Hiroshima J. Med. Sci.
Vol. 65, No. 3·4, 53~59, December, 2016
HIJM 65−8

Clinical Significance of Pharmacological Prophylaxis based on the Original Risk Classification of Venous Thromboembolism after Lower Abdominal Surgery

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ABSTRACT

Pharmacological prophylaxis was not routinely administrated following gastroenterological surgery because of concerns about bleeding complications. We tried to establish the original risk classification to determine the indication for pharmacological prophylaxis for selected patients at high risk of venous thromboembolism (VTE). One hundred and fifty-six consecutive patients who underwent lower abdominal elective surgery were divided into three groups (highest, high, and low risk groups) based on the original risk classification. Pharmacological prophylaxis was indicated for patients in the highest and high risk groups. We investigated safety and efficacy of the pharmacological prophylaxis based on this classification. Sixteen patients were classified in the highest, 50 in the high, and 90 in the low risk groups. Pharmacological prophylaxis was used for 59 cases (37.8%). There was no symptomatic pulmonary embolism or major bleeding complications. There were no significant differences in the occurrence of postoperative complications, analgesia use, and median postoperative pain scores for the three groups. In the highest and high risk groups administrated pharmacological prophylaxis, fibrin degradation products (FDP) and D-dimer did not change between postoperative day 1 and day 7. These data suggested the clinical significance of the pharmacological prophylaxis based on the original risk classification.

Key words: *Venous thromboembolism, Pharmacologic prophylaxis, Lower abdominal surgery*

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) are a set of life-threatening complications associated with surgery[5,9]. VTE has been reported as one of the most important potentially preventable conditions which increase morbidity and mortality[11]. The risk of VTE varies according to the patients' related thrombotic risk factors, such as age, sex, obesity, cancer, familial history, infection, heart disease, respiratory disease, hormone treatment, and poor functional status[7,16]. Major abdominal and pelvic surgery for cancer, puts these patients at a high risk of post-operative VTE[12,14].

The current American College of Chest Physicians (ACCP 2012) guideline, reported that general and abdominal-pelvic surgery patients, at high risk for VTE (~6.0%) were recommended pharmacological prophylaxis with low-molecular weight heparin (LMWH) or low-dose unfractionated heparin (UFH), in addition to mechanical prophylaxis with elastic stockings (ES) and intermittent pneumatic compression (IPC)[5,6]. The Caprini score is widely accepted for the identification of clinically high risk patients for VTE (score ≧5)[5]; however, the majority of patients who underwent gastroenterological surgery for malignant tumor are classified as a high risk group. The guidelines for VTE prophylaxis in Japan also categorized patients undergoing major cancer surgery as a high-risk group, for whom thrombo-prophylaxis with IPC or low-dose UFH was recommended.

Despite these recommendations, pharmacological prophylaxis after gastroenterological surgery was not widely administrated, especially in Japan, because of concerns about bleeding complications and epidural hematoma after epidural anesthesia.

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In order to minimize this disadvantage, more selective pharmacological prophylaxis is needed based on the risk classification, which can identify the patients at high risk for VTE.

In this study, we tried to establish the original risk classification to determine the indication of postoperative pharmacological prophylaxis for selected patients at high risk for VTE. We investigated the safety and efficacy of prophylaxis based on this risk classification of VTE after lower abdominal surgery.

PATIENTS AND METHODS

Patients

This study was the retrospective study using collected clinical data. One hundred and fifty-six consecutive patients who underwent elective lower abdominal surgery were enrolled (January 2013 to March 2014, Hiroshima University Hospital). Ninety male and sixty-six female patients were included in this study, with a mean age of 66 years (range, 21-93). Median body mass index was 21.9 (range 14.5-36.5). Open surgery was performed in 59 cases and laparoscopic surgery was performed in 97 cases. Details of the operative procedures are listed in Table 1.

Table 1. Operative procedures (n = 156)

Open/Laparoscopic	59/97
Colectomy	85
Proctectomy	40
Stoma closure	14
Tumor resection	4
Resection of small intestine	4
Repair of incisional hernia	4
Stoma creation	2
Total colectomy	1
Bypass	1
Incisional biopsy	1

Original risk classification of VTE in this study

Original risk classification of VTE in this study is demonstrated in Fig. 1. In detail, we defined the highest risk factors as the presence of VTE, a history of VTE, application of anticoagulant therapy and presence of a blood coagulation disorder. Malignant disease, obesity (body mass index, BMI: 30 or more), poor performance status (3 or 4), delayed ambulation, and age (60 years or more) were defined as 2 points of risk factor; and obesity (BMI: 28 to 30), age (40 to 60 years old), long operation time (more than 3 hrs), pelvic surgery, application of hormonal therapy, presence of varicose vein, heart failure, placement of central venous catheter (CV), and preoperative chemotherapy were defined as 1 point of risk factor. **The highest risk group** was defined as the patients who had any one of the highest risk factors. **The high risk group** was defined as the patients who had 6 points or more of risk factors, and **the low risk group** was defined as the patients who had 5 points or fewer of risk factors. These risk factors for VTE were based on the Caprini score and the Japanese VTE guideline.

Protocol of postoperative prophylaxis based on the original risk classification of VTE

VTE physiologic prophylaxis, including postoperative ES and IPC, was routinely administered to

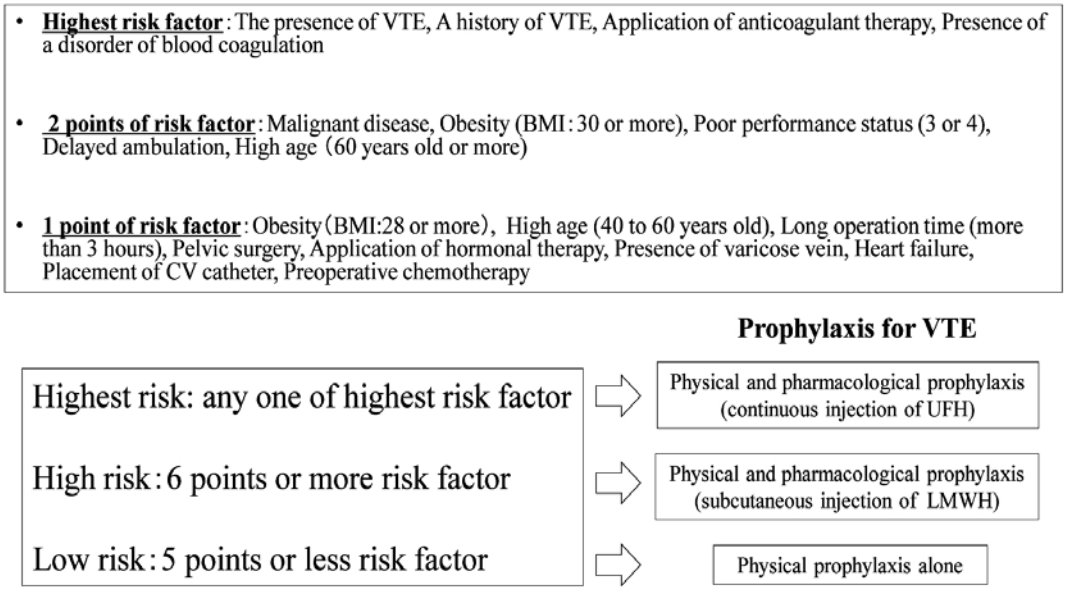


Fig. 1. Original risk classification of venous thromboembolism (VTE) in this study.
BMI, body mass index; CV, central vein; UFH, unfractionated heparin; LMWH, low-molecular weight heparin

all the patients. Postoperative pharmacological prophylaxis was indicated for the patients in **the highest risk group** and **the high risk group.** Principally, continuous injection of UFH was administered to the patients of **the highest risk group**, and subcutaneous injection of enoxaparin 20 mg twice daily was administered to the patients in **the high risk group**. Pharmacological prophylaxis was started 24-36 hrs after surgery, with the attending doctor's permission, and continued for 7 days. UFH was continuously infused and the value of APTT was maintained between 1.5 to 2 times from the reference value. For the patients with high risk of postoperative bleeding, on the attending doctor's decision, pharmacological prophylaxis was not applied, irrespective of the risk classification. In the patients who received pharmacological prophylaxis, postoperative pain control was administered through intravenous analgesia by opioid in place of epidural anesthesia.

Assessment

Short-term outcomes of the pharmacological prophylaxis based on the original risk classification of VTE, including thrombotic and bleeding complication, were assessed. In this study, postoperative examinations such as computed tomography and ultrasonography were not assessed to detect asymptomatic VTE. Therefore, we monitored perioperative fibrin related markers (D-dimer and fibrin degradation products (FDP)), and assessed the efficacy of pharmacologic prophylaxis based on the original risk classification in the view of these markers.

Before surgery, all the patients were provided with a detailed explanation of the risks and written informed consent was obtained from each patient. The complications were graded according to the method described by Dindo et al[4]. Complications with a grade above II were categorized as morbid. The postoperative ambulation day was defined as the first day on which the patient spent 50% or more of the daytime in the standing or sitting position.

Measurements in plasma samples

Blood samples were obtained from peripheral veins early in the morning, on the preoperative day, and on postoperative days(POD)1, 3, and 7. D-dimer (LIAS AUTO® D-dimer NEO, Sysmex, Kobe, Japan) and FDP (LIAS AUTO® P-FDP, Sysmex, Kobe, Japan) levels were measured by the latex agglutination method using a commercial immunoassay kit. All tests were performed on a Sysmex CS5100 analyzer (Sysmex, Kobe, Japan). The standard value amounted to ≦1 μg/ml for D-dimer and ≦5 μg/ml for FDP.

Statistical analyses

Statistical significance between the groups was analyzed by the chi-square test, Mann-Whitney U test, and paired t-test. In all analyses, statistical significance was set at a p value less than 0.05. All data are expressed as mean values ± standard deviation. All statistical analyses were performed using the IBM SPSS Statistic 20.0 software package.

RESULTS

Risk classification and validation

Among the 156 patients, 16 patients were classified in **the highest risk group**, 50 cases were classified in **the high risk group**, and 90 cases were classified in **the low risk group**, based on the original risk classification. The details of risk factors for VTE in this study are demonstrated in Table 2.

Firstly, we attempted to verify the validity of the original risk classification by using the Caprini score. The Caprini scores of the three groups are demonstrated in Fig. 2. Caprini scores of **the highest** and

Table 2. Risk factors for VTE in the study population

Risk factors	n
High age (60 years old or more)	125
High age (40 to 59 years old)	26
Malignant disease	135
Estimated operative time (3 hours or more)	126
Pelvic surgery	32
Obesity (BMI: 30 or more)	2
Obesity (BMI: 28 to 30)	9
Preoperative chemotherapy	6
Poor performance status	5
Placement of CV catheter	5
Application of hormone therapy	3
Presence of varicose vein	2

VTE, venous thromboembolism; BMI, body mass index; CV, central vein

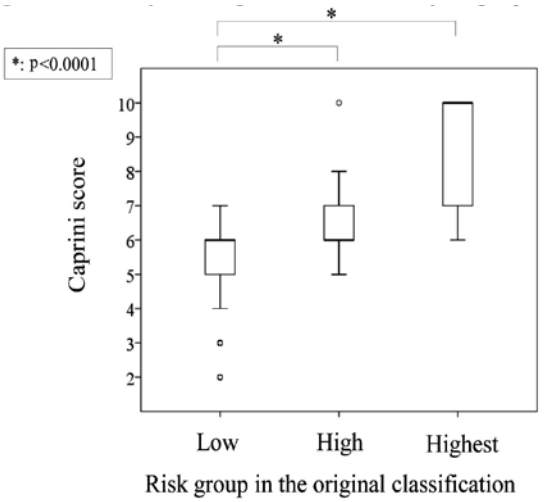


Fig. 2. The validation of the original risk classification by using Caprini score.
Caprini scores of **the highest** and **the high risk groups** were significantly higher than that of **the low risk group** ($p < 0.0001$).

the high risk groups were significantly higher than those of **the low risk group** ($p < 0.0001$). The patients selected for the pharmacological prophylaxis were therefore confirmed as clinically high risk patients for VTE by the Caprini score. In the Caprini score, postoperative anticoagulant therapy was recommended for the patients with 5 or more scores. As a result, pharmacological prophylaxis was recommended in 142 cases (91.0%) in our study. In the original classification, pharmacological prophylaxis was recommended in **the highest risk** and **the high risk** patients (66 cases, 42.3%). This demonstrated that this classification was more selective as the pharmacological prophylaxis was reserved for the high risk patient of VTE, in order to minimize the adverse effect.

Patient characteristics and pharmacologic prophylaxis

Patient characteristics of the three groups are demonstrated in Table 3. Among the three groups, there were no significant differences in sex ($p = 0.51$) and body mass index ($p = 0.48$). However, there were significant differences in the mean age ($p < 0.01$). There were also significant differences in the mode of pain control ($p < 0.01$): intravenous analgesia was mainly performed in **the high risk group** and **the highest risk group**, and epidural anesthesia was mainly performed in **the low risk group**.

Actually, postoperative pharmacologic prophylaxis was applied for 59 cases (37.8%). At the attending doctor's discretion, seven cases were not administered anticoagulant therapy because of the risk of postoperative bleeding, Continuous injection of UFH was applied in the highest risk group (14 cases) and subcutaneous injection of enoxaparin was applied in the high risk group (45 cases). Median day of initiation of anticoagulant therapy was postoperative day 2 (range, 1-5) in **the high risk group** and 2 (range, 0-3) in **the highest risk group**.

Outcome

There was no symptomatic pulmonary embolism in this study population. Post-operative bleeding complications, including subcutaneous bleeding and gross hematuria, occurred in 3.4% (2 of 59) of the patients (subcutaneous bleeding and gross hematuria). These bleeding complications were all classified as Grade 1, and major bleeding complications requiring blood transfusion or re-operation did not occur. There were no significant differences in the first flatus day ($p = 0.37$), the first defecation day ($p = 0.54$), the occurrence of postoperative complication ($p = 0.11$), and the decline of Hb levels (more than 2 g/dl) ($p = 0.65$) among the three groups (Table 3). However, there were significant differences in the postoperative ambulation day ($p < 0.01$) and postoperative hospital stay ($p < 0.01$).

There were no significant differences in the administration of routine oral Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) ($p = 0.32$), rescue use of oral NSAIDs ($p = 0.90$), and rescue use of intravenous NSAIDs ($p = 0.12$) among the three groups. There were no significant differences in the median pain score at any PODs for the three groups (Fig. 3). In the case of receiving the pharmacologic prophylaxis, postoperative pain control was through intravenous analgesia as a substitute for epidural anesthesia. However, increases of postoperative analgesia use and postoperative pain score were not observed.

Plasma FDP and D-dimer levels on POD 7 in **the high risk group** were significantly lower than those in **the highest** ($p < 0.01$) and **the low risk groups** ($p < 0.01$) (Fig. 4). There were no statistical

Table 3. Patient characteristics and postoperative courses in the three groups

		Low risk (n = 90)	High risk (n = 50)	Highest risk (n = 16)	p-value
Sex	Male / Female	49 / 41	32 / 18	10 / 6	0.51
Mean age (years old) (range)		65.0 (21 – 91)	68.5 (43 – 93)	78.3 (64 – 86)	<0.01
Body mass index (median, range)		21.6 (14.5 – 29)	22.3 (15.7 – 34)	22.3 (17.1 – 27.8)	0.48
Analgesia (case)	Epidural anesthesia/IV-PCA	77 / 13	6 / 43	0 / 16	<0.01
Postoperative outcomes					
First flatus day (median, range)		2.4 (1 – 5)	2.1 (0 – 7)	2.6 (1 – 9)	0.37
First defecation day (median, range)		3.5 (1 – 7)	3.3 (1 –7)	3.8 (1 – 8)	0.54
Postoperative ambulation day (median, range)		3.3 (1 – 15)	3.8 (1 – 14)	4.6 (3 – 10)	<0.01
Postoperative hospital stay (day, median, range)		13.0 (5 – 41)	16.7 (7 – 49)	17.6 (8 – 39)	<0.01
Postoperative complications (G2 or more) (case) (%)		13 (14%)	15 (30%)	3 (19%)	0.08
Decline of hemoglobin levels (more than 2 g/dl) (case) (%)		2 (2%)	2 (4%)	0 (0%)	0.65
Administration of routine oral NSAIDs (case) (%)		27 (30%)	19 (38%)	3 (19%)	0.32
Rescue use of oral NSAIDs (time, median, range)		2.3 (0 –18)	2.3 (0 – 10)	2.3 (0 – 12)	0.90
Rescue use of intravenous NSAIDs (time, median, range)		2.3 (0 – 15)	1.7 (0 – 12)	1.2 (0 – 7)	0.12

IV-PCA, intravenous patient control analgesia; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs

differences between FDP and D-dimer on POD 7 of **the highest risk group** and those of **the low risk group** ($p = 0.47$ and $p = 0.45$, respectively). In addition, in **the low risk group**, FDP and D-dimer on POD 7 were significantly increased than those on POD 1 ($p < 0.001$ and $p < 0.001$, respectively), however, in **the highest** and **the high risk group**, there were no significant differences between FDP and D-dimer on POD 1 and those on POD 7 ($p = 0.63$ and $p = 0.39$ in highest risk group, respectively, and $p = 0.75$ and $p = 0.22$ in high risk group, respectively). These results indicated the clinical significance of pharmacological prophylaxis in the view of these markers.

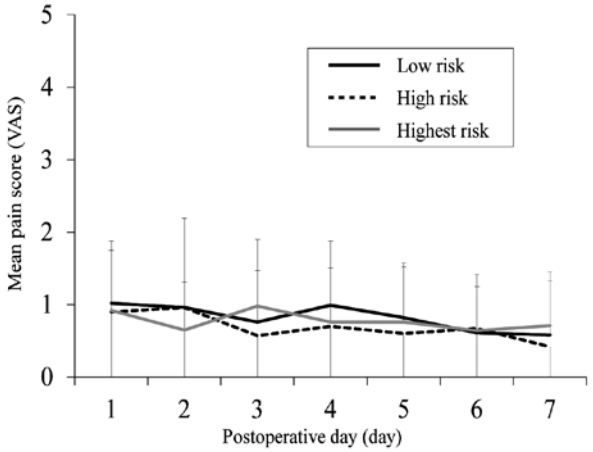
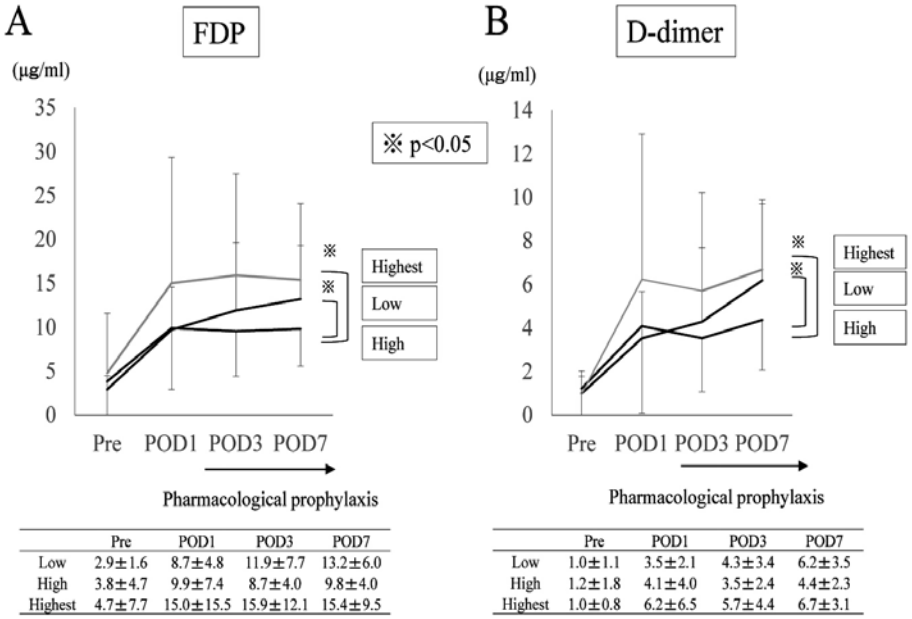


Fig. 3. Postoperative pain score of the three groups.
There were no significant differences in the median pain score at any postoperative days for three groups.
VAS, visual analogue scale

DISCUSSION

In the present study, we tried to establish the original risk classification to determine the indication of pharmacological prophylaxis in selected patients at high risk of VTE in order to minimize the complications of pharmacological prophylaxis. This classification can lead to more selective pharmacological prophylaxis than Caprini score and demonstrated the possible efficacy in the prevention of postoperative VTE.

Pharmacologic prophylaxis after gastroenterological surgery was not widely administrated, especially in Japan. Historically, VTE has been considered to be a rare surgical complication in Japan, however, the incidence of VTE in general surgery appears to be increasing[15]. The overall incidence of VTE has been reported to be 24.3% in Japanese patients, suggesting that pharmacological prophylaxis is essential to prevent VTE[16]. The other reasons were surgeons' concerns about bleeding complications and/or epidural hematoma after epidural anesthesia. We thought, therefore, more selective pharmacologic prophylaxis was needed based on the risk classification that could identify the patients at high risk for VTE. The present results showed that our established classification can lead to more selective pharmacological prophylaxis than previous criteria and guideline. In this classification, low risk group patients did not receive pharmacological prophylaxis, however, some part of the low risk group patients are recommended pharmacological prophylaxis as per Caprini score and/or Japanese guideline. Further investigation is mandatory whether such patients need to be on



	Pre	POD1	POD3	POD7
Low	2.9±1.6	8.7±4.8	11.9±7.7	13.2±6.0
High	3.8±4.7	9.9±7.4	8.7±4.0	9.8±4.0
Highest	4.7±7.7	15.0±15.5	15.9±12.1	15.4±9.5

	Pre	POD1	POD3	POD7
Low	1.0±1.1	3.5±2.1	4.3±3.4	6.2±3.5
High	1.2±1.8	4.1±4.0	3.5±2.4	4.4±2.3
Highest	1.0±0.8	6.2±6.5	5.7±4.4	6.7±3.1

Fig. 4. Postoperative kinetics of fibrin degradation products (FDP) (A) and D-dimer (B) in the three groups.
Plasma FDP and D-dimer levels on postoperative day 7 in **the high risk group** were significantly lower than those in **the highest** ($p < 0.01$) and **the low risk groups** ($p < 0.01$). All data are expressed as mean values ± standard deviation.

pharmacological prophylaxis to prevent VTE.

The present study also showed that the postoperative plasma levels of D-dimer (from POD 1 to POD 7) were not increased in the patients who were administered pharmacologic prophylaxis as determined by the original risk classification. The D-dimer level (POD7) is well known for high sensitivity of 79 to 95% and negative predictive value of nearly 100% for the presence of VTE[10,13,19]. Therefore, this result suggested the possible efficacy of the original classification in the prevention of postoperative VTE. However, D-dimer elevation also represent infection, malignancy, heart failure, chronic renal disease, liver disease[10]. This might not reflect the true VTE; therefore, further investigation is required regarding the actual preventative effect on VTE.

Epidural hematoma is rare, but the most serious complication of epidural anesthesia, and that is one of the reasons due to which pharmacological prophylaxis is not routinely used in gastroenterological surgery. Age, associated abnormalities of the spinal cord or vertebral column, the presence of an underlying coagulopathy, difficulty during needle placement, and an indwelling catheter during sustained anticoagulation have been reported to be the risk factors[8]. In the pharmacological prophylaxis using LMWH, indwelling catheters should be removed before initiation of LMWH or administration of LMWH should be delayed for two hours after catheter removal[8]. In the present study, postoperative pain control was administered through intravenous analgesia in place of epidural anesthesia, in the cases receiving pharmacological prophylaxis. Insufficient pain control and the delay of intestinal movement due to intravenous analgesia by opioid were the other concerns regarding pharmacological prophylaxis in the present study. We demonstrated that an increase of postoperative analgesia use and postoperative pain score was not observed in the cases receiving pharmacological prophylaxis. This result showed that postoperative intravenous analgesia was a useful substitute for epidural anesthesia without the complication of epidural hematoma.

Surgeons may withhold perioperative pharmacological prophylaxis due to the risk of bleeding complications. Major bleeding is reported to occur in 2.9 to 9.4% of patients during the period of pharmacological prophylaxis[1,17]. In the current study, post-operative bleeding complications, including subcutaneous bleeding and gross hematuria, occurred in 3.4% (2 of 59) of the patients, (subcutaneous bleeding and gross hematuria). These bleeding complications were all classified as Grade 1, and the major bleeding complications had not occurred. This suggested the safety of chemoprophylaxis after lower gastrointestinal surgery with respect to postoperative bleeding.

The optimal duration of thromboprophylaxis is still controversial. It has recently been clear that late thrombotic events can occur up to 6-7 weeks after surgery[2,18]. The Enoxaparin and Cancer II study has shown that, at least in high-risk patients, there is a significant benefit of an extended 4-week prophylactic period compared with the standard 1-week regimen[3]. The majority of patients who underwent gastroenterological surgery, were discharged one week after surgery, therefore, prolonged prophylaxis extending for several weeks may not be recommended for the Japanese population in general. In the present study, the duration of pharmacological prophylaxis was determined to be 7 days; however, it was necessary to pay attention to the occurrence of VTE for several weeks after discharge from the hospital.

In conclusion, our classification of VTE can lead to more selective application of the pharmacologic prophylaxis, to minimize the complications. The efficacy in the prevention of postoperative VTE has also been demonstrated. Further investigation is needed to evaluate the prophylactic effects in VTE.

ACKNOWLEDGEMENT

We would like to express our gratitude to the staff of our department for their assistance in the collection and registration of data and samples.

Conflict of interest statement

Manabu Shimomura and other co-authors have no conflict of interest.

(Received July 19, 2016)
(Accepted August 29, 2016)

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