Economic Impact of Venous Thromboembolism Following Major Orthopaedic Surgery in Japan

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ABSTRACT

Objectives: Venous thromboembolism (VTE) is the most frequent complication following major orthopaedic surgery (MOS). Although studies in Western populations have demonstrated significantly higher costs for patients with VTE versus those without VTE after MOS, there is a paucity of such data in Japan. This study was conducted to understand the costs and VTE rates in Japanese patients.

Methods: Data were extracted from a hospital claims database. MOS was defined as total hip replacement, total knee replacement, or hip fracture surgery. Subjects who underwent more than one MOS during the same admission were excluded. Identified VTE cases were matched on a 1:2 matching scheme on the basis of surgery type, hospital, and date of surgery (+6 months). The primary outcome was the difference in 90-day costs. Secondary outcomes included differences in total 6-month costs postsurgery and average length and cost of initial hospital stay.

Results: The 90-day cumulative VTE incidence was 0.774%, with 94% of the cases occurring within 30 days postsurgery. Total 90-day costs were significantly higher in patients with VTE (difference of 864,153 Japanese yen [US $10,538]). Average length of stay was longer for patients with VTE (66 days vs. 42 days). Costs incurred by patients with VTE were on average much higher than those incurred by patients without VTE throughout 5 months postsurgery.

Conclusions: The development of a VTE in patients undergoing MOS results in a 1.5-fold increase in the length of stay and a 1.7-fold increase in 90-day costs. Findings indicate that the avoidance of VTEs through more effective prophylaxis will help to reduce the economic burden associated with MOS.

Keywords: cost, incidence, orthopaedic surgery, VTE.

Conflict of Interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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Introduction

Venous thromboembolism (VTE) is the most frequent complication following major orthopaedic surgery (MOS) [1]. It can occur as a result of persistent venous injury or impaired venous function, prolonged immobilization, impairment of endogenous anticoagulant or fibrinolytic systems, or clots in the pelvic region or contralateral extremity, postoperatively [1,2]. Deep vein thrombosis (DVT) may be associated with sequelae including recurrent VTE and postthrombotic syndrome. Postthrombotic syndrome may, in turn, result in persistent symptoms of chronic edema, discomfort, dermatitis, ambulatory venous hypertension, and venous ulceration [1,3].

Prevalence of DVT has been found to be among the highest in orthopaedic procedures than in other surgery types. The incidence of pulmonary embolism (PE) is much less certain; however, 3% to 28% of the patients undergoing total hip replacement (THR) and total knee replacement (TKR) were found to be at a high risk of developing PE within 2 weeks following surgery. Moreover, VTE is the most common cause for hospital readmission after THR [1].

International consensus recommendations include routine thromboprophylaxis in patients undergoing MOS; however, pharmacological prophylaxis is not routinely administered in Asian populations because VTE incidence is thought to be low. These VTE incidence rates in Asian patients, however, have been reported to be similar to those in Western patients. In a prospective epidemiological study, the incidence of DVT in Asian patients who did not receive any pharmacological thromboprophylaxis was 58.1% after TKR and 42% after hip fracture surgery, compared with previously reported incidence rates of 40% to 74% and 36% to 60%, respectively, in Western patients [1]. Moreover, the incidence rates of asymptomatic DVT following TKR, hip fracture surgery, and THR were 43%, 24%, and 17%, respectively. The difficulty in diagnosing VTE because of frequently clinically silent events or unreliable clinical signs highlights the risk of PE-related sudden death being the first clinical manifestation [4]. Approximately 10% of the deaths during hospitalization are attributed to PE [1].

Despite the fact that PE has been identified as a major cause of sudden death following surgery, it is not diagnosed in 22% of the
cases before causing death [5]. A registry trial conducted with Western patients reported fatal initial PE and fatal recurrent PE rates of 1% and 0.3%, respectively, at 3 months after MOS [6]. However, DVT and PE following MOS have been shown to increase the mortality rates by nearly 5 times and nearly 66 times, respectively [7]. In Japan, the number of PE cases increased from 3492 cases in 1996 to 4020 cases in 2000 and mortality rates due to acute PE have increased by 20% to 40% [8,9]. According to the guidelines for VTE diagnosis, treatment, and prevention, published by the Japanese Circulation Society in 2009, the number of PE-related deaths have increased by approximately 1.5-fold in 2005 compared with 1995 [10]. In addition, mortality rates associated with PE are reportedly higher (11.9%) than those of acute myocardial infarction (7.3%) [11].

Symptomatic DVT and PE have been associated with serious and negative outcomes including considerable acute morbidity, substantial consumption of resources, and long-term clinical sequelae, which result in greatly increased health care costs [1]. Studies in Western populations have demonstrated significantly higher costs for patients with VTE than for patients without the complication after MOS. The occurrence of VTE was found to increase total hospitalization days by greater than 2-fold and time spent in the intensive care unit by almost 10-fold. These result in overall costs for patients with VTE that are twice those for patients without VTE [7]. Overall health care charges over a period of 3 months have been reported to increase by 63% because of postdischarge VTE following hip replacement, major knee surgery, or hip fracture repair (P < 0.01) [12]. There is a paucity of literature, however, that report the cost of VTE following MOS in Japan and other Asian countries.

Health care payers and policymakers would like to have information about the costs associated with diseases and their treatments. These data, however, are often not available from randomized clinical trials, which are the main source of clinical information. Specifically, because randomized clinical trials are often limited by atypical settings, artificial protocols, and highly selected populations due to strict screening criteria and short follow-up periods, their results may not reflect “real-world” outcomes. However, claims databases typically contain information from demographically and geographically diverse populations that are available for longer periods of time. These allow for better representation of the general population and real-life settings, which are more suitable for pharmacoeconomic evaluations [13]. Therefore, this study set out to analyze the costs associated with VTE following MOS using a claims database in Japan.

Methods

Data were extracted from the Medical Data Vision, Inc., database, a hospital claims database that contains detailed electronic hospital medical records from 13 private or governmental hospitals from Hokkaido, Tohoku, Kanto, Chubu, and Kansai prefectures. Data were extracted on major orthopaedic surgeries between January 1, 2003, and October 31, 2009.

Study Subjects

Major orthopaedic surgeries were defined as a principal procedure of THR, TKR, or hip fracture repair, and were identified by using ReceCodes, which are standardized codes used by the Ministry of Health, Labour and Welfare for electronic claims processing. These codes are associated to the following International Classification of Diseases, Ninth Revision, Clinical Modification, codes: 79.25, 81.51, 81.52, and 81.54. Inclusion criteria were aged 18 years or older, having at least 3 months of data prior to the index surgery, and having 3 to 6 months of postsurgery data available or died within this time period. Subjects who underwent more than one MOS during the same admission were excluded.

VTE Cases

Warfarin and heparin are commonly used for VTE prophylaxis. According to guidelines for the prophylaxis and treatment of VTE that were published in Japan in 2004, standard pharmacological treatment includes unfractionated heparin (UFH) followed by warfarin for at least 3 months, with the presence of risk factors that are reversible. Treatment may be administered for at least 6 months when there are no apparent risk factors associated with VTE incidence [10]. Given that prophylactic treatment cannot be prescribed without an associated diagnostic code, utilizing only the administration of low molecular weight heparin or warfarin would result in an excessively high false-positive VTE rate. Therefore, candidates VTE cases were identified by using ReceCodes associated with International Classification of Diseases, Tenth Revision, codes for PE (I269) and DVT (I801, I802, and I803), followed by additional strict criteria to ensure that subjects were true VTE cases. Following the identification of PE and DVT codes, subjects were required to have a DVT or PE diagnosis code up to 90 days after their first surgery and no diagnosis from 90 to 7 days before surgery. This allowed for the identification of a VTE up to 90 days post-surgery. Because prophylactic treatment may be administered prior to surgery, we allowed prophylaxis to be administered for up to 1 week prior to surgery. VTE codes identified earlier than this may be from prior VTE and therefore they would not be considered “at risk” of a VTE following surgery.

Subjects additionally need to have warfarin or UFH initiated within 1 day of VTE diagnosis, followed by anticoagulant use for more than 28 days after initiation. One day was selected to account for a delay in data entry within the hospital database. The use of UFH or warfarin for at least 28 days allowed for the exclusion of subjects assumed on prophylaxis treatment only, despite having a VTE diagnosis code. In addition, subjects with an inferior vena cava filter placement (International Classification of Diseases, Ninth Revision, Clinical Modification, code of 387.7) within 128 days of surgery were assumed to have a PE.

Matched Controls

Identified cases were matched to control subjects without VTE on a 1:2 matching scheme on the basis of surgery type, hospital, and date of surgery (±6 months). These criteria allowed for the reduction of impact of treatment practice changes that may influence the costs and resource utilization associated with surgery and VTE management. Control subjects were included in the study if their primary point of contact for clinical care was the hospital where they underwent surgery, to ensure that all treatment costs associated with the surgery and any postdischarge care were fully captured. Therefore, subjects were required to have at least a 3- to 6-month postsurgery visit.

Pharmacoeconomic Analyses

The primary outcome measure was the 90-day costs associated with surgery. The secondary outcomes were total costs for 6 months following surgery, average length of hospital stay for the initial admission, and cost of the hospital stay. Total costs consisted of pharmacy, laboratory, medical treatment, and room charges. Total costs between patients with VTE and patients without VTE were evaluated using a gamma-distributed generalized linear model with a log-link function. The gamma-distributed functional form is particularly useful because it avoids the issues with retransformation of skewed data.
Nonparametric bootstrapped mean differences in costs were analyzed on the basis of 1000 draws with replacement. Untransformed costs were evaluated by using t tests/analysis of variance, and median differences were tested by using the Mann-Whitney U/Wilcoxon rank-sum test. Costs are presented as Japanese yen (JPY) and US dollars ($2 JPY = US $1).

Results

The pool of potential cases consisted of 4650 patients who underwent MOS and did not have a prior diagnosis of VTE between 8 and 90 days prior to surgery. Among these, a total of 37 patients were identified to be true cases having had their first DVT and/or PE occurrence 0 to 7 days after surgery (12 patients), 8 to 14 days after surgery (19 patients), 15 to 30 days after surgery (3 patients), 31 to 60 days after surgery (2 patients), or 61 to 90 days after surgery (1 patient). These results are presented in Figure 1. One patient had more than one VTE occurrence. Therefore, within this cohort of MOS patients, there was a 90-day cumulative VTE incidence of 0.774%, with 94% of the cases occurring within the first 30 days following surgery.

Ten patients that were true cases did not have adequate data for the 90-day follow-up period, and therefore were not included in the demographics and cost analyses. A total of 26 cases had data for at least a 90-day follow-up period and were matched to 51 controls. One case could be matched to only one control instead of two. Twenty-five patients were identified as DVT cases with 49 matched controls. Eight patients were identified as PE cases with 15 matched controls. A total of 7 patients had both DVT and PE.

The mean age of the 26 patients with VTE was 75.4 ± 12.23 years, ranging from 40 to 96 years, and the mean age of the 51 matched controls was 76.5 ± 13.65 years, ranging from 24 to 98 years. Most were female patients in both the VTE (92.3%) and matched control (88.2%) groups, with more than half having a hip fracture repair. Demographic information for patients with at least 90 days of follow-up data is presented in Table 1. The greatest costs were incurred from the time of surgery to 30 days after the procedure for both patients with DVT and PE.

The composition of costs incurred during the 90-day period after surgery is presented in Figure 2. For each category, costs were greater in patients with VTE than in controls. The development of a VTE requires additional resources to diagnose, treat, and follow up the patient, resulting in the greater costs associated with each category (Table 2). Differences between the two groups for pharmacy, laboratory, medical, and room costs were large. These resulted in a difference of $3,394–$19,285 between the two groups of patients (bootstrapped 95% CI $-954,962.38 JPY to $2,098,639 JPY). Costs for patients with VTE were significantly higher when tested with the gamma-distributed log-link generalized linear model adjusted for age and gender (P < 0.0001).

Table 1 – Patient demographic information for VTE cases and matched controls with at least 90 d of follow-up data.

<table>
<thead>
<tr>
<th>Cases (n = 26)</th>
<th>Matched controls (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>Female</td>
<td>24 (92.3)</td>
</tr>
<tr>
<td>Age (y) at time of procedure</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>75.4 ± 12.23</td>
</tr>
<tr>
<td>Median</td>
<td>77.00</td>
</tr>
<tr>
<td>Min-Max</td>
<td>40.0–96.0</td>
</tr>
<tr>
<td>Age categorized (y), n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>7 (26.9)</td>
</tr>
<tr>
<td>70–79</td>
<td>9 (34.6)</td>
</tr>
<tr>
<td>≥80</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>Surgical intervention, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hip fracture repair</td>
<td>16 (61.5)</td>
</tr>
<tr>
<td>Hip replacement</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>Knee replacement</td>
<td>5 (19.2)</td>
</tr>
</tbody>
</table>

Note. Controls matched on MOS date, surgery type, and clinic. MOS, major orthopaedic surgery; VTE, venous thromboembolism.

VTE were significantly higher when tested with the gamma-distributed log-link generalized linear model adjusted for age and gender (P < 0.0001). The 90-day cost associated with surgery for patients with DVT was on average 1,910,365 JPY ($23,297) compared with 1,159,583 JPY ($14,141) for matched controls, resulting in a difference of 750,782 JPY ($9,156) (bootstrapped 95% CI 401,624.32 JPY–1,159,133.60 JPY) ($4,898–$14,136). For patients with PE, the 90-day cost associated with surgery was on average 1,998,479 JPY ($24,372) compared with 990,178 JPY ($12,075) for matched controls, resulting in a difference of 1,008,302 JPY ($12,296) (bootstrap 95% CI $728,525.72 JPY–1,581,357.60 JPY) ($3,394–$19,285). Costs for patients with DVT and PE were significantly higher than for their matched controls when tested with the gamma-distributed log-link generalized linear model adjusted for age and gender (P < 0.0001 and P = 0.0005, respectively). Patients with both DVT and PE had an average 90-day cost of 1,705,201 JPY ($20,795) associated with surgery compared with 2,098,639 JPY ($25,593) in patients with either DVT or PE only. These resulted in a difference of $393,438 JPY ($-4,798) between the two groups of patients (bootstrap 95% CI $-954,962.38 JPY to $215,616.42 JPY).

The cumulative costs associated with MOS from 30 days prior to the surgery date through 6 months after surgery are shown in Figure 3. The cumulative costs were greater in patients with VTE than in controls. The development of a VTE requires additional resources to diagnose, treat, and follow up the patient, resulting in the greater costs associated with each category (Table 2). Differences between the two groups for pharmacy, laboratory, medical, and room costs were large. These resulted in a difference of $3,394–$19,285 between the two groups of patients (bootstrap 95% CI $-954,962.38 JPY to $215,616.42 JPY).

The cumulative costs associated with MOS from 30 days prior to the surgery date through 6 months after surgery are shown in Figure 3. Examining the monthly costs, there was an immediate and large separation of costs between patients with VTE versus matched controls. The greatest costs were incurred from the time of surgery to 30 days after the procedure for both patients with

Fig. 1 – Time course of VTE incidence following MOS. MOS, major orthopaedic surgery; VTE, venous thromboembolism.
VTE and patients without VTE. The mean difference in costs between patients with VTE and controls increased to 363,893 JPY ($4,438) between 31 and 60 days after surgery, although the absolute costs for both groups decreased. This is most likely due to the added expenses of costly VTE treatment after surgery. Costs incurred in patients with VTE remain on average much higher than in patients without VTE throughout 5 months after surgery. Mean costs were the same among all the patients 6 months after surgery, which may indicate that patients with VTE no longer require treatment at this point. This result, however, may also be indicative of the lack of sufficient patient data.

Discussion

The development of a VTE in patients undergoing MOS results in a 1.5-fold increase in the length of hospitalization and a 1.7-fold increase in total costs over 90 days, resulting in a significant burden to the health care system. The additional costs patients incur are because of a VTE peak during the second month following surgery, likely because of additional treatments and testing following their VTE and perhaps because of the VTE occurring closer to 30 days postsurgery.

The reported cumulative incidence of 0.774% is slightly lower than what others have reported in the literature. Ollendorf et al. [7] reported an in-hospital incidence of 1.1% and White et al. [14] reported 0.9%. Oster et al. [12] reported a much higher incidence of VTE following MOS (2.2%). Oster et al. [12] used only a claim with a VTE diagnosis and the use of warfarin or UFH in defining their VTE population, likely overstating the true number of VTEs due to the use of prophylactic therapy and need for an associated diagnostic code to properly process the claim for reimbursement.

Data for the incidence rates of VTE following MOS in Japan are widely varied. In patients undergoing hip surgery and receiving thromboprophylaxis, the incidence rates of fatal PE, symptomatic PE, and asymptomatic DVT were 0%, 0.03%, and 0.1%, respectively [15]. In another study in which patients received a similar thromboprophylaxis regimen, the incidence rates of fatal PE, symptomatic PE, and proximal DVT were all 0%, but the incidence rate of asymptomatic DVT was 6% [16]. Higher DVT incidence rates of 22.6% and 43.6% were reported in Japanese patients undergoing total hip and total knee arthroplasties, respectively, without anticoagulant prophylactic therapy [17]. The 8 (0.17%) cases of PE found in the current study are supported by other researchers where PE after MOS was found to be between 0.01% and 1.45% [17,18]. Furthermore, most studies report the occurrence of unsymptomatic DVT while the present study evaluated symptomatic DVT.

Length of stay for the initial hospitalization was approximately six times what has been reported in the West. Oster et al. [12] reported a total length of stay of 6.5 days for patients without VTE and 11.1 days for patients with VTE, compared with 42.0 and 66.0 days, respectively, in our study. These findings are not surprising given the typically longer length of stay in Japan.

There are several limitations that need to be considered within this analysis. We used a very restrictive criteria for the identification of a VTE; however, this ensures confidence that these were highly probable true cases and therefore the cost differences seen are likely reflective of the true cost differences. It should be noted that some patients who discontinued anticoagulant treatment before 28 days postsurgery because of mild disease would have been excluded because of this restrictive criteria, suggesting that the resulting costs may have been higher due to more severe disease among the identified cases. It is also possible that a few VTE cases were classified as non-VTE cases because of our overly restrictive criteria, but this would have driven the cost differences toward no significant difference. The associated cumulative incidence is likely underestimated because of these restrictive criteria.

Another limitation results from the reliance on hospital electronic records in Japan. The current health care medical records databases are still underdeveloped compared with the West. Although these are developing rapidly, there remain limitations in their current breadth. The current database captures all electronic records for 13 hospitals from five prefectures. Therefore, the number of surgeries was quite small. Indeed, generalizability to the rest of Japan is somewhat problematic because of the limited number of hospitals; however, the database does include both Diagnosis Procedure Combination and non-Diagnosis Procedure Combination hospitals, reflecting the composition of care throughout Japan. Additional data from more rural hospitals and from the southern islands would be preferred.

Table 2 — Mean costs (JPY) by category for patients with VTE, patients with DVT, and patients with PE.

<table>
<thead>
<tr>
<th></th>
<th>VTE</th>
<th></th>
<th>DVT</th>
<th></th>
<th>PE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n = 26)</td>
<td>Controls (n = 51)</td>
<td>Cases (n = 24)</td>
<td>Controls (n = 49)</td>
<td>Cases (n = 8)</td>
<td>Controls (n = 15)</td>
</tr>
<tr>
<td>Mean</td>
<td>1,992,713</td>
<td>1,128,560</td>
<td>1,910,365</td>
<td>1,159,582</td>
<td>1,998,479</td>
<td>990,178</td>
</tr>
<tr>
<td>Pharmacy costs</td>
<td>162,872</td>
<td>44,892</td>
<td>156,426</td>
<td>45,943</td>
<td>144,718</td>
<td>37,925</td>
</tr>
<tr>
<td>Laboratory costs</td>
<td>142,547</td>
<td>50,425</td>
<td>139,065</td>
<td>50,861</td>
<td>179,061</td>
<td>62,016</td>
</tr>
<tr>
<td>Medical costs</td>
<td>700,486</td>
<td>440,716</td>
<td>697,128</td>
<td>447,562</td>
<td>626,376</td>
<td>424,436</td>
</tr>
<tr>
<td>Room costs</td>
<td>1,076,337</td>
<td>663,276</td>
<td>1,012,402</td>
<td>679,161</td>
<td>1,115,445</td>
<td>497,313</td>
</tr>
</tbody>
</table>

Note. Controls matched on the basis of qualified subjects.

DVT, deep vein thrombosis; JPY, Japanese yen; PE, pulmonary embolism; VTE, venous thromboembolism.
However, given the limitations of data in Japan, this small sample represents a tremendous step forward in understanding the economic burden of VTE on the health care system.

It is possible that patients who developed a VTE were at a higher risk of developing a VTE because of comorbid conditions. Unfortunately, we were not able to reliably develop a Charlson Index for subjects because of the use of hospital-based claims. We would be able to develop this comorbidity index only if each subject used the same hospital for his or her primary care and therefore, consistent recording of comorbid conditions could be extracted. We were able to control for several factors though. By matching on the hospital, surgery performed, and date of surgery (within 6 months), we were able to control for changes in practice patterns between hospitals and maintained the same balance of surgery type in the cases and controls. In addition, we controlled for age and gender in our multivariate analysis. Therefore, we feel as though the impact of comorbid conditions would only minimally impact our findings.

The results of this analysis highlight the significant increase in costs associated with the development of a VTE following MOS. In Japan, the use of pharmacologic VTE prophylaxis has been reported at only 17% [19]. VTE is an easily preventable disease with a substantial risk of morbidity and mortality in patients following surgery. However, it has been reported that few physicians in Asian countries use American College of Chest Physicians recommended types of prophylaxis [20]. This may be due to many factors, including physician awareness, risk of bleeding, availability of guidelines, education, or reimbursement. With a mortality rate of 32% in acute PE in Japanese subjects [21], the avoidance of VTEs (DVT and PE) is important from a clinical perspective. The avoidance of VTEs in Japanese patients through more effective prophylactic treatment will help to reduce the economic burden associated with MOS.

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REFERENCES


Fig. 3 – Cumulative mean costs (JPY) from 30 days prior to MOS through 6 months after surgery in patients with VTE and matched control patients. MOS, major orthopaedic surgery; VTE, venous thromboembolism.


