Table 10 Baseline and other characteristics of the propensity score-matched patients receiving fondaparinux or enoxaparin (THA)

	Fondaparinux n = 144	Enoxaparin n = 144	*P* value
Gender, male/female	20/124	23/121	0.620
Age, years			
Mean ± SD	67.3 ± 10.0	68.0 ± 8.8	0.707
Range	40-87	44-86	
Body mass index, kg/m^2			
Mean ± SD	23.4 ± 3.8	23.8 ± 3.6	0.386
History of venous thrombosis, n (%)	-	-	
malignant tumor	5 (3.5%)	0	0.030
Comorbidities, n (%)			
Hypertension	59 (41.0%)	54 (37.5%)	0.546
Ischemic heart disease	7 (4.9%)	6 (4.2%)	0.777
Diabetes	11 (7.6%)	10 (6.9%)	0.821
Cerebrovascular disease	4 (2.8%)	3 (2.1%)	0.702
Operation time, minutes			
Mean ± SD	124.6 ± 38.7	125.6 ± 47.3	0.931
Primary diseases, n (%)			
Rheumatoid arthritis	9 (6.3%)	5 (3.5%)	0.273
Osteoarthritis	129 (89.6%)	129 (89.6%)	1.000
Others	6 (4.2%)	10 (6.9%)	0.303
General anesthesia	141 (97.9%)	141 (97.9%)	1.000
Use of elastic stocking, n (%)	131 (91.0%)	133 (92.4%)	0.670
Use of foot pump, n (%)	138 (95.8%)	137 (95.1%)	0.777
Use of cement, n (%)	23 (16.0%)	24 (16.7%)	0.873
e-GFR, mL/min per 1.73 m^2			
Mean ± SD	81.9 ± 20.0	78.6 ± 16.8	0.220
Range	29.0-139.0	37.7-128.9	
Serum albumin, g/dL			
Mean ± SD	4.0 ± 0.5	4.1 ± 0.4	0.001
Range	2.4-5.0	2.6-5.1	
Platelet count, 10^4/μL			
Mean ± SD	27.7 ± 7.6	26.0 ± 7.7	0.048

Kruskal-Wallis rank test were performed on the means of continuous variables. For categorical variables, chi-squared tests were used. e-GFR, estimated glomerular filtrating ratio; SD, standard deviation; THA, total hip arthroplasty.

VTE in patients undergoing major orthopedic surgery of the lower limbs [33-36], these two agents were never compared directly in Japanese patients. When we compared their effectiveness in a propensity score-matched population, we found that fondaparinux significantly reduced the incidence of ultrasound-proven DVT compared with enoxaparin. In contrast, major bleeding, leading to a requirement for transfusion of at least one unit of blood or occurring in a critical organ, occurred more frequently

Table 11 Incidences of any DVT (up to POD10) and major bleeding (up to POD28) in propensity-matched fondaparinux- or enoxaparin-treated groups (TKA)

Events	Fondaparinux n = 204	Enoxaparin n = 204	Risk ratio (95% CI)	*P* value
DVT	28/204 (13.6%)	54/204 (26.2%)	0.70 (0.58-0.85)	0.002
Major bleeding	7/204 (3.4%)	1/204 (0.5%)	4.18 (0.67-26.20)	0.062

CI, confidence interval; DVT, deep vein thrombosis; POD, postoperative day; TKA, total knee arthroplasty.

in the fondaparinux- than in the enoxaparin-treated group. A meta-analysis of four randomized double-blind trials comparing fondaparinux with enoxaparin found that 2.5 mg/day fondaparinux was superior to approved enoxaparin regimens in preventing VTE [37]. Furthermore, the overall incidence of clinical-relevant bleeding did not differ between the two groups, and the benefit of fondaparinux was consistent across all studies. In one trial, however, the rates of major bleeding were significantly higher with fondaparinux than with enoxaparin [36]. The lack of consistency in defining "bleeding" in these studies, including ours, creates difficulties in interpreting the true benefit-harm balance. Pharmacological prophylaxis in patients undergoing major orthopedic surgery is of concern because of the increased risk of bleeding. Several previous studies have found an interaction between dose of fondaparinux and risk of major bleeding [38,39]. Overall, clinicians must make trade-offs between the benefits of reducing thrombosis and adverse effects, including bleeding, when using fondaparinux in Japanese patients.

Some methodological aspects and possible limitations of this study require comment. First, because of the non-interventional, open-label study design and limitations inherent to observational studies, the estimated risks were not unbiased. Owing to a lack of randomization, observational studies are confounded by indication. Although our study cohort was large and the study population was adjusted for a large number of confounding covariates, we could not adjust for all confounders. Thus, this observational study was not the equivalent of a randomized control trial. Second, indications for thromboprophylaxis varied widely among physicians and within hospitals, introducing an inherent selection bias. The incorporation

Table 12 Incidences of any DVT (up to POD10) and major bleeding (up to POD28) in propensity-matched fondaparinux- or enoxaparin-treated groups (THA)

Events	Fondaparinux n = 144	Enoxaparin n = 144	Risk ratio (95% CI)	*P* value
DVT	8/144 (5.6%)	16/144 (11.1%)	0.73 (0.53-0.99)	0.134
Major bleeding	7/144 (4.9%)	0/144 (0%)	-	0.022

CI, confidence interval; DVT, deep vein thrombosis; POD, postoperative day; THA, total hip arthroplasty.

of DVT into the composite primary efficacy end point of this study may be questionable [9]. However, DVT, both symptomatic and non-symptomatic, has been linked with symptomatic or fatal PE [40]. Venography is generally accepted as the gold standard in detecting DVT. A recent systematic review suggested that ultrasound is accurate for the postoperative diagnosis of DVT in asymptomatic orthopedic patients [13]. Additionally, the use of blinded investigators and independent adjudication may reduce some of the imprecision stemming from subjectivity and variability among observers [41]. Although the risk of VTE was shown to be extended by periods beyond the usual periods of hospitalization [42], the duration of pharmacological prophylaxis was relatively limited in our study. The association between mortality and major bleeding is strong in the first 30 days; however, it remains significant up to 3 years [43]. Our study did not determine whether in-hospital bleeding affects the long-term outcomes. Most asymptomatic DVTs detected by using the CUS method were distal, for which the diagnostic performance of CUS is poorer than for proximal DVT [44]. However, CUS yielded much better diagnostic performance in patients with asymptomatic DVT when performed by staff with substantial experience in ultrasonography and when a standardized examination procedure was used [45], as in our study. Even if the relative inaccuracy of CUS for detecting distal DVTs was real in our study, it would not explain the decreased incidences of DVT in patients receiving a certain thromboprophylaxis agent, because the same diagnostic procedure was used in all patients, regardless of thromboprophylactic agent. Propensity scores are estimated by using a large number of measured pretreatment covariates in a multivariate logistic regression model to predict exposure. Thus, propensity score-matched analysis of patients receiving fondaparinux and enoxaparin mimics a randomized trial. However, unmeasured characteristics and confounders are not completely balanced.

Our study represents the most comprehensive, hospital-based cohort study to date, with the outcomes in all enrolled patients completely followed. The participants in this study, in contrast to those in many clinical trials, were similar demographically to the general population undergoing joint replacement, suggesting that our findings are applicable to the general population. The J-PSVT has been able to recruit a large, diverse population of patients undergoing THA or TKA and therefore was able to identify factors affecting outcomes that may not be apparent in clinical trials.

Conclusions

This large, prospective, multicenter analysis assessed VTE risks and bleeding in patients undergoing joint replacement surgery under conditions reflecting routine "real-world" clinical practice in Japan. Our results suggest that fondaparinux prophylaxis can reduce DVT but that it is accompanied by a high risk of bleeding. These gaps between recommendations and real-world outcomes should be addressed by additional prospective studies or the registry.

Abbreviations

CUS: compression ultrasonography; DVT: deep vein thrombosis; J-PSVT: Japanese study of Prevention and Actual situation of Venous Thromboembolism after Total Arthroplasty; LMWH: low-molecular-weight heparin; NHO: National Hospital Organization; PE: pulmonary embolism; POD: post-operative day; THA: total hip arthroplasty; TKA: total knee arthroplasty; UFH: unfractionated heparin; VTE: venous thromboembolism.

Competing interests

SMi received research support and speaker honoraria from Daiichi Sankyo Co., Ltd (Tokyo, Japan), Mitsubishi Tanabe Pharma Corporation (Osaka, Japan), and CSL Behring K.K. (Tokyo, Japan). The other authors declare that they have no competing interests.

Authors' contributions

KM, SB, and SMo participated in the design of the study, helped to analyze the data, and helped to write the manuscript. MN and SMi participated in the design of the study. MK helped to analyze the data. MS, HKak, YuN, ToM, IF, YS, TTa, MY, HKan, IA, TaM, KI, SK, KS, HM, TS, YaN, and TTo helped to collect the clinical data. All authors read and approved the final manuscript.

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