

Methodology for Antithrombotic and Thrombolytic Therapy Guideline Development*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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The American College of Chest Physicians (ACCP) invited a panel of experts, researchers, information scientists, and guideline methodologists to develop the eighth edition of ACCP evidence-based guidelines on antithrombotic and thrombolytic therapy. The process began with guideline authors specifying the population, intervention and alternative, and outcomes for each clinical question and defined criteria for eligible articles, including methodologic criteria, for each recommendation. The McMaster University Evidence-Based Practice Center, in collaboration with the guideline authors and methodologists, developed strategies and executed systematic searches for evidence. The resulting guidelines are organized in chapters that present a clear link between the evidence and the resulting recommendations. The panel identified questions in which resource allocation issues were particularly important and obtained input from consultants with expertise in economic analysis for these issues. Authors paid careful attention to the quality of underlying evidence and the balance between risks and benefits, both reflected in grades of recommendations. For recommendations that are particularly sensitive to underlying values and preferences, the panel made explicit the values underlying the recommendations. Thus, the process of making recommendations for the ACCP guidelines included explicit definition of questions, transparent eligibility criteria for including studies, comprehensive searches and methodologic assessment of studies, and specification of values and preferences and resource implications underlying recommendations where particularly relevant. In combination with our previous practice of grading recommendations according to their strength and the methodologic quality of the supporting studies, these methods establish our guideline methodology as evidence based. (*CHEST 2008; 133:113S–122S*)

Key words: evidence-based medicine; grade; guideline development; guidelines; quality of evidence; recommendations

Abbreviations: ACCP = American College of Chest Physicians; EPC = evidence-based practice center; HSP = Health Science Policy; LMWH = low-molecular-weight heparin; RCT = randomized controlled trial; tPA = tissue plasminogen activator

The methodology for the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) built on the innovations of prior conferences. As with other iterations, the changing evidence base in the field of antithrombotic and thrombolytic research led to many updated and new recommendations. To further improve the quality of these guidelines, we have made additional

changes to the methodology. Evidence-based approaches to guideline development include acknowledgment of factors other than evidence that inevitably influence recommendations—values and preferences. For the first time, we involved consultants whose role was to focus on patient value and preference issues. We also implemented recommendations of a recent American College of Chest Physicians (ACCP) task force on integrating resource allocation in guideline develop-

ment by restricting resource expenditure consideration to a small number of recommendations for which they were particularly relevant.¹ To accomplish this task, we involved experts in economic analysis in developing these recommendations.^{1,2} In addition, for this iteration of the guidelines, we collaborated with the McMaster University Evidence-Based Practice Center (EPC) [Hamilton, ON, Canada], one of the 13 North American EPCs.

To maintain transparency of the guideline development, we followed explicit rules for managing conflicts of interest. Before participating on the panel, all participants submitted conflict-of-interest statements that were reviewed by the ACCP Health Science and Policy (HSP) Committee. Participants' potential conflicts are listed prominently in the front section of the guideline document.³ The panelists updated their conflict-of-interest disclosures again before the final conference and before publication. These disclosures are published with the guidelines and posted on the *CHEST* journal Web site (www.chestjournal.org).

The development of evidence-based guidelines includes explicitly defining the question that the guideline or recommendation is addressing; formulating eligibility criteria for evidence to be considered; conducting a comprehensive search for evidence; evaluating study quality; summarizing the studies; balancing the benefits and downsides of the alternative management strategies; and, finally, acknowledging values and preferences underlying the recommendations, including considerations on expenditures.^{4–6} This process ends with a recommendation for action and a grading of that recommendation according to the balance of desirable effects (benefits), undesirable effects (harms, burden, and resource expenditures), and the quality of the evidence. We followed the methodology for grading the quality of evidence and strength of recommendations that the ACCP codified during a recent ACCP task force meeting. The grading system adopted was a modification from that developed by the Grading

of Recommendations Assessment, Development and Evaluation Working Group.^{7–9} This article describes the methodology for guideline development for the *Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)*. Figure 1 summarizes this process.

GUIDELINE DEVELOPMENT FOR THE EIGHTH ACCP CONFERENCE ON ANTITHROMBOTIC AND THROMBOLYTIC THERAPY

Panel Selection Process

The criteria for panel selection were an established track record in the relevant clinical or research area, international and gender representation, prior involvement with the ACCP Conference on Antithrombotic and Thrombolytic Therapy, and absence of conflicts of interest that could not be resolved. The senior editors suggested individual chapter chairs as well as chapter members. Chapter chairs also made suggestions for the inclusion of chapter members. All panel members were approved by the ACCP HSP Committee after review of their curriculum vitae.

Defining the Clinical Question

Developing a clinical practice guideline should begin with specifying a clinical question that defines the relevant population, alternative management strategies (comparison), and outcomes.¹⁰ For the current ACCP guidelines, authors defined one question for each recommendation or set of recommendations. Readers can find these questions in the corresponding table of each chapter containing practice recommendations.

Presentation of Evidence and Recommendations

To provide a transparent, explicit link among questions, evidence, and recommendations, the section numbering in each chapter corresponds to numbers in the corresponding table in the chapters, which specifies the patients, interventions, and outcomes; the section numbering also corresponds to the numbering of the recommendations themselves.

Process of Searching for Evidence

Defining the clinical question provided the framework for formulating eligibility criteria that guided the search for relevant evidence. In specifying eligibility criteria, authors identified not only patients, interventions, and outcomes, but also methodologic criteria. For many recommendations, authors re-

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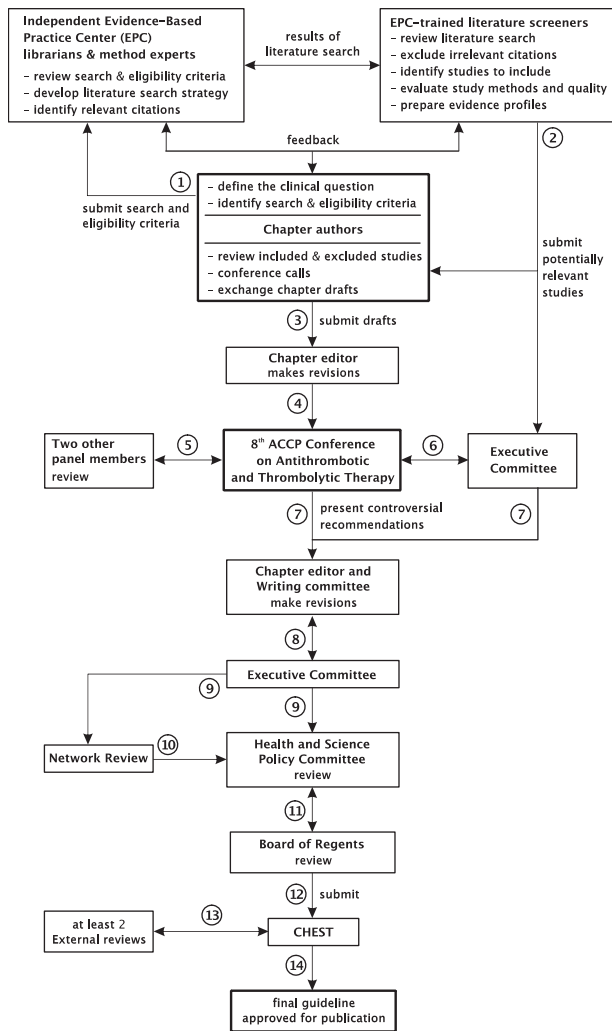


FIGURE 1. Methodology for guideline development and review. Process steps are indicated by the numbers adjacent to arrows in this algorithm. An executive committee comprising methodologists, content experts, and an HSP liaison coordinated the writing of chapters for the *Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)*.⁷ After identification of search and eligibility criteria by chapter authors, librarians in collaboration with two of the executive methodologists searched for evidence.^{1,2,7} Trained literature screeners reviewed citations and removed irrelevant citations under supervision of one executive methodologist and the chapter editors.^{1,2} Chapter authors revised previous chapters or wrote new chapters in close collaboration with all editors and authors of other chapters.^{3,4,5,8} The review process includes simultaneous reviews by the appropriate ACCP NetWork and the HSP before advancing to the Board of Regents.⁷⁻¹¹ Both of the latter two committees must approve the manuscript before it can be submitted to *CHEST*.¹² The editor-in-chief of the journal sends the manuscript to at least two external reviewers before acceptance for publication.^{13,14}

stricted eligibility to randomized controlled trials (RCTs). For example, as in previous editions, Albers et al¹¹ considered whether clinicians should offer thrombolytic therapy in acute stroke. They defined *patients* as anyone presenting with acute thrombotic

stroke (divided into presentation of < 3 h and > 3 h after onset of symptoms), *intervention* as any thrombolytic regimen compared to no intervention or placebo, and *outcome* as death or functional status based on assessment with a validated functional status instrument. The methodology was restricted to RCTs. This question yielded several recommendations, including whether patients with acute ischemic stroke presenting within 3 h of symptom onset should receive IV tissue plasminogen activator (tPA).

For many questions, randomized trials did not provide sufficient data, and chapter authors included observational studies when randomized trials were not the most appropriate design to address the research question. In particular, randomized trials are not necessarily the best design to understand risk groups, that is, the baseline or expected risk of a given event for certain subpopulations. Because no interventions are typically examined in questions about prognosis, one replaces interventions by the duration of exposure measured in time. For example, to obtain information about the risk of ischemic stroke in patients with atrial fibrillation in specific risk groups, the sensible question was: In patients with atrial fibrillation differing in age, BP, left ventricular function, or history of previous embolic events, what is the risk of stroke or death over a given time period?

Identifying the Evidence

To identify the relevant evidence, a team of librarians and research associates at the McMaster University EPC conducted comprehensive literature searches. Methodologic experts (including the editors) and the EPC librarians reviewed each question to ensure the development of a comprehensive search strategy. For example, for questions about antiplatelet agents, the EPC consulted chapter authors to ensure that the search included all relevant antiplatelet agents. More specifically, authors then decided whether to include dipyridamole in a search that already included aspirin, clopidogrel, and ticlopidine.

For each question the authors provided, the librarians searched the Cochrane Database of Systematic Reviews, MEDLINE, and Embase for published English-language literature and human studies between 2002 and May 2006. To filter MEDLINE and Embase search results for RCT evidence, the librarians used the search strategy developed by the Cochrane Collaboration. These searches updated our more comprehensive and sensitive searches conducted for the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines.^{3,6}

The EPC team conducted separate searches for systematic reviews; RCTs; and, if applicable, observational studies. For observational studies, searches were not restricted in terms of methodology. Although increasing the probability of identifying all published studies, this sensitive approach resulted in large numbers of citations for many of the defined clinical questions. Therefore, trained research assistants screened the citation list developed from the search using criteria of increased specificity to reduce the number of irrelevant citations that the authors received. These irrelevant citations included press news, editorials, narrative reviews, single-case reports, studies that included fewer participants than specified by authors as an inclusion criterion, animal studies (any nonhuman studies), and letters to the editor. Authors did not include data from abstracts of meetings for the development of recommendations, and we did not explicitly use Internet sources to search for research data. Authors were encouraged, however, to mention abstracts that reported on groundbreaking data that were particularly relevant to a specific question in the chapters in order to alert readers that new, fully published evidence might become available shortly.

Standard Consideration of Study Quality

High-quality clinical guidelines should pay careful attention to the methodologic quality of the studies that form the basis of their recommendations. Using the example of the prevention of venous thromboembolism during air travel, Table 1 shows the criteria for assessment of study quality (randomization, concealment or treatment allocation, blinding, completeness of follow-up, and whether the analysis was performed according to the intention-to-treat principle), and Table 2 shows the presentation of results that were circulated to the authors. Whereas all authors attended to these criteria, we have summarized the results of the quality assessment for only a minority of the recommendations. Readers can find these summaries in an online appendix to the recommendations (see online supplemental data).

In assessing the quality of observational studies, we did not make a distinction between prospective and retrospective because the key issues are unbiased sampling, high-quality measurement of patient characteristics and outcomes, and complete follow-up. Although it is more likely that these quality criteria will be achieved in prospective studies, prospective studies may fail to achieve them, and retrospective studies may succeed. We did make a key distinction about whether internal comparisons exist and their nature. Studies without internal comparisons received the label “case series” unless they met the

following criteria: (1) a protocol existed before the date of commencement of data collection; (2) a definition of inclusion and exclusion criteria was available; (3) the study reported the number of excluded patients; (4) the study conducted a standardized follow-up, including description of schedule of follow-up, investigation of suspected outcomes, and criteria used to define outcomes; and (5) the study reported all losses to follow-up.

We labeled studies that met these criteria “cohort studies without internal controls.” Studies with internal comparisons received the label “cohort studies with concurrent controls” or “cohort studies with historical controls.” These cohort studies may succeed or fail to ensure settings, similar time frames, adjustment for differences in patients’ characteristics, and follow-up with patients. These features were captured in descriptive tables provided to authors when requested from the EPC.

Summarizing Evidence

The electronic searches also included searches for systematic reviews. If authors were satisfied with a recent high-quality systematic review, evidence from that review provided a foundation for the relevant recommendation. For example, Albers et al¹¹ used a systematic review and metaanalysis as the foundation for their recommendation on IV streptokinase for acute ischemic stroke between 0 and 6 h of symptom onset (chapter on Stroke, Section 1.3). Geerts et al¹² used several metaanalyses for their recommendations (chapter on Prevention of Venous Thromboembolism, *eg*, Section 2).

For the first time for a small number of recommendations (see chapters Ansell et al, Warkentin et al, Geerts et al, Kearon et al, Albers et al, Harrington et al, Becker et al, Sobel and Verhaeghe, and Bates et al), we systematically examined the impact of quality of design and implementation of individual studies, precision, consistency and directness of results, likelihood of reporting bias, and presence of very large effects on the quality of the evidence. For recommendations in which we did so, we present tables that summarize these features. Table 3 provides an example.

Pooled analyses from high-quality systematic reviews formed summary data on which panelists based their recommendations wherever possible. Pooling offers the advantage of obtaining more precise estimates of treatment effects and allows for greater generalizability of results. However, pooling also bears the risk of spurious generalization. In general, the summary estimates of interest were the different types of outcomes conveying benefits and downsides (risk, burden, and cost). When pooled

Table 1—Example of Methodologic Evaluation of Studies*

Study, yr	Intervention	Randomization Concealed	Blinding	No Outcome, n/N (%)	Analysis	Comments
Travel socks						
Scurr/2001	No prophylaxis Socks: below-knee stockings (ankle pressure, 18–22 mm Hg), starting preflight	Yes: sealed envelope	Subjects: no Outcome assessors: yes	No prophylaxis: 16/116 (14) Socks: 15/115 (13%)	ITT	Designed as a pilot study
Belcaro/2002	No prophylaxis Socks: below-knee stockings (maximum ankle pressure, 25 mm Hg), starting 6–10 h preflight	Probably not (NR)	Subjects: no Outcome assessors: no	Combined: 52/885 (6)	NR	Subject recruitment process NR Exclusion criteria NR Method of randomization NR Specific stockings used NR DVT screening test not validated Dropouts/group NR
Belcaro/2002	No prophylaxis Socks: below-knee flight socks (ankle pressure, 14–17 mm Hg), starting 2–3 h preflight	Probably not (NR)	Subjects: no Outcome assessors: no	No prophylaxis: 17/331 (5) Socks: 11/326 (3)	ITT	Subject recruitment process NR Method of randomization NR DVT screening test not validated Source of funding NR
Cesarone/2003	No prophylaxis Socks: below-knee stockings (ankle pressure, 12–18 mm Hg), starting 2–3 h preflight	Probably not (NR)	Subjects: no Outcome assessors: no	No prophylaxis: 21/190 (11) Socks: 14/186 (8)	ITT	Subject recruitment process NR Exclusion criteria not defined Method of randomization NR DVT screening test not validated Source of funding NR
Cesarone/2003	No prophylaxis Socks: below-knee travel socks (ankle pressure, 20–30 mm Hg), starting 2–3 h preflight	Probably not (NR)	Subjects: no Outcome assessors: no	No prophylaxis: 6/144 (4) Socks: 2/140 (1)	ITT	Subject recruitment process NR Exclusion method of randomization NR DVT screening test not validated Unclear how many subjects were randomized in part II (n = 285 or 134) Source of funding NR Criteria not defined
Belcaro/2003	No prophylaxis + video Socks: below-knee flight socks (ankle pressure, 14–17 mm Hg), starting 3–4 h preflight + video	Probably not (NR)	Subjects: no Outcome assessors: no	No prophylaxis: 12/114 (11) Socks: 7/110 (6)	ITT	Subject recruitment process NR Exclusion criteria not defined Method of randomization NR DVT screening test not validated Source of funding NR
LMWH vs no prophylaxis						
Cesarone/2002	No prophylaxis Enoxaparin 1 mg/kg, 2–4 h preflight	Probably not (NR)	Subjects: no Outcome assessors: probably not	No prophylaxis: 17/100 (17) Enoxaparin: 18/100 (18)	Per protocol	Abstract reports an additional subject group (LMWH + socks) not mentioned in publication Subject recruitment process NR Flight duration NR Method of randomization NR DVT screening test not validated Source of funding NR

Table 1—Continued

Study, yr	Intervention	Randomization Concealed	Blinding	No Outcome, n/N (%)	Analysis	Comments
Aspirin vs no prophylaxis Cesarone/2002	No prophylaxis Aspirin 400 mg × 3 d, starting 12 h preflight	Probably not (NR)	Subjects: no Outcome assessors: probably not	No prophylaxis: 17/100 (17) Aspirin: 16/100 (16)	Per protocol	Abstract reports an additional subject group (LMWH + socks) not mentioned in publication Subject recruitment process NR Flight duration NR Method of randomization NR DVT screening test not validated Source of funding NR

*ITT = intention to treat; NR = not reported; DVT = deep vein thrombosis.

estimates of effects were not available, the EPC conducted metaanalysis to obtain pooled estimates for specific questions. These were questions that authors had specifically identified. Table 3 presents an example of a Grading of Recommendations Assessment, Development and Evaluation evidence profile prepared by the EPC.^{7,13}

Another chapter in this supplement details the basic grading of methodologic quality.⁸ In brief, consistent results from RCTs or observational studies with very strong effects result in Grade A recommendations; inconsistent results from RCTs or RCTs with important methodologic limitations receive Grade B, and observational studies without very strong effects result in Grade C quality of evidence.

Group-Specific Recommendations

The absolute magnitude of treatment effects may be very different in patients with varying levels of risk. For instance, although the relative risk reduction of warfarin vs aspirin in stroke prevention for atrial fibrillation patients is likely close to 50% across risk groups, this translates into absolute risk reductions of < 1% per year in the lowest risk groups, and in the vicinity of 5% per year in the highest risk groups. Clearly, optimal management must differ across risk groups, and this is reflected in the recommendations of our atrial fibrillation panel.

In general, we have endeavored to make our recommendations as specific as possible for patient subgroups differing according to risk. Whenever valid prognostic data were available, we used them to estimate absolute effects and made recommendations accordingly. Unfortunately, reliable prognostic indexes are not usually available, limiting the extent to which such group-specific recommendations are possible.

Acknowledge Values and Preferences and Resource Use Underlying Recommendations

Under ideal circumstances, knowledge of average patient values and preferences would be available for every recommendation, the panel members would summarize these values and preferences, and they would be integrated into the recommendations that guideline developers make. We asked all chapter chairs before beginning the searches for the relevant literature to identify recommendations that they believed were particularly sensitive to patients' values and preferences. Moderate-quality evidence regarding values and preferences bearing directly on the recommendations proved available for only the chapter that addresses antithrombotic therapy in patients with atrial fibrillation. Our panelists beared in mind what average patient values and preferences may be; the process, however, is speculative.¹⁴

Our main strategy for dealing with this unsatisfactory situation is to make the values and preferences underlying the recommendations explicit whenever the panelists believed that value and preference issues were crucial for a recommendation. For example, Albers et al¹¹ suggest for patients with acute ischemic stroke of > 3 h but < 4.5 h that clinicians do not use IV tPA (Grade 2A). For patients with acute stroke onset of > 4.5 h, we recommend against the use of IV tPA (Grade 1A). The authors noted in the corresponding values and preferences statement, "This recommendation assumes a relatively low value on small increases in long-term functional improvement, a relatively high value on avoiding acute intracranial hemorrhage and death, and a relatively high degree of risk aversion."

In addition, we involved three consultants with expertise in the area of values and preferences to collaborate with the chairs of two chapters and try to

Table 2—Example Randomized Trials of Thromboprophylaxis in Air Travelers (Partial Presentation of All Trials): Clinical Description and Results*

Study Year	Interventions	Risk Group/Flight Duration	Patients Analyzed		Time to Screening	DVT		SVT		Edema Mean (SD)	Comments
			No./Total (%)	No./Total (%)		No./Total (%)	No./Total (%)	RR (95% CI)	RR (95% CI)		
Travel socks											
Scurr, 2001	No prophylaxis Socks: below-knee stockings (ankle pressure 18–22 mm Hg), starting preflight	Low/18–36 h	No prophylaxis: 100/116 (86) Socks: 100/115 (87)	No prophylaxis: 12/100 (12) Socks: 0/100 RR: 0.04 (0.00–0.67)	< 48 h	No prophylaxis: 0/100 Socks: 4/100 (4%) RR: 9.00 (0.49–165.0)	NR	NR	No proximal DVT		
Belcaro, 2002	No prophylaxis Socks: below-knee stockings (maximum ankle pressure, 25 mm Hg)	High/10–15 h	Combined: 833/885 (94)	No prophylaxis: 19/422 (5) Socks: 1/411 (0%); 0/05 (0.01–0.40)	On arrival	No prophylaxis: 8/422 (2) Socks: 0/411; 0.06 (0.00–1.04)	NR	NR	Proximal DVT NR		
Belcaro, 2002	No prophylaxis Socks: below-knee flight socks (ankle pressure, 14–17 mm Hg), starting 2–3 h preflight	Low to medium/7–12 h	No prophylaxis: 314/331 (95) Socks: 315/326 (97)	No prophylaxis: 7/314 (2) Socks: 0/315; 0.07 (0.00–1.16)	On arrival	No prophylaxis: 5/314 (2) Socks: 0/315; 0.09 (0.01–1.63)	Short flight (7–8 h) No prophylaxis (n = 179): 6.7 Socks (n = 179): 2.2 (1.1) [p < 0.005] Long flight (11–12 h) No prophylaxis (n = 135): 8.1 (2.9) Socks (n = 136): 2.6 (1.6) [p < 0.05]	Subjects on 7- to 8-h flights randomized separately from those on 11- to 12-h flights 5/7 DVTs in no-prophylaxis group were proximal			

*RR = relative risk; SVT = superficial vein thrombosis; see Table 1 for expansion of abbreviations.

Table 3—Example of Evidence Profile*

No. of Studies	Design	Limitations	Consistency	Quality Assessment			Summary of Findings				
				Directness	Precision	Reporting Bias	Magnitude of Effect	Compression Stockings (Flight Socks)	Control	Relative Risk (95% CI)	Events Prevented per 1,000 Treated
DVT 6	RCT	See Table 2	No important inconsistency	No problems	No problems	No reporting bias	Not applicable†	2/1,239 (0.2)	46/1,245 (3.7)	0.09 (0.03–0.26)	High risk: 50 per 1,000 Low risk: 20 per 1,000
SVT 5	RCT	See Table 2	Some inconsistency	No problems	Some imprecision‡	No reporting bias	Not applicable†	5/754 (0.7)	10/751 (1.3)	0.47 (0.07–3.12)	Not significant

*See Tables 1 and 2 for expansion of abbreviations.

†All metaanalyses results are based on random effects models (more conservative), using Cochrane Collaboration Review Manager software (RevMan).

‡Despite the low relative risk, 0.1, do the methodologic limitations lower the confidence in this large effect?

§95% confidence interval includes no effect.

||Based on metaanalysis of four studies. One study reported no cases of superficial vein thrombosis in either the treatment (0/97 patients) or control group (0/98 patients) and was automatically dropped by RevMan during metaanalysis.

ensure that the guidelines adequately represented the views of patients.^{11,15} This collaboration led to extensive discussions among the chapter authors and the consultants and the reflection of these discussions in the associated values and preference statements.

In previous iterations of these guidelines, we did not have a standard or coherent approach to dealing with resource allocation (cost) issues. For these guidelines, we implemented recommendations of a recent ACCP task force on integrating resource allocation in clinical practice guidelines by restricting resource expenditure consideration to a small number of recommendations for which they were particularly relevant.¹ We relied on two consultants with expertise in economic assessment to help with the process of considering costs in those small numbers of recommendations that we considered very important to the decision. The methods and examples for this process are described in the article by Matchar and Mark in this supplement.² Recommendations highly sensitive to resource allocation now include value and preference statements regarding how cost issues were integrated.

Grading Strength of Recommendation

A systematic approach to grading the strength of treatment recommendations can minimize bias and aid interpretation of treatment recommendations. Chapter authors have graded their recommendations as strong (Grade 1, desirable effects much greater than undesirable effects or *vice versa*) and worded the recommendation accordingly as “we recommend” or as weak (Grade 2, desirable effects not clearly greater or less great than undesirable effects) and worded the recommendation as “we suggest.” They also have graded the methodologic quality of the underlying evidence. Another chapter in this supplement details our approach to grading recommendations.⁸

Finalizing and Harmonizing Recommendations

After having completed the steps we have described above, the guideline authors formulated draft recommendations before the conference, which laid the foundation for authors to work together and critique the recommendations. Fig 1 shows the process of guideline development and review. Drafts of chapters that included draft recommendations were usually distributed for peer review to at least two panel members and were always reviewed by at least one panel editor before the conference. Written critiques were prepared and returned to the authors for revision of their work. At the plenary conference, a representative of each

chapter presented potentially controversial issues in their recommendations. Chapter authors met to integrate feedback and consider related recommendations in other chapters and to revise their own guidelines accordingly. Authors continued this process after the conference until they reached agreement within their groups and with other author groups who provided critical feedback. The editors of this supplement harmonized the chapters and resolved remaining disagreements between chapters through facilitated discussion. All major correspondence and discussions at the meeting were recorded in written and audio protocols and are publicly available.

Review by ACCP and External Reviewers

The ACCP HSP established a process for the thorough review of all ACCP evidence-based clinical practice guidelines. After final review by the editors, the guidelines underwent review by appropriate NetWorks of the ACCP (for these guidelines, the Cardiovascular and Pulmonary Vascular NetWorks), the HSP, and the Board of Regents. The latter two have the right of approval or disapproval but usually work with the guideline authors and editors to make necessary revisions before final approval. Each group identified primary reviewers who read the full set of chapters as well as individual committee members who were responsible for reviewing one or more chapters. The reviewers considered both content and methodology as well as whether there was balanced, not biased, reporting and adherence to HSP processes. Finally, the *CHEST* editor-in-chief read and forwarded the manuscripts for nonbiased, independent, external peer review before acceptance for publication.

Limitations of These Guideline Development Methods

Limitations of these guidelines include the possibility that some authors followed this methodology more closely than others, although the development process was centralized by an EPC and supervised by the editors. Second, it is possible that we missed relevant studies in spite of the comprehensive searching process. Third, despite our efforts to begin centralizing the methodologic evaluation of all studies to facilitate uniformity in the validity assessments of the research incorporated into these guidelines, resources were insufficient to conduct this evaluation for all but a few of the recommendations in each chapter. Fourth, we performed only few statistical pooling exercises of primary study results. Finally,

sparse data on patient preferences and values represent additional limitations inherent to most guideline development methods.

FUTURE DIRECTIONS OF ACCP GUIDELINES

Future iterations of the current guidelines will continue to address the limitations of the current iteration. For example, we asked authors making clinical recommendations to consider concealment; blinding; loss to follow-up of individual studies; and precision, consistency, directness, and likelihood of reporting bias when assigning a grade (*ie*, A, B, or C) to the quality of the evidence for a given recommendation. Although final decisions regarding the quality of evidence must remain the prerogative of the panelists, a central process for initially generating these judgments would improve their uniformity. To further improve the quality of these evidence-based recommendations, our next objective is to extend the central assessment of methodologic quality of individual studies, overall judgments of evidence quality, and summaries of findings that we began in this iteration. This initiative will further enhance the consistency and transparency of the approach to grading quality of evidence and strength of recommendations for the *Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition)*.

CONCLUSION

For the eighth edition of the *Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines*, we have built on the methods of the 7th edition that introduced explicit definition of questions, transparent eligibility criteria for including studies, methodologic evaluation of RCTs included, and specification of values and preferences and resource considerations underlying recommendations where particularly relevant. In combination with our previous practice of grading recommendations according to their strength and the methodologic quality of the supporting studies, these methods establish our guideline methodology as evidence based.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Schünemann reports no personal payments from for-profit organizations, but he has received research grants and/or

honoraria that were deposited into research accounts or received by a research group that he belongs to from AstraZeneca (research grant, honoraria), Amgen (research grant), Barilla (research grant), Chiesi Foundation (honorarium), Lilly (honorarium), Pfizer (research grant, honorarium), Roche (honorarium), and UnitedBioSource (honorarium) for development or consulting regarding quality-of-life instruments for chronic respiratory diseases and as lecture fees related to the methodology of evidence-based practice guideline development and/or research methodology. He is documents editor for the American Thoracic Society and senior editor of the American College of Chest Physicians Antithrombotic and Thrombolytic Therapy Guidelines, and both organizations receive funding from for-profit organizations. Other institutions or organizations that he is affiliated with likely receive funding from for-profit sponsors that are supporting infrastructure and research that may serve his work.

Dr. Cook discloses that she received grant monies from the Canadian Institutes for Health Research and a dalteparin donation for a peer-review funded trial by the Canadian Institutes for Health Research.

Dr. Guyatt reveals no real or potential conflicts of interest or commitment.

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