Protocol-based Assessment of Thromboembolic Events (TEEs) after Intravenous Immune Globulin (IVIg) in the Sentinel Distributed Database (2006-2012)

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Funding and Disclosures

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- Conflict of interest statements:
  - E.M.A. is now employed in Johnson & Johnson's medical device epidemiology research division. The analyses for this project, as well as the drafting of the project report and associated manuscripts, were completed prior to his start in that role.
  - J.G.R. reports research grants from Amarin, Amgen, Astra-Zeneca, Eli Lilly, Esai, Glaxo-Smith Kline, Merck, Pfizer, Regeneron/Sanofi and Takeda, and consulting fees from Akcea/Ionis, Amgen, Eli Lilly, Esperion, Merck, Pfizer, and Regeneron/Sanofi.
  - Other workgroup members report no conflicts.

Background: Polyvalent intravenous immune globulin (IVIg) – Indications

- Humoral immunodeficiency
  - IVIg reduces the risk of infection
  - Typical treatment course: infusion of 0.4 g/kg every 3-4 weeks
- Autoimmune and inflammatory conditions
  - Higher doses (1-2 g/kg) can ameliorate some inflammatory disorders

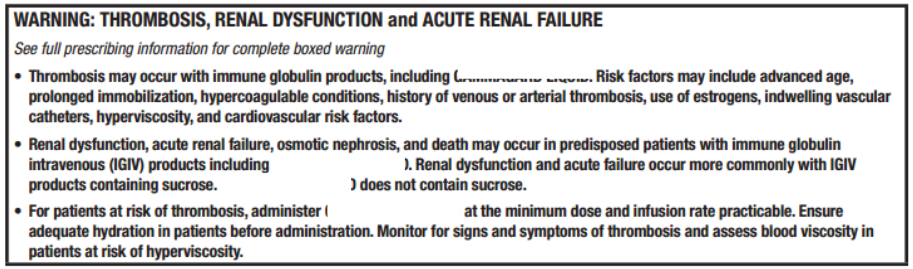
Table 1. Diseases for Which Intravenous Immune Globulin Has Been Shown to Be Beneficial.

FDA-approved indications
Primary immunodeficiency disease
Chronic lymphocytic leukemia
Pediatric HIV infection
Kawasaki's disease
Allogeneic bone marrow transplantation
Chronic inflammatory demyelinating polyneuropathy
Kidney transplantation involving a recipient with a high antibody titer or an ABO-incompatible donor
Multifocal motor neuropathy
Additional approved indications with criteria
Neuromuscular disorders
Guillain–Barré syndrome
Relapsing–remitting multiple sclerosis
Myasthenia gravis
Refractory polymyositis
Polyradiculoneuropathy
Lambert–Eaton myasthenic syndrome
Opsoclonus–myoclonus
Birdshot retinopathy
Refractory dermatomyositis
Hematologic disorders
Autoimmune hemolytic anemia
Severe anemia associated with parvovirus B19
Autoimmune neutropenia
Neonatal alloimmune thrombocytopenia
HIV-associated thrombocytopenia
Graft-versus-host disease
Cytomegalovirus infection or interstitial pneumonia in patients undergoing bone marrow transplantation
Dermatologic disorders
Pemphigus vulgaris
Pemphigus foliaceus
Bullous pemphigoid
Mucous-membrane (cicatricial) pemphigoid
Epidermolysis bullosa acquisita
Toxic epidermal necrolysis or Stevens–Johnson syndrome
Necrotizing fasciitis

Gelfand 2012; Eibl 2008; Silvergleid 2011; Orange 2006

Background: IVIg-associated TEEs

- 1986-present: >200 events reported to FDA (FAERS data) or published in the medical literature
- 2002: FDA requires manufacturers to include warning
- Voluntary product withdrawals:
  - Octagam (U.S., 2010)
  - Omr-IgG-am (Israel, 2011)
- 2013: Boxed warning required
- Reported TEE incidence rates among IVIG patients: 0.6-17%



WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning

- Thrombosis may occur with immune globulin products, including [illegible]. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.
- Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients with immune globulin intravenous (IGIV) products including [illegible]. Renal dysfunction and acute failure occur more commonly with IGIV products containing sucrose. [illegible] does not contain sucrose.
- For patients at risk of thrombosis, administer [illegible] at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk of hyperviscosity.

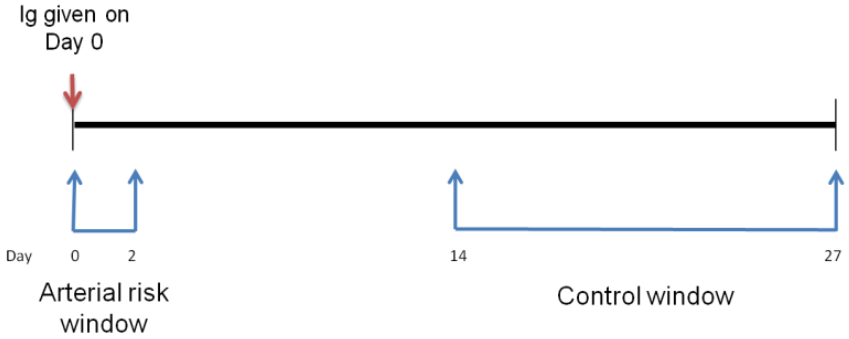
Daniel 2012; Menis 2013; Baxley 2011; Stangel 2003; Brannagan 1996; Caress 2003; Dalakas 1994; Huang 2011; Marie 2006; Okuda 2003; FDA 2002; FDA 2013; Paran 2005; Winiecki 2011; Turecek 2011; Ramirez 2014

Study design

- Self-controlled risk interval design
- Population: new IVIg users
  - Hospitalized patients excluded for venous TEE risk assessment

Arterial TEE (AMI + stroke)

- Risk window: 0-2d
- Control window: 14-27d



Venous TEE (LE DVT + PE)

- Risk window: 0-13d
- Control window: 14-27d

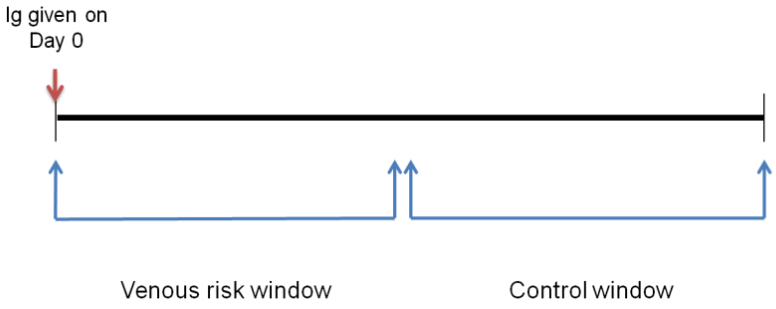


Chart validation of exposure and outcome

19,069 new IVIg users (34% age 60+ years) w/ 93,555 treatments

442 potential post-IVIg TEE cases identified in SDD

Charts requested from data partners

299 charts abstracted by trained nurses

Cases adjudicated by physicians

- Key elements
  - Occurrence of TEE
  - Exposure to IVIg
  - IVIg-TEE time interval

Frequency of confirmed arterial TEE cases by recency of exposure to IVIg

321 Potential events in SDD

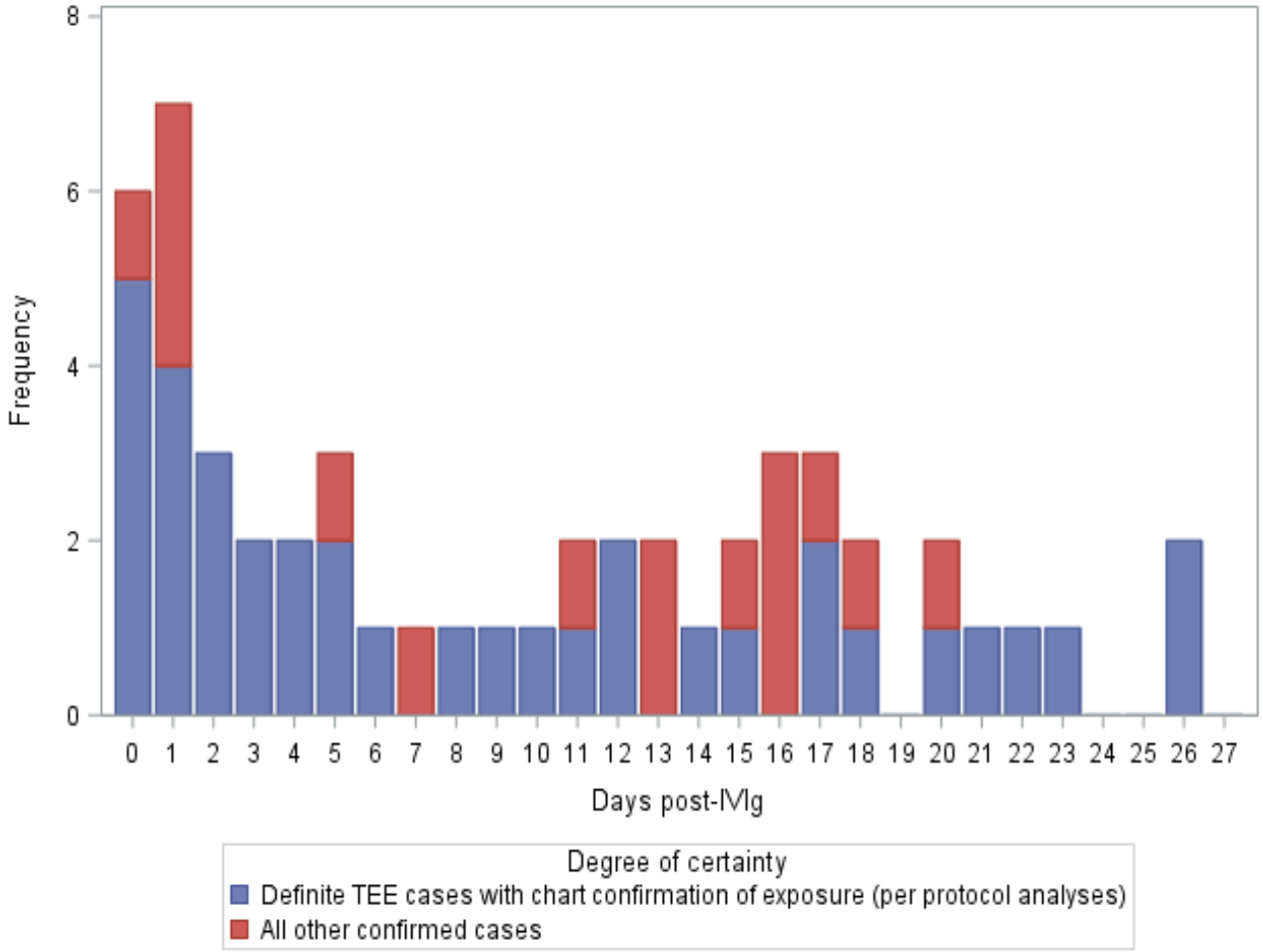
224 Adjudicated

92 Confirmed

5 Ineligible

112 Ruled out

15 Insufficient info



Frequency of confirmed venous TEE cases by recency of exposure to IVIg

121 Potential events in SDD

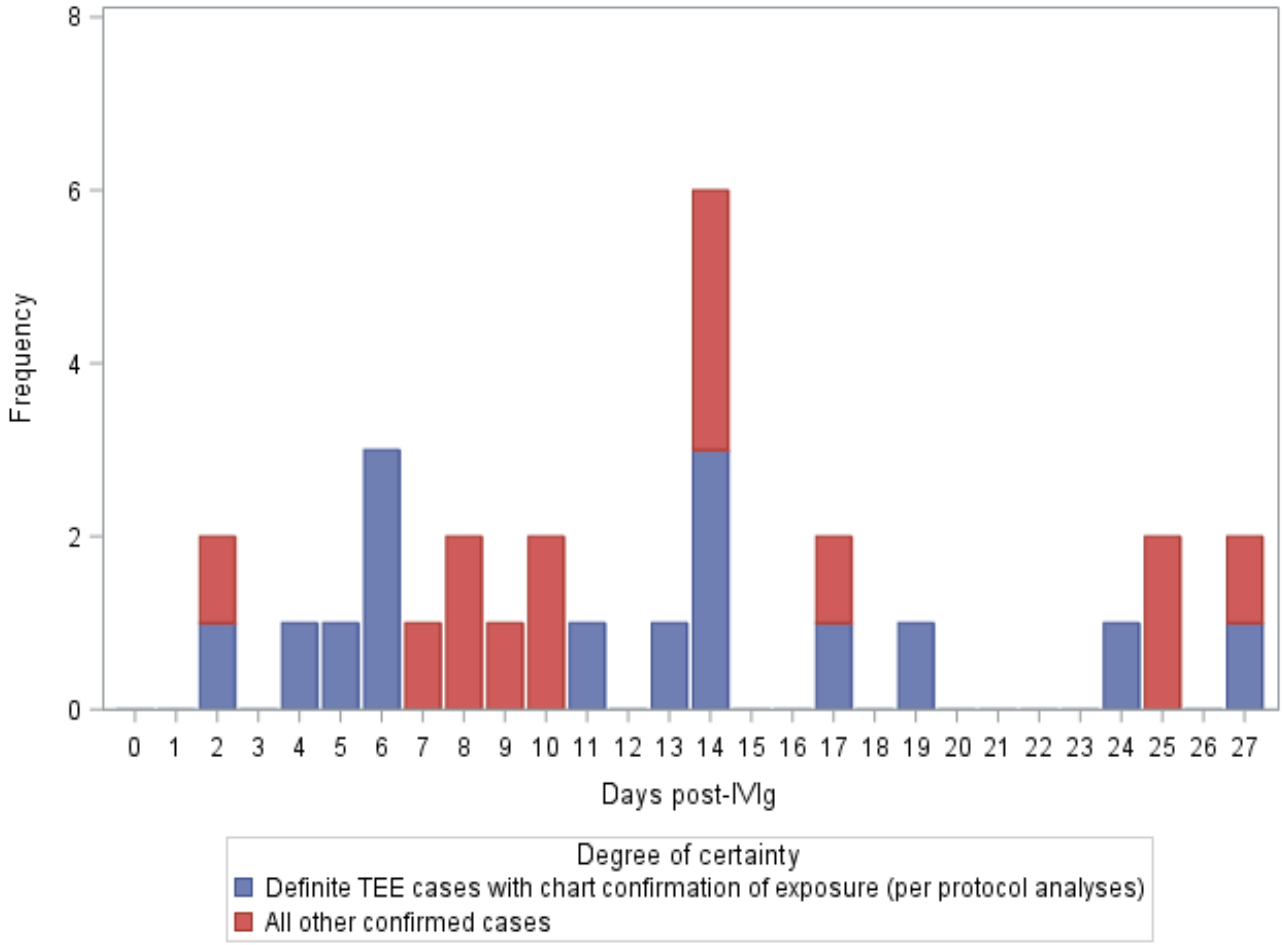
75 Adjudicated

37 Confirmed

8 Ineligible

17 Ruled out

13 Insufficient info



Patient-stratified conditional Poisson relative risk estimates

Endpoint	Rate ratio (95% CI)	Attributable event rates (95% CI) per 10,000 patients
Arterial TEE	3.72 (1.75, 7.84)	9.45 (3.64, 15.6)
Venous TEE	1.04 (0.47, 2.34)	0.81 (-13.6, 15.2)

Discussion

Strengths

- Large population-based cohort of new IVIg users
- Chart confirmation of outcome, exposure, and IVIg-TEE time interval
- Denominator data and absolute risk estimates

Limitations

- Missing data / lower than expected chart retrieval rates
- Venous TEE analysis excluded inpatient IVIg exposure patients
- Results sensitive to validity of
  - Risk/control window choices
  - Assumption of stable baseline risk for each patient

Conclusions

- Transient increased risk of arterial TEE during 0-2d post-IVIg (RR ≈ 3.7; absolute risk ≈ 1 per 1,000 new users)
- No significant increase in venous TEE risk during 0-13d post-IVIg (outpatient IVIg only)

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IVIg-TEE Workgroup

- Project Period: February 2013 – August 2016
- Workgroup Leads: Elizabeth Chrischilles and Ryan Carnahan
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- Kaiser Permanente Northern California: Bruce Fireman
- University of Pennsylvania: Charlie Leonard, Adam Cuker
- Many thanks are due to the 13 Data Partners who provided data and medical records used in the analysis.

Discussion: Unobtainable charts

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

Discussion: Arterial TEE risk overstated in administrative data due to spurious day zero events

Scenario	Rate ratio	Absolute risk
All chart-confirmed risk window (RW) or control window (CW) cases	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	16.1 (95% CI: 12.1, 21.7)	93.7 (95% CI: 85.1, 102.1) per 10,000 patients

No date/time stamping of inpatient procedure and diagnosis records in SDD

- Inpatient procedure and diagnosis records listed as occurring on the admission date