

Antihypertensive treatment in patients with peripheral vascular disease

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- **BACKGROUND** Some specific treatment goals are indicated for patients with hypertension complicated by peripheral vascular disease.
- **OBJECTIVE** To review the available information about treating hypertension in patients with atherosclerosis or aneurysms of the aorta or peripheral arteries.
- **SUMMARY** Patients with peripheral vascular disease and hypertension should be treated according to the general guidelines for all patients with hypertension. However, specific treatment goals include improvement or stabilization of intermittent claudication and associated conditions such as coronary artery disease, hyperlipidemia, and diabetes mellitus. The ideal therapy for most of these conditions is nonpharmacologic: achievement of ideal body weight, a diet low in cholesterol, saturated fat, and salt, and a regular exercise program will improve blood pressure control, lipid values, blood glucose control, insulin sensitivity, symptoms of intermittent claudication, and long-term survival. Patients who smoke should stop. Patients with aneurysms should receive beta blockers.
- **CONCLUSIONS** Antihypertensive therapy in patients with peripheral vascular disease should be part of a general program of risk-factor reduction.

■ INDEX TERMS: HYPERTENSION; PERIPHERAL VASCULAR DISEASES
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LITTLE PUBLISHED information exists regarding the treatment of hypertension in patients with peripheral vascular disease (atherosclerosis or aneurysmal disease of the aorta or the peripheral arteries).¹ The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V) contains no specific recommendations on this topic.² The goals for treating hypertension are essentially the same for all patients: optimal therapy should effectively and safely lower blood pressure, have minimum side effects, be administered as infrequently as possible to improve compliance, and be cost-effective.³ However, there are specific goals the physician should keep in mind when treating patients who have peripheral vascular disease (Table 1).

ARTERIOSCLEROSIS OBLITERANS

Patients with atherosclerosis of the aorta and lower-extremity arteries (arteriosclerosis obliterans, ASO) usually present with intermittent claudication (discomfort, aching, tiredness, pain, cramping,

TABLE 1
GOALS AND STRATEGIES IN TREATING HYPERTENSION
IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

For all hypertensive patients
Effectively and safely lower blood pressure
Minimize side effects of antihypertensive therapy
Administer medications as infrequently as possible to improve compliance
Use cost-effective therapy
For patients with peripheral arterial disease
Improve symptoms of intermittent claudication
Avoid beta blockers?
Prescribe a regular exercise program
Use therapy that will have beneficial effects on concomitant diseases
Atherosclerotic heart disease
Calcium antagonists
Beta blockers
Angiotensin-converting enzyme inhibitors (prevent ventricular dilation after anterior myocardial infarction)
Lipid abnormalities
Use lipid-neutral antihypertensive agents
Prescribe regular exercise
Diabetes mellitus
Use antihypertensive agents that do not worsen glucose intolerance or insulin resistance

or burning in the buttocks, hip girdle, thighs, calf muscles, or arch of the foot brought on by exercise and relieved by rest). The symptoms are reproducible from one day to the next, and the level of exercise that brings on the discomfort is consistent. When the patient stops walking, the discomfort commonly resolves within 2 to 5 minutes with simply standing.

Hypertension is a major risk factor for the development of ASO.⁴ Data from the Framingham study indicate the risk of intermittent claudication is 2.4 to 3.9 times higher in men and women with high blood pressure than in normotensive individuals.⁵ The JNC V states: "Effective control of pressure and other atherogenic factors may help retard or even reverse stiffening of the arteries."² However, although treating hypertension does decrease the incidence of stroke, congestive heart failure, and coronary artery disease, it has an unknown impact on the overall course of ASO.

Direct-acting vasodilators, calcium antagonists, alpha-1 blockers, and angiotensin-converting enzyme inhibitors all effectively dilate the arterioles, but they do not dilate atherosclerotic vessels, and therefore they do not improve the symptoms of intermittent claudication.^{6,7} In addition, these drugs have no measurable effect on walking distance or calf blood flow.

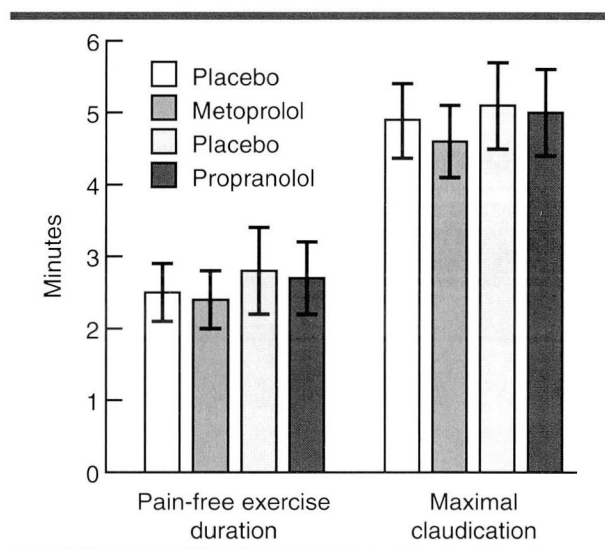


FIGURE 1. Time to onset of claudication and maximal claudication in 19 subjects receiving propranolol, metoprolol, or placebo in a crossover study. There was no significant difference in pain-free exercise duration and maximum exercise duration among the groups. Error bars indicate standard error of the mean. Data from Hiatt et al, reference 30.

Do beta blockers make intermittent claudication worse?

There is a commonly held belief that beta blockers may worsen intermittent claudication and reduce the amount of exercise that brings on discomfort in the extremity.⁸ Stimulation of beta-2 receptors in the periphery causes vasodilation in normal blood vessels. Because these agents block the vasodilatory beta receptors and leave the vasoconstrictive alpha receptors unopposed, some authors have suggested that beta blockers may cause increased vasoconstriction.⁹ However, numerous studies have demonstrated no difference in the walking distance, walking time, walking capacity, and calf blood flow in patients who receive cardioselective beta blockers, beta blockers with intrinsic sympathomimetic activity, or alpha-beta blockers compared with patients who receive non-selective beta blockers.^{7,10}

Despite the available data, some physicians continue to believe that beta blockers are contraindicated in patients who have intermittent claudication. What is the rationale for such a belief? In a carefully performed meta-analysis of the available randomized controlled trials, Radack and Deck¹⁰ concluded that there was no statistical difference in

TABLE 2
RANDOMIZED CONTROLLED TRIALS ASSESSING
THE EFFECTS OF BETA BLOCKERS ON INTERMITTENT CLAUDICATION*

Author	Reference	Year	Design	No. of subjects	Duration, weeks	Effect on exercise capacity
Reichert et al	11	1975	Crossover	7	8	No change
Clement	12	1980	Crossover	10	8	No change
Bogaert and Clement	13	1983	Crossover	10	8	No change
Lepantalo and von Knorring	14	1984	Crossover	10	8	No change
Hiatt et al	15	1985	Crossover	19	2	No change
Lepantalo	16	1985	Crossover	7	1.5	No change
Bostrom et al	17	1986	Crossover	7	4	No change
Svensen et al	18	1986	Crossover	14	8	No change
Roberts et al	7	1987	Crossover	20	4	Reduced

*Adapted from Radack and Deck, Arch Intern Med 1991; 151:1769-1776 (reference 10)

the degree of claudication between patients receiving a beta blocker and those receiving placebo. Exercise capacity was unchanged in eight of the nine studies designed to look at this outcome (Table 2).^{7,11-18} Only the study of Roberts and colleagues differed,⁷ showing that pain-free and maximum walking distances (measured on a treadmill) were decreased by atenolol, labetalol, and pindolol but not by captopril. However, the pooled results from all nine reports showed a treatment effect size for pain-free walking distance of -0.24 (95% confidence interval -0.62 to 0.14) and for maximum walking distance of -0.29 (95% confidence interval -0.70 to 0.12). Several studies used treadmill testing to measure pain-free exercise duration and maximum exercise duration, and none of them showed a difference between patients who received propranolol, metoprolol, or placebo (Figure 1).^{12,13,15} There was also no difference in peak (maximum) calf blood flow between patients who received metoprolol, propranolol, pindolol, or labetalol compared with placebo in the studies that examined this parameter.¹⁴⁻¹⁶

In an editorial accompanying this meta-analysis, Thandani and Whitsett¹⁹ stated that in spite of these pooled data, an occasional patient with asymptomatic ASO may experience the onset of intermittent claudication after treatment with beta blockers. Therefore, beta blockers may not be advisable in these individuals.

In our practice, we give beta blockers to patients with intermittent claudication if there is a compelling reason to do so (ie, for secondary prevention of myocardial infarction, to treat angina pectoris, for medical management of aortic dissection). If a pa-

tient experiences worsening exercise tolerance with beta blocker therapy and does not have an overwhelming reason to take a beta blocker, we discontinue it.

We agree with Thandani and Whitsett¹⁹ and try not to use beta blockers if critical limb ischemia is present (ischemic pain at rest, nonhealing ischemic ulceration) because these drugs may decrease cardiac output or increase unopposed alpha adrenergic receptor-mediated vasoconstriction and thus worsen the ischemia. However, this worsening has not been proven. Stopping beta blocker therapy alone will usually not improve symptoms in patients with ischemic pain at rest or with ischemic ulcerations, who often require surgery or other interventional therapy (percutaneous transluminal angioplasty, stents) to improve blood flow.

If beta blockers are to be discontinued, the dose should be tapered gradually. Psaty and colleagues²⁰ conducted a population-based case-controlled study in patients with coronary heart disease and high blood pressure. Subjects who had recently stopped using beta blockers had a transient fourfold increase in the relative risk of symptomatic coronary artery disease (relative risk 4.5; 95% confidence interval 1.1 to 18.5). In patients with known coronary artery disease, other antianginal agents such as calcium antagonists should be used if beta blockers are discontinued.

Patients with hypertension and vasospastic diseases such as Raynaud's phenomenon or pernio should generally not receive beta blockers because these medications may increase the amount of vasospasm. Under these circumstances, a calcium an-

TABLE 3
BENEFICIAL EFFECTS OF EXERCISE
IN PERIPHERAL ARTERIAL DISEASE*

Lowest blood pressure
Improves claudication symptoms
Increases pain-free walking distance
Increases maximum walking distance
Improves survival
Lowest triglycerides and raises high-density lipoprotein cholesterol
Improves glucose intolerance and insulin resistance

*From Olin, reference 1

tagonist or an alpha-adrenergic blocker would be preferred because they not only lower the blood pressure but also decrease the intensity and frequency of vasospasm.

Exercise improves symptoms

Patients with intermittent claudication and hypertension should undergo a structured exercise program, which can produce multiple beneficial effects (Table 3). On the average, 30 to 45 minutes of brisk walking 3 to 5 times per week will be beneficial.

Moderate aerobic physical activity can both prevent hypertension and lower high blood pressure,² decreasing systolic blood pressure by approximately 10 mm Hg in hypertensive patients, according to the World Hypertension League.²¹ Arrol and Beaglehole²² summarized the results of 13 controlled trials of sustained physical activity and found the average reduction in systolic and diastolic blood pressure to be 6 to 7 mm Hg—approximately the same as with single-drug therapy in some trials. The blood pressure-lowering effect of exercise was independent of weight loss. The exact mechanism by which exercise lowers blood pressure is not known, but proposed mechanisms include effects on the sympathetic nervous system, insulin sensitivity, electrolyte balance, neural and baroreflex mechanisms, and the vascular structure itself.²³

Besides lowering blood pressure, exercise has several other beneficial effects. Even moderate physical activity has been shown to decrease all-cause mortality.²⁴ Exercise improves glucose tolerance and insulin resistance,^{25,26} and it decreases the serum concentration of triglycerides by increasing their catabolism. Sustained exercise may also have an independent beneficial effect on high-density lipoprotein cholesterol.

In patients with intermittent claudication, exer-

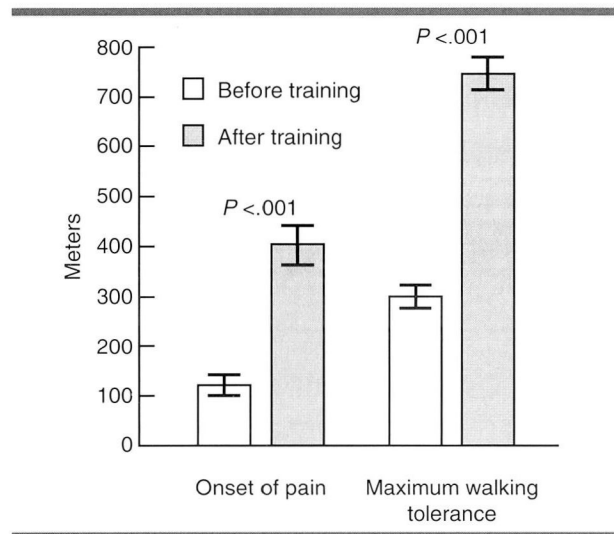


FIGURE 2. Improvement in walking tolerance after 4 to 6 months of physical training program in 129 subjects with intermittent claudication. Adapted from Ekroth et al, reference 31.

cise can increase walking tolerance. The exact mechanism for this is not known. Some have suggested a training effect, while others believe that walking increases the development of collateral blood vessels.²⁷ Some changes occur on the cellular level in patients who exercise regularly: the size and number of mitochondria increase, as does the oxidative capacity of the muscle cells involved in fatty acid oxidation. Exercise training may enhance the oxygen-carrying capacity of hemoglobin in patients with ASO and normalize the abnormal blood viscosity and flow that has been demonstrated in these patients.²⁸ Oxygen utilization in exercising muscles increases with physical training.²⁹

Hiatt and Regensteiner³⁰ summarized the data from 26 trials of exercise conditioning. The improvement in pain-free walking ranged from 44% to 290% (mean 134%), and the peak walking time increased 25% to 183% (mean 96%). These trials demonstrate that patients can walk farther, faster, and for a longer duration after they undergo a period of training. Figure 2 demonstrates the benefit of exercise on the onset of pain and the maximal walking tolerance before and after a walking program.³¹

The amount of exercise necessary to improve the symptoms of intermittent claudication is generally greater than that recommended for cardiovascular conditioning or for lowering blood pressure. Sev-

eral methods are used for exercise conditioning in patients with intermittent claudication. We generally ask patients to walk for approximately 45 minutes daily at one time. They are instructed to try to walk fast enough to bring on the intermittent claudication at approximately one half block. When claudication begins, they continue walking for a short time and then stop, stand still, and wait until the pain or discomfort disappears. They then resume walking until claudication returns, and this pattern is repeated for a total of 45 minutes. Patients will usually note an improvement in walking distance in a very short period of time. When this occurs, they are instructed to increase the pace of walking to try to bring on the claudication at approximately one half block. The beneficial effects of walking disappear quickly if the patient stops walking on a regular basis.

Although stopping cigarette smoking may not have a direct benefit on lowering blood pressure, it may be the single most important factor that determines whether ASO progresses. Therefore, it is important to encourage patients to stop smoking.

EFFECTS OF ANTIHYPERTENSIVE DRUG THERAPY ON ASSOCIATED CONDITIONS

Coronary artery disease

The Framingham study and others have clearly shown that hypertension is a predisposing factor in the development of ASO.⁵ The Framingham study also demonstrated that the risk of coronary artery disease in men with peripheral atherosclerosis is 2.4 times greater than in age- and sex-matched controls; in women it is 1.4 times greater.

A recent study by Vogt and colleagues³² has shown that the ankle/arm blood pressure index measured at rest is an important predictor of cardiovascular mortality (Table 4). In this study, approximately one fourth of women with an ankle/arm index of less than 0.9 died within 4 years. Several other studies have also shown that long-term survival in patients with intermittent claudication is poor: the mortality rate is approximately 25% at 5 years, 50% at 10 years, and 75% at 15 years.³³ Most of these deaths are due to cardiovascular disease. Criqui and colleagues³⁴ have shown that the 10-year mortality rate in patients with peripheral arterial disease is extremely high. The relative risk of dying from coronary heart disease in patients with peripheral arterial disease is 6.6 times that of a control population, and the relative

TABLE 4
ANKLE/ARM BLOOD PRESSURE INDEX
AND MORTALITY IN WOMEN*

Ankle/arm blood pressure index	Relative risk	95% confidence interval
> 1.0	1.0	—
1.0 to 0.9	1.4	0.7–2.6
0.9 to 0.8	5.3	2.6–10.9
≤ 0.8	4.0	2.0–8.3

*From Vogt et al, JAMA 1993; 270:465–469 (reference 32)

risk of dying from any cardiovascular disease is 5.9 times that of a control population.

Hertzner and associates³⁵ studied the cumulative 5-year survival of 977 patients undergoing peripheral vascular reconstruction. The cumulative survival was the worst in patients with inoperable, severe coronary heart disease: only approximately 22% survived 5 years. However, if patients either had normal coronary arteries at the time of cardiac catheterization or had severe coronary artery disease but underwent coronary artery bypass grafting, the 5-year survival was significantly better: 75% to 85%.

Therefore, it is important to consider the effects that various antihypertensive agents have on the coronary circulation, especially in patients with ASO. If there is clinical evidence of atherosclerotic heart disease, a calcium antagonist may be preferred to treat both conditions. If the patient has had a previous myocardial infarction, a beta blocker may be indicated to treat hypertension and for secondary prevention of myocardial infarction.³⁶ Recent data suggest that angiotensin-converting enzyme inhibitors can prevent progressive ventricular dilation (and future congestive heart failure) after an anterior-wall myocardial infarction.³⁷

Lipid abnormalities

It is also important to aggressively treat lipid disorders to prevent progression (or to cause regression) of atherosclerosis. There are increasing data that a large number of patients with ASO have concomitant lipid abnormalities: at our institution, 87% had one or more lipid abnormalities.³⁸ Patients may have high serum concentrations of triglycerides, total cholesterol, and low-density lipoprotein cholesterol, or low concentrations of high-density lipoprotein cholesterol, or both.

A nonpharmacologic approach to treating hypertension is ideal for patients with peripheral arterial disease because weight loss and exercise can allevi-

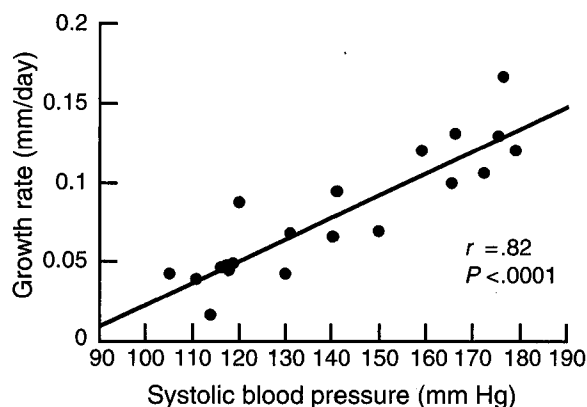


FIGURE 3. Relationship of blood pressure and growth rate of abdominal aortic aneurysm in rats. From Gadowski et al, reference 44.

ate claudication, lower high blood pressure, prolong survival, and correct or improve lipid disturbances. Therefore, we generally emphasize an aggressive program of life-style modification, including achieving ideal body weight, reducing cholesterol, saturated fat, and salt in the diet, and increasing physical activity.

Most long-term studies show that thiazide diuretics do not adversely affect total or low-density lipoprotein cholesterol concentrations, although they may increase triglycerides and decrease high-density lipoprotein cholesterol by approximately 10%. Some beta blockers may cause substantial increases in serum triglycerides and decreases in high-density lipoprotein cholesterol in susceptible individuals. Generally speaking, beta blockers with intrinsic sympathomimetic activity and alpha-beta blockers such as labetalol do not adversely affect lipids.³⁹

The National High Blood Pressure Education Program's working group report on the management of patients with hypertension and high blood cholesterol states: "The desire to avoid diuretics and beta blockers because of their adverse effect on blood lipids should be balanced by consideration of efficacy, tolerability, cost, and adherence."³⁹ We interpret this to mean that if there is a clear indication to use one of these classes of drugs, (ie, diuretics for systolic hypertension in the elderly or beta blockers after myocardial infarction), they should be used despite their effects on blood lipids.

Diabetes mellitus

Approximately one third of patients with lower extremity arterial disease have diabetes mellitus.³⁸ A nonpharmacologic approach may be initially indicated in overweight patients with type II diabetes. Central fat distribution (android obesity) has been associated with glucose intolerance, insulin resistance, and hypertension.⁴⁰ Achievement of ideal body weight in this situation may correct most of these underlying abnormalities.

As a general rule, diuretics or beta blockers should be avoided as initial therapy for hypertension because both of these classes of antihypertensive agents may worsen glucose tolerance and increase the degree of insulin resistance.⁴⁰

Emerging data show that angiotensin-converting enzyme inhibitors prevent or slow the progression of diabetic renal disease.⁴¹ Therefore, we use an angiotensin-converting enzyme inhibitor as the drug class of choice in patients with peripheral arterial disease, diabetes, and hypertension. If hyperkalemia limits the use of this class of drugs, a calcium antagonist is a reasonable alternative.

Aneurysms

Very little information has been published regarding the effect of hypertension on the expansion rate of arterial aneurysms. Nevertheless, most investigators believe that hypertension contributes to a more rapid expansion rate and eventual rupture of aneurysms and that treating it may prevent aneurysm enlargement.⁴²

Two recent studies showed that aneurysms grow much more rapidly in animals with arterial hypertension.^{43,44} Gadowski and colleagues⁴⁴ induced aneurysms in normotensive Wistar-Kyoto rats and a unique strain of genetically hypertensive Wistar-Kyoto rats by injecting elastase into isolated segments of their infrarenal abdominal aortas. The aneurysms in the hypertensive rats were significantly larger at 7 and 14 days than in the rats without hypertension. The mean growth rate of the aneurysms in the hypertensive rats was nearly twice that in the rats without hypertension. There was a strong linear relationship between the systolic blood pressure and the growth rate of the aneurysms (Figure 3).

In humans, the rate of expansion of abdominal aortic aneurysms ranges from 0.30 to 0.57 cm per year and averages approximately 0.40 cm per year.⁴⁵ Leach and colleagues⁴⁶ retrospectively analyzed the

TABLE 5
TREATMENT OF HYPERTENSION IN PATIENTS
WITH PERIPHERAL ARTERIAL DISEASE: EFFECT ON ASSOCIATED CONDITIONS

	Intermittent claudication	Coronary disease	Lipids	Diabetes, insulin resistance
Nonpharmacologic therapy	Improve	Improve	Improve	Improve
Diuretics	No effect	No effect	Worsen	Worsen
Beta blockers	No effect?	Improve	Worsen	Worsen
Angiotensin-converting enzyme inhibitors	No effect	Improve?	No effect	Improve?
Calcium antagonists	No effect	Improve	No effect	No effect
Alpha blockers	No effect	No effect	No effect or improve	No effect
Alpha-beta blocker	No effect	Improve?	No effect	No effect

rate of expansion of abdominal aortic aneurysms in 27 patients. Twelve patients received beta blockers in the long term and 15 patients received no beta blockers. The mean growth rate in the patients receiving beta blockers was 0.17 cm per year compared with 0.44 cm per year in the patients not receiving beta blockers. There was no difference in blood pressure between the two groups. Because of the small number of patients, these data were not statistically significant.

Gadowski, Pilcher, and Ricci⁴⁸ recently reported 128 patients with infrarenal abdominal aortic aneurysms. Eighty-three patients received no beta blocker therapy, while 38 patients received beta blockers. In patients receiving beta blockers, the expansion rate was $0.36 \pm .20$ cm/year, compared with an expansion rate of $0.68 \pm .64$ cm/year in patients who did not receive beta blocker therapy ($P < .05$). This study corroborates previously published reports showing that a reduced rate of expansion of large abdominal aortic aneurysms occurs in patients receiving beta blockers.

Based on the limited information available, our approach is to use beta blockers to treat hypertension in patients with abdominal aortic or peripheral arterial aneurysms, provided there are no contraindications. A prospective study comparing beta blockers with other forms of antihypertensive therapy is needed to answer the question of whether one antihypertensive agent is superior to another in slowing the growth rate of aneurysms.

CONCLUSIONS

There is preliminary evidence from the Treatment of Mild Hypertension Study⁴⁷ that treatment of hypertension decreases intermittent claudication and peripheral arterial occlusive disease. In addition, control of hypertension is considered to be important in the prevention of stroke, congestive heart failure, and ischemic heart disease.

Patients who have peripheral vascular disease and hypertension should be treated according to the general guidelines for all patients with hypertension, as recommended by the JNC V.² However, some specific treatment goals are indicated for this patient population: to improve or prevent the worsening of intermittent claudication and to use therapy that has beneficial effects on associated conditions such as coronary artery disease, hyperlipidemia, and diabetes mellitus. Patients with aneurysms should receive beta blockers.

The ideal therapy for most of these conditions is nonpharmacologic (Table 5).³ Achieving ideal body weight, adopting a diet low in cholesterol, saturated fat, and salt, and exercising regularly will improve blood pressure control, lipid values, blood glucose control, insulin sensitivity, symptoms of intermittent claudication, and long-term survival.

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