Effect of type 1 diabetes and type 2 diabetes on the risk of venous thromboembolism

Hinton, W.; Nemeth, B.; Lusignan, S. de; Field, B.; Feher, M.D.; Munro, N.; ... ; Whyte, M.B.

RESEARCH: COMPLICATIONS

DIABETIC Medicine

Effect of type 1 diabetes and type 2 diabetes on the risk of venous thromboembolism

William Hinton[1] | Banne Nemeth[2] | Simon de Lusignan[1,3,4] | Ben Field[3] | Michael
D. Feher[1] | Neil Munro[3] | Lara N. Roberts[5] | Roopen Arya[5] | Martin B. Whyte[3]

[1]Nuffield Department of Primary Care
Health Sciences, University of Oxford,
Oxford, UK

[2]Department of Clinical Epidemiology,
Leiden University, Leiden,
The Netherlands

[3]Faculty of Health & Medical Sciences,
University of Surrey, Guildford,
Surrey, UK

[4]Royal College of General Practitioners,
Royal College of General Practitioners
(RCGP) Research and Surveillance
Centre (RSC, London, UK

[5]King's Thrombosis Centre, Department
of Haematological Medicine, King's
College NHS Foundation Trust,
London, UK

Correspondence
Martin Whyte, 21PGM00, Leggett
Building, Daphne Jackson Road,
University of Surrey, Guildford, UK.
Email: m.b.whyte@surrey.ac.uk

Abstract

Aims: Whether diabetes increases venous thromboembolism (VTE) is unclear. Any greater risk may relate to insulin resistance, but many studies did not differentiate between type 1 diabetes and type 2 diabetes for VTE risk.

Methods: Retrospective cohort study of the Royal College of General Practitioners Research and Surveillance Centre, comprising over 530 primary care practices. We determined whether type 1 diabetes and/or type 2 diabetes are independent risk factors for VTE. The index date was 1 January 2009, individuals were followed to 31 December 2018, or censoring. Cox proportional hazard regression analysis was used to investigate the risk of VTE in people with type 1 diabetes and type 2 diabetes relative to no diabetes. The primary outcome was occurrence of VTE. The model was adjusted for potential confounders for VTE.

Results: There were 7086 people with type 1 diabetes and 95,566 with type 2 diabetes, diagnosed before 1 January 2009. The non-diabetes group consisted of 1,407,699 people. In the unadjusted analysis, there was no increased risk of VTE with type 1 diabetes (HR 1.00, 95% CI 0.76–1.33) but there was for type 2 diabetes (HR 2.70, 95% CI 2.57–2.84). In the fully adjusted model, VTE risk was increased in type 1 diabetes (HR 1.46, 95% CI 1.11–1.92), but not with type 2 diabetes (HR 1.06, 95% CI 0.98–1.14).

Conclusions: Type 1 diabetes was associated with a greater risk for VTE while type 2 diabetes was not. Further work is needed to determine the reason(s) for this.

KEYWORDS

cohort study, computerised medical records, primary care, type 1 diabetes, type 2 diabetes, venous thromboembolism

1 | INTRODUCTION

Diabetes carries an increased risk of complications from arterial atherothrombosis.[1] Important mediators for this are hypertension, smoking and dyslipidaemia. Diabetes is also considered a proinflammatory condition that itself may directly predispose to atherothrombosis.[1] The inflammatory cascade is also integral to venous thromboembolism (VTE) but whether diabetes carries a greater risk of VTE is less clear.

Animal studies and pre-clinical work in humans have highlighted several pathways, centred on coagulation and platelet reactivity, by which diabetes would plausibly predispose to VTE.[2] Diabetes is associated with increased tissue factor (TF) expression which activates thrombin,[3] converting fibrinogen into fibrin. Increased cellular synthesis of plasminogen activator inhibitor-1 (PAI-1) and fibrinogen, and reduced production of tissue plasminogen activator (t-PA), will augment the developing fibrin structure. Up-regulation of glycoproteins Ib and IIb/IIIa in people with diabetes triggers thrombus formation via interaction with von Willebrand Factor (vWF) and fibrin molecules.[1] Endothelial dysfunction will precipitate the rupture of the endothelium leading to the release of microparticles, which accelerate thrombus development through expression of procoagulant phospholipids.[4] Changes in plasma protein concentrations as well as plasma glucose levels lead to an increase in plasma viscosity in type 1 diabetes[5] and in type 2 diabetes.[6] The result is that thrombin generation (followed by measuring levels of the thrombin–antithrombin complex) is increased in individuals with type 1 diabetes or type 2 diabetes.[7,8]

A meta-analysis in 2008 reported greater risk of VTE in people with diabetes[9] but later analyses, found little to no increased risk.[10,11] A limitation to these studies is that many did not differentiate type 1 diabetes and type 2 diabetes. This is important as there are key differences between type 1 diabetes and type 2 diabetes in the prothrombotic *milieu*.[1,12,13] PAI-1 levels tend to be reduced in type 1 diabetes but raised (prothrombotic) in type 2 diabetes. HDL cholesterol (considered to have anticoagulant properties[14]) is often unchanged in type 1 diabetes but reduced in type 2 diabetes. Conversely, plasma levels of non-esterified fatty acids (which may cause endothelial dysfunction and destabilisation of the fibrin clot[15]) are raised in proportion to fat mass[16] – more in keeping with type 2 diabetes. These considerations would support an adverse role for insulin resistance in VTE pathogenesis.[12,13] However, a recent retrospective study including almost 5000 people in Taiwan has suggested that type 1 diabetes is an independent risk factor for VTE – although this did not report on VTE rate in type 2 diabetes.[17]

Therefore, we investigated whether diabetes is an independent risk factor for VTE. We hypothesised that the risk for VTE would be greater in type 2 diabetes than in type 1 diabetes.

2 | METHODS

2.1 | Study design

The study was a retrospective cohort study, of adults with and without diabetes, included in the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database.

What's new

What is already known

- Diabetes increases the risk for arterial atherosclerotic disease. Whether diabetes increases the risk for venous thromboembolism (VTE) is uncertain and may relate to failure to distinguish type 1 from type 2 diabetes.

What this study has found

- Diabetes increases the risk for arterial atherosclerotic disease. Whether diabetes increases the risk for venous thromboembolism (VTE) is uncertain and may relate to failure to distinguish type 1 from type 2 diabetes.

What are the clinical implications of the study

- Type 1 diabetes should be considered an at-risk group for VTE. The mechanism(s) underlying this requires further investigation. Attention should be paid to the type of diabetes when performing and analysing clinical studies on antithrombotic drugs.

2.2 | Data source

This comprises data from a sentinel network of primary care practices (general practices) distributed across England, which is representative of the general population.[18]

Until recently, clinical codes were recorded using the Read coding system (Read Version 2 and Clinical Terms Version 3 [CTV3]), which includes codes for diagnoses, medications, investigations and processes of care. In 2018, the Read classification was replaced by the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT).[19]

2.3 | Study population

We used a two-step process to identify type 1 diabetes and type 2 diabetes.[20] Step one identifies all people with diabetes (of any type), defined as those who had a diagnostic code (diagnosis of diabetes), clinical investigations (two or more fasted glucose, random glucose or glucose tolerance test values or HbA1c measurements consistent with diagnosis) or medication use (two or more prescriptions for oral diabetes medications [excluding metformin] or injectable therapies). Step two is the categorisation by diabetes type using a clinically based seven-step algorithm. This accounts for codes for type of diabetes, age (at first insulin

prescription), body mass index (BMI) and other key factors to determine type 1 diabetes or type 2 diabetes.[20] This step-wise categorisation algorithm allows over-riding of diagnostic codes where clinical characteristics are highly likely to indicate a specific type of diabetes. BMI is the final step.

We included all adults (age ≥18 years) in the RCGP RSC database prior to (1 January 2009).

2.4 | Exposure and outcome measures

We report the relationship of diabetes type to VTE outcomes. The following variables were identified from the literature as being potential confounders of the relationship of diabetes to VTE and were therefore adjusted for: age, sex, BMI, smoking, CKD (Stage 3–5), metformin, statin and aspirin therapy, presence of cancer, hormone replacement therapy, oral contraception and atrial fibrillation (AF) as a proxy for anticoagulation.[1,7,8,12,13,17,21] The most recently recorded entry (prior to 2009) was utilised. Comorbidities were defined using clinical codes for diagnosis, investigation and process of care. The primary outcome was VTE, including deep vein thrombosis (DVT) and pulmonary embolus (PE), codes are listed in Appendix S1. Ethnicity was defined using the Office of National Statistics (ONS) official UK ethnicity categories: this defines five major ethnic categories: White, Mixed/multiple ethnic groups (e.g. White and Black Caribbean), Asian (including Indian, Pakistani, Bangladeshi and Chinese), Black (including African and Caribbean) and Other (including Arab and other minority groups not classified elsewhere).[18]

2.5 | Statistical Methods

Continuous and categorical variables were presented as means, or proportions, as appropriate. Persons were subject to follow-up from the index date (1 January 2009) until the first diagnosis of VTE, withdrawal from the RCGP RSC, or 31 December 2018. At start of follow-up (1 January 2009) we assessed whether people had type 1 diabetes or type 2 diabetes, we did not perform a time-varying covariate analyses (e.g. in case people developed diabetes during follow-up, they did not switch from the no diabetes to the diabetes group). We calculated the incidence rate of VTE (per 10,000 person-years) as the number of VTE cases divided by the person-time at risk for both the diabetes and non-diabetes groups.

Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for the association between diabetes and VTE using Cox regression analyses. An unadjusted and adjusted analysis was performed to correct for potential confounders

(as stated above). Using life table techniques, Kaplan-Meier curves were generated to illustrate survival free from VTE in people with type 1 diabetes, type 2 diabetes and without diabetes. All analyses were performed using R statistical software version 3.5.3.

2.6 | Sensitivity analysis

Our primary analyses consisted of a complete case analysis. To verify these results, we repeated the Cox regression following multiple imputation for missing data. In addition, we excluded all people who developed diabetes during follow-up (people free from diabetes on 1 January 2009 who developed diabetes thereafter), and also performed an analysis with the index date 1 January 2014; after which the Cox regression analyses were repeated.

2.7 | Ethical considerations

All data were pseudonymised at the point of data extraction. No clinically identifiable information was available to researchers. The study was categorised as a service evaluation when assessed using the Health Research Authority (HRA) Medical Research Council (MRC) tool for identifying research. The study was also checked according to the University of Surrey Research Integrity and Governance Office Self-Assessment for Governance and Ethics tool, which advised that a formal ethics review was not required. Approvals for the use of the data were acquired from the RCGP RSC approvals committee.

3 | RESULTS

From the total RCGP RSC cohort of 1,510,351 adults from 293 primary care practices, 102,652 (7%) people were identified as having diabetes before 1 January 2009. Of these 95,566 (93%) were categorised as type 2 diabetes.

Mean follow-up time was 7.6 years. In total there were 50 VTE events in the type 1 diabetes group (crude incidence 9.6 per 10,000 person years), 1,798 events in type 2 diabetes (crude rate 25.8 per 10,000 person years) and 10,166 events (9.5 per 10,000 person years) in non-diabetes group. The characteristics of the diabetes and non-diabetes populations are shown in Table 1.

In the unadjusted analysis, diabetes increased risk of VTE (HR 2.58, 95% CI 2.46–2.71) (Table 2); adjusted for age and sex, the HR was 1.31 (95% CI 1.25–1.38). However, in the fully adjusted model (adjusted for age, sex, BMI, smoking status, CKD, metformin, statin or aspirin use and atrial fibrillation), there was no increased risk of VTE (HR 1.07, 95% CI

TABLE 1 Baseline characteristics of people with and without diabetes.

	No diabetes (*n* = 1,407,699)	Type 1 diabetes (*n* = 7086)	Type 2 diabetes (*n* = 95,566)
Age (mean, SD)	54.9 (18.9)	49.8 (16.9)	73.9 (13.3)
Male	49%	56%	55%
HbA1c (mmol/mol)	39 (7)	70 (19)	56 (16)
HbA1c (%)	5.7 (0.7)	8.5 (1.8)	7.3 (1.5)
Body mass index (mean, SD)	25.8 (5.5)	26.4 (5.3)	30.5 (6.4)
Smoking status			
Non-smoker	785,147 56%	3,908 55%	44,988 47%
Ex-smoker	264,598 19%	1,303 18%	30,649 32%
Active-smoker	357,954 25%	1,875 27%	19,929 21%
Venous thromboembolism (any type)	10,166	50	1,798
Venous thromboembolism			
Unspecified (n)	196	2	34
DVT (n)	5386	32	965
PE (n)	4584	16	799
Atrial fibrillation	25,188 1.8%	66 0.9%	6,671 7.0%
Chronic kidney disease	57,158 4.1%	604 8.5%	19,449 20%
Aspirin	132,153 9.4%	2,146 30%	53,778 56%
Statin	169,477 12%	3,376 48%	74,126 78%
Metformin	4,734 0.3%	775 11%	60,111 63%
Ethnicity[a]			
Asian	63,314	191	7796
Black	31,847	118	2779
Mixed	9489	48	530
Other	9267	24	448
White	917,278	5228	66,852

[a]Ethnicity missing for 395.142 individuals.

TABLE 2 Unadjusted and adjusted hazard ratios for diabetes type and VTE.

Covariates	No diabetes	Diabetes HR (95% CI)	Type 1 diabetes HR (95% CI)	Type 2 diabetes HR (95% CI)
Unadjusted	Reference	2.58 (2.46–2.71)	1.00 (0.76–1.33)	2.70 (2.57–2.84)
Age and sex	Reference	1.31 (1.25–1.38)	1.55 (1.18–2.05)	1.31 (1.24–1.38)
Fully adjusted model[a]	Reference	1.07 (0.99–1.15)	1.46 (1.11–1.92)	1.06 (0.98–1.14)

[a]Includes age, sex, body mass index, smoking status, chronic kidney disease, aspirin, metformin, statins and AF.

0.99–1.15). The HRs for VTE, with incremental adjustment for covariates, are shown in Figure 1. Kaplan-Meier curves (unadjusted analysis) illustrating freedom from VTE in people with type 1 diabetes, type 2 diabetes and people without diabetes are shown in Figure 2.

When considering *diabetes type*, type 2 diabetes was associated with VTE after adjustment for age and sex HR 1.31 (95% CI 1.24 – 1.38) but was not associated with increased risk of VTE in the fully adjusted model (HR 1.06, 95% 0.98 – 1.14).

However, the risk of VTE *was* increased in people type 1 diabetes in the fully adjusted model (HR 1.46, 95% CI 1.11–1.92). Additional adjustment for the presence of cancer, oral contraception or HRT use did not change the relationships of diabetes with VTE – type 1 diabetes HR 1.45 (95% CI 1.10–1.92), type 2 diabetes HR 1.05 (95% CI 0.97–1.13). Moreover, additional adjustment for pre-existing VTE did not alter the results.

In a sensitivity analyses, excluding all people who developed diabetes during follow-up, similar relationships
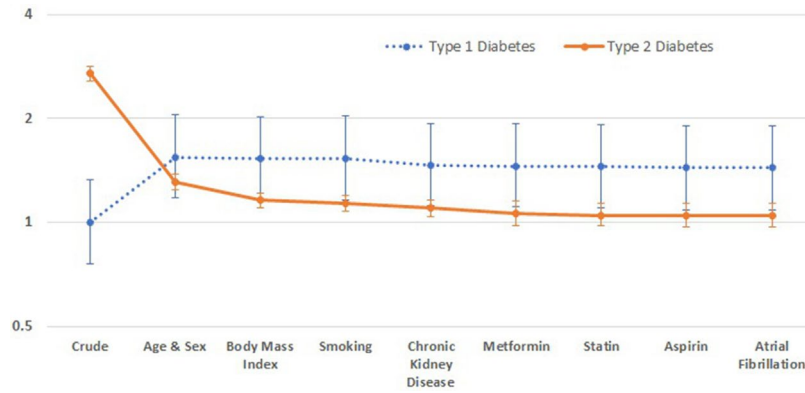
FIGURE 1 Hazard ratios for VTE, with incremental adjustment for covariates. AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease.
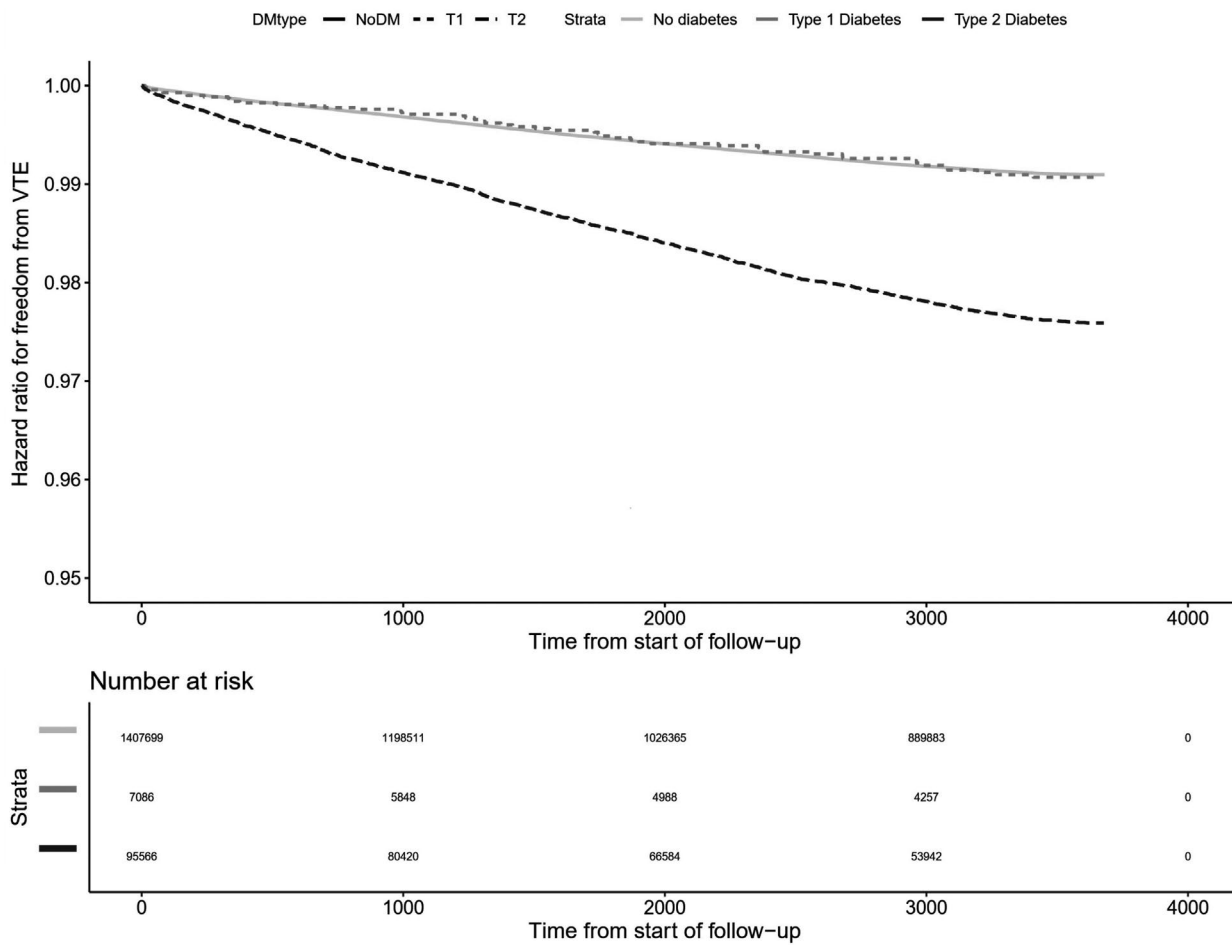

FIGURE 2 Unadjusted Kaplan Meier curves illustrating freedom from venous thromboembolism (VTE) in people with type 1 diabetes, type 2 diabetes and people without diabetes.

were found (for type 1 diabetes, HR 1.46, 95%CI 1.11–1.93 and for type 2 diabetes HR 1.05, 95% CI 0.97–1.14). Similarly, taking the index date from 1 January 2014, no difference in outcome was found: Type 1 diabetes ($n = 9558$) HR 1.26 (95% CI 0.86–1.86), multivariable HR 2.01 (95% CI 1.37–2.97); type 2 diabetes ($n = 134,885$) HR 2.56 (95% CI 2.39–2.75), multivariable 1.14 (95% CI 1.02–1.27). As a final sensitivity analysis, we used multiple imputation for missing values for explanatory variables, which did not change the relationships found— for type 1 diabetes, the HR was 1.47 (95% CI 1.22–1.92) for the multivariable model. For type 2 diabetes, the imputed results were HR was 1.08 (95% CI 1.00–1.17) for the multivariable model.

4 | DISCUSSION

Our data suggest a greater risk for VTE in people with type 1 diabetes compared to type 2 diabetes or controls. This was not anticipated. Although a recent publication showed a higher risk for VTE in type 1 diabetes than controls, it did not report rates in the type 2 diabetes population.[17]

Although challenged by recent analysis of the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) trial,[22] hyperglycaemia has traditionally been considered to contribute relatively little to the cardiovascular risk burden in diabetes.[23] Conversely, insulin resistance, adipose tissue dysfunction, inflammation and aberrant adipokine release have been implicated.[24] Similarly, insulin resistance has been proposed to have a role in venous thromboembolic disease.[12,13] We had therefore anticipated that type 2 diabetes would have a greater risk than type 1 diabetes. It may be that in these studies, insulin resistance was simply a surrogate for obesity, rather than an independent risk factor. We included BMI (a surrogate for obesity), as a covariate in our model which may contribute to difference in outcome. Alternatively, the widespread use of metformin (63% in the type 2 diabetes population), could have ameliorated the haemostatic consequence of insulin resistance,[25] although current metformin use was included in our fully adjusted model.

Other analyses have found that diabetes carries no independent risk of VTE.[10,11] However, type 2 diabetes accounts for over 90% of all diabetes and will therefore exert a proportionate impact on VTE risk in all cases of diabetes. Our work has shown no increased risk of VTE in individuals with type 2 diabetes compared to the population without diabetes, but that type 1 diabetes, when analysed separately, does so.

The 1.46-fold greater VTE risk in type 1 diabetes that we report was far lower than the 5.33-fold risk reported from a group in Taiwan.[17] The incidence of VTE in our no diabetes group was 9.5 per 10,000 person-years, which is in line with published data[26] but greater than the background (no diabetes) rate of 2.62 per 10,000 person years reported by Peng *et al*[17] This would have contributed to the effect of narrowing the HR for the type 1 diabetes group in our study.

The mechanism(s) that underpin the greater rate of VTE in type 1 diabetes merits further study. Virchow's triad represents three elements, each of which may predispose to thrombosis: a hypercoagulable state, vascular wall injury or circulatory stasis. A hypercoagulable state has been reported in type 1 diabetes, with a panoply of procoagulant mediators being raised: including vWF, Factor V, VIII, X and XI—all of which may relate to chronic inflammation.[27] Glycation of plasminogen in diabetes reduces the fibrinolytic activity of plasmin, which would predispose to thrombosis.[28] Few studies have looked at whether type 1 diabetes and type 2 diabetes have a differential influence on fibrin clot parameters or microparticles in thrombosis.[27] Vascular wall injury would arise from surgical procedures. However, hospital episode data may not reach primary care records, meaning that operations or periods of immobility may go unreported. In surgical patients, the length of hospital stay is up to 45% higher in those with diabetes,[29] putting them at greater thrombotic risk from immobility. Circulatory stasis might also ensue from atrial fibrillation (for which we adjusted) or heart failure,[30] although incidence rates of heart failure hospitalisation are no higher in type 1 diabetes than type 2 diabetes.[31]

4.1 | Limitations

The large size of the cohort and the robust nature of the diabetes case finding and algorithm for classification are major advantages of our study. Data quality of the RCGP RSC is high, complete case and multiple imputed analyses were similar. Hyperglycaemia may mediate a prothrombotic effect in diabetes.[5,6] As with Peng et al,[17] the model was not adjusted for glycated haemoglobin, due to missing data.

Although we adjusted for BMI, we were unable to identify phenotypes of type 2 diabetes. Furthermore, clinical coding for NALFD is poor in primary care.[32] Given that NAFLD is independently associated with VTE,[33] our approximation of risk in type 2 diabetes may have benefitted from distinguishing risks to subgroups of type 2 diabetes.

We did not perform a time-varying covariate analyses; this implicates that if people did not have diabetes at start of follow-up, they were classified accordingly for the entire duration of follow-up. This results in a slight overestimated baseline risk for VTE in the no diabetes group and consequently, a lower hazard for VTE for people with type 1 diabetes. However, a sensitivity analysis, excluding all people who developed diabetes during follow-up, showed comparable results to our primary model.

Theoretically, sodium-glucose cotransporter-2 inhibitors (SGLT2i) could increase blood viscosity, which may further increase risk of VTE. SGLT2i were introduced towards the end of our study period meaning too few data for interpretation. A recent meta-analysis that found no association between SGLT2i and risk of VTE among people with type 2 diabetes.[34] As prescribing of SGLT2i increases, re-analysis for risk should be undertaken.

To conclude, diabetes was associated with increased risk of VTE in the unadjusted analysis. However, after adjustment for confounders, this effect was negated. Any trend to greater VTE in the entire diabetes cohort may stem from the type 1 diabetes population.

CONFLICT OF INTEREST
The authors have no conflict of interest.

AUTHOR CONTRIBUTIONS
WH data analysis, manuscript writing; BN; data analysis; SdL data acquisition, data analysis; BF, MDF and NM data analysis; RA conception and design of the work; MBW and LR: conception and design of the work, data analysis and manuscript writing. All authors were involved in manuscript revision and approved the final version.

ORCID
Michael D. Feher 🄳 https://orcid.org/0000-0003-0631-6199
Martin B. Whyte 🄳 https://orcid.org/0000-0002-2897-2026

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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