**IVIg-exposure and thromboembolic event risk: findings from the UK Biobank**

Mahima Kapoor FRACP1,2, Ian Hunt PhD3, Jennifer Spillane PhD4,5, Laura Bonnett PhD6, Elspeth J Hutton PhD2, James McFadyen PhD7,8,9,10, John-Paul Westwood MD11, Michael P Lunn PhD,1,12, Aisling S Carr PhD1, Mary M Reilly FRCP1

1: Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London, UK.

2: Department of Neurosciences, Central Clinical School, Monash University, The Alfred Centre, Level 6, 99 Commercial Road, Melbourne, VIC, Australia

3: College of Sciences and Engineering, University of Tasmania, Tasmania, Australia

4: National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, Queen Square, London, UK

5: Guy's and St Thomas' NHS Foundation Trust, London, UK

6: Department of Health Data Science, University of Liverpool, Liverpool, UK

7: Atherothrombosis and Vascular Biology Laboratory, Baker Heart and Diabetes Institute, 75 Commercial Road, Melbourne, 3004 Victoria, Australia.

8: Department of Clinical Hematology, The Alfred Hospital, Melbourne, 3004 Victoria, Australia.

9: Department of Medicine, Central Clinical School, Monash University, Melbourne, 3004 Victoria, Australia.

10: Baker Department of Cardiometabolic Health, University of Melbourne, Melbourne, 3010 Victoria, Australia.

11: Department of Haematology, University College London Hospital, London, United Kingdom

12: Neuroimmunology and CSF Laboratory (NICL), UCL Queen Square Institute of Neurology, London, UK

**Corresponding Author:**

Mahima Kapoor

mahima.kapoor@monash.edu

Central Clinical School, Department of Neurosciences

Monash University, Level 6, 99 Commercial Road, Melbourne, VIC 3004, Australia

Ph: +61 3 9903 0781

Fax: +61 3 9903 8676

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**Abstract**

**Background**

Arterial and venous thromboembolic events (TEEs) have been associated with intravenous immunoglobulin (IVIg) use, but the risk has been poorly quantified. We aimed to calculate the risk of TEEs associated with exposure to IVIg.

**Methods**

We included participants from UK Biobank recruited over 3 years, with data extracted September 2020.

The study endpoints were the incidence of myocardial infarction, other acute ischemic heart disease, stroke, pulmonary embolism and other venous embolism and thrombosis.

Predictors included known TEE risk factors: age, sex, diagnosis of hypertension, smoking status, type 2 diabetes mellitus, hypercholesterolemia, cancer and past history of TEE. IVIg and six other predictors were added in the sensitivity analysis.

Information from participants was collected prospectively, while data from linked resources, including death, cancer, hospital admissions and primary care records were collected retrospectively and prospectively.

**Findings**

14 794 of 502 543 individuals had an incident TEE during the study period. The rate of incident events was 3-fold higher in those with prior history of TEE (8 ·7%) than those without previous history of TEE (3 · 0%).

In the prior TEE category, IVIg exposure was independently associated with increased risk of incident TEE (OR= 3 · 69, p=0 · 03) on multivariate analysis. The Number Needed to Harm by exposure to IVIg in those with a history of TEE was 5·8 (95% CI, 2·3-88·3).

IVIg exposure did not increase risk of TEE in those with no previous history of TEE.

**Interpretation**

IVIg is associated with increased risk of further TEE in individuals with prior history of an event with one further TEE for every 6 people exposed. In practice, this will influence how clinicians consent for and manage overall TEE risk upon IVIg exposure.

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**What is already known on this topic**

Arterial and venous thromboembolic complications of intravenous immunoglobulin (IVIg) have been reported, however, conflictingly, IVIg is also frequently used for inflammatory conditions which lead to increased risk of thromboses. The answer to the primary question of whether IVIg increases the risk of TEEs is inconsistent between reports. A systematic review and meta-analysis of randomised trials did not find the odds of developing a TEE with IVIg to be significantly increased, but a large longitudinal health insurance claims database cohort analysis found concerning rates of same-day TEEs after IVIg administration. These, and other studies, have been limited by insufficient details regarding other cardiovascular risk factors or relevant past history, and we did not find any comprehensive assessment of the impact of IVIg on the participants’ overall cardiovascular disease risk. Small sample sizes have also precluded meaningful subgroup analyses.

**What this study adds**

Our study is the largest investigation into factors linking IVIg exposure to an increased risk of recurrent thromboembolic events. Our findings show the significant increased odds of recurrent arterial and/or venous thromboembolic event after exposure to IVIg independent of other known cardiovascular risk factors. It highlights the number of patients who may be at increased risk, as any severity of previous thromboembolic event (from deep-vein thrombosis managed as an outpatient to patients admitted to hospital with pulmonary emboli or myocardial infarction) have an increased risk of future thromboembolism.

**How this study might affect research, practice and/or policy**

Given the increased risk of recurrent thromboembolic events, especially arterial, in people treated with IVIg, local secondary prevention guidelines should be closely implemented and reinforced in this cohort.

**Introduction**

Arterial and venous thromboembolic (TEE) complications of intravenous immunoglobulin (IVIg) have been reported for decades. A large cohort analysis of 11 785 patients using a longitudinal health insurance claims database found 122 persons (10 · 4 per 1000 persons exposed) had same-day TEEs after exposure to IVIg; the FDA subsequently mandated a black-box warning about the risk of thrombosis for all human Ig products.{Daniel, 2012 #8830;Blumberg, 2013 #245}

In a retrospective study in our hospital’s neuromuscular cohort on maintenance IVIg, we previously found a seven-fold increase in TEE incidence compared with contemporaneous population-based rates.{Kapoor, 2020 #9010}

The mechanism by which IVIg increases the risk of TEEs is uncertain and the rarity of this complication in neurology, haematology and immunology literature has limited a comprehensive assessment of the independent association between IVIg and TEEs.

Cardiovascular disease (CVD) risk is assessed by considering the effect of multiple risk factors (additive or synergistic). Moderate reductions in several risk factors are more effective in reducing overall CVD risk than trying to abolish any one factor alone. Any additional risk from IVIg should be clinically considered and incorporated into decision making for treatment. The classification of CVD risk differs between geographical regions, but absolute risk calculations are used to guide primary and secondary prevention decisions. In the UK guidelines, low risk is <10% incidence within the next 10 years and high risk is ≥ 20% probability of CVD within the next 10 years.{National Institute for Health and Care, 2021 #100;Hippisley-Cox, 2008 #9035}

Venous TEEs are divided in to unprovoked and provoked, which are further divided in to surgical and non-surgical, and transient or persistent. This classification is important as it impacts on the risk for recurrence and duration of anticoagulation.{Tran, 2019 #12841}

Analysing data from more than 500 000 participants in the UK Biobank, we investigated associations of several established TEE risk factors and IVIg exposure with the incidence of arterial and venous TEEs.

**Methods**

The risk prediction model was developed using the UK Biobank dataset (Project 45291, 43383).{Collins, 2012 #6851;Palmer, 2007 #6795;Sudlow, 2015 #8768}

**Participants**

The UK Biobank cohort includes 502 543 community-dwelling individuals, aged 40–73 recruited between April 2007 and December 2010. Data on demographics and a range of exposure and health-related outcomes continues to be collected. All participants are followed up for health outcomes through linkage to national electronic health-related data sets. Participants provided written informed consent to participate in research as previously described.{Sudlow, 2015 #8768} The volunteers tended to be healthier at baseline than the general UK population.{Fry, 2017 #8805}

Information from participants was collected prospectively, while data from linked resources, including death, cancer, hospital admissions and primary care records were collected retrospectively and prospectively.

We excluded participants with incomplete data on the outcomes. Our final analysis included 502 492 of these participants for whom data were available. UK Biobank was approved by the North West Multi­Centre Research Ethics Committee (reference 11/NW/0382).

**Study endpoints**

A TEE (study endpoint) was identified as any of the following: fatal or non-fatal myocardial infarction, other acute ischemic heart disease, stroke (haemorrhage or infarction), deep vein thrombosis, pulmonary embolism, portal vein thrombosis, and other venous embolism and thrombosis as defined by the UK Biobank. These diagnoses were identified from verbal interview. Further outcome adjudication involved linkage with hospital admissions data and national death register data to identify the date of the first known TEE and/or first date of IVIg exposure after the date of baseline assessment.

Two datasets were created from the 502 492 participants. For the first dataset, outcomes were defined by codes mapped to three-characters (I21, I24, I26, 163, I64, I81, I82) in the 10th edition of the International Classification of Diseases (ICD-10). For the second dataset, outcomes also included data-field codes corresponding to self-reported illness code for the above study endpoints. These were collected through a nurse-led interview, as per UK Biobank protocol. Follow-up started at inclusion in the UK Biobank study and our datasets was extracted on 22 Sep 2020, or on the first fatal or non-fatal venous or arterial event for all participants.

The study endpoints were ascertained in the following ways:

* Date of myocardial infarction, venous TEE, stroke, portal vein thrombosis, cerebral infarction, pulmonary embolism and ischaemic heart disease: These were provided as a single date based on algorithms developed by the UK Biobank and Outcome Adjudication group who combined coded information from UK Biobank’s baseline assessment data collection (and linked data from hospital admissions (diagnoses and procedures) and death registries.
* For the second dataset, patient-reported study endpoint information for arterial and venous was acquired at the assessment centre, where participants independently answered questions on a touchscreen. The questions for this section stated:
	+ ‘What was your age when the angina was first diagnosed?’
	+ ‘What was your age when the heart attack was first diagnosed?’
	+ ‘What was your age when the blood clot in the leg (DVT) was first diagnosed?’
	+ ‘What was your age when the blood clot in the lung was first diagnosed?’
	+ ‘What was your age when the stroke was first diagnosed?’

**Predictors**

The UK Biobank dataset contains 7 800 separate data points for each individual. We specified variables we intended to include in the model *a priori* based on traditional risk scores. We included the following arterial and venous TEE risk factors: age, sex, diagnosis of hypertension, type 2 diabetes mellitus, hypercholesterolemia, smoking status (never, ever), past history (Phx) of TEE and, history of cancer defined from the ICD-10 (Chapter 2: C00-C97), not including neoplasms in situ or benign neoplasms.{WHO, 2016 #443} Six potential additional CVD predictors were selected based on the literature and availability in the dataset: IVIg exposure and medications (antiplatelet, antihypertensive, lipid-lowering, insulin, oral hypoglycaemic agents).

The predictors were ascertained in the following ways:

* Medications for cholesterol, blood pressure and diabetes: At the assessment centre, participants independently answered questions on a touchscreen. The question for this section stated, ‘Do you regularly take any of the following medications? (you can select more than one answer)’
	+ Cholesterol lowering medication.
	+ Blood pressure medication.
	+ Insulin.
* Antiplatelets and warfarin: These medications were ascertained during a verbal interview with a clinic nurse at the assessment centre. The medications included in our analysis were labelled as the following and had an individual numerical code: aspirin 75 mg tablet, nu-seals aspirin 75 mg e/c tablet, aspirin, isosorbide mononitrate +aspirin, dipyridamole +aspirin, dipyridamole, clopidogrel, ticlopidine, warfarin and sodium warfarin. Other antiplatelets and antithrombotics: ticagrelor, prasugrel, eptifibatide and direct oral anticoagulants were not recorded in the dataset and hence, are not included in this analysis.
* Oral hypoglycaemics: These medications were ascertained during a verbal interview with a clinic nurse at the assessment centre. The medications included in our analysis were labelled as the following and had an individual numerical code: metformin, rosiglitazone 1 mg/metformin 500 mg tablet, glipizide, glipizide product, glimepiride, repaglinide, pioglitazone.
* Smoking: At the assessment centre, participants independently answered questions on a touchscreen. The questions for this section stated, ‘In the past, how often have you smoked tobacco?’ and ‘Do you smoke tobacco now?’
* Hypertension: At the assessment centre, participants independently answered questions on a touchscreen. The questions for this section stated, ‘Has a doctor ever told you that you have had any of the follow conditions (you can select more than one answer)?’
	+ Heart attack.
	+ Angina.
	+ Stroke.
	+ High blood pressure.
	+ None of the above.
	+ Prefer not to say.
* Cancer diagnosis: This predictor was determined from primary/main diagnosis codes and distinct secondary diagnoses codes a participant has had recorded across all their hospital inpatient records.
* Diabetes: At the assessment centre, participants independently answered questions on a touchscreen. The questions for this section stated, ‘Has a doctor ever told you that you have diabetes?’
* Intravenous Ig exposure: This predictor was determined from the main and secondary operation and procedure codes a participant has had recorded across all their hospital inpatient records. Operative procedures (including intravenous Ig administration) are coded according to the Office of Population Censuses and Surreys Classification of Interventions and Procedures, V.4. Only the first date of operation/procedure was provided in the dataset so an accurate time between last intravenous Ig and study endpoint could not be accurately calculated.

**Statistical Analysis**

**Data Handling**

Continuous variables were modelled as continuous to prevent biological implausibility and inefficient use of data.{Collins, 2016 #6767} All other variables were dichotomous.

**Missing Data**

Missing data were few (<1% for all variables), and therefore complete case analysis was used. Total numbers for each variable are shown in Table 1, for each model.

**Model Development**

Transparent reporting of a multivariate prediction model for individual prognosis or diagnosis (TRIPOD) guidelines for development and reporting were followed.{Collins, 2015 #8618}

The datasets were used to build multivariate cardiovascular disease risk prediction equations (Figure 1).

Dataset 1: Model 1 and Model 2

The dataset was divided into two groups: participants with and without a Phx of TEEs. Participants with no Phx but on an antiplatelet agent were excluded from the no Phx of TEE cohort. We developed two conditional multivariate logistic regression models from Dataset 1: Model 1 applies to those without a Phx of TEEs and Model 2 to those *with* a Phx of TEEs.

For each model, the variables of interest were tested for an (unadjusted) association with the outcome. This step was performed to detect associations, not to aid in variable selection. The *a priori* variables were included as a baseline model. Then models including first-order interactions between continuous and categorical variables were assessed by a series of pairwise likelihood ratio tests for each additional interaction term. Once the addition of further interaction terms did not improve a model’s performance, we added IVIg as a novel risk factor.

We used logistic regression analyses to assess the association between the traditional TEE risk factors, IVIg and use of medications (antiplatelet only in the model with Phx of TEE, others were included in both models) to determine whether treating traditional risk factors mitigates the overall incident TEE risk. We present the final models with their coefficients and odds ratios (OR) with 95% confidence intervals.

Dataset 2: Model 3 and Model 4

Dataset 2 adjudicated outcomes by also including data-field codes corresponding to self-reported illness code. Other variables were collected in the same method as dataset 1. The dataset was again divided into two groups: participants with and without Phx of TEEs. A similar approach to developing two conditional models was adopted. These are called Model 3 (without Phx of TEEs) and Model 4 (with Phx of TEEs).

We also examined the feasibility of exploratory models for Dataset 2 in which we made separate models conditional on the *type* of past TEE, arterial or venous and *type* of event, arterial or venous. However, these very fine-grained models were of little use because of the small sample size for those with IVIg exposure.

**Model Performance**

For Models 1-4, performance was assessed by measuring discrimination and calibration (see Figure 2 for the analysis of Model 2, for example). Discrimination was assessed using the C-statistic/Area under the Receiver Operating Curve.{Steyerberg, 2001 #8864} ﻿We also calculated the Brier score (a measure of goodness of fit where lower values indicate better accuracy) for each model.{Brier, 1950 #8673} Calibration was assessed by examining reliability diagrams based on risk deciles, and Hosmer-Lemeshow (H-L) tests.{Collins, 2016 #6767} Analyses were performed on ‘R’ (R Core Team, Vienna, Austria).

**Role of the funding source**

The funder of the study played no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author and ASC had full access to the study data and MPL and MMR had final responsibility for the decision to submit for publication.

**Results**

The characteristics of the cohorts are shown in Table 1 and differences are summarised below. Supplementary appendix 1 details characteristics of the IVIg group. We included 502 492 participants. For Dataset 1, 422 266 did not have a Phx of TEEs. 12 799 (3·0%) of those without TEE history, and 1 995 (8·7%) of those with previous TEE, had an incident TEE during follow up. For Dataset 2, 412 769 did not have a PHx of TEEs. 12 333 (2·3%) of those without TEE history, and 2 123 (5·1%) of those with previous TEE, had an incident TEE during follow up.

There is a difference between the total sizes of the datasets (table 1). In dataset 1, 57 970 participants were excluded from the ‘no past history’ group as they had no record of a relevant history but were on an antiplatelet agent (18 of these participants had exposure to intravenous Ig). In dataset 2, 47 921 participants were excluded from the ‘no past history’ group for the same reason (18 of these participants had exposure to intravenous Ig). The difference between the two datasets in the numbers of those on intravenous Ig in the ‘past history’ group is due to the method of collecting the information. There was one person on intravenous Ig in dataset 2 who had a history of a venous TEE, and another who reported a history of arterial TEE – both were not recorded in dataset 1. Only one extra post intravenous Ig TEE was recorded in dataset 2 compared with dataset 1.

**Univariate analysis**

In both datasets, increasing age, male sex, current or previous smoking, diabetes, hypertension, hypercholesterolemia, cancer, and being on treatment for the above risk factors were associated with increased risk of TEEs in univariate analyses (Table 2).

**Multivariate models**

Table 2 in the supplementary files presents details for Model 1 and Model 3. These show that IVIg was not associated with increased risk of TEE in those without a Phx of TEE.

Table 3 shows the ORs for predictors in Model 2 and Model 4, which are the models conditional on having a Phx of TEE. The salient feature of these models is that IVIg is a very significant risk factor for recurrent TEEs, with ORs of 3·69 and 5·14 in Model 2 and Model 4, respectively. Overall, most of other known risk factors for TEE (increasing age, male sex, smoking history, diabetes and hypertension) had statistically significant ORs in those with Phx of TEE. Treatments for these risk factors (antiplatelet and antihypertensive medications, and insulin) also had statistically significant ORs in all models. This likely represents the overall greater risk of events in those participants with these risk factors, rather than suggesting these treatments are not protective.

We assessed model performance using the H-L test statistic, and reliability diagrams for both models. We focus our discussion on Model 2, for participants with a Phx of TEE from Dataset 1, because it is the most important model in our paper. We display the reliability diagram for Model 2, which is indicative of the others, in Figure 2.{Huang, 2020 #9072}

Model 2 has good calibration (Figure 2), and an H-L test statistic and p-value of 9·18 and 0·33, respectively (the H-L statistic is based on ten bins of ordered probability predictions and Figure 2 presents results for both five and ten bins). Strong correlation and tight clustering on the reliability diagrams suggest that Model 2 makes reasonable probability predictions for a recurrent TEE, given the sample data. For Model 2, the Brier score is 0·08 (Model 4 Brier score= 0·05) and C-statistic is 0·61 (for Model 2 and 4), further suggesting that the model is useful at predicting the chances of a further TEE event.

**Impact of IVIg on Overall Risk of Recurrent TEE in Patients**

Our analysis focuses on Model 2 rather than Model 4, because Dataset 1 is a more conservative data set (or more “objective” because Dataset 2 includes patient-reported events). In this community-based cohort, there was a broad variation in individual risk from 2 to >40% (median estimated risk, 8%). In fact, 72·8% of participants were at relatively low risk (<10%) whereas only 0·02% were in the highest risk group in primary prevention, (> 30%).{Hippisley-Cox, 2008 #9035}

According to Model 2, IVIg exposure would have a substantial impact on the proportion of participants at high risk. If we assume that the OR for IVIg in Model 2 applies, then the median risk of recurrent event in those under 60 years of age increases from 6·1% to 19% and in those over 60 from 9·1% to 26.9% (moving nearly 50% of individuals into the high-risk category). A similar change in risk was seen if the cohort was divided by gender (Figure 3).

For Model 2, the number needed to harm (NNH) was calculated at 5·8 (95% CI, 2-88), or one further TEE for every 6 individuals with previous history of TEE on exposure to IVIg.

We explored the impact of IVIg exposure plus one, two or three risk factors (combinations of hypertension, hypercholesterolemia, and diabetes) to stratify those at highest risk. However, statistical significance was not reached, probably limited by small number of participants in these subgroups. Similarly, small numbers limited secondary analyses of the impact of risk factor modification (anti-hypertensive, anti-platelet, oral hypoglycaemic, statin treatment) on TEE risk with IVIg exposure.

**Discussion**

In this cohort study, exposure to IVIg in individuals with a previous TEE conferred an increased risk of TEEs. The multivariate analysis adjusted for the relevant variables showed an added risk from IVIg that was not explained by the other CVD risk factors, or cancer. IVIg exposure in those without Phx of TEE was not associated with increased risk of incident TEE.

Both dataset 1 and 2 were necessary because of the likely under-representation of deep-vein thrombosis (DVT) in hospital and death registry data. VTE (including DVT and pulmonary embolism) is the third commonest CVD.{Tran, 2019 #12841} DVT is frequently treated in the outpatient setting or presents initially to primary care physicians. IVIg increases risk of future event with any history of venous TEEs, uncomplicated or associated with hospital admission and higher morbidity and mortality. Clinically, this distinction highlights the importance of a complete medical history and the potential number of patients who may be at an increased risk of recurrent TEE if exposed to IVIg.

Many conflicting small observational and case-control studies of patients treated with IVIg have been conducted aiming to identify factors associated with increased risk of TEEs.{Guo, 2018 #8776} A systematic review and meta-analysis (n= 4 129 participants) of 28 RCTs in which IVIg was compared with placebo or no treatment found no evidence of increased TEE risk among patients who received IVIg (12 events) compared with placebo, or no treatment (8 events).{Ammann, 2016 #9149} However, the trials reviewed excluded patients with a history of TEE and did not collect details of traditional CVD risk factors, which we have shown greatly impact a patient’s overall risk of future TEEs.

In studies with only IVIg-exposed patients, there are conflicting results of whether age, gender and presence of other risk factors correlates with occurrence of TEEs. The independent risk conferred by IVIg exposure has not been well examined. Other studies have suggested a temporal association between IVIg infusion and the TEE event. In one case series, all seven patients who had a stroke or transient ischaemic attack did so within 24 hours of IVIg infusion.{Vucic, 2004 #8832} In a further study, two of 117 developed a DVT within three days of their infusion, and in a large series of 498 hospitalised patients receiving IVIg, 16 patients had a stroke, 14 (88%) of these during, or within 24 hours, of IVIg infusion.{Caress, 2003 #5714}

In 2010, activated factor XI was identified as the cause for higher-than-normal rates of TEEs with one brand of intravenous Ig. Since then, the European Pharmacopoeia and the FDA require immunoglobulin manufacturers to specifically report on the mechanisms they have undertaken to mitigate the TEE risk and reduce or remove thrombosis-generating agents in their products

IVIg may affect risk of TEEs by increasing plasma viscosity, although this remains unproven. One study measured plasma viscosity in 15 patients who received 2g/kg IVIg over 2-5 days and showed an 11% increase in serum viscosity at 24 hours.{Steinberger, 2003 #6576} Another study showed up to a four-fold increase in erythrocyte sedimentation rate post IVIg.{Bentley, 2012 #6571}. While the rise in viscosity is not a large absolute change, an acute change in these parameters in patients with other risk factors might contribute to the risk of clotting. Other potential mechanisms might be the effect of IVIg on platelets, cytokines and other naturally occurring pro-thrombotic factors. In a mouse brain ischaemia model, intravital microscopy was used to record cell trafficking in pial vessels before and after IVIg (0·4g/kg) injection. An hour after IVIg, the increase in leucocyte and platelet trafficking and aggregation was so great in the IVIg group that counting was not possible. Some of the immunomodulatory mechanism of IVIg might involve increasing interleukin-11 levels which stimulate platelets and other haemostatic factors.{Nguyen, 2021 #13071} In already diseased vessels, IVIg may bind to Fc receptors on platelets, triggering platelet-leucocyte interactions and potentiate haemostasis.{Lapointe, 2004 #9050} Theoretically, antiplatelet therapy could mitigate some of the risk, however, we could not demonstrate this here because of the relatively small event number.

Clinical Implications

Here we have shown that IVIg exposure has a substantial impact on an individual’s risk of recurrent TEE, with a NNH of 6, however, in some patients, IVIg remains the preferred first-line treatment option.{Vitiello, 2019 #12836} In specific neuromuscular conditions such as chronic inflammatory demyelinating polyradiculoneuropathy, Guillain-Barré syndrome and multifocal motor neuropathy, IVIg can lead to significant improvement in strength and function{Lunemann, 2015 #12835}

Our current study demonstrates that IVIg in those with a history of arterial and/or venous TEE increased the risk of recurrent arterial TEEs but did not show a specific increased risk of recurrent venous TEEs, the latter possibly limited by small numbers. Hence, we cannot justify a change in routine clinical practice to prevent future venous events.

This area needs further investigation and a method for risk stratification as recent data has demonstrated that patients with a history of unprovoked VTE, or VTE associated with a minor transient risk factor have a risk of recurrent VTE approximating 10% and 4%, respectively. Therefore, the use of short term VTE prophylaxis in this high-risk group could be considered to minimise the risk of TEE after intravenous Ig exposure. However, this approach would need to consider the potential bleeding risk associated with VTE prophylaxis since a significant subset of patients in our cohort received intravenous Ig for thrombocytopaenia and haematological malignancies.

Regarding, recurrent arterial events, our study suggests that optimising management of other CVD risk factors is the most sensible approach in patients with previous TEEs who need IVIg. Further research into the mechanisms of IVIg related exacerbations in already high-risk patients will further guide the best monitoring and management. Recurrence rates for any other CVD event in the year after a myocardial infarction is near 50%, and up to 75% of patients have a recurrent event within three years.{Bansilal, 2015 #12829} These patients should therefore be on appropriate arterial TEE secondary prevention after the primary events, which many are not (Table 1). When this is the case in clinical practice, and IVIg is considered, medications and non-pharmacological measures as per local guidelines for the secondary prevention of CVD should be optimised. As some indications for IVIg are for chronic conditions, this group will need treatment monitoring for life.{Bansilal, 2015 #12829} As there is convincing evidence for intensive risk-reduction therapies for secondary prevention, reinforcing adherence with secondary prevention guidelines will be beneficial in managing overall CVD risk when IVIg is considered in this group of adults.{Kleindorfer, 2021 #12876},{Roshandel, 2019 #13072}

The European Medical Agency, since at least 2004, has advised that ‘in patients at risk for… thromboembolic adverse reactions, intravenous Ig products should be administered at the minimum rate of infusion and dose practicable’ as an approach to mitigating the risk of TEEs. Our previous work did not identify intravenous Ig infusion factors that contributed to the risk. Other case–control studies have found that patients who developed a TEE were on higher doses (g/kg/day) than those who did not (mean 0.39 g/kg/day vs 0.59 g/kg/day) and another group found a significant (but small) correlation between daily intravenous Ig doses greater than 35 g with occurrence of TEE within 14 days of infusion. Both studies also found individual CVD risk factors and the number of CVD risk factors an individual had contributed to the risk of developing TEEs. Therefore, consideration to managing both patient and infusion related factors may minimise TEE risk.

**Strengths and limitations**

Our study is a population-based cohort and demonstrates the impact of IVIg in a real-life setting. It includes over half a million participants, providing at least enough arterial outcome events and adequate statistical power to explore important outcomes, potential predictors, and interactions.

Several potential limitations should also be considered. Hospital discharge records and death certificates can contain inaccuracies and misclassify disease outcomes, diluting the strength of the observed associations.

Using patient-reported health conditions has advantages but the validity of these reports has been questioned. The agreement between patient reports, clinician report and medical records vary depending on type of disease and patient characteristics.{Iecovich, 2013 #13068} The comprehensive data collected in the UK Biobank and the linkages with formal registries are a strength of the dataset, and the concordance between our results within the two models are reassuring.

The study did not record IVIg dose, formulation, and duration of use information. The lack of those data prevented an evaluation of dose-response associations. Finally, the small number of participants exposed to IVIg did not allow sensitivity analysis of the impact of the indication for IVIg on TEE risk.

**Conclusion**

We found an association of IVIg with TEE recurrence, independent of traditional CVD risk factors. IVIg also has a significant impact on the patients’ overall CVD risk, transitioning some patients to the highest risk group. This work provides a quantifiable risk to facilitate informed consent in an identifiable high-risk cohort. It suggests that proactive management of modifiable cardiovascular risk factors is sensible in all those exposed to IVIg.

**Contributors**

AC, MPL and MMR designed the original hypothesis and MK ran all the analyses in collaboration with IH and LJB. MK wrote the first draft of the report, apart from the model performance section and corresponding figure, which was written by IH. All authors interpreted the results, revised the text, and approved the final draft of the report.

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**Competing interests:**

MK reports Grifols sponsorship for attendance at meeting. ASC reports Grifols sponsorship for attendance at meeting and honorarium from CSL and Lupin for an advisory role. MPL was a Primary Investigator in studies for CSL Behring, UCB Pharma, Novartis, Octapharma. He has also received ad hoc consulting fees from CSL Behring, UCB and an honorarium from Terumo BCT.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Table 1: Baseline clinical characteristics for participants with and without a past history of cardiovascular disease Dataset 1 and Dataset 2

|  |  |  |
| --- | --- | --- |
|  | **Dataset 1: Hospital and death registry data for past history and incident events** | **Dataset 2: Hospital and death registry data plus patient-reported illnesses for past history and incident events** |
| **Characteristics** | **No Past History** **(n= 421,475)** | **Past History** **(n= 23,047)** | **No Past History** **(n= 412,769)** | **Past History** **(n= 41,802)** |
| Median (IQR range) age (years) | 57.6 (13.3) | 63.4 (8.9)  | 57.1 (13.3) | 63.4 (8.8)  |
| Sex (Male) | 179,921 (42.8%) | 15,314 (66.4%) | 176,653 (44.3%) | 24,810 (59.4%) |
| Ever Smoked | 182,280 (43.2%) | 14,121 (61.3%) | 121,912 (29.5%) | 26,216 (62.7%) |
| Diabetes | 12,684 (3%) | 3,642 (15.9%) | 12,076 (4.7%) | 6,058 (14.5%) |
| Hypertension | 95,477 (22.7%) | 11,403 (49.5%) | 92,483 (22.4%) | 19668 (47.1%) |
| Hypercholesterolemia | 37,858 (9.0%) | 7,764 (33.7%) | 51,698 (12.5%) | 15091 (36.1% |
| Cancer | 43,146 (10.2%) | 3,673 (15.9%) | 41,840 (10.1%) | 6,506 (15.6%) |
| IVIg | 98 (0.02%) | 14 (0.06%) | 96 (0.02%)  | 16 (0.04%) |
| Current Medications |  |  |  |  |
| Antiplatelet | 0 | 15,514 (67.3%) | 0 | 25,563 (61.2%) |
| Lipid-lowering  | 23,581 (5.6%) | 11,725 (50.9%) | 21,876 (5.3%) | 22,351 (53.5%) |
| Antihypertensives | 29,543 (7.0%) | 10,185 (44.2%) | 26,829 (6.5%)  | 19,764 (47.3%) |
| Insulin | 1,190 (0.3%) | 641 (2.8%) | 1,238 (0.3%) | 5,401 (12.9%) |
| Oral hypoglycaemics | 234 (0.06%) | 114 (0.5%) | 218 (0.05%) | 183 (0.4%) |
| Past History of Any TEE | 0 | 23,047  |  | 41,802  |
| Past History of Venous TEE | 0 | 4,436 (19.2%) | 0 | 13,000 (31.1%), 3,104 on warfarin |
| Past History of Arterial TEE  | 0 | 15,483 (67.2%) | 0 | 30,705 (73.5%) |
| Incident Cases of Arterial and/or Venous Thromboembolic Disease | 12,799 (3.0%) | 1,995 (8.7%) | 12,333 (2.3%) | 2123 (5.1%) |
| Incident Cases of Arterial Thromboembolic Disease |  |  | 9,352 (2.3%) | 1465 (3.5%) |
| Incident Cases of Venous Thromboembolic Disease |  |  | 3,232 (0.8%) | 709 (1.7%) |

Table 2: Univariate analysis of arterial or venous thromboembolic disease in the UK Biobank

|  |  |  |
| --- | --- | --- |
|  | **Dataset 1: Hospital and death registry data for past history and incident events** | **Dataset 2: Hospital and death registry data, plus patient-reported illnesses for past history and incident events** |
| **Variable** | **No Past History****(data for Model 1)** | **Past History****(data for Model 2)** | **No Past History****(data for Model 3)** | **Past History****(data for Model 4)** |
|  | **OR** | **95% CI**  | **Sig.** | **OR** | **95% CI**  | **Sig** | **OR** | **95% CI**  | **Sig** | **OR** | **95% CI**  | **Sig** |
| Age | 1.07 | 1.07-1.08 | \*\*\* | 1.04 | 1.03-1.04 | \*\*\* | 1.07 | 1.07-1.08 | \*\*\* | 1.0 | 1.03-1.05 | \*\*\* |
| Sex (Male) | 2.07 | 2.0-2.15 | \*\*\* | 1.36 | 1.23-1.51 | \*\*\* | 2.08 | 2.00-2.20 | \*\*\* | 1.26 | 1.15-1.38 | \*\*\* |
| Ever Smoked | 1.52 | 1.47-1.58 | \*\*\* | 1.33 | 1.2-1.46 | \*\*\* | 1.76 | 1.70-1.83 | \*\*\* | 1.26 | 1.15-1.39 | \*\*\* |
| Diabetes | 2.16 | 2.0-2.32 | \*\*\* | 1.76 | 1.58-1.96 | \*\*\* | 2.08 | 1.93-2.25 | \*\*\* | 1.58 | 1.42-1.76 | \*\*\* |
| HT | 1.84 | 1.78-1.91 | \*\*\* | 1.38 | 1.26-1.51 | \*\*\* | 1.85 | 1.78-1.92 | \*\*\* | 1.31 | 1.20-1.43 | \*\*\* |
| Hyperchol. | 1.41 | 1.34-1.49 | \*\*\* | 1.12 | 1.02-1.23 | 0.02 | 1.37 | 1.31-1.44 | \*\*\* | 1.07 | 0.98-1.17 | 0.14 |
| Cancer | 2.56 | 2.45-2.67 | \*\*\* | 1.49 | 1.33-1.67 | \*\*\* | 2.54 | 2.43-2.65 | \*\*\* | 1.88 | 1.70-2.08 | \*\*\* |
| **IVIg** | **1.01** | **0.32-3.18** | **0.99** | **4.23** | **1.3-13.5** | **0.03** | **1.05** | **0.26-2.79** | **0.937** | **6.24** | **1.74-17.9** | **0.002** |
| Antiplatelet |  |  |  | 1.47 | 1.32-1.63 | \*\*\* |  |  |  | 1.06 | 0.97-1.16 | 0.19 |
| Statin | 1.98 | 1.87-2.1 | \*\*\* | 1.3 | 1.18-1.42 | \*\*\* | 1.66 | 1.61-1.73 | \*\*\* | 1.13 | 1.04-1.24 | 0.006 |
| Anti-HT | 2.37 | 2.25-2.49 | \*\*\* | 1.34 | 1.23-1.47 | \*\*\* | 1.89 | 1.82-1.96 | \*\*\* | 1.24 | 1.14-1.35 | \*\*\* |
| Insulin | 3.47 | 2.86-4.21 | \*\*\* | 2.13 | 1.72-2.63 | \*\*\* | 1.45 | 1.40-1.51 | \*\*\* | 1.38 | 1.23-1.55 | \*\*\* |
| OHA | 2.66 | 1.65-4.31 | \*\*\* | 1.86 | 1.11-3.11 | 0.02 | 2.75 | 1.61-4.37 | \*\*\* | 2.57 | 1.60-3.93 | \*\*\* |

\*\*\* = p-value <0.001, OR= odds ratio, CI= confidence interval, HT= hypertension, anti-HT= antihypertensives, OHA=oral hypoglycaemic agents

Table 3: Multivariate model of arterial or venous thromboembolic disease in the UK Biobank

|  |  |  |
| --- | --- | --- |
|  | **Model 2****Dataset 1 (with Past History)** | **Model 4****Dataset 2 (with Past History)** |
| **Variable** | **OR** | **95% CI** | **P-value** | **OR** | **95% CI** | **P-value** |
| Age | 1.04 | 1.03-1.05 | <0.001 | 1.03 | 1.02-1.05 | <0.001 |
| Sex (Male) | 1.22 | 1.09-1.35 | <0.001 | 3.01 | 1.14-7.96 | <0.001 |
| Ever Smoked | 1.2 | 1.09-1.33 | <0.001 | 1.08 | .79-1.47 | 0.64 |
| Diabetes | 1.58 | 1.41-1.77 | <0.001 | 1.50 | 1.22-1.83 | <0.001 |
| Hypertension | 4.41 | 1.66-11.71 | <0.001 | 1.28 | 1.0-1.65 | 0.06 |
| Hypercholesterolemia | 1.00 | 0.91-1.10 | 0.98 | 1.07 | 0.87-1.31 | 0.52 |
| Cancer | 1.38 | 1.23-1.55 | <0.001 | 1.75 | 1.58-1.94 | <0.001 |
| **IVIg** | **3.69** | **1.15-11.92** | **0.03** | **5.14** | **1.64-16.1** | **0.005** |
| Age x hypertension\* | 0.98 | 0.97-1.0 | 0.01 |  |  |  |
|  | Model Intercept Coefficient ‑5.34 (P<0.001). Based on 23,047 observations (outcomes=1995 TEEs) | Model Intercept Coefficient ‑5.69 (P<0.001). Based on 41,802 observations (outcomes=2123 TEEs) |

Supplementary Table 1: Detailed clinical characteristics for participants with IVIg exposure

|  |
| --- |
| **Characteristics of IVIg Cohort (n=130)** |
| Median (IQR range) age (years) | 61.72 (13.0) |
| Sex (Male) | 57 (43.8%) |
| Indication for IVIg Identified | 96 (73.8%)Haematological- 49* Thrombocytopenia- 26
* Immunodeficiency- 23

Neurological- 43* Myasthenia Gravis- 15
* Guillain-Barre Syndrome- 10
* Other- 18
 |
| Ever SmokedCurrent Smoker | 59 (45.4%)16 (12.3%) |
| Diabetes |  10 (7.7%) |
| Hypertension | 44 (33.8%) |
| Hypercholesterolemia |  17 (13.1%) |
| Past History of Arterial or Venous Thromboembolic Disease | 14 (10.8%)8/14- myocardial infarctions4/14- pulmonary emboli2/14- cerebral infarction |
| Cancer  | 45 Solid Organ- 10Malignant Melanoma- 4Haematological- 23* CLL- 20
* Hodgkin’s Lymphoma- 1
* Non-Hodgkin’s Lymphoma- 2
 |
| Current Medications |  |
| Antiplatelet | 25 (19.2%) |
| Lipid-lowering  |  120 (92.3%) |
| Antihypertensives |  21 (16.2%) |
| Insulin |  0 |
| Oral hypoglycaemics |  0 |
| Incidence Cases of Arterial or Venous Thromboembolic Disease | 10 (7.7%)3/10= myocardial infarctions, 2= pulmonary emboli, 3= cerebral infarction, 2= Other |

Supplementary Table 2: Multivariate model of arterial or venous thromboembolic disease in the UK Biobank datasets *without* a history of TEE

|  |  |  |
| --- | --- | --- |
|  | **Dataset 1, Model 1** | **Dataset 2, Model 3** |
| **Variable** | **OR** | **95% CI** | **P-value** | **OR** | **95% CI** | **P-value** |
| Age | 1.07 | 1.06-1.07 | <0.001 | 1.08 | 1.07-1.08 | <0.001 |
| Sex (Male) | 1.99 | 1.92-2.06 | <0.001 | 5.50 | 3.99-7.58 | <0.001 |
| Ever Smoked | 1.28 | 1.24-1.33 | <0.001 | 1.16 | 1.05-1.29 | 0.003 |
| Diabetes | 1.22 | 0.58-2.51 | 0.34 | 1.25 | 0.59-2.64 | 0.55 |
| Hypertension | 4.62 | 3.24-6.56 | <0.001 | 3.90 | 2.70-5.63 | <0.001 |
| Hypercholesterolemia | 2.93 | 1.63-5.20 | <0.001 | 2.52 | 1.56-4.06 | <0.001 |
| Cancer | 1.98 | 1.89-2.07 | <0.001 | 2.00 | 1.91-2.09 | <0.001 |
| IVIg | 0.76 | 0.18-2.04 | 0.61 | 0.79 | 0.25-2.54 | 0.70 |
| Age x hypertension\* | 0.98 | 0.98-0.99 | <0.001 | 0.98 | 0.98-0.99 | <0.001 |
| Age x hypercholesterolemia\* | 0.98 | 0.98-0.99 | <0.001 | 0.98 | 0.98-0.99 | <0.001 |
| Age x diabetes\* | 1.00 | 0.99-1.02 | 0.50 | 1.00 | 0.99-1.02 | 0.61 |
| Age x sex\* |  |  |  | 0.98 | 0.98-0.99 | <0.001 |
|  | Model Intercept Coefficient ‑8.07 (P<0.001). Based on 421 475 observations (outcomes=12 799 TEEs) | Model Intercept Coefficient ‑8.58 (P<0.001). Based on 412 769 observations (outcomes=12 333 TEEs) |

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