Hyperglycemia, Assessed by HbA1c, and Future Risk of Venous Thromboembolism -The Tromsø Study

Running head: HbA1c and VTE

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Abbreviations:
BMI – Body mass index
CI – Confidence intervals
CVD – Cardiovascular disease
DM – Diabetes mellitus
DVT – Deep vein thrombosis
HbA1c – Glycated hemoglobin
HR – Hazard ratio
IR – Incidence rate
PE – Pulmonary embolism
VTE – Venous Thromboembolism

TOC category: population study
TOC subcategory: Thrombosis

Summary.

Background: Glycated hemoglobin (HbA1c), a marker of average plasma glucose during the last 8-12 weeks, is associated with future risk of cardiovascular disease (CVD) and all-cause mortality.

Objectives: To examine the association between hyperglycemia, assessed by HbA1c, and future risk of VTE in a population based cohort.

Methods: HbA1c was measured in 16 156 unique subjects (25-87 years) who participated in one or more surveys of the Tromsø study (Tromsø 4; 1994-95, Tromsø 5; 2001-2, and Tromsø 6; 2007-8). All subjects were followed, and incident VTE events were recorded through December 31, 2010.

Results: There were 333 validated first VTE events, of which 137 were unprovoked, during a median follow-up of 7.1 years. HbA1c was not associated with future risk of VTE in analysis treating HbA1c as a continuous variable, or in categorized analyses. The risk of VTE increased by 5% per 1 SD (0.7%) increase in HbA1c (multivariable-adjusted HR 1.05; 95% CI 0.97-1.14), and subjects with HbA1c ≥ 6.5% had 27% higher risk compared to those with HbA1c below 5.7% (multivariable-adjusted HR 1.27; 95% CI 0.72-2.26). There was no significant linear trend for increased risk of VTE across categories of HbA1c (p=0.27).

Conclusions: Serum levels of HbA1c were not associated with future risk of VTE in multivariable analysis. Our findings suggest that hyperglycemia does not play an important role in the pathogenesis of VTE.

Key words: Cardiovascular Diseases, Diabetes Mellitus, Glycated Hemoglobins, Glucose Metabolic Disorders, Venous Thromboembolism.

Introduction

Venous thromboembolism (VTE), a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disorder with serious short- and long-term complications, and a potential fatal outcome[1,2]. The incidence of VTE is 1 to 2 per 1000 persons per year in the general population, with a steep incline with age. Even though many environmental and inherited predisposing factors have been associated with VTE[1-5], still 30–50% of the events have no obvious provoking factors[6-8]. Thus, it is pivotal to identify biomarkers and risk behaviors of VTE that could be subject to modification in order to minimize the disease burden.

The prevalence of hyperglycemia is markedly increasing throughout the world, and hyperglycemia along with subsequent diabetes mellitus (DM) have become a particularly relevant public health challenge[9]. Glycated hemoglobin (HbA1c), which is formed by a simple chemical reaction between hemoglobin and blood glucose, reflects the average plasma glucose level in an individual over the preceding 8 to 12 weeks[10]. Experimental studies have suggested that hyperglycemia may facilitate thrombosis through activation of the coagulation system[11], as well as by impaired fibrinolysis[12], and a consistent relationship between HbA1c and arterial cardiovascular diseases (CVD)[13,14] has been suggested. Furthermore, both hyperglycemia and diabetes are known risk factors for arterial thromboembolic events[15,16].

Previous studies on the relation between hyperglycemia, DM and risk of VTE have yielded diverging results. Some studies have found increased risk[17-19], while others have failed to find an association[20-24]. The inconsistency between the studies may to some extent rely on differences in the definition of diabetes (e.g. non-

fasting or fasting glucose levels, self-reported data or use of antidiabetic drugs), as well as failure in controlling for important confounders such as obesity. Alternatively, other measures of hyperglycemia, rather than diabetes itself, may be more important in risk assessment of VTE[25,26]. Of note, the risk of arterial cardiovascular disease and all-cause mortality has been shown to increase across levels of HbA1c independent of the presence of diabetes[14]. Therefore, we set out to examine the association between hyperglycemia, assessed by HbA1c, and future risk of VTE in a general adult population.

Materials and methods

Study population

Participants were recruited from the fourth, fifth and sixth survey of the Tromsø study (conducted in 1994-95, 2001-2 and 2007-8, respectively)[27]. To these surveys, parts of the population aged ≥25 years living in the municipality of Tromsø, Norway, were invited to participate. The overall attendance rate was high, ranging from 78% in Tromsø 4 to 66% in Tromsø 6. A total of 18 080 individuals aged 25-87 years participated in at least one survey, and of these 6 140 participated in two or more surveys. A detailed description of study participation has been published elsewhere[27].Subjects who did not consent to medical research (n= 225), subjects not officially registered as inhabitants of the municipality of Tromsø at baseline (n= 18), and subjects with a known pre-baseline history of VTE (n= 121) were excluded from the study. Furthermore, subjects were excluded if they had missing HbA1c values in all visits (n= 1560). In total, 16 156 subjects were included in the study (fig.1), and followed from the date of enrollment through the end of the study period,

December 31, 2010. The study was approved by the regional committee of medical and health research ethics, and all participants gave their informed written consent to participate.

Measurements

Baseline information was collected by physical examinations, blood samples, and self-administered questionnaires[21]. Information on self-reported diabetes, CVD (angina pectoris, myocardial infarction (MI) and stroke), current daily smoking, and physical activity (≥ 1 hour per week) during leisure time was collected from the questionnaires. The self-reported diabetes data were supplemented with data on confirmed diagnosis on diabetes mellitus from the MI registry of the Tromsø Study. Height and weight were measured, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Non-fasting blood samples were collected from an antecubital vein, serum prepared by centrifugation after 1 h respite at room temperature, and further analyzed at the Department of Clinical Chemistry, University Hospital of North Norway. The Cobas Mira instrument was used to quantify HbA1c with an immunoturbidimetric method (Unimate 5 HbA1c, Hoffmann-La Roche). The normal reference range was 4.0% to 6.5%.

Venous thromboembolism ascertainment

All first-lifetime events of VTE among the participants during follow-up were recorded from the date of enrollment to the end of the study period, as previously described in detail [28]. Based on the presence of provoking factors at the time of diagnosis, the

VTE-event was classified as unprovoked (no provoking factors) or provoked (≥ one provoking factors). Major surgery, trauma or an acute medical condition (acute MI, ischemic stroke, or major infectious disease)[29,30] within 8 weeks prior to the event, active cancer at the time of the event, or marked immobilization (e.g. bed rest ≥ 3 days, wheelchair[31,32], or long distant travels ≥ 4 h within 14 days prior to the event), were considered provoking factors.

Statistical Analysis

Statistical analysis was carried out using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) and STATA version 12 (Stata corporation, College Station, TX, USA). The significance level was 0.05. PASS (Number Cruncher Statistical Systems, Kaysville, UT, USA) was used to estimate the lowest detectable effect size in our study population by a power of 0.80. Date of study enrollment for each individual was determined as the date of attendance in the first survey in which HbA1c measurements were available (fig.1). Person-years were accrued from enrollment through the date a VTE-event was first diagnosed. Subjects who did not experience an event during follow-up were censored from the date of migration or death or at the end of the study period (December 31, 2010).

Cox proportional hazards regression models were used to estimate age- and sex- and multivariable-adjusted hazard ratios (HR) with 95% confidence intervals (CI) for all VTE events, as well as for provoked and unprovoked VTE events by increasing levels of HbA1c. HbA1c was analyzed in predefined categories (<5.7 %; normal, 5.7-6.5%; pre-diabetes, and ≥ 6.5%; DM) according to the American Diabetes Association (ADA) [33] and the World Health Organization (WHO)

reports[34]. The lowest category of HbA1c was used as the reference group in each model. In the multivariate model we adjusted for age, sex, BMI, smoking, physical activity and history of CVD. The potential confounders were chosen due to their known association with HbA1c/diabetes [35-37] and possible association with VTE [38-40]. Potential interactions were tested by using cross product terms in the proportional hazards models for HbA1c with age and sex. The proportional hazard assumption was verified by evaluating the parallelism between the curves of the log-log survivor function for different categories of HbA1c.

Multivariable adjusted associations between HbA1c (as a continuous variable) and risk of VTE were visualized by a generalized additive regression plot. In this plot, HbA1c (log transformed) were modeled with a 4-degree of freedom smoothing spline fit in Cox proportional hazard models including the same co-variates as described above.

Additionally, a Cox-regression model with HbA1c entered as a time-varying covariate with multiple records per individual was performed to minimize the regression dilution effect. These analyses included individuals who had attended the second visit of Tromsø 4 and one or more of the following surveys (unless they had migrated or died before Tromsø 5) in which HbA1c and potential confounders were re-measured (n=5 647). If a subject had only two repeated measures (i.e. a recording of HbA1c from either Tromsø 5 or 6 was missing), the last HbA1c value was carried forward until a new value was obtained. Age was used as timescale in the time-dependent model.

Results

Baseline characteristics of participants across the predefined categories of HbA1c are shown in Table 1. Subjects with HbA1c value in the upper category (≥6.5%) were older, and more frequently women, compared to those in the lower categories. Furthermore, they had higher BMI, systolic blood pressure and triglycerides, whereas they had lower HDL-cholesterol and were less physically active. As expected, subjects within the upper categories of HbA1c had a higher proportion of concomitant diseases (diabetes and prior CVD).

There were 333 validated incident VTE events during a median of 7.1 years of follow-up. The overall crude incidence rate of VTE was 2.9 per 1000 person-years (95% CI: 2.61–3.24), reflecting the relatively high mean age of the study population. Characteristics of VTE patients at the time of the event are shown in Table 2. Among the subjects with VTE, 56.8% had DVT and 43.2% had PE, and 137 (41.1%) of the events were classified as unprovoked. Cancer was the most common provoking factor (24.3% of the VTE patients had a cancer-related VTE event), followed by immobilization (20.1%) (Table 2).

When analyzed as a continuous variable, no association was found between levels of HbA1c and VTE after adjustments for potential confounders (Fig.2).
In the categorized analysis adjusted for age and sex, subjects with HbA1c ≥6.5% had 67% higher risk of VTE compared to those with HbA1c <5.7% (HR 1.67; 95% CI 1.01-2.74), and there was a significant linear trend for increased risk of VTE across categories of HbA1c (*P* for trend 0.04) (Table 3). However, after further adjustments, in which BMI was the covariate with the largest influence, the risk estimates were attenuated and no longer statistically significant; multivariable HR 1.27 (95% CI 0.72-

2.26), *P* for trend 0.27. In separate analysis of unprovoked and provoked VTE, subjects with HbA1c ≥6.5% appeared to have a 1.6-fold higher risk of provoked VTE (multivariable HR 1.56; 95% CI 0.78-3.13) than those with HbA1c <5.7%, and the *P* for trend across categories was 0.09. No consistency was found in analyses of unprovoked VTE (multivariable HR for upper vs. lower category of HbA1c 0.89; 95% CI 0.32-2.49, *P* for trend 0.69). However, in these subgroup analyses the number of events in the upper category was low, and the results should therefore be interpreted with caution.

Repeated measures of HbA1c were carried out in 5647 participants (contributing to 13576 exposure periods) and there were 240 VTE events among these subjects during follow-up. In analyses with HbA1c level as a time-dependent exposure, all risk estimates remained essentially unchanged (multivariable HR for upper vs. lower category of HbA1c 1.18; 95% CI 0.73-1.90, p=0.8) (Table 4).

Discussion

In the present study, HbA1c was not associated with future risk of overall VTE in multivariable analyses, neither by a continuous nor by a categorical approach. Furthermore, HbA1c showed no significant association with either unprovoked or provoked VTE in subgroup analyses. However, a tendency of increased risk of provoked VTE was observed in subjects with HbA1c levels of 6.5% or more, suggesting that hyperglycemia may predispose for VTE through associated hospitalization or co-morbidities. Nevertheless, the number of events in the upper

category was low, and the results of these subgroup analyses should be interpreted with caution.

In contrast to our findings, a case-control study[25] suggested that hyperglycemia was related to increased risk of VTE, independently of known diabetes. However, in this study non-fasting glucose levels were measured on admission for a suspected DVT[25], and the elevated glucose levels in VTE patients could potentially be due to the inflammatory and counter-regulatory hormone action initiated by the VTE event itself[26].

The impact of hyperglycemia and diabetes on risk of VTE is controversial[17-25,41]. In a pilot study by Petrauskiene et al.[19] diabetes was a risk factor for VTE. However, the risk estimates were not adjusted for BMI. Abdominal obesity has previously been shown to be the main contributing risk factor for VTE among persons with metabolic syndrome[21]. Thus, high BMI in patients with diabetes may have confounded the observed association between diabetes and VTE. This notion was supported in our study where adjustment for BMI in the multivariable analyses highly attenuated the association between HbA1c and risk of VTE. The prevalence of insulin resistance is increased in obese individuals[42] and improves with weight loss[43-45]. Schouwenburg et al[46]showed that insulin resistance was not associated with risk of VTE after adjusting for BMI in a population-based cohort. In contrast, a recent report from the Iowa Women`s Health Study[18] found an association between diabetes and VTE in women, even after adjustment for BMI. However, self-reported data on weight and height in this study may have led to underestimation of BMI, and thereby attenuated the true confounding effect of BMI. Furthermore, the Longitudinal Investigation of Thromboembolism Etiology (LITE)

study[17], which combined information from two prospective cohorts (the Atherosclerotic Risk in Community (ARIC) study and the Cardiovascular Health Study (CHS)), showed that diabetes was a modest risk factor for VTE, whereas impaired fasting glucose was not related to VTE. However, in a later re-analysis of the ARIC data[23] no relationship was found between diabetes mellitus and VTE . The inconsistency between these two studies may be explained by the different study groups, and the fact that Wattanakit et al[23] performed time-dependent analysis. Furthermore, the LITE study only observed a significant association between diabetes and provoked VTE events. Thus, their finding that diabetes, but not impaired fasting glucose, was associated with VTE may be explained by other provoking factors rather than diabetes itself. Several other studies support our findings of no association between hyperglycemia and risk of VTE[20,22,24]. In a report by Heit et al[20], the observed link between diabetes and VTE was explained by more frequent hospitalizations of persons with diabetes, and thereby being predisposed for VTE. As diabetes and HbA1c are interlinked, this may explain the increased risk estimate for provoked events in subjects with HbA1c ≥6.5%. Hence, the apparent relationship between HbA1c and total VTE in our study may partly be mediated through provoking factors, such as arterial cardiovascular events or immobilization.

The main strengths of our study are the large number of participants and validated VTE events, the prospective design and long-term follow-up. To address the potential problem of regression dilution effects (i.e. that intra-individual changes in HbA1c during long term follow-up could bias the risk estimates towards the null) we additionally performed a time-dependent analysis which allowed for changes in

HbA1c and important covariates such as BMI over time in subjects who attended more than one visit. Our findings in the time-dependent analysis were similar to those using baseline measures only, supporting the robustness of our findings. The study has, however, some potential limitations. As some of the variables were self-reported measurements, misclassification may have occurred. Fasting glucose levels were not measured, and therefore we used HbA1c to assess hyperglycemia. In a systematic review of primary cross-sectional studies, no evidence was found for fasting plasma glucose to be superior to HbA1c in screening for diabetes or impaired glucose tolerance (IGT)[47]. The study provided sufficient statistical power for assessment of a HR of 1.16 for VTE by the continuous HbA1c variable. However, in the categorical analyses the number of events in the upper HbA1c category was low, and the study only provided sufficient statistical power (80%) for assessment of a HR of 1.97 for total VTE in the upper vs. lower category. Thus, as our non-significant finding may be due to a type II error we cannot rule out that subjects within the upper category may be at increased risk of VTE. Moreover, subgroup analyses had limited power, and firm conclusions regarding the association with provoked and unprovoked VTE could not be made. Information on concomitant treatment was not available in our study, and could therefore not be taken into consideration.

In our prospective population–based study, levels of HbA1c were not significantly associated with future risk of VTE after adjustment for BMI. Our findings suggest that hyperglycemia does not play an important role in the pathogenesis of VTE, and that obesity is a more important contributor to VTE in subjects with hyperglycemia.

Addendum

G. Lerstad and K.F. Enga carried out statistical analysis. G. Lerstad and E. Brodin interpreted the results and drafted the manuscript. S.K. Brækkan and J.B. Hansen designed the study, collected data, and critically revised the manuscript. G. Lerstad and S.K. Brækkan had full access to the data, and take full responsibility for its integrity and the accuracy of data analysis.

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Disclosure of Conflict of Interests: None

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Fig.1. Presentation of the follow-up of subjects included from the different Tromsø visits (94/95, 01/02 and 07/08). 5 647 subjects participated in two or more surveys.

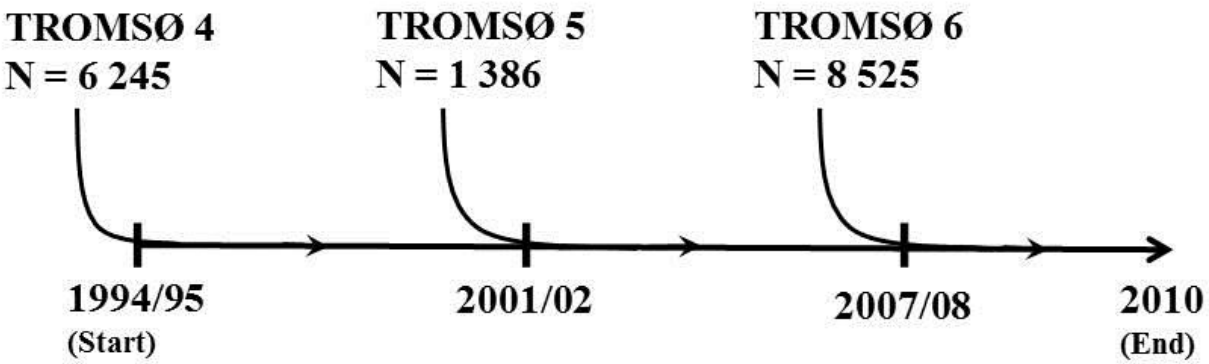

Fig. 2. Dose-response relationship between glycated hemoglobin (HbA1c) and risk of venous thromboembolism (VTE) obtained by generalized linear regression. The regression model is adjusted for age, sex, body mass index, smoking, physical activity and self-reported cardiovascular disease. The solid line shows hazard ratios and the shaded area shows 95% confidence intervals. Density plots show the distribution of HbA1c and white vertical lines indicate 2.5th, 25th, 50th, 75th and 97.5th percentiles.

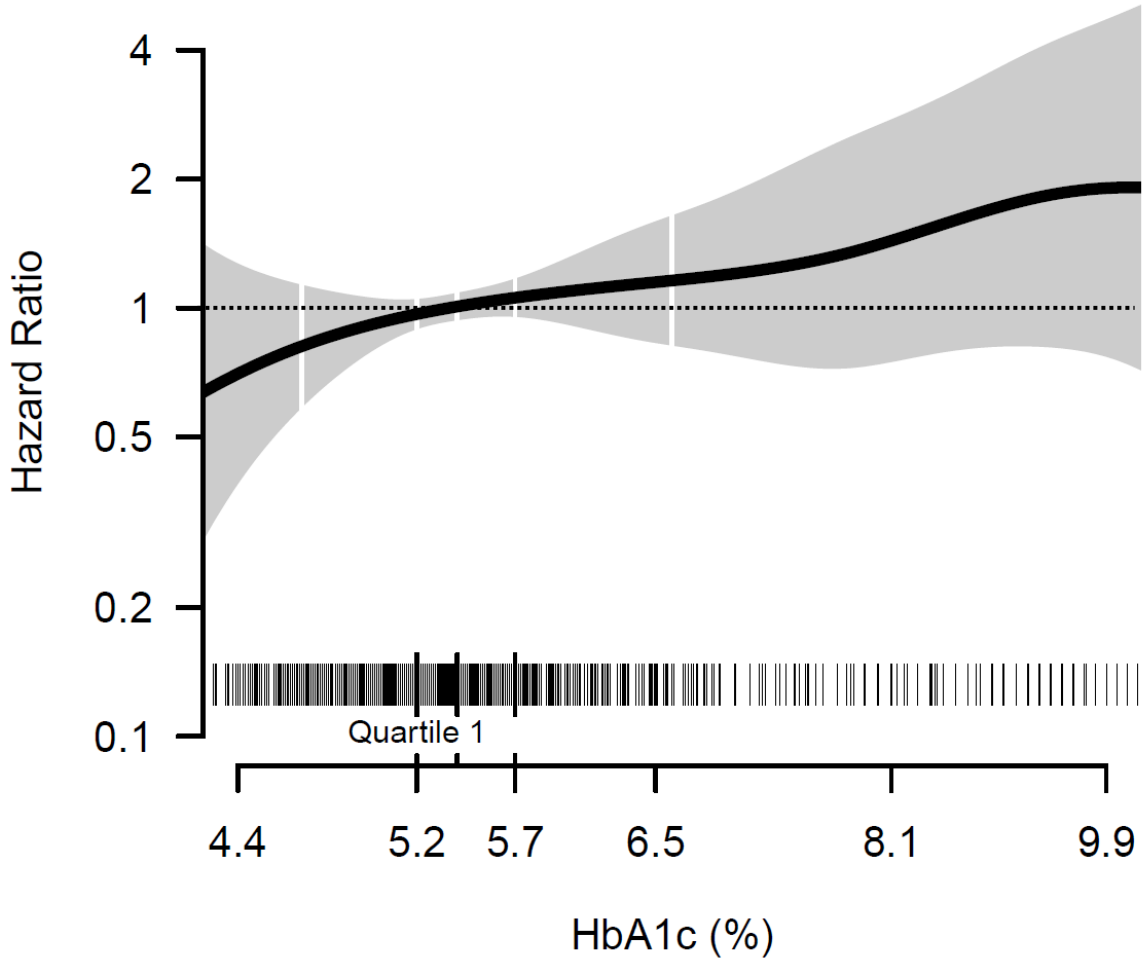

Table 1 Baseline characteristics of subjects enrolled in the Tromsø study (94/95, 01/02 and 07/08)

	HbA1c (%)		
	< 5.70%	5.70-6.50%	≥ 6.50%
Age (years)	54 ± 11	59 ± 9	61 ± 10
Sex (% women)	45 (5152)	51.2 (2099)	54.8 (339)
Body Mass Index (kg/m^2)	26.0 ± 3.9	27.4 ± 4.4	29.8 ± 5.1
Systolic Blood Pressure (mmHg)	135 ± 22	140 ± 23	145 ± 23
Diastolic Blood Pressure (mmHg)	80 ± 12	81 ± 12	81 ± 12
Triglycerides (mmol/L)	1.50 ± 0.90	1.78 ± 1.05	2.31 ± 2.16
Total cholesterol (mmol/L)	6.04 ± 1.29	6.23 ± 1.27	5.83 ± 1.48
HDL-cholesterol (mmol/L)	1.53 ± 0.43	1.45 ± 0.42	1.28 ± 0.38
Smoking (%)	25.6 (2909)	30.3 (1243)	21.8 (135)
Physical activity (%) *	51.4 (4377)	50.8 (1312)	42.0 (148)
Diabetes (%)	0.6 (63)	3.4 (138)	100 (619)
Cardiovascular disease (%)	7.2 (813)	13.1 (529)	26.3 (156)

Values are percentage with numbers in brackets or means ± 1 SD.

* Sweat production and breathlessness ≥1 hour per week during leisure time.

Table 2 Characteristics of venous thromboembolism (VTE) events (n=333). The Tromsø study (94/95, 01/02 and 07/08)

	% (n)
Deep vein thrombosis	56.8 (189)
Pulmonary embolism	43.2 (144)
Unprovoked ±	41.1 (137)
Clinical risk factors	
Estrogens (HRT, oral contraceptives)	5.7 (19)
Heredity†	2.7 (9)
Pregnancy	0 (0)
Other medical conditions‡	24.3 (81)
Provoking factors	
Surgery	18.3 (61)
Trauma	6.9 (23)
Acute medical conditions	14.4 (48)
Cancer	24.3 (81)
Immobilization(bed rest > 3 days, wheelchair)	20.1 (67)
Other §	4.5 (15)

Values are percentages with numbers in brackets.
±No provoking factors at the time of diagnosis.
†Heredity: Family history of VTE in first degree relative before the age of 60 years.
‡Other diseases within the previous year (myocardial infarction, ischemic stroke, heart failure, inflammatory bowel disease, chronic infections, chronic obstructive pulmonary disease or myeloproliferative disorders).
§Other factor specifically described as provoking in the medical record (e.g. intravascular catheter)
Abbreviations: VTE; Venous thromboembolism, HRP; Hormone replacement therapy

Table 3 Associations between categories of HbA1c and risk of for total VTE, provoked VTE and unprovoked VTE

	HbA1c (%)			
	<5.70	5.70 – 6.50	≥6.50	*P for trend*
Total VTE				
Person-years	85108	26009	3504	
Events	226	90	17	
IR*	2.66 (2.33-3.03)	3.46 (2.81-4.25)	4.85 (3.01-7.80)	
HR†	1.00 (reference)	1.17 (0.92-1.50)	1.67 (1.01-2.74)	*0.04*
HR‡	1.00 (reference)	1.12 (0.86-1.46)	1.27 (0.72-2.26)	*0.27*
Provoked VTE				
Person-years	84282	25794	3477	
Events	129	57	10	
IR*	1.53 (1.29-1.82)	2.21 (1.70-2.87)	2.88 (1.55-5.35)	
HR†	1.00 (reference)	1.31 (0.96-1.80)	1.74 (0.91-3.33)	*0.03*
HR‡	1.00 (reference)	1.27 (0.91-1.76)	1.56 (0.78-3.13)	*0.09*
Unprovoked VTE				
Person-years	84025	25591	3437	
Events	97	33	7	
IR*	1.15 (0.94-1.40)	1.29 (0.92-1.81)	2.04 (0.9-4.28)	
HR†	1.00 (reference)	0.99 (0.66-1.47)	1.56 (0.72-3.39)	*0.53*
HR‡	1.00 (reference)	0.92 (0.60-1.41)	0.89 (0.32-2.49)	*0.69*

*Incidence rate per 1000 person-years.
† Adjusted for age and sex.
‡ Adjusted for age, sex, body mass index, smoking, physical activity (hard) and self-reported CVD.

Table 4 Incidence rates (IR) and hazard ratios (HR) of VTE across categories of HbA1c. Time-dependent analysis of 5647 subjects with repeated measures (surveys 4, 5 and/or 6) in the Tromsø study 1994-2010.

	HbA1c (%)			
	< 5.70	5.70 – 6.50	≥ 6.50	*P for trend*
Person-years	55795	15053	3565	
Events	164	55	21	
IR*	2.9 (2.5-3.4)	3.6 (2.8-4.8)	5.9 (3.8-9.0)	
HR†	1.00 (reference)	0.99 (0.73-1.35)	1.43 (0.90-2.27)	*0.3*
HR‡	1.00 (reference)	0.93 (0.68-1.27)	1.18 (0.73-1.90)	*0.8*

Repeated measurements with age as time scale: 5647 subjects contributed to 13576 exposure periods and there were 240 VTE events during follow-up.
*Incidence rate per 1000 person-years.
† Adjusted for sex.
‡ Adjusted for sex, smoking, body mass index, physical activity (hard) and self-reported CVD.