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# Peripheral artery disease – current recommendations and best medical treatment

# Choroba niedokrwienna kończyn dolnych w świetle najnowszych wytycznych leczenia zachowawczego

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Summary

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis that is associated with a high risk of cardiovascular mortality and significant limitation in function because of limb ischemia. Patients with PAD should be considered to have significant coronary and cerebral arterial disease that requires aggressive risk factor management, including the prescription of antiplatelet drugs in order to lower the subsequent risk of myocardial infarction, stroke, and death. In the population with PAD, evidence supports the use of statin for lipid management, angiotensin-converting enzyme-1 inhibitors for blood pressure control, and aspirin or clopidogrel as antiplatelet agents. Once this is accomplished, the severity of limb symptoms should be assessed, and a structured exercise program or the selected use of drugs such as cilostazol to treat the intermittent claudication should be prescribed. In patients primarily considered for surgical treatment, antiplatelet and anticoagulant drug therapy can be used as a mean of promoting graft patency, and beta-adrenergic blockers can be used as a mean of reducing the perioperative risks associated with vascular surgery.

Key words: peripheral artery disease, medical treatment

Streszczenie

Manifestacje przewlekłego procesu miażdżycowego, takie jak choroba niedokrwienna serca, niedokrwienie OUN oraz przewlekłe niedokrwienie kończyn dolnych (PAD) stanowią prawie połowę przyczyn śmierci w Europie każdego roku. Przewlekłe niedokrwienie kończyn dolnych nie musi mieć ścisłego związku z objawami klinicznymi i bardzo często przebiega bezobjawowo. PAD jest nie tylko chorobą niedokrwienną kończyn, rozwój procesu miażdżycowego jest chorobą uogólnioną i dotyczy również mózgu, serca oraz innych organów wewnętrznych. W związku z tym pacjenci z PAD narażeni są na poważne komplikacje o charakterze naczyniowo-niedokrwiennym, w tym np. na zawał mięśnia sercowego lub niedokrwienie OUN. Liczba osób z PAD drastycznie wzrasta i w chwili obecnej osiąga 16% społeczeństwa w wieku ponad 55 lat, w związku z tym ta grupa pacjentów wymaga całościowego podejścia do tego problemu. Proces diagnostyczno-leczniczy powinien obejmować zarówno modyfikację czynników ryzyka rozwoju miażdżycy, jak również terapię lekami przeciwpłytkowymi mającymi na celu redukcję wystąpienie powikłań zakrzepowo-zatorowych. Najnowsze zalecenia obejmują również stosowanie statyn, celem leczenia hipercholesterolemii, inhibitorów ACE, celem redukcji nadciśnienia tętniczego oraz kwasu acetylosalicylowego lub klopidogrelu jako leków p/płytkowych. W leczeniu chromania przestankowego zaleca się początkowo wprowadzenie nadzorowanego treningu marszowego i/lub włączenie terapii cilostazolem, jako leku o najlepiej udowodnionej skuteczności. U pacjentów kwalifikowanych do operacji naczyniowych zaleca się stosowanie terapii antypłytkowej jako prewencji zakrzepowej. Rekomenduje się również stosowanie B-blokerów, celem redukcji powikłań okołooperacyjnych.

Słowa kluczowe: choroba niedokrwienna kończyn dolnych, leczenie zachowawcze

## INTRODUCTION

The peripheral arterial disease (PAD) is one of the most common and the most important manifestation of systemic atherosclerosis. The disease progresses with aging regardless from gender (1, 2). After the age of 40 years, there is two- to three-fold increase in risk of PAD development in each decade. PAD is closely related to coexistence of risk factors for the atherosclerosis development: smoking, diabetes mellitus, hyperlipidemia and hypertension (2-4).

**While PAD develops, risk of vascular and ischemic complications associated with myocardium**, and CNS increases, as well as risk of other vascular death (5). It is estimated that in patients with PAD, comparing to the remaining population of the patients, there is three-fold increase in risk of any vascular death, and six-fold increase in risk of cardiac death (6). In this case, gender does not matter, and risk is still high despite absence of the ischemic heart disease in the past (7, 8). It has been proven that together with increasing intensity of the peripheral arterial disease measured by the ankle-brachial index, risk of myocardial ischemia, ischemic stroke, and other vascular death, proportionally increases as well (9, 10). The main purpose of pharmacological treatment is an aggressive modification of risk factors, which is extremely important in inhibiting development of the peripheral arterial disease, as well as in lowering risk of other vascular complications. Introduction of antiplatelet therapy together with ACE inhibitors provides significant benefits in reducing occurrence of undesirable cardiovascular events.

The most common manifestation of the peripheral arterial disease is the intermittent claudication. Conservative treatment includes smoking cessation at the beginning, and then supervised exercises and pharmacological therapy in order to stop progress of the disease as well as reduce risk of occurrence of the vascular events. The patients with critical peripheral arterial disease require surgical treatment in order to supply the limb with blood, which provides optimum conditions for treatment of the ischemic lesions. In such cases, pharmacological therapy is an adjunctive therapy for the first-line surgical treatment.

Very important in the group of patients undergoing surgical treatment is to prevent myocardial ischemia during perioperative course and to provide long-term protection from coagulation in the vascular graft. In order to achieve these goals, beta-blockers and acetylsalicylic acid should be administered in the perioperative course.

This article presents review of current recommendations regarding conservative therapy of the peripheral arterial disease, which purpose is to modify risk factors for cardiovascular complications and to increase walking distance. Conservative treatment should also include prevention of the disease progress, treatment of coexisting diseases, improvement in the limb blood supply, prevention of necrotic lesions, and treatment of skin lesions.

As it was mentioned before, the patients with PAD constitute the group of patients with significantly increased risk of the cardiovascular event occurrence. It should be taken into consideration that majority of these patients have no symptoms of the peripheral arterial disease, and half of them have not yet experienced the cardiovascular event. Medical history and preliminary clinical examination may result in underestimation of the actual number of patients with PAD. Cirkulation 2001' published the article presenting positive correlation between coexisting PAD and the ankle-brachial index ABI ≤ 0.9 (11). Based on the article of A. Hirsch published in JAMA 2003' (12), ABI measurement was recommended in all symptomatic patients, in all patients in the age of 60-69 years with coexisting risk factors for the cardiovascular disease, and in all patients in the age of over 70 years.

The article listed recommendations of Trans-Atlantic Inter-Society Consensus – its second edition (TASC II) (13), regarding diagnostics and treatment of the peripheral arterial disease. The article is a result of cooperation among fourteen scientific societies from Europe and North America involved in problems regarding vascular diseases.

## PHARMACOLOGICAL MODIFICATION OF CARDIOVASCULAR RISK FACTORS

The patients with PAD are frequently burdened with many risk factors for cardiovascular complications. Many broad-spectrum studies confirmed basic role of their modification.

### Smoking cessation

Smoking cigarettes is associated with significant increase in risk of vascular complications and development of chronic ischemia of lower limbs at the background of atherosclerosis (14). Number of smoked cigarettes per year significantly correlates with increased risk of amputation, occlusion of the vascular graft, and death (15). In addition, during exercises on a treadmill, the smoking patients with PAD reported significantly less intensive pain in shanks than non-smoking patients (16). Therefore, smoking cessation is a significant factor for reducing cardiovascular complications, however, it has to be combined with formal program of nicotine replacement therapy (17) and administration of an antidepressant drug – bupropion (18). Introducing such regimen allows achieving 22% cessation rate within five years and if it is compared with 5% cessation rate achieved in patients with standard treatment, it becomes obvious how important is to apply aforementioned recommendations. The patients have to be informed about purpose of smoking cessation, which is not used in order to increase walking distance, but in order to significantly reduce risk factors for vascular and ischemic episodes. No broad-spectrum study explicitly proved that smoking cessation is associated with significant increase in walking distance (19, 20). The patients have to be aware of this fact in order to prevent losing effort put in therapy, if the patient is discouraged by noticing no increase in walking distance.

TASC II Recommendation 1.
Smoking cessation in peripheral arterial disease

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| AI patients who smoke should be strongly and repeatedly advised to stop smoking (B).<br>All patients who smoke should receive a program of physician advice, group counseling sessions, and nicotine replacement (A).<br>Cessation rates can be enhanced by the addition of antidepressant drug therapy (bupropion) and nicotine replacement (A). |

### Hyperlipidemia

**Independent risk factors for the lower limbs atherosclerosis include elevated level of total cholesterol, low-density lipoprotein (LDL) and triglycerides (TG)** (21). **Factor that is protective for the development of PAD is elevated high-density lipoprotein (HDL)** (22). Current recommendations for the management of lipid disorders in patients with PAD are to achieve LDL level in serum < 100 mg/dL, however, in patients with PAD and other vascular disease (e.g. coronary heart disease), concentration of LDL in serum should be at the level of < 70 mg/dL. Administration of statins is the main method for lowering level of LDL and reducing risk of the cardiovascular episode. Fibrates are recommended in order to lower concentration of triglycerides. Data coming from broad-spectrum, randomized study including population of over 20 thousand patients – Heart Protection Study (HPS), emphasizes the role of lowering LDL concentration in order to reduce undesired cardiovascular events. Use of simvastatin (40 mg/day) over the period of five years was associated with a 12% reduction in total mortality, 17% reduction in vascular mortality, 24% reduction in undesired vascular events and 27% reduction in all strokes (23). Moreover, HPS study revealed that long-term therapy with statins was associated with reduction in incidence of myocardial ischemia, stroke, and vascular death in patients with PAD.

TASC II Recommendation 2.
Lipid control in patients with peripheral arterial disease (PAD)

All symptomatic PAD patients should have their low-density lipoprotein (LDL)-cholesterol lowered to < 2.59 mmol/L (< 100 mg/dL) (A).
In patients with PAD and a history of vascular disease in other beds (e.g. coronary artery disease) it is reasonable to lower LDL cholesterol levels to < 1.81 mmol/L (< 70 mg/dL) (B).
All asymptomatic patients with PAD and no other clinical evidence of cardiovascular disease should also have their LDL-cholesterol level lowered to < 2.59 mmol/L (< 100 mg/dL) (C).
In patients with elevated triglyceride levels where the LDL cannot be accurately calculated, the LDL level should be directly measured and treated to values listed above. Alternatively, the non-HDL (high-density lipoprotein) cholesterol level can be calculated with a goal of < 3.36 mmol/L (< 130 mg/dL), and in high-risk patients the level should be <2.59 mmol/L (< 100 mg/dL).
Dietary modification should be the initial intervention to control abnormal lipid levels (B).
In symptomatic PAD patients, statins should be the primary agents to lower LDL cholesterol levels to reduce risk of cardiovascular events (A).
Fibrates and/or niacin to raise HDL-cholesterol levels and lower triglyceride levels should be considered in patients with PAD who have abnormalities of those lipid fractions (B).

### Hypertension

**Hypertension is the next independent factor associated with a two- to three-fold increased risk of the lower limbs ischemia at the background of atherosclerosis** (24). It is recommended to maintain the blood pressure in patients with atherosclerotic process at the level of 130/85 mm Hg (25). Beta-blockers are not contraindicated in therapy of the peripheral artery disease, as it was claimed in previous papers. Currently, it is believed that the patients qualified for surgical treatment of the peripheral artery disease should take beta-blockers due to their cardioprotective action in this group of patients (26). HOPE (Heart Outcomes Prevention Evaluation) study conducted on over four thousand of subjects proved positive effect of using ACE inhibitors on reduction of hypertension in the group of patients with PAD (27). Therefore, it is recommended to use ACE inhibitors in the group of patients with PAD and hypertension, who are at high risk of cardiovascular complications.

TASC II Recommendation 3.
Control of hypertension in peripheral arterial disease (PAD) patients

All patients with hypertension should have blood pressure controlled to <140/90 mmHg or <130/80 mmHg if they also have diabetes mellitus or renal insufficiency (A).
JNC VII and European guidelines for the management of hypertension in PAD should be followed (A).
Thiazides and ACE inhibitors should be considered as initial blood-pressure lowering drugs in PAD to reduce risk of cardiovascular events (B).
Beta-adrenergic-blocking drugs are not contraindicated in PAD (A).

### Diabetes mellitus

**In diabetes mellitus, there is approximately three-fold increase in risk of PAD and approximately five-fold increase in risk of intermittent claudication** (28). Risk of other complications, such as peripheral neuropathies or skin infections leading to non healing ulcerations, is also a few times higher within the course of diabetes mellitus. Several studies of both type 1 and type 2 diabetes mellitus have shown that aggressive blood-glucose lowering can prevent microvascular complications, particularly retinopathy. However, explicit positive effect of blood-glucose lowering on reduction of cardiovascular events and PAD development has not been proven (29). The current American Diabetes mellitus Association guidance recommends hemoglobin A1C level of 7%, however, it is unclear whether achieving this goal will effectively reduce PAD development.

TASC II Recommendation 4.
Control of diabetes mellitus in peripheral arterial disease (PAD)

Patients with diabetes mellitus and PAD should have aggressive control of blood glucose levels with a hemoglobin A1c goal of < 7.0% or as close to 6% as possible (C).

### Homocysteine

An elevated serum homocysteine level is an independent risk factor for PAD (30). However, no positive effect of using supplements with vitamin B on reduction of cardiovascular events has been proven.

TASC II Recommendation 5.
Use of folate supplementation in peripheral arterial disease (PAD)

Patients with PAD and other evidence of cardiovascular disease should not be given folate supplements to reduce their risk of cardiovascular events (B).

### Hypercoagulation

**Hypercoagulation is the most common cause of venous thrombosis, which has been proven in numerous studies** (31). Pathologies associated with coagulation in patients with PAD have been evaluated in not many studies, which provided evidence of coexisting elevated concentration of platelet activation markers and PAD (32).

### Antiplatelet therapy

Acetylsalicylic acid (ASA) is a well-recognized antiplatelet drug that has clear benefits in patients with cardiovascular diseases. Antithrombotic Trialists' Collaboration study proved efficacy of this drug in patients with ischemic heart disease (33). This study also proved that low doses of ASA (75-160 mg daily) are safe for the gastrointestinal tract. Thus, current recommendations would strongly favor the use of low doses of ASA in patients with cardiovascular diseases. Antiplatelet drugs are clearly indicated in the overall management of PAD, although the efficacy of ASA is shown only when PAD and cardiovascular disease coexist (34).

The thienopyridines are a class of antiplatelet agents that have been studied in terms of treatment of the peripheral artery disease. Despite benefits of administration of these drugs in patients with the peripheral artery disease, which are resulted from reduction in myocardial infarction, stroke and vascular death, its use is not recommended due to risk of side effects (neutropenia, thrombocytopenia) (35). As opposed to ticlopidine, clopidogrel was shown to be highly effective in reducing risk of vascular and ischemic episode in patients with PAD, with acceptable frequency of side effects. It was proven in Clopidogrel versus Aspirin in the Prevention of Recurrent Ischemic Events study (36, 37). In recent publications regarding patients with the acute coronary syndromes, it is suggested that combined therapy with ASA and clopidogrel is more effective than monotherapy with ASA, however it is associated with higher risk of bleeding (38). The last conducted study regarding this issue did not demonstrate general benefits resulted from combined therapy (ASA and clopidogrel) that are superior to monotherapy with ASA in preventing myocardial infarctions, strokes or vascular death (39). Therefore, combined therapy in patients with PAD is not recommended. If clopidogrel is considered, it should be used in monotherapy.

TASC II Recommendation 6.
Antiplatelet therapy in peripheral arterial disease (PAD)

All symptomatic patients with or without a history of other cardiovascular disease should be prescribed an antiplatelet drug long term to reduce risk of cardiovascular morbidity and mortality (A).
ASA is effective in patients with PAD who also have clinical evidence of other forms of cardiovascular disease (coronary or carotid) (A).
The use of ASA in patients with PAD who do not have clinical evidence of other forms of cardiovascular disease can be considered (C).
Clopidogrel is effective in reducing cardiovascular events in a subgroup of patients with symptomatic PAD, with or without other clinical evidence of cardiovascular disease (B).

## TREATMENT OF INTERMITTENT CLAUDICATION

### General management

At the beginning, treatment should include introduction of physical exercises, and in some patients, pharmacotherapy. Purpose of modification of risk factors and antiplatelet therapy is to reduce risk of cardiovascular episodes. If the patient does not respond to used conservative treatment, surgical treatment should be considered.

### Physical exercises

Conducting supervised exercises is the most effective, conservative therapy of intermittent claudication (40). Physical exercises 3 times a week are recommended. At the beginning, exercises should take 30 minutes, however, over the time, an exercise session should be prolonged to one hour. During exercises on a treadmill, its slope and its speed should be set in such manner that pain would occur within 3-5 minutes. Pain intensity should remain at moderate level. If the patient stops at the moment of pain occurrence, response to workout would be less effective. Workout should be repeated three times a week over at least three months.

TASC II Recommendation 14.
Exercise therapy in intermittent claudication

Supervised exercise should be made available as part of the initial treatment for all patients with peripheral arterial disease (A).
The most effective programs employ treadmill or track walking that is of sufficient intensity to bring on claudication, followed by rest, over the course of a 30-60 minute session. Exercise sessions are typically conducted three times a week for 3 months (A).

### Pharmacotherapy of intermittent claudication

All patients with intermittent claudication should receive suitable treatment and directions in order to modify risk factors for vascular diseases. However, radical improvement cannot be expected during conservative treatment. Despite promotion of many drugs, only small percentage of them reveal proven clinical effect. Therapeutic effect of physical exercises, which cannot be replaced by any pharmacological product, is still underestimated.

Formerly used vasodilator agents do not reveal documented therapeutic effect (41). In 1984, pentoxifylline was approved for treatment of intermittent claudication. However, the most recent clinical studies showed that in treatment of intermittent claudication this drug is not more effective than placebo (42).

**Cilostazol is the only drug with proven clinical effect in intermittent claudication, however, lack of marketing authorization of this drug in Poland makes its use impossible.** Its vasodilating, metabolic, and antiplatelet action is based on phosphodiesterase type 3 inhibition (43). Four clinical trials with enrolled over 1500 patients taking 100 mg of cilostazol twice daily showed obvious benefits resulted from administration of this drug comparing to placebo (statistically

significant increase in walking distance) (44). The studies comparing cilostazol and pentoxifylline showed that cilostazol is more effective (45). Use of cilostazol is contraindicated in patients, whose peripheral arterial disease is accompanied by heart failure (46). However, despite recent reports denying negative effect of cilostazol in this group of patients, it is still recommended to avoid therapy with this drug in patients with circulatory failure.

Acetylsalicylic acid and other antiplatelet drugs are important elements of long-term therapy of patients with PAD, which are used in order to reduce risk of cardiovascular events. However, no study demonstrated beneficial effect of antiplatelet or antithrombotic therapy in treatment of intermittent claudication (47).

Prostaglandins were evaluated in a few studies, however, there was no explicit evidence of benefits resulted from use of these drugs in treatment of intermittent claudication (48). Furthermore, other treatments formerly used in vascular diseases: buflomedil, vitamin E, chelation therapy, omega-3 fatty acids, and ginko biloba turned out to show no proven clinical effect (49).

TASC II Recommendation 15.
Pharmacotherapy for symptoms of intermittent claudication

A 3- to 6-month course of cilostazol should be first-line pharmacotherapy for the relief of claudication symptoms, as evidence shows both an improvement in treadmill exercise performance and in quality of life (A).
Naftidrofuryl can also be considered for treatment of claudication symptoms (A).

### Future treatment of intermittent claudication

**Since 1990s, the reports have been published on possible use of gene therapy in patients with the peripheral arterial disease** (50). **The studies focus on using multi-gene therapy in order to induce activity of angiogenic cytokines as well as other factors with basic significance in angiogenesis process, such as nitric oxide synthesis or angiopoietin.** In recent years, scientists are also interested in other angiogenic growth factors: vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). After intra-arterial administration of bFGF protein in patients with intermittent claudication, improvement occurred in form of increase in walking distance. The newest method of administration of angiogenic factors is gene therapy using viral vector in intramuscular injections. At the beginning, this method seemed to be very promising, however broad-spectrum clinical studies conducted on large group of patients showed no expected efficacy of treatment with VEGF (51). Therefore, it is necessary to conduct more studies on use of angiogenic growth factors in therapy of the peripheral arterial disease.

### Perioperative treatment

There is much evidence that chronic use of antiplatelet drugs, especially acetylsalicylic acid, contribute to reduction in vascular adverse events and prolonging patency of vascular grafts. Meta-analysis Antithrombotic Trialists' Collaboration showed that among 3000 patients after peripheral grafting surgery, who were taking acetylsalicylic acid, there was 16% of the graft occlusions comparing to 25% in the group taking placebo. Low doses of acetylsalicylic acid (50-100 mg) revealed similar efficacy as high doses (900-1000 mg) (52).

Justification for use of anticoagulant therapy in form of low molecular weight heparin administration following vascular surgeries in order to prolong the period of the graft patency was evaluated in many clinical trials. It was proven that prolonged use of low molecular weight heparin may positively influence long-term patency of the graft, but it is associated with increased postoperative bleeding (53).

Therapy with oral anticoagulant agents is more controversial. A few studies on therapy with warfarin used in patients after vascular grafting located below the inguinal ligament (venous grafts, prosthetic blood vessels and endarterectomy surgery) did not prove superiority of this treatment method over antiplatelet therapy resulted in prolonged period of patency of the graft or the vessel. In addition, use of warfarin was associated with increased risk of postoperative bleeding (54).

In a few clinical trials, effects of anticoagulant therapy were compared with effects of antiplatelet treatment. One trial included patients after vascular grafting with prosthetic blood vessel placed below the inguinal ligament. After surgery, the patients were randomized for treatment with low molecular weight heparin or combined therapy with acetylsalicylic acid (300 mg daily) and thienopyridine. Using heparin was associated with prolonged period of graft patency. There was no difference between the groups in terms of incidence of postoperative bleeding, however, slightly higher number of deaths was recorded in the group taking low molecular weight heparin (55).

In one of the largest clinical study comparing therapy with oral anticoagulants to therapy with acetylsalicylic acid (Dutch Bypass Oral Anticoagulants or Aspirin Study) in patients after vascular grafting located below the inguinal ligament, the authors suggest using therapy with oral anticoagulants in patients after vascular grafting with the patient's own vein, but in patients after vascular grafting with prosthetic blood vessel, better long-term effects were achieved in treatment with acetylsalicylic acid (56).

Many studies focus on combined therapy with oral anticoagulants and antiplatelet agents in patients with high risk of vascular complications. However, there is no evidence of definite superiority of combined therapy over therapy with acetylsalicylic acid alone, but simultaneous use of antiplatelet agents and oral anticoagulants is associated with higher risk of perioperative bleeding (57).

**To recap, antiplatelet therapy is important treatment in patients after vascular surgery.** It reduces

risk of occlusions of the vessels or the vascular grafts as well as it has positive effect on lowering frequency of adverse events such as myocardial ischemia and cerebral infarction. However, previous clinical studies did not provide clear answer for the following question – which group of the drugs or what combination of the drugs is the best long-term adjuvant therapy for the patients after vascular surgery. The safest and the most carefully evaluated drug seems to be acetylsalicylic acid. Recently published articles expressed concern that patients undergoing intervention due to the peripheral arterial disease do not receive proper treatment related to atherosclerosis. As it was mentioned before, all patients should undergo treatment related to atherosclerotic process regardless of any actions, which are necessary in order to save the limb.

TASC II Recommendation 41.
Antiplatelet drugs as adjuvant pharmacotherapy after revascularization

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| Antiplatelet therapy should be started preoperatively and continued as adjuvant pharmacotherapy after an endovascular or surgical procedure (A).<br>Unless subsequently contraindicated, this should be continued indefinitely (A). |

**Perioperative protection of myocardium**

Patients undergoing surgery due to vascular diseases are at high risk of cardiovascular complications (58). There are many publications suggesting stratification of preoperative risk in these patients by detailed interview and physical examination as well as evaluation of myocardial performance using minimally invasive methods (59). Basic and the most typical risk factors for cardiovascular complications in surgical patients include: age > 70 years, ischemic heart disease, past episode of myocardial ischemia, heart failure, infarction (60). Patients with symptoms of coronary instability should be referred to the cardiologist in order to initiate suitable treatment. In patients with stable coronary disease, treatment should depend on intensity of symptoms. In majority of patients with symptoms of coronary heart disease, it would be necessary to perform coronary angiogram in order to establish suitable method of revascularization. Adequate therapy should be initiated in all patients. In patients with no high risk of cardiovascular complications, preventive coronary revascularization in preparation to vascular surgery usually should not be performed, however, in majority of patients, perioperative use of beta-adrenolytic drugs is associated with lower cardiovascular risk (61).

TASC II Recommendation 7.
Management of coronary artery disease (CAD) in peripheral arterial disease patient

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| Patients with clinical evidence of CAD (angina, ischemic congestive heart failure) should be evaluated and managed according to current guidelines (C).<br>Patients with PAD considered for vascular surgery may undergo further risk stratification and those found to be at very high risk managed according to current guidelines for coronary revascularization (C).<br>Routine coronary revascularization in preparation for vascular surgery is not recommended (A). |

TASC II Recommendation 8.
Use of beta-blocking agents before vascular surgery

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| When there are no contraindications, beta-adrenergic blockers should be given perioperatively to patients with peripheral arterial disease undergoing vascular surgery in order to decrease cardiac morbidity and mortality (A). |

SUMMARY

Significant percentage of patients with chronic ischemia, who are coming to doctor's offices, are incorrectly diagnosed and treated. It happens that these patients are referred to the vascular surgeon with advanced ischemia of the limb, and in such condition possibilities of surgical treatment are limited. It is common that the patients with serious vascular problems do not receive adequate surgical assistance within the optimum time. Therefore, in order to prevent the disease development, therapy modifying risk factors for development of the atherosclerotic process should be initiated sufficiently early. The main elements of such management include smoking cessation, maintaining LDL cholesterol level below 100 mg/dL, maintaining blood pressure at <130/85 mm Hg and maintaining a hemoglobin A1c in diabetic patients at the level of < 7.0%. Recommended pharmacological treatment includes use of statins in order to reduce high level of LDL cholesterol, use of ACE inhibitors in order to treat hypertension and use of beta-blockers if not contraindicated. All patients should chronically use antiplatelet treatment. Besides reduction of risk factors for atherosclerosis, further treatment of the symptomatic patients with intermittent claudication includes introduction of supervised exercises. Cilostazol is the only drug approved for treatment of intermittent claudication; it is recommended to use one course of pharmacotherapy over at least three months in patients without contraindications, who are mentioned above. The patients, who underwent surgical treatment due to intermittent claudication or critical ischemia of the limb (surgery or angioplasty), have to take antiplatelet agents in order to prolong revascularization effect. Chronic use of acetylsalicylic acid is recommended. Multidrug therapy and its combinations are not approved in this population of patients.

BIBLIOGRAPHY

1. Criqui MH, Fronek A, Barrett-Connor E et al.: The prevalence of peripheral arterial disease in a defined population. Circulation 1985; 71: 510-5.
2. Hiatt WR, Hoag S, Hamman RF: Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley diabetes mellitus.

3. Newman AB, Siscovick DS, Manolio TA et al.: Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study (CHS) Collaborative Research Group. Circulation 1993; 88: 837-45.
4. Graham IM, Daly LE, Refsum HM et al.: Plasma homocysteine as a risk factor for vascular disease. The European Concerted Action Project. JAMA 1997; 277: 1775-81.
5. Ness J, Aronow WS: Prevalence of coexistence of coronary artery disease, ischemic stroke, and peripheral arterial disease in older persons, mean age 80 years, in an academic hospital-based geriatrics practice. J Am Geriatr Soc 1999; 47: 1255-6.
6. Criqui MH, Langer RD, Fronek A et al.: Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992; 326: 381-6.
7. Newman AB, Shemanski L, Manolio TA et al.: Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. Arterioscler Thromb Vasc Biol 1999; 19: 538-45.
8. Newman AB, Tyrrell KS, Kuller LH: Mortality over four years in SHEP participants with a low ankle-arm index. J Am Geriatr Soc 1997; 45: 1472-8.
9. McKenna M, Wolfson S, Kuller L: The ratio of ankle and arm arterial pressure as an independent predictor of mortality. Atherosclerosis 1991; 87: 119-28.
10. Vogt MT, McKenna M, Anderson SJ et al.: The relationship between ankle-arm index and mortality in older men and women. J Am Geriatr Soc 1993; 41: 523-30.
11. Kannel WB, Skinner JJ, Jr., Schwartz MJ, Shurtleff D: Intermittent claudication. Incidence in the Framingham Study. Circulation 1970; 41(5): 875-883.
12. Hirsch AT, Haskal ZJ, Hertzer NR et al.: ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extermity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interverntions, Society for Vascular Medicine and Biology, Society of Interventional Raidology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol 2006; 47: 1239-1312.
13. Norgren L, Hiatt WR, Dormady JA et al.: Trans-Atlantic Inter-Society Consensus (TASC II). Eur J Vasc End Surg 2007; 33, supl. I.
14. Hiatt WR, Hoag S, Hamman RF: Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley diabetes mellitus study. Circulation 1995; 91: 1472-9.
15. Criqui MH, Fronek A, Barrett-Connor E et al.: The prevalence of peripheral arterial disease in a defined population. Circulation 1985; 71: 510-5.
16. Gardner AW: The effect of cigarette smoking on exercise capacity in patients with intermittent claudication. Vasc Med 1996; 1: 181-6.
17. Fiore MC, Smith SS, Jorenby DE et al.: The effectiveness of the nicotine patch for smoking cessation: a meta-analysis. JAMA 1994; 271: 1940-7.
18. Berlin I, Said S, Spreux-Varoquaux O et al.: A reversible monoamine oxidase A inhibitor (moclobemide) facilitates smoking cessation and abstinence in heavy, dependent smokers. Clin Phar Ther 1995; 58: 444-52.
19. Jonason T, Bergstrom R: Cessation of smoking in patients with intermittent claudication. Acta Med Scand 1987; 221: 253-60.
20. Quick CRG, Cotton LT: The measured effect of stopping smoking on intermittent claudication. Br J Surg 1982; 69(Suppl): S24-6.
21. Hiatt WR, Hoag S, Hamman RF: Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley diabetes mellitus study. Circulation 1995; 91: 1472-9.
22. Johansson J, Egberg N, Hohnsson H et al.: Serum lipoproteins and hemostatic function in ntermittent claudication. Arterioscler Thromb 1993; 13: 1441-8.
23. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo controlled trial. Lancet 2002; 360: 7-22.
24. Gardner AW: The effect of cigarette smoking on exercise capacity in patients with intermittent claudication. Vasc Med 1996; 1: 181-6.
25. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997; 157: 2413-46.
26. Radack K, Deck C: Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. A meta-analysis of randomized controlled trials. Arch Intern Med 1991; 151: 1769-76.
27. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000; 342:
28. Kannel WB, McGee DL: Diabetes mellitus and cardiovascular disease. The Framingham Study. JAMA 1979; 241: 2035-8.
29. Effect of intensive diabetes mellitus management on macrovascular events and risk factors in the Diabetes mellitus Control and Complications Trial. Am J Cardiol 1995; 75: 894-903.
30. Valentine R, Kaplan HS, Green R et al.: Lipoprotein (a), homocysteine, and hypercoaguable states in young men with premature peripheral atherosclerosis: a prospective, controlled analysis. J Vasc Surg 1996; 23: 53-63.
31. Donaldson MC, Weinberg DS, Belkin M et al.: Screening for hypercoagulable states in vascular surgical practice: a preliminary study. J Vasc Surg 1990; 11: 825-31.
32. Catalano M, Russo U, Libretti A: Plasma beta-thromboglobulin levels and claudication degrees in patients with peripheral vascular disease. Angiology 1986; 37: 339-42.
33. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients 1. BMJ 2002; 324: 71-86.
34. Clagett P, Sobel M, Jackson M et al.: Antithrombotic therapy in peripheral arterial disease: The Seventh ACCP Conference on antithrombotic and thrombolytic therapy. Chest 2004; 126: S609- S626.
35. Janzon L, Bergqvist D, Boberg J et al.: Prevention of myocardial infarction and stroke in patients with intermittent claudication; effects of ticlopidine. Results from STIMS, the Swedish Ticlopidine Multicentre Study. J Intern Med 1990; 227(5): 301-308.
36. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348: 1329-39.
37. Bennett CL, Connors JM, Carwile JM et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. N Engl J Med 2000; 342: 1773-7.
38. Yusuf S, Zhao F, Mehta SR et al.: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345: 494-502.
39. Bhatt D, Fox K, Hacke W et al.: Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006; 354: 1706-1717.
40. Gardner AW, Poehlman ET: Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. JAMA 1995; 274: 975-80.
41. Coffman JD. Vasodilator drugs in peripheral vascular disease. N Engl J Med 1979; 300: 713-7.
42. Dawson DL, Cutler BS, Hiatt WR et al.: A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med 2000; 109: 523-30.
43. Kohda N, Tani T, Nakayama S et al.: Effect of cilostazol, a phosphodiesterase III inhibitor, on experimental thrombosis in the porcine carotid artery. Thromb Res 1999; 96: 261-8.
44. Beebe HG, Dawson DL, Cutler BS et al.: A new pharmacological treatment for intermittent claudication: results of a randomized, multicenter trial. Arch Intern Med 1999; 159: 2041-50.
45. Dawson D, Cutler B, Hiatt W et al.: A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med 2000; 109(7): 523-530.

46. Packer M, Carver JR, Rodeheffer RJ et al.: Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. N Engl J Med 1991; 325: 1468-75.
47. Cosmi B, Conti E, Coccheri S: Anticoagulants (heparin, low molecular weight heparin and oral anticoagulants) for intermittent claudication. Cochrane Database Syst Rev 2001; CD001999.
48. Lievre M, Morand S, Besse B et al.: Oral beraprost sodium, a prostaglandin I(2) analogue, for intermittent claudication: a double-blind, randomized, multicenter controlled trial. Beraprost et Claudication Intermittente (BERCI) Research Group. Circulation 2000; 102(4): 426-431.
49. de Backer T, Vander Stichele R, Bogaert M: Buflomedil for intermittent claudication. Cochrane Database Syst Rev 2001; CD000988.
50. Lederman R, Mendelsohn F, Anderson R et al.: Therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication (the TRAFFIC study): a randomised trial. Lancet 2002; 359(9323): 2053-2058.
51. Rajagopalan S, Mohler EI, Lederman R et al.: Regional angiogenesis with vascular endothelial growth factor in peripheral arterial disease: a phase II randomized, double-blind, controlled study of adenoviral delivery of vascular endothelial growth factor 121 in patients with disabling intermittent claudication. Circulation 2003; 108(16): 1933-1938.
52. Forbes TL, Friggatti P, Minar E et al.: Comp of effects of high dose and low dose of aspirine. Circulation 1995; 91
53. Samama CM, Gigou F, Ill P. Low-molecular weight heparin vs unfractionated heparin in morodistal reconstructive surgery: a multicenter open randomized study. Ann Vasc Surg 1995; 9: S45-S53.
54. Arfvidsson B, Lundgren F, Drott C et al.: Influence of coumarin treatment on patency and limb salvage after peripheral arterial reconstructive surgery. Am J Surg 1990; 159: 556-60.
55. Edmondson RA, Cohen AT, Das SK et al.: Low-molecular weight heparin versus aspirin and dipyridamole after femoropopliteal bypass grafting. Lancet 1994; 344: 914-8.
56. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. Lancet 2000; 355: 346-51.
57. Tangelder MJ, Lawson JA, Algra A et al.: Systematic review of randomized controlled trials of aspirin and oral anticoagulants in the prevention of graft occlusion and ischemic events after infrainguinal bypass surgery. J Vasc Surg 1999; 30: 701-9.
58. Hertzer NR, Beven EG, Young JR et al.: Coronary artery disease In peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. Ann Surg 84; 199: 223-33.
59. Eagle KA, Brundage BH, Chaitman BR et al.: Guidelines for perioperative cardiovascular valuation for noncardiac surgery. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery. Circulation 1996; 93: 1278-317.
60. Boersma E, Poldermans D, Bax JJ et al.: Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. JAMA 2001; 285: 1865-73.
61. McFalls EO, Ward HB, Moritz TE et al.: Coronary-artery revascularization before elective major vascular surgery. N Engl J Med 2004; 351(27): 2795-2804.

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