Risks of major bleeding and venous thromboembolism in patients undergoing total hip or total knee arthroplasty using therapeutic dosages of DOACs

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Risks of major bleeding and venous thromboembolism in patients undergoing total hip or total knee arthroplasty using therapeutic dosages of DOACs

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Abstract

About 1.5% of patients undergoing total hip (THA) or total knee arthroplasty (TKA) still develop postoperative venous thromboembolism (VTE), indicating that the current thromboprophylaxis strategy is not optimal. To evaluate the feasibility of therapeutic dosages of direct oral anticoagulants (DOACs) as thromboprophylaxis for high VTE risk patients, we determined the risks of major bleeding and VTE in patients who underwent THA/TKA and were treated with DOACs in therapeutic dosages for atrial fibrillation (AF). We conducted a registry-based cohort study from 2010 to 2018 in Denmark and included AF patients on therapeutic DOACs dose who underwent THA/TKA. AF patients were utilized as proxy since they have a life-long indication for therapeutic anticoagulant medication. The 49-days cumulative incidence (with death as competing risk) of major bleeding was assessed. The same was done for VTE at 49- and 90-days. 1,354 THA and TKA procedures were included. The 49-days cumulative incidence of major bleeding was 1.40% (95%Confidence Interval[CI] 0.88–2.14%). Most bleeding events occurred at the surgical site. The cumulative incidence of VTE at 49-days was 0.59% (95%CI 0.28–1.13%) and 0.74% (95%CI 0.38–1.32%) at 90-days. The incidence of major bleeding in THA/TKA patients on DOACs in therapeutic dosages was in line with previously reported incidences among THA/TKA patients on thromboprophylaxis dosages, while the incidence of VTE was relatively low. These data provide a solid basis for the design of randomized controlled trials to establish the safety and efficacy of therapeutic dosages of DOACs to prevent VTE in high-risk patients.

Essentials

- Some arthroplasty patients still develop venous thromboembolism (VTE), despite thromboprophylaxis.
- We assessed the feasibility of DOACs used in therapeutic dosage as thromboprophylaxis in high-risk THA/TKA patients.
- Observed risks of major bleeding and VTE were 1.40% (49-days) and 0.74% (90-days), respectively.
- A randomized clinical trial investigating the possible benefit of therapeutic dosages of DOACs as prophylactic strategy in high-risk arthroplasty patients seems a feasible next step.

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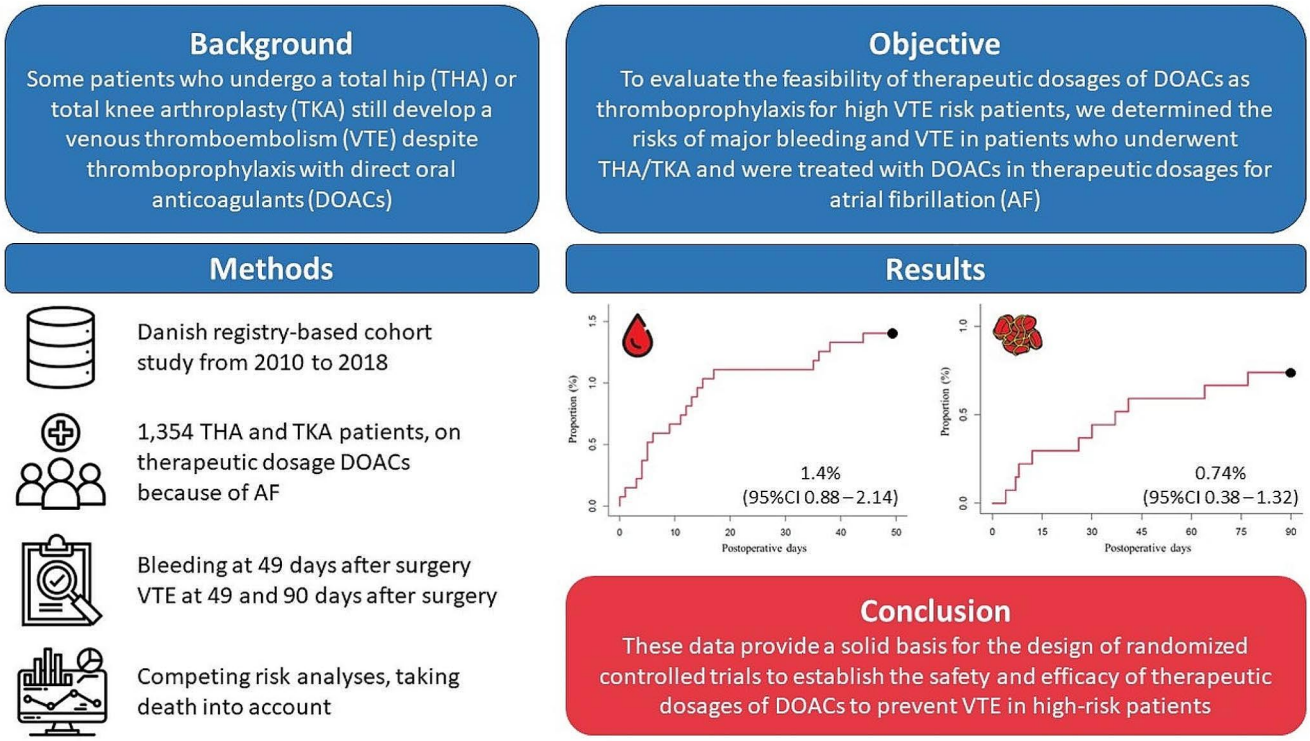
Graphical Abstract



Keywords Arthroplasty, replacement, hip · Arthroplasty, replacement, knee · Factor xa inhibitors · Hemorrhage · Venous thromboembolism

Introduction

On the population level, the incidence of venous thromboembolism (VTE) is still around 1.5% within the first 90-days following Total Hip (THA) and Total Knee Arthroplasty (TKA) despite thromboprophylaxis [1–5]. There are both low-risk patients (eligible for fast-track surgery) for whom the VTE risk is around 0.4% and high-risk patients who develop VTE despite the current "one-size-fits-all" thromboprophylaxis strategy [6, 7]. Hence, to optimize thromboprophylaxis and decrease the incidence of VTE as much as possible, we might need to step away from a universal preventive strategy and move towards personalized treatment. This can be done by distinguishing the low- from the high-risk patients and adapt the dose and/or duration of thromboprophylaxis accordingly [8, 9].

While fast-track treatment protocols seem very efficient in low-risk patients it is unknown how VTE can be prevented in high-risk patients. On a population level it has been studied whether extended thromboprophylaxis (up to 35 days), in all patients, reduces the incidence of VTE, as compared to standard duration prophylaxis (6–27 days), but results are conflicting [1, 2, 10]. Increasing the dosage of thromboprophylaxis might be the other logical intensified preventive strategy. To date, such an approach has not explicitly been studied, though in previous dose-ranging studies for Direct Oral Anticoagulants (DOACs), a dose-response relationship for preventing VTE was observed, which coincided with an increased risk of bleeding [11–17]. Yet, treatment was never continued after 2 weeks, while the VTE risk after THA and TKA is increased up to 90-days [4, 18, 19].

To prevent VTE in high-risk patients, we hypothesize that extended thromboprophylaxis for 6 weeks with therapeutic dosages (e.g., similar dose as administered to patients with atrial fibrillation [AF]) of anticoagulants might be an effective strategy. However, before exposing a large number of patients to such a strategy in a clinical trial, which could potentially increase the risk of bleeding, an indication of the size of the induced bleeding risk is necessary. Therefore, the aim of this study was to describe the risks of major bleeding and VTE in THA and TKA patients with extended duration therapeutic dosages of DOACs in a nationwide population study.

Methods

Study design

We conducted a cohort study by linking the Danish Hip and Knee Arthroplasty Registries to the Danish National Patient Registry and the Danish National Prescription Registry, all with known high completeness and validity of data [20–24]. The Danish Civil Registration System (CRS) assigns a unique personal identifier to all Danish residents, enabling linkage of data from numerous nationwide medical registries on an individual level and tracking of vital status and migration [25]. Danish residents have access to universal tax-supported healthcare system [26].

Study population

All primary, elective THA/TKA procedures for osteoarthritis from 2010 to 2018 were included. Since therapeutic dosage of thromboprophylaxis is not routinely administrated following THA/TKA, we used patients with AF as a proxy because they are chronically treated with anticoagulants. Hence, included patients had to have a diagnosis of AF and filled a prescription for DOACs matching therapeutic dosages (apixaban 5 mg, rivaroxaban 20 mg, dabigatran 150 mg, and edoxaban 60 mg), within 6 months preceding THA/TKA. To verify the assumption that these patients would also use DOACs in therapeutic dosages following the arthroplasty procedure, we assessed what percentage of included patients filled a prescription within the first 6 months postoperatively.

Exclusion criteria were: (1) filled prescription of Low Molecular Weight Heparin (LMWH) or Vitamin K antagonist within 6 months preceding THA/TKA, (2) another THA/TKA procedure within the previous year to ensure that any elevated VTE risk due to a previous THA/TKA had been removed.

Covariates

Age and sex were obtained from the CRS. A 5-year lookback period was utilized to assess comorbidities and calculate the Charlson Comorbidity Index (CCI) [27]. We further collected information on antiplatelet (aspirin, clopidogrel, prasugrel and ticagrelor) and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) use within 6 months before THA/TKA. Diagnoses were identified by ICD-coding while medication was identified by ATC-coding.

Outcome variables

The primary outcome was major bleeding at 49-days (7-weeks) postoperatively. This was chosen as endpoint to mimic a situation in which patients would be treated with therapeutic dosages of DOACs for 6 weeks following surgery. We extended follow-up by one more week to include events of patients who were admitted to the hospital with a delay. Bleeding was identified by hospital contacts for procedure/surgical site bleeding (including bleedings related to any medical procedure), intracranial bleeding, gastrointestinal bleeding, urinary bleeding, and bleeding of the airways. The secondary outcome was in-hospital or outpatient visit for symptomatic VTE within 49-days and 90-days. Follow-up for VTE was extended till 90-days as previous studies have shown that the risk is increased for this period [4, 18, 19].

Statistical analysis

Cumulative incidences of major bleeding and VTE separately were estimated with death as competing risk using the Aalen-Johansen estimator [28]. Follow-up time was calculated from the THA/TKA date until the end of study, death, major bleeding or VTE, or loss to follow-up, whichever occurred first. Revisions and other procedures after THA/TKA were not censored as censoring would violate the uninformative censoring assumption.

Due to Danish statutory privacy restrictions, we are not allowed to publish statistics that represent fewer than 5 patients.

Results

1,354 THA and TKA procedure were included (Fig. 1). Baseline characteristics are reported in Table 1. 95% of included patients filled a prescription for DOACs in therapeutic dosages in the first 6 months postoperatively. The cumulative incidence of major bleeding at 49-days was 1.40% (95%CI 0.88–2.14%) (Fig. 2a). 68% of bleedings occurred at the surgical site and the remaining 32% were either gastrointestinal or airway bleedings. The cumulative incidence of VTE was 0.59% (95%CI 0.28–1.13%) and 0.74% (95%CI 0.38–1.32%) at 49- and 90-days, respectively (Fig. 2b). Approximately 60% of VTE events were deep vein thrombosis and 40% pulmonary embolism.

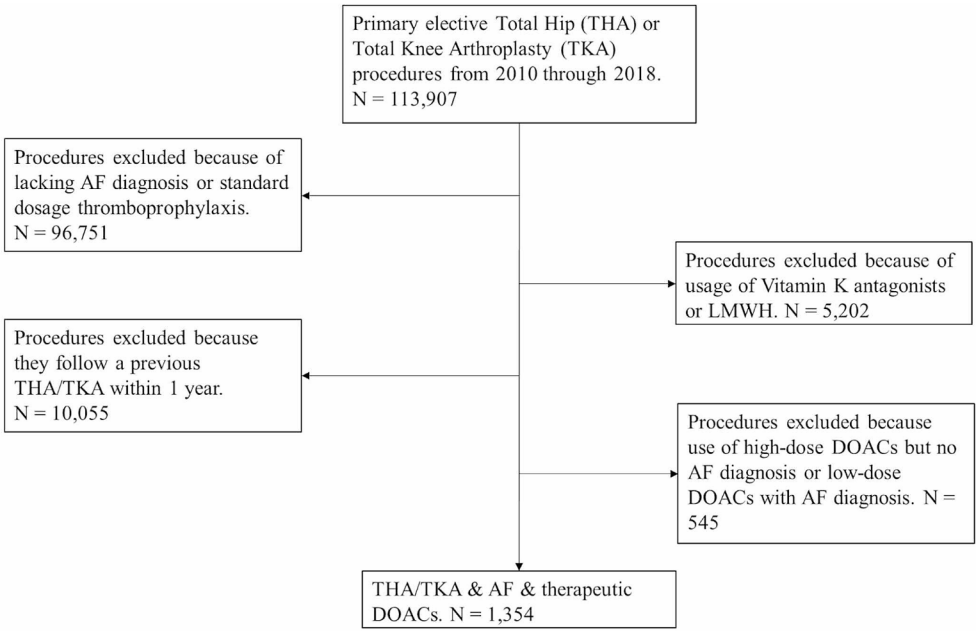


Fig. 1 Flowchart of patient inclusion. AF: Atrial Fibrillation, LMWH: Low-Molecular-Weight Heparin, DOACs: Direct Oral Anticoagulants

Table 1 General characteristics

Total procedures, *n*	1,354
Unique patients, n	1,297
Age, n (%)	
<65 years	144 (11)
65–75 years	724 (53)
>75 years	486 (36)
Female, n (%)	638 (47)
THA, n (%)	816 (60)
CCI score, n (%)	
0	699 (52)
1	340 (25)
2	173 (13)
3+	142 (10)
Hypertension, n (%)	661 (49)
History of bleeding, n (%)	116 (8.6)
History of VTE, n (%)	49 (3.6)
History of kidney/liver disease, n (%)	29 (2.1)
Apixaban[a], n (%)	425 (31)
Rivaroxaban[a], n (%)	435 (32)
Dabigatran[a], n (%)	483 (36)
Edoxaban[a], n (%)	11 (0.8)
Antiplatelet drugs, n (%)	116 (8.6)
Aspirin, n (%)	100 (7.4)
Clopidogrel, n (%)	23 (1.7)
Prasugrel, n (%)	0
Ticagrelor, n (%)	< 5 (< 0.5)[b]
NSAIDs, n (%)	335 (25)

Hypertension, history of bleeding and history of VTE within the 5 years preceding index data. Antiplatelet drugs and NSAIDs within the 6 months preceding index date. [a] DOACs in therapeutic dosage. [b] Numbers smaller than 5 needed to be masked due to privacy regulations by Statistics Denmark. CCI: Charlson Comorbidity Index, NSAID: Nonsteroidal anti-inflammatory drugs

Discussion

We found that the incidence of major bleeding in AF patients on therapeutic dosages of DOACs was 1.40% at 49-days following THA/TKA surgery and mainly consisted of surgical site bleedings. In the same population the risk of VTE was 0.74% at 90-days postoperatively.

Between 2004 and 2014, there have been 11 studies published on dose-ranging of DOACs as thromboprophylaxis for patients undergoing THA or TKA [11–17, 29, 30]. Some of these studies on apixaban, dabigatran and rivaroxaban found a dose-response relationship for both bleeding incidence (increase) as well as VTE incidence (decrease) with higher dosages [11, 13, 15]. Others, on rivaroxaban only, found a dose-response relationship for bleeding while the incidence of VTE was similar over all dosages [12, 16, 29]. Lastly, there are also studies on edoxaban and dabigatran that found a dose-response relationship for VTE incidence while the incidence of bleeding was similar across dosages [14, 17, 30]. These results show a varying pattern of harm and benefit of therapeutic dosages of DOACs as thromboprophylaxis. Possible explanations for this could be the patient selection in the different trials (with inclusion of low VTE risk patients) or random variation due to low sample sizes. Our findings add to these results by presenting the harms and benefits in a large nationwide population setting.

Two previous studies have estimated the risk of (major) bleeding in AF patients undergoing THA/TKA surgery but only one can be compared to our study, as it reports an absolute risk [31, 32]. This risk of major bleeding, during hospitalization, was approximately 0.3% while the risk of VTE was 1.9% [32]. This study was however limited

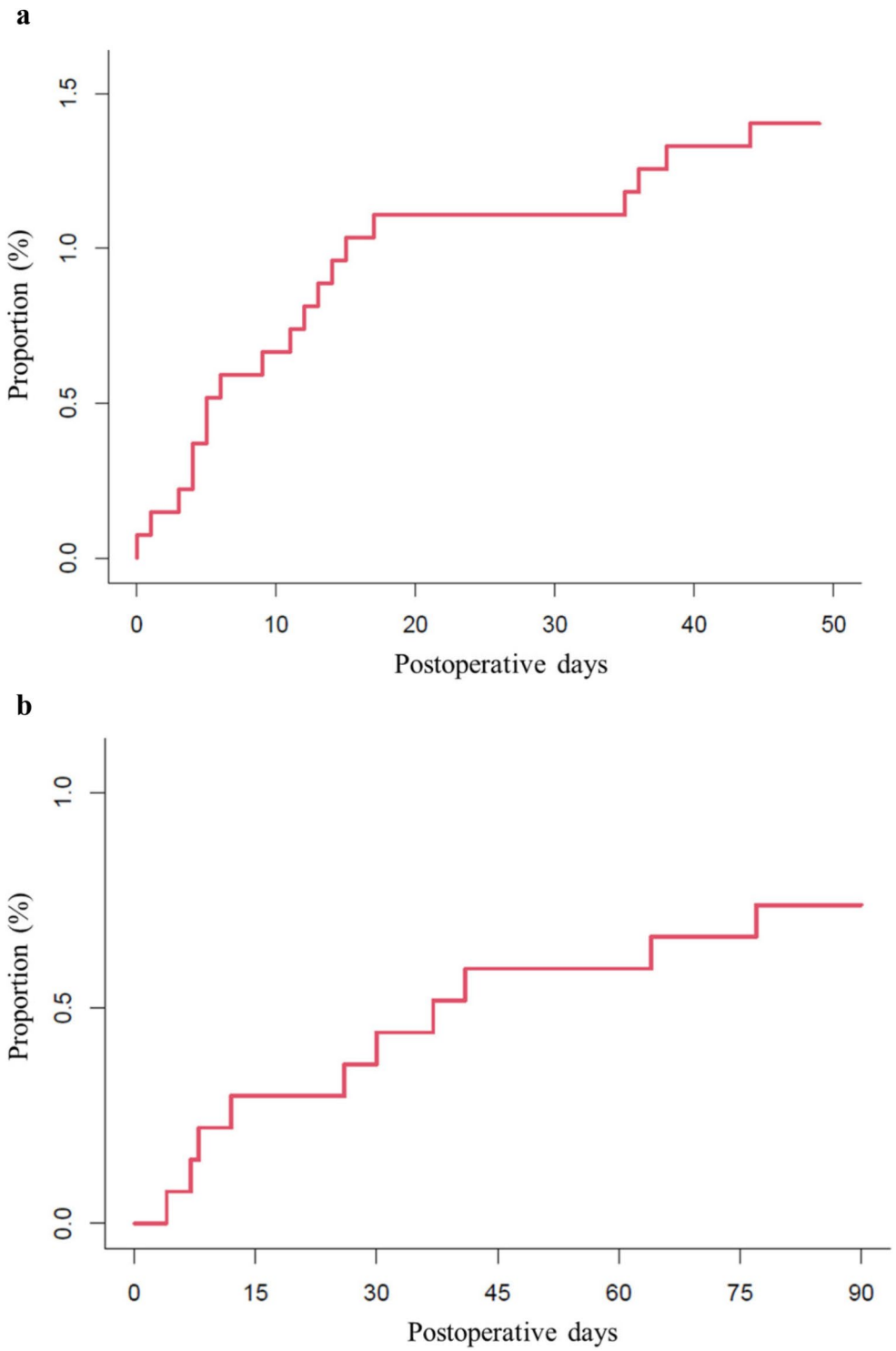


Fig. 2 **a** Cumulative incidence curve for major bleeding within 49-days & **b** Cumulative incidence curve for VTE within 90-days

to neurological and gastrointestinal bleedings only and bleeding events occurring after initial hospitalization were not included [32]. Furthermore, the authors did not report which type of anticoagulation patients were using [32]. In other studies, assessing (major) bleeding in all patients on prophylactic dosages of DOACs following THA or TKA, the incidence was found to be between 0.8% and 1.7%, which is similar to the incidence found in the present study [33–36]. Lastly, several studies have estimated the risk of symptomatic VTE in THA/TKA patients using prophylactic dosages of DOACs [35–38]. They found the risk of VTE to be between 0.4 and 3.0%, depending on the type of DOAC and the follow-up time.

Strengths of our study are the availability of well-established and complete Danish registry data and use of competing risk method. We have restricted the population to patients which had filled a prescription of DOACs in therapeutic dosages within 6 months before surgery increasing the likelihood that patients continued to take their DOACs after THA or TKA.

Although we used national registries, we still had relatively low numbers of THA/TKAs resulting in uncertainty of risk estimates. Lastly, the generalizability of major bleeding and VTE incidences in AF patients to future patients undergoing TKA/THA at a high risk of VTE is unknown. Nevertheless, AF patients are a selected, more comorbid, subgroup of the entire population of patients undergoing THA or TKA surgery. Because of their comorbidity, we expect their risks of major bleeding and VTE to be higher compared to the average THA/TKA patients and therefore, possibly, similar to the high VTE risk patients.

In summary, the risks of major bleeding in our study were similar compared to published studies of patients on prophylactic dosages of DOACs and bleedings mainly occurred at the surgical site. Furthermore, the point estimate of the risk of VTE was relatively low compared to previous literature. Hence, we conclude that further assessment of the benefit and harm of therapeutic dosages of DOACs, as thromboprophylaxis for 6 weeks in patients at high risk of developing VTE following THA/TKA in a RCT is likely to be sufficiently safe and feasible.

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Author contributions M. J. R. Smeets designed the study, analyzed the data and wrote the manuscript. E. B. Kristiansen constructed the dataset, contributed to the study design, analyses, interpretation of the results and revision of the manuscript. B. Nemeth, S. C. Cannegieter and A. B. Pedersen contributed to the study design, analyses, interpretation of the results and revision of the manuscript. M. V. Huisman contributed to the interpretation of the results and revision of the manuscript.

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Declarations

Ethical approval Registry based studies do not require formal ethical approval according to Danish law. The study was reported to the Danish Data Protection Agency through registration at Aarhus University (record number: AU-2016-051-000001, sequential number 880).

Disclosure of potential conflicts of interest The authors have no relevant financial or non-financial interests to disclose.

Competing interests The authors have no relevant financial or non-financial interests to disclose.

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