

Introduction

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 7th conference included efforts to reduce the number of authors to, wherever possible, 5 or less and to increase participation of female authors, and contributors from outside North America; the latter reflects 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 evolving knowledge and theory about producing guidelines and making recommendations, changes that we describe in detail in one of the supplement's chapters.ⁱ 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 two years, or stocks held, from companies that may benefit from the recommendations. This information is listed on page **xy – xy** in this supplement.ⁱⁱ

The change in the title from a conference emphasizing consensus (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 clear and explicit definition of each question,ⁱⁱⁱ 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 in acute stroke.^{iv} The authors defined patients as anyone presenting with acute thrombotic stroke (divided into presentation of less than and greater than 3 hours after 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 assessment with a validated functional status instrument.

In collaboration with guideline authors, a team of librarians conducted comprehensive literature searches for evidence relevant to these specific questions or recommendations. Authors reviewed 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 each chapter's summary table 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.^v If experts are very certain that benefits do, or do not, outweigh risks, burden, 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 risks, burden, and costs, and thus 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 generalization from RCTs Grade C⁺, inconsistent results from RCTs Grade B, and observational studies Grade C.

We have made one substantive change to the grading system presented in 2001. We now downgrade 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 (two-tailed p-value greater than 0.05) or if addition of a small number of adverse events to the treatment arm would render a result non-significant, we downgrade recommendations from otherwise strong randomized trials from A to B. In addition, we have adopted a terminology expressing the strength of the recommendation. We now use the terms “*we recommend*” for strong recommendations (Grade 1A, 1C⁺, 1B, 1C) and “*we suggest*” for weaker recommendations (2A, 2C⁺, 2B, 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, cost for low molecular weight heparin (LMWH) are high in the United States, but low in most European countries. Thus, in instances when small benefits accrue to patients from use of LMWH in

comparison to 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 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 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 CAPRIE trial that demonstrated a small benefit of clopidogrel over aspirin for prevention of vascular events, the authors of the chapter on stroke made a recommendation in favor of clopidogrel compared to aspirin for the prevention of ischemic stroke, designating the recommendation Grade 2 because of the high cost of clopidogrel compared with aspirin.^{iv} The authors of the chapter on peripheral arterial occlusive disease evaluated similar relevant evidence but chose to make a Grade 2 recommendation favoring aspirin over clopidogrel because of the high cost of clopidogrel in relation to the modest benefits.^{vi}

We have come a long way since the first publication of the 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 recommendation are made remains weak in 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.

ⁱ Schünemann HJ, Munger H, Brower S, et al. Developing evidence-based guidelines for the ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* (in this supplement)

ⁱⁱ Insert reference to declarations page.

ⁱⁱⁱ McKibbin A, Hunt D, Richardson SW, et al. Finding the evidence. In Guyatt G, Rennie D (eds): *Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice*. Chicago, American Medical Association Press, 16, 2002.

^{iv} Albers GW, Amarenco P, Easton JD, et al. Antithrombotic and Thrombolytic Therapy for Ischemic Stroke. *Chest* 2004 (in this supplement)

^v Guyatt G, Schünemann H, Cook D, et al. Grades of recommendation for antithrombotic agents. *Chest* 119: 3S-7S, 2001

^{vi} Clagett GP, Sobel M, Jackson MR, et al. *Chest* 2004 (in this supplement)