General

Guideline Title


Bibliographic Source(s)


Guideline Status

This is the current release of the guideline.


Recommendations

Major Recommendations

The grades of recommendation (1A, 1B, 1C, 2A, 2B, 2C) and the approach to rating the quality of evidence are defined at the end of the "Major Recommendations" field.

Vitamin K Antagonist (VKA)—Initiation of Therapy

Initial Dose Selection—Loading Dose

For patients sufficiently healthy to be treated as outpatients, the expert panel suggests initiating VKA therapy with warfarin 10 mg daily for the first 2 days followed by dosing based on international normalized ratio (INR) measurements rather than starting with the estimated maintenance dose (Grade 2C).

Initial Dose Selection and Pharmacogenetic Testing

For patients initiating VKA therapy, the expert panel recommends against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B).

Initiation Overlap for Heparin and VKA
For patients with acute venous thromboembolism (VTE), the expert panel suggests that VKA therapy be started on day 1 or 2 of low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) therapy rather than waiting for several days to start (Grade 2C).

Maintenance Treatment with VKAs

Monitoring Frequency for VKAs

For patients taking VKA therapy with consistently stable INRs, the expert panel suggests an INR testing frequency of up to 12 weeks rather than every 4 weeks (Grade 2B).

Management of the Single Out-of-Range INR

For patients taking VKAs with previously stable therapeutic INRs who present with a single out-of-range INR of ≤0.5 below or above therapeutic, the expert panel suggests continuing the current dose and testing the INR within 1 to 2 weeks (Grade 2C).

Bridging for Low INRs

For patients with stable therapeutic INRs presenting with a single subtherapeutic INR value, the expert panel suggests against routinely administering bridging with heparin (Grade 2C).

Vitamin K Supplementation

For patients taking VKAs, the expert panel suggests against routine use of vitamin K supplementation (Grade 2C).

Anticoagulation Management Services for VKAs

The expert panel suggests that health-care providers who manage oral anticoagulation therapy should do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions. (Best Practices Statement)

Patient Self-Testing and Self-Management

For patients treated with VKAs who are motivated and can demonstrate competency in self-management strategies, including the self-testing equipment, the expert panel suggests patient self-management (PSM) rather than usual outpatient INR monitoring (Grade 2B).

For all other patients, the expert panel suggests monitoring that includes the safeguards in the best practice statement listed above.

Dosing Decision Support

For dosing decisions during maintenance VKA therapy, the expert panel suggests using validated decision support tools (paper nomograms or computerized dosing programs) rather than no decision support (Grade 2C).

Remarks: Inexperienced prescribers may be more likely to improve prescribing with use of decision support tools than experienced prescribers.

VKA Drug Interactions to Avoid

For patients taking VKAs, the expert panel suggests avoiding concomitant treatment with nonsteroidal antiinflammatory drugs (NSAIDs), including cyclooxygenase (COX)-2-selective NSAIDs, and certain antibiotics (see Table 8 in the original guideline document) (Grade 2C).

For patients taking VKAs, the expert panel suggests avoiding concomitant treatment with antiplatelet agents except in situations where benefit is known or is highly likely to be greater than harm from bleeding, such as patients with mechanical valves, patients with acute coronary syndrome, or patients with recent coronary stents or bypass surgery (Grade 2C).

VKA—Monitoring

Optimal Therapeutic INR Range

For patients treated with VKAs, the expert panel recommends a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) rather than a lower (INR <2) or higher (INR 3.0-5.0) range (Grade 1B).

Therapeutic Range for High-Risk Groups

For patients with antiphospholipid syndrome with previous arterial or venous thromboembolism, the expert panel suggests VKA therapy titrated to a moderate-intensity INR range (INR 2.0-3.0) rather than higher intensity (INR 3.0-4.5) (Grade 2B).
VKA—Discontinuation of Therapy

For patients eligible to discontinue treatment with VKA, the expert panel suggests abrupt discontinuation rather than gradual tapering of the dose to discontinuation (Grade 2C).

Parenteral Anticoagulants

UFH—Dose Adjustment by Weight

For patients starting intravenous (IV) UFH, the expert panel suggests that the initial bolus and the initial rate of the continuous infusion be weight adjusted (bolus 80 units/kg followed by 18 units/kg per h for VTE; bolus 70 units/kg followed by 15 units/kg per h for cardiac or stroke patients) or use of a fixed-dose (bolus 5,000 units followed by 1,000 units/h) rather than alternative regimens (Grade 2C).

UFH—Dose Management of Subcutaneous (SC) UFH

For outpatients with VTE treated with SC UFH, the expert panel suggests weight-adjusted dosing (first dose 333 units/kg, then 250 units/kg) without monitoring rather than fixed or weight-adjusted dosing with monitoring (Grade 2C).

LMWH—Dosing

Should the Therapeutic Dose of LMWH Be Modified for Decreased Renal Function?

For patients receiving therapeutic LMWH who have severe renal insufficiency (calculated creatinine clearance <30 mL/min), the expert panel suggests a reduction of the dose rather than using standard doses (Grade 2C).

Fondaparinux—Dosing

Fondaparinux Dose Management by Weight

For patients with VTE and body weight over 100 kg, the expert panel suggests that the treatment dose of fondaparinux be increased from the usual 7.5 mg to 10 mg daily SC (Grade 2C).

Prevention and Management of Anticoagulant Complications

Vitamin K for Patients Taking VKAs with High INRs without Bleeding

For patients taking VKAs with INRs between 4.5 and 10 and with no evidence of bleeding, the expert panel suggests against the routine use of vitamin K (Grade 2B).

For patients taking VKAs with INRs >10.0 and with no evidence of bleeding, the expert panel suggests that oral vitamin K be administered (Grade 2C).

Clinical Prediction Rules for Bleeding While Taking VKA

For patients initiating VKA therapy, the expert panel suggests against the routine use of clinical prediction rules for bleeding as the sole criterion to withhold VKA therapy (Grade 2C).

Treatment of Anticoagulant-Related Bleeding

For patients with VKA-associated major bleeding, the expert panel suggests rapid reversal of anticoagulation with four-factor prothrombin complex concentrate (PCC) rather than with plasma (Grade 2C).

The expert panel suggests the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C).

Definitions:

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach to Rating Quality of Evidence

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Quality of Evidence</th>
<th>Lower if</th>
<th>Higher if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Trial →</td>
<td>High</td>
<td>Risk of bias</td>
<td>Large effect</td>
</tr>
<tr>
<td>Study Design</td>
<td>Mode of Evidence</td>
<td>-1 Serious Lower if</td>
<td>+1 Large Higher if</td>
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<tr>
<td>Observational Study →</td>
<td>Low</td>
<td>Inconsistency</td>
<td>Dose response</td>
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<td></td>
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<td>-2 Very serious</td>
<td>+1 Evidence of a gradient</td>
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<td></td>
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<td>Indirectness</td>
<td>All plausible confounding</td>
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<td>-2 Very serious</td>
<td>+1 Would produce a demonstrated effect or</td>
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<td></td>
<td></td>
<td>Imprecision</td>
<td>+1 Would suggest a spurious effect when result show no effect</td>
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<td></td>
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<td>-2 Very serious</td>
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<td></td>
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<td>Publication bias</td>
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<td></td>
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<td>-1 Likely</td>
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<td></td>
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<td>-2 Very likely</td>
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Scope

Disease/Condition(s)
Conditions requiring anticoagulant therapy

Guideline Category
Management
Prevention
Risk Assessment
Treatment

Clinical Specialty
Cardiology
Critical Care
Emergency Medicine
Family Practice
Hematology
Internal Medicine
Neurology
Oncology
Orthopedic Surgery
Pharmacology
Pulmonary Medicine
Surgery

Intended Users
Advanced Practice Nurses
Health Care Providers
Nurses
Pharmacists
Physician Assistants
Physicians

Guideline Objective(s)
To update evidence-based recommendations for the use of anticoagulant therapy for the management of thromboembolic conditions
To offer guidance for many common anticoagulation-related management problems
To optimize patient-important health outcomes and the processes of care for patients who have experienced or are at risk for thrombotic events

Target Population
Patients requiring anticoagulant therapy

Note: This guideline does not address anticoagulation management issues specific to pregnancy or to children. Issues believed to be specific to a particular diagnosis, such as venous thromboembolism (VTE) or atrial fibrillation, are dealt with in those specific articles of the original guideline supplement.

Interventions and Practices Considered

Treatment
1. Vitamin K antagonists (VKAs) (warfarin)
2. Unfractionated heparin or low-molecular-weight heparin (LMWH)
3. Reversal of VKAs:
   - Vitamin K
   - Fresh frozen plasma
   - Prothrombin complex concentrate (PCC)
   - Recombinant factor VIIa

Management
1. Systematic and coordinated approach
2. Prothrombin time (PT) monitoring
3. Targeting and monitoring international normalized ratio (INR)
4. Patient education
5. Pharmacogenetic testing for guiding doses of VKA (considered but not recommended routinely)
6. Vitamin K supplementation (not recommended)
7. Loading doses, initiation overlap, and monitoring frequency
8. Weight and renal function adjustment of doses
9. Patient self-management for INR monitoring versus outpatient monitoring
10. Use of validated decision support tools (paper nomograms or computerized dosing programs)
11. Avoiding use of concomitant nonsteroidal antiinflammatory drugs (NSAIDs), certain antibiotics, and antiplatelet agents
12. Discontinuation of anticoagulant therapy (abrupt versus gradual)
13. Prevention and management of bleeding complications

Major Outcomes Considered
- Incidence of thrombosis
- Recurrent thromboembolism
- Incidence of major and minor hemorrhage
- International normalized ratio (INR)
- Mortality

Methodology

Methods Used to Collect/Select the Evidence
Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Defining the Clinical Questions—Population, Intervention, Comparator, and Outcome

The thrombosis expert on the Executive Committee along with the deputy editors took primary responsibility for defining the scope of the clinical questions that each article would address. For each question, the topic editor and deputy editor defined the relevant population, alternative management strategies (intervention and comparator), and the outcomes (i.e., population, intervention, comparator, and outcome [PICO] format). Each clinical question provided the framework for formulating study inclusion and exclusion criteria and guided the search for relevant evidence (systematic reviews and original studies). Panels typically restricted included studies to randomized controlled trials (RCTs) for intervention questions but included observational studies when there was a paucity of RCT data addressing an intervention and for questions of risk assessment. Readers can find these PICO questions in the first table of each article. One or more recommendations could be formulated for each clinical question.

Identifying the Evidence

To identify the relevant evidence, a team of methodologists and medical librarians at the Oregon Health & Science University Evidence-based Practice Center conducted literature searches of Medline, the Cochrane Library, and the Database of Abstracts of Reviews of Effects. For each article, the team conducted a search for systematic reviews and another for original studies encompassing the main populations and interventions for that article. These searches included studies indexed from week 1, January 2005, forward because Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th Edition (AT8) searches were carried out up to that date (search strategies are available on request). Many articles supplemented these searches with more-focused searches addressing specific clinical questions. When clinical questions had not been covered in AT8, searches commenced at a date relevant to each intervention.

Titles and abstracts retrieved from bibliographic database searches generally were screened in duplicate, and full-text articles were retrieved for further review. Consensus on whether individual studies fulfilled inclusion criteria was achieved for each study between two reviewers. If consensus could not be achieved, the topic editor and other topic panelists were brought into the discussion. Deputy editors reviewed lists of included studies from the database searches in order to identify any potentially missed studies. Additional studies identified were then retrieved for further evaluation.

Topic panels also searched the same bibliographic databases for systematic reviews addressing each PICO question. The quality of reviews was assessed using principles embodied in prior instruments addressing methodologic quality of systematic reviews, and wherever possible, current high-quality systematic reviews were used as the source of summary estimates. Reviews were also used to identify additional studies to complement the database searches.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

<table>
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Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

General Methods

Assessing Studies and Summarizing Evidence

Evaluating Risk of Bias in Individual Studies

The expert panel developed and applied uniform criteria for evaluating the risk of bias associated with individual randomized controlled trials (RCTs) based on the criteria recommended by the Cochrane Collaboration (Table 1 in the methodology companion [see the "Availability of Companion Documents" field]). Although all authors assessed risk of bias for individual studies, because of resource limitations, the panel summarized the results of the risk of bias for only a minority of the recommendations. Readers can find these assessments in the online data supplements. For most recommendations for which such tables were not developed, Evidence Profiles that typically provide information on the risk of bias in footnotes were developed.

The panel also developed specific criteria for assessing the risk of bias of observational studies (cohort studies with concurrent controls, cohort studies with historical controls, case-control studies, or case series). Again, these were based on the evidence-based domains recommended by the Cochrane Collaboration for observational studies.

Studies without internal comparisons were termed "cohort studies without internal controls" if 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 all of the following: schedule of follow-up, investigation of suspected outcomes, and criteria used to define outcomes.
5. The study reported all losses to follow-up.

The panel labeled studies that did not meet these criteria as "case series." No distinction was made between prospective and retrospective studies because although prospective studies may on average be of higher quality, individual prospective studies may have a significant risk of bias and specific retrospective studies may not. For questions related to risk assessment, the panel evaluated the risk of bias of individual studies using the following criteria: valid outcome assessment, including blinding when appropriate; adjustment for between-group differences; and minimal loss to follow-up.

Evaluating Quality of Bodies of Evidence

The expert panel assessed evidence across studies on an outcome-by-outcome basis using criteria suggested by the Grading of Recommendations
Assessment, Development and Evaluation (GRADE) Working Group. The expert panel defined quality of evidence as their confidence in the estimate of the effect to support a recommendation. RCTs start as high-quality evidence and observational studies as low-quality evidence. Additional factors that affect this rating of quality include the risk of bias; precision, consistency, and directness of results; likelihood of publication bias; and presence of very large effects. The American College of Chest Physicians (ACCP) adaptation of the GRADE system differs only in that the quality of a body of evidence can be high (A), moderate (B), or low (C); GRADE also provides a category for very-low-quality evidence. See the "Rating Scheme for the Strength of the Evidence" field.

Often, the panel found that the quality of the evidence differed across outcomes. For example, in assessing the quality of evidence for thienopyridines vs warfarin in patients undergoing percutaneous coronary interventions, the panel determined the evidence to be of moderate quality for mortality, nonfatal myocardial infarction, and revascularization but of low quality for major bleeding.

The panel then made a rating of the quality of the entire body of evidence bearing on the effect of alternative management strategies for each clinical question. In other words, the panel assessed the quality across outcomes, including both benefits and harms. Quality for each recommendation was the lowest quality rating of the outcomes judged as critical (as opposed to important, but not critical).

Most patient-important outcomes in this guideline are binary or yes-no outcomes (death, stroke, venous thromboembolism [VTE], myocardial infarction, bleeding). In general, relative effects are similar across subgroups of patients, including those with varying baseline risk. The evidence summaries (Evidence Profiles and Summary of Findings tables), therefore, include a presentation of relative effects (where possible as relative risks because they are easier to understand than odds ratios [ORs]) of intervention vs control management strategies.

Trading off desirable and undesirable consequences (e.g., thrombosis vs bleeding) requires, however, estimates of absolute effect. For example, in patients with atrial fibrillation, warfarin results in a 66% relative risk reduction in nonfatal stroke. This comes at a cost of inconvenience, lifestyle restrictions, and risk of bleeding. For patients with a CHADS (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke) score of ≥3, the 66% relative risk reduction translates into an absolute reduction of 6.3% (63 in 1,000) per year. Virtually all patients will consider this worthwhile. On the other hand, for patients with a CHADS score of 0, the 66% reduction translates into an absolute risk reduction of only 0.5% (5 in 1,000) per year. Many patients may consider this reduction not worth the undesirable consequences of warfarin use.

The panel calculated absolute effects by applying relative risks to estimates of control group risk. For instance, if control group risk of thrombosis is 4% and relative risk with an intervention is 50%, then the absolute difference between intervention and control is 4% of 50% or 2%, and the number needed to treat to prevent an episode of thrombosis is 100/2 or 50. In many cases, the Summary of Findings tables present effects as events prevented (or caused) per 1,000 patients. In this hypothetical example, the effect would be 20 events per 1,000 patients.

Whenever valid prognostic data were available from observational studies, they were used to estimate control group risks. When credible results from observational and prognostic studies were not available, risk estimates from control groups of RCTs were used.

Considering Subgroup-Specific Relative and Absolute Effects

Whenever the expert panel identified credible evidence that the relative effects vary across distinguishable subgroups of patients (i.e., interaction between the intervention and a patient characteristic), the respective relative effects were considered separately. The panel then calculated the associated absolute effects.

Even when the relative effect is the same, the absolute magnitude of treatment effects may differ in patients with varying levels of risk. For instance, although the relative risk reduction of warfarin vs aspirin in stroke prevention for patients with atrial fibrillation is likely close to 50% across risk groups, this translates into an absolute risk reduction of <1% per year in the lowest-risk groups and ~5% per year in the highest-risk groups.

The expert panel included control group risks and absolute-effect estimates for different groups in the summaries of effect when (and only when) two conditions were present. First, they required validated prognostic models or, at the very least, credible strategies for clinicians to easily identify higher- and lower-risk patients. Second, the panel identified varying risk groups only when recommendations differed in strength or direction between groups. Both conditions were met, for instance, in the atrial fibrillation recommendations in which strong recommendations in favor of anticoagulation were restricted to the higher-risk patients.

Conducting Meta-analyses

When pooled estimates of effects were not available from existing high-quality systematic reviews, the panel performed meta-analyses if the data were sufficiently homogeneous. When pooling two studies, they used a fixed-effects model. When three or more studies were available for generating a pooled estimate, they used a random-effects model as the primary analysis and a fixed-effects model as a secondary analysis. If there were discrepancies between the two, the panel considered the following reasons: If there was substantial heterogeneity leading to wider confidence intervals (CIs) with the random-effects model, the panel considered that model more trustworthy, and if the discrepancy was due to a single large dominant study with a result substantially different from smaller studies, they considered the fixed-effects model more trustworthy. The panel also
assessed statistical heterogeneity using both a $\chi^2$ test and $I^2$ as well as assessed possible explanations of heterogeneity considering a priori-generated hypotheses.

**Summary Tables**

When resources permitted, the expert panel used a standardized approach for summarizing the evidence and methodology of individual studies. These summaries appear in the online data supplements. Wherever possible, the expert panel reported nonfatal events (e.g., nonfatal stroke) so that there is no overlap with the number of fatal events reported.

For a large number of recommendations, the expert panel summarized the quality of the body of evidence (see the "Rating Scheme for the Strength of the Evidence" field) and estimates of relative and absolute effect of alternative management strategies using the methods of the GRADE Working Group. Evidence Profiles summarize the quality of the body of evidence and when evidence comes from randomized trials, generally include a presentation of reviewer assessment of risk of bias, precision, consistency, directness, and publication bias associated with each outcome. As specified in GRADE methodology, the overall quality of evidence represents the lowest quality of any critical outcome.

Evidence Profiles can be found in the online data supplement. The format for these tables was determined through a formal survey of panelists that evaluated the panelists' preferences for alternative presentations and the impact of these presentations on their understanding of the evidence. The text in the printed version of Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9) recommendations includes more succinct Summary of Findings tables, which include the overall quality assessment as well as the relative and absolute effect sizes for each outcome. Use of an associated computer program facilitated the production of the Evidence Profiles and Summary of Findings tables which are listed in the original guideline document.

**Specific Methods for This Guideline**

The methods for the development of this article's recommendations follow those developed for the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Although the panel aimed to summarize and use RCT evidence to inform recommendations for clinicians, they found only lower-quality evidence to address most of their questions. At the onset of the review process, the panel decided to limit the recommendations to questions in which evidence met a minimum threshold for quality: at least one comparative study with ≥50 patients per group with contemporaneous or historical controls reporting on patient-important outcomes or closely related surrogates. Despite this low threshold, evidence was unavailable for several important clinical management questions. When randomized trials were available, confidence in estimates often decreased because of indirectness (surrogate outcomes) and imprecision (wide CIs).

**Methods Used to Formulate the Recommendations**

Expert Consensus (Consensus Development Conference)

**Description of Methods Used to Formulate the Recommendations**

**Composition and Selection of Topic Panel Members**

The American College of Chest Physicians (ACCP) Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9) Executive Committee selected panel members for each article. A topic editor and a deputy editor led each of the AT9 panels issuing recommendations. The topic editor was the person primarily responsible for each article and was required to be a methodologist without serious financial or intellectual conflict of interest for any of the article's recommendations. In all but one case, the topic editor also was a clinician. The Executive Committee chose these individuals on the basis of their previous experience with guideline development and, in particular, their familiarity with methods developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. These topic editors and all panel members were approved by the ACCP Health and Science Policy (HSP) Committee after review of their conflict of interest disclosures.

Criteria for selection of the remainder of the panel members, including the deputy editor-thrombosis expert, were an established record in the relevant clinical or research area, international and gender representation, and an absence of financial conflicts of interest that were judged unacceptable. Some of the panelists had prior experience on ACCP guidelines in this area and represented the thrombosis community, but there was substantial turnover from the previous edition. After an international request for applications broadcast through multiple medical societies, the Executive Committee nominated individual topic editors and deputy editors and collaborated with them to identify and nominate other topic panel members.
The ACCP HSP Committee reviewed all nominees and approved all panel members after review of their curricula vitae and conflict of interest disclosures. Of 150 nominees, 137 were approved, 18 were approved with management of conflicts of interest (i.e., regular disclosures and review of ongoing conflicts as the process progressed), and 13 were disapproved as a result of the magnitude of financial conflicts of interest. Articles associated with recommendations included from seven to 14 panel members. Patients or representatives of specific stakeholder groups were not included on topic panels.

Each topic panel also included a frontline physician working in the relevant area who was neither an expert in thrombosis nor a methodologist or clinical investigator. These individuals were chosen in consultation with the topic editors and the ACCP HSP Committee. These clinicians were charged with the following: (1) proposing important real-world clinical questions on the prevention, diagnosis, and treatment of thrombosis that were not addressed in Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th Edition (AT8) and (2) reviewing the draft manuscripts and recommendations to assess the usability of the guidelines and the feasibility of implementation of AT9 recommendations.

To address issues of economic efficiency six health economist-physicians were included on the AT9 topic panels charged with making recommendations. These resource consultants were selected and approved through identical procedures to those for topic editors and panel members.

Ensuring Consistency Across Articles

A number of strategies were used to ensure consistency across articles, and one panel member participated extensively in the formulation of clinical questions for each article. To ensure consistency of judgments regarding bleeding, another panel member was responsible for standardizing the approach to bleeding outcomes and participated in multiple topic panels. Additionally, to ensure consistency in the trade-offs between thrombotic and bleeding events, all articles used the same ratings of values and preferences (described in more detail in the methodology companion [see the "Availability of Companion Documents" field]). Because some of the same evidence summaries were relevant to several articles, five individuals were chosen to participate in each of the articles addressing coronary artery disease, stroke, and peripheral arterial disease.

In AT9, prevention of venous thromboembolism (VTE) is addressed in three articles as opposed to a single article as was done in AT8. The prevention topic editors and deputy editors and those of the stroke article (which includes thromboprophylaxis recommendations) participated in multiple conference calls to develop and harmonize the approach to prevention and to ensure consistency among final recommendations. Topic editors consulted with one another when issues overlapped. For example, the decision regarding the use of a vitamin K antagonist, aspirin, and clopidogrel simultaneously in patients with atrial fibrillation, valvular disease, and intravascular stents is relevant for the atrial fibrillation, coronary, and peripheral arterial disease articles. Topic panels deferred to the Evidence-Based Management of Anticoagulant Therapy AT9 topic panel for recommendations related to the dosing and monitoring of anticoagulation therapies.

The AT9 Executive Committee met at least once a month and regularly issued statements of clarification of methods to topic editors and deputy editors (e.g., use of fixed- or random-effects models for meta-analysis), conflict of interest, preparation of tables, and issues of style and presentation. All these statements were communicated directly to the topic editors and deputy editors and made available in a central repository accessible to all AT9 panelists. The chair of the Executive Committee was available for resolving any challenging issues related to the aforementioned topics. Between September 2009 and September 2010, two members of the Executive Committee held regular (every 3 months), separate conference calls with each topic editor and deputy editor during which they addressed questions and concerns. Finally, the chair of the Executive Committee reviewed every article to ensure consistency of evidence presentation, evaluation, and writing style. Refer to the methodology companion for further information on the approach used to ensure consistent language in writing.

Formulating Recommendations

Following approaches recommended by the GRADE Working Group, the topic editor, in some cases aided by a panelist without conflicts, formulated the draft recommendations. The formulation of recommendations considered the balance between the desirable and undesirable consequences of an intervention; the quality of evidence; the variability in patient values and preferences; and, on occasion, resource use issues. The recommendations were graded as strong when desirable effects were much greater than undesirable effects or vice versa. Strong recommendations were worded as "The expert panel recommends" and labeled 1. Recommendations were graded as weak when desirable effects were not clearly greater or less great than undesirable effects. Weak recommendations were worded as "The expert panel suggests" and labeled 2. The rating of the quality of the evidence—high, A; moderate, B; or low, C—is provided with the strength of each recommendation.

Finalizing Recommendations

The topic panel members without primary conflicts discussed draft recommendations. Initial discussions generally led to a consensus at the article level on the quality of evidence and the direction and strength of recommendations. At least two members of the Executive Committee reviewed in detail drafts of articles, including recommendations. Written critiques were prepared and returned to the authors for revision. Articles were then
Recommendations on which topic panels had difficulty coming to a consensus were discussed at a final conference in February 2011 attended by the topic editors and deputy editors and at least one other panel member from each article. Prior to the conference, all AT9 panelists updated their conflict of interest disclosures. The ACCP invited a number of clinical organizations with interest in the guideline topic to attend the final conference as observers.

At this final conference, a representative of each article presented potentially controversial issues in their article’s recommendations. Following discussion, which included those present and those attending by video conference, all panelists without primary conflicts of interest voted on each recommendation. The voting process used a GRADE grid and required that for a strong recommendation, ≥80% of those voting had to agree that a strong recommendation was appropriate.

The AT9 Executive Committee members harmonized the articles and resolved remaining disagreements among them through facilitated discussion with topic editors and deputy editors without primary conflicts. All major correspondence and decisions at the final conference were recorded in written and audio formats and are available on request to science@chestnet.org.

See the methodology companion (see the "Availability of Companion Documents" field) for information on accounting for patient values and preferences in recommendations.

### Rating Scheme for the Strength of the Recommendations

**Strength of the Recommendations Grading System**

<table>
<thead>
<tr>
<th>Grade of Recommendation*</th>
<th>Benefit vs. Risk and Burdens</th>
<th>Methodologic Quality of Supporting Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong recommendation, high-quality evidence, Grade 1A</td>
<td>Benefits clearly outweigh risk and burdens or vice versa</td>
<td>Consistent evidence from randomized controlled trials (RCTs) without important limitations or exceptionally strong evidence from observational studies</td>
<td>Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect</td>
</tr>
<tr>
<td>Strong recommendation, moderate-quality evidence, Grade 1B</td>
<td>Benefits clearly outweigh risk and burdens or vice versa</td>
<td>Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies</td>
<td>Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Strong recommendation, low- or very-low-quality evidence, Grade 1C</td>
<td>Benefits clearly outweigh risk and burdens or vice versa</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence</td>
<td>Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate</td>
</tr>
<tr>
<td>Weak recommendation, high-quality evidence, Grade 2A</td>
<td>Benefits closely balanced with risks and burden</td>
<td>Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies</td>
<td>The best action may differ depending on circumstances or patient or society values. Further research is very unlikely to change confidence in the estimate of effect</td>
</tr>
<tr>
<td>Weak recommendation, moderate-quality evidence, Grade 2B</td>
<td>Benefits closely balanced with risks and burden</td>
<td>Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies</td>
<td>Best action may differ depending on circumstances or patient or society values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Weak recommendation, low- or very-low-quality evidence, Grade 2C</td>
<td>Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence</td>
<td>Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate</td>
</tr>
</tbody>
</table>

*The guideline developers use the wording recommend for strong (Grade 1) recommendations and suggest for weak (Grade 2) recommendations.*
Cost Analysis

Resource Use Issues

In addressing resource use (cost) issues in Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9), the expert panel followed previously developed principles. In particular, the panel restricted economic evaluation to recommendations in which it was plausible that resource use considerations might change the direction or strength of the recommendation and in which high-quality economic evaluations were available. When this was not the case, the panel did not consider resource use in the recommendations.

Six clinicians with the requisite expertise in decision and economic analyses participated in the guideline development process; each article had the benefit of one of these experts as a full committee member. The following subsections present key points in the process of considering resource allocation issues in the recommendations.

Overview of the Process

Panelists, in consultation with resource use consultants, determined questions for which resource use might change the direction or strength of recommendations. For those questions, the panel sought high-quality economic analyses. If such analyses were available, the panel applied the evidence regarding resource use to the relevant recommendation. If net costs or marginal cost-effectiveness ratios were very high, panelists considered rating down the quality of evidence for an intervention from high to low or possibly changing the direction of the recommendation using guides described in the section "Criteria for Resource Allocation Issues to Affect Recommendations—Thresholds for Cost-Effectiveness" in the methodology companion (see the "Availability of Companion Documents" field).

Identifying the Literature

The Oregon Health & Science University Evidence-based Practice Center conducted thorough literature searches for economic analyses relevant to the different AT9 articles. The resource use experts supplemented these by searches focused on the specific questions of interest for each article. The searches were conducted in Medline and the Cochrane Central Register of Clinical Trials. On the basis that data from studies appreciably more than a decade old would not reflect the current situation, searches were restricted to published studies from 1999 forward. Thus, bibliographic database searches encompassed publications from January 1999 forward: The end date varied across articles and ranged between November 2009 and March 2010 when the searches were executed.

Evaluating the Evidence

A standardized data extraction form was used to ensure uniform evaluation of the quality of relevant economic analyses. Quality assessment was based on published criteria and included specification of perspective of analysis (e.g., societal, health system), appropriateness of time horizon (preferably lifetime), use of high-quality evidence for probabilities and rates, use of high-quality sources for costs (e.g., primary data, Medicare payments, claims data as proxies), use of appropriate methods for measurement of preferences, and performance of sensitivity analyses to explore uncertainty (both deterministic and probabilistic).

Criteria for Resource Allocation Issues to Affect Recommendations—Thresholds for Cost-Effectiveness

The results of economic analyses may either increase the strength of an otherwise weak recommendation or weaken the strength of a strong recommendation. If cost-effectiveness studies bolstered an already strong recommendation, no change to the recommendation was necessary. The panel chose the following thresholds for cost-effectiveness considerations affecting recommendations:

1. When the clinical evidence warrants a strong recommendation for A over B:
   a. Strong recommendation favoring A when high-quality evidence from economic evaluations shows that A costs <3 times the gross domestic product (GDP) per capita (approximately US $150,000) per quality-adjusted life year (QALY) gained relative to B
   b. Weak recommendation favoring A when high-quality evidence from economic evaluations shows that A costs 3 to 5 times the GDP per capita (~$150,000-$250,000) per QALY gained relative to B
   c. Weak recommendation favoring B when high-quality evidence from economic evaluations shows that A costs >5 times the GDP per capita (~$250,000) per QALY gained relative to B

2. When the clinical evidence warrants a weak recommendation for A over B:
   a. Strong recommendation favoring A if A results in cost savings of >10% to 20% of the GDP per capita (~$5,000-$10,000) relative to B (Cost savings must represent all downstream costs and not just the actual cost of the intervention, and analysis must demonstrate a high level of confidence that there is a cost savings.)
   b. Continued weak recommendation favoring A when B is marginally more costly than A (<10% the GDP per capita)
   c. Continued weak recommendation favoring A when A costs 0 to 5 times the GDP per capita per QALY gained relative to B
d. Weak recommendation favoring B if A costs >5 times the GDP per capita (~$250,000) per QALY gained relative to B

**Extension of Economic Analyses to Low- and Middle-Income Countries**

Although certain interventions may be cost-effective in high-income countries (e.g., <$20,000 per QALY gained), in poor countries, $20,000 gained per QALY may be prohibitive. The choice of a threshold will vary depending on who is making resource allocation decisions. To facilitate the use of already published cost-effectiveness analyses, the World Health Organization (WHO), through its WHO-CHOICE (Choosing Interventions that are Cost Effective) program has used criteria suggested by the Commission on Macroeconomics and Health. Interventions that cost <1 times the average per-capita income for a given country or region per QALY gained are considered very cost-effective. Interventions that cost up to three times the average per-capita income per QALY gained are still considered cost-effective, whereas those that exceed this level are not considered to be cost-effective. To facilitate this process, WHO has developed tables of such threshold values for different regions and countries around the world. Thus, the thresholds discussed in the previous section have been defined in terms of GDP per capita. Although referencing thresholds for cost-effectiveness to average per-capita income in middle- and low-income countries can help to extend results of economic analyses performed in high-income countries, such analyses may be less relevant in low-income countries because of significantly different material and labor costs and, thus, may be difficult to extrapolate. Furthermore, the comparator strategies may not be feasible or customary in these locales.

**Method of Guideline Validation**

External Peer Review

Internal Peer Review

**Description of Method of Guideline Validation**

The American College of Chest Physicians (ACCP) Health and Science Policy (HSP) Committee established a process for the thorough review of all ACCP evidence-based clinical practice guidelines. After final review by the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9) Executive Committee, the guidelines underwent review by the Cardiovascular and Pulmonary Vascular NetWorks of the ACCP, the HSP Committee, and the ACCP Board of Regents. The latter two groups had the right of approval or disapproval but usually worked with the topic panelists and editors to make necessary revisions prior to final approval. Both the HSP Committee and the Board of Regents identified primary reviewers who read the full set of articles, and the remaining HSP Committee members were responsible for reviewing several articles each. The reviewers considered both content and methodology as well as whether there was balanced reporting and adherence to HSP Committee processes. All reviewers were vetted through the same conflict of interest disclosure and management process as described in the "Description of Methods Used to Formulate the Recommendations" field. Finally, the Editor in Chief of CHEST read and forwarded the manuscripts for independent, external peer review prior to acceptance for publication. No recommendations or assessments of the quality of the evidence could be changed without the express approval of the topic panel members, AT9 Executive Committee, HSP Committee, and ACCP Board of Regents.

This guideline is endorsed by the American Association for Clinical Chemistry, the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, the American Society of Hematology, and the International Society on Thrombosis and Haemostasis.

**Evidence Supporting the Recommendations**

**Type of Evidence Supporting the Recommendations**

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

**Benefits/Harms of Implementing the Guideline Recommendations**

**Potential Benefits**

Appropriate use of anticoagulant therapy for the management of thromboembolic conditions
Potential Harms

- Vitamin K antagonists (VKAs) and other anticoagulants are associated with minor and major bleeding complications.
- The risk of bleeding increases significantly when the international normalized ratio (INR) exceeds 4.5. In a retrospective review, patients with mechanical heart valves had a risk of adverse events that increased logarithmically from two per 100 patient-years at INR 2.5 to 4.9, to 4.8 per 100 patient-years for INR 5 to 5.5, then to 75 per 100 patient-years for INR ≥6.5. Similarly, a case-control analysis of adults sustaining intracerebral bleeding while on warfarin noted a doubling of intracerebral bleeding for every 0.5-s increment in prothrombin time (approximately every 1-point increase in INR).
- When the INR becomes subtherapeutic, there may be an increased risk of thrombosis.
- There is a theoretical concern that abrupt VKA discontinuation may result in a temporary hypercoagulable state due to an imbalance in the rates of normalization of activity of the coagulation factors II, VII, IX, and X on the one hand and the natural inhibitors protein C and protein S on the other.
- Fresh frozen plasma has the disadvantage of potential allergic reaction or transmission of infection, preparation time, and higher volume.
- Intravenous injection of vitamin K is reported to cause anaphylaxis in 3 of 100,000 patients, resulting in advice to infuse slowly.

Contraindications

- For patients taking vitamin K antagonists (VKAs), the panel suggests avoiding concomitant treatment with nonsteroidal antiinflammatory drugs (NSAIDs), including cyclooxygenase (COX)-2-selective NSAIDs, and certain antibiotics. Refer to Table 8 in the original guideline document for more information.
- For patients taking VKAs, the panel suggests avoiding concomitant treatment with antiplatelet agents except in situations where benefit is known or is highly likely to be greater than harm from bleeding, such as patients with mechanical valves, patients with acute coronary syndrome, or patients with recent coronary stents or bypass surgery.

Qualifying Statements

- The evidence-based practice guidelines published by The American College of Chest Physicians ("ACCP") incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Guidelines are intended for general information only, are not medical advice, and do not replace professional medical care and physician advice, which always should be sought for any specific condition. Furthermore, guidelines may not be complete or accurate because new studies that have been published too late in the process of guideline development or after publication are not incorporated into any particular guideline before it is disseminated. The ACCP and its officers, regents, governors, executive committee, members and employees (the “ACCP Parties”) disclaim all liability for the accuracy or completeness of a guideline, and disclaim all warranties, express or implied. Guideline users always are urged to seek out newer information that might impact the diagnostic and treatment recommendations contained within a guideline. The ACCP Parties further disclaim all liability for any damages whatsoever (including, without limitation, direct, indirect, incidental, punitive, or consequential damages) arising out of the use, inavailability to use, or the results of use of a guideline, any references used in a guideline, or the materials, information, or procedures contained in a guideline, based on any legal theory whatsoever and whether or not there was advice of the possibility of such damages.
- Through a comprehensive and systematic literature review, the ACCP’s evidence-based clinical practice guidelines incorporate data from the existing peer-reviewed literature. This literature meets the prespecified inclusion criteria for the clinical research question, which ACCP considers, at the time of publication, to be the best evidence available for general clinical information purposes. This evidence is of varying quality from original studies of varying methodological rigor. The ACCP recommends that performance measures for quality improvement, performance-based reimbursement, and public reporting purposes should be based on rigorously developed guideline recommendations. However, not all recommendations graded highly according to the ACCP grading system (1A, 1B) are necessarily appropriate for development into such performance measures, and each one should be analyzed individually for importance, feasibility, usability, and scientific acceptability (National Quality Forum criteria). Performance measures developers should exercise caution in basing measures on recommendations that are graded 1C, 2A, 2B, and 2C, according to the ACCP Grading System as these should generally not be used in
performance measures for quality improvement, performance-based reimbursement, and public reporting purposes.

- Limitations of Methods: Although encouraged to use Evidence Profiles and Summary of Findings tables for all recommendations, there were some for which the authors were unable to produce such tables. However, those recommendations used an evidence-based systematic review and assessment of relevant studies. Some recommendations would have benefited from meta-analyses that would have clarified aspects of the evidence. Although panelists were instructed in completing the value and preference rating exercise to estimate patient values and preferences rather than to use their own, it cannot be assured that they succeeded in all instances.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the Availability of Companion Documents and Patient Resources fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)


Adaptation

Not applicable: The guideline was not adapted from another source.
Date Released

2004 Sep (revised 2012 Feb)

Guideline Developer(s)

American College of Chest Physicians - Medical Specialty Society

Source(s) of Funding

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The sponsors played no role in the development of these guidelines. Sponsoring organizations cannot recommend panelists or topics, nor are they allowed prepublication access to the manuscripts and recommendations.

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American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel

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Financial Disclosures/Conflicts of Interest

All panelists were required to disclose both financial conflicts of interest, such as receipt of funds for consulting with industry, and intellectual conflicts of interest, such as publication of original data bearing directly on a recommendation. Financial and intellectual conflicts of interest were classified as primary (more serious) or secondary (less serious). The operational definition of primary intellectual conflicts of interest included authorship of original studies and peer-reviewed grant funding (government, not-for-profit organizations) directly bearing on a recommendation. The operational definition of primary financial conflicts of interest included consultancies, advisory board membership, and the like from industry. Topic editors had no primary conflicts of interest, as noted. Some deputy editors, who were clinical experts in the topic of the article, had relevant primary conflicts of interest. The American College of Chest Physicians (ACCP) Health and Science Policy (HSP) Committee deemed some of these conflicts serious enough to require “management.” Management involved more frequent updates of disclosures than required of the approved panelists without any conflicts and recusal from activities relevant to that conflict.

Topic panel members, including the deputy editor, with primary conflicts related to a particular recommendation did not participate in the final deliberations that led to the decision regarding the direction or strength of a recommendation, nor did they vote on recommendations for which they were primarily conflicted. Panelists with primary conflicts could, however, participate in discussions and offer their opinions on interpretations of the evidence. Readers will find a record of panelist conflicts of interest on a recommendation-by-recommendation basis in the online data supplement.

In summary, the authors have reported to CHEST the following conflicts of interest: Dr Crowther has served on various advisory boards, has assisted in the preparation of educational materials, and has sat on data safety and monitoring boards. His institution has received research funds from the following companies: Leo Pharma A/S, Pfizer Inc, Boehringer Ingelheim GmbH, Bayer Healthcare Pharmaceuticals, 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 Guyatt is co-chair of the GRADE Working Group and Dr Vandvik is a prominent contributor to the GRADE Working Group. Drs Holbrook, Schulman, Witt, Fish, Kovacs, Svensson, and Veenstra have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Guideline panel members, including the chair, and members of the Health & Science Policy Committee are blinded to the funding sources. Further details on the Conflict of Interest Policy are available online at http://chestnet.org.

Guideline Endorser(s)

American Association for Clinical Chemistry, Inc. - Professional Association
American College of Clinical Pharmacy - Medical Specialty Society
American Society of Health-System Pharmacists - Professional Association
American Society of Hematology - Medical Specialty Society
International Society on Thrombosis and Haemostasis - Professional Association

Guideline Status

This is the current release of the guideline.


Guideline Availability


Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.
Availability of Companion Documents

The following are available:


Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on November 19, 2004. The information was verified by the guideline developer on January 12, 2005. This summary was updated by ECRI on December 7, 2005 following the U.S. Food and Drug Administration (FDA) advisory on NovoSeven. This summary was updated by ECRI on March 6, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin sodium). This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on September 7, 2007 following the revised U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin). This summary was updated by ECRI Institute on March 14, 2008 following the updated FDA advisory on heparin sodium injection. This NGC summary was updated by ECRI Institute on November 24, 2008. The updated information was verified by the guideline developer on January 7, 2009. This summary was updated by ECRI Institute on July 27, 2010 following the FDA drug safety communication on Heparin. This summary was updated by ECRI Institute on May 2, 2012. This summary was updated by ECRI Institute on March 10, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins.

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