Evaluation of the duration of thromboembolic prophylaxis after high-risk orthopaedic surgery: The ETHOS observational study

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Summary

Real-life data on post-discharge venous thromboembolism (VTE) prophylaxis practices and treatments are lacking. We assessed post-operative VTE prophylaxis prescribed and received in a prospective registry, compared with the 2004 American College of Chest Physicians (ACCP) guidelines in high-risk orthopaedic surgery patients. Consecutive patients undergoing total hip arthroplasty (THA), hip fracture surgery (HFS), or knee arthroplasty (KA) were enrolled at discharge from 161 centres in 17 European countries if they had received in-hospital VTE prophylaxis that was considered in accordance with the ACCP guidelines by the treating physician. Data on prescribed and actual prophylaxis were obtained from hospital charts and patient post-discharge diaries. Post-operative prophylaxis prescribed and actual prophylaxis received were considered adherent or adequate, respectively, if recommended therapies were used for ≥28 days (HFS and THA) or ≥10 days (KA). Among 4,388 patients, 69.9% were prescribed ACCP-adherent VTE prophylaxis (THA: 1,411/2,217 [63.6%]; HFS: 701/1,112 [63.0%]; KA: 955/1,059 [90.2%]). Actual prophylaxis received was described in 3,939 patients with an available diary after discharge (non-evaluability rate of 10%). Mean actual durations of pharmacological prophylaxis from surgery were: 28.4 ± 13.7 (THA), 29.3 ± 13.9 (HFS), and 28.7 ± 14.1 days (KA). ACCP-adequate VTE prophylaxis was received by 66.5% of patients (60.9% THA, 55.4% HFS, and 88.7% KA). Prophylaxis inadequacies were mainly due to inadequate prescription, non-recommended prophylaxis prescription at discharge, or too short prophylaxis prescribed. In high-risk orthopaedic surgery patients with hospital-initiated prophylaxis, there is a gap between ACCP recommendations, prescribed and actual prophylaxis received, mainly due to inadequate prescription at discharge.

Keywords

Hip fracture surgery, knee arthroplasty, prophylaxis, total hip arthroplasty, venous thromboembolism

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Introduction

Surgical patients are at risk of developing venous thromboembolism (VTE), and without thromboprophylaxis, up to 60% of high-risk orthopaedic surgery (OS) patients develop deep-vein thrombosis (DVT) (1). A recent study showed that bleeding, DVT and pulmonary embolism (PE), arising after knee arthroplasty (KA), are all independent predictors for death, stressing the importance of preventing these events in this patient population (2). Peri-operative thromboprophylaxis has been shown to significantly reduce the incidence of VTE in surgical patients (1, 3, 4).

In patients undergoing high-risk OS, including total hip arthroplasty (THA), KA, and hip fracture surgery (HFS), the risk for post-operative VTE persists for several weeks after hospital discharge (5–8), and extended post-discharge anticoagulant prophylaxis has been shown to be effective in preventing VTE (9–13). The 2004 American College of Chest Physicians (ACCP) guidelines recommend that thromboprophylaxis is extended for ≥28 days after HFS and THA, and ≥10 days following KA (14, 15).

Recent findings suggest that despite these recommendations, thromboprophylaxis is globally underused after OS even in hospital (8, 16–20). Substantially less data are available describing VTE prophylaxis prescription at/after hospital discharge (8) or regarding physicians' adherence to current guidelines for VTE prevention. Moreover, there is little or no information regarding the actual or "real-life" prophylaxis received by patients after discharge.

The Evaluation of duration of THromboembolic prophylaxis after major Orthopaedic Surgery (ETHOS) registry was a prospective, multinational, observational study for the evaluation of the adequacy of prophylaxis actually received by patients following high-risk OS, compared with the 2004 ACCP recommendations for VTE prophylaxis (14). To avoid including patients who received no form of prophylaxis in the study, only patients who received VTE prophylaxis that was considered in accordance with the ACCP

guidelines by the treating physician during their hospital stay after high-risk OS were considered. The ETHOS study evaluated the post-operative VTE prophylaxis prescribed (particularly with regard to the type of treatment and duration), and the actual VTE prophylaxis received during the full post-operative period (i.e. in-hospital stay and post-discharge) as compared with the 2004 ACCP recommendations. The ETHOS registry did not collect information on VTE and bleeding outcomes, as this was not an objective of the study.

Methods

Centres

In total, 17 European countries participated in the ETHOS registry. Orthopaedic wards were eligible for enrolment if they performed >50 high-risk OS procedures (HFS, THA, and KA) annually. Lists of all hospitals that perform high-risk OS were obtained in each country. Selection of potential eligible orthopaedic centres was performed at the country level. The ETHOS principal investigator in each country validated the list of eligible centres. An independent clinical research organisation (CRO) randomly selected the centres for study participation; randomisation stratified according to ward size (centres with more or less than 100 high-risk OS interventions annually). In each country, eligible centres began consecutive patient recruitment simultaneously and recruitment between centres was competitive. The ETHOS study was conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Epidemiology Practice. Locally appointed ethics committees approved the study research protocol, and informed consent was obtained from all patients.

The planned study sample size calculation per country was based on the two-sided 95% confidence interval (CI) of the frequency of patients treated according to the 2004 ACCP guidelines (14), which assumes a ~70% frequency of treatment and a non-evaluable rate of 20% for patients lost to follow-up. Per country, target enrolment was 200–630 patients, for an estimated precision of 4–7%. Overall, the study planned to recruit 5,000 patients, with ≥5 patients required per centre. Consecutive recruitment continued until the planned number of patients per country was achieved, thus recruitment duration varied from two weeks to three months across participating countries.

Patients

At hospital discharge, patients were eligible for inclusion if they were aged ≥18 years, had undergone THA, KA, or HFS in the previous 6 weeks, and had received in-hospital VTE prophylaxis that was considered in accordance with the ACCP guidelines by the treating physician. Patients were excluded if they: had a clinical VTE event or a major haemorrhage during hospitalisation; were receiving long-term anticoagulant therapy; were participating in a clinical study evaluating VTE prophylaxis; were pregnant; or if they did not provide informed consent.

Data collection

Information per centre was collected regarding: geographical location; number/distribution of high-risk OS procedures performed annually; involvement in teaching programs; past/ongoing involvement in clinical trials of VTE prophylaxis; specific ward protocols for VTE prophylaxis during hospitalisation and after discharge; and usual practices for patient/relative training in relation to injectable forms of VTE prophylaxis. Information was also gathered on the physicians' profile participating in patient follow-up.

In a screening log form, information on all ward patients who had undergone high-risk OS in the previous six weeks was collected, listing gender, type of surgery, date for discharge, and reason for non-enrolment.

The day of surgery was considered as day 1 of the study. The first patient visit occurred at hospital discharge and data collected included: medical history; primary diagnosis; type of surgery; type of anaesthesia; patient risk factors for VTE and bleeding; length of hospital stay; in-hospital complications; VTE prophylaxis prescribed during hospitalisation and at discharge; details on any/all mechanical methods of prophylaxis used; pharmacological antithrombotic/anticoagulant agents employed; plus dosages and durations for therapies.

After hospital discharge and until the scheduled second patient visit (4–6 weeks after surgery), patients completed a daily diary for 50 days with specific information on: daily intake of the prescribed VTE prophylaxis, person administering any injectable mode of prophylaxis, mechanical methods of prophylaxis used, and any reasons for not receiving/taking pharmacological prophylaxis as prescribed. Patient diary information was collected at the second patient visit and was reviewed by treating physicians and investigators to identify reasons for any temporary or definitive discontinuation of VTE prophylaxis. Data were then passed to the study CRO for analysis.

Data quality control was performed at 5% of randomly selected centres in each participating country by qualified, designated personnel. If specific issues were identified, the percentage of quality control in the concerned site/country was appropriately increased and corrective actions implemented. Management of clinical trial data was performed according to the following procedures: interactive data entry using Key Entry III® software (Lincoln, Boulogne-Billancourt, France); verification and validation using SAS® V8.2 (SAS Institute Inc., Cary, NC, USA); modifications in the database were traced using an audit trail.

Table 1: Criteria used to define VTE prophylaxis prescribed and actual VTE prophylaxis received as being according to 2004 ACCP guidelines.

Types of prophylaxis
• LMWH, fondaparinux, or VKA for THA and KA
• LMWH, fondaparinux, VKA, or UFH for HFS
• Intermittent pneumatic compression alone accepted for KA • Mechanical prophylaxis only (in all surgery types) in case of contraindication to pharmacological prophylaxis due to bleeding risk* • Discontinuation of prescribed prophylaxis regimen permanently or temporarily due to medical reasons*
Duration of prophylaxis
• ≥28 days for THA or HFS
• ≥10 days for KA

*Patients' bleeding risk was not defined a priori and was assessed on a patient-by-patient basis by the investigator. Patients were reviewed by the ETHOS Steering Committee. ACCP, American College of Chest Physicians; HFS, hip fracture surgery; KA, knee arthroplasty; LMWH, low-molecular-weight heparin; THA, total hip arthroplasty; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Table 2: Number of wards and enrolled/screened patients per surgery type and per country.

Country	Wards, n	Enrolled/screened patients, n/N			
		KA	THA	HFS	All surgery types
Austria	10	86/130	89/119	12/48	187/297
Belarus	8	14/20	167/327	19/51	200/398
Belgium	7	93/102	96/102	8/35	197/239
Bulgaria	10	26/29	98/139	126/164	250/332
Croatia	10	33/51	106/171	61/109	200/331
Georgia	4	4/4	83/83	13/13	100/100
Greece	10	121/151	89/102	107/177	317/430
Hungary	6	60/74	97/133	43/81	200/288
Lithuania	7	81/85	107/118	12/14	200/217
Poland	12	66/89	207/276	83/173	356/538
Portugal	8	92/96	64/71	45/83	201/250
Romania	10	24/30	127/162	223/342	374/534
Russia	24	43/48	213/336	239/341	495/725
Slovakia	7	121/140	274/307	30/56	425/503
Sweden	4	46/85	54/84	0/22	100/191
Ukraine	14	77/102	252/396	90/119	419/617
UK	10	89/145	104/199	7/22	200/366
Total	161	1,076/1,381	2,227/3,125	1,118/1,850	4,421/6,356*

*For 29 screened patients there was no information available on the type of surgery performed. HFS, hip fracture surgery; KA, knee arthroplasty; THA, total hip arthroplasty.

Assessment of post-operative VTE prophylaxis prescribed and actually received

Data on VTE prophylaxis prescribed in hospital from surgery to discharge, and at hospital discharge were obtained from case report forms (CRFs) collected at the first patient visit. Data on the actual VTE prophylaxis received were obtained from in-hospital data from CRFs and from data collected after hospital discharge from the patient diaries. All patients with data available on prophylaxis received during hospitalisation and after discharge, were eligible for analysis. If no prophylaxis was prescribed at discharge, patients were considered evaluable even if diary information was missing. When prophylaxis was prescribed at discharge, diary information was mandatory except in cases of hospitalisation lasting ≥28 days for HFS or ≥10 days for KA. One day missing in the patient diary was considered as no treatment intake that day.

Post-operative VTE prophylaxis prescribed and actual VTE prophylaxis received versus the 2004 ACCP guidelines

Post-operative VTE prophylaxis prescribed and actual VTE prophylaxis received were considered adherent or adequate, respectively, to the 2004 ACCP guidelines if they met the criteria listed in ▶Table 1.

Evaluation of adherence of post-operative VTE prophylaxis prescribed (ACCP-adherent) and adequacy of actual VTE prophylaxis received (ACCP-adequate) against the ACCP guidelines was limited to the minimum period for prophylaxis duration recommended in the 2004 guidelines (▶Table 1).

Post-operative VTE prophylaxis was also considered non-adherent if there was a prescription to start prophylaxis >day 2 following surgery. Additionally, actual VTE prophylaxis received was considered non-adequate if prophylaxis was provided for <80% days of the recommended period (21) or the patient had >2 consecutive days without prophylaxis.

Statistical analysis

Data were analysed overall and by type of surgery. Quantitative variables were summarised into counts of non-missing data, mean, and standard deviation; qualitative variables were summarised into counts of non-missing data, and percentage, accompanied with two-sided 95% confidence intervals (CIs) for the main criteria. SAS version 8.2 was used for all statistical analysis.

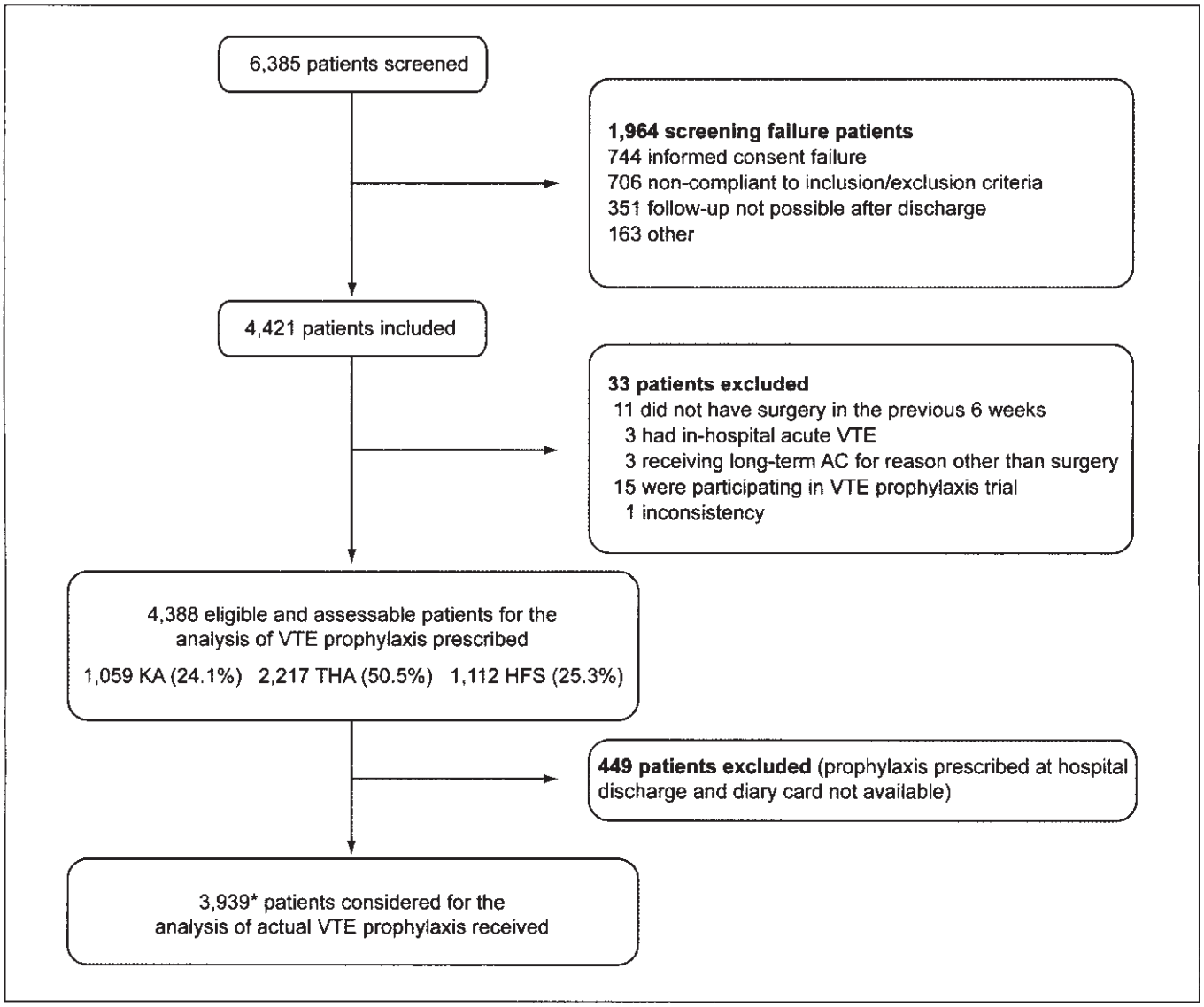

Figure 1: Patients considered for the analysis of prophylaxis prescribed and actual VTE prophylaxis received. *Among the 3,939 patients, 168 had no diary available and no prophylaxis prescription at discharge, and 64 had no diary available and a long hospitalisation duration. AC, anticoagulant; HFS, hip fracture surgery; KA, knee arthroplasty; THA, total hip arthroplasty; VTE, venous thromboembolism.

Results

The ETHOS study recruited patients from 161 orthopaedic wards in 17 European countries. Participating wards per country varied from four in Sweden and Georgia to 24 in Russia (▶Table 2). In total, 6,385 consecutive patients who had undergone high-risk OS were screened and of these 4,421 patients were enrolled into the ETHOS study (▶Fig. 1).

Patients and types of VTE prophylaxis prescribed during hospital stay

Of the 4,421 patients enrolled, 4,388 were eligible for the analysis of prophylaxis prescribed (▶Fig. 1). Patient characteristics and duration of hospitalisation of the eligible patients are listed in ▶Table 3. Of those undergoing HFS, 26% underwent osteosynthesis and 75% arthroplasty. The total average duration of hospitalisation ranged from 6.5 ± 1.5 days in Sweden to 25.2 ± 9.6 days in Russia.

The majority of patients were prescribed and received pharmacological prophylaxis according to the 2004 ACCP guidelines, from the day of surgery until discharge (in HFS patients, VTE prophylaxis was mainly used immediately from hospital admission).

	KA (n = 1,059)	THA (n = 2,217)	HFS (n = 1,112)	Total (N = 4,388)
Age, years	67.2 ± 8.9	61.6 ± 11.9	70.8 ± 14.0	65.3 ± 12.5
Female	755 (71.3)	1,318 (59.4)	770 (69.2)	2,843 (64.8)
Weight, kg	81.3 ± 14.1	77.7 ± 14.1	70.4 ± 12.5	76.8 ± 14.3
BMI, kg/m^2	29.8 ± 4.9	27.6 ± 4.5	25.5 ± 4.1	27.6 ± 4.7
Total hospitalisation duration, days	12.7 ± 6.6	14.8 ± 6.9	17.8 ± 8.8	15.0 ± 7.6
Duration of pre-operative hospital stay, days	2.0 ± 3.0	2.9 ± 3.7	4.9 ± 5.2	3.2 ± 4.2

Continuous data are shown as mean ± standard deviation. Dichotomous data are shown as n (%). BMI, body mass index; HFS, hip fracture surgery; KA, knee arthroplasty; THA, total hip arthroplasty.

Table 3: Patient characteristics by type of surgery.

Type of prophylaxis	KA (n = 1,059)	THA (n = 2,217)	HFS (n = 1,112)	Total (N = 4,388)
Pharmacological prophylaxis*	1,056 (99.7)	2,211 (99.7)	1,094 (98.4)	4,361 (99.4)
LMWH†	1,009 (95.3)	2,162 (97.5)	1,086 (97.7)	4,257 (97.0)
UFH	2 (0.2)	13 (0.6)	6 (0.5)	21 (0.5)
Fondaparinux‡	76 (7.2)	77 (3.5)	4 (0.4)	157 (3.6)
VKA‡	27 (2.5)	52 (2.3)	31 (2.8)	110 (2.5)
Mechanical prophylaxis	739 (69.8)	1,413 (63.7)	513 (46.1)	2,665 (60.7)
Elastic stocking/bandages	672 (63.5)	1,357 (61.2)	496 (44.6)	2,525 (57.5)
Elastic stocking/bandages and IPC	54 (5.1)	42 (1.9)	11 (1.0)	107 (2.4)
IPC	13 (1.2)	14 (0.6)	6 (0.5)	33 (0.8)
Mechanical and pharmacological prophylaxis	736 (69.4)	1,412 (63.6)	497 (44.6)	2,645 (60.2)
Duration of pharmacological prophylaxis, days	9.8 ± 4.5	10.9 ± 4.4	11.4 ± 4.9	10.8 ± 4.6
Pharmacological prophylaxis, daily dosage, mean ± SD				
LMWH, IU	4,039 ± 886	3,985 ± 747	3,940 ± 825	3,986 ± 803
UFH, IU	12,500 ± 10,607	5,000 ± 0	10,000 ± 0	7,143 ± 3,732
Fondaparinux, mg	2.5 ± 0	2.5 ± 0	2.5 ± 0	2.5 ± 0
VKA, mg	5.3 ± 5.3	6.7 ± 8.6	4.7 ± 6.8	5.8 ± 7.4

Continuous data are shown as mean ± standard deviation. Dichotomous data are shown as n (%). *Of the 4,388 patients, 27 did not receive pharmacological prophylaxis from the day of surgery until discharge. †In total, 183 patients received LMWH plus another concomitant treatment. ‡Only 1 patient received fondaparinux and VKA. HFS, hip fracture surgery; IPC, intermittent pneumatic compression; KA, knee arthroplasty; LMWH, low-molecular-weight heparin; THA, total hip arthroplasty; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Table 4: VTE prophylaxis prescribed during hospitalisation by type of surgery.

Types of prophylaxis received and the duration of pharmacological VTE prophylaxis during hospital stay are described in ▶Table 4. In total, 4,361 of 4,388 patients (99.4%) received pharmacological prophylaxis: 4,257 (97.0%) with a low-molecular-weight heparin (LMWH); 157 (3.6%) with fondaparinux; 21 (0.5%) with unfractionated heparin (UFH); and 110 (2.5%) with a vitamin K antagonist (VKA) (▶Table 4).

Only 27/4,388 patients (0.6%) did not receive recommended pharmacological prophylaxis from the day of surgery until discharge: 10 received mechanical prophylaxis alone; 10 mechanical prophylaxis and antiplatelet agents; 3 antiplatelet agents alone; 3 other (non-recommended) anticoagulant agents (hydroxychloroquine); and 1 received no VTE prophylaxis. Three patients receiving mechanical prophylaxis due to bleeding risk, were considered by the Steering Committee as receiving VTE prophylaxis according to the ACCP guidelines.

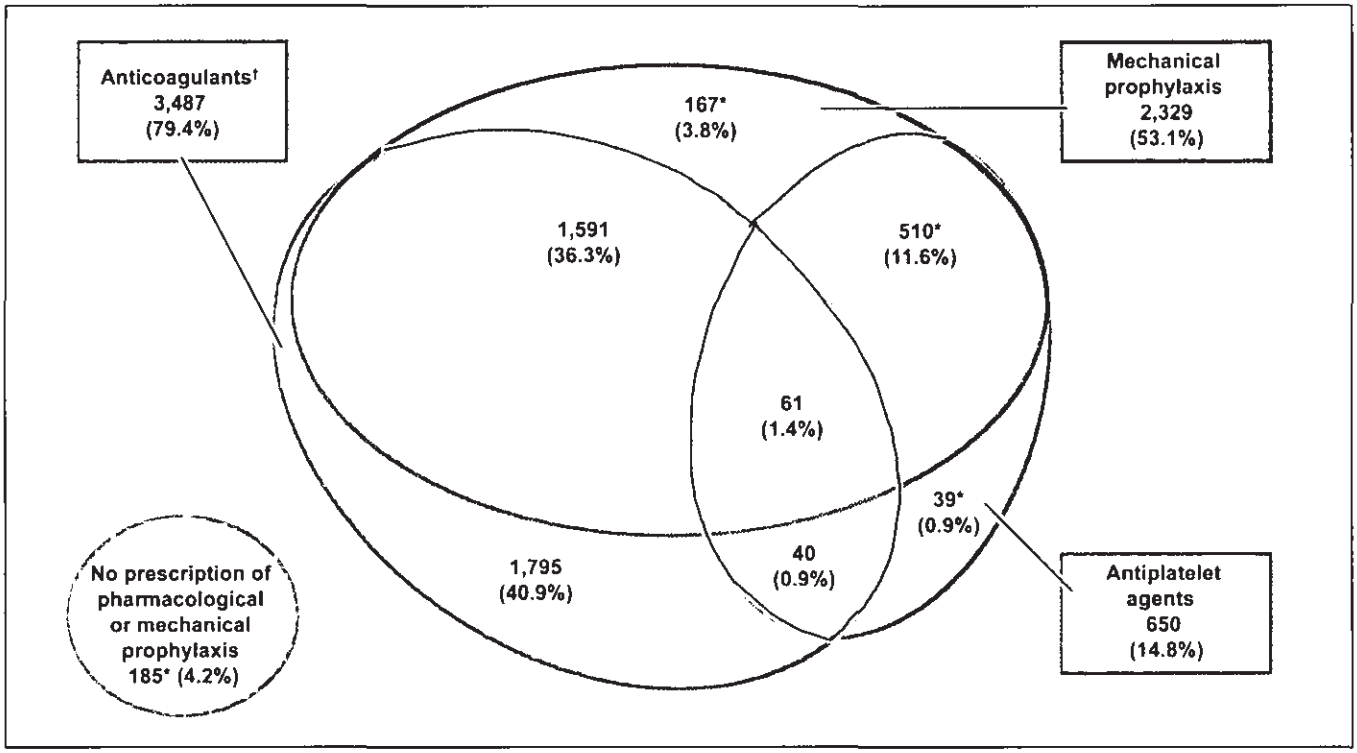

Figure 2: Venn diagram describing the venous thromboembolism (VTE) prophylaxis prescribed at hospital discharge (N = 4,388). *In total, 901 patients were not prescribed with any form of anticoagulant VTE prophylaxis at hospital discharge. †Patients receiving low-molecular-weight heparin, unfractionated heparin, fondaparinux, and vitamin K antagonists.

VTE prophylaxis prescribed at hospital discharge

Post-operative VTE prophylaxis was prescribed at discharge for 4,388 patients. Of these, 3,715 patients (84.7%) were discharged home and 560 (12.8%) patients were discharged to a convalescent home or rehabilitation centre. Fifty-five patients who underwent hip surgery were discharged from the hospital after ≥28 days and 538 KA patients were discharged after ≥10 days.

The types and combinations of VTE prophylaxis prescribed at hospital discharge are depicted in ▶ Figure 2. Overall, 185 (4.2%) patients received no pharmacological or mechanical prophylaxis prescription at discharge. A total of 3,487 patients (79.5%) were prescribed anticoagulant prophylaxis, 2,329 (53.1%) mechanical prophylaxis, and 650 (14.8%) antiplatelet agents. A total of 1,795 (40.9%) patients received anticoagulant VTE prophylaxis alone and 167 (3.8%) mechanical prophylaxis alone.

In total, 901 (20.5%) patients received no discharge prescription for anticoagulant VTE prophylaxis: 352 (8.0%) received no pharmacological prescription and 549 (12.5%) were prescribed with antiplatelet agents alone or in combination with mechanical prophylaxis. Over 50% of patients in Georgia, Russia, and Ukraine were prescribed antiplatelet agents alone (mainly aspirin) or combined with mechanical prophylaxis at discharge.

LMWHs were prescribed at discharge to 3,310 patients (75.4%) and were the most commonly prescribed form of pharmacological VTE prophylaxis, followed by VKA prescribed to 169 (3.9%) patients. Among patients who had undergone THA or KA, and prescribed with injectable prophylaxis, almost 50% self-injected their treatment and approximately 18% were given injections by relatives. The remaining patients were either injected by a nurse or by both a relative and a nurse. In HFS patients, the self-injection rate was 25.9%, whereas relatives and nurses performed 35.2% and 37.0% of required injections, respectively. The mean durations of pharmacological prophylaxis prescribed at discharge were 23.9 ± 15.4 days for KA patients, 24.2 ± 17.7 days for THA, and 26.0 ± 9.2 days for HFS.

Post-operative VTE prophylaxis prescribed as compared with the 2004 ACCP guidelines (ACCP-adherent)

Among the 4,388 eligible patients, 3,067 (69.9%; 95% CI 68.5–71.2%) received an ACCP-adherent post-operative VTE prophylaxis prescription (prescription received during hospitalisation plus prescription at discharge). ACCP-adherent post-operative prophylaxis was prescribed to 955 KA patients (90.2%; 95% CI 88.2–91.8%), 1,411 THA patients (63.6%; 95% CI 61.6–65.6%), and 701 HFS patients (63.0%; 95% CI 60.2–65.8%). Among patients who received a non-adherent post-operative VTE prophylaxis prescription (1,321/4,388; 30.1%), the main reason for non-

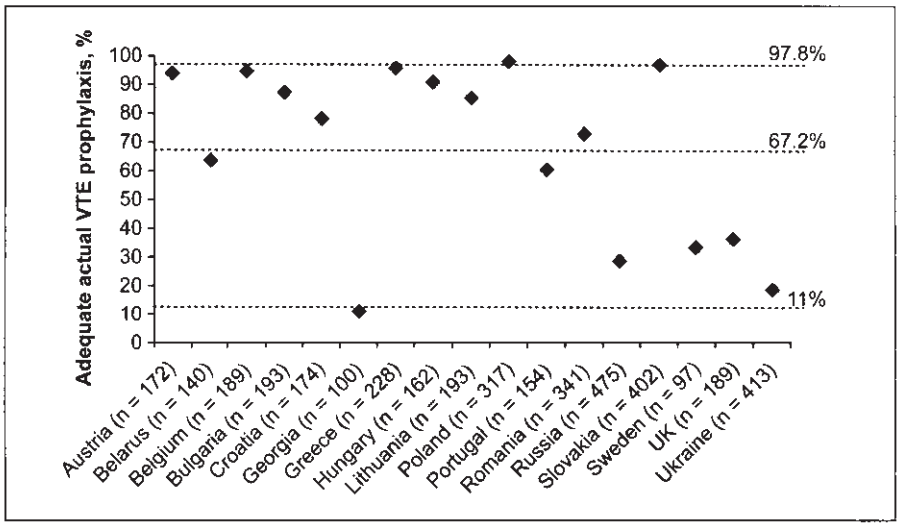

Figure 3: Proportions of patients receiving adequate actual venous thromboembolism (VTE) prophylaxis as compared with the 2004 American College of Chest Physician (ACCP) guidelines by country. Dotted lines represent highest (Poland with 97.8%), lowest (Georgia with 11%), and average proportions (67.2%) of patients receiving adequate actual VTE prophylaxis.

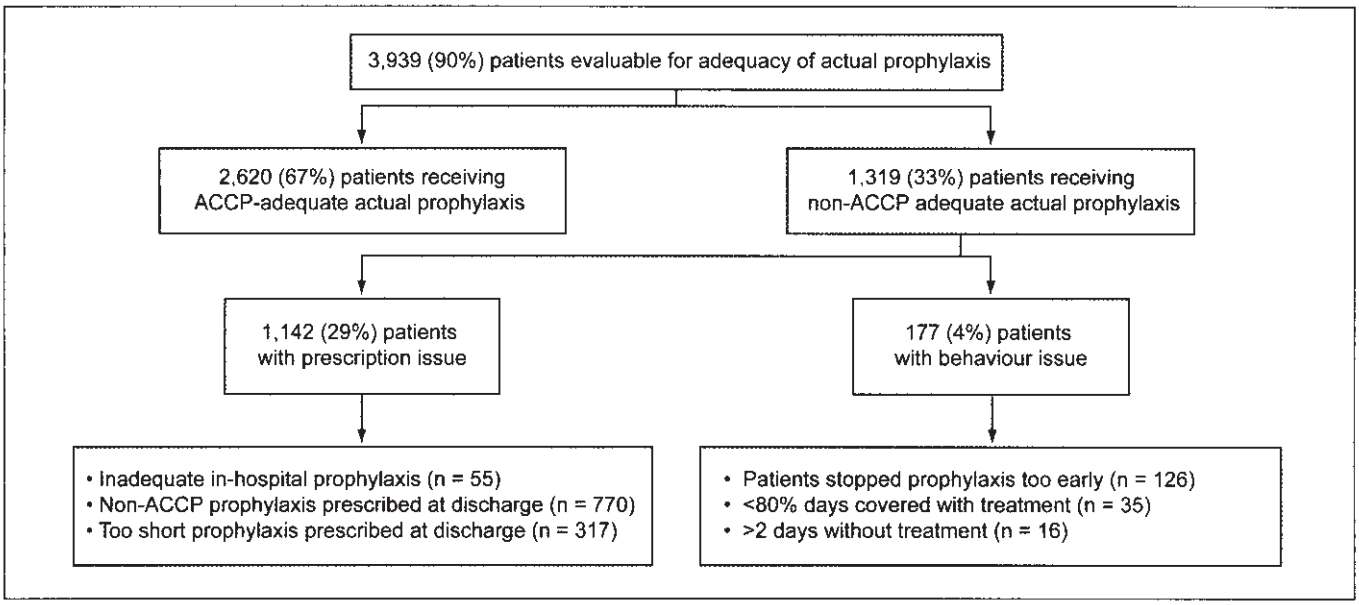

Figure 4: Reasons for discrepancies between actual venous thromboembolism prophylaxis received and 2004 American College of Chest Physicians (ACCP) guidelines.

adherence to ACCP recommendations was a too short prescription (1,256 patients; 28.6%). The mean post-operative prescription durations for VTE prophylaxis were 30.1 ± 17.7 days in KA patients, 30.1 ± 19.4 days in HA, and 31.5 ± 14.4 days in HFS.

Actual VTE prophylaxis received as compared with the 2004 ACCP guidelines (ACCP-adequate)

Among the 4,388 eligible patients, 449 were excluded from the analysis of actual prophylaxis received, leaving 3,939 patients who were considered for this analysis (▶Fig. 1).

The mean duration of actual pharmacological prophylaxis from surgery was 28.7 ± 13.8 days (28.7 ± 14.1 days in KA, 28.4 ± 13.7 in THA, and 29.3 ± 13.9 in HFS). In total, 2,620/3,939 patients (66.5%) received adequate actual VTE prophylaxis as compared with the ACCP guidelines: 872 KA (88.7%; 95% CI 86.6–90.5%), 1,231 THA (60.9%; 95% CI 58.7–63.0%), and 517 HFS (55.4%; 95% CI 52.2–58.6%). The proportion of patients that received adequate actual VTE prophylaxis varied by country (▶Fig. 3).

Among the 1,319 patients (33.5%) with non-adequate actual VTE prophylaxis, the main reason why prophylaxis did not meet ACCP criteria was inadequate prophylaxis prescription at discharge (1,087/3,939; 27.6%), mainly driven by insufficient duration of prophylaxis (▶Fig. 4). Only in 4.5% of cases was non

ACCP-adequate actual prophylaxis received due to patients' behaviour.

Discussion

The ETHOS registry is a prospective, observational study providing real-life data on both the VTE prophylactic practices, and the actual VTE prophylaxis received by patients who have undergone high-risk OS in European countries, and how these compare with the 2004 ACCP guidelines for VTE prevention.

ETHOS shows that in high-risk OS there is still a gap between the VTE prophylaxis that patients actually received (in-hospital plus post-discharge prophylaxis) and the 2004 ACCP recommendations (14) (66.5% of patients, who received in-hospital prophylaxis, received adequate actual VTE prophylaxis). The ETHOS study indicates that non-ACCP adherent prescription at discharge was the predominant cause of discrepancy from guideline-recommended practices. In particular, ETHOS reveals that approximately a quarter of patients are discharged with no prescription for prophylaxis, a prescription for an inadequate type of prophylaxis (including aspirin and other antiplatelet agents), or, in most cases, an adequate type of prophylaxis of inappropriate duration.

Recent literature has focused on the appropriateness of VTE prophylaxis (22–24); however, most of it has analysed patient discharge records retrospectively or focused on in-patient practices. The ENDORSE study assessed the at-risk patients receiving effective prophylaxis while in acute hospital care and showed that <60% of surgical patients with known risk for VTE and up to 88% of high-risk OS patients received ACCP-recommended prophylaxis (19). Analysis of U.S. patient discharge databases for surgical patients has reported that 67.7% of patients did not receive appropriate VTE prophylaxis according to ACCP guidelines, and found that high-risk OS patients were those most likely to receive an inappropriate duration of prophylaxis (25). The same database showed that the probability of DVT and PE were significantly lower among THA and KA patients who received ACCP-recommended VTE prophylaxis versus those who did not (26).

The Global Orthopaedic Registry (GLORY) highlights that full adherence in terms of optimal type of prophylaxis for type of surgery, and adherence of a prescription to recommendations for prophylaxis dosing and dose duration is only achieved in 47–62% of THA and 61–69% of KA patients (20). Compared to these observational studies, the ETHOS registry offers an overview of both in-hospital and at discharge prophylaxis practices. Furthermore, it provides insight on the prophylaxis actually received by patients post-discharge and on the reasons for differences in the prophylaxis prescribed at hospital discharge and the actual prophylaxis received by patients compared with the 2004 ACCP guidelines.

ETHOS suggests that a proportion of patients (13%) are prescribed with antiplatelet agents alone or combined with mechanical types of prophylaxis at discharge (>50% of patients in Georgia, Russia, and Ukraine). In the ETHOS study, the 2004 ACCP guidelines were used to define adequate VTE prophylaxis, and therefore aspirin was not considered as recommended prophylaxis in high-risk OS patients. Alternative guidelines issued by the American Academy of Orthopaedic Surgeons (AAOS) (27) recommend aspirin for the prevention of PE in THA and KA patients. However, inconsistencies regarding the evidence used from clinical studies by the AAOS guidelines are currently under debate (28). In addition, the frequent use of elastic stockings or bandages observed in the ETHOS study (60.7% among all surgery types) is remarkable considering that there is no scientific evidence for the benefits of administering mechanical prophylaxis on top of pharmacological prophylaxis. Moreover, the 2004 ACCP guidelines recommend against the sole use of mechanical prophylaxis.

Importantly, ETHOS shows that VTE prophylaxis after discharge is often insufficiently extended to match ACCP recommendations on duration, in spite of continued risk for VTE (8). Post-discharge records from another study in OS patients suggests that <20% of elderly patients are discharged with VTE thromboprophylaxis (29). However, our analysis also showed that in KA patients, the mean duration of actual pharmacological prophylaxis from surgery was much longer than the duration of prophylaxis recommended by the ACCP guidelines after KA (28.7 ± 14.1 days vs. 10–14 days). This discrepancy may be due to the re-assessment of KA patients' risks after hospital discharge in some countries.

Several reasons may explain the under-use of ACCP-recommended VTE prophylaxis in surgical patients, including phys-

What is known about this topic?

- Patients undergoing major orthopaedic surgery are well-recognised as being at high risk for venous thromboembolism (VTE) and the use of appropriate VTE prophylaxis has been shown to be effective in reducing the risk for thromboembolic events in this patient population.
- Consensus guidelines that describe which types of VTE prophylaxis may be effective, according to the type of surgery and the presence of individual patient risk factors for VTE and haemorrhagic complications, have been available for many years.
- Globally, many hospitalised patients do not receive adequate VTE prophylaxis as defined within currently available consensus guidelines.

What does this paper add?

- Despite receiving adequate VTE prophylaxis during hospitalisation, a substantial number of patients across 17 European countries do not receive effective VTE prophylaxis after hospital discharge.
- When patients are prescribed post-discharge VTE prophylaxis, the regimen actually received may still not meet the consensus guideline recommendations.
- The most common reasons for VTE prophylaxis provision not meeting recommended standards are: inadequate prescription, non-recommended prophylaxis prescription at hospital discharge, and prescription for prophylaxis shorter than the recommended time period.

icians' lack of guidelines awareness and perceived risks and difficulties regarding anticoagulant therapies (30). However, reassuring guidelines on the efficacy and safety profiles of recommended VTE prophylaxis modalities have been available for several years, and post-discharge prophylaxis is a feasible and acceptable option (31). Use of recommended VTE prophylaxis in surgical patients can be improved by implementing support systems and clinical audits of prophylaxis practice (32, 33), and training on the benefits of guideline adherence (34). Guidelines continue to support optimal uptake of VTE prophylaxis in orthopaedic patients (1, 27).

Country-to-country differences in hospital stay duration and timing of discharge may also play a part in inconsistent practices. Additionally, in terms of financial constraints on prescription practices, reimbursement policies differ greatly by country and limit the treatments availability for high-risk OS patients, resulting in prescription of cheaper options (such as aspirin) versus more effective treatments.

There are limitations in the ETHOS study. Not all European countries took part. At the time the ETHOS study was designed, the 2004 ACCP guidelines were the only available recommendations. Although the centres were randomly selected, the process followed may have increased awareness regarding the use of VTE prophylaxis. ETHOS was designed before data from the ENDORSE study were available, therefore under-use of appropriate VTE prophylaxis during hospital stay in surgical patients was not assumed or assessed. There were 449 (10%) missing diaries, and the level of adequate prophylaxis was probably lower in this subgroup of patients compared with the population having the follow-up visit and bringing back the diary. Some patients who were prescribed a short duration of prophylaxis at discharge may have received re-prescription from their family practitioner that was captured in the diary, but not in the discharge prescription. The ETHOS study focused on assessing the duration of prophylaxis, and type of prophylaxis used during hospital stay and at hospital discharge, but did not collect information on VTE or bleeding outcomes.

In conclusion, ETHOS highlights that in real-life practice, up to 66.5% of high-risk OS patients in Europe receive adequate actual VTE prophylaxis when compared to the ACCP guidelines. When looking at the reasons for discrepancies between the actual prophylaxis received and the ACCP guidelines, ETHOS shows that high-risk OS patients may not actually receive VTE prophylaxis of adequate duration to protect against the risks of post-operative VTE, mainly due to inappropriate prophylaxis prescription at discharge. Improvements in discharge prescribing practices may be important in ensuring more patients receive VTE prophylaxis which adheres to evidence-based, guideline-recommended management.

ETHOS registry investigators

Steering Committee: David Bergqvist, Juan I. Arcelus, Paulo Felicissimo. For the investigators who recruited patients for this registry see the *Appendix*.

Appendix

The following investigators recruited patients (principal investigator in bold): Austria—**Erich Minar**, Wolfgang Hochdaninger, Alfred Ungersböck, Friedrich Kroath, Gerhard Kaltenecker, Hans Krönigsberger, Josef Hochreiter, Martin Krismer, Norbert Freund, Oskar Kwasny, Peter Bösch; Belarus—**Siarhei Zaretski**, Ivan Minakouski, Alexey Maslov, Yuri Kos, Pavel Krasenkov, Yuri Azarov, Sergej Kisel, Viktor Klochkov, Vladimir Tsarev; Belgium—**Johan Bellemans**, Eric Meire, Rudi Pyls, Georges de Brouckère, Jean Colinet, Philippe Kinzinger, Herman Eelen, Johan Bogaert; Bulgaria—**Peter Tivchev**, Chavdar Shokov, Peter Bratoev, Dian Enchev, Valentin Ivanov, Nikolay Tivchev, Pavel Mishev, Panayot Tanchev, Atanas Atanasov, Plamen Nenov, Diko Boshnakov; Croatia—**Vladimir Zmak**, Tedi Cicvaric, Branko Tripkovic, Damir Kaplan, Miroslav Gluhinic, Antun Maricevic, Vladimir Boschi, Zvonimir Lovric, Aleksandar Nagy, Dragutin Bitunjac, Zoran Aleksijevic; Georgia—**Nikoloz Avazashvili**, Vazha Gaprindashvili, Tornike Nozadze, Zurab Avazashuili, Levan Teneishuili; Greece—**Kostantinos Malizos**, George Diakos, Theodoros Tsarouchas, Ioannis Krasoulis, George Kehagias, Antonios Asimakopoulos, Chris Dimitriou, Panagiotis Megas, Georgios Skouteris, George Kapetanos, Dionysios Verettas; Hungary—**Kálmán Tóth**, Endre Lénárt, István Zágh, István Szigeti, Tamás de Jonge, Tamás Moser, Tamás Gilicze; Lithuania—**Manvilius Kocius**, Robertas Mikalauska, Valdas Maciulis, Rimantas Tarasevicius, Vytautas Mockus, Alfredas Smailys, Manvilius Kocius, Filibertas Taucius; Poland—**Dariusz Chmielewski**, **Andrzej Górecki**, Krzysztof Czekaj, Krzysztof Mocko, Marek Wieczorek, Emil Taszkow, Marek Dolinski, Ireneusz Kotela, Jacek Majewski, Piotr Jeske, Zbigniew Wieczorek, Stanislaw Dawcewicz, Julian Dutka, Andrzej Kozlowski; Portugal—**Paulo Felicissimo**, Antonio Rodrigues, Herminio Loureiro, Abel Trigo Cabral, Antonio Meireles, Jacinto Loureiro, Jorge Mineiro, Rogério Palma Rodrigues; Romania—**Dinu Antonescu**, Ovidiu Alexa, Remus Caranfil, Radu Malancea, Ioan Baier, Dan Cristian Grecu, Nicolae Gogulescu, Tiberiu Bataga, Dan Poenaru, Alexandru Pop,Dan Osvald Lucaciu, Calin Tudor Hozan; Russia—**Anatoly Lazarev**, Igor Deev, Anatoly Bondarenko, Afanacy Peshkov, Joulia Ipatko, Sergey Abrosimov, Oganes Oganesyan, Sergey Ivanov, Pavel Zhukov, Anton Starkov, Pavel Boltaev, Ivan Vasin , Sergey Klushkin, Oleg Bogatyrev, Sergey Maslennikov, Andrey Milyukov, Fedor Lazko, Igor Lushnikov, Temur Kvetenadze, Alexander Kostyanov, Yuri Ezhov, Vladimir Ivanov, Anatoly Tyurchin, Stanislav Linnnik; Slovakia—**Miroslav Bdzoch**, Jan Cerny, Karol Gottschal, Martin Hromec, Andrej Hudec, Marek Ozorak, Peter Simko, Boris Steno; Sweden—**David Bergqvist**, Sari Ponzer, Björn Edshage, Annika Kragh-Ekstam, Ingemar Olsson; United Kingdom—**Ian Jeffery**, Mohammad Maqsood, Dand Shardlow, Sohail Quraishi, Arpit Patel, Ronan Banin, Ivan Brenkel, Edward Crawfurd, Peter Kay, Peter Cnudde, Riad Adam; Ukraine—**Oleksandr Kosaykov**, Vladimir Gavrilov, Oleg Drobotun, Yaroslav Linko, Andriy Pidlisetskyy, Yaroslav Vasylchyshyn, Olena Shevchenko, Andriy Gerasymenko, Olexandr Polyvoda, Valeriy Vakulenko, Igor Shishka, Olexandr Loskutov, Gennadiy Olinichenko, Myckaylo Arshulik, Igor Spesivyj.

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Conflict of interest

None declared.

References

1. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133 (6 Suppl): 381S–453S.
2. Guijarro R, Montes J, San Román C, et al. Venous thromboembolism and bleeding after total knee and hip arthroplasty. Findings from the Spanish National Discharge Database. Thromb Haemost 2011; 105: 610–615.
3. Collins R, Scrimgeour A, Yusuf S, et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med 1988; 318: 1162–1173.
4. Agnelli G. Prevention of venous thromboembolism in surgical patients. Circulation 2004; 110 (Suppl 1): IV4–IV12.
5. Bergqvist D, Lindblad B. A 30-year survey of pulmonary embolism verified at autopsy: an analysis of 1274 surgical patients. Br J Surg 1985; 72: 105–108.
6. Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 2002; 346: 975–980.
7. Bergqvist D. The postdischarge risk of venous thromboembolism after hip replacement. The role of prolonged prophylaxis. Drugs 1996; 52 (Suppl 7): 55–59.
8. Warwick D, Friedman RJ, Agnelli G, et al. Insufficient duration of venous thromboembolism prophylaxis after total hip or knee replacement when compared with the time course of thromboembolic events: findings from the Global Orthopaedic Registry. J Bone Joint Surg Br 2007; 89: 799–807.
9. Bergqvist D, Benoni G, Björgell O, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. N Engl J Med 1996; 335: 696–700.
10. Planes A, Vochelle N, Darmon JY, et al. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. Lancet 1996; 348: 224–228.
11. Hull RD, Pineo GF, Stein PD, et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. Ann Intern Med 2001; 135: 858–869.
12. Friedman RJ. Extended thromboprophylaxis after hip or knee replacement. Orthopedics 2003; 26 (2 Suppl): S225–S230.
13. Eikelboom JW, Mazzarol A, Quinlan DJ, et al. Thromboprophylaxis practice patterns in two Western Australian teaching hospitals. Haematologica 2004; 89: 586–593.
14. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126 (3 Suppl): 338S–400S.
15. Cardiovascular Disease Educational and Research Trust; Cyprus Cardiovascular Disease Educational and Research Trust; European Venous Forum; et al. Prevention and treatment of venous thromboembolism. International Consensus Statement (guidelines according to scientific evidence). Int Angiol 2006; 25: 101–161.
16. Arnold DM, Kahn SR, Shrier I. Missed opportunities for prevention of venous thromboembolism: an evaluation of the use of thromboprophylaxis guidelines. Chest 2001; 120: 1964–1971.
17. Vallano A, Arnau JM, Miralda GP, et al. Use of venous thromboprophylaxis and adherence to guideline recommendations: a cross-sectional study. Thromb J 2004; 2: 3.
18. Tapson VF, Hyers TM, Waldo AL, et al. Antithrombotic therapy practices in US hospitals in an era of practice guidelines. Arch Intern Med 2005; 165: 1458–1464.
19. Cohen AT, Tapson VF, Bergmann JF, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet 2008; 371: 387–394.
20. Friedman RJ, Gallus AS, Cushner FD, et al. Physician compliance with guidelines for deep-vein thrombosis prevention in total hip and knee arthroplasty. Curr Med Res Opin 2008; 24: 87–97.
21. Karve S, Cleves MA, Helm M, et al. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. Curr Med Res Opin 2009; 25: 2303–2310.
22. Bikdeli B, Sharif-Kashani B, Raeissi S, et al. Chest physicians' knowledge of appropriate thromboprophylaxis: insights from the PROMOTE study. Blood Coagul Fibrinolysis 2011; in press.
23. Weigelt JA, Lal A, Riska R. Venous thromboembolism prophylaxis in surgical patients: identifying a patient group to maximize performance improvement. Jt Comm J Qual Patient Saf 2011; 37: 178–83.
24. Schleyer AM, Schreuder AB, Jarman KM, et al. Adherence to guideline-directed venous thromboembolism prophylaxis among medical and surgical inpatients at 33 academic medical centers in the United States. Am J Med Qual 2011; 26: 174–180.
25. Amin AN, Stemkowski S, Lin J, et al. Preventing venous thromboembolism in US hospitals: are surgical patients receiving appropriate prophylaxis? Thromb Haemost 2008; 99: 796–797.
26. Borah B, McDonald H, Henk J, et al. Alignment to ACCP prophylaxis guidelines and VTE outcomes in THR and TKR patients [abstract]. Blood 2008; 112: Abstract 170.
27. American Academy of Orthopaedic Surgeons clinical guideline on prevention of pulmonary embolism in patients undergoing total hip or knee arthroplasty, May 2007. http://www.aaos.org/Research/guidelines/PE_guideline.pdf. Accessed February 21, 2011.
28. Eikelboom J, Karthikeyan G, Fagel N, et al. American Association of Orthopedic Surgeons and American College of Chest Physicians guidelines for venous thromboembolism prevention in hip and knee arthroplasty differ: what are the implications for clinicians and patients? Chest 2009; 135: 513–520.
29. Rahme E, Dasgupta K, Burman M, et al. Postdischarge thromboprophylaxis and mortality risk after hip-or knee-replacement surgery. CMAJ 2008; 178: 1545–1554.
30. Labarère J, Bosson JL, Bergmann JF, et al. Agreement of four competing guidelines on prevention of venous thromboembolism and comparison with observed physician practices: a cross-sectional study of 1,032 medical inpatients. J Gen Intern Med 2004; 19: 849–855.
31. Spyropoulos AC. Outpatient-based primary and secondary thromboprophylaxis with low-molecular-weight heparin. Clin Appl Thromb Hemost 2008; 14: 63–74.
32. Beeler PE, Kucher N, Blaser J. Sustained impact of electronic alerts on rate of prophylaxis against venous thromboembolism. Thromb Haemost. 2011; 106: 734–738.
33. Fiumara K, Piovella C, Hurwitz S, et al. Multi-screen electronic alerts to augment venous thromboembolism prophylaxis. Thromb Haemost. 2010; 103: 312–317.
34. Tooher R, Middleton P, Pham C, et al. A systematic review of strategies to improve prophylaxis for venous thromboembolism in hospitals. Ann Surg 2005; 241: 397–415.