

## Peripheral arterial disease – towards extended awareness and improved prevention of ischaemic events

‘Increased awareness of peripheral arterial disease (PAD) among the older at-risk population could assist specialists in their efforts to reduce cardiovascular events in this vulnerable population’, noted Prof Barry Jacobson, chairman of the newly formed SA Society of Thrombosis and Haemostasis.

A recent international specialist initiative, the Prevention of Atherothrombotic Disease Network, funded by unrestricted educational grants from major pharmaceutical companies, has called for a more aggressive approach to the diagnosis and treatment of PAD. The first South African Summit, sponsored by Sanofi-Synthelabo, was held in major centres in the country recently. Prof Andries Brink, editor, attended the Cape Town meeting and recommended that this report be prepared for publication.

There are some 6.3 million individuals diagnosed with symptomatic, established PAD in the USA and Europe, while epidemiological studies indicate a real prevalence worldwide of more than 53 million. In South Africa, a recent A.C. Nielsen Research Project indicated that in excess of one million South Africans might experience undiagnosed PAD symptoms, based on their indicative admission of experiencing pain when walking.

‘PAD is a highly prevalent, under-recognised, under-reported, under-treated disease that often leads to fatal ischaemic events. However, screening with a simple ankle-brachial index (ABI), a test that can be performed in the primary-care physician’s office, and greater awareness among clinicians of the protective effects of antiplatelet agents such as clopidogrel and ASA (acetyl salicylic acid) would ease the burden of this disease considerably’, said Dr van Marle, a vascular surgeon in Pretoria.

Recent developments in the diagnosis and management of PAD are the key drivers of this new initiative. A.M. Hirsch recently reviewed evidence for the use of the ankle-brachial

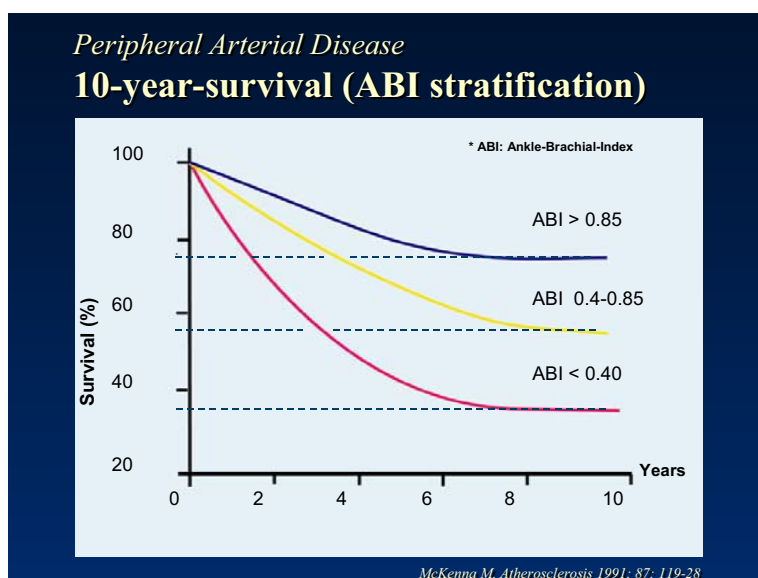


Fig. 1. PAD: 10-year survival (ABI stratification).

*Peripheral Arterial Disease*  
**PAD risk factor for myocardial infarction and ischemic stroke**

Original event	Increased risk vs. general population (%)	
	Myocardial infarct	Stroke
<b>Myocardial infarct</b>	<b>5–7 x greater risk<sup>1</sup></b> (includes death)	<b>3–4 x greater risk<sup>2</sup></b> (includes TIA)
<b>Peripheral arterial disease</b>	<b>4 x greater risk<sup>4</sup></b> (includes only fatal heart attack & other CHD death <sup>4</sup> )	<b>2–3 x greater risk<sup>3</sup></b> (includes TIA)

1. Adult Treatment Panel II. *Circulation* 1994; 89:1333–63. 2. Kannel WB. *J Cardiovasc Risk* 1994; 1: 333–9.  
3. Willebrandt JI, Easton JD. *Arch Neurol* 1992; 49: 857–63. 4. Criqui MH et al. *N Engl J Med* 1992; 326: 381–6.

Fig. 2. PAD risk factor for myocardial infarction and ischaemic stroke.

index,<sup>1</sup> which uses a definitive diagnosis of PAD based on an ABI measurement of less than 0.9. ‘An ABI of less than 0.9 is associated with higher morbidity and mortality from cardiovascular and cerebrovascular events’, stated Prof Iris Baumgartner of the University Hospital, Bern, Switzerland (Figs 1, 2).

### Anti-platelet therapy is the key component of PAD management

The meta-analysis, carried out by the Antithrombotic Trialists’ Collaboration, of 9 214 PAD patients receiving antiplatelet therapy demonstrated a

23% proportional reduction in serious vascular events. In the CAPRIE trial, there were differences in the treatment effect among patients with MI, stroke and PAD. In the 6 452 patients with PAD, the primary end-point occurred at an annual rate of 4.9% in patients given aspirin, and 3.7% in patients given clopidogrel, a calculated adjusted risk reduction of 23.8% (95% CI 8.9 to 36%,  $p < 0.05$ ). This treatment effect was greater than that in patients with MI or stroke. These data are included in Fig. 3, which encompasses all relevant trials.

The number of ischaemic events is recognised to be substantially greater in clinical practice. In the CAPRIE Actual Practice Rates Analysis (CAPRA), the ischaemic event rate during follow-up in a clinical practice setting was 2.3 times for patients with CAD, 2.5 times for patients with cerebrovascular disease, but 3.8 times for patients with PAD at baseline (Fig. 4).

### Anti-platelet therapy following vascular reconstructive therapy

The Cochrane Collaboration has shown that ASA alone, or in combination with dipyridamole, versus placebo, gave a 42% risk reduction for re-occlusion within 12 months of graft surgery. Ticlopidine improved the long-term patency of lower-extremity saphenous vein bypass grafts in 243 patients two years after randomisation (66.4% of patients in the ticlopidine group versus 51.2% in the placebo group). It is thought that clopidogrel combined with ASA may give benefits above that of ASA alone due to a dual antiplatelet effect. Two studies have been designed to address this question, CAMPER (Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularisation) and CASPAR (Clopidogrel and Acetylsalicylic Acid in bypass Surgery for Peripheral Arterial disease).

## Peripheral Arterial Disease Protective Effect of Antiplatelet Therapy Antithrombotic Trialists' Collaboration

Treatment	No. of trials with data	No. of patients	% odds reduction (MI, stroke, or vascular death)
All trials	195	144,051	25 <sup>1</sup>
Any ASA	64	59,395	23 <sup>1</sup>
Dipyridamole	15	5,430	16 <sup>1</sup>
Ticlopidine	42	5,430	32 <sup>1</sup>
Clopidogrel*	1	19,185	30 <sup>2</sup>

ASA = acetylsalicylic acid MI = myocardial infarction

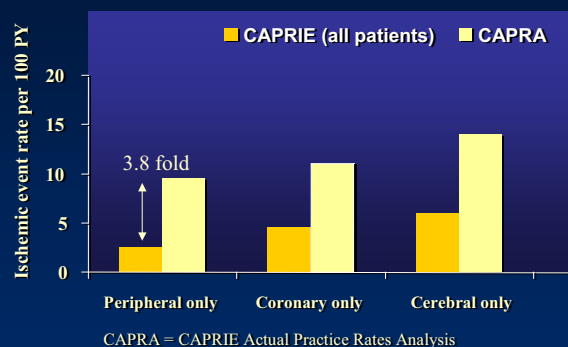
\*% odds reduction for clopidogrel is a statistical analysis that uses data from the Antithrombotic

Trialists' Collaboration and the CAPRIE trial to estimate the effect of clopidogrel vs placebo

1. Antithrombotic Trialists' Collaboration. *BMJ* 2002; 324: 71–86. 2. *Am Heart J* 2001; 141: 26–32.

Fig. 3. Protective effect of antiplatelet therapy.

## Actual Practice Rates are Higher



*Lancet* 1996; 348(9038):1329–39.  
*Caro et al: Atherosclerosis* 1999; 9:(suppl.1):17.

Fig. 4. Number of ischaemic events in CAPRIE versus CAPRA.

### Maximising therapy after ACS

‘There are substantial and continuing risks of thrombotic events after presentation with an acute coronary syndrome’, noted Keith Fox, Professor of Cardiology at the University of Edinburgh, Scotland. Chronic treatment options have been improved following recent anti-platelet therapy studies (Fig. 5).

The CURE trial with clopidogrel has demonstrated a reduction in the rate of CV death/MI/stroke from 11.5% to 9.3%. The treatment effect is evident within the first 24 hours and occurs in low-, medium- and higher-risk patients. The lowest bleeding risk is achieved by combining clopidogrel with less than 100 mg of aspirin. The results of the CREDO trial reinforce the findings of CURE and in particular PCI-CURE.

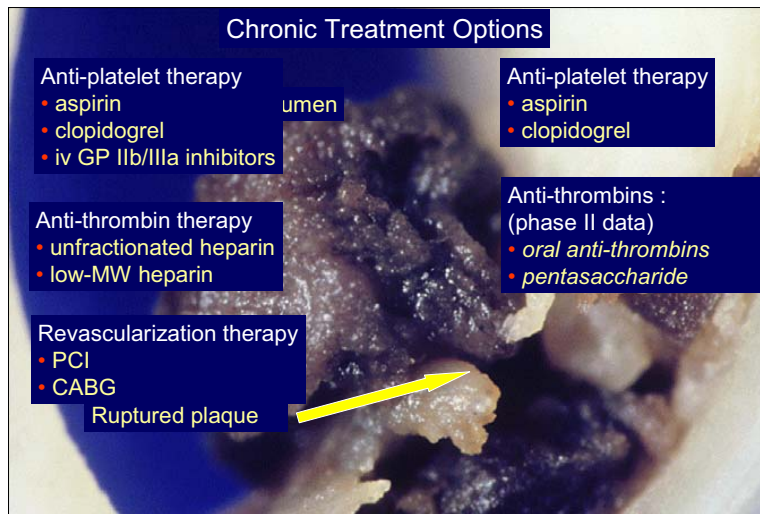


Fig. 5. Chronic treatment options.

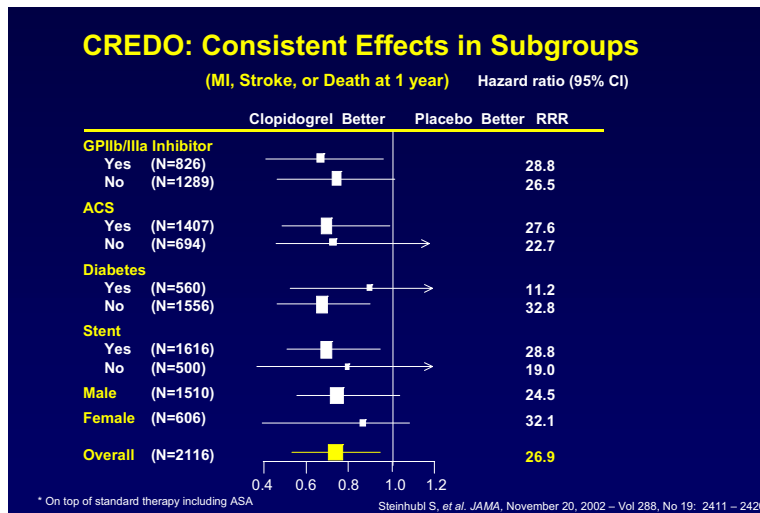


Fig. 6. CREDO: consistent effects in subgroups.

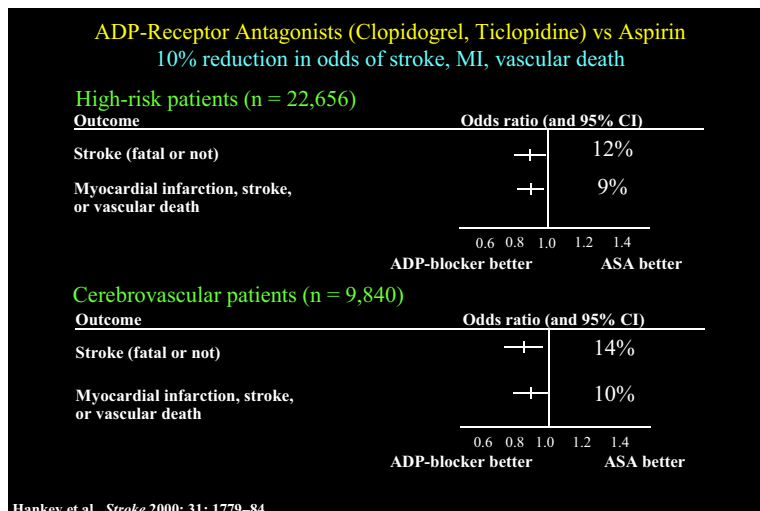


Fig. 7. ADP-receptor antagonists (clopidogrel, ticlopidine) versus aspirin.

The CREDO results<sup>2</sup> (Fig. 6) demonstrate that similar benefits of clopidogrel were seen in the presence of glycoprotein 11b/111a inhibitors. These results have led to the inclusion of clopidogrel in the class 1 recommendations of the ACC/AHA and in the European Guidelines for the management of patients with acute coronary syndrome. Prof Fox indicated that the National Institute of Clinical Excellence (NICE) in the UK has recently recommended the use of clopidogrel in ACS for nine to 12 months.

### Effective longer-term secondary prevention after stroke

Prof Graeme Hankey, consultant neurologist and head of the Stroke Unit at the Royal Perth Hospital, Western Australia discussed both the short- and long-term treatment options following a stroke.

Effective longer-term secondary prevention strategies should comprise carotid endarterectomy (and perhaps stenting) for patients with severe symptomatic extracranial internal carotid artery stenosis; lowering blood pressure by means of perindopril (the PROGRESS study results are compelling) or ramipril (HOPE results), and indapamide for almost all stroke survivors, irrespective of stroke pathology, baseline blood pressure or ethnicity; lowering blood cholesterol, by means of simvastatin or pravastatin for survivors of atherothrombo-embolic ischaemic stroke, irrespective of the patient's age, gender or baseline blood cholesterol concentration; antiplatelet therapy with aspirin 75-150 mg daily, clopidogrel 75 mg daily or the combination of aspirin and dipyridamole 200 mg bd for patients in sinus rhythm with ischaemic stroke due to presumed arterial thrombo-embolism; anticoagulation with warfarin for patients with embolism of thrombus from the heart (atrial fibrillation, valvular heart disease).

Prof Hankey noted that the systematic review of all unconfounded ran-

domised trials comparing ADP-receptor antagonists (ticlopidine or clopidogrel) directly with aspirin, conducted in collaboration with the Cochrane Stroke Group, found four trials consisting of a total of 22 656 patients with either cerebrovascular, coronary or peripheral arterial disease, with results showing a 10% reduction in the odds of a stroke, MI or vascular death using these agents (Fig. 7).

Referring to new trials currently

underway, Prof Hankey noted in particular the Vitamins to Prevent Stroke (VITATOPS) study, of which he is principal investigator, the P<sub>RO</sub>FESS study, which involves clopidogrel, aspirin and telmisartan, the MATCH study comparing clopidogrel alone and in combination with aspirin for high-risk patients with recent TIA/ischaemic stroke, and the CHARISMA study of clopidogrel and aspirin versus aspirin alone.

Better management of PAD can assist in the prevention of cardiovascular events and reduce its negative impact on the South African economy and on the individual patient.

### References

1. Hirsch AM, *et al. JAMA* 2001; **286**(19): 1317–1324.
2. Steinbuhl S, *et al. JAMA* 2002; **288**(19): 2411–2420.