

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.^{1,2} 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.^{3,4}

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.⁴ 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.⁵

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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.⁶ 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.⁶

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.^{1,2,7}

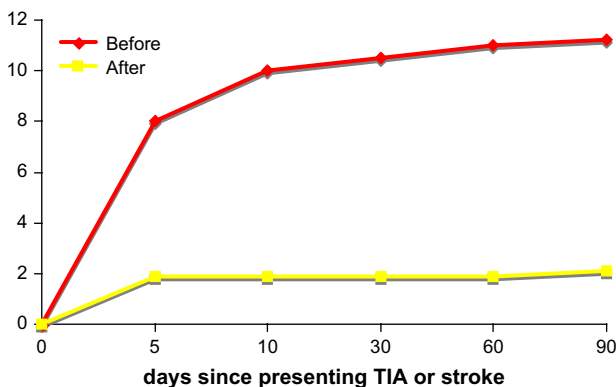


Fig. 1. 90 day risk of stroke following presentation of initial TIA or stroke. "Before" Refers to previous treatment algorithm, "After" refers to new practice to expedite assessment and start 'best medical treatment'.

The risk of any atherosclerotic complications (vascular death, myocardial infarction & stroke) may be as high as 7–10% per year or more.⁸ 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.⁹ 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.¹⁰ 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).

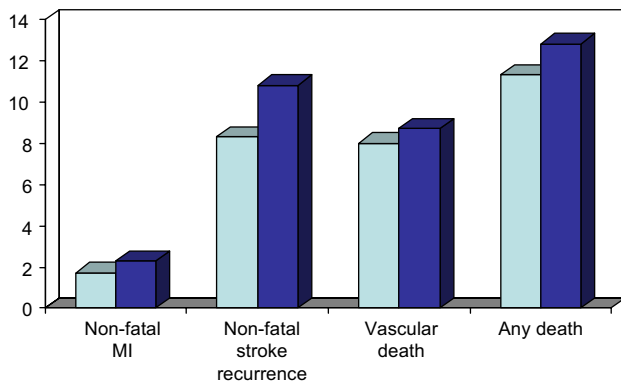


Fig. 2. Effect of antiplatelet agents on non-fatal myocardial infarction (MI), non-fatal stroke, vascular death and any death in patients with previous stroke or TIA. Bars indicate incidence in percent (mean duration of treatment 3 years).⁹

The European Stroke Prevention Study compared aspirin to placebo, dipyridamole to placebo, aspirin + dipyridamole to placebo and aspirin alone in patients with recent stroke or TIA.¹¹ Aspirin on its own conferred an RRR of 18% in late stroke, as compared with 16% for dipyridamole alone. The maximum benefit, however, was seen in patients randomised to combination therapy (RRR in stroke = 37%).

The CHARISMA trial compared Aspirin and Clopidogrel against aspirin alone in patients with symptomatic atherosclerotic disease and those asymptomatic patients with risk factors.¹² Analysing all of the patients on an intention-to-treat basis showed a non-significant 7% RRR in the risk of future ischemic events (death, myocardial infarction, and stroke). However, a secondary analysis comprising only symptomatic patients from CHARISMA revealed a 12% RRR in favour of combination therapy which just reached statistical significance.

Based on the available evidence in symptomatic patients (and without knowledge of whether they did or did not have carotid stenosis), the following recommendations can be made with reasonable certainty in symptomatic patients:

1. Antiplatelet agents are proven to be beneficial for patients with previous cerebrovascular disease. It should, therefore, be assumed that this finding also holds true for symptomatic patients with carotid stenosis.
2. There may be differences in the benefit conferred by individual antiplatelet agents. Clopidogrel is a more potent antiplatelet agent than aspirin but due consideration must also be given to the risk of excess bleeding should the patient require surgery.
3. Low dose aspirin therapy is just as effective as high-dose aspirin.

4. Combination therapy (aspirin plus dipyridamole or aspirin plus clopidogrel) may increase the overall benefit, especially in patients not being considered for surgery or angioplasty.

(2) Asymptomatic patients with carotid stenosis

It is much more difficult to make recommendations based on evidence in this category of patient as they have never been subjected to scientific scrutiny. Accordingly, some have suggested that primary prophylaxis (with aspirin) may not be appropriate in every patient because the prevalence of side-effects may outweigh any clinical benefit.¹³ However, patients with asymptomatic carotid disease have proven atherosclerosis and a rate of ischemic events that exceeds the rate observed in persons without carotid disease.⁷ The European Stroke Initiative currently recommends anti-platelet therapy in patients with asymptomatic carotid disease (primarily) for the prevention of cardiac events.¹⁴

Statin Therapy

The SPARCL Trial, which randomised 4732 patients with recent stroke or TIA to atorvastatin 80 mg per day or placebo, reported a 16% reduction in the risk of future stroke.¹⁵ A subgroup analysis from the SPARCL study looked at the effect of statin in 1007 patients with a documented carotid stenosis.⁸ Here they observed a 33% RRR in the risk of late stroke, a 42% RRR in major coronary events and a 56% reduction in the need for carotid revascularisation in the group taking 80 mg atorvastatin.⁸

Unlike the Express study summarised earlier, SPARCL was not an 'acute' study. Patients were eligible for entry if they had had suffered a TIA/stroke within 1 to 6 months.¹⁵ In fact, the average time from ischemic event to randomisation was 90 days. When one considers that the 30-day recurrent stroke rate is approximately 10% in patients with an ipsilateral carotid stenosis, many potentially eligible patients would have suffered their stroke before entering the trial. The question therefore remains; how much more benefit would have accrued had the patients been recruited earlier.

Although not a stroke trial, the MIRACL Study provides further support for rapid intervention with statin therapy. In this study, patients who presented with an acute coronary syndrome (ACS) were randomised to atorvastatin 80 mg or placebo within 24–48 hours.²⁰ By sixteen weeks, aggressive early treatment

with Atorvastatin was associated with a 16% RRR in secondary coronary events.¹⁶

The Heart Protection Study (HPS randomised patients to simvastatin 40 mg or placebo and showed that in patients with a history of prior cerebrovascular symptoms, statin therapy conferred a 23.6% RRR in the composite endpoint of vascular death, myocardial infarction, stroke and need for revascularisation.¹⁷ However, the incidence of late stroke (alone) was not reduced by statin therapy and it is possible that these patients probably gained more benefit from cardiac protection. An alternative explanation for this otherwise unexpected finding may be the fact that patients were randomised (on average) 4.3 years after the qualifying event.

Accordingly, in symptomatic patients with carotid disease, there is compelling evidence for starting statin therapy as soon as possible. However, is there a cholesterol level below which statins do not work? Are there some patients who do not need the drug? There is accumulating evidence that the lower the cholesterol level (while on statin therapy), the fewer the atherosclerotic complications and this is NOT at the expense of a higher prevalence of serious side effects.^{15,18–20} In SPARCL, the mean on treatment LDL cholesterol level throughout the 5 years of the trial was 73 mg/dl (1.8 mmol/l) with no difference being observed in the prevalence of adverse effects between the treatment and placebo groups. In the TNT trial (which included 10,000 patients with stable ischaemic heart disease), the maximum overall benefit conferred by statin therapy was observed in the quintile of patients recording the lowest LDL (mean LDL cholesterol of 53 mg/dl (1.3 mmol/l)) but without an increase in clinical side effects.¹⁸

For patients with asymptomatic carotid disease there are no data from large randomised trials in asymptomatic patients to guide practice. However, the European Stroke Initiative have recommended that statin therapy be implemented in patients with asymptomatic carotid disease unless contraindicated.¹⁴

Ongoing research will report whether Ezetimibe (a novel agent, for inhibiting cholesterol absorption from the intestine) confers a significant reduction in stroke risk, while drugs designed to increase HDL cholesterol are under development. At present, there are no data to support the preferential use of these agents over statins (Table 1).

Antihypertensive Therapy

It is beyond the scope of this paper to overview the randomised trials testing different antihypertensive

drugs and how to initiate and titrate treatment. The reader is advised to consult the European Guidelines which otherwise provide a comprehensive review of the literature.²¹ In summary, however, control of hypertension remains one of the cornerstones of risk-factor management and blood pressure should (preferably) be maintained <140/90 mmHg for non-diabetic patients with carotid stenosis and <130/80 mmHg for patients with diabetes.

There is emerging evidence that some antihypertensive medications may exert their beneficial effect in ways other than by reducing blood pressure. In the HOPE Study, it was observed that a daily 5 mg dose of Ramipril (which did not really alter blood pressure) conferred a significant reduction in the risk of late ischemic events.²² Subsequent studies showed that patients with peripheral arterial disease appeared to benefit more than others.²³ More recently, the latest class of drugs working on the renin-angiotensin system seem to offer more benefit than that conferred by betablockers for the same reduction in blood pressure. It is conceded, however, that 74% of the patients randomised in this trial did not have symptomatic atherosclerotic disease²⁴ and it is therefore difficult to know whether the same applies in patients with carotid disease.

Diabetes

Diabetes is another major risk factor for vascular disease whose management is again outwith the scope of this article.²⁵ Interestingly, tight glycaemic control does not seem to reduce the long term risk of stroke but meticulous attention to risk factor control (especially hypertension) has been proven to reduce the risk of late stroke by 40%.²⁶

Life Style Changes

Smoking, physical inactivity and eating habits are important risk factors for the development of vascular disease. It is very important to understand that although preventive medications are easy to prescribe, modification of lifestyle is equally important in order to reduce the risk of stroke in patients with carotid artery disease.

How to provide secondary prevention

There are many types of lifestyle clinic, most linked with a service to ensure that 'best medical therapy' is also delivered to the patient. The following is a

Table 1. Summary of recommendations for 'best medical therapy' in patients with asymptomatic and symptomatic carotid disease derived from the European Stroke Initiative¹⁴

Treatment	Asymptomatic	Symptomatic
BP < 140/90 mmHg or <130/80 mmHg in diabetics	Level I	Level I
Glycaemic control to prevent other diabetic complications	Level III	Level III
Statin therapy	Level I	Level I
Stop smoking	Level II	Level II
Avoid heavy consumption of alcohol	Level I	Level I
Regular physical activity	Level II	Level II
Low salt, low saturated fat, high fruit and vegetable diet rich in fibre	Level II	Level II
If BMI elevated, reduce weight	Level II	Level II
HRT should not be used for stroke prevention in women	Level I	Level I
Aspirin	To prevent MI level IV	Level I
Aspirin & Dipyridamole	Not recommended level IV	Level I
Clopidogrel	Not recommended level IV	Level I

summary of how such a service is organised and implemented in Copenhagen. As will be seen it involves close co-operation between nurses and vascular surgeons.

The typical patient course is as follows. A newly referred patient with stroke/TIA (or aneurismal/peripheral vascular disease) is seen by a consultant who evaluates the patient's symptoms and considers whether an intervention is appropriate. Irrespective of this judgement, the patient's medication is reviewed. The nurses ensure that all patients are prescribed at least 40 mg simvastatin and 75 mg of aspirin. If the patient has high levels of LDL cholesterol a more potent statin may be used from the outset. The patient is then questioned about life style and given information about which modifications should be made. Thereafter, a decision is made as to whether the patient would benefit from our attending the rehabilitation clinic. This will obviously depend on which medical disciplines are already involved. For example, most diabetic/cardiac patients already attend specialist clinics and risk-factor control etc can therefore be devolved to them, thus avoiding duplication of effort. However, if the patient is not attending other clinics and if the patient is motivated, he/she is offered the chance to participate. This initiative involves a minimum of 4 visits including one at 6 weeks, 3 months, 6 months and then 1 year. On each occasion, smoking cessation advice is given and medical therapy reviewed. If blood tests show a need for an increase in dose or a change in the type of statin, the clinic nurse ensures that this happens. Using this approach, approximately 90% of patients will be taking platelet inhibitors and statins by the 2nd visit and cholesterol levels are (on average) 0.5 mmol/l below national treatment targets which means that approximately 80% of patients are reaching their target. A fuller description of the methodology and results from this lifestyle service has been described in detail elsewhere.²⁷

How might new improvements in 'best medical therapy' affect the evidence from the surgical trials upon which we currently base management decisions?

As mentioned in the introduction, the trials that established that CEA conferred significant benefit were largely undertaken in an era when much of what now constitutes 'best medical therapy' was unavailable. Accordingly, it might not be unreasonable to speculate that were the trials to be repeated, the number of strokes observed in the medical limb of the trials would be significantly fewer. Accordingly, if one assumed that improved, modern medical care resulted in a 40% RRR in the risks of stroke observed in the medical limbs of the symptomatic and asymptomatic trials, most of the significant benefits conferred by CEA would probably disappear. This 40% figure is not unreasonable as statin therapy alone might be expected to confer a 30% RRR in the rates of stroke observed 20 years ago.

As a consequence, the available evidence from ECST, NASCET, ACAS and ACST is outdated and it is inappropriate to continue to uncritically extrapolate data to justify practice in the modern era. To this author, at least, any new trial comparing CEA with angioplasty (especially in asymptomatic patients) should also include a medical treatment limb.

Conclusion

The concept of 'best medical therapy' has advanced dramatically over the last two decades and requires all of us to enforce lifestyle modification, (dual) anti-platelet and statin therapy in practically all of our patients along with meticulous attention to blood pressure control especially in diabetics. Since there does not seem to be a lower cholesterol value below which statins cease to confer benefit, aggressive lipid lowering therapy is probably beneficial in almost every patient with a carotid stenosis.

References

- 1 European Carotid Surgery Trialists' Collaborative Group. MRC European carotid surgery trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. *Lancet* 1991;**337**:1235–1243.
- 2 North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;**325**:445–453.
- 3 Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid stenosis. *JAMA* 1995;**273**:1421–1428.
- 4 MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;**363**:1491–1502.
- 5 ROTHWELL PM, ELIASZIW M, GUTNIKOV SA, WARLOW CP, BARNETT HJ. Carotid Endarterectomy Trialists Collaboration: Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004;**363**:915–924.
- 6 ROTHWELL PM, GILES MF, CHANDRATHEVA A, MARQUARDT L, GERAGHTY O, REDGRAVE JNE *et al.* Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet* 2007;**6**:953–960.
- 7 HENNERICI M, HUELSBOEMER HB, HEFTER H, LAMMERTS D, RAUTENBERG W. Natural history of asymptomatic extracranial disease. Results of a long-term prospective study. *Brain* 1987;**110**:777–791.
- 8 SILLESEN H, AMARENCO P, SZAREK M, CALLAHAN A, GOLDSTEIN L, HENNERICI M *et al.* on behalf of the SPARCL Investigators. Atorvastatin treatment in patients with carotid stenosis is associated with a marked reduction in the risk stroke, cardiac events and endarterectomy. A substudy of the Stroke Prevention with Aggressive Reduction in Cholesterol Levels (SPARCL) Trial. *Stroke* 2007;**38**:457.
- 9 Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of anti-platelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
- 10 CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–1339.
- 11 DIENER HC, CUNHA L, FORBES C, SIVENIUS J, SMETS P, LOWENTHAL A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci.* 1996 Nov;**143**(1–2):1–13.
- 12 BHATT DL, KIETH AA, FOX MB, BERGER GP, BLACK HR, BODEN WE *et al.* for the CHARISMA investigators: Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. *N Engl J Med* 2006:354.
- 13 NELSON MR, LIEW D, BERTRAM M, VOS T. Epidemiological modelling of routine use of low dose aspirin for the primary prevention of coronary heart disease and stroke in those aged > or =70. *BMJ* 2005 Jun 4;**330**(7503):1306.
- 14 The European Stroke Initiative Executive Committee and the EUSI Writing Committee. European stroke initiative recommendations for stroke management – update 2003. *Cerebrovasc Dis* 2003;**16**:311–337.
- 15 AMARENCO P, BOGOUSLAVSKY JC, CALLAHAN A, GOLDSTEIN L, HENNERICI M, SILLESEN H *et al.* A placebo-controlled trial of high-dose atorvastatin in patients with recent stroke or transient ischemic attack. The Stroke Prevention with Aggressive Reduction in Cholesterol Levels (SPARCL) Study. *New England Journal of Medicine* Aug 10, 2006;**355**(6):549–559.
- 16 SCHWARTZ GG, OLSSON AG, EZEKOWITZ M, GANZ P, OLIVER MF, WATERS DD *et al.* Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001 Apr 4;**285**(13):1711–1718.
- 17 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:1–12.
- 18 LA ROSA JC, GRUNDY SM, WATERS DD, SHEAR C, BARTER P, FRUCHART JC *et al.* Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005 Apr 7;**352**(14):1425–1435.
- 19 CANNON CP, BRAUNWALD E, McCABE CH, RADER DJ, ROULEAU JL, BELDER R. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004 Apr 8;**350**(15):1495–1504.
- 20 PEDERSEN TR, FAERGEMAN O, KASTELEIN JJ, OLSSON AG, TIKKANEN MJ, HOLME I *et al.* High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005 Nov 16;**294**(19):2437–2445.
- 21 European Society for Hypertension. ESH-ESC guidelines management of arterial hypertension <www.eshonline.org>, 2007.
- 22 The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin converting enzyme inhibitor, Ramipril, on cardiovascular events in high risk patients. *N Engl J Med* 2000;**342**:145–153.
- 23 ÖSTERGREN J, SLEIGHT P, DAGENAIS G, DANISA K, BOSCH J, QILONG Y *et al.* Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. *European Heart Journal* 2004;**25**:17–24.
- 24 DAHLÖF B, DEVEREUX RB, KJELSDEN SE, JULIUS S, BEEVERS G, DE FAIRE U *et al.* Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;**359**:995–1003.
- 25 International diabetes federation guidelines to treatment of diabetes <www.idf.org>
- 26 GAEDE P, VEDEL P, LARSEN N, JENSEN GV, PARVING HH, PEDERSEN O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003 Jan 30;**348**(5):383–393.
- 27 SILLESEN H, MADELUNG S, ELDRUP N, ROED M. Organising a nurse-driven PAD rehabilitation clinic within the vascular surgical department: what is required and are treatment goals reached – a prospective study? *Eur J Vasc Endovasc Surg* 2007 Jan;**33**(1):26–32.

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