

## CAROTID MASTERCLASS

### What Does ‘Best Medical Therapy’ Really Mean?

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*Carotid disease is like any other atherosclerotic manifestation, a condition, which may induce thrombosis, in this case with subsequent cerebral ischemia. Carotid endarterectomy has proven effective in preventing ipsilateral stroke, however, the studies providing the evidence were conducted before the use of statins, newer antiplatelet and antihypertensive drugs, and at a time when less emphasis was on lifestyle modification. Therefore, it is likely that, not only would all patients with carotid stenosis benefit from modern medical treatment, in addition, some patients could have similar risk reduction to that of endarterectomy, were these effective preventive drugs used systematically, as recommended, in this patient group.*

*This article reviews the evidence that is available concerning medical therapy for patients with carotid stenosis, with special emphasis on antiplatelet and statin therapy. An example on how this treatment may be organised is given.*

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#### Introduction

It is important to recognise that the evidence used to develop international guidelines for the surgical treatment of patients with carotid artery disease is based upon trials that were conducted up to 20 years ago when the concept of ‘best medical therapy’ was fairly rudimentary (i.e. essentially ‘stop smoking and take aspirin’). The two principle symptomatic trials (NASCET and ECST) randomised patients throughout the 1980s, reporting their positive results for the management of severe stenosis in 1991.<sup>1,2</sup> The two trials in asymptomatic patients (ACAS and ACST) were undertaken in the 1990s and the beginning of the current century, reporting in 1995 and 2004.<sup>3,4</sup>

#### *What has changed?*

During the last 20 years, major advances have been made regarding medical therapy (antiplatelet, statin, and hypertension) alongside changes in lifestyle (e.g.

greater emphasis on smoking cessation). These have to be considered when planning the management of patients with carotid disease. For example, it is an indisputable fact that hypertension is now managed much better than 20 years ago with treatment goals set at stricter blood pressure thresholds than those advocated in the 1980s. Statin therapy, perhaps the single most important pharmacological advance in cardiovascular risk factor management was not available when ECST, NASCET and ACAS were recruiting. Even in the recently published ACST trial, only 30% of patients were on statin therapy when they were randomised.<sup>4</sup> Third, there are now several new classes of antiplatelet agent some of which when administered as ‘dual’ therapy confer enhanced benefit. Accordingly, not only is there is the potential for offering improved antiplatelet activity, but there are now also therapeutic alternatives to the 10% of patients with aspirin intolerance or resistance.

#### *Rapid access ‘best medical therapy’?*

Emerging evidence suggests that carotid endarterectomy (CEA) confers maximum benefit if it is performed within 2 weeks of onset of symptoms.<sup>5</sup>

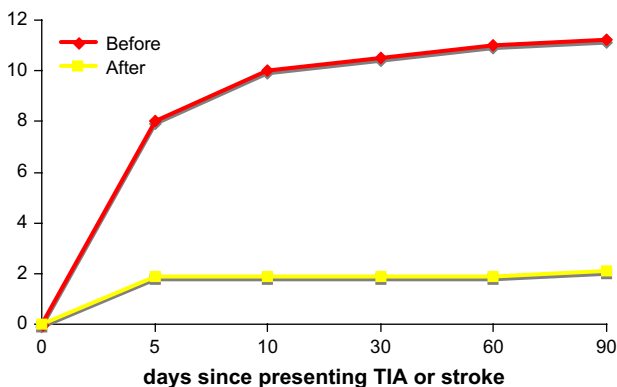
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However, few observers have considered whether rapid implementation of 'best medical therapy' could have just as beneficial an effect. This is largely because most clinicians believe that there is an inevitable 'lag phase' (lasting many months) before medical therapy can take effect. The potential importance of starting medical therapy as soon as possible was highlighted in the recently published Express Study.<sup>6</sup> Here, the 90-day stroke rate was reduced from 10.2% to 2.1% as a consequence of simply changing clinical practices so as to minimise delays in assessment, investigation and treatment of patients with symptomatic cerebral vascular disease (Fig. 1). Medical therapy (aggressive antiplatelet, statin and anti-hypertensive therapy) was instituted in the majority of cases within 24 hours of onset of symptoms. Although this strategy also reduced delays to CEA, approximately 85% of the observed reduction in recurrent stroke was attributed to the fact that 'best medical therapy' had been instituted as soon as possible.<sup>6</sup>

#### Surgeons and 'best medical therapy'

Why is it so important for the vascular surgeon/specialist to be aware of the value of improvements in medical therapy in patients with carotid stenosis? First of all, having any kind of atherosclerotic disease (coronary, cerebrovascular, renovascular, mesenteric or peripheral) indicates that there is a systemic effect on the arterial system. In other words, the patient with carotid disease is not only at risk of stroke but also of myocardial infarction and other ischemic complications. In reality, the annual risk of death/myocardial infarction is much higher than that of ipsilateral stroke in patients with asymptomatic carotid stenosis.<sup>1,2,7</sup>



**Fig. 1.** 90 day risk of stroke following presentation of initial TIA or stroke. "Before" Refers to previous treatment algorithm, "After" refers to new practice to expedite assessment and start 'best medical treatment'.

The risk of any atherosclerotic complications (vascular death, myocardial infarction & stroke) may be as high as 7–10% per year or more.<sup>8</sup> Put simply, it is no use simply treating a carotid stenosis by surgery or angioplasty to the exclusion of all other aspects of care.

"Best medical treatment" can be an overused and over-simplified term. This paper will review new and emerging data from the literature, predominantly relating to antiplatelet and statin therapy. All of the data and recommendations regarding medical therapy in patients with carotid disease are derived from general studies on stroke prevention, atherosclerosis prevention and (wherever possible) primary and secondary analyses from stroke prevention studies involving patients with carotid disease.

### Antiplatelet Therapy

#### (1) Symptomatic patients with carotid stenosis

Aspirin has been shown to reduce the risk of stroke in patients with previous cerebrovascular symptoms (TIA or stroke). The latest meta-analysis from the Anti-thrombotic Trialists Collaboration reviewed 21 placebo controlled trials (including more than 22,000 patients with previous stroke or TIA) and found that treatment with an anti-platelet agent resulted in a 22% relative risk reduction (RRR) in the combined end-point of vascular death, myocardial infarction and stroke.<sup>9</sup> Fig. 2 summarises the principle benefits conferred by three years of antiplatelet therapy in patients who had initially presented with TIA or stroke. This meta-analysis also reviewed studies looking at different aspirin doses and observed that 75–150 mg daily was just as effective as higher doses, but with fewer side effects.

Several contemporary studies have also evaluated the role of alternative and/or dual antiplatelet therapy regimes. The CAPRIE Study compared aspirin 75 mg daily with clopidogrel 75 mg daily.<sup>10</sup> This trial randomised more than 19,000 patients with atherosclerotic disease and demonstrated an 8.7% RRR in the combined endpoint of vascular death, myocardial infarction and stroke favouring clopidogrel. The benefit in the subset of patients with a prior history of cerebrovascular disease was similar to that of the overall, intention-to-treat population. Interestingly, patients who at randomisation had reported symptoms from more than one vascular territory (e.g. coronary, cerebrovascular and/or peripheral arterial) appeared to gain greater benefit (22% RRR).

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