Incidence, Characteristics and Management of Venous Thromboembolism in Japan During 2011

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Background: This study aimed to determine the incidence, characteristics and management of venous thromboembolism (VTE) in Japan during 2011.

Methods and Results: A retrospective study assessed responses to a questionnaire regarding treating newly diagnosed VTE at all admitting hospitals throughout Japan during 2011. More individuals were diagnosed with VTE than ever before, with 16,096 cases of diagnosed pulmonary embolism (PE) and 24,538 cases of diagnosed deep vein thrombosis (DVT). Almost half (47.2%) of the PE patients had a relatively mild condition with no right ventricular overload. Similarly, almost half (43.8%) of the DVT patients had a relatively mild condition with isolated calf thrombus. Most of PE patients were treated by anticoagulation, and fewer were treated using thrombolytic agent or inferior vena cava (IVC) filter.

Conclusions: The present study showed a remarkable increase in the incidence of VTE in Japan during 2011. Relatively mild conditions such as non-massive PE and isolated calf DVT were frequently diagnosed. Among PE patients, thrombolytic therapy or IVC filter implantation decreased compared with previous surveys. The appropriate management of isolated calf DVT requires further investigation.

Key Words: Deep vein thrombosis; Pulmonary embolism; Venous thromboembolism

Although the annual incidence and management of venous thromboembolism (VTE) in Japan was investigated during 1996, 2000, 2004 and 2009 using questionnaires, the subsequent analyses following these surveys remain insufficient. Furthermore, circumstances surrounding VTE in Japan have changed rapidly. For example, an increasing trend towards a non-traditional lifestyle, increasing incidence of both obesity and cancer, and a higher usage of oral contraceptives have increased the risk of developing VTE. In addition, accumulating evidence about diagnosis, treatment and prophylaxis might have affected the management of VTE.

We therefore implemented another questionnaire survey to determine the incidence, features and management of VTE in Japan during 2011.

Methods

The Ethics Committee of Mie University approved this retrospective study of VTE. Questionnaires were mailed to all clinical departments (internal medicine and surgery, pediatrics, obstetrics and gynecology, orthopedics, otorhinolaryngology, ophthalmology, dermatology, and urology) at all university schools of medicine or medical colleges, and admitting hospitals with over 20 beds in Japan. The questionnaire asked about the number of patients with VTE managed at each hospital during the period from November 1 to December 31, 2011. The annual number of patients diagnosed for the first time with VTE was assessed based on the responses. Details of the patients included age, sex, height, weight, circumstances of onset, symptoms, underlying risk factors, severity, diagnostic methods, treatment, and in-hospital outcome.

The numbers of patients diagnosed with pulmonary embolism (PE) or deep vein thrombosis (DVT) was calculated by the same method previously reported as: number of patients with PE (or DVT) per 2 months × response rate. Because PE occurs secondarily to DVT, PE and DVT often coexist. In such cases, patients were enrolled as PE or DVT belong to the first diagnosis in this study.

PE was definitively diagnosed by enhanced computed tomography, pulmonary angiography, pulmonary scintig-
arrhythmia, hypovolemia, or sepsis). Submassive PE was defined as acute PE with stable hemodynamics accompanied by right ventricular overload determined by echocardiography. Non-massive PE was defined as PE other than those described above. DVT was classified as proximal or isolated calf DVT. Proximal DVT was defined when the presenting part of the thrombus was located in a proximal deep vein above the popliteal vein to inferior vena cava (IVC). Isolated calf DVT was defined as thrombus located solely in the calf vein. Immobilization was defined as strict bed rest for at least 3 continuous days within the previous 3 months.

### Statistical Analysis

Data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were analyzed using
overload. Isolated calf DVT was identified among 43.8% of all DVT cases, and 40.1% of all DVT were asymptomatic. Among patients diagnosed with PE, only 33% of them had leg symptoms.

Treatment for VTE

All types of PE was treated by anticoagulation in 92.4%, by thrombolysis in 14.0%, and by IVC filter implantation in 29.4% (permanent type: 46.6%, retrievable type: 30.1%, temporary type: 23.3%). Significantly more patients who were diagnosed as PE with residual proximal DVT had an IVC filter implanted than those with PE without proximal DVT (38.9% vs. 17.3%, P<0.001). The rates of surgical thrombectomy (0.4%) and catheter intervention (2.2%) were very low.

Table 2. Treatments in Japan According to Severity of VTE

<table>
<thead>
<tr>
<th></th>
<th>PE</th>
<th>DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arrest at onset (n=39)</td>
<td>Massive (n=64)</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>31 (79.5)</td>
<td>60 (93.8)</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>13 (33.3)</td>
<td>15 (23.4)</td>
</tr>
<tr>
<td>IVC filter implantation</td>
<td>3 (7.7)</td>
<td>17 (26.6)</td>
</tr>
<tr>
<td>Surgical thrombectomy</td>
<td>2 (5.1)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Catheter intervention</td>
<td>3 (7.7)</td>
<td>8 (12.5)</td>
</tr>
</tbody>
</table>

Table 3. In-Hospital Mortality With/Without Thrombolysis for Severe PE (Except Arrest at Onset)

<table>
<thead>
<tr>
<th>Type of PE</th>
<th>Thrombolysis (+)</th>
<th>Thrombolysis (−)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massive</td>
<td>1/15 (6.7)</td>
<td>14/49 (28.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Submassive</td>
<td>1/43 (2.3)</td>
<td>9/199 (4.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 4. In-Hospital Mortality With/Without IVC Filter for Severe VTE (Except Arrest at Onset)

<table>
<thead>
<tr>
<th>Severe PE/Type of PE</th>
<th>IVC filter (+)</th>
<th>IVC filter (−)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massive</td>
<td>2/17 (11.8)</td>
<td>13/47 (27.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Submassive</td>
<td>1/77 (1.3)</td>
<td>9/165 (5.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With PE</td>
<td>13/175 (7.4)</td>
<td>28/240 (11.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Without PE</td>
<td>10/144 (6.9)</td>
<td>22/400 (5.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are shown as n (%). IVC, inferior vena cava. Other abbreviations as in Table 1.

Results

Incidence, Risk Factors and Severity of VTE

We mailed the questionnaire to 9,383 institutions and received 2,722 (29.0%) valid responses, from 1,005 of 2,797 (35.9%) clinical departments at university schools of medicine or medical colleges, and from 1,717 of 6,586 (26.1%) admitting hospitals. The numbers of patients with newly diagnosed PE and DVT during the 2-month study period were 778 and 1,186, respectively. From these results, the annual incidence of PE and DVT in Japan was calculated as 16,096 and 24,538, respectively.

Table 1 shows the characteristics of the patients. In the DVT group, the rate of in-hospital onset was higher, age was more advanced, body mass index was lower, and the percentage of women was higher than in the PE group. The all-cause in-hospital mortality rate was significantly higher among patients with PE than those with DVT. The major underlying risk factors for VTE were similar between patients with PE and DVT (malignancy 25.8% vs. 22.8%; prolonged immobilization, 21.6% vs. 26.9%; postoperative status, 13.2% vs. 27.2%; Figure 1). Figure 2 shows the severity of VTE. Almost half (47.2%) of the PE patients had a relatively mild condition with no right ventricular overload. Isolated calf DVT was identified among 43.8% of all DVT cases, and 40.1% of all DVT were asymptomatic. Among patients diagnosed with PE, only 33% of them had leg symptoms.

Treatment for VTE

All types of PE was treated by anticoagulation in 92.4%, by thrombolysis in 14.0%, and by IVC filter implantation in 29.4% (permanent type: 46.6%, retrievable type: 30.1%, temporary type: 23.3%). Significantly more patients who were diagnosed as PE with residual proximal DVT had an IVC filter implanted than those with PE without proximal DVT (38.9% vs. 17.3%, P<0.001). The rates of surgical thrombectomy (0.4%) and catheter intervention (2.2%) were very low. Table 2 shows treatment strategies applied according to the severity of VTE. The prognosis for severe VTE patients treated by IVC filter or thrombolysis was better than for the patients treated without them, but there were no significant differences between the 2 groups (Tables 3–4).

Treatment for DVT

Most patients with DVT were treated by anticoagulation (88.1%). Thrombolysis was applied to 5.1% of all DVT cases, and 15.3% of patients were implanted with an IVC filter that was permanent (36.7%), retrievable (43.2%) or temporary (20.1%). Table 2 shows the treatment strategies applied according to the severity of DVT. Most cases of proximal DVT and approximately 75% of cases of isolated calf DVT were treated by anticoagulation.
Discussion

Incidence of VTE

VTE is the third most frequent type of cardiovascular disease, with an overall annual incidence of 100–200 per 100,000 inhabitants in Europe and the USA. The relative risk of VTE in European and Asian patients after age standardization is 4.02. The present study found that 16,096 and 24,538 individuals in Japan were diagnosed with new PE and DVT, respectively, during 2011, which represented overall annual incidences of 12.6 and 19.2 per 100,000, respectively. Table 5 shows the changes in the annual numbers of patients diagnosed as PE in Japan determined from previous surveys. Although the incidence of VTE in Japan remains lower than in Western countries, the annual rate of PE has been increasing gradually. The major reasons for this increase include a shift towards a westernized lifestyle, increasing rates of obesity and cancer, and the widespread use of oral contraceptives. Another factor that has contributed to this increase seems to be greater recognition of the risk for VTE. Screening even asymptomatic patients at high risk for VTE has become prevalent since the guidelines were formulated in Japan. The findings from our present study support this hypothesis because in almost half of the cases VTE the patients had a relatively mild condition such as non-massive PE and isolated calf DVT.

The rate of in-hospital onset was higher in patients with DVT. This might have been because DVT, especially asymptomatic DVT, was diagnosed among many patients who were screened after hospital admission to treat other diseases. Prolonged immobilization, recent major surgery and malignancy, which were major risk factors for VTE in this study, have been previously considered as risk factors for PE and therefore such patients are always candidates for screening.

Underlying gynecological, orthopedic or other disorders that are more prevalent in women might have affected the predominance of female patients with DVT.

Adequate Treatment of VTE

Improving the prognosis is a critical issue for any disease and past reports indicated that only anticoagulation could improve the prognosis of PE. Anticoagulation has been established as an effective treatment for PE and was performed equally in this study, whereas thrombolytic therapy and IVC filter implantation were applied less frequently than before. The frequency of administering tissue plasminogen activator (t-PA) was predicted to increase after 2005, when the Japanese Ministry of Health, Labor and Welfare approved it as a treatment for PE. However, it rather decreased in this study, possibly because nearly half of the patients in the present study had relatively mild conditions that did not justify thrombolysis, and many of the patients in this study had high potential risk of bleeding because of malignancy, perioperative status or advanced age. The present study could not indicate superiority of thrombolysis. Previous findings in other countries also indicate there is little evidence that thrombolysis improves the prognosis of PE. This is one of the reasons why thrombolysis is not implemented. Only one small randomized trial has compared the effects on survival between thrombolysis and anticoagulation among patients with massive PE; 4 patients treated by thrombolysis survived whereas 4 others treated by anticoagulation died within a few hours. Thrombolytic therapy might be able to save more patients with massive PE regardless of the risk of fatal bleeding. More information about how to use t-PA, including indications and dosage, is needed.

The application of IVC filters seems to have decreased over the years. The present study found that outcomes were poorer for patients diagnosed as PE than DVT. Because the main cause of PE is thought to be the embolization of thrombus from veins of the lower limbs or intra-pelvic veins, an IVC filter seems to be a rational approach to preventing PE. However, recent reports describe adverse effects of IVC filters such as the migration and embolization of device components, IVC perforation, and filter fracture. Furthermore, increased risk of recurrent VTE determined in the PREPIC STUDY has discouraged the implantation of permanent IVC filters. The Japanese guideline recommends IVC filter implantation when anticoagulation is contraindicated or invalid. Reduced cardiopulmonary reserve is recommended as a Class Ila indication for an IVC filter but in this study filters did not improve the prognosis of patients with severe PE or proximal DVT (Table 4). These findings imply that indications for IVC filters should be reconsidered.

Features of DVT Causing PE

Most PE occurs as a sequela of DVT but not all patients with DVT develop PE. For this reason, it is very important to assess the type of DVT that causes the development of PE in order to apply the optimal therapeutic strategy, including IVC filter implantation. The present survey attempted to identify such types. Because proximal DVT is often associated with acute PE, we compared contributing factors between patients with PE and those with proximal DVT without PE. Symptoms caused by a thrombus in the leg were significantly less prevalent among PE patients than among those with proximal DVT alone. We previously reported that leg symptoms were not frequent among patients with DVT accompanied by PE. In DVT patients, most leg symptoms are caused by disruption.

Table 5. Changes in Annual Numbers of Patients Diagnosed With PE Between 1996 and 2011 in Japan

<table>
<thead>
<tr>
<th>First author</th>
<th>Study period</th>
<th>Annual number of persons diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumasaka N1</td>
<td>Aug. 1–Sept. 30, 1996</td>
<td>3,492</td>
</tr>
<tr>
<td>Kitamura K2</td>
<td>Aug. 1–Sept. 30, 2000</td>
<td>4,022</td>
</tr>
<tr>
<td>Sakuma M4</td>
<td>Aug. 1–Sept. 30, 2006</td>
<td>7,864</td>
</tr>
<tr>
<td>Present study</td>
<td>Nov. 1–Dec. 31, 2011</td>
<td>16,096</td>
</tr>
</tbody>
</table>

PE, pulmonary embolism.
of venous return with thrombi. Thus, occlusive-thrombi involve leg symptoms, whereas free-floating thrombi seem to cause less venous obstruction and still cause leg symptoms, but this type of thrombi easily embolize with venous flow to the pulmonary artery.\textsuperscript{28,29} Therefore, identifying distal DVT, including isolated calf DVT, with the potential to extend into the proximal vein and form a floating thrombus might be important. Calf DVT is more often asymptomatic, which causes difficulties with diagnosis. However, because of the recent increase of awareness about VTE, asymptomatic isolated calf DVT has become diagnosed more frequently by screening test. Thus, Japan is now at the next stage of PE prevention through the appropriate management of calf DVT. The 9th American College of Chest Physicians’ guidelines recommend anticoagulation for isolated calf DVT as the initial treatment if patients have severe symptoms or exacerbating risk factors.\textsuperscript{30} However, insufficient evidence is available about the risk factors, particularly among Asian populations, including Japan. This point is very important to justify this strategy. The present study indicated that although isolated calf DVT is treated less frequently by anticoagulation than proximal DVT, 78.8\% of patients with isolated calf DVT were actually treated by anticoagulation. The appropriate management of isolated calf DVT in Japan requires further investigation because anticoagulation carries a risk of bleeding.

Study Limitations

This survey was performed more than 5 years ago, and medical therapy for VTE has changed markedly, especially with the advent of direct oral anticoagulants. For this reason, some of the results derived from our study are not applicable to the current situation.

The low response rate to the questionnaire in this retrospective study might have generated some bias. But that is a key issue with such epidemiological investigative studies. Prior surveys had also been performed and estimated the incidence of VTE and we used similar methodology in order to be able to compare our results with the previous incidence of VTE and we used similar methodology in order to be able to compare our results with the previous surveys. But some studies have revealed no seasonal variation in the prevalence of VTE were not taken into consideration. This survey was performed in a different season from that of the previous survey. The past study was performed in August and September. Initially, we had planned to perform the present survey in the same time period, but a terrible natural disaster, known as the “Great East Japan earthquake”, occurred. Circumstances were still confused in August and we decided to postpone the survey until the end of the year. This might be a limitation of study for comparison with data from previous studies. But some studies have revealed no seasonal variation in the incidence of VTE in Japan.\textsuperscript{31,33}

In an analysis of prognosis based on all-cause in-hospital mortality, the primary cause of death might include not only VTE but other factors. Some patients with a predicted poor prognosis might have had less therapy or contraindications to therapy, but the background data of each patient did not include such information. It is definitely important to mention the deaths, which are regretted, because we did not ask about this aspect in our questionnaire.

Conclusions

The present study showed there was a remarkable increase in the incidence of VTE in Japan during 2011. Relatively mild conditions such as non-major PE and isolated calf DVT were frequently diagnosed. Among PE patients, the cases of thrombolytic therapy or IVC filter implantation had decreased compared with previous surveys. The appropriate management of isolated calf DVT requires further investigation.

Financial Support

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References