



## Introduction to the Ninth Edition

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

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**The Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines differs substantially from the prior versions both in process and in content. In this introduction, we describe some of the differences and the rationale for the changes.** *CHEST 2012; 141(2)(Suppl):48S–52S*

**Abbreviations:** ACCP = American College of Chest Physicians; AT6 = Sixth ACCP Consensus Conference on Antithrombotic Therapy; AT7 = Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines; AT8 = Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition); AT9 = Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; GRADE = Grades of Recommendations, Assessment, Development, and Evaluation

We would like to begin by acknowledging the contributions of the visionaries whose work on past editions of these guidelines have allowed the current panel to develop this edition using the changes noted herein. First, James E. Dalen, respected clinician

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and researcher, while President of the American College of Chest Physicians (ACCP), had the foresight not only to propose the original consensus conference on the controversial issues of the indications for anti-thrombotics, antiplatelet agents, and thrombolytics for the prevention and treatment of cardiovascular disorders but also to invite Jack Hirsh, an extremely productive scientist and leader in the field of thrombosis, to join him in leading this important project. Drs Hirsh and Dalen brought a panel of leading experts together for the first antithrombotic guideline<sup>1</sup> in 1986. Dr Dalen was co-editor of the first six guidelines from 1986 to 2001.

Dr Hirsh is, to an extraordinary extent, responsible not only for creating the platform that has made Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians

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Evidence-Based Clinical Practice Guidelines (AT9) possible but also for the advances from Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) (AT8) to AT9. It was not only the creation of an expert panel—a standard feature of specialty society clinical practice guidelines from the outset—that made the antithrombotic guidelines extremely successful. Dr Hirsh, an accomplished basic science researcher and a brilliant clinical trialist, deeply understood the value of what was to become more than a decade later evidence-based medicine. He recruited one of the world leaders in the burgeoning field of clinical epidemiology, David Sackett, to play a major role in the guidelines. Drs Hirsh and Sackett developed and applied an innovative system of rating the quality of evidence and strength of recommendations that was at the time unique to specialty guidelines. The combined impact of the authoritative, carefully considered recommendations and explicit acknowledgment of the quality of evidence and strength of recommendations immediately made these guidelines the reference standard for antithrombotic therapy around the world.

Under Dr Hirsh's leadership, the guidelines more than kept pace with advances in the science of guideline methodology and continued to improve with each iteration. Each new edition provided a model incorporating not only the latest evidence regarding antithrombotic therapy but also advances in specialty-based guidelines and therefore maintained preeminence in the field of thrombosis.

As Dr Hirsh was stepping down from the leadership of the guidelines in 2007, his insight led him to question the reliance on expert opinion that provided the basis for the first eight iterations of the antithrombotic guidelines. Reviewing his experience—and in the process giving new life to an idea suggested decades earlier but seldom applied<sup>2</sup>—Dr Hirsh concluded that the conflict of interest of leading experts was highly problematic.<sup>3</sup> Furthermore, the problem arose not only from their financial but equally or perhaps more important, their intellectual conflict of interest. This revelation and the changes in process that Dr Hirsh suggested as a solution to the problem had a profound impact on the leadership to whom he was passing the torch. These changes underlie all the innovations in AT9.

#### THE NEW PROCESS IN AT9—DEALING WITH CONFLICT OF INTEREST

The solution that Dr Hirsh proposed was endorsed by the ACCP leadership and implemented in AT9. That solution is to give primary leadership and

**Table 1—Major Innovations in AT9**

1. Unconflicted methodologists as topic editors. Conflicted experts did not participate in final process of making recommendations.
2. Many evidence profile and summary of finding tables.
3. New insights into evidence (asymptomatic thrombosis, aspirin).
4. Quantitative specification of values and preferences based on systematic review of relevant evidence and formal preference rating exercise.
5. Article addressing diagnosis of DVT.

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responsibility for each article not to a thrombosis expert but to a methodologist who, in almost all cases, also is a practicing physician without important conflicts of interest<sup>4,5</sup> (Table 1). These editors of each article had specific training in ACCP's approach to rating the quality of evidence and grading strength of recommendations (see "Evidence Summaries" section). Further, building on the work of prior guideline groups,<sup>6</sup> the process stipulated that although conflicted thrombosis experts could engage in discussion and even draft evidence summaries, they would be excluded from the final decisions regarding quality of evidence and direction and strength of recommendations. Intellectual conflicts received the same attention as financial conflicts. Readers of the guidelines can find in the online data supplements to AT9 articles a recommendation-by-recommendation accounting of the intellectual and financial conflicts of each panel member. The most important changes in AT9 content have flowed directly from this change in process.

#### EVIDENCE SUMMARIES

The Sixth ACCP Consensus Conference on Antithrombotic Therapy (AT6),<sup>7</sup> published in 2001, adopted an approach to rating quality of evidence and strength of recommendations<sup>8</sup> that presaged that of the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) working group,<sup>9</sup> itself adopted with minor modifications for AT8<sup>10</sup> and for all ACCP guidelines.<sup>11</sup> AT8, like AT6 and the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines (AT7),<sup>12</sup> underwent thorough editing and review of the quality of evidence, including in many cases a careful assessment of single studies by topic editors and the guideline executive committee. Nevertheless, many of the topic editors did not have methodologic training or, as was the case in AT8, specific training in the ACCP-GRADE approach. The result was that in AT8, the ACCP-GRADE approach often was not applied with optimal rigor, and authors

produced very few of the summary tables that are the hallmark end product of the GRADE process.

There are two types of such tables: evidence profiles and summary of findings. Evidence profiles summarize the quality of a body of evidence for each relevant outcome and, when evidence comes from randomized trials, include a presentation of reviewers' assessment of risk of bias, precision, consistency, directness, and publication bias.<sup>5</sup> Readers of AT9 can find the evidence profiles in the online data supplements. The text in the main AT9 articles includes the more succinct summary of findings tables, which include the overall quality assessment as well as relative and absolute effect sizes for each outcome. We did not succeed in the lofty goal of producing a summary of findings table for each recommendation, but readers will find these for most major and potentially controversial recommendations. Readers will find >10 such tables in most articles and >20 in some articles.

Producing these tables forces a rigor of thinking achievable in few other ways. Creating a large number of evidence profiles provides deep insight into the ACCP-GRADE approach to assessing the quality of evidence and strength of recommendations. Along with recruitment of GRADE-expert topic editors, production of evidence profiles and summary of findings tables is responsible for the increased methodologic rigor of AT9.

We also tried to apply a rigorous approach to choosing the format of these tables, an issue that has generated some controversy within the GRADE working group. Per Olav Vandvik, Holger Schünemann, and Nancy Santesso led the group in a formal study in which AT9 panelists expressed their view of the optimal presentation of the tables.<sup>5</sup> The results have not only guided the presentation of evidence profiles and summary of findings in AT9 but also provided one of the recommended options for the GRADE working group.

## REEVALUATION OF EVIDENCE

Relying on the perspective of unconflicted methodologists, rigorously applying the GRADE approach, and excluding those with financial and intellectual conflict of interests from bottom-line decisions regarding the quality of evidence and strength of recommendations led to reevaluations of previously existing evidence (Table 1). For instance, application of the ACCP-GRADE approach requires the distinction between patient-important and surrogate outcomes. The first eight editions of the antithrombotic guidelines failed to fully recognize the implications of a surrogate widely used in thrombosis prevention

trials—asymptomatic, screening-detected thrombosis. Use of this surrogate creates major problems in making the trade-off between patient-important outcomes (thrombosis and serious bleeding). For instance, if one knows that an intervention increases serious bleeding by 20 events in 1,000 patients but reduces asymptomatic thrombosis by 100 in 1,000, what is the net benefit? Establishing net benefit in outcomes important to patients requires knowing the symptomatic DVT and symptomatic pulmonary embolism reduction represented by the reduction in 100 asymptomatic events. Dr Hirsh and John Eikelboom led the prevention topic editors in developing innovative approaches to dealing with the problem of inferring the impact of thromboprophylaxis on symptomatic thrombosis from studies that relied to a considerable extent on detection of asymptomatic events.<sup>13</sup> The available approaches, although representing a step forward, all have limitations and highlight the need for studies that directly measure symptomatic thrombosis without venographic or ultrasound surveillance.

As a result of a reevaluation led by Dr Eikelboom, one consequence of the recognition that measurement of patient-important events in a naturalistic clinical setting (as opposed to in the context of venographic or ultrasonographic screening for asymptomatic thrombosis) was a differing perspective on the use of aspirin in thromboprophylaxis in orthopedic surgery. The authors of AT8 had concluded that there was high-quality evidence justifying a strong recommendation against aspirin as the sole agent for thromboprophylaxis in surgical patients. Authors of AT9 focused on results from a very large trial using concealed randomization and blinding and achieving near-complete follow-up.<sup>14</sup> After an exhaustive and repeated discussion involving the authors of all the prevention articles, and ultimately the entire panel, AT9 authors concluded that the trial provides moderate-quality evidence supporting the use of aspirin, which is now offered as an option for thromboprophylaxis in patients undergoing major orthopedic procedures.<sup>15</sup> AT9 authors concluded that there is low-quality evidence supporting a weak recommendation of low-molecular-weight heparin over aspirin in these patients.

The GRADE approach defines quality of evidence as our level of confidence in estimates of diagnostic or treatment effect to support a particular recommendation.<sup>16</sup> In general, the changing perspectives on evidence led to the conclusion that we often could not be as confident in estimates of effect as previously believed. Readers of AT9 will often find, therefore, that some of the evidence previously rated as high quality is now moderate, and evidence previously rated as moderate quality is now low.

## VALUES AND PREFERENCES

Serial iterations of AT9 dating back to AT6 have gradually put increasing emphasis on patient values and preferences. For the first time, the AT7 panel made the assumptions about values and preferences explicit. The AT9 panel has accelerated that process by conducting a systematic review<sup>17</sup> of the relevant research of empirical investigations of values and preferences of patients regarding antithrombotic therapy. Based on that review, AT9 panelists conducted a value rating exercise that provided the basis for values and preference judgments within AT9, judgments that are summarized in the introductory section of each article.<sup>13</sup> The judgments are more explicit and quantitative than any previous guideline. For example, we estimated that on average, patients experience the disutility of a GI bleed more or less equally to that of VTE but only one-third of the disutility of a stroke.

Among the findings of the systematic review of patient values and preferences regarding antithrombotic treatment are the heterogeneity of results between studies and the wide variability in values and preferences among patients. Because the core characteristic of a strong recommendation is the belief that across the range of values and preferences, virtually all informed patients will make the same choice, the wide variability in patient values and preferences makes strong recommendations less likely.<sup>18</sup>

### IMPACT OF INNOVATIONS ON THE RECOMMENDATIONS

Readers of AT9 will find many weak recommendations replacing the strong recommendations of AT8. One major reason for this change is the more critical look at the evidence and the resulting inferences that some evidence is lower quality than previously believed. A second is the recognition of variability in values and preferences. Third, in the small number of controversial recommendations that came to a formal vote using anonymous electronic voting, we required the endorsement of >80% of panelists to make a strong recommendation. Finally, the exclusion of conflicted experts, who often hold strong opinions about optimal management approaches, from final decisions regarding quality of evidence and strength of recommendations also may have contributed.

### OTHER INNOVATIONS IN AT9

For the first time, each panel included a frontline clinician not involved in thrombosis research. The goal of including these individuals was to ensure that recommendations considered the full realities of clinical practice as viewed by those outside the research

environment and to support efforts to make the phrasing of recommendations more user friendly and implementable.

A limitation of AT8 was the very inconsistent approaches to assessing bleeding risk. Sam Schulman, author of the bleeding risk article in AT8,<sup>19</sup> took responsibility for developing the AT9 approach to bleeding and ensuring that it was consistently applied across chapters.<sup>5</sup>

To address issues of economic efficiency, we included “resource use consultants” on the AT9 article panels charged with making recommendations. They developed a transparent and systematic methodology to address questions for which resource use might change the direction or strength of recommendations.<sup>5</sup>

We made an intensive effort to remove duplication between articles and to harmonize recommendations between related articles. An important strategy was to include topic editors and deputy editors as panelists from both articles when two had overlapping issues.

Finally, for the first time, the antithrombotic guidelines have addressed issues of diagnosis. Shannon Bates and Roman Jaeschke led a panel that took on the challenging task of applying the newly developed GRADE methodology for recommendations regarding the diagnosis of DVT.<sup>20</sup>

## CONCLUSION

Building on the seminal work of Drs Hirsh and Dalen and their colleagues over the 20-year history of the ACCP antithrombotic guidelines, AT9 has made a number of changes in process, resulting in differences in the approach to making recommendations and their content. Past iterations of these guidelines have celebrated new high-quality evidence and the strong recommendations that such evidence warrants. The insights from AT9 include the persisting limitations in evidence quality (particularly with respect to the use of surrogate outcomes in prophylaxis trials) and the appropriateness of weak recommendations that reflect our lack of confidence in effect estimates and the variability in patient values and preferences. We believe that the objective, rigorous application of the science of guideline development will ultimately best serve our patients.

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Octapharm AG, CSL Behring, and Artisan Pharma. Personal total compensation for these activities over the past 3 years totals less than US \$10,000. Dr Gutterman has had the following relationships that are entirely unrelated to the AT9 guidelines: ACCP President, GlaxoSmithKline plc grant to study vasodilation in adipose tissue, National Institutes of Health grant to study human coronary dilation, and GE Healthcare consultation on a study for ECG evaluation of chronic heart disease. Drs Guyatt and Schünemann are co-chairs of the GRADE Working Group, and Dr Akl is a member and prominent contributor to the GRADE Working Group. Dr Lewis is a full-time employee of the ACCP.

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