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Effectiveness and safety of thromboprophylaxis in total hip arthroplasty – a register study comparing new oral anticoagulants and low molecular weight heparin

Degree Project in Medicine

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©Swedish Hip Arthroplasty Register

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Abstract

Introduction:

Venous thromboembolism (VTE) is a common and potentially lethal complication after total hip arthroplasty (THA). While low molecular weight heparin (LMWH) remains the gold standard antithrombotic medication after THA in Nordic countries, recent randomized trials have demonstrated superior efficacy in new oral anticoagulants (NOAC) such as dabigatran and rivaroxaban compared to LMWH. In this register study we compared established efficacy and safety outcomes between patients who had received LMWH and NOAC as thromboprophylaxis after THA.

Method:

Data was collected from the Swedish Hip Arthroplasty Register (SHAR), the National Patient Register (NPR) and the Prescribed Drug Register (PDR) to form a database from which 32633 patients were selected. These included all primary THA procedures for patients with osteoarthritis. Patients who had an earlier VTE diagnosis or received a potent anticoagulant were excluded from the analysis. A binary logistic regression model adjusted for age, sex and previous antiaggregant medication was used to calculate odds ratios (OR) for VTE-incidence up till 3 months after surgery.

Results:

26881 patients received LMWH and 5752 patients were treated with NOAC. The VTE-incidence in the LMWH group was 1.0% (n=264) and 0.4% (n=24) in the NOAC group. Adjusted OR for VTE was 0.42 (95% CI: 0.28-0.64, p<0.0001); deep venous thrombosis (DVT) 0.46 (95% CI: 0.28-0.76, p=0.002); pulmonary embolism (PE) 0.34 (95% CI:0.17-

0.71, p=0.004); major bleeding events 0.96 (95% CI: 0.72-1.27, p=0.756); and minor bleeding events 0.75 (95% CI: 0.32-1.79, p=0.521) in the NOAC group.

Conclusion:

The incidence of VTE following THA was lower for patients with NOAC compared to those with LMWH as thromboprophylactic medication. There were no differences in adverse events including bleeding, reoperation and death. Similar, but less pronounced differences have been reported previously. Although, there may be residual confounding due to selection bias the magnitude of the difference warrants a call for change of practice.

Abbreviations	
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
VTE	Venous thromboembolism
DVT	Deep venous thrombosis
PE	Pulmonary embolism
SHAR	Swedish Hip Arthroplasty Register
PDR	Prescribed Drug Register
NPR	National Patient Register
LMWH	Low molecular weight heparin
NOAC	New oral anticoagulants
OR	Odds ratio
CI	Confidence interval
BMI	Body mass index
ASA	American Society of Anesthesiologists

Background/Introduction

Total hip arthroplasty (THA) is a major orthopedic procedure in practice since the 1960's. THA is often referred to as one of the most successful surgical procedures in medical history. This has been facilitated by advancements in bioengineering technology that has increased both function and sustainability in hip prostheses (1).

The original purpose of THA was solely to alleviate pain and restore mobility for patients with osteoarthritis (2). However, the population is demographically shifting towards a higher age and physically demanding activity among senior citizens is increasing. The former has led to a rising demand for THA procedures and the latter a need for more durable prostheses (1).

Venous Thromboembolism (VTE)

One of the most common and feared complications with THA is venous thromboembolism (VTE), i.e. a blood clot is formed in one of the deep veins of the leg or deep venous thrombosis (DVT). These clots are partly induced by the state of hypercoagulability associated with major joint surgery such as THA. Additionally, venous stasis and endothelial damage to blood vessels can attribute to DVT.

In some instances a part of the blood clot, an embolus, loosens and travels upwards via the blood stream. When the embolus bypasses the liver and the heart, it can lead to a pulmonary embolism (PE). This is when an embolus plugs one of the pulmonary vessels, preventing the blocked sections of the lung from receiving blood, reducing oxygen uptake. This often presents clinical symptoms such as dyspnea and tachypnea and the state of hypoxia is potentially lethal.

Nonetheless, not all VTE is diagnosed as a result of clinical symptoms, e.g. DVT can be detected via ultrasound, fibrinogen analysis or ascending venography in patients who show no clinical signs of DVT such as pain and swelling of the leg. This is referred to as asymptomatic DVT or VTE and is much more common than symptomatic VTE, but its clinical significance has been disputed (3).

Multiple studies have assessed the probability of acquiring symptomatic and asymptomatic VTE after THA that ranges between 0.8-2.8% the first 3 months after surgery (4-8), 1.6-2.7% after 6 months (7, 9) and 2.6% 1 year after surgery (4). A Danish cohort study (7) reported on THA patients during 1995-2010 (n=85 965) of which 0.79% had a symptomatic VTE event during the first 3 months postoperatively. An additional 0.29% of the patients were diagnosed during the remainder of the first postoperative year. This also demonstrates that VTE is most common in the early postoperative period. This study also reported a relative risk of 15.8 to suffer symptomatic VTE in the THA group compared to the general population (7). Even though the documented postoperative VTE incidence can vary between studies, THA undisputedly carries with it an increased risk of VTE.

Without intervention asymptomatic DVT occurs for 40-60% of the THA patients and symptomatic VTE seems to appear for 5% (10, 11). Randomized trials between untreated control groups and patients who have received antithrombotic treatment have reported a significant decrease in both symptomless DVT and symptomatic VTE (9, 12). This emphasizes the importance of thromboprophylactic medication in the prevention of VTE.

Thromboprophylaxis

The most widely used antithrombotic treatment for patients undergoing THA in Sweden is low molecular weight heparin (LMWH). LMWH mediates its anticoagulant effect by binding to antithrombin, thus enhancing its inhibitory activity towards thrombin and the coagulation

factor Xa (13). The introduction of LMWH in the 1980's was an important milestone for the reduction of VTE correlated to major surgery as it facilitated the administration being subcutaneously (s.c.), decreased side effects, required less monitoring, and enabled earlier discharges (14).

That is not to say there are no difficulties with the use of LMWH's in clinical practice. While outpatient administration was enabled, there is an issue with compliance as not all patients are comfortable with needles. This results in a high economic burden as home-care visits and patient education often is required (15).

As with most interventions in health care, there are undesired side effects, thromboprophylaxis is not an exception. The anticoagulant effect has to be weighed against the risk of bleeding. This is reflected in clinical trials that measure both VTE and bleeding as endpoints, in the hope of finding a gold standard treatment that maximizes both efficacy and safety.

Besides the evolution of thromboprophylactic agents several other steps have been taken to achieve this goal. Historically, the length of stay in hospitals for THA patients could exceed weeks (16, 17). The introduction of fast-track protocols with a multimodal approach using early mobilization and effective postoperative pain relief enables discharges 2-3 days after surgery. There are reports on reduced risk of VTE and other surgical complications after introduction of fast-track (17-21).

The use of mechanical prophylaxis such as anti-embolism stockings and foot impulse devices has also been of aid postoperatively for patients struggling to regain mobility due to comorbidity (22).

Another crucial element is the recommended treatment period. The current guidelines promote antithrombotic treatment for at least 10-14 days with an extended continuation up to

35 days (22-24), a strategy that has received support from studies financed by pharmaceutical companies. However, skeptics have argued that extended duration treatment forces an unnecessary economic burden and increases the risk of side effects for THA patients (25, 26).

NOAC (New Oral Anticoagulants)

However, it could be argued that the most important advance in VTE prevention was the introduction of new oral anticoagulants (NOAC) that happened in recent years. NOAC is increasingly used in clinical practice to prevent VTE. NOAC can be administered orally, arguably making compliance less of an obstacle (27). NOAC also seems to be a more cost-effective alternative but this has yet to be proven significant (28).

One of the criticisms raised towards NOAC is wound complications following surgery requiring prolonged wound drainage and therefore longer hospital stay. This critique has been directed mostly towards rivaroxaban (29, 30).

There are currently three NOACs that have gone through phase-III-trials and are approved as VTE prophylaxis. The direct thrombin inhibitor dabigatran etexilate and the selective Xa factor inhibitors rivaroxaban and apixaban (13).

In the ADVANCE-III double-blind study apixaban was compared with enoxaparin (a LMWH) after both primary and revision THA (31). 5407 patients were randomized to extended duration thromboprophylaxis with either 40 mg subcutaneous (sc) enoxaparin daily or 2.5 mg of apixaban orally twice daily for a total of 35 days. 3866 patients were used in the primary efficacy analysis. The approximate 30% loss of subjects happened in both study groups and were due to evaluation of DVT not being possible. The primary efficacy outcome included asymptomatic and symptomatic DVT, non-fatal PE or death from any cause during the treatment period. These outcomes occurred in 1.4% in the apixaban group and 3.9% in the

enoxaparin group, giving an absolute risk reduction of 2.5% and relative risk of 36% for apixaban. No significant increase in bleeding events was seen for apixaban (31).

Dabigatran etexilate has been compared with enoxaparin after THA in two randomized phase-III trials, RE-NOVATE and RE-NOVATE II (32, 33). In RE-NOVATE it was confirmed that both 150 mg and 220 mg dose of dabigatran orally once daily was non-inferior to enoxaparin in terms of reducing the primary efficacy outcome. This was determined via a non-inferiority margin for the absolute risk difference between dabigatran and enoxaparin. If the upper limit for the 95% confidence interval [CI] in absolute risk difference exceeds the non-inferiority margin of 7.7%, dabigatran would be considered inferior to enoxaparin. The margin of 7.7% was based on pooled data from enoxaparin vs. placebo trials (34-36).

As a result of the RE-NOVATE trial in 2007 which was mainly conducted in Europe, 220 mg once-daily dose of dabigatran was approved for use in more than 75 countries as thromboprophylaxis after THA. To further establish the non-inferiority of dabigatran in a more diverse population the RE-NOVATE II trial was initiated.

The RE-NOVATE II trial included 2055 patients that were randomly assigned to oral dabigatran 220 mg or s.c. enoxaparin once daily. 1577 (76.7%) patients were eligible for primary efficacy analysis. Similar to the ADVANCE-III trial for apixaban, the exclusion of almost 500 patients for the primary efficacy analysis was mostly due to lack of or non-interpretable venographic data.

As in the RE-NOVATE trial, no significant difference was seen between dabigatran and enoxaparin in terms of reducing primary efficacy events. The absolute risk difference was 1.1% ($p=0.43$). However, as the 95% CI did not exceed the 7.7% margin, dabigatran was again shown to be non-inferior to enoxaparin, without any significant rise in bleeding (33).

Rivaroxaban has been studied in two phase-III trials (RECORD-I and RECORD-II) and recently a phase IV-trial (XAMOS) (37-39).

In RECORD-I 4541 THA patients were randomized to extended duration thromboprophylaxis with either 40 mg s.c. enoxaparin or 10 mg of oral rivaroxaban once daily plus a placebo tablet or injection. In RECORD-II 2509 patients scheduled for THA were randomly split into two groups, one receiving extended duration treatment with 10 mg once-daily oral rivaroxaban and the other short-term treatment with 40 mg of s.c. enoxaparin (10-14 days). Primary efficacy analyses in both studies were performed in a modified intention-to-treat groups which consisted of all patients who had undergone surgery, received at least one dose of study medication and had adequate assessment of thromboembolism, 69% of the patients who had been randomized (in both RECORD-I and RECORD-II).

Similar to the RE-NOVATE trials the aim of the RECORD-I trial was primarily to ascertain the non-inferiority of rivaroxaban compared to enoxaparin. Therefore a non-inferiority analysis for primary efficacy outcome preceded the superiority analysis on the modified intention-to-treat cohort. RECORD-I found an absolute risk reduction in primary efficacy outcome of 2.6% ($p<0.001$) and relative risk reduction of 70% for rivaroxaban in the modified intention-to-treat population.

The primary goal of RECORD-II was to determine if extended duration treatment with rivaroxaban was superior to short-duration treatment with enoxaparin. RECORD-II reported an absolute risk reduction of 7.3% ($p<0.001$) for primary efficacy outcome for extended-duration rivaroxaban in the modified intention-to-treat cohort. No significant elevation in risk of bleeding was seen in the rivaroxaban group.

All the above mentioned studies use strict inclusion and exclusion criteria that make it difficult to determine if the results are applicable to routine clinical practice. Phase-IV studies

provide a real-world setting that can further establish the superior efficacy of NOAC compared to LMWH. It was for this reason that the XAMOS study was launched (39).

17701 patients who underwent either THA or TKA were enrolled in the XAMOS study and multiple clinical outcomes such as thromboembolism, bleeding, wound complications and death were recorded. Patients were assigned to receive rivaroxaban or standard-of-care (of which 81.7% received LMWHs and 5.5% received dabigatran). The incidence of symptomatic VTE was 0.65 % in the rivaroxaban group and 1.02 % in the standard-of-care group with an odds ratio [OR] of 0.63 (95% CI, 0.45-0.89) for rivaroxaban. No significant difference was found for any bleeding or adverse events.

The XAMOS and preceding phase III studies have given a solid foundation for suggesting NOAC as an alternative to LMWH where daily injections are an inconvenience. Yet, among critics there is still skepticism for offering NOAC instead of LMWH due to believed risk of bleeding and lack on long-term safety data (40).

A meta-analysis assessing a total of 16 randomized trials for NOAC in major joint surgery found that NOAC had similar efficacy and safety to LMWH but higher efficacy and was often associated with a rise in bleeding events. Compared with enoxaparin, the incidence of symptomatic VTE was lower with rivaroxaban (relative risk 0.48, 95% CI 0.31-0.75), but did not differ significantly with dabigatran (0.71, 0.23 to 2.12) and apixaban (0.82, 0.41 to 1.64). Using clinically relevant bleeding as a safety outcome they found that when compared to enoxaparin, the risk was higher with rivaroxaban (1.25, 1.05 to 1.49) and similar with dabigatran (1.12, 0.94 to 1.35) and lower with apixaban (0.82, 0.69 to 0.98) (41).

The Swedish Hip Arthroplasty Register (SHAR)

The SHAR was founded in 1979 as a national quality register to evaluate and provide guidelines for THA procedures. The clinical data from SHAR is used for multiple purposes:

The assessment of health care institutions and their activities, the continuous encouragement for clinical improvement and clinical research (42).

The SHAR also has an important role in post-market surveillance of implants. This has for instance led to discontinued use of some implants that have not performed well according to standards. Sweden has one of the lowest THA revision rates globally which has been largely credited to the activity of SHAR (43).

The information relayed to the SHAR is reliant upon the treating units that are supplying it. Therefore, the register examines the data quality and the completeness of the data (number of reported hip replacements/number of performed hip replacements) on an annual basis. The data completeness has been measured at 98-99% despite the participation from health care institutions not being mandatory (42).

Furthermore, SHAR documents approximately 16500 THA in their annual report for 2015 (44). With such a large number of patients undergoing THA the SHAR has access to data from hundreds of thousands of THA procedures, offering enough statistical power to permit the study of rare complications such as VTE.

Still, what SHAR can evaluate via medical research is limited to the data that is collected. Incidence of VTE is regrettably not included in the database. However, by interlinking SHAR with other registers researchers are able to perform analysis on variables from multiple databases. This is facilitated by the 10-digit personal identity number (PIN) maintained by the Swedish Tax Agency.

With access to data from the NPR and the Prescribed Drug Register (PDR), both governed by the National Board of Health and Welfare, we can assess the occurrence of VTE and adverse events after THA after controlling for the prescribed thromboprophylaxis. The cross-linking of these registers and the vast amount of data collected offers a unique opportunity to

extensively evaluate the effectivity and safety of LMWH and NOAC after THA. We hope this study will offer robust evidence for the ongoing debate on thromboprophylaxis and potentially be used as a springboard for change in Nordic health care policy.

Objectives

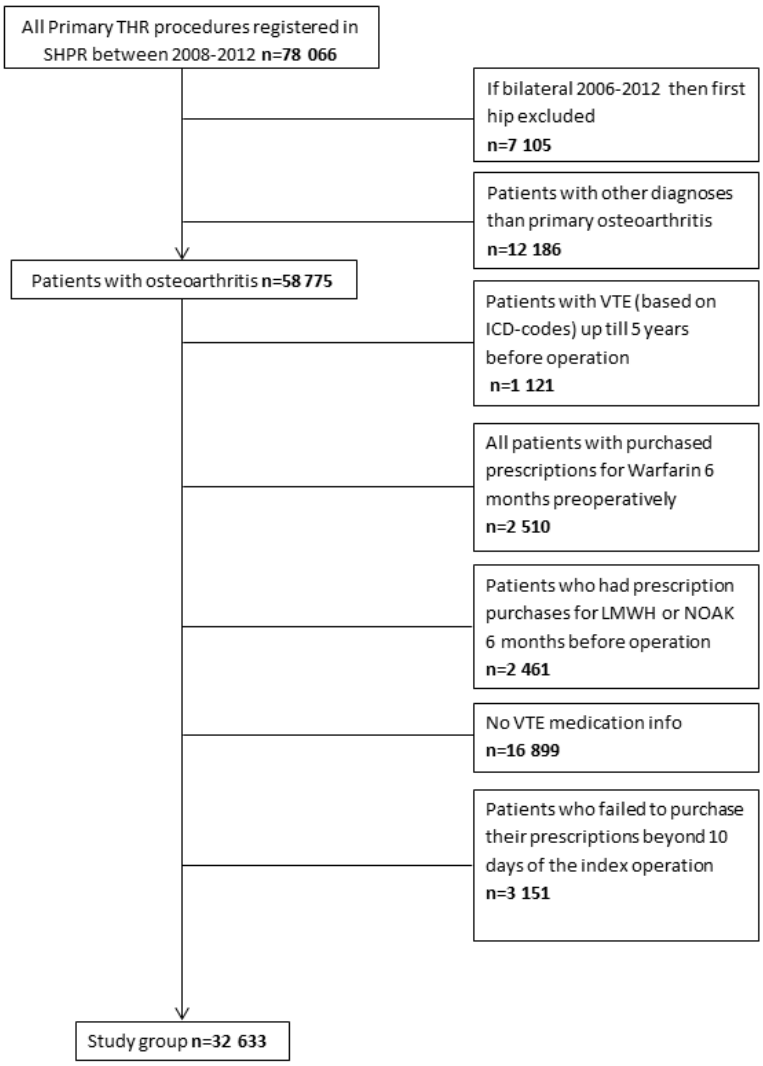
The aim was to explore differences in VTE incidence after THA for patients treated with LMWH or NOAC. Furthermore, we assessed the association between medication and adverse events such as bleeding, reoperation and mortality.

Methods

Data was previously collected from the SHAR, the NPR and the PDR (both governed by the National Board of Health and Welfare) to form a cross-linked register database in another study (43). A formal request of access was filed via the SHAR to make the data available to the author. No additional data collection was necessary.

A cohort consisting of 32 663 patients was selected from the interlinked registers. The selection process included multiple steps (Figure 1). We included all primary THA procedures between 2008 and 2012 in patients suffering from osteoarthritis. Patients with high risk of developing VTE including those with other diagnoses than osteoarthritis (e.g tumors, congenital disorders or hip fractures), previous VTE diagnosis or a prescription of a potent anticoagulant (warfarin, LMWH or NOAC) 6 months preoperatively were excluded.

Figure 1. Study group selection flow chart



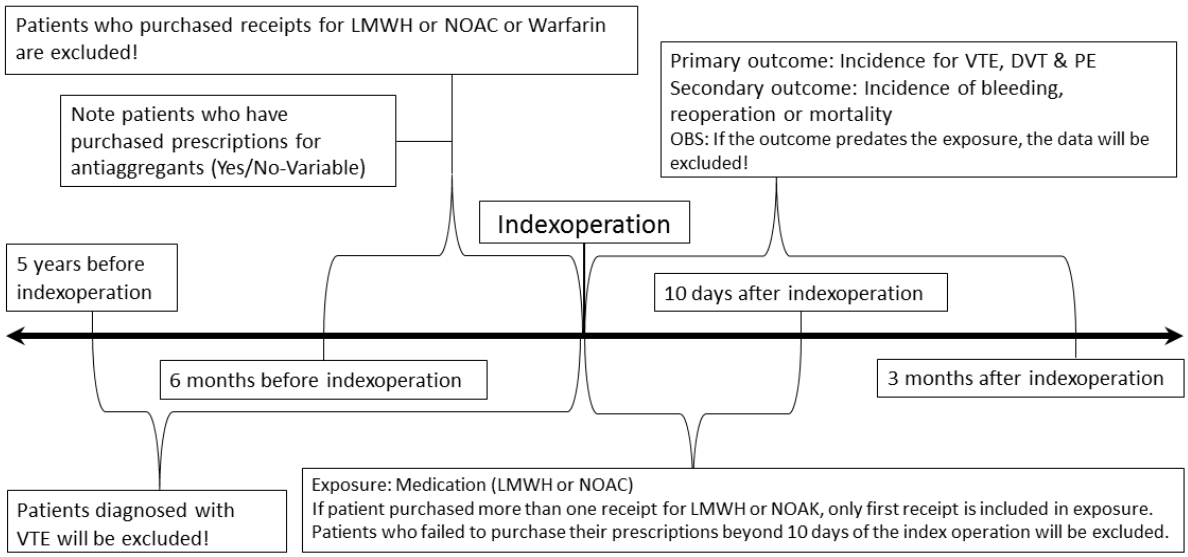
Exposure was defined as thromboprophylaxis after THA. Patients who had received LMWH or NOAC were divided into two separate study cohorts for statistical analysis. In order to be included in the analysis exposure had to precede all potential outcomes and the prescription had to have been purchased within 10 days of the index operation (Figure 2).

Exposure data was selected from ATC-codes reported in the register from the National Board of Health and Welfare. Three ATC-codes for LMWH (B01AB04, B01AB05, B01AB10) corresponding to dalteparin (Fragmin), enoxaparin (Klexane) and tinzaparin (Innohep) were

included. NOAC consisted of two ATC-codes (B01AE07, B01AF01) standing for dabigatran etexilate (Pradaxa) and rivaroxaban (Xarelto).

Occurrences of VTE, DVT and PE up till 3 months postoperatively were our primary endpoints. Adverse events were also measured in the same time frame as secondary outcomes. These included major bleeding, minor bleeding, reoperation and mortality. Mortality and reoperations are reported for every THA in the SHAR and were directly applicable for analysis.

Figure 2. Time axis used in study design



However, VTE, DVT, PE, major and minor bleeding were all diagnostic outcomes that required specific definitions before analysis could be performed. Since this data was not available in SHAR we used ICD-10 codes reported in the NPR to define these outcomes.

A search with the keywords “thrombosis”, “bleeding” and “haematoma” was performed in an ICD-10 database. Specific ICD-10 codes corresponding to every outcome were selected by the research group. See appendix for the ICD-10 list for each of these outcomes. The separation between what was considered major and minor bleeding events was based on a

research article that had examined the definition of bleeding as a secondary outcome in clinical trials reporting on THA (45).

Originally the study population included patients from 2006-2012. This period was later changed to 2008-2012 for several reasons. Firstly, there was only a single patient registered for 2007 after the data had bypassed our selection criteria, whereas, the other years the number of patients exceeded at least 3500 per year. Secondly, BMI had not been recorded in SHAR earlier than 2008. Finally, no patients in the NOAC group were registered prior to 2008.

Setting the time frame for purchasing prescriptions was based on the distribution of data from the interlinking registers. A plotted histogram over the days between index operation and purchased prescriptions revealed that the majority of patients had already bought it after 3-5 days. From this we concluded that setting a margin of 10 days postoperatively would not exclude a large portion of THA operations. It would also limit the inclusion of high-risk patients, excluding those who were unable to get an early discharge due to comorbidity.

Statistical methods

The statistical analysis was performed using IBM SPSS software, version 21. The data was analyzed in a binary logistic regression model to determine the odds ratio [OR] with a 95% confidence interval. A p-value below 0.05 was considered statistically significant.

Each of the observed outcomes was used as the dependent variable in a binary logistic regression. We calculated the OR both in a univariate unadjusted and a multivariate adjusted analysis with sex, age and previous antiaggregant medication as confounders.

Ethics

This study was approved by a Regional Ethical Review Board in Gothenburg (entry number 271-14).

This was a register study that didn't require any contact with the patient. The data in SPSS could only be accessed via a remote desktop server called SODA (Secure Online Data-Access) requiring dual step identification. The data could not be transferred or copied from SODA and hence all the analyses were done via this network. The patients were anonymously listed in the database and the key to unlock the identity of the patient was not available to the research team. We determine the possibility of reidentifying individuals by anyone in the research team to be close to non-existent.

Furthermore, SHAR is a well-established national register with a research record of over 40 years. Without the use of SHAR, it would prove very difficult to gather the large number of patients required for studying the primary endpoints described in this paper. Considering the effort of clinicians who report patient data to the SHAR and the National Board of Health and Welfare we are as researchers obligated to use that information to continuously evaluate current treatment policies and find areas where improvement is achievable.

Results

The distribution of gender was equal across both groups with an expected domination of women. (Table 1).

Table 1. Demographic and clinical characteristics of the study population

**standard deviation*

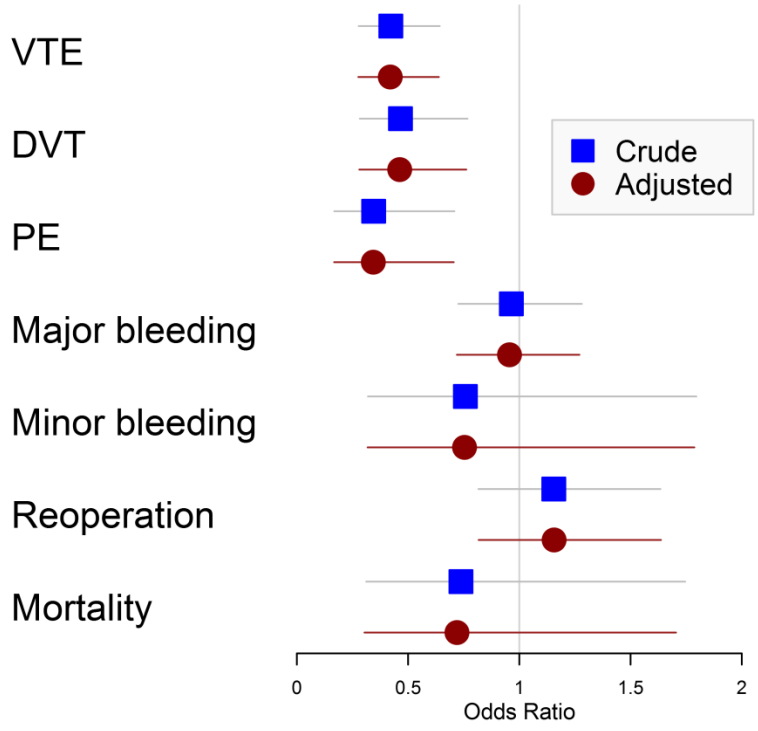
	NOAC	**LMWH**	**p-value**
N	5752	26881	
Gender = female - n (%)	3329 (57.9)	15339 (57.1)	0.264
Age - mean (sd*)	68.19 (9.97)	67.75 (9.95)	0.002
BMI (kg/m^2) - mean (sd)	27.45 (4.45)	27.28 (5.29)	0.031
ASA - n (%)			<0.001
Healthy (I)	1605 (29.2)	6926 (26.5)	
Mild (II)	3280 (59.7)	15913 (60.9)	
Severe (III)	598 (10.9)	3228 (12.3)	
Life-threatening (IV)	7 (0.1)	70 (0.3)	
Moribund (V)	0 (0.0)	1 (0.0)	
Elixhauser - mean (sd)	0.76 (0.93)	0.63 (0.93)	<0.001
Education - n (%)			<0.001
Low	1929 (33.6)	8616 (32.1)	
Middle	2447 (42.6)	11113 (41.4)	
High	1372 (23.9)	7120 (26.5)	
Civil state – n (%)			0.205
Couple	3260 (56.7)	15254 (56.8)	
Single	1622 (28.2)	7774 (29.0)	
Widow	866 (15.1)	3822 (14.2)	
Fixation – n (%)			<0.001
Cemented	4142 (72.1)	17123 (64.0)	
Uncemented	888 (15.5)	4371 (16.3)	
Hybrid	93 (1.6)	210 (0.8)	
Reversed hybrid	609 (10.6)	4607 (17.2)	
Resurfacing	13 (0.2)	463 (1.7)	

Education showed a trend towards a higher standard in the LMWH group. Two measures for comorbidity, the American Society of Anesthesiologists (ASA) classification and Elixhauser comorbidity index were included, where a higher value indicates further comorbidity.

Interestingly, the ASA classification, in contrast with the Elixhauser comorbidity index, shows a slightly lower comorbidity in the NOAC population. 29.2% in the NOAC group were classified as ASA I, compared to 26.5% in the LMWH group whilst the mean Elixhauser comorbidity index was almost 21% greater among NOAC patients. Data on prosthesis fixation showed that there was a higher tendency towards cementation in the NOAC group and lower use of reversed hybrid fixation.

VTE events occurred in 264 of 26881 patients (1.0%) in the LMWH group and 24 of 5752 patients (0.4%) in the NOAC group. The adjusted OR in the NOAC group was 0.42 (95% confidence interval [CI], 0.28-0.64; p<0.0001). This analysis showed that NOAC is superior compared to LMWH in terms of effectiveness.

Figure 3. The forest plot presents crude (blue) and adjusted (red) odds ratios for NOAC with LMWH as reference.



DVT was diagnosed in 170 of 26881 patients (0.6%) in the LMWH group and 17 of 5752 patients (0.3%) in the NOAC group. Adjusted OR in the NOAC group was 0.46 (95% CI,

0.28-0.76; p=0.002). PE was identified in 108 of 26881 patients (0.4%) in the LMWH group and 8 of 5752 patients (0.1%) in the NOAC group. Adjusted OR in the NOAC group was 0.34 (95% CI, 0.17-0.71; p=0.004).

Major bleeding events occurred in 281 of 26881 patients (1.0%) in the LMWH group and 58 of 5752 (1.0%) in the NOAC group. Adjusted OR in the NOAC group was 0.96 (95% CI, 0.72-1.27; p=0.756).

Minor bleeding events were suffered by 37 of 26881 patients (0.1%) in the LMWH group and 6 of 5752 (0.1%) in the NOAC group with an adjusted OR of 0.75 in the NOAC group (95% CI, 0.32-1.79; p=0,521)

Death during follow-up was confirmed in 38 of 26881 patients (0.1%) in the LMWH group and 6 of 5752 patients (0.1%) in the NOAC group. Adjusted OR was 0.72 in the NOAC group (95% CI, 0.30-1.70; p=0.455).

A total of 202 patients underwent reoperation. 162 patients were from the LMWH group (0.6%) and 40 patients were from the NOAC group (0.7%). Adjusted OR in the NOAC group was 1.16 (95% CI, 0.82-1.64; p=0.412).

Discussion

This explorative study was conducted in order to describe any potential significant differences in VTE incidence and adverse events between NOAC and LMWH after primary THA in patients suffering from osteoarthritis.

The results reveal a significantly lower occurrence of VTE in patients who were given NOAC compared to LMWH. Risk of developing VTE, DVT and PE remained significantly lower in the NOAC group after adjusting for sex, age and previous antiaggregant medication.

Furthermore, the analysis did not show any significant difference for reoperations, bleeding or mortality between NOAC and LMWH.

Comparison to similar studies

Our findings are in accordance with those found in phase III clinical trials for NOAC and the XAMOS Phase IV-study comparing rivaroxaban (NOAC) with enoxaparin (LMWH) (31-33, 37-39). However, important to note is that these trials did not use the same primary endpoints as this study and therefore are not directly comparable.

To the best of our knowledge, these calculations affirm a greater superiority with NOAC than previously published in the literature. As a result of this, we suspected that a fraction of the 288 patients that suffered VTE could have been receiving treatment for an unregistered VTE instead of prophylaxis. Due to LMWH being the most commonly prescribed medication for VTE in most Swedish hospitals this could have resulted in patients being falsely classified as LMWH.

Using the data from the PDR, we confirmed that all (except three) patients belonging to the LMWH group had received a prophylaxis dose of LMWH preceding VTE treatment. It is still possible that these patients had been offered prophylaxis but not via prescription. Regardless if these three cases were categorized correctly or not, we assume that this limited number does not have any impact on our results.

There is constantly a risk of confounding bias caused by differences in demographic and clinical characteristics between patient cohorts. We found a significantly higher Elixhauser comorbidity index in the NOAC group. This could arguably have influenced our results, yet the effect would be a higher incidence of complications in the NOAC population, including VTE. The higher comorbidity in the NOAC cohort likely was not a source of confounding for superior effectiveness with NOAC.

Moreover, there was a tendency towards more cemented fixation in the NOAC group. Studies have reported cementation as a potential risk factor for VTE (46, 47). Assuming that cementation increases the risk for VTE, the same principle as above can be applied, since it would not contribute to decreasing the amount of VTE events in the NOAC group.

Additionally, the symptomatic VTE-incidence recorded in our study is generally lower compared to those found in randomized trials. The RECORD-I trial reported a VTE-incidence of 1.1% in the rivaroxaban group and 3.7% in the enoxaparin group despite a follow-up of 36 days, almost three times shorter than our follow-up (37). The XAMOS study documented a 3-month-VTE-incidence at 0.89% for rivaroxaban and 1.35% for standard-of-care (82% enoxaparin) (39).

One potential explanation is the rigid selection criteria in this study. Only primary THA procedures for osteoarthritic patients that had not suffered VTE in the last 5 years were included. In comparison, the XAMOS study included all patients aged above 18 who were to undergo THA, TKA or hip fracture surgery where rivaroxaban was indicated (39).

Another reason for low VTE-incidence could be underreporting in the NPR. However, this would affect the registration of VTE events for both NOAC and LMWH, hence our results are still comparable.

Strengths and weaknesses of study

Surprisingly, there was a large portion of the patient cohort (n=16899) that did not contain any data from the PDR. It is very unlikely that all of these patients were not offered antithrombotic medicine. One possible explanation is that certain hospitals may have a specific treatment regimen that does not include prescriptions for LMWH or NOAC during discharge. For example, one might allow patients to take LMWH injections home with them bypassing the pharmacy or only offer antithrombotic treatment during hospitalization.

Regardless, due to the lack of information on this patient group it is impossible to draw any conclusion in regards to our measured outcomes, therefore we excluded this group from the analysis.

We performed an exclusion analysis on these patients to determine if their removal from the study group affected our results. We found that the VTE-incidence for the patients that had been excluded was similar to the study group (0.4 %). See appendix.

One of the selection criteria for the study group was that the patient needed to have purchased their prescription within 10 days of the index operation. This was intended to exclude highly comorbid patients but could have also unintentionally excluded a portion of NOAC patients that were forced to remain in the hospital longer due to wound drainage.

Our study only included patients who underwent primary THA and had been diagnosed with osteoarthritis. Yet, there are other large patient groups such as hip fractures, tumors etc. that undergo hip surgery. Despite the magnitude of the difference in effectiveness recorded, it is important to further investigate safety risks associated with NOAC that was not captured within the framework of this study. The optimal way of pursuing this objective is via phase-IV clinical studies such as the XAMOS study for rivaroxaban (39).

Nonetheless, the magnitude of the difference between the NOAC and LMWH population in terms of effectiveness challenges the traditional mindset of LMWH being the gold standard thromboprophylactic medication after THA. Future studies will have to examine this relationship further in other patient cohorts going through THA.

Populärvetenskaplig sammanfattning (In Swedish)

I Sverige utförs fler än tiotusen höftprotesoperationer varje år och så stora kirurgiska ingrepp medför alltid en risk för patienten att drabbas av komplikationer efter operationen. En av de vanligaste komplikationerna är uppkomsten av blodproppar i benen som kan föras vidare via blodbanan och ge upphov till en livshotande propp i lungan.

För att förhindra detta behandlas samtliga höftprotespatienter med proppförebyggande läkemedel under en till flera veckor efter operation. Behandlingen ges vanligen genom sprutor med lågmolekylärt heparin (LMH) men de senaste åren används även s.k. NOAK-tabletter.

I denna studie har vi jämfört förekomsten av proppar upp till tre månader efter operationen hos patienter som tagit LMH och NOAK. Studien baseras på data från svenska höftprotesregistret för tidsperioden 2008-2012 vilka i en tidigare studie samkörts med läkemedelsregistret och patientregistret. 30000 patienter behandlades med LMH och 5700 patienter med NOAK. Förekomsten av proppar i LMH-gruppen var 1.0% och i NOAK-gruppen 0.4%. Vi fann ca 60% lägre risk att få proppar hos NOAK-gruppen och vi fann ingen märkbar skillnad vad avser blödningar, omoperationer eller dödsfall mellan grupperna.Våra resultat överensstämmer med tidigare forskning, men nu för första gången med en större grupp patienter.

Således har denna studie bättre än tidigare studier klargjort risken för proppar och andra biverkningar efter en höftprotesoperation. Dock krävs ytterligare forskning för att också studera andra eventuella risker med användandet av NOAK vilka inte inkluderats i denna studie.

Våra resultat talar dock starkt för den enklare och för patienten mer skonsamma NOAK metoden och emot den traditionella LMH metoden som den effektivaste behandlingen mot proppbildning efter en höftprotesoperation.

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Appendix

Table 2. ICD-10 codes used to define outcome.

VTE	DVT	PE	Major bleeding				Minor bleeding	
I82.8	I81.9	I26.0	R04.1	K27.0	H43.1	I61.4	J38.3J	K625
I82.2	I82.9	I26.9	R04.8	K27.2	H45.0*	I61.5	O90.2	L608J
I82.3	I82.8		R04.9	K27.4	I60.0	I61.6	O71.7	N421
I26.0	I82.2		R23.3	K27.6	I60.1	I61.8	T14.5	N501A
I26.9	I82.3		R23.3W	K28.0	I60.2	I61.9	N89.7	N922
I81.9			R58.9	K28.2	I60.3	I62.0	N83.6	N923
I82.9			S06.4	K28.4	I60.4	I62.1	N83.7	N924
			S06.40	K28.6	I60.5	I62.9	AAD10	N930
			S06.41	D62.9	I60.6	I85.0	AAD05	N938
			T81.0	H31.3	I60.7	I98.3*	AAB30	N939
			K92.2	H35.6	I60.8	K22.6	AAD15	N950
			K25.6	H35.6A	I60.9	K25.0	AAD00	N950A
			K26.0	H35.6B	I61.0	K25.2	ABB40	N950B
			K26.2	H35.6C	I61.1	K25.4	TQX05	N950W
			K26.4	H35.6W	I61.2		H113	N950X
			K26.6	H35.6X	I61.3		H922	T140A

Table 3. Treating units with missing data from Prescribed Drug Register

Unit	Missing (n)	Existing (n)	Total (n)	Missing (%)	VTE (n)	DVT (n)	PE (n)
Aleris Specialistvård Elisabethsjukhuset	4	309	313	1%	0	0	0
Aleris Specialistvård Motala	1028	68	1096	94%	8	5	3
Aleris Specialistvård Nacka	8	406	414	2%	0	0	0
Aleris Specialistvård Sabbatsberg	4	456	460	1%	0	0	0
Alingsås	152	648	800	19%	0	0	0
Art Clinic Jönköping	1	6	7	14%	0	0	0
Arvika	5	644	649	1%	0	0	0
Bollnäs	12	932	944	1%	0	0	0
Borås	28	458	486	6%	0	0	0
Capio Movement	750	115	865	87%	0	0	0
Capio Ortopediska Huset	25	1560	1585	2%	1	0	1
Capio S:t Göran	166	1275	1441	12%	2	1	1
Carlanderska	11	388	399	3%	0	0	0
Danderyd	68	942	1010	7%	1	1	0
Eksjö	696	84	780	89%	5	2	3
Enköping	31	1009	1040	3%	0	0	0
Eskilstuna	117	147	264	44%	1	0	1
Falköping	11	497	508	2%	0	0	0
Falun	154	1051	1205	13%	0	0	0
Frölunda Specialistsjukhus	54	293	347	16%	0	0	0
Gällivare	11	295	306	4%	0	0	0
Gävle	58	378	436	13%	1	0	1
Halmstad	317	408	725	44%	0	0	0
Helsingborg	75	63	138	54%	0	0	0
Hudiksvall	2	366	368	1%	0	0	0
Hässleholm-Kristianstad	2599	368	2967	88%	12	4	8
Jönköping	576	132	708	81%	3	1	2
Kalmar	478	56	534	90%	0	0	0
Karlshamn	12	792	804	1%	0	0	0
Karlskoga	4	494	498	1%	0	0	0
Karlskrona	2	26	28	7%	0	0	0
Karlstad	15	594	609	2%	0	0	0
Karolinska/Huddinge	48	647	695	7%	1	0	1
Karolinska/Solna	62	474	536	12%	1	0	1
Katrineholm	416	564	980	42%	1	0	1
Kungälv	94	535	629	15%	0	0	0
Köping	44	10	54	81%	0	0	0
Lidköping	8	534	542	1%	0	0	0
Lindesberg	13	720	733	2%	0	0	0
Linköping	125	23	148	84%	0	0	0
Ljungby	533	56	589	90%	3	2	1
Lycksele	575	605	1180	49%	3	1	2
Mora	40	719	759	5%	1	1	0

Motala	447	47	494	90%	1	1	0
Norrköping	689	67	756	91%	1	0	1
Norrtälje	19	349	368	5%	0	0	0
Nyköping	512	44	556	92%	0	0	0
Ortho Center IFK-kliniken	2	42	44	5%	0	0	0
Oskarshamn	780	57	837	93%	1	0	1
Piteå	14	1437	1451	1%	0	0	0
Skellefteå	10	279	289	3%	1	0	1
Skene	18	381	399	5%	0	0	0
Skövde	3	468	471	1%	0	0	0
Sollefteå	12	438	450	3%	1	0	1
Sophiahemmet	16	647	663	2%	0	0	0
Spenshult	50	365	415	12%	0	0	0
SU/Mölndal	42	851	893	5%	2	2	0
SU/Östra	12	98	110	11%	0	0	0
Sunderby	2	25	27	7%	0	0	0
Sundsvall	163	461	624	26%	0	0	0
SUS/Lund	72	16	88	82%	0	0	0
SUS/Malmö	72	25	97	74%	0	0	0
Södersjukhuset	80	1009	1089	7%	1	1	0
Södertälje	38	375	413	9%	1	0	1
Torsby	6	371	377	2%	0	0	0
Trelleborg	1979	386	2365	84%	8	6	3
Uddevalla	176	910	1086	16%	2	0	2
Umeå	27	208	235	11%	0	0	0
Uppsala	176	487	663	27%	1	1	0
Varberg	88	707	795	11%	0	0	0
Visby	102	318	420	24%	1	0	1
Värnamo	446	70	516	86%	2	1	1
Västervik	365	32	397	92%	2	1	1
Västerås	124	1031	1155	11%	1	0	1
Växjö	393	45	438	90%	1	0	1
Ängelholm	34	408	442	8%	0	0	0
Örebro	458	66	524	87%	1	0	1
Örnsköldsvik	4	610	614	1%	0	0	0
Östersund	32	791	823	4%	1	1	0

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