The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

Evidence-Based Guidelines

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Since the Sixth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy, the results of clinical trials have provided important new information on the management of thromboembolic disorders, and the science of developing recommendations has advanced. In the accompanying supplement, we provide the new and previously existing recommendations and review several important changes that we have made in our guideline development process. We made a conscious effort to increase the participation of female authors and of contributors from outside North America, with the latter reflecting the widespread use and dissemination of these guidelines internationally. The change in the title from a conference emphasizing consensus to “ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines” reflects the evidence-based approach to making recommendations. The recommendations follow the grading system described in the 2001 recommendations. If the guideline developers are very certain that benefits do, or do not, outweigh risks, burdens, and costs, they will make a strong recommendation (in our formulation, Grade 1). If they are less certain of the magnitude of the benefits and the risks, burdens, and costs, and thus of their relative impact, they make a weaker Grade 2 recommendation. Consistent results from RCTs generate Grade A recommendations, observational studies with very strong effects or secure generalizations from randomized clinical trials (RCTs) generate Grade C+ recommendations, inconsistent results from RCTs generate Grade B recommendations, and observational studies generate Grade C recommendations. We now use the language “we recommend” for strong recommendations (ie, Grades 1A, 1C+, 1B, and 1C) and “we suggest” for weaker recommendations (ie, Grades 2A, 2C+, 2B, and 2C). While evidence on which recommendation are made remains weak in the fields of pediatric thrombosis, thrombosis in pregnancy, and thrombosis in valvular heart disease, rigorous studies in other fields have resulted in new and strong evidence-based recommendations for many indications.

(CHEST 2004; 126:1725–1735)

Since the last publication of the conference guidelines, 3 years ago, the results of clinical trials have provided important new information on the management of thromboembolic disorders. A number of new antithrombotic agents have been approved and introduced into the clinic. In addition, other new anticoagulants have been evaluated in phase 3 clinical trials. In this supplement, we not only provide the new and previously existing recommendations, but also review several important changes that we have made in our guideline development process.

Our planning for the seventh conference included efforts to reduce the number of authors to, wherever possible, five or fewer and to increase the participation of female authors and of contributors from outside North America, with the latter reflecting the widespread use and dissemination of these guidelines internationally. We have made some progress in all these areas and plan to continue with similar efforts for the next set of guidelines.

We also made several organizational and policy changes that reflect the evolving knowledge and theory about producing guidelines and making recommendations, changes that we describe in detail in one of the supplement articles. One change reflects increasing concern regarding potential conflicts of interest. All participants of the conference have been asked to declare honoraria or research funding obtained in the previous 2 years, or stocks held, from companies that may benefit from the recommendations. This information is listed on pages 167 to 171 in this supplement.

The change in the title from a conference emphasizing consensus (ie, “Seventh American College of Chest Physicians [ACCP] Consensus Conference on Antithrombotic Therapy”) to “ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines” reflects the emphasis on an evidence-based approach to making recommendations. The development of evidence-based guidelines requires a clear and explicit definition of each question, a definition that specifies eligibility criteria, including the relevant population, alternative management strategies, and the outcomes. For the current ACCP guidelines, authors defined clinical questions including these components for each recommendation or set of recommendations.

For example, Albers et al. considered whether clinicians should offer thrombolytic therapy to patients experiencing acute stroke. The authors defined those patients as anyone presenting with acute thrombosis stroke (divided into presentation at < 3 h and > 3 h after the onset of symptoms), the intervention as any thrombolytic regimen compared to no intervention or placebo, and the outcome as death or functional status based on the results of an assessment with a validated functional status instrument.

In collaboration with guideline authors, a team of librarians conducted comprehensive literature searches for evidence that was relevant to these specific questions.
or recommendations. Authors reviewed the citations and applied the predefined criteria to ascertain whether studies contributed to the evidence that underlies the recommendations.

We have emphasized transparency and explicitness among questions, evidence, and recommendations. When applicable, we also included a numbering scheme to ensure that the number associated with the explicitly defined questions presented in the summary table for each article corresponds to the number of the section laying out the evidence, as well as any corresponding recommendation. This scheme will allow readers to quickly identify the underlying question associated with each recommendation and the relevant evidence.

In general, the recommendations presented here follow the grading system described in 2001. If experts are very certain that benefits do, or do not, outweigh risks, burdens, and costs, they will make a strong recommendation (in our formulation, Grade 1). If they are less certain of the magnitude of the benefits and the risks, burdens, and costs, and thus of their relative impact, they make a weaker Grade 2 recommendation. Consistent results from randomized clinical trials (RCTs) generate Grade A recommendations, observational studies with very strong effects or secure generalizations from RCTs generate Grade C+ recommendations, inconsistent results from RCTs generate Grade B recommendations, and observational studies generate Grade C recommendations.

We have made one substantive change to the grading system presented in 2001. We now downgrade the methodological quality of recommendations in favor of treatments that carry greater risk, inconvenience, and cost than the alternatives if sample size is small or event rates are low. Specifically, if the results are not statistically significant (ie, p > 0.05 [two-tailed]) or if the addition of a small number of adverse events to the treatment arm would render a result nonsignificant, we downgrade recommendations from otherwise strong randomized trials from Grade A to Grade B. In addition, we have adopted a terminology expressing the strength of the recommendation. We now use the language “we recommend” for strong recommendations (ie, Grades 1A, 1C+, 1B, and 1C) and “we suggest” for weaker recommendations (ie, Grades 2A, 2C+, 2B, and 2C).

While conference participants agreed that recommendations should reflect economic considerations, incorporating costs is fraught with difficult challenges. For most recommendations, formal economic analyses are unavailable. Even when analyses are available, they may be methodologically weak or biased. Furthermore, costs differ radically across jurisdictions, and even sometimes across hospitals within jurisdictions. For example, the cost for low-molecular-weight heparin (LMWH) is high in the United States, but low in most European countries. Thus, in instances in which small benefits accrue to patients from the use of LMWH in comparison to the use of unfractionated heparin, the choice in favor of LMWH may be clear in Europe, but much less clear in North America.

Because of these challenges, we consider economic factors only when the costs of one therapeutic option over another are substantially different within major jurisdictions in which clinicians make use of our recommendations. As a result, in jurisdictions in which resource constraints are severe, alternative allocations may serve the health of the public far better than some of the interventions that we designate as Grade 1A. This will likely be true for all less industrialized countries and, with the increasing promotion of expensive drugs with marginal benefits, may be increasingly true for wealthier nations. Furthermore, recommendations change (either in direction or with respect to grade) only when we believe that costs are high in relation to benefits. We label instances in which costs have influenced recommendations in the “values and preferences” statements associated with the recommendation.

Values and preferences are by nature subjective and may even differ across expert groups. For example, focusing on data from the Clopidogrel versus Aspirin in Patients at risk of Ischemic Events trial that demonstrated a small benefit of therapy with clopidogrel over therapy with aspirin for the prevention of vascular events, the authors of the article on stroke made a recommendation in favor of clopidogrel therapy compared to aspirin therapy for the prevention of ischemic stroke, designating the recommendation as Grade 2 because of the high cost of clopidogrel compared with aspirin. The authors of the article on peripheral arterial occlusive disease evaluated similar relevant evidence but chose to make a Grade 2 recommendation favoring aspirin over clopidogrel therapy because of the high cost of clopidogrel in relation to the modest benefits.

We have come a long way since the first publication of these guidelines in 1986. The number of antithrombotic agents available to the clinician has trebled, the rigor with which they are evaluated has improved dramatically, and our grading system for making recommendations has been refined. While evidence on which recommendations are made remains weak in the fields of pediatric thrombosis, thrombosis in pregnancy, and thrombosis in valvular heart disease, rigorous studies in other fields have resulted in new and strong evidence-based recommendations for many indications.

REFERENCES