Symptomatic In-Hospital Deep Vein Thrombosis and Pulmonary Embolism Following Hip and Knee Arthroplasty Among Patients Receiving Recommended Prophylaxis

A Systematic Review

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Context Symptomatic venous thromboembolism (VTE) after total or partial knee arthroplasty (TPKA) and after total or partial hip arthroplasty (TPHA) are proposed patient safety indicators, but its incidence prior to discharge is not defined.

Objective To establish a literature-based estimate of symptomatic VTE event rates prior to hospital discharge in patients undergoing TPHA or TPKA.

Data Sources Search of MEDLINE, EMBASE, and the Cochrane Library (1996 to 2011), supplemented by relevant articles.

Study Selection Reports of incidence of symptomatic postoperative pulmonary embolism or deep vein thrombosis (DVT) before hospital discharge in patients who received VTE prophylaxis with either a low-molecular-weight heparin or a subcutaneous factor Xa inhibitor or oral direct inhibitor of factors Xa or IIa.

Data Extraction and Synthesis Meta-analysis of randomized clinical trials and observational studies that reported rates of postoperative symptomatic VTE in patients who received recommended VTE prophylaxis after undergoing TPHA or TPKA. Data were independently extracted by 2 analysts, and pooled incidence rates of VTE, DVT, and pulmonary embolism were estimated using random-effects models.

Results The analysis included 44 844 cases provided by 47 studies. The pooled rates of symptomatic postoperative VTE before hospital discharge were 1.09% (95% CI, 0.85%-1.33%) for patients undergoing TPKA and 0.53% (95% CI, 0.35%-0.70%) for those undergoing TPHA. The pooled rates of symptomatic DVT were 0.63% (95% CI, 0.47%-0.78%) for knee arthroplasty and 0.26% (95% CI, 0.14%-0.37%) for hip arthroplasty. The pooled rates for pulmonary embolism were 0.27% (95% CI, 0.16%-0.38%) for knee arthroplasty and 0.14% (95% CI, 0.07%-0.21%) for hip arthroplasty. There was significant heterogeneity for the pooled incidence rates of symptomatic postoperative VTE in TPKA studies but less heterogeneity for DVT and pulmonary embolism in TPKA studies and for VTE, DVT, and pulmonary embolism in TPHA studies.

Conclusion Using current VTE prophylaxis, approximately 1 in 100 patients undergoing TPKA and approximately 1 in 200 patients undergoing TPHA develops symptomatic VTE prior to hospital discharge.

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POSTOPERATIVE VENOUS thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism, is an important safety issue in acute care hospitals.[1] Without prophylaxis, VTE (both symptomatic and asymptomatic) is the most frequent surgical adverse event after infections.[2] In the absence of prophylactic therapy, the incidence of postoperative VTE is particularly high after orthopedic surgery: the incidence of DVT (as detected by screening tests) varies from 42% to 57% after hip arthroplasty and from 41% to 85% after knee arthoplasty; the incidence of pulmonary embolism varies from 0.9% to 28% after hip arthroplasty

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CME available online at www.jamaarchivescme.com and questions on p 312.

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and from 1.5% to 10% after knee arthroplasty.[3] Although asymptomatic VTE is more common than symptomatic VTE, available data demonstrate that symptomatic VTE is clinically important, while the clinical relevance of asymptomatic VTE is less clear.[3-5]

Systematic prophylaxis of VTE has been implemented for more than 20 years,[4] supported by numerous guidelines.[3,4,6-10] For example, low-molecular-weight heparin (LMWH), a proven efficacious prophylactic therapy, has been increasingly used since 1995.[11] More recently, other efficacious prophylactic therapies have been studied, including indirect and direct inhibitors of factors Xa and IIa.[12]

Large numbers of patients worldwide undergo hip and knee replacement procedures annually, and VTE is a widely acknowledged complication. Yet no estimate of symptomatic VTE risk prior to hospital discharge is available from the literature that can be conveyed to patients in the informed consent process. Furthermore, rates of in-hospital VTE are often studied and reported, in the context of safety reviews, without a benchmark based on expected rates of events. Accordingly, there is a need to fully understand the risk of symptomatic VTE when appropriate prophylactic therapy is given perioperatively. In this systematic review, we establish a contemporary literature-based estimate of symptomatic VTE event rates prior to hospital discharge in patients undergoing total or partial hip arthroplasty (TPHA), and total or partial knee arthroplasty (TPKA) who received recommended VTE prophylaxis during their hospitalization.

METHODS

We searched studies that reported symptomatic postoperative DVT, pulmonary embolism, or both that occurred during the hospital stay in adult patients undergoing TPKA, TPHA, or both who received recommended VTE prophylaxis. We followed the PRISMA statement for conduct and reporting of systematic reviews.[13]

Search Strategy and Data Sources

We conducted a systematic search of publications listed in MEDLINE, EMBASE, and the Cochrane Library from January 1, 1996, to September 30, 2011. We used keywords targeting surgical intervention (TPHA, TPKA, or both), VTE prophylaxis, VTE outcomes, and study design. The detailed search strategy is presented in eTable 1, available at http://www.jama.com). This search strategy was applied to titles and abstracts, without language restrictions. We identified additional articles by contacting authors working in this field and searching cited references of relevant articles.

Inclusion Criteria

We included randomized clinical trials (RCTs) testing efficacious VTE prophylaxis regimens and observational studies of patients receiving VTE prophylaxis that reported confirmed postoperative symptomatic VTE that occurred before hospital discharge following TPHA, TPKA, or both in adult (≥18 years) inpatients. We included only patients allocated to receive recommended VTE prophylaxis (guidelines[3,4,6-10] and drug agencies' recommendations): LMWH or direct and indirect Xa and IIa factor inhibitors.[14,15]

Because there are no standardized diagnostic criteria for both proximal and distal symptomatic DVT, we accepted diagnoses based on a clinical suspicion confirmed by venography or ultrasonography[16-18] or one of these tests combined with impedance plethysmography.[19] For pulmonary embolism, a standard definition exists, based on clinical symptoms confirmed by perfusion/ventilation scintigraphy, pulmonary angiography, or spiral computed tomography.[20,21]

Two investigators (J.M.J., G.C.) independently screened titles and abstracts and eventually examined the full text of original articles for study inclusion.

Data Extraction and Quality Assessment

We extracted data that described the studies, patients, type of prophylaxis, and VTE events. Study characteristics comprised study design (RCT, observational), study year, number of centers, country, and potential conflict of interest. Patients characteristics included average age, proportion of women, hip vs knee arthroplasty, and the study population inclusion and exclusion criteria. To characterize VTE events, we recorded the mean length of stay, opportunities to detect VTE, number of symptomatic postoperative VTE events that occurred between surgery and hospital discharge (numerator), and methods used for determining symptomatic postoperative DVT and pulmonary embolism. We also extracted the number of risk-exposed study population (denominator) for calculating the VTE rate.

Two investigators (J.M.J., B.B.) assessed study quality following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[22] Because GRADE is designed to compare interventions, whereas our goal was to provide a benchmark value for VTE events in patients receiving this intervention, we used only the appropriate elements of GRADE: allocation concealment, blinding, sparse data, attrition bias, indirectness (external validity), potential measurement bias, and potential conflict of interest, at study level. Other elements were considered at group level: risk of bias, imprecision, inconsistency, indirectness, and publication bias.

Statistical Analysis

We calculated pooled proportions of symptomatic postoperative DVT and pulmonary embolism. We used a fixed-effects model where appropriate, weighting each estimate by its standard error, using the Mantel-Haenszel method and a random-effects model according to the method of DerSimonian and Laird.[23,24] We

evaluated heterogeneity using I^2 statistics,[25,26] interpreting a value of $I^2 > 50\%$ as substantial heterogeneity; when I^2 statistics indicated substantial heterogeneity using a fixed-effects model, we considered intracluster homogeneity as not assessed.

We thus used a random-effects model to evaluate subgroup characteristics. Using stratified analyses, we explored the following predefined sources of potential heterogeneity: proportion of women (<60% vs ≥60%), average age (<65 years vs ≥65 years), length of stay between surgery and hospital discharge (<8 days vs ≥8 days), type of VTE prophylaxis (LMWH vs direct Xa or IIa factor inhibitors vs indirect Xa or IIa factor inhibitors), study design (RCT vs observational), country (mostly Europe vs mostly North America vs others), study publication year (1996 to 2005 vs 2006 to 2011), potential limitations (yes vs no), and potential generalizibility (yes vs no). We included cutpoints for patient sex, age, and length of stay, defined empirically based on the variables' distribution from the studies, in our systematic review (eg, average of the mean value or average/median proportion in the studies). In addition, we investigated potential publications bias in our meta-analysis.[27,28] We used the updated commands METAN and METABIAS in Stata version 11.0 for the analyses.

RESULTS

Eight-hundred forty citations were found, from which 47 studies were eventually included (eFigure 1). Of these, 6 were observational studies[29-34] and 41 were RCTs.[35-75] Twenty-one studies included patients undergoing hip arthroplasty,[35-55] 20 included those undergoing knee arthroplasty,[29,30,56-72,75] and 6 included both.[31-34,73,74] More than 1 prophylactic drug was used in several studies (eg, case group using pentassacharide and control group using enoxaparin). Thus, there were 38 active treatment groups for hip arthroplasty and 39 for knee arthroplasty.

The 47 studies recruited 44 844 patients[29-75] (21 369 undergoing TPHA and 23 475 undergoing TPKA). eTables 2-4 summarize, respectively, the characteristics of the 21 TPHA studies,[35-55] the 20 TPKA studies,[29,30,56-72,75] and the 6 studies for both TPHA and TPKA,[31-34,73,74] which reported 443 cases of symptomatic postoperative VTE that occurred between surgery and patient hospital discharge, 288 in the patients undergoing knee arthroplasty and 155 in those undergoing hip arthroplasty. Of these cases, 275 were DVT (182 in the TPKA group and 93 in the TPHA group) and 149 were pulmonary embolism (106 in the TPKA group and 43 in the TPHA group). Symptomatic DVT was confirmed by means of ultrasonography, bilateral venography, or both in 32 studies (68%),* by duplex ultrasonography in 5 studies (11%),[29-31,43,56] and by one of these in 10 studies (21%).† Pulmonary embolism was confirmed by one of the following methods in all studies: lung ventilation/perfusion scintigraphy, spiral computed tomography, pulmonary angiography, or autopsy in patients who died.

Description of Studies and Population

Study and population characteristics, including prophylactic treatments, are presented in eTables 2-4 for studies including patients undergoing TPHA, those undergoing TPKA, and those undergoing both TPHA and TPKA. Of the 47 studies, 22 were conducted primarily in Europe, 14 primarily in North America, and 11 primarily in several countries, including studies conducted worldwide.

Study sample sizes ranged from 40 to 1599 for TPKA and from 21 to 2512 for TPHA. The proportion of women ranged from 12% to 85%; it was less than 60% in 8 of 32 treatment groups for TPKA and 29 of 32 for TPHA. The mean patient age ranged from 62.0 years to 74.0 years for TPKA and from 58.0 years to 70.0 years for TPHA. The mean durations of follow-up after surgery were 13 (SD, 6) days (range, 8-35) for TPKA and 13 (SD, 2) days (range, 8-17) for TPHA. In 1 study,[34] postoperative pulmonary embolism was fatal in 2 of 3 cases of pulmonary embolism reported among patients undergoing TPKA.

Pooled Incidence Rates of Venous Thromboembolism Complications and Heterogeneity

FIGURE 1 and FIGURE 2 show the pooled incidence rates of symptomatic postoperative VTE across studies, using random-effects models, among patients undergoing TPHA and TPKA, respectively. Similarly, eFigures 2 through 5 show the pooled incidence rates of symptomatic postoperative DVT and pulmonary embolism. In patients undergoing TPHA, the pooled incidence rates were 0.53% (95% CI, 0.35%-0.70%) for symptomatic postoperative VTE, 0.26% (95% CI, 0.14%-0.37%) for DVT, and 0.14% (95% CI, 0.07%-0.21%) for pulmonary embolism (Figure 1, eFigures 2 and 3).

In patients undergoing TPKA, the pooled incidence rates were 1.09% (95% CI, 0.85%-1.33%) for symptomatic postoperative VTE, 0.63% (95% CI, 0.47%-0.78%) for DVT, and 0.27% (95% CI, 0.16%-0.38%) for pulmonary embolism (Figure 2, eFigures 4 and 5).

In patients undergoing TPKA, the pooled incidence rates of symptomatic postoperative VTE were significantly heterogeneous ($I^2 = 55.7\%$ [$P < .001$]); the pooled incidence rates of symptomatic postoperative DVT and pulmonary embolism indicated less heterogeneity ($I^2 = 36.0\%$ [$P = .02$] and $I^2 = 39.4\%$ [$P = .007$], respectively). For patients undergoing TPHA, similar heterogeneity was observed for the pooled incidence rates of symptomatic postoperative VTE and DVT ($I^2 = 49.4\%$ [$P < .001$] and $I^2 = 37.0\%$ [$P = .01$], respectively). The pooled incidence rates of symptomatic postoperative pulmonary embolism were associated with $I^2 = 0.0\%$ ($P > .99$).

*References 33, 35-38, 40-42, 45-47, 50-52, 54, 55, 57-64, 66-69, 71, 73-75.
†References 32, 34, 39, 44, 48, 49, 53, 65, 70, 72.

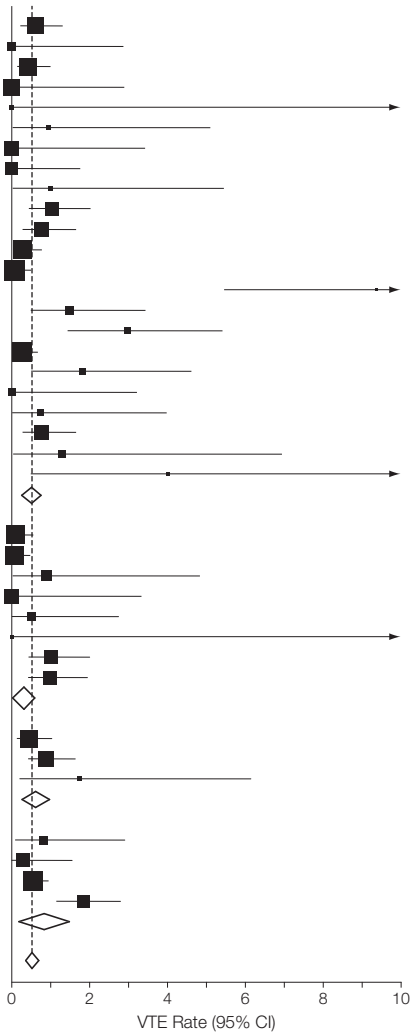
Stratified Analysis

The TABLE reports stratified pooled incidence rates of symptomatic postoperative VTE by characteristics potentially contributing to heterogeneity. Heterogeneity between studies was present in all strata, for TPHA as well as TPKA studies. This stratified analysis provided different estimates of the pooled incidence rates for VTE and DVT between subgroups and between TPHA and TPKA. The incidence of VTE differed according to the type of prophylaxis therapy.

For patients treated with LMWH prophylaxis, the pooled incidence rates of VTE were 1.42% (95% CI, 1.02%-1.83%) in TPKA studies and 0.58% (95% CI, 0.35%-0.81%) in TPHA studies. With oral direct inhibitors of factor Xa or IIa, the pooled incidence rates of VTE were 0.81% (95% CI, 0.54%-1.07%) for TPKA studies and 0.31% (95% CI, 0.03%-0.59%) for TPHA studies. In addition, there were different estimates between TPKA and TPHA for studies with an average proportion of women less than 60%, for studies with an average proportion of patients younger than 65 years, and for studies set mostly in Europe vs mostly in North America (eTable 1).

Figure 1. Forest Plots and Pooled Event Rates of Symptomatic VTE That Occurred Before Hospital Discharge in Postoperative TPHA Patients Receiving Recommended VTE Prophylaxis

Subgroup/Source	Sample Size, No.	Events, No. DVT	PE	VTE	VTE Rate (95% CI)
RCTs—LMWH					
Eriksson et al,[35] 2011 (RE-NOVATE II)	992	4	2	6	0.60 (0.22-1.31)
Eriksson et al,[36] 2010 (ONYX-2)	127	0	0	0	0.00 (0.00-2.86)
Kakkar et al,[37] 2008 (RECORD2)	1172	1	4	5	0.43 (0.14-0.99)
Lassen et al,[38] 2008 (DRIVE)	126	0	0	0	0.00 (0.00-2.89)
Eriksson et al,[39] 2007 (ONYX)	31	0	0	0	0.00 (0.00-11.22)
Eriksson et al,[40] 2006 (OXIDa-OD-HIP)	107	1	0	1	0.93 (0.02-5.10)
Erikson et al,[41] 2006 (OXIDa-HIP)	106	0	0	0	0.00 (0.00-3.42)
Eriksson et al,[73] 2005 (BISTRO II)	208	0	0	0	0.00 (0.00-1.76)
Pitto et al,[43] 2004	100	1	0	1	1.00 (0.03-5.45)
Colwell et al,[44] 2003	775	8	0	8	1.03 (0.45-2.02)
Eriksson et al,[74] 2003 (METRO III)	789	5	1	6	0.76 (0.28-1.65)
Lassen et al,[46] 2002 (EPHESUS)	1123	1	2	3	0.27 (0.06-0.78)
Turpie et al,[45] 2002 (PENTATHLON 2000)	1128	0	1	1	0.09 (0.00-0.49)
Turpie et al,[47] 2001	171			16	9.36 (5.44-14.75)
Hull et al,[48] 2000	337	5	0	5	1.48 (0.48-3.43)
Hull et al,[48] 2000	336	10	0	10	2.98 (1.44-5.41)
Colwell et al,[49] 1999	1516	2	2	4	0.26 (0.07-0.67)
Planès et al,[50] 1999	219	3	1	4	1.83 (0.50-4.61)
Lassen et al,[51] 1998 (DaPP)	113	0	0	0	0.00 (0.00-3.21)
Warwick et al,[52] 1998	138	1	0	1	0.72 (0.02-3.97)
Eriksson et al,[53] 1997	785	4	2	6	0.76 (0.28-1.66)
Samama et al,[54] 1997	78	1	0	1	1.28 (0.03-6.94)
Yoo et al,[55] 1997	50	1	1	2	4.00 (0.49-13.71)
Subtotal (I^2 = 45.4%, P = .01)					0.51 (0.26-0.76)
RCTs—oral direct factor Xa/IIa inhibitor					
Eriksson et al,[35] 2011 (RE-NOVATE II)	1001	0	1	1	0.10 (0.00-0.56)
Kakkar et al,[37] 2008 (RECORD2)	1183	0	1	1	0.08 (0.00-0.47)
Eriksson et al,[40] 2006 (OXIDa-OD-HIP)	113	0	1	1	0.88 (0.02-4.83)
Eriksson et al,[41] 2006 (OXIDa-HIP)	109	0	0	0	0.00 (0.00-3.33)
Eriksson et al,[73] 2005 (BISTRO II)	201	0	1	1	0.50 (0.01-2.74)
Eriksson et al,[42] 2004 (BISTRO I)	21	0	0	0	0.00 (0.00-16.11)
Colwell et al,[44] 2003	782	4	4	8	1.02 (0.44-2.01)
Eriksson et al,[74] 2003 (METRO III)	806	8	0	8	0.99 (0.43-1.95)
Subtotal (I^2 = 32.8%, P = .07)					0.31 (0.03-0.59)
RCTs—indirect factor Xa/IIa inhibitor					
Lassen et al,[46] 2002 (EPHESUS)	1129	3	2	5	0.44 (0.14-1.03)
Turpie et al,[45] 2002 (PENTATHLON 2000)	1126	5	5	10	0.89 (0.43-1.63)
Turpie et al,[47] 2001	115	2	0	2	1.74 (0.21-6.14)
Subtotal (I^2 = 0.0%, P = .38)					0.62 (0.26-0.97)
Observational studies—LMWH					
Kerr and Linkins,[31] 2010	246	1	1	2	0.81 (0.10-2.91)
Abad et al,[32] 2007	356	1	0	1	0.28 (0.01-1.56)
Bjørnarå et al,[33] 2006	2512	9	5	14	0.56 (0.31-0.93)
Leclerc et al,[34] 1998	1142	15	6	21	1.84 (1.14-2.80)
Subtotal (I^2 = 67.3%, P = .23)					0.83 (0.19-1.48)
Overall (I^2 = 49.4%, P <.001)					0.53 (0.35-0.70)



Systematic literature review of studies published between January 1, 1996, and September 31, 2011. Random-effects model. DVT indicates deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; TPHA, total or partial hip arthroplasty; VTE, venous thromboembolism. Data marker sizes correspond to the weight each study contributed to the analysis.

No differences were observed between RCTs and observational studies for LMWH prophylaxis (1.24% [95% CI, 0.87%-1.60%] vs 1.71% [95% CI, 0.56%-2.86%] in patients undergoing TPKA and 0.51% [95% CI, 0.26%-0.76%] vs 0.83% [95% CI, 0.19%-1.48%] in those undergoing TPHA) (Figures 1 and 2).

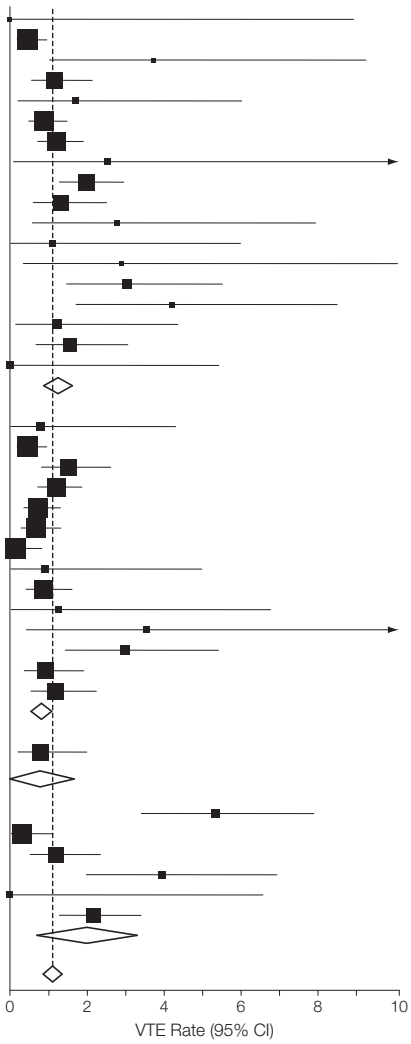
Testing for Publication Bias and Summaries of GRADE Evaluation

The potential for publication bias was assessed using Begg funnel plots of effect size against standard error in TPKA and TPHA treatment groups. In TPKA studies, the incidence rate distributions of symptomatic postoperative VTE in LMWH (RCTs), oral direct factor Xa/IIa inhibitor (RCTs), and LMWH (observational studies) groups were broadly symmetrical, with insignificant statistical testing of funnel plot asymmetry for 2 of these 3 groups (P=.18, P=.04, and P=.14, respectively).

In TPHA studies, the incidence rate distribution of symptomatic

Figure 2. Forest Plots and Pooled Event Rates of Symptomatic VTE That Occurred Before Hospital Discharge in Postoperative TPKA Patients Receiving Recommended VTE Prophylaxis

Subgroup/Source	Sample Size, No.	Events, No. DVT	PE	VTE	VTE Rate (95% CI)
RCTs—LMWH					
Windisch et al,[56] 2011	40	0	0	0	0.00 (0.00-8.81)
Lassen et al,[58] 2010 (ADVANCE 2)	1529	7	0	7	0.46 (0.18-0.94)
Weitz et al,[59] 2010	109	2	2	4	3.67 (1.01-9.13)
Ginsberg et al,[60] 2009 (RE-MOBILIZE)	868	5	5	10	1.15-0.55-2.11)
Lassen et al,[61] 2009 (TREK)	119	1	1	2	1.68 (0.20-5.94)
Lassen et al,[62] 2009 (ADVANCE 1)	1596	7	7	14	0.88 (0.48-1.47)
Turpie et al,[63] 2009 (RECORD4)	1508	10	8	18	1.19 (0.71-1.88)
Turpie et al,[64] 2009 (EXPERT)	40	1	0	1	2.50 (0.06-13.16)
Lassen et al,[65] 2008 (RECORD3)	1217	20	4	24	1.97 (1.27-2.92)
Eriksson et al,[66] 2007 (RE-MODEL)	685	8	1	9	1.31 (0.60-2.48)
Lassen et al,[75] 2007 (APROPOS)	109	1	2	3	2.75 (0.57-7.83)
Eriksson et al,[73] 2005 (BISTRO II)	92	1	0	1	1.09 (0.03-5.91)
Turpie et al,[68] 2005	70	2	0	2	2.86 (0.35-9.94)
Eriksson et al,[74] 2003 (METRO III)	333	9	1	10	3.00 (1.45-5.45)
Navarro-Quilis et al,[70] 2003	168	5	2	7	4.17 (1.69-8.40)
Navarro-Quilis et al,[70] 2003	165	2	0	2	1.21 (0.15-4.31)
Bauer et al,[71] 2001	517	4	4	8	1.55 (0.67-3.03)
Blanchard et al,[72] 1999	67	0	0	0	0.00 (0.00-5.36)
Subtotal (I^2 = 36.7%, P = .06)					1.24 (0.87-1.60)
RCTs—oral direct factor Xa/IIa inhibitor					
Fuji et al,[57] 2010	129	1	0	1	0.78 (0.02-4.24)
Lassen et al,[58] 2010 (ADVANCE 2)	1528	3	4	7	0.46 (0.18-0.94)
Ginsberg et al,[60] 2009 (RE-MOBILIZE)	857	7	6	13	1.52 (0.81-2.58)
Lassen et al,[62] 2009 (ADVANCE 1)	1599	3	16	19	1.19 (0.72-1.85)
Turpie et al,[63] 2009 (RECORD4)	1526	6	5	11	0.72 (0.36-1.29)
Lassen et al,[65] 2008 (RECORD3)	1201	8	0	8	0.67 (0.29-1.31)
Eriksson et al,[66] 2007 (RE-MODEL)	675	1	0	1	0.15 (0.00-0.82)
Lassen et al,[75] 2007 (APROPOS)	111	1	0	1	0.90 (0.02-4.92)
Colwell et al,[67] 2005 (EXULT B)	1151	8	2	10	0.87 (0.42-1.59)
Eriksson et al,[73] 2005 (BISTRO II)	81	0	1	1	1.23 (0.03-6.69)
Turpie et al,[68] 2005	57	0	2	2	3.51 (0.43-12.11)
Eriksson et al,[74] 2003 (METRO III)	340	9	1	10	2.94 (1.42-5.34)
Francis et al,[69] 2003 (EXULT A)	757	5	2	7	0.92 (0.37-1.90)
Francis et al,[69] 2003 (EXULT A)	769	7	2	9	1.17 (0.54-2.21)
Subtotal (I^2 = 42.5%, P = .047)					0.81 (0.54-1.07)
RCT—indirect factor Xa/IIa inhibitor					
Bauer et al,[71] 2001	517	3	1	4	0.77 (0.21-1.97)
Subtotal					0.77 (0.00-1.65)
Observational studies—LMWH					
Kerr and Linkins,[31] 2010	437	3	20	23	5.26 (3.37-7.79)
Abad et al,[32] 2007	653	2	0	2	0.31 (0.04-1.10)
Bjørnarå et al,[33] 2006	675	6	2	8	1.19 (0.51-2.32)
Hitos and Fletcher,[29] 2006	283	9	2	11	3.89 (1.96-6.85)
Niazi et al,[30] 2006	55	0	0	0	0.00 (0.00-6.49)
Leclerc et al,[34] 1998	842	15	3[a]	18	2.14 (1.27-3.36)
Subtotal (I^2 = 84.0%, P < .001)					1.98 (0.69-3.27)
Overall (I^2 = 55.7%, P < .001)					1.09 (0.85-1.33)



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[a]Two fatal PE included.

Table. Pooled Event Rates of Symptomatic VTE That Occurred Before Hospital Discharge in Postoperative Patients Receiving Recommended VTE Prophylaxis for TPHA or TPKA, Stratified by Patient Characteristics and Study Quality Factors[a]

Variables	Symptomatic VTE in Patients Undergoing TPHA					Symptomatic VTE in Patients Undergoing TPKA				
	No.		Pooled Event Rate, % (95% CI)	Heterogeneity		No.		Pooled Event Rate, % (95% CI)	Heterogeneity	
	Studies	Sample		I^2 (%)	*P* Value[b]	Studies	Sample		I^2 (%)	*P* Value[b]
Total	38	21 369	0.53 (0.35-0.70)	49.4	<.001	39	23 475	1.09 (0.85-1.33)	55.7	<.001
Women, %										
<60	29	16 049	0.47 (0.28-0.66)	50.4	.001	8	3740	2.00 (1.23-2.77)	49.8	.49
≥60	3	773	1.85 (0.77-2.94)	0.0	.40	24	18 119	0.85 (0.62-1.07)	48.4	.12
Missing	6	4547	0.58 (0.33-0.84)	0.0	.68	7	1616	1.54 (0.84-2.25)	10.0	.42
Average age, y										
<65	16	8994	0.42 (0.19-0.65)	42.2	.04	6	4477	1.70 (0.81-2.59)	73.4	.64
≥65	15	7778	0.66 (0.29-1.02)	63.2	.001	28	17 477	0.93 (0.69-1.18)	49.3	.15
Missing	7	4597	0.59 (0.34-0.84)	0.0	.65	5	1521	1.77 (0.91-2.63)	13.7	.15
Time of outcome measurement, d										
<14	27	4981	0.72 (0.44-1.01)	53.9	.001	18	8089	1.22 (0.78-1.66)	61.6	<.001
≥14	5	4567	0.25 (0.01-0.49)	43.1	.13	17	14 101	0.92 (0.68-1.16)	36.4	.07
Missing	6	4821	0.40 (0.19-0.60)	0.0	.70	4	1285	2.23 (0.11-4.35)	73.8	.01
Prophylaxis										
LMWH	27	14 783	0.58 (0.35-0.81)	51.8	.001	24	12 177	1.42 (1.02-1.83)	60.4	<.001
Oral direct factor Xa or IIa inhibitor	8	4216	0.31 (0.03-0.59)	32.8	.14	14	10 781	0.81 (0.54-1.07)	42.5	.047
Indirect factor Xa or IIa inhibitor	3	2370	0.62 (0.26-0.97)	0.0	.38	1	517	0.77 (0.21-1.97)	NA	NA
Design										
Observational	4	4256	0.83 (0.19-1.48)	67.3	.03	6	2945	1.98 (0.69-3.27)	84.0	<.001
RCT	34	17 113	0.47 (0.29-0.65)	42.9	.005	33	20 530	0.97 (0.76-1.19)	40.4	.01
Countries										
Mostly North America	11	7674	1.05 (0.55-1.56)	79.9	<.001	13	6991	1.41 (0.97-1.85)	45.6	.04
Mostly Europe	23	11 190	0.39 (0.25-0.53)	0.0	.83	14	6392	1.12 (0.61-1.62)	63.8	.001
Worldwide	2	2355	0.21 (0.00-0.53)	47.3	.17	9	9625	0.77 (0.53-1.00)	26.4	.21
Other	2	150	1.43 (0.00-3.94)	0.0	.41	3	467	1.65 (0.00-3.95)	58.9	.09
Year of publication										
2006-2011	14	8181	0.26 (0.12-0.39)	0.0	.64	24	17 549	0.98 (0.70-1.27)	62.6	<.001
1996-2005	24	13 188	0.75 (0.47-1.02)	60.9	<.001	15	5926	1.31 (0.92-1.69)	17.8	.25
Allocation concealment										
No	10	6231	0.67 (0.29-1.06)	43.1	.07	8	3052	1.67 (0.53-2.81)	78.1	<.001
Yes	27	15 025	0.50 (0.30-0.70)	52.0	.001	30	20 383	0.99 (0.77-1.21)	45.2	.004
Uncertain	1	113	0.00 (0.00-3.21)	NA	NA	1	40	2.50 (0.06-13.16)	NA	NA
Blinding, both patients/professionals										
No	10	6112	0.63 (0.27-0.99)	37.2	.11	9	3092	1.69 (0.58-2.80)	75.1	<.001
Yes	25	14 858	0.45 (0.28-0.63)	40.8	.02	30	20 383	0.99 (0.77-1.21)	45.2	.004
Uncertain	3	399	3.20 (0.00-7.64)	85.8	.001				NA	NA
Sparse data										
No	9	8888	1.00 (0.61-1.39)	64.1	.004	21	16 943	1.03 (0.74-1.32)	68.6	<.001
Yes	29	12 481	0.23 (0.12-0.33)	0.0	.63	18	6532	1.28 (0.82-1.74)	34.8	.06
Attrition bias										
No	15	8660	0.91 (0.62-1.20)	24.3	.18	18	8569	1.55 (1.05-2.04)	62.6	<.001
Yes	22	12 659	0.31 (0.15-0.47)	33.4	.06	20	14 866	0.84 (0.61-1.07)	41.5	.03
Uncertain	1	50	4.00 (0.49-13.71)	NA	NA	1	40	0.00 (0.00-8.81)	NA	NA
Indirectness, external validity										
No	20	10 066	0.53 (0.28-0.77)	45.3	.02	27	20 208	1.10 (0.83-1.36)	61.6	<.001
Yes	7	4321	0.77 (0.35-0.70)	21.5	.26	3	1025	1.63 (0.00-3.46)	61.8	.07
Uncertain	11	6982	0.44 (0.12-0.75)	59.8	.006	9	2242	0.93 (0.31-1.55)	24.4	.23
Potential measurement bias										
No	32	18 057	0.51 (0.32-0.69)	48.2	.001	34	21 205	0.98 (0.77-1.18)	39.3	.01
Yes	6	3312	0.72 (0.03-1.40)	60.8	.03	4	2215	2.65 (0.64-4.67)	90.2	<.001
Uncertain				NA	NA	1	55	0.00 (0.00-6.49)	NA	NA
Potential conflict of interest										
No	1	246	0.81 (0.10-2.91)	NA	NA	1	437	5.26 (3.37-7.79)	NA	NA
Yes	33	16 941	0.49 (0.30-0.69)	50.3	.001	34	21 985	0.99 (0.77-1.21)	47.8	.001
Uncertain	4	4182	0.65 (0.38-0.92)	0.0	.43	4	1053	1.52 (0.06-3.09)	43.2	.15

Abbreviations: LMWH, low-molecular-weight heparin; NA, not applicable; RCT, randomized controlled trial; TPHA, total or partial hip arthroplasty; TPKA, total or partial knee arthroplasty; VTE, venous thromboembolism.

[a] Studies that examined effectiveness of VTE prophylaxis in hip and knee arthroplasty patients published between January 1, 1996, and May 30, 2011. Two tables presenting the same results for deep vein thrombosis and pulmonary embolism are available from authors.

[b] For evaluation of subgroups characteristics heterogeneity using random effects by I^2 statistic.

postoperative VTE in LMWH (RCTs), oral direct factor Xa/IIa inhibitor (RCTs), indirect factor Xa/IIa inhibitor (RCTs), and LMWH (observational studies) groups was broadly symmetrical, with insignificant statistical testing results in 3 of these 4 groups ($P=.01$, $P=.19$, $P=.60$, and $P=.497$, respectively).

eTable 5 presents a summary of quality assessment, using GRADE, of the included studies, which showed some limitations. Individual subgroup and pooled estimates showed consistency, but large confidence intervals indicated lack of precision; indeed, 95% CI estimates ranged widely for all RCT and observational studies. A potential measurement bias was present in less than 13% of RCTs, whereas it was present in between 67% and 75% of observational studies. Indirectness of evidence varied largely between subgroups (0%-93%).

COMMENT

This meta-analysis reports pooled in-hospital incidence rates of symptomatic postoperative VTE of approximately 1% after TPKA and approximately 0.5% after TPHA in patients who received recommended VTE prophylaxis during their hospitalization. These pooled rate estimates indicate that, under contemporary prophylactic regimens, approximately 1 in every 100 patients undergoing TPKA and 1 in every 200 patients undergoing TPHA will experience a VTE event before hospital discharge. These estimates are of value to individual patients and clinicians in the consideration of risks and benefits of TPKA and TPHA, as well as to individuals and organizations seeking to evaluate institutional VTE event rates against contemporary benchmarks. Our above-mentioned rate estimates provide these contemporary benchmarks.

Most published studies report 2% to 3% and 2% to 5% rates of symptomatic VTE occurring during the 3-month period after TPKA and TPHA, respectively,[3,76-80] and find that a large proportion of symptomatic postoperative VTEs occur after hospital discharge.[3] In our review, 37 studies assessed patients after discharge; symptomatic VTE was reported in 21 studies, showing an occurrence rate ranging from 0% to 3.4% at 4 to 12 weeks after discharge. Interestingly, and consistently with the study by Douketis et al,[76] we found pooled incidence rates of symptomatic VTE after TPKA higher than rates after TPHA before hospital discharge. This contrasts with the observation that VTE occurred significantly more commonly after TPHA than after TPKA when the postdischarge period is included.[3,76-78] Indeed, White et al[78] observed that VTE was diagnosed before discharge in 53% and 24% of patients undergoing TPKA or TPHA, respectively. One explanation may be related to the site of venous injury: TPKA tends to injure smaller calf veins which, if thrombosed, become symptomatic faster, whereas TPHA tends to injure larger femoral veins, which would take more time to become occluded and manifest with symptoms.

Our results allow us to propose a benchmark value for the incidence of postoperative VTE that could be used to examine the validity of a patient safety indicator based on routinely collected data such as the Patient Safety Indicators from the Agency for Healthcare Research and Quality.[81,82] Given that these rates are based on the results of rigorous studies, they may represent a lower incidence than actual rates observed in clinical practice, in which patients are selected less rigorously and prophylaxis is administered less assiduously. In addition, our inclusion of studies that examined different types of prophylaxis allows us to provide expected rates for several treatments. The expected value also could be adjusted to the type of therapy proposed in a given setting or country. Actually, the oral direct inhibitors of factor Xa or IIa were associated with lower pooled incidence rates of DVT in both TPKA and TPHA compared with prior treatments. However, we cannot make assertions regarding comparative efficacy among treatments, because our meta-analyses did not directly compare LMWH with oral direct inhibitors of factor Xa or IIa, as an efficacy meta-analysis would have done.

If the rate of postoperative VTE events were to become a widely used patient safety indicator, one may wonder how the observation window could be enlarged to encompass a longer period (eg, 3 months) to obtain a more stable and accurate estimate of such events. The problem is the availability of the information that could not be derived from hospital discharge data. Yet another element to be considered is the lower postoperative VTE incidence in the more recent studies, when compared with older studies. The pooled incidence rates of symptomatic DVT were 0.50% in the 2006 to 2011 period and 0.94% in the 1996 to 2005 period for patients undergoing TPKA. In comparison, the pooled incidence rates of symptomatic DVT were 0.09% in the most recent period (2006-2011) and 0.43% between 1996 and 2005 in patients undergoing TPHA. Similar secular time trends have been observed in patients undergoing TPKA.[80] Although asymptomatic DVT occurs more frequently than symptomatic DVT, the latter unequivocally is considered clinically important, whereas there is limited evidence as to the importance of venographically detected asymptomatic DVT, the vast majority of such thrombi being limited to the calf.[4,5] Symptomatic DVT could thus be considered an indicator of patient safety, not the true rate of postoperative DVT.

A strength of this study is that we included studies with symptomatic VTE as the primary outcome occurring before patients' hospital discharge. All symptomatic VTE outcomes were confirmed by objective tests. In the studies included in this systematic review, all patients received evidence-based VTE prophylaxis,[3,4,6-10] on average for 8 days.

This study has some limitations. Our search strategy may have missed

some studies, especially observational studies, which were not published or not found. Most studies included in this meta-analysis were RCTs. Thus, the case-mix of participants in these RCTs may be different from clinical characteristics of patients outside of a clinical trial setting. Indeed, we found limitations in external validity. A lower VTE occurrence rate may thus be expected because patients with comorbid conditions would tend to be excluded from RCTs. However, the attentive follow-up of patients in RCTs also may have contributed to a higher discovery rate of symptomatic VTE events than in usual care. The observed heterogeneity across the RCTs selected to estimate the incidence rate of VTE and DVT indicates that there may not only be 1 universal expected value for such events. In addition, the value of DVT as a patient safety indicator remains controversial among experts.[83] All agree that the main goal of thromboprophylaxis in patients undergoing knee or hip arthroplasty is to prevent postoperative pulmonary embolism. However, all detected cases of DVT would be considered clinically important and would warrant anticoagulant therapy, because they are symptomatic and occurred after a major provoking risk factor.

Additional possible limitations include potential interactions between thromboprophylaxis and other factors (eg, year of publication, country).[2] For example, the studies reporting the effectiveness of oral direct inhibitors of factors Xa or IIa have been published since 2006, in contrast with many of the LMWH studies published earlier. Last, the differing event rates across methods of prophylaxis should not be interpreted as evidence on comparative efficacy, because the treatments were not assessed in a randomized comparison in a common pool of patients.

In conclusion, using current VTE prophylaxis, approximately 1 in every 100 patients undergoing TPKA and approximately 1 in every 200 patients undergoing TPHA develops symptomatic VTE prior to hospital discharge. These values could be used as a benchmark to evaluate patient safety indicators derived from routinely collected data.

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Study concept and design: Januel, Chen, Quan, Colin, Ghali, Burnand.
Acquisition of data: Januel, Chen, Quan.
Analysis and interpretation of data: Januel, Chen, Ruffieux, Quan, Douketis, Crowther, Burnand.
Drafting of the manuscript: Januel, Chen, Quan, Burnand.
Critical revision of the manuscript for important intellectual content: Chen, Ruffieux, Quan, Douketis, Crowther, Colin, Burnand.
Statistical analysis: Januel, Chen, Ruffieux, Quan.
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Administrative, technical, or material support: Chen, Quan, Crowther, Ghali, Burnand.
*Study supervision:*Crowther, Colin, Ghali, Burnand.
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