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Chapter III: Management of Cardiovascular Risk Factors and Medical Therapy

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Abstract Critical limb ischaemia (CLI) is a particularly severe manifestation of lower limb atherosclerosis posing a major threat to both limb and life of affected patients. Besides arterial revascularisation, risk-factor modification and administration of antiplatelet therapy is a major goal in the treatment of CLI patients.

Key elements of cardiovascular risk management are smoking cessation and treatment of hyperlipidaemia with dietary modification or statins. Moreover, arterial hypertension and diabetes mellitus should be adequately treated.

In CLI patients not suitable for arterial revascularisation or subsequent to unsuccessful revascularisation, parenteral prostanoids may be considered. CLI patients undergoing surgical revascularisation should be treated with beta blockers. At present, neither gene nor stem-cell therapy can be recommended outside clinical trials. Of note, walking exercise is contraindicated in CLI patients due to the risk of worsening pre-existing or causing new ischaemic wounds.

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CLI patients are oftentimes medically frail and exhibit significant comorbidities. Co-existing coronary heart and carotid as well as renal artery disease should be managed according to current guidelines.

Considering the above-mentioned treatment goals, interdisciplinary treatment approaches for CLI patients are warranted.

Aim of the present manuscript is to discuss currently existing evidence for both the management of cardiovascular risk factors and treatment of co-existing disease and to deduct specific treatment recommendations.

Critical issue

Most of the outlined recommendations apply to peripheral arterial disease (PAD) patients in general. Thus, it has to be kept in mind that recommendations are frequently extrapolated to the subgroup of PAD with critical limb ischaemia (CLI).

1. Smoking

Smoking is the most important risk factor in PAD patients. The extent of smoking exposure correlates with PAD disease severity, rates of lower limb amputation, bypass re-occlusion as well as with mortality.[1–3] Thus, CLI patients should be advised to quit smoking with the aim to reduce the risk of adverse cardiovascular events and amputation.

Physician smoking cessation advice coupled with a formal smoking cessation programme and nicotine replacement was shown to be associated with a 22% cigarette smoking cessation rate out to 5 years.[1] In this randomised controlled trial (RCT), cessation rate was only 5% in the group of patients not undergoing this programme. Fourteen years post randomisation, the group of patients on this programme still exhibited a significant survival benefit as compared to the control group.

The clinical utility of nicotine replacement therapy was assessed in a Cochrane review[4] for which a total of 132 RCTs were summarised. All of the commercially available forms of nicotine replacement therapy (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) were shown to increase the odds of successfully stopping cigarette smoking by 50–70%.

A number of RCTs supported the use of bupropion, an antidepressive agent, in cigarette smokers with cardiovascular disease. Abstinence rates were reported to be 34%, 27% and 22% at 3-, 6- and 12-month follow-up as compared with 15%, 11% and 9%, respectively, with placebo treatment.[5]

Finally, the efficacy of nicotine receptor partial agonists was assessed in a recently published systematic Cochrane review summarising 11 RCTs with more than 10,300 patients.[6] In this analysis, the pooled risk ratio for continuous smoking abstinence at 6 months or longer for varenicline vs. placebo was 2.31 (95% CI 2.01–2.66). Moreover, varenicline was shown to be superior to bupropion [pooled RR for varenicline vs. bupropion at 1 year: 1.52 (95% CI 1.22–1.88)].

Of note, smoking cessation may be associated with important benefits such as improvement of respiratory symptoms[7] and vascular tone already during short-term follow-up.[8]

Recommendations

CLI patients should be strongly and repeatedly advised to stop smoking. **(Level 2a; Grade B)**

Smoking cessation rates can be improved by offering medical advice, group counseling session, nicotine replacement, nicotine receptor partial agonists (varenicline) or antidepressant drug therapy (bupropion). **(Level 1a; Grade A)**

2. Hyperlipidaemia

Increased cholesterol, low-density lipoprotein (LDL), triglyceride and lipoprotein (a) concentrations are independent major PAD risk factors. Moreover, PAD is considered a coronary heart disease risk equivalent.[9]

The Heart Protection Study assessed the impact of statin intake on mortality and fatal and non-fatal vascular events.[10] For that purpose, a total of 20,536 patients with coronary artery disease (CAD), other arterial occlusive disease or diabetes mellitus were randomly assigned to 40 mg simvastatin daily vs. placebo. In that study, all-cause mortality and cardiac death were significantly reduced by statins irrespective of the patients' cholesterol concentration. Importantly, simvastatin reduced major vascular events by 22% in the subgroup of PAD patients. Remarkably, there was no threshold cholesterol value below which statin therapy was not associated with clinical benefits.

In the 4S study (Scandinavian Simvastatin Survival Study), a total of 4444 coronary heart disease patients were randomised to simvastatin vs. placebo.[11] In the statin group, the risks for mortality, stroke and intermittent claudication were significantly reduced. The authors concluded that long-term treatment with simvastatin is safe and improves survival in coronary heart disease patients.

In the PREVENT III study a total of 1404 CLI patients undergoing lower extremity bypass grafting were randomised to edifoligide vs. placebo aimed at preventing neointimal hyperplasia and vein graft failure.[12] In that trial, statin use was associated with a significant reduction of 1-year mortality in a propensity-score adjusted model.

In a Cochrane review including 18 RCTs with 10,049 participants the clinical utility of statins in PAD patients was scrutinised.[13] Lipid-lowering medication was shown to be associated with a beneficial effect on the incidence of total cardiovascular events, primarily due to an overall reduction in coronary events (OR: 0.8; 95% CI 0.7–0.9). Statins were identified as the only type of drug for which consistent, clear evidence of a beneficial effect on total cardiovascular events, total coronary events and stroke was

available. The greatest evidence was with simvastatin in people with a blood cholesterol level of at least 3.5 mmol/L (i.e. 63 mg/dL).

At present, there is no study indicating that diet alone impacts on cardiovascular events in patients with atherosclerosis. It is recommended, however, that therapy for increased cholesterol concentrations begins with lifestyle modifications aimed at lowering elevated cholesterol.[14] Thus, dietary modification and pharmacologic intervention for dyslipidaemia should be tailored to meet the current guidelines for high-risk patients.

In addition to the above-described benefits, statins may prevent plaque instability and thrombosis due to their pleiotropic effects such as improvement of endothelial function, reduction of inflammation, and stabilisation of atherosclerotic plaques.[15]

Current recommendations for the management of lipid disorders in PAD are to achieve an LDL cholesterol level of <100 mg/dL and to treat the pattern of increased triglyceride and low high-density lipoprotein (HDL).[16,17]

Recommendations

In CLI patients, statins should be the primary agents to lower LDL cholesterol levels to reduce the risk of cardiovascular events. **(Level 1a; Grade B)**

For CLI patients, LDL cholesterol should be <100 mg/dL. **(Level 5; Grade D)**

Dietary modification is aimed at controlling body weight and lipid disorders. **(Level 5; Grade D)**

Statins are indicated for secondary prevention of cardiovascular events in patients with CLI. **(Level 1a; Grade B)**

3. Arterial hypertension

Arterial hypertension is a major independent risk factor for PAD. Current hypertension guidelines advocate aggressive treatment of elevated bood pressure in patients with atherosclerosis. Current treatment goals of antihypertensive therapy are arterial blood pressures of <140/90 mmHg. Moreover, blood pressure should be <130/80 mmHg if the patient also has diabetes or renal insufficiency.[18,19] To achieve these results, all drugs capable of lowering arterial blood pressures can be considered for the prevention of vascular events. Many patients may require agents of various classes to achieve the above-mentioned blood pressure goals. Evidence for specific blood-pressure lowering drugs in PAD patients is only available for angiotensin-converting-enzyme (ACE) inhibitors and beta blockers. It has to be kept in mind, however, that an acute reduction of blood pressure may result in a further impairment of lower limb perfusion in CLI patients not undergoing revascularisation.

The specific benefit of ramipril, an ACE inhibitor, in PAD patients was documented by results from the HOPE (Heart Outcomes Prevention Evaluation) study in 4046 patients.[20] In the subgroup of PAD patients, there was a 22% risk reduction in the composite endpoints of myocardial infarction, stroke or cardiovascular death in patients randomised to ramipril as compared to placebo. Interestingly, this clinical benefit was independent of lowering of blood pressure. Thus, ACE inhibitors may exert beneficial effects such as plaque stabilisation and prevention of atherosclerosis progression beyond those of lowering arterial blood pressure. However, it has to be kept in mind that this study was not carried out exclusively in CLI patients. Thus, as for other risk factor interventions, data are largely extrapolated from a general PAD but not specifically CLI population.

Based on results from initial studies with non-selective beta blockers such as propanolol, beta-adrenergic blocking drugs have previously been discouraged in PAD due to their potential to reduce cardiac output and to prevent beta-2-receptor-mediated skeletal muscle vasodilation.[21] Two meta-analyses of studies published in patients with mild and moderate lower limb ischaemia did not confirm the intake of beta blockers to be associated with exacerbation of PAD symptoms.[22,23] Thus, the above-mentioned concern might have been overstated, especially in patients treated with a beta-1 selective drug, especially since PAD patients with coronary disease may have additional cardiac protection with beta blockers. Therefore, beta-adrenergic-blocking agents may be considered for the treatment of arterial hypertension in PAD patients.

The clinical utility of peri-operative administration of beta blockers is controversial. Use of beta blockers was shown to be associated with significant reductions of peri-operative myocardial ischaemia and infarction in various surgical settings.[24] In the POISE (peri-operative ischaemic evaluation) study, a total of 8351 patients with, or at risk of, atherosclerotic disease who were undergoing non-cardiac surgery were randomised to extended-release metoprolol succinate (n = 4174) vs. placebo (n = 4177).[25] Study treatment had been started 2–4 hours before surgery and continued for 30 days. The primary endpoint, a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal cardiac arrest, was more frequently observed in the beta-blocker cohort (5.8%) as compared to the placebo group (6.9%) (HR: 0.84, 95% CI 0.70–0.99; $p = 0.0399$). Fewer patients in the metoprolol group experienced myocardial infarction (4.2% vs. 5.7%, HR: 0.73, 95% CI 0.60–0.89; $p = 0.0017$). However, both mortality (3.1% vs. 2.3%, HR: 1.33, 95% CI 1.03–1.74; $p = 0.0317$) and stroke (1.0% vs. 0.5%, HR: 2.17, 95% CI 1.26–3.74; $p = 0.0053$) rates were higher in the metoprolol compared to the placebo group. Of note, the dose of beta blockers administered in the POISE trial was higher as compared to that used in earlier studies.[26]

Recommendations

CLI patients with arterial hypertension should be treated with antihypertensive medical therapy aimed at lowering cardiovascular mortality. **(Level 1a; Grade B)**

Treatment goals for CLI patients with arterial hypertension: arterial blood pressure should be <140/90 mmHg and <130/80 mmHg in case of concomitant diabetes mellitus or renal insufficiency. **(Level 1a; Grade B)**

ACE inhibitors are recommended in CLI patients. **(Level 2a; Grade B)**

Beta-adrenergic blocking drugs are not contraindicated in CLI patients. **(Level 1a; Grade B)**

Beta-adrenergic blocking drugs may be administered to patients undergoing surgical lower limb revascularisation. **(Level 1a; Grade D)**

4. Diabetes mellitus

Diabetes mellitus is independently associated with PAD and its progression to CLI. Limb salvage rates in diabetic CLI patients have been reported to be lower as compared to those of non-diabetic patients, and diabetes was shown to be an independent risk factor for amputation and complications in CLI patients.

In the STENO-2 study, 160 diabetics were randomly assigned to either intensified or conventional therapy (control of blood glucose, statins, antithrombotic therapy, blood pressure control). After 13.3 years, intensive therapy was associated with a significant reduction of risks of all-cause death (HR: 0.54, 95% CI 0.32–0.89; $p = 0.02$, risk reduction: 20%) and cardiovascular death (HR: 0.43, 95% CI 0.19–0.94; $p = 0.04$, risk reduction: 13%).[27]

In the UKPDS study (United Kingdom Prospective Diabetes study), a total of 5000 patients with newly diagnosed diabetes mellitus were randomised to conventional therapy (dietary restrictions as primary treatment approach) vs. intensified therapy (either sulfonylurea or insulin or metformin).[28] Although between-group differences in HbA1c levels perished after the first year, intensified therapy was associated with risk reductions for microvascular disease, myocardial infarction and death from any cause as well as for any diabetes-related endpoint.

In contrast to these findings, it has recently been called into doubt if intensive glucose lowering is truly beneficial: In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial, a total of 11,140 patients with type 2 diabetes were randomised to undergo either standard glucose control or intensive glucose control to achieve a glycated haemoglobin value of 6.5% or less.[29] In that study, rates of microvascular complications, but not macrovascular complications or cardiovascular deaths were improved by intensive diabetes therapy during a follow-up of 5 years.

Moreover, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study randomised participants with type 2 diabetes and cardiovascular disease or additional cardiovascular risk factors to receive intensive therapy (targeting a HbA1c <6.0%) or standard therapy (targeting a level of 7–7.9%).[30] The study was prematurely stopped after 3.4 years due to an increased mortality in the intensively treated group, although the rates of non-fatal myocardial infarction and stroke were lower in the intensively treated group by that time. At 5 years, the use of intensive therapy for 3.7 years reduced 5-year non-fatal myocardial infarctions but increased 5-year mortality.

Whether the above-mentioned benefits of thorough diabetes control yield improvements in functional lower limb outcomes such as limb salvage or freedom from repeated revascularisation in CLI patients has yet to be determined.

Recommendation

Blood glucose levels should be monitored in CLI patients with a haemoglobin A1c (HbA1c) goal of <7.0%. **(Level 5; Grade D)**

5. Antiplatelet therapy

While the clinical utility of antiplatelet therapy for secondary prevention of patients with atherothrombosis is without controversy, there are currently no convincing data showing a delay or reduction of the progression of lower limb atherothrombotic lesions by antiplatelet therapy. In contrast, studies assessing antiplatelet therapy for primary prevention or peripheral vascular events are scarce and results have been conflicting so far.[31]

The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial demonstrated that the combined risk of death from vascular causes, myocardial infarction, and stroke was significantly, albeit moderately (number-needed-to-treat with clopidogrel in comparison with aspirin: 87 patients) lower with clopidogrel (75 mg/day) compared with aspirin (325 mg/day).[32] Of note, the benefits of clopidogrel were most pronounced in the subgroup of PAD patients in that trial.

The Antithrombotic Trialists' Collaboration meta-analysis found a 23% reduction in serious vascular events in 9214 PAD patients within 42 trials.[33] In the primary meta-analysis, however, no significant reduction of cardiovascular events could be demonstrated for PAD patients without further atherothrombotic lesions in other arterial territories. In a subsequent summary including study data on various antiplatelet drugs such as acetylsalicylic acid, clopidogrel, ticlopidine, dipyridamole and picotamide, a 23% risk reduction of ischaemic results could be shown for all PAD patients.[34] Moreover, since clinically inapparent concomitant coronary heart disease is present in many PAD patients,[35] it might be logical to extend the administration of antiplatelet therapy to asymptomatic PAD patients, although various questions related to this issue are still pending.

The precise daily dose for aspirin remains to be determined. Low-dose aspirin (75–325 mg) is as effective as higher doses.[36] However, higher doses of aspirin result in increased bleeding rates[37] and very low doses (<75 mg) are less effective.[36]

The daily dose of clopidogrel for secondary prevention of PAD patients is 75 mg. Ticlopidin was assessed within various PAD studies and reduces the risk for myocardial infraction, stroke and vascular death.[38] However, its clinical utility is limited by potential side effects such as neutropenia and thrombopenia.

In the absence of other indications for oral anticoagulation, the latter is not indicated in PAD patients. Even more so, it was shown to be associated with higher bleeding rates if added to aspirin, without lowering rates of cardiovascular events.[39]

Two RCTs analysed whether or not antiplatelet therapy may improve patency rates subsequent to lower limb endovascular therapy. In the first study,[40] a total of 199 patients undergoing femoropopliteal angioplasty were randomised to dipyridamole (225 mg) combined with 900 mg of aspirin vs. dipyridamole (225 mg) with 300 mg of aspirin vs. placebo. Patients from both dipyridamole arms showed higher patency rates as compared to those on placebo. In the second study,[41] a total of 223 patients after iliac or femoropopliteal angioplasty were randomised to placebo vs. 50 mg of aspirin plus 400 mg of dipyridamole. Primary patency was comparable in both groups. However, a substantial limitation of that study was that a significantly higher number of iliac angioplasties had been included in the placebo arm, which was shown to be associated with lower restenosis rates.

Moreover, the CASPAR study randomised a total of 425 patients undergoing below-the-knee bypass grafting to either aspirin 75–100 mg per day alone or aspirin 75–100 mg per day plus clopidogrel 75 mg per day.[42] In that trial a combination of clopidogrel plus aspirin did not improve lower limb or systemic outcomes. However, dual antiplatelet therapy was associated with a lower rate of a composite of index-graft occlusion or revascularisation, above-ankle amputation of the affected limb, or death as compared to aspirin alone without increasing bleeding risks.

Four studies analysed whether a high dose (90–1000 mg) of aspirin is more potent in inhibiting reocclusions subsequent to endovascular therapy.[43–45] Six months post-interventionally, there was no benefit of high-dose aspirin, whereas the rates of gastrointestinal side effects increased with higher doses.

In line with current standards in coronary endovascular revascularisation,[46] a combination of aspirin with clopidogrel is used subsequent to peripheral arterial stent implantation. However, at present there are no dedicated study data for the peripheral arteries. The CAMPER (Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularisation) study had been started in the USA to evaluate the combined administration of aspirin and clopidogrel in patients undergoing endovascular revascularisation of the femoropopliteal arteries. Due to insufficient numbers of patients randomised, this study was stopped prematurely.

Recommendations

Antiplatelet (aspirin or clopidogrel) therapy is indicated in patients with symptomatic peripheral arterial disease. **(Level 1a; Grade A)**

Both aspirin and clopidogrel reduce rates of cardiovascular events in patients with symptomatic peripheral arterial disease. **(Level 1b; Grade A)**

In line with recommendations for patients with coronary heart disease, an intermittent administration of dual antiplatelet therapy (aspirin plus clopidogrel) may be considered for patients undergoing stent implantation or drug-eluting balloon angioplasty of femoropopliteal or infrapopliteal arteries. **(Level 5; Grade D)**

A combination of clopidogrel and aspirin may be considered as antithrombotic regimen in patients undergoing below-the-knee prosthetic bypass grafting. **(Level 1b; Grade A)**

6. Vasoactive drugs

In patients with CLI not eligible for arterial reconstruction, prostanoids are the only vasoactive drugs with proven efficacy. The currently available data support the use of prostanoids in patients unsuitable for lower limb revascularisation or in patients in whom revascularisation attempts have failed.

Two randomised double-blind studies with prostaglandin E-1 have shown a clinical benefit with regard to the reduction of ulcer size.[47,48] A further RCT with iloprost showed higher limb salvage and survival rates in the prostanoid group.[49]

Creutzig recently concluded, in a meta-analysis of randomised placebo-controlled trials[50] including data from 7 studies totalling 643 patients, that for patients with PAD stage III or IV PGE1 therapy not only has significant beneficial effects over placebo on ulcer healing and pain relief, but also increases the rate of patients surviving with both legs after 6 months follow-up.

A further meta-analysis has shown that a 2- to 4-week treatment with iloprost reduces rest pain and ulcer size.[51] Moreover, iloprost was associated with a higher rate of amputation-free survival at 6 months. It has to be kept in mind, however, that the use of iloprost is not approved in all European countries.

Further vasoactive drugs such as naftidrofuryl, buflomedil or pentoxifylline did not show additional benefit with regard to reduction of amputations and wound healing.[2,52]

Recommendation

Parenteral prostanoids can be used in patients with critical limb ischaemia not suitable for arterial revascularisation or after unsuccessful revascularisation. **(Level 1b; Grade B)**

7. Gene and stem-cell therapy

The clinical utility of gene and stem-cell therapy is not yet fully understood. While it has been shown that both treatment approaches are well tolerated, a significant clinical benefit has yet to be shown for either method.

Gene therapy has been clinically evaluated since 1994 within at least 6 placebo-controlled randomised clinical phase II studies and within one placebo-controlled phase III study. The four studies assessing gene therapy in CLI patients were positive for various endpoints.[53–56] However, only amputation and mortality should be considered clinically relevant endpoints in this regard. Only the application of riferminogen pecaplasmid [non-viral gene construct for the fibroblast growth factor 1 (NV1FGF)] was shown to be associated with a reduction of the rate for major amputations and improved amputation-free survival as compared to placebo within the TALISMAN 201 study.[54] Further positive endpoints of other studies included angiographically verified improvements of arterial vascularisation during follow-up, improvements in transcutaneously measured oxygen partial pressure and further haemodynamic parameters.

Based on positive results from the above-mentioned TALISMAN 201 study,[54] the currently largest gene therapy trial was initiated including 525 CLI patients without any option for endovascular or surgical revascularisation from 30 countries and 171 hospitals. With 2-week intervals eight injections of a gene construct vs. placebo were applied into thigh and calf of the affected limb. After 12 months, there was no significant difference in amputation-free survival and time to major amputation comparing the NV1FGF with the placebo group.[57]

Since progenitor cells have been identified as a participant in angiogenesis, their role in therapeutic clinical applications has been assessed. The first clinical trial investigating the use of progenitor cells in CLI patients was published in 2002.[58] Use of bone-marrow-derived mononuclear cells was associated with improvements in ABI, $TcPO_2$ and pain-free walking time out to 6 months. Subsequent to this trial with a small sample size, this concept was investigated in various non-randomised studies with small sample sizes.[59] To date, there are no double-blind RCTs assessing the use

of bone-marrow-derived or mobilised mononuclear cells in PAD patients. The scientific community is currently waiting for results of at least 10 randomised controlled cell therapy trials.[59,60] Until data from these studies are availabe, the application of stem cells cannot be recommended outside clinical studies.

Recommendation

Neither gene nor stem cell therapy can be recommended as a treatment for CLI outside clinical trials. **(Level 5; Grade D)**

8. Exercise and lower limb rehabilitation

In contrast to patients with intermittent claudication, no data assessing the efficacy of walking exercise in CLI are available. Considering the risk of causing or worsening already present ischaemic wounds, walking exercise is contraindicated in patients with CLI not undergoing revascularisation.

Recommendation

Due to the risk of worsening pre-existing or causing new ischaemic wounds in the affected lower limb, walking exercise may be contraindicated in CLI patients not undergoing revascularisation. **(Level 5; Grade D)**

9. Treatment of co-existing disease

This section covers the management of typical co-existing diseases in patients presenting with CLI and with important impact on morbidity and mortality.

9.1. Coronary artery disease (CAD)

Patients with PAD have a high prevalence of CAD, which strongly increases the risk for cardiac mortality and morbidity.[61,62] Therefore, all PAD patients should be considered at high risk for clinically significant ischaemic heart disease, for which guidelines exist.[63,64] Cardiac risk is related to urgency, extent, type and duration of the intervention planned. Patients should be evaluated for evidence of CAD. Treatment decisions for coexisting CAD should be based on current practice guidelines and the intended treatment modality. Patients with unstable symptoms (acute coronary syndrome, congestive heart failure) should be referred to a cardiovascular physician for appropriate diagnosis and treatment. Most patients with severe cardiac symptoms will require coronary angiography to determine the appropriate means for revascularisation. For patients with stable CAD, management should be guided by the severity of the symptoms and comorbid conditions. All patients should be given appropriate medical therapy to treat symptoms and atherosclerotic risk factors. Cardiac assessment scores may be useful in the context of patients being considered for peripheral revascularisation.[65] In patients with a high cardiac risk assessment score, current guidelines recommend further evaluation of the patient for possible coronary revascularisation.[24] However, in the recent Coronary Artery Revascularization Prophylaxis (CARP) trial of patients with peripheral vascular disease who were considered high risk for peri-operative complications and had significant CAD, coronary revascularisation did not reduce peri-operative myocardial infarction or overall mortality.[66]

Delay to vascular surgery was significantly longer in patients who underwent coronary revascularisation compared to patients who did not, which in CLI patients is often counterproductive. Therefore, the strategy of a pre-emptive coronary revascularisation prior to urgent peripheral vascular surgery should not normally be pursued. In most patients, peri-operative use of beta-adrenergic-blocking agents is associated with reduced cardiovascular risks of surgery. Recent studies have shown that beta-adrenergic blockade with bisoprolol significantly decreases the risk for cardiovascular events during vascular surgery and afterwards.[67,68] Besides controlling symptoms of myocardial ischaemia, treatment with beta-blocking agents also has the benefit of favourably influencing prognosis in these patients.[69] Starting beta-adrenergic-blocking treatment shortly before surgery (POISE), however, was not proven to be beneficial in terms of mortality and stroke as outlined above.[25]

Recommendations

Routine treatment with beta blockers before vascular surgery is recommended. **(Level 1b; Grade B)**

Routine coronary revascularisation before vascular surgery is not recommended. **(Level 1b; Grade B)**

9.2. Carotid artery disease

The prevalence of carotid artery disease in patients with PAD is 10–30%, and there are no specific data for CLI. Since PAD patients are at an increased risk of stroke it might be reasonable to screen those patients for carotid artery disease routinely. Further evaluation and consideration for revascularisation should be based on current guidelines.[70] One must keep in mind that CLI patients with limited life expectancy will hardly benefit from carotid endarterectomy or stenting for asymptomatic carotid disease.

9.3. Renal artery disease

PAD patients are at an increased risk for renovascular hypertension. The management of patients with atherosclerotic renal artery disease and PAD is focused on preservation of renal function and control of hypertension. Patients with hypertension should be assessed by renovascular ultrasound imaging. In the presence of significant renal artery stenosis treatment should be based on current guidelines.[2,71–74] These patients should be referred to an appropriate vascular physician. Again, one must keep in mind that CLI patients will hardly benefit from treatment of renal artery stenosis.

10. Health economics of risk-factor interventions

Unlike in PAD patients,[2] no literature is available on health economics of risk-factor intervention specifically in CLI patients. CLI patients differ importantly from claudicants. CLI patients are suffering from ischaemic lower

limb pain, depression, social isolation and fear of losing their limb. They tend to adhere more to their habits and changing any life style issue can be an important task.

Measuring compliance of chronic patients to risk-factor interventions is difficult since these patients are treated by numerous health professionals at the same time. Health and economic benefits are obviously worse in CLI patients than in primary preventions since life expectancy in CLI patients is significantly reduced. An additional difficulty is that health and economic benefits are delayed while resources for treatment have to be expended at once. Moreover, given that numerous interventions are performed by means of a variety of drugs, costs differ importantly between health-economic systems in different countries. Costs in health economics can be expressed as average costs for 1 year of life gained.

10.1. Cost-effectiveness of smoking cessation interventions

No publications are available for CLI patients. Although there is good evidence for smoking cessation in peripheral artery disease, cessation programmes might not be successful in CLI patients. Training and group counseling sessions may not be followed in normal range. Antidepressant therapy (bupropion) and nicotine replacement could therefore still be considered by the treating physician.[5]

10.2. Cost-effectiveness of pharmacologic interventions

Studies on diabetes, dyslipidaemia and hypertension have shown for primary intervention that compliance with guidelines is usually cost effective with a range of $20,000 to $30,000 per year of life gained.[75,76] Statin drug costs represented between 45% and 68% of the overall primary preventive cost of coronary heart disease.[77] The specific costs differ depending on the guidelines used. Studies on cost-effectiveness in CLI patients are currently lacking. Considering that CLI patients would benefit from the same medication as claudicants, i.e. treatment by a combination of aspirin, a statin, a beta blocker and a diuretic,[78] the costs per additional quality-adjusted life year (QALY) would be £20,000 to £40,000. On top of that in CLI patients pain-relief medication, antibiotics, ACE inhibitors and more should be added.

Recently the term "cost per major event averted" has been created since studies have failed to show a benefit on mortality. For example, the cost effectiveness of 40 mg/day simvastatin in high-risk patients is £4500 (95% CI £2300–7400) per major vascular event averted, but the result is highly dependent on the cost of statin.[79]

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None

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