REVI EWS

Current Medical Therapies for Patients with Peripheral Arterial Disease: A Critical Review

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There is a paucity of trials that specifically evaluate the benefits of cardiovascular risk reduction therapies in patients with peripheral arterial disease. We therefore sought to describe the data supporting the use of therapies for lowering cardiovascular risk, preventing ischemic events, as well as managing intermittent claudication, in these patients. A search for randomized, placebo-controlled trials in peripheral arterial disease was conducted using Medline and reference lists of relevant articles. These trials served as the primary sources of data and treatment recommendations, while observational studies and case series were included as sources of commonly accepted treatment recommendations that were not fully supported by the randomized trial. Data from the primary sources support the use of antiplatelet therapy and, potentially, of angiotensin-converting enzyme inhibitors, for preventing ischemic events. In contrast, the evidence demonstrates a nonsignificant trend for treating dyslipidemia to prevent mortality and does not specifically support intensive glycemic control in persons with diabetes or estrogen use in these patients. However, observational data and data derived from trials in persons with other manifestations of cardiovascular disease may be generalized to support the importance of treating key risk factors, such as smoking, diabetes, dyslipidemia, and hypertension. Data supporting the use of estrogen to reduce cardiovascular risk are less clear. Studies do demonstrate improvement in walking ability resulting from exercise rehabilitation programs, as well as from use of cilostazol and, to a more modest degree, pentoxifylline. The consensus is to treat risk factors of peripheral arterial disease patients similarly to patients with other manifestations of atherosclerosis and to use exercise rehabilitation or cilostazol to treat the subset of patients with claudication. Am J Med. 2002;112:49–57. ©2002 by Excerpta Medica, Inc.
normal activities substantially (17) and because improvement in the absence of an intervention is rare, therapy to relieve intermittent claudication is also essential. We sought in this review to describe and evaluate the evidence for treating systemic atherosclerosis, as well as intermittent claudication, in patients with peripheral arterial disease.

SELECTION CRITERIA

We searched Medline and the reference lists of relevant articles for treatment trials that included patients with peripheral arterial disease. Disease-related terms included peripheral arterial disease, peripheral vascular disease, peripheral atherosclerosis, claudication, and intermittent claudication. Risk factor–related or drug-related terms included lipids, dyslipidemia, hyperlipidemia, hypertension, diabetes, smoking, estrogen, menopause, antiplatelet, angiotensin-converting enzyme (ACE), aspirin, ticlopidine, and clopidogrel. Terms referring to treatment for claudication included exercise therapy, exercise rehabilitation, pentoxifylline, and cilostazol.

Outcome Measures

Primary outcome measures included death from heart disease and stroke. Cardiovascular morbidity (including nonfatal myocardial infarction and stroke) was another primary outcome. The primary endpoint with relevance to claudication therapy was maximal walking distance on the treadmill. We also considered measures of community-based walking ability and health-related quality of life in these patients.

Types of Studies

Levels of evidence 1 or 2 were essential to warrant a data-based treatment recommendation. Level 1 data were obtained from large randomized trials with clearcut results (and low risk of error) (18). Level 2 data were obtained from small randomized trials with uncertain results (and moderate to high risk of error). Data from a level 3 (nonrandomized, contemporaneous controls) or lower study were included to provide evidence for consensus opinions only.

We found 2466 publications describing cardiovascular risk reduction, antiplatelet therapy, and ACE inhibitor therapy in peripheral arterial disease. Of these, 272 randomized controlled trials were identified and evaluated. Eight of these trials met the criteria for inclusion (levels of evidence 1 or 2 and direct evaluation of therapies in the peripheral arterial disease population), including one meta-analysis (19–26) (Table 2). In addition, 300 papers related to the medical treatment of claudication were found, of which 67 were randomized controlled trials, but only 26 met the criteria for inclusion. Because each of these trials had relatively few patients, we report the results of recent meta-analyses that included these trials (27–30) (Table 3).

LOWERING THE RISK OF ISCHEMIC EVENTS

Antiplatelet Therapy

The Antiplatelet Trialists’ Collaboration evaluated the efficacy of prolonged (1 month or longer) antiplatelet ther-

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Table 1. Risks of Death from All Causes and from Cardiovascular Causes in Patients with Peripheral Arterial Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>Sex</th>
<th>No. of Subjects</th>
<th>Controls</th>
<th>Patients with Peripheral Arterial Disease</th>
<th>RR (95% CI)</th>
<th>Patients Without Cardiovascular Disease at Entry</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent per year</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>2.0</td>
<td>6.1 (without symptoms)</td>
<td></td>
<td>2.4 (1.6–3.7)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>4.5</td>
<td>7.8</td>
<td></td>
<td>1.5 (1.2–1.9)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>1.3</td>
<td>3.8</td>
<td></td>
<td>2.7 (1.6–4.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>1.0 (without symptoms)</td>
<td></td>
<td>2.8 (1.4–5.5)</td>
<td></td>
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</tr>
</tbody>
</table>

* RR denotes relative risk, and CI confidence interval. Dashes indicate that no data were presented.

Table 2. Effects of Treatments on Systemic Cardiovascular Morbidity and Mortality in Peripheral Arterial Disease

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Trial (Reference)</th>
<th>Primary Endpoint</th>
<th>Controls</th>
<th>Treated Patients</th>
<th>Relative Risk or Odds Ratio, with 95% Confidence Interval</th>
<th>Absolute Risk Reduction (%)</th>
<th>Number Needed to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiplatelet therapy</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin*</td>
<td>ATC (patients with claudication) (19)</td>
<td>Composite endpoint of death, nonfatal MI, and stroke</td>
<td>195/1649 (11.8)</td>
<td>160/1646 (9.7)</td>
<td>OR = 0.78 (0.50–1.10)</td>
<td>2.1</td>
<td>48</td>
</tr>
<tr>
<td>Ticlopidine§</td>
<td>STIMS (20)</td>
<td>Composite endpoint of fatal or nonfatal MI, or stroke, and TIA</td>
<td>99/341 (29.0)</td>
<td>89/346 (25.7)</td>
<td>RR = 0.66 (0.45–0.96)</td>
<td>3.3</td>
<td>30</td>
</tr>
<tr>
<td>Ticlopidine§</td>
<td>EMATAP (21)</td>
<td>Cluster of outcome events: sudden death, fatal or nonfatal MI or stroke, and cardiovascular intervention</td>
<td>20/311 (6.4)</td>
<td>5/304 (1.6)</td>
<td>RR = 0.26 (0.10–0.67)</td>
<td>4.8</td>
<td>21</td>
</tr>
<tr>
<td>Clopidogrel§</td>
<td>CAPRIE[II] (peripheral arterial disease subgroup only) (22)</td>
<td>Composite endpoint of MI, stroke, and vascular death</td>
<td>277/3229 (8.6)</td>
<td>215/3223 (6.7)</td>
<td>RR = 0.24 (0.09–0.36)</td>
<td>1.9</td>
<td>53</td>
</tr>
<tr>
<td><strong>ACE inhibitor therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramipril§</td>
<td>HOPE (23)</td>
<td>Composite endpoint of MI, stroke, and cardiovascular death</td>
<td>459/2085 (22)</td>
<td>316/1966 (16)</td>
<td>RR = 0.73 (0.61–0.86)</td>
<td>6.0</td>
<td>17</td>
</tr>
<tr>
<td><strong>Lipid-lowering therapy</strong></td>
<td>(25)</td>
<td>Mortality</td>
<td>8/268 (2.9)</td>
<td>2/269 (0.7)</td>
<td>OR = 0.21 (0.03–1.17)</td>
<td>2.2</td>
<td>45</td>
</tr>
</tbody>
</table>

* Similar nonsignificant results observed for peripheral angioplasty or peripheral grafts.
† Meta-analysis.
‡ Data estimated from information in article.
§ Positive trial in peripheral arterial disease.
∥ Aspirin used as a control.

ATC = Antiplatelet Trialists’ Collaboration; CAPRIE = Clopidogrel versus Aspirin in Patients At Risk of Ischemic Events; EMATAP = Estudio Multicéntrico Argentino de la Ticlopidine en las Arteriopatías Periféricas; HOPE = Heart Outcomes Prevention Evaluation; MI = myocardial infarction; OR = odds ratio; RR = relative risk; STIMS = Swedish Ticlopidine Multicentre Study; TIA = transient ischemic attack.
apy (in most cases, aspirin) in preventing vascular events, including nonfatal myocardial infarction, stroke, and vascular death (19). This meta-analysis combined data from 145 randomized studies involving more than 100,000 patients, including approximately 70,000 high-risk patients with evidence of cardiovascular disease, such as myocardial infarction, stroke, or transient ischemic attack.

The analysis showed an overall 27% reduction in odds ratio in the composite primary endpoint for high-risk patients compared with controls, a finding that was confirmed in all groups listed above. However, when a subset of 3295 claudicating patients was analyzed, the risk reduction in these endpoints after a mean of 27 months of follow-up was not statistically significant (19) (Table 2).

These results do not completely support the use of aspirin to prevent cardiovascular events and death from stroke and myocardial infarction in patients with peripheral arterial disease, although the risk reduction is similar in peripheral arterial disease and cardiovascular disease. Aspirin has not been approved by the Food and Drug Administration (FDA) for the treatment of patients with peripheral arterial disease, possibly because of the nonsignificant trend observed in the claudicating subpopulation (31). However, it has been recommended by other groups, such as the American College of Chest Physicians (32).

Ticlopidine has been reported to reduce cardiovascular and thrombotic events significantly in patients with intermittent claudication. In the Swedish Ticlopidine Multicentre Study (20), which compared ticlopidine (250 mg twice daily) with placebo in the prevention of fatal and nonfatal myocardial infarction, stroke, and transient ischemic attack in 687 patients, a significant reduction in coronary and cerebrovascular events and total mortality was observed in an “on-treatment” analysis (Table 2). Similarly, in the Estudio Multicéntrico Argentino de la Ticalopidina en las Arteriopatias Periféricas trial (21), ticlopidine (250 mg twice daily) significantly reduced the number of thrombotic events (sudden death, fatal or nonfatal myocardial infarction, stroke, and cardiovascular interventions) and vascular surgery in 615 patients, as compared with placebo (Table 2).

The Clopidogrel versus Aspirin in Patients At Risk of Ischemic Events (CAPRIE) study was the first to evaluate aspirin versus clopidogrel in patients with recent stroke, myocardial infarction, or stable peripheral artery disease (N = 19,185) (22). Study results showed that clopidogrel 75 mg, administered once daily, had a relative risk reduction of 8.7% [95% confidence interval (CI), 0.3% to 16.5%; P = 0.04] for myocardial infarction, ischemic stroke, and vascular death, compared with aspirin 325 mg, administered once daily. Similarly, clopidogrel was associated with a risk reduction of about 24% compared with aspirin in a subgroup analysis of over 6000 patients in the study (22) (Table 2). Furthermore, clopidogrel was shown to be as safe as medium-dose aspirin. Based on these results, clopidogrel was approved by the FDA for the reduction of ischemic events in patients with peripheral arterial disease.

Aspirin, ticlopidine, and clopidogrel are associated with potential adverse effects. Aspirin causes upper gastrointestinal disturbances in some patients, although it is generally well tolerated. In the CAPRIE study, 18% of patients who received aspirin experienced this adverse effect compared with 15% of those who were treated with

### Table 3. Effects of Treatments for Improving Walking Ability in Patients with Claudication*

<table>
<thead>
<tr>
<th>Claudication Treatments (Reference)</th>
<th>Number of Trials</th>
<th>No. of Patients Control</th>
<th>No. of Patients Treated</th>
<th>Change in Maximal Walking Time or Maximal Walking Distance</th>
<th>Difference in Maximal Walking Time or Maximal Walking Distance, Change between Treated and Control Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise rehabilitation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leng et al. (27)</td>
<td>6</td>
<td>56 64</td>
<td></td>
<td>5.8 min 12.3 min</td>
<td>6.5 min (112)</td>
</tr>
<tr>
<td>Girolami et al. (28)</td>
<td>5</td>
<td>55 58</td>
<td></td>
<td>338.2 m 599.6 m</td>
<td>261.4 m (77)</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girolami et al. (28)</td>
<td>7</td>
<td>279 288</td>
<td></td>
<td>264.4 m 370.6 m</td>
<td>106.2 m (40)</td>
</tr>
<tr>
<td>Hood et al. (29)</td>
<td>8</td>
<td>258 253</td>
<td></td>
<td>311.9 m 456.0 m</td>
<td>144.1 m (46)</td>
</tr>
<tr>
<td>Cilostazol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regensteiner and Hiatt (30)</td>
<td>6</td>
<td>730 740</td>
<td></td>
<td>50.0 m 100.0 m</td>
<td>50.0 m (100)</td>
</tr>
<tr>
<td>Graded</td>
<td></td>
<td></td>
<td></td>
<td>27.0 m 76.0 m</td>
<td>49.0 m (181)</td>
</tr>
</tbody>
</table>

Graded = treadmill protocol that increases in grade over time; constant load = treadmill protocol that maintains the same work load throughout the test.

* All trials included are positive meta-analyses in peripheral arterial disease, and include levels of evidence 1 or 2, or both. Pharmacologic treatments are included only if approved for use in the United States.
clopidogrel (*P < 0.05*) (22). Ticlopidine increases the risk of rash and diarrhea by more than twofold as compared with aspirin, whereas clopidogrel is associated with a one-third increase (33).

Patients taking ticlopidine also require extensive hematologic monitoring because of the risk of neutropenia (seen in 2.3% of patients) and thrombotic thrombocytopenia purpura (seen in 1 in 2000 to 4000 patients) (33,34). Although it has been observed that patients taking clopidogrel did not have the same risk of thrombotic thrombocytopenia purpura as those taking ticlopidine (about 1 in 1600) (34), Bennett et al. (35) identified 11 cases during a 2-year period of active surveillance, and subsequently reported nine other cases. To date, over 3 million people have received clopidogrel, and in all but one case, thrombotic thrombocytopenia purpura developed after a treatment of 2 weeks’ duration or less.

**ACE Inhibitors**

Results of the Heart Outcomes Prevention Evaluation study showed that ramipril (23), an ACE inhibitor, significantly reduced the rate of cardiovascular death, myocardial infarction, and stroke in a broad range of patients at high risk of cardiovascular death (relative risk [RR] = 0.78; 95% CI, 0.70 to 0.86; *P < 0.001*). Of the 9297 patients in this study, 4051 had peripheral arterial disease, defined by a history of peripheral arterial disease, claudication, or an ankle-brachial index of less than 0.90. These patients had a similar reduction in the primary endpoint when compared with those without peripheral arterial disease (Table 2), thus demonstrating that ramipril was effective in lowering the risk of fatal and nonfatal ischemic events among patients with peripheral arterial disease. Results of the study, however, could not be explained by the effects of ramipril on lowering blood pressure, because the majority of patients did not have hypertension at study baseline and the mean decrease in blood pressure was about 2 mm Hg.

Similar to the CAPRIE trial, conclusions about the efficacy of ramipril were drawn from a subgroup analysis, and the role of ACE inhibitors has not been studied in prospective, randomized trials in the peripheral arterial population alone. Such trials would be beneficial before making definite treatment recommendations.

**TREATMENT OF CARDIOVASCULAR RISK FACTORS**

The most common cardiovascular risk factors for peripheral arterial disease include smoking, diabetes, hypertension, dyslipidemia, and abnormalities of homocysteine metabolism, as well as lower estrogen levels after menopause. There is insufficient level 1 or 2 evidence to support the relation between treatment of these risk factors and improved cardiovascular outcomes in persons with peripheral arterial disease. Nonetheless, expert consensus publications strongly recommend treating these risk factors based on extrapolation of results from trials of patients with other forms of cardiovascular disease.

**Cigarette Smoking**

Tobacco use is perhaps the single most important risk factor. In patients with peripheral arterial disease, smoking is associated with increased progression of atherosclerosis as well as increased risk of amputation (36). Results from a longitudinal study of 5209 men and women in Framingham, Massachusetts, suggested that smoking correlated more closely with the development of intermittent claudication than did any other risk factor (37). To date, most data on the importance of smoking cessation for improving cardiovascular endpoints are derived from the general population of smokers or from patients with cardiovascular disease. So although level 1 or 2 evidence is lacking, consensus clearly supports smoking cessation in these patients (38,39).

**Diabetes**

Patients with diabetes have a two- to fourfold increase in the risk of developing intermittent claudication compared with nondiabetic patients (40–42). In the Framingham Study, which had a 16-year follow-up, the age-adjusted risk of developing intermittent claudication in persons with diabetes compared with controls was increased by fivefold in men and threefold in women (40–42). Cardiovascular disease causes approximately 65% of deaths in persons with type 2 diabetes (43).

In the United Kingdom Prospective Diabetes Study, patients with type 2 diabetes were randomly assigned to intensive or conventional glycemic treatment with sulfonylureas and insulin (24). Intensive treatment reduced diabetes-related endpoints, diabetes-related deaths, and myocardial infarction. It was not associated with a significant reduction in the risk of amputation resulting from peripheral arterial disease (RR = 0.51; 99% CI, 0.01 to 19.64). In fact, the major reduction in adverse endpoints was the result of decreased microvascular rather than macrovascular endpoints. Although it is likely that many patients with peripheral arterial disease were included in this study, the prevalence of the disease was not defined. Therefore, conclusions from this study may not directly relate to a predefined study in patients with diabetes and peripheral arterial disease.

Current guidelines for treating patients with diabetes recommend the target hemoglobin (Hb) A1C level to be less than 7% (44).

**Hypertension**

Hypertension is associated with the development of atherosclerosis, particularly in the coronary and cerebral circulations, as well as with a two- to threefold increased risk of claudication (45–47). However, the effects of treating
hypertension on the natural history of atherosclerotic disease have not been evaluated in patients with peripheral arterial disease specifically. In the absence of such data, consensus still supports the management of hypertension in these patients. For example, guidelines such as the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure include peripheral arterial disease as a marker of cardiovascular disease (48) and call for maintaining a blood pressure level less than 130/85 mm Hg in these patients.

**Dyslipidemia**

It has not been shown that treating dyslipidemia decreases cardiovascular morbidity and mortality in patients with peripheral arterial disease. In a meta-analysis of randomized trials in 698 patients with peripheral arterial disease treated by a variety of therapies, Leng et al. (25) reported a nonsignificant reduction in mortality (Table 2) and no change in nonfatal cardiovascular events. In contrast to the lack of effect on ischemic events, the study concluded that the severity of claudication was reduced by lipid-lowering treatment. Similarly, in the Scandinavian Simvastatin Survival Study, the reduction in cholesterol level by simvastatin was associated with a 38% reduction in the risk of new or worsening symptoms of intermittent claudication in a subgroup analysis (49). Consensus supports the treatment of dyslipidemia according to the National Cholesterol Education Program (Third Report) guidelines, which recommend maintaining a low-density lipoprotein (LDL) cholesterol level less than 100 mg/dL (50).

**Homocysteine Levels**

An elevated homocysteine level is emerging as a prevalent and strong risk factor for atherosclerotic vascular disease in the peripheral, coronary, and cerebral vessels (51–53). In addition, the rate of progression of intermittent claudication has also been found to be significantly associated with plasma homocysteine levels (53). There are currently, however, no studies examining whether treating this problem reduces ischemic events, so recommendations cannot be made.

**Estrogen**

Findings of increased risk of coronary artery disease after menopause or oophorectomy have suggested that estrogen has a protective effect against cardiovascular disease. Some case-control studies have also proposed that supplemental estrogen lowers this risk (54–56). Conversely, data from the Heart and Estrogen/Progestin Replacement Study do not support these findings (26). In this study, 2763 postmenopausal women with coronary heart disease were randomly assigned to placebo or estrogen replacement therapy. The primary outcome was nonfatal myocardial infarction or death from coronary heart disease, and the secondary outcomes included peripheral arterial disease (defined as acute obstruction, dissection, or rupture of the peripheral arteries). There were no significant differences between placebo and estrogen replacement groups in the primary and secondary outcomes. Additionally, more women on hormone replacement therapy developed deep vein thrombosis and pulmonary emboli (26). Thus, estrogen supplementation was not shown to be beneficial in preventing cardiovascular endpoints.

### MEDICAL TREATMENT OF CLAUDICATION

Medical therapy for claudication includes exercise rehabilitation as well as two drugs approved by the FDA. There are other therapeutic agents in development for this indication, but they await further development.

**Exercise Rehabilitation**

A walking exercise program has been recommended since 1966, when the first randomized, controlled trial of exercise training in persons with peripheral arterial disease demonstrated a marked improvement in treadmill walking ability (57). The primary outcome in this and subsequent studies has been maximal walking time (or distance) and pain-free walking time (or distance) on the treadmill, using either a graded or constant-load treadmill protocol.

Many trials have since demonstrated the efficacy of walking rehabilitation compared with placebo, reporting an increase in pain-free and maximal treadmill walking duration (15,16,57–64). The consistency of these findings and the strength of the data suggest that exercise training programs have a clinically important impact on functional capacity in patients with peripheral arterial disease despite the small size of each trial. Table 3 presents the results of two recent meta-analyses showing the benefits of exercise rehabilitation. A significant improvement in community-based walking ability and health-related quality of life has also been reported (17). Exercise therapy has minimal associated morbidity and is effective in almost all participants. In contrast to other claudication treatments, it is likely to improve the cardiovascular risk factor profile (65).

**Pharmacologic Therapies**

**Pentoxifylline.** Pentoxifylline, a hemorheologic agent, was approved in 1984 for treating claudication. In an early trial (66), pentoxifylline increased maximal walking distance by 12% compared with placebo, but the differences were not statistically significant when baseline walking ability was compared with walking distance at the end of treatment. Similarly, a nonsignificant 21% increase in treadmill walking distance over placebo was re-
ported in a later study (67). Hood et al. (29) and Girolami et al. (28) concluded in their meta-analyses that there was a significant improvement in the absolute claudication distance, albeit of small magnitude (Table 3). The effects of pentoxifylline on quality of life, however, were not evaluated.

Cilostazol. Cilostazol, a phosphodiesterase inhibitor, was the second drug to gain FDA approval for treating intermittent claudication. With significant antiplatelet and vasodilatory capacity as well as vascular antiproliferative properties (68–70), cilostazol has been shown to be effective in increasing maximal walking time (30,71–75) (Table 3), in addition to improving functional status and quality of life. Importantly, use of this drug is contraindicated if any degree of heart failure is present.

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TREATING PERIPHERAL ARTERIAL DISEASE: EVIDENCE VERSUS CONSENSUS

Evidence available for cardiovascular risk reduction therapies in patients with peripheral arterial disease supports the use of antiplatelet drugs, in particular clopidogrel. Similarly, data also suggest that ACE inhibitor therapy is likely to be effective. However, these conclusions were derived from subgroup analyses of trials in patients with a broad range of atherosclerotic disease manifestations. Consensus opinion based on evidence from trials in patients with other manifestations of atherosclerosis, but not level 1 or 2 evidence, supports an aggressive approach to risk factor modification, including lowering LDL cholesterol levels (less than 100 mg/dL), smoking cessation, lowering blood pressure levels (less than 130/85 mm Hg), and managing diabetes (HbA1C less than 7%). In contrast to the case with risk factor treatment in peripheral arterial disease, therapies for claudication have been more thoroughly investigated, and this is an area of continuing research.

Despite the lack of data on cardiovascular risk in patients with peripheral arterial disease, these patients should not be treated less intensively. Until additional prospective, randomized trials are undertaken to evaluate the benefits of treating the risk factors in this patient population, patients can be treated with strategies based on current recommendations for other manifestations of atherosclerosis.

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25. Leng GC, Price JF, Jepson RG. Lipid-lowering for lower limb atherosclerosis (Cochrane Review). *Cochrane Database Syst Rev.* 2000;2:CD000123 ELSEVIER: This publication is formatted as such; no page numbers.


