Complete Summary

GUIDELINE TITLE

Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.

BIBLIOGRAPHIC SOURCE(S)

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. [119 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Ginsberg JS, Greer I, Hirsh J. Use of antithrombotic agents during pregnancy. Chest 2001 Jan;119(1 Suppl):122S-131S.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

- Pregnancy complications associated with thrombophilia (presence of antiphospholipid antibodies or hereditary thrombophilia)
- Venous thromboembolism or pulmonary embolism during pregnancy
- Venous thromboembolism associated with cesarean section
- Systemic thromboembolism associated with mechanical heart valves during pregnancy

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Internal Medicine
Obstetrics and Gynecology
Pulmonary Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide evidence-based recommendations on the management of thromboembolic complications during pregnancy

TARGET POPULATION

- Pregnant women with or at risk of developing thromboembolic complications
- Pregnant women with mechanical heart valves
- Pregnant women with thrombophilia (antiphospholipid antibodies, factor V Leiden, prothrombin gene mutation, hyperhomocysteinemia, protein S deficiency, protein C deficiency, antithrombin deficiency)
- Pregnant women with a prior history of venous thromboembolism
- Symptomatic pregnant women with clinical suspicion of deep vein thrombosis (DVT) or pulmonary embolism (PE)

INTERVENTIONS AND PRACTICES CONSIDERED

Prevention, Management, and Treatment

1. Screening, as appropriate, for congenital thrombophilia and antiphospholipid antibodies (APLAs).
2. Antithrombotic pharmacotherapy, including:
    - Heparin; mini-dose unfractionated heparin (UFH); moderate-dose UFH; adjusted-dose UFH; prophylactic low-molecular-weight-heparin (LMWH; for example, dalteparin or enoxaparin); adjusted-dose LMWH (weight-adjusted, full-treatment doses of LMWH)
    - Postpartum anticoagulant therapy (warfarin in combination with initial UFH or LMWH overlap)
    - Aspirin therapy, such as antepartum aspirin; low-dose aspirin therapy in combination with anticoagulant therapy, as appropriate, during pregnancy

Note: Aspirin therapy alone (rather than in combination with anticoagulant therapy) is considered but not recommended during pregnancy.

3. Folic acid supplementation
4. Surveillance of women with symptoms suspicious of deep vein thrombosis (DVT) or pulmonary embolism (PE), and of women who are at increased risk of venous thromboembolism (VTE) or thrombophilia
5. Screening with noninvasive tests for DVT, such as compression ultrasound
6. Laboratory testing and monitoring:
    - Anti-factor Xa levels
    - Activated partial thromboplastin time (aPTT)
7. Patient education/counseling, such as pre-pregnancy counseling of risks associated with pregnancy in women receiving long-term anticoagulation therapy

MAJOR OUTCOMES CONSIDERED

Effectiveness and safety of antithrombotic therapy as evidenced by the following:

- Rates of fetal complications (e.g., spontaneous abortions, fetal hemorrhage, congenital fetal anomalies, fetal wastage) with maternal antithrombotic therapy
- Rates of maternal complications including mortality, major bleeding episodes, venous thromboembolism (VTE), heparin-induced thrombocytopenia (HIT), and heparin-associated osteoporosis.

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. Prior to searching for the evidence, methodological experts and librarians reviewed each question to ensure that the librarians could derive a comprehensive search strategy.

In specifying eligibility criteria, authors not only identified patients, interventions, and outcomes, but also methodological criteria. For most therapeutic studies, authors restricted eligibility to randomized controlled trials (RCTs).

For many questions, RCTs did not provide sufficient data, and article authors also included observational studies. This was also true when randomized trials were not the most appropriate design to use for addressing the research question. In particular, randomized trials are not necessarily the best design to understand risk

groups (e.g., the baseline or expected risk of a given event for certain subpopulations). Because there are no interventions examined in questions about prognosis, one replaces interventions by the exposure, which is time.

Identifying the Evidence

To identify the relevant evidence, a team of librarians at the University at Buffalo conducted comprehensive literature searches. For each question the authors provided, the librarians developed sensitive (but not specific) search strategies, including all languages, and conducted separate searches for systematic reviews, RCTs, and, if applicable, observational studies. The librarians searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness and Cochrane Register of Controlled Trial, the ACP Journal Club, MEDLINE, and Embase for studies published between 1966 and June 2002 in any language. To filter MEDLINE and Embase search results for RCT evidence, the librarians used the search strategy developed by the Cochrane Collaboration (full strategy available in Appendix online at: http://www.chestjournal.org/content/vol126/3_suppl_1).

For observational studies, they restricted their searches to human studies. Searches were not further restricted in terms of methodology. While increasing the probability of identifying all published studies, this sensitive approach resulted in large number of citations for many of the defined clinical questions. Therefore, trained research assistants screened the citation list developed from the search and removed any apparently irrelevant citations. These irrelevant citations included press news, editorials, narrative reviews, single case reports, animal studies (any nonhuman studies), and letters to the editor. Authors included data from abstracts of recent meetings if reporting was transparent and all necessary data for the formulation of a recommendation were available. The guideline developers did not explicitly use Internet sources to search for research data.

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, C+, or C). See "Rating Scheme for the Strength of the Recommendations."

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 searching 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, wherever possible, the evidence base of the recommendations. Pooling offers the advantage of obtaining more precise estimates of treatment effects and allows for a 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 benefit and downsides (i.e., risk, burden, and cost).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The strength of any recommendation depends on the following two factors: the trade-off between the benefits and the risks, burdens, and costs; and the strength of the methodology that leads to the treatment effect. The guideline developers grade the trade-off between benefits and risks in the two categories: 1, in which the trade-off is clear enough that most patients, despite differences in values, would make the same choice; and 2, in which the trade-off is less clear, and individual patients´ values will likely lead to different choices.

When randomized trials provide precise estimates suggesting large treatment effects, and the risks and costs of therapy are small, treatment for average patients with compatible values and preferences can be confidently recommended.

If the balance between benefits and risks is in doubt, methodologically rigorous studies providing Grade A evidence and recommendations may still be weak (Grade 2). Uncertainty may come from less precise estimates of benefit, harm, or costs, or from small effect sizes.

There is an independent impact of validity and consistency, and the balance of positive and negative impacts of treatment on the strength of recommendations. In situations in which there is doubt about the value of the trade-off, any recommendation will be weaker, moving from Grade 1 to Grade 2.

Grade 1 recommendations can only be made when there is a relatively clear picture of both the benefits and the risks, burdens, and costs, and when the balance between the two clearly favors recommending or not recommending the intervention for the typical patient with compatible values and preferences. A number of factors can reduce the strength of a recommendation, moving it from Grade 1 to Grade 2. Uncertainty about a recommendation to treat may be

introduced if the following conditions apply: (1) the target event that is trying to be prevented is less important (confident recommendations are more likely to be made to prevent death or stroke than asymptomatic deep vein thrombosis); (2) the magnitude of risk reduction in the overall group is small; (3) the probability of the target event is low in a particular subgroup of patients; (4) the estimate of the treatment effect is imprecise, as reflected in a wide confidence interval (CI) around the effect; (5) there is substantial potential harm associated with therapy; or (6) there is an expectation for a wide divergence in values even among average or typical patients. Higher costs would also lead to weaker recommendations to treat.

The more balanced the trade-off between benefits and risks, the greater the influence of individual patient values in decision making. Virtually all patients, if they understand the benefits and risks, will take aspirin after experiencing a myocardial infarction (MI) or will comply with prophylaxis to reduce the risk of thromboembolism after undergoing hip replacement. Thus, one way of thinking about a Grade 1 recommendation is that variability in patient values is unlikely to influence treatment choice in average or typical patients.

When the trade-off between benefits and risks is less clear, individual patient values may influence treatment decisions even among patients with average or typical preferences.

Grade 2 recommendations are those in which variation in patient values or individual physician values will often mandate different treatment choices, even among average or typical patients. An alternative, but similar, interpretation is that a Grade 2 recommendation suggests that clinicians conduct detailed conversations with patients to ensure that their ultimate recommendation is consistent with the patient's values.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
1A	Clear	Randomized controlled trials (RCTs) without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1C+	Clear	No RCTs, but strong RCT results can be unequivocally extrapolated, or	Strong recommendation; can apply to most patients in most circumstances

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
		overwhelming evidence from observational studies	
1B	Clear	RCTs with important limitations (inconsistent results, methodological flaws*)	Strong recommendation; likely to apply to most patients
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	RCTs without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2C+	Unclear	No RCTs, but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	RCTs with important limitations (inconsistent results, methodological	Weak recommendation; alternative approaches likely to be better for some patients

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
		flaws*)	under some circumstances
2C	Unclear	Observational studies	Very weak recommendation; other alternatives may be equally reasonable

*These situations include RCTs with both lack of blinding and subjective outcomes, where the risk of bias in measurement of outcomes is high, or RCTs with large loss to follow-up.

COST ANALYSIS

While conference participants agreed that recommendations should reflect economic considerations, incorporating costs is fraught with difficult challenges. For most recommendations, formal economic analyses are unavailable. Even when analyses are available, they may be methodologically weak or biased. Furthermore, costs differ radically across jurisdictions, and even sometimes across hospitals within jurisdictions.

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

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guideline authors formulated draft recommendations prior to the conference that served as the foundation for authors to work together and critique the

recommendations. Drafts of all articles including draft recommendations were available for review during the conference. A representative of each article presented potentially controversial issues in their recommendations at plenary meetings. Article authors met to integrate feedback, to consider related recommendations in other articles, 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 had provided critical feedback. Finally, the editors of this supplement harmonized the articles and resolved remaining disagreements through facilitated discussion.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The rating scheme is defined at the end of the "Major Recommendations" field.

When describing the various regimens of unfractionated heparin (UFH) and low-molecular-weight-heparin (LMWH), the guideline developers use the following terminology:

- Mini-dose UFH: UFH 5,000 U subcutaneous (SC) every 12 hours
- Moderate-dose UFH: UFH SC every 12 hours in doses adjusted to target an anti-Xa level of 0.1 to 0.3 U/mL
- Adjusted-dose UFH: UFH SC every 12 hours in doses adjusted to target a mid-interval activated partial thromboplastin time (aPTT) into the therapeutic range
- Prophylactic LMWH: e.g., dalteparin 5,000 U SC every 24 hours, or enoxaparin 40 mg SC every 24 hours (although at extremes of body weight modification of dose may be required)
- Intermediate-dose LMWH: e.g., dalteparin 5,000 U SC every 12 hours, or enoxaparin 40 mg SC every 12 hours
- Adjusted-dose LMWH: weight-adjusted, full-treatment doses of LMWH administered once or twice daily (e.g., dalteparin 200 U/kg, or tinzaparin 175 U/kg once daily, or dalteparin 100 U/kg every 12 hours, or enoxaparin 1 mg/kg every 12 hours). As the half-life of LMWH is shorter in pregnancy, twice-daily dosing is preferable, at least in the initial treatment phase.
- Postpartum anticoagulants: warfarin for 4 to 6 weeks with a target international normalized ratio (INR) of 2.0 to 3.0, with initial UFH or LMWH overlap until the INR is $\geq$2.0
- In addition, the term surveillance refers to clinical vigilance and aggressive investigation of women with symptoms suspicious of deep vein thrombosis (DVT) or pulmonary embolism (PE).

Management of Women Receiving Long-Term Vitamin K Antagonist (VKA) Therapy Who Are Considering Pregnancy

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

Treatment of Venous Thromboembolism (VTE) during Pregnancy

1. In women with acute VTE, the guideline developers recommend either adjusted-dose LMWH throughout pregnancy or intravenous (IV) UFH (bolus followed by a continuous infusion to maintain the aPTT in the therapeutic range) for at least 5 days, followed by adjusted-dose UFH or LMWH for the remainder of the pregnancy. Anticoagulants should be administered for at least 6 weeks postpartum (Grade 1C+).
2. In women receiving adjusted-dose LMWH or UFH therapy, the guideline developers recommend discontinuing the heparin 24 hours prior to elective induction of labor (Grade 1C).

Prevention of VTE during Pregnancy

Prior VTE and Pregnancy

1. In patients with a single episode of VTE associated with a transient risk factor that is no longer present, the guideline developers recommend clinical surveillance and postpartum anticoagulants (Grade 1C). If the previous event is pregnancy or estrogen-related or there are additional risk factors (such as obesity), the guideline developers suggest antenatal anticoagulant prophylaxis (Grade 2C).
2. In patients with a single idiopathic episode of VTE who are not receiving long-term anticoagulants, the guideline developers suggest prophylactic LMWH, or mini-dose UFH, or moderate-dose UFH, or clinical surveillance plus postpartum anticoagulants (Grade 2C).
3. In patients with a single episode of VTE and thrombophilia (confirmed laboratory abnormality) or strong family history of thrombosis and not receiving long-term anticoagulants, the guideline developers suggest prophylactic or intermediate-dose LMWH, or mini-dose or moderate-dose UFH, plus postpartum anticoagulants (Grade 2C).
4. In antithrombin-deficient women, compound heterozygotes for prothrombin G20210A and factor V Leiden and homozygotes for these conditions with a history of VTE, the guideline developers suggest intermediate-dose LMWH prophylaxis or moderate-dose UFH (Grade 2C).
5. In patients with multiple (two or more) episodes of VTE and/or women receiving long-term anticoagulants (e.g., single episode of VTE—either idiopathic or associated with thrombophilia) the guideline developers suggest adjusted-dose UFH or adjusted-dose LMWH followed by resumption of long-term anticoagulants postpartum (Grade 2C).
6. In all women with previous DVT, antenatally and postpartum, the guideline developers suggest use of graduated elastic compression stockings (Grade 2C).

Thrombophilia and VTE Associated with Pregnancy

1. In antithrombin-deficient women, compound heterozygotes for prothrombin G20210A and factor V Leiden, and homozygotes for these conditions with no prior VTE, the guideline developers suggest active prophylaxis (Grade 2C).
2. In all other patients with no prior VTE and thrombophilia (confirmed laboratory abnormality), the guideline developers suggest surveillance or

prophylactic LMWH or mini-dose UFH, plus postpartum anticoagulants (Grade 2C).

Thrombophilia and Pregnancy Complications

1. For women with recurrent pregnancy loss (three or more miscarriages) and women with prior severe or recurrent preeclampsia, abruptions, or otherwise unexplained intrauterine death, the guideline developers suggest screening for congenital thrombophilia and antiphospholipid antibodies (APLAs) (Grade 2C).
2. For pregnant patients with APLAs and a history of multiple (two or more) early pregnancy losses or one or more late pregnancy losses, preeclampsia, intrauterine growth retardation (IUGR), or abruption, the guideline developers suggest administration of antepartum aspirin plus mini-dose or moderate-dose UFH or prophylactic LMWH (Grade 2B).
3. For women who are homozygous for thermolabile variant (C677T) or MTHFR, the guideline developers suggest folic acid supplements prior to conception or, if already pregnant, as soon as possible, and throughout pregnancy (Grade 2C).
4. For women with a congenital thrombophilic deficit and recurrent miscarriages, a second-trimester or later loss, severe or recurrent preeclampsia, or abruption, the guideline developers suggest low-dose aspirin therapy plus either mini-dose heparin or prophylactic LMWH therapy (Grade 2C). The guideline developers also suggest that postpartum anticoagulants be administered to these women (Grade 2C).
5. Patients with APLAs and a history of venous thrombosis are usually receiving long-term oral anticoagulation therapy because of the high risk of recurrence. During pregnancy, the guideline developers recommend adjusted-dose LMWH or UFH therapy plus low-dose aspirin and resumption of long-term oral anticoagulation therapy postpartum (Grade 1C).
6. Patients with APLAs and no prior VTE or pregnancy loss should be considered to have an increased risk for the development of venous thrombosis and, perhaps, pregnancy loss. The guideline developers suggest one of the following approaches for these women: surveillance, mini-dose heparin, prophylactic LMWH, and/or low-dose aspirin, 75 to 162 mg daily (all Grade 2C).

Prophylaxis in Patients with Mechanical Heart Valves

In women with prosthetic heart valves, the guideline developers recommend:

1. Adjusted-dose, twice-daily LMWH throughout pregnancy in doses adjusted either to keep a 4-hour postinjection anti-Xa heparin level at approximately 1.0 to 1.2 U/mL (preferable) or according to weight (Grade 1C), or
2. Aggressive adjusted-dose UFH throughout pregnancy: i.e., administered SC every 12 hours in doses adjusted to keep the mid-interval aPTT at least twice control or to attain an anti-Xa heparin level of 0.35 to 0.70 U/mL (Grade 1C), or
3. UFH or LMWH (as above) until the thirteenth week, change to warfarin until the middle of the third trimester, and then restart UFH or LMWH (Grade 1C).

Remark: Long-term anticoagulants should be resumed postpartum with all regimens.

4. In women with prosthetic heart valves at high risk, the guideline developers suggest the addition of low-dose aspirin, 75 to 162 mg/day (Grade 2C).

Definitions

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
1A	Clear	Randomized controlled trials (RCTs) without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1C+	Clear	No RCTs, but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1B	Clear	RCTs with important limitations (inconsistent results, methodological flaws*)	Strong recommendation; likely to apply to most patients
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	RCTs without important limitations	Intermediate-strength recommendation;

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
			best action may differ depending on circumstances or patients' or societal values
2C+	Unclear	No RCTs, but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	RCTs with important limitations (inconsistent results, methodological flaws*)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Observational studies	Very weak recommendation; other alternatives may be equally reasonable

*These situations include RCTs with both lack of blinding and subjective outcomes, where the risk of bias in measurement of outcomes is high, or RCTs with large loss to follow-up.

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

- The appropriate use of antithrombotic agents during pregnancy can help prevent and treat venous thromboembolism or systemic embolism, while decreasing the risk and rate of negative maternal and fetal health outcomes.
- Low-molecular-weight heparins (LMWHs) have potential advantages over unfractionated heparin (UFH) during pregnancy because they cause less heparin-induced thrombocytopenia (HIT), have a longer plasma half-life and a more predictable dose response than UFH, with the potential for once-daily administration, and are likely associated with a lower risk of heparin-induced osteoporosis.
- Heparin and LMWHs are not secreted into breast milk and can be safely administered to nursing mothers.

POTENTIAL HARMS

General

- Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) is problematic because it involves long-term parenteral unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). Both are expensive, inconvenient, painful to administer, and are associated with risks for bleeding, osteoporosis, and heparin-induced thrombocytopenia (HIT), although these complications , particularly HIT, are very uncommon with LMWH.
- Allergic skin reactions to both LMWH and UFH can occur. These take the form of itchy, erythematous infiltrated plaques, which may resolve when preparations are switched, although cross-reactivity can occur. As HIT can present with isolated skin manifestations, this entity should be excluded when skin lesions develop.

Fetal Complications of Anticoagulants during Pregnancy

- There are two potential fetal complications of maternal anticoagulant therapy: teratogenicity and bleeding. Neither UFH nor LMWH cross the placenta; therefore, these agents do not have the potential to cause fetal bleeding or teratogenicity, although bleeding at the uteroplacental junction is possible.
- In contrast, coumarin derivatives cross the placenta and have the potential to cause both bleeding in the fetus and teratogenicity. Coumarin derivatives can cause an embryopathy, consisting of nasal hypoplasia and/or stippled epiphyses, after in utero exposure to vitamin K antagonists (VKAs) during the first trimester of pregnancy, and central nervous system (CNS) abnormalities after exposure to such drugs during any trimester.
- In addition, VKAs cause an anticoagulant effect in the fetus, which is a concern, particularly at the time of delivery, when the combination of anticoagulant effect and trauma of delivery can lead to bleeding in the neonate.

Maternal Complications of Anticoagulant Therapy during Pregnancy

- In a cohort study, the rate of major bleeding in pregnant patients treated with UFH therapy was 2%, which is consistent with the reported rates of bleeding associated with heparin therapy in nonpregnant patients and with warfarin therapy when used for the treatment of DVT. In addition, adjusted-dose subcutaneous (SC) UFH can cause a persistent anticoagulant effect at the time of delivery, which can complicate its use prior to labor. In a small study, an anticoagulant effect persisted for up to 28 hours after the last injection of adjusted-dose SC UFH, resulting in deliveries that were complicated by a prolonged activated partial thromboplastin time (aPTT).
- Bleeding complications appear to be very uncommon with low molecular weight heparin.

HIT

- Approximately 3% of nonpregnant patients receiving UFH acquire immune, IgG-mediated thrombocytopenia, which is frequently complicated by extension of preexisting VTE or new arterial thrombosis.

Heparin-Induced Osteoporosis

- Long-term heparin therapy has been reported to cause osteoporosis in both laboratory animals and humans.

Safety of Aspirin during Pregnancy

- Potential complications of aspirin during pregnancy include birth defects and bleeding in the neonate and in the mother. Both a meta-analysis and a large randomized trial that enrolled >9,000 patients reported that low-dose (60 to 150 mg/day) aspirin therapy administered during the second and third trimesters of pregnancy in women at risk for pregnancy-induced hypertension or intrauterine growth retardation (IUGR) was safe for the mother and fetus. Thus, based on current evidence, low-dose aspirin (<150 mg/day) during the second and third trimester appears to be safe. The safety of higher doses of aspirin and/or aspirin ingestion during the first trimester remains uncertain.

Subgroups Most Likely to be Harmed

Pregnant women with prosthetic heart valves

CONTRAINDICATIONS

CONTRAINDICATIONS

- Coumarins are contraindicated in pregnancy in North America due to fetal concerns.
- European experts have recommended warfarin therapy throughout pregnancy in view of the reports of bad maternal outcomes with heparin and their impression that the risk of embryopathy with coumarin derivatives has been overstated. Although this latter approach is reasonable, it is fraught with

medicolegal concerns, because the package insert states that warfarin is contraindicated during pregnancy. The guideline developers believe that warfarin should be avoided between 6 weeks and 12 weeks of gestation (to avoid embryopathy) and close to term (to avoid delivery of an anticoagulated fetus). Although the risks associated with warfarin during the remainder of pregnancy have been considered smaller, the recent association with neurodevelopment problems with mid-pregnancy exposure must also be considered.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Interpreting the Recommendations

Clinicians, third-party payers, institutional review committees, or the courts should not construe these guidelines in any way as absolute dictates. In general, anything other than a Grade 1A recommendation indicates that the article authors acknowledge that other interpretations of the evidence, and other clinical policies, may be reasonable and appropriate. Even Grade 1A recommendations will not apply to all circumstances and all patients. For instance, the guideline developers have been conservative in their considerations of cost and have seldom downgraded recommendations from Grade 1 to Grade 2 on the basis of expense. As a result, in jurisdictions in which resource constraints are severe, alternative allocations may serve the health of the public far better than some of the interventions that are designated as Grade 1A. This will likely be true for all less industrialized countries and, with the increasing promotion of expensive drugs with marginal benefits, may be increasingly true for wealthier nations.

Similarly, following Grade 1A recommendations will at times not serve the best interests of patients with atypical values or preferences or of those whose risks differ markedly from those of the usual patient. For instance, consider patients who find anticoagulant therapy extremely aversive, either because it interferes with their lifestyle (e.g., prevents participation in contact sports) or because of the need for monitoring. Clinicians may reasonably conclude that following some Grade 1A recommendations for anticoagulation therapy for either group of patients will be a mistake. The same may be true for patients with particular comorbidities (e.g., a recent gastrointestinal bleed or a balance disorder with repeated falls) or other special circumstances (e.g., very advanced age) that put them at unusual risk.

The guideline developers trust that these observations convey their acknowledgment that no recommendations or clinical practice guidelines can take into account the often compelling and unique features of individual clinical circumstances. No clinician, and no body charged with evaluating a clinician's actions, should attempt to apply our recommendations in a rote or blanket fashion.

Limitations of Guideline Development Methods

The limitations of these guidelines include the possibility that some authors followed this methodology more closely than others, although the development process was centralized and supervised by the editors. Second, it is possible that the guideline developers missed relevant studies despite the comprehensive searching process. Third, the guideline developers did not centralize the methodological evaluation of all studies to facilitate uniformity in the validity assessments of the research incorporated into these guidelines. Fourth, if high-quality meta-analyses were unavailable, the guideline developers did not statistically pool primary study results using meta-analysis. Finally, sparse data on patient preferences and values, resources, and other costs represent additional limitations that are inherent to most guideline development methods.

Pregnant Patients with Mechanical Heart Valves

There are still insufficient grounds to make definitive recommendations about optimal antithrombotic therapy in pregnant patients with mechanical heart valves because properly designed studies have not been performed. Substantial concern remains about the fetal safety of warfarin, the efficacy of subcutaneous (SC) heparin and of low-molecular-weight heparin (LMWH) in preventing thromboembolic complications, and the risks of maternal bleed with various regimens.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Guideline Implementation Strategies

A full review of implementation strategies for practice guidelines is provided in the companion document titled "Antithrombotic and Antithrombolytic Therapy: From Evidence to Application." The review suggests that there are few implementation strategies that are of unequivocal, consistent benefit, and that are clearly and consistently worth resource investment. The following is a summary of the recommendations (see "Major Recommendations" for a definition of the recommendation grades).

To encourage uptake of guidelines, the guideline developers recommend that appreciable resources be devoted to distribution of educational material (Grade 2B).

They also suggest that:

- Few resources be devoted to educational meetings (Grade 2B)
- Few resources be devoted to educational outreach visits (Grade 2A)
- Appreciable resources be devoted to computer reminders (Grade 2A)
- Appreciable resources be devoted to patient-mediated interventions to encourage uptake of the guidelines (Grade 2B)
- Few resources be devoted to audit and feedback (Grade 2B)

IMPLEMENTATION TOOLS

Patient Resources
Personal Digital Assistant (PDA) Downloads
Quick Reference Guides/Physician Guides
Resources
Slide Presentation
Tool Kits

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)

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. [119 references] PubMed

ADAPTATION

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

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GUIDELINE DEVELOPER(S)

American College of Chest Physicians - Medical Specialty Society

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American College of Chest Physicians Consensus Panel on Antithrombotic and Thrombolytic Therapy

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Bates has no conflicts of interest to disclose.

Dr. Greer has received honoraria for his participation on advisory boards and/or as a speaker at educational events from Aventis.

Dr. Hirsh has received research funding from AstraZeneca and has received honararia for his participation on advisory boards and/or as a speaker at educational events from AstraZeneca, Aventis Pharma, Sanofi-Synthelabo-Organon, Bristol-Myers Squibb, GlaxoSmithKline and Asahi.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Ginsberg JS, Greer I, Hirsh J. Use of antithrombotic agents during pregnancy. Chest 2001 Jan;119(1 Suppl):122S-131S.

GUIDELINE AVAILABILITY

Electronic copies: Available from 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:

- The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Evidence-based guidelines. Northbrook, IL: ACCP, 2004 Sep.
- Methodology for guideline development for the Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.
- Applying the grades of recommendation for antithrombotic and thrombolytic therapy: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.
- Hemorrhagic complications of anticoagulant treatment: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.
- Antithrombotic and thrombolytic therapy: from evidence to application: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.
- Platelet-active drugs: the relationships among dose, effectiveness, and side effects: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.

Electronic copies: Available from the Chest - The Cardiopulmonary and Critical Care Journal Web site.

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

The following is also available:

- Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-based guidelines; quick reference guide. Northbrook, IL: ACCP, 2004 Sep. Personal Digital Assistant (PDA) download available at ACCP Web site.

Additional implementation tools are also available:

- Clinical resource: antithrombotic and thrombolytic therapy. Northbrook, IL. ACCP, 2004. Ordering information: Available from the ACCP Web site.

PATIENT RESOURCES

The following is available:

- A patient's guide to antithrombotic and thrombolytic therapy. In: Clinical resource: antithrombotic and thrombolytic therapy. Northbrook (IL): American College of Chest Physicians (ACCP). 2004.

Ordering information is available from the ACCP Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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.

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