Family History of Myocardial Infarction and Cause-Specific Risk of Myocardial Infarction and Venous Thromboembolism – the Tromsø Study

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Abstract

Background: A family history of myocardial infarction (FHMI) has been shown to increase the risk of venous thromboembolism (VTE). The mechanism underlying the association remains unclear. Therefore, we aimed to determine the risks of myocardial infarction (MI) and VTE by FHMI using a cause-specific model, and to explore whether atherosclerotic risk factors could explain the association between FHMI and VTE in a population-based cohort.

Methods and Results: The study included 21 624 subjects recruited from the Tromsø Study in 1994-95 and 2001-02. Incident MI and VTE events were registered from date of enrollment to end of follow-up, December 31, 2010. There were 1 311 MIs and 428 VTEs during a median follow-up of 15.8 years. FHMI was associated with a 52% increased risk of MI (adjusted HR 1.52; 95% CI 1.35-1.70) and a 26% increased risk of VTE (adjusted HR 1.26; 95% CI 1.02-1.55) in the cause-specific Cox model. Similar results were found using the traditional Cox model. The risk estimates by status of FHMI were highest for unprovoked deep vein thrombosis (DVT) (adjusted HR 1.69; 95% CI 1.12-2.56), and the risk increased with increasing number of affected relatives. Modifiable atherosclerotic risk factors slightly altered the association between FHMI and MI, but had a negligible impact on the association between FHMI and VTE.

Conclusions: FHMI was associated with increased risk of both MI and VTE in a cause-specific model. Apparently, the association between FHMI and VTE applied to unprovoked DVT and was not explained by modifiable atherosclerotic risk factors.

Key words- Myocardial infarction, thrombosis, epidemiology, follow-up studies

Introduction

A family history of myocardial infarction (FHMI) is an established risk factor for myocardial infarction (MI), and atherosclerotic risk factors (e.g. smoking, hypertension, hypercholesterolemia, obesity and diabetes mellitus) are known to slightly modify the association between FHMI and MI.[1-5] Recently, FHMI has also been shown to be associated with increased risk of venous thromboembolism (VTE).[6-9] However, it is uncertain how FHMI contributes to the increased risk of VTE. The association may potentially be explained by aggregation of common atherosclerotic risk factors, other shared genetic or environmental risk factors for MI and VTE, or mediated through a direct impact of MI on VTE risk in subjects with FHMI.

It has been suggested that atherosclerotic risk factors may partly explain the association between arterial and venous thrombosis found in observational studies.[10-18] However, growing evidence supports the notion that atherosclerotic risk factors including diabetes mellitus, hypertension and dyslipidemia are not associated with VTE.[19-23] Obesity and advancing age were the only shared risk factors for arterial and venous thrombosis in cohort studies investigating the influence of atherosclerotic risk factors on risk of MI and VTE within the same population.[19, 20] The impact of atherosclerotic risk factors on the association between FHMI and risk of VTE remains unsettled. Moreover, to the best of our knowledge, no previous study has considered the effect of FHMI on risk of VTE in the complete absence of MI in a general population. In a cause-specific model, the impact of MI on VTE risk is eliminated, and risks of MI and VTE are estimated in a population with equal distribution of exposure and potential unrecognized confounders.

We aimed to determine the absolute and relative risks of MI and VTE by FHMI in a population-based cohort study, and to explicitly compare the impact of FHMI on risks of MI

and VTE by applying a cause-specific model. Moreover, we aimed to explore whether the association between FHMI and VTE could be explained by atherosclerotic risk factors.

Methods

Study population

Study participants were recruited from the fourth (1994-95) and fifth survey (2001-02) of the Tromsø Study. To these surveys, the entire population (Tromsø 4) or parts (Tromsø 5) of the population aged ≥ 25 years living in the municipality of Tromsø, Norway, were invited to participate. The overall attendance rate was high, 77% in Tromsø 4 and 79% in Tromsø 5, and a total of 27 806 subjects (26 957 subjects from Tromsø 4, and 849 unique subjects from Tromsø 5 that did not participate in Tromsø 4) aged 25-97 years participated in at least one of the surveys. The study population has been described in detail elsewhere.[24] The study was approved by the Regional Committee of Medical and Health Research Ethics North Norway, and all subjects gave their informed written consent to participate. Subjects who did not consent to medical research (n= 222), subjects not officially registered as inhabitants of the municipality Tromsø at baseline (n= 45), subjects with VTE (n= 57) or MI (n= 686) before baseline, and subjects with missing values of body mass index (BMI), systolic or diastolic blood pressure, triglycerides, total cholesterol, high density lipoprotein (HDL), smoking, diabetes mellitus or family history of MI before the age of 60 years (n= 5 394) were excluded. In total, 21 624 subjects were included and followed from the date of enrollment through the end of the study period, December 31, 2010.

Baseline measurements

Baseline information was collected by self-administered questionnaires, blood samples and physical examinations. Questionnaires were used to obtain information on current smoking, physical activity, history of diabetes mellitus or cancer, and family history of MI. To identify family history of MI, 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. Height, weight, blood pressure, and non-fasting serum lipids were measured as previously described.[19] BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Registry of VTE

All first-time VTE events during follow-up were identified by searching the hospital discharge diagnosis registry, the autopsy registry, and the radiology procedure registry of the University Hospital of North Norway as previously described.[25] The medical record for each potential VTE case was reviewed by trained personnel, and a VTE event was verified and recorded when presence of clinical signs and symptoms of deep vein thrombosis (DVT) or pulmonary embolism (PE) were combined with an objective confirmatory radiology procedure (compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan, pulmonary angiography, or autopsy), and resulted in a VTE diagnosis that required treatment.[25] For patients derived from the autopsy registry, a VTE-event was recorded when the autopsy record indicated PE as cause of death or as a significant condition contributing to death.

Verified VTE events were classified as unprovoked or provoked based on the presence of provoking factors at the time of diagnosis. An event was defined as provoked if one or

more of the following factors were present: recent surgery or trauma within the previous 8 weeks before the event, acute medical conditions (acute MI, stroke or major infectious disease), active cancer at the time of the event, marked immobilization (bed rest for > 3 days, wheelchair use, or long-distance travel exceeding 4 hours within the last 14 days) or any other factor described by a physician in the medical record (e.g. intravascular catheter).

Registry of MI

Incident events of MI during follow-up were identified by searching the hospital and out-of hospital medical records, autopsy records and death certificates, as previously described.[19] The national unique 11-digit identification number allowed linkage to national and local diagnosis registries and to the National Causes of Death Registry at Statistics Norway. Medical records were case validated by an independent endpoint committee. Modified WHO MONICA/MORGAM criteria for myocardial infarction were used and these included clinical symptoms and signs, findings in electrocardiograms, values of cardiac biomarkers, and autopsy reports when applicable.

Statistical analyses

In the traditional model, each participant contributed with separate person-years of follow-up from (i) the baseline inclusion date (1994-95 or 2001-02) to the date of a diagnosis of MI, the date the participant died or moved from the municipality of Tromsø, or until the end of the study period (December 31, 2010), and from (ii) the baseline inclusion date to the date of a diagnosis of VTE, the date of death or migration, or until the end of the study period. In the cause-specific model, person-years for each participant were counted from the date of

enrollment to the date of an incident diagnosis of MI or VTE, the date of death or migration, or until the end of the study period, whichever came first. All subjects had at most 1 of the 2 outcomes (i.e. MI or VTE) on the date of first occurrence in the cause-specific model. Subjects who died (n=2 359) or moved from Tromsø (n=3 488) during follow-up were censored at the date of death or migration.

Statistical analyses were performed with STATA version 12.0 (Stata Corporation, College Station, TX). Crude incidence rates (IR) of MI and VTE were calculated and expressed as number of events per 1000 person-years at risk. Cox proportional hazard regression models were used to estimate crude and multivariable adjusted hazard ratios (HR) with 95 % confidence intervals (CI) for MI, unprovoked and provoked VTE, DVT and PE by family history of MI. The multivariable HRs were adjusted for age, sex, BMI, mean systolic and diastolic blood pressure, total cholesterol, HDL, triglycerides, self-reported smoking and diabetes mellitus. Percent change in the adjusted compared with the crude HR was calculated by the formula (100 * (crude HR – adjusted HR) / (crude HR – 1)). Previous studies have reported synergistic interaction between FHMI and lipids on risk of MI.[2-4] Statistical interactions between FHMI and age, sex, BMI, blood pressure, total cholesterol, HDL, triglycerides, smoking or diabetes mellitus for MI and VTE were tested by including cross product terms in the proportional hazards model. In addition, statistical interactions between FHMI and age or sex were tested in analyses with unprovoked DVT as the outcome. The proportional hazard assumption was verified by evaluating the parallelism between the curves of the log-log survivor function. Furthermore, a test of the proportional hazard assumption using Schoenfeld residuals was performed for all the relevant variables.

Attributable risk (AR%), the proportion of events among the exposed subjects that can be explained by the exposure, was calculated from incidence rates of MI, VTE, DVT and PE in the population with (I_e) and the population without a family history of MI (I_0) (100% * (I_e -

I_0) / I_e)). Population attributable risk fraction (PAR%), the proportion of events in the study population attributable to the exposure, was calculated using the incidence rates of MI, VTE, DVT and PE in the general population (I_p) and in the population without a family history of MI (I_0) (100% * (I_p – I_0) / I_p).

Results

We identified 1 311 subjects with a validated diagnosis of incident MI and 428 subjects with an incident VTE event during a median of 15.8 years of follow-up. Characteristics of the study participants at baseline are shown in Table 1. Subjects who were diagnosed with VTE during follow-up were on average younger, had lower blood pressure, total cholesterol and triglyceride levels, higher HDL cholesterol levels, comprised lower proportions of men, smokers and subjects with diabetes mellitus, and a higher proportion of subjects with cancer than those diagnosed with MI (Table 1).

Incidence rates and hazard ratios for MI and VTE among subjects with and without FHMI are displayed in Table 2. Among subjects with FHMI (n=5 194), 510 MI events (IR 7.5 per 1000 person-years) and 147 VTE events (IR 2.1 per 1000 person-years) were identified during follow-up, while there were 801 MI events (IR 3.7 per 1000 person-years) and 281 VTE events (IR 1.3 per 1000 person-years) among subjects without FHMI (n=16 430) (Table 2). Overall, FHMI was associated with a 53% increased risk of MI (adjusted HR 1.53; 95% CI 1.37-1.71) and a 27% increased risk of VTE (adjusted HR 1.27; 95% CI 1.04-1.56) (Table 2). The adjustment for modifiable atherosclerotic risk factors (Table 2, model 2), in addition to age and sex, caused a 17% and 8% risk reduction in the risk estimates for MI and VTE, respectively. Age, BMI and cholesterol had multiplicative effects with FHMI on the risk of MI, whereas no statistical interactions were found with FHMI for VTE or unprovoked DVT.

The risk estimates for DVT (adjusted HR 1.29; 95% CI 1.00-1.68) by FHMI were somewhat higher than the risk estimates for PE (adjusted HR 1.25; 95% CI 0.91-1.72) in stratified analysis (Table 2). Further stratification depending on the presence or absence of provoking factors for VTE revealed that the association between and FHMI and VTE was confined to unprovoked events, in particular unprovoked DVT. FHMI was associated with a 45% higher risk of unprovoked VTE (adjusted HR 1.45; 95% CI 1.07-1.97) and a 63% higher risk of unprovoked DVT (adjusted HR 1.63; 95% CI 1.08-2.46). There was no significant association between FHMI and risk of PE, neither provoked nor unprovoked, in our population.

There were 52 subjects who had both incident MI and incident VTE event during follow-up. In order to eliminate the impact of a direct interaction of MI and VTE on the apparent associations between FHMI and MI/VTE, we conducted survival analysis in a cause-specific model. Incidence rates and hazard ratios for the cause-specific survival analysis of MI and VTE by FHMI, according to type and number of affected first-degree relatives, are shown in Table 3. The risks of VTE by FHMI, and separate entities stratified by location and predisposing factors, were similar in the traditional Cox model and in the cause-specific Cox model (Tables 2 and 3). The risk estimates for unprovoked VTE events were higher than for provoked events. The higher risk estimates for unprovoked events appeared to be driven by a strong association between FHMI and unprovoked DVT. FHMI was associated with a 69% higher risk of unprovoked DVT (adjusted HR 1.69; 95% CI 1.12-2.56) (Table 3). Adjustment for modifiable atherosclerotic risk factors in addition to age and sex did not affect the risk estimate. A family history of ≥ 2 subjects with MI increased the risk of unprovoked DVT (adjusted HR 2.64; 95% CI 1.12-6.24). A parental history of MI was associated with higher risk of VTE than a history of affected siblings.

Subjects with ≥ 1 first-degree relative with a history of MI had 1.5-fold higher risk of MI (adjusted HR 1.52; 95% CI 1.35-1.70). A parental history of MI was associated with a 54% increased risk of MI (adjusted HR 1.54; 95% CI 1.34-1.76), while subjects with a sibling with a history of MI had a 61% increased risk of MI (adjusted HR 1.61; 95% CI 1.39-1.86). A family history of ≥ 2 subjects with MI augmented the risk of MI (adjusted HR 1.85; 95% CI 1.44-2.36). The risk of MI by FHMI was similar in the traditional Cox model and in the cause-specific Cox model (Tables 2 and 3).

In order to explore whether our assumption that loss to follow-up due to death was non-informative, we fit a Fine and Grey proportional subdistribution hazard model to assess the impact of treating death as competing risk on the association between FHMI and MI and VTE. We reached the same conclusion as that when death was treated as censoring (data not shown).

The attributable risk of MI, total VTE, unprovoked VTE and unprovoked DVT due to a family history of MI was 50.1%, 38.0%, 46.5% and 52.6%, respectively. The proportion of events in the study population attributed to FHMI (population attributable risk), however, was 19.4%, 12.7%, 17.2% and 20.6% for MI, total VTE, unprovoked VTE and unprovoked DVT, respectively.

Discussion

In the present study, subjects with a family history of MI had increased risk of both incident myocardial infarction and venous thromboembolism. For VTE, the association with FHMI applied to unprovoked events, and appeared to be primarily related to unprovoked deep vein thrombosis. Modifiable atherosclerotic risk factors slightly altered the risk of MI associated with FHMI, but had a negligible impact on the association between FHMI and VTE. The risk

estimates for MI and VTE by FHMI were not affected by a direct interaction between the two diseases, and increased with increasing number of affected first-degree relatives. The population attributable risks of MI and VTE by FHMI were 19% and 13%, respectively.

The increased risk of incident MI associated with FHMI found in our study is in agreement with the results of observational studies.[1-5] However, our risk estimates for MI obtained from a cohort recruited from a general population were lower than those reported in previous cohort[5] and case-control[1-4] studies in which non-fatal MI cases,[1, 2] hospitalized controls,[1, 3, 4] or registered relatives of MI patients[5] were included. We also confirmed our previous original finding,[6] later supported by two independent observational studies[7, 9] with similar risk estimates for the association between FHMI and VTE, using an extended cohort with longer follow-up.

Modifiable atherosclerotic risk factors including hypertension, dyslipidemia and diabetes mellitus are affected by genetic[26] and life-style[27, 28] factors. In our study, modifiable atherosclerotic risk factors influenced the association between FHMI and MI by weakening the risk estimates in the multivariable adjusted model. Furthermore, FHMI had a synergistic effect with age, BMI and cholesterol on the risk of MI. Environmental factors are therefore likely to contribute to the increased risk of MI associated with FHMI. This is further supported by the high risk of MI found in subjects reporting ≥ 1 siblings with a history of MI, which may be explained by an interaction between shared genes and environmental factors. In contrast, modifiable atherosclerotic risk factors only modestly affected the risk of VTE by FHMI, and no statistical interactions were found between FHMI and one or more atherosclerotic risk factors. Taken together, these findings indicate that atherosclerotic risk factors do not explain the observed association between FHMI and VTE, and are in agreement with the hypothesis that traditional atherosclerotic risk factors such as diabetes mellitus, hypertension, and dyslipidemia do not play an important role in the etiology of VTE.[19-23]

Accordingly, the impact of FHMI on VTE risk has to be mediated through different mechanisms potentially including other shared genetic or environmental risk factors.

The association between FHMI and VTE was mainly attributed to unprovoked VTE events. Furthermore, the risk of VTE increased with increasing number of affected relatives with a history of MI. Thus, there is strong circumstantial evidence that inherited factors contribute to the association between FHMI and VTE. Several genes encoding risk factors for VTE are shown to be related to heart disease, and may potentially explain the increased risk of VTE in subjects with FHMI. In a genome-wide association study,[29] MI was found to be associated with the alleles on the ABO locus encoding the highly prevalent non-O blood groups,[29] which are known to predominantly increase the risk of unprovoked VTE.[30, 31] In addition, common inherited thrombophilic abnormalities such as factor V Leiden and prothrombin G20210A are identified as risk factors for coronary heart disease.[32] Factor V Leiden is shown to be associated with DVT rather than isolated PE,[33] and may explain the high risk of unprovoked DVT found in subjects with FHMI. Furthermore, a combination of the inherited risk factors related to MI could potentially underlie the association between FHMI and VTE, as non-O blood groups and factor V Leiden are found to have an additive effect on the risk of VTE.[30, 31] Finally, unrecognized genetic variants may partly explain the association between FHMI and VTE, which encourage an untargeted approach to reveal novel genetic risk factors common for arterial and venous thrombosis.

It is also possible that the increased risk of VTE found in subjects with FHMI is explained by shared environmental risk factors. In a large registry-based study, spouses of MI patients were shown to have increased risk of VTE.[8] Thus, shared family environment may contribute to the observed association between FHMI and VTE. Concordantly, some environmental psychosocial factors, such as stress at home and at work and stressful life events, have been reported as risk factors for both MI and VTE.[34, 35] This is further supported

by an observed synergistic effect between job strain and family history of coronary heart disease on the risk of MI in women.[2] Shared socioeconomic status and diet could potentially explain the association between FHMI and VTE. Socioeconomic status including household income is found to be inversely associated with coronary heart disease and VTE.[21, 36] Diet, however, is reported to influence the risks of MI and VTE differently.[37, 38]

Numerous observational studies have shown an independent association between arterial and venous thrombotic diseases.[10-18] However, the risk estimates for MI and VTE by FHMI in our study were similar in the traditional Cox model and in the cause-specific Cox model, implying that the associations between FHMI and MI and VTE were not affected by a direct interaction between VTE and MI. From a public health perspective, we found FHMI to be a considerable risk factor for VTE with a predictive value comparable to family history of VTE,[39] explaining 13% of the VTE events in the study population. Thus, FHMI may be used in clinical practice to improve the identification of those at high risk of VTE likely to benefit from targeted preventive interventions.

The main strengths of our study include the prospective design, the large number of participants recruited from a general population and the high attendance rate. Moreover, the cause-specific model eliminates the impact of MI on risk of VTE, and facilitates risk estimation of MI and VTE by FHMI simultaneously in a population with equal distribution of potential unrecognized confounders. Conversely, the study has some limitations. Analyses were restricted to subjects who had provided information on FHMI. Most likely, the majority of subjects with missing information on FHMI (n= 5 038) did not answer this question because they did not have a first-degree relative with a history of MI. When we investigated the extreme scenarios, i.e. performed analyses under the assumptions that all subjects with missing did not have a FHMI, or that all subjects with missing did have a FHMI, the risk estimates for MI and VTE did not change notably, which supports our use of complete case

analyses. Among those who reported FHMI, over- or underreporting is possible, and this may have led to over- or underestimation of the true risk. Underestimation is most likely as a high specificity and a lower sensitivity of self-reported FHMI previously has been demonstrated in a validation study.[40] Furthermore, modifiable atherosclerotic risk factors such as FHMI, smoking, diabetes mellitus, hypertension and hypercholesterolemia may change over time, and residual confounding by these factors cannot be ruled out. Finally, unrecognized confounders may be present, and could potentially explain the observed associations between FHMI and MI and VTE.

In conclusion, subjects with a history of myocardial infarction in a first-degree relative before the age of 60 years had increased risk of both incident myocardial infarction and venous thromboembolism in a cause-specific model. Apparently, the association between FHMI and VTE applied to unprovoked deep vein thrombosis and was not explained by modifiable atherosclerotic risk factors. Moreover, the risk of unprovoked DVT increased with increasing number of affected first-degree relatives with a history of MI. Our findings support the hypothesis that family members share yet unknown genetic or environmental risk factors for VTE.

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Disclosures

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Table 1. Baseline characteristics of participants with subsequent myocardial infarction (MI) or venous thromboembolism (VTE) or no event during follow-up, stratified by family history of MI (n = 21 624). The Tromsø Study, 1994-2010.

	No family history of MI			**Family history of MI**		
	No event	**MI**	**VTE**	**No event**	**MI**	**VTE**
	(n= 15 376)	**(n= 801)**	**(n= 281)**	**(n= 4 561)**	**(n= 510)**	**(n= 147)**
% (n)/ mean ± SD						
Age (years)	42 ± 13	61 ± 13	57 ± 14	46 ± 13	59 ± 12	58 ± 14
Sex (male)	46.2 (7 097)	68.3 (547)	49.1 (138)	43.5 (1 984)	57.5 (293)	44.9 (66)
BMI (kg/m^2)	24.8 ± 3.7	26.6 ± 4.1	26.6 ± 4.6	26.4 ± 3.6	26.5 ± 3.7	26.9 ± 4.0
Systolic BP (mmHg)	131 ± 18	150 ± 24	142 ± 23	134 ± 19	151 ± 23	144 ± 24
Diastolic BP (mmHg)	76 ± 11	86 ± 14	82 ± 14	79 ± 12	86 ± 13	82 ± 13
Total cholesterol (mmol/L)	5.78 ± 1.23	6.83 ± 1.24	6.50 ± 1.34	6.20 ± 1.28	6.90 ± 1.21	6.68 ± 1.17
HDL (mmol/L)	1.51 ± 0.41	1.39 ± 0.38	1.54 ± 0.44	1.50 ± 0.40	1.40 ± 0.40	1.46 ± 0.40
Triglycerides (mmol/L)	1.45 ± 0.96	1.95 ± 1.19	1.62 ± 0.86	1.58 ± 1.03	1.96 ± 1.16	1.76 ± 1.05
Diabetes mellitus*	0.9 (137)	4.7 (38)	2.5 (7)	1.5 (69)	6.3 (32)	2.0 (3)
Cancer*	2.4 (370)	5.2 (42)	7.5 (21)	3.0 (137)	4.1 (21)	9.5 (14)

Smoking*†	34.8 (5 350)	43.1 (345)	32.4 (91)	39.8 (1 815)	42.2 (215)	38.8 (57)
Physical activity*‡	34.8 (5 356)	21.5 (172)	22.4 (63)	28.9 (1 319)	22.5 (115)	18.4 (27)

* Self-reported.

†Daily smoking of cigarettes, cigars or pipe, yes/no.

‡ > 1 hour of hard physical activity per week, yes/no.

Table 2. Incidence rates (IR) and hazard ratios (HR) with 95 % confidence interval (CI) for myocardial infarction (MI), provoked and unprovoked venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE) by family history of MI (FHMI) before the age of 60 years. The Tromsø Study, 1994-2010.

	Person-years	**Events**	**Crude IR (95 % CI)***	**Crude HR (95 % CI)**	**HR (95 % CI)†**	**HR (95 % CI)‡**
MI						
No FHMI	215 730	801	3.71 (3.46-3.98)	Ref.	Ref.	Ref.
FHMI	67 726	510	7.53 (6.90-8.21)	2.03 (1.82-2.27)	1.70 (1.52-1.90)	1.53 (1.37-1.71)
VTE						
All						
No FHMI	217 636	281	1.29 (1.15-1.45)	Ref.	Ref.	Ref.
FHMI	69 355	147	2.12 (1.80-2.49)	1.64 (1.35-2.01)	1.32 (1.08-1.62)	1.27 (1.04-1.56)
Unprovoked						
No FHMI	216 231	117	0.54 (0.45-0.65)	Ref.	Ref.	Ref.
FHMI	68 652	68	0.99 (0.78-1.26)	1.83 (1.36-2.47)	1.47 (1.09-1.99)	1.45 (1.07-1.97)

Provoked						
No FHMI	216 533	164	0.76 (0.65-0.88)	Ref.	Ref.	Ref.
FHMI	68 740	79	1.15 (0.92-1.43)	1.52 (1.16-1.99)	1.22 (0.93-1.60)	1.16 (0.88-1.52)
DVT						
All						
No FHMI	216 515	168	0.8 (0.67-0.90)	Ref.	Ref.	Ref.
FHMI	68 743	88	1.28 (1.04-1.58)	1.65 (1.28-2.14)	1.33 (1.03-1.72)	1.29 (1.00-1.68)
Unprovoked						
No FHMI	215 616	59	0.27 (0.21-0.35)	Ref.	Ref.	Ref.
FHMI	68 334	38	0.56 (0.40-0.76)	2.03 (1.35-3.05)	1.63 (1.08-2.46)	1.63 (1.08-2.46)
Provoked						
No FHMI	216 027	109	0.50 (0.42-0.61)	Ref.	Ref.	Ref.
FHMI	68 446	50	0.73 (0.55-0.96)	1.45 (1.04-2.02)	1.17 (0.83-1.64)	1.12 (0.80-1.57)
PE						
All						
No FHMI	216 249	113	0.52 (0.43-0.63)	Ref.	Ref.	Ref.

FHMI	68 648	59	0.86 (0.67-1.11)	1.65 (1.20-2.26)	1.32 (0.96-1.81)	1.25 (0.91-1.72)
Unprovoked						
No FHMI	215 743	58	0.27 (0.21-0.35)	Ref.	Ref.	Ref.
FHMI	68 354	30	0.44 (0.31-0.63)	1.63 (1.05-2.53)	1.31 (0.84-2.05)	1.28 (0.82-2.00)
Provoked						
No FHMI	215 634	55	0.26 (0.20-0.33)	Ref.	Ref.	Ref.
FHMI	68 330	29	0.42 (0.19-0.61)	1.67 (1.06-2.62)	1.33 (0.84-2.09)	1.23 (0.78-1.94)

* Per 1000 person-years.

† Adjusted for age and sex.

‡ Adjusted for age, sex, BMI, mean systolic blood pressure, mean diastolic blood pressure, cholesterol, HDL, triglycerides, diabetes mellitus and smoking.

Table 3. Incidence rates (IR) and hazard ratios (HR) with 95 % confidence interval (CI) for the cause-specific risk of myocardial infarction (MI), provoked and unprovoked venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE) by family history of MI (FHMI) according to number and type of affected first degree relatives. The Tromsø Study, 1994-2010.

	Person-years	**Events**	**Crude IR (95 % CI)***	**Crude HR (95 % CI)**	**HR (95 % CI)†**	**HR (95 % CI)‡**
MI						
No FHMI	214 565	768	3.58 (3.33-3.84)	Ref.	Ref.	Ref.
≥ 1 relative	67 157	482	7.18 (6.56-7.85)	2.01 (1.79-2.25)	1.69 (1.50-1.89)	1.52 (1.35-1.70)
≥ 2 relatives	4 848	72	14.85 (11.79-18.71)	4.19 (3.29-5.33)	2.39 (1.87-3.05)	1.85 (1.44-2.36)
Parent	54 791	300	5.48 (4.89-6.13)	1.53 (1.34-1.75)	1.74 (1.52-1.99)	1.54 (1.34-1.76)
Sibling	16 948	250	14.75 (13.03-16.70)	4.16 (3.61-4.80)	1.81 (1.56-2.10)	1.61 (1.39-1.86)
VTE						
All						
No FHMI	214 565	267	1.24 (1.10-1.40)	Ref.	Ref.	Ref.
≥ 1 relative	67 157	134	2.00 (1.68-2.36)	1.61 (1.31-1.98)	1.30 (1.06-1.60)	1.26 (1.02-1.55)
≥ 2 relatives	4 848	14	2.89 (1.71-4.88)	2.37 (1.38-4.05)	1.36 (0.79-2.34)	1.32 (0.76-2.27)
Parent	54 791	94	1.72 (1.40-2.10)	1.38 (1.09-1.74)	1.43 (1.13-1.81)	1.36 (1.07-1.73)
Sibling	16 948	53	3.13 (2.39-4.09)	2.57 (1.91-3.45)	1.15 (0.85-1.56)	1.12 (0.83-1.52)
Unprovoked						
No FHMI	213 275	114	0.53 (0.44-0.64)	Ref.	Ref.	Ref.
≥ 1 relative	66 552	66	0.99 (0.78-1.26)	1.86 (1.38-2.52)	1.51 (1.12-2.05)	1.49 (1.09-2.02)
≥ 2 relatives	4 795	8	1.67 (0.83-3.34)	3.20 (1.56-6.55)	1.79 (0.87-3.69)	1.86 (0.90-3.86)
Parent	54 384	49	0.90 (0.68-1.19)	1.68 (1.20-2.35)	1.73 (1.24-2.42)	1.68 (1.20-2.36)
Sibling	16 698	25	1.50 (1.01-2.22)	2.88 (1.86-4.43)	1.29 (0.82-2.01)	1.30 (0.83-2.04)
Provoked						
No FHMI	213 500	153	0.72 (0.61-0.84)	Ref.	Ref.	Ref.
≥ 1 relative	66 569	68	1.02 (0.81-1.30)	1.43 (1.08-1.91)	1.15 (1.86-1.53)	1.10 (0.82-1.47)
≥ 2 relatives	4 779	6	1.26 (0.56-2.79)	1.78 (0.79-4.02)	1.03 (0.46-2.34)	0.95 (0.42-2.15)
Parent	54 333	45	0.83 (0.62-1.11)	1.16 (0.83-1.61)	1.21 (0.87-1.69)	1.13 (0.81-1.59)

Sibling	16 749	28	1.67 (1.15-2.42)	2.38 (1.59-3.55)	1.05 (0.69-1.59)	1.01 (0.66-1.52)
DVT						
All						
No FHMI	213 518	161	0.75 (0.65-0.88)	Ref.	Ref.	Ref.
≥ 1 relative	66 631	84	1.26 (1.02-1.56)	1.68 (1.29-2.18)	1.35 (1.04-1.77)	1.32 (1.01-1.73)
≥ 2 relatives	4 809	10	2.08 (1.12-3.86)	2.78 (1.47-5.27)	1.61 (0.85-3.06)	1.52 (0.80-2.90)
Parent	54 401	58	1.07 (0.82-1.38)	1.41 (1.05-1.91)	1.46 (1.08-1.98)	1.41 (1.04-1.91)
Sibling	16 773	35	2.09 (1.50-2.91)	2.80 (1.94-4.03)	1.26 (0.87-1.85)	1.23 (0.84-1.79)
Unprovoked						
No FHMI	212 684	58	0.27 (0.21-0.35)	Ref.	Ref.	Ref.
≥ 1 relative	66 262	38	0.57 (0.42-0.79)	2.11 (1.40-3.17)	1.70 (1.13-2.57)	1.69 (1.12-2.56)
≥ 2 relatives	4 777	6	1.26 (0.56-2.80)	4.64 (2.00-10.76)	2.53 (1.08-5.91)	2.64 (1.12-6.24)
Parent	54 145	27	0.50 (0.34-0.73)	1.83 (1.16-2.89)	1.88 (1.19-2.96)	1.83 (1.16-2.91)
Sibling	16 630	17	1.02 (0.64-1.64)	3.78 (2.20-6.50)	1.67 (0.95-2.93)	1.68 (0.96-2.96)
Provoked						
No FHMI	213 044	103	0.48 (0.40-0.59)	Ref.	Ref.	Ref.
≥ 1 relative	66 334	46	0.69 (0.52-0.93)	1.44 (1.02-2.03)	1.16 (0.82-1.65)	1.12 (0.79-1.60)
≥ 2 relatives	4 758	4	0.84 (0.32-2.24)	1.75 (0.65-4.76)	1.05 (0.38-2.85)	0.93 (0.34-2.55)
Parent	54 183	31	0.57 (0.40-0.81)	1.18 (0.79-1.77)	1.23 (0.82-1.84)	1.17 (0.78-1.75)
Sibling	16 643	18	1.08 (0.68-1.72)	2.26 (1.37-3.73)	1.03 (0.62-1.73)	0.99 (0.59-1.66)
PE						
All						
No FHMI	213 256	106	0.50 (0.41-0.60)	Ref.	Ref.	Ref.
≥ 1 relative	66 490	50	0.75 (0.57-0.99)	1.52 (1.09-2.13)	1.23 (0.87-1.72)	1.17 (0.83-1.64)
≥ 2 relatives	4 765	4	0.84 (0.32-2.24)	1.75 (0.64-4.75)	0.98 (0.36-2.67)	0.97 (0.36-2.67)
Parent	54 316	36	0.66 (0.48-0.92)	1.33 (0.91-1.94)	1.39 (0.95-2.04)	1.30 (0.89-1.91)
Sibling	16 675	18	1.08 (0.68-1.71)	2.26 (1.37-3.72)	0.98 (0.59-1.64)	0.96 (0.57-1.61)
Unprovoked						
No FHMI	212 800	56	0.26 (0.20-0.34)	Ref.	Ref.	Ref.
≥ 1 relative	66 255	28	0.42 (0.29-0.61)	1.61 (1.03-2.54)	1.32 (0.84-2.08)	1.28 (0.81-2.02)
≥ 2 relatives	4 744	2	0.42 (0.11-1.69)	1.67 (0.41-6.84)	0.96 (0.23-3.94)	1.00 (0.24-4.14)
Parent	54 165	22	0.41 (0.27-0.62)	1.54 (0.94-2.52)	1.59 (0.97-2.60)	1.53 (0.93-2.51)

Sibling	16 568	8	0.48 (0.24-0.97)	1.92 (0.91-2.03)	0.87 (0.40-1.85)	0.88 (0.41-1.89)
Provoked						
No FHMI	212 665	50	0.24 (0.18-0.31)	Ref.	Ref.	Ref.
≥ 1 relative	66 200	22	0.33 (0.22-0.50)	1.43 (0.86-2.36)	1.13 (0.68-1.87)	1.05 (0.63-1.75)
≥ 2 relatives	4 748	2	0.42 (0.11-0.17)	1.84 (0.45-7.57)	1.00 (0.24-4.14)	0.94 (0.23-3.93)
Parent	54 077	14	0.26 (0.15-0.44)	1.10 (0.61-2.00)	1.18 (0.65-2.14)	1.07 (0.59-1.94)
Sibling	16 606	10	0.60 (0.32-1.12)	2.65 (1.34-5.22)	1.10 (0.55-2.20)	1.04 (0.51-2.09)

* Per 1000 person-years.

† Adjusted for age and sex.

‡ Adjusted for age, sex, BMI, mean systolic blood pressure, mean diastolic blood pressure, cholesterol, HDL, triglycerides, diabetes mellitus and smoking.