CURRENT CONCEPTS REVIEW

Is Pharmacologic Prophylaxis for Venous Thromboembolism Necessary in People With Hemophilia After Total Knee and Hip Arthroplasty?

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Received: 2 June 2025 *Accepted: 23 June 2025*

Abstract

Pharmacologic thromboprophylaxis for postoperative venous thromboembolism (VTE) after total knee arthroplasty (TKA) and total hip arthroplasty (THA) in people with hemophilia (PWH) is highly controversial. In PWH the prevalence of symptomatic VTE after TKA and THA is between 0 to 5%, while the prevalence of asymptomatic VTE is between 7.5% and 10%. In PWH many clinicians have not used pharmacologic thromboprophylaxis. Others have used low molecular weight heparin (LMWH) and reduced doses of DOAC [direct oral anticoagulants (thrombin inhibitors and Factor Xa inhibitors)]. It appears that pharmacologic thromboprophylaxis should only be carried out in PWH undergoing TKA and THA who have VTE risk factors [e.g., old age, prior VTE, varicose veins, general anesthesia, cancer, Factor V (Leiden) mutation, and obesity]. After TKA and THA in PWH, early mobilization is essential. Some authors have advocated additional mechanical thromboprophylaxis (pneumatic compression devices). In conclusion, for all PWH experiencing TKA and THA mechanical prophylaxis is sensible. Some form of pharmacologic prophylaxis should be strongly considered for PWH with clear risk factors. The main area of doubt is in PWH without risk factors. More prospective multicenter studies are required. Difficulties will be getting agreement on universal regimes to be followed; and the relatively small numbers of PWH experiencing TKA and THA.

Level of evidence: III

Keywords: Hemophilia, Mechanical thromboprophylaxis, Pharmacologic thromboprophylaxis, Postoperative venous thromboembolism, Total hip arthroplasty, Total knee arthroplasty

Introduction

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are major surgical interventions with proven good outcomes in people with hemophilia (PWH).[1-9] However, it is still unclear what the answer is to the following question: should PWH receive postoperative pharmacologic prophylaxis to prevent venous thromboembolism (VTE) [deep vein thrombosis (DVT) and pulmonary embolism] as is usually recommended for people without hemophilia? This article attempts to answer that question.

In 2004, Dargaud et al stated that postoperative pharmacologic prophylaxis of VTE was not systematically carried out in PWH.[10] Perez Botero et al (2015) reported that pharmacologic prophylaxis of VTE was routinely utilized in people without hemophilia. However, for PWH, pharmacologic prophylaxis was controversial because of the inherent risk of bleeding.[11] In 2014 Siboni et al analyzed 32 orthopedic procedures (6 minor, 26 major) performed over a 33-year period in 23 PWH. Minor surgery included three hand procedures, one foot procedure, and two others). Major surgery included 7 joint arthroplasties (TKA and THA), 9 arthroscopic procedures, two foot procedures, and 8 others). Pharmacologic prophylaxis of VTE was used in four cases only.[12]

According to Ono and Takedani (2020), VTE remained controversial in PWH undergoing major orthopedic

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THE ONLINE VERSION OF THIS ARTICLE ABJS.MUMS.AC.IR

surgery. They did not detect DVT on ultrasonography (US) after TKA in 36 Japanese PWH.[13]

In 2024, Santagata et al stated that VTE was a well-recognized complication after TKA and THA in PWH. However, persons with hemophilia A or B were considered at low postoperative risk of VTE, and performing pharmacologic thromboprophylaxis was frequently contraindicated.[14]

In August 2023, Rodriguez-Merchan published a narrative review of the literature entitled "Pharmacological thromboprophylaxis in PWH experiencing orthopedic surgery".[15] This article included the most relevant publications found in PubMed up to July 31, 2023. Given the scarcity of information on the subject of VTE in PWH, the purpose of this article was to carry out a new review of the literature (after July 2023). The keywords used for this article were "hemophilia postoperative venous thrmoboembolism". A total of 40 articles were found, of which 14 were included as they were directly related to the title of the article.

Main body

Main data on postoperative VTE after TKA and THA in PWH: type of surgery, rate of VTE and hemostatic control during surgery

In 2015, Perez Botero *et al.* analyzed 42 PWH who underwent 71 THAs or TKAs over a period of 39 years. They also analyzed the literature to calculate the prevalence of VTE following arthroplasty. All PWH utilized compression stockings for up to 6 weeks after the surgical procedures; besides, 6 individuals (10.5%) used sequential intermittent compression devices, and 2 subjects (2.8%) postoperatively received LMWH (low molecular weight heparin). One patient (1.4%), who had received LMWH, suffered a symptomatic, lower-limb, VTE 10 days after hip arthroplasty following traumatic fracture. None of the other 70 surgical cases had symptomatic VTE within the first three months post-surgically. The analysis of the pooled data from published series of PWH experiencing arthroplasty showed an estimated incidence of symptomatic VTE of 0.5%.[11]

In 2015 Pan *et al*. analyzed 11 patients (12 THAs and 14 TKAs) undergoing arthroplasty for hemophilic arthropathy, including one case of simultaneous bilateral TKA. Patients were treated with personalized thrombus prevention regime by adjusting the dosage of recombinant human coagulation factor (F) VIII (Kogenate FS). No patient had postoperative VTE.[16]

In 2016, Hermans *et al.* reported the outcomes of three prospective studies performed in three major hospitals from Italy, Belgium and Norway assessing by systematic US-Doppler imaging the prevalence of subclinical VTE in PWH referred for major orthopedic surgery over more than 10 years.[17] In total, 214 individuals with hemophilia (191 hemophilia A, 23 hemophilia B) experiencing 136 TKAs and 34 THAs were analyzed. PWH were treated with continuous infusion or bolus of concentrates. They did not receive antithrombotic pharmacologic prophylaxis. US Doppler of both lower extremities was carried out between days 5 and 10 post-op. No case of clinical VTE was detected. In total, 11 cases of distal subclinical DVT involving 1 (5) or 2 (6) calf veins were detected, of which six were treated with a low-dose and short course of LMWH. The prevalence of subclinical DVT was 4.7% (11/231) and ranged in the three hospitals from 3.4% in Norway (1/29), 4% in Italy (6/148) and 7.4% in Belgium (4/54). They concluded that the risk of clinically significant VTE after TKA and THA in PWH was very low and, therefore, systematic pharmacologic thromboprophylaxis is for most patients not required.[17]

In a multicenter study (11 centers) of 46 patients reported by Buckner *et al*. (2016), the prevalence of US-detectable, asymptomatic VTE in PWH following TKA or THA was low. However, the incidence of symptomatic VTE (4.3 %, 95 % CI, 0.5-14.8 %) appeared similar to the incidence in the general population without pharmacologic thromboprophylaxis.[18] Lower limb venous duplex US was carried out before the surgical procedures and 4-6 weeks following the surgical procedures. In the perioperative period, 6 individuals (13%) received bypassing drugs [recombinant FVII activated (rFVIIa) or FVIII inhibitor bypassing agent (FEIBA)]; the remaining 40 individuals were treated with FVIII or FIX replacement. In the postoperative period, intermittent pneumatic compression devices were utilized in 23 subjects (50%), and 4 subjects (8.7%) also were given LMWH prophylaxis. One subject (2.2%) with moderate hemophilia A suffered a distal DVT on day 6 following TKA. One subject (2.2%) with severe hemophilia A suffered a pulmonary embolism on day 9 following bilateral TKA. No subjects were diagnosed on US with an asymptomatic DVT.[18]

Zhai *et al.* (2017) reported one lower limb DVT postoperatively in 19 PWH (20 hips) who underwent primary cementless procedures.[19] In 2019, Peng et al studied the incidence of clinically significant VTE in PWH experiencing THA and TKA without pharmacologic thromboprophylaxis and a modified coagulation factor substitution. A total of 98 male individuals were analyzed. Thirty-one individuals underwent 39 primary THAs (including only 1 case of hemophilia B) and 67 individuals experienced 101 primary TKAs (5 cases with hemophilia B). There was only 1 hemophilia B patient with symptomatic VTE. None of the other 97 individuals had symptomatic VTE within 6 months after surgery (prevalence of 1.02%). None of the individuals received prophylactic anticoagulation. All individuals were subjected to a standardized postoperative protocol with routine mechanical prophylaxis against VTE. Peng et al stated that given the low incidence (1.02%) of VTE in this series, routine pharmacologic prophylaxis in PWH experiencing THA and TKA might not be required.[20]

In a prospective study, Ono and Takedani (2020) assessed the incidence of DVT after TKA among 11 hemophilic A patients (11 TKAs) using US and contrast-enhanced computed tomography (CT). A pneumatic compression device was employed from the start of the surgical procedure until the subject was able to carry out standing exercises (day 2). To identify asymptomatic lower limb DVTs, US was carried out prior to and after the surgical procedure (day 2). Later, to identify any VTEs, contrast-enhanced CT was carried out on day 7 post-operatively. D-dimer levels were measured pre-surgery and post-surgery. DVTs were not identified by US on either pre- or postoperative examinations, however, contrast-enhanced CT detected DVTs in two individuals. No patients showed clinical signs for VTE during hospitalization, and no additional treatment for VTE was performed.

In 2021, Rosas *et al.* analyzed 4,034 PWH among Medicare beneficiaries who had experienced TKA. They found an odds ratio (OR) of DVT of 2.3 (95% CI: 1.8-2.8), and an OR of pulmonary embolism of 2.9 (95% CI: 2.1-3.9).[21] Gillinov *et al.* (2022) stated that PWH had greater odds of experiencing of a VTE episode (DVT, OR 2.67; pulmonary embolism, OR 4.01). Five hundred eighteen hemophilia THA patients were matched, at a ratio of 1:10, with 5,193 non-hemophilia patients. These authors stated that PWH experiencing THA had elevated risk of VTE (DVT and pulmonary embolism) relative to matched controls.[22]

In 2024 Zhang *et al.* studied the prevalence of DVT in PWH undergoing simultaneous bilateral TKAs with no pharmacologic prophylaxis (38 subjects, 76 surgical procedures). All patients used mechanical thromboprophylaxis. D-dimer levels were measured before surgery, on the day of the surgical procedure and after surgery (day 1, week 1 and week 2). In order to identify any DVT, US of the lower extremities was carried out prior to (the surgical procedure and after surgery (day 3; week 2). The patients were followed up for 2 years. Almost half the individuals (47.3%) had D-dimer concentrations above the threshold of 10μg/mL on day 7 and 39.5% on week 2. No individuals had a DVT on postoperative US. No subjects had symptomatic DVT or pulmonary embolism during the 2-year follow-up. These authors affirmed that pharmacologic prophylaxis perhaps was not required.[23]

In 2009 Dindo *et al.* reported that the D-dimer is elevated after major surgery making interpretation difficult and questioning its validity in detecting VTE episodes.[24] Therefore, it seems that D-dimers are not helpful post-major surgery.

A systematic review (Santagata *et al.*, 2024) analyzed the incidence of VTE in PWH undergoing total joint replacements (THA and TKA) of the lower limbs involving a total of 1,181 procedures. Postoperative pharmacologic thromboprophylaxis was used in only 1.3% of the individuals (15 procedures). Seventeen VTEs occurred (1.4%; 95% CI, 0.9%-2.3%), including 6.6% after the surgical procedures with postoperative US VTE screening and 0.7% after the surgical procedures without postoperative US screening. In this systematic review, thromboprophylaxis protocols were specified in 21 studies. This information was not accessible for 29% of the reported procedures.[14] Table 1 summarizes the main data on postoperative VTE in the literature [Table 1]. [11,13,14,16-23]

Table 1. People with hemophilia (PWH): main data on postoperative venous thromboembolism (VTE) after TKA and THA in the literature.

AUTHORS [REFERENCE]	YEAR	TYPE OF SURGERY	RATE OF POST-OP. VTE	ODDS RATIO	HEMOSTATIC CONTROL DURING SURGERY
Perez Botero, et al [11]	2015	TKA and THA	1.4% (1/71) – symptomatic DVT	NA	FVIII or FIX concentrate.
Pan, et al [16]	2015	TKA and THA	0% (0/15)	NA	Recombinant human coagulation FVIII (Kogenate FS).
Hermans, et al [17]	2016	TKA and THA	0% (0/231)	NA	NA
Buckner, et al [18]	2016	TKA and THA	2.1% (2/46) – symptomatric DVT	NA	In the perioperative period 6 individuals (13%) received bypassing drugs; the remaining 40 individuals were treated with FVIII or FIX replacement.
Zhai, et al [19]	2017	THA	5% (1/20) – symptomatic DVT	NA	Based on WFH guidelines, a modified coagulation factor substitution regime was adopted.
Peng, et al [20]	2019	TKA and THA	1.03% (1/97) – symptomatic DVT	NA	Based on WFH guidelines, a modified coagulation factor substitution regimen was adopted.
Ono and Takedani [13]	2020	TKA	9% (2/11) – asymptomatic DVT	NA	FVIII or FIX concentrate.
Rosas, et al [21]	2021	TKA	NA	Odds ratio of DVT: 2.3; Odds ratio of pulmonary embolism: 2.9	NA

Table 1. Continued

Gillinov, et al [22]	2022	THA	NA	Odds ratio of DVT: 2.67; Odds ratio of pulmonary embolism: 4.01	NA
Zhang, et al [23]	2024	TKA	0% (0/76)	NA	All individuals received a modified coagulation factor substitution regimen. Tranexamic acid was utilized for hemostasis in all individuals during surgery.
Santagata, et al [13]	2024	TKA and TKA	1.4% (17/1181) – symptomatic DVT	NA	NA

DVT = deep vein thrombosis; FVIII = factor VIII; FIX = factor IX; TKA = total knee arthroplasty; THA = total hip arthroplasty; NA = not available; WFH = World Federation of Hemophilia.

Results of pharmacologic thromboprophylaxis in the prevention of VTE in PWH

The conclusions of the study by Perez Botero *et al.* (2015) suggested that in PWH, joint arthroplasties can be performed safely without pharmacological prophylaxis of VTE and without increasing the risk of VTE. The authors ventured that pharmacological prophylaxis of VTE might be considered in select patients with known additional risk factors for VTE.[11]

In 2015, Pan *et al.* affirmed that, in PWH undergoing joint arthroplasty, it was important to determine how to control the balance between postoperative thrombus prevention, hemostasis, and coagulation factor replacement therapy. Pan et al stated that postoperative mobilization had proven helpful in PWH, especially in diminishing the risk of hemostasis and reducing hospital in-patient stays.[16] In PWH experiencing surgery, Ahmed *et al.* (2018) made certain recommendations which are shown in [Table 2].[25]

In 2023, Tripodi *et al.* stated that multicenter prospective trials were required to address the value of pharmacologic prophylaxis to avoid postoperative VTE in PWH, especially during major orthopedic surgery when regular pharmacologic prophylaxis is supplemented with additional coagulation factor products or bypassing agents. Tripodi et al concluded that, until this information is available, PWH experiencing major orthopedic surgery, whilst on antihemorrhagic prophylaxis supplemented with coagulation factor concentrates or bypassing agents, should, as a minimum, receive intermittent pneumatic compression.[26]

Table 2. European guidelines on perioperative venous thromboembolism (VTE) prophylaxis in people with hemophilia (PWH) [25]

RECOMMENDATION	GRADE OF EVIDENCE
VTE risk should be balanced against the increased bleeding risk associated with anticoagulant utilization in PWH.	1C
In PWH experiencing major surgery, the recommendation is not to use routine postoperative pharmacologic prophylaxis, especially for patients with hemophilia A and B.	1B
Glomerular filtration rate should be evaluated prior to the initiation of each direct oral anticoagulant, and also at least once a year or more frequently as required, such as postoperatively before the resumption of therapeutic direct oral anticoagulant administration, when it is suspected that renal function could decline or deteriorate	1C
Reduced dosages of LMWHs may be utilized relatively safely during transient severe (<50 × 10 L) thrombocytopenia.	2C
Monitoring of anti-Xa levels may be used to adjust the doses of LMWH in patients with moderate or severe thrombocytopenia.	2C
The delay between major gastrointestinal bleeding and resuming warfarin should be at least 7 days.	2C
For PWH at a high risk of VTE and with a high bleeding risk after surgery, administering a reduced dose of direct oral anticoagulant on the evening after surgery and on the following day (first postoperative day) after surgery can be considered a good practice.	2B

LMWH = low molecular weight heparin; L = liter.

Results dealing with the risk of bleeding after surgery in hemophilia

In a multicenter study published in 2022, Kleiboer *et al*. assessed the percentage of patients experiencing excessive bleeding during the postoperative period after THA or TKA. One hundred and thirty-one procedures were analyzed and 39 (29.8%) were complicated by major postoperative bleeding. The risk of major bleeding was increased by the existence of an inhibitor, increased body mass index (BMI), and non-usage of an antifibrinolytic drug. Pharmacologic thromboprophylaxis was not associated with bleeding risk.[27]

Considerations on possible reduced doses of DOACs (direct oral anticoagulants) and LMWH

In 2018, Ahmed *et al.* stated that for PWH at high risk of VTE and with an elevated bleeding risk after surgery, a reduced dose of DOAC on the evening after surgery and on the first postoperative day after surgery was good practice.[25] Standard doses of DOACs are the following: thrombin inhibitors (dabigatran, 150 mg oral/12 h); activated FXa inhibitors (rivaroxaban, 20 mg oral/24 h; apixaban, 5 mg oral/24 h); and subcutaneous fondaparinux (2.5 mg/24 h subcutaneously).[15] However, information on what constitutes a reasonable reduced dose of LMWH has not been found in the literature.

Summary: high risk surgery and case in whom to consider pharmacologic thromboprophylaxis in the prevention of VTE in PWH

According to Rodriguez-Merchan (2023), the hemophilia literature states that the use of pharmacologic thromboprophylaxis should only be carried out in PWH undergoing TKA and THA who have additional VTE risk factors, such as old age, prior VTE, varicose veins, general anesthesia, cancer, FV (Leiden) mutation, obesity, and treatment with the oral contraceptive pill (in females with von Willebrand's illness).[15]

In 2023, Schutgens *et al*. [EHA (European Hematology Association) –ISTH (International Society on Thrombosis and Hemostasis) – EAHAD (European Association of Hemophilia and Allied Disorders) -ESO (European Stroke Organization) clinical practice guidance] confirmed that after assessing the low incidence of postoperative VTE in PWH and the potential chance of bleeding adverse events, they did not advise the routine use pharmacologic thromboprophylaxis in the perioperative period. Additionally, they advised for an individual approach towards surgical patients with elevated VTE risk. They advised against extended durations of pharmacologic thromboprophylaxis. They did not advise routine pharmacologic thromboprophylaxis in PWH that are medically otherwise well and they advised mechanical over pharmacologic thromboprophylaxis, if indicated.[28]

Rodriguez-Merchan (2023) advised that if various risk factors for VTE in PWH undergoing orthopedic surgery are identified, similar pharmacologic thromboprophylaxis regimes advised for non-hemophilia individuals should be followed: LMWHs, such as enoxaparin; or DOACs, either FXa inhibitors (rivaroxaban, apixaban, or subcutaneous fondaparinux). Nonetheless, the PWH literature review has demonstrated that only a few authors have utilized pharmacologic prophylaxis with LMWH (subcutaneous enoxaparin), for a short time period (10-14 days), in some individuals with VTE risk factors. Only one group of authors utilized a low dose of DOAC, in the evening after the surgical procedure and on the next day, specifically in individuals at elevated VTE risk and elevated risk of bleeding after the surgical procedure.[15]

For individuals treated with bypassing agents and emicizumab, Schutgens et al did not advise the routine use of pharmacologic thromboprophylaxis in surgical PWH.[27] Information on the risk of VTE after surgery due to replacement therapy with fitusiran has not been found in the literature.

Conclusion

For all PWH experiencing TKA and THA mechanical prophylaxis is sensible. Some form of pharmacologic prophylaxis should be strongly considered for PWH with clear risk factors. The main area of doubt is in PWH without risk factors. More prospective multi-center studies are required. Difficulties will be getting agreement on universal regimes to be followed; and relatively small numbers of PWH experiencing TKA and THA.

Acknowledgement

N/A

Authors Contribution: Author who conceived and designed the analysis: ECR-M, HDlC-R, WJR/ Author who collected the data: ECR-M, HDlC-R, WJR/Author who contributed data or analysis tools: ECR-M, HDlC-R, WJR/Author who performed the analysis: ECR-M, HDlC-R, WJR/Author who wrote the paper: ECR-M, HDlC-R and WJR

Declaration of Conflict of Interest: The authors do NOT have any potential conflicts of interest for this manuscript.

Declaration of Funding: The authors received NO financial support for the preparation, research, authorship, and publication of this manuscript.

Declaration of Ethical Approval for Study: Our institutions do not require ethical approval for reporting retrospective studies.

Declaration of Informed Consent: The authors declare that there is no information (names, initials, hospital identification numbers, or photographs) in the submitted manuscript that can be used to identify patients.

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