Treatment of venous thromboembolism: focus on patient characteristics and bleeding complications
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Sex-specific differences in the presenting location of a first venous thromboembolism

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Abstract

Background The risk of venous thromboembolism (VTE) differs between men and women. Some risk factors seem to influence the presenting location of VTE. Sex-specific differences in presenting VTE location have not been studied extensively.

Methods We analysed data from the MEGA case-control study and the Hokusai-VTE study, and used published data from the RIETE registry. Data from patients with a symptomatic first VTE were included (MEGA n=4953; Hokusai-VTE n=6720; RIETE n=40028). Distributions of deep vein thrombosis (DVT), pulmonary embolism (PE) and combined DVT and PE as presenting VTE location were calculated for men and women and presented as proportions with 95% confidence intervals (95%CI). Sex-specific differences were explored for different age categories and for unprovoked and provoked events.

Results In the MEGA study, PE was the presenting location in 35.5% of women and in 29.5% of men with VTE (difference 6.0%, 95%CI 3.4-8.6). In the Hokusai-VTE study these proportions were 35.1% for women and 25.2% for men (difference 10.0%, 95%CI 7.8-12.2). In the RIETE registry, PE (with or without DVT) was also observed more often as the presenting location in women (53.3%) compared with men (47.7%) with a difference of 5.6% (95%CI 4.7-6.6). The observed higher proportion of PE as presenting location in women was present in all age groups and most prominent amongst unprovoked VTE events.

Conclusion In three large studies, the distribution of presenting VTE location differed consistently between the sexes, where PE was relatively more often the primary location of presentation in women than in men.
Introduction

The incidence, risk factors, clinical presentation and course of a disease often differ between men and women (1). Identification of these differences and their causes is of importance to optimise diagnosis and management of a disease by means of sex-specific strategies (2). Sex-specific differences also exist for venous thromboembolism (VTE) which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). Women are at higher risk during their fertile life, mainly due to the effects of endogenous and exogenous hormones (3). In contrast, men are at higher risk at older ages (4). In addition, several risk factors seem to influence the presenting location of VTE. Some are observed more often in DVT compared with PE, while other risk factors are associated with a higher PE incidence. For example, oral contraceptive use and carriership of Factor V Leiden (which is known as the Factor V Leiden paradox) affect the risk of DVT much more than that of PE (5-7) whereas pulmonary diseases seem stronger risk factors for PE than for DVT (8-10). Also, patients with a DVT are more likely to recur with DVT than with PE, and vice versa (11-13). The presenting location of a VTE is relevant, as the impact of a PE is often higher than that of a DVT (14).

The underlying mechanism which influences presenting VTE location is poorly understood. Moreover, sex-specific differences in presenting VTE location have not been studied extensively. Therefore we set out to explore sex-specific differences in presenting VTE location.

Methods

For the evaluation of differences in the distributions of DVT, PE and combined DVT and PE as presenting location among men and women with a first episode of VTE, data from the MEGA study were first analysed (15). The Hokusai-VTE study was used as a validation (16). Finally, confirmation was obtained by using published data from the RIETE registry (17).

MEGA case-control study

The Multiple Environmental and Genetic Assessment (MEGA) of risk factors for venous thrombosis study is a large case-control study of which the details of the design have been described before (15). Briefly, consecutive patients aged 18-70 with a first VTE were included from one of six (Amersfoort, Amsterdam, The Hague, Leiden, Rotterdam, and Utrecht) anticoagulation clinics in the Netherlands between March 1999 and September 2004. Eighty-six percent of eligible patients participated in the MEGA study. Participants completed a detailed questionnaire on VTE risk factors and were asked to provide a blood sample and DNA. Detailed information on diagnosis was acquired from hospital.
discharge reports and data from general practitioners. All participants provided written informed consent. The study was approved by the Medical Ethical Committee of the Leiden University Medical Center, Leiden, the Netherlands. For the current analyses patients with a chromosomal disorder (n=1) of the sex chromosomes (e.g. Klinefelter syndrome) or persons undergoing a sex change (n=2) were excluded.

**Hokusai-VTE study**
The Hokusai-VTE study (ClinicalTrials.gov identifier: NCT00986154) was a large, international randomized double-blind study recruiting from January 2010 through October 2012 that compared heparin/edoxaban with heparin/warfarin in patients with acute symptomatic DVT or PE (16). Patients aged ≥18 years could participate if they had and objectively diagnosed acute symptomatic DVT of the popliteal, femoral, or iliac veins, or an acute symptomatic PE (with or without DVT). In the Hokusai-VTE study there was a minimum ratio of PE:DVT events of 2:3. Edoxaban (or placebo) was started at a dose of 60 mg once daily (or dose adjusted according to specific criteria), warfarin (or placebo) was dosed according to the international normalized ratio (INR). The primary efficacy outcome of the Hokusai-VTE study was a composite of recurrent DVT, nonfatal or fatal PE. Pregnant patients could not participate in the study. All patients provided written informed consent. The institutional review board at each participating centre approved the protocol. The Hokusai-VTE study was funded by Daiichi-Sankyo.

**RIETE registry**
We used data from the Registro Informatizado de Enfermedad TromboEmbólica (RIETE) registry, that were published previously by Blanco-Molina and colleagues (17). This is a large ongoing registry (initiated in 2001) of acute symptomatic VTE patients that runs in over 10 countries.

**Presenting location of VTE**
In all three studies a VTE diagnosis was guided by presenting symptomology, for example if chest symptoms were the major way of coming to medical attention, chest imaging was ordered. In case of a PE diagnosis, in absence of DVT symptoms, ultrasound of the legs is typically not routinely performed in clinical practice. A diagnosis was confirmed by objective imaging tests such as ultrasonography or venography for DVT and computed tomography, lung scintigraphy or pulmonary angiography for PE. In the MEGA and Hokusai-VTE study the presenting locations could be classified into DVT, PE and combined DVT and PE. From the published data of the RIETE-registry only a subdivision into DVT or PE with or without DVT could be made.
Statistical analysis
Proportions and differences in proportions (Δ) of DVT, PE and combined DVT and PE of first VTE events were calculated with their 95% confidence intervals (95%CI) for men and women. Next, these differences were explored in different age categories, i.e. <30, 30-45, 46-60 and >60 years. Subsequently, we investigated differences in presenting VTE location among unprovoked and provoked events. In the MEGA study provoked events were defined as a VTE triggered by one or more of the following: recent surgery, trauma or immobilization, pregnancy or puerperium, long haul travel, active malignancy in the past 5 years or the use of estrogen containing drugs. In the Hokusai-VTE dataset the definition for provoked events was a VTE triggered by one or more of the following: recent surgery, trauma or immobilization, puerperium, active cancer, sitting more than 4 hours, active cancer, known thrombophilic condition or the use of estrogen containing drugs. Finally, as use of oral contraceptives in women and carriership of the Factor V Leiden variant are known influences of VTE location (e.g. predominance of DVT compared with PE) (5-7) these risk factors were explored in detail in available data of the MEGA study.

Results
Data on the presenting VTE location of participants of the MEGA (n=4953), the Hokusai-VTE (n=6720) and the RIETE registry (n=40028) with a first episode of VTE were included in the current analysis. General characteristics of the MEGA and Hokusai-VTE study populations were available and are shown in Table 5.1.

Table 5.2 shows the distribution of DVT, PE, and combined DVT and PE as presenting location for each of the three studies. In the MEGA study, PE was the presenting location in 35.5% of all women and in 29.5% of the men (difference 6.0%, 95%CI 3.4-8.6), in the Hokusai-VTE study PE was the presenting location in 35.1% of women and 25.2% of the men (difference 10.0%, 95%CI 7.8-12.2). In the RIETE registry, PE (with or without DVT) as the presenting location was also more frequently observed in women (53.3%) compared with men (47.7%) with a difference in proportion of 5.6% (95%CI 4.7-6.6). In respect to this classification in the RIETE, in women in the MEGA and Hokusai-VTE studies PE with or without DVT was also more frequently the presenting location compared with men, difference between women and men: 3.2% (95%CI 0.3-5.9) and 8.5% (95%CI 6.2-10.9), respectively.

Table 5.3 depicts the sex-specific distribution of DVT, PE and combined DVT and PE as presenting location for a total of 11671 patients with a first VTE in different age categories from the MEGA and Hokusai-VTE studies (Supplementary Figure 1 provides a summary of these findings). The observed higher proportion of PE as a presenting location in women compared with men was observed in all age groups. The largest differences in the
proportion of PE as presenting location were detected in the age categories 30-45 years (difference women vs. men, MEGA: 5.6%, 95%CI 0.6-10.5; and Hokusai-VTE: 8.0%, 95%CI 3.5-12.6) and older than 60 years (difference women vs. men, MEGA: 12.9%, 95%CI 7.0-18.7; and Hokusai-VTE: 11.3%, 95%CI 7.8-14.8). Only in the youngest age group (<30 years), there was no clear difference in the proportion of presenting location between men and women in the MEGA study (difference -1.1%, 95%CI -11.7 to 8.7). However, in the Hokusai-VTE study, PE as presenting location was again found more often in women vs. men in this age group, i.e., 16.0% (95%CI 7.9-23.7). This discrepancy might be explained by inclusion of pregnant women in the MEGA study, while pregnant patients were excluded in the Hokusai-VTE (17).

The proportion of unprovoked VTE events was smaller in women than in men (Table 5.4), particularly in the Hokusai-VTE study (1545/2928 [52%] of all women had an unprovoked VTE compared with 2702/3792 [71%] of all men). Amongst unprovoked VTE events, the difference between men and women in PE as a presenting location was most pronounced (difference women vs. men, 15.0%, 95%CI 9.6-20.3 in the MEGA; 10.9%, 95%CI 8.1-13.8 in the Hokusai-VTE).

In the MEGA study, in 67/329 (20.4%) of female patients with a heterozygous Factor V Leiden variant PE was the presenting location, this was the case in 50/317 (15.8%) of the men which carried this variant (difference 4.6%, 95%CI -1.4 to 10.5). In the group without a heterozygous Factor V Leiden mutation, 747/1983 (37.7%) of the women and 527/1626 (32.4%) of the men PE was the presenting location (absolute difference 5.3%, 95%CI 2.1-8.4).

Of all women aged 50 years or younger in the MEGA study who used oral contraceptives, 342/1103 (31%) had a PE as presenting location, this were 214/531 (40.3%) women aged 50 years or younger who did not use oral contraceptives (absolute difference 9.3%, 95%CI 4.3-14.3).
Table 5.2. Proportions of DVT, PE and combined DVT and PE as presenting location of a first venous thromboembolism in the MEGA, Hokusai-VTE studies and the RIETE registry

<table>
<thead>
<tr>
<th>Study</th>
<th>MEGA N=4953</th>
<th>Hokusai-VTE N=6720</th>
<th>RIETE N=40028</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women n=2679</td>
<td>Men n=2274</td>
<td></td>
</tr>
<tr>
<td>DVT, n (%)</td>
<td>1522 (56.9)</td>
<td>1364 (60.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Δ Difference women vs. men, % (95%CI)</td>
<td>1642 (56.1)</td>
<td>2449 (64.6)</td>
</tr>
<tr>
<td>PE, n (%)</td>
<td>951 (35.5)</td>
<td>670 (29.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Δ Difference women vs. men, % (95%CI)</td>
<td>1029 (35.1)</td>
<td>955 (25.2)</td>
</tr>
<tr>
<td>Combined, n (%)</td>
<td>206 (7.6)</td>
<td>240 (10.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Δ Difference women vs. men, % (95%CI)</td>
<td>257 (8.8)</td>
<td>388 (10.2)</td>
</tr>
<tr>
<td>PE+/- DVT, n (%)</td>
<td>1157 (43.1)</td>
<td>910 (40)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Δ Difference women vs. men, % (95%CI)</td>
<td>1286 (43.9)</td>
<td>1343 (35.4)</td>
</tr>
</tbody>
</table>

*Numbers estimated from available data from (17). DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism; CI: confidence interval.
### Table 5.3. Sex-specific proportions of DVT, PE and combined DVT and PE as a presenting location in different age categories for patients with a first VTE in the MEGA and Hokusai-VTE studies

<table>
<thead>
<tr>
<th>Age Category</th>
<th>MEGA N=4953</th>
<th>Hokusai-VTE N=6720</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women n=2679</td>
<td>Men n=2274</td>
</tr>
<tr>
<td></td>
<td>Δ Difference women vs. men, % (95%CI)</td>
<td>Women n=2928</td>
</tr>
<tr>
<td>Age &lt; 30 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT, n (%)</td>
<td>254 (61.7)</td>
<td>56 (56.6)</td>
</tr>
<tr>
<td>PE, n (%)</td>
<td>133 (32.2)</td>
<td>33 (33.3)</td>
</tr>
<tr>
<td>Combined, n (%)</td>
<td>25 (6.1)</td>
<td>10 (10.1)</td>
</tr>
<tr>
<td>Age 30-45 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT, n (%)</td>
<td>534 (56.7)</td>
<td>326 (59.6)</td>
</tr>
<tr>
<td>PE, n (%)</td>
<td>344 (36.5)</td>
<td>168 (30.7)</td>
</tr>
<tr>
<td>Combined, n (%)</td>
<td>64 (6.8)</td>
<td>53 (9.7)</td>
</tr>
<tr>
<td>Age 46-60 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT, n (%)</td>
<td>533 (58.4)</td>
<td>588 (60.4)</td>
</tr>
<tr>
<td>PE, n (%)</td>
<td>299 (32.7)</td>
<td>275 (28.3)</td>
</tr>
<tr>
<td>Combined, n (%)</td>
<td>81 (8.9)</td>
<td>110 (11.3)</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT, n (%)</td>
<td>201 (48.8)</td>
<td>394 (60.2)</td>
</tr>
<tr>
<td>PE, n (%)</td>
<td>175 (42.5)</td>
<td>194 (29.6)</td>
</tr>
<tr>
<td>Combined, n (%)</td>
<td>36 (8.7)</td>
<td>67 (10.2)</td>
</tr>
</tbody>
</table>

VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; CI: confidence interval
Sex-specific differences in first venous thromboembolism location

In this analysis, which entailed data from three large independent studies, we observed consistent differences in the proportions of predominant presenting VTE location between men and women, where the presenting location was more often PE in women and more often DVT in men. This finding was most prominent amongst unprovoked VTE cases and was consistent amongst age groups.

For the interpretation of these results we should emphasize that our results are conditional probabilities, i.e. given that a person has developed VTE, the likelihood of presenting with PE is higher in women than in men. To be able to fully understand our findings, absolute risks, i.e. incidence rates are needed. From most incidence studies that

**Table 5.4.** Sex-specific proportions of DVT, PE and combined DVT and PE as a presenting location for patients with a first provoked and unprovoked VTE in the MEGA and Hokusai-VTE studies

<table>
<thead>
<tr>
<th></th>
<th>MEGA N=4953</th>
<th>Hokusai-VTE N=6720</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unprovoked VTE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>Men</td>
<td>△ Difference</td>
</tr>
<tr>
<td>n=2679</td>
<td>n=2274</td>
<td>Women vs. men, %</td>
</tr>
<tr>
<td>DVT, n (%)</td>
<td>222 (48.9)</td>
<td>584 (59.0)</td>
</tr>
<tr>
<td>PE, n (%)</td>
<td>201 (44.3)</td>
<td>290 (29.3)</td>
</tr>
<tr>
<td>Combined, n (%)</td>
<td>31 (6.8)</td>
<td>116 (11.7)</td>
</tr>
</tbody>
</table>

| **Provoked VTE**† |         |                      |
| Women           | Men       | △ Difference         | Women         | Men         | △ Difference         |
| n=2225          | n=1284    |                        | n=1383        | n=1090      |                        |
| DVT, n (%)      | 1300 (58.4) | 780 (60.7)            | 750 (54.0)    | 635 (58.0)  | -2.3% (-5.7;-1.1)    |
| PE, n (%)       | 750 (33.7)  | 380 (29.6)            | 493 (36.0)    | 313 (29.0)  | +4.1% (0.9;7.3)      |
| Combined, n (%) | 175 (7.9)  | 124 (9.7)             | 140 (10.0)    | 142 (13.0)  | -1.8% (-3.8;0.2)     |

*MEGA study: VTE triggered by one or more of the following: active malignancy in the past 5 years; recent surgery, trauma or immobilization, pregnancy or puerperium, or long haul travel; use of estrogen containing drugs. †Hokusai-VTE: VTE triggered by one or more of the following: active cancer; recent surgery, trauma or immobilization; use of estrogen containing drugs, puerperium, sitting more than 4 hours; known thrombophyllic condition. VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; CI: confidence interval

**Discussion**

In this analysis, which entailed data from three large independent studies, we observed consistent differences in the proportions of predominant presenting VTE location between men and women, where the presenting location was more often PE in women and more often DVT in men. This finding was most prominent amongst unprovoked VTE cases and was consistent amongst age groups.

For the interpretation of these results we should emphasize that our results are conditional probabilities, i.e. given that a person has developed VTE, the likelihood of presenting with PE is higher in women than in men. To be able to fully understand our findings, absolute risks, i.e. incidence rates are needed. From most incidence studies that
are available it appears as if these rates often do not differ considerably between men and
women (19-26). This finding is, however, in contrast with incidence rates for recurrence,
which are consistently found to be about two-fold higher in men than in women (27-31).
This paradox can be explained because women are exposed to more risk factors than men,
i.e. in addition to all regular risk factors, to hormone use and pregnancy. These common
exposures ‘artificially’ raise the risk of first VTE in women. Indeed, in a recent study where this
was taken into account, we found that the risk in men for a first event is also about 2 times
higher than in women, thus explaining the paradox (4). We can therefore assume that men
have a higher intrinsic VTE risk, and women a higher extrinsic VTE risk (due to more exposure
to risk factors). Moreover, female-specific risk factors such as use of oral contraceptives and
pregnancy lead to a larger DVT than PE risk (5). This is reflected in our results, where the
proportion of PE becomes even higher in women when these factors are disregarded, i.e.
in the unprovoked cases.

With the findings from our study we can merely speculate on potential underlying
mechanisms for the observed differences in presenting location. A first mechanism, that
has been proposed before, which could explain a higher proportion of DVT as presenting
location in men is that men are on average taller and have longer legs than women. This
may lead to more susceptibility to stasis in the lower extremities in men (24). Increased
stasis in the lower extremities could hereby increase DVT risk. A second explanation for
the observed differences is the possibility that clot composition in women is more fragile
or instable than in men, potentially leading to increased embolization rates. A third option
could be that there is variability between men and women in the anatomical origin of
thromboses, as is exemplified by cerebral venous sinus thrombosis which predominantly
occur in women (32). Women might be more prone to the development of a local thrombus
in the pulmonary arteries or right side of the heart. The potential association between
atrial fibrillation and pulmonary embolism has not been fully elucidated and might play
a role (33). Although the incidence of atrial fibrillation is higher in men, the incidence of
thrombotic of events is higher in women with atrial fibrillation (34). Thrombus formation
could also occur at yet another sex-specific anatomical site, such as the ovarian or uterine
veins, and embolise to the lungs, hence not leading to symptoms of DVT. Ovarian vein
thrombosis is rare, although symptoms are often ambiguous and diagnosis is difficult with
imaging without contrast (35, 36). Furthermore, another possible explanation could be
that in women an asymptomatic May-Turner syndrome with silent proximal DVT is more
prevalent than in men. A last possibility would be that men and women experience signs
and symptoms in a different way, as is the case in many (cardiovascular) diseases. Men
might be more aware of symptoms of the leg or calf, where women might notice chests
symptoms earlier. Another possibility is that men with chest pain are typically suspected of
myocardial infarction where women with chest pain might be suspected of PE earlier on.
A major strength of this study is the use of combined data from three large studies including more than 50,000 subjects. Moreover, all three studies had different designs increasing the generalisibility of the observed results. Although the included populations in the studies slightly differ, the distributions of presenting location of first VTE in the studies are consistent.

A limitation of this study as mentioned above, is that only relative occurrence could be determined. Therefore further research is necessary to complement the current results. Incidence data are needed which allow stratification for the sexes, by age and exposure to women-specific risk factors for the outcomes PE, DVT and PE with DVT separately. Another limitation is that in the data from the RIETE registry only distributions of DVT or PE with or without DVT as presenting location were available. Despite this, the larger proportion of PE with or without DVT in women compared with men definitely points towards a higher PE proportion in women and is therefore consistent with the MEGA and Hokusai-VTE observations. A third limitation, selection bias could have explained the findings if, for example, men with PE or women with DVT would have been less likely to participate in any of the three studies. However, it is very unlikely that this has occurred at such a large scale in all three studies. Lastly, it is possible that diagnostic strategies slightly differed among participating sites in the three studies, however this would unlikely change the results. For example, if hypothetically a selection of patients with a PE diagnosis would have also undergone a routine ultrasound of the lower extremities, in absence of DVT symptoms, this would only influence the results in the unlikely scenario that this would have systematically been done in men only but not in women or vice versa.

To our knowledge, this is the first study to extensively analyse differences in presenting VTE location between men and women. The findings show that the distribution of the presenting location of a first VTE differed consistently between the sexes, where PE was more often the primary location of presentation in women than in men. This finding was independent of age and more pronounced in unprovoked VTE events. The underlying mechanism is unknown and urges further investigation. The results of this study may have some clinical relevance, as VTE which presents as PE is associated with decreased survival rates compared with DVT as the presenting location (14). This study emphasizes the sex-specific differences in VTE.
Chapter 5

References


Sex-specific differences in first venous thromboembolism location


Supplementary Figure 1. Sex-specific proportions of DVT, PE and combined DVT and PE as a presenting location in different age categories for patients with a first VTE in the MEGA and Hokusai-VTE studies

Supplementary Figure 1 depicts the sex-specific distributions of deep vein thrombosis (DVT), pulmonary embolism (PE) and PE +/- DVT as presenting location of a first venous thromboembolism in the MEGA and Hokusai-VTE study for different age groups, A) <30 years, B) 30-45 years, C) 46-60 years and D) >60 years. The bottom columns represent the observed PE (black), the middle PE +/- DVT (grey) and the top DVT (white) proportions in percentages.