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Effective Health Care

Bulletin on the effectiveness of health service interventions for decision makers

NHS Centre for Reviews and Dissemination, University of York

Management of stable angina

- People with stable angina are at increased risk of heart attack and death. Targeting this group with effective treatments is an important component of a coronary heart disease strategy.
- Initial treatment choice should take into account disease severity. In less severe disease, medical treatment is as effective as angioplasty (PTCA) in relieving symptoms, and has better survival rates than PTCA or coronary artery bypass grafting (CABG). In more severe disease, invasive procedures are more appropriate.
- CABG is slightly better at relieving angina than PTCA and is more appropriate for patients with more severe or extensive disease. Many patients receiving PTCA require retreatment.
- There is a need for research-based guidance on clinical indications for further investigation and invasive procedures in order to increase the appropriateness and cost-effectiveness of treatment.
- Many patients will benefit from long-term low-dose aspirin and lipid-lowering therapies either as primary treatment or as an adjunct to invasive procedures.
- Despite little evidence that coronary stents are more cost-effective than standard angioplasty they are increasingly being used. The adoption of this or other new technologies should be managed in line with the results of reliable trials.
- There is evidence of unequal access to testing and revascularisation, by gender, ethnic group and social class. This suggests a need to monitor access in order to promote equity.

The contents of this bulletin are likely to be valid for around nine months, by which time significant new research evidence may have become available.

A. Background

A.1 The burden of illness: Coronary heart disease (CHD) (narrowing of the coronary arteries) is the leading cause of death in the UK. People are at varying risk of CHD depending on their age, sex, constitution and a number of modifiable risk factors such as socioeconomic conditions, serum cholesterol, blood pressure, obesity, smoking, diet, physical activity and alcohol intake. Population strategies seek to change overall population risk by altering some of these risk factors e.g. through lifestyle changes. In addition, people at higher risk may be targeted for risk factor modification which may also involve treatment e.g. lipid-lowering drugs. These will be considered in more detail in a future *Effective Health Care* bulletin.

People with symptoms of CHD such as angina are at particularly high risk of dying from CHD. Symptoms of stable angina are experienced as regular or predictable pain in the chest, arm or jaw. It is estimated that, in a 1-year period, 1% of the population present with anginal symptoms to a GP[1] and within about 1-year around 1 in 10 will either have a non-fatal heart attack, or die from coronary causes.[2] Because people with angina are at significantly elevated risk of having an adverse cardiac event, and are easily identifiable, they constitute an important group to target with effective interventions.

A.2 Types of intervention: Treatment aims are twofold; to reduce symptoms and to reduce the rate of, or even reverse, the progress of the underlying vascular disease thereby reducing the risk of myocardial infarction (MI) or death. Optimal medical management can also prevent stroke and peripheral vascular disease. Interventions should always be accompanied by risk factor modification such as smoking cessation, increasing exercise, reducing weight, and dietary change.

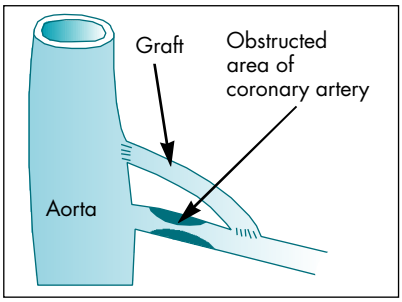

Fig. 1 Coronary artery bypass graft

Patients are often referred for further investigations to assess the pattern and extent of the underlying coronary artery disease, and other prognostic factors which may affect the appropriateness of invasive procedures.

There are two main types of invasive procedures: coronary artery bypass grafting (CABG) in which a section of vein or artery is used to reroute the blood supply round the obstructed area (Fig. 1) and percutaneous transluminal coronary angioplasty (PTCA), in which the stenosed artery is widened by introducing and inflating a balloon catheter (Fig. 2). CABG involves major surgery: patients spend about two weeks in hospital and several months convalescing. Recovery following PTCA, on the other hand, takes a few days. Following CABG, and more commonly after PTCA, the artery may become narrowed resulting in a re-occurrence of symptoms and a need for further invasive treatment.

This bulletin examines the evidence for the effectiveness and cost-effectiveness of medical therapy, CABG and PTCA in treating patients with stable angina. The bulletin is based on a systematic review of randomised controlled trials (RCTs) with at least 6 months follow-up, which was commissioned by the NHS Health Technology Assessment programme.[3]

B. Medical treatments

In practice most patients with angina will be treated medically by their GP, though many will need to be referred for further investigations and interventions.[4]

B.1 Medical therapies for relief of symptoms: There are only a few published long-term comparisons of the effectiveness of different classes of drugs in relieving symptoms of angina. These show no major differences between the main classes of drug treatment such as beta-blockers, nitrates and calcium channel blockers.[5–12] There is no evidence that combination therapy is more effective than monotherapy.[11,13,14]

Secondary prevention of cardiac events

B.2 Antiplatelet therapy: A meta-analysis of RCTs showed that antiplatelet drugs significantly reduce the incidence of MI among patients with stable angina.[15] Antiplatelet therapy showed even greater reductions in the incidence of MI, stroke and vascular death in high-risk patients, such as those with a past history of MI 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).

B.3 Lipid-lowering therapy: Using evidence from a large RCT,[16] the Standing Medical Advisory Committee has recommended that patients with angina who have a total cholesterol level of 5.5mmol/l or more (or LDL 3.7 mmol/l or more) should be considered for treatment with statins.[17]

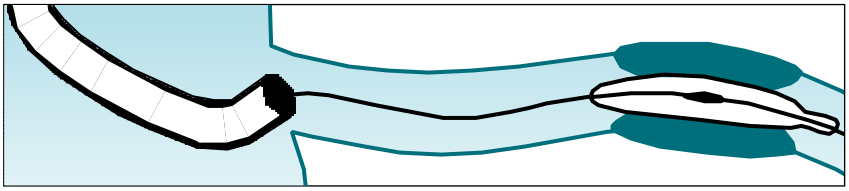

Fig. 2 Percutaneous transluminal coronary angioplasty (PTCA)

Table 1 Meta-analyses of trials of interventions in stable angina, and details of RITA-2 trial

Study	Study details	Patients	Main results
Antiplatelet Trialists Collaboration -I, 1994[15]	Meta-analysis of 145 RCTs of prevention of vascular events in high- and low-risk patients by antiplatelet therapy Average follow-up: 2 yrs	Subgroup analysis of 551 patients with stable angina in 5 trials	Reduction in odds of MI, stroke or vascular death (10% vs 15%; p=0.04). Inclusion of subsequent large RCT in meta-analysis shows significant reduction in MI in patients with stable angina
Yusuf et al, 1994[24]	Meta-analysis of 7 RCTs (2649 patients) comparing effects of CABG and medical therapy on survival Average follow-up: 10 yrs	Mean age 51 yrs. 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 yrs. CABG results in 4 mths longer survival than medical therapy at 10 yrs (p=0.003). Additional survival benefit of CABG varies with severity: LMA disease=19 mths; 3 vessel disease= 6 mths; 1 or 2 vessel disease=2 mths (p=0.02 for trend)
Pocock et al, 1995[25]	Meta-analysis of 8 RCTs comparing PTCA with CABG in angina (3371 patients) Average follow-up: mean of 2.7 yrs	Single 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 (p=0.01 for interaction). Need for reintervention within 1 yr lower with CABG (3% vs 34%; p>0.0001). Angina prevalence higher in PTCA group at 1 yr (RR=1.56; 95%CI:1.3,1.9), and slightly higher at 3 yrs (RR=1.23; 95%CI:0.99,1.5).
Antiplatelet Trialists' Collaboration -II, 1994[35]	Meta-analysis of 46 RCTs of antiplatelet therapy vs control, in the maintenance of vascular graft or arterial patency (including peripheral arteries). Average length of therapy: PTCA= 6 mths; CABG=7 mths	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% (p<0.0001). (Occlusion rates: PTCA: aspirin vs control: 4% vs 8%; CABG: aspirin vs control: 21% vs 30%) 1 excess fatal bleed per 1000 patients with antiplatelet therapy (95%CI:0, 3).
RITA-2 trial, 1997[19]	Multicentre (UK & Ireland) RCT. PTCA vs medical therapy (beta-blockers, calcium antagonists, nitrates, plus aspirin) in 1018 patients with significant stenosis in at least one major coronary artery. Average follow-up: 2.7 yrs	Median age=58 yrs. 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% vs 3%, p=0.02) but no statistically significant difference in deaths alone (2% vs 1%, p=0.32). No difference in need for subsequent CABG (8% vs 6%, p=0.2). Angina improvement greater with PTCA at 6 mths (p<0.001), but little difference between treatments at 2 yrs (p=0.05). No treatment effect on angina for patients with no or grade 1 angina by 6 mths.

C. PTCA/CABG vs medical therapy

C.1 PTCA compared to medical therapy: RCTs have shown that PTCA is more effective at relieving anginal symptoms than medical treatments such as beta-blockers, nitrates and calcium channel antagonists.[18, 19] The advantages of PTCA are greatest in patients with more severe baseline angina. These decrease over time however, with little difference remaining at 3 years, because of the high rate of restenosis.[19, 20] There appears to be little additional benefit for patients with few symptoms.

Even though PTCA can improve symptom relief in some patients it has not been shown to improve survival. The RITA-2 trial – the only RCT to compare the effectiveness of PTCA and medical treatment on cardiac events – showed that PTCA was associated with an increased rate of non-fatal MI and death compared to medical therapy, mainly due to early procedure-related events (Table 1).[19]

C.2 CABG compared to medical therapy: CABG improves symptoms of angina and other indicators of quality of life (QoL) over 10 years compared to medical therapy.[21]

CABG, however, carries greater initial risks of MI or death than medical treatment: in-hospital or 30-day mortality rates for CABG are approximately 1–3%.[22–24] The potential benefits of CABG in improving event-free survival, therefore, are only likely to be realised in patients at high-risk of CHD mortality. This is shown in a meta-analysis of 7 RCTs which found that, whilst on average mortality was reduced in patients treated by CABG compared to those treated medically, this was confined to patients at higher risk (expected annual mortality rate on medical treatment $\geq$ 2%; Table 1).[24] There was a non-significant trend towards greater mortality in lower risk patients receiving CABG.

C.3 Cost-effectiveness of CABG and PTCA vs medical therapy: There are no recent cost-effectiveness analyses comparing either CABG or PTCA with medical therapy.

D. PTCA vs CABG

D.1 Relative effectiveness: A meta-analysis of individual patient data from 8 RCTs comparing angioplasty with CABG found that at 1 year, CABG was better at alleviating anginal symptoms in both single- and multivessel disease (Table 1).[25] PTCA also had a higher rate of repeat intervention over the first year (34% vs 3%). There was substantial variation between the trials in the rate of repeat revascularisation after PTCA, ranging from 20% to over 40%. This may reflect differences in patient populations, criteria for retreatment and possible bias due to awareness of previous randomised procedure. No difference in mortality was found between the treatments though the number of patients analysed was small.

These results are consistent with those from a recent trial involving patients with multivessel disease which found that angina prevalence was higher at 5 years (21% vs 15%, p=0.007), and revascularisation was more likely with PTCA.[26]

PTCA is not suitable for patients with left main coronary stenosis (and no existing bypass to protect it) and others at very high risk such as those with multivessel disease and/or those with completely occluded arteries.[27] The risk–benefit ratio is generally in favour of using 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 increase survival.

A range of diagnostic procedures to assess the degree and distribution of stenosis and the condition of the heart muscle are available to help decide the most appropriate management (see G.2). The performance of different investigative technologies is not reviewed here.

D.2 Relative cost-effectiveness: A UK cost-analysis found the initial costs of PTCA and CABG were approximately £3,000 and £6,000 respectively in a non-London centre at 1993/4 prices.[28] However, because of the high re-intervention rate, PTCA total costs rose to over 80% of the costs of CAGB at 2-year follow-up.

E. Adjunctive therapy

CABG and PTCA are essentially local interventions for what is a systemic disease, and patients with angina are at raised risk of stroke and peripheral vascular disease. Medical therapy used as an adjunct to invasive procedures may therefore both reduce the risk of restenosis after intervention and have additional benefits for secondary prevention. Cardiac rehabilitation is also sometimes used after treatment in order to improve levels of functioning, psychological well-being and promote risk factor modification. This is likely to be reviewed in a future bulletin.

E.1 Medical adjuncts to PTCA: A meta-analysis of RCTs has reported that antiplatelet therapy significantly reduces the risk of MI, stroke or vascular death in post-PTCA patients (Table 1).[15] Calcium antagonist treatment[29] and fish oils[30] may also reduce the risk of vascular occlusion, though further evaluation in large trials is required.

Several studies have investigated glycoprotein IIb/IIIa receptor blocking drugs. One of these, abciximab, (not licensed for use in the UK) has been found to reduce in-hospital MI and re-intervention rates in patients at high risk of abrupt vessel closure, though use of the drug increased the risk of bleeding.[31] A 3-year follow-up from one study reported reductions in the need for re-intervention and MI at 1-year without increased bleeding in angioplasty patients at high risk of complications, though no overall reduction in mortality was found.[32] Trapidil, an antagonist of platelet-derived growth factor, has been found to reduce restenosis and angina compared to aspirin at 6 months,[33] and an antioxidant, probucol, reduced restenosis rates and the need for repeat angioplasty compared to placebo at 6 months in patients with 1 or 2 vessel disease.[34]

E.2 Medical adjuncts to CABG: A meta-analysis of 20 trials of antiplatelet drugs found that antiplatelet therapy significantly reduced reocclusion rates compared to control in post-CABG patients (21% vs 30%; Table 1).[35] Lipid-lowering therapy has also been found to reduce progression of atherosclerosis, risk of non-fatal MI, cardiac death and need for revascularisation compared to placebo in CABG patients.[36]

E.3 Cost-effectiveness of adjunctive therapy in PTCA and CABG: A US economic assessment found that abciximab increased the overall mean cost per patient by $293.[37] No studies have examined the cost-effectiveness of medical adjuncts to CABG. It is unclear whether these newer adjunctive medical therapies are as effective or cost-effective as cheaper alternatives such as aspirin. Larger, long-term studies comparing aspirin and lipid-lowering with other medical adjuncts would be useful to help identify optimal treatment following revascularisation.

F. Newer technology

F.1 Intracoronary stents: are used to prevent abrupt closure of the artery and longer term restenosis after PTCA by inserting a metal tube or coil in the stenosed artery. Two trials with 6-months and 1-year follow-up (the STRESS and BENESTENT studies) reported that stents reduce the need for subsequent revascularisation.[38,39] In the STRESS study, although angiographically-detected restenosis was lower in the stent group (32% vs 42%, p=0.046), no significant differences in angina, mortality, stroke or MI were observed at 6 months.[38] In BENESTENT, restenosis and the need for further PTCA was reduced in the stent group at 1 year, although there were also no differences in angina, mortality, stroke, MI or need for CABG (Table 2).[39]

A recent critical appraisal has highlighted several problems with these trials.[40] Lack of blinding in the BENESTENT trial may have resulted in the investigators performing more revascularisations in patients receiving PTCA alone. Given the greater rate of vascular complications in stent patients, differences in adverse outcomes may also emerge over longer periods of follow-up. In the STRESS study there were no differences in restenosis rates when data were reanalysed on an intention-to-treat basis.

Table 2 RCTs of standard balloon angioplasty compared to intracoronary stenting (see F1 for commentary)

Study	Methods	Patients	Results (standard PTCA vs stents)
Fischman et al, 1994[38] STRESS trial International multicentre	PTCA alone (n=203) vs. Palmaz-Schatz stent n=(207) in patients with >=70% stenosis, lesion <=15mm length which could be spanned by a single stent and vessel diameter >=3mm. Follow-up: 6 mths	% Male: 73% (PTCA) vs 83% (stent) (p<=0.05). 1-vessel disease: 68 vs 64%. 2-vessel disease: 21% vs 27% 3-vessel disease: 11% vs 9%. Mean age: 60 yrs in both groups. Ejection fraction: 61% both groups. Lesion length: 8.7mm vs 9.6mm (p<0.001). % stenosis: 75%, both groups. Diabetes: 16% vs 15%. Hypertension: 45% vs 43%. Unstable angina: 48% vs 47%	Restenosis: 43% vs 32% (p=0.05) Re-intervention: 15% vs 10% (p=0.06) Freedom from angina: 71% vs 79% (p=0.08) Event-free survival (inc. mortality): 76% vs 81% (p=0.16)
Macaya et al, 1996[39] BENESTENT trial European multicentre	PTCA (n=258) vs. PalmazSchatz stents (n=262) in patients with stable angina and single new lesions, aged >=30 & <=75. Follow-up: 1 yr	% Male: 82% (PTCA) vs 80% (stent). Mean age: 58 vs 57 yrs. Prior CABG: 2% vs 0%. Prior PTCA: 3% vs 2%. Concentric lesion: 46% vs 50%. Length of lesion: 6.96mm vs 7.06mm. Diabetes: 6% vs 7%. Angina CCS class III or IV: 59% vs 54%	No significant differences in mortality (0.8% vs 1.2%), MI (5% vs 4.2%), need for CABG (5% vs 7%), or % angina-free (86 vs 82%). Need for repeat PTCA 21% vs 10%, (p=0.001)
Sirnes et al, 1996[41] SICCO Norway & Sweden multicentre	PTCA (n=59) vs PTCA+stents (n=58) in patients >18 yrs undergoing PTCA of a chronically occluded coronary artery Follow-up: 6 mths	Mean age= 58 yrs. % Males: 20% (PTCA) 16% (stent) Mean no. of diseased vessels: 1.5 in each group. % with 1-vessel disease: 62% each group. Mean EF: 63% each group. % CCS class I/II: 24% vs 22%	No difference in deaths or MI rates. Freedom from angina 24% vs 57% (p=<0.001). Restenosis: 74% vs 32% (p<0.001).
Versaci et al, 1997[42] Italy	PTCA (n=60) vs stents (n=60) in patients with angina, MI or both. Follow-up: 12 mths	Mean age: 57 (PTCA) vs 58 yrs (stent). % Males: 83% vs 92%. Previous MI: 25% vs 28%. Angina Class I: 8% vs 7%; Class II: 45% vs 37%; Class III: 18% vs 30%;Class V:10% vs 10%. Mean EF: 54 vs 52.	Event free survival: 70% vs 87% (p=0.04). Restenosis: 40% vs 19% (p=0.02). Recurrence of angina: 25% vs 10% (p=0.05).

More recently, the SICCO trial found that stenting reduced the rates of angina, and restenosis and reocclusion at 6 months in the very small minority of patients with a chronically occluded coronary artery,[41] though 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 angina recurrence and restenosis rates at 12 months.[42] However, the outcome assessment was not systematic and was not blinded to treatment allocation. No differences in MI or cardiac-related mortality were found, though the study is small. Stents were associated with higher vascular complication rates in part attributable to the use of intensive anticoagulation regimens. Vascular complications are less problematic when aspirin and ticlopidine are used rather than intensive anticoagulation.[73]

These trials raise serious questions about the extent to which stents are being used routinely: around 30–60% of PTCA procedures now involve stents. The suggestive results of these few RCTs have been enthusiastically extrapolated to almost every other patient and lesion subset,[74] and new types of stent are being rapidly adopted before they have been adequately evaluated. Several evaluations are due to be reported in the near future.[74]

F.2 Laser angioplasty; directional and rotational atherectomy; radiotherapy: Two other new, but rarely used, approaches to opening the obstructed artery rely on the physical removal of atheroma. Trials have reported that laser angioplasty, directional and rotational coronary atherectomy are no more effective than standard PTCA.[43–48] Catheter-based radiotherapy has also been reported to reduce restenosis at six months following stent implantation, though the study may be too small to detect differences in clinical outcomes. Further evaluation of this technology is required.[49]

F.3 Cost-effectiveness of intracoronary stents and atherectomy: Two economic studies report that stents increase overall costs at 1 year compared to standard PTCA.[50, 51] Thus there is no evidence of improved cost-effectiveness. Studies comparing PTCA with atherectomy suggest that atherectomy is more costly, and no more effective.[45, 52, 53] No studies have examined the costs of laser angioplasty.

G. Organisation of services

G.1 Equity and access: Referral rates for further investigation and revascularisation rates vary widely within the UK.[54, 55] There is some evidence of gender inequities in access to revascularisation,[56, 57] and referral rates for hospital investigations are lower in women than in men with a similar severity of angina.[58] Revascularisation rates have also been shown to be lower for people living in deprived areas, despite their higher prevalence of angina and CHD mortality.[59, 60] Referral rates for angiography have also been reported to be lower in patients of Asian origin.[61]

G.2 Appropriateness: The rate of invasive procedures has been

increasing over the last decade. Though there are no precise thresholds for investigation and invasive treatments, there is some evidence that some people likely to benefit from revascularisation may not be receiving it, and that others may be receiving inappropriate treatment.[62–64] For example, there is little research evidence to justify the increased use of PTCA for patients with 2- and 3-vessel disease.[27]

Improvements in the appropriateness and equity of care may be achieved if regularly-updated guidelines are developed which include agreed referral criteria for assessment of the pattern and extent of disease. These should specify indications or thresholds for intervention, based on best available evidence and should take into account measures of disease severity or risk based on factors such as age, class of angina, history of MI, ejection fraction, coronary anatomy, and other CHD risk factors. Such guidance could also play a role in ensuring the greatest cost-effectiveness of treatments and should take into account the needs of local populations, and patient preferences.[65] Examples of these have been developed in New Zealand[66] and Canada.[67]

G.3 Volume and quality: The risk of hospital mortality may be reduced in centres carrying out more than 100–200 CABG procedures per year.[68] At present most UK units operate above this threshold. There is some evidence that the incidence of major complications and MI following PTCA decreases with increasing hospital volume.[69, 70]

H. Implications

- As there are no important differences in the effectiveness of medical treatments used in the reduction of anginal symptoms, the choice should be based on the consideration of adverse effects, compliance and on the overall cost of treatment.
- Whichever treatment is used to alleviate symptoms, there is a strong case for the use of secondary prevention measures such as lifestyle change and treatment with aspirin and statins.
- Local research-based guidance should be developed to provide an agreed framework for the management of stable angina, including indications for referral, further assessment and, where appropriate, revascularisation. Guidance should be based on the assessment of disease severity and other risk factors, the likely benefits and risks of treatment, and costs. For example, in patients with less severe coronary artery disease, the risks of invasive treatment may outweigh the benefits. It may be reasonable in these cases to defer intervention while continuing medical treatment. Guidance may also reduce unnecessary treatment and improve access for those likely to derive significant benefit from treatment.
- Health authorities should consider ways of promoting equitable access to treatment e.g. through regular equity audits to monitor use. Routine activity data from the minimum contract dataset, linked to measures of need (e.g. death rates from CHD) and socioeconomic variables, may provide one framework for monitoring.[71]
- Both CABG and PTCA substantially improve symptoms of angina. However, PTCA is probably more useful as a palliative treatment in less severely ill patients who are inadequately controlled by medical treatment or other patients for whom surgery is not advisable. CABG improves survival compared to PTCA in patients with severe disease and requires less re-intervention. In the minority of patients in whom both procedures are equally appropriate, patients' preferences will be important in determining the choice of treatment.
- Antiplatelet therapy and lipid-lowering treatment can reduce restenosis and cardiac events in patients after invasive procedures. Patients should, therefore, be considered for dietary modification, help with smoking cessation, lipid-lowering agents and antiplatelet treatment (e.g. aspirin)[72] as an adjunct to invasive treatments.
- Newer technologies, such as stents, have not been reliably shown to be more cost-effective than PTCA or CABG. NHS decision-makers should therefore exercise caution in expanding the use of stents until such evidence becomes available. The results of future trials need to be carefully appraised to assess whether claims of increased effectiveness for stenting are justified.

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The Research Team:

This bulletin is based on a review commissioned by the NHS Health Technology Assessment Programme from Brunel and York Universities and carried out by Mark Sculpher, Mark Petticrew, Martin Buxton, Jo Kelland, Rachel Elliott and Diana Holdright.

Writing of the bulletin, additional research, analysis and production was carried out by the following staff at the NHS Centre for Reviews & Dissemination, University of York:

- Sally Baker
- Mark Petticrew
- Paula Press
- Frances Sharp
- Trevor Sheldon
- Amanda Sowden
- Mary Turner-Boutle
- Ian Watt

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