Quantification of risk factors for venous thromboembolism: a preliminary study for the development of a risk assessment tool

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Background. Venous thromboembolism is a frequent and serious disorder influenced by numerous factors. As the first step in creating a tool to assess an individual patient's risk of venous thromboembolism, we carried out a literature review in order to quantify risk factors for venous thromboembolism.

Evidence and Information Sources. Risk factors were identified as being either predisposing, that is, those risks presented by a patient prior to hospital admission, or exposing, that is, those risks occurring when a patient is hospitalized for a certain medical condition or surgical procedure. Predisposing risk factors were classified with regard to the patients' characteristics (including general characteristics and inherent risk factors), and recent and chronic clinical conditions.

Results. The major predisposing factors among the patients' characteristics were age, hormonal therapy and personal history of venous thromboembolism, along with inherited coagulation factor abnormalities. Clinical situations associated with the highest risk of venous thromboembolism were recent surgery, hospitalization for medical conditions and immobilization, moderate to severe congestive heart failure, and malignancy.

Conclusions. This literature review will assist in the development of a suitable risk assessment tool for aiding healthcare professionals to decide whether to employ thromboprophylaxis, and, if so, to select the appropriate type and duration of prophylaxis.

Key words: venous thromboembolism, risk factor, prophylaxis.

Haematologica 2003; 88:1410-1421
http://www.haematologica.org/2003_12/1410.htm

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Venous thromboembolism (VTE) remains a major cause of morbidity and mortality for a large group of patients undergoing medical or general surgical procedures. Studies performed during the last decade indicate that the incidence of diagnosed VTE in the general population is 1 to 2 per 1000 persons per year[1-3] with the 90-day survival after VTE being 69%.[4] Thromboprophylaxis is therefore an important aim of modern medicine.

Current prophylactic strategies are based on assigning groups of patients to risk categories according to the presence of VTE risk factors. Risk assessment models have been designed to facilitate this process. The use of scores, of variable complexity, allows stratification of patients into risk groups, typically either three or four groups. The majority of patients are therefore considered in stereotypic standard clusters. Thrombosis is, however, a multifactorial disease and patients may have multiple risk factors simultaneously.[4] Even in situations with an intrinsically low VTE risk, a sudden, unexpected VTE event may occur because of the superimposition of this single event on other chronic and/or transient risk factor(s) for VTE. Accordingly, thromboprophylaxis would be improved if it were feasible to obtain individual VTE risk profiles which could then be used to guide the choice of prophylactic method on an individual basis. A Taskforce Group was formed to develop a risk assessment tool that would be capable of linking the risk profile to appropriate prophylaxis on an individual basis to be used within a routine setting. As a preliminary step in the development of this model, a review of the evidence for each risk factor was required. Risk factors were identified as being either predisposing, that is, those risks presented by a patient prior to hospital admission, or exposing, that is, those risks occurring when a patient is hospitalized for a certain medical condition or surgical procedure. The quantification of the predisposing risks, based upon the results of the literature review, is the focus of the present manuscript.

Methodology

We conducted a literature review of current evidence concerning predisposing risk factors for VTE. To identify all relevant published studies on this topic, electronic databases (MEDLINE, EMBASE) were searched using the following terms: thrombosis, thromboembolism, pulmonary embolism, deep-vein thrombosis, risk factors, epidemiology, case control study, cohort study, and randomized controlled trial, in combination with previously identified individual risk factors. Thrombophilia factors were evalu-

ated using the following key words: antithrombin, protein C, protein S deficiency, activated protein C resistance, factor V Leiden and prothrombin or factor II mutations. Pregnancy, which may involve specific mechanisms and therapeutic management, was not investigated. The majority of information was extracted from case-control and cohort studies, systematic reviews, and randomized studies in which multivariate analyses were used to identify independent risk factors. The majority of studies assessed symptomatic VTE, although some evidence is presented concerning asymptomatic deep-vein thrombosis (DVT). In addition, our study focused more specifically on predisposing risk factors for a first episode of VTE.

Statistical analyses

Independent risk factors for VTE determined using multivariate analyses were extracted from the studies identified. Quantification of the level of risk was reported using odds ratio (OR), relative risk (RR), hazard ratio (HR), relative hazard (RH) or rate ratio (RRo). These variables all represent measures of association between a factor and the subsequent risk of developing VTE. Case-control studies express these proportions of risk as OR, while cohort studies express them as RR, HR or RH. RRo is utilized in descriptions of large population-based analyses. For example, the odds ratio (OR) represents the proportional odds (number of events divided by the number of non-events) in the treated or exposed group compared to the odds in the control group. Epidemiological studies generally try to identify factors that cause harm — those with the OR greater than one. The magnitude of the risk above one represents the degree of harm. All data are presented with the 95% confidence intervals (CI) and pooled data are presented in tables.

Results

Predisposing risk factors were classified according to the patients' characteristics (general characteristics and inherent risk factors) and clinical situations (both acute and chronic). Pooled data showing the risk associated with these factors are summarized in Tables 1-3.

Patients' general characteristics

Gender

The association between gender and VTE is controversial with different studies yielding conflicting results. Two retrospective cohort studies and one case-control study identified a slightly higher risk (OR: 1.2-1.7) of symptomatic VTE in males.[3,5,6] Similarly, the Longitudinal Investigation of Thromboembolism Etiology (LITE) study[7] identified an increased risk of VTE (HR: 1.4 [95% CI: 1.1-1.9]) among males. In contrast, a French study identified a slightly higher incidence of VTE among females (OR: 1.3), confined mainly to the age groups 20-39 years and above 75 years.[1] The risk of symptomatic VTE was also found to be higher in females undergoing total hip arthroplasty (OR: 1.4 [95% CI: 1.0-1.9]) than in males undergoing the same operation.[8] Nordstrom *et al*., however, found no gender difference in the incidence of DVT.[2]

Table 1. Range of venous thromboembolism risk according to patients' general characteristics and major inherent risk factors (excluding coagulation factor abnormalities) in the different studies using multivariate analysis.*

Risk factors	*Risk°*
Age[7,9]	from 1.8 to 14.8
Hyperhomocysteinemia (low methylfolate in red blood cells)[19]	7.1
Antipsychotics[40]	7.1
Oral contraceptives[19,24,25]	from 2.2 to 6.9
Personal history of venous thromboembolism[9,25,42,43]	from 1.7 to 4.7
Obesity[7,8,15,17-20]	from 1.0 to 4.5
Secondary antiphospholipid syndrome[6]	4.3
Family history of venous thromboembolism[19,25]	from 3.3 to 3.4
Smoking[6,7,17,18,21]	from 1.0 to 3.3
Hormone replacement therapy[15,24,34,35]	from 2.1 to 2.7
Black ethnicity (compared to white ethnicity)[7]	1.4
Male gender[7,8]	from 0.6 to 1.4
Aspirin[7,15]	from 0.5 to 1.0
Statin[15,38]	from 0.5 to 0.8

**The risk due to myeloproliferative disorder and primary antiphospholipid syndrome, not evaluated using multivariate analysis, is not presented. °The risk includes odds ratio, relative risk, relative hazard, and hazard ratio.*

Age

Advanced age is a well-accepted independent risk factor for VTE[3] (Figure 1). In patients hospitalized for VTE, Anderson *et al*. found an exponential relationship between VTE incidence and age with a 1.9-fold increase per decade.[5] Similarly, Oger

Table 2. Range of venous thromboembolism risk according to coagulation factor abnormalities.

Coagulation factor abnormality	*Risk of VTE in case-control studies**	*Risk of VTE in family studies**
Factor V Leiden + prothrombin gene mutation[69,70]	20	58.6
Antithrombin, protein C or protein S deficiency[57-59,61]	from 1.7 to 6.5	from 5.0 to 42.8
Factor VIII > 90-95th percentile (*versus* lowest quartile)[51,52]	from 3.8 to 11	–
Factor V Leiden heterozygote[19,58,59,62,63,66]	from 4.9 to 9.7	from 2.5 to 16.3
Prothrombin gene mutation heterozygote[62,66-68]	from 2.8 to 3.8	from 2.0 to 3.6
Factor VII >95th percentile (*versus* lowest quartile)[51]	2.4	–
Factor IX >90th percentile (*versus* lowest quartile)[53]	2.2	–
Factor XI >90th percentile (*versus* lowest quartile)[54]	1.9	–

*This table presents risks obtained using univariate or multivariate analysis, depending on the study. *The risk includes odds ratio, relative risk, and hazard ratio.*

Table 3. Range of venous thromboembolism risk according to clinical situations in the different studies using multivariate analysis.*

Risk factors	*Risk°*
Recent surgery[15,25,43]	from 3.7 to 21.7
Non-surgical hospitalization or immobilization[22,39]	from 5.7 to 11.1
Congestive heart failure[15,43,71]	from 1.4 to 9.6
Malignancy + chemotherapy[43]	6.5
Venous catheter[43,79]	from 5.6 to 6.0
Myocardial infarction[15]	5.9
Malignancy[6,7,9,15,19]	from 2.4 to 5.6
Venous insufficiency[9,21,43]	from 0.9 to 4.2
Ischemic stroke[15,43]	from 2.0 to 3.0

**The risks due to inflammatory bowel disease, nephrotic syndrome, chronic obstructive pulmonary disease and prolonged travel, not evaluated using multivariate analysis, are not presented. °The risk includes odds ratio, relative risk, and relative hazard.*

identified that the incidence of VTE increased markedly with age, especially in people aged over 75 years, in whom the annual incidence of VTE was twice that in the age group 60-74 years.[1] The LITE study,[7] too, found that age independently increased the risk of VTE by approximately 2-fold per decade with patients 85 years or over having a 15-fold higher risk than those aged 45-54 years (HR: 14.8 [95% CI: 6.3-35.1]). In an outpatient setting, patients aged over 65 years had a higher risk of developing DVT (OR: 1.8 [95% CI: 1.2-2.3]) when compared with younger patients.[9] Patients undergoing hip or knee arthroplasty[10] show an increased risk of symptomatic VTE with age (OR: 1.15 per decade > 50 years of age).

Blood group

Non-O blood group has consistently been demonstrated to be associated with an increased risk of VTE.[2,11,12] However, whereas univariate analysis showed non-O blood group to be associated with a significantly higher risk of VTE compared with O blood group (OR: 1.5 [95% CI: 1.0-2.2]), this higher risk was no longer significant when multivariate analysis accounted for plasma levels of factor VIII, indicating that the increased VTE risk was largely due to higher levels of factor VIII.[11]

Geography and ethnicity

Several studies have demonstrated differences in the incidence of VTE among different ethnic groups living in the same region.[13,14] In California,[13] African Americans were found to have a higher risk than whites of developing idiopathic DVT (RRo: 1.3 [95% CI: 1.1-1.5]), while Asians and Pacific Islanders had a significantly lower risk (RRo: 0.3 [95% CI: 0.2-0.3]). In the LITE study,[7] black ethnicity was independently associated with an increased VTE risk when compared with white ethnicity (HR: 1.4 [95% CI: 1.0-1.9]).

Obesity

Whereas the Heart and Estrogen/progestin Replacement Study (HERS) study[15] showed no association between obesity and VTE, several other studies have demonstrated the association.[7,8,16-20] For example, in the Nurses' Health study,[17] patients with a body mass index of over 29 kg/m^2 had a 3-fold increase (RR: 2.9 [95% CI: 1.5-5.4]) in

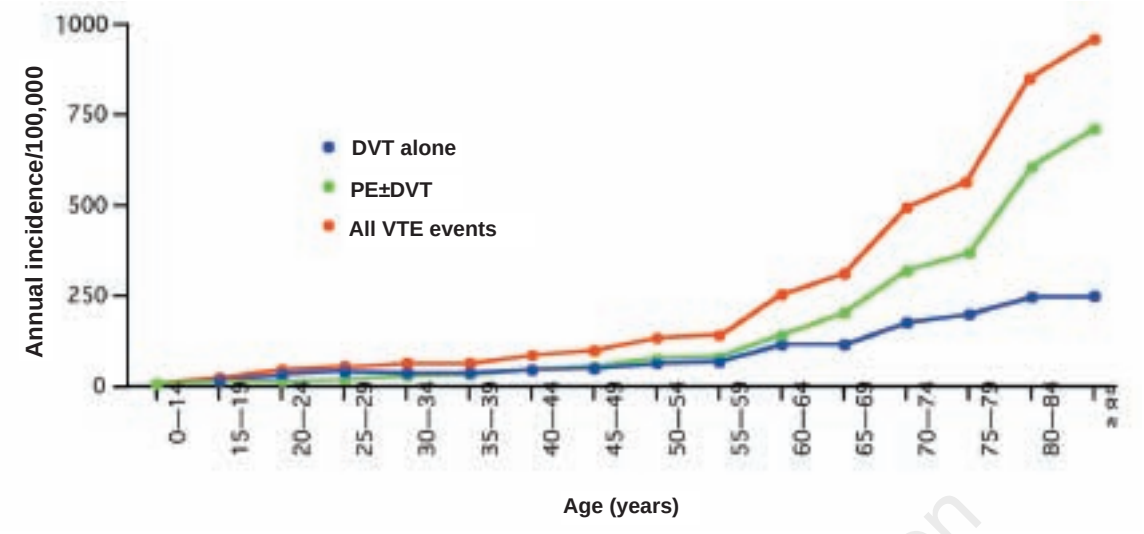

Figure 1. Annual incidence of deep-vein thrombosis (DVT) alone, pulmonary embolism ± deep-vein thrombosis (PE ± DVT) and all venous thromboembolic events (VTE) among residents of Omsted County, Minnesota, from 1966 to 1990, by age.[3]

the risk of pulmonary embolism (PE). Hansson *et al*.,[18] demonstrated that middle-aged men with a waist circumference of 100 cm or more had an increased risk of symptomatic DVT (adjusted RR: 3.9 [95% CI: 2.1-7.3]).

Smoking

Cigarette smoking is an established risk factor for atherosclerotic vascular disease; however, its relationship with VTE remains controversial. While the Nurses' Health Study,[17] showed cigarette smoking to be an independent predictor of PE (RR: 3.3 [95% CI: 1.7-6.5]), and a population-based study[18] showed an elevated VTE risk among men who smoked 15 cigarettes per day (adjusted RR: 2.8 [95% CI: 1.3-6.1]), other studies have failed to find any association between smoking and VTE.[6,7,21]

Specific Drug Use

Oral contraceptive

Numerous studies have confirmed the association between VTE and use of oral contraceptives. Caution should, however, be adopted when interpreting the data, since the baseline risk among young women is low, being approximately 0.3/10,000 per year.[22] Reviewing 22 studies of similar design, Douketis *et al*.[23] found a 2- to 4-fold increase in the risk of VTE among users of any oral contraceptive compared with placebo. In the Nurses' Health Study,[24] current users of oral contraceptives had a 2-fold increased risk of PE (RR: 2.2 [95% CI: 0.8-5.9]), although past use did not confer the same level of risk (RR: 0.8 [95% CI: 0.5-1.2]). Two other studies[19,25] confirmed that users of oral contraceptives had a higher risk of VTE with an OR of 4.9 (95% CI: 1.8-13.1) and 6.9 (95% CI: 1.9-25.4), respectively. Several studies [3,26,27] have demonstrated that third-generation pills (containing a gonane progesterone such as desogestrel) are associated with a greater VTE risk (OR: 1.7-5.0) than are second-generation pills (containing the progestogen levanorgestrel). Finally, the increased risk of VTE seems to be predominant in the first year of use,[28,29] and compounded in patients with additional risk factors, such as obesity[20] or factor V Leiden.[30]

Hormone replacement therapy

Several observational and case-control studies initially suggesting a 2- to 4-fold increased risk of VTE[23,31-33] with the use of hormone replacement therapy were subsequently confirmed by larger studies using multivariate analysis. The Nurses' Health Study[24] identified a 2-fold increased risk of PE among users of postmenopausal hormone therapy (RR: 2.1 [95% CI: 1.2-3.8]), while past use produced no increase in risk (RR: 1.3 [95% CI: 0.7-2.4]). In the HERS study,[15] 2763 women randomized to hormone replacement therapy had a 3-fold higher risk of VTE (RH: 2.7 [95% CI: 1.4-5.0]) than did the women randomized to placebo. This effect was additive to that of other risk factors, and was highest in the first two years following initiation of therapy. The VTE risk declined (RH: 1.4 [95% CI: 0.6-3.1]) in women who continued therapy for a further 2.7 years.[34] Over the total 6.8 years of therapy, the risk was, however, still doubled (OR: 2.1 [95% CI: 1.3-3.4]). Similar results were obtained in the recently completed Women's Health Initiative study in which 16,608 women were randomized to hormone

replacement therapy or placebo.[35] Following a mean follow-up of 5.2 years, women receiving hormone replacement therapy had a 2-fold increased risk of DVT (HR: 2.1 [95% CI: 1.1-3.7]) and PE (HR: 2.1 [95% CI: 1.0-4.5]). Again, the risk was greatest in the first year of use. As the baseline risk of VTE is higher in women using hormone replacement therapy than in younger women using oral contraceptives, the absolute risk of VTE is much higher in the former group.[36]

Aspirin

The potential benefit of aspirin in preventing VTE is uncertain. In the Pulmonary Embolism Prevention study,[37] there was a 36% reduction (95% CI: 19-50%) in symptomatic VTE associated with the use of aspirin among patients undergoing hip fracture surgery; however, the true effect of aspirin in this trial is uncertain since the endpoint diagnoses were not clearly defined and other forms of prophylaxis were allowed, in particular heparins which were used in about 40% of patients. Whereas aspirin use was associated with a halving of VTE risk (RH: 0.5 [95% CI: 0.2-0.8]) in subgroup analysis from the HERS study,[15] it was not associated with reduced VTE risk (HR: 1.0 [95% CI: 0.8-1.3]) in the LITE study.[7]

Statins

While it is recognized that statins are effective in the secondary prevention of arterial thrombosis, current evidence also suggests additional benefit in preventing VTE. One cohort study,[38] showed a 20% reduction in DVT risk (HR: 0.8 [95% CI: 0.7-0.9]), and the HERS trial,[15] showed a 50% reduction in VTE risk (RH: 0.5 [95% CI: 0.2-0.9]). Data concerning the risk of VTE among patients with dyslipidemia are, however, conflicting.[7,17,18,39]

Psychotropic drugs

In a case-control study,[40] current exposure to conventional antipsychotic drugs was associated with an increased risk of idiopathic VTE (adjusted OR: 7.1 [95% CI: 2.3-22.0]). Low-potency antipsychotic drugs (chlorpromazine and thioridazine) seem to confer a higher risk (OR: 24.1 [95% CI: 3.3-172.7]) than do high-potency drugs (haloperidol) (OR: 3.3 [95% CI: 0.8-13.2]), with the risk being highest during the first few months of drug use. Benzodiazepine use has not been shown to confer a significant increase in the risk of VTE.[41]

Inherent risk factors

Previous history of venous thromboembolism

A previous history of VTE is an established strong risk factor for subsequent thromboembolic events. A French case control study[25] showed a past history of VTE to be one of the strongest risk factors for development of DVT (OR: 4.7 [95% CI: 2.4-8.9]). Comparable findings (OR: 1.7) were seen in patients developing DVT either as outpatients[9] or following major surgery.[42] Furthermore, patients with prior superficial vein thrombosis[43] were also shown to have a higher risk of subsequent VTE events (OR: 4.3 [95% CI: 1.8-10.6]). Unfortunately, most studies did not separately analyze patients with an idiopathic VTE and those in whom thrombus formation was associated with additional risk factors.

Family history of venous thromboembolism

A family history of VTE among patients presenting with idiopathic thrombotic events is often suggestive of a thrombophilia condition. Among patients hospitalized for DVT,[25] a family history of VTE was shown to confer a 3-fold increase in risk (OR: 3.3 [95% CI: 1.8-5.9]). Another case-control study[19] showed similar findings (OR: 3.4 [95% CI: 1.8-6.7]).

Thrombophilia

Antiphospholipid syndrome. The association between antiphospholipid syndrome and thrombosis is well recognized. A strong association exists between symptomatic VTE and both primary (without systemic lupus erythematous [SLE]) and secondary (with SLE) antiphospholipid syndromes.[6,44,45] Secondary antiphospholipid syndrome was found[6] to be associated with a 4-fold increased risk of VTE (OR: 4.3 [95% CI: 3.1-5.5]). Among patients with SLE,[45] those with lupus anticoagulant have a much greater VTE risk (OR: 5.6 [95% CI: 3.8-8.3]) than those without lupus anticoagulant. Similarly, patients with anticardiolipin antibodies have a greater VTE risk (OR: 2.2 [95% CI: 1.5-3.1]) than those without anticardiolipin antibodies.[45]

Myeloproliferative disorders. Polycythemia vera, essential thrombocythemia, and chronic myeloid leukemia have all been identified in descending order of magnitude as conferring an increased risk for VTE, particularly thrombosis of hepatic or portal veins.[46,47] In patients with occult cancers,[48] polycythemia vera was associated with an increased risk of VTE (standardized incidence ratio: 12.9 [95% CI: 8.6-18.7]). However, in a population-based case-control study,[43] the increased risk of VTE associated with myeloproliferative disorders was not statistically significant (OR: 4.0 [95% CI: 0.9-18.9]).

Hyperhomocysteinemia. Hyperhomocysteinemia is an established risk factor for atherosclerosis and vascular disease. One meta-analysis of 10 case-control studies,[49] showed that patients with a fasting plasma homocysteine concentration above the 95th percentile or mean plus two standard deviations have a 2-fold increase in the risk of VTE (OR: 2.5 [95% CI: 1.8-3.5]). A subsequent meta-analysis confirmed these findings (OR: 3.0 [95% CI: 2.1-4.2]),

and identified a greater risk among patients younger than 60 years.[50] Low folate levels are a major determinant of high homocysteine levels: patients with low red blood cell methylfolate concentration had a higher VTE risk (OR 7.1 [95% CI: 3.2-15.8]) than did patients with normal red blood cell methylfolate concentration.[19]

Elevated plasma levels of coagulation factors. In the LITE study,[51] subjects with a factor VII plasma level above the 95th percentile had double the risk of VTE when compared to subjects with a factor VII plasma level in the lowest quartile (adjusted HR: 2.4 [95% CI: 1.2-4.8]). Several studies showed that the risk of VTE was related to factor VIII plasma levels.[11,51,52] Patients with factor VIII plasma levels above 200 IU/dL had an 11-fold higher risk of a first episode of VTE (OR: 11 [95% CI: 2-71]) than did patients with plasma factor VIII concentration below 100 IU/dL.[52] Similarly, in the LITE study,[51] patients with factor VIII levels above the 95th percentile had a higher risk of VTE than did those with levels in the lowest quartile (adjusted HR: 3.8 [95% CI: 2.0-7.2]). The LEiden Thrombophilia Study (LETS) study[53] identified a 2-fold increase (adjusted OR: 2.2 [95% CI: 1.3-3.6]) in the risk of VTE among patients with factor IX levels exceeding the 90th percentile (129 U/dL); the risk was even higher when both factor VIII and factor IX plasma levels were above the 90th percentile (OR: 8.2 [95% CI: 3.6-18.4]). In the same study group,[54] factor XI levels above the 90th percentile (121 U/dL) doubled the risk of VTE (adjusted OR: 1.9 [95% CI: 1.3-2.9]). In contrast, high plasma levels of fibrinogen[51] or factor X[55] did not confer an increased risk of VTE.

Inherited thrombophilia conditions

The thrombotic risk conferred by inherited thrombophilia conditions depends on whether the examined studies are case-controlled or involve relatives of affected patients, the risk being higher in the latter group (Table 2).

Deficiency in antithrombin, protein C or protein S

Deficiencies of these three core inhibitors of the coagulation cascade are rare, being detectable in less than 1% of the general population and in less than 10% of unselected patients with VTE.[56] Their implication for the development of VTE is, however, high with the RR for VTE reported to be 5, 6.5 and 1.7 in subjects with antithrombin, protein C or protein S deficiency, respectively.[57]

In a family study,[58] patients with any of these deficiencies had an 11-fold increase in risk of spontaneous VTE when compared with subjects without the deficiencies (RR: 10.6 [95% CI: 2.7-41.2]). Another family study[59] found a high level of VTE risk among patients with antithrombin, protein C or protein S deficiency, with an adjusted RR of 42.8 (95% CI: 10.2-180.3), 31.3 (95% CI: 7.0-138.8), and 35.7 (95% CI: 7.9-160.1), respectively. Bucciarelli *et al*. in their family study,[60] showed that the VTE risk was 2- to 3-fold higher in patients with antithrombin deficiency than in those with protein C or protein S deficiency, respectively. Finally,[61] patients with protein S deficiency and a specific defect in the protein S gene (PROS1) had a 5-fold higher risk of VTE (RR: 5.0 [95% CI: 1.5-16.8]).

Factor V Leiden

A point mutation in the factor V gene called factor V Leiden results in resistance to activated protein C. One case-control study ,[19] showed that the factor V Leiden mutation conferred a 10-fold increase in VTE risk (OR: 9.7 [95% CI: 3.4-27.3]). A pooled analysis of 8 case-control studies[62] confirmed these findings (OR 4.9 [95% CI: 4.1-5.9]). Interestingly, the frequency of factor V Leiden was lower in patients with PE than in patients with DVT alone.[62] Compared to patients without factor V Leiden, patients heterozygous for factor V Leiden had a 6- to 8-fold higher risk of VTE and patients homozygous for factor V Leiden had a 30- to 140-fold higher risk.[63] Two retrospective studies,[64,65] confirmed that there was a 4-fold higher risk of thrombosis in factor V Leiden homozygotes than in heterozygotes.

In a study in relatives of patients with factor V Leiden, the adjusted RR for VTE was 10.1 (95% CI: 2.3-43.7) in carriers of this mutation.[59] Similarly, another family study,[66] showed a 16-fold increase in the risk of VTE in patients heterozygous for factor V Leiden (OR: 16.3 [95% CI: 8.5-31.1]). The risk was not as high in a cohort study by Simioni *et al*.[58] in family members of unselected patients with VTE (RR: 2.5 [95% CI: 0.6-10.6]).

Prothrombin gene mutation

The G20210A prothrombin gene mutation is associated with high plasma levels of factor II.[67] In the LETS study,[67] the risk of first VTE was increased 3-fold (OR: 2.8 [1.4-5.6]) in patients with this mutation. Similarly, in a pooled analysis of 8 case-control studies,[62] OR for VTE was 3.8 (95% CI: 3.0-4.9). These findings were confirmed by several family studies.[66,68]

Combined thrombophilia

The presence of combined defects further increases the risk of a first thrombotic event. Emmerich *et al*. identified a much higher risk of VTE (OR: 20.0 [95% CI: 11.1-36.1]) among patients heterozygous for both factor V Leiden and the prothrombin gene mutation.[62] In another study, co-presence of factor V Leiden and the prothrombin gene mutation gave an OR of 58.6 (95% CI: 22.1-155.2) for the risk of VTE when compared with the risk in patients without the mutations.[66] However, the VTE risk in patients with factor V Leiden and inherited protein C or protein S deficiencies[65] is

higher than that in patients with combined factor V Leiden and prothrombin gene mutation (adjusted HR; 17.5 [95% CI: 3.8-81.2] and 1.3 [95% CI: 0.5-3.8], respectively versus factor V Leiden only).

Clinical situations

Recent surgery

Major surgery is one of the most well recognized risk factors for VTE. Surgery within the last 45-90 days confers a 4- to 22-fold increase in the risk of VTE.[15,25,43] The wide variation in the level of risk reflects the variable risk posed by different surgical procedures, not only during the perioperative period, but also for several months later, especially in high-risk patients such as those undergoing cancer surgery.

Non-surgical hospitalization or immobilization

Hospitalization not involving surgery is recognized to be a strong independent factor influencing the risk of VTE. A review of medical records from a cohort of patients experiencing VTE[69] identified the average annual age- and sex-adjusted incidence of VTE among hospitalized patients to be 100-times greater than that in the community. The LETS study[36] confirmed that hospitalization within the previous year, without any surgical procedure having been performed, was associated with an increased risk of VTE (OR: 11.1 [95% CI: 4.7-25.9]). Similarly, the HERS study,[15] identified that hospitalization was associated with an increased risk of symptomatic VTE during the subsequent 90 days (RH: 5.7 [95% CI: 3.0-10.8]). An 8-fold increased risk of VTE (OR: 8.0 [95% CI: 4.5-14.2]) was demonstrated among patients hospitalized or confined to nursing homes within the previous three months.[43] Unfortunately these studies did not identify the specific medical conditions requiring hospitalization. Immobilization, due to either prolonged bed rest or limb immobilization, was recorded in up to 25% of patients developing in-hospital VTE.[70] In a case-control study of patients presenting with a DVT to their general practitioner,[16] univariate analysis showed that immobilization, defined as total confinement to bed or to bed and armchair, was associated with a 5.6 fold (95% CI: 2.3-13.7) increase in DVT. Interestingly, a large study by Tsai *et al*. failed to demonstrate any association between low physical activity and VTE.[7]

Congestive heart failure

Congestive heart failure is generally considered to be an independent risk factor for VTE, although few studies have attempted to assess the level of risk according to the severity of the heart failure. One study using univariate analysis showed that congestive heart failure conferred a 3-fold increased risk of DVT.[16] Similarly, a retrospective case-control study,[71] confirmed that congestive heart failure was associated with an increased risk of symptomatic VTE (OR: 2.6 [95% CI: 1.4-4.7]), with the risk increasing as the ejection fraction decreased (OR: 38.3 [95% CI: 9.6-152.5]). Heit *et al*.[43] identified congestive heart failure to be independently associated with post-mortem VTE that was not categorized as a cause of death (OR: 9.6 [95% CI: 2.4-38.1]). However, it was not a risk factor for VTE when the latter was either manifested before death or categorized as a cause of death (OR: 1.4 [95% CI: 0.7-2.7]). Multivariate analysis from the HERS study failed to confirm that congestive heart failure conferred an increased risk of VTE.[15]

Malignancy

The association between malignancy and VTE is well recognized. Both case-control and randomized studies using multivariate analyses have shown a 2- to 6-fold increase in risk of symptomatic DVT or PE among patients with confirmed malignancy.[6,7,9,15,19] The risk of postoperative VTE is also approximately 2-fold higher among cancer patients than among non-cancer controls.[42,72]

A further increase in the risk of VTE is seen among cancer patients receiving chemotherapy. Heit *et al*.,[43] showed a higher risk of DVT in patients undergoing chemotherapy than among those not receiving chemotherapy. The exact level of increased risk with chemotherapy is difficult to quantify since studies have not directly evaluated chemotherapy versus no chemotherapy. Similarly most studies have evaluated patients receiving chemotherapy for breast cancer and it is not known whether patients with other types of tumor have similar levels of risk. One study[73] showed that women receiving adjunct tamoxifen therapy for breast cancer had a 7-fold further increase in the risk of VTE over that in the group of patients who had never received tamoxifen therapy or had done so in the past (RR: 7.1 [95% CI: 1.5-33]), while the increase in VTE risk was not significant (OR: 2.7 [95% CI: 0.7-10.1]) in another large study.[43] Thalidomide, which is often used in combination with chemotherapeutic agents to treat multiple myeloma and other tumors, has been reported to be associated with an increased risk of VTE, but the level of this risk has yet to be defined.[74,75]

A number of epidemiological studies have examined the risk of VTE according to tumor type. Rickles and Edwards[76] determined that the types of cancer most commonly associated with VTE were lung cancer (25.6%), followed by pancreatic (17.4%), gastric (16.8%), and colon (15.2%) cancers. Another study revealed the strongest associations to be with carcinomas of the pancreas, ovary, liver and brain and non-Hodgkin's lymphoma.[77] Similarly, Baron *et al*.[48] showed that the tumor sites most

commonly associated with VTE were ovary, pancreas, brain and liver, with standardized incidence ratios of between 11.4 and 6.6. A recent analysis of over nine million hospitalized patients aged over 65 years,[78] showed the most common malignancies associated with VTE to be uterine (RR: 3.4), brain (RR: 2.4), ovarian (RR: 2.2) and pancreatic (RR: 2.1). In contrast, patients with tumors involving the head/neck, bladder and breast, with RR of 0.3, 0.4 and 0.4 respectively, appeared to have a lower risk of VTE than patients hospitalized for reasons other than cancer.

Myocardial infarction

Traditionally, myocardial infarction has been recognized as a strong risk factor for VTE, however, with current treatment strategies involving multiple antithrombotic and antiplatelet therapies, the exact level of VTE risk is uncertain. Subgroup analysis of women participating in the HERS study[15] demonstrated that the risk is greatest during the first 90 days following a myocardial infarction (RH: 5.9 [95% CI: 2.3-15.3]), although it is still elevated four years following the event (overall RH: 2.1 [95% CI: 0.9-5.3]).

Venous catheter

Indwelling central venous catheters are commonly associated with PE or upper limb DVT. Catheter or pacemaker insertion was found[43] to confer a 6-fold increase in risk of developing PE or upper limb DVT (OR: 5.6 [95% CI: 1.6-19.6]). Similarly, the placement of a femoral venous catheter in critically ill patients[79] is a risk factor for development of an iliofemoral DVT (RR: 6.0 [95% CI: 1.5-23.5]).

Venous insufficiency

The degree of risk associated with varying severity of lower limb venous dysfunction remains poorly defined. Ferrari *et al*. identified varicose veins as a risk factor for VTE in patients in whom no other etiology was found.[70] Similarly, in another study,[9] varicose veins were an independent risk factor for DVT (OR: 2.6 [95% CI: 1.9-3.3]). Heit *et al*.[43] noted that the risk of VTE conferred by varicose veins varied inversely with the patients' age, being higher in those aged 45 years (OR: 4.2) than in those aged 75 years (OR: 0.9). In contrast, the Framingham Study did not identify varicose veins as an independent predictor of major PE discovered at autopsy.[21] Leg ulcers were found[42] to confer a 4-fold increased VTE risk among patients undergoing major abdominal surgery (OR: 4.2 [95% CI: 1.8-9.9]).

Ischemic stroke

In the HERS study,[15] stroke or transient ischemic attack was not found to be a significant risk factor for VTE (RH: 2.0 [95% CI: 0.8-5.3]). In contrast, Heit *et al*.,[43] identified that neurological disease with peripheral paresthesia conferred a 3-fold increase in risk for initial VTE (OR: 3.0 [95% CI: 1.3-7.4]). VTE was documented in 11% of patients undergoing rehabilitation for stroke, occurring, on average, 60 days after the stroke;[80] the risk of VTE was significantly higher (OR: 17.6 [95% CI: 2.2-143.5]) in patients who were bedridden or wheelchair-bound at the time of admission.

Chronic obstructive pulmonary disease

The epidemiological evidence for an independent association between chronic obstructive pulmonary disease and VTE is not strong and indeed three large studies[15,16,43] failed to demonstrate the association. However, the diagnosis of PE in this group is particularly difficult and therefore, the true frequency has not been well established. In a prospective cohort study, in which 196 patients with chronic obstructive pulmonary disease in a respiratory intensive care unit were studied on the day of admission, DVT was demonstrated in 10.7% patients by ultrasound.[81] A study of 223 patients mechanically ventilated for decompensated chronic obstructive pulmonary disease identified that DVT was present among 28% of patients not receiving prophylaxis.[82]

Nephrotic syndrome

Although nephrotic syndrome has been identified as a risk factor for VTE in an overview of this disease,[83] few studies have been published concerning the risk of VTE in patients with nephrotic syndrome.

Inflammatory bowel disease

A population-based cohort study[84] showed that patients with inflammatory bowel disease had a 3-fold increased risk of VTE. The significant increase in risk was seen among patients with Crohn's disease or ulcerative colitis. Although the highest rates of VTE were seen in patients over 60 years old, the incidence rate ratios for these events were highest in patients less than 40 years old. Inflammatory bowel disease did not, however, significantly increase VTE risk (OR: 0.8 [95% CI: 0.2-3.0]) in the population-based study by Heit *et al*.[43]

Prolonged travel

The role of prolonged travel as a risk factor for VTE is uncertain. In a case-control study,[85] at least one travel episode of more than four hours during the preceding four weeks was reported four times more often in patients hospitalized for acute DVT than among age-matched controls (OR: 4.0 [95% CI: 1.9-8.4]). However, questions have been raised concerning the validity of the control group. A second study,[16] using a univariate analysis identified long-distance travel to be more frequent in outpa-

tients presenting with DVT (OR: 2.4 [95% CI: 1.5-3.8]). In contrast, a Dutch study of 788 patients presenting with DVT within the previous three months[86] showed no increase in risk (OR: 1.0 [95% CI: 0.3-3.0]) associated with air travel alone even when this was longer than five hours. In addition, no association was recorded for any of the other modes of transport (car/bus and train/boat). In a recent pooled analysis of three case-control studies of patients referred for suspected VTE,[87] the pooled OR of the association between any travel and symptomatic VTE was 0.9 (95% CI: 0.6-1.4). The result was non-significant whatever the type of transport. When the overall median travel time was 7 hours, among a subgroup of patients travelling for 10-15 hours, the risk doubled (OR: 2.5 [95% CI: 1.0-6.2]).

Other factors

Various other factors have been investigated in several studies. Cogo *et al*.[6] found that intermittent claudication was associated with a 2-fold increased risk of VTE (OR: 1.9 [95% CI: 1.3-2.5]). Diabetes mellitus was shown to be independently associated with an increased risk of VTE (HR: 1.5 [95% CI: 1.0-2.1]) in the LITE study,[7] although this was not demonstrated in other studies.[17,18,21] A subanalysis of the Nurses' Health Study[17] indicated that hypertension was associated with an increased risk of PE (RR: 1.9 [95% CI: 1.2-2.8]), however, this association was statistically not significant in the LITE (HR: 1.2 [95% CI: 0.9-1.6]) and the HERS (RH: 1.5 [95% CI: 0.9-2.7]) studies.[7,15] Finally, violent effort or muscular trauma was associated with an increased risk of VTE (OR: 7.6) in one study.[16]

Conclusions

As underlined in a recent review, risk factors for VTE can have important implications for the type and duration of appropriate prophylaxis and should be carefully analyzed to assess the overall risk of VTE in each patient.[88] On the basis of our literature review, we divided risk factors for VTE according to whether they were related to the patients' characteristics or clinical situations. We identified the major predisposing factors in terms of patients' characteristics to be age, treatment with psychotropic drugs, hormonal therapy and personal history of VTE, along with inherited coagulation factor abnormalities. Clinical situations associated with the highest risk of VTE were recent surgery, non-surgical hospitalization and immobilization, congestive heart failure, and malignancy.

Our study has several limitations, reflecting the difficulty in attempting to apportion levels of weight to risk factors for VTE based on heterogeneous epidemiological studies.[89] Risk factors were derived from a wide spectrum of predominantly retrospective community-based studies. Generally, these studies had different designs and goals, that is, they differed in terms of representativeness of sample, quality of documentation of the thrombotic events and number of putative risk factors investigated. In addition, due to the small sample sizes in a number of the epidemiological studies, detailed analysis of certain risk factors was not possible due to lack of statistical power. Although VTE has multiple causes,[30] the use of multivariate analysis can potentially adjust for the known influence of confounding variables and demonstrate the value of putative risk factors independently of other factors. Such analyses were not always available in several studies and their results were dependent on the putative risk factors included in the statistical model of the original studies. Nevertheless, in an effort to minimize these issues, we predominantly used methodologically robust and recent studies, and where possible used only multivariate analyses for identification of risk factors. The application of results from predominantly outpatient studies to hospitalized patients may not be appropriate in all situations; however we believe that the majority of risk factors identified are adaptable to both situations. It is important to emphasize that our literature review was not meant to be exhaustive, but was performed to provide a basis for individual opinions using the most recent studies. Similarly it is recognized that case-control studies have the potential to answer important epidemiological questions, but only when the patients and control subjects are appropriately selected. Ideally, the two groups of subjects compared must be alike in all respects except for the characteristic of interest. Multifactorial processes such as VTE may be ill suited to analysis by this method, since it is seldom possible to control all the relevant variables, many of which are unrecognized.

In summary, we believe that the present classification adequately reflects a valid attempt to qualify and quantify the different levels of risk conferred by the various factors potentially presented by a patient. It will serve as a starting point from which an international panel of medical and surgical experts will develop a risk assessment model. This model will be a tool for healthcare providers to use in decision-making processes considering when to use thromboprophylaxis, what type of prophylaxis to use and the appropriate duration of treatment.

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Pre-publication Report

Contributions

MMS: primary responsibility for the paper; DJQ: author of all tables and figures. All authors devised the study, participated in the interpretation of results, and reviewed and approved the final version of the manuscript. The order of authorship was decided of a common accord.

Funding

This work was supported by a grant from Sanofi-Synthelabo.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by an Associate Editor. The final decision to accept this paper for publication was taken by the Editors. Manuscript received July 11, 2003; accepted October 3, 2003.