Association between duration of anticoagulant thromboprophylaxis and revision rate in primary total hip arthroplasty: a Danish and Norwegian nationwide cohort study

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Background and purpose — There are concerns that bleeding following primary total hip arthroplasty (THA) contributes to prolonged wound drainage and prosthetic joint infection (PJI). We examined whether short (1–5 days), medium (6–14 days), and extended (≥ 15 days) duration of thromboprophylaxis is associated with the 5-year revision rate after THA due to osteoarthritis.

Patients and methods — We performed a cohort study based on data from hip arthroplasty and administrative registries in Denmark and Norway (2008–2014). The outcome was revision surgery due to PJI, aseptic loosening or any cause, and patient mortality. Adjusted cause-specific hazard ratios (HRs) were analyzed with Cox regression analyses.

Results — Among 50,482 THA patients, 8,333 received short, 17,009 received medium, and 25,140 received extended thromboprophylaxis. The HRs for revision due to PJI within 5 years were 1.0 (95%CI 0.7–1.3) and 1.1 (CI 0.9–1.3) for short and extended vs. medium treatment, whereas HR for extended vs. medium prophylaxis was 1.5 (CI 1.2–2.0) within 3 months. The HRs for revision due to aseptic loosening within 5 years were 1.0 (CI 0.7–1.4) and 1.1 (CI 0.9–1.4) for short and extended vs. medium treatment. The HRs for any revision within 5 years were 0.9 (CI 0.8–1.1) and 0.9 (CI 0.8–1.0) for short and extended vs. medium treatment. Extended vs. medium prophylaxis was associated with a decreased 0–3 month mortality. The absolute differences at 5 years were ≤ 1%.

Conclusion — Our data suggests no association between duration of anticoagulant thromboprophylaxis and revision rate within 5 years of primary THA. The extended thromboprophylaxis might be associated with early increased revision rate due to PJI but also with lower mortality; however, the clinical relevance of this finding requires further research.

All patients undergoing total hip arthroplasty (THA) are recommended anticoagulant thromboprophylaxis to prevent venous thromboembolism (VTE) (1-3). Recommendations on the duration of thromboprophylaxis are ambiguous. Depending on the guideline used, THA patients are recommended to use thromboembolic prophylaxis for 6–35 days postoperatively, and less than 5 days if fast-track THA surgery is performed (1-5).

Periprosthetic joint infection (PJI) is responsible for 24% of all revisions after THA corresponding to a revision rate of 1–2% of all primary THAs (6,7). The risk of infection has been shown to increase with the use of anticoagulant thromboprophylaxis due to postoperative bleeding and wound drainage (8-10). Both rivaroxaban and warfarin used as anticoagulant thromboprophylaxis have shown increased risk of surgical site infection, and early PJI has been associated with the use of rivaroxaban (10,11). Warfarin is reported to be associated with a higher risk of deep infection and revision compared with aspirin, but not compared with low-molecular-weight heparin (LMWH) (12). No difference has been observed in revision rates due to aseptic loosening when comparing aspirin with warfarin (13). The overall mortality after THA seems to be higher with the use of enoxaparin compared with rivaroxaban, but similar when comparing enoxaparin with dabigatran (14). Short-term anticoagulant thromboprophylaxis after THA has been associated with increased 90-day mortality (15), but no studies have investigated the long-term mortality. The use of non-vitamin K antagonist oral anticoagulants (NOAC) has been associated with slightly lower revision rate due to infection compared with LMWH, but higher revision rates due to aseptic loosening and all-cause revision (16).

We have previously investigated whether various durations of anticoagulant thromboprophylaxis are associated with 90-day

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risk of VTE or major bleeding after THA, showing no clinically relevant difference (15). Another study on major orthopedic surgery patients has reported conflicting results regarding major and minor bleeding compared with our previous study (15,17). No studies have investigated whether the duration of anticoagulant thromboprophylaxis affects revision due to PJI and aseptic loosening. This is important as the clinical decisions regarding the utility of thromboprophylaxis require the simultaneous consideration of both efficacy and safety.

We examined whether short (1–5 days), medium (6–14 days), and extended (≥ 15 days) duration of thromboprophylaxis was associated with the 5-year revision rate due to PJI in patients undergoing elective THA in Denmark and Norway. In addition, we examined risk of revision due to aseptic loosening and due to any cause. In view of general patient safety, long-term mortality was also studied.

Patients and methods

Study design and setting

This multinational, population-level cohort study was conducted using prospectively collected data, available from the Nordic Arthroplasty Register Association (NARA) database. All Danish, Norwegian, Swedish, and Finnish citizens are assigned a unique civil registration number at birth. This allows unambiguous linkage between hip registries and other medical databases in each country, as well as the tracking of deceased or emigrated patients. The study is reported according to the RECORD guidelines.

Study population

Due to individual-level data on anticoagulant thromboprophylaxis, only patients operated on in Denmark and Norway were identified through the NARA database and included in this study.

Inclusion criteria were primary THAs due to primary osteoarthritis (OA) between January 1, 2010 and December 31, 2014 from Denmark (n = 34,625) and between January 1, 2008 and December 31, 2013 from Norway (n = 34,801). This cohort is the same as was used in our previous study on short-term risks with thromboprophylaxis (15).

As in the previous study, after exclusions, 23,940 patients from Denmark and 26,542 from Norway, a total of 50,482 with 1st-time unilateral THA due to primary OA, were available for the complete-case analysis. For details on patient exclusions see Pedersen et al. (15).

The data in the Danish Hip Arthroplasty Registry and Norwegian Arthroplasty Register is documented to have a completeness higher than 95% for primary arthroplasties and around 85–93% for revisions (18,19). In addition, the accuracy of OA diagnosis in the Danish Hip Arthroplasty Registry and Norwegian Arthroplasty Register is more than 95% (19,20). Further, the completeness and accuracy of antithrombotic treatment in the Danish Hip Arthroplasty Registry is 99% and 78%, respectively (21). The accuracy of duration of thromboprophylaxis treatment has not been evaluated but given the high accuracy of other variables included in Danish and Norwegian arthroplasty registries we have no reason to suspect that opposite is applicable to our exposure.

Duration of anticoagulant thromboprophylaxis

The duration of anticoagulant thromboprophylaxis for each individual patient is registered in the NARA database. The duration is based on the number of days the patient was planned to receive thromboprophylaxis after THA by surgeon, including the planned days of treatment after discharge. The planned duration is based on the recommendations of the clinical practice guidelines for thromboprophylaxis in Denmark and Norway (4,5). Duration of thromboprophylaxis in relation to THA surgery was categorized as short term (1–5 days), medium (6–14 days), or extended (≥ 15 days). The following anticoagulant agents were included: parenteral LMWH (including enoxaparin, dalteparin, and tinzaparin), fondaparinux, and NOACs (dabigatran and rivaroxaban), administered both pre- and postoperatively. Dosage of treatment was not available for this study.

Outcome

The primary outcome was revision due to PJI. The secondary outcomes were THA revision due to aseptic loosening, revision due to any cause, and patient death. Information on revisions was obtained from the NARA database. The causes of revision are registered in NARA based on clinical signs before and during the surgery, and diagnostic work-up. Microbiology results after surgery are not registered in the NARA database (18). The registration of causes of revision in NARA database will not be changed even if positive cultures later change the cause of revision.

The Danish Civil Registration System and Statistics Norway were used to obtain information on death for each patient in the national registries before transferring the data to NARA.

Variables and covariates

Information on comorbidity was collected from the Danish National Patient Registry (DNRP) and the Norwegian Patient Registry (NPR), before transferring data to the NARA database (22,23). All primary and secondary discharge diagnoses for all hospitalizations and hospital outpatient visits occurring 1 year before primary THA were identified for all included THA patients. The Charlson Comorbidity Index (CCI) was then computed for each patient at the time of surgery and patients were classified according to 1 of the 3 comorbidity levels: a score of 0 (low); a score of 1–2 (medium); and a score of ≥ 3 (high).

Information on age (in the categories: 10–59, 60–69, 70–79, and ≥ 80 years), sex, fixation type (cemented, uncemented, and hybrid fixation), as well as the start of thromboprophylaxis

(pre- or postoperative) and length were collected from the NARA database. Furthermore, the Danish National Database of Reimbursed Prescriptions and the Norwegian Prescription Database were used to collect information on the use of acetylsalicylic acid (Anatomical Therapeutic Chemical [ATC] code: N02BA01), low-dose and high-dose vitamin-K antagonists (VKA) (ATC code: B01AA), and platelet inhibitors (clopidogrel, prasugrel, and ticagrelor [ATC code: B01AC04, B01AC22, B01AC24]) 2 years prior to primary THA.

Statistics

Cumulative incidence function was used to compute the 5-year risk of revision due to PJI. Revision due to aseptic loosening and revision due to other causes were included as a competing risk event in analyses of revision due to PJI. Similarly, revision due to aseptic loosening was calculated, with revision due to PJI and revision due to other causes as competing risk. Death was not added as a competing risk for revision based on published recommendations (24). Kaplan–Meier (KM) was used to calculate the risk for any cause of revision and for death. Cox regression was used for the analysis of cause-specific hazard ratios (HRs) adjusted for potential confounding factors with 95% confidence intervals (CIs).

The following variables were included as potential confounders: age, sex, CCI, use of anticoagulant prior to THA, type of fixation, duration of surgery, start of thromboprophylaxis, and type of anticoagulant thromboprophylaxis in relation to THA. Furthermore, stratification was done on the same variables to examine the potential effect modification of these variables on outcome. In addition, country-level stratification was performed. By inspecting Schoenfeld residuals, the Cox proportional hazards models were found to be reasonable to use. We also evaluated the proportional hazards assumptions by calculating HRs for the follow-up time intervals: 0–3 months, 3–6 months, 0.5–1 year, 1–2 years, and 2–5 years (Table 1, see Supplementary data).

Ethics, funding, data sharing, and disclosures

The Norwegian Arthroplasty Register has permission from the Norwegian Data Inspectorate to collect patient data based on written consent from patients (ref. 24.1.2017: 16/1622-3/CDG) and for this study from the Regional Ethical Committee of western Norway (ref. 2015/880/REK Vest). The Danish Data Protection Agency has approved the study (j. nr. 1-16-02-54-17). The study was supported by a grant from Aarhus University Research Foundation. No competing interests were declared. Data sharing is not possible due to existing legislation (18-21).

Table 2. Baseline characteristics of 50,482 patients undergoing primary total hip arthroplasty (THA) in Denmark from 2010–2014 and Norway from 2008–2013 by short (1–5 days), medium (6–14 days), and extended (≥ 15 days) thromboprophylaxis treatment. Values are count (%)

Baseline characteristics	Short	Medium	Extended	Total
Total number	8,333	17,009	25,140	50,482
Age group				
10–59	1,487 (18)	2,790 (16)	3,811 (15)	8,088 (16)
60–69	2,819 (34)	5,646 (33)	8,665 (35)	17,130 (34)
70–79	2,890 (35)	6,129 (36)	8,971 (38)	17,990 (36)
≥ 80	1,137 (14)	2,444 (14)	3,693 (15)	7,274 (14)
Female sex	4,586 (55)	10,326 (61)	15,975 (64)	30,887 (61)
Charlson Comorbidity Index [a]				
Low	7,354 (88)	14,201 (83)	20,586 (82)	42,141 (83)
Medium	864 (10)	2,486 (15)	3,975 (16)	7,325 (15)
High	115 (2)	322 (2)	579 (2)	1,016 (2)
Used before surgery				
Acetylsalicylic acid	1,739 (21)	3,901 (23)	5,938 (24)	11,578 (23)
Antiplatelet drugs [b]	226 (3)	374 (2)	413 (2)	1,103 (2)
Anticoagulants [c]	634 (8)	1,245 (7)	1,170 (5)	3,049 (6)
Type of fixation [d]				
Missing data	16 (0)	178 (1)	343 (1)	537 (1)
Cemented	481 (6)	5,164 (30)	8,971 (36)	14,616 (29)
Uncemented	5,934 (71)	8,625 (51)	9,123 (36)	23,682 (47)
Hybrid A	1,691 (20)	855 (5)	774 (3)	3,320 (7)
Hybrid B	211 (3)	2,187 (13)	5,929 (24)	8,327 (16)
Anticoagulant thromboprophylaxis at THA				
Start				
Missing data	51 (1)	555 (3)	1,866 (7)	2,472 (5)
Preoperative	2,677 (32)	4,892 (29)	6,334 (25)	13,903 (27)
Postoperative	5,605 (67)	11,562 (68)	16,940 (67)	34,107 (68)
Type				
Dabigatran	86 (1)	830 (5)	3,277 (13)	4,193 (8)
Dalteparin	1,962 (24)	8,177 (48)	13,299 (53)	23,438 (48)
Enoxaparin	1,259 (15)	4,859 (29)	4,460 (18)	10,578 (21)
Fondaparinux	865 (10)	465 (3)	53 (1)	1,383 (3)
Rivaroxaban	3,663 (44)	1,040 (6)	3,904 (16)	8,607 (17)
Tinzaparin	476 (5.7)	1,568 (9)	16 (1)	2,060 (4)
Other	22 (1)	70 (1)	131 (1)	223 (1)

[a] After tabulating CCI by exposure the number of patients in some exposure groups was < 5, and thus details cannot be given due to ethics constrain. These patients were for the table purpose moved into "low" CCI group.
[b] Clopidogrel, prasugrel, ticagrelor.
[c] Warfarin, marcoumar, dagigratran, apixaban, rivaroxaban.
[d] Hybrid A = cemented stem, Hybrid B = uncemented stem.

Results

Description of the study population

Approximately 15% of THA patients received thromboprophylaxis for a short period, 31% for medium, and 45% for an extended period (Table 2). Data regarding the duration of thromboprophylaxis was missing in 9% of the patients and these were excluded from the complete-case analysis. These patients' characteristics (age, sex, CCI) were similar to the characteristics of patients included in the study population (data not shown).

Patients in the short-duration group were slightly younger, included fewer females, had lower CCI scores, and had lower

Table 3. Effect of thromboprophylaxis treatment duration on the risk of revision due to prosthetic joint infection (PJI), revision due to aseptic loosening, all-cause revision, and death in total hip arthroplasty (THA) patients within 5 years of surgery, with medium-duration treatment as a reference. Values are count, hazard ratio (HR) and cumulative incidence percentage with 95% confidence intervals

Outcome Duration of thromboprophylaxis	Events	Number at risk	Crude HR	Adjusted HR [a]	Cumulative incidence
Revision due to PJI					
Short	68	8,333	0.8 (0.6–1.0)	1.0 (0.7–1.3)	0.9 (0.7–1.1)
Medium	180	17,009	Reference	Reference	1.1 (0.9–1.3)
Extended	281	25,140	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.2 (1.0–1.3)
Revision due to aseptic loosening					
Short	50	8,333	1.0 (0.7–1.4)	1.0 (0.7–1.4)	0.7 (0.5–0.9)
Medium	116	17,009	Reference	Reference	0.8 (0.7–1.0)
Extended	225	25,140	1.3 (1.1–1.7)	1.1 (0.9–1.4)	1.1 (0.9–1.2)
All-cause revision					
Short	317	8,333	1.0 (0.9–1.2)	1.0 (0.7–1.3)	4.3 (3.8–4.9) [b]
Medium	677	17,009	Reference	Reference	4.4 (4.0–4.8) [b]
Extended	924	25,140	0.9 (0.8–1.0)	0.9 (0.8–1.0)	4.0 (3.8–4.4) [b]
Death					
Short	506	8,333	1.0 (0.9–1.1)	0.9 (0.8–1.1)	8.8 (8.0–9.6) [b]
Medium	1,253	17,009	Reference	Reference	9.0 (8.5–9.5) [b]
Extended	1,620	25,140	0.9 (0.8–1.0)	0.9 (0.8–0.9)	8.0 (7.7–8.4) [b]

[a] Adjusted HR was adjusted for: age, sex, Charlson Comorbidity Index, type of fixation, regular use of acetylsalicylic acid, clopidogrel/prasugrel/ticagrelor, warfarin/marcumar/dabigatran/apixaban/rivaroxaban before THA, start of anticoagulant thromboprophylaxis in relation to THA, type of anticoagulant thromboprophylaxis drug used in relation to THA (LMWH-group (dalteparin, enoxaparin, tinzaparin)/NOAC-group (dabigatran, rivaroxaban)/Other-group (other, fondaparinux)).
[b] 1–KM survival (95% CI).

acetylsalicylic acid use, but were more often prescribed VKA and platelet inhibitors than patients in the medium-duration group. Patients in the extended-duration group were also slightly younger, included more females, had higher CCI scores, and fewer had VKA and platelet inhibitors prescribed than patients in the medium-duration group. A larger proportion of patients in the short-duration group received NOACs, whereas LWMH was more often prescribed in the medium- and extended-duration group. A larger proportion in the extended-duration group received dabigatran compared with the short- and medium-duration group. A more detailed description of characteristics can be found in our previous study (15).

Revision due to PJI

The cumulative incidences for revision due to PJI are presented in Table 3 and Figure 1. The adjusted HRs for revision due to PJI within 5 years were 1.0 (CI 0.7–1.3) for short and 1.1 (CI 0.9–1.3) for extended thromboprophylaxis vs. medium thromboprophylaxis (Table 3).

However, the adjusted HRs for revision due to PJI within 3 months were 1.0 (CI 0.7–1.5) and 1.5 (CI 1.2–2.0) for short and extended vs. medium thromboprophylaxis. The risk of revision due to PJI was not increased beyond the first 3 months (Table 1, see Supplementary data).

Revision due to aseptic loosening

The cumulative incidences for revision due to aseptic loosening are presented in Table 3 and Figure 2. The HRs within 0–5 years were 1.0 (CI 0.7–1.4) for the short-duration and 1.1 (CI 0.9–1.4) for the extended-duration when compared with the medium-duration group (Table 3). The follow-up time-intervals' specific HR estimates were similar to those for 0–5 years (Table 1, see Supplementary data).

All-cause revision

The 1-KM estimates for all-cause revision are presented in Table 3 and Figure 3. The HRs within 5 years were 0.9 (CI 0.8–1.1) for the short-duration and 0.9 (CI 0.8–1.0) for the extended-duration when compared with the medium-duration treatment group (Table 3). The follow-up time-intervals' specific HR estimates were similar to those of 0–5 years, except that HR was 0.5 (CI 0.3–0.8) in the time interval 3–6 months for extended vs. medium duration (Table 1, see Supplementary data).

Death

The 1–KM estimates for death are presented in Table 3 and Figure 4. The HRs for death within 5 years were 0.9 (CI 0.8–1.0) for the short-duration and 0.9 (CI 0.8–0.9) for the extended-duration when compared with the medium-duration treatment group (Table 3). The adjusted HRs for death within 3 months were 1.0 (CI 0.6–1.5) and 0.7 (CI 0.5–1.0) for short and extended vs. medium thromboprophylaxis. Some, but not all, subsequent follow-up time-intervals' specific HR estimates for death indicate a trend towards lower mortality for extended vs. medium thromboprophylaxis (Table 1, see Supplementary data).

At all endpoints, the absolute differences in cumulative incidences were less than 1% after 5 years.

Stratified analyses

The country-specific HRs (Table 4, see Supplementary data) did not differ from the overall HRs. The same applies to analyses stratified on age, sex, CCI, fixation, and start of thromboprophylaxis (data not shown). Statistical precision of HRs from the stratified analyses was low, expressed by wide CI and a low number of outcomes.

Discussion

We found no difference in revision rate due to PJI, aseptic loosening, all-cause revision, or death within 5 years, with

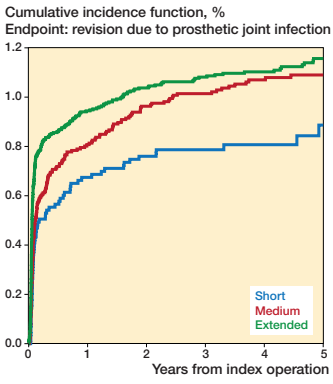

Figure 1. Cumulative incidences for revision due to periprosthetic joint infection in total hip arthroplasty patients within 5 years of surgery with other causes of revision as competing risk.

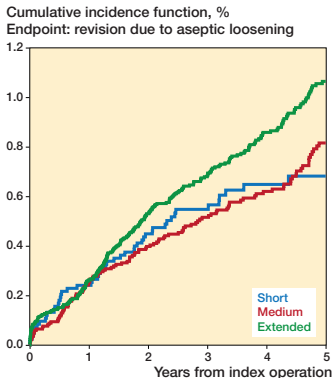

Figure 2. Cumulative incidences for revision due to aseptic loosening in total hip arthroplasty patients within 5 years of surgery with other causes of revision as competing risk.

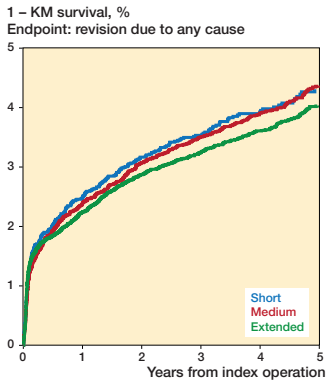

Figure 3. Cumulative revision rate (1 – KM revision-free survival) for revision due to all causes in total hip arthroplasty patients within 5 years of surgery.

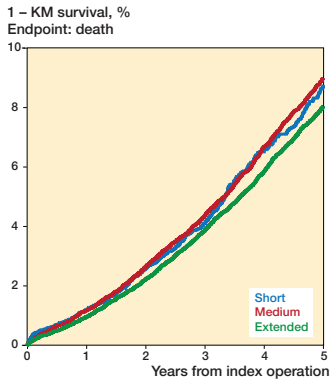

Figure 4. Cumulative mortality rate (1 – KM survival) in total hip arthroplasty patients within 5 years of surgery.

respect to the duration of thromboprophylaxis among THA patients. There was an indication that extended prophylaxis was associated with increased risk of revision due to PJI but lower mortality within 3 months compared with medium prophylaxis, which requires further research.

The risk of surgically relevant complications such as revision surgery due to duration of thromboprophylaxis has not been evaluated previously. Several studies have suggested that specific anticoagulants, such as rivaroxaban and LWMH, have an impact on development of infection after hip or knee arthroplasty (**9,10**). In these studies, rivaroxaban was administered for more than 14 days or for 28–35 days in accordance with the NICE guidelines. Bleeding and hematoma formation can result in prolonged wound drainage, which may predispose to infections. A Cochrane systematic review on randomized control trials concluded that extended duration of anticoagulants was associated with increased risk of minor bleeding after hip or knee arthroplasty (**25**). This observation was further supported by studies on medical patients with or without cancer, showing that extended duration of thromboprophylaxis with apixaban, enoxaparin, and rivaroxaban increases the risk of major bleeding (**26**). In line with this, the extended-duration group in our study had a larger proportion of NOAC users than the medium-duration group, but not all studies have reported increased risk of bleeding with extended anticoagulant treatment (**15**). However, in our previous study surgical bleeding and hematoma formation around the joint were not studied, in terms of either risk of reoperation or revision arthroplasty due to infection. Our present finding of an association between extended duration of thromboprophylaxis and the early risk of revision due to PJI is consistent with previous reports that bleeding might lead to prolonged wound drainage and development of infections that require revision (**8-10**).

Previous studies in unselected patients from routine clinical practice showed no difference in the 90-day risk of death with respect to duration of thromboprophylaxis (**15,27**); point estimates were below 1, but not statistically significant. Our study indicates that compared with patients receiving prophylaxis for 6–14 days, extended duration was a predictor of slightly lower early mortality. The difference between the studies is that in our study we have adjusted for type of anticoagulant drug used in relation to THA, which was not the case in previous studies. Lower mortality in extended-prophylaxis groups could also be due to residual confounding and selection bias. Nevertheless, the benefits of treatment (lower mortality for extended duration of treatment) should be weighed against safety of treatment (increased PJI risk for extended treatment) and surgery performed in fast-track settings (**28**).

With differences in revision and mortality rate of less than 1% after 5 years, clinicians should continue to follow current national and local guidelines, but with increased focus on early devastating complications such as PJI.

Strengths and weaknesses

A study based on databases is only as accurate as the data submitted to the specific databases. Our study consists of quality data with high completeness from well-established databases (**18-21**). The relatively low incidence of PJI requires large numbers of patients/events to obtain appropriate statistical power, making the use of large databases optimal. However, the definition of infection might vary between surgeons, hospitals, and countries, and is often based on pre- and intraoperative findings. In addition, the results of tissue sampling with intraoperative cultures are usually not available at the time when registration of revision cause is reported to arthroplasty registries. This will lead to misclassification of PJI diagnosis. Gundtoft et al. found that the "true" incidence of PJI after primary THA might be as much as 40% higher when looking at several registries as opposed to the national registries alone (**18**). Thus, misclassification of revision due to PJI exists, but it is most likely not related to exposure in our study due to prospective registration of data.

The selection bias in our study is low because all THA patients treated were included, regardless of department, specific patient characteristics, or willingness to participate in the study. It is unlikely that the missing data on duration of treatment occurred systematically as data on duration of treatment and subsequent outcomes of interest was prospectively collected. Even though patients have received anticoagulant drugs (pills) from the hospital or through prescription, we cannot be sure about the patients' compliance with treatment. Theoretically, if patients' compliance with planned treatment is low, which would be most alarming for patients in the extended-treatment group, then this change could have affected our results in any direction. However, 1 previous study has shown that adherence to treatment prescribed by general practitioners in Denmark is more than 90% (29). Further, even though the patient potentially could switch from one to another exposure group because planned duration of treatment has changed for various reasons, we have analyzed our data following the intention-to-treat principle, similar to the principle used in randomized trials. Thus, the patient stayed in a specific exposure group planned at the time of surgery.

As we assume that orthopedic surgeons are familiar with and follow the general guidelines on anticoagulation treatment of medical patients, THA patients are likely to receive different duration of treatment depending on their individual risk. Thus, high-risk patients with a history of VTE or cancer will more likely receive extended prophylaxis. However, we do not have specific information as to whether this is true or not for patients with a history of VTE or cancer, but we have partly adjusted for this with CCI. Off-label use of NOACs could be explained by increasing use of fast-track THA surgery in both countries and a national guideline recommending NOACs only during hospitalization, which is less than 5 days (28).

Although we adjusted for several potential confounders, other factors might have an impact on our results. Newer studies suggest that socioeconomic status might affect revision after THA (30). Data was not available on smoking, which is shown to increase the overall revision rate, risk of aseptic loosening, and PJI (31). However, it is questionable whether these factors are true confounders, because they also relate to selected exposure. Lastly, we did not consider the body mass index (BMI) of patients, despite BMI being a significant risk factor for PJI (32). It is possible that BMI is a confounder if the dose and duration of thromboprophylaxis is modified in patients with high BMI.

In conclusion, in this large cohort study including 50,482 THA patients from Denmark and Norway, there was no association between the duration of pharmacological thromboprophylaxis and a clinically relevant rate of revision due to PJI, aseptic loosening, revision of any cause, or death within 5 years of THA. However, there is an indication that extended thromboprophylaxis is associated with increased revision rate due to PJI but lower mortality within 3 months of THA. The absolute differences in cumulative incidences after 5 years were all < 1%.

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Supplementary data

Table 1. Adjusted hazard ratios (aHR) at different follow-up periods for revision due to prosthetic joint infection (PJI), revision due to aseptic loosening, all-cause revision, and death

Outcome / Duration of thromboprophylaxis	0–3 months Events	0–3 months aHR [a] (CI)	3–6 months Events	3–6 months aHR [a] (CI)	0.5–1 year Events	0.5–1 year aHR [a] (CI)	1–2 years Events	1–2 years aHR [a] (CI)	2–5 years Events	2–5 years aHR [a] (CI)
Revision due to PJI										
Short	42	1.0 (0.7–1.5)	5	0.6 (0.2–1.7)	9	1.4 (0.6–3.5)	7	0.6 (0.2–1.5)	5	1.1 (0.4–3.1)
Medium	104	Reference	18	Reference	15	Reference	26	Reference	17	Reference
Extended	207	1.5 (1.2–2.0)	9	0.3 (0.1–0.7)	21	0.9 (0.5–2.0)	23	0.5 (0.3–0.9)	21	1.0 (0.5–2.0)
Revision due to aseptic loosening										
Short	8	1.0 (0.4–2.8)	7	3.5 (1.0–12.0)	5	0.4 (0.2–1.2)	17	1.3 (0.6–2.5)	13	0.9 (0.5–1.7)
Medium	13	Reference	6	Reference	24	Reference	24	Reference	49	Reference
Extended	31	1.4 (0.7–3.0)	7	0.9 (0.3–2.8)	28	0.7 (0.4–1.2)	66	1.5 (0.9–2.5)	93	1.1 (0.8–1.6)
All-cause revision										
Short	142	1.0 (0.8–1.3)	27	0.7 (0.4–1.2)	37	0.9 (0.6–1.4)	56	1.0 (0.7–1.4)	55	0.9 (0.6–1.3)
Medium	270	Reference	58	Reference	79	Reference	112	Reference	158	Reference
Extended	417	1.1 (0.9–1.3)	46	0.5 (0.3–0.8)	100	0.8 (0.6–1.1)	155	0.9 (0.7–1.1)	206	0.9 (0.7–1.1)
Death										
Short	43	1.0 (0.6–1.5)	15	0.6 (0.3–1.2)	41	1.0 (0.7–1.5)	116	0.8 (0.6–1.0)	291	0.9 (0.8–1.1)
Medium	68	Reference	41	Reference	89	Reference	250	Reference	805	Reference
Extended	79	0.7 (0.5–1.0)	44	0.7 (0.5–1.2)	117	1.0 (0.7–1.3)	316	0.8 (0.7–1.0)	1,064	0.9 (0.8–1.0)

[a] Adjusted HR with 95% confidence intervals (CI), see footnote Table 3.

Table 4. Country specific stratified data on revision due to prosthetic joint infection (PJI), revision due to aseptic loosening, all-cause revision, and death within 5 years of surgery with medium-duration treatment as reference

Outcome	Duration of thromboprophylaxis	Adjusted HR [a] (CI) Denmark	Adjusted HR [a] (CI) Norway
Revision due to PJI	Short	1.2 (0.8–1.8)	0.5 (0.1–1.5)
	Extended	1.5 (0.9–2.3)	0.9 (0.7–1.1)
Revision due to aseptic loosening	Short	1.0 (0.6–1.5)	1.9 (0.7–5.4)
	Extended	1.3 (0.9–2.1)	1.3 (0.9–1.8)
All-cause revision	Short	1.0 (0.9–1.2)	0.7 (0.4–1.4)
	Extended	1.1 (0.9–1.4)	0.8 (0.7–1.0)
Death	Short	0.9 (0.8–1.0)	0.7 (0.5–1.1)
	Extended	1.0 (0.9–1.2)	0.9 (0.8–1.0)

[a] Adjusted HR with 95% confidence intervals (CI), see footnote Table 3.