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?

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The recently published American Association of Orthopedic Surgeons (AAOS) guidelines for the prevention of venous thromboembolism (VTE) in patients undergoing hip or knee surgery conflict with long-established and widely used American College of Chest Physicians (ACCP) guidelines. Both guidelines accepted that the most important goal of thromboprophylaxis in patients undergoing hip or knee replacement is to prevent pulmonary embolism (PE). The ACCP guidelines included asymptomatic (and symptomatic) deep vein thrombosis (DVT) detected by venography as a measure of the efficacy of thromboprophylaxis, whereas the AAOS rejected DVT as a valid outcome because the panelists considered the link between DVT and PE to be unproven. The AAOS position is inconsistent with evidence from imaging studies linking DVT with PE and from clinical studies demonstrating a parallel reduction of DVT and PE when antithrombotic agents are compared with placebo or untreated controls. The AAOS panel ignored the randomized data demonstrating that thromboprophylaxis reduces both DVT and PE, and many of their recommendations are based on expert opinion and lack a scientific basis. We recommend the ACCP guidelines because the methodology is explicit and rigorous and the treatment recommendations reflect all of the evidence from the randomized trials. Adoption of the ACCP guideline will ensure that patients undergoing hip and knee arthroplasty receive the best available therapies for prevention of VTE and reduce disability and death due to this common and potentially preventable condition. *(CHEST 2009; 135:513–520)*

Key words: arthroplasty; guidelines; venous thromboembolism prevention

Abbreviations: AAOS = American Association of Orthopedic Surgeons; ACCP = American College of Chest Physicians; DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PEP = Pulmonary Embolism Prevention (trial); RCT = randomized controlled trial; UFH = unfractionated heparin; VTE = venous thromboembolism

Clinicians should base treatment decisions for their patients on the best available evidence. The highest quality evidence comes from methodologically rigorous randomized controlled trials (RCTs). Observational and mechanistic studies usually provide lower quality evidence, whereas expert opinion represents the lowest quality evidence and should determine treatment decisions only when higher quality evidence is lacking.

For > 20 years, the American College of Chest Physicians (ACCP) has published guidelines for the prevention of venous thromboembolism (VTE).[1,2] The ACCP guidelines are widely used in North America and worldwide, and they have had a major impact on the use of thromboprophylaxis in patients undergoing total hip or knee arthroplasty. In December 2008, for the first time, the American Association of Orthopedic Surgeons (AAOS) published

	ACCP[2]	AAOS*[3,4]
Year of publication	No restriction	Patient recruitment since 1996
Criteria for inclusion of studies to assess efficacy and safety	RCTs and metaanalyses of RCTs, $\geq$ 10 per treatment group	RCTs ($\geq$ 10 per treatment group) and prospective studies ($\geq$ 100 per treatment group)
Analysis	Narrative review	Pooled event rates drawn from treatment arms of RCTs and nonrandomized cohorts
	Randomized data only	Observational data only
Main efficacy outcome	Objectively diagnosed DVT (asymptomatic or symptomatic) or objectively diagnosed PE	Objectively diagnosed symptomatic PE

*Methods apply only to recommendations concerning chemoprophylaxis. Other recommendations by AAOS are based on "consensus development methods."

guidelines for the prevention of VTE in patients undergoing total hip or knee arthroplasty.[3,4] The AAOS had access to the same clinical trial data as the ACCP but used different methods and criteria to assess efficacy (Table 1) and reached very different conclusions (Table 2). In this commentary, we critically examine and compare the ACCP and AAOS guideline recommendations for the prevention of VTE in patients undergoing total hip or knee arthroplasty and consider the implications of the disagreements for clinicians and patients.

The most important disagreement between the ACCP and AAOS guidelines concerns the validity of deep vein thrombosis (DVT) as a surrogate for pulmonary embolism (PE). Both guideline panels accepted prevention of fatal PE as the most important goal of thromboprophylaxis. However, the ACCP included asymptomatic (and symptomatic) DVT detected by venography as a measure of the efficacy of thromboprophylaxis, whereas the AAOS rejected DVT (both asymptomatic and symptomatic) as a valid outcome because the panelists considered the link between DVT and PE in patients undergoing hip or knee surgery to be unproven.[3,4] Thus the AAOS only accepted symptomatic PE and fatal PE as valid outcomes and limited their analysis to studies reporting this outcome. In this article, we first consider the validity of the premise that DVT is an acceptable surrogate for PE because this is a major source of disagreement between the two organizations. Thereafter we review the differences in the AAOS and ACCP guidelines and the methods used to collect the evidence to support their respective recommendations.

Validity of DVT as a Surrogate for PE

The evidence linking DVT, both asymptomatic and symptomatic, with symptomatic or fatal PE is derived from two main sources. The first is the consistent association, demonstrated by imaging studies, between DVT and PE in patients who present with either symptomatic DVT or with symptomatic PE.[5] The second, which is more relevant to the issue under consideration, is the demonstration in adequately powered RCTs and metaanalysis of RCTs of a parallel reduction of DVT and PE when antithrombotic agents are compared with placebo or untreated controls. The RCTs supporting an association between DVT and PE were performed in both orthopedic and nonorthopedic patients and evaluated aspirin, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and fondaparinux.

Aspirin

The Pulmonary Embolism Prevention (PEP) trial of 13,356 patients undergoing hip fracture surgery

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ACCP		AAOS		
Recommendation	Grade and Level of Evidence†	Patient Risk	Recommendation	Grade and Level of Evidence‡
LMWH Fondaparinux VKA (adjusted dose)	Grade I, Level A	Standard risk of both PE and major bleeding	Aspirin LMWH Fondaparinux Warfarin	Grade B, Level III
		Elevated risk of PE and standard risk of major bleeding	LMWH Fondaparinux Warfarin	Grade B, Level III
		Standard risk of PE and elevated risk of major bleeding	Aspirin Warfarin None	Grade C, Level III
		Elevated risk of both PE and major bleeding	Aspirin Warfarin None	Grade C, Level III

*IPC = intermittent pneumatic compression; LDUH = low-dose unfractionated heparin; VKA = vitamin K antagonist.
†ACCP: Grade 1 recommendations are strong and indicate that the benefits do or do not outweigh risks, burden, and costs. Grade 2 suggestions imply that individual patient values may lead to different choices. Level A denotes high-quality evidence, Level B denotes moderate quality evidence, and Level C denotes low-quality evidence.
‡AAOP: Grade A denotes good evidence (level I studies with consistent finding) for recommending intervention. Grade B denotes fair evidence (level II or III studies with consistent findings) for recommending intervention. Grade C denotes poor quality evidence (level IV or V) for recommending intervention. Level I evidence is from high-quality randomized clinical trials, level II evidence is from cohort studies, level III evidence is from case-control studies, level IV evidence is from an uncontrolled case series, and level V evidence is from expert opinion.

showed that, compared with placebo, low-dose aspirin significantly reduced the risk of any DVT by 29%, any PE by 43%, and fatal PE by 58%.[6] A metaanalysis of aspirin trials in 26,890 high-risk medical, general surgical, and orthopedic patients that included the PEP trial results showed that aspirin compared with control (placebo or no treatment) reduced the risk of DVT by 37% and PE by 53%.[6]

UFH

Collins and colleagues performed a metaanalysis of clinical trials that evaluated the effect of UFH on asymptomatic and symptomatic VTE in 8,874 patients undergoing general, orthopedic, or urological surgery. They showed that UFH compared with placebo (or no heparin) significantly reduced any DVT by 68%, nonfatal PE by 40%, and fatal PE by 64%.[7]

LMWH

A metaanalysis of RCTs comparing LMWH with placebo in 5,520 patients undergoing general surgery showed that LMWH significantly reduced venographic DVT by 72% and any PE by 65%.[8] A similar pattern of reduced DVT and PE was shown in several other metaanalyses comparing LMWH with placebo,[9–11] although in these other metaanalyses the reductions in PE were of borderline statistical significance. Thus in a metaanalysis of 987 patients undergoing general or major orthopedic surgery, LMWH compared with placebo reduced any DVT by 69% and any PE by 61%.[9] In a metaanalysis of 3,999 patients undergoing major orthopedic surgery, LMWH compared with placebo reduced venographic DVT by 52%, symptomatic DVT by 59%, and any PE by 57%.[11] In a metaanalysis of 8,357 medical patients, LMWH (or fondaparinux in one study) compared with placebo reduced any DVT by 40% and any PE by 46%.[10]

Fondaparinux

In the Artemis study involving 849 medical patients, fondaparinux compared with placebo significantly reduced venographic DVT by 47% and fatal PE by 58%.[12]

Active Comparator Trials

Results of clinical trials comparing two active and effective interventions can also be used to examine the relationship between reductions of DVT and PE, but because the absolute event rates in these trials are much lower than in the control group of placebo-controlled trials, such studies often lack statistical power. Further, there is evidence that thromboprophylaxis reduces the size of thrombi and because smaller thrombi are less likely to cause symptomatic

PE, an even lower rate of PE could be anticipated in the active comparator trials. Despite these limitations, there is a consistent pattern of association between DVT and PE in trials directly comparing two pharmacologic thromboprophylaxis strategies. Thus a metaanalysis of RCTs comparing LMWH with UFH in patients undergoing general or orthopedic surgery showed a significant 15% reduction in any DVT and 41% reduction in PE.[9] A consistent pattern of numerically fewer DVT and PE events was evident in randomized trials and metaanalyses of randomized trials comparing LMWH with UFH,[8,13,14] LMWH with warfarin,[15–16] and rivaroxaban with LMWH[17] in orthopedic or general surgical patients and in medical patients, although the observed reductions were not statistically significant for both DVT and PE. Other RCTs and metaanalyses have shown an increase in PE despite a reduction in DVT,[18–21] but in each of these cases the comparisons were underpowered for PE as evidenced by wide confidence intervals around the estimates that did not exclude a reduction in PE.

Summary of Association Between DVT and PE in Large Thromboprophylaxis RCTs and Metaanalyses

We have summarized in Figures 1 and 2 the evidence for association between DVT and PE from all published RCTs and metaanalyses of RCTs involving at least 500 patients that examined the efficacy of pharmacologic methods of thromboprophylaxis (placebo-controlled: aspirin,[6] UFH,[7] LMWH,[8–11,22–24] fondaparinux[12,25]; active-comparator: LMWH vs UFH,[8,9,13,14,26,27] LMWH vs warfarin[15,16,28,29]; fondaparinux vs LMWH[19,30] dabigatran vs LMWH,[20,21] rivaroxaban vs LMWH[31–33]).

FIGURE 1. Summary of relative risks of venographic and symptomatic VTE from large (n ≥ 500) RCTs and metaanalyses of RCTs comparing pharmacologic thromboprophylaxis with placebo in surgical or medical patients. For a list of references of included studies, see text.
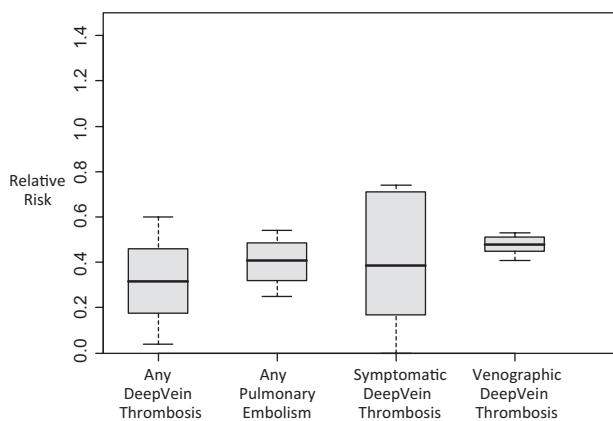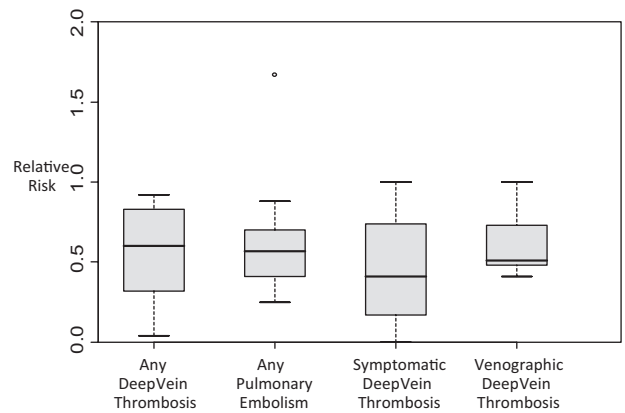

FIGURE 2. Summary of relative risks of venographic and symptomatic VTE from large (n ≥ 500) RCTs and metaanalyses of RCTs comparing pharmacologic thromboprophylaxis with placebo or active control in surgical or medical patients. For a list of references of included studies, see text.

Box plots summarizing the effects of thromboprophylaxis for the prevention of any DVT, any PE, symptomatic DVT, and asymptomatic (mainly venographic) DVT in placebo-controlled trials (Fig 1) and in all trials combined (Fig 2) demonstrate an association between DVT (irrespective of whether it is asymptomatic or symptomatic) and PE. We have previously shown there is a close relationship between venographic DVT and symptomatic VTE in RCTs where patients routinely underwent venography, and symptomatic VTE in trials where patients did not undergo venography.[34]

Collectively these data support the conclusion that DVT is a valid surrogate for PE irrespective of whether the DVT is symptomatic or asymptomatic (venographic).

The AAOS and ACCP Guidelines

The AAOS contention that there is no association between DVT and PE is based on their analysis of studies evaluating prophylaxis for total hip or knee arthroplasty that recruited patients since 1996. In individual randomized trials they noted that various antithrombotic agents are effective in reducing the incidence of DVT, but there was not a statistically significant difference in PE rates. Pooling the data from randomized and nonrandomized studies also failed to demonstrate a statistically significant difference in PE rates. The AAOS argument is flawed because it excluded data from important and relevant clinical trials. The AAOS analysis did not include data from randomized trials and metaanalyses of randomized trials that showed aspirin,[6] UFH,[7] LMWH,[8,9] and fondaparinux[12] are effective for preventing both DVT and PE in patients undergoing major orthopedic surgery and in other clinical set-

No.	Page†	Statement	Evidence Cited by AAOS in Support of Their Statement Where Applicable	Comment
1	2, 12	Patients with known contraindications to anticoagulation should be considered for vena cava filter replacement	Nil	No RCTs have evaluated the efficacy and safety of prophylactic filters[2]
2	5	Although current appropriately powered clinical trials have demonstrated statistically significant differences in DVT rates among selected agents, as this guideline will demonstrate by way of a systematic literature review, the concurrently reported PE rates for all prophylactic modalities are not statistically different	Selective and incomplete	Statistically significant reductions in PE were shown with ASA by the PEP Trialists,[6] with UFH by Collins et al,[7] with LMWH by Mismetti et al[8] and Leizorovicz et al 1992,[9] and in the ARTEMIS trial[12]
3	6	The selection of an appropriate prophylactic regimen against PE in hip and knee replacement should be based on a balance between bleeding-related risks and medical adverse effects, on one hand, and the expected effectiveness in preventing symptomatic PEs, on the other		This approach disregards symptomatic DVT, which is frequently accompanied by PE and can cause acute and chronic symptoms[5]
4	12	All patients should be assessed preoperatively for elevated risk (greater than standard risk) of pulmonary embolism	Nil	All patients undergoing total hip or knee arthroplasty are at high risk of VTE[2]
5	12	Careful history taking and physical examination in combination with clinical judgment, which integrates knowledge of specific risk factors with the patient's clinical status is the cornerstone of PE risk management for patients undergoing hip or knee replacement	Nil	There is no evidence that clinical assessment of patients undergoing total hip or knee arthroplasty can identify groups at low enough risk of PE to justify no prophylaxis
6	13	Although routine serological tests to screen patients for potential bleeding problems are not indicated, they may be useful in patients where there is a high level of suspicion of a predisposition for bleeding	Nil	There is no evidence that "serological testing" is useful to identify patients at risk of bleeding
7	14	There is only circumstantial evidence that regional anesthesia, as part of a multimodal prophylaxis protocol, reduces the prevalence of symptomatic and fatal PE	Expert opinion; metaanalysis data not cited	Metaanalysis data indicate that regional anesthesia reduces risk of PE[36;37]
8	15, 16	Patients . . . should be considered for . . . aspirin, 325 mg 2x/d (reduce to 81 mg 1x/d if gastrointestinal symptoms develop), starting the day of surgery, for 6 weeks	Nil	The PEP study evaluated aspirin at a dose of 162 mg/d[6]. There is no evidence that 650 mg/d is more effective than 162 mg/d or that 6 wk of treatment is needed to prevent VTE
9	15, 16	Patients . . . should be considered for . . . LMWH, dose per package insert, starting 12–24 h postoperatively (or after an indwelling epidural catheter has been removed), for 7–12 days (N.B., the LMWHs have not been sufficiently evaluated for longer periods to allow recommendation beyond this period)	Nil	RCTs have shown the effectiveness of extended duration prophylaxis for preventing symptomatic VTE in patients undergoing elective hip or knee surgery[11]
10	16	Patients . . . should be considered for . . . none (no thromboprophylaxis)	Nil	There is no evidence to support this recommendation
11	18	All evaluations (of the effectiveness of different thromboprophylaxis strategies) were based on indirect comparisons across different arms (cohorts) of different studies	Nil	Randomized comparisons were not considered

(Continued)

Table 3—(*Continued*)

No.	Page†	Statement	Evidence Cited by AAOS in Support of Their Statement Where Applicable	Comment
12	25, 26	In the setting of elevated risk of both PE and major bleeding . . . aspirin, with its attendant very low risk of bleeding and warfarin, which can be dosed to lower INRs in high-risk bleeding situations are the agents recommended if chemoprophylaxis is deemed necessary	Nil	There is no evidence that lower intensity warfarin is effective for primary prevention of VTE
13	27	The reduction of DVT does not appear to have a significant effect on the PE rate, and this calls into question the long assumed epidemiologic if not pathophysiologic link between the two processes	Based on indirect comparisons, low event rates, and type 2 error. The absence of a significant difference in underpowered studies is not evidence of no difference	Randomized trials demonstrating a parallel reduction in DVT and PE were disregarded (see No. 2 above)
14	28	None of the studies was designed to investigate PE as a primary outcome		The PEP study in patients with hip fracture or hip arthroplasty was designed to investigate PE as a primary outcome[6]

*INR = international normalized ratio.
†Page numbers correspond to reference 3.

tings. Instead, they limited their analyses to individual studies conducted in patients undergoing total hip and knee arthroplasty that were underpowered to show true differences in PE. Lack of a statistically significant difference in PE rates among various methods of prophylaxis should not be taken as an indication that true differences do not exist.

Many of the AAOS guideline recommendations are not linked to the results of their analysis, which failed to show benefit for any individual agent over another or over no treatment. Further some of their recommendations have little scientific basis and conflict with evidence from RCTs (Table 3). The AAOS recommended routine preoperative assessment for risk of PE and bleeding and stratified their recommendations for thromboprophylaxis according to whether patients are "standard risk" or "high risk" for PE and bleeding. They did not discuss the issue of dose adjustments in the elderly or those with renal dysfunction, which are the most important indicators of high bleeding risk. Further, there is no validated or even accepted approach to stratify patients undergoing hip or knee surgery according to their risk of PE. The AAOS recommended that "serological testing" may be useful in patients if there is a high level of suspicion of a predisposition for bleeding and that clinicians should consider thromboprophylaxis with aspirin at a dose of 325 mg twice daily for 6 weeks. These recommendations are not supported by the literature and can at best be considered "expert" opinion. The recommendation by the AAOS panel for no pharmacologic prophylaxis in patients deemed to be at high risk of bleeding is particularly concerning because, if adopted, it is likely to expose patients to an increased risk of fatal PE.

The most important strengths of the ACCP guidelines are that they considered only high-quality evidence from randomized trials, based their recommendations on patient-important outcomes or on a valid surrogate thereof, used explicit criteria to grade the evidence, and made explicit the underlying preferences and values of the guideline panel.

Conflicting guidelines are confusing for healthcare providers and third-party insurers who use guidelines to develop performance measures that influence payment. Even more importantly, conflicting guidelines can negatively impact patient outcomes because clinicians who read both guidelines might conclude that disagreement reflects uncertainty about the benefits of thromboprophylaxis and fail to use prophylaxis altogether, thereby increasing the risk of preventable morbidity and mortality. The Office of the Surgeon General in the United States recently called for a coordinated plan to reduce the incidence of DVT and PE in the United States.[35] We believe that as part of this call to action, addressing disagreement between the guidelines is an urgent priority. A meeting between guideline committees to debate differences that also involves methodologists and regulators has been organized and might help to

resolve some areas of disagreement based on the existing evidence and to identify areas of uncertainly that can be addressed in future research efforts.

What should clinicians and patients do when faced with conflicting ACCP and AAOS guidelines? We recommend the ACCP guidelines because the methodology is explicit and rigorous and the treatment recommendations reflect all of the evidence from the randomized trials. Adoption of the ACCP guideline will ensure that patients undergoing hip and knee arthroplasty receive the best available therapies for prevention of VTE and reduce disability and death due to this common and potentially preventable condition.

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