# Complete Summary

## GUIDELINE TITLE

Antithrombotic therapy in peripheral arterial occlusive disease. In: Sixth ACCP Consensus Conference on Antithrombotic Therapy.

## BIBLIOGRAPHIC SOURCE(S)

Jackson MR, Clagett GP. Antithrombotic therapy in peripheral arterial occlusive disease. Chest 2001 Jan;119(1 Suppl):283S-299S. [207 references]

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## SCOPE

### DISEASE/CONDITION(S)

Peripheral arterial occlusive disease, including:

- Chronic extremity arterial insufficiency
- Acute extremity arterial insufficiency

### GUIDELINE CATEGORY

Treatment

### CLINICAL SPECIALTY

Cardiology
Emergency Medicine
Family Practice
Internal Medicine
Surgery

### INTENDED USERS

Physicians

## GUIDELINE OBJECTIVE(S)

To provide evidence-based recommendations on the use of antithrombotic therapy in patients with peripheral arterial occlusive disease

## TARGET POPULATION

- Patients with acute or chronic peripheral arterial occlusive disease
- Patients requiring peripheral vascular reconstructive surgery
- Patients requiring carotid endarterectomy

## INTERVENTIONS AND PRACTICES CONSIDERED

Antithrombotic pharmacologic treatment in chronic extremity arterial insufficiency:

1. Aspirin therapy alone
2. Aspirin therapy in combination with dipyridamole
3. Clopidogrel
4. Pentoxifylline
5. Cilostazol therapy

   Note: Other agents were considered for the treatment of intermittent claudication, but not recommended, including: ticlopidine, ketanserin, suloctidil, nifedipine, fish oil supplementation, naftidrofuryl, ethylenediaminetetraacetic acid chelation therapy, and L-carnitine.

Antithrombotic pharmacologic treatment in acute extremity arterial insufficiency:

1. Heparin therapy
2. Intra-arterial thrombolytic therapy

Antithrombotic pharmacologic treatment in peripheral vascular reconstructive surgery:

1. Aspirin therapy
2. Aspirin therapy in combination with dipyridamole
3. Clopidogrel

   Note: Other agents were considered, but not recommended, including ticlopidine and dextran.

Anticoagulation Treatment:

1. Warfarin therapy
2. Warfarin therapy in combination with aspirin therapy
3. Heparin therapy (regional or systemic); heparin reversal, as needed, by protamine sulfate

Antithrombotic pharmacologic treatment in carotid endarterectomy:

1. Aspirin therapy

MAJOR OUTCOMES CONSIDERED

Efficacy and safety of treatment as evidenced by the following:

- Rates of vascular mortality
- Rates of surgical intervention required for treatment
- Rates of morbidity related to complications of peripheral vascular disease, such as nonfatal stroke, myocardial infarction, and limb amputation
- Patency of vein grafts following peripheral vascular reconstructive surgery

## 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

The participants reviewed information from an exhaustive review of the literature.

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) (see "Rating Scheme for the Strength of the Recommendations") and the methodologic quality of the underlying evidence (A, B, C+, or C).

Grades of evidence for antithrombotic agents:

1A
Methodological strength of supporting evidence: randomized controlled trials without important limitations

1B
Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws*)

1C+
Methodological strength of supporting evidence: no randomized controlled trials, but randomized controlled trial results can be unequivocally extrapolated; or, overwhelming evidence from observational studies

1C
Methodological strength of supporting evidence: observation studies

2A
Methodological strength of supporting evidence: randomized controlled trials without important limitations

2B
Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws*)

2C
Methodological strength of supporting evidence: observational studies

* Such situations include randomized controlled trials with lack of blinding, and subjective outcomes, in which the risk of bias in measurement of outcomes is high; and randomized controlled trials with large loss to follow-up.

## METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

## 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 two factors: the trade-off between benefits and risks, and the strength of the methodology that leads to estimates of the treatment effect. The rating scheme used for this guideline captures these factors. The guideline developers grade the trade-off between benefits and risks in two categories: (1) the trade-off is clear enough that most patients, despite differences in values, would make the same choice; and (2) the trade-off is less clear, and each patient's values will likely lead to different choices.

When randomized trials provide precise estimates suggesting large treatment effects, and 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 uncertain, 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/consistency and the balance of positive and negative impacts of treatment on the strength of recommendations. In situations when 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 are precise estimates of both benefit and harm, and the balance between the two clearly favors recommending or not recommending the intervention for the average patient with compatible values and preferences. Table 2 of the original guideline document summarizes how 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 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 venous thrombosis); if the magnitude of risk reduction in the overall group is small; if the risk is low in a particular subgroup of patients; if the estimate of the treatment effect, reflected in a wide confidence interval (CI) around the effect, is imprecise; if there is substantial potential harm associated with therapy; or if 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. If they understand the benefits and risks, virtually all patients will take aspirin after myocardial infarction or will comply with prophylaxis to reduce thromboembolism after hip replacement. Thus, one way of thinking about a grade 1 recommendation is that variability in patient values or individual physician 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 will 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.

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) and the methodologic quality of the underlying evidence (A, B, C+, or C) (see "Rating Scheme for the Strength of the Evidence").

<u>Grades of recommendation for antithrombotic agents</u>:

1A
Clarity of risk/benefit: risk/benefit clear
Implications: strong recommendation; can apply to most circumstances, without reservation

1B
Clarity of risk/benefit: risk/benefit clear
Implications: strong recommendation; likely to apply to most patients

1C+
Clarity of risk/benefit: risk/benefit clear
Implications: strong recommendation; can apply to most patients in most circumstances

1C
Clarity of risk/benefit: risk/benefit clear
Implications: intermediate-strength recommendation; may change when stronger evidence available

2A
Clarity of risk/benefit: risk/benefit unclear
Implications: intermediate strength recommendation; best action may differ, depending on circumstances or patients' societal values

2B
Clarity of risk/benefit: risk/benefit unclear
Implications: weak recommendation; alternative approaches likely to be better for some patients under some circumstances

2C
Clarity of risk/benefit: risk/benefit unclear
Implications: very weak recommendation; other alternatives may be equally reasonable

## COST ANALYSIS

While the American College of Chest Physicians conference participants considered cost in deciding on the strength of recommendations, the paucity of rigorous cost-effective analyses and the wide variability of costs across jurisdictions led the guideline developers to take a conservative approach to cost issues. That is, cost considerations influenced the recommendations and the grades of those recommendations only when the gradient between alternatives was very large.

## METHOD OF GUIDELINE VALIDATION

Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The initial guidelines were prepared by the chapter committee (the primary authors) and then reviewed separately by the Committee Co-Chairs and

methodology experts and finally by the entire group of Consensus Guideline participants.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

Excerpted by the National Guideline Clearinghouse (NGC):

The grading scheme is defined at the end of the Major Recommendations.

Preamble: For patients with clinical evidence of cerebrovascular disease or coronary artery disease, the recommendation for aspirin use is grade 1A. The following recommendations refer to patients who do not have evidence of cerebrovascular disease or coronary artery disease.

#### Chronic Extremity Arterial Insufficiency

1. Aspirin alone or in combination with dipyridamole may modify the natural history of intermittent claudication from arteriosclerosis. In addition, because these patients are at high risk of future cardiovascular events (stroke and myocardial infarction), the guideline developers recommend treatment with life-long aspirin therapy (81 to 325 mg/day) in the absence of contraindications (grade 1C+).
2. Clopidogrel may be superior to aspirin in reducing ischemic complications in patients with peripheral vascular disease and intermittent claudication, and the guideline developers recommend that clinicians consider clopidogrel for treatment (grade 2A).
3. The guideline developers recommend that pentoxifylline should not be routinely used in patients with intermittent claudication (grade 1B).
4. For patients experiencing disabling claudication, particularly when lifestyle modification alone is ineffective and revascularization cannot be offered or is declined by the patient, the guideline developers recommend a trial of cilostazol therapy (grade 2A). Cilostazol is not recommended for routine use in all patients with intermittent claudication because of its high cost and modest clinical benefit.

#### Acute Extremity Arterial Insufficiency

1. The guideline developers recommend that patients who suffer acute arterial thrombi or emboli undergo systemic anticoagulation with heparin to prevent proximal and distal thrombotic propagation. The guideline developers recommend the use of heparin followed by oral anticoagulation to prevent recurrent embolism in patients undergoing thromboembolectomy (grade 1C).
2. The guideline developers recommend that intra-arterial thrombolytic therapy be considered in patients with short-term (<14 days) thrombotic or embolic

occlusive disease provided that there is a low risk of myonecrosis developing during the time to achieve revascularization by this method (grade 2B).

Peripheral Vascular Reconstructive Surgery

1. The guideline developers recommend that clinicians do not use antithrombotic therapy to maintain patency of vascular reconstructions involving high-flow, low-resistance arteries >6 mm in diameter in the absence of other indications for antithrombotic therapy (grade 1C).
2. However, if aspirin therapy is indicated as a result of arteriosclerotic disease, the guideline developers recommend life-long aspirin therapy in these patients to reduce long-term cardiovascular morbidity and mortality (grade 1C+).
3. The guideline developers recommend that clinicians use aspirin (81 to 325 mg/day) in patients having prosthetic, femoropopliteal bypass operations, and antiplatelet therapy should be begun preoperatively (grade 1A). The addition of dipyridamole (75 mg three times daily) to aspirin may provide additional benefit (grade 2B).
4. In patients undergoing saphenous vein femoropopliteal or distal bypass, the guideline developers recommend the use of aspirin therapy, 81 to 325 mg/day, to reduce the incidence of myocardial infarction and stroke (grade 1C+). The guideline developers recommend that clinicians administer life-long aspirin therapy in these patients (grade 1C+). In patients unable to take aspirin, the guideline developers recommend that clinicians use clopidogrel (grade 1C+).

Anticoagulation

1. The guideline developers recommend that clinicians use long-term oral anticoagulation with warfarin with or without aspirin in selected patients after infrainguinal bypass and other vascular reconstructions (grade 2B). For patients undergoing infrainguinal bypass who are at high risk of graft thrombosis, the guideline developers recommend combination treatment of warfarin and aspirin. (grade 1A).
2. The guideline developers recommend that patients undergoing major vascular reconstructive operations undergo systemic anticoagulation with heparin at the time of application of cross-clamps (grade 1A). The best route of administration (regional versus systemic) and optimal doses are unknown, and the desirability of reversing or not reversing heparin by protamine sulfate has not been established. Heparin reversal is subject to wide practice variations among surgeons.

Carotid Endarterectomy

1. The guideline developers recommend that clinicians give aspirin, 81 mg to 325 mg daily, preoperatively and continue treatment indefinitely in patients undergoing carotid endarterectomy to prevent subsequent transient ischemic attacks and stroke (grade 1A).

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) and the methodologic quality of the underlying evidence (A, B, C+, or C).

Definitions:

Grades of recommendations:

1A

Clarity of risk/benefit: risk/benefit clear
Methodological strength of supporting evidence: randomized controlled trials without important limitations
Implications: strong recommendation; can apply to most circumstances, without reservation

1B

Clarity of risk/benefit: risk/benefit clear
Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws*)
Implications: strong recommendation; likely to apply to most patients

1C+

Clarity of risk/benefit: risk/benefit clear
Methodological strength of supporting evidence: no randomized controlled trials, but randomized controlled trial results can be unequivocally extrapolated; or, overwhelming evidence from observational studies
Implications: strong recommendation; can apply to most patients in most circumstances

1C

Clarity of risk/benefit: risk/benefit clear
Methodological strength of supporting evidence: observation studies
Implications: intermediate-strength recommendation; may change when stronger evidence available

2A

Clarity of risk/benefit: risk/benefit unclear
Methodological strength of supporting evidence: randomized controlled trials without important limitations
Implications: intermediate strength recommendation; best action may differ, depending on circumstances or patients' societal values

2B

Clarity of risk/benefit: risk/benefit unclear
Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws*)
Implications: weak recommendation; alternative approaches likely to be better for some patients under some circumstances

2C

Clarity of risk/benefit: risk/benefit unclear
Methodological strength of supporting evidence: observational studies
Implications: very weak recommendation; other alternatives may be equally reasonable

* Such situations include randomized controlled trials with lack of blinding, and subjective outcomes, in which the risk of bias in measurement of outcomes is high; and randomized controlled trials 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 for each recommendation (refer to "Major Recommendations").

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Overall

Antithrombotic therapy in peripheral arterial occlusive disease may reduce the rates of vascular mortality, nonfatal myocardial infarction, stroke, and limb loss, in addition, to possibly improving bypass patency.

Specifically

In chronic peripheral arterial occlusive disease, antithrombotic therapy may have the following benefits:

- Relieve ischemic symptoms
- Alleviate disability
- Prevent progression that might lead to gangrene and limb loss
- Prevent thrombotic occlusion
- Prevent thrombotic complications after vascular reconstructions and other interventions

In acute arterial occlusion, antithrombotic therapy may have the following general benefits:

- Restore blood flow
- Preserve life and limb

In acute arterial occlusion from embolism or thrombosis, effective anticoagulant therapy may have the following benefits:

- Prevent propagation of thrombi into proximal and distal arterial branches with attendant compromise of collateral flow
- Prevent reocclusion after surgical or interventional procedures to reestablish flow
- In the case of embolism, prevent recurrence

Subgroups Most Likely to Benefit:

Subgroup analysis revealed that virtually all of the benefit associated with clopidogrel was observed in the group with symptomatic peripheral vascular disease, who as a group sustained significantly fewer myocardial infarctions and vascular-related deaths than did the aspirin-treated group.

## POTENTIAL HARMS

There are risks for adverse events from antithrombotic therapy, particularly bleeding.

# QUALIFYING STATEMENTS

## QUALIFYING STATEMENTS

### Interpreting the Recommendations

The authors of these guidelines offer recommendations that should not be construed as dictates by the readers, including clinicians, third-party payers, institutional review committees, and courts. In general, anything other than a 1A recommendation indicates that the chapter 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 1 to 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 more than some of the interventions that the developers designate grade 1A. This will likely be true for all less-industrialized countries. However, a weak recommendation (2C) that reduces resource consumption may be more strongly indicated in less-industrialized countries.

Similarly, following grade 1A recommendations will at times not serve the best interests of patients with atypical values or preferences. For instance, consider patients who find anticoagulant therapy extremely aversive, either because it interferes with their lifestyle (prevents participation in contact sports, for instance) or because of the need for monitoring. For such patients, clinicians may reasonably conclude that following some grade 1A recommendations for anticoagulation will be a mistake. The same may be true for patients with particular comorbidities (such as a recent GI bleed or a balance disorder with repeated falls) or other special circumstances (such as very advanced age).

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

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Getting Better
Living with Illness

### IOM DOMAIN

Effectiveness
Safety

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Jackson MR, Clagett GP. Antithrombotic therapy in peripheral arterial occlusive disease. Chest 2001 Jan;119(1 Suppl):283S-299S. [207 references]

### ADAPTATION

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

### DATE RELEASED

2001 Jan

### GUIDELINE DEVELOPER(S)

American College of Chest Physicians - Medical Specialty Society

### SOURCE(S) OF FUNDING

Funding was supplied by DuPont Pharmaceuticals.

### GUIDELINE COMMITTEE

American College of Chest Physicians Consensus Panel on Antithrombotic Therapy

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## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

## GUIDELINE STATUS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

## GUIDELINE AVAILABILITY

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

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 is available:

- Sixth ACCP Consensus Conference on Antithrombotic Therapy (2001): quick reference guide for clinicians. Northbrook, IL: ACCP, 2001.

Electronic copies: Available in from the American College of Chest Physicians Web site. (Downloadable files intended for use with Palm OS compatible devices are available.)

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348, or by calling 1 (800) 343-2227.

## PATIENT RESOURCES

None available

## NGC STATUS

This summary was completed by ECRI on July 30, 2001. The information was verified by the guideline developer on September 27, 2001.

## COPYRIGHT STATEMENT

This NGC summary is based on the original guideline, which may be subject to the guideline developer's copyright restrictions.

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