Effect of prothrombotic genotypes on the risk of venous thromboembolism in patients with ischemic stroke. The Tromsø Study

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Abstract

Background: Patients with ischemic stroke have a transient increased risk of subsequent venous thromboembolism (VTE). Prothrombotic genotypes may augment VTE risk under conditions of high thrombosis risk related to the stroke.

Aims: To investigate the effect of prothrombotic genotypes in patients with ischemic stroke on the risk of VTE in a population-based case-cohort study.

Methods: Cases with incident VTE (n=660) and a randomly selected age-weighted sub-cohort (n=1803) were sampled from 3 surveys of the Tromsø Study (1994-2008). Participants were genotyped for *ABO* (rs8176719), *F5* (rs6025), *F2* (rs1799963), *FGG* (rs2066865) and *F11* (rs2036914) single nucleotide polymorphisms (SNPs). Cox regression models were used to calculate hazard ratios (HR) for incident VTE according to individual SNPs and categories of risk alleles (the 5-SNP score; 0-1, 2, 3-4 and ≥5) in participants with and without ischemic stroke.

Results: There were 263 patients with incident stroke, of whom 60 developed VTE during a median of 15.3 years of follow-up. The risk alleles of individual SNPs augmented the elevated risk brought about by ischemic stroke for VTE. In stroke patients, one category increase in the genetic risk score was associated with 54% higher risk of overall VTE (HR 1.54, 95% CI 1.35-1.75) and 76% higher risk of provoked VTE (HR 1.76, 95%CI 1.51-2.06). Stroke patients with ≥5 risk alleles had a 12-fold (HR 11.8, 95%CI 4.17-33.3) higher VTE risk than stroke-free participants with 0-1 risk alleles.

Conclusions: Prothrombotic genotypes increased the risk of VTE in stroke patients, and the risk increased with increasing number of risk alleles.

Introduction

Recent studies have shown that patients with arterial cardiovascular disease (i.e. myocardial infarction and ischemic stroke) have increased risk of subsequent venous thromboembolism (VTE) [1, 2]. In patients with ischemic stroke, the incidence of VTE is high, particularly of deep vein thrombosis (DVT) [3]. Even though clinically overt pulmonary embolism (PE) occurs in only 1% of stroke patients during the first 14 days after an acute stroke [4, 5], PE may account for up to 25-50% of deaths after acute stroke [5, 6]. Recently, we reported a transiently 20-fold increased risk of VTE within the first month after ischemic stroke in a population-based cohort study [7].

Simulation studies have shown that genetic profiling may be useful to discriminate between persons with high and low risk of disease [8, 9]. To identify individuals with high risk of a first VTE, de Haan *et al*. created a genetic score based on 31 single nucleotide polymorphisms (SNPs) previously reported to be associated with VTE [10]. SNPs with the highest odds ratios of VTE were added one-by-one to construct a genetic risk score using the most parsimonious model with fewer SNPs. This resulted in a score of 5 SNPs which included rs8176719 (non-O blood type) in *ABO*, rs6025 (factor V Leiden [FVL]) in *F5*, rs1799963 (prothrombin G20210A) in *F2*, rs2066865 in fibrinogen gamma gene (*FGG*), and rs2036914 in *F11*. The genetic risk score based on these 5 SNPs performed similarly to the score of all 31 SNPs [10].

Ischemic stroke is a heterogeneous multicausal disorder, and epidemiological data have provided substantial evidence for a genetic component to the disease [11, 12]. Hypercoagulability has a more pronounced effect on the risk of ischemic stroke than the risk of myocardial infarction [13]. The genes in the 5-SNP score are not only associated with increased risk of VTE but also with stroke. In a large meta-analysis, FVL and prothrombin

G20210A were found to be associated with a 33% and 44% increased risk of stroke, respectively [14]. Furthermore, non-O blood type was associated with 83% increased risk of stroke [15], and an association between *F11* variation and overall ischemic stroke was reported in individuals below 70 years of age [16]. Increased levels of plasma fibrinogen were associated with increased risk of stroke [17], but variants in *FGG* were not related to higher risk of stroke [18].

Even though ischemic stroke increases the risk of VTE and prothrombotic genotypes are associated with both stroke and VTE, the joint effect of prothrombotic genotypes and stroke on the risk of VTE has not been explored. Identification of genetic risk factors that particularly increase the risk of VTE instroke patients may guide decisions on thromboprophylaxis in stroke patients. Therefore, the aim of the present study was to investigate the combined effect of ischemic stroke and the SNPs included in the 5-SNP risk score [10] on the risk of VTE in a population-based case-cohort.

Methods

Study population

The Tromsø Study is a single-center, prospective, population-based study, with repeated health surveys of the inhabitants of Tromsø, Norway. Study participants (n=30,371) were recruited from the fourth, fifth and sixth surveys of the Tromsø Study, conducted in 1994–1995, 2001-2002, and 2007–2008, respectively. The overall attendance rates were high with 77% in the fourth survey, 79% in the fifth survey, and 66% in the sixth survey. A detailed description of the Tromsø Study has been published elsewhere [19]. The Tromsø study was approved by the Regional Committee for Medical and Health Research Ethics in Northern Norway, and all participants provided informed written consent to participation.

All subjects (n=30,371) were followed from the date of inclusion until a verified incident VTE event, migration, death, or end of follow-up (December 31, 2012). Incident VTE events were identified by searching the hospital discharge diagnosis registry, the radiological procedure registry and the autopsy registry at the University Hospital of North Norway, and adjudicated by an end-point committee, as previously described by Brækkan *et al* [20]. A VTE event was classified as either a DVT or PE. When these events occurred concurrently, the event was classified as a PE. VTE events were further classified as provoked or unprovoked according to the presence of provoking risk factors at the time of diagnosis [20]. Major surgery or trauma within 8 weeks prior to the event, active cancer at the time of diagnosis, marked immobilization (i.e. bed rest > 3 days, confinement to wheelchair, or long-distance travel > 4 hours within the last 14 days prior to the event) or other potential provoking factors specifically described by a physician in the medical record (e.g. intravascular catheter), were considered provoking factors. Ischemic stroke, myocardial infarction, or other acute medical conditions were not included in the definition of provoked VTE.

A total of 737 individuals without previous VTE experienced a VTE during follow-up. Out of these, 45 did not have blood samples available or of sufficient quality for DNA analysis. Thus, the remaining 692 subjects were included as cases in our study. A subcohort (n=2016) was created by randomly sampling participants from the three surveys weighted for the age of the cases in 5-year age-groups. Due to the case-cohort design, 71 of the cases were sampled and included in the subcohort. Study participants with a history of ischemic stroke (n=63) or with missing values for at least one of the risk allele variants (n=182) were excluded. Thus, our final case-cohort included 2463 participants, consisting of 660 VTE cases and 1803 sub-cohort members (Figure 1).

Baseline measurements

Information about the study participants at study entry was collected by physical examinations, blood samples, and self-administered questionnaires at each survey. Blood samples were collected from an antecubital vein and analyzed at the Department of Clinical Chemistry at the University Hospital of North Norway. DNA was isolated from whole blood and stored at -70°C at the national CONOR biobank, located at the HUNT Biobank in Levanger, Norway.

Body weight and height were measured in study participants wearing light clothing and no shoes. Body mass index (BMI) was calculated by the weight in kilograms (kg) divided by the height in meters (m) squared (kg/m^2). Information regarding a history of cardiovascular disease (myocardial infarction, angina or stroke) prior to inclusion in the cohort, diabetes mellitus, smoking status (yes/no), physical activity and level of education was obtained by using self-reported questionnaires. The baseline variables have been described in detail elsewhere [19].

Genetic risk factors of VTE

We genotyped the following SNPs: rs8176719 (non-O blood type) in *ABO*, rs6025 (FVL) in *F5*, rs1799963 (prothrombin G20210A) in *F2,* and rs2036914 in *F11*, with the Sequenom platform, and rs2066865 in *FGG* with the TaqMan platform, as previously described [21]. For Sequenom, which uses single-base extension followed by mass spectrometry to measure the molecular mass of the extended primers, samples were genotyped with the Sequenom iPlex Gold Assay according to the recommended protocol, with an initial input of 10–20 ng of DNA, and were analyzed with the MassARRAY Analyzer 4. Only genotypes with a high quality score of ‘A. Conservative’ or ‘B. Moderate’ were used. When multiple attempts were made

to genotype an individual, one of the highest-quality genotypes across all attempts was chosen for each SNP. For TaqMan, an initial input of 100 ng of DNA was used. Samples were genotyped with the Applied Biosystems 7900HT (Foster City, CA, USA) according to the recommended protocol, and processed with SDS 2.4 (Thermo Fisher, Foster City, CA, USA). Genotypes passing a quality value threshold of 95 were used.

Participants were considered carriers of the prothrombotic risk gene when one or two risk alleles were present. We did not differentiate in hetero- and homozygotes due to few homozygote study participants. The only genetic variant with a minor allele associated with reduced risk of VTE was the rs2036914 in *F11*, and in this case, we considered the common allele as the risk allele. The 5-SNP score conceived by de Haan *et al*. was created by summarizing the number of risk alleles from the five sequenced SNPs [10].

Assessment of ischemic stroke

Ischemic stroke was during follow-up defined according to the World Health Organization definition when computed tomography or magnetic resonance imaging or autopsy had ruled out brain hemorrhage [22]. An end-point committee performed validation of hospitalized and out-of-hospital events of ischemic stroke based on data from hospital and out-of-hospital journals, autopsy records, and death certificates, as previously described [7].

Statistical methods

Statistical analyses were performed using STATA version 15.0 (Stata Corporation, College Station, TX, USA). Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for incident VTE according to the individual SNPs or categories of risk alleles (the 5-SNP score categories; 0-1, 2, 3-4 and ≥5 risk alleles) in

study participants with and without ischemic stroke. The joint risk conferred by ischemic stroke and the individual SNP was calculated using participants without stroke and with no risk allele as the reference category. When the 5-SNP score was assessed instead of the individual SNPs, participants without stroke and with 0-1 risk allele were used as the reference category. Age was used as time scale in the Cox model, with the age of the participants at study enrollment defined as entry time, and the age at the VTE event or censoring event (i.e., death, migration, or the date of study end) defined as exit time. Ischemic stroke was included as a time-dependent covariate in the Cox model. Thus, participants who developed stroke during follow-up contributed person-years in both the unexposed and exposed group. All analyses were adjusted for age (as time scale) and sex. Because of the size of the subcohort, we did not make adjustment to the partial likelihood in the Cox regression analyses [23]. Subgroup analyses were performed according to the anatomical localization of the thrombotic event (DVT and PE), and the presence of provoking risk factors at the time of diagnosis. The proportional hazards assumption was tested using Schoenfeld residuals and found not violated.

To investigate whether the effect of ischemic stroke on the risk of VTE differed across strata of prothrombotic risk alleles, the presence of interaction on an additive scale between these 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. These three measures of interaction with their corresponding 95% CIs were calculated according to Andersson *et al.* [24], using an excel sheet (epinet.se/res/xls/epinetcalculation.xls).

Results

In our cohort, 263 participants had incident ischemic stroke during a median of 15.3 years of follow-up. Baseline characteristics of the study participants are shown in Table 1. The mean age was higher in stroke patients than in those without stroke, 67 years versus 57 years, respectively. The proportion of study participants with hypertension, hypercholesterolemia and diabetes mellitus were higher in stroke patients, while mean BMI and the proportion of males and current smokers was similar in both groups. The prevalence of risk alleles for each of the SNPs studied was similar in the two groups (Table 1). In the 5-SNP score, the distribution of individuals across number of risk alleles was virtually the same in participants with and without ischemic stroke (Figure 2).

In total, 60 of the 660 VTEs in our study occurred in patients with ischemic stroke. Characteristics of the VTE events in participants with and without stroke are shown in Table 2. The distribution of DVT and PE (60% and 40% respectively) was similar in both groups. The proportion of provoked VTE was higher in patients with ischemic stroke (75%) than in those without stroke (48%). Moreover, the proportion of patients immobilized before the VTE was substantially higher in those with stroke (62% versus 16%). Ischemic stroke was associated with an age- and sex-adjusted overall 2.1-fold (HR 2.06, 95% CI 1.56-2.71) increased risk of VTE, 2.3-fold (HR 2.36, 95% CI 1.65-3.37) higher risk of DVT, and 1.7-fold (HR 1.73, 95% CI 1.12-2.65) higher risk of PE, compared with study participants without stroke.

The risk estimates of VTE according to the individual SNPs in study participants with and without ischemic stroke are shown in Table 3. In the absence of ischemic stroke, non-O blood type (rs8176719), FVL (rs6025) and prothrombin G20210A (rs1799963) all increased the risk of VTE, whereas no effect on VTE risk was observed for the SNPs in *FGG* (rs2066865) and *F11* (rs2036914). For all the individual SNPs, the combinations of ischemic stroke and ≥1

risk alleles were associated with increased risk of VTE. The highest risk of VTE was conferred by the joint exposure of ischemic stroke and FVL (HR 4.42, 95% CI 2.28-8.59) or prothrombin G20210A (HR 9.62, 95% CI 1.32-69.0). As depicted in Table 4, measures quantifying interaction on an additive scale (i.e. RERI, AP, and synergy index) suggested a positive interaction between ischemic stroke and each of the prothrombotic SNPs, with the exception of the non-O blood type.

When the 5-SNP score was used (Table 3), the risk of VTE increased gradually across categories of number of risk alleles (0-1, 2, 3-4, and ≥ 5 risk alleles) in both study participants with and without stroke compared to participants without stroke and 0-1 risk allele. Of note, the dose-response relationship was even more pronounced in stroke patients. When the score was analyzed as an ordinal variable, the risk of VTE increased 24% (HR 1.24, 95% CI 1.05-1.46) per increase of genetic risk category in study participants without stroke, and 54% (HR 1.54, 95% CI 1.34-1.75) among those with stroke. We found a synergistic effect between the number of risk alleles and ischemic stroke on the risk of VTE. Patients with ischemic stroke and ≥5 risk alleles had 12-fold (HR 11.8, 95% CI 4.17-33.3) higher risk of VTE than study participants without stroke and 0-1 risk alleles. This was higher than expected on the basis of the individual effects of ischemic stroke and ≥ 5 risk alleles. Indeed, all measures of interaction described in Table 4 suggested a positive interaction between the two exposures. For instance, the AP revealed that 84% of the total VTE events in participants with stroke and ≥5 risk alleles were due to the interaction between the two exposures. In subgroup analyses, having both stroke and ≥5 risk alleles resulted in a hazard ratio of 13.3 (95% CI 3.08-57.5) for DVT and 9.97 (95% CI 2.38-43.5) for PE (Supplementary Table 1). As in the overall analysis, measures of interaction suggested a positive interaction between stroke and ≥5 risk alleles on the risk of either DVT or PE (Supplementary Table 2).

The risk estimates of provoked and unprovoked VTE according to the individual SNPs in participants with and without stroke are shown in Supplemental Table 3. For non-O blood type, FVL, and the SNPs in *FGG* and *F11*, the risk estimates for provoked events were higher than those for unprovoked events in study participants jointly exposed to stroke and ≥1 risk alleles. In patients with stroke, the risk estimates for VTE across categories of risk alleles in the 5-SNP score were higher for provoked than for unprovoked events (Table 5). The risk of provoked events increased almost 80% per increase of risk category (HR 1.76, 95% CI 1.41-2.06), while no association was observed for unprovoked events (HR 1.17, 95% CI 0.92-1.50). Participants jointly exposed to ≥5 risk alleles and stroke had an almost 23-fold (HR 22.6 95% CI 7.71-66.2) higher risk of provoked VTE compared with study participants without stroke and 0-1 risk alleles. In participants without stroke, the risk estimates for unprovoked VTE were higher than those for provoked VTE in all risk categories (Table 5).

Discussion

In the present case-cohort study with participants recruited from the general population, we found a synergistic effect of ischemic stroke and prothrombotic genotypes on the risk of VTE. The combined exposure to ischemic stroke and each of the individual SNPs (i.e. FVL, prothrombin G20210A, or variations in *FGG* or *F11)* resulted in an effect on VTE risk that exceeded the sum of the separate effects. When the 5-SNP risk score [10] was applied the number of prothrombotic risk alleles displayed a dose-response relationship with VTE risk, both in participants with and without stroke. The dose-response was particularly pronounced in stroke patients, and the risk of overall VTE and provoked VTE increased on average by 54% and 76%, respectively, per category increase in the genetic score. Furthermore, the combination of ischemic stroke and the high-risk category of the genetic

score (i.e. ≥5 risk alleles) yielded an effect on VTE risk that was greater than the sum of the separate effects. Of note, more than 80% of the VTE events occurring among study participants jointly exposed to ischemic stroke and the high-risk category of the genetic score appeared to be attributable to the interaction between the two risk factors. As risk estimates for provoked VTE were higher than for unprovoked events, our findings suggest that the increased risk of VTE in stroke patients was mainly driven by a combination of stroke-related provoking factors and genetic risk factors.

Recently, we reported that patients with ischemic stroke have a transient increased risk of VTE [7], which is consistent with previous registry-based population studies investigating the temporal relationship between ischemic stroke and VTE [1, 25]. This transient nature of VTE risk after stroke underscores the role of stroke-related factors as the main contributors to the development of thrombotic events. Indeed, measures of stroke severity have been shown to be strongly associated with risk of subsequent VTE [26]. Accordingly, our risk estimates were consistently higher for provoked than for unprovoked VTE events in study participants jointly exposed to stroke and prothrombotic risk genes. Therefore, it is likely that complications to acute stroke, such as prolonged immobilization, leg paralysis and secondary infections, which are all established risk factors of VTE [27-30], may contribute to the VTE risk. Previous studies have shown that individuals under prolonged immobilization [31, 32] or with upper respiratory tract infections [33], who are also carriers of prothrombotic risk genes, have increased risk of VTE that exceeds the sum of the separate effects of the risk factors. However, to the best of our knowledge, no other study have explored the joint effect of ischemic stroke and prothrombotic risk genes on the VTE risk.

Our findings of an increased risk of VTE after stroke in individuals with prothrombotic genotypes appear to be consistent with the thrombosis potential model. In this model, the thrombosis potential reflects the risk for VTE that is present during an individual's life, and each risk factor contributes to increase the thrombosis potential [34]. When sufficient risk factors have been accumulated, the thrombosis potential exceeds the 'thrombosis threshold' and a thrombotic event occurs [34]. Stroke is a strong risk factor of VTE [7]. Still, when the 5-SNP score was applied, the risk of VTE in stroke patients with one or no risk allele was not increased compared with participants without stroke. Our findings infer that the combination of stroke-related risk factors and prothrombotic risk genes are needed to sufficiently rise the thrombosis potential, leading to an incident VTE event. Moreover, the addition of risk alleles resulted in a dose-dependent increased risk of VTE. Stroke patients with ≥5 risk alleles had almost 12-fold higher risk of VTE than participants without stroke and ≤1 risk allele. All measures of interaction (i.e. RERI, AP and synergy index) between risk alleles and ischemic stroke on VTE risk were pointing towards a substantial synergistic effect. When these findings were analyzed in light of the thrombosis potential model, our findings suggest that ischemic stroke and the high-risk category of the 5-SNP score yielded a higher thrombosis potential together than separately [34].

Even though our results on the interaction between stroke and prothrombotic genotypes do not allow conclusions about biological mechanisms, as interaction is defined in numerical terms [34], one may still speculate on the pathophysiology behind these findings. A potential mechanism includes an association between prothrombotic genotypes and severity of stroke. If the prothrombotic genotypes are somehow related to severity of stroke, this may lead to a more pronounced or prolonged immobilization after acute stroke. However, whether the prothrombotic genotypes assessed in this study influence the

outcome of ischemic stroke is as yet unclear, as studies on this topic are scarce, and often limited by small sample sizes [16]. The risk of VTE in stroke patients could be further amplified by the hypercoagulable state associated with the prothrombotic genotypes, either through resistance to activated protein C due to FVL [35, 36], increased levels of prothrombin or factor XI in the presence of prothrombin G20210A or *F11* variation, respectively [37, 38], or changes in levels of fibrinogen γ', a product of alternative splicing of *FGG* that is inversely related to thrombotic risk [39]. The present study was not designed to investigate these proposed mechanisms. Still, our results may form the basis for further studies to confirm the interaction and to investigate the underlying mechanism(s).

International guidelines for VTE prevention after stroke suggest prophylactic-dose heparin (unfractionated or low-molecular-weight heparin) or intermittent pneumatic compression devices over no prophylaxis in patients with acute ischemic stroke and restricted mobility [40]. Prophylaxis should be initiated as early as possible and should be continued throughout the hospital stay or until the patient regains mobility. However, the guidelines are mainly based on one randomized study (the Clots in Legs or Stockings after Stroke [CLOTS] study), in which no information was provided regarding the prevalence of prothrombotic risk genes in the study population [41]. Despite the recommendation of anticoagulant use during the hospitalization, the high incidence of VTE observed after stroke indicates that VTE prophylaxis in stroke patients is inadequate. Indeed, data from clinical practice have shown that less than 50% of ischemic stroke patients at risk of VTE receive any form of thromboprophylaxis [42, 43]. This may be due to poor compliance following guidelines, or uncertainty on how to assess patients at increased risk of VTE. The Padua prediction score uses both ischemic stroke and known thrombophilic conditions to predict VTE in hospitalized patients [44]. However, the Padua score does not differentiate between

number of risk alleles, and external validation of the prediction score showed limited performance for predicting VTE among hospitalized medical patients [45]. Our finding of an increased risk of VTE after stroke with increasing number of prothrombotic risk alleles suggests that the number of prothrombotic risk alleles could be considered when assessing thrombosis risk in patients with ischemic stroke. Identification of patients in whom supra-additive effects on VTE risk are present due to the combination of stroke-related risk factors and prothrombotic risk alleles, would allow the implementation of more effective thromboprophylaxis, which may reduce the incidence of VTE after stroke. Therefore, new studies are warranted to explore to what extent assessment of prothrombotic genotypes in stroke patients would improve risk stratification of VTE and aid clinical decisions of therapeutic interventions.

Major strengths of our study include the prospective design with participants recruited from the general population, the large number of genotyped participants, the long-term follow-up, the wide age distribution and the validated events of both ischemic stroke and VTE. The high participation rate in the Tromsø Study and the broad age range formed a cohort that is representative of the general population and minimized selection bias in the sub-cohort. Some limitations merit attention. Even though our study was derived from a large cohort, the number of VTE events was low in some subgroups, particularly for the rare genetic variants, which resulted in limited statistical power. Our results on the measures that quantify interaction should therefore be interpreted with caution. Unfortunately, we did not have information about stroke severity or the number of patients with leg-paralysis or prolonged immobilization.

In conclusion, we found a synergistic effect of ischemic stroke and prothrombotic genotypes on the risk of subsequent VTE. In stroke patients, increasing number of risk alleles

showed a dose-dependent increased risk of VTE, particularly of provoked VTE events. Our findings suggest that genetic risk factors play an important role in the development of VTE after stroke, and may imply that the number of risk alleles could be considered when assessing the VTE risk in patients with ischemic stroke.

Addendum

L. B. Rinde and V.M. Morreli analyzed the data and drafted the manuscript. J.-B. Hansen and S. K. Brækkan designed the study, organized data collection, interpreted the results and revised the manuscript. F. R. Rosendaal,and B. Småbrekke interpreted the results and critically reviewed the manuscript. E. N. Smith and K. A. Frazer genotyped the case-cohort. I. Njølstad, E. B. Mathiesen, and M.-L. Løchen were responsible for data collection and revision of the manuscript. T. Wilsgaard provided statistical support and revision of the manuscript.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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Tables

Table 1. Baseline characteristics of the study population with and without stroke (n = 2463). The Tromsø Study

	No stroke (n= 2200)	**Stroke (n=263)**
Age (years)	57 ± 14	67 ± 10
Sex (male)	44.4 (976)	46.0 (121)
BMI (kg/m^2)	26.0 ± 4.1	26.9 ± 4.4
Total cholesterol (mmol/L)	6.53 ± 1.31	6.87 ± 1.25
HDL (mmol/L)	1.54 ± 0.42	1.47 ± 0.40
Triglycerides (mmol/L)	1.63 ± 1.00	1.87 ± 1.06
Systolic blood pressure (mmHg)	142 ± 22	158 ± 27
Diastolic blood pressure (mmHg)	81 ± 13	88 ± 16
Hypertension*	52.0 (1144)	79.8 (210)
Hypercholesterolemia†	49.5 (1089)	58.9 (155)
Smoking ‡	34.0 (749)	31.9 (84)
Physical activity §	22.1 (486)	14.1 (37)
Education ‖	21.7 (478)	10.6 (28)
Self-reported diabetes mellitus	2.7 (60)	7.2 (19)
rs8176719 (*ABO*)		
≥1 risk allele	63.1 (1389)	67.7 (178)
rs6025 (*F5*)		
≥1 risk allele	8.8 (193)	8.4 (22)
rs1799963 (*F2*)		
≥1 risk allele	1.6 (34)	0.8 (2)
rs2066865 (*FGG*)		
≥1 risk allele	45.7 (1006)	43.7 (115)
rs2036914 (*F11*)		
≥1 risk allele	81.5 (1792)	78.7 (207)

Values are % (n) or mean ± SD
BMI indicates body mass index
Genes related to the single nucleotide polymorphisms are depicted between parentheses
*Mean systolic/diastolic blood pressure ≥140/≥90 mm Hg
†Total cholesterol ≥6.5 mmol/L
‡Self-reported daily smoking, yes/no.
§≥1hours of moderate or hard physical activity per week, yes/no.
‖>15 years of education.

Table 2. Characteristics of venous thromboembolism events (n = 660). The Tromsø Study

	No stroke (n = 600)	Stroke (n = 60)
Clinical characteristics % (n)		
Deep vein thrombosis	56.7 (340)	60.0 (36)
Pulmonary embolism	43.3 (260)	40.0 (24)
Provoked	48.3 (290)	75.0 (45)
Unprovoked	51.7 (310)	25.0 (15)
Clinical risk factors % (n)		
Estrogen*†	5.8 (35)	6.7 (4)
Pregnancy/puerperium*	0.8 (5)	-
Heredity‡	3.8 (23)	-
Provoking factors % (n)		
Surgery	16.8 (101)	11.7 (7)
Trauma	8.5 (51)	8.3 (5)
Cancer	27.2 (163)	16.7 (10)
Immobility§	16.3 (98)	61.7 (37)
Other||	6.0 (36)	3.3 (2)

*Only women included in the analysis.
†Current or previous use of hormone replacement therapy or oral contraceptives.
‡Venous thromboembolism in a first-degree relative before 60 years of age.
§Bed rest> 3 days, journeys of > 4 h by car, boat, train or air within the last 14 days, or other types of immobilization.
||Other provoking factor described by a physician in the medical record (e.g. intravascular catheter)

Table 3. Hazard Ratios of venous thromboembolism for individual single nucleotide polymorphisms and categories of the 5-SNP score according to ischemic stroke exposure. The Tromsø Study

	Risk Alleles	Events	HR (95 % CI)*
SNP (Gene)			
rs8176719 (*ABO*)			
No stroke	0	195	1 (Reference)
	≥1	405	1.32 (1.11-1.57)
Stroke	0	17	2.38 (1.44-3.92)
	≥1	43	2.49 (1.78-3.48)
rs6025 (*F5*)			
No stroke	0	511	1 (Reference)
	≥1	89	2.11 (1.68-2.64)
Stroke	0	51	2.02 (1.50-2.72)
	≥1	9	4.42 (2.28-8.59)
rs1799963 (*F2*)			
No stroke	0	586	1 (Reference)
	≥1	14	1.64 (0.96-2.78)
Stroke	0	59	2.04 (1.55-2.69)
	≥1	1	9.62 (1.32-69.04)
rs2066865 (*FGG*)			
No stroke	0	328	1 (Reference)
	≥1	272	1.02 (0.86-1.19)
Stroke	0	30	1.61 (1.10-2.36)
	≥1	30	2.90 (1.98-4.26)
rs2036914 (*F11*)			
No stroke	0	108	1 (Reference)
	≥1	492	1.06 (0.86-1.31)
Stroke	0	12	1.99 (1.09-3.63)
	≥1	48	2.20 (1.56-3.12)

Table 3. *(Continued)*

	Risk Alleles	Events	HR (95 % CI)*
5-SNP score			
No stroke	0-1	101	1 (Reference)
	2	161	1.07 (0.83-1.37)
	3-4	292	1.30 (1.04-1.63)
	≥ 5	46	1.97 (1.39-2.80)
	HR per increase of risk category		1.24 (1.05-1.46)
Stroke	0-1	6	0.96 (0.42-2.20)
	2	15	1.81 (1.03-3.17)
	3-4	35	3.54 (2.35-5.33)
	≥ 5	4	11.8 (4.17-33.3)
	HR per increase of risk category		1.54 (1.35-1.75)

CI, confidence interval; HR, hazard ratio; single nucleotide polymorphisms (SNP)
*Adjusted for age (as time scale) and sex.

Table 4. Measures of interaction on an additive scale between ischemic stroke and the individual single nucleotide polymorphisms or 5 or more risk alleles in the 5-SNP score. The Tromsø Study

	RERI (95% CI)	AP (95% CI)	Synergy index (95% CI)
SNP (Gene)			
rs8176719 (*ABO*)	-0.21 (-1.59 to 1.16)	-0.09 (-0.65 to 0.48)	0.87 (0.38 to 2.03)
rs6025 (*F5*)	1.29 (-1.70 to 4.28)	0.29 (-0.20 to 0.78)	1.61 (0.65 to 4.00)
rs1799963 (*F2*)	6.94 (-12.04 to 25.92)	0.72 (0.16 to 1.28)	5.13 (0.53 to 50.2)
rs2066865 (*FGG*)	1.28 (0.07 to 2.48)	0.44 (0.15 to 0.73)	3.03 (0.98 to 9.36)
rs2036914 (*F11*)	0.15 (-1.16 to 1.46)	0.07 (-0.52 to 0.65)	1.14 (0.34 to 3.85)
5-SNP score	9.84 (-2.13 to 21.82)	0.84 (0.67 to 1.00)	11.6 (3.18 to 42.1)

CI, confidence interval; single nucleotide polymorphisms (SNP); RERI, Relative excess risk due to interaction; AP, Proportion due to interaction

Table 5. Hazard Ratios for provoked and unprovoked venous thromboembolism for categories of the 5-SNP Score according to ischemic stroke exposure. The Tromsø Study

		Provoked VTE		Unprovoked VTE	
	Risk Alleles	**Events**	**HR (95 % CI)***	**Events**	**HR (95 % CI)***
5-SNP score					
No stroke	0-1	55	1 (Reference)	46	1 (Reference)
	2	86	1.06 (0.75-1.48)	75	1.08 (0.75-1.57)
	3-4	130	1.07 (0.78-1.46)	162	1.58 (1.14-2.19)
	≥ 5	19	1.48 (0.88-2.50)	27	2.57 (1.59-4.14)
	HR per increase of risk category		1.07 (0.93-1.23)		1.35 (1.18-1.55)
Stroke	0-1	5	1.51 (0.59-3.83)	1	0.33 (0.05-2.45)
	2	10	2.22 (1.10-4.46)	5	1.33 (0.52-3.44)
	3-4	26	5.10 (3.10-8.39)	9	1.79 (0.84-3.83)
	≥ 5	4	22.6 (7.7-66.2)	0	-
	HR per increase of risk category		1.76 (1.51-2.06)		1.17 (0.92-1.50)

CI, confidence interval; HR, hazard ratio; single nucleotide polymorphisms (SNP)
*Adjusted for age (as time scale) and sex.

Figures

Figure 1. Flowchart illustrating the composition of the case–cohort study. FVL, Factor V Leiden; n, number of participants; VTE, venous thromboembolism

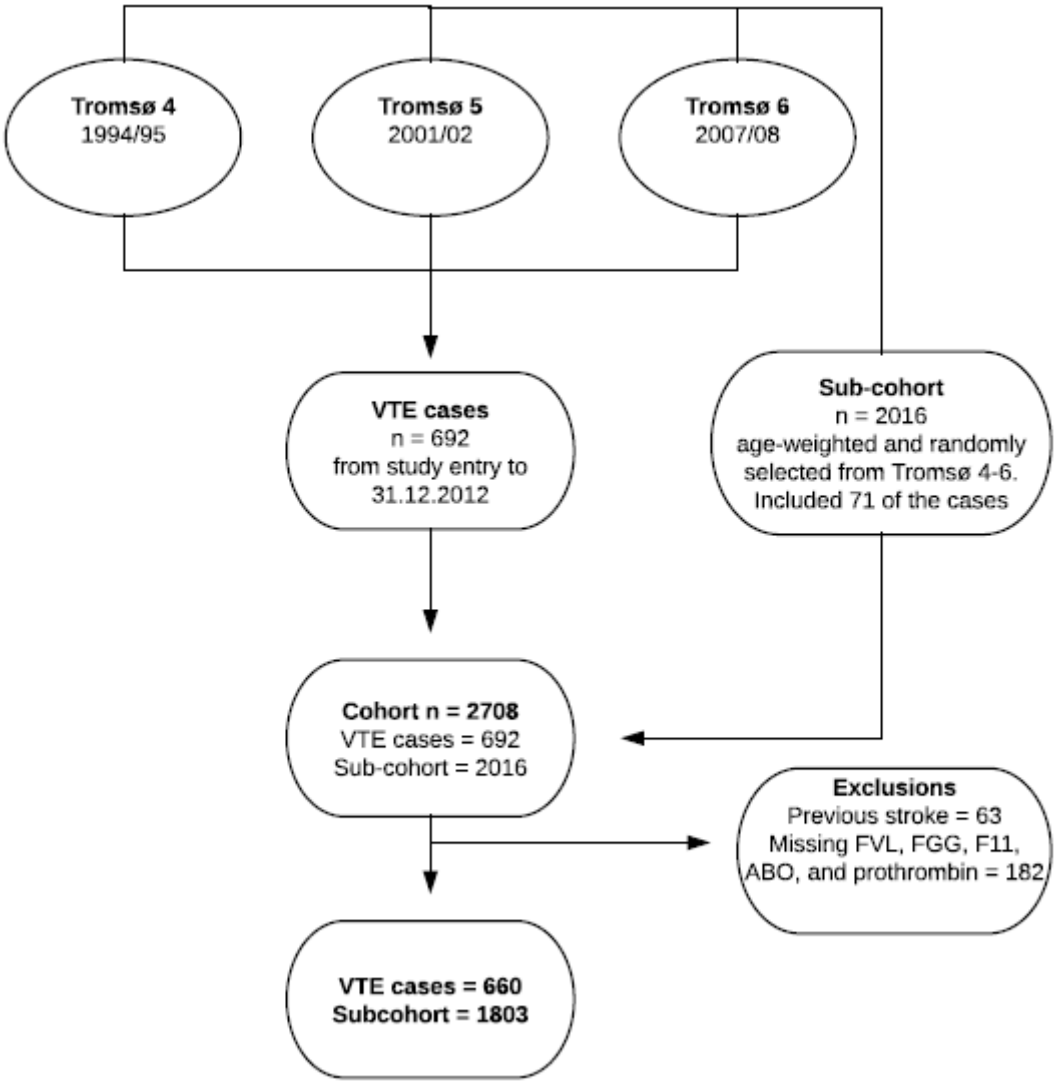
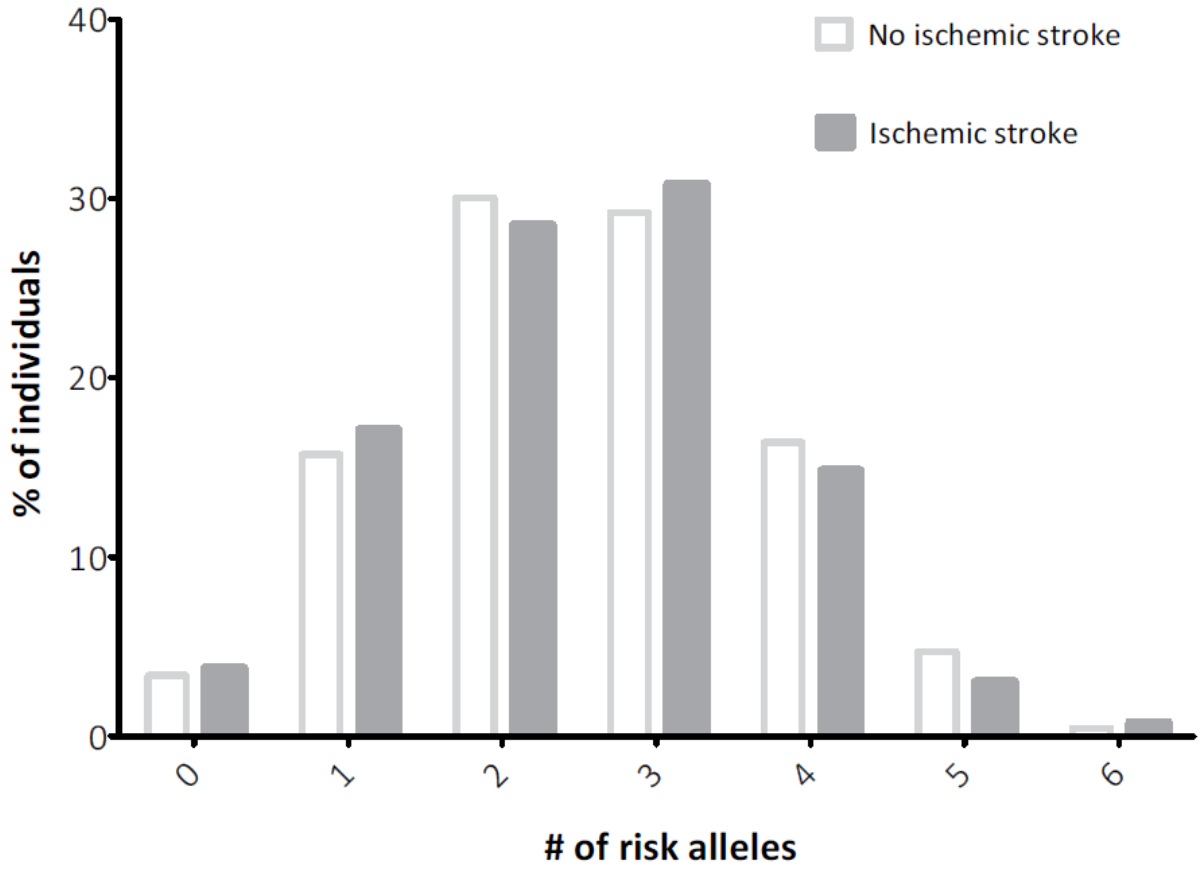


Figure 2. Distribution (%) of individuals across number of risk alleles in study participants with and without previous ischemic stroke



Supplementary material

Supplementary Table 1. Hazard Ratios for deep vein thrombosis and pulmonary embolism for individual single nucleotide polymorphisms and categories of the 5-SNP Score according to ischemic stroke exposure. The Tromsø Study

		Deep vein thrombosis		Pulmonary embolism	
	Risk Alleles	**Events**	**HR (95 % CI)***	**Events**	**HR (95 % CI)***
SNPs (Gene)					
rs8176719 (*ABO*)					
No stroke	0	103	1 (Reference)	92	1 (Reference)
	≥1	237	1.44 (1.14-1.82)	168	1.19 (0.92-1.53)
Stroke	0	14	3.95 (2.24-6.95)	3	0.82 (0.26-2.61)
	≥1	22	2.57 (1.61-4.12)	21	2.37 (1.46-3.85)
rs6025 (*F5*)					
No stroke	0	275	1 (Reference)	236	1 (Reference)
	≥1	65	2.82 (2.15-3.70)	24	1.26 (0.83-1.92)
Stroke	0	28	2.21 (1.48-3.30)	23	1.82 (1.17-2.82)
	≥1	8	7.84 (3.85-15.96)	1	0.98 (0.14-6.98)
rs1799963 (*F2*)					
No stroke	0	334	1 (Reference)	252	1 (Reference)
	≥1	6	1.20 (0.53-2.68)	8	2.26 (1.12-4.58)
Stroke	0	35	2.30 (1.60-3.31)	24	1.76 (1.14-2.70)
	≥1	1	16.51 (2.28-119.48)	0	-
rs2066865 (*FGG*)					
No stroke	0	184	1 (Reference)	144	1 (Reference)
	≥1	156	1.03 (0.83-1.28)	116	1.00 (0.78-1.27)
Stroke	0	19	1.97 (1.22-3.19)	11	1.23 (0.66-2.28)
	≥1	17	3.16 (1.90-5.25)	13	2.62 (1.47-4.68)
rs2036914 (*F11*)					
No stroke	0	60	1 (Reference)	48	1 (Reference)
	≥1	280	1.09 (0.82-1.44)	212	1.02 (0.75-1.40)
Stroke	0	8	2.59 (1.23-5.46)	4	1.36 (0.49-3.77)
	≥1	28	2.51 (1.58-3.97)	20	1.87 (1.10-3.19)

Supplementary Table 1. (Continued)

		Deep vein thrombosis		Pulmonary embolism	
	Risk Alleles	**Events**	**HR (95 % CI)***	**Events**	**HR (95 % CI)***
5-SNP score					
No stroke	0-1	55	1 (Reference)	46	1 (Reference)
	2	89	1.08 (0.77-1.52)	72	1.05 (0.72-1.52)
	3-4	169	1.37 (1.01-1.86)	123	1.22 (0.87-1.70)
	≥ 5	27	2.08 (1.31-3.29)	19	1.85 (1.08-3.17)
	HR per increase of risk category		1.24 (1.09-1.41)		1.16 (1.00-1.35)
Stroke	0-1	4	1.38 (0.49-63.87)	2	0.58 (0.14-2.40)
	2	10	2.47 (1.22-4.97)	5	1.16 (0.45-2.98)
	3-4	20	4.51 (2.62-7.77)	15	2.63 (1.42-4.88)
	≥ 5	2	13.30 (3.08-57.5)	2	9.97 (2.28-43.5)
	HR per increase of risk category		1.67 (1.41-1.98)		1.39 (1.14-1.69)

CI, confidence interval; HR, hazard ratio; single nucleotide polymorphisms (SNP)
*Adjusted for age (as time scale) and sex.

Supplementary Table 2. Measures of interaction on an additive scale between ischemic stroke and five or more risk alleles in the 5-SNP score in deep vein thrombosis and pulmonary embolism. The Tromsø Study

	RERI (95% CI)	AP (95% CI)	Synergy index (95% CI)
Deep vein thrombosis	10.85 (-8.28 to 30.0)	0.82 (0.55 to 1.08)	8.42 (1.54 to 46.7)
Pulmonary embolism	8.54 (-5.78 to 22.9)	0.86 (0.66 to 1.05)	20.88 (1.88 to 232)

CI, confidence interval; single nucleotide polymorphisms (SNP); RERI, Relative excess risk due to interaction; AP, Proportion due to interaction

Supplementary table 3. Hazard Ratios for provoked and unprovoked venous thromboembolism for individual single nucleotide polymorphisms according to ischemic stroke exposure. The Tromsø Study

		Provoked VTE		Unprovoked VTE	
	Risk Alleles	**Events**	**HR (95 % CI)***	**Events**	**HR (95 % CI)***
SNP (Gene)					
rs8176719 (*ABO*)					
No stroke	0	100	1 (Reference)	95	1 (Reference)
	≥1	190	1.21 (0.95-1.55)	215	1.44 (1.13-1.84)
Stroke	0	11	2.90 (1.55-5.44)	6	1.78 (0.78-4.09)
	≥1	34	3.82 (2.56-5.70)	9	1.07 (0.53-2.13)
rs6025 (*F5*)					
No stroke	0	255	1 (Reference)	256	1 (Reference)
	≥1	35	1.65 (1.16-2.35)	54	2.58 (1.92-3.46)
Stroke	0	39	3.08 (2.17-4.37)	12	0.95 (0.53-3.72)
	≥1	6	5.74 (2.54-12.99)	3	3.03 (0.97-9.50)
rs1799963 (*F2*)					
No stroke	0	285	1 (Reference)	301	1 (Reference)
	≥1	5	1.20 (0.50-2.91)	9	2.05 (1.06-3.99)
Stroke	0	45	3.17 (2.28-4.40)	14	0.95 (0.55-1.64)
	≥1	0	-	1	20.21 (2.78-146.85)
rs2066865 (*FGG*)					
No stroke	0	161	1 (Reference)	167	1 (Reference)
	≥1	129	0.98 (0.78-1.24)	143	1.05 (0.84-1.31)
Stroke	0	23	2.44 (1.56-3.82)	7	0.76 (0.36-1.64)
	≥1	22	4.39 (2.78-6.92)	8	1.49 (0.72-3.06)
rs2036914 (*F11*)					
No stroke	0	60	1 (Reference)	48	1 (Reference)
	≥1	230	0.89 (0.67-1.19)	262	1.27 (0.93-1.73)
Stroke	0	10	2.93 (1.49-5.75)	2	0.76 (0.18-3.15)
	≥1	35	2.86 (1.87-4.39)	13	1.35 (0.73-2.52)

CI, confidence interval; HR, hazard ratio; single nucleotide polymorphisms (SNP)
*Adjusted for age (as time scale) and sex.