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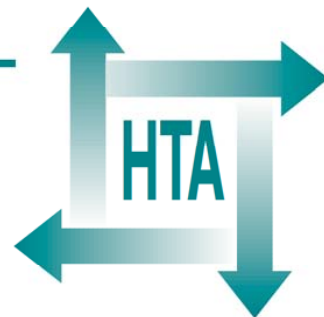
Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review

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**Health Technology Assessment
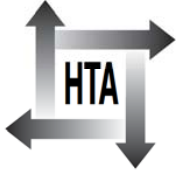NHS R&D HTA Programme**

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Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review

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Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context but a glossary is provided for the non-specialist reader. In some cases usage differs in the literature but the term has a constant meaning throughout this review.

Glossary

Abciximab A glycoprotein IIb/IIIa antagonist, used to inhibit blood clotting.

Acute coronary syndrome Severe symptomatic coronary artery disease including unstable angina and non-Q wave myocardial infarction.

Angina Pain in the heart muscle due to lack of blood-borne oxygen, it is usually induced by exercise and relieved by rest.

Angiography Radiographic technique using contrast medium to show outline of coronary artery lumens.

Angioplasty Short for percutaneous transluminal coronary angioplasty (PTCA).

Atherosclerosis A disease of the arteries in which fatty plaques develop on their inner walls leading to reduced blood flow or obstruction.

Bailout stent Stent inserted as an emergency during PTCA because of dissection of the vessel wall.

Braunwald Classification Classification of unstable angina.

Cardiac catheterisation Passing a catheter from femoral artery into coronary arteries for angiography or percutaneous coronary intervention (PCI).

Clopidogrel Drug that inhibits platelet function, now used instead of warfarin during stent placement.

Creatinine kinase A cardiac enzyme, the blood levels of which are raised during myocardial infarction.

ECG Electrocardiogram – maps electrical activity in the heart muscle. ECG findings might include Q waves or ST elevation

Exercise stress test Diagnostic test used to find exercise-induced ECG changes indicating myocardial ischaemia

Elective Non-emergency treatment.

Graft (saphenous vein) Insertion of graft vessel into coronary artery during coronary artery bypass grafting (CABG).

Heterogeneity Variability or differences between studies.

Hypertension High blood pressure.

Invasive treatment Used in this report to refer to PCI or CABG.

Ischaemia Lack of blood flow or oxygen.

Lumen The space within a blood vessel.

MEDLINE A database of medical journal articles.

Meta-analysis Method of combining results from different studies to produce a summary statistic.

Minimally invasive CABG CABG technique using a small thoracotomy only and not always requiring stopping of the heart during the operation.

Myocardium Heart muscle.

Myocardial infarction Death of a segment of heart muscle because of severe ischaemia.

Ostial lesion Lesion of the ostium of coronary artery (which is difficult to stent).

continued

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Glossary *contd*

Platelets Blood constituents involved in blood clot formation.

Provisional stenting Stent placement depending on suboptimal result of PTCA.

Q wave An abnormal wave on ECG indicating past myocardial infarction.

Reocclusion Repeat complete blockage of coronary artery.

Restenosis Re-narrowing of coronary artery.

Revascularisation Maintaining or improving coronary artery blood supply.

Silent ischaemia Ischaemia of heart muscle found with exercise stress test where patient has no angina symptoms.

Stent Small prosthesis inserted into coronary artery to keep the lumen open.

Subacute ischaemic heart disease All manifestations of ischaemic heart disease except acute myocardial infarction.

Thrombus Blood clot.

Ticlopidine Drug that inhibits platelet function, now used instead of warfarin during stent placement.

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List of abbreviations

AMI	acute myocardial infarction (see myocardial infarction)	MLD	minimal lumen diameter of coronary artery
BCIS	British Cardiovascular Intervention Society	MVD	multi-vessel coronary disease*
CABG	coronary artery bypass graft(ing)	N/A	not applicable*
		N/C	not clear*
CAD	coronary artery disease	NR	not recorded*
CEA	cost-effectiveness analysis*	NS	not statistically significant*
CI	confidence interval (95%)	NHSEED	NHS Economic Evaluations Database
CK-MB	creatine kinase		
CO	chronic coronary occlusion*	NICE	National Institute for Clinical Excellence
cost/EFS	cost per event-free survivor		
CU	cost–utility study*	NSF	National Service Framework
CVA	cerebrovascular accident (stroke)*	OR	odds ratio
		PCI	percutaneous coronary intervention (includes PTCA, atherectomy, excimer laser, rotablator, stents)
DARE	Database of Abstracts of Reviews of Effectiveness		
DEC	Development and Evaluation Committee	PMI	previous myocardial infarction*
DFl	Dutch Guilder	PTCA	percutaneous transluminal coronary angioplasty
eCABG	emergency CABG*		
EFS	event-free survival or survivor	PYAR	person years at risk
EUROQOL	standardised assessment method for quality of life (used in cost–utility studies)*	QALY	quality adjusted life-year
		QOL	quality of life*
		RCT	randomised controlled trial
IHD	ischaemic heart disease	SA	stable angina*
INR	International Normalised Ratio*	SD	standard deviation*
LAD artery	left anterior descending coronary artery	SF-36	Short Form 36
		SMR	standardised mortality ratio
LMW heparins	low molecular weight heparins (used for blood anticoagulation)*	SVD	single vessel coronary disease*
LoS	length of stay*	TIMI flow grade	Thrombolysis In Myocardial Infarction flow grade [0 (poor) – 4 (good)]*
LVEF	left ventricular ejection fraction (measure of heart performance)*		
		TLR	target lesion revascularisation
MACCE	major adverse coronary and cerebrovascular events*	TVR	target vessel revascularisation
MACE	major adverse coronary events*	UA	unstable angina*
		YLL	years of life lost
MI	myocardial infarction (heart attack)		

* Used only in tables

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Executive summary

Background

Coronary artery stents are prosthetic linings inserted into coronary arteries via a catheter to widen the artery and increase blood flow to ischaemic heart muscle. They are used in the treatment of ischaemic heart disease (IHD).

IHD is a major cause of morbidity and mortality (123,000 deaths per annum) in the UK and a major cost to the NHS. Clinical effects of IHD include subacute manifestations (stable and unstable angina) and acute manifestations (particularly myocardial infarction [MI]). Treatment includes attention to risk factors, drug therapy, percutaneous invasive interventions (PCIs) (including percutaneous transluminal coronary angioplasty [PTCA] and stents) and coronary artery bypass graft surgery (CABG).

In the last decade there has been a steady and significant increase in the rate of PCIs for IHD. In the UK, rates per million population increased from 174 in 1991 to 437 in 1998. Stents are now used in about 70% of PCIs. Data from the rest of Europe suggest there is potential for PCI and stent rates to increase considerably. In the UK there is evidence of under-provision and inequity of access to revascularisation procedures.

Objectives

The following questions were addressed.

1. What are the effects and effectiveness of elective stent insertion versus PTCA in subacute IHD, particularly stable angina and unstable angina?
2. What are the effects and effectiveness of elective stent insertion versus CABG in subacute IHD, particularly stable angina and unstable angina?
3. What are the effects and effectiveness of elective stent insertion versus PTCA in acute MI (AMI)?
4. What are best estimates of UK cost for elective stent insertion, PTCA and CABG in the circumstances of review questions 1 to 3?
5. What are best estimates of cost-effectiveness and cost–utility for elective stent insertion relative to PTCA or CABG in the circumstances of review questions 1 to 3?

Methods

A systematic review addressing the objectives was undertaken.

Data sources

A search was made for RCTs comparing stents (inserted during a PTCA procedure) with PTCA alone or with CABG in any manifestation of IHD. The search strategy covered the period from 1990 to November 1999 and included searches of electronic databases (MEDLINE, EMBASE, BIDS ISI, The Cochrane Library), Internet sites, and handsearches of cardiology conference abstracts and 1999 issues of cardiology journals. Lead researchers and local clinical experts were contacted. Manufacturers' submissions to the National Institute for Clinical Excellence were searched.

The search strategy was expanded to look for relevant economic analyses and information to inform the economic model (including searching MEDLINE, the NHS Economic Evaluation Database and the Database of Abstracts of Reviews of Effectiveness). Searches focused on research that reported costs and quality of life data associated with IHD and interventional cardiology.

Study selection

For the review of clinical effectiveness, inclusion criteria were: (i) RCT design; (ii) study population comprising adults with IHD in native or graft vessels (including patients with subacute IHD or AMI); (iii) procedure involving elective insertion of coronary artery stents; (iv) elective PTCA (including PTCA with provisional stenting) or CABG as comparator; (v) outcomes defined as one or more of: combined event rate (or event-free survival), death, MI, angina, target vessel revascularisation, CABG, repeat PTCA, angiographic outcomes; (vi) trials that had closed and reported results for all or almost all recruited patients.

For the economic evaluation, studies of adults with IHD were included if they were of the following types: studies reporting UK costs; comparative economic evaluation combining both costs and outcomes; economic evaluations reporting costs and outcomes separately for the years 1998 and 1999 (to ensure current practice was included).

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Data extraction

For the review of clinical effectiveness, data were extracted into data extraction forms and RCT quality was assessed using standard methods. Decisions relating to data extraction and quality were made by two independent reviewers. Disagreements were resolved by discussion and with the aid of a third party if there was any residual discrepancy. The quality assessment of cost-effectiveness analyses was based on a pre-determined check-list.

Data synthesis

For the review of clinical effectiveness, abstracted data were collated in summary tables. Whenever possible, analysis was on an intention-to-treat basis. Meta-analyses were carried out when adequate data were available.

For the economic evaluation, cost data and health economic assessments were documented and evaluated.

Results

Effects and effectiveness

Thirty-five RCTs which fulfilled the study criteria were found: 25 compared stent with PTCA for subacute IHD; three compared stents with CABG for subacute IHD; seven compared stents with PTCA following AMI. In general, the trials were open to bias, which introduced uncertainty. Despite this, convincing evidence of impact was identified in the following.

1. Elective stent insertion versus PTCA in subacute IHD for:
    * event rates (generally death, MI, repeat PTCA and CABG) – odds ratio (OR), 0.68 (95% confidence interval [CI], 0.59 to 0.78)
    * repeat PTCA – OR, 0.57 (95% CI, 0.48 to 0.69)
2. Elective stent insertion versus PTCA in AMI for:
    * event rates (generally death, MI, repeat PTCA and CABG) – OR, 0.39 (95% CI, 0.28 to 0.54)
    * repeat PTCA – OR, 0.44 (95% CI, 0.26 to 0.74).

There was no clear evidence of impact on deaths, MI or CABG in comparison (1) or (2) above. Although trials were identified, there was insufficient evidence to draw any conclusions on the effectiveness of elective stent insertion versus CABG in subacute IHD.

Costs and economic analyses

The information identified contributes only to conclusions concerning elective stent insertion compared with PTCA in subacute IHD. There was wide variation in the estimates of cost, cost-effectiveness and cost–utility. Cost estimation, particularly for wider costs, was generally poor. It was probably conducted best in the context of the cost-effectiveness studies. These generally showed that cost/event-free survivor for elective stenting was equivalent to or less than that of PTCA. They support the view that higher initial costs of stents are outweighed by savings from reduced requirement for repeat PTCA. The majority of cost–utility studies reported cost/ QALY estimations in the range of £20,000–£30,000. Reasons why these estimates should be treated with caution were identified.

The efficiency of the use of stents compared with CABG in subacute IHD or stents compared with PTCA in AMI is unknown.

Conclusions

In subacute IHD (especially stable angina and unstable angina), there is evidence for the effectiveness of elective stents in reducing the need for repeat PTCA. This appears to represent an efficient use of resources. However, this assertion could be made with more confidence if the resource neutrality of stents could be confirmed using more rigorously derived cost data. There is currently insufficient evidence to assess the effectiveness of the extension of stent use to patients with baseline risks or indications different from those of the patients in the trials reviewed (for review question 1).

Recommendations for further evaluation and research

1. For many important stenting applications, research is ongoing and a reassessment of research evidence and health economic evaluations in 1–2 years' time would be valuable.
2. Further research on the use of stents is needed to: acquire better cost data, using explicit micro-costing; investigate the impact of stents on severity of angina and quality of life; evaluate the effectiveness of newer technologies.
3. It is very important to establish clearly the effectiveness and efficiency of stents compared with CABG, and even though there is considerable ongoing research in this area, further targeted research may be valuable.

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Chapter 1

Review aims and background

Aims

- To assess the effectiveness of coronary artery stents compared with other established revascularisation procedures (percutaneous transluminal coronary angioplasty [PTCA] alone and coronary artery bypass grafting [CABG]) in the main manifestations of ischaemic heart disease (IHD).
- To assess the costs, cost-effectiveness and cost–utility of the above.

Introduction

A coronary artery stent is a metal tube, coil or mesh that is inserted into a coronary artery, via a catheter inserted in an artery in the groin or arm, in order to widen the coronary artery and improve the blood flow to ischaemic heart muscle.

Interventional cardiologists are increasingly using coronary artery stents to treat IHD.[1] The procedure is carried out in a cardiac catheterisation laboratory. The stents can be inserted as an elective procedure (elective stenting), or after a PTCA with sub-optimal results ('provisional stenting') or where there is an acute closure of the artery after PTCA (emergency or 'bailout' stenting).

Description of health problem

Disease

IHD is caused by an insufficient supply of oxygen to the heart muscle. It can be 'silent' (when the patient has no symptoms) or can cause angina, unstable angina, myocardial infarction (MI) or death.

In this report we distinguish between **acute myocardial infarction** (AMI) and the subacute manifestations of IHD, particularly angina and unstable angina.

Pathology

IHD is generally caused by constriction or blockage of the coronary arteries supplying the heart. This is also known as **coronary artery disease** (CAD). The vast majority of IHD is due to atheroma and its complications. **Atheroma** occurs when there is damage to the linings of arteries leading to the formation of raised patches of fibrous and fatty material, known as **atheromatous plaques**.

Epidemiology

IHD is the major cause of death of men and women in the UK.[2] In 1997 there were 122,780 deaths due to IHD in the UK (22% of all deaths and 25% of deaths in men).[3]

Although deaths from IHD have fallen over by over two-thirds in the last 30 years, UK rates remain higher than in many countries (e.g. the death rate in the UK is over three times that of France, the EU country with the lowest death rate).[4] When measured in terms of years of life lost (YLL), IHD accounts for 15.6% of all years of life lost (1,365,995 YLL per year). The figure is 19.3% for men.[3]

It is estimated that, in Europe, IHD is the leading single cause of disability accounting for 9.7% of total disability adjusted life-years.[5] Given the high incidence of IHD in England and Wales, the figure will be even higher here.

The results of the 1998 Health Survey for England[6] indicate an overall prevalence of IHD of 7.1% in men and 4.6% in women. Prevalence increases markedly with age, reaching 23.4% in men and 18.4% in women aged over 75 years. The point prevalence of angina is estimated to be 3.2% for men and 2.5% for women; 5.3% of men and 3.9% of women reported ever having had angina. Overall 4.2% of men and 1.8% of women reported having had a heart attack (0.6% of men and 0.3% of women reported having it within the last 12 months).[6]

The Fourth General Practice Morbidity Survey (1991–1992)[7] gives the prevalence and incidence rates per 10,000 person years at risk (PYAR) for AMI and angina pectoris[8] (*Table 1*). Comparison of the Fourth Survey with the Third General Practice Morbidity Survey (1981) suggests that the rates for angina are rising.[7]

Aetiology

Cigarette smoking and other tobacco use are associated with an increase in atheroma and

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TABLE I *Prevalence and incidence rates of AMI and angina per 10,000 person years at risk (PYAR)*[7]

	Prevalence		Incidence	
	Men	**Women**	**Men**	**Women**
AMI	38	20	29	16
Angina	130	98	55	49

are a major risk factor for IHD. Diabetes mellitus, hypertension, raised cholesterol, genetic predisposition, diet, lack of exercise and obesity are also risk factors.

Many of these risk factors can be modified and IHD has been identified as a major contributor to **avoidable** mortality. Reduction in circulatory disease mortality is a major UK government target in the strategy to improve the nation's health.[9]

Treatments of established IHD
Introduction
Although preventing IHD is important, this paper is concerned with the treatments that aim to reduce both the morbidity and the mortality in patients with established IHD. Treatment of IHD has many modalities:

- modification of risk factors
- medical management
- percutaneous invasive treatments (carried out by interventional cardiologists)
- surgical interventions.

Medical treatments have many mechanisms of action and rationales. They may aim to:

- reduce risk factors causing IHD
- reduce the physical demand on the heart
- improve the blood flow within the heart
- alter the clotting characteristics of blood.

There are now many well established treatments for both IHD and many of its risk factors. Many clearly contribute to both alleviation of symptoms and prevention of adverse events, such as AMI and death. The aims of treatment are to prolong life, prevent MI, prevent damage to the heart and heart failure, relieve painful and disabling angina and other symptoms, and improve quality of life.

This paper does not review the evidence for all of these treatments or discuss their relative merits, but concentrates on coronary artery stenting and the alternative established methods of

revascularisation (PTCA and CABG), which are increasingly being replaced by stenting.

It is useful to have a brief overview of revascularisation techniques over the last 30 years in order to understand why stents were developed. Initially, revascularisation began in order to provide alternative therapy when medical treatments failed to control symptoms. The basic aim of all revascularisation procedures is to provide a better lumen in the vessel supplying heart muscle to improve blood flow.

CABG
CABG is a surgical technique that involves opening the chest wall and bypassing a blocked or narrowed section of a coronary artery, usually by using a vein or artery taken from elsewhere in the patient's body.

CABGs began in the late 1960s. They are carried out by cardiothoracic surgeons and can be undertaken as planned or emergency procedures. They are usually reserved for more severe cases of CAD[10] and are used to treat patients with chronic stable angina or unstable angina, following MI or following complications from PTCA. CABGs were also considered more appropriate for complex disease patterns (e.g. multi-vessel disease, disease of the left anterior descending [LAD] artery and diffuse disease). Techniques have been evolving (e.g. the development of minimally invasive CABG). The advantages and disadvantages of CABG are summarised in *Box 1*.

BOX 1 Advantages and disadvantages of CABG

Advantages
Complete relief from angina in 60–90% of patients at 1 year[11,12]

A slight decrease in mortality when compared with medical treatment[11,12]

Lower revascularisation rates after 1 year when compared with PTCA[11,13]

Disadvantages
High cost. A longer time is spent in hospital and for convalescence: the mean length of stay post-operatively in uncomplicated cases is 7–10 days[11,14]

There is a slightly higher rate of MI when compared with medical treatment[11]

Following hospital discharge, recovery takes longer after CABG when compared with PTCA[11,12,15]

Some patients are not fit enough to undergo such a major operation

In the longer term, progression of CAD often occurs in native or graft vessels[30]

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PTCA

PTCA is a technique in which the narrowed or blocked part of a coronary artery is dilated by passing a radiographically guided catheter with a small balloon, usually through the femoral artery, into the narrowed section of the coronary artery. The balloon is then inflated to a high pressure for a short time. The inflated balloon produces longitudinal and circular splits in the atheromatous plaque. The balloon is then deflated and withdrawn. Because the plaque has elastic properties, it retracts where it has split leaving the coronary artery with a wider lumen than before the procedure but with a very disrupted surface.[16]

PTCA was first used in the late 1970s[17] and its use has grown steadily. PTCAs are undertaken by interventional cardiologists in a cardiac catheterisation laboratory.

PTCA is generally considered when medical treatment has failed to control symptoms.[10] It is most commonly used in single or double vessel disease.[18] Indications for PTCA have widened, and the procedure is now used to treat patients with chronic stable angina, unstable angina, stenosed CABG grafts, or cardiogenic shock, as well as patients with asymptomatic IHD and those for whom CABG is deemed inappropriate. PTCA can be repeated if symptoms return.

PTCA is also used to achieve reperfusion following MI and has the advantage of lower bleeding rates than with fibrinolytic ('clot-busting') therapy. Also, PTCA produced better short-term clinical outcomes than older fibrinolytic treatment regimens. The use of PTCA in AMI is not common because of the limited immediate availability of cardiac catheterisation laboratories and resultant delays in 'time to balloon'.[19]

The advantages and disadvantages of PTCA are summarised in *Box 2*.

When compared with medical therapy, studies have shown that PTCA is probably more successful in treating angina, but at the cost of higher subsequent rates for MI (inflating the balloon temporarily blocks blood flow through the artery, there can be acute closure of the artery, side branch occlusion or distal embolisation) and need for CABG.[21,25] Evidence suggests that more patients have angina 1 year after PTCA than after CABG, but the difference is not so marked after 3 years.[13] Mortality and MI rates are similar for both treatments but the re-intervention rates are greater for

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BOX 2 Advantages and disadvantages of PTCA

Advantages

In randomised controlled trials (RCTs), PTCA has been shown to have improved outcomes compared with medical therapy[20,21]

PTCA does not require a general anaesthetic or necessitate opening the chest wall so it is useful in patients for whom operations carry a high risk

Length of stay in hospital is short (this is gradually decreasing: for elective and emegency cases, the mean was 4.3 days in 1994[22] and 3.7 days in 1996/1997[14])

PTCA can be carried out as a day case – there were 75 day cases (0.53% of all PTCA cases) in the UK in 1998[14]

It is useful for people considered not fit enough for a CABG

There is no need for prolonged convalescence

Disadvantages

Acute closure: during the procedure the artery may close abruptly, leading to an MI or, in rare cases, death. Abrupt closure during PTCA has been reported in 2–10% of patients[23] and this has required emergency CABG back-up to be available.[16,18] 'Bailout' stenting now provides an alternative to CABG in many of these cases (see 'Bailout stenting' page 4)

Restenosis: between 15 and 52% of target arteries show narrowing on angiography after a few months (restenosis) following an initial successful PTCA.[13,24] These patients may then require further treatment which could be CABG, PTCA (known as target vessel revascularisation [TVR]) or, where these options are not indicated, medical treatment. In the RITA-I RCT comparing PTCA with CABG, mortality was no different at 6 months, the incidence of angina was higher in PTCA patients, and 31% of these patients compared with 11% of CABG patients required revascularisation. Similar results have been found in meta-analysis.[13] As, however, complications following PTCA occur mostly in the first 6 months whereas complications following CABG may occur over a longer period, the picture may change to some extent when longer term follow-up from the trials becomes available

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PTCA.[13] Compared with CABG, PTCA is cheaper, involves a shorter hospital stay and is less painful for the patient.[11]

Recent new antithrombotic strategies developed in conjunction with stent insertion but not used widely in PTCAs may have important implications when interpreting evidence about the relative effectiveness and adverse effects of the two technologies (see page 5).

3

Technology under evaluation: coronary artery stents
Introduction

Coronary artery stents are short prosthetic linings for coronary arteries which are used as an adjunct to PTCA in the invasive management of CAD or are inserted directly. They were developed to address the two main disadvantages of PTCA: the need for emergency CABG if PTCA fails, and restenosis (see *Box 2*).

A coronary artery stent is a metal tube, coil or mesh that is inserted into the coronary artery via a catheter inserted into an artery in the groin or arm. Before stent placement, the artery is usually widened using a balloon. Stents are made from stainless-steel, nitinol or tantalum wire bent in a variety of ways to make coils or slotted tubes. They can have radio-opaque end markers or can be coated with heparin.[26,27] Stents are inserted into coronary arteries and expanded onto the artery wall by using the pressure from a balloon or a balloon catheter, or by retraction of a sheath.

Despite being a relatively new technology, stents are frequently used (see 'Stent rates' page 7) and are being used in an increasing range of lesions and patient subgroups. Stents are the most widely diffused of the new additions to PTCA. Since the use of stents in patients was first reported by Sigwart in 1987,[26] their design and use has been rapidly and continually evolving. The first generation of stents has now been replaced by improved designs.[28] It has been suggested that some 40 or more stents are available in Europe and elsewhere,[29] but only a limited number of these are said to be in routine use in the UK.

More than one stent may be fitted during a procedure, depending on the length of the lesion or whether there are multiple lesions suitable for stenting in different coronary arteries. The time taken to insert the stent successfully depends partly on the operator's ability and experience and partly on the anatomy of the lesion to be stented.

Causes of restenosis after PTCA are complex – the growth of new scar tissue, vessel recoil and vessel 'remodelling' (a narrowing of the lumen of a vessel which has been widened in an angioplasty) all play a role. By providing a permanent support structure or 'scaffold' for the vessel wall, it was thought that stents might reduce both vessel recoil and remodelling.

There are several strategies for the use of coronary artery stents[26,30] including bailout

stenting, elective stenting and provisional stenting, which are considered below. Elective stenting is the technology that is evaluated in this report. Both bailout stenting and provisional stenting occur in the control arms of PTCA trials for ethical reasons. Moreover, provisional stenting is often the control procedure with which elective stenting is compared.

The potential advantages and disadvantages of stenting are summarised in *Box 3*.

BOX 3 Potential advantages and disadvantages of stenting

Potential advantages

Stenting takes very little longer than PTCA on its own

The use of a stent may reduce the need for subsequent repeat intervention

The stay in hospital for elective stent procedures is short (up to 3 days only, with some patients being suitable for treatment as day cases[22,31])

Stenting is suitable for some patients for whom CABG would have been indicated in preference to PTCA but who are insufficiently fit to undergo a major operation

Compared with PTCA, it diminishes the risk of having to undergo an emergency CABG

Stenting is less traumatic than CABG for the patient

Potential disadvantages

Stent thrombosis: stents are 'foreign bodies' permanently implanted into arterial walls so there is a risk of blood clots forming and blocking the coronary artery

In-stent restenosis: this occurs when there is narrowing of the lumen within a stent. Mostly this is related to overgrowth of the intima, the elastic membrane inside the artery, and is promoted by the trauma of stent insertion[32]

If the procedure is inadequate in preventing symptoms, future interventions (e.g. further PTCA) may be more difficult and patients may have to undergo open heart surgery (CABG) instead

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Bailout stenting

As discussed above, PTCA can cause acute closure of an artery. Stents can be used to tack back flaps of the arterial wall caused by rupture of a plaque to keep the coronary artery open and, if successful, prevent the need for emergency CABG. This use of stents is known as 'bailout' or rescue stenting. There is no strong evidence from RCTs of the superiority of bailout stenting over emergency CABG or other emergency treatments (e.g.

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prolonged perfusion balloon). However, evidence of this type would be logistically hard to obtain because of the emergency nature of the situation. Bailout stenting has received widespread accept-ance as an alternative to emergency CABG. Poor outcomes associated with emergency CABG suggest that current practice seems reasonable. Bailout stenting is not considered further in this report.

Elective stenting

Elective or 'primary' stenting is the planned insertion of a stent irrespective of angioplasty results. The aim of elective stenting is to reduce the incidence of restenosis in the treated artery in the longer term compared with PTCA, thus reducing the need for further invasive inter-vention. Stenting can, in theory, prevent gradual closure of the artery and long-term restenosis by increasing the lumen diameter after the procedure and mechanically reinforcing the vessel wall.[33]

Elective stenting may be used in subacute IHD and also as a reperfusion therapy in the early hours of an AMI (as an alternative or in addition to fibrinolytic therapy).

Provisional stenting

Contingent use of a stent, dependent on the angiographic result of a PTCA, is known as 'provisional stenting'. Where angiography suggests that the result of a PTCA is sub-optimal, stents are used to prevent restenosis and potential acute arterial closure.

Antithrombotic therapy in stent use

Because early studies reported high rates of stent thrombosis,[34,35] aggressive antiplatelet and anticoagulant therapy, incorporating anti-coagulation with heparin for up to 96 hours after deployment, was introduced to prevent these potentially fatal complications.[36] For the first few years that stents were being used, patients were given aspirin, dipyridamole, dextran, heparin, warfarin and calcium antagonists or a similar combination. The use of these regimens in early stent trials resulted in more bleeding compli-cations and longer hospital stays with stents than with PTCA alone.[32] Antithrombotic therapy is a rapidly changing field, and regimens used in early stent trials are no longer current practice.[37] Bleeding complication rates have decreased, as the increasing use of antiplatelet therapy with aspirin and ticlopidine has meant that lower doses of anticoagulants are now current practice, resulting in decreased bleeding complications and hence shorter hospital

stays.[18,38–40] Neutropenia has been reported with ticlopidine, but not with clopidogrel, another antiplatelet agent, which is now used routinely in preference.

An important development in antiplatelet therapy is the licensing of abciximab, a monoclonal antibody that inhibits platelet glycoprotein IIb/IIIa receptors, for high-risk patients undergoing PTCA. A recent RCT found a lower rate of death, MI or urgent revascularisation in stent with abciximab than in stent with placebo (5.3% compared with 10.8%; hazard ratio 0.48 [95% confidence interval, CI, 0.33 to 0.69]).[41] Six-month outcomes were reported in the EPILOG trial,[42] in which there was no difference in the pre-specified endpoint between abciximab and low-dose heparin or placebo, although there was a difference between abciximab and standard dose heparin or placebo. Attenuation of the 30-day risk difference largely resulted from the lack of any impact of abciximab on non-urgent revascularisation. The CAPTURE trial also found no difference in deaths or MI at 6 months.[43] Results in favour of abciximab at 30 days have been reported for stent subgroups in the CAPTURE and EPILOG trials,[44] but the use of stents was discouraged in these trials, so patients are unlikely to be repre-sentative. Treat-ment with this drug adds substantially to the cost (£670 for a typical patient; E Grant, West Midlands Drug Information Unit: personal communication, 1999), and a full evaluation of the effectiveness and cost-effectiveness of this class of drugs in the treatment of IHD is needed.

Aggressive antithrombotic strategies do not appear to have been rigorously tested in PTCA.

Developments in percutaneous coronary interventions (PCIs)

The nature and design of stents, methods of insertion and adjuvant therapies are continuously evolving. For example, manufacturers are seeking to make stents that are non-thrombogenic[32] or conformable so that 'dead space' between the stent and the vessel wall (which predisposes to clot formation) is eliminated. There are also developments in PTCA and other PCIs that do not involve stent placement. There are trials in progress comparing different stents and looking at direct stenting. New technological develop-ments to prevent or deal with in-stent stenosis include medical treatments, laser treatments, debulking, atherectomy, cutting balloon angioplasty, stent coatings, therapeutic ultrasound and radiotherapy.[32,45]

The range of indications for which stents are being used is expanding. Proponents argue that stents not only improve the outcome in situations where PTCA would have been used previously, but also extend the range of circumstances in which PCIs are appropriate. That is to say that stents are appropriate in some of the circumstances in which CABG was indicated because of the complexity of the disease pattern (e.g. multi-vessel disease) or when PTCA was felt to be too risky.

Current service provision

Introduction

Before the introduction of stents, PTCA alone was the standard treatment, and provided an alternative to open heart surgery for many patients. Improvements in PTCA technology, the introduction of stents and adjunctive anti-thrombotic drug therapy have resulted in a rapid increase in the number of PCIs carried out, and their use in a wider range of patients.

This section will examine the current service provision and activity levels for PCIs and CABGs. However, it must be remembered that IHD is treated in every section of the NHS, especially in primary care and in non-specialist hospitals, and that any changes in service provision will have a knock-on effect on these services.

Provision of interventional or diagnostic centres

The number of centres undertaking diagnostic tests or performing interventions has increased steadily over the last decade. In 1998 there were 126 such centres in the UK,[31] 111 of which are in the NHS (46 interventional and 65 diagnostic only). All 15 centres in the private sector are interventional. The activity of NHS interventional centres also increased between 1991 and 1998 with a doubling of the mean number of PCIs undertaken per centre (from 191 in 1991 to 408 in 1998).

Cardiac catheterisations

According to national statistics, in 1996/1997 there were 57,046 NHS patient episodes categorised as cardiac catheterisations (for angiography or PCI) in the UK.[14] Of these, 42% were day cases and 68% were carried out in men. According to the British Cardiovascular Intervention Society (BCIS) returns (see below), there were 100,023 cardiac catheterisations in the NHS and private intervention centres in 1998.

Number of PCIs

PCIs include PTCA alone, atherectomy, excimer laser, rotablator and PTCA with stent. According to the audit data from the BCIS, in 1998 there were 24,899 PCIs. The number of PCIs has increased 2.5-fold from 1991 to 1998 (*Table 2*).[31]

Although there is a striking increase in PCIs, comparisons with activity levels in other countries suggest that there is potential for considerable further growth. Germany had a rate of over 1800/million population in 1998. *Figure 1* shows a comparison of the UK with the rest of Europe.

Compared with the UK, European countries such as Portugal, Italy, France and Spain have very low rates of IHD (age-adjusted mortality rates per 100,000 for men aged 45–74 years in 1990–1992: Portugal, 207; Italy, 224; France, 42; Spain, 181; England and Wales, 515; Scotland, 655). In the light of these low rates of IHD in other European countries, the UK's relatively low rate of PCI activity is even more striking.

TABLE 2 *Total UK PCI procedures*[31]

Year	No. of centres	Total no. of PCIs	Increase over previous year (%)	Rate (per million population)
1991	52	9,933	–	174
1992	52	11,575	16.5	203
1993	53	12,937	11.8	227
1994	54	14,624	13.0	256
1995	54	17,344	18.6	304
1996	53	20,511	18.1	359
1997	58	22,902	11.7	402
1998	61	24,899	8.7	437

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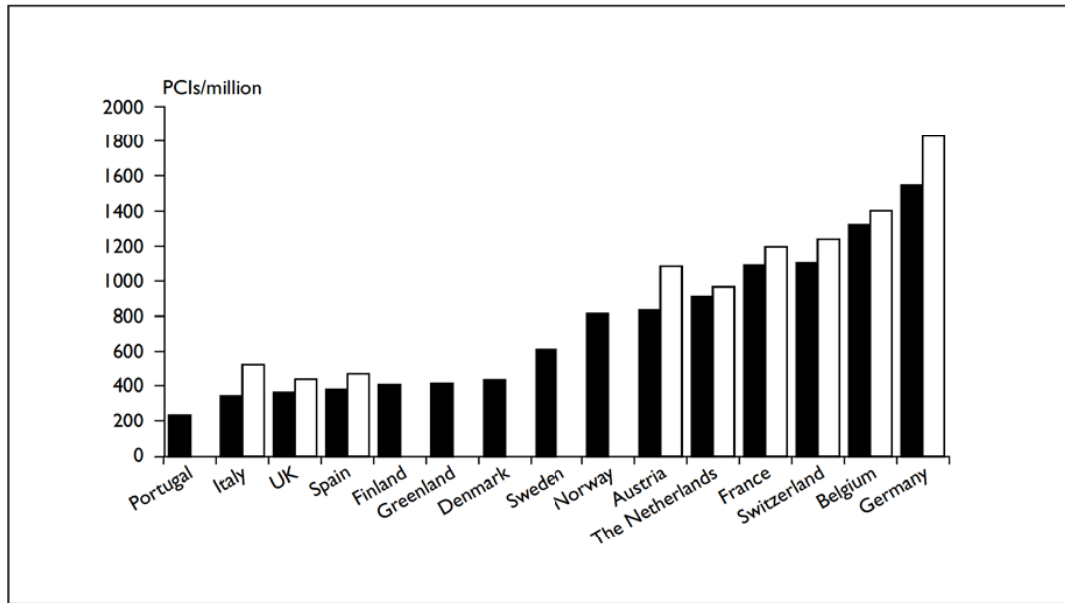
FIGURE I *PCIs: UK compared with other European countries 1996 (■) and 1998 (□)*

UK data[31] show that the overwhelming majority of PCIs are either PTCA alone or PTCA with stent. The BCIS audit data show that 31% of PCIs do not involve stents (i.e. approximately 17,200 procedures). National statistics show that there were 14,023 patient episodes for PTCA in 1998 with a median and modal length of stay of 1–2 days.[14]

Stent rates

The rate of stent insertion in PTCA has been increasing. The rate increased 23-fold from 13 to 302/million UK population between 1993 and 1998. The use of stents has also increased as a proportion of PCIs and now about 70% of PCIs will involve the use of stents (*Figure 2*).[31]

CABG rates

National statistics for CABGs in the UK (excluding Northern Ireland) show that there were 16,780 patient episodes in 1998, of which 13,297 (79%) were in men and 3483 (21%) were in women. The mean length of stay was 9 days.[14] These numbers give a rate of about 320/million population. Only 3.23% of these patient episodes were emergency admissions; the others were either elective (88%) or admissions from other NHS providers (8.64%).[14]

Proponents of stenting argue that rates of emergency CABG following PTCA have dropped as the percentage of PTCAs involving stents has

gone up (*Figure 3*), as have repeat procedures for acute closure (*Figure 4*) and repeat procedures for restenosis (*Figure 5*).

The data in *Figures 3–5* come from the registry run by the BCIS. However, caution must be used before drawing strong conclusions from the data because complete outcome data are not received from all centres and it is possible that there is some reporting bias.

Geographical variation

There is considerable geographical variation in both patient need (for investigation and revascularisation) and service provision. The two are not necessarily correlated. Discussion with clinicians and public health consultants concerned with services for IHD suggests that revascularisation activity and guidelines for access to services and treatment in different districts may be determined more by service supply and clinician interest than by patient need. It is also possible that different attitudes to the treatment of elderly people may underlie some of difference in activity levels between areas with similar standardised mortality ratios (SMRs).

Need

There are differences in SMRs for IHD between regions in the UK. *Table 3* shows the figures for the old regional structure for 1993–1995 when SMRs ranged between 88 and 113.

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Medtronic Exhibit 1414
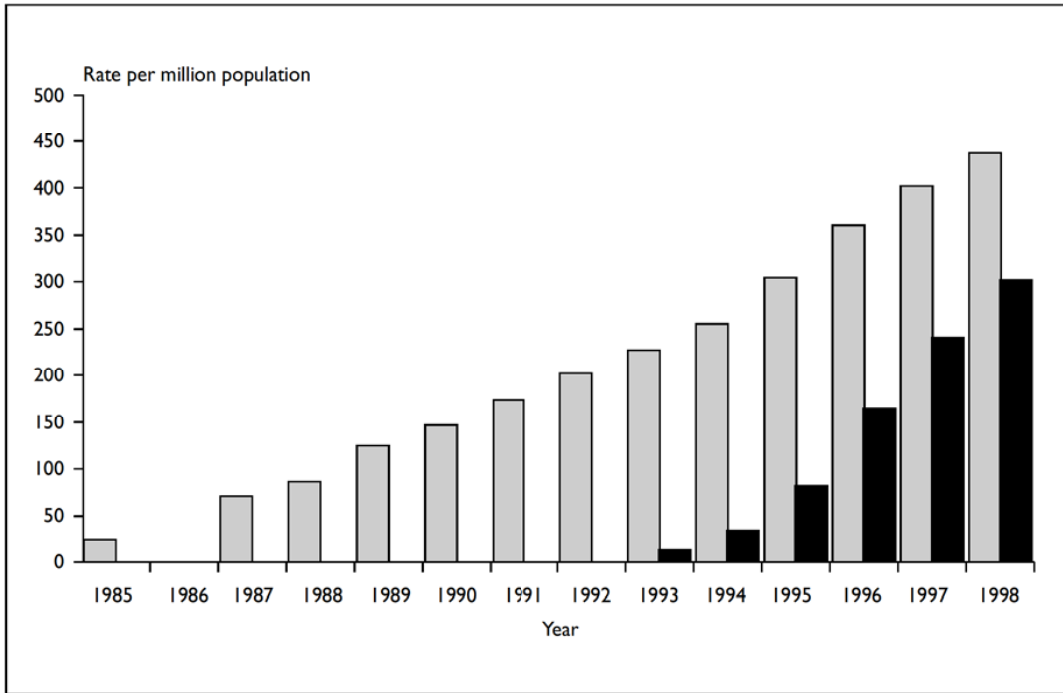
FIGURE 2 *Rates of PCIs and PTCA plus stent in the UK, 1985–1998 (□, all PCI procedures; ■, stents)*
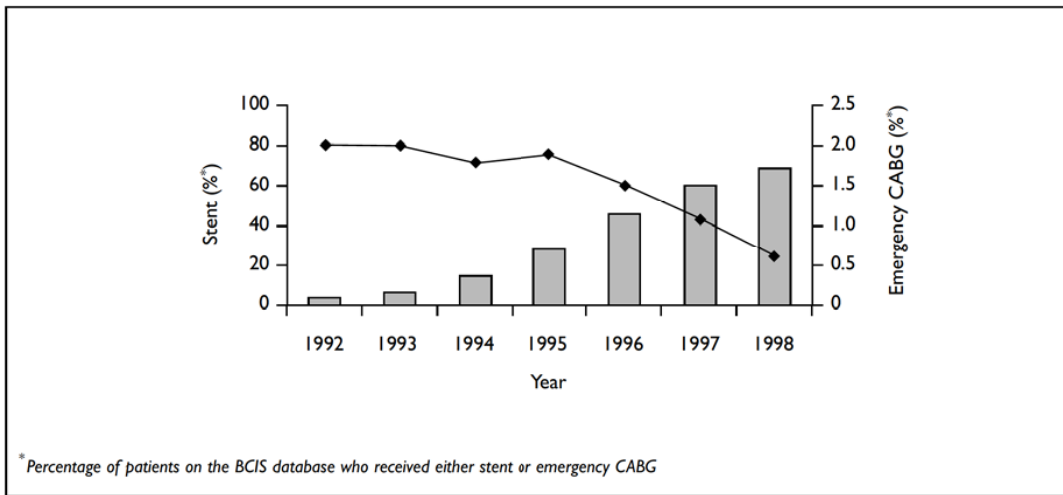
FIGURE 3 *Stenting and the need for emergency CABG (□, stent; ◆, emergency CABG)*

Percentage of patients on the BCIS database who received either stent or emergency CABG

Activity

Access to facilities and revascularisation rates vary greatly across the country with a five-fold difference in revascularisation rates between different regions.[46] Similar differences can be found within regions. An example follows for the West Midlands Region for the years 1990–1997 (*Table 4*). There were over two-fold differences between districts for CABG rates, and more than six-fold differences in PTCA rates (data from Hospital Episode Statistics dataset). It can be seen from *Table 4* that access and need do not correlate: Solihull has the

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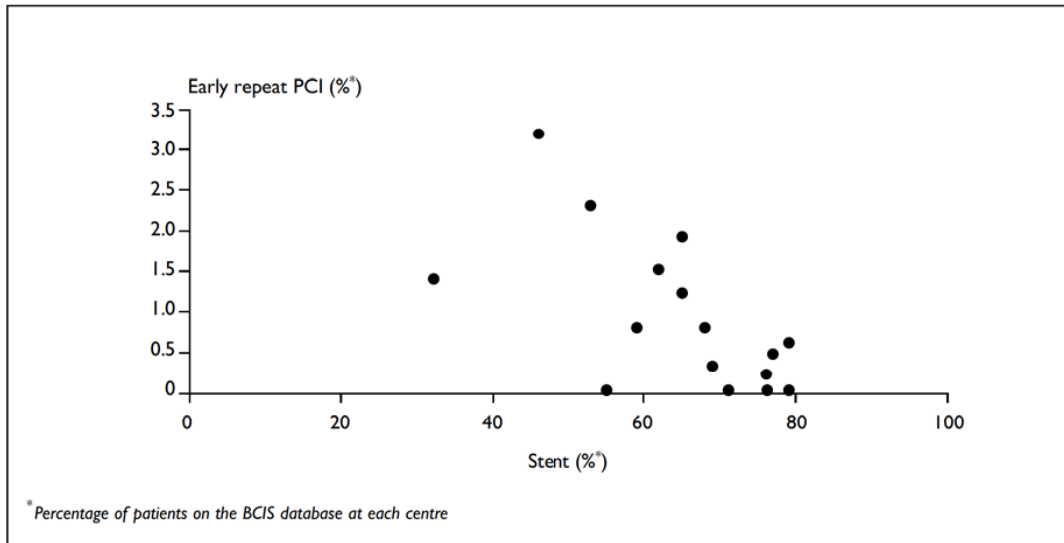
FIGURE 4 *Stenting and early repeat PCI for acute closure 1998[31] (data from 16 centres)*
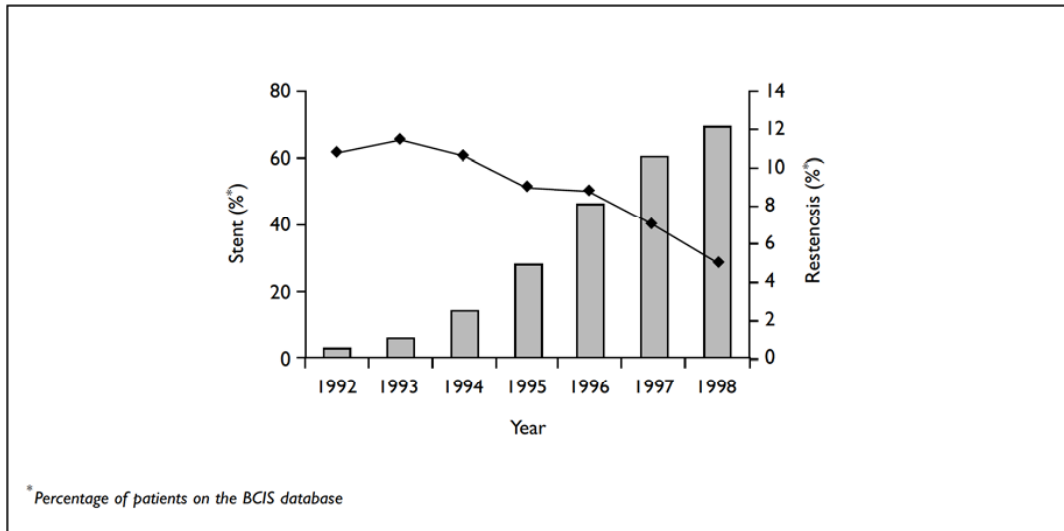
FIGURE 5 *Stenting and procedures for restenosis[31] (data from 25 centres) (◻, stent; ◆, restenosis)*

lowest SMR and the highest revascularisation rate, whereas Walsall has the highest SMR and the lowest revascularisation rate.

Implications for the NHS

It is reasonable to assume that populations with relatively high SMRs for IHD will require higher rates of revascularisation than populations with lower SMRs, provided that interventions are being used appropriately. Thus the comparisons of revascularisation rates in the UK with those of other European countries (*Figure 1*), suggest that there is probably under-provision of services in this country. This is true whether or not one concludes that stenting is more effective or cost-effective than PTCA alone.

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TABLE 3 *SMRs for Regions in England 1993–1995*

Region	SMR for IHD, 1993–1995
Northern & Yorks	113
Trent	105
Anglia & Oxford	88
North Thames	92
South Thames	88
South West	91
West Midlands	105
North West	116

The British Cardiac Society suggested in a statement issued in 1994 that a realistic target for 1996–1997 should be 1000 revascularisations per million population (with a split of 6:4 for CABGs:PTCA).[46] A prospective study of patients referred from a random sample of general practitioners to a special open-access chest pain clinic estimated a crude annual incidence of 830/million population, of whom about one-third had exercise test results that would suggest referral for revascularisation.[47]

The National Service Framework (NSF) has been published[48] since completion of this report in December 1999. The NSF has set standards for the prevention and treatment of IHD including revascularisation. It offers advice on the indications for investigation and treatment. Now that this is available, the size, nature and location of any under-provision ought to become clearer.

TABLE 4 *Revascularisation rates and SMRs for IHD, West Midlands Region*

Health Authority	CABG/million population, 1996	PTCA/million population, 1996	Total	SMRs for IHD, 1993–1995
Region	*543*	*274*	*817*	*105*
Coventry	297	577	874	100
Warwickshire	354	589	943	92
Walsall	457	141	598	131
Sandwell	472	151	623	119
Wolverhampton	499	192	691	107
Herefordshire	522	91	613	92
South Staffordshire	523	262	785	111
North Staffordshire	537	253	790	113
Worcester	598	196	794	90
Shropshire	615	171	786	102
Birmingham	652	226	878	108
Dudley	676	256	932	104
Solihull	687	407	1094	89

Data from Hospital Episode Statistics dataset

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Chapter 2
Methods

Review questions

The following questions are addressed in this review.

- What are the effects and effectiveness of elective stent insertion versus PTCA in subacute IHD, particularly stable angina and unstable angina?
- What are the effects and effectiveness of elective stent insertion versus CABG in subacute IHD, particularly stable angina and unstable angina?
- What are the effects and effectiveness of elective stent insertion versus PTCA in acute MI?
- What are best estimates of UK cost for elective stent insertion, PTCA and CABG in the circumstances of review questions 1 to 3?
- What are best estimates of cost-effectiveness and cost–utility for elective stent insertion relative to PTCA or CABG in the circumstances of review questions 1 to 3?

The methods of the reviews generally followed the guidance laid out in the West Midlands Development and Evaluation Service Handbook[49] and the NHSCRD Report No. 4.[50]

Search strategy

A scoping search was undertaken, focusing on existing reviews and other key papers, as well as the identification of RCTs likely to be included. The yield from this search and a 1998 West Midlands Development and Evaluation Committee (DEC) report on coronary artery stents[1] was used to develop the protocol for the review including inclusion and exclusion criteria and a data abstraction form. Although the scoping review identified recent systematic reviews comparing stents with PTCA,[51,52] this technology is developing so rapidly that any review quickly becomes out of date and so the existence of these systematic reviews did not preclude the need for an up-to-date review.

A search was made for RCTs comparing stents, inserted during a PTCA procedure, with PTCA alone or with CABG in any manifestation of CAD using the NHS Centre for Reviews and Dissemination search strategy for RCTs.[50] The

search strategy covered the period from 1990 to November 1999, as it was in the early 1990s that work on the development of coronary artery stents first began. Key components of the formal search were as follows.

- Electronic databases were searched: MEDLINE (including Pre-MEDLINE); EMBASE; BIDS ISI; The Cochrane Library; York HTA. A combination of index terms (including 'stent' and 'coronary artery disease') and textwords (including 'stent*' and 'coronary') were used.
- A general search of Internet sites was made using medical search engines including OMNI and the general search engine Google, using general search terms such as 'cardiology' or 'stent*'. A search of specific cardiology Internet sites (including the American College of Cardiology website) was carried out.
- Contact was made with lead researchers on existing reviews and RCTs and local clinical experts.
- Handsearches of cardiology conference abstracts, in journals and on websites, were carried out.
- Handsearches were made of recent issues (1999) of cardiology journals.
- Citations were checked in reviews and RCTs identified by the searches.
- A search was made of manufacturers' submissions to NICE (see appendix 1).

For MEDLINE and EMBASE search strategies see appendix 2.

The search strategy was expanded to look for relevant economic analyses and for information to inform the economic model. Searches focused on research that reported costs and quality of life data associated with CAD and interventional cardiology.

Additional elements to the search strategy included:

- specific searches on MEDLINE for relevant cost and cost-effectiveness studies
- searching specialised health economics sources such as NHS Economic Evaluation Database (NHSEED) and the Database of Abstracts of Reviews of Effectiveness (DARE).

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For cost and cost-effectiveness search strategies see appendices 3 and 4.

Inclusion and exclusion criteria (clinical effectiveness)

Two independent reviewers using explicit pre-determined criteria made the inclusion and exclusion decisions. Disagreements were resolved through discussion with a third party. Inclusion and exclusion decisions were made independently of the detailed scrutiny of the results.

Inclusion criteria

Studies were only included in the final analysis of the review if they met the criteria in *Box 4*.

BOX 4 Criteria for inclusion of studies in the final analysis of clinical effectiveness	
Study design	RCTs
Population	Adults with CAD in native or graft vessels. Patient groups included subacute IHD and with AMI
Intervention	Coronary artery stents inserted as an elective procedure
Comparator	Elective PTCA and CABG (i.e. established invasive treatments) including PTCA with provisional stenting (i.e. where stenting is conditional upon immediate angiographic results)
Outcomes	Studies were only included in the review if they reported results of one or more of: combined event rate (or event-free survival), death, MI (Q wave, non-Q wave and total), angina rate, target vessel revascular-isation, CABG, repeat PTCA, angiographic outcomes
Reporting	Only trials that had closed and had reported results for all or almost all recruited patients were included

The primary outcomes for this review were the medium term (3 to < 12 month) and long-term (1–5 year) clinical results. The secondary outcomes were considered to be short-term (< 3 month) clinical results and the angiographic results. Although trials with only angiographic outcomes were included, preferred outcomes were patient-, rather than coronary artery-, centred. Angiographic outcomes may be biased because the stent is visible in angiographic film.

This review included RCTs that have been fully published in peer-reviewed journals and also as conference abstracts. When RCTs were published as conference abstracts only, efforts were made to obtain more complete data from the trialists by writing to the first named author. Trialists had 4–6 weeks to reply. Trials published as abstracts were only included if the trial had closed and some follow-up effectiveness results were available for all or almost all trial participants.

Exclusion criteria

The exclusion criteria were as follows.

1. RCTs that had not finished recruiting (as of latest abstract available).
2. RCTs that published interim results only.
3. RCTs that published results for only some of the trial participants.
4. RCTs for which there were no details of the numbers of patients in each arm of the trial.
5. RCTs that did not compare elective stenting with PTCA or CABG.

The review did not address:

- bailout stenting compared with PTCA (prolonged perfusion balloon) for failed initial PTCA (RCTs of bailout stenting are logistically difficult)
- stents compared with medical treatment
- stents compared with newer technologies (e.g. atherectomy, excimer laser or angioplasty cutting balloon)
- stents compared with stents (i.e. comparisons of effectiveness of different stent types).

Note was made of any RCTs found during the searches and subsequently excluded under points 1–5 above.

Inclusion and exclusion criteria (economic evaluation)

One reviewer, using explicit, predetermined criteria, made the inclusion and exclusion decisions for the cost and cost-effectiveness studies.

Studies were included in the final review if they met the criteria shown in *Box 5*.

As costs from other countries, particularly the USA, may not be comparable with costs in the UK, only costs calculated in the UK are included in the cost analysis.

> **BOX 5 Criteria for inclusion of studies in the final analysis of cost and cost-effectiveness**
>
> | | |
> |---|---|
> | Population | Adults with CAD AND |
> | Economic study type | Studies reporting UK costs OR |
> | | Comparative economic evaluation combining both costs and outcomes OR |
> | | Economic evaluation in which costs and outcomes are reported separately for the years 1998 and 1999 (to ensure current practice has been included) |

This review excludes any studies published before 1996. Practice has changed significantly in recent years, in particular with respect to replacing the anti-coagulation treatment with an anti-thrombotic regimen which allows earlier discharge and fewer bleeding complications. Stent technology has changed, and the patients treated have changed from low risk (discrete single-vessel lesions) to those with more complex multi-vessel disease. The costs of the procedures are changing rapidly, so costs calculated during the last 3 years (1996–1999) only have been included.

Data abstraction (clinical effectiveness)

Two independent reviewers undertook the data abstraction using a data extraction form developed during the protocol stage of the review. Disagreements were resolved by discussion and with the aid of a third party when there was any residual discrepancy.

The following data were extracted:

- overall study design sufficient to allow an assessment of the validity of the study such as size, duration, randomisation procedure, concealment of allocation, blinding, drop-outs, crossovers, and losses to follow-up for each patient group
- details of the study populations such as percentages of patients with stable and unstable angina and previous MI
- details of the intervention such as type of stent and anticoagulation/antiplatelet treatment used
- individual outcomes measured such as use of survival analysis or event rates and the results,

as percentages and/or ideally as raw numbers, plus any summary measure given (standard deviation, p value and CIs where possible).

Data abstraction (economic evaluation)

For the UK cost study the following data were extracted:

- source of information, reference, date, and potential problems with source
- nature of intervention costed
- nature of costing (procedure only, hospital costs or wider costs including follow-up time) and whether point estimate or range
- estimate of cost and range.

For the cost-effectiveness study the following data were extracted:

- details of the study design
- details of the study population
- details of the intervention used, for example, primary stenting, versus PTCA or secondary stenting
- details of individual outcome measures used
- details of and sources of effectiveness data in economic models
- details of sources of quality of life data
- methods of collecting cost data
- assumptions used in economic models.

Quality assessment (clinical effectiveness)

Two independent reviewers undertook the quality assessment. Disagreements were resolved by discussion and with the aid of a third party when there was any residual discrepancy.

The quality of RCTs was assessed in standard ways[50] including the use of the Jadad[53] score. A judgement on the quality and reliability of each study, and of each outcome within the study, was made on the basis of the abstracted information.

Quality assessment (economic evaluation)

The quality assessment of cost-effectiveness analyses was based on the 35-point checklist used by the *British Medical Journal* to assist referees of

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economic analyses.[54,55] When studies were available only in abstract form or summarised in an industry submission there was insufficient information to do a formal quality assessment.

Data synthesis (clinical effectiveness)

Results are presented for the review questions listed above. All abstracted data were collated in summary tables indicating the general pattern of results. Where possible all results were analysed on an intention to treat basis.

Where sufficient information was available and the studies were considered sufficiently clinically and statistically homogeneous for combination to be informative, meta-analyses were carried out using Cochrane Collaboration Review Manager 3.01 software (Update Software Ltd). Analyses were made for the clinical outcome measures of death, MI, angina rate, TVR, CABG, repeat PTCA and total event rate for stents versus PTCA in IHD and following acute MI.

Possible explanations of heterogeneity were considered such as differences between the subgroups specified below and the potential impact of study quality.

In the review of stents versus PTCA in IHD, the following prespecified patient subgroups were considered:

- patients with small coronary arteries
- patients with chronic occlusion
- stenting compared to PTCA with stent insertion dependent upon immediate angiographic results (provisional stenting).

Data synthesis (economic evaluation)

The purpose of the review of economic evaluation was to document existing cost data and health economic assessments, with a view to explaining variation in them, particularly in light of the systematic review of effectiveness information in the preceding sections. These data are used to draw overall conclusions on the likely cost-effectiveness and cost–utility of the use of elective stenting in CAD. This review has not undertaken a cost–utility estimate or directly modelled the data.

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Chapter 3
Results

Introduction

The clinical effectiveness and economic evaluation results are presented in separate sections of this report. Overall, 108 references were identified for this systematic review.[27,41,51,56–160]

Effectiveness results

Results of the searches
Full results of the searches are reported in appendix 2.

Excluded trials
Twenty-five RCTs were found which did not meet the inclusion criteria (15 trials of stent versus PTCA in IHD,[56–69,155,156,158,159] four trials of stent versus CABG in IHD,[70–73] three trials of stent versus PTCA in patients with MI,[74–76] and three trials of other comparisons[75,77,78]). Details of these excluded trials are shown in appendix 5 (pages 69–72).

Most of the trials were excluded because the trial had not yet finished enrolment of patients. Other reasons for exclusion included no details of number of patients in each arm of the RCT and reporting of results for only a small proportion of trial participants. Almost all of the excluded trials were reported as conference abstracts only. Where only abstracts were available, letters requesting further information were sent to first authors. For some of the fully reported trials the longer term follow-up results were only available in abstract form, but no letters were sent to the investigators in those trials. STRESS II[79] was a continuation of the STRESS trial, and data from STRESS I alone has been used here in view of the *ad hoc* decision to continue the STRESS trial and the fuller reporting of the STRESS I data.

Coronary artery stent technology is in a phase of rapid development. This is evidenced by the number of trials in progress which were excluded from this review. New evidence on all of the questions addressed is likely to become available over the coming years.

Included trials
Thirty-five RCTs were found which met the inclusion criteria for this report:

- 25 comparing elective stenting with PTCA in subacute CAD
- three comparing elective stenting with CABG (or minimally invasive CABG) in CAD
- seven comparing stents with PTCA following AMI.

Replies from authors provided substantial further information for two trials on AMI patients, STENTIM II and PASTA. A further abstract was received for the PSAAMI study.

A level of statistical significance of $p < 0.05$ has been used throughout the results.

Effectiveness of elective stenting compared with PTCA in subacute IHD
Trial reporting
Of the 25 trials in this category, 16[27,41,80–107] were fully reported in peer-reviewed journals. The remaining nine[108–117] were available as abstracts only or in a press release that appeared to use information from a conference presentation in March 1999 (OPUS; included in Cordis industry submission)[116] or from another systematic review (WIN).[51,109]

In the tables, the 25 trials are presented in the order of oldest trials first (BENESTENT[80–84] to WIDEST[111]), then subgroups of trials of: saphenous vein graft lesions (SAVED[96]), stent + abciximab versus PTCA + abciximab (EPISTENT[41,97]), chronic coronary occlusion (SICCO[98–100] to CORSICA[113]) and then elective stenting versus PTCA with provisional stenting (OCBAS[107] to OPUS[116]).

Follow-up varied from 6 months to 5 years. The clinical results tables have been split into three groups: immediate, in hospital or up to 1 month follow-up, 3 to < 12 months follow-up, and 1 to 5 years follow-up. Only the medium- and long-term results have been discussed in the results section and meta-analyses.

There were sufficient trials for the possibility of publication or small study bias to be considered in a funnel plot. The outcome chosen for the

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Medtronic Exhibit 1414

plot was the medium-term event rate, and those trials which reported this outcome in sufficient detail to be included in a meta-analysis (see below) were included in the plot (*Figure 6*). The plot gives no clear indication of publication or small study bias.

Patients

Patient characteristics are reported in appendix 5 (pages 73–77). All of the trials included patients who could have been treated either with PTCA alone or with stents. In some of the earlier trials (BENESTENT,[80–84] Eeckhout,[90] GISSOC[101]) it was specified that all patients also had to be eligible for CABG.

The BENESTENT[80–84] trial, one of the earliest, included only patients with stable angina. All other trials included various proportions of patients with stable or unstable angina.

All trials but DEBATE II[114,115,117] (for which little information on trial design was available) and Restenosis SSG[95] excluded small coronary artery stents. The latter included only patients with restenosis following PTCA. Some trials only included new lesions (BENESTENT,[80–84] STRESS,[85–89] Eeckhout,[90] Versaci,[91] BENESTENT II,[27] AS,[110] SICCO[98–100]) whereas the other trials (which gave details) included both new and restenotic lesions.

One trial included only lesions in saphenous vein grafts (SAVED[96]). All of the other trials looked at lesions in native vessels only.

A large subgroup of eight trials included patients whose vessels had chronic and total occlusion only (SICCO,[98–100] GISSOC,[101] Hancock,[102] TOSCA,[103,104] SPACTO,[105] SARECCO,[106] STOP,[112] CORSICA[113]) whereas other trials specifically excluded total occlusion (Versaci,[91] START[93,94]).

Although four trials[57,64,65,68] considered the use of stenting in small coronary vessels, none of them could be included in the review because no complete results were available.

Most trials did not report what proportion of potential patients were eligible for the trial, or indeed what proportion of eligible patients were randomised (see appendix 5, pages 78–83). Where this was reported (Eeckhout,[90] EPISTENT,[41,97] SICCO,[98–100] Hancock,[102] TOSCA,[103,104] SPACTO,[105] OCBAS[107]), most trials appeared to have included only highly selected groups. Thus trial results may not be generalisable to typical PCI patients.

Interventions and comparators
Stents

The type of stent used in the RCTs varied but more used Palmaz-Schatz than any other stent type (see appendix 5, pages 73–77). Two of the
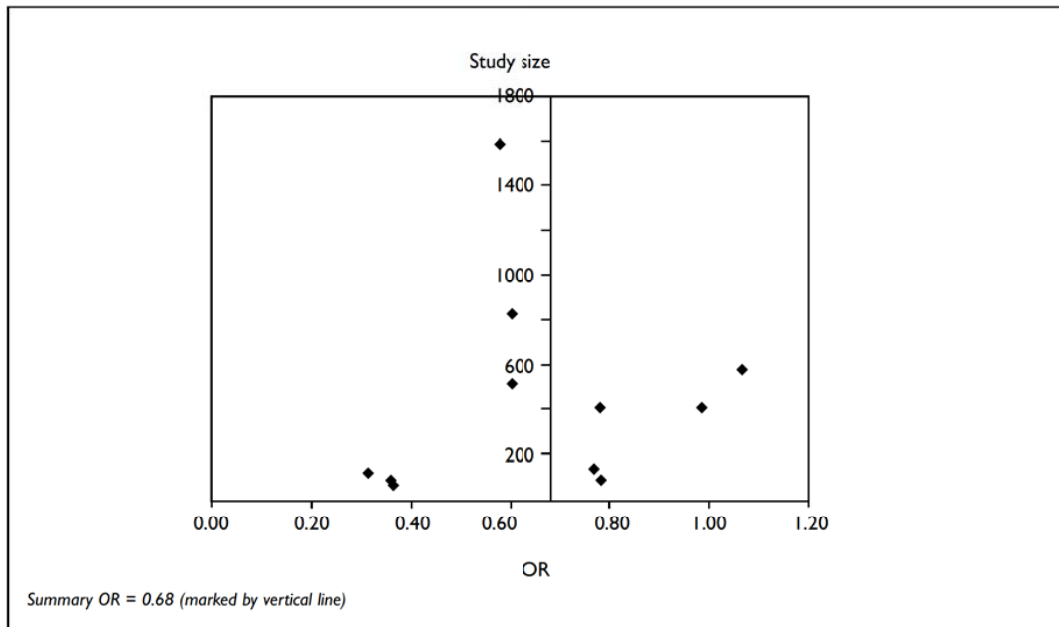
FIGURE 6 *Funnel plot: odds ratios (ORs) for 4–11 month event rate against study size – stent versus PTCA*

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trials used Palmaz-Schatz heparin-coated stents (BENESTENT II,[27] TOSCA[103,104]).

Antithrombotic regimens

The standard anticoagulation/antiplatelet drug treatments have changed in the last 5 years. When the first trials were undertaken (BENESTENT,[80–84] STRESS,[85–89] Versaci,[91] START,[93,94] SAVED,[96] SICCO,[98–100] GISSOC,[101] Hancock[102]), warfarin for the stent group was standard practice but the PTCA groups did not receive the same drug treatment. Since then warfarin has not been used because of increased bleeding complications and ticlopidine has been used instead. In some trials (WIDEST,[111] TOSCA,[103,104] SPACTO[105]) the drug regimen for the stent patients changed from warfarin to ticlopidine midway through the trial. In only a few trials (AS,[110] EPISTENT,[41,97] CORSICA[113]) does it appear that the same drug regimen was given to the stent and PTCA groups (see appendix 5, pages 84–87). In the vast majority of trials antithrombotic therapy was more intensive in the stent arm than in the PTCA arm, leaving open the possibility that some of the difference in observed outcomes may be attributable to this.

In the EPISTENT[41,97] trial there was a third arm to the trial (stent + placebo) but the only results included in this review are for the stent + abciximab and PTCA + abciximab groups. Abciximab was used in a small proportion of patients in other RCTs in this review (TOSCA[103,104]).

It might be expected that bleeding complication rates and also length of hospital stay would have varied depending upon the anticoagulation regimen used.

Comparators

In most of the trials, the intention was to treat the PTCA group with PTCA only. However, some patients in the PTCA-only groups did receive stents. Patients either received emergency stent placement because the target artery had not remained patent after the PTCA (bailout stent), or a stent because there was uncertainty as to whether the artery would have remained patent (provisional stent). In these trials the number of patients in the PTCA group who received a stent was recorded as a treatment crossover. In a few of the trials (OCBAS,[107] DEBATE II,[114,115,117] OPUS[116]) the strategy of provisional stenting for an unacceptable PTCA result was part of the trial design. In these trials, patients allocated to PTCA received a stent if the immediate angiographic results were considered 'suboptimal' (not 'stent-like'), as well as

when there was an emergency requirement for a bailout stent. In this review, the number of patients in the PTCA group who received a stent is recorded as a treatment crossover whatever the reason for crossover, regardless of different trial design (see appendix 5, pages 84–87). No crossovers were allowed in some trials.

The crossovers from stent to PTCA treatment ranged from 0% to 9.3%. The crossovers from PTCA to stent treatment ranged from 0% to 37%. Of the four trials with a crossover from PTCA to stents of > 30%, only one was a trial of PTCA with provisional stenting versus elective stenting.

Another important difference between trial designs is the point at which randomisation occurs. This was sometimes before catheterisation, sometimes after the guidewire had been passed, and sometimes after a successful PTCA had been achieved. The further along this pathway randomisation occurs, the more selected the patient group.

Summary

The trials are not simply comparing stenting in PTCA with PTCA alone. The interventions and comparisons in these trials are packages comprising selection at different stages in the catheterisation pathway, different policies with regard to crossover to stent in the PTCA arm of the trial, and antithrombotic regimens which in most cases were different for stent and for PTCA and which in some cases were changed part way through the trial.

Trial quality

Where reported, the baseline characteristics of stent and PTCA groups within each trial were mostly similar. Any differences are described in appendix 5 (pages 78–83). The most conspicuous difference was in the SPACTO[105] trial, in which men made up 57% of the patient population in the stent arm of the trial and 81% in the PTCA arm ($p = 0.02$), suggesting that confounding factors might not have been balanced between the trial arms.

All of the RCTs were graded using the Jadad scale[53] (see appendix 5, pages 84–87). This score incorporates points for blinding, randomisation, concealment of allocation and reporting of follow-up – all factors that have been shown to be important in prevention of bias. A score of 3 or more indicates a trial of good quality in these respects. The scores ranged from 1 to 3 only. None of the trials was described as double blind, as this would be impossible to achieve. It

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appears that neither physicians nor patients were blinded to the treatment received in any of the trials. The Jadad score is included to give an indication of the quality of trial execution, but in this case it also reflects the quality of reporting, largely in those trials published only in abstract form. The main reason for a fully reported RCT receiving a score of less than 3 was because there were no details of the randomisation process. All of the RCTs reported as abstracts only had a Jadad score of 1.

The number of drop-outs after randomisation was usually very small (see appendix 5, pages 78–83).

As blinding of patients and clinicians was not possible in these trials, it is possible that some degree of bias has entered into trial execution and reporting, because trialists often have a subconscious bias in favour of the new treatment, in this case stents. This has been acknowledged by stent trialists.[27]

A further source of bias is introduced by angiographic follow-up. It is not possible to blind angiographic assessment of outcomes, but a further potentially important problem is that it is probable that healthy rather than unhealthy patients are lost to or refuse angiographic follow-up. In this review, clinical outcomes are considered to be the primary endpoints, although angiographic outcome data are reported in appendix 5 (pages 92–93).

In general, the clinical follow-up rates are high, even for long-term follow-up. Where it is completely unclear as to how many patients have been followed up, blanks have been left in the tables in appendix 5. Although percentages were sometimes given in the trial reports, absence of any absolute numbers often made it impossible to include data in the meta-analysis.

Short-term clinical outcomes
Short-term outcomes are reported in appendix 5 (pages 88–89 and 90–91). The bleeding complication rate appears to be influenced by the anticoagulant regimen, rather than by stent insertion, as it varies according to the anticoagulation used. In particular, where major bleeding complications were recorded, differences between stent and PTCA arms were minimal in those trials which did not incorporate formal anticoagulation with warfarin and used ticlopidine instead (that is, BENESTENT II,[27] EPISTENT,[41,97] and SARECCO[106]). Bleeding complications, costs and hospital stay were increased when heavy anticoagulation was used.

Definitions of major bleed varied between the trials. Where descriptions of bleeding complications were given, major bleed was taken to include any bleeding that had resource implications (e.g. need for vascular repair or blood transfusion).

Angiographic outcomes
Angiographic follow-up for all trials varied from 4 to 9 months but was mostly carried out at approximately 6 months. Initial minimal lumen diameter of the coronary artery (MLD) and percentage stenosis and follow-up restenosis rates are reported in appendix 5 (pages 92–93).

Stenting produced better post-procedural angiographic results than PTCA but the difference between the two groups declined over time. Angiographic results from the trials tend to show a statistically significant improvement for the stent group compared with the PTCA group post procedure and at follow-up (4 to 9 months), but angiographic results are not well correlated with clinical results and so will not be discussed further in this report.

Medium-term (4 to 11 months) clinical outcomes
Results covering periods of follow-up of between 4 and 11 months are reported in appendix 5 (pages 95–96 and 97–98).

Where full information on the numbers of patients in each arm and the number of events was available, trials were included in meta-analyses produced using the Cochrane Collaboration Revman 3.01 software (Update Software Ltd) and are reported in Forest plots. A fixed effect model and the Peto OR have been used. Results which were clearly based on actuarial survival analysis with variable lengths of follow-up were not included in the meta-analyses. The following outcomes were considered: composite event rates (for definition used in each trial, see appendix 5, page 94), death, MI, target vessel or lesion revascularisation (TVR or TLR), CABG, repeat PTCA and angina status. Trials are ordered as follows: general CAD trials in order of year of publication, followed by EPISTENT,[41,97] the abciximab trial, followed by chronic occlusion trials in order of year of publication.

Event rate
The medium-term event rate was the primary clinical endpoint of most trials. Composite event rates included death, MI and repeat revascularisation. The last of these accounted for the majority of the events. Details of individual

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trial event rate definitions are given in appendix 5 (page 94). Composite event rates reported at between 4 and 11 months follow-up tended to favour stent (*Figure 7*), with a summary OR of 0.68 (95% CI, 0.59 to 0.78). Some heterogeneity between the ORs was present, but it was not obviously related to patient characteristics or to patient subgroups (e.g. chronic occlusion).

Two trials were neutral between stent and PTCA. They were WIN,[51,109] which appeared to have unusually high event rates and consistently different results, and TOSCA,[103,104] one of the chronic occlusion trials. The latter used a sensitive definition of MI (≥ 5 times the normal creatinine kinase [CK-MB] elevation) that might in part account for this result if stenting in itself produced CK-MB elevation. This result can also be seen in the L'Abbe plot in *Figure 8*. The event rates in the SICCO[98–100] and SPACTO[105] trials were high, consistent with the

relatively longstanding and confirmed disease in patients in these trials. In the case of SPACTO,[105] this was compounded by the exclusion of patients with no angiographic follow-up (21%) from the reporting of results. BENESTENT II[27] and EPISTENT[41,97] had particularly low event rates.

Impact of crossovers on event rate
The possibility that the event rate was influenced by the proportion of PTCA patients who crossed over to stent is explored in *Figure 9* which plots crossover rates against the OR for the event rate. There is no evidence of a clear relationship between effect size and crossover, which is surprising.

Impact of method of follow-up on event rate
The BENESTENT II trial[27] provides some important information on the impact of method of follow-up on event rates. To quote the investigators, "we wanted to document the natural

Study	Event rate		Weight (%)	Peto OR (95% CI, fixed)
	Experiment (n/N)	Control (n/N)		
BENESTENT	52/259	76/257	12.2	0.60 (0.40 to 0.90)
STRESS	40/205	48/202	8.8	0.78 (0.49 to 1.25)
Eeckhout	10/42	12/42	2.1	0.78 (0.30 to 2.06)
BENESTENT II	53/413	79/410	14.1	0.62 (0.43 to 0.90)
WIN	84/299	77/287	14.8	0.07 (0.74 to 1.53)
EPISTENT (Abciximab)	103/794	163/796	28.1	0.58 (0.45 to 0.76)
SICCO (CO)	12/58	27/59	3.3	0.33 (0.15 to 0.70)
Hancock (CO)	4/30	9/30	1.3	0.38 (0.11 to 1.29)
TOSCA (CO)	47/202	49/208	9.3	0.98 (0.62 to 1.55)
SPACTO (CO)	12/40	22/40	2.5	0.36 (0.15 to 0.88)
CORSICA (CO)	16/72	19/70	3.4	0.77 (0.36 to 1.64)
Total (95% CI)	433/2414	581/2401	100.0	0.68 (0.59 to 0.78)

Chi-square 17.12 (df = 10) Z = 5.39

0.1 0.2   1   5 10

Favours treatment   Favours control

CO = chronic occlusion, df = degrees of freedom

FIGURE 7 *Event rates at 4 to 11 months: stent compared with PTCA in IHD*
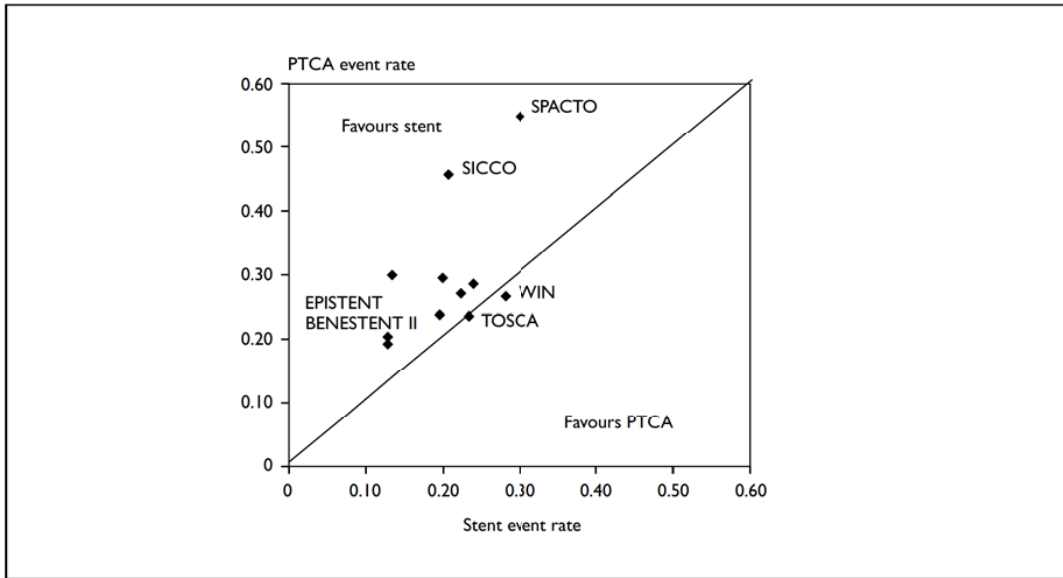
FIGURE 8 *L'Abbe plot: event rates at 4 and 11 months – stent versus PTCA*
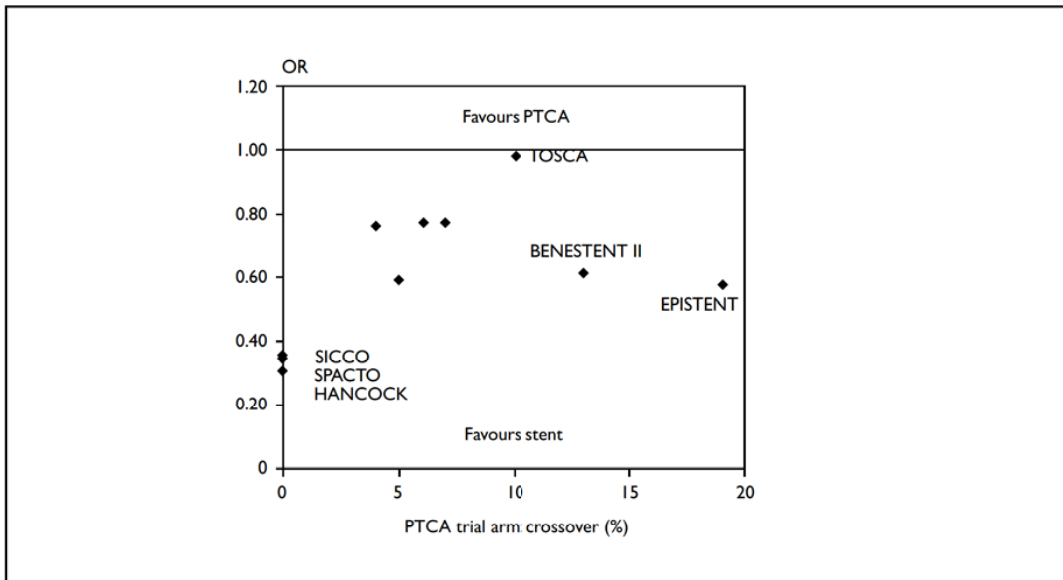
FIGURE 9 *ORs for event rates at 4–11 months – stent versus PTCA by stent crossover rate in PTCA*

TABLE 5 *Impact of method of follow-up on BENESTENT II EFS (Kaplan–Meier method) at 12 months*

Patient group	EFS (%)		
	Stent	**PTCA**	**p value (log-rank test)**
All patients	84.3	77.6	0.01
Patients with angiographic follow-up	79.3	76.6	0.39
Patients with clinical follow-up alone	89.3	78.6	0.003

course of the disease and the spontaneous behaviour of the interventional cardiologists, taking into account their current psychological diagnostic and therapeutical bias". This was achieved by a sub-randomisation to clinical follow-up alone or to clinical and angiographic follow-up. The difference between the stent and PTCA arms in event free survival (EFS) was almost entirely attributable to the differences found in the group randomised to clinical follow-up alone (*Table 5*). The reason for the difference is unclear. Apart from the BENESTENT II[27] sub-randomisation, EPISTENT[41,97] was the only trial without angiographic follow-up.

Event rate summary

In summary, analysis on an intention-to-treat basis shows that stenting is associated with a reduction in clinical events in the medium term compared with PTCA. Event rates are lower overall where there is no angiographic follow-up, as a result of reduced intervention rates, but in these circumstances the relative difference in event rates is greater and favours stent. This difference could result from clinician behaviour, as well as from real need to intervene.

The separate components of the clinical event rates are considered below.

Death rate

Death rates at between 4 and 11 months for PTCA compared with stent are shown in *Figure 10*.

Death is a relatively rare outcome at this period of follow-up and as indicated by the CIs in

Study	Event rate Experiment (n/N)	Control (n/N)		Weight (%)	Peto OR (95% CI, fixed)
BENESTENT	2/259	1/257		5.4	1.94 (0.20 to 18.71)
STRESS	3/205	3/202		10.6	0.99 (0.20 to 4.93)
Eeckhout	0/42	0/42		0.0	Not estimable
BENESTENT II	1/413	2/410		5.4	0.51 (0.05 to 4.91)
Restenosis SSG	2/178	2/176		7.1	0.99 (0.14 to 7.08)
WIN	9/229	10/287		32.4	1.13 (0.45 to 2.85)
EPISTENT (Abciximab)	3/794	14/796		30.2	0.27 (0.10 to 0.71)
SICCO (CO)	0/58	0/59		0.0	Not estimable
GISSOC (CO)	0/56	1/54		1.8	0.13 (0.00 to 6.58)
Hancock (CO)	0/30	1/30		1.8	0.14 (0.00 to 6.82)
TOSCA (CO)	1/202	1/208		3.6	1.03 (0.06 to 16.53)
SPACTO (CO)	1/40	0/40		1.8	7.39 (0.15 to 372.41)
SARECCO (CO)	0/55	0/55		0.0	Not estimable
Total (95% CI)	22/2561	35/2616		100.0	0.68 (0.40 to 1.14)
Chi-square 8.80 (df = 9) Z = 1.46					

```
        0.1  0.2      1      5   10
      Favours treatment   Favours control
```

FIGURE 10 *Death rates at 4 to 11 months: stent compared with PTCA in IHD*

Figure 10, the trials are not powerful enough collectively to provide any evidence on this outcome. The high event rate in WIN[51,109] results in narrower CIs, but WIN event rates are not typical, and perhaps result from some unidentified clinical heterogeneity in a trial with limited reporting. EPISTENT,[41,97] the largest trial, shows a difference in favour of stent with abciximab in comparison to PTCA with abciximab. This finding may not be generalisable to stent and/or PTCA without abciximab. Few patients in the other trials had abciximab. The trials other than WIN[51,109] and EPISTENT,[41,97] individually or collectively, provide no evidence on the impact of stents on mortality.

MI rate

Rates of MI at between 4 and 11 months for PTCA compared with stent are shown in *Figure 11*. Where Q wave and non-Q wave MIs were reported separately, data have been combined. There may

be some rounding errors from back calculation from percentages.

The trials display no statistical heterogeneity. No trial favours either stent or PTCA. As with mortality, low underlying event rates reduce the power of the trials to provide definitive information. The TOSCA[103,104] trial's definition of MI was CK-MB elevation more than five times the norm. This sensitive definition may include false positive diagnoses of MI and is inconsistent with the definitions used in the other trials. Again, the high event rate in WIN[51,109] is not typical of the other trials. WIN,[51,109] BENESTENT[80-84] and BENESTENT II[27] have relatively precise CIs and show no difference between stent and PTCA. In summary, the trials provide no evidence of an effect on MI.

Those trials that report Q-wave MI separately (*Figure 12*) have homogeneous results and show

	MI rate					
Study	**Experiment (n/N)**	**Control (n/N)**			**Weight (%)**	**Peto OR (95% CI, fixed)**
BENESTENT	11/259	10/257			15.1	1.10 (0.46 to 2.62)
STRESS	13/205	14/202			18.9	0.91 (0.42 to 1.98)
Eeckhout	0/42	0/42			0.0	Not estimable
BENESTENT II	13/413	15/410			20.2	0.86 (0.40 to 1.82)
Restenosis SSG	8/178	2/176			7.3	3.39 (0.96 to 11.89)
WIN	26/299	18/287			30.4	1.42 (0.77 to 2.62)
SICCO (CO)	1/58	0/59			0.7	7.52 (0.15 to 378.94)
Hancock (CO)	0/30	1/30			0.7	0.14 (0.00 to 6.82)
TOSCA (CO)	5/202	2/208			5.1	2.46 (0.55 to 10.94)
SPACTO (CO)	0/40	0/40			0.0	Not estimable
SARECCO (CO)	1/55	1/55			1.5	1.00 (0.06 to 16.19)
Total (95% CI)	78/1781	63/1766			100.0	1.23 (0.88 to 1.72)
Chi-square 7.12 (df = 8) Z = 1.19						

0.1 0.2   1   5 10

Favours treatment   Favours control

FIGURE 11 *MI rates at 4 to 11 months: stent compared with PTCA in IHD*

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no difference between stent and PTCA on this more precise definition of MI.

Results for non-Q wave MI also showed no difference between stent and PTCA (*Figure 13*).

Angina rate
Only five trials reported on the angina status of the patients at 4 to 11 months, despite the important impact of this outcome on patient quality of life. Where possible, angina-free survival

	Q wave MI rate				
Study	Experiment (*n/N*)	Control (*n/N*)		Weight (%)	Peto OR (95% CI, fixed)
BENESTENT	7/259	4/257		25.0	1.73 (0.52 to 5.71)
STRESS	7/205	7/202		31.4	0.98 (0.34 to 2.86)
BENESTENT II	7/413	5/410		27.5	1.39 (0.45 to 4.35)
Restenosis SSG	5/178	1/176		13.7	3.82 (0.76 to 19.16)
SARECCO (CO)	0/55	1/55		2.3	0.14 (0.00 to 6.82)
Total (95% CI)	26/1110	18/1100		100.0	1.43 (0.79 to 2.61)
Chi-square 3.39 (df = 4) *Z* = 1.18					

0.1 0.2   1   5 10

Favours treatment   Favours control

FIGURE 12 *Q wave MI rates at 4 to 11 months: stent compared with PTCA in IHD*

	Non-Q wave MI rate				
Study	Experiment (*n/N*)	Control (*n/N*)		Weight (%)	Peto OR (95% CI, fixed)
BENESTENT	4/259	6/257		32.2	0.66 (0.19 to 2.31)
BENESTENT II	6/413	10/410		51.5	0.60 (0.22 to 1.60)
Restenosis SSG	3/178	1/176		13.0	2.71 (0.38 to 19.41)
SARECCO (CO)	1/55	0/55		3.3	7.39 (0.15 to 372.41)
Total (95% CI)	14/905	17/898		100.0	0.81 (0.40 to 1.66)
Chi-square 3.14 (df = 3) *Z* = 0.56					

0.1 0.2   1   5 10

Favours treatment   Favours control
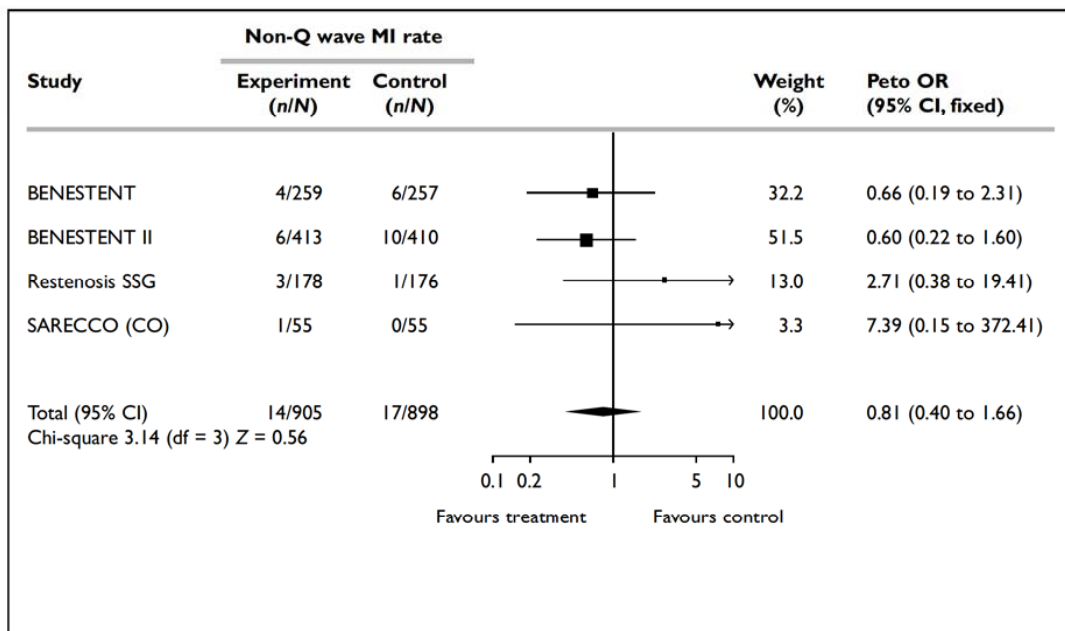
FIGURE 13 *Non-Q wave MI rates at 4 to 11 months: stent compared with PTCA in IHD*

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rates have been recalculated as angina rates. The results are heterogeneous, with BENESTENT[80–84] tending to favour PTCA and the others tending to favour stent. There are statistically significant results from the BENESTENT II trial,[27] a recent and relatively good quality trial, and the SICCO trial[98–100] (*Figure 14*). There are no obvious clinical explanations for these differences. The BENESTENT II trial[27] yields a number needed to treat of 13 to achieve one extra angina-free patient at 6 months. Angina is an important outcome that occurs frequently but has been poorly evaluated. Further trials will be needed if the impact of stents on angina is to be addressed adequately.

TVR rate
TVR comprises repeat PCIs and CABGs that address restenosis in the vessel originally treated. Some trials specify TLR. TVR and TLR have been combined here. All but one of the trials favours stent (*Figure 15*). WIN[51,109] once again introduces some heterogeneity and is neutral between stent and PTCA. As a whole the results favour stent.

CABG rate
The outcome CABG includes any CABG, not just CABG procedures that address problems with the target vessel. Low event rates again mean that trial results are very imprecise (*Figure 16*). They are however consistent and homogeneous with relatively precise CIs, and collectively favour neither stent nor PTCA.

Repeat PTCA rate
The outcome PTCA includes any PTCA, not just PTCA procedures that address problems with the target vessel, except for a few of the trials in which only repeat PTCA of the target vessel was reported. Repeat PTCA was by far the more common form of repeat intervention, and trial results are accordingly more precise (*Figure 17*). There is some heterogeneity in the results: WIN[51,109] was neutral between stent and PTCA, whereas the other trials favoured stent, so that on balance stent reduces the repeat PTCA rate relative to initial PTCA (summary OR, 0.57; 95% CI, 0.48 to 0.69). Repeat PTCAs to the target vessel make the largest contribution to the event rate.

Medium-term outcomes summary
There is a lower event rate with stent than with PTCA at periods of follow-up of between 4 and 11 months. Composite event rates, however, include both deaths and MIs and re-interventions. Death and MIs might be considered the more important outcomes, but as these events are relatively rare in the trials, the trials provide no clear evidence on

Study	Angina rate			Weight (%)	Peto OR (95% CI, fixed)
	Experiment (n/N)	Control (n/N)			
BENESTENT	88/259	68/257		33.9	1.43 (0.98 to 2.08)
BENESTENT II	97/413	125/410		50.4	0.70 (0.52 to 0.95)
Eeckhout	6/42	7/42		3.5	0.84 (0.26 to 2.71)
SICCO (CO)	25/58	45/59		8.8	0.25 (0.12 to 0.53)
SPACTO (CO)	4/40	9/40		3.4	0.40 (0.12 to 1.31)
Total (95% CI) Chi-square 20.43 (df = 4) Z = 1.94	220/812	254/808		100.0	0.81 (0.65 to 1.00)

0.1 0.2   1   5 10

Favours treatment   Favours control

FIGURE 14 *Angina rates at 4 to 11 months: stent compared with PTCA in IHD*

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Study	TVR rate			Weight (%)	Peto OR (95% CI, fixed)
	Experiment (n/N)	Control (n/N)			
Restenosis SSG	16/156	42/158		10.6	0.34 (0.19 to 0.60)
WIN	63/299	58/287		21.4	1.05 (0.71 to 1.57)
EPISTENT (Abciximab)	69/794	123/796		37.6	0.53 (0.39 to 0.72)
SICCO (CO)	12/58	23/59		5.5	0.42 (0.19 to 0.93)
GISSOC (CO)	3/56	12/54		2.9	0.24 (0.08 to 0.72)
TOSCA (CO)	17/202	32/208		9.6	0.52 (0.28 to 0.94)
SARECCO (CO)	13/55	30/55		5.9	0.28 (0.13 to 0.59)
CORSICA (CO)	16/72	24/70		6.4	0.55 (0.27 to 1.15)
Total (95% CI) Chi-square 18.80 (df = 7) Z = 6.45	209/1692	344/1687		100.0	0.54 (0.45 to 0.65)

0.1 0.2   1   5   10

Favours treatment   Favours control

FIGURE 15 *TVR rates at 4 to 11 months: stent compared with PTCA in IHD*

either outcome. Differences in re-intervention rates largely account for the superiority of stents in the trials. This outcome is, however, potentially susceptible to bias, as clinicians might investigate PTCA patients more intensively, leading to increased intervention.

Long-term clinical outcomes

One-year follow-up information was available for the BENESTENT,[84] STRESS,[86] Versaci,[91] BENESTENT II,[27] and WIDEST[111] trials. Follow-up data were available at 2 years for the AS[110] and SARECCO[118] trials, at 3 years (plus or minus 6 months) for the SICCO trial,[99] at 4 years for the START trial[92] and at 5 years for the BENESTENT trial.[81] Follow-up at between 9 and 23 months was available for OCBAS.[107] Longer term outcomes are tabulated in appendix 5 (pages 99 and 100).

Event rate

There was some heterogeneity in the ORs for event rates (*Figure 18*), but ORs generally favoured

stent, with Versaci,[91] START,[92] BENESTENT II[27] and SICCO[99] trials having statistically significant ORs in favour of stent. BENESTENT favoured stent at 1 year,[84] but there was no significant difference in the event rate for PTCA and for stent at the 5 years follow-up.[81] The 4 years follow-up of the START trial,[92] however, favoured stent.

Death rate

Even with longer follow-up, deaths occur too rarely for the trials individually to produce evidence on this outcome. The summary OR of 1.13 (95% CI, 0.67 to 1.97) shows no difference between stent and PTCA (*Figure 19*) and provides more convincing evidence than the medium-term results of stents having no impact on death rates.

MI rate

There are no differences in MI rates between stent and PTCA in any of the longer term follow-ups as shown in *Figure 20*. The summary OR was 0.95 (95% CI, 0.65 to 1.37).

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	CABG rate					
Study	Experiment (n/N)	Control (n/N)			Weight (%)	Peto OR (95% CI, fixed)
BENESTENT	13/259	10/257			20.8	1.30 (0.56 to 3.00)
STRESS	10/205	17/202			23.9	0.57 (0.26 to 1.23)
Eeckhout	3/42	1/42			3.6	2.82 (0.38 to 20.78)
BENESTENT II	6/413	6/410			11.2	0.99 (0.32 to 3.10)
Restenosis SSG	6/178	2/176			7.4	2.74 (0.68 to 11.12)
WIN	8/299	5/287			12.0	1.54 (0.51 to 4.61)
SICCO (CO)	3/58	1/59			3.7	2.84 (0.39 to 20.70)
GISSOC (CO)	2/56	4/54			5.4	0.48 (0.09 to 2.46)
Hancock (CO)	1/30	2/30			2.7	0.50 (0.05 to 5.02)
TOSCA (CO)	3/202	4/208			6.5	0.77 (0.17 to 3.43)
SPACTO (CO)	1/40	2/40			2.8	0.50 (0.05 to 4.99)
SARECCO (CO)	0/55	0/55			0.0	Not estimable
Total (95% CI)	56/1837	54/1820			100.0	1.03 (0.70 to 1.50)
Chi-square 8.68 (df = 10) Z = 0.13						

```
       0.1  0.2        1      5   10
       Favours treatment    Favours control
```

FIGURE 16 *CABG rates at 4 to 11 months: stent compared with PTCA in IHD*

In the case of BENESTENT, the non-Q wave MI rates are less at 5 years follow-up[81] than at 1 year follow-up.[84] This might result from a hierarchical definition of event rates, where only the most serious event is counted. Q wave and non-Q wave MIs are reported separately in appendix 5 (page 99).

Angina rate
Three of the four trials that reported this outcome, BENESTENT at 1 year,[84] STRESS[86] and SICCO,[99] found no difference between stent and PTCA at 1 year, 1 year and 3 years (± 6 months) respectively (*Figure 21*). The Versaci trial[91] reported a reduced OR in favour of stent at 1 year (OR, 0.36; 95% CI, 0.14 to

0.91). The trials display most heterogeneity on this outcome.

TVR rate
There was some heterogeneity in the results, but all except one trial (OCBAS[107]) favoured stent (*Figure 22*).

CABG rate
Figure 23 illustrates that there was no heterogeneity and no evidence for a difference between stent and PTCA for this outcome.

Repeat PTCA rate
There was some heterogeneity for this outcome with some trials (BENESTENT,[84] Versaci,[91]

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	Repeat PTCA rate				
Study	Experiment (*n/N*)	Control (*n/N*)		Weight (%)	Peto OR (95% CI, fixed)
BENESTENT	26/259	53/257		14.4	0.44 (0.27 to 0.71)
STRESS	23/205	25/202		9.1	0.90 (0.49 to 1.63)
Eeckhout	5/42	7/42		2.2	0.68 (0.20 to 2.29)
BENESTENT II	33/413	56/410		17.1	0.56 (0.36 to 0.86)
WIN	57/299	54/287		19.4	1.02 (0.67 to 1.54)
EPISTENT (Abciximab)	10/794	24/796		7.2	0.43 (0.22 to 0.85)
SICCO (CO)	10/58	24/59		5.2	0.32 (0.15 to 0.72)
GISSOC (CO)	3/56	10/54		2.5	0.29 (0.09 to 0.91)
Hancock (CO)	3/30	5/30		1.5	0.57 (0.13 to 2.48)
TOSCA (CO)	25/202	41/208		11.9	0.58 (0.34 to 0.98)
SPACTO (CO)	10/40	16/40		3.8	0.51 (0.20 to 1.29)
SARECCO (CO)	13/55	30/55		5.7	0.28 (0.13 to 0.59)
Total (95% CI)	218/2453	345/2440		100.0	0.57 (0.48 to 0.69)
Chi-square 18.33 (df = 11) Z = 5.99					

0.1 0.2   1   5 10

Favours treatment   Favours control

FIGURE 17 *Repeat PTCA rates at 4 to 11 months: stent compared with PTCA in IHD*

BENESTENT II[27] and SICCO[99]) favouring stent, whereas STRESS[86] and OCBAS[107] favoured neither stent nor PTCA (*Figure 24*).

Health-related quality of life
Generic and disease-specific health-related quality of life were measured at between 6 and 18 months in the STRESS trial[87] using the Short Form 36 (SF-36), a modification of the Rose Angina Questionnaire, with functional status assessed by modified versions of the Duke Activity Status Index and the Canadian Cardiovascular Society Classification. There were 160 (80%) responders out of 199 consecutive patients. The stent group had significantly better scores on the SF-36 bodily

pain index. There were, however, no other differences in generic or disease-specific health-related quality of life, although 88% of the stent group reported that bodily pain did not interfere with normal work compared with 73% of the PTCA group ($p < 0.05$).

Long-term outcomes summary
Relatively few trials have yet reported long-term outcomes. Stenting was generally associated with lower event rates at 1 year or longer, although this was not the case in the only 5 year follow-up. No conclusions could be drawn on death rates, and what evidence there was indicated no difference between stents and PTCA in MI rates. Evidence

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Study	Event rate			Weight (%)	Peto OR (95% CI, fixed)
	Experiment (*n/N*)	Control (*n/N*)			
BENESTENT	60/259	81/257		21.1	0.66 (0.45 to 0.97)
BENESTENT II	65/413	92/410		26.2	0.65 (0.46 to 0.92)
SICCO (CO)	14/58	35/59		5.9	0.24 (0.11 to 0.50)
START	38/225	63/211		16.0	0.48 (0.31 to 0.75)
STRESS	51/205	61/202		16.7	0.77 (0.50 to 1.18)
Versaci	8/60	18/60		4.2	0.38 (0.16 to 0.90)
WIDEST	32/154	28/146		9.9	1.10 (0.63 to 1.94)
Total (95% CI)	268/1374	378/1345		100.0	0.62 (0.52 to 0.74)

Chi-square 14.10 (df = 6) *Z* = 5.28

0.1 0.2 1 5 10

Favours treatment   Favours control

FIGURE 18 *Event rates, variable follow-up (≥ 1 year): stent compared with PTCA in IHD*

Study	Death rate			Weight (%)	Peto OR (95% CI, fixed)
	Experiment (*n/N*)	Control (*n/N*)			
BENESTENT 5 year	15/248	8/243		40.4	1.85 (0.80 to 4.27)
STRESS	3/205	4/202		12.7	0.74 (0.17 to 3.28)
OCBAS (Provis)	0/57	1/59		1.8	0.14 (0.00 to 7.06)
Versaci	1/60	1/60		3.6	1.00 (0.06 to 16.18)
START	6/225	5/211		19.7	1.13 (0.34 to 3.73)
BENESTENT II	4/413	4/410		14.6	0.99 (0.25 to 3.99)
SICCO (CO)	1/58	3/59		7.2	0.36 (0.05 to 2.66)
Total (95% CI)	30/1266	26/1244		100.0	1.13 (0.67 to 1.93)

Chi-square 4.03 (df = 6) *Z* = 0.46

0.1 0.2 1 5 10

Favours treatment   Favours control

Provis = provisional stenting

FIGURE 19 *Death rates, variable follow-up (≥ 1 year): stent compared with PTCA in IHD*

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	MI rate				Weight (%)	Peto OR (95% CI, fixed)
Study	**Experiment** (*n/N*)	**Control** (*n/N*)				
SICCO (CO)	1/58	2/59			2.6	0.52 (0.05 to 5.06)
BENESTENT 5 year	22/248	14/243			30.0	1.58 (0.80 to 3.11)
STRESS	13/205	16/202			24.2	0.79 (0.37 to 1.68)
Versaci	3/60	4/60			6.0	0.74 (0.16 to 3.39)
START	5/225	6/211			9.6	0.78 (0.23 to 2.57)
BENESTENT II	14/413	18/410			27.6	0.77 (0.38 to 1.55)
Total (95% CI)	58/1209	60/1185			100.0	0.95 (0.65 to 1.37)
Chi-square 3.24 (df = 5) Z = 0.29						

```
        0.1 0.2    1    5  10
      Favours treatment   Favours control
```
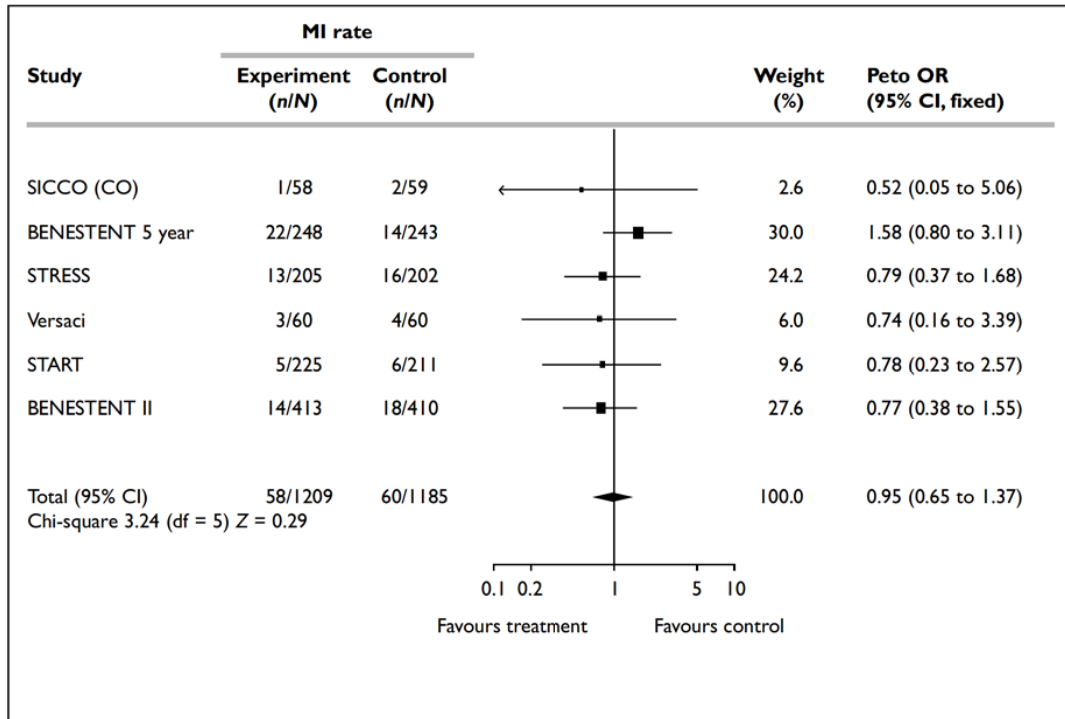
FIGURE 20 *MI rates, variable follow-up (≥ 1 year): stent compared with PTCA in IHD*

	Angina rate				Weight (%)	Peto OR (95% CI, fixed)
Study	**Experiment** (*n/N*)	**Control** (*n/N*)				
BENESTENT	43/259	37/257			43.1	1.18 (0.73 to 1.90)
STRESS	26/161	25/155			27.3	1.00 (0.55 to 1.82)
Versaci	6/60	15/60			11.1	0.36 (0.14 to 0.91)
SICCO (CO)	33/58	33/59			18.5	1.04 (0.50 to 2.15)
Total (95% CI)	108/538	110/531			100.0	0.97 (0.71 to 1.32)
Chi-square 5.08 (df = 3) Z = 0.22						

```
        0.1 0.2    1    5  10
      Favours treatment   Favours control
```
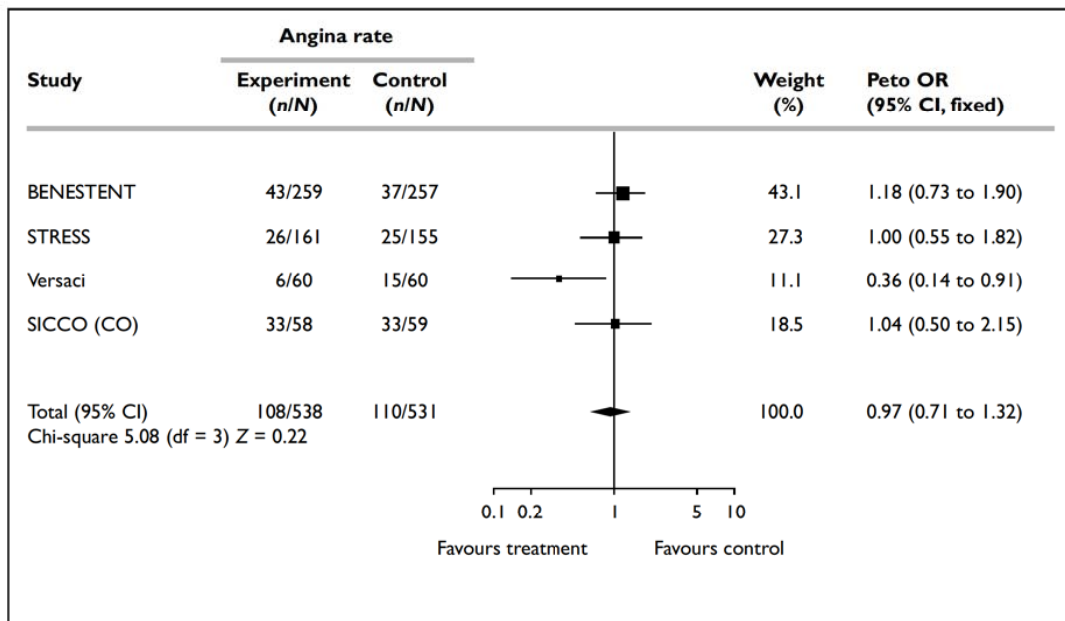
FIGURE 21 *Angina rates, variable follow-up (≥ 1 year): stent compared with PTCA in IHD*

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Study	TVR rate			Weight (%)	Peto OR (95% CI, fixed)
	Experiment (*n/N*)	Control (*n/N*)			
BENESTENT 5 year	43/248	66/243		27.5	0.57 (0.37 to 0.87)
STRESS	24/205	38/202		17.1	0.58 (0.34 to 0.99)
START	27/225	52/211		21.0	0.43 (0.26 to 0.70)
AS Trial	31/192	48/196		20.4	0.60 (0.37 to 0.98)
SICCO (CO)	14/58	31/59		9.0	0.30 (0.14 to 0.64)
OCBAS (Provis)	10/57	8/59		5.0	1.35 (0.50 to 3.68)
Total (95% CI)	149/985	243/970		100.0	0.53 (0.43 to 0.67)
Chi-square 6.68 (df = 5) *Z* = 5.50					

0.1 0.2   1   5   10

Favours treatment   Favours control
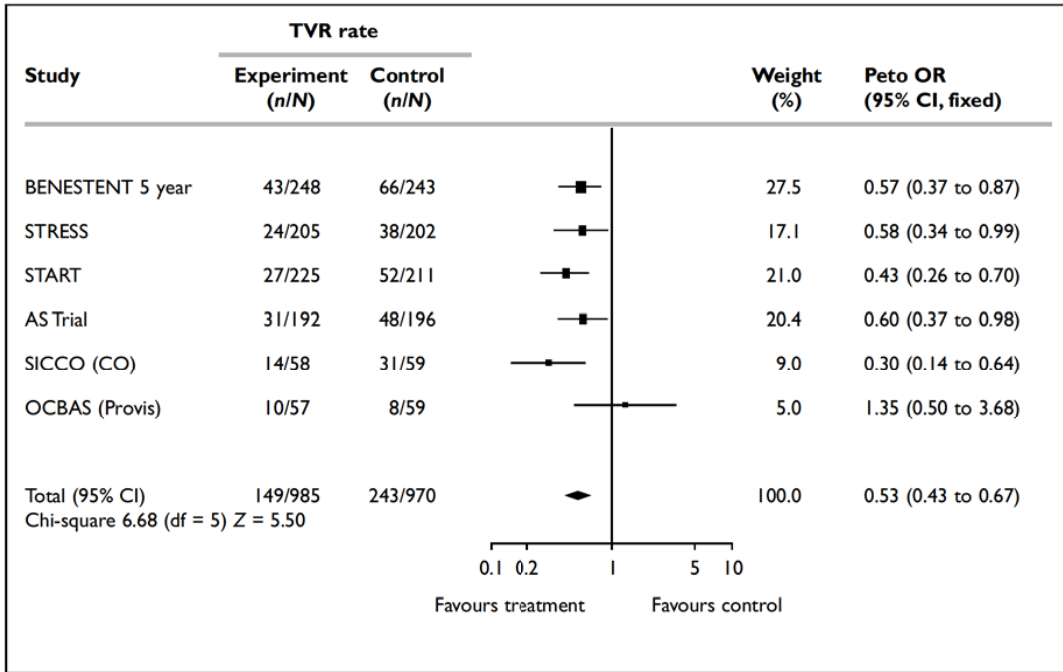
FIGURE 22 *TVR rates, variable follow-up (≥ 1 year): stent compared with PTCA in IHD*

Study	CABG rate			Weight (%)	Peto OR (95% CI, fixed)
	Experiment (*n/N*)	Control (*n/N*)			
BENESTENT 5 year	30/248	23/243		43.2	1.31 (0.74 to 2.32)
STRESS	12/205	18/202		25.4	0.64 (0.30 to 1.34)
Versaci	4/60	3/60		6.1	1.35 (0.30 to 6.18)
BENESTENT II	8/413	6/410		12.6	1.33 (0.46 to 3.82)
SICCO (CO)	5/58	4/59		7.6	1.29 (0.33 to 5.01)
OCBAS (Provis)	4/57	2/59		5.2	2.08 (0.41 to 10.70)
Total (95% CI)	63/1041	56/1033		100.0	1.12 (0.77 to 1.63)
Chi-square 3.24 (df = 5) *Z* = 0.61					

0.1 0.2   1   5   10

Favours treatment   Favours control

FIGURE 23 *CABG rates, variable follow-up (≥ 1 year): stent compared with PTCA in IHD*

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Study	PTCA rate			Weight (%)	Peto OR (95% CI, fixed)
	Experiment (*n/N*)	Control (*n/N*)			
BENESTENT	26/259	53/257		24.4	0.44 (0.27 to 0.71)
STRESS	39/205	42/202		23.6	0.90 (0.55 to 1.46)
Versaci	4/60	13/60		5.4	0.29 (0.11 to 0.82)
BENESTENT II	39/413	64/410		32.8	0.57 (0.38 to 0.86)
SICCO (CO)	12/58	30/59		9.9	0.27 (0.13 to 0.58)
OCBAS (Provis)	6/57	6/59		3.9	1.04 (0.32 to 3.42)
Total (95% CI)	126/1052	208/1047		100.0	0.55 (0.43 to 0.69)
Chi-square 10.55 (df = 5) *Z* = 4.99					

0.1 0.2   1   5 10

Favours treatment   Favours control

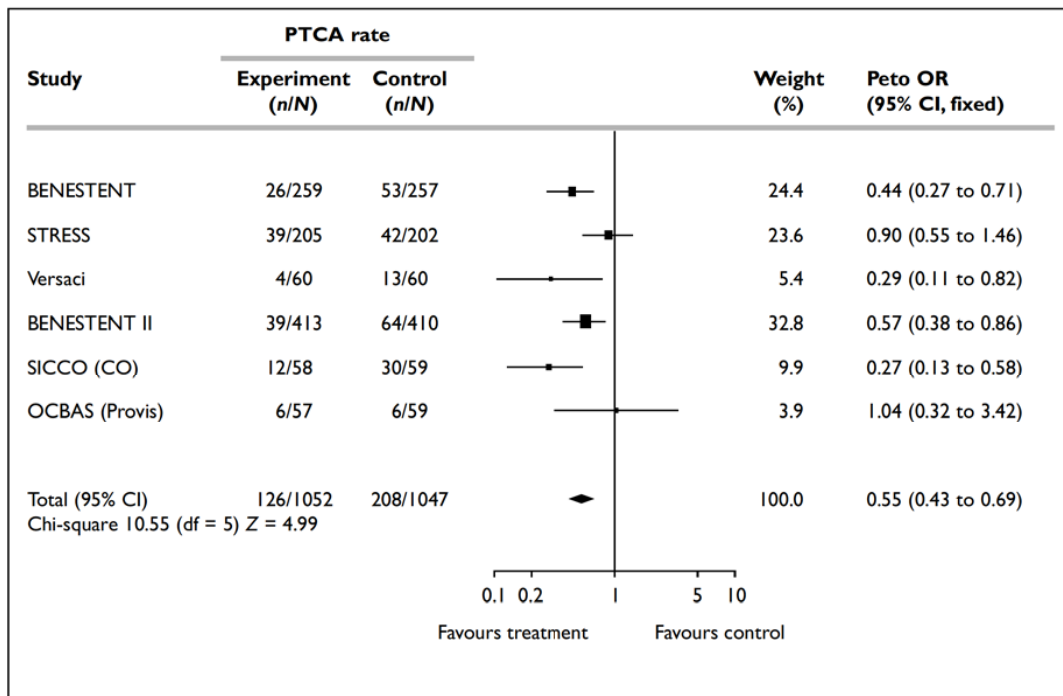**FIGURE 24** *PTCA rates, variable follow-up (≥ 1 year): stent compared with PTCA in IHD*

on angina was conflicting, although no trials favoured PTCA. Stent was associated with a relative reduction in revascularisation rates.

Summary
The trials broadly favoured stents over PTCA in trials of planned stenting. There are, however, some caveats.

- The nature of intervention meant that neither clinicians nor patients could be blinded to treatment, and so the trials may be biased in favour of stent to some degree.
- Most of the trials allowed some crossover to stent from PTCA – in some trials to the extent that effectively different stenting policies (immediate or provisional) were under review, not a straight choice between stent and PTCA.
- The trials individually and collectively did not have the statistical power to provide precise outcomes on mortality and MI, which are relatively rare but important outcomes.
- Event rates favourable to stents reflected reduced intervention rates, not reduced mortality or coronary events.
- Although angina is an important outcome, it was not often reported, results were

inconsistent, and little can be said about the impact of stents on the recurrence of angina or its severity.

Effectiveness of elective stenting compared with CABG in subacute IHD
Trial reporting
Each of the three trials[120–122] is reported as an abstract only. Letters were sent to all three trialists but no replies were received.

Patients
The largest trial (ERACI II[120]) included only people with multi-vessel disease. The other two trials included LAD lesions only (see appendix 5, page 101).

Interventions
One of the trials (Spyrantis[122]) compared a new technique of minimally invasive CABG with stents. The other two trials used standard CABG (see appendix 5, page 101).

Trial quality
Because only abstracts were available, details of trial design were not available. Each of the trials had a Jadad score of 1, possibly as a consequence of lack of full publication (see appendix 5,

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page 103). None of the trials reported the proportion of eligible patients randomised (see appendix 5, page 102). Baseline characteristics were reported to be similar in both arms of each of the three trials (see appendix 5, page 102). One trial, ERACI II,[120] reported statistically significant differences in favour of stent for 30-day event rate, deaths and MI. The SIMA[121] trial, however, found no such differences in in-hospital outcome (see appendix 5 pages 104 and 105).

The one trial (SIMA[121]) that reported complications found a significant difference in favour of stents for an outcome that included major bleeding and arrhythmias.

Angiographic outcomes
Angiographic follow-up is not fully reported in this group of trials. The only trial[122] to report restenosis rates at follow-up shows a larger restenosis rate for the stent group compared with the CABG group (see appendix 5, page 106).

Medium term (4 to 11 months) clinical outcomes
Very few results are available for these three trials. ERACI II[120] shows a significantly higher rate of TVR in the stent group and Spyrantis[122] shows a significantly higher rate of repeat PTCA in the stent group at 6 months follow-up (see appendix 5, page 107). No numbers for outcomes death, MI or angina rate were given in the reports of any of the trials.

No results beyond 6 months were available.

Summary
Full evaluation of stent against CABG in CAD must await completion of trials in progress and full publication.

Results so far indicate that stenting is associated with higher re-intervention rates at 6 months than CABG.

Effectiveness of stents compared with PTCA in acute MI
Trial reporting
Of the seven trials in this category, three[119,123,124] have been fully reported in peer-reviewed journals. Letters were sent to the investigator for the other four trials,[125–128] which resulted in three replies, including page proofs (PASTA[125]), a manuscript (STENTIM II[128]) and a further abstract (PSAAMI[127]). The largest trial by far in this group is the PAMI-Stent trial.[126] Although this trial appears to have finished recruiting and

follow-up, it has not been fully published at the time of writing. Twenty-five abstracts were available for this trial, and those that appeared to be based on completed recruitment were used to abstract data. It was impossible to identify the number of patients in each arm of the PSAAMI trial at follow-up, and data from this trial could not be used in meta-analyses.

Patients
All of the trials include patients within 12–24 hours of MI symptom onset in whom the culprit lesion is in a 'stentable' artery. Cardiogenic shock is included in some of the trials (GRAMI,[119] FRESCO,[123] PSAAMI[127]) and excluded in others (PAMI-Stent.[126] STENTIM II[128]) (see appendix 5, pages 108–109).

Interventions and comparators
Stent
The type of stent used varied (Palmaz-Schatz, Gianturco-Roubin, Wiktor). One trial used a heparin-coated stent (PAMI-Stent[126]) and one used a silicon carbide-coated Tantal stent (PSAAMI[127]) (see appendix 5, pages 108–109).

Antithrombotic regimens
Most of the trials used ticlopidine rather than anticoagulation, but the ESCOBAR[124] trial changed from warfarin to ticlopidine after 20% patients had been treated. In the PSAAMI trial,[127] abciximab was used in approximately 50% patients (see appendix 5, pages 108–109).

Comparators
PTCA was the comparison in all trials, with stenting conditional upon initial PTCA in the PTCA arm of the STENTIM II trial[128] (appendix 5, pages 108–109).

Crossovers
Rates of crossover in the stent arms of the trials ranged from 0% to 3%, whereas in the PTCA arms they ranged from 0% to 36%. Thus in the PTCA arms of the trials, the chances of patients receiving the intervention rather than the control treatment varied (see appendix 5, page 110).

Trial quality
The Jadad scores[53] ranged from 1 to 3 (see appendix 5, page 111). It is possible that the low scores of PSAAMI[127] and PAMI-Stent[126] reflect reporting in abstract form rather than poor execution in terms of concealment of allocation and follow-up, but without full publication, quality cannot be assumed to be high. As patients and

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clinicians cannot be blinded to treatment in these trials, it is possible that some degree of bias has entered into trial execution and reporting.

Short-term clinical outcomes

Two out of the three trials that reported short-term event rates (GRAMI[119] and PASTA[125]) found significant differences in favour of stent (see appendix 5, page 113). Event rate definitions are given in appendix 5 (page 94). None of the trials reported significant differences in deaths or MI, and the differences that did exist arose from differences in re-intervention rates (see appendix 5, page 113). The PAMI-Stent[126] and FRESCO[123] trials found significant differences in TVR in favour of stents.

Definitions of major bleed vary between the trials. Where descriptions of bleeding complications were given, major bleed was taken to include any bleeding that had resource implications (e.g. need for vascular repair or blood transfusion). There were no significant differences in bleeding complications reported in any of the trials (see appendix 5, page 112). This may reflect the use of ticlopidine, rather than intensive anticoagulant therapy, in these trials.

Angiographic outcomes

Angiographic results from three trials (FRESCO,[123] PASTA,[125] STENTIM II[128]) all show a statistically significant improvement for the stent group compared with the PTCA group post-procedure and at follow-up (6 months) (see appendix 5, page 114).

Clinical outcomes at 6 to 12 months

Two trials, FRESCO[123] and ESCOBAR,[124] reported at 6 months only. One trial, GRAMI,[119] reported at 1 year only, whereas PASTA,[125] PAMI-Stent[126] and PSAAMI[127] reported at 6 and 12 months. Results at both 6 months (see appendix 5, pages 115 and 116) and 12 months (see appendix 5, pages 117 and 118) are reported in the tables in appendix 5, but the results at 12 months are used in preference to those at 6 months in the meta-analyses.

Event rate

There were lower event rates in the stent group (summary OR, 0.39; 95% CI, 0.28 to 0.54) with no heterogeneity (see *Figure 25*). This yielded numbers needed to treat ranging from 4 in PASTA[125] to 12 in STENTIM II.[128]

Death rate

In all seven trials, there were no significant differences in death rates between the stent and PTCA groups. Death is a relatively rare outcome at this period of follow-up, and as indicated by the CIs in *Figure 26*, the trials are not powerful enough collectively to provide any evidence on this outcome.

Study	Event rate			Weight (%)	Peto OR (95% CI, fixed)
	Experiment (n/N)	Control (n/N)			
ESCOBAR	6/112	23/115		17.8	0.27 (0.12 to 0.59)
FRESCO	10/75	24/75		18.6	0.35 (0.16 to 0.74)
GRAMI	9/52	18/52		14.2	0.41 (0.17 to 0.98)
PASTA	15/67	34/69		22.2	0.31 (0.16 to 0.63)
STENTIM II	20/101	31/110		27.2	0.63 (0.34 to 1.19)
Total (95% CI) Chi-square 3.62 (df = 4) Z = 5.59	60/407	130/421		100.0	0.39 (0.28 to 0.54)

0.1 0.2 1 5 10

Favours treatment   Favours control
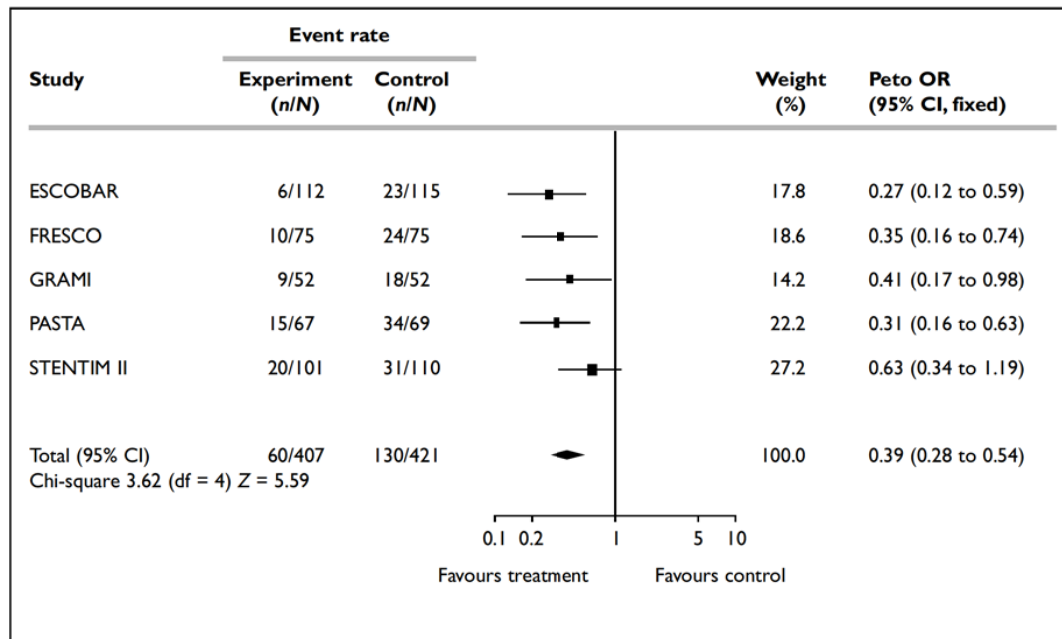
FIGURE 25 *Event rates, 6 to 12 months follow-up: stent compared with PTCA in AMI*

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	Death rate				Weight (%)	Peto OR (95% CI, fixed)
Study	**Experiment** (*n/N*)	**Control** (*n/N*)				
ESCOBAR	2/112	3/115			9.1	0.68 (0.12 to 4.01)
FRESCO	1/75	4/75			9.0	0.29 (0.05 to 1.72)
GRAMI	2/52	4/52			10.5	0.50 (0.10 to 2.56)
PAMI-Stent	15/448	11/444			46.7	1.36 (0.62 to 2.97)
PASTA	3/67	6/69			15.6	0.51 (0.13 to 1.95)
STENTIM II	3/101	2/110			9.0	1.64 (0.28 to 9.65)
Total (95% CI)	26/855	30/865			100.0	0.87 (0.51 to 1.49)
Chi-square 4.34 (df = 5) *Z* = 0.50						

0.1 0.2   1   5 10
Favours treatment   Favours control

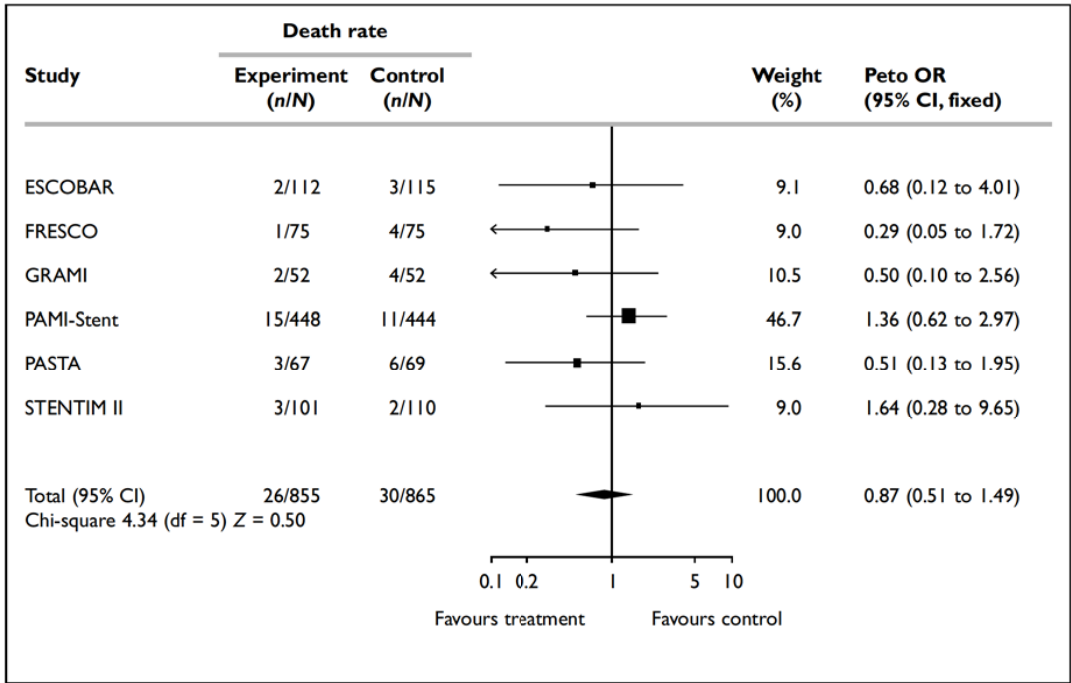**FIGURE 26** *Death rates, 6 to 12 months follow-up: stent compared with PTCA in AMI*

MI rate

As shown in *Figure 27* all trials that measured this outcome suggested benefit. However, only in ESCOBAR[124] was the result statistically significant. When the results of the trials were combined there was reduced MI in the stent group compared with the PTCA group, but it should be noted that the 95% CI for the summary OR still includes 1.0, that the result is based on a very small number of outcomes and that only

	MI rate				Weight (%)	Peto OR (95% CI, fixed)
Study	**Experiment** (*n/N*)	**Control** (*n/N*)				
ESCOBAR	1/112	8/115			17.6	0.20 (0.05 to 0.77)
FRESCO	1/75	2/75			6.0	0.51 (0.05 to 4.97)
PAMI-Stent	13/448	16/444			57.0	0.80 (0.38 to 1.68)
STENTIM II	4/101	6/110			19.4	0.72 (0.20 to 2.56)
Total (95% CI)	19/736	32/744			100.0	0.60 (0.34 to 1.05)
Chi-square 3.19 (df = 3) *Z* = 1.79						

0.1 0.2   1   5 10
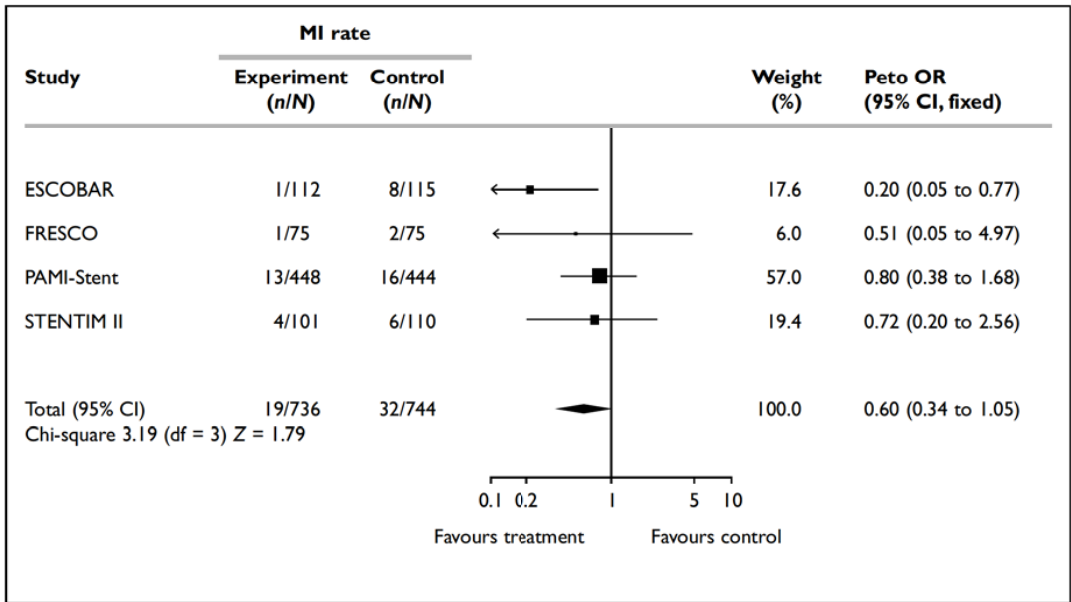Favours treatment   Favours control

FIGURE 27 *MI rates, 6 to 12 months follow-up: stent compared with PTCA in AMI*

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provisional results were available for the largest trial, PAMI-Stent.[126] Q wave and non-Q wave MI were not reported separately.

Angina rate

Only one trial reported angina rates at follow-up (PAMI-Stent[126]). There was a significant difference in angina status at 6 months, with 10.1% of the stent group having angina, in comparison with 15.5% of the PTCA group ($p < 0.05$) (calculated from reporting of diabetic and non-diabetic subgroup results).

TVR rate

When the trials were combined, there was a significant decrease in TVR rates for the stent group compared with the PTCA group (summary OR, 0.41; 95% CI, 0.31 to 0.56), with no heterogeneity in the results (see *Figure 28*).

CABG rate

There were only four CABGs in the two trials that reported this outcome, FRESCO[123] and STENTIM II,[128] and so the results provide no useful information on CABG rate.

Repeat PTCA

When the two trials reporting this outcome were combined, stenting was associated with a reduction in repeat PTCA rates with little

heterogeneity (summary OR, 0.44; 95% CI 0.26 to 0.74) (see *Figure 29*).

Summary

Of seven trials, three were published in peer-reviewed publications, for two information was obtained from authors, and for two (including the largest trial) publication was only in abstract form.

The trials consistently favoured stents over PTCA in trials of stenting in acute MI. There are, however, some caveats.

- The nature of intervention meant that neither clinicians nor patients could be blinded to treatment, so that the trials may be biased in favour of stent to some degree.
- Crossover rates from PTCA to stent ranged from 0% to 36%, indicating that different policies were operating with regard to crossover to stent in the PTCA arms of the trials.
- The trials individually and collectively did not have the statistical power to provide precise outcomes on mortality.
- There were no differences between stent and PTCA in reinfarction rates.
- Event rates favourable to stents largely reflected reduced intervention rates, not reduced mortality or coronary events.
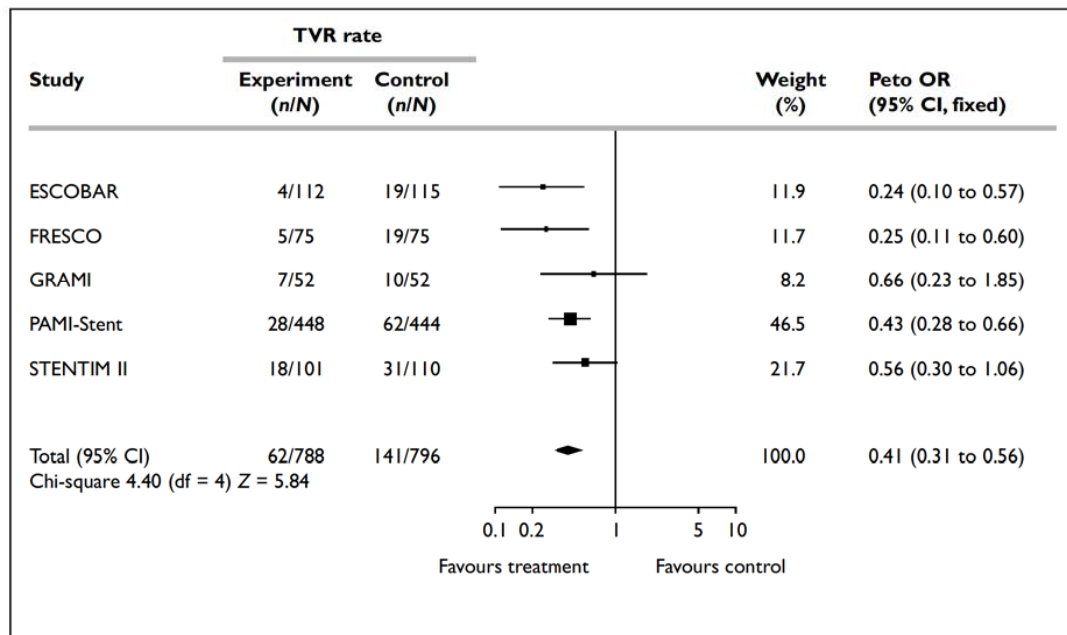
Study	TVR rate			Weight (%)	Peto OR (95% CI, fixed)
	Experiment (n/N)	Control (n/N)			
ESCOBAR	4/112	19/115		11.9	0.24 (0.10 to 0.57)
FRESCO	5/75	19/75		11.7	0.25 (0.11 to 0.60)
GRAMI	7/52	10/52		8.2	0.66 (0.23 to 1.85)
PAMI-Stent	28/448	62/444		46.5	0.43 (0.28 to 0.66)
STENTIM II	18/101	31/110		21.7	0.56 (0.30 to 1.06)
Total (95% CI)	62/788	141/796		100.0	0.41 (0.31 to 0.56)
Chi-square 4.40 (df = 4) Z = 5.84					

0.1 0.2   1   5   10

Favours treatment   Favours control

FIGURE 28 *TVR rates, 6 to 12 months follow-up: stent compared with PTCA in AMI*

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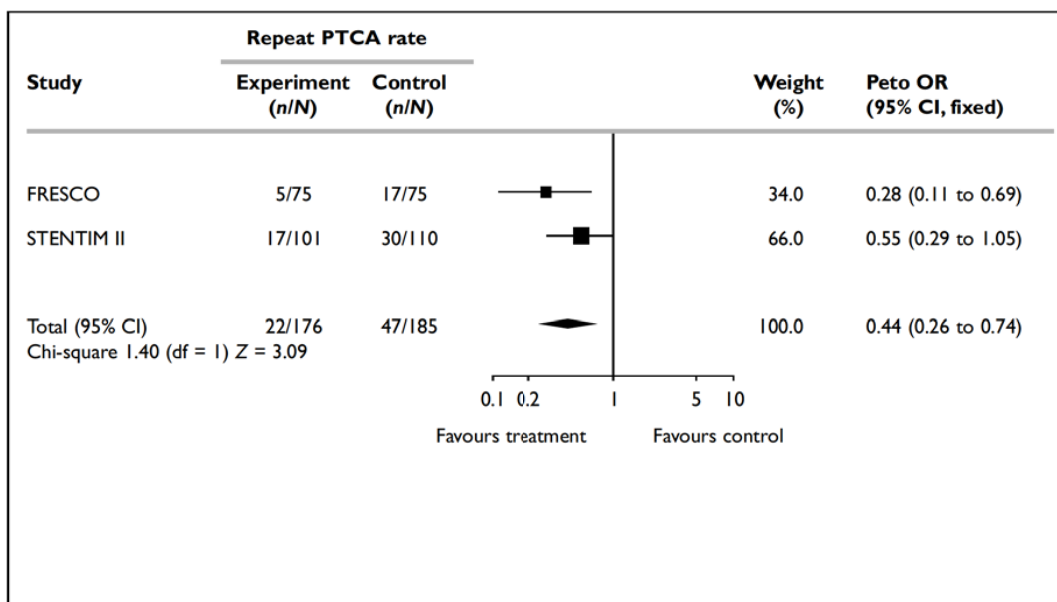|	Repeat PTCA rate				
Study	Experiment (n/N)	Control (n/N)		Weight (%)	Peto OR (95% CI, fixed)
FRESCO	5/75	17/75		34.0	0.28 (0.11 to 0.69)
STENTIM II	17/101	30/110		66.0	0.55 (0.29 to 1.05)
Total (95% CI)	22/176	47/185		100.0	0.44 (0.26 to 0.74)
Chi-square 1.40 (df = 1) Z = 3.09					

FIGURE 29 *Repeat PTCA rates, 6 to 12 months follow-up: stent compared with PTCA in AMI*

- The only trial that considered angina found in favour of stent. This trial has not as yet been fully published at the time of writing.

Results of economic evaluations review

Studies reporting costs
Number of studies
Nine studies reported the costs of PTCA in the UK. Five of these also reported stent costs and seven reported the cost of CABG. Four of the studies are included in the section on cost-effectiveness analyses. Three RCTs from the clinical effectiveness review are included in the cost-effectiveness/cost–utility review.[70,116,129]

Design of cost studies
The cost studies came from a variety of study types. Studies either presented costs only[130] or were part of cost-effectiveness studies.[1,131–137] Most provided minimal detail on costing methods used. As a result, important factors such as bailout stenting and trends towards using multiple stents may not have been taken into account. Costs were obtained from three systematic reviews.[1,132,133] The most detailed cost analysis was a micro-costing study,[131] which we have used as the pivotal study. The costs from this study lie midway in the range of hospital costs.

NHS costs for PTCA, stents and CABG
The costs for PTCA, PTCA with stent and CABG are shown in *Table 6* and in detail in appendices 6–8 (pages 119–126).

The costs in the appendices are presented in date order (earliest first). A separate table shows the current prices of some stents. The costs have been separated into three main groups for each intervention:

- Costs for the procedure include staff time and equipment costs used during the procedure itself.
- Hospital costs include length of stay in hospital and associated costs in addition to procedural costs.
- Wider costs include in addition the treatment costs incurred during the follow-up of a cohort of patients for a specified length of time following the initial procedure and include the procedure and hospital costs.

The costs should increase as more factors are taken into account. However, the summary of costs does not show this trend. Apparently, for stents the wider costs are less than the procedure costs and hospital costs. This is an anomaly resulting from the small number of studies contributing information to particular cells in *Table 6*.

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TABLE 6 *Summary of costs (in £) for PTCA, stent and CABG*

	PTCA			Stents			CABG		
	Procedure only	Hospital costs	Wider costs	Procedure only	Hospital costs	Wider costs	Procedure only	Hospital costs	Wider costs
Mean	2408	2850	3156	4700*	4340	3999*	5144	6028	5065*
Range	1053–4944	1125–4325	2683–3630	–	2664–5697	2484–5290	2105–9123	3197–10,770	–
Number of data sources	7	9	2	1	5	2	5	9	1
Pivotal study[131]	–	2357	–	–	4144†	–	–	5539	–

* *Caution required in interpreting these figures as they are based on small numbers of studies (see text for further discussion)*
† *Cost for a repeat PTCA and stent*

The difference in mean hospital cost between stent and PTCA is £1490, and for the pivotal study £1787. However for the figure from the pivotal study it should noted that this is based on costs for a **repeat** PTCA with stent (mean cost £4144), and is hence likely to be an overestimate of the true difference. The difference in mean costs, for the wider cost studies, is £843. Again this may be biased by the small number of studies ($n = 2$). However, in the most recent study, examining wider costs in both PTCA and stents, the cost differential was £919.[1] Thus it seems reasonable to conclude that the cost differential between PTCA and stent is less for wider costs than for procedural costs.

PTCA procedure costs appear to increase over time. However, there are no time trends in hospital and wider costs. This is also true of the procedural, hospital and wider costs of stents. This is likely to be an artefact because of the small number of studies available. The trends of stent prices appear to be decreasing over time (information from industry data on file). The main variation in the data appears to be the variation in costs from different sources.

The difference in mean hospital cost between CABG and stent is £1688, and for the pivotal study £1395. Because of the limitations of the information available it is impossible to comment on the difference between wider costs. There do not appear to be any time trends in the procedural, hospital or wider costs but even fewer data were available than for stents versus PTCA.

Studies reporting cost-effectiveness/ cost–utility
Number of studies
A total of 16 studies that compared the cost-effectiveness of coronary stenting with PTCA were

identified. In all except one, the comparison arm was PTCA, but in the OPUS study the comparison was between PTCA and provisional stenting. One further study comparing the cost-effectiveness of stenting with that of CABG in multi-vessel disease was identified.[70]

Few of the studies are directly comparable. They are based on a range of effectiveness data, costs have been collected at different time periods, they use a range of outcome measures, and the PTCA groups compared with stenting used a spectrum of policies from all PTCA, to PTCA with bailout stenting, or provisional stenting.

Study design
Six of the studies were cost-effectiveness analyses,[18,27,70,134,138–146] six were cost–utility analyses[1,133,146–150] and five reported costs and outcomes separately.[116,137,151–153] Three studies were RCTs,[27,70,116] five were observational studies[134,137,151–153] and eight used modelling techniques.[18,133,138–150]

Appendix 9 (page 127) shows the characteristics of the studies and the type of cost-effectiveness analysis used. The studies based on models are tabulated in detail in appendix 10 (pages 129–132) and the individual studies are tabulated in appendix 11 (page 133–137). We concentrated on the cost-effectiveness and cost–utility analyses. We did not examine in depth the studies in which the costs and outcomes were reported separately because they were mainly based on observational effectiveness data. These have the advantage of reporting current routine practice, and thus may produce results that are more generalisable. They have the major disadvantage of potential bias due to baseline differences in the groups. Three of the studies provide sufficient baseline