



Approach to Outcome Measurement in the Prevention of Thrombosis in Surgical and Medical Patients

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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This article provides the rationale for the approach to making recommendations primarily used in four articles of the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines: orthopedic surgery, nonorthopedic surgery, nonsurgical patients, and stroke. Some of the early clinical trials of antithrombotic prophylaxis with a placebo or no treatment group used symptomatic VTE and fatal PE to measure efficacy of the treatment. These trials suggest a benefit of thromboprophylaxis in reducing fatal PE. In contrast, most of the recent clinical trials comparing the efficacy of alternative anticoagulants used a surrogate outcome, asymptomatic DVT detected at mandatory venography. This outcome is fundamentally unsatisfactory because it does not allow a trade-off with serious bleeding; that trade-off requires knowledge of the number of symptomatic events that thromboprophylaxis prevents. In this article, we review the merits and limitations of four approaches to estimating reduction in symptomatic thrombosis: (1) direct measurement of symptomatic thrombosis, (2) use of asymptomatic events for relative risks and symptomatic events from randomized controlled trials for baseline risk, (3) use of baseline risk estimates from studies that did not perform surveillance and relative effect from asymptomatic events in randomized controlled trials, and (4) use of available data to estimate the proportion of asymptomatic events that will become symptomatic. All approaches have their limitations. The optimal choice of approach depends on the nature of the evidence available. *CHEST 2012; 141(2)(Suppl):e185S–e194S*

Abbreviations: AT9 = Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; IPC = intermittent pneumatic compression; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; RCT = randomized controlled trial; RR = risk ratio; UFH = unfractionated heparin; VKA = vitamin K antagonist

This article provides the rationale for the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (AT9) approach to estimating the effect of antithrombotic prophylaxis on patient-important outcomes of pulmonary embolism (PE) and symptomatic venous thrombosis.

1.0 THROMBOPROPHYLAXIS REDUCES FATAL PE IN MEDICAL AND SURGICAL PATIENTS

Although some studies have limitations of lack of concealment and blinding, evidence from meta-analyses of randomized controlled trials (RCTs) strongly suggests that prophylaxis with an anticoagulant or aspirin reduces symptomatic VTE and fatal

PE in medical and surgical patients (Table 1). In patients undergoing orthopedic, general, or urological surgery, unfractionated heparin (UFH) reduces the risk of fatal PE by about two-thirds¹; in patients undergoing hip or knee arthroplasty or hip fracture surgery, vitamin K antagonists (VKAs) reduce the risk of symptomatic VTE by about four-fifths²; in patients undergoing hip or knee arthroplasty, extended-duration low-molecular-weight heparin (LMWH) or warfarin reduces the risk of symptomatic VTE by about three-fifths³; in medical patients at highest risk, UFH, LMWH, danaparoid, or fondaparinux reduces the risk of PE by about two- to three-fifths^{4,5}; and in patients undergoing abdominal or pelvic surgery, LMWH reduces the risk of symptomatic VTE by about four-fifths.⁶ Antiplatelet therapy also is effective for the prevention of VTE in the highest-risk surgical or medical patients, reducing the risk of PE by about one-half and DVT by about three-fifths.⁷ Similar relative risk reductions are seen in trials comparing the efficacy of anticoagulant prophylaxis with placebo or no treatment based on a surrogate outcome; compared with placebo or no treatment, prophylactic anticoagulants reduce the relative incidence of silent DVT diagnosed through screening venography by 30% to 70%.⁸

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The effects of antithrombotic prophylaxis on bleeding were inconsistent. In some meta-analyses, major or total bleeding was increased, whereas in others, there was no excess of bleeding (Table 1).

Collectively, the meta-analysis data indicate that prophylactic anticoagulants are effective for the prevention of patient-important VTE and that the benefit-risk trade-off justifies their use in patients who are at sufficiently high risk of symptomatic VTE. Identifying characteristics of surgical procedures and individual patients that predict VTE risk is necessary to wisely select patients for consideration of prophylaxis.

2.0 EVIDENCE IS STRONGER FOR ANTICOAGULANTS AND ASPIRIN THAN FOR MECHANICAL PROPHYLAXIS

Mechanical methods of thromboprophylaxis include graduated compression stockings, intermittent pneumatic compression (IPC) devices, and the venous foot pump. Relative to anticoagulants and aspirin, these methods have the advantage of not increasing bleeding. Moreover, comparisons of these agents against no prophylaxis suggest that they are effective in reducing thrombosis.

Unfortunately, these studies and others comparing mechanical and pharmaceutical agents are relatively few and small in size.⁹ Therefore, the compelling evidence of a decrease in fatal PE that exists for anticoagulants and for aspirin does not exist for mechanical methods.

3.0 COMPARISONS OF ALTERNATIVE ANTITHROMBOTIC AGENTS PRESENT CHALLENGES

All the RCTs comparing two different antithrombotic agents have used asymptomatic DVT by mandatory venography as the primary outcome measure or as a component thereof. In general, any improvement in efficacy with any one agent was accompanied by an increase in bleeding. These studies are difficult to interpret because they do not provide information on the trade-off between benefits and risks in patient-important events.

The use of asymptomatic DVT detected by venography as a surrogate for a patient-important event is based on two premises. The first is that most thrombi start as small calf vein thrombi, which often remain asymptomatic but can grow to form symptomatic venous thrombi, which in turn can break off to cause asymptomatic PE, symptomatic PE, or fatal PE. The second is that a reduction in asymptomatic venous thrombosis by antithrombotic prophylaxis is paralleled by a similar reduction in symptomatic VTE and

Table 1—Summary of the Results of Meta-analyses of Randomized Controlled Trials Comparing Anticoagulant Prophylaxis or Antiplatelet Therapy to Placebo or No Antithrombotic Prophylaxis in High-Risk Medical or Surgical Patients

Study/Year	No.	Population	Intervention	All-Cause Mortality	Fatal PE	Symptomatic VTE	Asymptomatic DVT	Bleeding
Collins ¹ /1988	> 70 studies; 15,598 subjects	General, orthopedic, urological surgery	UFH	RRR 0.21 ^a <i>P</i> < .02	64% odds reduction <i>P</i> < .0001	N/A	N/A	66% odds increase in any bleeding
Mismett ² /2004	8 studies; 813 subjects	THR, TKR, HFS	VKA	RR 0.78 (95% CI, 0.56-1.09; <i>P</i> = .14)	N/A	Clinical PE RR 0.23 (95% CI 0.09-0.59, <i>P</i> = .002)	N/A	Major bleeding 16/270 vs 9/268, <i>P</i> = ns Wound hematoma RR 2.91 (95% CI, 1.09-7.75; <i>P</i> = .03)
Eikelboom ³ /2001	9 studies; 3,999 subjects	THR, TKR; extended-duration prophylaxis	UFH, LMWH, warfarin	OR 0.68 (95% CI, 0.25-1.88)	N/A	OR 0.38 (95% CI, 0.24-0.61)	OR 0.48 (95% CI, 0.36-0.63)	Major bleeding OR 0.62 (95% CI, 0.22-1.75)
Dental ⁴ /2007	9 studies; 19,958 subjects	Medical inpatients	UFH, LMWH, fondaparinux	RR 0.97 (95% CI, 0.77-1.21)	RR 0.38 (95% CI, 0.21-0.69)	All PE: RR 0.43 (95% CI, 0.26-0.71) DVT: RR 0.47 (95% CI, 0.22-1.00)	N/A	Major bleeding RR 1.32 (95% CI, 0.73-2.37)
Wein ⁵ /2007	26 studies; 43,732 subjects	Medical inpatients	UFH, LMWH, danaparoid, factor Xa inhibitor	RR 0.95 (95% CI, 0.89-1.02; <i>P</i> = .16)	N/A	All PE: RR 0.57 (95% CI, 0.45-0.72)	N/A	Total bleeding RR 1.90 (95% CI, 1.69-2.14)
Rasmussen ⁶ /2009	4 studies; 901 subjects	Major abdominal or pelvic surgery; extended-duration prophylaxis	LMWH	OR 1.12 (95% CI, 0.65-1.93)	N/A	OR 0.22 (95% CI, 0.06-0.80)	N/A	Bleeding complications OR 1.12 (95% CI, 0.62-1.97)
PEP study report ⁷ /2000	63 studies; 26,890 subjects	Surgical and medical patients	Antiplatelet therapy			PE: 53% odds reduction (41-63; <i>P</i> < .00001) DVT: 37% odds reduction (29-44; <i>P</i> < .000001)		

HFS = hip fracture surgery; LMWH = low-molecular-weight heparin; N/A = not available; ns = not significant; PE = pulmonary embolism; PEP = Pulmonary Embolism Prevention; RR = risk ratio; RRR = relative risk reduction; THR = total hip replacement; TKR = total knee replacement; UFH = unfractionated heparin; VKA = vitamin K antagonist.

^aEstimated from observed event rate (3.33% vs 4.23%).

fatal PE. Pooled data from RCTs show that on average, the relative reduction is similar for silent DVT and patient-important VTE.¹⁰ This is true for placebo-controlled (or no-treatment) trials as well as active-controlled trials. It does not necessarily, however, mean that the relative effects of asymptomatic and symptomatic events will be similar.

Even if we assume that the reduction in asymptomatic DVT is associated with a similar relative risk reduction in symptomatic VTE, this alone would not be sufficient reason to recommend the use of one antithrombotic agent over another. Rather, the recommendation of a particular anticoagulant over another should be based on the trade-off between the absolute reduction in patient-important VTE and the absolute increase in patient-important bleeding. To complicate matters further, there is controversy (based on uncertainty) regarding the relative importance of symptomatic VTE and bleeding to the patient, to the physician, and to the health-care system.

The potential consequences of DVT are the discomfort associated with symptomatic DVT, the postthrombotic syndrome, the inconvenience and side effects of treatment, and the development of PE. The risk of postthrombotic syndrome following silent DVT is likely to be low, whereas up to 40% of patients with symptomatic DVT develop postthrombotic syndrome, which is debilitating in ~15% of those who develop the syndrome.¹¹ The most important consequence of PE is death, although thromboembolic pulmonary hypertension, which occurs in up to 4% of patients with PE, is also important.¹²

Bleeding associated with the use of antithrombotic agents varies widely in severity. Apart from intracranial bleeding, little is known about the long-term patient-important consequences of bleeding. Of particular relevance to major orthopedic surgery, in patients receiving anticoagulants for the prevention of VTE, the incidence of bleeding into joints and the impact of wound and joint bleeding on functional patient outcomes are unknown. Specifically, there are no published data addressing the relationship between wound or joint bleeding and either wound infection or long-term joint function.

Based on our lack of knowledge about the consequences of asymptomatic thrombi and wound bleeds, it is difficult to formulate a trade-off between risk and benefits among antithrombotic agents. Nevertheless, clinicians must make decisions regarding thromboprophylaxis, and guidelines serving clinicians must provide guidance. Estimates of the frequency of symptomatic VTE and bleeding and their consequences are necessary for making appropriate recommendations.

In AT9, we considered possible strategies for estimating the absolute difference in the frequency of VTE associated with alternative approaches to antithrombotic management. To estimate the absolute benefit of one antithrombotic regimen over another in reducing VTE requires an estimate of the control group event risk and the relative risk reduction associated with the alternative or experimental antithrombotic regimen. In this section, we review the strategies we considered and discuss their relative merits. Table 2 summarizes the strategies and their key limitations.

4.1 Strategy 1: Use Direct Estimates of Symptomatic Events From RCTs

One approach to estimating the absolute difference among VTE across management strategies is to simply use the number of symptomatic and fatal events observed (ie, the number of fatal and nonfatal PEs, the number of symptomatic DVTs). Using this strategy, estimates of both control event risk and relative effect come from symptomatic events. The implication of using this approach is that unless there is convincing evidence of a difference in symptomatic events, panelists recommend the strategy with the lowest bleeding rates.

In dealing with prophylaxis for nonsurgical patients in this guideline, Kahn et al¹³ initially considered this approach in addressing the impact of anticoagulant prophylaxis (LMWH, UFH, fondaparinux) in hospitalized medical patients.¹ They found moderate-quality evidence (rated down for imprecision) from a systematic review of four RCTs (risk ratio [RR], 0.47; 95% CI, 0.22-1.0).

This approach has the merit of simplicity. In addition, it uses events that have been observed and, thus, requires no questionable assumptions. Taking a perspective of *primum non nocere*, it is conservative, which some may perceive as an advantage.

The approach, however, does have a number of limitations. First, even in populations labeled as high risk, symptomatic thrombotic events in patients treated with antithrombotic agents typically are uncommon. Estimates of effect are, therefore, imprecise, and CIs are wide (as in the example from Kahn et al¹³). These wide CIs could, however, be seen as an advantage: They capture the true uncertainty associated with estimates of the effect of the intervention on patient-important events.

Second, the approach may have limitations of generalizability. Patients enrolled in RCTs are likely to be at a different risk than the populations to whom the results will be applied. If this is so, estimates of absolute difference may be misleading.

Table 2—Strategies for Estimating Absolute Benefit in Symptomatic Venous Thromboembolic Events in Comparisons of Alternative Thromboprophylaxis Strategies

	Source of Control Group Risk	Source of Relative Risk	Limitations
Strategy 1	Symptomatic events	Symptomatic events	Yields imprecise estimates of relative risk reduction Upward and downward biases in control group risk due to venographic and ultrasound surveillance
Strategy 2	Symptomatic events	Composite of symptomatic and asymptomatic events	Assumes that relative risk reduction in asymptomatic events applies to symptomatic events, which may not be the case Upward and downward biases in control group risk due to venographic and ultrasound surveillance
Strategy 3	Observational studies or randomized controlled trials without venographic or ultrasound surveillance	Composite of symptomatic and asymptomatic events	Assumes that relative risk reduction in asymptomatic events applies to symptomatic events, which may not be the case Ideal observational studies may not be available
Strategy 4	Symptomatic events plus 10% (or range of 3%-50%) of asymptomatic events	Composite of symptomatic and asymptomatic events	Assumes that relative risk reduction in asymptomatic events applies to symptomatic events, which may not be the case Limitations in data and questionable assumptions make estimates of proportion of asymptomatic events that become symptomatic questionable

Third, estimates of absolute symptomatic events from studies that included mandatory venography may be misleading. If mandatory venography is positive, patients typically will receive antithrombotic treatment. Had venography not been undertaken and anticoagulant therapy not been administered, some of these patients likely would have developed symptomatic VTE. To the extent that this is the case, the number of symptomatic VTE and the benefit of any treatment that reduces VTE will be underestimated.

There is also the possibility of bias in the opposite direction. What might otherwise have been considered minor swelling or pain in the leg not warranting investigation could be labeled, after a positive mandatory venogram, a symptomatic leg event. What might otherwise have been considered a minor transient episode of dyspnea not warranting further investigation might be considered, after a positive mandatory venogram (with or without direct testing for pulmonary emboli), a symptomatic pulmonary embolus. To the extent that these phenomena occur, the number of symptomatic VTE and the benefit of any treatment that reduces VTE will be overestimated.

There is no evidence that allows confident estimates of the relative impact of the downward and upward biases on the estimates of symptomatic events that result from mandatory venography. One might speculate that the downward bias as a result of the treatment of asymptomatic events is likely to be greater than the upward bias as a result of labeling of clinically trivial events as symptomatic. To the extent

that this is true, estimates of benefit of one treatment over another would be conservative. Depending on one's perspective, one might view this conservatism in estimates as desirable or undesirable.

Considering all these issues, estimates of reduction in patient-important events using this strategy are likely, if they err, to underestimate the true effect. Therefore, despite their limitations, if well-conducted RCTs have been sufficiently large to yield precise estimates suggesting a reduction in symptomatic VTE, this constitutes high-quality evidence of benefit. Smaller studies with wider CIs will yield, at best, moderate confidence in estimates.

Eventually, Kahn et al¹³ determined that the baseline risk of medical patients enrolled in RCTs was too heterogeneous and used stratified baseline risks from symptomatic events from a risk assessment model.

4.2 Strategy 2: Asymptomatic Events for Relative Risks, Symptomatic Events From RCTs for Baseline Risk

A second approach would be to use estimates of the relative effect of the interventions under comparison from the combined end point of symptomatic and asymptomatic VTE or, if this is not available, the relative effect from asymptomatic events. One would use this relative risk estimate (often reasonably precise) rather than that derived from symptomatic events alone. One would apply this estimate of relative effect to the proportion of the absolute number

of symptomatic events in the control intervention to generate a best estimate of the absolute number of events in experimental intervention.

For instance, assume that the relative risk of the combined end point of asymptomatic and symptomatic VTE pooled across relevant RCTs was 0.6, a relative risk reduction of 40%. Of the control patients, 1% experienced a symptomatic pulmonary embolus and 4% experienced symptomatic DVT (again, for both estimates, pooling across relevant studies). The absolute reductions in pulmonary embolus with the experimental treatment would therefore be 0.4% (40% of 1%, or one in 250 patients) for pulmonary embolus and 1.6% (40% of 4%, or one in ~63 patients) for DVT.

For example, in the article addressing thromboprophylaxis in orthopedic surgical patients, Falck-Ytter et al¹⁴ used the event rate in trials of LMWH, adjusted for the effect of LMWH from previous trials of LMWH against placebo or no treatment, to generate a control group risk.² To estimate the absolute reduction in symptomatic DVT event rates with UFH, they applied the RR from the relevant RCTs for the combined end point of symptomatic and asymptomatic events (of which most were asymptomatic) to the control group risk derived from the LMWH trials. Their estimate of RR was 0.42 (95% CI, 0.36-0.5), their control group risk over the first 14 days after surgery was 1.8%, and their estimate of absolute benefit was 10 fewer events per 1,000 (95% CI, from nine fewer to 12 fewer). The very tight CI leaves no need to rate down for imprecision, but using asymptomatic events to generate that tight CI requires rating down for indirectness, and the quality evidence is, as a result, only moderate.

The advantage of this approach over the first, as the example from the orthopedic prophylaxis article¹⁴ shows, is that it provides a more precise estimate of relative risk than one would obtain from the much fewer symptomatic events. It requires, however, the assumption that the relative effect on symptomatic and asymptomatic events is the same (thus, the need to rate down for indirectness). Furthermore, it shares the following disadvantages with the first approach: It uses RCT populations that are likely to be unrepresentative of real-world practice; because the number of symptomatic events is small, the precision of the estimates of baseline control group risk of symptomatic events will be imprecise; and estimates of baseline control group risk of an asymptomatic event are subject to both the upward and the downward biases presented in the discussion of strategy 1. Because of these limitations and the uncertainty resulting from the substitution of the relative effect on symptomatic and asymptomatic VTE for the relative effect on symp-

tomatic VTE, this approach can yield, at best, moderate confidence in estimates.

4.3 Strategy 3: Baseline Risk Estimates From Studies That Do Not Perform Surveillance, Relative Effect From Asymptomatic Events in RCTs

In the third approach, one would begin by identifying observational studies of risks of symptomatic VTE from relevant medical or surgical populations in which venographic or ultrasound surveillance was not undertaken. One would then apply the relative risk reductions from the combined end point of symptomatic and asymptomatic DVT from RCTs to those baseline estimates of risk. The approach is similar to the second strategy, but baseline risk estimates now come from observational studies without surveillance rather than from RCTs with surveillance. If satisfactory observational studies were not available, one could use control event risks from RCTs that did not perform venographic or ultrasound surveillance.

The advantages of this approach are threefold: Baseline risk estimates would, if one used observational studies, come from real-world populations; they would not be subject to the biases associated with treatment of asymptomatic events or with attribution of questionable symptoms to VTE after discovery of a venographic DVT; and if sample sizes were large enough, estimates of risk would be reasonably precise. These are compelling advantages.

One disadvantage would be the persisting assumption that relative effects of treatment on symptomatic and asymptomatic events are identical. A second would arise if the observational studies were conducted only on patients not receiving thromboprophylaxis. When applying risks from observational populations to comparisons of two active treatments, one would have to model results from RCTs of controlled active interventions vs no thromboprophylaxis and then apply the resulting risk estimates to the experimental VTE prophylaxis strategy.

Our judgment is that the advantages of this third strategy outweigh its disadvantages, given one crucial proviso. It requires the existence of large observational studies with a low risk of bias. To achieve a low risk of bias, observational studies would need to enroll representative populations; avoid exclusions; minimize loss to follow-up; and institute a rigorous, reproducible, and comprehensive strategy for ascertaining symptomatic VTE. The authors would also specify the number of patients receiving some sort of prophylaxis and ideally report results separately for those receiving and not receiving prophylaxis. Unfortunately, studies meeting all these criteria are rarely available. In situations in which there are large, high-quality observational studies available, if one is ready

to believe that it is very likely that the relative effect on asymptomatic VTE in the particular context is very similar to the relative effect on symptomatic VTE, one could argue that it is possible for this approach to yield high confidence in effect estimates. Greater skepticism regarding application of the relative effect on asymptomatic events to symptomatic events would suggest that this strategy yields, at best, moderate confidence in effect estimates.

In the article on nonorthopedic surgery thromboprophylaxis, Gould et al¹⁵ used this strategy to address the effect of IPC on symptomatic VTE.³ The control group risk of VTE came from an observational study of 8,216 general, vascular, and urological surgery patients, most of whom received either mechanical or pharmacologic prophylaxis.⁴ The observational study enrolled a representative population, had minimal loss to follow-up, provided information about use of prophylaxis (which allowed adjustment for the effect of treatment in estimating untreated risk), and used the best available risk stratification strategy. It was limited in that it relied on recorded clinical diagnosis abstracted by trained nurses (ie, the approach to diagnosis of VTE was not systematic). Gould et al¹⁵ estimated that 26 of 1,000 moderate-risk patients would experience VTE if they received no prophylaxis. IPC lowered the risk of asymptomatic DVT substantially, with a narrow CI (OR, 0.48; 95% CI, 0.22-0.74), resulting in an estimate of 13 fewer VTE per 1,000 patients (95% CI, 7-20). Unfortunately, in addition to the consequent indirectness on estimates of relative effect coming from asymptomatic events, the RCTs also suffered from high risk of bias; therefore, the overall confidence in estimates is low.

In the nonorthopedic surgical prophylaxis article, Gould et al¹⁵ used a variant of this strategy that could potentially yield high-quality evidence. In calculating the likely effect of LMWH on reducing symptomatic VTE, their estimate of baseline risk came from the relatively high-quality observational study described in the previous paragraph and their estimate of relative effect from three RCTs that reported symptomatic events. Unfortunately, the studies were judged as suffering from a high risk of bias, and so the overall confidence in estimates was only moderate.

4.4 Strategy 4: Use Available Data To Estimate the Proportion of Asymptomatic Events That Will Become Symptomatic

The fourth strategy provides an estimate of the frequency with which asymptomatic events will become symptomatic, and uses this estimate to add some proportion of the asymptomatic events to symptomatic events in generating the control group risk. It uses available data to provide this estimate.

What data should drive an informed estimate? Intuitively, one might estimate the proportion of asymptomatic events that would become, in the absence of antithrombotic therapy, symptomatic by looking at the ratio between symptomatic and asymptomatic events. Using this approach, we estimate that about one in 10 patients with asymptomatic DVT detected by mandatory venography develop symptomatic DVT.

To see how one would apply this estimate, let us take a hypothetical example in which 1% of the control patients experience symptomatic VTE and 10% experience asymptomatic VTE. If we estimate that of the asymptomatic events, one in 10 will become symptomatic, then the total symptomatic events in the control group will be $1\% + (10\%/10) = 1\% + 1\% = 2\%$. One then would apply the relative risk reduction associated with the composite of symptomatic and asymptomatic events to this control group risk. For example, if the relative risk reduction were 40%, the absolute reduction in events would $2\% \times 4/10 = 0.8\%$.

This approach is fraught with limitations, five of which are particularly challenging:

1. There is likely to be an upward bias in clinically trivial events being labeled symptomatic when venography is positive. To the extent that this is the case, it will inflate the ratio of asymptomatic events that would eventually become symptomatic. To consider only the downward bias from the prevention of events that ultimately become symptomatic is problematic.
2. The ratio of asymptomatic to symptomatic events varies widely across settings. The ratio of asymptomatic to symptomatic thrombosis varies from as high as 2:1 to as low as 30:1 among different patient groups.
3. At least in select orthopedic prophylaxis studies, the center interpreting the venography appears to influence the ratio; for example, the reported frequency of venographic DVT is consistently lower in studies adjudicated by McMaster University compared with the University of Gothenburg, resulting in lower ratios of asymptomatic to symptomatic thrombosis in studies adjudicated by McMaster compared with Gothenburg.¹⁶
4. The ratio reflects the number of symptomatic events occurring before or labeled at the time of venography (we do not know which) vs the number asymptomatic venographic events. What we are trying to estimate, however, is the proportion of symptomatic events that occur after venography. It is quite possible that the number of symptomatic events that would occur following venography would be quite different from the

number occurring before. (Using this approach, we are assuming that they would be the same.)

5. A fifth problem, perhaps less troubling than the others, is the assumption that the nature of symptomatic events that will develop in those patients who are asymptomatic at the time of positive venography is such that the relative risk reduction generated from prior symptomatic and asymptomatic events will apply to late symptomatic events.

One merit of this approach is that to the extent that the downward bias is greater than the upward bias when one uses symptomatic events alone, the approach may bring us closer to the true number of VTE events prevented by an experimental treatment. The most important limitation is the uncertainty of the best estimate, and because of this uncertainty, this approach can provide only low confidence in estimates.

We also considered a variation on strategy 4 that acknowledges the uncertainty associated both with the upward bias resulting from clinically trivial events being labeled as important because of a positive venogram and with the uncertainty in the estimate of venographic events that would become symptomatic. Instead of a single best estimate of the proportion of asymptomatic events that ultimately will be symptomatic, this approach generates upper and lower boundaries of the estimate, that is, the lowest plausible ratio and the highest plausible ratio. The available evidence suggests that this range varies from 2:1 to 30:1.

Thus, rather than using a conventional CI around the magnitude of effect, one might generate what could be called an "uncertainty interval." We illustrate how this might work using the hypothetical example we present here for strategy 4. Of the control patients, 1% experienced symptomatic VTE, and 10% experienced asymptomatic VTE. We estimated that of the asymptomatic events, one in 10 would become symptomatic; the control event rate would be 2%; and with a relative risk reduction of 40%, the absolute reduction in events would be 0.8%. The point estimate of the relative risk reduction is associated with a CI of, say, between 10% and 70%. Assuming one boundary, 10%, the absolute reduction in risk would be 10% of 2%, or 0.2%. Assuming the other boundary of 70%, the absolute reduction in risk would be 70% of 2%, or 1.4%.

What are the consequences if we acknowledge the uncertainty around our estimate of a 10:1 ratio between asymptomatic and symptomatic events (as low as 2:1 and as high as 30:1)? Without belaboring the arithmetic, this would generate an uncertainty interval that suggests that the absolute benefit could be as low as 1.03% or as high as 4.5%.

This approach has the same fundamental advantages and disadvantages of the basic strategy 4. It has the advantage, however, of fully acknowledging the uncertainty around estimates of the ratio between asymptomatic and symptomatic events. Its disadvantage, relative to strategy 4, is that some may find the approach conceptually challenging, and others may be uncomfortable with the width of the uncertainty interval. We would argue, however, that this range accurately reflects the limited inferences one can make on the basis of the present evidence and the low confidence in estimates that this approach generates.

Kahn et al¹³ used this approach (almost) in only one recommendation. To estimate the impact of LMWH on PE in critically ill patients, they calculated the point estimate of the absolute reduction in asymptomatic DVT from two RCTs (22 per 1,000). For their point estimate (a reduction of four events per 1,000), they estimated that for each of five asymptomatic DVTs there would be one fewer PE. In generating a CI around this estimate (from eight fewer to one more PE), they used both 1:5 and 1:10 ratios and presented the widest CI consistent with these estimated ratios. Because of concerns about, in addition to the uncertainty about, the ratio of asymptomatic DVT to clinically significant PE, risk of bias, inconsistency, and imprecision, the data provided only very low confidence in the effect estimate. Ultimately, the authors abandoned the approach, preferring strategy 3 in which they obtained baseline risk from observational studies and relative risk reduction from asymptomatic events in RCTs.

5.0 THE AT9 APPROACH TO ESTIMATING SYMPTOMATIC VTE

Under different circumstances, with different bodies of evidence, any of strategies 1 to 3 might generate the highest-quality evidence. In the presence of rigorous observational studies and in the absence of large RCTs that show significant differences in symptomatic events between competing antithrombotic agents, strategy 3 will yield the highest-quality evidence. When large RCTs show convincing differences in symptomatic events between agents, strategy 1 will yield the highest-quality evidence. When neither of these conditions exist, it is likely that strategy 2 will yield the highest-quality evidence. It is unlikely that strategy 4 will ever yield the highest confidence in estimates.

In general, AT9 uses the best available evidence to generate estimates of the magnitude of intervention effects on patient-important outcomes. This is the approach we have adopted for estimating the

reduction in symptomatic VTE with competing antithrombotic agents. Depending on the evidence in a particular situation, AT9 guideline panels have chosen the approach, among strategies documented here, that yields the highest confidence in estimates.

6.0 TRADING OFF SYMPTOMATIC VTE AND BLEEDING

Having established best estimates of VTE and bleeding, making recommendations requires deciding on whether net benefit is optimized by administering or withholding antithrombotic prophylaxis. The relevant nonfatal events in medical and surgical prophylaxis are pulmonary embolus, DVT, and GI and surgical site bleeding. AT9 panelists¹⁷ rated the disutility (aversiveness or importance) of these events and judged them to be of similar importance to patients (DVT slightly less important; PE, GI, and perioperative bleeding very similar). Thus, considering nonfatal events alone, if an antithrombotic regimen prevents more VTE events than it causes bleeding events compared with an alternative, recommendations will favor that regimen; if therapy causes more bleeding events than it prevents VTE events, recommendations will favor withholding (or administering less aggressive) antithrombotic prophylaxis. Given a constant relative risk reduction in VTE for patient groups at relatively high risk of symptomatic VTE, the former situation is likely to hold, and for those at very low risk, the latter.

The approach to trading off presented thus far has two limitations. First, it ignores the most important events—fatalities. As we have noted, antithrombotic prophylaxis, relative to no prophylaxis, reduces deaths from pulmonary embolus in both medical and surgical patients enrolled in RCTs and may reduce all-cause mortality in surgical patients (Table 1), providing a compelling rationale for recommending prophylaxis in patients who meet the profile of those enrolled in the trials that demonstrated the reduction in mortality from pulmonary embolus.

Once one has decided to administer antithrombotic prophylaxis to patients at sufficiently high risk of VTE, the issue of lower mortality from pulmonary embolus becomes less compelling. The administration of any effective antithrombotic prophylaxis is likely to substantially reduce the number of fatal pulmonary emboli, which already is very rare. Thus, any further reduction in absolute risk from more-intensive antithrombotic therapy will be, in absolute terms, very small. Furthermore, an inference that any additional reduction in fatal pulmonary emboli will occur at all is based on indirect evidence from the impact on nonfatal and often largely asymp-

tomatic thrombi and on the evidence from comparisons of antithrombotic prophylaxis vs no antithrombotic prophylaxis.

In this article, we have outlined the limitations associated with evidence quality in ascertaining best estimates of treatment impact on VTE. In the individual articles that present recommendations, we describe the limitations regarding the evidence quality for differences in bleeding. Our judgment is that in comparisons of alternative antithrombotic regimens, inferences regarding fatalities are even more tenuous. Therefore, for decisions regarding which antithrombotic agent or regimen to use, we largely base inferences on evidence in nonfatal VTE prevention vs increases in nonfatal bleeding.

The second limitation is that the judgment that bleeding events have more or less the same disutility as VTE events is fraught with uncertainty. Studies of patient values and preferences that would lead to confidence in this judgment do not exist; therefore, recommending one antithrombotic agent over another requires a substantial benefit-risk gradient between therapies, with a high level of confidence in that gradient.

CONCLUSION

None of the approaches we have suggested for estimating the effect of antithrombotic prophylaxis is without problems arising from the conduct of screening ultrasound and venography. Subsequent studies should rely on clinical surveillance to detect symptomatic events.

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Dr Guyatt: served as a Topic Editor and was responsible for drafting the entire article, with the exception of the first part on evidence regarding the impact of antithrombotic prophylaxis on mortality, and for final editing and content.

Dr Eikelboom: served as a panelist and was responsible for drafting the first part of this article dealing with the evidence regarding the impact of antithrombotic prophylaxis on mortality.

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