ARTICLE

# RECENT TRENDS IN THE MANAGEMENT OF PERIPHERAL VASCULAR DISEASE IN HIGH RISK PATIENTS

**Mr Sherif Sultan, Consultant Vascular and Endovascular Surgeon, and Dr Niamh Hynes, Vascular Research Fellow, Western Vascular Institute, University College Hospital Galway.**

## INTRODUCTION

Arterial disease is the most prevalent disease in the developed world. Atherosclerotic arterial disease can slowly progress to a clinical syndrome and the main burden is acute ischaemic vascular events. The age-adjusted prevalence of peripheral vascular disease (PVD) is 12% in both men and women.[1] The risk increases two- to three-fold for every 10-year increase in age above the age of 40 years. PVD is closely associated with cardiovascular risk factors such as smoking, diabetes mellitus, hyperlipidaemia, hypertension, poor renal function and increases in homocysteine levels.[2-4]

The most important of these risk factors are diabetes mellitus and smoking, each with a relative risk for PVD of three- to four-fold.[2,3] Both C-reactive protein and fibrinogen are strongly associated with PVD, suggesting a role for inflammation in the pathogenesis of PVD and may predispose these patients to a marked increased risk of myocardial infarction, ischaemic stroke and vascular death.[5]

In patients with PVD, the adjusted all-cause mortality risk rate is increased three-fold and the cardiovascular mortality rate is increased six-fold.[6] Critical limb ischaemia (CLI) represents the most advanced stage of PVD and is associated with high rates of cardiovascular mortality, morbidity, diminished quality of life and major limb amputation. Mortality rates in patients with CLI are typically in the range of 20% by one year. Case fatalities increase with age and, in contrast to other arterial fields, namely coronary and cerebrovascular, where mortality is often overestimated, death certificates consistently underestimate the burden of acute peripheral vascular events.

Only with experience and a high deliberate practice volume (DPV) can one determine, firstly, if revascularisation is technically feasible, secondly, how co-morbid factors influence outcome and, thirdly, which treatment modality is best suited to the situation.

## PHARMACOTHERAPY

Potential benefits of anti-thrombotic therapy include improved patency of lower extremity angioplasty/bypass grafts and a reduction in amputations. Lipid-lowering drugs, particularly the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins), have demonstrated significant benefit in numerous secondary prevention trials.[7-9] Statin therapy has been associated with decreased peri-operative mortality in patients undergoing major vascular surgery.[10] The benefits of peri-operative cardio-selective blocker use in vascular patients appear to extend well beyond the period of operative stress.[11,12]

All our patients are treated with aspirin, a statin and a cardio-selective β-blocker peri- and post-operatively. Post-operatively, we add clopidogrel for one year. This 'magic bullet' aims to reduce cardiovascular morbidity and mortality, and failures due to thrombosis, myointimal hyperplasia or further progression of atherosclerosis. We have previously shown that this treatment statistically improves the overall outcome of high risk patients with PVD.[13]

## INTERVENTION

Despite the increasingly complex medical and surgical challenge associated with CLI, excellent outcomes can still be achieved by an aggressive policy to attempt revascularisation for all patients who have a chance of maintaining independence, provided that the limb is salvageable and the patient is fit for surgery.[14] We have previously demonstrated that specialised vascular care and the increasing use of minimally-invasive techniques has significantly lowered the peri-operative death and morbidity rates in this high risk patient population.[15]

However, because of the palliative nature of CLI treatment, although initial benefits are achievable, the question remains as to whether these high risk patients actually live long enough to benefit from their revascularisation.[16] In our unit, 10 year survival

rates were 42.5% (SE 2.7%) for primary amputation and 44.4% (SE 2.09%) for bypass surgery. However, with advances in percutaneous minimally-invasive techniques and the increase in the application of endovascular therapy for arterial occlusive disease of the lower extremities, the long-term outlook for CLI patients is improving.

In our unit, in the last decade of the 20th century, 98% of revascularisations were performed by bypass, with only 2% performed by angioplasty. Since the turn of the century, 52% of revascularisations are performed endovascularly with less than 48% performed by bypass. The primary amputation rate has decreased from 33% in the period 1990-2000 to 21% in the period 2001-2005.

## ENDOVASCULAR TECHNIQUES

Considerable advances have been made over the last decade in percutaneous technology for treatment of atherosclerotic diseases in the iliac, femoropopliteal and distal tibio-peroneal arteries. While treatment strategies are well defined in the ilio-femoral segment, where angioplasty and stenting perform well in appropriately selected lesions, the search for a durable transcatheter therapy for femoropopliteal and distal occlusive disease continues. The spectrum of treatment alternatives to angioplasty ranges from transcatheter plaque excision to laser ablation, rotational atherectomy, cryoplasty, brachytherapy and stenting.[17]

The success, durability and cost-effectiveness of iliac artery stenting has been well established, with patency rates that rival those of standard surgical procedures. Patency rates are even comparable with aorto-bi-femoral grafting, one of the most successful and durable of vascular procedures.[14,18] The presence of poor run-off, external iliac artery disease and female gender are independent predictors of poor outcome after iliac stenting.[19] However, iliac angioplasty and stenting has been successful even for Trans-Atlantic Society Consensus Working Group (TASC) D lesions and occlusions, once thought to be suitable only for surgical reconstruction.[14]

Subintimal angioplasty (SIA) is increasingly being recognised as an option in the treatment of chronic CLI.[20-22] In this process, the subintimal space, proximal or distal to the occlusion, is entered, traversing the occlusion in the subintimal channel to exit downstream in the natural lumen. This technique is primarily effective in lengthy occlusions and the tibio-peroneal vessels. Subintimal PTA is indicated for CLI or in patients unfit for anaesthesia or without a suitable venous conduit for bypass. However, it is our first-line management in CLI.

Previous studies by our group have shown that SIA can achieve symptomatic patency rates of 95% and a reduction in length of hospital stay by minimally-invasive means.[14] The minimal invasiveness of the procedure allows treatment of this elderly population, the majority of whom have significant co-morbidity, even if they have multi-level occlusive disease. We have previously shown that SIA is equivocal to bypass surgery in the management of CLI without compromising limb salvage, patient survival and subsequent vascular intervention rates, even in lesions classified as C or D by the TASC group.[14,15]

In our unit, four years' survival rate is 17% higher for SIA compared to bypass (p=0.0017, relative risk [RR] =0.62, 95% confidence interval [CI] =0.47-0.81). Furthermore, patients are more likely to be discharged to their home, rather than a further healthcare facility or nursing home, if they are treated by SIA than if they had bypass surgery or primary amputation, reflecting an increased ambulatory rate and degree of independence.

Due to the fact that primary success of femoropopliteal stenting is very high, the possibility of coating a stent with an anti-proliferative agent may maintain initial patency and eliminate or dramatically reduce the need for secondary intervention. The question of whether to stent primarily in CLI or whether to reserve stenting for the management of elastic recoil, dissection, perforation and thrombosis remains unsolved.

## DIABETES

The incidence of diabetes, especially type 2, in our population is increasing as our population ages.[23,24] Diabetes is known to be associated with increased calcification, multi-level disease and infrapopliteal lesions, as well as a mortality rate up to 10 times higher than in those without diabetes.[25] However, it has been shown that people with diabetes can benefit from a bypass operation to the same degree as those without diabetes in terms of patency and limb salvage.[26]

Although SIA has been shown to successfully achieve recanalisation of long occluded arterial segments,[14,27,28] its specific role in patients with diabetes has not been widely studied. We found that people with diabetes were more likely to have a primary amputation than those without diabetes,[15] a finding reflected in previous studies.[29]

However, in those patients deemed suitable for revascularisation, including those with multi-level disease and infrapopliteal lesions, there was no statistical significant difference in the limb salvage rate between people with diabetes and those without diabetes. This is, again, in accordance with other studies.[27] However, we found that people with diabetes were more likely to have an amputation after bypass surgery than after SIA.[15]

For patients with diabetes, strict glycaemic control should be mandatory prior to undergoing vascular intervention. We perform routine measurement of plasma HbA1c levels for all patients undergoing vascular surgery. We have found that more than 50% of those without diabetes presenting to our unit have chronic hyperglycaemia as determined by plasma HbA1c >6% and ≤7%. We also found that the majority of patients with diabetes presenting for vascular surgery have suboptimal HbA1c levels (HbA1c >7%).

Raised glucose levels in the circulation may speed up the process of atherosclerosis through putative mechanisms, such as oxidative stress and protein glycation of vessel walls.[31] In patients with diabetes, reducing plasma HbA1c levels by tight glycaemic control lowers the risk of subsequent microvascular disease. However, the relation of reduced HbA1c levels with macrovascular outcomes (e.g. stroke, ischaemic heart disease, PVD) is less clear.[32]

Studies have concluded that a progressive relation between glucose concentrations and cardiovascular disease extends below the current threshold used to define diabetes mellitus.[33,34] Therefore, patients who do not have diabetes with suboptimal HbA1c levels may have a level of dysglycaemia that may not meet the criteria for a diagnosis of diabetes mellitus, but may still contribute to an adverse post-operative outcome.

In a study to determine whether or not patients with diabetes and those without diabetes with suboptimal HbA1c levels had a worse post-operative outcome than those patients with optimal HbA1c levels in a vascular surgical population, we found that both non-diabetes and diabetes patients with suboptimal HbA1c levels had a higher incidence of 30-day post-operative morbidity, compared to non-diabetes and diabetes patients with optimal HbA1c levels. Multivariate analysis revealed that, in non-diabetic patients, a plasma HbA1c >6% and ≤7% was a significant independent predictor of overall 30 day morbidity. A suboptimal HbA1c level, therefore, may have prognostic significance in patients without diabetes undergoing vascular surgery.

## ALTERNATIVE TREATMENT MODALITIES

In light of the poor long-term outcome associated with primary amputation, we have successfully introduced treatments for patients unsuitable for either SIA or bypass and in whom amputation would previously have been inevitable.

Our initial experience with non-operative management of CLI using a mechanical sequential compression device (ArtAssist) mirrors the experience of other centres using similar devices,[35,36] and has allowed limb salvage and reduced hospital stay in patients with no option of revascularisation.

## CONCLUSION

We have shown that significant improvements in salvaging limbs are possible with high DPVs. Although some authors have voiced concerns that, in this high risk cohort, an inverse relationship may actually exist between limb salvage and survival, we have shown that, in our practice, a judicious approach to high risk revascularisation can result in significant improvement in long-term survival.

The danger with management of CLI is that treatment can be focused on graft and limb, with only modest understanding of the effects of treatment on patient morbidity, function and long-term survival. Only with specialist vascular training and deliberate practice can one appreciate that endovascular therapy and open vascular surgery have advantages and disadvantages.

A single therapeutic option is rarely ideal for all patients. Only a vascular and endovascular specialist, who is expert in both techniques, can appreciate which technique to use, how to combine modalities for hybrid techniques, what alternatives are available when neither technique is applicable and how to optimise overall care.

The evolution of endovascular therapy over the last decade has led to the development of simpler, safer and more durable techniques for limb salvage. Exciting developments in the areas of drug-eluting stents, stem cell therapy, angiogenesis and nanotechnology will undoubtedly bring solutions for patients with long SFA occlusions and durable results for patients with limb-threatening ischaemia.

## REFERENCES


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 Study. Circulation 1995; 91: 1472-9.*
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, ischaemic 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. New Engl J Med 1992; 326: 381-6.

7. Group SSSS. Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383-9.
8. Downs J, Clearfield M, Weis S. Primary prevention of acute coronary events with iovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998; 279: 1615-22.
9. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7-22.
10. Poldermans D, Bax J, Kertai M et al. Statins are associated with a reduced incidence of peri-operative mortality in patients undergoing major non-cardiac vascular surgery. Circulation 2003; 107: 1848-51.
11. Mangano D, Layug E, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after non-cardiac surgery. Multi-centre Study of Peri-operative Ischaemia Research Group. New Engl J Med 1996; 335: 1713-20.
12. Poldermans D, Boersma E, Bax J et al. Bisoprolol reduces cardiac death and myocardial infarction in high-risk patients as long as 2 years after successful major vascular surgery. Eur Heart J 2001; 22: 1353-8
13. Oaikhinan K, Hirpara K, Akhtar Y et al. An observational parallel group comparative study with and without the 'magic bullet' (MB: Aspirin, cardioselective β-blocker, pravastatin and clopidogrel) in the peri-operative and postoperative period for abdominal aortic aneurysms surgery and femoral-popliteal segment revascularisation. Does the magic bullet improve the 30-day morbidity and mortality outcome? Br J Surg 2004; 91 (1): 113-4.
14. Hynes N, Akhtar Y, Manning B et al. Subintimal angioplasty as a primary modality in the management of critical limb ischaemia: comparison to bypass grafting for aorto-iliac and femoropopliteal occlusive disease. J Endovasc Ther 2004; 11 (4): 460-71.
15. Hynes N, Mahendran B, Manning B et al. The influence of subintimal angioplasty on level of amputation and limb salvage rates in lower limb critical ischaemia: a 15 year experience. Eur J Vasc Endovasc Surg 2005; 30 (3): 291-9.
16. Nehler MR, Hiatt WR, Taylor LM. Is revascularisation and limb salvage always the best treatment for critical limb ischaemia? J Vasc Surg 2003; 37: 704-8.
17. Bates MC, AbuRahma AF. An update on endovascular therapy of the lower extremities. J Endovasc Ther 2004; 11 (2): II107-127.
18. TASC Working Group. Management of peripheral arterial disease. Outcome assessment methodology in peripheral arterial disease. J Vasc Surg 2000; 31: S97-S120.
19. Timaran CH, Prault TL, Stevens SL et al. Iliac artery stenting versus surgical reconstruction for TASC type B and type C iliac lesions. J Vasc Surg 2003; 38: 272-8.
20. Bolia A, Fishwick G. Recanalisation of iliac artery occlusion by subintimal dissection using the ipsilateral and the contralateral approach. Clin Radiol 1997; 52: 684-7.
21. Yilmaz S, Sindel T, Lüleci E. Subintimal versus intraluminal recanalisation of chronic iliac occlusions. J Endovasc Ther 2004; 11: 107-18.
22. Lipsitz EC, Ohki T, Veith FJ et al. Does subintimal angioplasty have a role in the treatment of severe lower extremity ischaemia? J Vasc Surg 2003; 37: 386-391
23. Onkamo P, Vä änänen S, Karvonen M, Tuomilehto J. Worldwide increase in incidence of type I diabetes: the analysis of the data on published incidence trends Diabetologia 1999; 42: 1395-403.
24. Valle T, Tuomilehto J, Eriksson J. Epidemiology of NIDDM in europids. In: Alberti KGMM, Zimmet P, Defronco RA, Keen H Editors, International textbook of diabetes mellitus. New York, Wiley, 1997. pp125-47.
25. Melliere D, Berrahal D, Desgranges P et al. Influence of diabetes on revascularisation procedures of the aorta and lower limb arteries: early results. Eur J Vasc Endovasc Surg 1999; 17 (5): 438-41.
26. Wolfle KD, Bruijnen H, Loeprecht H et al. Graft patency and clinical outcome of femerodistal arterial reconstruction in diabetic and non-diabetic patients: results of a multi-centre comparative analysis. Eur J Vasc Endovasc Surg 2003; 25: 229-34.
27. Lazaris AM, Tsiamis AC, Fishwick G et al. Clinical outcome of primary infrainguinal subintimal angioplasty in diabetic patients with critical lower limb ischaemia. J Endovasc Ther 2004; 11 (4): 447-53.
28. Tartari S, Zattoni L, Rolma G, Sacco A. Subintimal angioplasty of infrapopliteal artery occlusions in the treatment of critical limb ischaemia. Short-term results. Radiol Med (Torino) 2004; 108 (3): 265-74.
29. Da Silva AF, Desgranges P, Holsworth J et al. The management and outcome of critical limb ischaemia in diabetic patients: results of a national survey. Diabetic Med 1996; 13: 726-8.
30. O'Sullivan CJ, Andrews EJ, Hynes N et al. Haemoglobin A1c (HbA1c) in non-diabetic vascular patients. Is HbA1c an independent risk factor and predictor of adverse outcome? Ir J Med Sci 2005; 174 (3): S1, 49.
31. Gernstein HC. Glucose: a continuous risk factor for cardiovascular disease. Diabetic Med 1997; 14: S25-31.
32. UK Prospective Diabetes Study Group. Intensive blood group with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-53.

33. *Park S, Barrett-Connor E, Wingard DL et al. GHb is a better predictor of cardiovascular disease than fasting or postchallenge plasma glucose in women without diabetes. The Rancho Bernardo Study. Diabetes Care 1996; 19: 5: 450-6.*
34. *Briguori C, Condorelli G, Airoldi F et al. Impact of glycaemic and lipid control on outcome after percutaneous coronary interventions in diabetic patients. Heart. 2004; 90 (12): 1481-2.*
35. *Mahendran B, Tawfik S, Hynes N et al. Non-operative management of critical limb ischaemia (CLI): initial short term experience with a biomechanical device. Ir J Med Sci 2005; 174 (3): S1: 51.*
36. *Louridas G, Saadia R, Spelay J et al. The ArtAssist device in chronic lower limb ischaemia: a pilot study. Int Angiol 2002; 21 (1): 28-35.*