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, 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. 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.

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. 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, which formed the basis for part of a recent Effective Health Care Bulletin 1997 vol 3.

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).

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. There is also no evidence that combination treatment is more effective than monotherapy, 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. 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. 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. 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).
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, although with greater procedure related risks of myocardial infarction or death. 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). 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). 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 revascularisation 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.

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, 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. 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>
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<th>Study</th>
<th>Methodological details</th>
<th>Patients and interventions</th>
<th>Main results</th>
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<tr>
<td>Antiplatelet Trialists Collaboration-I 1994</td>
<td>Meta-analysis of 145 RCTs of prevention of vascular events in high and low risk patients by antiplatelet therapy; Follow up: average 2 y</td>
<td>Subgroup analysis of 551 patients with stable angina in 5 trials</td>
<td>Reduction in odds of MI, stroke or vascular death (10% v 15%; p=0.04). Inclusion of subsequent large RCT in meta-analysis shows significant reduction in MI in patients with stable angina</td>
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<tr>
<td>Yusuf et al 1994</td>
<td>Meta-analysis of 7 RCTs (2649 patients) comparing effects of CABG and medical therapy on survival; Follow up: 10 y</td>
<td>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%</td>
<td>Total mortality lower with CABG at 5, 7, and 10 y. CABG results in 4 mths longer survival than medical therapy at 10 y (p=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 (p=0.02 for trend)</td>
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<td>Pocock et al 1995</td>
<td>Meta-analysis of 8 RCTs comparing PTCA with CABG in angina (3371 patients); Follow up: mean of 2.7 y</td>
<td>1 Vessel disease=22% (3 trials) Multivessel disease=78% (6 trials)</td>
<td>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 (p=0.01 for interaction) Need for reintervention within 1 y lower with CABG (3% v 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)</td>
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<tr>
<td>Antiplatelet Trialists’ Collaboration-II 1994</td>
<td>Meta-analysis of 46 RCTs of antiplatelet therapy v control, in the maintenance of vascular graft or arterial patency (including peripheral arteries); Average duration of therapy: PTCA= 6 months; CABG=7 months</td>
<td>Patients receiving additional antiplatelet therapy: PTCA: 3 trials (833 patients) CABG: 20 trials (5323 patients)</td>
<td>For PTCA or CABG, therapy reduced odds of vascular occlusion by 41% (2p=0.0001) (Oclusion rates: PTCA patients: aspirin v control: 4% v 8% CABG patients: aspirin v control: 21% v 30%) 1 excess fatal bleed/1000 patients with therapy (95%CI:0.3)</td>
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<td>RITA-2 trial 1997</td>
<td>Multicentre (United Kingdom and Ireland) RCT PTCA v antanginal 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</td>
<td>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%</td>
<td>Death or MI more frequent with PTCA (6% v 3%; p=0.02) but no difference in deaths alone (2% v 1%, p=0.32) No difference in need for subsequent CABG (8% v 6%, p=0.2). Angina improvement greater with PTCA at 6 months (p&lt;0.001), but little difference between treatments at 2 y (p=0.05). Little difference at 6 months between PTCA and medical therapy, in patients with no or grade 1 angina at baseline</td>
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**Table 2** RCTs of standard balloon angioplasty compared with intracoronary stenting

<table>
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<tr>
<th>Study</th>
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<th>Patients</th>
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<tr>
<td>Macaya et al 1996&lt;sup&gt;46&lt;/sup&gt; Serruys et al 1994&lt;sup&gt;47&lt;/sup&gt; BENESTENT trial</td>
<td>PTCA (n=258) v Palmaz-Schatz stents (n=262) in patients with stable angina and single new lesions, aged ≥30 and ≤75</td>
<td>Follow up: 1 y</td>
<td>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)</td>
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<tr>
<td>Sirnes et al 1998&lt;sup&gt;48&lt;/sup&gt; SICCO Norway and Sweden multicentre</td>
<td>PTCA (n=59) v PTCA+stents (n=58) in patients &gt;18 y undergoing PTCA of a chronically occluded coronary artery Follow up: 6 months</td>
<td>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%</td>
<td>No difference in deaths or MI rates Freedom from angina 24% v 57% (p&lt;0.001) Restenosis: 74% v 32% (p&lt;0.001)</td>
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<tr>
<td>Versaci et al 1997&lt;sup&gt;49&lt;/sup&gt; Italy</td>
<td>PTCA (n=60) v stents (n=60) in patients with angina, MI, or both Follow up: 12 months</td>
<td>Mean age: 57 (PTCA) v 58 y (stent) % Men: 83% v 92%</td>
<td>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)</td>
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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 adjacents 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).<sup>18</sup> Treatment with calcium channel blockers<sup>30</sup> and fish oils<sup>31</sup> 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. 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.<sup>32</sup> Trapidil, an antagonist of platelet derived growth factor, has been found to reduce restenosis and angina compared with aspirin at 6 months,<sup>34</sup> 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.<sup>35</sup>

**Medical adjacents 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).<sup>16</sup> 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.<sup>37</sup>

**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.<sup>38</sup> 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, longer term comparative studies would be useful to help identify optimal treatment after revascularisation.

**NEWER TECHNOLOGIES: STENTS, LASER ANGIOPLASTY, AND ATHRECTION**

**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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{40}

A recent systematic review highlighted several problems with these trials.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{45}

\textbf{Laser angioplasty; directional and rotational atherectomy; radiotherapy}

Laser angioplasty, and directional and rotational coronary atherectomy are no more effective than standard PTCA.\textsuperscript{46–51} Catheter based radiotherapy has been reported to reduce restenosis at up to 6 months after stent implantation, though the study may be too small to detect differences in clinical outcomes.\textsuperscript{52} Further evaluation of this technology (and of newer procedures—such as minimally invasive CABG) is required.

\textbf{Cost effectiveness of intracoronary stents and atherectomy}

Two economic evaluations have reported that stents increase overall costs at 1 year compared with standard PTCA.\textsuperscript{53,54} One of these\textsuperscript{53} 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.\textsuperscript{48,55,56} No studies have examined the costs of laser angioplasty.

\textbf{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 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.

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

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<th>Study</th>
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<th>Patients</th>
<th>Main results</th>
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<tr>
<td>Destors et al 1989</td>
<td>Multicentre RCT, calcium channel blocker (bepridil) v β blocker (propranolol) v placebo; n=191 Follow up: 24 weeks</td>
<td>Patients with exercise induced angina; % Male: 64% v 73% v 57%; Mean age: 56 v 56 v 54 y</td>
<td>Increased exercise duration: 31% v 24% v 8% Increased workload: 25% v 30% v 14% No significant difference between drug groups</td>
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<tr>
<td>Vliegen et al 1991</td>
<td>Multicentre RCT, calcium channel blocker (diltiazem) v β blocker (metoprolol); n=56 Follow up: 32 weeks</td>
<td>Patients with stable angina for at least 3 months, &gt;3 angina attacks/week., aged 21–79</td>
<td>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</td>
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<tr>
<td>Nahrendorf et al 1992</td>
<td>RCT, vasodilating β blocker (carvedilol) v β blocker/nitrate combination (propranolol/ESDN); n=31 Follow up: 6 months</td>
<td>Patients with exertion induced angina, 100% male Mean age 54 y</td>
<td>After 6 months no therapeutic efficacy of the combination was found, whereas the acute therapeutic effects of carvedilol were maintained</td>
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<td>Boberg et al 1992</td>
<td>Multicentre RCT, β blocker with intrinsic sympathomimetic activity (epanolol) v β blocker (atenolol); n=173 Follow up: 1 y</td>
<td>Patients with stable angina, 85% male Mean age 58 y</td>
<td>Exercise tolerance: 718 s v 700 s NS Median angina attack rate/day: 0.17 v 0.15 NS No differences in energy, wellbeing or activity scores.</td>
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<tr>
<td>Singh et al 1993</td>
<td>Multicentre RCT, calcium channel blocker (amlodipine) v β blocker (nadolol); n=80 Follow up: 26 weeks</td>
<td>Patients with symptoms of stable angina Mean duration of angina 79 months % Male: 88% v 90% Mean age:65 v 62 y</td>
<td>No significant difference in increase in total exercise time Angina attack rate/reduce: reduced in each group to 0.3 week; NS, decrease in ST segment depression: 9% v 21% NS</td>
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<tr>
<td>Guermontprez et al 1993</td>
<td>Multicentre RCT, calcium channel blocker (diltiazem) v potassium channel activator (nicorandil); n=60 Follow up: initially 3 months</td>
<td>Patients with stable angina of average duration approx 3.7 y; 35% in each group had previous MI % Male: 86% v 90% Mean age: 61 v 60 y 1 Vessel disease:32% v 37% 2 Vessel:29% v 33% 3 Vessel: 36% v 30%</td>
<td>No significant differences in exercise tolerance or angina attack frequency, or in adverse effects</td>
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<tr>
<td>Dargie et al 1996</td>
<td>Multicentre RCT, β blocker (atenolol) v calcium channel blocker (nifedipine) v combination; n=682 Follow up: 1-3 y</td>
<td>% Male: 87% v 82% v 88% Mean age: 59 v 60 v 60 y Previous MI: 34% v 31% v 34%</td>
<td>Cardiac death: 3% v 6% v 4% Non-fatal MI: 14% v 15% v 7% Unstable angina: 12% v 4% v 8% CABG: 7% v 6% v 4% PTCA: 1% v 0% v 0% All above primary end points NS</td>
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<tr>
<td>Rehnqvist et al 1996</td>
<td>Multicentre RCT, β blocker (metoprolol) v calcium channel blocker (verapamil); n=809 Follow up: 3 y</td>
<td>% Male: 73% v 66% Mean age: 59 y both groups Duration of angina 2 y both groups NYHA angina class I: 27% v 25% NYHA class II: 68% v 69%</td>
<td>Mortality: 5.45 v 6.2% (p=0.63) Non-fatal cardiovascular events: 26% v 24% (p=0.56)</td>
</tr>
<tr>
<td>Kawanishi et al 1992</td>
<td>RCT, β blocker (propranolol) v calcium channel blocker (nifedipine) v combination; n=74 Follow up: 6 months</td>
<td>Mean age: 54 y 6% male. NYHA class: I 14%, II 73%, III 23%</td>
<td>Angina attack frequency and exercise tolerance showed no greater improvement with combination therapy than with sole agents at follow up.</td>
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<tr>
<td>Gapinski et al 1993</td>
<td>Meta-analysis of 7 RCTs of omega-3 fatty acids</td>
<td>Patients undergoing PTCA with restenosis defined using angiography or stress testing</td>
<td>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%)</td>
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<tr>
<td>Study</td>
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<td><strong>EPIC investigators 1994</strong>&lt;sup&gt;15&lt;/sup&gt; <strong>Topol et al 1997</strong>&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Multicentre RCT; c7E3 Fab as bolus or infusion (with placebo bolus or infusion as appropriate) v both v placebo; n=2099 Follow up: up to 3 y</td>
<td>Patients at high risk of abrupt vessel closure, but not bleeding, aged &lt;80 y</td>
<td>At 3 y, death, MI or revascularisation occurred in 41% (bolus+infusion) v 47% (bolus only) v 47% (placebo) (p=0.09, bolus+infusion v placebo) Mortality: 7% v 8% v 9% (p=0.20, bolus+infusion v placebo) ME: 11% v 12% v 13% (p=0.08, bolus+infusion v placebo) Revascularisation: 35% v 39% v 40% (p=0.02, bolus+infusion v placebo) Overall bolus improved outcomes at short and long term follow up</td>
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<td><strong>Mareota et al 1994</strong>&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Multicentre RCT, trapidil v aspirin for 6 months; n=254</td>
<td></td>
<td>No deaths Angina at follow up: 74% v 56%; MI: 2.4% v 1.6%; CABG: 0.8% both groups.</td>
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<td><strong>Tardi et al 1996</strong>&lt;sup&gt;18&lt;/sup&gt;</td>
<td>RCT, probucol v multivitamins, v both, v placebo, for 6 months; n=317</td>
<td></td>
<td>Rates of repeated angioplasty: 11% v 24% v 16% v 27% (p=0.009 for probucol v no probucol, p=0.75 for vitamins v no vitamins).</td>
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<td><strong>Azem et al 1996</strong>&lt;sup&gt;19&lt;/sup&gt;</td>
<td>RCT, colestipol/niacin plus diet v placebo plus diet; initial n=162 (n=103 at 4 y) Follow up at 2 and 4 y</td>
<td>Patients undergoing elective angioplasty Mean age: 59 v 58 v 60 y; % male: 81% v 85% v 65% v 77% CCS angina grade I: 15% v 8% v 11% v 5%; grade II: 54% v 67% v 55% v 62%; grade III: 18% v 23% v 17% v 23%; grade IV: 3% v 1% v 1% v 0% No of diseased vessels: 1:35% v 42% v 49% v 29% v 24% v 3% v 22% v 23% v 22%</td>
<td>2 y results show decreased atherosclerosis progression and increased regression At 4 y: atherosclerosis non-progression 52% v 15%; regression: 18% v 6%; development of new lesions in native arteries:14% v 40%; new lesions in bypass grafts: 16% v 38%</td>
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<td><strong>Schomig et al 1996</strong>&lt;sup&gt;20&lt;/sup&gt;</td>
<td>RCT, antiplatelet (ticlopidine plus aspirin) v anticoagulant (intravenous heparin, phenprocoumon and aspirin) therapy; n=257 Follow up of 1 month</td>
<td>Patients undergoing placement of Palmaz-Schatz coronary artery stents Mean age: 62 y % male: 23% v 24% Previous ME: 42% v 45% Previous PTCA: 47% v 54% Previous CABG: 8% v 13%</td>
<td>Primary cardiac end point: 6% v 2% (p=0.01) Fewer non-cardiac events in antiplatelet group (1% v 12%, p&lt;0.001) Combined clinical end point: 3% v 17% (p&lt;0.001) Occlusion of stented vessel: 1% v 5% (p=0.044).</td>
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<td><strong>Appelman et al 1996</strong>&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Multicentre RCT, excimer laser angioplasty v balloon angioplasty; n=308 Follow up: 6 months</td>
<td>Patients with stable angina and lesions &gt;10 mm suitable for PTCA % Male:76% v 73% Mean age: 58 v 59 y 1 Vessel disease: 55% v 50% Previous CABG: 7% v 8% Previous PTCA: 11% v 16%</td>
<td>No angina: 60% both groups In hospital ME: 1.3% both groups Overall MI: 5% v 6% (p=0.67) CABG: 11% both groups Repeat PTCA: 20% v 17% (p=0.45)</td>
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<tr>
<td><strong>Reifart et al 1997</strong>&lt;sup&gt;22&lt;/sup&gt;</td>
<td>RCT, balloon angioplasty v excimer laser angioplasty v rotational atherectomy; n=685 Follow up: 1 y</td>
<td>Patients with symptomatic coronary artery disease warranting PTCA for a complex lesion Mean age 62 all groups; % male: 81 v 78 v 80 y Previous ME: 45% v 42% v 47% 1 Vessel disease: 48% v 47% v 42% 2 Vessel disease: 41% all groups 3 Vessel disease: 11% v 11% v 18%</td>
<td>Clinical end point (death, Q wave MI, CABG, or repeated angioplasty): 37% v 48% v 46% (p=0.06 for three group comparison; p=0.015 for PTCA v excimer laser; p=0.04 for PTCA v atherectomy) % CCS class 0/1 at follow up: 64% v 62% v 63%</td>
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<td><strong>Adelman et al 1993</strong>&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Multicentre RCT, PTCA v atherectomy; n=274 Follow up: 6 months</td>
<td>Patients with angina or evidence of myocardial ischaemia and a stenosis of &gt;60% in the proximal third of the left anterior descending artery % Male: 87% v 80% Mean age: 55 v 58 y Multivessel disease: 20% v 27%</td>
<td>Mortality: 0% v 1% % Class III/IV angina: 20% v 30% (p=0.11) Long term MI: 1% v 0% Subsequent CABG: 4% v 5% PTCA 22% v 23%</td>
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</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study details</th>
<th>Patients</th>
<th>Main results</th>
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<tr>
<td>Holmes et al 1995&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Multicentre RCT, PTCA vs directional atherectomy; n=305 Follow up: 6 months</td>
<td>Patients with previous CABG and de novo saphenous vein graft lesions % Male: 85% vs 83% Mean age 65 y both groups Angina class III/IV: 85% vs 80% 1 Lesion targeted: 84% vs 89% 2 Lesions targeted: 15% vs 10%</td>
<td>Survival: 92% vs 95% (p=0.41) Angina class I or less: 64% vs 66% (p=0.8) MI: 16% vs 20% (p=0.5) CABG: 5% vs 5% Any percutaneous intervention: 27% vs 19% (p=0.04)</td>
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<td>Elliott et al 1995&lt;sup&gt;19&lt;/sup&gt; ; Topol et al 1993&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Multicentre RCT, PTCA vs excisional atherectomy; n=1012 Follow up: at least 1 y</td>
<td>Patients with diseased native coronary vessels &gt;60% stenosis, and lesion length &lt;12 mm % Male: 70% vs 75% Mean age 59 y both groups Single vessel disease: 65% vs 66%</td>
<td>1 y Mortality: 0.6 vs 2.2% (p=0.04) 1 y MI 4% vs 9% (p=0.05) Restenosis at 6 months: 57% vs 50% (p=0.06) Combined end points: death or MI: 5% vs 10% (p&lt;0.001); death, MI, bypass surgery, or target lesion intervention: 34% vs 37% (p=0.32); death, MI, bypass surgery, or percutaneous intervention: 39% vs 42% (p=0.22)</td>
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<td>Teirstein et al 1997&lt;sup&gt;24&lt;/sup&gt;</td>
<td>RCT, catheter-based radiotherapy with iridium-192 vs placebo; n=55 Follow up: 6 months</td>
<td>Patients with restenosis undergoing coronary stenting and balloon dilation % Male: 73% vs 76% Mean age: 70 vs 69 y Previous MI: 34 vs 38% Previous restenoses: 2.1 vs 2.0</td>
<td>Angiographically defined restenosis: 17% vs 54% (p=0.01)</td>
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</tbody>
</table>

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