Association of perioperative thromboprophylaxis on revision rate due to infection and aseptic loosening in primary total hip arthroplasty – new evidence from the Nordic Arthroplasty Registry Association (NARA)

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Background and purpose — Results regarding the impact of anticoagulants on revision rate are conflicting. We examined the association between the use of low molecular weight heparin (LMWH) or non-vitamin K oral anticoagulants (NOACs) as thromboprophylaxis after primary total hip arthroplasty (THA) and the revision rate due to infection, aseptic loosening, and all causes.

Patients and methods — We conducted a cohort study (n = 53,605) based on prospectively collected data from the national hip arthroplasty registries from Denmark and Norway. The outcome was time to revision due to infection, aseptic loosening, and all causes, studied separately. Kaplan–Meier (KM) survival analysis and a Cox proportional hazard model was used to estimate implant survival and cause-specific hazard ratios (HRs) with 95% confidence intervals (CI) adjusting for age, sex, Charlson Comorbidity Index, fixation type, start, and duration of thromboprophylaxis, and preoperative use of Vitamin K antagonists, NOAC, aspirin, and platelet inhibitors as confounders.

Results — We included 40,451 patients in the LMWH group and 13,154 patients in the NOAC group. Regarding revision due to infection, the 1-year and 5-year KM survival was 99% in both the LMWH group and in the NOAC group. During the entire follow-up period, the adjusted HR for revision due to infection was 0.9 (CI 0.7–1.1), 1.6 (CI 1.3–2.1) for aseptic loosening, and 1.2 (CI 1.1–1.4) for all-cause revision for the NOAC compared with the LMWH group. The absolute differences in revision rates between the groups varied from 0.2% to 1%.

Interpretation — Compared with LMWH, NOACs were associated with a slightly lower revision rate due to infection, but higher revisions rates due to aseptic loosening and all-cause revision. The absolute differences between groups are small and most likely not clinically relevant. In addition, the observed associations might partly be explained by selection bias and unmeasured confounding, and should be a topic for further research.

Anticoagulant thromboprophylaxis is recommended to all total hip arthroplasty (THA) patients according to current guidelines (1,2). However, some studies suggest that anticoagulants may play an important role in the risk of developing infection (3,4). The possible mechanism may be due to anticoagulants' contribution to a greater risk of bleeding-related complications such as oozing, hematoma, and wound drainage (5), which may enhance prolonged healing, bacterial virulence, and subsequently the development of infection (3,6,7).

Subcutaneous low-molecular weight heparin (LMWH) and non-vitamin K antagonist oral anticoagulants (NOACs) are the recommended anticoagulant thromboprophylactic agents in Norway and Denmark (8). LMWH has been associated with higher rates of bleeding-related complications, including wound infections and revisions (5,9,10), but sufficient evidence is currently missing regarding the use of NOACs as thromboprophylaxis for THA patients. Some studies reported that rivaroxaban is associated with a higher wound compli-

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cation rate following lower limb arthroplasty surgery (11) and with higher risk of early deep postoperative surgical site infections after THA and total knee arthroplasty (4). Current observational studies are limited by short observation time, small study populations, and varying definition of infection (5,6,12,13). Thus, it remains unresolved as to whether NOACs increase the risk of infection and subsequent revision surgery compared with LMWH.

Therefore, we performed a population-based prospective cohort study based on the Nordic Arthroplasty Register Association (NARA) database with the primary aim of examining the association between the use of NOACs compared with LMWH in patients undergoing primary THA and the revision rate due to infection. Our secondary aim was to examine the association between NOAC versus LMWH and the revision rate due to aseptic loosening of the prosthesis and the overall revision rate.

Patients and methods

Study design and setting

This population-based cohort study was conducted using prospectively collected data available from the NARA database (14). All Danish and Norwegian citizens are assigned a unique identification number permitting unambiguous linkage between the Danish National Patient Registry and the Norwegian Patient Registry along with the Danish National Database of Reimbursed Prescriptions and the Norwegian Prescription Database. This also enables tracking of deceased and emigrated patients.

Study population

We included all primary THAs performed due to osteoarthritis and registered in the NARA database between January 1, 2010 and December 31, 2014 from Denmark (n = 26,250) and between January 1, 2008 and December 31, 2013 from Norway (n = 29,290) and assessed their preoperative and surgery-related records. 2 patients died on the day their follow-up time started and were thus censored, and 36 patients were lost to follow-up due to emigration. Primary THA was defined as insertion of a unilateral total hip prosthesis due to primary osteoarthritis (thus only first-time THAs on the left or right side were included). Because we were interested in NOAC and comparison with the most common treatment with LMWH, we excluded 1,589 patients from Denmark and 346 patients from Norway who received fondaparinux or other types of anticoagulants, leaving 24,661 Danish and 28,944 Norwegian THAs patients in the study population. Patient with missing information on type of thromboprophylaxis were not considered at all in our study.

Perioperative anticoagulant treatment

The exposure was defined as anticoagulant thromboprophylaxis in relation to the primary THA (initiated during hospitalization shortly before or after THA surgery). We compared NOACs (dabigatran, rivaroxaban, apixaban, edoxaban) with LMWH (dalteparin, enoxaparin, tinzaparin). Patients will receive the same anticoagulants depending on the department's local guidelines. In Denmark, the surgeon may select only 1 type of thromboprophylactic agent when reporting to the Danish Hip Arthroplasty Register, which comprises source data for the NARA database. Although in Norway surgeons may select 1 or more agents, patients were included in our study based on their 1st (being the main) agent.

Revision surgery

We defined the following 3 outcomes: (i) time to 1st revision surgery due to infection, (ii) time to 1st revision due to aseptic loosening, and (iii) time to any first-time revision of the prosthesis irrespective of cause. A revision was defined as any secondary surgical procedure involving removal or exchange of prosthesis components of a primary THA.

Covariates

From the NARA database we obtained information on age at primary THA (in categories: ≤ 59, 60–69, 70–79, and ≥ 80 years of age), sex, fixation type (in categories: cemented, uncemented, and hybrid/inverse hybrid fixation), duration and start (pre- or postoperatively) of anticoagulant treatment. The duration of perioperative anticoagulant thromboprophylaxis prescribed by a surgeon in connection with THA surgery was defined as short term (1–5 days), standard (6–14 days), or extended (> 15 days) treatment, based on current evidence and available international guidelines for thromboprophylaxis and clinical practice in Denmark and Norway (8). Information on comorbidity 2 years before primary THA was obtained from the Danish National Patient Registry and Norwegian Population Register before transferring to the NARA database. We summarized comorbid diseases using the Charlson Comorbidity Index (CCI) score classified as low comorbidity (CCI score of 0), defined as no previous record of disease included in the CCI, medium comorbidity (CCI of 1–2), and high comorbidity (CCI of 3 or higher).

As potential confounders, we also included data on other anticoagulants defined as at least 1 redeemed prescription within 12 months preceding the day of primary THA. The Danish National Database of Reimbursed Prescriptions and Norwegian Prescription Database provided data on dispensed prescriptions on acetylsalicylic acid, vitamin K antagonists, NOACs, and platelet inhibitors (clopidogrel, prasugrel, and ticagrelor).

Statistics

Data was described using total counts (%) distributed on type of thromboprophylactic treatment (NOAC or LMWH). We used Kaplan–Meier (KM) survival analysis to assess implant survival probability with 95% confidence intervals (CI) by type of thromboprophylactic treatment. We have also performed a

competing risk analysis (data not shown), but the results were not different from the KM estimates. We presented KM estimates in the paper as competing risk analyses of non-fatal outcomes may introduce collider bias (15). A Cox proportional hazards regression model was used to estimate crude and adjusted cause-specific hazard ratios (HRs) with 95% confidence intervals (CIs) for infection, aseptic loosening, and all-cause revision within 1 and 5 years of primary THA. Crude and adjusted HRs were calculated including age, sex, CCI, fixation type, duration and start of thromboprophylaxis, and preoperative use of Vitamin K antagonists, NOAC, aspirin, and platelet inhibitors, as confounding factors. We included these factors as potential confounders a priori based on established impact of the association between chemical thromboprophylaxis and revision surgery (16), due to their unequal distribution between exposure groups and because they are unlikely to be intermediate factors. Specific sub-analyses were performed by stratifying on country of origin (Denmark and Norway) and fixation type (cemented and uncemented). Due to small sample size, we were not able to stratify on other fixation types. The period of observation started on the day of primary THA and ended when the patient experienced 1 of the following events: revision outcome (defined previously), emigration, death, or when the follow-up period ended (December 31, 2016), whichever came first. The assumption of proportional hazards was evaluated visually with log-minus-log plots and was fulfilled in all models.

All statistical analyses were performed using Stata, version 16.0 (Stat Corp, College Station, TX, USA).

This paper was reported following the STROBE and the RECORD statements.

Ethics, funding, and potential conflicts of interest

The Norwegian Arthroplasty Register has permission from the Norwegian Data Inspectorate to collect patient data based on written consent from the 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 by any author.

Table 1. Characteristics of the study population. Values are count (%) unless otherwise specified

Factor	LMWH	NOACs	Total
Total	40,451 (75)	13,154 (25)	53,605 (100)
Age groups			
< 60	6,170 (15)	2,290 (17)	8,460 (16)
60–69	13,472 (33)	4,629 (35)	18,101 (34)
70–79	14,688 (36)	4,563 (35)	19,251 (36)
> 80	6,121 (15)	1,672 (30)	7,793 (15)
Sex			
Female	25,220 (62)	7,577 (58)	32,797 (61)
Male	15,231 (38)	5,577 (42)	20,808 (39)
Preoperative Charlson Comorbidity Index			
Low	32,652 (81)	11,721 (89)	44,373 (83)
Medium	6,618 (16)	1,259 (10)	7,877 (15)
High	938 (2.0)	153 (30)	1,091 (2.0)
Missing	243 (1.0)	21 (0)	264 (0)
Type of fixation			
Cemented	14,134 (35)	1,687 (30)	15,821 (30)
Uncemented	14,256 (35)	10,087 (77)	24,343 (45)
Hybrid	2,578 (6)	1,032 (8)	3,610 (7)
Reverse hybrid	8,933 (22)	295 (2.0)	9,228 (17)
Missing	550 (1.0)	53 (0)	603 (1.0)
Start of thromboprophylaxis			
Preoperatively	14,635 (36)	385 (3)	15,020 (28)
Postoperatively	22,614 (56)	12,634 (96)	35,248 (66)
Missing	3,202 (8.0)	135 (1.0)	3,337 (6.0)
Duration of postoperative thromboprophylaxis			
Short	3,697 (9)	3,749 (29)	7,446 (14)
Standard	14,604 (36)	1,870 (14)	16,474 (31)
Extended	17,775 (44)	7,181 (55)	24,956 (47)
Missing	4,375 (11)	354 (2.7)	4,729 (8.8)
ASA prior to primary THA [a]			
No	30,653 (76)	10,533 (80)	41,186 (77)
Yes	9,798 (24)	2,621 (20)	12,419 (23)
ADP receptor inhibitor prior to primary THA [a]			
No	39,711 (98)	12,817 (97)	52,528 (98)
Yes	740 (1.8)	337 (2.6)	1,077 (2.0)
VKA prior to primary THA [a]			
No	37,967 (94)	12,741 (97)	50,708 (95)
Yes	2,484 (6.1)	413 (3.1)	2,897 (5.4)
NOACs prior to primary THA [a]			
No	40,273 (99.6)	12,815 (97)	53,088 (99)
Yes	178 (0.4)	339 (2.6)	517 (1.0)

LMWH = low molecular weight heparin, NOACs = non-vitamin K oral anticoagulants (dabigatran/rivaroxaban/apixaban/edoxaban), ASA = acetylsalicylic acid, VKA = Vitamin K antagonists, ADP = adenosine diphosphate (clopidogrel/prasugrel/ticagrelor).
[a] Dispensing up to 12 months prior to the date of primary THA.

Results

53,605 patients were included in this study, of whom 40,451 (75%) received LMWH and 13,154 (25%) received a NOAC as thromboprophylaxis. In both cohorts, the majority of patients were between 60 and 79 years old at the time of THA and there was a higher proportion of females (Table 1). Only 2% of Norwegian patients received NOACs in comparison with 52% of Danish patients. Compared with patients who received LMWH, patients who received NOACs more often underwent uncemented THA, started anticoagulant treatment postoperatively, received treatment for less than 5 days, and had a lower prevalence of comorbidity. The median (range) follow-up time was 4.4 years (1.1–5.9).

The 1-year KM-based survival rate in terms of revision due to infection was 99% (CI 99–99) in the LMWH group and 99% (CI 99–99) in the NOAC group (Table 2). The absolute revision rate difference between NOACs and LMWH was 0.2% after both 1-year and 5-year follow-up. Throughout the entire follow-up period, the adjusted HR for revision due to infection was 0.9 (CI 0.7–1.1) when comparing NOACs with LMWH. The corresponding adjusted HRs were 1.6 (CI 1.3–

Table 2. KM survival estimates in terms of revision due to infection, aseptic loosening, and all causes

Outcome Type of thromboprophylaxis	1-year KM, % (95% CI)	5-year KM, %(95% CI)
Revision due to infection		
LMWH	99 (99–99)	99 (99–99)
NOAC	99 (99–100)	99 (99–99)
Revision due to aseptic loosening		
LMWH	100 (100–100)	99 (99–99)
NOAC	100 (100–100)	100 (99–99)
All-cause revision		
LMWH	98 (98–98))	96 (96–96)
NOAC	97 (97–98)	95 (95–96)

LMWH = low molecular weight heparin, NOAC = non-vitamin K oral anticoagulants, CI = confidence interval.

Table 3. Hazard ratios (HRs) of revision due to infection, aseptic loosening, and all causes

Outcome Type of thrombo-prophylaxis	Revised	Number at risk	Person-years at risk	Crude HR (95% CI)	Adjusted [a] HR (95% CI)
Revision due to infection					
LMWH	450	40,451	185,963	1 (reference)	1 (reference)
NOAC	114	13,154	525,221	0.8 (0.7–1.0)	0.9 (0.7–1.1)
Revision due to aseptic loosening					
LMWH	350	40,449	185,963	1 (reference)	1 (reference)
NOAC	129	13,154	525,221	1.3 (1.1–1.6)	1.6 (1.3–2.1)
All-cause revision					
LMWH	1,546	40,449	185,977	1 (reference)	1 (reference)
NOAC	574	13,154	525,537	1.2 (1.1–1.4)	1.2 (1.1–1.4)

For abbreviations, see Table2.
[a] Adjusted for sex, age, CCI, fixation type, start of thromboprophylaxis and duration of thromboprophylaxis and acetylsalicylic acid, clopidogrel/prasugrel/ticagrelor, warfarin/marcumar, and dabigatran/apixaban/rivaroxaban used before surgery.

Table 4. Hazard ratios (HRs) of revision due to infection, aseptic loosening, and all causes, stratified by fixation type

Outcome	Cemented (n = 15,821)				Uncemented (n = 24,343)			
Type of thrombo-prophylaxis	Revised	Number at risk	Crude HR (95% CI)	Adjusted [a] HR (95% CI)	Revised	Number at risk	Crude HR (95% CI)	Adjusted [a] HR (95% CI)
Revision due to infection								
LMWH	189	14,134	1 (reference)	1 (reference)	132	14,256	1 (reference)	1 (reference)
NOAC	17	1,687	0.8 (0.5–1.3)	0.8 (0.5– 1.4)	89	10,087	0.98 (0.8–1.3)	0.8 (0.6–1.1)
Revision due to aseptic loosening								
LMWH	144	14,134	1 (reference)	1 (reference)	105	14,256	1 (reference)	1 (reference)
NOAC	22	1,687	1.7 (1.1–2.7)	1.9 (1.1–3.1)	85	10,087	1.3 (0.9–1.7)	1.3 (0.9–1.9)
All-cause revision								
LMWH	570	14,134	1 (reference)	1 (reference)	585	14,256	1 (reference)	1 (reference)
NOAC	60	1,687	0.99 (0.8–1.3)	1.04 (0.8–1.4)	449	10,087	1.1 (1.0–1.3)	1.2 (1.02–1.4)

For abbreviations, see Table 2.
[a] Adjusted for sex, age, CCI, start of thromboprophylaxis and duration of thromboprophylaxis and acetylsalicylic acid, clopidogrel/prasugrel/ticagrelor, warfarin/marcumar, and dabigatran/apixaban/rivaroxaban used before surgery.

Table 5. Hazard ratios (HRs) of revision due to infection, aseptic loosening, and all causes, stratified by country

Outcome	Denmark (n = 24,661)				Norway (n = 28,944)			
Type of thrombo-prophylaxis	Revised	Number at risk	Crude HR (95% CI)	Adjusted [a] HR (95% CI)	Revised	Number at risk	Crude HR (95% CI)	Adjusted [a] HR (95% CI)
Revision due to infection								
LMWH	82	12,017	1 (reference)	1 (reference)	368	28,434	1 (reference)	1 (reference)
NOAC	107	12,644	1.3 (1.0 –1.7)	1.0 (0.6–1.5)	7	510	1.1 (0.5– 2.3)	1.02 (0.4–2.5)
Revision due to aseptic loosening								
LMWH	84	12,017	1 (reference)	1 (reference)	266	28,434	1 (reference)	1 (reference)
NOAC	122	12,644	1.5 (1.1–1.9)	1.3 (0.9–2.0)	7	510	2.1 (1.0–4.4)	2.2 (0.9–5.6)
All-cause revision								
LMWH	435	12,017	1 (reference)	1 (reference)	1,111	28,434	1 (reference)	1 (reference)
NOAC	553	12,644	1.2 (1.1–1.4)	1.1 (0.9–1.3)	21	510	1.2 (0.8–1.9)	1.3 (0.75–2.1)

For abbreviations, see Table 2.
[a] Adjusted for sex, age, CCI, start of thromboprophylaxis, and duration of thromboprophylaxis.

2.1) for aseptic loosening and 1.2 (CI 1.1– 1.4) for all-cause revision for NOACs versus LMWH (Table 3) and the absolute revision rate difference was less than 1% after 5 years.

Stratification on fixation type and country of origin showed HRs that were consistent with HRs based on the main analysis (Table 4 and 5).

Discussion

In this cohort study, use of NOACs compared with LMWH was associated with a slightly lower revision rate due to infection, but increased revision rates due to aseptic loosening and all-cause revision. However, the absolute rate differences between the groups were less than 1% and likely to be not clinically relevant.

Strengths and weaknesses

To our knowledge, this is the largest evaluation of the effects of thromboprophylaxis on revision rates among THA patients using a large-scale cohort design comprising 53,605 primary total hip replacements. Completeness and validity of data on primary THAs in the Danish Hip Arthroplasty Registry and Norwegian Arthroplasty Register has been documented to be greater than 95% (17,18). However, completeness of registration of revision due to infection in the Danish Hip Arthroplasty Registry was recently found to be only 67% (19). Thus, our absolute cumulative incidences on revision due to infection are underestimated. In addition, the positive predictive value of revision due to infection in the Danish Hip Arthroplasty Registry has been estimated at 77% (19) and thus we have a misclassification of our outcome. However, this misclassification is most likely not related to registration of exposure in our study due to prospective collection of data, thus we have non-differential misclassification, and bias towards the null. We do not know if the similar issue concerning validity of revision due to infection is the case in Norway but it is most likely due to the similar method of registration of revisions in arthroplasty registries. The positive predictive value and completeness of registration of thromboprophylactic treatment in the Danish Hip Arthroplasty Registry is generally high, reducing the risk of misclassification of exposure (20). Compliance with the treatment during hospitalization for THA is high; however, the compliance after discharge is hard to evaluate but is likely to correspond to relatively high compliance in the general population (21).

Further, we obtained information on deceased and emigrated patients from the Danish Civil Registration System and Norwegian Patient Registry, allowing for nationwide cohort studies with complete follow-up.

We included several covariates obtained from national patient registries and national prescription databases along with the NARA database. Alcohol (22), smoking (23,24), and higher BMI (3) have previously been identified as risk factors for infection. Although we did not obtain information regarding these factors, CCI may act, to some extent, as a surrogate marker for diseases caused by unhealthy lifestyle. We cannot rule out the possibility that developing an infection and undergoing surgery for revision is related to these or other factors, thus unmeasured confounding could still bias our results. In addition, we adjusted for variables such as duration of postoperative thromboprophylaxis, type of fixation, and CCI with missing data on 1% to 9% of cases; thus, residual confounding could bias our results. The country-specific estimates were subject to statistical uncertainty as seen by wide confidence intervals.

Comparison with other studies

Excessive anticoagulation may result in increased wound complications and postoperative infections (25), but no studies have to our knowledge investigated the revision rate due to infection when comparing NOACs with LMWH. Current studies investigating the effects of thromboprophylaxis on infection and subsequent revision compare rivaroxaban with undefined anticoagulants or tinzaparin, and thus may offer limited comparison with our findings (3-5).

Our cumulative incidences of revision due to infection are in accordance with other studies reporting similar findings (26), thus supporting the fact that revisions due to infection are rare after primary THAs. Brimmo et al. (4) compared early deep postoperative surgical site infection and subsequent reoperation rates (within 30 days of surgery) in THA and total knee arthroplasty (TKA) patients treated with rivaroxaban or other forms of chemical thromboprophylaxis. The authors reported that deep surgical site infections occurred in 3% of patients treated with rivaroxaban as thromboprophylaxis compared with only 0.2% in the control group. This association did not remain statistically significant when restricted to THA patients only (4). Similar observations were reported in a study performed by Jensen et al. observing 3% of patients developing deep infection and returning to theatre when treated with rivaroxaban compared with only 1% in patients receiving tinzaparin (27). Likewise, when separating THA and TKA patients, the differences in revision rates no longer reached statistical significance (27). In comparison with our study, the incidence of revision rate due to infection was 0.7% in patients receiving NOACs compared with 0.9% in patients receiving LMWH, and this absolute difference in revision rate of less than 0.2% should be taken into consideration when interpreting the study results. As infection is a rare complication, it is dubious as to whether the studies by Brimmo et al. (4) and Jensen et al. (27) achieved adequate power to provide evidence on revision rates when comparing rivaroxaban with other types of thromboprophylactic treatment. Further, our adjusted HR of revision due to infection suggested a lower revision rate in patients receiving NOACs compared with LMWH, although the confidence interval was relatively wide. In support of our findings, a large randomised controlled trial (n = 3,449) on DVT patients found rivaroxaban to be non-inferior in regard to major bleeding in comparison with enoxaparin followed by warfarin (28), suggesting that rivaroxaban would be considered a safer choice.

Conversely, our results indicate higher revision rates due to aseptic loosening and all-cause revision in patients receiving NOACs compared with LMWH. The possible biological expla-

nation could be that NOACs interfere with initial bone healing by, e.g., causing micro bleeding resulting in low or even no bone ingrowth to the implant surface. However, this possible mechanism has not yet been addressed in the literature. A second, and perhaps more likely explanation for the results in this study is the influence of country differences revealing that a considerably small proportion of Norwegian patients received NOACs (2%) in comparison with almost half (51%) of the Danish patients, and uncemented THAs are more commonly used in Denmark than in Norway. Thus, when stratifying on country of origin, the adjusted HRs only showed weak evidence of an association between choice of thromboprophylaxis and revision rate due to infection. In addition, the wide confidence intervals implied non-sufficient power to detect an association with strong statistical support although large study populations were included. When comparing our results with results of other studies it is relevant to consider selection of patients for NOAC and LMWH treatment in Norway and Denmark, which might be different from selection criteria posed in other countries. For example, use of aspirin for thromboprophylaxis in THA patients is common in the UK, whereas aspirin is not used in Denmark and used in less than 0.5% of patients in Norway. Thus, users of NOACs and LMWH could be selectively different from users of these agents in the UK (29).

Conclusion

We found a slightly lower revision rate due to infection for NOACs compared with LMWH users. However, NOACs were associated with a higher revision rate due to aseptic loosening and all-cause revision compared with LMWH. The small absolute differences, selection bias, and unmeasured confounding have to be taken into consideration when interpreting these results. It can be debated whether the absolute revision rate differences of less than 1% are clinically relevant to lead to change in clinical practice regarding the usage of one rather than another anticoagulant.

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