Safety of fondaparinux for prevention of postoperative venous thromboembolism in urologic malignancy

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Short running title

FPX for postoperative thromboprophylaxis

Abstract

Objectives

To prospectively evaluate safety of postoperative fondaparinux in comparison to low molecular weight heparin.

Methods

This study was a prospective, single-blind randomized trial. A total of 359 patients undergoing surgery for urologic malignancy were enrolled from January 2011 to December 2012; 298 of those subjects (fondaparinux group; 152, low molecular weight heparin group; 146) were evaluable for intention-to-treat-analysis. Patients were randomly assigned to low dose unfractionated heparin, 5000 units twice daily until postoperative day 1 plus either fondaparinux 2.5 mg once daily or low molecular weight heparin 2,000 units twice daily until postoperative day 5. Postoperative bleeding and adverse events were evaluated. D-dimer and soluble fibrin monomer complex levels were measured perioperatively. Clinical signs of venous thromboembolism or elevated D-dimer ($\geq$15 μg/ml) were followed up with multidetector-row computed tomography.

Results

No significant differences were detected in the incidence of postoperative bleeding or adverse events between groups. Bleeding occurred in 21 patients (12 in the

in fondaparinux group and 9 in low molecular weight heparin group, respectively). Overall incidence of venous thromboembolism was 0.7% (2 patients in low molecular weight group). The D-dimer was elevated on postoperative day 1 in one patient (16.6 μg/ml). In the other patient, the soluble fibrin monomer complex was elevated (109 μg/ml).

Conclusions

The favorable safety profiles of fondparinux support its prophylactic use as an alternative to low molecular weight heparin after surgery for urologic malignancy. Larger studies will be required to confirm these findings.

Keywords: thromboprophylaxis; urologic malignancy; urologic surgery; venous thromboembolism

Abbreviations and Acronyms

FPX = fondaparinux

DVT = deep venous thrombosis

VTE = venous thromboembolism

PTE = pulmonary thromboembolism

UFH = unfractionated heparin

LDUH = low dose unfractionated heparin

LMWH = low molecular weight heparin

HIT = heparin induced thrombocytopenia

MDCT = multidetector-row computed tomography

DD = D-dimer

SFMC = soluble fibrin monomer complex

POD = postoperative day

eGFR = estimated glomerular filtration rate

AST = Aspartate aminotransferase

ALT = Alanine aminotransferase

CTCAE = Common Terminology Criteria for Adverse Events

Lap = laparoscopic

LRP = laparoscopic radical prostatectomy

RRP = radical retropubic prostatectomy

EBL = estimated blood loss

GCS = graduated compression stockings

IPC = intermittent pneumatic compression

AUA = American Urological Association

ACCP = American College of Chest Physicians

NYHA = New York Heart Association

NA = not applicable

Introduction

DVT is a serious complication after surgical intervention, potentially resulting in fatal PTE. Recent recognition of the close causality between these two classes of events has led to wider use of the term "VTE" for both DVT and PTE.[1,2]

The AUA advocates prevention of DVT in its best-practice statement for patients undergoing urologic surgery. Nevertheless, up to 18.1% of urologic oncologists and laparoscopic/robotic surgeons do not routinely use thromboprophylaxis.[3]

Since timely detection and treatment of PTE is difficult, thromboprophylaxis can be an effective option for preventing such surgery-related mortality. Cancer surgery seems to have at least twice the risk of postoperative DVT and more than 3 times the risk of fatal PTE than similar procedures in non-cancer patients.[4] The incidence of VTE thus remains an issue, despite mechanical and pharmacological thromboprophylaxis, ranging from 0.5% to 7.2% after radical prostatectomy,[5,6] 4.3% to 24% after radical cystectomy,[5,7] 1.0% to 7.1% after nephrectomy[5,8] and 0% to 11.1% after nephroureterectomy. [9,10]

The use of heparin as thromboprophylaxis has been extensively investigated over the past thirty years.[11-13] The ACCP and the AUA recommend the use of LDUH

(Grade 1B) or LMWH (Grade 1B) plus mechanical prophylaxis following general or abdominal-pelvic surgery in high-risk cancer patients.[14,15]

FPX is the first of a new class of synthetic antithrombotic agent that is equivalent or more effective than LMWH without introducing additional bleeding risk after general surgery.[16] FPX specifically inhibits factor Xa without directly affecting thrombin (factor IIa).[17] However, only low-level supporting evidence is available due to the paucity of clinical trials related to abdominal-pelvic cancer surgery. FPX is not listed in the AUA recommendations.[15] To the best of our knowledge, there have been no randomized controlled trials directly comparing FPX with LMWH for prophylaxis of VTE after surgery for urologic malignancy.

Early detection of VTE is a challenge. Both DD and SFMC have been suggested as blood anticoagulation markers for predicting postoperative VTE.[18,19] Their performance has never been evaluated in surgery in urologic malignancy.

The aim of this study was to prospectively evaluate the safety of postoperative FPX in comparison to LMWH in the prevention of VTE in high- to highest-risk patients undergoing surgery for urologic malignancy.

Methods

Patient selection

This study was planned as a prospective, single-blind randomized trial. Patients with urologic malignancy, 40 yr or older, scheduled for surgery at Jikei University Hospital from January 2011 to December 2012, considered candidates for open or laparoscopic surgery of >45 minutes in length, and with a life expectancy of at least 6 months after surgery were eligible for participation. Exclusion criteria included body weight less than 40kg, hypersensitivity to FPX or LMWH, contraindication to anticoagulant therapy, active bleeding, documented bleeding disorder or thrombocytopenia, perioperative VTE within the previous year, severe hepatic dysfunction, severe renal dysfunction (eGFR < 30ml/min/1.73m^2), concurrent disorder such as gastrointestinal ulceration or diverticulitis, colitis, bacterial endocarditis, severe diabetes mellitus, severe hypertension or disseminated intravascular coagulation; hemorrhagic stroke; brain, spine or eye surgery within the previous 3 months; HIT; or pregnancy. Patients were to one of two groups (FPX or LMWH) and stratified by risk based on ACCP and AUA guidelines before surgery.[15,20]

Ten surgeons participated in the study; all were blinded to drug allocation until the end of the surgical procedure. If patients were taking anticoagulant or antiplatelet

agents prior to surgery, that use was temporarily suspended and restarted at an appropriate time. This study was performed under the Declaration of Helsinki and applicable clinical practice. The institutional ethics committees approved the study protocol and informed consent was obtained from all patients.

VTE prophylaxis

Mechanical thromboprophylaxis was used in all patients until fully ambulatory. If epidural anesthesia was combined with general anesthesia, the epidural catheter was removed immediately after surgery. Six hours after surgical wound closure and confirmation of no severe bleeding, LDUH (5000 units) was injected subcutaneously; administration was continued every 12 hours until the day after surgery. FPX patients received 2.5mg subcutaneous FPX (Arixtra®; Sanofi-Synthelabo, Paris, France) once daily, and LMWH patients received 2000 units LMWH, i.e. enoxaparin (Clexane®; Aventis Pharma, Bridgewater, NJ, USA) subcutaneously twice daily. Both treatments were administered from POD 2 to 5. If eGFR ranged from 30 to 50ml/min/1.73m^2 and the risk of bleeding was high, FPX and LMWH could be reduced to 1.5mg and 2,000 units daily, respectively, at the discretion of the attending physician.

Evaluation

Blood DD and SFMC levels were measured by latex immunoagglutination assay (LSI Medience Corporation, Tokyo, Japan) before surgery, on PODs 1, 3 and 5, and whenever VTE or other complications were suspected. Adverse events were evaluated using CTCAE (the Common Terminology Criteria for Adverse Events) version 4.0. If preoperative DD was a ≥1.5μg/ml, if clinical symptoms or signs of VTE developed, or if postoperative DD was ≥15μg/ml, contrast enhanced 16-row MDCT of the chest to the lower limbs was performed. Two radiologists evaluated the MDCT images. No SFMC threshold was set for decision-making, because 1 week was required before the results could be obtained. (An SFMC level of < 6.1μg/ml was considered normal.)

Study endpoints

The primary objective was to evaluate the safety of the anticoagulants. Major bleeding was defined as fatal bleeding, bleeding at vital organs, bleeding or hematoma around the surgical beds necessitating reoperation, or bleeding necessitating transfusion of > 400mL red blood cells prepared from whole blood, or >2g/dL decrease in hemoglobin level within 48 hours after bleeding onset.[21] Minor bleeding was defined as clinically abnormal bleeding that could not be described as major. The following specific adverse events were compared: incidence of lymphocele formation, decreased

thrombocyte count including HIT, elevation of AST and ALT. Changes in perioperative blood coagulation markers in relation to VTE events were also investigated.

Statistical analysis

All the analyses were performed in the intention-to-treat cohort (all randomly assigned patients). For the evaluation of changes in perioperative blood coagulation markers, per-protocol analysis was also performed (**Fig. 1)**. For nonparametric testing, chi-square test was used. For continuous variables, unpaired t test depending on data normality was performed. GraphPad PRISM, version 5 (GraphPad Software, San Diego, California, USA) was used for all statistical analyses. A *P* value of <0.05 was considered statistically significant.

Results

Patient characteristics

During the study period, 359 consecutive patients underwent surgery for urologic malignancies (**Fig. 1**). Sixty-one patients were excluded: 39 did not meet the inclusion criteria, two declined to participate, and 20 withdrew their consent for various reasons. The remaining 298 patients were evaluated in intention-to-treat analysis (**Fig.**

1). Sixteen patients did not receive the assigned treatment after randomization owing to intraoperative or postoperative bleeding, or immediate reoperation. The preoperative characteristics were similar between the two patient groups (**Table 1**). Based on the AUA Best Practices Statement, 64 and 234 patients were in the high- and highest-risk groups, respectively[15]; by ACCP classification, all patients were high-risk.[20] One patient in FPX group had VTE 3 years previously, which was successfully treated with anticoagulation therapy. Surgical and therapeutic details are summarized in **Table 2**. In total, 244 radical prostatectomies, 22 radical nephroureterectomies, and 32 radical nephrectomies were performed. Operation time, estimated blood loss, time to ambulation, and transfusion rates did not differ significantly between the two groups.

Complications

No significant between-group differences were noted in the incidence of major and minor postoperative bleeding between two groups; there were 1 (0.7%) and 2 (1.3%) major bleeding events in the LMWH and FPX groups, respectively (**Table 3**). Red blood cell transfusion was required in all the patients who had hematoma in the pelvis. Minor bleeding episodes developed in 8/146 LMWH patients (5.5%) and 10/152 FPX patients (6.6%) (p=0.81). These included bloody drain discharge (n=3 and n=5, respectively), gross hematuria (n=1 in both groups), surgical site hematoma (n=1 and

n=2, respectively), hemoglobin <2g/dl (n = 2 in both group) and 1 hematoma of pelvis only in LMWH group. Lymphocele occurred in 3 prostatectomies with concomitant pelvic lymphadenectomy irrespective of whether open or laparoscopic. There were no VTE events in these cases. One patient in LMWH group and two patients in FPX group showed thrombocytes <10.0 x 10^4/μl, but these decreases resolved spontaneously without discontinuation of pharmacological prophylaxis. Transaminase elevation was the most frequently observed adverse event, but the incidence did not differ significantly between the two groups. Grade 1 or 2 AST/ALT elevation was noted in 60 patients in LMWH group and 47 patients in FPX group, but those values returned to baseline without further treatment.

DD and SFMC

Ten LMWH patients and 3 FPX patients had preoperative DD values $\geq$ 1.5μg/ml. MDCT, conducted in 8 of the LMWH patients and all 3 FPX patients, showed no preoperative VTEs. Twelve LMWH patients and 9 FPX patients had preoperative SFMC concentrations above the normal range (< 6.1μg/ml). Overall, DD values were significantly elevated after surgery compared with preoperative baseline values, over 15μg/ml in 4 patients (2 in each group) on POD 1. No patients showed DD values above 15μg/ml on POD 3 or 5. No significant difference was noted in these values between

groups (p>0.05, **Fig. 2**). SFMC values in both groups peaked on POD 1 (LMWH group: POD 1 vs before surgery, p=0.04; vs POD 3, p=0.02; vs POD 5, p<0.0001. FPX group: POD 1 vs before surgery, p<0.0001; vs POD 3, p<0.0001; vs POD 5, p<0.0001). No significant difference was observed between groups (p>0.05, **Fig. 3**). However, in the per-protocol cohort, DD values on POD 5 had a tendency to be lower in the FPX group than in the LMWH group (p=0.0505, data not shown).

Development of VTE

Table 4 summarizes VTE events observed in this study. Three VTEs occurred in 2 LMWH patients (0.7%). No events occurred in the FPX group. Proximal DVT accompanied by non-fatal PTE was detected in 1 patient, who presented with right leg edema 1.5 months after open radical prostatectomy; DD and SFMC levels were 8.5μg/ml and 109μg/ml on POD 1. The other patient, who had undergone laparoscopic radical prostatectomy, developed dyspnea with elevated DD (16.6μg/ml), and was diagnosed with non-fatal PTE without DVT on POD 1 while still on LDUH. Both patients were treated with intravenous UFH and oral anticoagulant. An inferior vena cava filter was implanted in the former patient. Both were treated successfully without any sequelae.

Discussion

To the best of our knowledge, this is the first reported study to prospectively compare FPX with LMWH for thromboprophylaxis in patients undergoing surgery for urologic malignancy. In our intention-to-treat-analysis, the incidence of major and minor postoperative bleeding was comparable in both groups. Though none of these events necessitated surgical intervention, discontinuation of the study drug was considered mandatory in the affected patients.

Postoperative bleeding in the FPX group occurred at a rate similar to that reported by Leonardi *et al*., in a prospective study of various anticoagulation agents including LMWH and FPX for general, gynecologic, thoracic, and urological surgeries.[22] However, pharmacological prophylaxis was discontinued at a higher rate in our study than in that study (8.1% vs. 2.0%). Turpie *et al*., in a meta-analysis of anticoagulant prophylaxis performed for orthopedic surgeries, showed that FPX did not increase the risk of clinically relevant bleeding compared with LMWH.[23] Anticoagulation agents were discontinued in all patients with bleeding in our study, even those with minor bleeding, at the discretion of the attending physician. Other adverse events were not serious and resolved spontaneously. No statistically significant differences were found between the groups.

The overall incidence of VTE in our study was 0.7% (n=2 in the LMWH group), lower than for previous studies without thromboprophylaxis, but comparable to those studies involving the prophylactic use of anticoagulants.[6,8] The meta-analysis by Turpie *et al*. showed no difference in the incidence of VTE between LMWH (0.4%) and FPX (0.6%).[23] Agnelli *et al*. reported similar findings in high-risk abdominal surgery. In the subgroup of patients undergoing surgery for malignancy, FPX reduced the relative risk of VTE by 38.6%.[16] Meanwhile, Benjamin CJ *et al*. suggested that lymphocele was an independent risk factor for VTE and pharmacological thromboprophylaxis increased the rate of lymphocele formation.[24] Lymphocele was diagnosed in 3 patients who had undergone prostatectomy with concomitant pelvic lymphadenectomy in the present study. However, there were no VTE events in these cases.

Results of our study suggest that the safety of FPX and LMWH were similar. Whether FPX performs better than LMWH remains unconfirmed, owing to the limited number of patients. Potential disadvantages in the use of FPX include lack of a reversal agent, non-applicability in patients with severe renal dysfunction, and temporal restrictions in combination with epidural anesthesia. Nevertheless, FPX should be included among the reasonable thromboprophylactic options for high- to highest-risk patients undergoing urologic surgery in safety.

DD and SFMC threshold values have been widely investigated for the detection of VTE after various types of surgery. Those values vary by surgery type and by report, ranging from 2.0 to 20 μg/ml for DD and 3.6 to 20.8 μg/ml for SFMC.[19,25-27]In the present study, we set the postoperative DD threshold at 15 μg/ml. DD exceeded this threshold in 4 patients (2 in each group) on POD 1. However, only 1 of the 2 patients who developed VTE showed levels higher than this threshold. The other had DD of 8.5 μg/ml, well below the cutoff, but interestingly his SFMC on POD 1 was high (109 μg/ml). Our DD cut-off threshold may thus not be sufficiently sensitive for the detection of VTE; the combined use of DD and SFMC may be more useful. Yoshioka et al. found no difference in DD between patients with or without VTE until POD 3, but patients with VTE had significantly higher DD levels on POD 7.[19] There may have been additional subclinical VTE in our study, since DD was monitored only up to POD 5. The lower DD values at POD 5 in FPX group of the per-protocol population may indicate potentially more efficient thromboprophylaxis than in the LMWH group.

Several limitations should be considered in the interpretation of our study data. First, the two patient groups were too small for us to determine the true incidence of VTE in similar patients. Second, LDUH was used during the first 24 hours before

starting FPX and LMWH, as required under the Japanese health care system, because neither FPX nor LMWH is approved for use immediately after surgery in Japan. The design of this study was thus to evaluate LDUH plus either FPX or LMWH. VTE was detected on POD 1, before starting LMWH, in one patient. Last, though no further cases of symptomatic VTE were noted up to 3 months after surgery, many VTE events could have been overlooked due to inappropriate DD cut-off values.

In conclusion, the present study showed that the safety of FPX thromboprophylaxis in patients undergoing surgery for urologic malignancy were comparable to LMWH. However, larger studies will be required to confirm these findings.

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Conflict of interest

None declared

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Figure legends

Fig. 1

Flow diagram for treatment

Fig. 2

Changes in perioperative DD levels

Fig. 3

Changes in perioperative SFMC levels

Table 1 Baseline demographics and clinical characteristics of patients.

	LMWH (n=146)	FPX (n=152)	P value
Age (yrs , mean ± SD, range)	63.9± 7.5 (40-82)	64.7 ± 7.5 (40-86)	>0.05
Gender (male / female)	138 / 8	144 / 8	>0.05
Body mass index (kg/m^2, mean±SD, range)	23.9 ± 2.6 (18.1-32.1)	23.7 ± 2.6 (17.0-31.4)	>0.05
Brinkman index (median, range)	430 (0-2700)	327 (0-2000)	>0.05
AUA guidelines (No. pts, %)	high 32 (21.9) highest 114 (78.1)	high 32 (21.1) highest 120 (78.9)	>0.05
9^{th} ACCP guideline (No. pts, %)	high 146 (100)	high 152 (100)	>0.05
Preoperative drugs (No. pts, %)			
Antiplatelet drugs	12 (8.2)	13 (8.6)	>0.05
Anticoagulation drugs	4 (2.7)	4 (2.6)	
Prior VTE (No. pts, %)	0 (0)	1 (0.7)	>0.05
Prior congestive heart failure (NYHA grade Ⅲ or Ⅳ, No. pts, %)	0 (0)	0 (0)	NA
Chronic obstructive pulmonary disease (No. pts, %)	4 (2.7)	1 (0.7)	>0.05
Inflammatory bowel disease (No. pts, %)	4 (2.7)	3 (2.0)	>0.05
Other malignancy (No. pts, %)	8 (5.5)	10 (6.6)	>0.05

Table 2 Surgical and therapeutic characteristics of patients.

	LMWH (n=146)		FPX (n=152)		P value
Surgical procedures (No. pts)	LRP RRP Lap nephrectomy Open nephrectomy Lap nephroureterectomy Open nephroureterectomy	106 18 12 3 7 0	LRP RRP Lap nephrectomy Open nephrectomy Lap nephroureterectomy Open nephroureterectomy	106 14 17 0 14 1	NA
Time from skin incision to closure (min, mean ± SD, range)	298.0 ± 75.6 (150-617)		290.9 ± 67.3 (115-588)		>0.05
EBL (ml, mean ± SD, range)	549.0 ± 590.5 (0-3,510)		488.0 ± 535.6 (0-3,240)		>0.05
Time to ambulation (d, mean ± SD, median)	1.52 ± 0.78 (1)		1.44 ± 0.73 (1)		>0.05
Intraoperative or perioperative transfusion (No. pts, %)	18 (12.3)		15 (9.9)		>0.05
Concomitant treatment (No. pts, %)					
GCS	146 (100)		152 (100)		NA
IPC	146 (100)		152(100)		

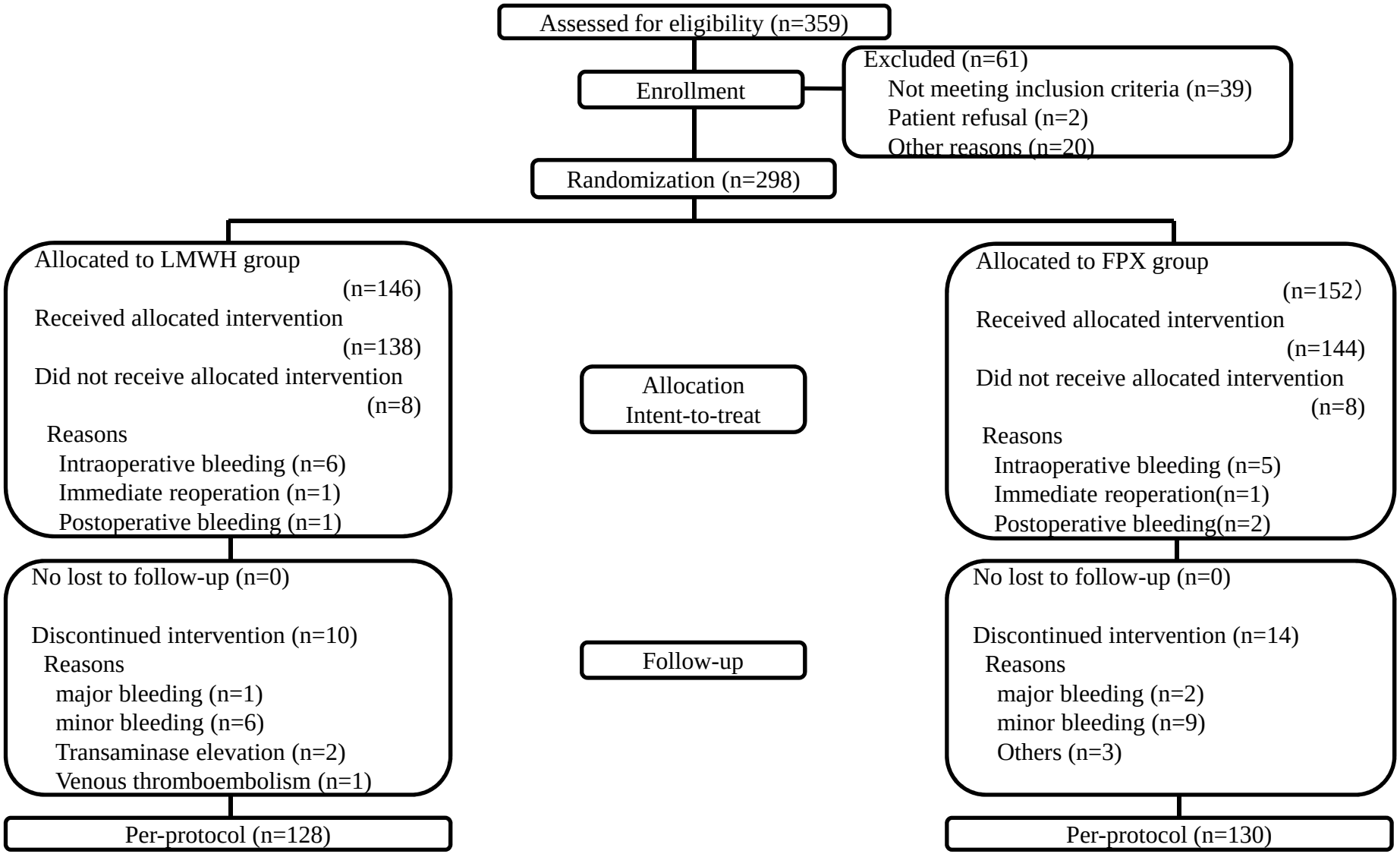
Table 3 Safety outcomes during treatment.

	LMWH (n=146) No. pts (%)	FPX (n=152) No. pts (%)	P value
Major bleeding	1 (0.7)	2 (1.3)	>0.05
Minor bleeding	8 (5.5)	10 (6.6)	>0.05
Lymphocele	2 (1.3)	1 (0.7)	>0.05
Thrombocytes decrease less than $10.0x10^4/\mu l$	1 (0.7)	3 (2.0)	>0.05
Elevated AST/ALT	G1 54 (37.0) G2 6 (4.1)	G1 47 (30.9) G2 0 (0)	>0.05

Table 4 Venous thromboembolic events.

	LMWH (n=146)	FPX (n=152)	P value
All VTE	2*	0	>0.05
DVT			
Distal	0	0	NA
Proximal	1	0	>0.05
Non-fatal PTE	2	0	>0.05
Fatal PTE	0	0	NA

Fig. 1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Enrollment
Excluded (n=61)
Not meeting inclusion criteria (n=39)
Patient refusal (n=2)
Other reasons (n=20)
Randomization (n=298)
Allocated to LMWH group (n=146)
Received allocated intervention (n=138)
Did not receive allocated intervention (n=8)
Reasons
Intraoperative bleeding (n=6)
Immediate reoperation (n=1)
Postoperative bleeding (n=1)
Allocated to FPX group (n=152）
Received allocated intervention (n=144)
Did not receive allocated intervention (n=8)
Reasons
Intraoperative bleeding (n=5)
Immediate reoperation(n=1)
Postoperative bleeding(n=2)
Allocation
Intent-to-treat
No lost to follow-up (n=0)
Discontinued intervention (n=10)
Reasons
major bleeding (n=1)
minor bleeding (n=6)
Transaminase elevation (n=2)
Venous thromboembolism (n=1)
No lost to follow-up (n=0)
Discontinued intervention (n=14)
Reasons
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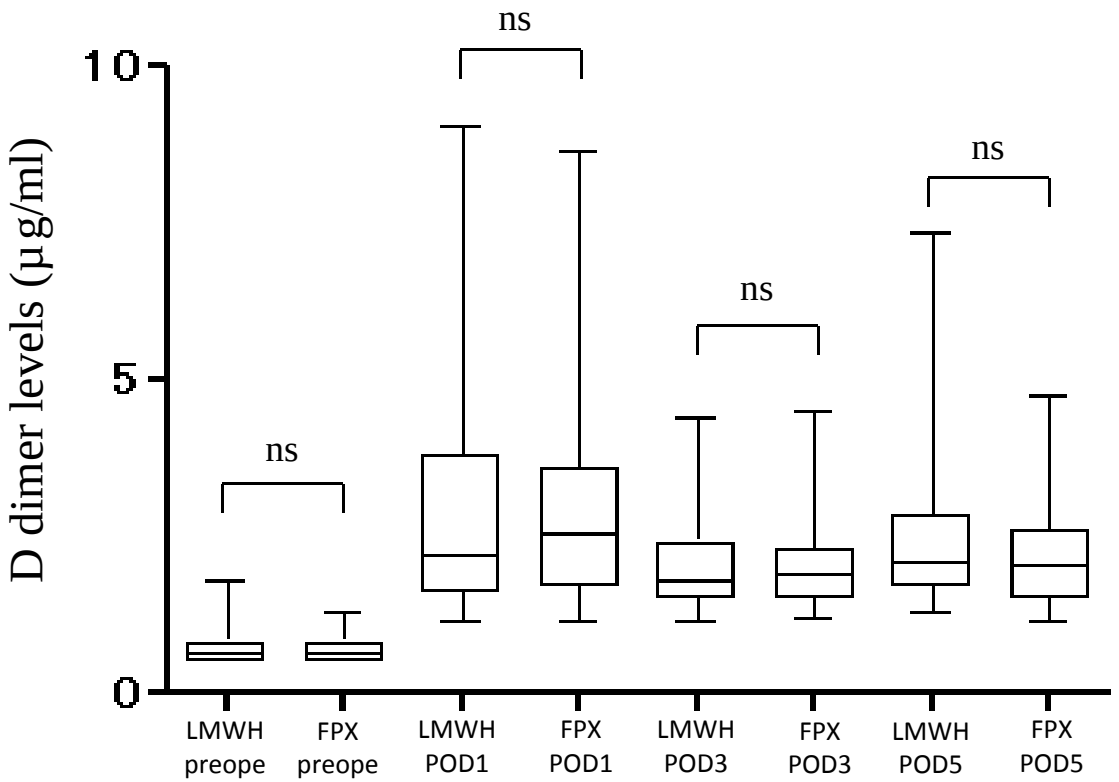
minor bleeding (n=9)
Others (n=3)
Follow-up
Per-protocol (n=128)
Per-protocol (n=130)

Fig. 2


ns
ns
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10
5
0
D dimer levels (μg/ml)
LMWH preope
FPX preope
LMWH POD1
FPX POD1
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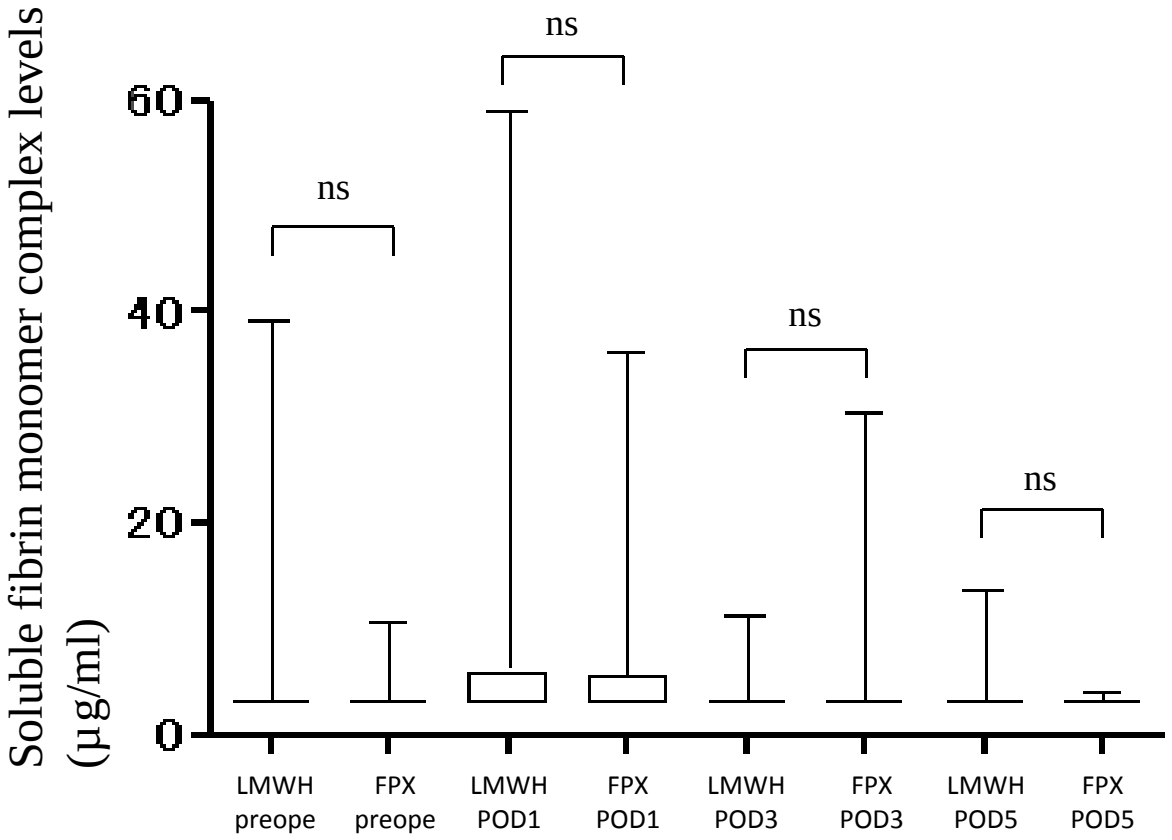
FPX POD3
LMWH POD5
FPX POD5

Fig. 3


Soluble fibrin monomer complex levels (μg/ml)
60
40
20
0
ns
ns
ns
ns
LMWH preope
FPX preope
LMWH POD1
FPX POD1
LMWH POD3
FPX POD3
LMWH POD5
FPX POD5