Effective management of stable angina

Mark Petticrew, Mark Sculpher, Jo Kelland, Rachel Elliott, Diana Holdright, Martin Buxton

Introduction

Coronary heart disease is the leading cause of death in the United Kingdom. People with symptoms of coronary heart disease—such as angina pectoris—are at particularly high risk of death from coronary heart disease. It is estimated that, in a one year period, 1% of the population present with anginal symptoms to a general practitioner,¹ and within about one year of initial consultation, around one in 10 patients will either have a non-fatal myocardial infarction, or die from coronary causes.² Interventions for angina aim to reduce symptoms, increase functioning, and reduce the risk of myocardial infarction and death. As well as modification of lifestyle—such as stopping smoking and reducing weight—the mainstay of treatment of angina in general practice is the use of drugs—such as β blockers, nitrates, calcium channel blockers, and aspirin. The Standing Medical Advisory Committee has also recommended that patients with angina who have high concentrations of total cholesterol or low density lipoprotein should be considered for cholesterol lowering medical treatment to prevent progression of coronary artery disease.³

Patients are often referred for further investigations to assess the pattern and extent of the underlying coronary artery disease and other prognostic factors which determine severity of disease and the appropriateness of invasive procedures. There is evidence that United Kingdom referral rates vary widely.^{4–5}

The main invasive treatments are percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG).

This paper examines the evidence for the effectiveness and cost effectiveness of medical treatment, CABG, and PTCA in patients with stable angina. It is based on a review commissioned by the National Health Service (NHS) health technology assessment programme,⁶ which formed the basis for part of a recent *Effective Health Care Bulletin* 1997 vol 3.⁷

Methods

The review included randomised controlled trials of non-drug interventions and drug treatment (for which at least 6 months of follow up was required for inclusion). Medical treatments were included if they compared different classes of drug. Publications on clinical effectiveness, and cost and cost effectiveness were

identified by a search of computerised databases. Details of the studies included can be found in the main systematic review (appendix).⁷

Results

MEDICAL TREATMENTS

Relief of symptoms

There are few long term comparisons of the effectiveness of different classes of drugs in relieving symptoms of angina. These studies show no major differences between the main classes of drug treatment.^{8–15} There is also no evidence that combination treatment is more effective than monotherapy,^{16–17} and no evidence of major treatment related differences in health related quality of life.

Secondary prevention of cardiac events

A meta-analysis has shown that antiplatelet drugs significantly reduce the incidence of myocardial infarction among patients with stable angina.¹⁸ Antiplatelet treatment showed even greater reductions in the incidence of myocardial infarction, stroke, and vascular death in high risk patients—such as those with a history of myocardial infarction or stroke. There is no evidence that dipyridamole, used alone or in combination with aspirin, is more effective than the cheaper option of aspirin alone (table 1).

PTCA AND CABG COMPARED WITH MEDICAL TREATMENT

PTCA compared with medical treatment

Angioplasty is more effective at relieving angina than medical treatments.^{19–20} The advantages of PTCA are greatest in patients with more severe angina at baseline, and there seems to be little extra benefit for patients with few symptoms. The advantage of PTCA in relief of symptoms decreases over time, with little difference at 3 years, because of the high rate of restenosis after the initial procedure.^{20–21} However, although PTCA can relieve symptoms in some groups of patients, it has not been shown to improve survival. The second randomised intervention treatment of angina (RITA-2) trial showed that PTCA was associated with an increased rate of adverse cardiac events (non-fatal myocardial infarction and death) compared with medical treatment, mainly due to early procedure related events (table 1).²¹

NHS Centre for Reviews and Dissemination, University of York, York
Mark Petticrew, research fellow

Health Economics Research Group, Brunel University, Uxbridge, Middlesex, UK
Mark Sculpher, senior research fellow
Martin Buxton, professor of health economics
Jo Kelland, research fellow

School of Pharmacy and Pharmaceutical Sciences, University of Manchester, UK
Rachel Elliott, clinical lecturer

Middlesex Hospital, London, UK
Diana Holdright, consultant cardiologist

Correspondence to:
Dr Mark Petticrew, NHS Centre for Reviews and Dissemination, University of York, York YO1 5DD, UK.

Accepted for publication
2 April 1998

CABG compared with medical treatment

Grafting improves symptoms of angina and other indicators of health related quality of life over 10 years compared with medical treatment,²² although with greater procedure related risks of myocardial infarction or death.^{23–25} The potential benefits of CABG in improving event free survival are therefore only likely to be realised in patients at higher risk of mortality from coronary heart disease. For example, a meta-analysis of seven randomised controlled trials showed that, although on average mortality was reduced in patients treated by CABG compared with those treated medically, this benefit was confined to higher risk patients (table 1).²⁵ There was a non-significant trend towards greater mortality after CABG in lower risk patients.

There are no recent cost effectiveness analyses of these alternatives; further evaluation of newer procedures such as minimally invasive CABG is also required.

PTCA COMPARED WITH CABG

A meta-analysis of eight randomised controlled trials comparing angioplasty with grafting found that at 1 year CABG was better at alleviating anginal symptoms in both single and multivessel disease than PTCA (table 1).²⁶ Angioplasty also had a higher rate of repeat intervention over the first year (34% *v* 3%; *p*<0.0001). There was substantial variation between the trials in the rate of repeat revascu-

larisation after PTCA, ranging from 20% to >40%. This may reflect differences in patient populations, criteria for retreatment, and possible bias due to awareness of previous randomised procedures. No difference in mortality was found between the treatments although the sample of patients analysed was small. These results are consistent with those from a recent trial which found that prevalence of angina was higher at 5 years in patients with multivessel disease (21% *v* 15%, *p*=0.007), and revascularisation more likely after PTCA.²⁷

Angioplasty is not generally suitable for patients with left main coronary stenosis (and no existing bypass graft to protect it), and those with severe diffuse disease,²⁸ although it may still occasionally be carried out in these patients. The balance of risks and benefits generally favours use of PTCA for palliation in patients with less severe disease who are not getting adequate symptom relief on medical treatments, but there is little evidence that this will improve survival.

Relative costs

A United Kingdom cost-analysis found that the initial costs of PTCA and CABG were about £3000 and £6000 respectively in a non-London centre at 1993–4 prices.²⁹ However, because of its high reintervention rate the total NHS cost of PTCA rose to over 80% of the costs of CABG after 2 years. Publication of five year follow up data from this study is expected.

Table 1 Meta-analyses of trials of interventions in stable angina, and details of the 2nd randomised intervention treatment of angina (RITA-2) trial

Study	Methodological details	Patients and interventions	Main results
Antiplatelet Trialists Collaboration-I 1994 ¹⁸	Meta-analysis of 145 RCTs of prevention of vascular events in high and low risk patients by antiplatelet therapy Follow up: average 2 y	Subgroup analysis of 551 patients with stable angina in 5 trials	Reduction in odds of MI, stroke or vascular death (10% <i>v</i> 15%; <i>p</i> =0.04). Inclusion of subsequent large RCT in meta-analysis shows significant reduction in MI in patients with stable angina ⁵⁷
Yusuf <i>et al</i> 1994 ²⁵	Meta-analysis of 7 RCTs (2649 patients) comparing effects of CABG and medical therapy on survival Follow up: 10 y	Mean age 51 y Angina severity: class I/II: 54% III/IV: 35% No of vessels diseased: LMA: 7%; 1 vessel: 10%; 2 vessel: 32%; 3 vessel: 51%	Total mortality lower with CABG at 5, 7, and 10 y. CABG results in 4 mths longer survival than medical therapy at 10 y (<i>p</i> =0.003). Additional survival benefit of CABG varies with severity: LMA disease=19 months; 3 vessel disease= 6 months; 1 or 2 vessel disease=2 months (<i>p</i> =0.02 for trend)
Pocock <i>et al</i> 1995 ²⁶	Meta-analysis of 8 RCTs comparing PTCA with CABG in angina (3371 patients) Follow up: mean of 2.7 y	1 Vessel disease=22% (3 trials) Multivessel disease=78% (6 trials)	No difference in mortality at follow up (RR=1.08, 95% CI: 0.8, 1.5) Risk of cardiac death and MI lower for CABG than PTCA in single vessel disease, but no difference for multivessel disease (<i>p</i> =0.01 for interaction) Need for reintervention within 1 y lower with CABG (3% <i>v</i> 34%) Angina prevalence lower in CABG group at 1 y (RR=1.56; 95% CI: 1.3–1.9), and slightly lower at 3 y (RR=1.23; 95% CI: 0.99–1.5)
Antiplatelet Trialists' Collaboration-II 1994 ³⁶	Meta-analysis of 46 RCTs of antiplatelet therapy <i>v</i> control, in the maintenance of vascular graft or arterial patency (including peripheral arteries). Average duration of therapy: PTCA= 6 months; CABG=7 months	Patients receiving additional antiplatelet treatment: PTCA: 3 trials (833 patients) CABG: 20 trials (5323 patients)	For PTCA or CABG, therapy reduced odds of vascular occlusion by 41% (2 <i>p</i> <0.0001) (Occlusion rates: PTCA patients: aspirin <i>v</i> control: 4% <i>v</i> 8% CABG patients: aspirin <i>v</i> control: 21% <i>v</i> 30%) 1 excess fatal bleed/1000 patients with therapy (95% CI: 0, 3)
RITA-2 trial 1997 ²⁰	Multicentre (United Kingdom and Ireland) RCT PTCA <i>v</i> antianginal medical therapy (β blockers, calcium antagonists, nitrates, plus aspirin) in 1018 patients with significant stenosis in at least one major epicardial vessel Average follow up=2.7 y	Median age=58 y Women=18% Angina grade: none=20%; 1 or 2=60%; grade 3 or 4= 20%. 1 vessel disease=60%; 2 vessel disease=33%; 3 vessel disease=7%	Death or MI more frequent with PTCA (6% <i>v</i> 3%, <i>p</i> =0.02) but no difference in deaths alone (2% <i>v</i> 1%, <i>p</i> =0.32) No difference in need for subsequent CABG (8% <i>v</i> 6%, <i>p</i> =0.2). Angina improvement greater with PTCA at 6 months (<i>p</i> <0.001), but little difference between treatments at 2 y (<i>p</i> =0.05). Little difference at 6 months between PTCA and medical therapy, in patients with no or grade 1 angina at baseline

MI=myocardial infarction; RTC=randomised controlled trial; NYHA=New York Heart Association; CCS=Canadian cooperative study; PTCA=percutaneous transluminal coronary angioplasty; CABG=coronary artery bypass grafting; LMA=???

Table 2 RCTs of standard balloon angioplasty compared with intracoronary stenting

Study	Methods and patient inclusion criteria	Patients	Results (standard PTCA v stents)
Fischman <i>et al</i> 1994 ³⁹ STRESS trial International multicentre	PTCA alone (n=203) v Palmaz-Schatz stent n=(207) in patients with ≤70% stenosis, lesion ≤15 mm length which could be spanned by a single stent and vessel diameter ≤3 mm Follow up: 6 months	% Male: 73% (PTCA) v 83% (stent) (p<0.05) 1 Vessel disease: 68% v 64% 2 Vessel disease: 21% v 27% 3 Vessel disease: 11% v 9% Mean age: 60 y in both groups Ejection fraction: 61% both groups. Lesion length: 8.7 mm v 9.6 mm (p<0.001) % Stenosis: 75%, both groups Diabetes: 16% v 15% Hypertension: 45% v 43%. Unstable angina: 48% v 47%	Restenosis: 43% v 32% (p=0.05) Re-intervention: 15% v 10% (p=0.06) Freedom from angina: 71% v 79% (p=0.08) Event free survival (including mortality): 76% v 81% (p=0.16)
Macaya <i>et al</i> 1996 ⁴⁰ Serruys <i>et al</i> 1994 ³⁸ BENESTENT trial European multicentre	PTCA (n=258) v Palmaz-Schatz stents (n=262) in patients with stable angina and single new lesions, aged ≥30 and ≤75 Follow up: 1 y	% Male: 82% (PTCA) v 80% (stent) Mean age: 58 v 57 y Previous CABG: 2% v 0% Previous PTCA: 3% v 2% Concentric lesion: 46% v 50% Length of lesion: 6.96mm v 7.06mm Diabetes: 6% v 7% Angina CCS class III or IV: 59% v 54%	No significant differences in mortality (0.8% v 1.2%), MI (5% v 4.2%), need for CABG (5% v 7%), or % angina free (86 v 82%) Need for repeat PTCA lower in stent group (21% v 10%, p=0.001)
Sirnes <i>et al</i> 1996 ⁴² SICC0 Norway and Sweden multicentre	PTCA (n=59) v PTCA+stents (n=58) in patients >18 y undergoing PTCA of a chronically occluded coronary artery Follow up: 6 months	Mean age 58 y, % men: 80% (PTCA) 84% (stent) Mean No of diseased vessels: 1.5 in each group % With 1 vessel disease: 62% each group. Mean ejection fraction: 63% each group % CCS class I/II: 24% v 22%	No difference in deaths or MI rates Freedom from angina 24% v 57% (p<0.001) Restenosis: 74% v 32% (p<0.001)
Versaci <i>et al</i> 1997 ⁴³ Italy	PTCA (n=60) v stents (n=60) in patients with angina, MI, or both Follow up: 12 months	Mean age: 57 (PTCA) v 58 y (stent) % Men: 83% v 92% Previous MI: 25% v 28% Angina class I: 8% v 7%; class II: 45% v 37%; class III: 18% v 30%; class V: 10% v 10% Mean ejection fraction: 54 v 52	Event free survival: 70% v 87% (p=0.04) Restenosis: 40% v 19% (p=0.02) Recurrence of angina: 25% v 10% (p=0.05)

MI=myocardial infarction; RTC=randomised controlled trial; NYHA=New York Heart Association; CCS=Canadian cooperative study; PTCA=percutaneous transluminal coronary artery; CABG=coronary artery bypass grafting.

ADJUNCTIVE MEDICAL TREATMENT

Both CABG and PTCA are essentially local interventions for what is a systemic disease, and patients with angina are at increased risk of stroke and peripheral vascular disease. Adjunctive medications may, therefore, have additional benefits for secondary prevention.

Medical adjuncts to PTCA

A meta-analysis has reported that antiplatelet treatment significantly reduces the risk of myocardial infarction, stroke, and vascular death in patients after PTCA (table 1).¹⁸ Treatment with calcium channel blockers³⁰ and fish oils³¹ may also reduce the risk of vascular occlusion although further evaluation in large trials is required.

Several studies have investigated glycoprotein IIb/IIIa receptor blocking drugs. One of these, abciximab, has been found to reduce in hospital myocardial infarction and reintervention rates in patients at high risk of abrupt vessel closure.³² Three year follow up from one study reported reductions in the need for reintervention and myocardial infarction after PTCA in patients at high risk of complications, although no overall reduction in mortality was found.³³ Tirofiban, an antagonist of platelet derived growth factor, has been found to reduce restenosis and angina compared with aspirin at 6 months,³⁴ and an antioxidant, probucol, reduced restenosis rates and the need for repeat angioplasty compared with placebo at 6 months in patients with one or two vessel disease.³⁵

Medical adjuncts to CABG

A meta-analysis of 20 trials found that antiplatelet treatment significantly reduced reocclusion rates compared with controls in patients after CABG (21% v 30%; table 1).³⁶ Lipid lowering treatment has also been found to reduce the risk of cardiac events and the need for revascularisation compared with placebo in patients with CABG.³⁷

Cost effectiveness of adjunctive medications in PTCA and CABG

A United States cost analysis found that abciximab reduced repeat admissions to hospital after PTCA but increased the overall mean cost per patient (including the cost of admission to hospital during the study period, 1991–2) by \$293.³⁸ No studies have examined the cost effectiveness of medical adjuncts to CABG.

It is unclear whether these newer adjunctive medical treatments are as effective or cost effective as cheaper alternatives—for example, aspirin. Larger, long term comparative studies would be useful to help identify optimal treatment after revascularisation.

NEWER TECHNOLOGIES: STENTS, LASER ANGIOPLASTY, AND ATHERECTOMY

Intracoronary stents

Stents involve placing a metal coil or tube within the stenosed artery and are used to prevent abrupt closure of the artery after PTCA and prevent longer term restenosis. The STRESS and BENESTENT studies reported

that stents reduce the need for subsequent revascularisation.^{39 40} In the STRESS study, angiographically-detected restenosis was lower in the stent group at 6 months. No significant differences in angina were found.³⁹ In BENESTENT, restenosis and the need for further PTCA were reduced in the stent group at 1 year. There were no differences in angina or need for CABG (table 2).⁴⁰

A recent systematic review highlighted several problems with these trials.⁴¹ Lack of blinding in the BENESTENT trial may have resulted in the investigators performing more revascularisations in patients receiving PTCA alone. In the STRESS study there were no differences in rates of restenosis when data were reanalysed on an intention to treat basis.

More recently, the SICCO trial found that stenting reduced the rates of angina, restenosis, and reocclusion at 6 months in the few patients with a chronically occluded coronary artery,⁴² although the assessment of this outcome was unblinded. Another recent trial found patients with isolated stenosis of the left anterior descending coronary artery who received stents had lower rates of recurrence of angina and restenosis at 12 months.⁴³ However, the outcome assessment was unsystematic and unblinded. Although the initial studies of stents reported high vascular complication rates, this is likely to have been due to the use of an intensive anticoagulation regimen. This has since been replaced with aspirin and ticlopidine, which produce fewer complications.⁴⁴

Stents rapidly came into routine use before being fully evaluated, and around 30%–60% of PTCA procedures now involve stents. Clinical belief, based on practical experience, is that they are beneficial for patients. As stent technology has evolved rapidly, the results of earlier studies are now becoming outdated, and continuing evaluation of this rapidly diffusing technology is therefore essential. Several trials are due to be reported in the near future.⁴⁵

Laser angioplasty; directional and rotational atherectomy; radiotherapy

Laser angioplasty, and directional and rotational coronary atherectomy are no more effective than standard PTCA.^{46–51} Catheter based radiotherapy has been reported to reduce restenosis at six months after stent implantation, though the study may be too small to detect differences in clinical outcomes.⁵² Further evaluation of this technology (and of newer procedures—such as minimally invasive CABG) is required.

Cost effectiveness of intracoronary stents and atherectomy

Two economic evaluations have reported that stents increase overall costs at 1 year compared with standard PTCA.^{53 54} One of these⁵³ reported that they were more cost effective given the improved outcomes; however, many of the studies it was based on are now outdated, as some are >10 years old. Studies comparing PTCA with atherectomy suggest that atherectomy is more costly, and no more

effective.^{48 55 56} No studies have examined the costs of laser angioplasty.

Conclusions

There is little evidence of important differences in the effectiveness and cost effectiveness of the principal classes of medical treatments for angina, used singly or in combination. The choice of medical treatment should, therefore, be based on the consideration of adverse effects and compliance, and on overall costs.

Both CABG and PTCA substantially improve symptoms of angina. Grafting improves survival in patients with severe disease and leads to less reintervention. However, PTCA is probably more useful as a palliative treatment in less severely ill patients whose symptoms are inadequately controlled by medical treatment, or other patients for whom surgery is not advisable. In those patients in whom both procedures are equally appropriate, patients' preferences for trade offs between degree of symptom relief and speed of recovery may be the key factors in determining choice of treatment.

More recent approaches to revascularisation, such as stents, have not been reliably shown to be more cost effective than standard PTCA or CABG; continuing evaluation is required, and the results of future trials need to be carefully appraised to determine the effectiveness of stenting in angioplasty.

Several areas for further research were identified by the review, including assessment of the effectiveness and cost effectiveness of the new generation medical and non-medical adjuncts to PTCA and CABG; cost and cost effectiveness of PTCA compared with medical treatment; and investigation of patients' treatment and health related preferences about stable angina. Further economic evaluations of alternative treatments for stable angina are also needed.

Finally, improvements in the appropriateness and equity of care may be achieved if regularly updated guidelines are developed to include agreed referral criteria for assessment of the pattern and extent of CHD. These should specify indications or thresholds for intervention, based on best available evidence, and take into account measures of disease severity or risk. Such guidance could also play a part in ensuring more cost effective treatment.

We are grateful to the large panel who advised us in the preparation of the systematic review and to the referees who commented on the *Effective Health Care Bulletin*. We thank Trevor Sheldon for helpful advice and Julie Glanville and the information staff at the NHS Centre for Reviews and Dissemination for help with the search strategies. The Health Economics Research Group receives funding through the Department of Health Policy Research Programme, and the systematic review on which this paper is based was commissioned by the NHS Health Technology Assessment Programme. The views expressed are those of the authors alone.

- 1 McCormick A, Fleming D, Charlton J. *Morbidity statistics from general practice: fourth national study 1991–2*. 1995: HMSO: London.
- 2 Ghandhi MM, Lampe FC, Wood DA. Incidence, clinical characteristics, and short-term prognosis of angina pectoris. *Br Heart J* 1995;73:193–8.
- 3 Standing Medical Advisory Committee. *The use of statins*. London: Department of Health, May 1997.
- 4 Black N, Langham S, Petticrew M. Trends in the age and sex of patients undergoing coronary revascularisation in the United Kingdom 1987–93. *Br Heart J* 1994;72:317–20.

- 5 Black NA, Langham S, Petticrew M. Coronary revascularisation: why do rates vary geographically in the UK? *J Epidemiol Community Health* 1995;49:408–12.
- 6 Sculpher M, Petticrew M, Buxton M, *et al.* *Resource Allocation in Chronic Stable Angina: a systematic review of the effectiveness, costs and cost-effectiveness of alternative interventions.* London: Health Economics Research Group, Brunel University, 1997.
- 7 Management of stable angina. *Effective Health Care* 1997;3:1–8.
- 8 Destors JM, Boissel JP, Philippon AM, *et al.* Controlled clinical trial of bepridil, propranolol and placebo in the treatment of exercise induced angina pectoris. *Fundam Clin Pharmacol* 1989;3:597–611.
- 9 Vliegen HW, van der Wall EE, Niemeyer MG, *et al.* Long-term efficacy of diltiazem controlled release versus metoprolol in patients with stable angina pectoris. *J Cardiovasc Pharmacol* 1991;18:S55–60.
- 10 Nahrendorf W, Rading A, Steinig G, *et al.* A comparison of carvedilol with a combination of propranolol and isosorbide dinitrate in the chronic treatment of stable angina. *Cardiovasc Pharmacol* 1992;19:S114–6.
- 11 Boberg J, Larsen FF, Pehrsson SK. The effects of β blockade with (epanolol) and without (atenolol) on intrinsic sympathomimetic activity in stable angina pectoris. *Clin Cardiol* 1992;15:591–5.
- 12 Singh S. Long term double blind evaluation of amlodipine and nadolol in patients with stable exertional angina pectoris. *Clin Cardiol* 1993;16:54–8.
- 13 Guernonprez JL, Blin P, Peterlongo F. A double-blind comparison of the long-term efficacy of a potassium channel opener and a calcium antagonist in stable angina pectoris. *Eur Heart J* 1993;14:30–4.
- 14 Dargie HJ, Ford I, Fox KM. Total Ischaemic Burden European Trial (TIBET). Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. *Eur Heart J* 1996;17:104–12.
- 15 Rehnqvist N, Hjelm Dahl P, Billin E, *et al.* Effects of metoprolol *vs* verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS). *Eur Heart J* 1996;17:76–81.
- 16 Kawanishi DT, Reid CL, Morrison EC, *et al.* Response of angina and ischemia to long term treatment in patients with chronic stable angina: a double-blind randomised individualised dosing trial of nifedipine, propranolol and their combination. *J Am Coll Cardiol* 1992;19:409–17.
- 17 Savonitto S, Ardissio D, Egstrup K, *et al.* Combination therapy with metoprolol and nifedipine versus monotherapy in patients with stable angina pectoris. Results of the International Multicenter Angina Exercise (IMAGE) Study. *J Am Coll Cardiol* 1996;27:311–6.
- 18 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81–106.
- 19 Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. *N Engl J Med* 1992;326:10–6.
- 20 RITA-2 trial participants. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. *Lancet* 1997;350:461–8.
- 21 Folland ED, Hartigan PM, Parisi AF. Percutaneous transluminal coronary angioplasty versus medical therapy for stable angina pectoris: outcomes for patients with double-vessel versus single-vessel coronary artery disease in a Veterans Affairs Cooperative randomized trial. Veterans Affairs ACME Investigators. *J Am Coll Cardiol* 1997;29:1505–11.
- 22 Rogers WJ, Coggins CJ, Gersh BJ, *et al.* Ten year follow up of quality of life in patients randomised to receive medical therapy or coronary artery bypass graft surgery. *Circulation* 1990;82:1647–58.
- 23 Schmuziger M, Christenson JT, Maurice J, *et al.* Reoperative myocardial revascularization: an analysis of 458 reoperations and 2645 single operations. *Cardiovasc Surg* 1994;2:623–9.
- 24 Jaglal SB, Tu JV, Naylor CD. Higher in-hospital mortality in female patients following coronary artery bypass surgery: a population-based study. Provincial Adult Cardiac Care Network of Ontario. *Clin Invest Med* 1995;18:99–107.
- 25 Yusuf S, Zucker D, Peduzzi P, *et al.* Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994;344:563–70.
- 26 Pocock SJ, Henderson RA, Rickards AF, *et al.* Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *Lancet* 1995;346:1184–9.
- 27 Bypass Angioplasty Revascularisation Investigators (BARI). Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 1996;335:217–25.
- 28 De Bono D. Coronary angioplasty. In: Weatherall DJ, Ledingham JG, Warrell DA, eds. *Oxford textbook of medicine.* Oxford: Oxford University Press, 1996:2349–53.
- 29 Sculpher MJ, Seed P, Henderson RA, *et al.* Health service costs of coronary angioplasty and coronary artery bypass surgery: the randomised intervention treatment of angina (RITA) trial. *Lancet* 1994;344:927–30.
- 30 Hillegass WB, Ohman EM, Leimberger JD, *et al.* A meta-analysis of randomised trials of calcium antagonists to reduce restenosis after coronary angioplasty. *Am J Cardiol* 1994;73:835–9.
- 31 Gapinski JP, VanRuiswyk JV, Heudebert GR, *et al.* Preventing restenosis with fish oils following coronary angioplasty. A meta-analysis. *Arch Intern Med* 1993;153:1595–601.
- 32 EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;330:956–61.
- 33 Topol EJ, Ferguson JJ, Weisman HF, *et al.* Long-term protection from myocardial ischemic events in a randomized trial of brief integrin beta 3 blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa Inhibition for Prevention of Ischemic Complication. *JAMA* 1997;278:479–84.
- 34 Maresta A, Balducci M, Cantini L, *et al.* Triazolinolopyrimidine, a platelet-derived growth factor antagonist, reduces restenosis after percutaneous transluminal coronary angioplasty. Results of the randomised double-blind STARC study. Studio Triadil versus Aspirin nella Restenosi Coronarica. *Circulation* 1994;90:2710–5.
- 35 Tardiff JC, Cote G, Lesperance J, *et al.* Probulol and multivitamins in the prevention of restenosis after coronary angioplasty. *N Engl J Med* 1997;337:365–72.
- 36 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. *BMJ* 1994;308:159–68.
- 37 Azen SP, Mack WJ, Cashin-Hemphill L, *et al.* Progression of coronary artery disease predicts clinical coronary events. Long term follow up from the cholesterol lowering atherosclerosis study. *Circulation* 1996;93:34–41.
- 38 Mark DB, Talley JD, Topol EJ, *et al.* Economic assessment of platelet glycoprotein IIb/IIIa inhibition for prevention of ischemic complications of high-risk coronary angioplasty. EPIC Investigators. *Circulation* 1996;94:629–35.
- 39 Fischman DL, Leon MB, Baim DS, *et al.* A randomised comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994;331:496–501.
- 40 Macaya C, Serruys PW, Ruygrok P, *et al.* Continued benefit of coronary stenting versus balloon angioplasty: one year clinical follow up of Benestent trial. Benestent Study Group. *J Am Coll Cardiol* 1996;27:255–61.
- 41 Savoie I, Sheps S. *Coronary stents: an appraisal of controlled clinical studies.* Vancouver: British Columbia Office of Health Technology Assessment, 1996.
- 42 Sirnes PA, Golf S, Myrnes Y, *et al.* Stenting in chronic coronary occlusion (SICCO): a randomised, controlled trial of adding stent implantation after successful angioplasty. *J Am Coll Cardiol* 1996;28:1444–51.
- 43 Versaci F, Gaspardone A, Tomai F, *et al.* A comparison of coronary-artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery. *N Engl J Med* 1997;336:817–22.
- 44 Schomig A, Neumann FJ, Kastrati A, *et al.* A randomised comparison of antiplatelet and anticoagulant therapy after coronary artery stents. *N Engl J Med* 1996;334:1084–9.
- 45 Balcon R, Beyar R, Chierchia I, *et al.* Recommendations on stent manufacture, implantation and utilization. *Eur Heart J* 1997;18:536–47.
- 46 Appelman YE, Pick JJ, Strikwerda S, *et al.* Randomised trial of excimer laser angioplasty versus balloon angioplasty for treatment of obstructive coronary artery disease. *Lancet* 1996;347:79–84.
- 47 Reifart N, Vandormael M, Krajcar M, *et al.* Randomized comparison of angioplasty of complex coronary lesions at a single center. Excimer laser, rotational atherectomy, and balloon angioplasty comparison (ERBAC) study. *Circulation* 1997;96:91–8.
- 48 Topol EJ, Leya F, Pinkerton CA, *et al.* A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. *N Engl J Med* 1993;329:221–7.
- 49 Adelman AG, Cohen EA, Kimball BP, *et al.* A comparison of directional atherectomy with balloon angioplasty for lesions of the left anterior descending coronary artery. *N Engl J Med* 1993;329:228–33.
- 50 Holmes DR Jr, Topol EJ, Califf RM, *et al.* A multicentre, randomised trial of coronary angioplasty versus directional atherectomy for patients with saphenous vein bypass graft lesions. CAVEAT-II Investigators. *Circulation* 1995;91:1966–74.
- 51 Elliott JM, Berdan LG, Holmes DR, I *et al.* One year follow up in the coronary angioplasty versus excisional atherectomy trial (CAVEAT I). *Circulation* 1995;91:2158–66.
- 52 Teirstein PS, Massullo V, Jani S, *et al.* Catheter-based radiotherapy to inhibit restenosis after coronary stenting. *N Engl J Med* 1997;336:1697–703.
- 53 Cohen DJ, Breall JA, Ho KK, *et al.* Evaluating the potential cost-effectiveness of stenting as a treatment for symptomatic single-vessel coronary disease. Use of a decision-analytic model. *Circulation* 1994;89:1859–74.
- 54 Cohen DJ, Krumholz HM, Sukin CA, *et al.* In-hospital and one-year economic outcomes after coronary stenting or balloon angioplasty. Results from a randomised clinical trial. *Circulation* 1995;92:2480–7.
- 55 Dick RJ, Popma JJ, Muller DW, *et al.* In hospital costs associated with new percutaneous coronary devices. *Am J Cardiol* 1991;68:879–85.

- 56 Guzman LA, Simpfendorfer C, Fix J, *et al.* Comparison of costs of new atherectomy devices and balloon angioplasty for coronary artery disease. *Am J Cardiol* 1994;74:22–5.
- 57 Juul-Moller S, Edvardsson N, Jahnmatz B, *et al.* Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. *Lancet* 1992;340:1421–5.
- 58 Serruys PW, de Jaegere P, Kiemeneij F, *et al.* A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994;331:489–95.

Appendix: Additional included studies assessing the long term effectiveness of treatments for stable angina

Study	Study details	Patients	Main results
Destors <i>et al</i> 1989 ⁸	Multicentre RCT, calcium channel blocker (bepridil) <i>v</i> β blocker (propranolol) <i>v</i> placebo; n=191 Follow up: 24 weeks	Patients with exercise induced angina; % Male: 64% <i>v</i> 73% <i>v</i> 57%; Mean age: 56 <i>v</i> 56 <i>v</i> 54 y History of MI: 26% <i>v</i> 29% <i>v</i> 11%	Increased exercise duration: 31% <i>v</i> 24% <i>v</i> 8% Increased workload: 25% <i>v</i> 30% <i>v</i> 14% No significant difference between drug groups
Vliegen <i>et al</i> 1991 ⁹	Multicentre RCT, calcium channel blocker (diltiazem) <i>v</i> β blocker (metoprolol); n=56 Follow up: 32 weeks	Patients with stable angina for at least 3 months, >3 angina attacks/week., aged 21–79	No significant difference in increase in exercise duration between groups No difference in frequency of anginal attacks per week; no difference in incidence or severity of side effects
Nahrendorf <i>et al</i> 1992 ¹⁰	RCT, vasodilating β blocker (carvedilol) <i>v</i> β blocker/nitrate combination (propranolol/ISDN); n=31 Follow up: 6 months	Patients with exertion induced angina, 100% male Mean age 54 y	After 6 months no therapeutic efficacy of the combination was found, whereas the acute therapeutic effects of carvedilol were maintained
Boberg <i>et al</i> 1992 ¹¹	Multicentre RCT, β blocker with intrinsic sympathomimetic activity (epanolol) <i>v</i> β blocker (atenolol); n=173 Follow up: 1 y	Patients with stable angina, 85% male Mean age 58 y	Exercise tolerance: 718s <i>v</i> 700s NS Median angina attack rate/day: 0.17 <i>v</i> 0.15 NS No differences in energy, wellbeing or activity scores.
Singh <i>et al</i> 1993 ¹²	Multicentre RCT, calcium channel blocker (amlodipine) <i>v</i> β blocker (nadolol); n=80 Follow up: 26 weeks	Patients with symptoms of stable angina Mean duration of angina 79 months % Male: 88% <i>v</i> 90% Mean age: 65 <i>v</i> 62 y	No significant difference in increase in total exercise time Angina attack rate/week: reduced in each group to 0.3/week, NS; decrease in ST segment depression: 9% <i>v</i> 21% NS
Guermonprez <i>et al</i> 1993 ¹³	Multicentre RCT, calcium channel blocker (diltiazem) <i>v</i> potassium channel activator (nicorandil); n=60 Follow up: initially 3 months	Patients with stable angina of average duration approx 3.7 y; 35% in each group had previous MI % Male: 86% <i>v</i> 90% Mean age: 61 <i>v</i> 60 y 1 Vessel disease: 32% <i>v</i> 37% 2 Vessel 29% <i>v</i> 33% 3 Vessel 36% <i>v</i> 30%	No significant differences in exercise tolerance or angina attack frequency, or in adverse effects
Dargie <i>et al</i> 1996 ¹⁴	Multicentre RCT, β blocker (atenolol) <i>v</i> calcium channel blocker (nifedipine) <i>v</i> combination; n=682 Follow up: 1–3 y	% Male: 87% <i>v</i> 82% <i>v</i> 88% Mean age: 59 <i>v</i> 60 <i>v</i> 60 y Previous MI: 34% <i>v</i> 31% <i>v</i> 34%	Cardiac death: 3% <i>v</i> 6% <i>v</i> 4% Non-fatal MI: 14% <i>v</i> 15% <i>v</i> 7% Unstable angina: 12% <i>v</i> 4% <i>v</i> 8% CABG: 7% <i>v</i> 6% <i>v</i> 4% PTCA: 1% <i>v</i> 0% <i>v</i> 0% All above primary end points NS
Rehnqvist <i>et al</i> 1996 ¹⁵	Multicentre RCT, β blocker (metoprolol) <i>v</i> calcium channel blocker (verapamil); n=809 Follow up: 3 y	% Male: 73% <i>v</i> 66% Mean age: 59 y both groups Duration of angina 2 y both groups NYHA angina class I: 27% <i>v</i> 25% NYHA class II: 68% <i>v</i> 69%	Mortality: 5.45 <i>v</i> 6.2% (p=0.63) Non-fatal cardiovascular events: 26% <i>v</i> 24% (p=0.56)
Kawanishi <i>et al</i> 1992 ¹⁶	RCT, β blocker (propranolol) <i>v</i> calcium channel blocker (nifedipine) <i>v</i> combination; n=74 Follow up: 6 months	Mean age: 54 y 66% male. NYHA class: I 4%, II 73%, III 23%	Angina attack frequency and exercise tolerance showed no greater improvement with combination therapy than with sole agents at follow up.
Gapinski <i>et al</i> 1993 ³¹	Meta-analysis of 7 RCTs of omega-3 fatty acids	Patients undergoing PTCA with restenosis defined using angiography or stress testing	Significant relation between restenosis and dose (p=0.03) For studies using angiography, absolute difference in restenosis rates=14% (95% CI: 3,25%) For studies using stress testing, absolute difference in restenosis rates=5% (95% CI: -4 to 14%)

Appendix: Additional included studies assessing the long term effectiveness of treatments for stable angina

Study	Study details	Patients	Main results
EPIC investigators 1994 ³² Topol <i>et al</i> 1997 ³³	Multicentre RCT, c7E3 Fab as bolus or infusion (with placebo bolus or infusion as appropriate) <i>v</i> both <i>v</i> placebo; n=2099 Follow up: up to 3 y	Patients at high risk of abrupt vessel closure, but not bleeding, aged <80 y	At 3 y, death, MI or revascularisation occurred in 41% (bolus+infusion) <i>v</i> 47% (bolus only) <i>v</i> 47% (placebo) (p=0.09, bolus+infusion <i>v</i> placebo) Mortality: 7% <i>v</i> 8% <i>v</i> 9% (p=0.20, bolus+infusion <i>v</i> placebo) MI: 11% <i>v</i> 12% <i>v</i> 13% (p=0.08, bolus+infusion <i>v</i> placebo) Revascularisation: 35% <i>v</i> 39% <i>v</i> 40% (p=0.02, bolus+infusion <i>v</i> placebo) Overall bolus improved outcomes at short and long term follow up
Maresta <i>et al</i> 1994 ³⁴	Multicentre RCT, trapidil <i>v</i> aspirin for 6 months; n=254	Patients with successful PTCA for coronary stenosis $\geq 70\%$, and significant ischaemia % male: 78% <i>v</i> 80% Mean age: 58 <i>v</i> 57 y CCS Class III angina: 54% <i>v</i> 49% Class IV angina: 11% <i>v</i> 12%	No deaths Angina at follow up: 74% <i>v</i> 56%; MI: 2.4% <i>v</i> 1.6%; CABG: 0.8% both groups.
Tardiff <i>et al</i> 1997 ³⁵	RCT, probucol <i>v</i> multivitamins, <i>v</i> both, <i>v</i> placebo, for 6 months; n=317	Patients undergoing elective angioplasty Mean age: 59 <i>v</i> 58 <i>v</i> 58 <i>v</i> 60 y. % male: 81% <i>v</i> 85% <i>v</i> 65% <i>v</i> 77% CCS angina grade I: 15% <i>v</i> 8% <i>v</i> 11% <i>v</i> 5%; grade II: 54% <i>v</i> 67% <i>v</i> 55% <i>v</i> 62%; grade III: 18% <i>v</i> 23% <i>v</i> 17% <i>v</i> 23%; grade IV: 3% <i>v</i> 1% <i>v</i> 1%, 0% No of diseased vessels: 1:35% <i>v</i> 42% <i>v</i> 49% <i>v</i> 29% 2:43% <i>v</i> 38% <i>v</i> 35% <i>v</i> 49% 3: 22% <i>v</i> 13% <i>v</i> 23% <i>v</i> 22%	Rates of repeated angioplasty: 11% <i>v</i> 24% <i>v</i> 16% <i>v</i> 27% (p=0.009 for probucol <i>v</i> no probucol, p=0.75 for vitamins <i>v</i> no vitamins).
Azen <i>et al</i> 1996 ³⁷	RCT, colestipol/niacin plus diet <i>v</i> placebo plus diet; initial n=162 (n=103 at 4 y) Follow up at 2 and 4 y	40–59 y old men with previous CABG, cholesterol between 4.79 and 9.07 mmol/l and confirmed lipid lowering response to study medications	2 y results show decreased atherosclerosis progression and increased regression At 4 y: atherosclerosis non-progression 52% <i>v</i> 15%; regression: 18% <i>v</i> 6%; development of new lesions in native arteries: 14% <i>v</i> 40%; new lesions in bypass grafts: 16% <i>v</i> 38%
Schomig <i>et al</i> 1996 ⁴⁴	RCT, antiplatelet (ticlopidine plus aspirin) <i>v</i> anticoagulant (intravenous heparin, phenprocoumon and aspirin) therapy; n=257 Follow up of 1 month	Patients undergoing placement of Palmaz-Schatz coronary artery stents Mean age: 62 y % male: 23% <i>v</i> 24% Previous MI: 42% <i>v</i> 45% Previous PTCA: 47% <i>v</i> 54% Previous CABG: 8% <i>v</i> 13%	Primary cardiac end point: 6% <i>v</i> 2% (p=0.01) Fewer non-cardiac events in antiplatelet group (1% <i>v</i> 12% p<0.001) Combined clinical end point: 3% <i>v</i> 17% (p<0.001) Occlusion of stented vessel: 1% <i>v</i> 5% (p=0.004).
Appelman <i>et al</i> 1996 ⁴⁶	Multicentre RCT, excimer laser angioplasty <i>v</i> balloon angioplasty; n=308 Follow up: 6 months	Patients with stable angina and lesions >10 mm suitable for PTCA % Male: 76% <i>v</i> 73% Mean age: 58 <i>v</i> 59 y 1 Vessel disease: 55% <i>v</i> 50% Previous CABG: 7% <i>v</i> 8% Previous PTCA: 11% <i>v</i> 16%	No angina: 60% both groups In hospital MI: 1.3% both groups Overall MI: 5% <i>v</i> 6% (p=0.67) CABG: 11% both groups Repeat PTCA: 20% <i>v</i> 17% (p=0.45)
Reifart <i>et al</i> 1997 ⁴⁷	RCT, balloon angioplasty <i>v</i> excimer laser angioplasty <i>v</i> rotational atherectomy; n=685 Follow up: 1 y	Patients with symptomatic coronary artery disease warranting PTCA for a complex lesion Mean age 62 all groups; % male: 81 <i>v</i> 78 <i>v</i> 80 y Previous MI: 45% <i>v</i> 42% <i>v</i> 47% 1 Vessel disease: 48% <i>v</i> 47% <i>v</i> 42% 2 Vessel disease: 41% all groups 3 Vessel disease: 11% <i>v</i> 11% <i>v</i> 18%	Clinical end point (death, Q wave MI, CABG, or repeated angioplasty): 37% <i>v</i> 48% <i>v</i> 46% (p=.06 for three group comparison; p=0.015 for PTCA <i>v</i> excimer laser; p=0.04 for PTCA <i>v</i> atherectomy) % CCS class 0/1 at follow up: 64% <i>v</i> 62% <i>v</i> 63%
Adelman <i>et al</i> 1993 ⁴⁹	Multicentre RCT, PTCA <i>v</i> atherectomy; n=274 Follow up: 6 months	Patients with angina or evidence of myocardial ischaemia and a stenosis of $\geq 60\%$ in the proximal third of the left anterior descending artery % Male: 87% <i>v</i> 80% Mean age: 55 <i>v</i> 58 y Multivessel disease: 20% <i>v</i> 27%	Mortality: 0% <i>v</i> 1% % Class III/IV angina: 20% <i>v</i> 30% (p=0.11) Long term MI: 1% <i>v</i> 0% Subsequent CABG: 4% <i>v</i> 5% PTCA 22% <i>v</i> 23%

Appendix: Additional included studies assessing the long term effectiveness of treatments for stable angina

Study	Study details	Patients	Main results
Holmes <i>et al</i> 1995 ⁵⁰	Multicentre RCT, PTCA <i>v</i> directional atherectomy; n=305 Follow up: 6 months	Patients with previous CABG and de novo saphenous vein graft lesions % Male: 85% <i>v</i> 83% Mean age 65 y both groups Angina class III/IV: 85% <i>v</i> 80% 1 Lesion targeted: 84% <i>v</i> 89% 2 Lesions targeted: 15% <i>v</i> 10%	Survival: 92% <i>v</i> 95% (p=0.41) Angina class 1 or less: 64% <i>v</i> 66% (p=0.8) MI: 16% <i>v</i> 20% (p=0.5) CABG: 5% <i>v</i> 5% Any percutaneous intervention: 27% <i>v</i> 19% (p=0.04)
Elliott <i>et al</i> 1995 ⁵¹ ; Topol <i>et al</i> 1993 ⁴⁸	Multicentre RCT, PTCA <i>v</i> excisional atherectomy; n=1012 Follow up: at least 1 y	Patients with diseased native coronary vessels $\geq 60\%$ stenosis, and lesion length <12 mm % Male: 70% <i>v</i> 75% Mean age 59 y both groups Single vessel disease: 65% <i>v</i> 66%	1 y Mortality: 0.6% <i>v</i> 2.2% (p=0.04) 1 y MI 4% <i>v</i> 9% (p=0.005) Restenosis at 6 months: 57% <i>v</i> 50% (p=0.06) Combined end points: death or MI: 5% <i>v</i> 10% (p<0.001); death, MI, bypass surgery, or target lesion intervention: 34% <i>v</i> 37% (p=0.32); death, MI, bypass surgery, or percutaneous intervention: 39% <i>v</i> 42% (p=0.22)
Teirstein <i>et al</i> 1997 ⁵²	RCT, catheter-based radiotherapy with iridium-192 <i>v</i> placebo; n=55 Follow up: 6 months	Patients with restenosis undergoing coronary stenting and balloon dilation % Male: 73% <i>v</i> 76% Mean age: 70 <i>v</i> 69 y Previous MI: 34 <i>v</i> 38% Previous restenoses: 2.1 <i>v</i> 2.0	Angiographically defined restenosis: 17% <i>v</i> 54% (p=0.01)

MI=myocardial infarction; RTC=randomised controlled trial; NYHA=New York Heart Association; CCS=Canadian cooperative study; PTCA= percutaneous transluminal coronary angioplasty; CABG=coronary artery bypass grafting.