



Complete Summary

GUIDELINE TITLE

Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy. American College of Chest Physicians evidence-based clinical practice guidelines (8th edition).

BIBLIOGRAPHIC SOURCE(S)

Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):844S-86S. [230 references] [PubMed](#)

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):627S-44S.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [February 28, 2008, Heparin Sodium Injection](#): The U.S. Food and Drug Administration (FDA) informed the public that Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection and their heparin lock flush solutions. Alternate heparin manufacturers are expected to be able to increase heparin production sufficiently to supply the U.S. market. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **

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SCOPE

DISEASE/CONDITION(S)

Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy

GUIDELINE CATEGORY

Prevention
Treatment

CLINICAL SPECIALTY

Cardiology
Critical Care
Emergency Medicine
Family Practice
Hematology
Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Nurses
Patients
Pharmacists
Physician Assistants
Physicians
Psychologists/Non-physician Behavioral Health Clinicians
Social Workers

GUIDELINE OBJECTIVE(S)

To provide evidence-based guidelines on the treatment of pregnant patients with venous thromboembolism, thrombophilia, or receiving antithrombotic therapy

TARGET POPULATION

Pregnant patients with venous thromboembolism, thrombophilia, requirement for antithrombotic therapy

INTERVENTIONS AND PRACTICES CONSIDERED

Management

1. Vitamin K antagonist (VKA) exposure in utero
2. Management of women receiving long-term VKAs who are considering pregnancy (unfractionated heparin [UFH], low-molecular weight heparin [LMWH] substitution)
3. Anticoagulant use in lactating women (warfarin, UFH, LMWH, fondaparinux, danaparoid, rhirudin)
4. LMWH therapy during pregnancy
5. Thrombosis risk assessment for women undergoing cesarean section
6. Thromboprophylaxis following cesarean section
 - UFH
 - LMWH
 - Graduated compression stockings
 - Intermittent pneumatic compression
 - Extended prophylaxis
7. Treatment of VTE during pregnancy
 - UFH
 - LMWH
 - Postpartum duration of therapy
 - Discontinuation of therapy prior to induction of labor
8. Monitoring (activated partial thromboplastin time [APTT], anti-Xa LMWH or UFH levels)
9. Prevention of recurrent VTE in pregnant women
 - Clinical surveillance antepartum
 - Anticoagulant prophylaxis antepartum
 - Anticoagulant prophylaxis postpartum (UFH, LMWH, VKAs), graduated compression stockings
10. Individualized risk assessment for prevention of pregnancy-related VTE in women with thrombophilia
11. Prevention of pregnancy complications in women with thrombophilia
 - Screening for antiphospholipid antibodies (APLAs) (in women with recurrent early pregnancy loss or unexplained late pregnancy loss, severe or recurrent preeclampsia or intrauterine growth restriction [IUGR])
 - Antepartum UFH or LMWH and aspirin in women with APLAs and recurrent pregnancy loss or late pregnancy loss
12. Prevention of recurrent preeclampsia in high-risk women without thrombophilia (low dose aspirin)
13. Anticoagulant management of mechanical prosthetic valves in pregnant women
 - Assessment of additional risk factors for thromboembolism
 - LMWH
 - UFH
 - VKAs

MAJOR OUTCOMES CONSIDERED

- Mortality
- Fetal loss
- Congenital malformation
- Thromboembolism
- Recurrent thromboembolism
- Major and minor hemorrhage
- Intrauterine growth restriction
- Placental abruption
- Preeclampsia

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
 Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Process of Searching for Evidence

Defining the clinical question provided the framework for formulating eligibility criteria that guided the search for relevant evidence. In specifying eligibility criteria, authors identified not only patients, interventions, and outcomes, but also methodologic criteria. For many recommendations, authors restricted eligibility to randomized controlled trials (RCTs).

For many questions, randomized trials did not provide sufficient data, and chapter authors included observational studies when randomized trials were not the most appropriate design to address the research question. In particular, randomized trials are not necessarily the best design to understand risk groups, that is, the baseline or expected risk of a given event for certain subpopulations. Because no interventions are typically examined in questions about prognosis, one replaces interventions by the duration of exposure measured in time.

Identifying the Evidence

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

For each question the authors provided, the librarians searched the Cochrane Database of Systematic Reviews, MEDLINE, and Embase for published English-language literature and human studies between 2002 and May 2006. To filter MEDLINE and Embase search results for RCT evidence, the librarians used the

search strategy developed by the Cochrane Collaboration. These searches updated the more comprehensive and sensitive searches conducted for the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines.

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

Standard Consideration of Study Quality

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

In assessing the quality of observational studies, the guideline developers did not make a distinction between prospective and retrospective because the key issues are unbiased sampling, high-quality measurement of patient characteristics and outcomes, and complete follow-up.

Although it is more likely that these quality criteria will be achieved in prospective studies, prospective studies may fail to achieve them, and retrospective studies may succeed. The guideline developers did make a key distinction about whether internal comparisons exist and their nature. Studies without internal comparisons received the label "case series" unless they met the following criteria: (1) a protocol existed before the date of commencement of data collection; (2) a definition of inclusion and exclusion criteria was available; (3) the study reported the number of excluded patients; (4) the study conducted a standardized follow-up, including description of schedule of follow-up, investigation of suspected

outcomes, and criteria used to define outcomes; and (5) the study reported all losses to follow-up.

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

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

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) and the methodological quality of the underlying evidence (A, B, or C). See "Grades of recommendations for antithrombotic agents" in the "Availability of Companion Documents" field and the "Rating Scheme for the Strength of the Recommendations." field.

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

Summarizing Evidence

The electronic searches also included searches for systematic reviews. If authors were satisfied with a recent high-quality systematic review, evidence from that review provided a foundation for the relevant recommendation.

Pooled analyses from high-quality systematic reviews formed summary data on which panelists based their recommendations wherever possible. Pooling offers the advantage of obtaining more precise estimates of treatment effects and allows for greater generalizability of results. However, pooling also bears the risk of spurious generalization. In general, the summary estimates of interest were the different types of outcomes conveying benefits and downsides (risk, burden, and cost). When pooled estimates of effects were not available, the McMaster University Evidence based practice center (EPC) conducted meta-analysis to obtain pooled estimates for specific questions. These were questions that authors had specifically identified.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Group-Specific Recommendations

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

Acknowledge Values and Preferences and Resource Use Underlying Recommendations

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

The guideline developer's main strategy for dealing with this unsatisfactory situation is to make the values and preferences underlying the recommendations explicit whenever the panelists believed that value and preference issues were crucial for a recommendation.

In addition, the guideline developers involved three consultants with expertise in the area of values and preferences to collaborate with the chairs of two chapters and try to ensure that the guidelines adequately represented the views of patients. This collaboration led to extensive discussions among the chapter authors and the consultants and the reflection of these discussions in the associated values and preference statements.

Finalizing and Harmonizing Recommendations

After having completed the steps the guideline developers have described above, the guideline authors formulated draft recommendations before the conference, which laid the foundation for authors to work together and critique the recommendations. Figure 1 in the methodology companion (see "Availability of Companion Documents" field) shows the process of guideline development and review. Drafts of chapters that included draft recommendations were usually

distributed for peer review to at least two panel members and were always reviewed by at least one panel editor before the conference. Written critiques were prepared and returned to the authors for revision of their work. At the plenary conference, a representative of each chapter presented potentially controversial issues in their recommendations. Chapter authors met to integrate feedback and consider related recommendations in other chapters and to revise their own guidelines accordingly. Authors continued this process after the conference until they reached agreement within their groups and with other author groups who provided critical feedback. The editors of this supplement harmonized the chapters and resolved remaining disagreements between chapters through facilitated discussion. All major correspondence and discussions at the meeting were recorded in written and audio protocols and are publicly available.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading Recommendation			
Grade of Recommendation*	Benefit vs. Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
Strong recommendation, high-quality evidence, Grade 1A	Desirable effects clearly outweigh undesirable effects, or <i>vice versa</i>	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; further research is very unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate-quality evidence, Grade 1B	Desirable effects clearly outweigh undesirable effects, or <i>vice versa</i>	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, low or very low-quality evidence, Grade 1C	Desirable effects clearly outweigh undesirable effects, or <i>vice versa</i>	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and

Grading Recommendation			
Grade of Recommendation*	Benefit vs. Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
			may well change the estimate
Weak recommendation, high-quality evidence, Grade 2A	Desirable effects closely balanced with undesirable effects	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient or society values; further research is very unlikely to change our confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade 2B	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Best action may differ depending on circumstances or patient or society values; higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Weak recommendation, low or very low-quality evidence, Grade 2C	Desirable effects closely balanced with undesirable effects	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate

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

COST ANALYSIS

For these guidelines, the guideline developers implemented recommendations of a recent American College of Chest Physicians (ACCP) task force on integrating resource allocation in clinical practice guidelines by restricting resource expenditure consideration to a small number of recommendations for which they were particularly relevant. The guideline developers relied on two consultants with expertise in economic assessment to help with the process of considering costs in those small numbers of recommendations that the guideline developers considered very important to the decision.

Recommendations highly sensitive to resource allocation now include value and preference statements regarding how cost issues were integrated.

Refer to "Strategies for incorporating resource allocation and economic considerations" (see "Availability of Companion Documents" field) for details of the cost analyses.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

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

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The grades of recommendation (1A, 1B, 1C, 2A, 2B, 2C) are defined at the end of the "Major Recommendations" field.

Fetal Complications of Anticoagulant Therapy during Pregnancy

Vitamin K Antagonists (VKA) Exposure in Utero

1. For women receiving anticoagulation for the management of venous thromboembolism (VTE) who become pregnant, the guideline developers recommend that VKAs be substituted with unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) (**Grade 1A**).
2. For women with mechanical valves who become pregnant, the guideline developers suggest either adjusted-dose twice a day (bid) LMWH or UFH throughout pregnancy or adjusted-dose bid LMWH or UFH until the thirteenth week with substitution by VKAs until LMWH or UFH are resumed close to delivery (**Grade 1C**). In pregnant women with high-risk mechanical valves (e.g., older-generation valve in the mitral position or history of

thromboembolism), the guideline developers suggest the use of oral anticoagulants over heparin **(Grade 2C)**.

Underlying values and preferences: The suggestion to utilize VKAs during the first 12 weeks of pregnancy places similar value on avoiding maternal thromboembolic complications as on avoiding fetal risks.

Management of Women Receiving Long-term VKAs Who Are Considering Pregnancy

For women requiring long-term VKAs who are attempting pregnancy and are candidates for UFH or LMWH substitution, the guideline developers suggest performing frequent pregnancy tests and substituting UFH or LMWH for VKAs when pregnancy is achieved **(Grade 2C)**.

Underlying values and preferences: This recommendation places a higher value on avoiding the risks, inconvenience, and costs of UFH or LMWH therapy of uncertain duration while awaiting pregnancy compared to minimizing the risks of early miscarriage associated with VKA therapy.

Use of Anticoagulants in Nursing Women

1. For lactating women using warfarin or UFH who wish to breastfeed, the guideline developers recommend continuing these medications **(Grade 1A)**.
2. For lactating women using LMWH, danaparoid, or r-hirudin who wish to breastfeed, the guideline developers suggest continuing these medications **(Grade 2C)**.
3. For breastfeeding women, the guideline developers suggest alternative anticoagulants rather than pentasaccharides **(Grade 2C)**.

Maternal Complications of Anticoagulant Therapy

LMWH Therapy

For pregnant patients, the guideline developers suggest LMWH over UFH for the prevention and treatment of VTE **(Grade 2C)**.

VTE Following Cesarean Section

Risk of VTE Following Cesarean Section

1. The guideline developers suggest that a thrombosis risk assessment be carried out in all women undergoing cesarean section to determine the need for thromboprophylaxis **(Grade 2C)**.
2. In patients without additional thrombosis risk factors undergoing cesarean section, the guideline developers recommend against the use of specific thromboprophylaxis other than early mobilization **(Grade 1B)**.

Thromboprophylaxis Following Cesarean Section

1. For women considered at increased risk of VTE after cesarean section because of the presence of at least one risk factor in addition to pregnancy and cesarean section, the guideline developers suggest pharmacologic thromboprophylaxis (prophylactic LMWH or UFH) or mechanical prophylaxis (graduated compression stockings or intermittent pneumatic compression) while in hospital following delivery (**Grade 2C**).
2. For women with multiple additional risk factors for thromboembolism who are undergoing cesarean section and are considered to be at very high risk of VTE, the guideline developers suggest that pharmacologic prophylaxis be combined with the use of graduated compression stockings and/or intermittent pneumatic compression (**Grade 2C**).
3. For selected high-risk patients in whom significant risk factors persist following delivery, the guideline developers suggest extended prophylaxis (up to 4 to 6 weeks after delivery) following discharge from the hospital (**Grade 2C**).

VTE during Pregnancy

Treatment of VTE during Pregnancy

1. For pregnant women with acute VTE, the guideline developers recommend initial therapy with either adjusted-dose subcutaneous (SC) LMWH or adjusted-dose UFH (IV bolus, followed by a continuous infusion to maintain the activated partial thromboplastin time (aPTT) within the therapeutic range or subcutaneous therapy adjusted to maintain the APTT 6 hours after injection into the therapeutic APTT range) for at least 5 days (**Grade 1A**).
2. For pregnant women with acute VTE, after initial therapy, the guideline developers recommend that subcutaneous LMWH or UFH should be continued throughout pregnancy (**Grade 1B**).
3. For pregnant women with acute VTE, the guideline developers suggest that anticoagulants should be continued for at least 6 weeks postpartum (for a minimum total duration of therapy of 6 months) (**Grade 2C**).
4. For pregnant women receiving adjusted-dose LMWH or UFH therapy, the guideline developers recommend discontinuation of the heparin at least 24 hours prior to elective induction of labor (**Grade 1C**).

Prevention of VTE in Pregnant Women With Prior Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE)

Prevention of Recurrent VTE in Pregnant Women

1. For pregnant women with a single episode of VTE associated with a transient risk factor that is no longer present and no thrombophilia, the guideline developers recommend clinical surveillance antepartum and anticoagulant prophylaxis postpartum (**Grade 1C**).
2. If the transient risk factor associated with a previous VTE event is pregnancy or estrogen related, the guideline developers suggest antepartum clinical surveillance or prophylaxis (prophylactic LMWH/UFH or intermediate-dose LMWH/UFH) plus postpartum prophylaxis, rather than routine care (**Grade 2C**).
3. For pregnant women with a single idiopathic episode of VTE but without thrombophilia and who are not receiving long-term anticoagulants, the

- guideline developers recommend one of the following, rather than routine care or adjusted-dose anticoagulation: prophylactic LMWH/UFH or intermediate-dose LMWH/UFH or clinical surveillance throughout pregnancy plus postpartum anticoagulants **(Grade 1C)**.
4. For pregnant women with thrombophilia (confirmed laboratory abnormality) who have had a single prior episode of VTE and are not receiving long-term anticoagulants, the guideline developers recommend one of the following, rather than routine care or adjusted-dose anticoagulation: antepartum prophylactic or intermediate-dose LMWH or prophylactic or intermediate-dose UFH or clinical surveillance throughout pregnancy; plus postpartum anticoagulants **(Grade 1C)**.
 5. For women with "higher-risk" thrombophilias (e.g., antithrombin deficiency, persistent positivity for the presence of antiphospholipid antibodies; compound heterozygosity for prothrombin G20210A variant and factor V Leiden or homozygosity for these conditions) who have had a single prior episode of VTE and are not receiving long-term anticoagulants, the guideline developers suggest, in addition to postpartum prophylaxis, antepartum prophylactic or intermediate-dose LMWH or prophylactic or intermediate-dose UFH, rather than clinical surveillance **(Grade 2C)**.
 6. For pregnant women with multiple (≥ 2) episodes of VTE not receiving long-term anticoagulants, the guideline developers suggest antepartum prophylactic, intermediate-dose, or adjusted-dose LMWH or prophylactic, intermediate-dose or adjusted-dose UFH followed by postpartum anticoagulants rather than clinical surveillance **(Grade 2C)**.
 7. For pregnant women receiving long-term anticoagulants for prior VTE, the guideline developers recommend LMWH or UFH throughout pregnancy (either adjusted-dose LMWH or UFH, 75% of adjusted-dose LMWH, or intermediate-dose LMWH) followed by resumption of long-term anticoagulants postpartum **(Grade 1C)**.
 8. For all pregnant women with previous DVT, the guideline developers suggest the use of graduated elastic compression stockings both antepartum and postpartum **(Grade 2C)**.

Underlying values and preferences: This recommendation places a high value on uncertain incremental benefit with stockings and a low value on avoiding discomfort and inconvenience.

Prevention of VTE in Pregnant Women with Thrombophilia and No Prior VTE

Risk of Pregnancy-Related VTE in Women with Thrombophilia

For pregnant patients with thrombophilia but no prior VTE, the guideline developers recommend that physicians do not use routine pharmacologic antepartum prophylaxis but instead perform an individualized risk assessment **(Grade 1C)**.

Prevention of Pregnancy-Related VTE in Women with Thrombophilia

1. For pregnant women with no history of VTE but antithrombin deficiency, the guideline developers suggest antepartum and postpartum prophylaxis **(Grade 2C)**.

2. For all other pregnant women with thrombophilia and no prior VTE, the guideline developers suggest antepartum clinical surveillance or prophylactic LMWH or UFH, plus postpartum anticoagulants **(Grade 2C)**.

Thrombophilia and Pregnancy Complications

Risk of Pregnancy Complications in Women with Thrombophilia

1. For women with recurrent early pregnancy loss (three or more miscarriages) or unexplained late pregnancy loss, the guideline developers recommend screening for antiphospholipid antibodies (APLAs) **(Grade 1A)**.
2. For women with severe or recurrent preeclampsia or IUGR, the guideline developers suggest screening for APLAs **(Grade 2C)**.

Prevention of Pregnancy Complications in Women with Thrombophilia

For women with APLAs and recurrent (three or more) pregnancy loss or late pregnancy loss and no history of venous or arterial thrombosis, the guideline developers recommend antepartum administration of prophylactic or intermediate-dose UFH or prophylactic LMWH combined with aspirin **(Grade 1B)**.

Management of Women with a History of Preeclampsia and No Thrombophilia

Prevention of Recurrent Preeclampsia in Women Without Thrombophilia

1. For women considered high risk for preeclampsia, the guideline developers recommend low-dose aspirin therapy throughout pregnancy **(Grade 1B)**.
2. For women with a history of preeclampsia, the guideline developers suggest that UFH and LMWH should not be used as prophylaxis in subsequent pregnancies **(Grade 2C)**.

Maternal and Fetal Risks Related to Anticoagulation During Pregnancy for Mechanical Prosthetic Valves

Anticoagulant Management of Mechanical Prosthetic Valves in Pregnant Women

1. For pregnant women with mechanical heart valves the guideline developers recommend that the decision about anticoagulant management during pregnancy include an assessment of additional risk factors for thromboembolism including valve type, position, and history of thromboembolism and that the decision should also be influenced strongly by patient preferences **(Grade 1C)**.
2. For pregnant women with mechanical heart valves, the guideline developers recommend one of the following anticoagulant regimens in preference to no anticoagulation:
 - a. Adjusted-dose bid LMWH throughout pregnancy **(Grade 1C)**. The guideline developers suggest that doses be adjusted to achieve the manufacturer's peak anti-Xa LMWH 4 hours after SC injection **(Grade 2C)** or

- b. Adjusted-dose UFH throughout pregnancy administered SC every twelve hours (q12h) in doses adjusted to keep the mid-interval aPTT at least twice control or attain an anti-Xa heparin level of 0.35 to 0.70 U/mL **(Grade 1C)**
- c. UFH or LMWH (as above) until the thirteenth week with warfarin substitution until close to delivery when UFH or LMWH is resumed **(Grade 1C)**.

In women judged to be at very high risk of thromboembolism in whom concerns exist about the efficacy and safety of UFH or LMWH as dosed above (e.g., older-generation prosthesis in the mitral position or history of thromboembolism), the guideline developers suggest VKAs throughout pregnancy with replacement by UFH or LMWH (as above) close to delivery, rather than one of the regimens above; after a thorough discussion of the potential risks and benefits of this approach **(Grade 2C)**.

Underlying values and preferences: In contrast to our other recommendations, which place a high value on avoiding fetal risk, the recommendation for women at very high risk of thromboembolism places equal value on avoiding maternal complications.

Remark: For all the recommendations above, usual long-term anticoagulants should be resumed postpartum.

- 3. For pregnant women with prosthetic valves at high risk of thromboembolism, the guideline developers recommend the addition of low-dose aspirin, 75 to 100 mg/d **(Grade 2C)**.

Definitions:

Grading Recommendation			
Grade of Recommendation*	Benefit vs. Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
Strong recommendation, high-quality evidence, Grade 1A	Desirable effects clearly outweigh undesirable effects, or <i>vice versa</i>	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; further research is very unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate-quality evidence, Grade 1B	Desirable effects clearly outweigh undesirable effects, or	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws,	Recommendation can apply to most patients in most circumstances; higher quality research may well have an important impact on our

Grading Recommendation			
Grade of Recommendation*	Benefit vs. Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
	<i>vice versa</i>	indirect or imprecise), or very strong evidence from observational studies	confidence in the estimate of effect and may change the estimate
Strong recommendation, low or very low-quality evidence, Grade 1C	Desirable effects clearly outweigh undesirable effects, or <i>vice versa</i>	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak recommendation, high-quality evidence, Grade 2A	Desirable effects closely balanced with undesirable effects	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient or society values; further research is very unlikely to change our confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade 2B	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Best action may differ depending on circumstances or patient or society values; higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Weak recommendation, low or very low-quality evidence, Grade 2C	Desirable effects closely balanced with undesirable effects	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate

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

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

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

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate monitoring and management of pregnant patients with venous thromboembolism, thrombophilia, or receiving antithrombotic therapy

POTENTIAL HARMS

Antithrombotic therapy is associated with an increased risk of hemorrhage. Certain antithrombotic agents may be associated with risks to the fetus.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Limitations of These Guideline Development Methods

Limitations of these guidelines include the limited quantity and quality of available studies for some patient groups. Second, it is possible that some authors followed this methodology more closely than others, although the development process was centralized by an evidence-based practice center (EPC) and supervised by the editors. Third, it is possible that the guideline developers missed relevant studies in spite of the comprehensive searching process. Fourth, despite their efforts to begin centralizing the methodologic evaluation of all studies to facilitate uniformity in the validity assessments of the research incorporated into these guidelines, resources were insufficient to conduct this evaluation for all but a few of the recommendations in each chapter. Fifth, the guideline developers performed only few statistical pooling exercises of primary study results. Finally, sparse data on patient preferences and values represent additional limitations inherent to most guideline development methods.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy includes local educational programs and tools offered through the American College of Chest Physicians (ACCP) Board of Governors and select other locations. The Veterans Administration (VA) will also participate in a pilot project.

IMPLEMENTATION TOOLS

Resources

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
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):844S-86S. [230 references] [PubMed](#)

ADAPTATION

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

DATE RELEASED

2001 Jan (revised 2008 Jun)

GUIDELINE DEVELOPER(S)

American College of Chest Physicians - Medical Specialty Society

SOURCE(S) OF FUNDING

American College of Chest Physicians

GUIDELINE COMMITTEE

American College of Chest Physicians (ACCP) Expert Panel on Antithrombotic and Thrombolytic Therapy

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Bates discloses grant monies received from the Canadian Institute of Health Research, the Heart and Stroke Foundation of Ontario, and bioMérieux. She received consultant fees from, and was on advisory committees for, GlaxoSmithKline, Dade Behring, and Trinity Biotech. Dr. Bates also has received an honorarium from LEO Pharma.

Dr. Greer discloses that he has received grant monies from the British Health Foundation and the Chief Scientist's Office (Scotland). He has also received honoraria for lectures for Sanofi-Aventis and Leo, and has served on an advisory committee for Sanofi-Aventis.

Dr. Pabinger discloses that she has received grant monies from CSL Behring and Pfizer. She is also on the speaker bureaus for CSL Behring, Bayer, Pfizer, Aventis, Baxter, and Biotest, and is on advisory committees for Novo, Bayer, and Wyeth. Dr.Pabinger also holds a fiduciary position on the Board of Gesellschaft für Thrombose und Hämostaseforschung.

Dr. Hirsh discloses that he has received partial support for writing two books, one on fondaparinux and one on low-molecular-weight heparin.

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

ENDORSER(S)

American College of Clinical Pharmacy - Medical Specialty Society
American Society of Health-System Pharmacists - Professional Association

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):627S-44S.

GUIDELINE AVAILABILITY

Electronic copies: Available to subscribers of the [Chest - The Cardiopulmonary and Critical Care Journal](#).

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:

Executive Summary:

- Antithrombotic and thrombolytic therapy executive summary. Chest 2008 Jun; 133:71S-109S.

Background Articles:

- Antithrombotic and thrombolytic therapy. Chest 2008 Jun; 133:110S-112S.

- Methodology for antithrombotic and thrombolytic therapy guideline development. Chest 2008 Jun; 133:113S-122S.
- Grades of recommendation for antithrombotic agents. Chest 2008 Jun; 133:123S-131S.
- Strategies for incorporating resource allocation and economic considerations. Chest 2008 Jun; 133:132S-140S.

Electronic copies: Available to subscribers of the [Chest - The Cardiopulmonary and Critical Care Journal](#).

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 summary was completed by ECRI on July 12, 2001. The information was verified by the guideline developer on October 2001. This NGC summary was updated by ECRI on December 9, 2004. The updated information was verified by the guideline developer on January 12, 2005. 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 December 9, 2008. The updated information was verified by the guideline developer on January 7, 2009.

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