event: difference was 14-27 days. In the SDD, inpatient diagnosis and procedure codes are typically assigned the date of the hospital admission. In ascertaining potential cases, we made no assumptions about when these events actually took place during multi-day inpatient stays. For this reason, for a small number of cases, the difference between the IGIV procedure date and TEE date was <0 or >27 in the SDD, but these cases were still identified as potential RW or CW cases depending on when exposure and outcome actually occurred during the patient's hospital stay(s). In the graph above, IGIV-TEE intervals <0 days were rounded up to 0, and those >27 days were rounded down to 27.

Figure G 2. Missing data rates for potential arterial TEE cases by IGIV-TEE interval, as recorded in the SDD



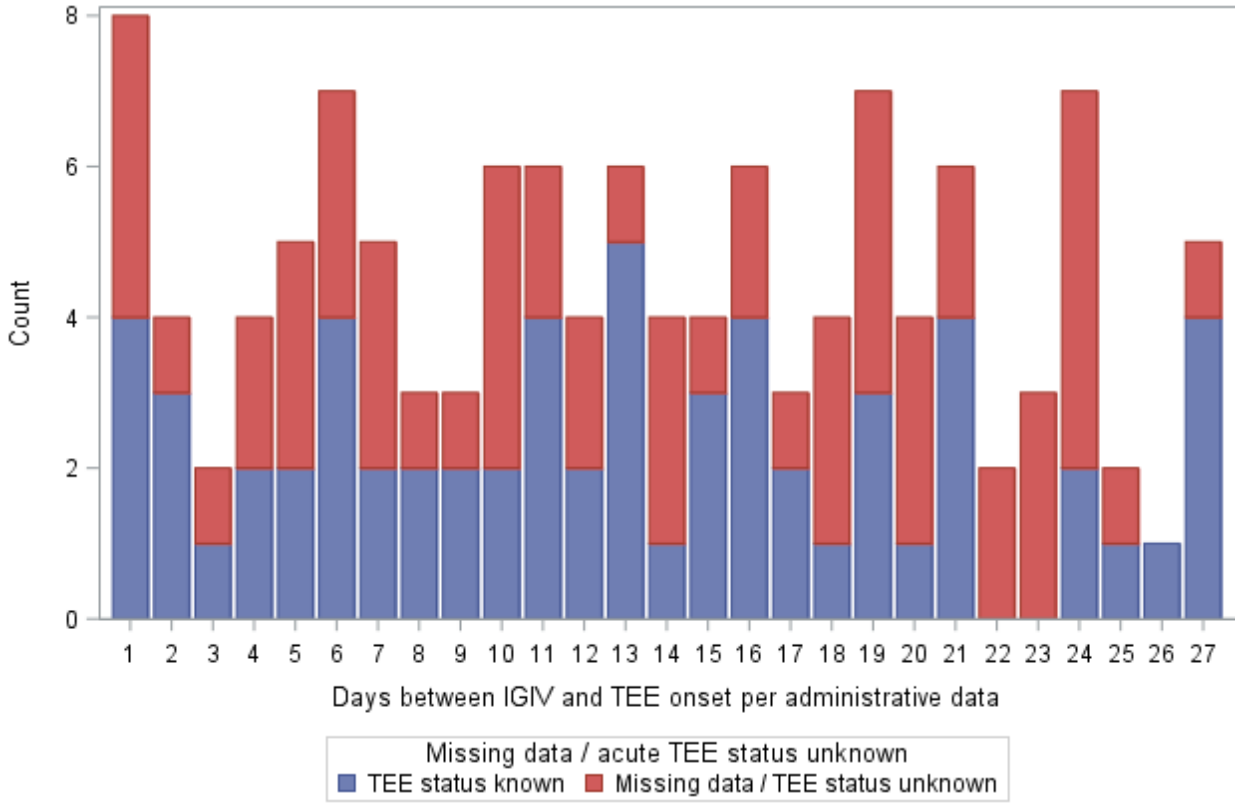
Note: In the SDD, inpatient diagnosis and procedure codes are typically assigned the date of the hospital admission. In ascertaining potential cases, we made no assumptions about when these events actually took place during multi-day inpatient stays. For this reason, for a small number of cases, the difference between the IGIV procedure date and TEE date was <0 or >27 in the SDD, but these cases were still identified as potential RW or CW cases depending on when exposure and outcome actually occurred during the patient's hospital stay(s). In the graph above, IGIV-TEE intervals <0 days were rounded up to 0, and those >27 days were rounded down to 27.

Figure G 3. Disposition of all potential venous TEE cases by the time interval between IGIV and TEE, as recorded in the SDD



Note: Potential RW event: difference between TEE date and IGIV date, as recorded in the SDD, was 0-13 days; potential CW event: difference was 14-27 days. Venous TEE risk assessment had no washout period, and was restricted to outpatient IGIV exposures. In the SDD, inpatient diagnosis and procedure codes are typically assigned the date of the hospital admission. In ascertaining potential cases, we made no assumptions about when these events actually took place during multi-day inpatient stays. For this reason, for a small number of cases, the difference between the IGIV procedure date and TEE date was <0 or >27 in the SDD, but these cases were still identified as potential RW or CW cases depending on when exposure and outcome actually occurred during the patient's hospital stay(s). In the graph above, IGIV-TEE intervals <0 days were rounded up to 0, and those >27 days were rounded down to 27.

Figure G 4. Missing data rates for potential venous TEE cases by IGIV-TEE interval, as recorded in the SDD



Note: In the SDD, inpatient diagnosis and procedure codes are typically assigned the date of the hospital admission. In ascertaining potential cases, we made no assumptions about when these events actually took place during multi-day inpatient stays. For this reason, for a small number of cases, the difference between the IGIV procedure date and TEE date was <0 or >27 in the SDD, but these cases were still identified as potential RW or CW cases depending on when exposure and outcome actually occurred during the patient's hospital stay(s). In the graph above, IGIV-TEE intervals <0 days were rounded up to 0, and those >27 days were rounded down to 27.

H. APPENDIX H: RESULTS FROM OBJECTIVE D1 EXPLORATORY COHORT ANALYSES

Table H 3. Objective D1 exploratory cohort analyses: Cohort identification steps

Inclusion criteria	Patient count
01. New IG users (outpatient setting only)	27395
02. Restrict to patients with a recognized IG indication	19416
03. Exclude pregnant women	19006
04A. Exclude patients with recent arterial TEE (arterial TEE analyses)	18984
04V. Exclude patients with recent venous TEE (venous TEE analyses)	18960

Table H 4. Objective D1 exploratory cohort analyses: Cohort baseline characteristics

Covariate	D1 cohort analysis: Arterial TEE risk assessment new user cohort (N = 18,948). N (%)	D1 cohort analysis: Venous TEE risk assessment new user cohort (N = 18,960). N (%)
0-19 years	2662 (14%)	2661 (14%)
20-39 years	2835 (15%)	2827 (15%)
40-59 years	7019 (37%)	7012 (37%)
60-79 years	5678 (30%)	5670 (30%)
80+ years	790 (4%)	790 (4%)
Female	10090 (53%)	10079 (53%)
Autoimmune/inflammatory condition	10444 (55%)	10426 (55%)
Immune deficiency	8390 (44%)	8374 (44%)
Infection	2090 (11%)	2077 (11%)
Pre- or post-exposure prophylaxis against infection	586 (3%)	586 (3%)
Bone marrow or hematopoietic stem cell transplant	1232 (6%)	1223 (6%)
Other indication	4455 (23%)	4440 (23%)
Myocardial infarction	427 (2%)	439 (2%)
Angina	1861 (10%)	1864 (10%)
Atrial fibrillation or flutter	928 (5%)	927 (5%)
Ischemic stroke	360 (2%)	366 (2%)
Peripheral vascular disease	984 (5%)	980 (5%)
Hypertension, uncomplicated	6304 (33%)	6298 (33%)
Hypertension, complicated	1111 (6%)	1112 (6%)

Covariate	D1 cohort analysis: Arterial TEE risk assessment new user cohort (N = 18,948). N (%)	D1 cohort analysis: Venous TEE risk assessment new user cohort (N = 18,960). N (%)
Diabetes	3264 (17%)	3258 (17%)
Venous thromboembolism	752 (4%)	710 (4%)
Oral anticoagulant use	949 (5%)	925 (5%)
Hospitalization	5573 (29%)	5549 (29%)
Condition associated with immobility	5230 (28%)	5208 (27%)
Cancer	5557 (29%)	5535 (29%)

Table H 5. Objective D1 exploratory cohort analyses: Arterial TEE risk estimates by recency of IG exposure

	IG recency	Events	Person-years	Incidence density per 1000 person-years (95% CI)	Adjusted hazard ratio (95% CI)
Main results: all IG exposures p = 0.87	Days 1-2	3	542.0	5.5 (1.1, 16.2)	1.04 (0.30, 3.59)
	Days 3-13	15	2531.1	5.9 (3.3, 9.8)	1.14 (0.59, 2.22)
	Days 14-27	14	2431.4	5.8 (3.1, 9.7)	1.33 (0.68, 2.59)
	Days 28-90	16	2668.7	6.0 (3.4, 9.7)	1.00 (reference)
	Days 91-180	7	2064.3	3.4 (1.4, 7.0)	1.00 (reference)
	Days 181+	9	2559.6	3.5 (1.6, 6.7)	1.00 (reference)
Route subgroup analysis: intramuscular IG products Zero events outside of reference period: model not fit to data.	Days 1-2	0	25.5	0.0 (0.0, 144.8)	--
	Days 3-13	0	131.9	0.0 (0.0, 28.0)	--
	Days 14-27	0	146.1	0.0 (0.0, 25.3)	--
	Days 28-90	2	504.5	4.0 (0.5, 14.3)	1.00 (reference)
	Days 91-180	1	625.7	1.6 (0.0, 8.9)	1.00 (reference)
	Days 181+	1	1122.3	0.9 (0.0, 5.0)	1.00 (reference)
Route subgroup analysis: subcutaneous IG products Zero events: model not fit to data.	Days 1-2	0	73.4	0.0 (0.0, 50.2)	--
	Days 3-13	0	261.7	0.0 (0.0, 14.1)	--
	Days 14-27	0	179.0	0.0 (0.0, 20.6)	--
	Days 28-90	0	73.5	0.0 (0.0, 50.2)	1.00 (reference)
	Days 91-180	0	37.1	0.0 (0.0, 99.3)	1.00 (reference)
	Days 181+	0	31.7	0.0 (0.0, 116.4)	1.00 (reference)

	IG recency	Events	Person-years	Incidence density per 1000 person-years (95% CI)	Adjusted hazard ratio (95% CI)
Route subgroup analysis: route-unspecified IG products p = 0.94	Days 1-2	0	33.9	0.0 (0.0, 108.7)	--
	Days 3-13	1	158.6	6.3 (0.2, 35.1)	--
	Days 14-27	1	153.4	6.5 (0.2, 36.3)	--
	Days 28-90	0	178.4	0.0 (0.0, 20.7)	1.00 (reference)
	Days 91-180	0	131.1	0.0 (0.0, 28.1)	1.00 (reference)
	Days 181+	3	151.1	19.9 (4.1, 58.0)	1.00 (reference)
Route subgroup analysis: intravenous IG products p = 0.83	Days 1-2	3	409.2	7.3 (1.5, 21.4)	1.53 (0.43, 5.37)
	Days 3-13	14	1979.0	7.1 (3.9, 11.9)	1.11 (0.55, 2.24)
	Days 14-27	13	1952.9	6.7 (3.5, 11.4)	1.33 (0.65, 2.69)
	Days 28-90	14	1912.3	7.3 (4.0, 12.3)	1.00 (reference)
	Days 91-180	6	1270.4	4.7 (1.7, 10.3)	1.00 (reference)
	Days 181+	5	1254.5	4.0 (1.3, 9.3)	1.00 (reference)
Indication subgroup analysis: patients with possible autoimmune/ inflammatory indication p = 0.58	Days 1-2	3	294.0	10.2 (2.1, 29.8)	1.56 (0.42, 5.77)
	Days 3-13	11	1352.6	8.1 (4.1, 14.6)	1.26 (0.57, 2.79)
	Days 14-27	11	1253.1	8.8 (4.4, 15.7)	1.71 (0.78, 3.75)
	Days 28-90	11	1419.8	7.7 (3.9, 13.9)	1.00 (reference)
	Days 91-180	3	1011.1	3.0 (0.6, 8.7)	1.00 (reference)
	Days 181+	8	1082.7	7.4 (3.2, 14.6)	1.00 (reference)
Indication subgroup analysis: patients with possible immune deficiency indication p = 0.52	Days 1-2	0	183.6	0.0 (0.0, 20.1)	--
	Days 3-13	4	870.7	4.6 (1.3, 11.8)	0.90 (0.19, 4.38)
	Days 14-27	1	854.5	1.2 (0.0, 6.5)	0.18 (0.02, 1.84)
	Days 28-90	5	581.4	8.6 (2.8, 20.1)	1.00 (reference)
	Days 91-180	0	339.6	0.0 (0.0, 10.9)	1.00 (reference)
	Days 181+	0	326.0	0.0 (0.0, 11.3)	1.00 (reference)
Indication subgroup analysis: patients with another indication type p = 0.92	Days 1-2	0	64.5	0.0 (0.0, 57.2)	--
	Days 3-13	0	307.8	0.0 (0.0, 12.0)	--
	Days 14-27	2	323.8	6.2 (0.7, 22.3)	1.92 (0.30, 12.11)
	Days 28-90	0	667.5	0.0 (0.0, 5.5)	1.00 (reference)
	Days 91-180	4	713.7	5.6 (1.5, 14.4)	1.00 (reference)
	Days 181+	1	1150.9	0.9 (0.0, 4.8)	1.00 (reference)

	IG recency	Events	Person-years	Incidence density per 1000 person-years (95% CI)	Adjusted hazard ratio (95% CI)
Baseline TEE risk subgroup analysis: lowest 8 risk deciles p = 0.65	Days 1-2	1	448.2	2.2 (0.1, 12.4)	0.68 (0.09, 5.33)
	Days 3-13	10	2090.4	4.8 (2.3, 8.8)	1.43 (0.63, 3.22)
	Days 14-27	5	1992.3	2.5 (0.8, 5.9)	0.75 (0.27, 2.08)
	Days 28-90	10	2183.2	4.6 (2.2, 8.4)	1.00 (reference)
	Days 91-180	5	1725.5	2.9 (0.9, 6.8)	1.00 (reference)
	Days 181+	5	2187.8	2.3 (0.7, 5.3)	1.00 (reference)
Baseline TEE risk subgroup analysis: highest 2 risk deciles p = 0.20	Days 1-2	2	93.8	21.3 (2.6, 77.0)	1.57 (0.31, 7.88)
	Days 3-13	5	440.7	11.3 (3.7, 26.5)	0.77 (0.23, 2.54)
	Days 14-27	9	439.1	20.5 (9.4, 38.9)	2.39 (0.94, 6.10)
	Days 28-90	6	485.5	12.4 (4.5, 26.9)	1.00 (reference)
	Days 91-180	2	338.8	5.9 (0.7, 21.3)	1.00 (reference)
	Days 181+	4	371.8	10.8 (2.9, 27.5)	1.00 (reference)

Table H 6. Objective D1 exploratory cohort analyses: Venous TEE risk estimates by recency of IG exposure

	IG recency	Events	Person-years	Incidence density per 1000 person-years (95% CI)	Adjusted hazard ratio (95% CI)
Main results: all IG exposures p = 0.002	Days 1-2	10	540.7	18.5 (8.9, 34.0)	3.51 (1.67, 7.40)
	Days 3-13	24	2524.2	9.5 (6.1, 14.1)	1.75 (1.01, 3.02)
	Days 14-27	13	2425.9	5.4 (2.9, 9.2)	0.85 (0.44, 1.64)
	Days 28-90	18	2664.0	6.8 (4.0, 10.7)	1.00 (reference)
	Days 91-180	11	2062.2	5.3 (2.7, 9.5)	1.00 (reference)
	Days 181+	5	2558.8	2.0 (0.6, 4.6)	1.00 (reference)
Route subgroup analysis: intramuscular IG products Unstable parameter estimates due to sparse data: model not fit.	Days 1-2	1	25.5	39.3 (1.0, 218.9)	--
	Days 3-13	0	131.8	0.0 (0.0, 28.0)	--
	Days 14-27	0	146.0	0.0 (0.0, 25.3)	--
	Days 28-90	1	504.3	2.0 (0.1, 11.0)	1.00 (reference)
	Days 91-180	1	625.4	1.6 (0.0, 8.9)	1.00 (reference)
	Days 181+	0	1121.8	0.0 (0.0, 3.3)	1.00 (reference)
Route subgroup analysis:	Days 1-2	0	73.4	0.0 (0.0, 50.2)	--
	Days 3-13	2	261.5	7.6 (0.9, 27.6)	--

	IG recency	Events	Person-years	Incidence density per 1000 person-years (95% CI)	Adjusted hazard ratio (95% CI)
subcutaneous IG products. Unstable parameter estimates due to sparse data: model not fit.	Days 14-27	3	178.8	16.8 (3.5, 49.0)	--
	Days 28-90	0	73.3	0.0 (0.0, 50.3)	1.00 (reference)
	Days 91-180	0	36.9	0.0 (0.0, 100.0)	1.00 (reference)
	Days 181+	0	31.6	0.0 (0.0, 116.7)	1.00 (reference)
Route subgroup analysis: route-unspecified IG products p = 0.86	Days 1-2	1	33.8	29.6 (0.7, 164.9)	--
	Days 3-13	1	158.0	6.3 (0.2, 35.3)	3.46 (0.22, 55.78)
	Days 14-27	0	152.8	0.0 (0.0, 24.1)	--
	Days 28-90	1	178.5	5.6 (0.1, 31.2)	1.00 (reference)
	Days 91-180	1	131.3	7.6 (0.2, 42.4)	1.00 (reference)
	Days 181+	0	151.2	0.0 (0.0, 24.4)	1.00 (reference)
Route subgroup analysis: intravenous IG products p = 0.006	Days 1-2	8	408.0	19.6 (8.5, 38.6)	3.45 (1.50, 7.96)
	Days 3-13	21	1972.9	10.6 (6.6, 16.3)	1.71 (0.96, 3.08)
	Days 14-27	10	1948.3	5.1 (2.5, 9.4)	0.75 (0.36, 1.58)
	Days 28-90	16	1907.9	8.4 (4.8, 13.6)	1.00 (reference)
	Days 91-180	9	1268.6	7.1 (3.2, 13.5)	1.00 (reference)
	Days 181+	5	1254.2	4.0 (1.3, 9.3)	1.00 (reference)
Indication subgroup analysis: patients with possible autoimmune/ inflammatory indication p = 0.0003	Days 1-2	9	293.0	30.7 (14.0, 58.3)	6.75 (2.76, 16.47)
	Days 3-13	12	1347.3	8.9 (4.6, 15.6)	1.50 (0.71, 3.16)
	Days 14-27	9	1248.8	7.2 (3.3, 13.7)	0.98 (0.42, 2.29)
	Days 28-90	11	1416.3	7.8 (3.9, 13.9)	1.00 (reference)
	Days 91-180	8	1010.0	7.9 (3.4, 15.6)	1.00 (reference)
	Days 181+	3	1082.3	2.8 (0.6, 8.1)	1.00 (reference)
Indication subgroup analysis: patients with possible immune deficiency indication p = 0.57	Days 1-2	1	183.5	5.5 (0.1, 30.4)	0.87 (0.09, 8.19)
	Days 3-13	8	870.4	9.2 (4.0, 18.1)	1.81 (0.61, 5.38)
	Days 14-27	3	854.0	3.5 (0.7, 10.3)	0.75 (0.19, 3.02)
	Days 28-90	3	580.3	5.2 (1.1, 15.1)	1.00 (reference)
	Days 91-180	3	338.8	8.9 (1.8, 25.9)	1.00 (reference)
	Days 181+	1	325.5	3.1 (0.1, 17.1)	1.00 (reference)
Indication	Days 1-2	0	64.2	0.0 (0.0, 57.5)	--

	IG recency	Events	Person-years	Incidence density per 1000 person-years (95% CI)	Adjusted hazard ratio (95% CI)
subgroup analysis: patients with another indication type p = 0.63	Days 3-13	4	306.6	13.0 (3.6, 33.4)	2.95 (0.59, 14.66)
	Days 14-27	1	323.2	3.1 (0.1, 17.2)	1.49 (0.16, 14.33)
	Days 28-90	4	667.4	6.0 (1.6, 15.3)	1.00 (reference)
	Days 91-180	0	713.5	0.0 (0.0, 5.2)	1.00 (reference)
	Days 181+	1	1150.9	0.9 (0.0, 4.8)	1.00 (reference)
Baseline TEE risk subgroup analysis: lowest 8 risk deciles p = 0.002	Days 1-2	8	449.3	17.8 (7.7, 35.1)	4.96 (2.07, 11.90)
	Days 3-13	15	2095.9	7.2 (4.0, 11.8)	2.05 (1.02, 4.14)
	Days 14-27	9	2000.4	4.5 (2.1, 8.5)	1.08 (0.48, 2.43)
	Days 28-90	10	2198.0	4.5 (2.2, 8.4)	1.00 (reference)
	Days 91-180	6	1751.4	3.4 (1.3, 7.5)	1.00 (reference)
	Days 181+	4	2226.3	1.8 (0.5, 4.6)	1.00 (reference)
Baseline TEE risk subgroup analysis: highest 2 risk deciles p = 0.50	Days 1-2	2	91.4	21.9 (2.6, 79.0)	1.59 (0.34, 7.42)
	Days 3-13	9	428.3	21.0 (9.6, 39.9)	1.36 (0.57, 3.26)
	Days 14-27	4	425.5	9.4 (2.6, 24.1)	0.57 (0.18, 1.77)
	Days 28-90	8	466.1	17.2 (7.4, 33.8)	1.00 (reference)
	Days 91-180	5	310.8	16.1 (5.2, 37.5)	1.00 (reference)
	Days 181+	1	332.4	3.0 (0.1, 16.8)	1.00 (reference)

I. APPENDIX I: RESULTS FROM OBJECTIVE D2 EXPLORATORY COHORT ANALYSES

Table I 1. Objective D2 exploratory cohort analyses: Cohort identification steps

Inclusion criteria	Patient count
01. Patients with >183 days of eligible enrollment and a recognized IG indication	2,159,854
02. Exclude pregnant women	2,067,337
03. Exclude prevalent IG users	2,045,978
04A. Exclude patients with recent arterial TEE (arterial TEE analyses)	2,033,045
04A2. Count of arterial TEE cohort members who initiated IG during follow-up	11,861
04V. Exclude patients with recent venous TEE (venous TEE analyses)	2,040,588
04V2. Count of venous TEE cohort members who initiated IG during follow-up	11,840

Table I 2. Objective D2 exploratory cohort analyses: Cohort baseline characteristics

Covariate	D2 cohort analysis: Arterial TEE risk assessment new user cohort (N = 2,033,045). N (%)	D2 cohort analysis: Venous TEE risk assessment new user cohort (N = 2,040,588). N (%)
0-19 years	284,596 (14%)	284,568 (14%)
20-39 years	423,555 (21%)	423,568 (21%)
40-59 years	690,574 (34%)	692,044 (34%)
60-79 years	515,506 (25%)	519,441 (25%)
80+ years	118,814 (6%)	120,967 (6%)
Female	1,231,898 (61%)	1,235,126 (61%)
Autoimmune/inflammatory condition	1,332,147 (66%)	1,339,687 (66%)
Immune deficiency	615,806 (30%)	616,137 (30%)
Infection	63,959 (3%)	64,739 (3%)
Pre- or post-exposure prophylaxis against infection	272,269 (13%)	272,368 (13%)
Bone marrow or hematopoietic stem cell transplant	10,523 (1%)	10,506 (1%)
Other indication	168,905 (8%)	169,164 (8%)
Myocardial infarction	56,105 (3%)	63,784 (3%)
Angina	207,081 (10%)	213,373 (10%)
Atrial fibrillation or flutter	89,986 (4%)	92,410 (5%)
Ischemic stroke	39,821 (2%)	45,196 (2%)
Peripheral vascular disease	126,187 (6%)	128,711 (6%)
Hypertension, uncomplicated	708,714 (35%)	715,555 (35%)

Covariate	D2 cohort analysis: Arterial TEE risk assessment new user cohort (N = 2,033,045). N (%)	D2 cohort analysis: Venous TEE risk assessment new user cohort (N = 2,040,588). N (%)
Hypertension, complicated	149,283 (7%)	152,500 (7%)
Diabetes	463,424 (23%)	468,660 (23%)
Venous thromboembolism	39,404 (2%)	35,237 (2%)
Oral anticoagulant use	74,401 (4%)	74,155 (4%)
Hospitalization	336,858 (17%)	344,401 (17%)
Condition associated with immobility	270,080 (13%)	272,994 (13%)
Cancer	238,693 (12%)	239,030 (12%)

Table I 3. Objective D2 exploratory cohort analyses: Arterial TEE risk estimates by recency of IG exposure

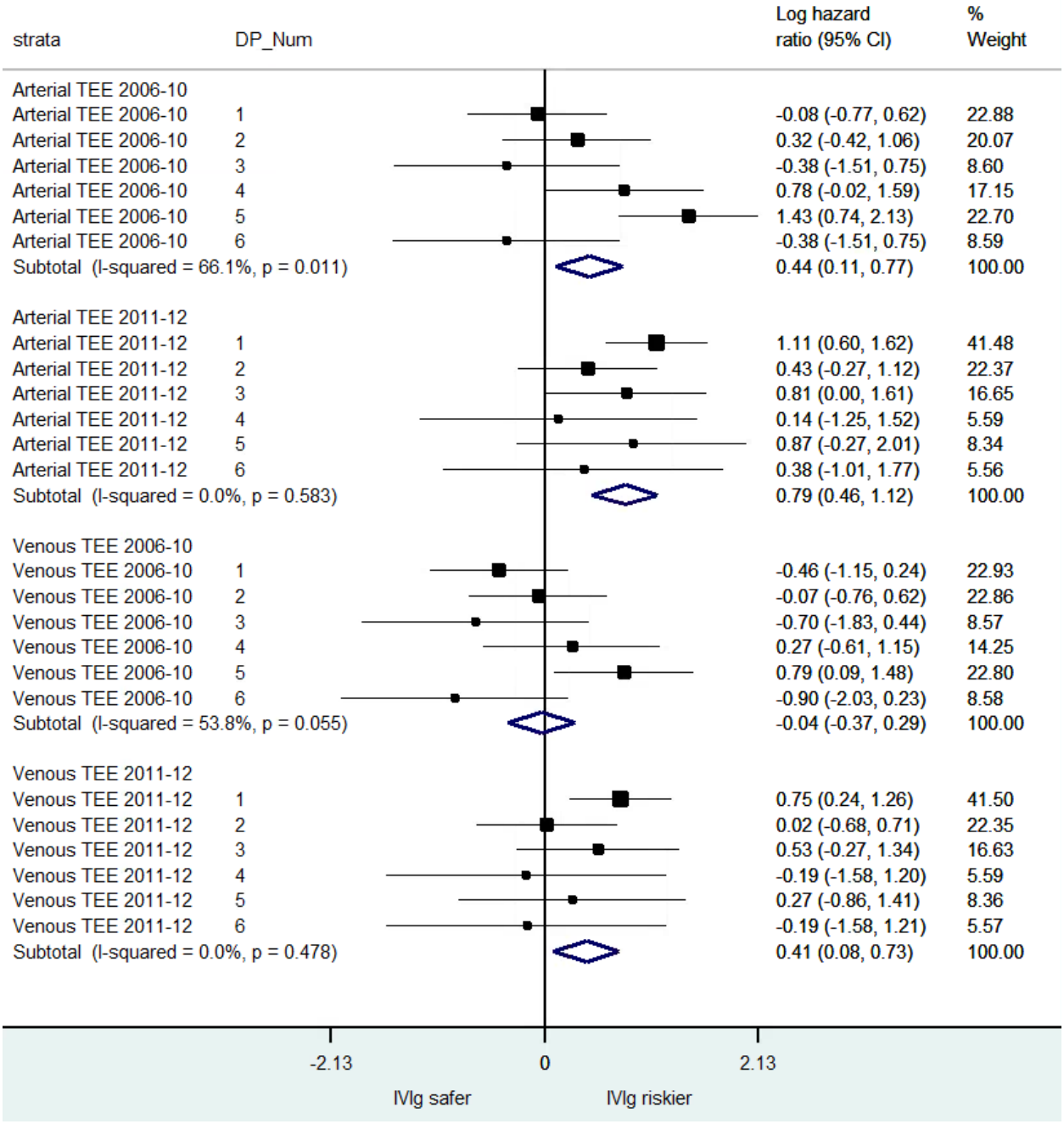
	IG recency	Events	Person-years	Incidence density per 1,000 person-years (95% CI)	Adjusted hazard ratio (95% CI)
Main results: all IG exposures p = 0.0004	Unexposed	18429	1,627,662.6	11.3 (11.2, 11.5)	1.00 (reference)
	Days 0-60	71	4,025.0	17.6 (13.8, 22.3)	1.60 (1.27, 2.02)
	Days 61+	34	2,745.7	12.4 (8.6, 17.3)	1.06 (0.76, 1.49)
Calendar year subgroup analysis: 2006-2010 p = 0.29	Unexposed	13169	1,143,700.0	11.5 (11.3, 11.7)	1.00 (reference)
	Days 0-60	35	2,541.4	13.8 (9.6, 19.2)	1.29 (0.92, 1.80)
	Days 61+	18	1,770.1	10.2 (6.0, 16.1)	0.90 (0.57, 1.43)
Calendar year subgroup analysis: 2011-2012 p < 0.0001	Unexposed	5260	483,962.6	10.9 (10.6, 11.2)	1.00 (reference)
	Days 0-60	36	1,483.5	24.3 (17.0, 33.6)	2.10 (1.51, 2.91)
	Days 61+	16	975.6	16.4 (9.4, 26.6)	1.34 (0.82, 2.19)

Table I 4. Objective D2 exploratory cohort analyses: Venous TEE risk estimates by recency of IG exposure

	IG recency	Events	Person-years	Incidence density per 1,000 person-years (95% CI)	Adjusted hazard ratio (95% CI)
Main results: all IG exposures p = 0.18	Unexposed	19980	1,631,975.4	12.2 (12.1, 12.4)	1.00 (reference)
	Days 0-60	71	4,014.3	17.7 (13.8, 22.3)	1.05 (0.83, 1.32)
	Days 61+	34	2,742.9	12.4 (8.6, 17.3)	0.73 (0.52, 1.03)
Calendar year subgroup analysis: 2006-2010 p = 0.06	Unexposed	14321	1,146,574.5	12.5 (12.3, 12.7)	1.00 (reference)
	Days 0-60	35	2,532.5	13.8 (9.6, 19.2)	0.83 (0.60, 1.16)
	Days 61+	18	1,768.4	10.2 (6.0, 16.1)	0.61 (0.38, 0.97)
Calendar year subgroup analysis: 2011-2012 p = 0.12	Unexposed	5659	485,400.9	11.7 (11.4, 12.0)	1.00 (reference)
	Days 0-60	36	1,481.8	24.3 (17.0, 33.6)	1.41 (1.02, 1.96)
	Days 61+	16	974.5	16.4 (9.4, 26.7)	0.96 (0.59, 1.57)

Note: we verified that the identical arterial and venous TEE case counts for the days 0-60 and days 61+ post-IG exposure categories were a coincidence and not a data analysis or copy/paste error.

Figure I 1. D2 exploratory cohort analyses: Thromboembolic event (TEE) hazard ratio (HR) estimates for days 0-60 post-IG relative to untreated patients, stratified by TEE class, calendar year period, and Data Partner* (DP)



*Due to data sparseness, smaller Data Partners were grouped together (DP numbers 5 and 6 above).

VIII. ACKNOWLEDGEMENTS

Many thanks are due to those who participated in this project:

Data Partners who provided medical records and data used in the analysis: Aetna (Aetna Informatics, Blue Bell, PA), HealthCore (HealthCore, Inc. Government & Academic Research, Alexandria, VA), Harvard Pilgrim (Harvard Pilgrim Health Care Institute, Boston, MA), Health Partners (HealthPartners Institute for Education and Research, Saint Paul, Minnesota), Humana (Humana, Inc., Comprehensive Health Insights, Miramar, FL), KPCO (Kaiser Permanente Colorado Institute for Health Research, Denver, CO), KPHI (Kaiser Permanente Center for Health Research Hawai'i, Honolulu, HI), KPNC (Kaiser Permanente Northern California, Division of Research, Oakland, CA), KPNW (Kaiser Permanente Northwest Center for Health Research, Portland, OR), KPWA (Kaiser Permanente Washington, Seattle, WA), Meyers (Meyers Primary Care Institute, a joint endeavor of Fallon Community Health Plan, Worcester, MA), Optum (OptumInsight Life Sciences Inc., Waltham, MA), Vanderbilt (Vanderbilt University School of Medicine, Department of Preventive Medicine, Nashville, TN [we are indebted to the Tennessee Bureau of TennCare of the Department of Finance and Administration which provided data]).

Sentinel Operations Center: Carolyn Balsbaugh, Jennifer Popovic, Katherine Yih, Tiffany Woodworth, Noelle Cocoros, PRISM Chart Validation Team

IGIV-TEE Workgroup: Joshua Gagne, Mike Mueller, Casey Covarrubias, Carly Comins, Elena Letuchy, Vinutha Vijayadeva, Cynthia Nakasato

Programmers: Rick deFreisse, StatLog, Robert Jin

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