Impact of prothrombotic genotypes on the association between family history of myocardial infarction and venous thromboembolism

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Essentials

- Venous thromboembolism (VTE) is associated with family history of myocardial infarction (FHMI)
- VTE cases and a sub-cohort from the Tromsø and the Nord-Trøndelag Health Studies were genotyped
- The risk of VTE by FHMI could not be explained by the prothrombotic genotypes
- The combination of FHMI and prothrombotic genotypes had an additive effect on VTE risk

Summary

Background: Family history of myocardial infarction (FHMI) is known to increase the risk of venous thromboembolism (VTE).

Objectives: To investigate the effect of prothrombotic genotypes on the association between FHMI and VTE in a case-cohort recruited from a general population.

Methods: Cases with a first VTE (n=1,493) and a sub-cohort (n=13,072) were sampled from the Tromsø study (1994-2012) and the Nord-Trøndelag health (HUNT) study (1995-2008). DNA-samples were genotyped for rs8176719 (*ABO*), rs6025 (*F5*), rs1799963 (*F2*), rs2066865 (*FGG*) and rs2036914 (*F11*). Participants with missing information on risk alleles (n=175), FHMI (n=2769) and BMI (n=52) were excluded. Cox-regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CI) for VTE. To explore the role of prothrombotic genotypes for the association between FHMI and VTE, we (i) included the genotypes in the multivariable-adjusted models, and (ii) assessed the joint effects between FHMI and genotypes on VTE risk.

Results: FHMI was associated with a 1.3-fold increased risk of VTE (HR 1.32, 95% CI 1.16-1.50) and 1.5-fold increased risk of unprovoked VTE (HR 1.47, 95% CI 1.22-1.78). The risk of VTE by FHMI did not alter after adjustment for the five genotypes. The combination of FHMI and the different prothrombotic genotypes did not result in an excess VTE risk (i.e. no biological interaction).

Conclusions: Our findings suggest that the risk of VTE by FHMI is not explained by rs8176719 (*ABO*), rs6025 (*F5*), rs1799963 (*F2*), rs2066865 (*FGG*) and rs2036914 (*F11*). FHMI combined with prothrombotic genotypes had an additive effect on VTE risk.

Keywords: Genotype – Myocardial infarction – Prospective studies – Risk factors – Venous thromboembolism

Introduction

Traditionally, arterial thrombotic diseases (e.g. myocardial infarction [MI] and stroke) and venous thromboembolism (VTE) (deep vein thrombosis [DVT] and pulmonary embolism [PE]) have been considered as separate disease entities with different pathophysiology and treatment. However, both registry-based studies and cohorts recruited from the general population have demonstrated bidirectional associations between arterial and venous thromboembolic diseases [1-4]. The relationship between arterial and venous thrombosis may be attributed to shared environmental or genetic risk factors, or it may be a causal association through mediating factors, such as hospitalization accompanied by immobilization and infection, or via a transient prothrombotic state following an arterial event [5]. Results from population-based cohorts have revealed that among the well-known cardiovascular risk factors, only advancing age, obesity and family history of MI (FHMI) were shared risk factors for arterial and venous thromboembolic diseases [6-11].

FHMI is a well-established risk factor for MI [11-13], and during recent years, FHMI has also been found to be associated with an increased risk of VTE [9-11, 14]. The population attributable fraction (PAF) of MI and VTE by FHMI has been estimated to be 19% and 13%, respectively [11], indicating that 19% of the total incidence of MI and 13% of the total incidence of VTE could be explained by FHMI-related risk factors. Due to the impact of FHMI on the risk of MI and VTE, it is important to unravel underlying mechanisms and potential common pathways. Although it is unclear how FHMI contributes to the risk of VTE, it might be due to shared environmental or genetic risk factors or mediated by an effect of a previous arterial cardiovascular disease. Previously, we reported that modifiable cardiovascular risk factors slightly attenuated the association between FHMI and MI, but had no effect on the association between FHMI and VTE. Furthermore, by applying a cause-specific model to eliminate the effect of MI on VTE, we showed that MI did not mediate the effect of FHMI on the risk of VTE [11].

As the risk of VTE by FHMI was particularly pronounced for unprovoked VTE events and increased with the number of affected relatives [11], it is plausible to assume that prothrombotic genotypes accumulating in families with arterial cardiovascular disease might explain the association between FHMI and VTE. Several genetic polymorphisms associated with an increased risk of VTE have been discovered during the last decades [15]. Some of these prothrombotic genotypes, such as rs8176719 (*ABO*), rs6025 (*F5*), rs1799963 (*F2*), have also been shown to increase the risk of arterial thrombosis in some studies [16-18].

It is unknown whether prothrombotic genotypes are shared risk factors for FHMI and VTE, and how a combination of these factors influence the VTE risk. We therefore aimed to (i) investigate whether the association between FHMI and VTE was explained by the presence of prothrombotic genotypes and to (ii) explore the combined effects of FHMI and prothrombotic genotypes on the risk of VTE, using a case-cohort recruited from the general population.

Methods

Study population

Study participants were recruited from the fourth survey of the Tromsø study (Tromsø 4) conducted in 1994-1995 [19], and the second survey of the Nord-Trøndelag Health Study (HUNT 2), conducted in 1995-1997 [20]. The Tromsø Study and the HUNT Study are population-based cohorts of inhabitants in Tromsø municipality and Nord-Trøndelag County, Norway, respectively. To Tromsø 4, the entire population aged ≥25 years living in the municipality of Tromsø was invited to participate, and 27,158 participants attended (77%). To HUNT 2, all residents in Nord-Trøndelag County aged 20 years and older were invited to participate, and 66,140 participants attended (71%) [20]. More detailed descriptions of the studies have been published elsewhere [19, 20].

All participants from these surveys were followed from the date of inclusion until a verified VTE event, migration, death or end of follow-up (December 31, 2008 in the HUNT Study, and December

31, 2012 in the Tromsø Study). In the Tromsø Study, all incident VTE events were identified by searching the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University Hospital of North Norway. The medical record for each potential case of VTE was reviewed by trained personnel, and adjudication criteria for VTE were the presence of clinical signs and symptoms of DVT or PE combined with objective confirmation by radiologic procedures that resulted in treatment initiation (unless contraindications were specified). In the HUNT study, VTE events were identified by searching the hospital discharge diagnosis registry and the radiology procedure registry at the two local hospitals in the county (Levanger Hospital and Namsos Hospital) and by searching the discharge diagnosis registry of the tertiary-care center of the region, St. Olav's Hospital in Trondheim (Sør-Trøndelag County). The medical records for potential VTE cases were reviewed and validated by two physicians, and the VTE diagnosis required positive objective confirmation by radiologic procedures. Detailed descriptions of identification and validation of VTE events in the two studies have been published elsewhere [21, 22].

All cases with an incident VTE (n=1,493) and a randomly selected sub-cohort (n=13,072) of participants without previous VTE were included in our study (Figure 1). Due to the study design, in which all participants in the original cohort has an equal chance of being included in the sub-cohort, 217 cases were included in the sub-cohort. Participants not officially registered as inhabitants in Tromsø or Nord-Trøndelag at baseline (n=3) were excluded. Further, we excluded participants with missing values for at least one of the single nucleotide polymorphisms (SNPs) studied (n=175), and participants with missing data on FHMI (n=2,769) and BMI (n=52). Consequently, 1,164 incident VTEs and 10,402 sub-cohort participants were included in the study. The study was approved by the Regional Committees for Medical and Health Research Ethics, and all study participants provided informed written consent.

Classification of VTE events

VTE events were classified as provoked and unprovoked, depending on the presence of provoking factors at the time of diagnosis. In the Tromsø Study, provoking factors were active cancer, acute medical conditions (including acute MI, ischemic stroke or major infections), recent surgery or trauma within the previous eight weeks, immobilization (bed rest over three days, wheelchair use or long distance travel exceeding four hours the last 14 days prior to the event) or any other provoking factors described by a physician in the medical record (e.g. intravascular catheter). In the HUNT study, provoking factors included active cancer at the time of the event or within six months after the event, trauma, surgery or marked immobilization (paresis, paralysis, prolonged bed rest due to an acute medical illness or travel exceeding 8 hours) within the last three months, pregnancy or puerperium at the time of the event and oral contraceptives used at the time of the event or up to one month prior to the event.

Cardiovascular risk factors

Baseline information on cardiovascular risk factors was collected by physical examinations, blood samples, and self-administered questionnaires. Height and weight were measured with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meter (kg/m^2). Blood pressure was measured three times with an automatic device (Dinamap Vital Signs Monitor in the Tromsø Study and Dinamap 845XT [Critikon] in the HUNT study) in a sitting position after two minutes of rest. The average of the two last readings was used in the analyses. Non-fasting blood samples were collected from an antecubital vein and total cholesterol, triglycerides and high-density lipoprotein (HDL) were measured, as previously described [7, 20]. Self-administered questionnaires were used to obtain information on diabetes, smoking (current daily smoking, yes/no) and FHMI. To identify FHMI, subjects were asked to report whether their mother, father, sister, brother, child or none in the family had a history of MI before the age of

60 years. A positive family history was regarded as ≥ 1 first-degree relative with a history of MI before the age of 60 years.

Prothrombotic genotypes

The following single nucleotide polymorphisms (SNPs) were genotyped and used in the present study: rs8176719 in *ABO* (non-O blood type), rs6025 in *F5* (Factor V Leiden), rs1799963 in *F2* (prothrombin G20210A), rs2066865 in *FGG* and rs2036914 in *F11*. In the Tromsø Study, rs8176719 (*ABO*), rs6025 (*F5*), rs1799963 (*F2*) and rs2036914 (*F11*) were genotyped with the Sequenom platform, and rs2066865 (*FGG*) with the TaqMan platform, as previously described [23]. The HUNT study performed genotyping using the Illumina HumanCore Exome array.

Participants were considered carriers of the prothrombotic risk gene when one or two risk alleles were present. We did not differentiate between hetero- and homozygous carriers due to the low number of homozygous carriers. For rs2036914 in *F11*, the minor allele was associated with reduced risk of VTE, and in this case, we considered the common allele as the risk allele [24]. For rs8176719 (*ABO*), zero risk alleles were classified as O blood type, whereas one or two risk alleles were classified as non-O blood type. The 5-SNP score conceived by de Haan and colleagues was created by summarizing the number of risk alleles from the five sequenced SNPs [25]. As homozygous individuals have two risk alleles, the potential maximum number of risk alleles in the 5-SNP score would be 10.

Statistical analysis

Statistical analyses were carried out using STATA version 14.0 and 15.0 (Stata Corporation, College Station, TX, USA). For each participant, person-years of follow-up were counted from the date of enrollment (1994-1995 in the Tromsø Study and 1995-1997 in the HUNT Study) to the date of an incident VTE event, the date the participant died or moved from Tromsø or Nord-Trøndelag County,

or until the end of the study period (December 31, 2008 in the HUNT study and December 31, 2012 in the Tromsø Study). Participants who died or moved from Tromsø or Nord-Trøndelag County during follow-up were censored at the date of death or migration.

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for VTE by FHMI and prothrombotic genotypes. Age was used as the time-scale, with the age of the participants at study enrolment defined as entry time, and the age at the VTE or censoring event defined as exit time. All analyses were adjusted for age (as time-scale), sex and BMI. We estimated the risk of total VTE, as well as unprovoked VTE and provoked VTE, by FHMI and according to ≥ 1 affected relatives or ≥ 1 affected parent, respectively. In order to assess the role of prothrombotic genotypes on the association between FHMI and VTE, the five SNPs were entered into the regression models. Furthermore, to investigate combined effects, we calculated HRs of VTE according to categories of FHMI and the individual SNPs as well as categories of the 5-SNP score (0-1, 2, 3-4 and ≥ 5 risk alleles). The presence of biological interaction between the two exposures was assessed by calculating the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP) and the synergy index (SI) with corresponding 95% CIs [26]. Briefly, the RERI can be interpreted as part of the total effect on the outcome that is due to interaction, and the AP as the proportion of cases in the combined group that is due to an interaction between the two exposures. RERI and AP > 0 and SI > 1.0 suggest positive interaction, i.e., the effect of the joint exposures to two risk factors is greater than the sum of the separate effects [26].

Because of the size of the sub-cohort, we did not make adjustments to the partial likelihood in the Cox regression analyses [27]. The proportional hazard assumption was tested using Schoenfeld residuals. Lastly, we performed a sensitivity analysis in which participants with missing information on FHMI were included in the study and categorized as not having FHMI (i.e. assuming that all missings would be due to no FHMI).

Results

The baseline characteristics of the cases and the sub-cohort are shown in Table 1. Participants who experienced a VTE were older and had slightly higher systolic blood pressure, BMI, triglycerides, and cholesterol levels compared with participants in the sub-cohort. Serum levels of triglycerides and total cholesterol along with the proportion of smokers and participants with self-reported diabetes were higher in the group with a FHMI. Compared to the sub-cohort, VTE patients had a higher proportion of participants with ≥ 1 risk allele(s) in all SNPs, and rs8176719 (*ABO*), rs6025 (*F5*), and rs1799963 (*F2*) in particular. The prevalence of the SNPs did not differ according to FHMI.

The distribution of individuals (%) across numbers of risk alleles for subjects with and without FHMI is shown in Figure 2, panel A. The number of risk alleles ranged from zero to seven with a median of two for both groups, and participants with and without FHMI had a similar distribution of the number of risk alleles. The risk of VTE (Figure 2, panel B) increased with increasing number of risk alleles when compared to zero risk alleles (p for trend<0.001). Subjects with ≥ 5 risk alleles had a 2.4-fold higher risk of VTE (HR 2.43, 95% CI 1.64-3.59) compared with those without risk alleles.

Table 2 shows HRs for total, unprovoked and provoked VTE by FHMI. In models adjusted for age (as time-scale), sex and BMI, subjects with ≥ 1 affected first-degree relative or ≥ 1 affected parent had increased risk of VTE with a HR of 1.32 (95% CI 1.16-1.50) and 1.40 (95% CI 1.20-1.64), respectively. The point estimate for unprovoked VTE (HR 1.47, 95% CI 1.22-1.78) was higher than for provoked VTE (HR 1.20, 95% CI 1.00-1.43). Similarly to total VTE, the risk estimates for unprovoked VTE were higher in the analysis of ≥ 1 affected parent (HR 1.52, 95% CI 1.20-1.93) in comparison with ≥ 1 affected first-degree relative (HR 1.47, 95% CI 1.22-1.78). Adjustments for the five prothrombotic genotypes had a negligible effect on the risk estimates for VTE. Sensitivity analyses where participants with missing information on FHMI were included in the no FHMI group yielded similar results (Supplementary Table 1).

Table 3 shows HRs with 95% CI for total VTE and unprovoked VTE by combinations of FHMI and prothrombotic genotypes, adjusted for age (as time-scale), sex and BMI. For each of the individual SNPs, the risk of VTE was increased in participants having a positive FHMI and no risk alleles, and in participants without FHMI and ≥ 1 risk alleles. However, the combined effect of having both FHMI and ≥ 1 risk alleles did not exceed the sum of the effects of the individual risk factors. For instance, having both FHMI and non-O blood type (rs8176719) was associated with a 1.8-fold increased risk of VTE (HR 1.78, 95% CI 1.49-2.13), which approximated the sum of having only FHMI (HR 1.35, 95% CI 1.07-1.71) or non-O blood type (HR 1.38, 95% CI 1.19-1.59). The combination of FHMI and the high-risk category of the 5-SNP score (i.e. ≥ 5 risk alleles) did not have a synergistic impact on the VTE risk (RERI 0.37, 95% CI -0.89 to 1.63 and AP 0.14, 95% CI -0.29 to 0.56). Thus, combinations of FHMI and prothrombotic genotypes had merely additive effects on the VTE risk, as suggested by the estimated measures of biological interaction (i.e. RERI, AP, and SI) described in Supplementary Tables 2 and 3.

Discussion

In this case-cohort study with participants recruited from the general population, we found that the association between FHMI and VTE could not be explained by common prothrombotic genotypes, such as rs8176719 (*ABO*), rs6025 (*F5*), rs1799963 (*F2*), rs2066865 (*FGG*), and rs2036914 (*F11*). Adjustment for prothrombotic genotypes did not alter the association between FHMI and VTE, and the combination of FHMI and prothrombotic genotypes had merely an additive effect on the VTE risk.

The increased risk of VTE, and particularly unprovoked VTE, by a FHMI is in agreement with results from other observational studies [9-11, 14]. In two previous studies with data from the entire Tromsø cohort, FHMI was associated with a 1.3-fold increased risk of VTE [9, 11], and a 1.5-fold increased risk of unprovoked VTE [9, 11]. Adjustment for traditional cardiovascular risk factors had a negligible effect on the risk of VTE [9, 11], whereas the risk of MI was attenuated [11], indicating that cardiovascular risk factors were confounders for the association between FHMI and MI, but not for the

association between FHMI and VTE [11]. Similar results were reported in a case-cohort derived from the second survey of the HUNT study [10], and a case-control study derived from the Genetic Attributes and Thrombosis Epidemiology (GATE) study [14]. Sub-group analyses from the different studies revealed that the risk of VTE increased with increasing number of affected relatives [11, 14], and when a relative aged < 50 years experienced an MI [14]. Further, the reported risk estimates for DVT and PE were similar, but the risk was highest for unprovoked DVTs [11]. A FHMI is not considered to be a causal factor for thrombosis, but rather an indicator of genetic or environmental risk factors accumulating in certain families, which have the potential to affect the risk of VTE. Due to the particularly increased risk of unprovoked VTE, and because the risk increases with increasing numbers of affected relatives, it was suggested that the association between FHMI and VTE was caused by shared genetic risk factors [9-11, 14].

In the present study, rs8176719 (*ABO*), rs6025 (*F5*), rs1799963 (*F2*), rs2066865 (*FGG*), and rs2036914 (*F11*) did not act as confounders in the association between FHMI and VTE, as adjustments for these prothrombotic genotypes had a negligible effect on the risk estimates. Furthermore, combinations of FHMI and the prothrombotic genotypes had an additive effect on the risk of VTE. For instance, having both FHMI and rs8176719 (*ABO*) was associated with a 1.8-fold increased risk of VTE, which was equal to the sum of having only FHMI or rs8176719 (*ABO*). Similar results were found for FHMI in combination with the other individual SNPs and the combined 5-SNP score. Our results suggest that FHMI and the five prothrombotic genotypes included in this study are unrelated risk factors of VTE and that these prothrombotic genotypes do not influence the association between FHMI and VTE.

Two risk factors acting through the same pathophysiological mechanism can have both synergistic and additive effects on an outcome. For instance, obesity and rs6025 (*F5*), which are associated with hypercoagulability, had synergistic effects on VTE risk [28]. Similarly, the risk of VTE in obese women using oral contraceptives has been shown to exceed the sum of the effects of the individual risk factors [29]. However, a cohort study of 66,000 genotyped participants found additive effects on VTE risk when different prothrombotic genotypes, all causing hypercoagulability, were

combined [30]. Consequently, our results do not allow us to determine the mechanisms behind the association between FHMI and VTE, and do not exclude the possibility that other unrecognized genetic variants can partly explain the association between FHMI and VTE.

Even though the prothrombotic genotypes included in our study are associated with both arterial and venous thrombosis [15-18], our results indicate that these genotypes do not explain the association between FHMI and VTE. However, on the basis of the present and previous findings [9, 11], it is likely to assume that genetic risk factors are one of the main contributors to the association between FHMI and VTE. Furthermore, environmental risk factors clustering within families may potentially act as contributors to this association. Although the association between FHMI and VTE is independent of traditional cardiovascular risk factors [9-11], other environmental risk factors related to both FHMI and VTE, such as stress and socioeconomic status [31-33], might partly explain the association.

The main strengths of our study include the long-term follow-up, the large number of genotyped participants, the high attendance rate in the parent cohorts, and the thorough outcome assessment. The study cohorts represent a general and homogenous Caucasian population, which limits confounding by ethnicity in the sub-cohort [34]. Some limitations of this study need to be addressed. First, analyses were restricted to subjects with information on FHMI. It is likely to assume that the majority of subjects with missing information on FHMI did not answer the question because they did not have, or did not know if they had, any first-degree relatives with a history of MI before the age of 60 years. It is noteworthy, however, that the association between FHMI and VTE, albeit slightly attenuated, remained when participants with missing data on FHMI were classified as having no FHMI (Supplementary table 1). Second, data on FHMI was self-reported and both under-reporting and over-reporting of affected relatives were possible. Validation of FHMI in the Tromsø Study showed high concurrence between reported and confirmed diagnosis [35], and a validation study by Kee et al. found high specificity (97%) and lower sensitivity (68%) of a positive FHMI [36]. Hence, underestimation of the risks associated with FHMI is more likely. Third, even though our study was

derived from large cohorts, the number of VTE events was low in some subgroups, particularly for the rare exposures, which resulted in limited statistical power. Our results on the measures that quantify interaction should therefore be interpreted with caution. Lastly, due to the observational nature of our study, unknown confounders could be present and lead to residual confounding.

In conclusion, our study provides evidence that the association between FHMI and VTE is not explained by rs8176719 (*ABO*), rs6025 (*F5*), rs1799963 (*F2*), rs2066865 (*FGG*) or rs2036914 (*F11*). FHMI and the prothrombotic genotypes had an additive effect on VTE risk, indicating no biological interaction between the risk factors.

Addendum

Birgit Småbrekke analyzed the data and drafted the manuscript. Ludvig B. Rinde, Line H. Evensen, Vania M. Morelli, Inger Njølstad, Ellisiv B. Mathiesen and Frits R. Rosendaal were involved in the interpretation of the results and revision of the manuscript. Kristian Hveem and Maiken E. Gabrielsen were involved in data collection and revision of the manuscript. Sigrid K. Brækkan and John-Bjarne Hansen were involved in conception and design of the study, data collection and revision of the manuscript. The manuscript has been read and approved for submission to Journal of Thrombosis and Haemostasis by all authors.

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Disclosure of Conflict of interests

The authors state that they have no conflict of interest.

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Tables

T**able 1.** Baseline characteristics by family history of myocardial infarction (FHMI) and incident venous thromboembolism (VTE).

	No FHMI		FHMI	
	Sub-cohort	**VTE**	**Sub-cohort**	**VTE**
Participants, n	8376	851	2026	313
Age, years	49.8±17	60.7±15	52.7±15	59.9±14
Male sex	46.0 (3857)	49.6 (422)	42.9 (869)	42.5 (133)
Systolic BP, mmHg	137±21	144±24	140±21	144±23
Diastolic BP, mmHg	80±12	83±13	82±12	82±12
BMI, kg/m^2	26.1±4.1	27.5±4.6	26.5±4.2	27.4±4.2
Triglycerides, mmol/L	1.68±1.04	1.80±0.99	1.82±1.09	1.95±1.32
Cholesterol, mmol/L	5.88±1.26	6.34±1.28	6.26±1.32	6.63±1.28
HDL, mmol/L	1.41±0.39	1.43±0.41	1.41±0.40	1.42±0.41
Self-reported diabetes	2.9 (244)	3.8 (32)	3.9 (80)	4.5 (14)
Smoking	27.1 (2269)	25.7 (219)	31.9 (646)	31.6 (99)
rs8176719 (*ABO*)*	61.4 (5139)	69.1 (588)	63.4 (1284)	69.0 (216)
rs6025 (*F5*)*	6.8 (571)	15.3 (130)	7.2 (146)	16.0 (50)
rs1799963 (*F2*)*	1.2 (104)	1.8 (15)	1.5 (31)	3.2 (10)
rs2066865 (*FGG*)*	41.9 (3508)	44.1 (375)	44.6 (903)	50.2 (157)
rs2036914 (*F11*)*	78.5 (6572)	80.4 (684)	76.7 (1553)	82.1 (257)

Values are % (n) or mean±SD. BP indicating blood pressure; BMI, body mass index; HDL, high-density lipoprotein.

* Percentage of participants with ≥1 risk allele

Table 2. Hazard ratios (HR) with 95% confidence intervals (CI) for total, unprovoked and provoked venous thromboembolism (VTE) by family history of myocardial infarction (FHMI).

	N	Events	HR (95% CI)*	Adjusted HR (95% CI)†
Total VTE		1164		
No FHMI	9227	851	Ref.	Ref.
≥ 1 first-degree relative	2339	313	1.32 (1.16-1.50)	1.30 (1.14-1.48)
≥ 1 affected parent	1673	197	1.40 (1.20-1.64)	1.41 (1.20-1.65)
Unprovoked VTE		513		
No FHMI	9227	363	Ref.	Ref.
≥ 1 first-degree relative	2339	150	1.47 (1.22-1.78)	1.45 (1.20-1.76)
≥ 1 affected parent	1673	90	1.52 (1.20-1.92)	1.53 (1.21-1.93)
Provoked VTE		651		
No FHMI	9227	488	Ref.	Ref.
≥ 1 first-degree relative	2339	163	1.20 (1.00-1.43)	1.19 (0.99-1.42)
≥ 1 affected parent	1673	107	1.32 (1.07-1.63)	1.32 (1.07-1.63)

*Adjusted for age (as time-scale), sex and body mass index

†Adjusted for age (as time-scale), sex, body mass index, rs8176719 (*ABO*), rs6025 (*F5*), rs1799963 (*F2*), rs2066865 (*FGG*), and rs2036914 (*F11*)

Table 3. Hazard ratios (HR) with 95% confidence intervals (CI) for venous thromboembolism (VTE) by combined categories of family history of myocardial infarction (FHMI) and prothrombotic genotypes.

			Total VTE		Unprovoked VTE	
		N	Events	HR (95% CI)*	Events	HR (95% CI)*
FHMI	**rs8176719 (*ABO*)†**					
-	-	3500	263	Ref.	107	Ref.
+	-	839	97	1.35 (1.07-1.71)	49	1.67 (1.19-2.34)
-	+	5727	588	1.38 (1.19-1.59)	256	1.47 (1.17-1.84)
+	+	1500	216	1.78 (1.49-2.13)	101	2.04 (1.55-2.68)
FHMI	**rs6025 (*F5*)†**					
-	-	8526	721	Ref.	296	Ref.
+	-	2143	263	1.31 (1.14-1.51)	129	1.56 (1.27-1.92)
-	+	701	130	2.31 (1.92-2.79)	67	2.92 (2.24-3.81)
+	+	196	50	3.09 (2.32-4.12)	21	3.16 (2.03-4.93)
FHMI	**rs1799963 (*F2*)†**					
-	-	9108	836	Ref.	355	Ref.
+	-	2298	303	1.30 (1.14-1.49)	145	1.46 (1.20-1.77)
-	+	119	15	1.41 (0.85-2.35)	8	1.77 (0.88-3.57)
+	+	41	10	2.49 (1.33-4.64)	5	2.91 (1.20-7.04)
FHMI	**rs2066865 (*FGG*)†**					
-	-	5344	476	Ref.	198	Ref.
+	-	1279	156	1.22 (1.02-1.47)	76	1.42 (1.09-1.86)
-	+	3883	375	1.10 (0.96-1.26)	165	1.17 (0.95-1.43)
+	+	1060	157	1.56 (1.30-1.87)	74	1.77 (1.35-2.31)
FHMI	**rs2036914 (*F11*)†**					
-	-	1971	167	Ref.	60	Ref.
+	-	529	56	1.16 (0.86-1.57)	20	1.15 (0.69-1.91)
-	+	7256	684	1.11 (0.94-1.31)	303	1.37 (1.04-1.80)
+	+	1810	257	1.50 (1.24-1.83)	130	2.11 (1.55-2.87)
FHMI	**5-SNP score‡**					
-	0-1	2117	154	Ref.	53	Ref.
+	0-1	484	46	1.16 (0.83-1.61)	21	1.52 (0.92-2.52)
-	2	2888	217	1.03 (0.84-1.26)	98	1.35 (0.96-1.88)
+	2	716	83	1.38 (1.06-1.80)	37	1.77 (1.16-2.69)
-	3-4	3833	420	1.49 (1.24-1.80)	186	1.92 (1.41-2.60)
+	3-4	1026	160	2.02 (1.62-2.52)	80	2.94 (2.07-4.16)
-	≥5	389	60	2.16 (1.60-2.91)	26	2.73 (1.71-4.36)
+	≥5	113	24	2.69 (1.75-4.13)	12	3.88 (2.07-7.28)

*Adjusted for age (as time-scale), sex and body mass index

†Positive indicating subjects with one or two risk alleles

‡Number of risk alleles

Figures

Figure 1. Study population. Participants were recruited from the fourth survey of the Tromsø Study (1994-2012), and from the second survey of the Nord-Trøndelag Health (HUNT) Study (1995-2008). VTE indicates venous thromboembolism; SNPs, single nucleotide polymorphisms; FHMI, family history of myocardial infarction.

Figure 2. Panel A. Distribution (%) of individuals across number of risk alleles and family history of myocardial infarction (FHMI).

Figure 2. Panel B. Hazard ratios with 95% confidence intervals for the risk of venous thromboembolism (VTE) by number of risk alleles in the 5-SNP score.