■ HIP

Increased one-year risk of symptomatic venous thromboembolism following total hip replacement

A NATIONWIDE COHORT STUDY

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We examined the one-year risk of symptomatic venous thromboembolism (VTE) following primary total hip replacement (THR) among Danish patients and a comparison cohort from the general population. From the Danish Hip Arthroplasty Registry we identified all primary THRs performed in Denmark between 1995 and 2010 (n = 85 965). In all, 97% of patients undergoing THR received low-molecular-weight heparin products during hospitalisation. Through the Danish Civil Registration System we sampled a comparison cohort who had not undergone THR from the general population (n = 257 895). Among the patients undergoing THR, the risk of symptomatic VTE was 0.79% between 0 and 90 days after surgery and 0.29% between 91 and 365 days after surgery. In the comparison cohort the corresponding risks were 0.05% and 0.12%, respectively. The adjusted relative risks of symptomatic VTE among patients undergoing THR were 15.84 (95% confidence interval (CI) 13.12 to 19.12) during the first 90 days after surgery and 2.41 (95% CI 2.04 to 2.85) during 91 to 365 days after surgery, compared with the comparison cohort. The relative risk of VTE was elevated irrespective of the gender, age and level of comorbidity at the time of THR.

We concluded that THR was associated with an increased risk of symptomatic VTE up to one year after surgery compared with the general population, although the absolute risk is small.

Mortality has been reported to be higher for patients who undergo total hip replacement (THR) than for the corresponding general population within 30 days after surgery,[1] and THR is a recognised major risk for venous thromboembolism (VTE).[2,3] The risks of suffering symptomatic or asymptomatic VTE within three months after THR have been reported in randomised studies to range from 1.4% to 6%.[4,5] In the few available observational cohort studies, the cumulative risk of symptomatic VTE was found to be 2.8% and 1.7% at three months,[6,7] 1.3% at six months[8] and 2.6% one year after surgery.[9]

The benefits of pharmacological and non-pharmacological thromboprophylaxis in this group of patients has been clearly shown.[2] Extended thromboprophylaxis for four weeks after THR[4,10] is therefore recommended in current clinical guidelines.[2,11] However, clinical trials are often characterised by limited follow-up, a small sample size, and by being restricted to patients with few or no comorbidities, despite various comorbidities being well-known risk factors for VTE.[3] The findings from such trials may therefore be difficult to translate into clinical practice.[12] Furthermore, to our knowledge, only one study among middle-aged women has compared the risk of VTE after THR with the risk in the general population, reporting that within 12 weeks after surgery the risk of VTE after THR was higher than in the general population.[13] Comparing these two groups will allow the excess risk conferred by the surgery to be identified and to clarify whether the currently used methods of thromboprophylaxis are appropriate.

This observational population-based study involved using prospectively collected data from databases in Denmark to estimate the overall risk of VTE, including deep venous thrombosis (DVT) and pulmonary embolism (PE), among patients within one year of THR. We also compared the VTE risk in patients in different gender, age and comorbidity groups, with that in the general population.

Patients and Methods

Denmark has a total population of approximately 5.5 million inhabitants, who receive free medical care for both emergency and elective admissions to hospitals and outpatient clinics. At birth, all Danes are assigned a unique ten-digit personal identification number that allows unambiguous linkage between all Danish medical databases.[14]

The Danish Hip Arthroplasty Registry (DHR) contains data on > 95% of all patients

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Table I. Characteristics of patients who underwent total hip replacement (THR) and the comparison cohort, in Denmark, between 1995 and 2006 (VTE, venous thromboembolism)

	THR patients (n = 85 965)	Comparison cohort (n = 257 895)
Gender (n, %)		
Women	49 839 (58)	149 517 (58)
Men	36 126 (42)	108 378 (42)
Age group (n, %)		
10 to 59 years	17 480 (20)	52 627 (20)
60 to 69 years	26 083 (30)	78 084 (30)
70 to 79 years	28 873 (34)	86 625 (34)
≥ 80 years	13 529 (16)	40 559 (16)
Charlson score (n, %)		
Low (0)	54 598 (*64*)	171 671 (*67*)
Moderate (1 to 2)	24 770 (*29*)	67 707 (*26*)
High (≥ 3)	6597 (*8*)	18 517 (*7*)
VTE during 0 to 365 days after surgery (n, %)	924 (*1.06*)	437 (*0.17*)
VTE during entire follow-up (n, %)	2318 (*2.70*)	3331 (*1.29*)

undergoing primary or revision THR in Denmark since 1 January 1995.[15] The Danish Civil Registration System, a national registry of all Danish residents established in 1968, maintains data on vital status and residence for the entire Danish population.[16] The Danish National Registry of Patients contains data on all hospital admissions since 1977, and since 1995 for all hospital outpatient and emergency visits, including the dates of admission and discharge, and up to 20 discharge diagnoses recorded according to the International Classification of Diseases (ICD)[17] (Eighth edition until the end of 1993, Tenth edition thereafter).

Study population. We used the DHR to identify all patients undergoing their first primary THR between 1 January 1995 and 31 December 2010. Of these, 30 947 (36%) received dalteparin low-molecular-weight heparin (LMWH) (Fragmin; Pfizer ApS Denmark, Ballerup, Denmark), 31 804 (37%) received enoxaparin LMWH (Klexane; Sanofi-Aventis Denmark A/S, Horsholm, Denmark), 16 333 (19%) received tinzaparin LMWH (Innohep; LEO Pharma Nordic, Malmö, Sweden), 3438 (4%) received fondaparinux (Arixtra; GlaxoSmithKline Pharma A/S, Brondby, Denmark), and 3440 (4%) received a combination of drugs during hospitalisation. Information on the duration of thromboprophylaxis is not included as these data are only available after 2009 and have not yet been validated.

Using the Civil Registration System, for each patient who underwent THR we selected three subjects for comparison from the general population who had not undergone THR. These subjects were matched for gender and age at the time of surgery, and also had to be alive at the date of the corresponding THR patient's surgery (the index date). We used the National Registry of Patients to obtain information on all patients and comparison subjects who were treated for VTE (including DVT and PE) at an outpatient clinic, or hospitalised with VTE at a private or a public hospital, after the index date. ICD codes I26, I80.1–I80.9 and I82.1–I82.9 were used. We did not include diagnoses from emergency room visits without subsequent hospitalisation for VTE.[18]

Statistical analysis. Patients who underwent THR and comparison subjects entered the study on the date of surgery/index date and were followed until the date of first outpatient visit for symptomatic VTE, first inpatient admission (hospitalisation) for symptomatic VTE, death, emigration, or 1 January 2012, whichever came first. Comorbidity data were retrieved from the National Registry of Patients and included all primary and secondary diagnoses for all hospitalisations from 1 January 1977 and outpatient visits from 1 January 1995 until the surgery/index date. These data were used to compute Charlson comorbidity index (CCI) scores,[19] described in detail elsewhere[20] (Table I).

We computed the rate of hospitalisation for VTE as the number of VTE cases per 1000 person-years at risk and associated 95% confidence intervals (CI). A Kaplan–Meier life-table technique was used to calculate the cumulative risk of VTE. Analyses were conducted from 0 to 90 days and from 91 to 365 days following surgery. We also calculated the difference in rate by subtracting the VTE rates in the comparison cohort from the VTE rates in the patients undergoing THR, and the risk difference by subtracting the VTE risk in the comparison cohort from the VTE risk in the patients undergoing THR. In addition, the number needed to harm was calculated[21] as the inverse of the rate difference, which indicates how many patients need to undergo THR over a specific period to cause VTE in one patient who would not otherwise develop VTE. Cox's proportional hazards regression was used to estimate the crude and adjusted relative risk (RR) of VTE with 95% CI in order to study the association between THR and VTE. We stratified according to gender, age and CCI score at the time of surgery. The study was approved by the Danish Data Protection Agency.

Results

Descriptive data. A total of 85 965 patients who underwent THR and 257 895 comparison subjects were included in the study (Table I). The patients undergoing THR had slightly more comorbid conditions than the comparison cohort: the prevalence of CCI score of 1 or 2 at the time of surgery was 29% among patients undergoing THR *vs* 26% of the comparison cohort. Patient- and surgery-related characteristics of those undergoing THR have been described in detail elsewhere.[3]

0 to 90 days follow-up after THR. Within the first 90 days after surgery the risk of VTE was 0.79% among the patients undergoing THR and 0.05% in the comparison cohort, corresponding to a risk difference of 0.74% (95% CI 0.70 to 0.78) (Fig. 1a). The number needed to harm associated with THR was 134 (95% CI 127 to 149).

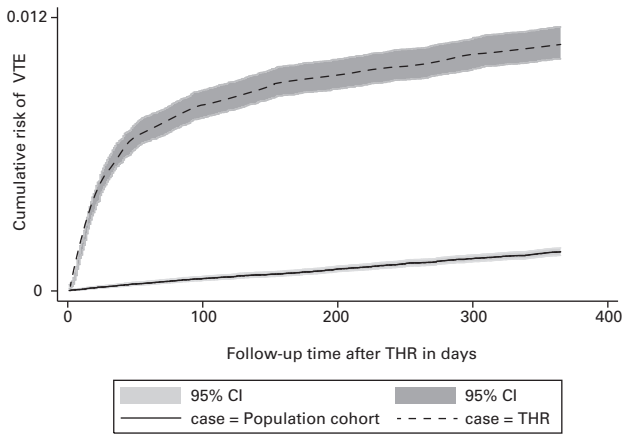

Fig. 1a

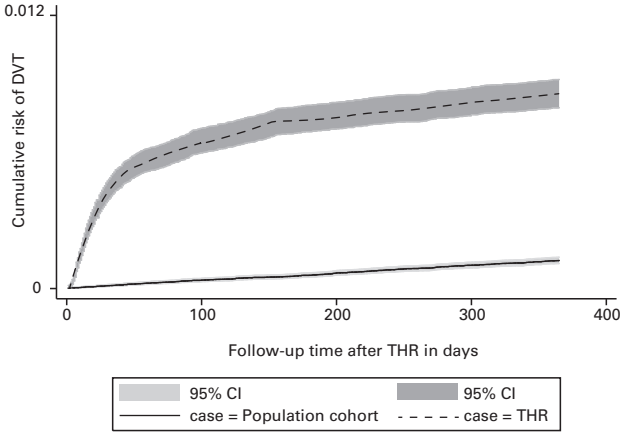

Fig. 1b

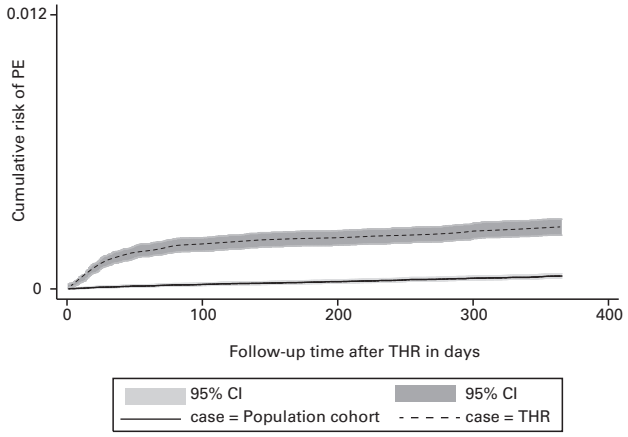

Fig. 1c

Kaplan–Meier estimates of the cumulative risk of a) venous thromboembolism (VTE), b) deep-vein thrombosis (DVT) and c) pulmonary embolism (PE) within 365 days of total hip replacement (THR) with 95% confidence intervals (CI).

During this period the rate of VTE in patients undergoing THR was 32.47 cases per 1000 person-years (95% CI 30.11 to 35.00), compared with 2.04 cases per 1000 person-years (95% CI 1.72 to 2.42) in the comparison cohort. Compared with the comparison cohort, patients undergoing THR were at a substantially increased risk of VTE within the first 90 days after surgery, with an RR of 15.84 (95% CI 13.12 to 19.12) and a rate difference of 30.43 (95% CI 27.96 to 32.92) VTE cases per 1000 person-years (Table II). The RR was particularly high in the first 30 days after surgery, at 26.97 (95% CI 20.19 to 36.02) and declining to 11.92 (95% CI 8.35 to17.02) during the 31 to 60 days and 5.32 (95% CI 3.61 to 7.85) during the 61 to 90 days after surgery.

Within the first 90 days after surgery the risk was 0.62% *vs* 0.03% for DVT and 0.19% *vs* 0.02% for PE in those undergoing THR and the comparison cohort, respectively (Figs 1b and 1c). The rates of DVT and PE within 90 days of surgery in THR patients and the comparison cohort are presented in Table II. We found the patients undergoing THR to have an RR of 18.24 (95% CI 14.56 to 22.86) for DVT and an RR of 10.65 (95% CI 7.68 to 14.78) for PE compared with the comparison cohort within 90 days of surgery.

91 to 365 days follow-up after THR. During the 91 to 365 days after surgery the risk of VTE was 0.29% among patients undergoing THR and 0.12% for the comparison cohort, corresponding to a risk difference of 0.17% (95% CI 0.14 to 0.20) (Fig. 1a). The number needed to harm associated with THR was 588 (95% CI 500 to 714). During this period the overall rate of VTE was 3.94 cases per 1000 person-years (95% CI 3.47 to 4.46) among patients undergoing THR and 1.62 cases per 1000 person-years (95% CI 1.45 to 1.81) among the comparison cohort. During the 91 to 365 days following THR the difference in rate was 2.32 (95% CI 1.79 to 2.84) VTE cases per 1000 person-years and the adjusted RR for VTE among patients undergoing THR was 2.41 (95% CI 2.04 to 2.85) compared with the comparison cohort (Table II).

In patients undergoing THR the rate of VTE was highest during the 91 to 150 days following THR, with 6.76 cases

Table II. Risk rates with 95% confidence intervals (CI) of venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE), in patients undergoing total hip replacement (THR) and the comparison cohort, according to time since surgery. The numbers of DVT and PE events separately is higher than the number of VTE events, because few patients who experienced more than one event were counted once in VTE

	THR patients (n = 85 965)	Comparison cohort (n = 257 895)	Adjusted relative risk (95% CI)
0 to 90 days after THR			
VTE (n/risk, %)	678 (*0.79*)	129 (*0.05*)	-
DVT (n/risk, %)	534 (*0.62*)	88 (*0.03*)	-
PE (n/risk, %)	163 (*0.19*)	46 (*0.02*)	-
VTE rate per 1000 person-years	32.47 (30.11 to 35.00)	2.04 (1.72 to 2.42)	15.84 (13.12 to 19.12)
DVT rate per 1000 person-years	25.54 (23.46 to 27.80)	1.39 (1.13 to 1.71)	18.24 (14.56 to 22.86)
PE rate per 1000 person-years	7.76 (6.66 to 9.05)	0.73 (0.54 to 0.97)	10.65 (7.68 to 14.78)
91 to 365 days after THR			
VTE (n/risk, %)	246 (*0.29*)	308 (*0.12*)	-
DVT (n/risk, %)	193 (*0.23*)	226 (*0.09*)	-
PE (n/risk, %)	65 (*0.08*)	97 (*0.04*)	-
VTE rate per 1000 person-years	3.94 (3.47 to 4.46)	1.62 (1.45 to 1.81)	2.41 (2.04 to 2.85)
DVT rate per 1000 person-years	3.08 (2.68 to 3.55)	1.19 (1.04 to 1.36)	2.58 (2.13 to 3.12)
PE rate per 1000 person-years	1.03 (0.81 to 1.31)	0.51 (0.42 to 0.62)	2.01 (1.46 to 2.75)

Table III. Effect of gender, age and Charlson comorbidity score at the time of surgery on the association between total hip replacement (THR) and the risk of venous thromboembolism (VTE) according to time since surgery

	0 to 90 days after THR			91 to 365 days after THR		
	THR cohort (no. VTEs, %)	Comparison cohort (no. VTEs, %)	Adjusted relative risk (95% CI)	THR cohort (no. VTEs, %)	Comparison cohort (no. VTEs, %)	Adjusted relative risk (95% CI)
Gender						
Women	393/49 839 (*0.78*)	72/149 517 (*0.04*)	16.44 (12.79 to 21.14)	111/48 687 (*0.23*)	180/148 189 (*0.12*)	1.86 (1.47 to 2.35)
Men	285/36 126 (*0.78*)	57/108 378 (*0.21*)	15.07 (11.34 to 20.03)	135/35 268 (*0.38*)	128/107 284 (*0.12*)	3.19 (2.51 to 4.07)
Age						
10 to 59 years	170/17 480 (*0.96*)	18/52 627 (*0.03*)	28.38 (17.46 to 46.15)	45/17 204 (*0.26*)	54/52 544 (*0.10*)	2.50 (1.68 to 3.71)
60 to 69 years	243/26 083 (*0.92*)	39/78 084 (*0.05*)	18.70 (13.34 to 26.23)	78/25 645 (*0.30*)	84/77 697 (*0.11*)	2.79 (2.05 to 3.80)
70 to 79 years	190/28 873 (*0.65*)	52/86 625 (*0.06*)	11.04 (8.12 to 14.99)	89/28 231 (*0.31*)	120/85 694 (*0.14*)	2.25 (1.71 to 2.95)
≥ 80 years	75/13 529 (*0.55*)	20/40 559 (*0.05*)	11.44 (6.99 to 18.74)	34/12 875 (*0.26*)	50/39 538 (*0.13*)	2.07 (1.34 to 3.21)
Charlson score						
Low (0)	436/54 598 (*0.79*)	75/171 671 (*0.04*)	18.54 (14.51 to 23.69)	151/53 748 (*0.28*)	181/171 071 (*0.11*)	2.64 (2.13 to 3.28)
Moderate (1 to 2)	200/24 770 (*0.80*)	38/67 707 (*0.06*)	14.24 (10.07 to 20.15)	76/24 000 (*0.32*)	91/66 659 (*0.14*)	2.33 (1.72 to 3.17)
High (≥ 3)	42/6597 (*0.63*)	16/18 514 (*0.09*)	7.21 (4.05 to 12.83)	19/6207 (*0.31*)	36/17 743 (*0.20*)	1.52 (0.87 to 2.64)

per 1000 person-years (95% CI 5.12 to 8.29), declining to 3.14 cases per 1000 person-years (95% CI 2.68 to 3.68) during the 151 to 365 days following THR. Among the comparison cohort the rates were similar during the entire 91 to 365-day period, being 1.41 cases per 1000 person-years (95% CI 1.09 to 1.82) during the 91 to 150 days after surgery and 1.68 cases per 1000 person-years (95% CI 1.50 to 1.91) during the 151 to 365 days after surgery. The adjusted RR estimate was 4.80 (95% CI 3.45 to 6.62) during the 91 to 150 days following THR, declining to 1.85 (95% CI 1.51 to 2.27) during the 151 to 365 days following THR.

During the 91 to 365 days after surgery the risk was 0.23% *vs*. 0.09% for DVT and 0.08% *vs* 0.04% for PE in patients undergoing THR and the comparison cohort, respectively (Figs 1b and 1c). We found patients undergoing THR to have an RR of 2.58 (95% CI 2.13 to 3.12) for DVT and of 2.01 (95% CI 1.46 to 2.75) for PE compared with the comparison cohort during the 91 to 365 days after surgery.

Effect of gender, age and comorbidity on the association between THR and VTE. Within the first 90 days after surgery the relative VTE risk was markedly increased for both women (RR 16.44 (95% CI 12.79 to 21.14)) and men (RR 15.07 (95% CI 11.34 to 20.03)). In the same period, the relative VTE risk was 10 to 30 times higher in patients undergoing THR in different age categories, but particularly high for patients aged < 60 years (RR 28.38 (95% CI 17.46 to 46.15)). In addition, patients undergoing THR had a 7- to 18-fold higher risk of VTE than the comparison cohort, depending on the CCI score at the time of surgery (Table III).

During the 91 to 365 days after surgery the relative VTE risk was one to three times higher for patients undergoing

THR than for the comparison cohort, irrespective of age, gender and CCI score at the time of surgery.

Discussion

Our large nationwide population-based study involving 85 965 patients undergoing THR provides evidence that THR is associated with an increased risk of symptomatic VTE up to one year after surgery compared with a comparison cohort from the general population, although the absolute risk is small. The VTE risk was elevated irrespective of the THR patient's gender, age and comorbidity at the time of surgery.

Main findings compared with other studies. The VTE risk within 90 days after surgery observed in this study is lower than that previously reported in randomised clinical trials.[4,5] Such trials typically follow a standardised protocol with ultrasound screening of patients, and include both symptomatic and asymptomatic VTE events, whereas our study focused on symptomatic events that required hospitalisation. The length of follow-up in clinical trials is often restricted to 90 days after surgery. The long-term VTE risk beyond 90 days among orthopaedic patients has therefore not been studied in randomised clinical trials. Two observational cohort studies reported three-month post-operative rates of symptomatic VTE of 1.7% and 2.8%, respectively, a six-month rate of 1.3%[8] and a one-year post-operative rate of 2.6%,[9] which are slightly higher than our findings. In both studies patients were not routinely screened for VTE.

The absolute estimates of VTE rates among patients undergoing THR are important in the management of these patients, but have to be compared with the VTE risk in the absence of THR. In a cohort study, Sweetland et al[13] found that within 12 weeks after surgery the risk of VTE in patients undergoing THR was > 130 relative to subjects not having surgery, which is much higher than the RR of about 15.84 found in our study in the same post-operative period. The study by Sweetland et al[13] was based on healthy middle-aged women with a mean age of 56 years, and does not reflect the average THR population, who in Denmark have a mean age of about 68 years.[22] Nevertheless, the 12-week incidence rate of VTE after hip and knee replacement among these younger women was 92 per 1000 person-years, compared with 32.47 per 1000 person-years among our older patients undergoing THR. Thus, these women were for some reason highly susceptible to VTE. Further, in the study by Sweetland et al[13] the general population had a very low VTE incidence rate of 0.7 per 1000 person-years, compared with 2.04 per 1000 person-years in our general population. Another difference between the studies relates to the outcome, as Sweetland et al[13] included patients who died if VTE was registered as an underlying cause of death, and we did not. Thus, the true magnitude of the association between THR and VTE risk is likely to be overestimated in their study, although the results of both studies point in the same direction.

The duration of pharmacological thromboprophylaxis currently recommended in the American College of Chest Physicians (ACCP) guidelines (9th edition) from 2012[2] is four weeks. Our study presents evidence that the risk for VTE after surgery among patients undergoing THR is substantial within 90 days after surgery, far beyond the current duration of hospitalisation, which is a mean of < ten days,[23] and beyond the four weeks of pharmacological thromboprophylaxis recommended in Denmark.[11] However, we accept that our study does not permit us to state whether or not the use of thromboprophylaxis conferred any benefit on the incidence of VTE in patients undergoing THR.

It is an interesting finding that the absolute VTE risk decreased with greater age in patients undergoing THR, whereas the absolute risk among the comparison cohort was consistently low across age groups. The increased RR among younger patients undergoing THR might reflect system-related factors, such as a lower level of awareness by health professionals towards the prevention, detection and treatment of thromboembolic complications in patients considered to be at low risk. In theory, younger patients might suffer from more severe comorbidities, or physicians may be less prone to record all comorbidities in younger patients undergoing THR than in controls, but this is hard to prove.

Several mechanisms underlying the short-term association between THR and VTE have been suggested.[24,25] Long-term elevation of the risk of VTE after surgery is also supported by increasing evidence that the activation of the coagulation–fibrinolytic system occurs during surgery and persists for at least two months.[26] This was confirmed in our study, as VTE rates among patients undergoing THR dropped substantially after 90 days, approaching the VTE rates of the general population, albeit still twice as high. Given previous research showing that VTE may be associated with mortality,[27] recurrent VTE,[28] venous stasis syndrome[29] and long-term risk of subsequent arterial cardiovascular events,[30] it is clear that patients undergoing THR require careful post-operative observation far beyond the hospitalisation period.

Methodological considerations. The validity of our findings is dependent on the accuracy of the registry data used. A previous study[15] documented high data quality in the Danish Hip Arthroplasty Registry. A diagnosis of VTE in the National Registry of Patients could, after review of the medical records, be confirmed in 75% to 95% of the patients,[18,20] and the accuracy of the VTE diagnosis is most likely to be independent of THR status. On the other hand, we cannot exclude the possible surveillance bias that might include a higher level of awareness by physicians towards the detection and use of VTE diagnosis in high-risk THR patients compared with the background population. We included both inpatient and outpatient symptomatic VTE diagnoses, which enables comparison with studies from other countries where most patients with VTE are treated as outpatients. We focused on symptomatic VTE, which should be kept in mind when comparing our results to studies based

on screening for VTE. Screening of patients after THR is not part of standard clinical practice in Denmark. Furthermore, we were able to adjust for a wide range of comorbid conditions,[20] but we lacked information on their severity. In addition, data on potential confounders such as smoking, alcohol, body mass index, physical activity and use of drugs such as non-steroidal anti-inflammatory drugs were not available in the registries used. We lack the autopsy results producing more conservative estimates of the overall VTE risk, but this would not have affected the relative risk estimates. Information on pharmacological thromboprophylaxis (yes/no) in relation to THR surgery has been collected by the DHR, but has yet not been validated.

In conclusion, THR was associated with an increased risk of symptomatic VTE up to one year after surgery compared with the general population, although the absolute risk was small. The risk of VTE was elevated irrespective of the gender, age or level of comorbidity at time of undergoing THR.

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