Sex Differences in Clinical Characteristics and Outcomes of Patients With Venous Thromboembolism — From the COMMAND VTE Registry —

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Background: It remains controversial whether sex category is a risk for recurrent venous thromboembolism (VTE) and major bleeding among VTE patients.

Methods and Results: The COMMAND VTE Registry is a multicenter registry enrolling 3,027 consecutive acute symptomatic VTE patients from 29 centers in Japan between January 2010 and August 2014. We compared the clinical characteristics and outcomes of men and women. Men accounted for 1,169 (39%) and women 1,858 (61%). Compared with women, men were younger (64.9±14.7 vs. 68.6±15.6 years old, P<0.001), more often had prior VTE (7.2% vs. 5.1%, P=0.02), and less often had transient risk factors for VTE (30% vs. 40%, P<0.001). The proportions of active cancer and pulmonary embolism were comparable between men and women (24% vs. 22%, P=0.26; 56% vs. 57%, P=0.48, respectively). The cumulative 3-year incidences of recurrent VTE, major bleeding, and all-cause death were not significantly different between men and women (7.0% vs. 8.6%, P=0.47; 10.6% vs. 9.2%, P=0.25; 25.2% vs. 23.4%, P=0.35, respectively). The adjusted risks of men relative to women for recurrent VTE and for major bleeding remained insignificant (HR 0.83, 95% CI 0.63–1.09, P=0.17; HR 1.15, 95% CI 0.90–1.47, P=0.25, respectively).

Conclusions: In real-world VTE patients, the clinical characteristics differed between men and women, but there was not a large sex-related difference in the risks for recurrent VTE or major bleeding.

Key Words: Recurrence; Sex differences; Venous thromboembolism

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a major health problem worldwide. It has a long-term risk of recurrence, which can be prevented by anticoagulation therapy. The current guidelines recommend specific durations of anticoagulation therapy for the prevention of recurrence depending on risk.3–6 Although several risk factors for recurrent VTE have been reported, it remains controversial whether sex affects the risk for recurrent VTE. Some studies reported that men had a higher risk of recurrence than women, whereas others showed no association between sex and recurrent VTE.12
rence.13,14 This may be partly because these studies included different populations, conducted crude comparison without adjusting confounders, and assessed clinical events only under or after discontinuation of anticoagulation therapy.

There are very few studies of the sex-related differences of VTE patients that included consecutive patients in daily clinical practice. Furthermore, the influence of sex on recurrence has been reported to vary depending on race.9 To date, there is scarce data on sex differences in the clinical characteristics and outcomes of VTE patients among Asian populations. Clarification of the association between sex and clinical outcome would be clinically important to identify high-risk patients requiring prolonged duration of anticoagulation therapy. Therefore, we sought to evaluate the clinical characteristics and outcomes of men and women with VTE in a large observational study in Japan.

Methods

Study Population

The COMMAND VTE (COntemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism) Registry is a physician-initiated, multicenter cohort study enrolling consecutive patients with acute symptomatic VTE objectively confirmed by imaging examination (ultrasound, contrast-enhanced computed tomography, ventilation-perfusion lung scintigraphy, pulmonary angiography, or contrast venography) or by autopsy in 29 centers in Japan between January 2010 and August 2014.15 The relevant review boards or ethics committees in all 29 participating centers (Supplementary Appendix 1) approved the research protocol. Written informed consent from each patient was waived because we used clinical information obtained in routine clinical practice, and none of the patients refused to participate in the study when contacted for follow-up. This method was concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare in Japan.

We referred to the hospital charts for clinical diagnosis and imaging examinations, and enrolled consecutive patients who met the definition of acute symptomatic VTE diagnosed within 31 days from symptom onset during the study period.16 The symptoms of VTE were defined as follows: for PE — sudden-onset dyspnea, pleuritic chest pain, substernal chest pain, cough, fever, hemoptysis, and syncope; for DVT — erythema, warmth, pain, swelling, tenderness, and pain on dorsiflexion of the foot.17,18 Additionally, sudden-onset abnormalities in vital signs such as a decrease in arterial oxygen saturation and hypotension were also regarded as symptoms of PE. The presence or absence of symptoms was evaluated at the time of the imaging studies. Patient management, including the duration of anticoagulation, was left to the discretion of the attending physicians in each participating hospital.

Data Collection and Definitions

Baseline data were collected from hospital charts or hospital databases according to prespecified definitions, using an electronic case report form in a web-based database system. The study investigators at each institution were responsible for data entry, and data were automatically checked for missing or contradictory input and values out of the expected range. Additional data monitoring were performed at the general office of the registry.

Transient risk factors for VTE included recent surgery (within 2 months prior to VTE), recent immobilization (defined as non-surgical bed-rest within 2 months prior to VTE), long-distance travel (travel lasting ≥6 h in the previous 3 weeks), central venous catheter use, pregnancy or puerperium, severe infection, and estrogen use.19 Patients with active cancer were defined as those on treatment for cancer such as chemotherapy or radiotherapy, those scheduled to undergo surgery for cancer, those with metastasis to other organs, and/or those with terminal cancer (expected life expectancy ≤6 months) at the time of diagnosis of VTE. Anemia was diagnosed if the value of hemoglobin was <13 g/dL for men and <12 g/dL for women, and thrombocytopenia as platelet count <100×10^9/L.

Initial anticoagulation therapy was defined as parenteral anticoagulation therapy in the acute phase (heparin or fondaparinux) for ≤10 days after the diagnosis, whereas anticoagulation therapy beyond the acute phase was defined as anticoagulation therapy (warfarin, direct oral anticoagulant, or heparin) for >10 days after the diagnosis.19 Detailed definitions of other patients’ characteristics are given in Supplementary Appendix 2.

Clinical Follow-up and Outcomes

Follow-up information was mainly collected by reviewing hospital charts, and additional follow-up information was obtained by phone and/or mail to patients, relatives, and/or referring physicians, regarding vital status, recurrent VTE, bleeding, invasive procedures, acute myocardial infarction, stroke and status of anticoagulation therapy beyond the acute phase was defined as anticoagulation therapy. Data were collected between July 2016 and March 2017, with a median follow-up duration of 1,218 (interquartile range [IQR] 847–1,764) days for surviving patients (95.1% follow-up at 1 year).

The primary outcome measures were recurrent VTE and major bleeding. Recurrent VTE was defined as PE and/or DVT with symptoms accompanied by confirmation of new thrombus or exacerbation of the thrombus by objective imaging and/or autopsy.20 Major bleeding was defined as International Society of Thrombosis and Hemostasis (ISTH) major bleeding, which consisted of a reduction in the hemoglobin level by at least 2 g/dL, transfusion of at least 2 units of blood or symptomatic bleeding in a critical area or organ.21 Another outcome measure was all-cause death. The Independent Clinical Event Committee (members listed in Supplementary Appendix 3) were unaware of the patients’ characteristics and reviewed all the study outcomes, and classified the causes of death as PE, cardiac event, cancer, bleeding event, other non-cardiac event, or unknown cause.22 Discontinuation of anticoagulation ther-
### Table 1. Baseline Characteristics of the Male and Female Patients With Venous Thromboembolism

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All (n=3,027)</th>
<th>Men (n=1,169)</th>
<th>Women (n=1,858)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*.†</td>
<td>67.2±15.3</td>
<td>64.9±14.7</td>
<td>68.6±15.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.2±4.4</td>
<td>23.3±4.1</td>
<td>23.1±4.6</td>
<td>0.17</td>
</tr>
<tr>
<td>BMI &gt;30*</td>
<td>169 (5.6%)</td>
<td>55 (4.7%)</td>
<td>114 (6.1%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Previous VTE*</td>
<td>178 (5.9%)</td>
<td>84 (7.2%)</td>
<td>94 (5.1%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,161 (38%)</td>
<td>460 (39%)</td>
<td>701 (38%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>386 (13%)</td>
<td>194 (17%)</td>
<td>192 (10%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic kidney disease†</td>
<td>572 (19%)</td>
<td>245 (21%)</td>
<td>327 (18%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dialysis</td>
<td>21 (0.7%)</td>
<td>12 (1.0%)</td>
<td>9 (0.5%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Previous heart failure</td>
<td>101 (3.3%)</td>
<td>38 (3.3%)</td>
<td>63 (3.4%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Varicose vein*</td>
<td>139 (4.6%)</td>
<td>48 (4.1%)</td>
<td>91 (4.9%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Liver cirrhosis†</td>
<td>26 (0.9%)</td>
<td>15 (1.3%)</td>
<td>11 (0.6%)</td>
<td>0.045</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>271 (9.0%)</td>
<td>134 (11%)</td>
<td>137 (7.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>145 (4.8%)</td>
<td>77 (6.6%)</td>
<td>68 (3.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>53 (1.8%)</td>
<td>33 (2.8%)</td>
<td>20 (1.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>84 (2.8%)</td>
<td>50 (4.3%)</td>
<td>34 (1.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>129 (4.3%)</td>
<td>62 (5.3%)</td>
<td>67 (3.6%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>270 (8.9%)</td>
<td>125 (11%)</td>
<td>145 (7.8%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Previous major bleeding†</td>
<td>231 (7.6%)</td>
<td>88 (7.5%)</td>
<td>143 (7.7%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>244 (8.1%)</td>
<td>71 (6.1%)</td>
<td>173 (9.3%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

#### Transient risk factors of VTE*..†
- Traveling: 1,086 (36%) vs. 346 (30%) vs. 740 (40%) <0.001
- Immobilized: 352 (12%) vs. 115 (9.8%) vs. 237 (13%) 0.01
- Central venous catheter: 64 (2.1%) vs. 31 (2.7%) vs. 33 (1.8%) 0.10
- Pregnancy: 45 (1.5%) vs. 0 (0.0%) vs. 45 (2.4%) NA
- Trauma: 119 (3.9%) vs. 28 (2.4%) vs. 91 (4.9%) <0.001
- Surgery: 406 (13%) vs. 122 (10%) vs. 284 (15%) <0.001
- Estrogen therapy: 52 (1.7%) vs. 4 (0.3%) vs. 48 (2.6%) <0.001
- Unprovoked VTE: 1,442 (48%) vs. 623 (53%) vs. 819 (44%) <0.001
- Active cancer*..†: 695 (23%) vs. 281 (24%) vs. 414 (22%) 0.26
- History of cancer: 938 (31%) vs. 391 (33%) vs. 547 (29%) 0.02

#### Presentation**..†
- Pulmonary embolism: 1,715 (57%) vs. 653 (56%) vs. 1,062 (57%) 0.48
- With hypoxemia: 850/1,715 (50%) vs. 299/653 (46%) vs. 551/1,062 (52%) 0.01
- With shock: 179/1,715 (10%) vs. 56/653 (8.6%) vs. 123/1,062 (12%) 0.048
- With cardiac arrest/collapse: 80/1,715 (4.7%) vs. 25/653 (3.8%) vs. 55/1,062 (5.2%) 0.20
- DVT only: 1,312 (43%) vs. 516 (44%) vs. 796 (43%) 0.48

#### Laboratory data at diagnosis
- Anemia†: 1,627 (54%) vs. 537 (46%) vs. 1,090 (59%) <0.001
- Thrombocytopenia†: 167 (5.5%) vs. 79 (6.8%) vs. 88 (4.8%) 0.02
- eGFR (mL/min/m², n=3,001): 70.5±30.4 vs. 71.0±29.7 vs. 70.1±30.8 0.42
- eGFR <60mL/min/m²: 1,123 (37%) vs. 425 (37%) vs. 698 (38%) 0.56
- D-dimer (μg/mL, n=2,852): 10.2 [5.0–20.4] vs. 9.8 [4.7–19.8] vs. 10.7 [5.3–20.9] 0.01
- Thrombophilia*: 147 (4.9%) vs. 68 (5.8%) vs. 79 (4.3%) 0.053

#### Treatment in the acute phase
- Initial anticoagulation therapy: 2,534 (84%) vs. 985 (84%) vs. 1,549 (83%) 0.52
- Heparin: 2,417 (95%) vs. 949 (96%) vs. 1,468 (95%) 0.07
- Fondaparinux: 168 (66%) vs. 55 (5.6%) vs. 113 (7.3%) 0.09
- Thrombolysis: 430 (17%) vs. 186 (19%) vs. 244 (16%) 0.041
- Inferior vena cava filter: 720 (24%) vs. 293 (25%) vs. 427 (23%) 0.19
- Ventilation support: 92 (11%) vs. 30 (9.1%) vs. 62 (12%) 0.14
- PCPS: 39 (4.2%) vs. 14 (4.2%) vs. 25 (5.0%) 0.61

(Table 1 continued the next page.)
Figure 1. (A) Study flowchart, and (B) age distribution by sex category. The men were significantly younger than the women, most of whom were elderly, while the distribution of younger men and women was balanced. VTE, venous thromboembolism, including pulmonary embolism and deep vein thrombosis.
Sex Differences in VTE Patients

Consistent with previous reports, we selected 8 risk-adjusting variables for recurrent VTE and 9 risk-adjusting variables for major bleeding, listed in Table 1. As a sensitivity analysis, to adjust for the status of anticoagulation therapy, we constructed a multivariable Cox proportional hazard model incorporating the status of anticoagulation therapy (on vs. off) as a time-updated covariate together with the same risk-adjusting variables as in the main analysis, and estimated the risk of men relative to women for recurrent VTE and major bleeding. The detailed method is described in Supplementary Appendix 5. Also as a sensitivity analysis, we took into consideration the competing risk of death for each primary outcome measure in the survival analysis and used Fine and Gray’s method because a substantial proportion of the patients died during the follow-up period. All the statistical analyses were conducted by a physician.

Table 2. Anticoagulation Therapy Beyond the Acute Phase

<table>
<thead>
<tr>
<th>Anticoagulation therapy beyond the acute phase</th>
<th>All (n=3,027)</th>
<th>Men (n=1,169)</th>
<th>Women (n=1,858)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2,803 (93%)</td>
<td>1,090 (93%)</td>
<td>1,713 (92%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Warfarin</td>
<td>2.676/2.803 (95%)</td>
<td>1.051/1.090 (96%)</td>
<td>1.625/1.713 (95%)</td>
<td>0.053</td>
</tr>
<tr>
<td>TTR for PT-INR 1.5–2.5 (%)</td>
<td>71.7 [43.8–91.0]</td>
<td>73.7 [47.3–92.0]</td>
<td>69.8 [42.0–90.7]</td>
<td>0.02</td>
</tr>
<tr>
<td>TTR for PT-INR 2.0–3.0 (%)</td>
<td>28.7 [6.9–55.5]</td>
<td>31.2 [8.7–56.4]</td>
<td>28.4 [6.0–54.8]</td>
<td>0.15</td>
</tr>
<tr>
<td>Direct oral anticoagulant</td>
<td>78/2,803 (2.8%)</td>
<td>23/1,090 (2.1%)</td>
<td>55/1,713 (3.2%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Heparin</td>
<td>49/2,803 (1.8%)</td>
<td>16/1,090 (1.5%)</td>
<td>33/1,713 (1.9%)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Categorical variables are presented as numbers and percentages. Continuous variables are presented as median and interquartile range. TTR was calculated by the Rosendaal method. PT-INR, prothrombin time-international normalized ratio; TTR, time in therapeutic range.

Figure 2. Kaplan-Meier curves of the cumulative 3-year incidence of discontinuation of anticoagulation therapy during the follow-up period: men vs. women. The patients who received anticoagulation therapy beyond the acute phase of venous thromboembolism (VTE: n=2,803 in total; 1,090 men and 1,713 women) were assessed.

apy was defined as withdrawal of anticoagulant drug for ≥14 days. Detailed definitions of other clinical outcomes are given in Supplementary Appendix 4.

Statistical Analysis

Categorical variables are presented as numbers and percentages, and continuous variables are presented as mean and standard deviation or median and IQR based on their distributions. Categorical variables were compared by the chi-squared test. Continuous variables were compared by Student’s t-test or Wilcoxon’s rank sum test based on their distributions. Cumulative incidences were estimated by the Kaplan-Meier method and differences were assessed by the log-rank test. To adjust for clinically relevant covariates, we constructed a multivariable Cox proportional hazard model to estimate the hazard ratio (HR) and 95% confidence interval (CI) of men relative to women for the primary outcome measure, and major bleeding. Consistent with previous reports, we selected 8 risk-adjusting variables for recurrent VTE and 9 risk-adjusting variables for major bleeding, listed in Table 1. As a sensitivity analysis, to adjust for the status of anticoagulation therapy, we constructed a multivariable Cox proportional hazard model incorporating the status of anticoagulation therapy (on vs. off) as a time-updated covariate together with the same risk-adjusting variables as in the main analysis, and estimated the risk of men relative to women for recurrent VTE and major bleeding. The detailed method is described in Supplementary Appendix 5. Also as a sensitivity analysis, we took into consideration the competing risk of death for each primary outcome measure in the survival analysis and used Fine and Gray’s method because a substantial proportion of the patients died during the follow-up period. All the statistical analyses were conducted by a physician.
Figure 3. Kaplan-Meier curves of the cumulative 3-year incidences of (A) recurrent venous thromboembolism (VTE) and (B) major bleeding: men vs. women.
Sex Differences in VTE Patients

Table 3. Clinical Outcomes at 3 Years for Men vs. Women

<table>
<thead>
<tr>
<th></th>
<th>No. of patients with event (Cumulative incidence)</th>
<th>Log-rank P</th>
<th>Adjusted HR [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>Men (n=1,169)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women (n=1,858)</td>
<td>0.47</td>
<td>0.83 [0.63–1.09]</td>
<td>0.17</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>69 (7.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>129 (8.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>104 (10.6%)</td>
<td>0.25</td>
<td>1.15 [0.90–1.47]</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>143 (9.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from VTE</td>
<td>272 (25.2%)</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>407 (23.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cancer</td>
<td>146 (14.4%)</td>
<td>0.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>238 (14.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from bleeding</td>
<td>10 (1.0%)</td>
<td>0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17 (1.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cumulative incidences estimated by the Kaplan-Meier method. The HRs represent the risks of men relative to women for each clinical outcome. HR, hazard ratio; VTE, venous thromboembolism.


drew to a time-updated covariate was performed with SPSS version 25.0 (IBM Corp.). All the other analyses were performed with R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). The reported P-values were 2-sided and P<0.05 was considered statistically significant.

Results

Patients' Characteristics

After screening 19,634 consecutive patients with suspected VTE for eligibility through chart review by the physicians at each institution, a total of 3,027 consecutive patients who had acute symptomatic VTE were enrolled in the current registry. We divided the entire cohort into male and female groups. Among the 3,027 patients, there were 1,169 men (39%) and 1,858 women (61%) (Figure 1A). The men were significantly younger than the women. Most of the women were elderly, but the distribution of younger men and women was balanced (Figure 1B). As compared with the women, the men were more likely to have a history of VTE, diabetes mellitus, chronic kidney disease, liver cirrhosis, anemia, chronic lung disease, ischemic heart disease, atrial fibrillation and previous stroke, whereas the women were more likely to have a connective tissue disease, and transient risks for VTE. Prevalence of active cancer was not different between groups. The proportion of those with PE was similar for men and women (Table 1).

Therapeutic Management and Clinical Outcomes

Treatment for VTE in the acute phase was similar for men and women, except for thrombolysis (Table 1). The prevalence of anticoagulation therapy beyond the acute phase was not different for men and women. During the follow-up period, time in therapeutic range of warfarin was significantly higher in men than in women (Table 2). Of those who underwent anticoagulation therapy beyond the acute phase of VTE, the duration of anticoagulation therapy was longer for men than for the women. The cumulative incidence of discontinuation of anticoagulation therapy was significantly higher in women than in men (Figure 2).

The cumulative 3-year incidence of recurrent VTE was not significantly different for men and women (Figure 3A), nor was the cumulative 3-year incidence of major bleeding (Figure 3B). The cumulative 3-year incidence of all-cause death did not differ significantly between groups (Table 3).

After adjusting for potential confounders, the risk of men relative to women for recurrent VTE was not significant (HR 0.83, 95% CI 0.63–1.09, P=0.17). The adjusted risk of men relative to women for major bleeding was also not significant (HR 1.15, 95% CI 0.90–1.47, P=0.25) (Table 3). In the sensitivity analysis using the multivariable Cox proportional hazard model with a time-updated covariate of anticoagulation therapy status, the risks of men relative to women for recurrent VTE and for major bleeding remained insignificant (HR 0.91, 95% CI 0.69–1.20, P=0.51, and HR 1.14, 95% CI 0.90–1.46, P=0.29) (Supplementary Appendix 5). Also in the sensitivity analysis using Fine and Gray's method for each primary outcome measure, the HRs were not statistically significant for either recurrent VTE or major bleeding (Supplementary Appendix 6).

Discussion

The main findings of the current study were as follows: in real-world VTE patients, the clinical characteristics and management of anticoagulation therapy were different for men and women, but there was not a large sex-related difference in the risks for recurrent VTE and major bleeding. The previous reports suggesting male sex as a risk for recurrent VTE had some exclusion criteria, such as cancer and precedent hormonal therapy.7–12 Exclusion criteria, especially of clinically important factors, can lead to selection bias such that the results may not be generalizable to the patient population of interest.23 Additionally, some of the studies only assessed patients who had already discontinued anticoagulation therapy, and hence the intervals from diagnosis of VTE probably varied from one patient to another. This would have led to significant treatment and selection bias. In contrast, the current registry consisted of patients presenting as acute symptomatic VTE without exclusion criteria and demonstrated that the risk for recurrent VTE was not significantly different for men and women. One of the strengths of our study is that we evaluated consecutive patients and took clinically relevant factors into account as risk-adjusting factors. The results are in line with the report from the large observational registry of consecutive patients (the RIETE Registry).13 Sex category may be a risk for VTE recurrence under some conditions but not any longer in unselected populations.

Various characteristics were different between the men and women, especially the higher proportion of women with transient risk factors of VTE when compared with men. In the current population, the duration of anticoagulation therapy significantly differed between men and women, probably because a shorter duration of anticoagulation therapy is recommended for those with transient risk factors of VTE.3–6 This might have influenced the incidence of recurrent VTE. In the current study, however, the mul-
tivariable analysis adjusting for other risks showed no large sex-related difference. Even the sensitivity analysis considering the effect of anticoagulation therapy did not demonstrate any difference between men and women. Another difference in the treatment for VTE between men and women was that men more frequently underwent thrombolysis during the acute phase of VTE than women, although hemodynamic instability was more often seen in women than in men (Table 1). Actually, we do not have data on the reasons why some patients received thrombolysis and the others not; nevertheless, several patient characteristics might explain that difference. Patients in the female group were older and more often had anemia than the men. These factors have been reported to be risk factors for bleeding23,24 and thus might have affected the decision of the attending physicians.

There have been relatively few reports on the sex difference in bleeding risk of VTE patients. Anticoagulation therapy reduces thrombotic events, but is likely to increase bleeding events. Thus, attention should be paid to the bleeding risk when deciding the duration of anticoagulation therapy after VTE. Women are reported to have a higher risk for bleeding during anticoagulant treatment for VTE in the era of warfarin25 and new oral anticoagulants.26 However, those reports were based on randomized clinical trials, whereas the RIETE registry, which derived from real-world clinical situation, showed no large sex-related difference in bleeding risk.13 The result of the current registry is in line with the RIETE registry (i.e., no large sex-related difference). Therefore, this study’s results suggested that sex category can be disregarded when deciding the duration of anticoagulation therapy after VTE.

Previous literature reported no consistent data regarding a sex-related difference in the incidence of VTE, although oral contraceptives and postmenopausal hormone replacement have been associated with a higher incidence of VTE.27 In the current registry, the proportion of women was higher than that of men, which would be explained by the difference in the age distribution between men and women (Figure 1B). A number of studies have reported that the incidence of VTE rises exponentially with age.28 The age distribution and the majority of women in the present study were consistent with previous reports23 and reflected a real-world population of VTE patients.

Study Limitations
First, this study was observational. Anticoagulation therapy was left to the discretion of physicians and hence there may have been treatment selection bias and residual confounding. Second, most of the anticoagulation therapy in the current registry was vitamin K antagonist, but an increasing number of VTE patients are treated by direct oral anticoagulant in contemporary clinical practice. The results might be less generalizable because of the mode of anticoagulation therapy. However, both men and women were treated under the same conditions and thus that would have had little influence on sex-related differences.

Conclusions
In real-world VTE patients, the clinical characteristics and duration of anticoagulation were different between men and women. However, there was no large sex-related difference in the risk for recurrent VTE or major bleeding.

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Conflicts of Interest
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Supplementary Files

Please find supplementary file(s):