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ORIGINAL ARTICLE

Myocardial infarction, prothrombotic genotypes, and venous thrombosis risk: The Tromsø Study

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Abstract

Background: The risk of venous thromboembolism (VTE) is increased after a myocardial infarction (MI). Some prothrombotic genotypes associated with VTE have also been associated with risk of MI. Whether prothrombotic single-nucleotide polymorphisms (SNPs) further increase the risk of VTE in MI patients is scarcely investigated.

Aim: To study the combined effect of MI and prothrombotic SNPs on the risk of VTE.

Methods: Cases with incident VTE (n = 641) and a randomly sampled subcohort weighted for age (n = 1761) were identified from the 4 to 6 surveys of the Tromsø Study (1994-2012). DNA was genotyped for rs8176719 (*ABO*), rs6025 (*F5*), rs1799963 (*F2*), rs2066865 (*FGG*), and rs2036914 (*F11*). Hazard ratios (HRs) for VTE with 95% confidence intervals (CIs) were estimated by categories of risk alleles and MI status.

Results: Patients with MI had a 1.4-fold increased risk of VTE, and adjustments for the 5 SNPs, either alone or in combination, did not affect this relationship (adjusted HR, 1.52; 95% CI, 1.12-2.07). In subjects without MI, an increased risk of VTE was observed for each of the individual SNPs (≥1 vs. 0 risk alleles), and the risk increased linearly with increasing number of risk alleles in the 5-SNP score. The combination of MI and prothrombotic genotypes, either as individual SNPs or in the 5-SNP score, did not result in an excess risk of VTE.

Conclusion: The relationship between MI and VTE was not explained by these 5 prothrombotic genotypes. Prothrombotic genotypes did not yield an excess risk of VTE in patients with MI.

KEYWORDS

epidemiology, genetics, myocardial infarction, pulmonary embolism, risk factors, thromboembolism, venous

Essentials

- The risk of venous thromboembolism (VTE) is increased after myocardial infarction (MI).
- Whether this association is explained by common prothrombotic genotypes is scarcely investigated.
- We investigated the combined impact of MI and prothrombotic genotypes on risk of VTE.
- In patients with MI, prothrombotic genotypes did not yield excess risk of VTE.

1 | INTRODUCTION

Several studies have indicated that patients with myocardial infarction (MI) have increased risk of subsequent venous thromboembolism (VTE).[1–3] The risk is highest during the first months after an MI[2,3] and appears to be particularly pronounced for pulmonary embolism (PE).

VTE is a multicausal disease encompassing both genetic and environmental risk factors, and a number of prothrombotic genotypes have been linked with VTE risk.[4] In a prediction study, de Haan and coworkers[5] investigated whether a set of 31 known VTE-associated single-nucleotide polymorphisms (SNPs) could be used to identify subjects with high risk of VTE. SNPs with the highest odds ratios in the literature were added one by one to build a risk score, ultimately using the most parsimonious model. A 5-SNP score, which consisted of rs8176719 (*ABO*), rs6025 (*F5*, factor V Leiden [FVL]), rs1799963 (*F2*, prothrombin G20210A), rs2066865 (*FGG*), and rs2036914 (*F11*), predicted VTE with an area under the receiver operating characteristic curve of 0.69.

The mechanism for the relationship between MI and VTE is not well understood. However, growing evidence indicates that atherosclerotic risk factors[6,7] and subclinical atherosclerosis[8–11] are not associated with VTE, and therefore cannot serve as common risk factors for the 2 conditions. It has been reported that certain SNPs associated with VTE risk also predisposes to acute MI.[5,12–15] Additionally, family history of MI has been demonstrated to be a risk factor for VTE in several studies,[16–18] and this risk is not explained by intermediate development of MI.[19] Whether the relationship between MI and VTE can be explained by common prothrombotic genotypes has not been well addressed. Therefore, the aim of this study was to investigate the combined effect of MI and the SNPs included in the 5-SNP risk score on VTE risk in a population-based case cohort.

2 | MATERIALS AND METHODS

2.1 | Study population

As described elsewhere,[20] the Tromsø Study is a unique Norwegian follow-up study with consecutive health surveys of the inhabitants of Tromsø. For the fourth survey (1994-1995), all inhabitants of the municipality of Tromsø aged >24 years of age were invited to participate. The overall attendance rate was high (77%) and 27 158 individuals participated. Repeated surveys were conducted in 2001-2002 and 2007-2008, with attendance rates of 78% and 66%, respectively. In total, 30 586 unique participants aged 25 to 97 years partook in ≥1 of the surveys, and of these, 30 361 consented to contribute to medical research.

From the date of inclusion in 1 of the 3 surveys until the follow-up ended (December 31, 2012), all incident VTE events were identified by performing an extensive search in the registries (diagnosis registry, autopsy registry, and radiology registry) at the University Hospital of North Norway (UNN). The UNN is the only hospital in the region, and all hospital care and relevant diagnostic radiological procedures is provided exclusively by this hospital. Each VTE was adjudicated and recorded after extensive review of medical records, as previously described.[21] The adjudication criteria for VTE were presence of signs and symptoms of deep vein thrombosis (DVT) or PE combined with objective confirmation by radiological procedures, which resulted in treatment initiation (unless contraindications were specified). A VTE was classified as either a DVT or PE, and if DVT and PE occurred concurrently, the VTE was classified as a PE.

During follow-up, 737 incident VTE events occurred. Subjects for whom blood samples were not available or of insufficient quality for DNA analysis were excluded (n = 45). The remaining 692 subjects were included as cases, and a subcohort (n = 2016) was created by randomly sampling participants from the source cohort weighted for the age distribution of the cases in 5-year age groups. As a consequence of the case-cohort design, 71 cases were also sampled to, and included in, the subcohort. Participants with MI before the enrollment date of the study were excluded (n = 135). Further, participants with at least 1 missing value for the risk allele variants were also excluded from the study (n = 171). Our final case cohort therefore comprised a total of 2402 subjects, consisting of 641 VTE cases and 1761 subjects in the subcohort (Figure 1). The regional committee for medical and health research ethics in Northern Norway approved the study. All participants provided informed written consent to participate.

2.2 | Baseline measurements

Baseline information was collected by questionnaires, physical examination, and blood samples. Nonfasting blood samples were collected from an antecubital vein, and citrated plasma and DNA were stored at −70°C in biobanks.

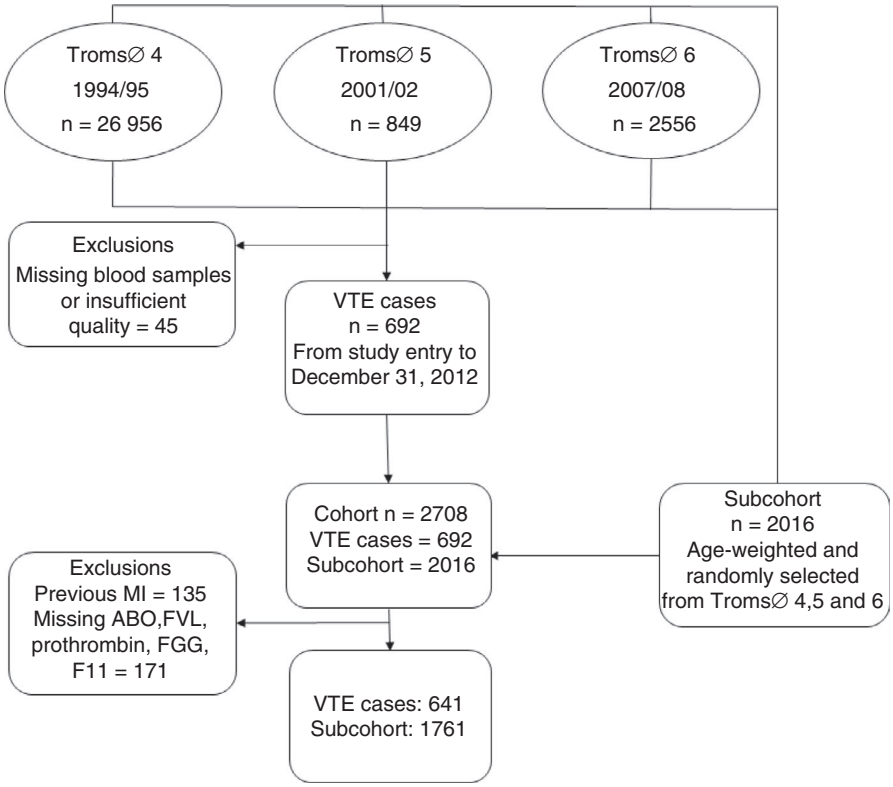

FIGURE 1 Flowchart illustrating the composition of the case-cohort study. FVL, factor V Leiden; VTE, venous thromboembolism

Hypertension was defined as mean systolic blood pressure ≥140 mm Hg or mean diastolic blood pressure ≥90 mm Hg or current use of antihypertensives. Hypercholesterolemia was defined as total cholesterol ≥6.5 mmol/L. From the self-administered questionnaires, baseline data on diabetes mellitus, cardiovascular disease (myocardial infarction, angina, or stroke), smoking (never/former/current), physical activity habits, and education level was obtained. Education level was categorized into basic schooling (7-10 years), high school/vocational school, and college/university. Further information about the baseline variables in the Tromsø Study can be found elsewhere.[20]

2.3 | Assessment of myocardial infarction

Identification of MI patients was performed searching hospital medical records and out-of-hospital medical records, autopsy records, and death certificates. The national 11-digit identification number facilitated linkage to local and national diagnosis registries. Possible cases of MI were identified by searching the hospital discharge registry at the UNN using relevant International Classification of Diseases codes, as previously described.[3] The medical records were reviewed, and all possible events were validated by an independent end-point committee. MONICA/MORGAM criteria were used to adjudicate MI cases, and these included clinical signs and symptoms of ischemic cardiac disease, findings on electrocardiograms, and elevated cardiac biomarkers. The autopsy record was used when applicable.

2.4 | Prothrombotic genotypes

We genotyped the SNPs rs8176719 in *ABO* (ABO blood group), rs6025 in *F5* (FVL), rs1799963 in *F2* (prothrombin G20210A), and rs2036914 in *F11* using the Sequenom platform, and rs2066865 in *FGG* using the TaqMan platform, as previously described.[22] For Sequenom, samples were genotyped using the Sequenom iPlex Gold Assay according to the recommended protocol, using an initial input of 10 to 20 ng DNA, and were analyzed using the MassARRAY Analyzer 4 (Agena Bioscience, San Diego, CA, USA). For TaqMan, an initial input of 100 ng of DNA was used, and samples were genotyped using the 7900HT (Applied Biosystems, Foster City, CA, USA) according to the recommended protocol.

Subjects were categorized as carriers of the prothrombotic risk gene when ≥1 risk allele was present. For rs2036914, the minor allele was associated with lower risk of VTE, and therefore we considered the major allele as the risk allele. Based on the paper by de Haan et al,[5] we composed a 5-SNP score by summarizing the number of risk alleles from the 5 sequenced SNPs. These were further categorized into 0 to 1, 2, 3, and ≥4 risk alleles.

2.5 | Statistical analysis

Statistical analysis was carried out using the STATA software version 15.0 (StataCorp, College Station, TX, USA). Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for VTE by MI status, adjusted for each of

the prothrombotic genotypes individually and in a multivariable model. Further, we estimated HRs for combinations of MI and the individual SNPs. Participants without MI and with no risk alleles was used as the reference group. Moreover, we estimated HRs according to combinations of MI and categories of the 5-SNP score, using those without MI and 0 to 1 risk alleles as the reference group. Age was used as time scale in the Cox model, and MI was included as a time-dependent covariate in the Cox model. Thus, those who developed MI during follow-up contributed with both unexposed and exposed person-time (ie, unexposed person-time from baseline to the date of MI, and thereafter with exposed person-time from MI to the end of follow-up). All analyses were adjusted sex. The proportional hazards assumption was tested using Schoenfeld residuals and found not violated.

3 | RESULTS

Baseline characteristics of the study participants are shown in Table 1. In our cohort, 274 subjects experienced an incident MI during the median of 15.7 years of follow-up. On average, those who developed MI were older and had higher values of cardiometabolic risk factors, including total cholesterol, triglycerides, and body mass index than those who did not experience an MI. The proportion of men, smokers, and subjects with hypertension, hypercholesterolemia, and diabetes mellitus was higher in those with MI than in those without MI. The proportion of participants with ≥1 risk allele(s) for the SNPs investigated were essentially similar between the groups (Table 1).

Table 2 shows features of the VTE events in participants with and without MI in our study. In total, 47 of the 641 VTE events occurred in subjects with MI. The proportion of PEs was higher among subjects suffering from MI than among subjects who did not experience an MI (55% and 42%, respectively). The proportion of provoked events was higher in the MI group than in the non-MI group (62% and 53%, respectively).

Subjects with MI had an overall 1.4-fold higher risk of developing VTE (HR, 1.44; 95% CI, 1.07-1.96) compared to subjects without MI. Further adjustments for each of the prothrombotic SNPs did not alter the risk estimates (data not shown), and the HR for MI in the model that included all 5 SNPs was 1.52 (1.12-2.07).

The risk estimates for VTE by categories of the individual SNPs and MI status are shown in Table 3. In subjects with non-O

TABLE 1 Baseline characteristics of the study population with and without MI (n = 2402): The Tromsø study

	No MI (n = 2128)	MI (n = 274)
Age, y	57 ± 14	67 ± 10
Sex, male	41.9 (892)	54.0 (148)
Body mass index, kg/m^2	25.9 ± 4.2	26.7 ± 4.4
Total cholesterol, mmol/L	6.49 ± 1.31	7.17 ± 1.23
High-density lipoprotein, mmol/L	1.55 ± 0.42	1.47 ± 0.43
Triglycerides, mmol/L	1.60 ± 0.97	1.94 ± 1.08
Systolic blood pressure, mm Hg	142 ± 23	154 ± 23
Diastolic blood pressure, mm Hg	82 ± 13	87 ± 14
Hypertension[a]	52.0 (1107)	74.8 (205)
Hypercholesterolemia[b]	48.0 (1021)	71.5 (196)
Smoking[c]	33.7 (716)	38.1 (104)
Physical activity[d]	23.0 (484)	14.8 (40)
Education[e]	23.6 (503)	8.76 (24)
Self-reported diabetes mellitus	2.79 (59)	6.23 (17)
rs8176719 (*ABO*), ≥1 risk allele[f]	63.3 (1347)	65.3 (179)
rs6025 (*F5*), ≥1 risk allele[f]	9.1 (194)	5.1 (14)
rs1799963 (*F2*), ≥1 risk allele[f]	1.6 (35)	0.4 (1)
rs2066865 (*FGG*), ≥1 risk allele[f]	45.4 (966)	43.8 (120)
rs2036914 (*F11*), ≥1 risk allele[f]	81.6 (1736)	80.3 (220)

Note: Values are % (n) or mean ± standard deviation.

[a]Mean systolic/diastolic blood pressure ≥140/≥90 mm Hg or current use of antihypertensives.

[b]Total cholesterol ≥6.5.

[c]Self-reported daily smoking, yes/no.

[d]≥1 hour of moderate or hard physical activity per week, yes/no.

[e]>10 years of education.

[f]Percentage of participants with ≥1 risk allele(s).

TABLE 2 Baseline characteristics of VTE events (n = 641): The Tromsø Study

	No MI (n = 594)	MI (n = 47)
Clinical characteristics, % (n)		
DVT	58.1 (345)	44.7 (21)
PE	41.9 (249)	55.3 (26)
Provoked	52.7 (313)	61.7 (29)
Unprovoked	47.3 (281)	38.3 (18)
Clinical risk factors, % (n)		
Estrogen[a,b]	12.2 (36)	3.85 (1)
Pregnancy/ puerperium[a]	1.9 (5)	–
Heredity[c]	3.71 (22)	–
Provoking factors, % (n)		
Surgery	14.8 (88)	21.3 (10)
Trauma	7.9 (47)	6.4 (3)
Cancer	23.4 (139)	27.7 (13)
Immobility[d]	21.0 (125)	21.3 (10)
Other[e]	5.1 (30)	4.3 (2)

[a]Only women included in the analysis.

[b]Current or previous use of hormone replacement therapy or oral contraceptives.

[c]Venous thromboembolism in a first-degree relative before 60 y of age.

[d]Bed rest >3 d; journeys of >4 h by car, boat, train, or air within the past 14 d; or other types of immobilization.

[e]Other provoking factor described by a physician in the medical record (eg, intravascular catheter).

TABLE 3 HRs with 95% CIs for VTE by combined categories of MI and prothrombotic genotypes: The Tromsø Study

	Risk alleles	Events	HR (95% CI)[a]
rs8176719 (*ABO*)			
No MI	0	181	Reference
	≥1	413	1.44 (1.21-1.72)
MI	0	23	2.38 (1.54-3.69)
	≥1	24	1.48 (0.97-2.29)
rs6025 (*F5*)			
No MI	0	499	Reference
	≥1	95	2.20 (1.76-2.73)
MI	0	45	1.54 (1.13-2.11)
	≥1	2	2.46 (0.61-9.91)
rs1799963 (*F2*)			
No MI	0	579	Reference
	≥1	15	1.64 (0.98-2.73)
MI	0	47	1.46 (1.10-2.00)
	≥1	0	–
rs2066865 (*FGG*)			
No MI	0	320	Reference
	≥1	274	1.06 (0.90-1.25)
MI	0	30	1.59 (1.08-2.32)
	≥1	17	1.34 (0.82-2.19)
rs2036914 (*F11*)			
No MI	0	106	Reference
	≥1	488	1.05 (0.85-1.30)
MI	0	8	1.21 (0.59-2.48)
	≥1	39	1.58 (1.10-2.30)
De Haan score			
No MI	0-1	87	Reference
	2	157	1.18 (1.00-1.54)
	3	185	1.47 (1.14-1.90)
	≥4	165	1.78 (1.37-2.31)
MI	0-1	14	2.19 (1.24-3.87)
	2	13	1.60 (0.89-2.87)
	3	10	1.68 (0.87-3.24)
	≥4	10	2.70 (1.40-5.21)

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; VTE, venous thromboembolism.

[a]Adjusted for age (as time scale) and sex.

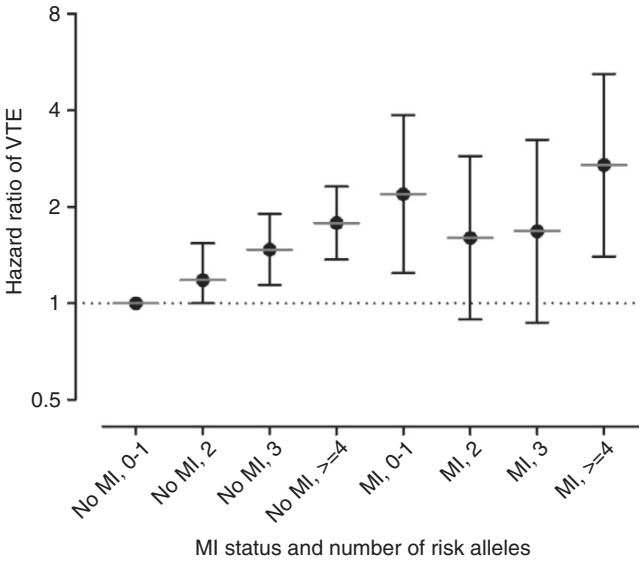

FIGURE 2 In individuals without MI, the risk of VTE increased linearly with increasing number of risk alleles in the 5-SNP score. In contrast, there was no association between increasing number of risk alleles and risk of VTE in MI patients. MI, myocardial infarction; SNP, single-nucleotide polymorphism; VTE, venous thromboembolism

blood type and no MI, the risk of VTE was 1.4-fold increased (HR, 1.44; 95% CI, 1.21-1.72) compared to subjects with blood type O without MI (reference category). In subjects with blood type O and MI, the risk was 2.4-fold higher (HR, 2.38; 95% CI, 1.54-3.69) than the reference category. However, the combination of non-O blood type and MI yielded a 1.5-fold increase (HR, 1.48; 95% CI, 0.97-2.29) in VTE risk compared to the reference category. In subjects without MI, FVL was associated with a 2-fold increased risk (HR, 2.20; 95% CI, 1.76-2.73) of VTE. Subjects with MI without FVL had a 1.5-fold increased risk (HR, 1.54; 95% CI, 1.13-2.11) of VTE, and MI patients with ≥1 risk alleles of FVL had a 2.5-fold higher (HR, 2.46; 95% CI, 0.61-9.91) risk of VTE than subjects without FVL and no MI. There was no association between *FGG* SNP and VTE risk in participants either with or without MI. In subjects without MI, the prothrombin mutation was associated with a 1.6-fold increased risk of VTE (HR, 1.64; 95% CI, 0.98-2.73). Due to lack of cases with MI and the prothrombin mutation, no combined effect could be calculated. In subjects without MI, there was no association between *F11* SNP and risk of VTE (HR, 1.05; 95% CI, 0.85-1.30). Subjects with MI and no risk alleles at *F11* had a HR for VTE of 1.21 (95% CI, 0.59-2.48), whereas MI patients with ≥1 allele had a 1.6-fold increased risk of VTE (HR, 1.58; 95% CI, 1.10-2.30).

In subjects without MI, the risk of VTE increased linearly across increasing categories of risk alleles of the 5-SNP score. In those with 2, 3 and ≥4 risk alleles, the risk was 1.2-fold (HR, 1.18; 95% CI, 1.00-1.54), 1.5-fold (HR, 1.47; 95% CI, 1.14-1.90) and 1.8-fold (HR, 1.78; 95% CI, 1.37-2.31) increased compared to subjects with 0 to 1 risk alleles. In patients with MI, there was no increased risk across categories of the 5-SNP score (Table 3 and Figure 2).

In subgroup analysis, we found that MI patients with ≥1 risk allele at *F11* had 1.8-fold higher risk of PE (HR, 1.79; 95% CI, 1.05-3.05). Otherwise, subgroup analysis on the association between the other SNPs studied and MI in relation to the risk of DVT and PE (Table S1), as well as provoked and unprovoked VTE, (Table S2) showed essentially similar results as those for overall VTE.

4 | DISCUSSION

We investigated the role of 5 prothrombotic genotypes as potential common risk factors for MI and VTE. Subjects with MI had increased risk of VTE, but adjustment for the 5 prothrombotic SNPs, either individually or as a score, did not influence this relationship. In individuals without MI, the risk of VTE increased with increasing number of risk alleles in the 5-SNP score. In contrast, there was no association between increasing number of risk alleles and risk of VTE in MI patients. Our findings suggest that the increased risk of VTE in patients with MI cannot be explained by these 5 prothrombotic genotypes.

Several studies,[1,2] including a former report from the Tromsø Study,[3] have shown that MI patients are at increased risk of VTE, particularly the initial months after the MI. Several lines of evidence support that this relationship is not explained by common atherosclerotic risk factors or subclinical atherosclerosis. A large meta-analysis of 9 population-based cohorts, including more than 240 000 individuals, showed no association between traditional atherosclerotic risk factors and VTE.[7] In the Tromsø Study, the risk of VTE after MI remained after adjustment for atherosclerotic risk factors.[3] Moreover, previous cohorts,[11] including the Tromsø Study,[8,9] consistently showed that subclinical atherosclerosis was not associated with VTE.

Non-O blood group, FVL, prothrombin G20210A, and SNPs in *FGG* and *F11* are recognized risk factors for VTE,[23–25] and some of these SNPs have also been associated with coronary artery disease.[13,14,26,27] For instance, non-O blood group is associated with a modestly increased risk of coronary heart disease,[28,29] and 2 meta-analyses[14,30] concluded that the FVL and prothrombin G20210A variants have weak or moderate associations with MI risk. Moreover, in a case-control study comprising only men, Doggen et al[31] reported a higher risk of MI in individuals with factor XI levels in the highest versus lowest quintile. In our study, rs2036914 in *F11* was the only SNP that showed an association with VTE in MI patients. However, the risk allele in the *F11* SNP was the most frequent allele (ie, major allele), and adjustment for this allele did not influence the association between MI and VTE, indicating that the aforementioned SNP could not explain the increased risk of VTE after MI. Indeed, all our adjustment models indicated that the presence of these 5 prothrombotic genotypes, either evaluated as individual SNPs or combined in a genetic risk score, could not explain the higher VTE risk observed in patients with MI compared to the general population.

The increased risk of VTE after MI could be explained by mechanisms other than shared risk factors such as obesity and advancing age.[32] Indeed, the short-term nature of the increased VTE risk reported in several studies points toward mechanisms related to the MI itself or subsequent complications after the MI.[1–3] Potential mechanisms may be venous stasis because of heart failure or disturbances in the electromechanical function of the heart (eg, atrial fibrillation),[33] or release of procoagulant extracellular vesicles following hypoxia and myocardial damage.[34] Furthermore, the short-term risk of provoked VTE after MI[3] infers that complications related to the MI may be important contributors. Concomitant presence of transient risk factors such as infection, immobilization, or cardiac surgery following an acute MI could give rise to a short period with particularly high thrombosis risk.[35–37] Our finding of no combined effect of prothrombotic SNPs and MI on VTE risk, indicates that the pathogenesis of VTE in subjects with MI probably involves mechanisms related to pathways other than those that lead to a hypercoagulable state in the presence of prothrombotic genotypes.

Developing a risk assessment model to distinguish MI patients with high and low risk of VTE is pivotal, and future studies should aim at identifying predictors of VTE following MI. The findings from this study may indicate that the SNPs included in the 5-SNP score are not critical in the risk assessment of VTE in MI patients.

Our study has several strengths, such as the prospective design, recruitment of participants from a general population, well-validated events of both VTE and MI, and the long follow-up period. The high participation rate and the broad age range formed a source cohort that presumably is representative of a general Caucasian population. The study was limited by a low number of VTE events in certain subgroups, particularly for the SNPs with a low prevalence (eg, the prothrombin mutation). Hence, the risk estimates must be interpreted with caution. Further studies with more statistical power are warranted to explore this association is subgroups of MI patients. Both statins and antithrombotic medications are frequently used after MI, and these therapies also reduces the risk of VTE. Unfortunately, we lacked information on the use of medications after MI. However, the use of such medications would presumably be evenly distributed among the prothrombotic genotypes and categories of the 5-SNP score, and thus, not serve as confounders. However, if the effect of these therapies were sufficient to counterbalance the risk of VTE due to prothrombotic genotypes in MI patients, they may have contributed to dilute or underestimate the effect of prothrombotic genotypes. Finally, as in all observational studies, the potential presence of residual confounding cannot be ruled out.

The combination of MI and 5 prothrombotic genotypes, either as individual SNPs or as a 5-SNP score, did not result in an excess risk of VTE. Our findings imply that the increased risk of VTE after an acute MI is not explained by these 5 prothrombotic genotypes.

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RELATIONSHIP DISCLOSURE

The authors report nothing to disclose.

AUTHOR CONTRIBUTIONS

JKS analyzed the data and drafted the manuscript. VMM was involved in interpretation of the results and critical revision of the

manuscript. SKB and JBH designed the study and were involved in data collection, interpretation of results, and critical revision of the manuscript.

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SUPPORTING INFORMATION

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

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