Family history of venous thromboembolism as a risk factor and genetic research tool

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Summary
Familial clustering of venous thromboembolism (VTE) was described as far back as 1905 by Briggs. Although Egeberg discovered inherited deficiency of antithrombin in 1965, it was not until Dahlbäck discovered resistance to activated protein C in 1993 that it became clear that genetic factors are common risk factors of VTE. Several genes have been linked to familial aggregation of VTE and genome-wide association studies have found several novel gene loci. Still, it has been estimated that much of the heritability for VTE remains to be discovered. Family history (FH) of VTE is therefore still important to determine whether a patient has an increased genetic risk of VTE. FH has the potential to represent the sum of effects and interactions between environmental and genetic factors. In this article the design, methodology, results, clinical and genetic implications of FH studies of VTE are reviewed. FH in first-degree relatives (siblings and/or parents) is associated with a 2–3 times increased familial relative risk (FRR). However, the FRR is dependent on age, number of affected relatives, and presentation of VTE (provoked/unprovoked). Especially high familial risks are observed in individuals with two or more affected siblings (FRR> 50). However, the familial risk for recurrent VTE is much lower or non-significant. Moreover, FH of VTE appears mainly to be important for venous diseases (i.e. VTE and varicose veins). The familial associations with other diseases are weaker. In conclusion, FH of VTE is an important research tool and a clinically potential useful risk factor for VTE.

Keywords
Familial thrombosis, venous thrombosis, pulmonary embolism, epidemiological studies, thrombophilia

Introduction
Hippocrates included observations regarding family history (FH) of disease in his clinical case histories (1). He noted that disease type and severity often runs in families. Even today, when the advances arising from the Human Genomic Project have added new genomic tools, FH is still relevant and will remain so for years to come (2). FH has long since been of major importance in the caring for Mendelian or single gene disorders such as von Willebrand’s disease, polycystic kidney disease and sickle disease (2). However, we do our patients a disservice if we do not consider FH in common multifactorial disorders as well (2). FH is a feasible and comprehensive genetic risk assessment method for common conditions such as hypertension, type 2 diabetes, coronary heart disease (CHD), breast cancer, colon cancer and prostate cancer (3). In this review the importance of FH of venous thromboembolism (VTE) will be reviewed.

Family history
FH is not only of importance in the clinical situation and in epidemiology but also in genetic epidemiology (4). If a disease does not aggregate in families an important genetic cause of a disease is unlikely. However, familial aggregation of a disease is not sufficient to infer a genetic cause of a disease. As well as genes, environmental and cultural influences may also aggregate in families, leading to an increased familial risk (5–7). Studies of twins or adoptees give the opportunity to disentangle genetic and environmental influences (5). The study of familial risks in spouses is a way to estimate the effect of adult shared family environment (5, 7). Studies of half-siblings may also help to disentangle genetic and non-genetic contributions to FH (8). Moreover, extended family studies may also separate heritable, since individuals outside the nuclear family are less likely to have shared the same environmental exposure(s) (9, 10). Heritability is a measure of the genetic contribution to the observed differences on a trait among individuals of a popu-
Heritability thus analyses the relative contributions of differences in genetic and non-genetic factors to the total phenotypic variance in a population. Another possibility to test for the extent of environmental sharing is to calculate familial risks according to age difference between siblings (a proxy for the time of shared environment) or year difference in time of diagnosis between proband and relative (11). For instance, invasive pneumococcal disease (IPD) aggregates in families in Denmark (12), but only regarding events within one year of the index IPD diagnosis (rate ratio = 7.4). After one year, there was no increased risk of IPD in first degree relatives. Thus, genetic susceptibility appears of little importance in the development of IPD.

The familial relative risk (FRR), i.e. the ratio of the risk of those with and without an FH) is often expressed as a recurrence risk ratio (λ), which is the prevalence of the disease in relatives with affected relatives divided by the prevalence in the general population (4). Another way to express the FRR is with standardised incidence ratio (SIR, i.e. incidence rate of the disease in individuals with a FH compared with the incidence rate in those without a FH) (6). SIR is a method for cohort studies. Other measures of the familial aggregation of a disease are the odds ratio (OR, the ratio of the odds of disease of those with and without an FH) and hazard ratio (HR, the ratio of rates) (6).

Methods

We used PubMed (http://www.ncbi.nlm.nih.gov/) to search for all relevant studies on associations between FH and VTE that were published before February 2015. Medical Subject Heading terms (Mesh terms) "venous thromboembolism", "venous thrombosis", "pulmonary embolism", "thrombophlebitis", and key phrases “venous thrombosis”, "venous thromboembolism", "vein thrombosis", "pulmonary embolism", and "thrombophlebitis" were used to identify articles about VTE. The search results for VTE were then combined with Mesh terms for "family/history", "heredity ", "family", and key phrases "familial risk", "familial aggregation", "familial clustering", "familial history", and "familial risks". Included were: 1) original research papers, 2) papers published in the English language and 3) cross-sectional, case-control or cohort studies that investigated the association of FH of VTE and risk of VTE. Case reports, editorials and reviews were excluded. Studies where cases or relatives were defined with a combination of VTE and arterial thrombosis were also excluded. A total of 1,541 articles were identified. One reviewer (B.Z.) screened all titles and abstracts of papers identified by the electronic search. After screening the titles 101 papers remained and after screening the abstract 37 papers remained. One author (B.Z.) reviewed full text copies of all remaining potentially relevant papers. References from relevant articles, letters, reviews and editorials were searched to identify any additional relevant studies. A total of 30 papers about FH of VTE were identified in this way.

Familial clustering of VTE – a historic review

The first case of possible venous thrombosis in a leg was described in the 13th century by the Parisian surgeon Henri du Perchle (13, 14). The patient was a 20-year-old man from Normandy named Raoul who developed unilateral swelling of a leg. As pointed out by Mannucci, the young age of Raoul leads us to suspect that he had a thrombophilic condition (14). However, it was not until 1905 when Briggs was the first to report clustering of venous thrombophlebitis in a family (15). The patient was a 35-year-old man with eight recurrent episodes of venous thrombophlebitis in the lower extremities since 1887. Eight of 16 adult relatives were affected by venous diseases like varicose veins, haemorrhoids and thrombosis during the puerperium period or after acute infections. In 1956 Jordan and Nandorff further described a familial tendency for thromboembolic disease (16). They reported 21 cases with VTE with a familial tendency from their own clinic (Medical Department, University Hospital, Utrecht). Moreover, they made a literature review of 22 published cases with familial tendency for VTE. Thus, a theoretical ground for a possible genetic cause of VTE was laid by Jordan and Nandorff. In 1965 Egeberg described the first family with inherited antithrombin deficiency associated with familial aggregation of thrombosis (17). In 1981 Griffin et al. described the first family with inherited deficiency of protein C linked to a familial tendency of VTE (18). In 1984 inherited protein S deficiency was linked to familial inheritance of VTE by Comp and Esmon (19). However, these deficiencies are rare, and it was not until 1993 when Dahlback et al. described the first family with resistance to activated protein C (APC-resistance) that a large number of familial cases could be explained (20). APC-resistance was in the majority of familial cases linked to the same single factor V mutation that results in the replacement of Arg506 in one of the APC-cleavage sites with a Gln (21–25). After the discovery of APC-resistance it became clear from several family studies that more than one inherited thrombophilic defect segregates in many thrombophilic families (26–28). In 1996 Poort et al. found another common genetic cause of VTE linked to familial clustering of VTE (29). Still, only 30% of familial cases have any of these inherited defects (thrombophilias) (30). Bezemier et al. found that FH of VTE is a risk factor for VTE both in the presence or absence of the known thrombophilias (30). Other researchers have also reported that the known thrombophilias only explain a fraction of familial cases (31–42). However, the frequency of thrombophilias is dependent on the number of affected relatives and their ages (36). Thus, the importance of FH is still of great interest to study. FH of a disease represents the concerted action of genes and environmental influence. In the present study we will dissect FH of VTE both from a clinical point of view but also from a genetic point of view.

Family history of VTE – Nature or nurture

Though a large number of studies have found familial aggregation of VTE it was not until after the millennium the familial risks of...
having an affected relative was determined. In three case-control studies FH increased the risk for venous thrombosis by approximately 2.5-fold, with ORs of 2.2, 2.3 and 2.7, respectively (30, 43, 44). Several studies have tried to disentangle genetic from environmental contribution to the observed familial risks of VTE. In 2003 Larsen et al. studied Danish twins (45). For men, the concordance rates for mono- and dizygotic twin pairs, respectively, were 0.22 (95% confidence interval [CI] 0.14 to 0.30) and 0.08 (0.04–0.12). The OR was 13.5 (7.3–24.8) among monozygotic twins and 3.8 (1.8–8.3) among dizygotic twins. The proportion of the variance attributable to genetic effects on VTE in males was 55% (39%-68%). The remaining variation could be attributed to men’s non-familial environments. Perhaps surprisingly they found no intra-twin pair similarity for VTE among women. Thus, they found differences in genetic susceptibility to VTE between the sexes, with genetic factors playing a substantially stronger role in males than in females. However, this may be related to the limited study size.

Another way to disentangle genetic from environmental contribution is to do extended family analysis. Souto et al. examined 398 individuals in 21 extended pedigrees (46). The authors found that more than 60% of the variation in susceptibility to common venous and arterial thrombosis is attributable to genetic factors. Of the 53 symptomatic cases 40 (75.5%) had had VTE and 17 (32.1%) an atrial thrombosis. In 2004 Heit et al. studied 751 probands with VTE and their relatives (47). A multifactorial non-Mendelian inheritance model was favored as the cause for VTE, while a model postulating a purely environmental cause was rejected. VTE is probably a result of multi-genic action as well as environmental exposures (48).

Using nationwide family studies other approaches have also indicated the importance of genes to the familial aggregation of VTE (49). A nationwide study of adoptees showed a stronger correlation with disease in biological than in adoptive parents (50). Moreover, in a nationwide extended family study the familial risk was determined in not only first-degree relatives but also second and third degree relatives (51). There was a strong correlation between OR and the degree of relatedness. A further approach is to study spouses that share adult familial environment. However, spouse risk of VTE was not only low but also much lower than risk among first-, second- and third degree relatives (51). Also, age difference among siblings did not affect the familial risk to any significant degree, which would be expected if familial environment effects were important (11, 12).

Familial risk of VTE in first-degree relatives

Cross-sectional and case–control studies

In all, one cross-sectional and seven case-control studies were identified that provided risks of VTE by FH of VTE in first-degree relatives (30, 42–56). Table 1 details the characteristics of these studies. Sample sizes ranged from 116 to 1,288 VTE cases. The types of control subjects used varied between studies. Data on the VTE status of relatives were collected from the index case. The familial risk for the cross-sectional study was 4.6. The familial risks calculated from the case-control studies were between 2.2 and 3.0. All cross-sectional and case-control studies included all VTE or deep-vein thrombosis (DVT) and pulmonary embolism (PE) events.

Cohort studies

Table 2 details the characteristics of the six cohort studies that have investigated the relationship between FH and VTE risk (11, 57–62). The study by Rojnuckarin et al. was performed on hospital patients in Thailand and differs very much from the other cohort studies, cross-sectional and case control studies (57). The study was, however, small with only 27 cases with VTE among hospitalised patients. In another study by Bosson et al. of medical outpatients from France the adjusted FRR was 1.68 (58). However, the German community based cohort study by Spannagl et al. (3.4 crude FRR and 2.4 adjusted FRR) and the four nationwide studies gives more similar familial risks between 1.96 and 3.08 depending on first degree relative and VTE manifestation (11, 59–62). Sample sizes ranged from 19,599 to 45,362 VTE cases in the nationwide studies. Thus, the large nationwide cohort studies (Table 2) give similar familial risks as the case-control studies (Table 1). The nationwide cohort studies are the only studies where FH was not collected from the index case (11, 60–62). Instead the diagnosis was collected from nationwide hospital registers. Only one study has determined separate familial risks for PE (61).

Age dependence of familial risks

Several studies have determined age dependence of FH of VTE. Couturaud et al. have studied predictive factors of thrombosis in relatives of patients with VTE (63,64). Thrombosis at a young age was a predictive factor (OR=0.97 per year older, 95% CI .96–0.99 (63) including in relatives of unprovoked cases (OR=3.27 in patients < 45 years compared with patients > 71 years, 95% CI 1.68–6.38) (64). In the study by Mili et al. there was no major age difference in familial risks among blacks or whites (55). Bezemer et al., however, found the FRR to be 2.7 for those with an affected relative under 50 years of age compared to an FRR of 2.2 when all subjects were considered (30). Sørensen et al. found a strong association between age in index case and VTE risk (60), and Zöller et al. found that the FRR is highly age-dependent (11, 65). This age dependence was observed for both venous thrombosis in the legs, PE, and other forms of venous thromboembolic events (65).

Family history of VTE and rare VTE manifestations

In a nationwide study of 1,824 patients with rare manifestations of VTE the familial risks were determined (66). The SIR (sibling/or parent) were significantly increased for migrating thrombophlebitis (1.81; 95% CI 1.40–2.31), portal vein thrombosis (2.35; 95% CI 1.81–3.02) and deep-venous thrombosis (DVT) (3.58; 95% CI 2.8–4.5).
1.77–3.06), vena cava thrombosis (1.96; 95 % CI 1.42–2.64) and cerebral venous thrombosis (1.74; 95 % CI 1.30–2.28). Budd-Chiari syndrome (SIR, 0.92; 95 % CI 0.24–2.38) and renal vein thrombosis (SIR, 1.72; 95 % CI 0.62–3.77) were not significantly associated with FH of VTE. However, these two conditions were rare and we cannot draw firm conclusions from this negative finding. Thus, FH of VTE is an important risk factor for the most unusual forms of VTE (66).

### Shared familial susceptibility for different VTE manifestations

The Factor V Leiden has been shown to be a stronger risk factor for DVT of the lower extremities than for PE, which is named the factor V paradox (67, 68). Zöller et al. therefore determined whether DVT of the legs, PE and other forms of VTE share familial susceptibility (69). However, concordant (same VTE manifestation in case and relative) and discordant (different VTE manifestation in case and relative) familial risks showed no major differences indicating shared familial susceptibility for DVT of the legs, PE and other forms of thromboembolic manifestations (69).

*In study by Kucher et al. of risk factors for symptomatic pulmonary embolism (PE) in DVT patients FH of DVT/PE was associated with symptomatic PE (p<0.001) (70). However, FH was not an independent risk factor for PE among DVT patients.*

### Multiplex families

Familial risks of VTE in families with several affected members are of special interest, i.e. multiplex families. In Swedish multiplex families with two or more affected siblings we have found very high risks for VTE and PE (11, 61). The SIR for siblings with 2 and ≥3 affected probands were 51.87 (95 % CI, 31.47 to 85.00) and 53.69 (95 % CI, 25.59 to 108.50), respectively (11). Considering only PE the SIR for siblings with two affected probands was 114.29 (95 % CI 56.57–223.95) (61). These high risks are close to what is

#### Table 1: Characteristics of cross-sectional and case-control studies examining the relationship between family history of VTE and risk of VTE in first degree-relatives.

<table>
<thead>
<tr>
<th>1st Author, Year, Country</th>
<th>Study design</th>
<th>VTE cases (n)</th>
<th>Age range (years)</th>
<th>Females (%)</th>
<th>Relatives included</th>
<th>Familial risk 95 % CI</th>
<th>Settings</th>
<th>VTE type cases</th>
<th>VTE type relatives</th>
<th>Adjusted Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dowling, 2002, USA [44]</td>
<td>Case-control</td>
<td>370</td>
<td>49.2***</td>
<td>189 (51 %)</td>
<td>Not reported</td>
<td>2.3 (1.4–3.8)</td>
<td>Hospital</td>
<td>DVT, PE</td>
<td>Not reported</td>
<td>Age, sex, race, education</td>
</tr>
<tr>
<td>Lidegaard, 2002, Denmark [53]</td>
<td>Case-control</td>
<td>987</td>
<td>15–44</td>
<td>987 (100 %)</td>
<td>Not reported</td>
<td>3.0 (2.3–4.0)</td>
<td>Nationwide</td>
<td>VTE</td>
<td>VTE</td>
<td>Age, oral contraceptive use, years of schooling, family acute myocardial infarction, hypertension.</td>
</tr>
<tr>
<td>Tosetto, 2003, Italy [52]</td>
<td>Cross-sectional</td>
<td>116</td>
<td>53***</td>
<td>74 (64 %)</td>
<td>All first-degree relatives</td>
<td>4.5 (2.4–8.5)</td>
<td>Population based</td>
<td>VTE</td>
<td>VTE</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Blom, 2005, Netherlands [54]</td>
<td>Case-control</td>
<td>179</td>
<td>45, 20.5–67.2*</td>
<td>100 (55.9 %)</td>
<td>Parents under the age of 50 years</td>
<td>2.8 (1.6–4.9)</td>
<td>Population based</td>
<td>Upper extremity DVT</td>
<td>DVT</td>
<td>Age and sex</td>
</tr>
<tr>
<td>Noboa, 2008, France [43]</td>
<td>Case-control</td>
<td>698</td>
<td>67±18**</td>
<td>382 (55 %)</td>
<td>All first degree relatives</td>
<td>2.7 (1.8–3.8)</td>
<td>Hospital</td>
<td>DVT, PE</td>
<td>VTE</td>
<td>Factor V Leiden, FII G20210A</td>
</tr>
<tr>
<td>Bezemer, 2009, Netherlands [30]</td>
<td>Case-control</td>
<td>1605</td>
<td>50, 27–68*</td>
<td>833 (52 %)</td>
<td>Parents, siblings</td>
<td>2.2 (1.9–2.6)</td>
<td>Anticoagulation clinics</td>
<td>DVT and PE</td>
<td>DVT</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Milli, 2011, USA [55]</td>
<td>Case-control</td>
<td>1094</td>
<td>50.0, 25–68*</td>
<td>545 (50 %)</td>
<td>All first-degree relatives</td>
<td>2.9 (2.0–4.1) blacks 2.7 (1.9 3.7) whites</td>
<td>Hospital</td>
<td>DVT, PE</td>
<td>VTE</td>
<td>Education</td>
</tr>
<tr>
<td>Sonnevi, 2013, Sweden [56]</td>
<td>Case Control</td>
<td>1288</td>
<td>18–64</td>
<td>1288 (100 %)</td>
<td>Parents, siblings</td>
<td>2.2 (1.8–2.7)</td>
<td>Nationwide</td>
<td>DVT, PE</td>
<td>VTE</td>
<td>Age, BMI, surgery/cast, CHC, HT, Factor V Leiden, G20210A</td>
</tr>
</tbody>
</table>

*median age and 5th-95th percentile; ** mean age and standard deviation (SD) for those with no major risk factors. The mean age was 62 and SD 18 years for those with a major risk factor; ***median age; ****mean age.
observed in patients with combined genetic defects, for instance combined Factor V Leiden and protein S deficiency (28).

Family history and second and third degree relatives

Most studies have focused on familial risks in first degree relatives (Table 1 and Table 2). However, first degree relatives usually share a household but second and third degree relatives generally do not. However, half-siblings who are second degree relatives may or may not share a household. In Sweden paternal half-siblings usually do not share a household but maternal half-siblings do (50). The finding of a OR 1.52 in maternal half-siblings (1.26–1.85), 2.34 in paternal half-siblings (2.00–2.73), 1.69 in cousins (1.33–1.64), therefore indicate an important genetic contribution to the increased familial risks of VTE (50).

### Table 2: Characteristics of cohort studies (including historical cohort studies) examining the relationship between family history of VTE and risk of VTE.

<table>
<thead>
<tr>
<th>1st author, year, country</th>
<th>Study design</th>
<th>VTE cases (n)</th>
<th>Age range (%)</th>
<th>Relatives</th>
<th>Familial risk 95% CI</th>
<th>Settings</th>
<th>VTE type cases</th>
<th>VTE type relatives</th>
<th>Adjusted variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosson, 2006, France [58]</td>
<td>Cohort</td>
<td>164</td>
<td>39–103 **</td>
<td>Not reported</td>
<td>1.68 (1.17–2.42)</td>
<td>Medical outpatient</td>
<td>VTE</td>
<td>VTE</td>
<td>Varicose veins, thrombophylaxis, cancer, previous VTE, myeloproliferative disorder</td>
</tr>
<tr>
<td>Spannagl, 2005, Germany [59]</td>
<td>Cohort</td>
<td>34</td>
<td>26±8.6*</td>
<td>Not reported</td>
<td>Crude: 3.4 (1.6–7.1) Adjusted: 2.4 (1.0–5.4)</td>
<td>Community based</td>
<td>VTE</td>
<td>VTE</td>
<td>Age, BMI, hormone use, smoking, personal history of VTE, thrombophilies, family history of varicose veins, myocardial infarction, and stroke</td>
</tr>
<tr>
<td>Rojnuckarin, 2011, Thailand [57]</td>
<td>Cohort</td>
<td>27</td>
<td>58***</td>
<td>Not reported</td>
<td>120.28 (6.89–2101)</td>
<td>Hospitalised patients</td>
<td>PE, DVT</td>
<td>VTE</td>
<td>Comorbidities</td>
</tr>
<tr>
<td>Sørensen, 2011, Denmark [60]</td>
<td>Cohort</td>
<td>19599</td>
<td>0–57</td>
<td>Siblings</td>
<td>3.08 (2.80–3.39)</td>
<td>Nationwide</td>
<td>DVT, PE</td>
<td>DVT, PE</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Zöller (parents), 2011, Sweden [62]</td>
<td>Cohort</td>
<td>45362</td>
<td>0–75</td>
<td>Parents</td>
<td>2.00 (1.94–2.05)</td>
<td>Nationwide</td>
<td>VTE</td>
<td>VTE</td>
<td>Age, sex, time period, socioeconomic status, region of residence</td>
</tr>
<tr>
<td>Zöller (siblings), 2011, Sweden [11]</td>
<td>Cohort</td>
<td>45362</td>
<td>0–75</td>
<td>Siblings</td>
<td>2.45 (1.66–3.61)</td>
<td>Nationwide</td>
<td>VTE</td>
<td>VTE</td>
<td>Age, sex, time period, socioeconomic status, region of residence</td>
</tr>
<tr>
<td>Zöller, 2012, Sweden [61]</td>
<td>Cohort</td>
<td>20860</td>
<td>0–76</td>
<td>Parents, siblings</td>
<td>1.96 (1.86–2.06) parents 2.67 (1.74–4.09) siblings</td>
<td>Nationwide</td>
<td>PE</td>
<td>PE</td>
<td>Age, sex, time period, socioeconomic status, region of residence</td>
</tr>
</tbody>
</table>

*mean age and standard deviation for the whole cohort. ** The whole cohort. *** mean years.
Family history of VTE and unprovoked VTE

In a study by Couturaud et al. the risk for VTE in first-degree relatives was higher if the index cases had an unprovoked compared with a provoked VTE (OR, 2.38; 95% CI, 1.43–3.85) (63). Thus, relatives to patients with spontaneous thrombosis and especially at younger age (below 45 years) have a substantial risk for VTE (63, 64).

Family history of VTE and surgery

Cook et al. identified that a combined variable of personal or FH of VTE (HR 4.0, 95% CI 1.5–10.3) was a risk factor for VTE medical-surgical patients in intensive care (77). Markovic-Denic prospectively followed 499 adult patients undergoing total hip and knee replacement (78). Family history of VTE was an independent risk factor for postoperative VTE (OR=6.61 95% CI 1.33–32.90) (78). Sonnevi et al. found that self-reported FH of VTE was associated with an increased odds of VTE in connection with surgery or plaster (56). However, in prospective analysis of 3,289 consecutive patients managed, with total hip or total knee arthroplasty, by Lewis et al. FH of VTE was not a risk factor for postoperative VTE during 90 days follow-up (79). Pannucci et al. used FH of VTE in a weighted risk index for postoperative thrombosis including a total of seven VTE risk factors in two cohorts of surgical patients (80). The areas under the receiver-operator curve (ROC) were 0.72 and 0.70, respectively. An 18-fold variation in 90-day VTE rate was identified with the used risk index (80).

Family history of VTE and cancer

In a study by Kristinsson et al. myeloma patients with a FH of VTE had an OR for VTE of 2.2 (95% CI 1.8–2.7) compared to myeloma patients without a FH of VTE (81). In a study by Srkalovic et al. the HR for VTE was even higher in myeloma patients with a FH of VTE compared with those without a FH (HR=9.59, 95% CI 1.29–71.20) (82). In another study by Kröger et al. of 507 patients with different cancer types FH of VTE was suggested to be a risk factor for VTE, with an approximate two-fold increase OR of borderline significance (p=0.0498) (83). Milli et al. found an association between FH of DVT and VTE in black but not white cancer patients (OR=6.4, 95% CI 1.3–31.9 and OR=2.0, 95% CI 0.72–5.4) (55).

Family history and oral contraceptives

In a study of 50 women with VTE using oral contraceptives, 16% had a FH of VTE (33). In a case-control study of women with VTE, aged 18–64 years, self-reported FH of VTE in combination with combined oral contraceptive use gave a very high OR for VTE of 15.3 (95% CI = 6.1–38), compared with non-users without a family history of VTE (56). Roach et al. found a high risk of VTE in users of oral contraceptives (OR 14.2; 95% CI, 6.7–30.0) or hormone replacement therapy (OR 2.4; 95% CI, 1.4–4.1) with FH of VTE compared with women who were non-users and lacked FH of VTE (84).

Family history of VTE and seasonal variation of VTE

Seasonal variation in VTE incidence in individuals with familial predisposition to VTE was explored in a nationwide study (85). Seasonal variation in VTE incidence, mostly with a peak during the winter, was observed among persons with and without FH with overall peak-to-low ratios (PLRs) of 1.15 and 1.21, respectively. The peak day was December 25 for persons with a FH of VTE and February 1 for persons without FH of VTE. Seasonal variation was most pronounced among persons aged >50 years. Among persons aged 0–25 years with a FH, the peak for VTE was in July (PLR = 1.20). Significant seasonal variation was observed for both PE and DVT incidence. However, among persons with FH no seasonal variation was observed for DVT incidence (PLR = 1.01). This study supports the presence of a modest seasonal variation of VTE among individuals with and without a FH of VTE. However, young age and FH may modify and attenuate the effect of season on VTE (85).

Predicting VTE with a combination of family history and genetic variants

An interesting focus of research is whether a combination of a clinical risk score including FH and a risk score of known genetic risk factors better predicts VTE than FH or genetic risk score alone. Bruzelius et al. found that seven SNPs (F5 rs6025, F2 rs1799963, ABO rs514659, FGG rs2066865, F11 rs2289252, PROC rs1799810 and KNG1 rs710446) contributed to the genetic risk score for VTE, with an area under the curve (AUC) of 0.66 (95% CI, 0.64–0.68) (86). The AUC for a clinical risk score (including height, body mass index (BMI), immobilisation, long-distance flight, hormonal use, FH of VTE) was 0.80 (95% CI 0.79–83). After adding the clinical risk score, the AUC reached 0.84 (95% CI, 0.82–0.85). Cohen et al. used a five-variable score, named the MARNI score, derived from FH score of VT, von Willebrand factor antigen levels, age, severity of thrombophilia, and FGG rs2066865 in families with inherited VTE (87). The risk of VT ranged from 0.2% for individuals with a score of 0 (n = 186) to >70% for individuals with a score of ≥7 (n = 27). Thus, a combination of genetic variants, FH and other risk markers appears to be a promising novel avenue for risk assessment.

Biochemical properties linked to familial clustering of VTE

The association of an intermediate phenotype in VTE facilitates the discovery of new familial risk factors. Linking biochemical
properties to familial clustering of VTE would allow for GWAS (genome-wide association study) and identification of potential novel VTE loci. Wichers et al. determined overall haemostasis assays (i.e. thrombin generation time (TGT), endogenous thrombin potential (ETP), prothrombin fragment 1+2 (F1+2) and activated protein C-sensitivity ratio (APC-sr) and clot-lysis time (CLT)) in families with unexplained thrombophilic inheritance (88). Only ETP was associated with VTE (OR 1.03 for each % increase, 95% CI, 1.01–1.05) (88). Thus, increased ETP may serve as a correlate phenotype for VTE and may be used to discover novel inherited risk factors by GWAS and genetic linkage analysis. In a similar study FVIII levels were significantly (P=0.038) clustered within families in which a member showed high FVIII levels after previous VTE (89).

**Accuracy of family history for detection of major thrombophilias**

Several reports have determined whether FH of VTE is associated with thrombophilias among patients with or without a personal history of VTE (31–42). The selection of patients, definitions of FH and included thrombophilias have varied between these studies. In a systematic review by Grimes et al. the value of FH to identify inherited thrombophilias a sensitivity ranging from 16 to 63% and a positive predictive value of 6–50% was reported (38). Grimes et al. concluded that FH of VTE, even in high prevalence populations, has a low predictive value. In Table 3 studies of FH of VTE as a predictor for major thrombophilias (i.e. F5 rs6025, F2 rs1799963, and deficiencies of protein S, protein C and antithrombin) in women without a personal history of VTE are presented. The sensitivity and positive predictive value of FH of VTE for thrombophilias were low, suggesting the presence of other, today unknown, familial and possible genetic factors.

**Pleiotropic effects**

Pleiotropy is when one gene has an effect on multiple phenotypes or diseases (90, 91). The molecular mechanisms of pleiotropy may be related to multiple molecular functions of a single gene product or multiple consequences of a single molecular function (90). GWAS have identified a growing number of gene variants that affects multiple traits, indicating that pleiotropic effects on human complex traits may be widespread (90, 91). Pleiotropy may also be reflected in shared familial susceptibility. If there is no shared familial susceptibility then it is unlikely that the disorders share strong and common genetic variants.

**Family history of VTE and myocardial infarction**

Lind et al. found that FH of myocardial infarction increased risk of VTE (HR, 1.26; 95% CI, 1.02–1.55) in a cause-specific Cox model (92). This confirms a previous study from the same Tromø study by Brøkkkan et al. that found that FH of myocardial infarction (HR 1.3; 95% CI, 1.04–1.65) was significantly associated with VTE (93). Milli et al. found that FH of myocardial infarction was a risk factor for VTE among whites (OR 1.3; 95% CI, 1.03–1.8) but not blacks (OR 1.2; 95% CI, 0.89–1.5) (94). However, in a large Swedish nationwide study the association with CHD was weaker (95). For instance, the offspring of parents with CHD had an increased risk of VTE (SIR 1.03; 95% CI, 1.01–1.04). In spouses of CHD patients risk of VTE was increased by a minor amount (SIR 1.03; 95% CI, 1.02–1.03). Subanalyses of cases of myocardial infarction and PE/DVT showed similar results. The familial background of CHD and myocardial infarction in this study was different from that of VTE (95). The study suggests that it is unlikely that major shared disease-causing mutations exist to a large extent in the Swedish population. This was confirmed at the molecular level by Bruzelius et al. (96). Among 39 single nucleotide polymorphisms in 32 loci associated with coronary artery disease in GWAS only rs579459 in the ABO locus demonstrated a significant association with VTE (96).

**Family history of VTE and ischaemic stroke**

In a Swedish nationwide study Zöller et al. determined whether VTE shares familial susceptibility with ischaemic stroke (97). Offspring of parents with VTE were at increased risk for ischaemic

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**Table 3: Characteristics of studies examining the sensitivity and positive predictive value of family history of VTE for the five major thrombophilias (i.e. F5 rs6025, F2 rs1799963, and deficiencies of protein S, protein C and antithrombin) among women without personal history of VTE.**

<table>
<thead>
<tr>
<th>1st Author, Year, Country</th>
<th>Cases, N</th>
<th>Age range</th>
<th>Females</th>
<th>Relatives</th>
<th>Family history (%)</th>
<th>Settings</th>
<th>Sensitivity (%)</th>
<th>Positive predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosmi, 2001, Italy [31]</td>
<td>324</td>
<td>15–49</td>
<td>100</td>
<td>First and second degree</td>
<td>34 (10)</td>
<td>Gynaecological outpatients</td>
<td>3/19 (16)</td>
<td>3/34 (9)</td>
</tr>
<tr>
<td>Cosmi, 2003, Italy [32]</td>
<td>479</td>
<td>15–49</td>
<td>100</td>
<td>First and second degree</td>
<td>49 (10)</td>
<td>Family planning clinic</td>
<td>3/36 (8.3)</td>
<td>3/49 (6.1)</td>
</tr>
<tr>
<td>Horton, 2010, USA* [41]</td>
<td>5168</td>
<td>21–29</td>
<td>100</td>
<td>First and second degree</td>
<td>412 (8)</td>
<td>Multicenter study of women with singleton pregnancy</td>
<td>23/140 (16)</td>
<td>23/412 (5.6)</td>
</tr>
</tbody>
</table>

*Only Factor V Leiden was determined.
stroke: OR, 1.10 (95% CI, 1.06–1.14). Siblings of probands with VTE had no increased risk of ischaemic stroke: OR, 1.05 (95% CI, 1.00–1.11). Spouses of probands with VTE were at increased risk for ischaemic stroke: OR, 1.18 (95% CI, 1.10–1.27). Conversely, the risks for VTE in relatives of probands with ischaemic stroke were OR, 1.15; 95% CI, 1.10–1.21 (offspring); OR, 1.07; 95% CI, 1.02–1.12 (siblings); and OR, 1.21; 95% CI, 1.11–1.32 (spouses). The study shows VTE does not share strong familial susceptibility with ischaemic stroke in the Swedish population. Moreover, familial non-genetic factors contributed to the observed minor familial associations. Thus it is unlikely that shared strong disease-causing mutations exist to a large extent in the Swedish population for ischaemic stroke and VTE (97).

Family history of VTE and cancer
Cancer and VTE are associated disorders. In a nationwide study, Zöller et al. analysed the risk of cancer in siblings, offspring and spouses of individuals hospitalised for VTE (and vice versa) in order to identify shared familial risk factors for cancer and VTE (98). No overall associations between cancer and VTE were observed in parent-offspring pairs. The risk of cancer was slightly increased in siblings of VTE patients (1.03, 95% CI 1.01–1.06), and the risk of VTE was also increased in siblings of cancer patients (1.07, 95% CI 1.04–1.10). Risks of cancer were also slightly increased in the husbands (1.09, 95% CI 1.07–1.11) and wives (1.02, 95% CI 1.00–1.05) of individuals with VTE. Thus, VTE and common cancers shared only minor familial risk factors. Moreover, these factors are expected to be mainly environmental because of the positive associations in the spouse and sibling analyses and negative associations in the parent-offspring analysis, although the possibility of shared genetic risk factors also exists (98).

Family history of VTE and preeclampsia/eclampsia
Divergent results exist whether Factor V Leiden and other thrombophilias are risk factors for preeclampsia/eclampsia (99, 100). Zöller et al. therefore determined whether FH of VTE is a risk factor for preeclampsia/eclampsia (101). Family history of VTE had only minor effects on the risk of preeclampsia/eclampsia (101), suggesting that genetic factors associated with VTE are unlikely to be strong and common risk factors for preeclampsia/eclampsia, though the possibility of some shared genetic risk factors exists.

Family history of VTE and varicose veins
Varicose veins have previously been associated with VTE (102). In a nationwide study Zöller et al. determined whether VTE shares familial susceptibility with varicose veins (103). An increased risk of VTE was observed in persons whose siblings had varicose veins (FRR 1.30; 95% CI 1.26–1.33), whereas persons whose siblings had VTE had an increased risk of varicose veins (FRR 1.30; 95% CI, 1.27–1.34). If two or more siblings were affected by VTE, the risk for varicose veins was 1.70 (95% CI, 1.53–1.88). Conversely, if two or more siblings were affected by varicose veins, the risk for VTE was 1.52 (95% CI 1.38 to 1.67). In spouses the association between VTE and varicose veins was weak. Thus, varicose veins and VTE share familial susceptibility, which suggests the existence of shared familial and possibly genetic factors (103).

Family history of VTE and sudden death
In a case-control study by Prandoni et al, a positive FH of VTE or sudden death increased the risk of VTE by 3.7 (95% CI 2.9–4.7) and 2.2 (95% CI 1.4–3.4), respectively (104). This study suggests that among patients with sudden death, familial PE may constitute a significant proportion.

Family history of VTE and psychological aspects
Few studies have determined the psychological aspects of FH of VTE. Klok et al. found that quality of life (QoL) was higher in PE patients with FH of VTE (105). The presence of family members who have a history of the same condition was associated with improved social status, decreased intensity of complaints and a smaller amount of emotional complaints. The authors hypothesised that this phenomenon might be related to enhanced social support, which is an important aspect of QoL (105).

Parrott et al. examined the in-depth life reflection interviews of 20 women who experienced a first venous blood clot between the ages of 18 and 50 years, identifying causal attributions the women made for thrombosis after the event (106). Four women were aware of a FH of VTE when the event occurred, 13 had such a history but lacked awareness until the VTE event, and three had no known history. VTE diagnosis occurred sooner among women with awareness of their FH of VTE. Thus, awareness of FH of VTE may promote survival and efficiencies in health care due to earlier diagnosis (106).

Discussion
The findings from our review of the published literature on familial aggregation of VTE are consistent with a two- to three-fold increased risk of VTE associated with FH of VTE in first-degree relatives with evidence of risk being related to early age of diagnosis, number of relatives affected, provoking factors and genetic distance to affected relative. Moreover, FH is not explained more than partially by major thrombophilias. Family history studies remain the most easily accessible way of measuring the hereditary component of a disease and they represent the overall interaction between environmental, epigenetic and genetic factors (2). Family history will remain highly relevant for years to come (2) even when sequencing a patient’s genome may cost less than $1,000 in the future. The interpretation of family studies always requires caution: while familial risks are compatible with genetic predisposition, they could reflect common exposures (4, 5). Cohort studies of twins are classically used to separate genetic and environmental influences on familial aggregation of a disease but only one twin study has been published (42). However, three extended
family studies and one adoption study further indicates an important genetic contribution to the familial risks of VTE (46, 47, 50, 51). The contribution of shared adult environmental risk factors to familial VTE risk may also be tested through risk estimation associated with an affected spouse since concordance of lifestyle habits between spouse pairs has been reported. However, only small spouse risks were observed for VTE and remained lower than the risk associated with an affected relative which is consistent with possible genetic factors (11, 50, 62).

Information from family studies could be useful when planning studies to identify new genetic variants associated with VTE. It is evident that the importance of FH is dependent on age, number of affected relatives and presentation of VTE (unprovoked or provoked), and degree of relatedness. The present review suggests that gene hunt for novel thrombophilias will be most successful in families with two or more affected siblings and also in individuals with spontaneous thrombosis at younger ages especially before the age of 50. In a recent study of siblings a novel VTE susceptibility locus on chr7 has been found suggesting that this is a feasible approach (107), although this association remains to be replicated.

Family studies may also be used to generate hypothesis and discover new associations. For instance an association between varicose veins and VTE FH suggests that common familial and possible genetic factors exist for these conditions (103). However, for most other tested potential pleiotropic association for VTE and other disorders the familial risks are low. Thus, the familial inherited factors involved in VTE are most important in venous disorders, though minor associations with other diseases exist such as CHD, ischaemic stroke, cancer, and preeclampsia/eclampsia. The association between FH of VTE and sudden death is also interesting and suggests that PE contributes significantly to sudden death (104).

A limitation of nationwide family studies is the lack of information on smoking, weight, height, BMI and laboratory analysis. However, in the Swedish medical birth register and the military conscript register information on smoking, weight, height and BMI may be found. The large size of nationwide studies is a major advantage because they offer powerful data sets. Moreover, nationwide family studies may be conducted relatively cheaply as long-term follow-up register based data already exists for the entire population. Thus, it is faster to test hypotheses and generate new ideas using nationwide registers and to predict long-term follow-up risks.

An issue inherent in many case–control studies is that of recall bias. The diagnosis of VTE in an individual may bring to light knowledge or awareness of VTE in relatives. Bias from this source can be eliminated by collecting the FH data before diagnosis (prospective/cohort study design). Alternatively, verification of VTE or cause of death among relatives from medical records or death certificates will eliminate recall bias. However, most case control studies were similar to results from register based cohort studies (Table 2). Selection bias may also exist in case control studies.

An important issue is the predictive values of FH. The predictive value depends not only on the sensitivity and specificity of a test (i.e. FH) but also on the prevalence rate of the disease in the population (i.e. VTE) (108). If the prevalence of a disease is low, even a valid test with high sensitivity will yield a low predictive value if the specificity is low. In populations with a high prevalence of the disease, the predictive value of a test increases dramatically. Thus, establishing the clinical validity of FH tools will require research involving the use of FH tools in different populations, and careful interpretations of results from case-control studies.

Future opportunities could be to include FH of VTE in risk index scores (80, 86, 87). This could further increase the value of FH in clinical risk assessment. Though FH of unprovoked VTE is most important, the present review indicates that FH of VTE is also important in specific risk situations such as oral contraceptives, surgery and cancer. Another interesting issue that is worth further elucidation is why FH of VTE is less important for recurrent than for primary VTE (72–74).

In summary, FH of VTE is a clinical relevant risk factor for VTE. This systematic review finds a significant increase of VTE risk associated with having an affected relative. The risk being further increased with earlier age of onset of the disease and with multiple affected family members. This suggests that VTE risk may be in part genetically determined. Furthermore, a twin study, an adoptee study and three extended family studies together with the low risk among spouses favor an important genetic susceptibility. Unknown genetic variants are likely to exist, as known thrombophilias are only present in 30% of cases with VTE. Ultimately, verification of a genetic predisposition must come from the identification of causal mutations. Until then, FH of VTE will remain important for risk assessment of VTE.

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Conflicts of interest

None declared.

References


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