Preventing VTE following total hip and knee arthroplasty: Is prediction the future?

Banne Nemeth1,2 | Rob Nelissen2 | Roopen Arya3 | Suzanne Cannegieter1,4

1Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands
2Department of Orthopaedic Surgery, Leiden University Medical Center, Leiden, The Netherlands
3King’s Thrombosis Centre, King’s College Hospital NHS Foundation Trust, London, United Kingdom
4Division of Thrombosis and Haemostasis, Leiden University Medical Center, Leiden, The Netherlands

Correspondence
Banne Nemeth, Departments of Clinical Epidemiology and Orthopaedic Surgery, Albinusdreef 2, 2333 ZA Leiden, The Netherlands.
Email: b.nemeth@lumc.nl

Abstract
Venous thromboembolism (VTE) is a common complication following total hip arthroplasty (THA) and total knee arthroplasty (TKA). Many guidelines advise on the ideal pharmacological thromboprophylaxis strategy; however, despite its use, approximately 1.5% of patients still develop symptomatic VTE. Considering the large number of THAs and TKAs performed worldwide (2.5 million in total), the impact of VTE following these interventions is enormous. This paper discusses a concept how to further lower rates of VTE and bleeding complications following surgery. By stratifying patients according to their risk, we can optimize the balance between VTE and bleeding for each individual. This way, low-risk patients may be safely withheld from treatment (and avoid unnecessary bleeding complications and costs), whereas high-risk patients should receive adequate therapy (for instance, an increased thromboprophylaxis dosage and duration). An individualized strategy requires a well-functioning VTE prediction model following THA and TKA to help physicians to decide on optimal thromboprophylaxis therapy.

KEYWORDS
decision modelling, hip replacement arthroplasty, knee replacement arthroplasty, risk, venous thromboembolism

1 | THE INCIDENCE OF POSTOPERATIVE VENOUS THROMBOEMBOLISM FOLLOWING THA AND TKA

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are associated with an increased risk of venous thromboembolism (VTE), comprising both deep vein thrombosis and pulmonary embolism. In the 1960s, patients undergoing THA or TKA developed asymptomatic VTE in approximately 30% of cases without the administration of any type of mechanical or pharmacological thromboprophylaxis. Because of the introduction of anticoagulants such as low molecular weight heparins (LMWH) in the 1970s, the cumulative incidence of symptomatic VTE declined to approximately 5% to 10% in the 1990s (Figure S1). Thereafter, improvements in thromboprophylactic strategies, for instance an extended thromboprophylaxis regimen up to 4 to 6 weeks, have further reduced the incidence of symptomatic VTE to a current 1.5% within 3 months postoperatively.

It is important to realize that not only the introduction of pharmacological thromboprophylaxis has led to this strong decline in
postoperative VTE. New surgical techniques (eg, minimal invasive procedures, less traumatic surgery) and improvement in postoperative care have also contributed. For instance, fast-track surgery, a treatment protocol with neuraxial/regional anesthesia, early mobilization, and hospital discharge within 3 days, has been a great enhancement in orthopedic care. It has been shown consistently that shorter hospitalization, as a result of early mobilization, reduces VTE risk considerably. Large registry studies of patients included in such fast-track treatment protocols have shown very low symptomatic VTE rates (<1%). Interestingly, in some of these studies, patients only received pharmacological thromboprophylaxis (any type) for a maximum of 5 days postoperatively. It has even been challenged by some whether THA or TKA patients in such fast-track protocols need thromboprophylaxis at all.

2 | DESPITE THROMBOPROPHYLAXIS, 1.5% OF PATIENTS STILL DEVELOP VTE

As discussed previously by Jørgensen and colleagues, many guidelines advice on the optimal type and duration of thromboprophylaxis, but there may be little consensus. The American College of Chest Physicians’ guidelines on thromboprophylaxis suggest to treat patients undergoing THA or TKA for a minimum of 10 to 14 days postoperatively with (any) pharmacological thromboprophylaxis rather than no prophylaxis (grade 1B). Even more, an extended duration of therapy is advised up to 35 days, with a lower grade of evidence (grade 2B). The UK National Institute for Health and Care Excellence advises to treat for a minimum duration of 28 days by either an LMWH or the combination of aspirin followed by LMWH. For TKA, a treatment duration of 14 days is advised. An extended treatment is not advised because this coincides with a high risk of (major) bleeding.

In spite of all these implemented guidelines on thromboprophylaxis therapy following THA and TKA, about 1.5% of patients still develop symptomatic VTE, which may be explained by several factors. First, thromboprophylaxis is not 100% effective, for example, the effectiveness of LMWH on VTE prevention following THA and TKA is estimated to be approximately 50%. Thus, some patients still develop VTE despite pharmacological thromboprophylactic strategies. Second, drug compliance may be an issue that results in reduced effectiveness of the drug and finally, VTEs can occur after the treatment has stopped.

Considering the large number of annually performed THA and TKA worldwide (respectively, 1.4 and 1.1 million), and given the high mortality and morbidity associated with VTE, the impact of VTE for both patients as well as society is enormous (despite its low incidence). Long-term complications such as postthrombotic syndrome, chronic thromboembolic pulmonary hypertension, and recurrent VTE all have a harmful effect on patients’ wellbeing. The current strategy in thromboprophylaxis management for elective arthroplasty surgery therefore needs improvement, which raises the question: how?

3 | HOW TO FURTHER REDUCE VTE RATES FOLLOWING THA AND TKA?

Patients undergoing THA or TKA are heterogenous in several aspects. Orthopedic surgeons individualize the type and size of the implant to match patient specific needs and anatomical characteristics, known as “individualized therapy or personalized medicine.” In contrast, however, for thromboprophylaxis this does not necessarily seem to be the case. Despite individualized antithrombotic treatment often being used in medical patients, in the majority of elective orthopedic surgeries thromboprophylaxis is administered according to hospital protocol; a similar thromboprophylactic regimen for all patients undergoing THA or TKA is advised (ie, a population-based approach). For instance, patients with a history of VTE, patients without any comorbidities, and patients who are discharged within 2 days are all considered to be equal in terms of VTE risk and hence receive the same dosage and duration of thromboprophylaxis. There might be some variance in the type of prophylaxis (LMWH, direct-acting oral anticoagulant, aspirin), but the dosage is almost never increased to above or even therapeutic levels. Although this population-based approach has led to a strong decline in VTE rates, it is difficult to further lower VTE rates without increasing the risk of major bleeding in all patients. A more rational approach would be to intensify thromboprophylactic strategies, by increasing the dosage, duration of therapy or both, only in high-risk patients. Likewise, low-risk patients may not need prophylaxis at all, or just for the duration of hospitalization. By this individualized approach, both bleeding and VTE rates can be lowered by tailoring thromboprophylaxis to individual patient characteristics. An individual’s thrombosis risk is determined by many factors which can be grouped into three categories (genetic [eg, factor V Leiden mutation or non-O blood type], acquired [eg, increasing age, chronic kidney disease], and environmental factors [eg, surgery, infection, immobilization]). Thrombosis occurs when an individual’s thrombosis potential/threshold is crossed, which usually happens when multiple factors coincide. A prediction model can help identifying patients at high risk of VTE by combining information of all permanent (eg, increasing age) and transient factors (eg, infection, surgery) that are predictive of VTE.

4 | CURRENT PREDICTIVE MODELS FOR VTE FOLLOWING THA OR TKA

Currently, there are five available models to predict symptomatic VTE following joint replacement surgery. Although some of these models show promising results, none are routinely used or advised in clinical practice. This may be because they are either very extensive (ie, up to 26 predictors), lack performance, are impractical (ie, include blood measurements), or not properly validated (Table S1). Moreover, unfortunately, none report any performance measures and therefore do not give objective information for potential users. Furthermore, important predictors such as start of mobilization...
or length of hospital stay are often missing. Hence, the development and validation of a well-functioning prediction model is highly needed.

To illustrate the effect of individualized thromboprophylaxis therapy on VTE and bleeding rates, three strategies (current, intensified, individualized approach) are shown in Table 1. Of note, these data are meant to show proof of concept and do not represent clinical data. In this example, we assume that of 1000 patients undergoing THA or TKA, 30 would develop VTE without any form of thromboprophylaxis (for each strategy; baseline risk of 3%, as estimated by the American College of Chest Physicians guidelines7). In the current situation (strategy 1), 1.5% of patients develop postoperative VTE despite the use of thromboprophylaxis therapy, assuming drug effectiveness of 50%. Consequently, assuming a baseline major bleeding risk of 0.15% and relative risk for major bleeding from thromboprophylaxis of 5.0, 0.75% of patients develop postoperative major bleeding,9,10 leading to a total of 22.5/1000 complications (15 VTEs + 7.5 bleedings). To further lower VTE rates, the only option is to intensify thromboprophylaxis (strategy 2).

The effect of an intensified thromboprophylaxis strategy for all patients undergoing THA/TKA is shown in strategy 2. An increased dosage and duration of thromboprophylaxis improves the effectiveness on VTE (from a relative risk of 0.50 to 0.25); however, the risk of major bleeding also increases (relative risk of 5.0 to 10). Overall, 7.5 fewer VTEs occur at the expense of 7.5 bleedings induced by intensified thromboprophylaxis. Altogether, this leads to a total of 22.5/1000 complications (15 VTEs + 7.5 bleedings). To further lower VTE rates, the only option is to intensify thromboprophylaxis (strategy 2).

The concept of individualized thromboprophylaxis is illustrated in strategy 3. Again, a total of 1000 patients undergo THA/TKA. The model identifies 200/1000 patients at high risk of VTE (with a test sensitivity of 80% in this case). The high-risk group versus 800/1000 patients are stratified according to their VTE/bleeding risk. Considering the test sensitivity of 80%, in this example 24/200 (12%) patients will develop VTE in the high-risk group versus 6/800 (0.75%) patients in the low-risk group. The high-risk group can be treated with a longer and higher dosage of anticoagulants (similarly to strategy 2), and the low-risk group can be treated with a shorter duration of therapy. Because the low-risk group can be treated with a shorter duration of therapy, the overall effect is substantial. 27% risk reduction from current to individualized thromboprophylaxis strategy (total: 22.5 events → 16.5 events).

### TABLE 1

Three thromboprophylactic strategies for THA and TKA patients

| No. patients | VTE risk | RR  | VTE risk | Major Bleeding | Bleeding risk | RR  | Total Complications | Risk/Benefit Ratio |
|--------------|----------|-----|----------|----------------|---------------|-----|---------------------|--------------------|
|              | Baseline | Postoperative | Baseline | Postoperative |              |     |                      |                    |
| Strategy 1. Current thromboprophylaxis strategy | 1000 | 3.00% | 0.50 | 1.50% | 0.15% | 5.0 | 0.75% | 15 | 75 | 22.5 | 67 | 167 | 2.5 |
| Strategy 2. Intensified thromboprophylaxis | 1000 | 3.00% | 0.25 | 0.75% | 0.15% | 10 | 1.5% | 7.5 | 15 | 22.5 | 44 | 74 | 1.67 |
| Strategy 3. Individualized thromboprophylaxis | 200 | 12.00% | 0.25 | 3.00% | 0.15% | 10 | 1.5% | 6 | 3 | 9 | 11 | 28 | 2.52 |
| | 800 | 0.75% | 0.75 | 0.56% | 0.15% | 2.5 | 0.38% | 4.5 | 3 | 7.5 | 533 | 444 | 0.83 |

Note: The current strategy in which 1.5% of patients still develop VTE despite pharmacological thromboprophylaxis. The intensified thromboprophylaxis in all patients and the individualized strategy in which patients are stratified according to their VTE risk. 27% risk reduction from current to individualized thromboprophylaxis strategy (total: 22.5 events → 16.5 events).

Abbreviations: NNH, number needed to harm; NNT, number needed to treat; No, number; RR, relative risk; VTE, venous thromboembolism.
of 27% compared with the current thromboprophylaxis strategy (22.5/1000 complications). Moreover, the number needed to harm and number needed to treat (NNH/NNT) ratio improves in high-risk patients (NNH/NNT 6.67), whereas in low-risk patients it is evident we could even consider to stop treatment altogether (NNH/NNT 0.8). In low-risk patients, for every 444 patients treated with thromboprophylaxis, one major bleeding is induced, whereas 533 patients have to be treated to save one patient from a VTE. This implies more harm than benefit. An individualized approach thus saves 800 low-risk patients from the costs and burden (bleeding) of thromboprophylaxis.

6 | PREVENTING VTE FOLLOWING TOTAL HIP AND KNEE ARTHROPLASTY: IS PREDICTION THE FUTURE?

In this paper, we discuss the concept of individualized thromboprophylaxis therapy to reduce both VTE and bleeding complications. High-risk patients may need intensified thromboprophylaxis treatment to reduce their risk, whereas thromboprophylaxis in low-risk patients may be safely withheld. However, before such a strategy can be implemented in clinical practice, several challenges lie ahead. First, there is an urgent need for (the development of) a well-performing and validated prediction model for VTE risk following THA/TKA. This can help physicians to determine an individual’s risk and to decide on pharmacological thromboprophylaxis therapy. Model performance is expressed in terms of risk calibration, discrimination, and overall performance. Calibration is the ability to accurately estimate an individual’s risks. Discrimination is the ability to discriminate between individuals who develop an event versus those who do not (ie, differentiating between low- and high-risk patients). The discriminative ability of a model to select a population that may benefit from an intensified thromboprophylaxis regimen is therefore paramount. For more details on model development techniques and statistics we refer to Steyerberg.²¹

Besides good performance measures, the model needs to be user friendly to successfully implement its use in clinical practice, the number of predictors should therefore be kept to a minimum while maintaining good performance. This balance between usability in clinical practice and optimal model performance is challenging: too many predictors will scare off potential users, whereas a limited number of predictors can hamper model performance.

Following the development phase, a second step would be to implement the score in clinical practice to prospectively validate its performance. Good model performance in a wide variety of clinical settings is vital for successful implementation. Finally, a randomized controlled clinical trial is necessary to test whether an individualized approach is indeed superior compared with the current “one-size-fits-all” strategy. In such a trial, low-risk patients will receive minimal or no thromboprophylaxis, whereas high-risk patients receive an intensified regimen. The preferable dose and duration of thromboprophylaxis will depend upon the average VTE and bleeding risk in the high-risk group. Hence, at this point, detailed advice on a specific intensified regimen (for example, a double or even therapeutic dose of either a LMWH, direct-acting oral anticoagulant, or aspirin) is too speculative. Because the overall incidence of VTE will be low, for both a randomized controlled clinical trial and model development and validation, international collaboration within a best evidence-based perioperative protocol is vital to reach adequate study power and success.

CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

All authors contributed to the concept and design. Banne Nemeth wrote the initial draft and revised it accordingly. Rob G.H.H. Nelissen, Roopen Arya, and Suzanne C. Cannegieter critically revised the intellectual content. All authors approved the final manuscript for publication.

ORCID

Banne Nemeth https://orcid.org/0000-0002-1214-5923
Suzanne Cannegieter https://orcid.org/0000-0003-4707-2303

TWITTER

Banne Nemeth@bannenemeth
Roopen Arya@AryaRoopen

REFERENCES

1. Harris WH, Salzman EW, Desanctis RW. The prevention of thromboembolic disease by prophylactic anticoagulation. A controlled study in elective hip surgery. J Bone Joint Surg Am. 1967;49(1):81-89.
2. Turpie AG, Levine MN, Hirsh J, et al. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. N Engl J Med. 1986;315(15):925-929.
3. Forster R, Stewart M. Anticoagulants (extended duration) for prevention of venous thromboembolism following total hip or knee replacement or hip fracture repair. Cochrane Database Syst Rev. 2016;3:CD004179.
4. Lassen MR, Borris LC. Mobilisation after hip surgery and efficacy of thromboprophylaxis. Lancet. 1991;337(8741):618.
5. Petersen PB, Kehlet H, Jorgensen CC. Safety of in-hospital only thromboprophylaxis after fast-track total hip and knee arthroplasty: a prospective follow-up study in 17,582 procedures. Thromb Haemost. 2018;118(12):2152-2161.
6. Jorgensen CC, Petersen PB, Reed M, Kehlet H. Recommendations on thromboprophylaxis in major joint arthroplasty - many guidelines, little consensus? J Thromb Haemost. 2019;17(2):250-253.
7. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):e278S-e325S.
8. National Institute for Health and Care Excellence. NICE guideline [NG89] Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. 2018. https://www.nice.org.uk/guidance/ng89
9. Pedersen AB, Andersen IT, Overgaard S, et al. Optimal duration of anticoagulant thromboprophylaxis in total hip arthroplasty: new evidence in 55,540 patients with osteoarthritis from the Nordic Arthroplasty Register Association (NARA) group. Acta Orthop. 2019;90(4):298-305.

10. Pedersen AB, Mehnert F, Sorensen HT, Emmeluth C, Overgaard S, Johnsen SP. The risk of venous thromboembolism, myocardial infarction, stroke, major bleeding and death in patients undergoing total hip and knee replacement: a 15-year retrospective cohort study of routine clinical practice. Bone Joint J. 2014;96-B(4):479-485.

11. Petersen PB, Jorgensen CC, Kehlet H. Venous thromboembolism despite ongoing prophylaxis after fast-track hip and knee arthroplasty: a prospective multicenter study of 34,397 procedures. Thromb Haemost. 2019;119(11):1877-1885.

12. Flinterman LE, van Hylckama Vlieg A, Cannegieter SC, Rosendaal FR. Long-term survival in a large cohort of patients with venous thrombosis: incidence and predictors. PLoS Med. 2012;9(1):e1001155.

13. Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med. 1996;125(1):1-7.

14. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. J Thromb Thrombolysis. 2009;28(4):465-476.

15. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. Eur Respir J. 2017;49(2):1601792.

16. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet. 2003;362(9383):523-526.

17. Cobben MRR, Nemeth B, Lijfering WM, Cannegieter SC. Validation of risk assessment models for venous thrombosis in hospitalized medical patients. Res Pract Thromb Haemost. 2019;3:217-225.

18. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet. 1999;353(9159):1167-1173.

19. Nemeth B, Cannegieter SC. Venous thrombosis following lower-leg cast immobilization and knee arthroscopy: from a population-based approach to individualized therapy. Thromb Res. 2019;174:62-75.

20. Kunutsor SK, Beswick AD, Whitehouse MR, Blom AW. Systematic review of risk prediction scores for venous thromboembolism following joint replacement. Thromb Res. 2018;168:148-155.

21. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J. 2014;35(29):1925-1931.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Nemeth B, Nelissen R, Arya R, Cannegieter S. Preventing VTE following total hip and knee arthroplasty: Is prediction the future?. J Thromb Haemost. 2021;19:41-45, https://doi.org/10.1111/jth.15132