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REVIEW ARTICLE

What Constitutes Best Medical Therapy for Peripheral Arterial Disease?

P. Burns, E. Lima and A. W. Bradbury*

University Department of Vascular Surgery, Heartlands Hospital, Birmingham, U.K.

Peripheral arterial disease (PAD) is associated with a high morbidity and mortality, largely from coronary and cerebrovascular disease, which often overshadows the PAD itself. Best Medical Therapy (BMT), comprising smoking cessation, antiplatelet agent use, cholesterol reduction, exercise therapy, and the diagnosis and treatment of hypertension and diabetes mellitus; is evidenced based and can result in significant reductions in cardiovascular risk, as well as some improvement in PAD. Previous data have largely been restricted to patients with coronary artery disease, and their relevance to PAD has been extrapolated. However, data are now starting to become available, such as the Heart Protection Study, with data specific to PAD patients. This article reviews the data regarding the use of BMT in patients with PAD, and based on this, makes recommendations for the use of BMT in this group of patients.

Key Words: Best medical therapy; Peripheral arterial disease.

Introduction

Peripheral arterial disease (PAD) is common, with over 20% of the population having asymptomatic disease, and up to 5% having lower limb symptoms; most commonly, intermittent claudication.[1] Although intermittent claudication is relatively benign in terms of limb-loss (1–2% per year), it is associated with a vascular mortality (5–10% per year) 2–4 times greater than that of an age and sex matched non-claudicant population; a risk that is, in fact, greater than that experienced by patients with angina.[2] There are several reasons for this.

- PAD is a marker for severe, multi-system atherosclerosis affecting the cerebral, visceral and coronary arteries.[3]
- In the presence of exercise-limiting intermittent claudication, even severe ischaemic heart disease may be asymptomatic and thus go unrecognised and untreated.
- There is some evidence that repeated ischaemia-reperfusion of leg muscles may lead to a systemic inflammatory response that accelerates atherosclerosis and promotes thrombotic events.[4]
- But most importantly, research into the benefits of risk factor modification and best medical treatment (BMT) in PAD patients has lagged far behind that directed towards symptomatic ischaemic heart disease. This in turn has resulted in:
  - a less compelling evidence base for treatment.
  - a lack of awareness of the vascular risk faced by these patients.
  - a belief that the costs of instituting BMT in patients with PAD could not be justified.

For these reasons, rather than viewing the PAD patient in a holistic way as a vascular "time-bomb", those treating PAD have tended to focus on the arterial lesion and its surgical or endovascular (angioplasty, stenting) treatment. Unfortunately, with the notable exception of carotid intervention for high-grade symptomatic disease,[5–7] there is little or no level 1 evidence to support intervention for PAD that is not immediately life or limb-threatening. What little data are available suggest that invasive intervention for claudication can lead to an early (1 year) improvement in symptoms, but there is no evidence this is sustained.[8–11] Such interventions are expensive,

* Please address all correspondence to: A. W. Bradbury, Professor of Vascular Surgery, Lincoln House (Research Institute), Birmingham Heartlands Hospital, Bordesley Green East, Birmingham, B9 5SS, U.K.

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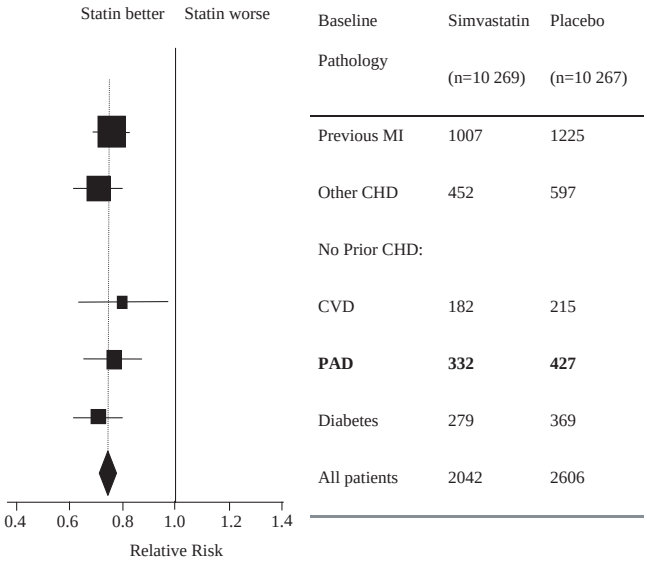
potentially hazardous, usually of limited durability and do not impact upon the patients' high underling vascular risk.[10,11] By contrast, there is increasing and compelling evidence that BMT comprising anti-smoking strategies, antiplatelet agents, lipid lowering and exercise programmes dramatically reduce the vascular risk and significant increase functional status.[12,13] BMT is also relatively inexpensive and virtually free from risk. With the release of data from the Heart Protection Study, which included over 6000 patients with PAD and confirmed the benefits of lipid lowering, it is timely to review what BMT should comprise and how it can be instituted universally in patients with PAD.[14]

Anti-smoking strategies

There is overwhelming evidence that smoking is the single most important risk factor for the development and progression of PAD and that it significantly increases the risk, and reduces the success, of peripheral arterial intervention.[12,15–20] Despite the clear benefits of smoking cessation in PAD patients, only a minority (11–48%) of patients manage to quit.[21] Simple oral advice is ineffective,[22] but more intensive counselling has been shown to be effective in unselected smokers, although not in PAD patients.[23–25] Nicotine replacement therapy, whether delivered by patch, gum, intranasal spray, inhaler or sublingual tablet, is safe, and leads to significant improvements in smoking cessation (odds ratio 1.72, 95% confidence interval 1.60–1.84); at least in the short term.[26,27] Bupropion is at least as effective as nicotine replacement therapy, but appears to confer no additional benefit in combination with nicotine replacement therapy.[28] The Cochrane group on tobacco addiction has found alternative therapies such as acupuncture, hypnotherapy, and "aversive smoking", to be ineffective.[29–31]

Hypercholesterolaemia

Hypercholesterolaemia is clearly an independent risk factor for the development and progression of PAD.[2,15,16,32] Cholesterol lowering has been shown to slow the progression of peripheral atherosclerosis in a number of large, including randomised, anatomical and pathological studies,[33,34] although none have shown benefit with respect to PAD symptoms. The recently concluded Heart Protection Study has, for the first time, demonstrated a benefit of statins in PAD patients by reducing coronary events by 20%. Furthermore, this was achieved irrespective of starting total cholesterol[35] (Fig. 1). Detailed, peer-reviewed



Baseline Pathology	Simvastatin (n=10 269)	Placebo (n=10 267)
Previous MI	1007	1225
Other CHD	452	597
No Prior CHD:		
CVD	182	215
PAD	**332**	**427**
Diabetes	279	369
All patients	2042	2606

Fig. 1. Benefit of 40 mg simvastatin from The Heart Protection Study. Number of vascular events by prior disease. Data taken from www.hpsinfo.org. MI: myocardial infarction; CHD: coronary heart disease; CVD: cerebrovascular disease.

results are awaited, but this could have significant implications for cholesterol lowering in patients with PAD. Whether there is benefit from raising high density lipoproteins, and reducing triglycerides levels is less clear.[36]

In summary, all patients with PAD should have their cholesterol reduced with aggressive statin therapy, regardless of starting total cholesterol. In the longer term it seems possible that statin therapy will be indicated for any patient with objective evidence of asymptomatic PAD; for example, as demonstrated by a reduced ankle : brachial pressure index. As patents expire, and generic drugs become available, the financial consequences of these massive changes in prescribing practice will ease and, of course, the prevention of large numbers of vascular events will also help to offset the costs.

Antiplatelet Therapy

Early studies suggested antiplatelet agents could produce angiographic improvement,[37] increase walking distance,[38,39] and reduce the requirement for vascular intervention.[40] There is overwhelming evidence from the Antiplatelet Trialists' Collaboration that the prescription of an anti-platelet agent, usually aspirin, reduces vascular death in patients with symptomatic atherosclerotic disease by about 25%.[41] Most of the studies were in patients with ischaemic heart disease and, when taken in isolation, data from the few studies looking specifically at patients with PAD were

not conclusive. However, more recently, a review of 24 trials has shown that, when compared with placebo, APA treatment reduced the risk of death by about a quarter in patients with PAD.[42]

In summary, all patients with PAD should be on an antiplatelet agents because it reduces vascular event and death, improves the patency rates of surgery and endovascular interventions and may improve walking distance. For reasons of cost, non-enteric aspirin (75 mg) is a reasonable first-line choice as there is no clear evidence that a higher dose is more effective (but will cause more adverse events) or that enteric coating is associated with less gastric upset (and is more expensive). Patients who cannot take aspirin should be considered for clopidogrel.

Exercise

There is little doubt that exercise leads to a significant improvement in exercise tolerance (most studies show at least a doubling in walking distance) in patients with PAD.[43–45] It is also likely, though not specifically proved, that exercise will reduce vascular risk. However, clinicians and academics alike have largely neglected this simple, inexpensive and effective therapy; and as such, many important questions remain unanswered.

How does exercise work? Whilst early animal studies suggested that exercise may improve blood flow by the development of collaterals, studies in humans using venous occlusion plethysmography, Xenon-133 clearance and duplex ultrasonography have not confirmed this.[46] Despite this, exercise training can lead to increased clearance of Xenon-133 injected into calf muscles, possibly indicating that blood is being diverted towards more active muscles. Exercise training in claudicants leads to increases in oxidative enzymes, and enhanced utilization of fatty acids in the calf muscles, maximising the use of oxygen delivered to the tissues. Improvements in walking distance may also be due to improvements in walking biomechanics[47] and blood rheology.[48]

What is the best form of exercise? It has generally been thought to be walking but recent data have suggested that arm exercise, may be at least as beneficial, which further questions the mechanism by which exercise achieves its benefit.[49]

Does exercise have beneficial effects on risk factor profile? A small non-randomised controlled trail showed that exercise training for claudicants, can lead to modest reductions in blood pressure, cholesterol and glucose levels.[51] Whether this translates to a significant improvement in cardiovascular risk, has not been specifically determined in claudicants, but data from ischaemic heart disease patients suggests that it may.[50]

Should exercise be supervised and, if so, how and for how long? Supervised exercise programmes would seem intuitively to be better, but there is little evidence to support this. Gardner and Poehlman reviewed 21 studies of exercise therapy in PAD, and found that supervised exercise programmes were no better than unsupervised. A small randomised study of 54 patients, comparing a 12 week supervised exercise programme and unsupervised exercise, did suggest that the supervised programme was superior (improvement in maximum walking distance 207 vs 70% at 6 months). What is unclear, is the durability of any benefit. It might be speculated that any advantage of supervised exercise will diminish with time, although there is no evidence to support this.

Until these issues are addressed one must approach this aspect of care in a pragmatic way based upon local resources. PAD patients should certainly be repeatedly and specifically informed that exercise is beneficial and that it is not (as far as we know) harmful to try to "walk through" their claudication pain. Written advice may be a useful adjunct although this suggestion is not evidence-based. Although supervised programmes may be superior, at least in the U.K., such programmes are not widely available. The ongoing, U.K.-based, Heath Technology Assessment funded Exercise versus angioplasty in claudication trial (EXACT) will provide more information about the relative benefits of exercise and angioplasty when it reports (for more information please contact the senior author).

Diabetes

Diabetics have a 3–5 fold increased risk of PAD, and are at increased risk of progression from intermittent claudication to critical limb ischaemia.[52,53] The U.K. Prospective Diabetes Study has shown that intensive control decreased the risk of microvascular but not macrovascular vascular complications of the disease.[54] However, it is extremely important that the diagnosis of diabetes be specifically confirmed or excluded in patients with PAD because it will affect other areas of their treatment, such as blood pressure and lipid control.[55,56]

Blood Pressure Control

Hypertension, particularly, systolic hypertension, is associated with a three-fold increase in the risk

of developing PAD.[57–59] No study has specifically investigated PAD patients but it is quite clear that in general the treatment of hypertension significantly reduces coronary events and stroke.[60] Traditionally, blood pressure has been treated to a level of 160/90, but more recent data suggest that tighter control (130–140/85 mmHg) might confer additional benefits.[61] It is frequently taught that β blockers are contra-indicated PAD, but there is no evidence to support this.[62]

Other Risk Factors

Hyperhomocysteinaemia is becoming increasingly recognised as an important risk factor for development of atherosclerosis, and cross-sectional studies have linked it specifically to PAD.[63] However, the effect of reducing homocysteine levels has yet to defined, but should be answered by several ongoing trials. Observational studies have suggested that low levels of anti-oxidant vitamins are associated with PAD, although no studies, including the Heart Protection Study, have yet shown any benefit from vitamin supplementation.[14,64,65]

The relationship between alcohol and PAD appears to be J shaped, with minimal risk occurring at around 2 units of alcohol per day.[66] Excess alcohol consumption is clearly associated with an increased vascular risk. Oestrogen has been proposed as being cardio protective, on the basis of reduced cardiovascular morbidity and mortality in women taking hormone replacement therapy, but a recent randomised controlled trials showed no difference in cardiovascular events between groups randomised to oestrogen/progestogen, and placebo.[67] In summary, these factors may represent important risk factors in PAD, but at present there is insufficient evidence to justify targeting them for treatment.

Prevalence of BMT use in PAD

Despite the overwhelming evidence for BMT in patients with PAD, clinical experience and the literature indicated that it has been poorly applied in the past (Table 1). The proportion of patients taking any kind of anti-thrombotic therapy or warfarin ranges from 39% to 66%, and prevalence of cholesterol lowering therapy ranges from 5% to 46%. Patients who also have symptomatic ischaemic heart disease seem more likely to be treated but, in general there seems little or no relationship between the prevalence of treatment, the severity of the underlying disease and thus the potential benefits of BMT.[68–71] In other words, treatment is haphazard rather that the result of evidence.

The current situation is unacceptable, and clearly strategies need to be put in place to ensure that PAD patients do not miss out on evidence-based life saving treatment. The initial step needs to be the education of health professionals working with PAD patients about the increased cardiovascular risk of these patients, and the benefits of BMT. Articles such as this should raise the profile of these important issues. One strategy to increase the institution of BMT is the use of record cards (Fig. 2). These chart the level of individual risk factors over time, and allow easy recognition for healthcare professionals of untreated, or inadequately treated risk factors. These charts could be held in the case notes, or by the patient. Another possibility for increasing BMT use is to have dedicated staff in out-patient clinics. This is an ideal role for clinical nurse specialists, who are increasing in number. Whatever technique is employed, it is important to co-ordinate the patient's care with primary care.

Summary

There is overwhelming evidence for the efficacy of BMT in PAD, in terms of cardiovascular risk reduction, and improvement in PAD symptoms. Recommendations for the use of BMT, based on the best evidence available to date are presented in Table 2. Despite the evidence of benefit, BMT is grossly

Table 1. The use of cholesterol-lowering and anti-thrombotic therapy (antiplatelet agent of warfarin) in patients with PAD.

Study	*n*	Patient population	*n* with IHD (%)	*n* receiving	
				Cholesterol-lowering therapy (%)	Anti-thrombotic therapy (%)
Clark *et al*. (1999)[68]	299	Admitted for angiography	106 (36)	26 (9)	140 (47)
Anand *et al*. (1999)[70]	195	Admitted for peripheral arterial surgery	106 (54)	31 (16)	94 (49)
Bismuth *et al*. (2000)[69]	147	Critical limb ischaemia	66 (45)	8 (5)	58 (39)
McDermott *et al*. (1997)[71]	202	ABPI < 0.9 or abnormal Doppler waveform	103 (51)	93 (46)	133 (66)

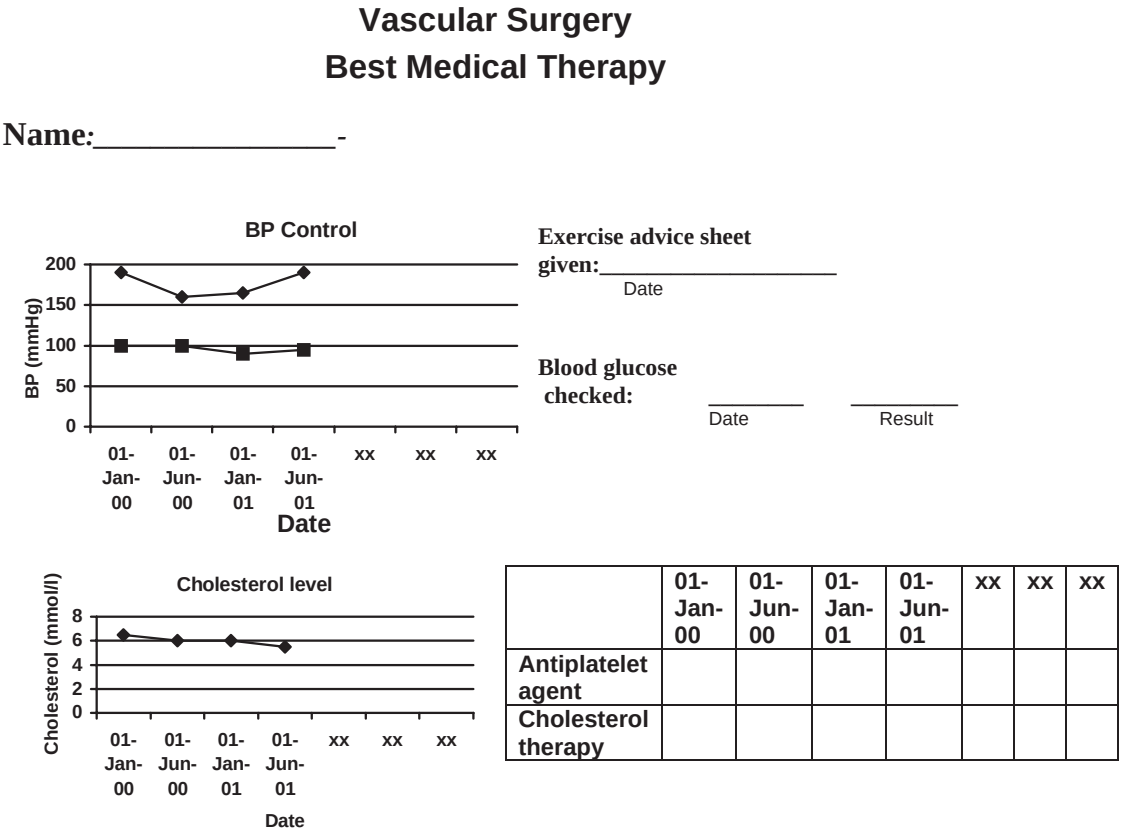


Fig. 2. Best Medical Therapy chart.

Table 2. Recommendations for best medical therapy (BMT) in patients with PAD.

Component of BMT	Recommendation
Smoking cessation	Repeated advice Nicotine replacement therapy Behavioural therapy (Smoking cessation classes)
Cholesterol reduction	Cholesterol checked yearly Statin therapy if total cholesterol >5.0 Additional treatment will be required if HDL low, or triglycerides high (Referral to lipid clinic)
Antiplatelet agent	Aspirin Clopidogrel if aspirin intolerant
Diabetes mellitus	Screen for diabetes mellitus
Blood pressure	Reduce blood pressure to $<140/80$ mmHg
Exercise	Patients with lower limb disease should be prescribed a supervised exercise programme

underused in PAD patients. If BMT use increases, this will lead to a decrease in cardiovascular morbidity and mortality, a reduction in the requirement for peripheral vascular intervention, and an improvement in outcome for those interventions that are required. It is imperative that those involved in the care of patients with PAD are aware of the benefit of BMT, and develop strategies to help improve its implementation.

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