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Effectiveness and safety of different duration of thromboprophylaxis in 16,865 hip replacement patients - A real-word, prospective observational study

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ABSTRACT

Introduction: Clinical trials have provided evidence about efficacy and safety of extended thromboprophylaxis among total hip replacement (THR) patients. There is a lack of evidence on effectiveness and safety of extended treatment in unselected patients from routine clinical practice. We examined the effectiveness and safety of short (1-6 days) and standard (7-27 days) compared with extended (≥28 days) thromboprophylaxis using population-based design.

Material and methods: Among all primary THR procedures performed in Denmark from 2010 through 2012 (n = 16,865), we calculated adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for risk of symptomatic venous thromboembolism (VTE) and major bleeding, in addition to net clinical benefit, defined as the number of VTE avoided minus the number of excess bleeding events occurring among patients prescribed short-term and standard versus extended treatment.

Results: The 90-day risks of VTE were 1.1% (short), 1.4% (standard), and 1.0% (extended), yielding aHRs of 0.83 (95% CI: 0.52-1.31) and 0.82 (95% CI: 0.50-1.33) for short and standard versus extended treatment. The risk of major bleeding was 1.1% (short), 1.0% (standard), and 0.7% (extended), resulting in aHRs of 1.64 (95% CI: 0.83-3.21) and 1.24 (95%CI: 0.61-2.51) for short and standard versus extended thromboprophylaxis. Direct comparison between benefits and harms using net clinical benefit analyses did not favor any of the three treatment durations. The same results were found for VTE or death.

Conclusions: In a real-word observational cohort of unselected THR patients, we observed no difference in the risks of symptomatic VTE, VTE/ death or bleeding with respect to thromboprophylaxis duration.

Introduction

Venous thromboembolism (VTE) is a well-recognized complication after total hip replacement (THR) surgery. Among patients receiving thromboprophylaxis, rates of symptomatic VTE within 90 days of THR ranged from 1% to 4% [1–5]. There has been less interest in arterial thromboembolic events after THR, although 0.3%-1.8% of patients have a myocardial infarction (MI) [6,7] and 0.2% [8,9] have an ischemic stroke in-hospital or within 90 days after THR surgery.

The thromboprophylaxis after major orthopedic surgery including THR is a well-accepted treatment, but the duration of the treatment has been a matter of debate for years [10]. The most recent version of the American College of Chest Physicians (ACCP) guidelines, from 2012, recommends use of anticoagulation drugs for a minimum of 10 to 14 days with grade 1B evidence and suggests extending prophylaxis for up to 35 days with grade 2B evidence [11]. The National Institute for Health and Care Excellence (NICE) guidelines from 2012 also recommended prophylaxis for 28-35 days, depending on the summary of product characteristics for the individual agent being used [12], whereas the guidelines from the American Academy of Orthopedic Surgeons (AAOS) from 2011 recommend individual assessment of the most optimal duration of thromboprophylaxis without any elaboration regarding which THR patients might benefit from extended prophylaxis [13]. Administration of extended thromboprophylaxis after THR has proven difficult in many clinical settings [14], and concerns about treatment benefit and risk in routine clinical practice have remained.

Successive clinical trials generally have been designed to compare the benefits and harms of standard (7-10 days) versus extended treatment duration [15], reporting the absolute risk reduction for VTE and bleeding or using the number needed to treat or harm measures. Estimates of these measures are almost always presented separately. In

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order to directly compare benefits and harms according to the duration of thromboprophylaxis we summarized all benefit and harmful outcomes into a single relative estimate used net clinical benefit analyses [16]. Thus, there is a lack of knowledge about the effectiveness and safety of treatment duration in unselected patients that are currently treated in routine clinical practice.

The primary objective of this study was to examine the risk of symptomatic VTE and major bleeding associated with short-term (1-6 days) and standard (7-27 days) thromboprophylaxis compared with extended (≥28 days) therapy. We also aim to directly quantify the net clinical benefit of short- and standard compared with extended treatment in a "real world" population-based unselected cohort of THR patients. The risk of MI and stroke are also reported.

Material and Methods

Study Design and Setting

We conducted this population-based cohort study using prospectively collected data available from nationwide Danish medical registries. The Danish National Health Service provides tax-supported healthcare for all Danish citizens; free medical care is guaranteed for emergency and general hospital admissions, as well as for outpatient clinic visits. The Danish Civil Registration System has maintained data on vital status, date of death, residence, and migration for the entire Danish population since 1968. All Danish citizens are assigned a unique 10-digit personal identification number at birth or upon immigration. This system permits unambiguous linkage among all Danish administrative and health registries, as well as tracking of patients that die, emigrate, or are transferred between hospitals [17].

Study Population

We used the Danish Hip Arthroplasty Registry (DHR) to identify all patients that underwent primary THR between 1 January 2010 and 31 December 2012 and to access their preoperative and surgery-related records. Primary THR was defined as first-time insertion of a unilateral total hip prosthesis [18] owing to primary osteoarthritis based on the surgeon's decision. In total, data on 18,928 THR patients, all of whom received pharmacological thromboprophylaxis, were extracted from DHR. We excluded 2,063 (10%) patients that lacked data regarding thromboprophylaxis duration or were registered as not receiving any thromboprophylaxis, leaving 16,865 THR patients in the analysis.

Pharmacological Thromboprophylaxis

We categorized the duration of pharmacological thromboprophylaxis prescribed in conjunction with THR as short-term (1-6 days), standard (7-27 days), or extended (>28 days) based on available guidelines for thromboprophylaxis and clinical practice in Denmark [19,20]. Allocation of duration of treatment was almost solely dependent on the local guidelines at the individual departments, thus, all patients operated at one department will receive the same length of treatment irrespective of their risk. Pharmacological agents included parenteral low-molecular-weight heparin (including enoxaparin, dalteparin, and tinzaparin) and fondaparinux, dabigatran, and rivaroxaban, initiated both pre- and post-operatively. Mechanical thromboprophylaxis is not widely used in Danish departments; when used, it is combined with pharmacological thromboprophylaxis [21].

VTE, MI, Stroke, Bleeding Events, and Death

Data regarding symptomatic VTE, major bleeding and other cardiovascular events were obtained from the Danish National Registry of Patients (DNRP). The DNRP has maintained data regarding all admissions to non-psychiatric hospitals in Denmark since 1977 and regarding all emergency room visits and visits to hospital specialty clinics since 1995. Recorded data include dates of admission and discharge, as well as up to 20 discharge diagnoses. The discharge diagnoses were classified according to the 8th edition of the *International Classification of Diseases* (ICD-8) until the end of 1993, and according to the 10th edition (ICD-10) thereafter.

The primary effectiveness outcome in our analyses was VTE, including deep venous thrombosis (DVT) and pulmonary embolism (PE) after THR. The primary safety outcomes were major bleeding events, including intracranial bleeding, gastrointestinal bleeding, and urinary/lung bleeding (see Table 1 in appendix for ICD codes).

As secondary outcomes we further assess the risk of MI and ischemic stroke after THR.

The proportion of hospitalized patients correctly registered in the DNRP with cardiovascular events and major bleeding has been reported as 75% to 95% [22–25]. Both primary and secondary diagnoses, which were coded by the physician at the discharge from the hospital or during the out-patient visit, were included in our study. The validity of diagnostic codes in emergency room contacts not leading to hospitalization is most likely low [24] because they are working diagnoses. We therefore did not include these contacts in the analyses. We did not have data from the general practitioners. However, any suspicion to VTE in Denmark would lead to hospitalization or out-patient clinic visit of the patients to confirm the diagnosis and initiate the treatment. No general practitioners in Denmark will start treatment for VTE without sending the patients pass the hospital.

Information on death due to any cause after THR surgery was collected from The Danish Civil Registration System.

Potential Confounding Factors

We obtained information on patient age and sex from the DHR (Table 1). The DNRP provided the complete hospitalization history of all patients for 10 years preceding the date of primary THR [26]. As a measure of comorbidity, we computed the Charlson Comorbidity Index (CCI) score [25,27] for each patient at the time of surgery (see Table 2 in appendix for ICD codes). We defined three comorbidity levels: a score of 0 (low), given to patients with no previous record of

Table 1
Characteristics of 16,865 patients that underwent total hip replacement in 2010, 2011, and 2012 in Denmark.

Patient characteristics	Short, 0-6 days, N = 4804, n (% of N)	Standard, 7-27 days, N = 6362, n (% of N)	Extended, +28 days, N = 5699, n (% of N)
Age, years			
10-49	357 (7.4%)	344 (5.4%)	303 (5.3%)
50-59	697 (14.5%)	784 (12.3%)	705 (12.3%)
60-69	1531 (31.9%)	1972 (31.0%)	1969 (34.5%)
70-79	1480 (30.8%)	2138 (33.6%)	1917 (33.6%)
80+	739 (15.4%)	1124 (17.7%)	805 (14.1%)
Sex, Female	2635 (54.8%)	3658 (57.5%)	3282 (57.8%)
Charlson Comorbidity Index score			
Low score (0)	3582 (76.6%)	4535 (71.3%)	4273 (74.9%)
Medium score (1,2)	995 (20.7%)	1459 (22.9%)	1156 (20.3%)
High score (≥3)	227 (4.7%)	368 (5.8%)	270 (4.7%)
Use of other drugs within 5 years of THR			
Acetylsalicylic acid, yes	1132 (23.6%)	1496 (23.5%)	1261 (22.1%)
Other platelet inhibitors, yes	155 (3.2%)	210 (3.3%)	178 (3.1%)
Vitamin K antagonist, yes	323 (6.7%)	417 (6.5%)	236 (4.1%)
Type of anticoagulation drug			
Enoxaparin	952 (19.8%)	249 (3.9%)	45 (0.8%)
Dalteparin	1197 (24.9%)	3784 (59.5%)	397 (6.9%)
Tinzaparin	273 (5.7%)	1341 (21.1%)	18 (0.3%)
Fondaparinux	862 (17.9%)	346 (0.5%)	7 (0.1%)
Dabigatran	35 (0.7%)	124 (1.9%)	2798 (49.1%)
Rivaroxaban	1485 (30.9%)	518 (8.1%)	2434 (42.7%)