Economic Burden of Venous Thromboembolism in Patients Undergoing Major Abdominal Surgery

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ABSTRACT

Background: Venous thromboembolism (VTE) is a serious complication that arises after major abdominal surgery. VTE poses risks of negative outcomes and health care burden. The literature on the cost of VTE in Japanese surgical patients, however, is scarce. Objective: This study was conducted to investigate the economic consequences of VTE in Japanese patients with major abdominal surgery, using a hospital claims database. Methods: This is a retrospective, matched cohort study. Patients who had a VTE event up to 90 days after their first major abdominal surgery and initiated warfarin or heparin within 1 day of VTE diagnosis with continued treatment for more than 4 weeks were matched with controls for surgery type, hospital, and date of surgery ≤ 6 months in a 1:2 scheme. The primary outcome was 90-day costs associated with major abdominal surgery. The secondary outcomes were 6-month total costs, average length of initial inpatient stay, and cost of initial inpatient stay. Results: The 90-day cumulative incidence of VTE was 4.89%. The development of a VTE event in patients undergoing major abdominal surgery resulted in a 1.5-fold increase in the length of hospitalization and a 2.8-fold increase in total costs 90 days after the surgery. Total costs further increased to 3.4-fold at 6 months. Overall, costs incurred in patients with VTE are on average much higher than in patients without VTE throughout 6-month postsurgery. Conclusions: The preventive care for VTE using more effective prophylactic treatment is recommended to reduce the economic burden associated with major abdominal surgery.

Keywords: cost, incidence, Japan, major abdominal surgery, VTE.

Introduction

Venous thromboembolism (VTE), defined as either deep vein thrombosis (DVT) or pulmonary embolism (PE), is a serious, common complication that arises after major abdominal surgery. It can occur in patients as a result of prolonged immobilization, impairment of venous function, or impairment of endogenous anticoagulant or fibrinolytic systems [1]. Recurrent VTE and postthrombotic syndrome are both serious sequelae of DVT, and postthrombotic syndrome may further cause persistent symptoms such as chronic edema, dermatitis, ambulatory venous hypertension, and venous ulceration [1,2]. Postthrombotic syndrome is characterized by swelling, pain, and discomfort that are typically most pronounced at the end of the day and are aggravated by standing and walking [3]. PE is a major cause of sudden death after surgery and is manifested by clinical symptoms including dyspnea, chest pain, and syncope [4].

In Japan, the incidence of clinical PE after general surgery was reported to be 0.33% [5]. The mortality rate of patients with PE was 31%, and fatal PE was reported in 0.08% of the surgical population [5]. In addition, evidence suggests that in some patients, the risk of developing VTE may persist for several weeks after a triggering event such as a major abdominal surgery [6]. Although the occurrence of VTE has been reported to be relatively low in the Asian population, its incidence has increased rapidly in the past decade in Japan to 0.02% of total births and 0.08% of total gynecological operations in Japan between 1991 and 2000 [7]. The number of PE cases in obstetrics and gynecology was reported to have increased by 6.5-fold over the past 10 years. One more recent study reported the incidence of postoperative
VTE in patients without chemical thromboprophylaxis to be 7.7% in Japan [8]. The incidence of VTE was also observed in 24.3% of the 173 Japanese patients undergoing open major laparotomy [9], which was slightly more but comparable to that of the Caucasian patient population undergoing general or gynecologic surgery (15%–19%) [9–11]. Furthermore, besides the increasingly similar VTE incidence in Asian and Western populations, the literature suggests that patients in both regions may share the same risk factors and VTE disease pattern [12].

VTE brings serious risks of negative outcomes to patients after major surgery [1]. Its recurrence and complications also pose an enormous burden on health care resources for its management [13]. The age-adjusted mortality rate of patients with PE has increased rapidly in the last 50 years in Japan [14]. Risk factors for developing postoperative VTE include age over 40 years, obesity, and stage III/IV cancer [1,12,15], and patients with gynecological cancer undergoing major abdominal surgery demonstrated a 14-fold greater probability of developing PE than did patients with benign disease (P < 0.001) [16]. In addition, pharmacologic thromboprophylaxis including low-molecular-weight heparin (LMWH) is associated with an increased incidence of postoperative bleeding complications that can be life-threatening [16].

Warfarin and heparin are used as common prophylaxis treatments to prevent VTE. According to the Japan guideline for prophylaxis and treatment of VTE [17], standard treatment includes unfractionated heparin followed by warfarin for at least 3 months for patients with reversible risk factors. Treatment can also be administered for a longer time when there are no apparent risk factors or when patients have cancer or recurrent VTE [17].

Although several studies have investigated the cost associated with VTE in Western countries, there is a paucity of literature describing the true costs associated with VTE after major abdominal surgery in Japan [18–21]. The present study investigated the incidence and economic consequences of having a VTE event after major abdominal surgery, using electronic hospital medical records.

Methods

Data Source

Data were obtained from the database developed by Medical Data Vision, Inc., an electronic hospital claims database containing hospital medical records from hospitals across Japan. The database contains health insurance claims for about 1 million patients since 2003 [22], providing a large number of patient samples needed to evaluate the incidence of clinical VTE. Anonymous information including patient background, disease, medications, tests, surgeries, and diagnosis procedure combination claims is included in this database [22]. Data were extracted on all major abdominal surgeries in the time frame between January 1, 2003, and October 31, 2009, to ensure an adequate number of events given the expected low incidence.

Study Subjects

A major abdominal surgery was defined as a principal procedure of gastrointestinal surgery, urological surgery, and male and female genitourinary surgery and was identified using receipt codes, which are standardized codes used by the Ministry of Health, Labour and Welfare for electronic claims processing. These codes were associated with 68 International Classification of Diseases, Ninth Revision, Clinical Modification codes. Patients who underwent the defined major abdominal surgery comprised the primary population for the analysis. Patients who were aged 18 years or older and had at least 3 months data before the index surgery and 3 to 6 months postsurgery follow-up available were included in the analysis. Patients who underwent more than one of these procedures during the same inpatient admission were excluded.

VTE Cases

The Japanese guideline for prophylaxis and treatment of VTE suggests that unfractionated heparin followed by warfarin may be used for the treatment of VTE and/or prevention of VTE before the surgery or immediately after the surgery, depending on the risk of VTE [17]. Given that prophylactic treatment cannot be prescribed without an associated diagnostic code, utilizing only the administration of unfractionated heparin or warfarin would result in an excessively high false-positive VTE rate. Therefore, candidate VTE cases were grouped into PE (using receipt codes equivalent to the International Classification of Diseases, Tenth Revision code I269) or DVT (International Classification of Diseases, Tenth Revision code equivalence: 1801, 1802, and 1803). After being identified by PE and DVT codes, patients were considered potential cases if they had a DVT or PE diagnosis code up to 90 days after their first major abdominal surgery. Patients were also required to have no VTE diagnosis from 90 to 7 days before surgery to reduce the risk of patients with prior VTE being included. In addition, those patients who received anticoagulants up to 1 week before surgery or immediately after surgery as prophylaxis may not be true VTE candidates despite the diagnosis code. Thus, it is possible for the identified VTE code to be from prior VTE, and it would not be considered as a potential postoperative VTE case. Therefore, additional criteria that require warfarin or heparin to be initiated within 1 day of VTE diagnosis to account for a delay in data entry and patients to receive an anticoagulant for more than 28 days were added. Those patients who used an anticoagulant for 28 days or less were assumed to be on prophylaxis treatment only and were thus excluded. In addition to the criteria mentioned above, patients with an inferior vena cava filter placement (receipt codes equivalent to the International Classification of Diseases, Ninth Revision, Clinical Modification code of 38.7) within 128 days of surgery were assumed to have a PE. The very strict criteria of inclusion were intentionally used here to ensure that all included cases were credible VTE cases and to avoid the risk of reporting false incidence or costs resulting from false VTE cases.

Matched Controls

Identified cases were matched to control cases on a 1:2 matching scheme. Cases were matched on the basis of same surgery type, at the same hospital, and a date of surgery ± 6 months. Because of anticipated limited sample sizes, age and sex were not included in the matching process. These criteria were expected to reduce the impact of treatment practice changes that may influence the costs and resource utilization associated with surgery and the treatment of complications, including VTE.

To make sure patients’ eligibility for the analysis, it was ensured that the patients’ primary point of contact for clinical care was the matched hospital. If the patient attended the hospital only for a surgery and received treatment for postdischarge VTE elsewhere, neither the comprehensive treatment costs for the “episode of care” for the surgical intervention nor the possible postdischarge occurrence of VTE was captured. Therefore, all patients with at least one additional visit during the 6-month period after surgery were included.

Pharmacoeconomic Analyses

The primary outcome measure was 90-day costs associated with major abdominal surgery. Secondary outcomes included total 6-
month costs after surgery, average length of initial hospital stay, and cost of hospital stay. Costs were broken down into pharmacy, laboratory, medical treatment, and room charges. The analysis was conducted from a health care perspective.

Nonparametric bootstrapped mean difference in costs between cases and controls were presented on the basis of 1000 draws. Given that cost data are usually skewed, costs were also evaluated with either a \( \gamma \)-distributed generalized linear model (GLM) with a log-link function or ordinary least squares on log-transformed costs, using a smearing estimate to the retransformed costs to evaluate between-group differences. The \( \gamma \)-distributed functional form is particularly useful because it avoids issues with the retransformation of skewed data. Potential covariates that were not included in the matching but may affect costs such as age or sex were included in the model as covariates to obtain an adjusted analysis. Covariates were retained if they were significant at the 0.10 level. Costs were presented as Japanese yen (JPY) and US dollar (US $). The exchange rate was calculated as US $1 = 102 JPY (Google Finance May 14, 2014) [23].

### Results

#### Study Population

A total of 348 patients who underwent major abdominal surgery were selected as potential VTE cases. Among the pool of potential cases, a total of 17 patients were identified to be true VTE cases, including 5 patients having had their first DVT and/or PE occurrence 0 to 7 days after surgery, 4 patients 8 to 14 days after surgery, 3 patients 15 to 30 days after surgery, 3 patients 31 to 60 days after surgery, and 2 patients 61 to 90 days after surgery. The incidence of VTE after major abdominal surgery in true VTE cases is presented in Figure 1. The 90-day VTE cumulative incidence was 4.89% in patients undergoing major abdominal surgery, and 71% occurred in the first 30 days after the surgery.

One patient who was a true case but did not have adequate data for the 90-day follow-up period was not included in demographic and cost analyses. Sixteen patients with VTE had both 90-day and 6-month follow-up data and were matched to 31 controls. One VTE case could not be matched to two controls and was matched to one control instead. A total of 12 patients were identified as DVT cases with 23 matched controls, and 7 patients were identified as PE cases with 14 matched controls.

#### 90-Day Evaluation

The average 90-day surgery-related costs were 2,106,047 ± 1,729,493 JPY ($20,648 ± 19,956) for patients with VTE and 747,703 ± 569,434 JPY ($7,330 ± 5,588) for matched controls, with a difference of 1,358,344 JPY ($13,317) (bootstrapped 95% confidence interval [95% CI] 598,232.64–2,268,952.25 JPY [5,865–$22,245]). When tested with the \( \gamma \)-distributed log-link GLM adjusted for age and sex, costs for patients with VTE were significantly higher than for control patients (\( P < 0.0001 \)). For patients with DVT, the 90-day surgery-related costs were on average 719,669 ± 552,332 JPY ($7,055 ± 5,415) for the controls, with a difference of 1,006,223 JPY ($15,231) (bootstrapped 95% CI 598,232.64–2,268,952.25 JPY [5,865–$22,245]). When tested with the \( \gamma \)-distributed log-link GLM adjusted for age and sex, costs for patients with VTE were significantly higher than for control patients (\( P < 0.0001 \)). For patients with PE, the 90-day surgery-related costs were on average 569,943 JPY ($7,330 ± 5,588) for matched controls, with a difference of 1,006,223 JPY ($15,231) (bootstrapped 95% CI 598,232.64–2,268,952.25 JPY [5,865–$22,245]). Notably, room cost data were missing for 1 VTE case and 14 controls matched to VTE cases, 1 DVT case and 10 controls matched to DVT cases, and 1 PE case and 8 controls matched to PE cases (Table 2).

Three patients had both DVT and PE while 13 patients had either DVT or PE only.

The mean age of patients with VTE (\( n = 16 \)) with both 90-day and 6-month follow-up data was 66.1 ± 15.45 years, ranging from 38 to 87 years. The mean age of matched controls (\( n = 31 \)) was 61.2 ± 17.32 years, ranging from 25 to 83 years. The majority were female in both the VTE group (75.0%) and the control group (74.2%), with more than half undergoing a gastrointestinal procedure.

#### Cost Analysis

The 90-day surgery-related costs were on average 2,440,599 ± 1,553,647 JPY ($23,927 ± 17,500); \( P = 0.0004 \). The 90-day surgery-related costs were on average 2,268,952.25 JPY ($5,865–$22,245). When tested with the \( \gamma \)-distributed log-link GLM adjusted for age and sex, costs for patients with VTE were significantly higher than for control patients (\( P < 0.0001 \)). For patients with DVT, the 90-day surgery-related costs were on average 1,725,892 ± 1,255,512 JPY ($17,500±12,309) for the patients and 719,669 ± 552,332 JPY ($7,055 ± 5,415) for the controls, with a difference of 1,006,223 JPY ($15,231) (bootstrapped 95% CI 598,232.64–2,268,952.25 JPY [5,865–$22,245]). Notably, room cost data were missing for 1 VTE case and 14 controls matched to VTE cases, 1 DVT case and 10 controls matched to DVT cases, and 1 PE case and 8 controls matched to PE cases (Table 2).

The 90-day total costs after surgery are presented in Figure 2. Costs for patients with VTE were higher than those for controls in each category. Because it requires additional health care resources

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 16)</th>
<th>Matched controls (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4 (25.0)</td>
<td>8 (25.8)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (75.0)</td>
<td>23 (74.2)</td>
</tr>
<tr>
<td>Age (y) at time of procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>66.1 ± 15.45</td>
<td>61.2 ± 17.32</td>
</tr>
<tr>
<td>Median</td>
<td>70.50</td>
<td>65.00</td>
</tr>
<tr>
<td>Min–Max</td>
<td>38.0–87.0</td>
<td>25.0–83.0</td>
</tr>
<tr>
<td>Age categorized (y)</td>
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<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>7 (43.8)</td>
<td>20 (64.5)</td>
</tr>
<tr>
<td>70–79</td>
<td>6 (37.5)</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>≥80</td>
<td>3 (18.8)</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal procedure</td>
<td>9 (56.3)</td>
<td>18 (58.1)</td>
</tr>
<tr>
<td>Urology procedure</td>
<td>3 (18.8)</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>Male genital procedure</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Female genital procedure</td>
<td>4 (25.0)</td>
<td>7 (22.6)</td>
</tr>
</tbody>
</table>

Note. Values represent n (%) except where indicated. VTE, venous thromboembolism.

* Controls matched on major abdominal surgery date, surgery type, and clinic.

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![Fig. 1 – Time course of VTE incidence after major abdominal surgery. VTE, venous thromboembolism.](image)

Table 1 – Patients’ demographic information for VTE cases and matched controls
Table 2  Mean 90- and 6-month costs (JPY) by category for patients with VTE, patients with DVT, and patients with PE

<table>
<thead>
<tr>
<th>Category</th>
<th>Cases (n = 12)</th>
<th>Controls (n = 7)</th>
<th>Controls matched with VTE cases (n = 14)</th>
<th>Controls matched with PE cases (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Room costs</td>
<td>1,725,892 ± 1,255,512</td>
<td>719,669 ± 552,332</td>
<td>1,263,192 JPY ($12,312)</td>
<td>1,163,047 JPY ($11,960)</td>
</tr>
<tr>
<td>Pharmacy costs</td>
<td>275,378 ± 86,421</td>
<td>106,007 ± 46,755</td>
<td>193,903 JPY ($1,911)</td>
<td>196,966 JPY ($1,945)</td>
</tr>
<tr>
<td>Medical costs</td>
<td>295,377 ± 105,974</td>
<td>92,214 ± 49,877</td>
<td>196,966 JPY ($1,945)</td>
<td>196,966 JPY ($1,945)</td>
</tr>
<tr>
<td>Room costs</td>
<td>1,263,192 JPY ($12,312)</td>
<td>1,163,047 JPY ($11,960)</td>
<td>1,163,047 JPY ($11,960)</td>
<td>1,163,047 JPY ($11,960)</td>
</tr>
</tbody>
</table>

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

* Controls matched on the basis of qualified patients.

Data were missing for 1 VTE case and 14 controls matched with VTE cases; 1 DVT case and 10 controls matched with DVT cases; 1 PE case and 8 controls matched with PE cases.

6-Month Evaluation

All patients with at least 90-day follow-up data also had adequate 6-month follow-up data available. The 6-month total costs after surgery were on average 2,705,929 JPY ($21,418 ± $14,711) for patients with VTE and 759,980 JPY ($7,451 ± $5,663) for controls. The difference was 1,946,949 JPY ($18,962) (bootstrapped 95% CI 1,050,811–2,301,754.58 JPY [$10,295–$29,429]). The average total 6-month cost in patients with VTE was significantly greater than in control patients, when tested with the γ-distributed log-link GLM adjusted for age and sex (P < 0.0001).

The 6-month costs associated with surgery were on average 2,184,604 JPY ($15,102 ± $11,312) for patients with VTE and 759,980 JPY ($7,451 ± $5,663) for controls. The difference was 1,424,624 JPY ($13,661) (bootstrapped 95% CI 1,050,811–2,301,754.58 JPY [$10,295–$29,429]).

The composition of costs in the 6-month period after surgery is presented in Table 2. For each category, costs were greater in patients with VTE than in matched controls. Differences between the VTE group and the control group for pharmacy, laboratory, medical, and room costs were 333,369 JPY ($3,268), 143,439 JPY ($1,406), 254,107 JPY ($2,491), and 984,879 JPY ($9,656), respectively. Costs for each category were greater in the DVT and PE patient groups than in the control groups (Table 2).

Initial Hospitalization

The total costs associated with the initial hospital stay were on average 1,873,159 JPY ($18,364 ± $19,570) for patients with VTE and 864,086 JPY ($8,474 ± $7,836) for matched controls, with a mean difference of 1,008,773 JPY ($9,890) (bootstrapped 95% CI 134,986–2,159,696.54 JPY [$1,323–$21,173]). Costs were significantly higher for patients with VTE in the γ-distributed log-link GLM test adjusted for age and sex (P = 0.0158). The total costs associated with the initial hospital stay were 1,491,176 JPY ($14,619 ± $13,057) for patients with VTE and 830,542 JPY ($8,142 ± $7,580) for matched controls, with a mean difference of 660,534 JPY ($6,477) (bootstrapped 95% CI 48,520.91 to 1,479,818.51 JPY [$476 to $14,508]). The total costs associated with the initial hospital stay were 2,352,533 JPY ($22,735) (bootstrapped 95% CI 1,577,807.55–3,625,241.40 JPY [$1,547–$35,542]). Costs for the DVT and PE patient groups were not significantly higher than those for
controls in the $\gamma$-distributed log-link GLM test adjusted for age and sex ($P = 0.0936$ and $0.0601$, respectively).

Cost Time Course
The overall costs associated with major abdominal surgery from 30 days before the surgery date through 6 months after surgery are presented in Figure 3. There was an immediate and large separation of costs between patients with VTE and matched controls. The absolute costs for the 30-day period before the surgery were approximately the same for both groups. The mean difference in costs, however, markedly increased to 677,165 JPY ($6,639) 30 days after the procedure when the greatest costs were incurred for both groups. Costs for patients with VTE remained generally much higher than those for controls throughout the 6 months after surgery, with costs for controls quickly decreasing 31 to 60 days after surgery and the average amount starting to plateau past 61 days after surgery below 30,000 JPY ($294). The cumulative costs of VTE peaked at 6 months, resulting in the greatest difference in mean costs of 1,866,109 JPY ($18,295) between the VTE patient and control groups. The cumulative costs incurred demonstrated the large economic impact of VTE on the health care system.

Discussion
To our knowledge, this study is the first study describing the true costs associated with VTE after major abdominal surgery in Japan. The 90-day cost was found to be 2,106,047 JPY ($20,648). There was a 1.5-fold increase in the length of hospitalization and a 2.8-fold increase in total costs over 90 days in patients with VTE.
undergoing major abdominal surgery, which is consistent with the other VTE cost study [24]. The study investigating the cost of VTE after major orthopedic surgery reported a mean cost of 1,992,713 JPY for the VTE group, compared with 1,128,560 JPY in the non-VTE matched control group [24]. They also found that patients with VTE had a 1.5-fold increase in the length of hospitalizations [24]. An annual VTE cost of around $10,000 to $33,000 was reported in the United States [18–20]. A more recent matched-cohort study indicated that the annual cost of patients with VTE was significantly higher than that of patients without VTE ($33,531 vs. $15,914). Similarly, another study in Italy reported that the total median cost for VTE was approximately 4 times higher than for the non-VTE group ($1348.68 vs. $373.03) [21]. Although the difference in health care systems and medical practices as well as different methods and criteria used in the previous literature make the results not directly comparable, our results are consistent with previous findings in that VTE brought significant economic burden to the health care system.

The cumulative incidence of 4.89% in this study is similar to but slightly lower than what has been reported in the literature for patients with clinical VTE undergoing major abdominal surgery with pharmacological prophylaxis [8,25,26]. In a recent study in the Japanese population, the incidence of VTE in patients without chemical thromboprophylaxis was reported to be 7.7% [8]. In a meta-analysis of three randomized trials, Bottaro et al. [25] reported an incidence of 5.92% for patients on extended LMWH prophylaxis. They [25] also found that the incidence of VTE increased to 6.2% over 3 months after major abdominal surgery. In another meta-analysis of four randomized trials, the incidence of overall VTE after major abdominal or pelvic surgery was reported to be 14.3% in patients receiving placebo or no treatment and 6.1% in patients receiving out-of-hospital LMWH [26]. A possible reason of the slightly lower incidence compared with that in the literature is that patients may have been receiving mechanical prophylaxis in the present study. The routine preventive care for VTE in Japan is mechanical prophylaxis such as elastic stocking or intermittent pneumatic compression. The cost of this mechanical prophylaxis was included in this study. Therefore, it is very important to investigate whether the additional pharmacological prophylaxis is effective or not, not only clinically but also cost-effectively. In other words, it is important to determine whether the cost for pharmacological prophylaxis in all surgical patients exceeds the cost to be spent for the treatment of VTE, that is, the greatest difference between patients with VTE and control patients. In a similar clinical setting to this study, a short-term (7–14 days) perioperative administration of enoxaparin, one of available anticoagulants for thromboprophylaxis in Japan, was shown to drastically reduce the incidence of VTE from 19.4% (control group) to 1.2% (enoxaparin group) [27]. In the current setting, the maximum total cost per patient that can be spent for VTE prophylaxis with enoxaparin is calculated as 85,608 JPY ($839.29), calculated as the proportion of risk reduction attributed to thromboprophylaxis: [(19.4% – 1.2%)/19.4%] times the cost difference for VTE (1,866,109 JPY) and VTE rate (4.89%). This is equivalent to the cost of enoxaparin (2,072 JPY [$20.31/d]) administration for 41 days. Likewise, it is equivalent to the 38-days administration cost of another available anticoagulant, fondaparinux (2,207 JPY [$21.64/d]). Thus, the pharmacological thromboprophylaxis in addition to mechanical prophylaxis would be considered cost-effective in major abdominal surgery in Japan.

This study also has several limitations. First, very restrictive criteria were used for the identification of VTE in this study, which ensured that the selected cases were credible true cases and therefore the costs are highly reflective of the true costs. Still, a few VTE cases were possibly classified as non-VTE cases because of the restrictive criteria, but this would have driven the cost differences toward no significant difference. The associated cumulative incidence can also be underestimated because of these restrictive criteria and would be considered a lower bound.

Second, there is limitation resulting from the use of hospital electronic records in Japan. Compared with the Western countries, the current health care medical records databases in Japan are still largely underdeveloped. Despite the accelerated development of these databases, their current breadth remains a limitation. Because the database used in this study captures electronic records for 13 hospitals throughout Japan, the number of surgeries was quite small. Generalization to the rest of Japan can be problematic because of the limited number of hospitals. Nevertheless, both diagnosis procedure combination and non-diagnosis procedure combination hospitals are included in the database, which can reflect the real-world composition of health care situation in Japan. For a more comprehensive study throughout Japan, data from more rural hospitals and hospitals in the southern islands would be required. Given the limitations of data availability, the present study has taken a huge step forward in analyzing the economic burden brought by postoperative VTE.

There may have been some potential bias due to the lack of matching on age and sex; however, there were surgeries specific to men and women, such as hysterectomy or uterine tumor surgery, which would account for lack of sex matching. Matching on age would have required a large range, which may not have been useful. The specificity of the surgery matching may have accounted in part for similar ages. Both age and sex were included as covariates in the $\gamma$-distributed log-link GLM analysis, which should help control for some of their influence.

Last, our patients with VTE were at a higher risk of developing a VTE caused by comorbidities. However, we were not able to develop a reliable Charlson comorbidity index because of the use of hospital-based claims in the present study. A comorbidity index could not be developed unless consistent recording of comorbid conditions could be extracted, meaning that the patients would need to use the same hospital for their primary care. Instead, we managed to control several factors. Using the matching scheme of the hospital, the surgery type, and the date of surgery (within 6 months), we controlled for changes in practice patterns between hospitals and were thus able to maintain the same balance of surgery type in the VTE cases and control groups. We also controlled for age and sex in our multivariate analysis. Hence, although it is possible that comorbidities might affect our findings, our adjusting other factors hope to limit it to the minimal extent.

In conclusion, the development of VTE after major abdominal surgery has brought an enormous economic burden on the health care system. Because VTE is a preventable disease, pharmacological prophylaxis should be recommended as a common practice to reduce both the clinical and economic burden in Japan [25,26]. Prevention through more effective prophylactic treatment in Japanese patients will help to reduce the significant cost caused by postoperative VTE.

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