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R Hill, A Bagust, A Bakhai, R Dickson, Y Dündar, A Haycox, R Mujica Mota, A Reaney, D Roberts, P Williamson and T Walley

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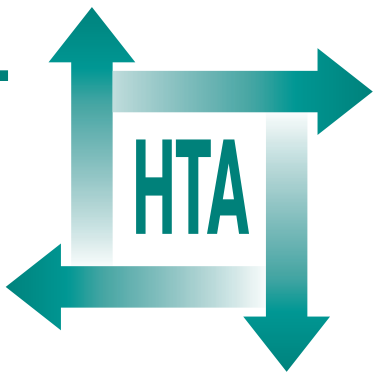

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Abstract

Coronary artery stents: a rapid systematic review and economic evaluation

R Hill,[1] A Bagust,[1] A Bakhai,[2] R Dickson,[1*] Y Dündar,[1] A Haycox,[1] R Mujica Mota,[1] A Reaney,[3] D Roberts,[4] P Williamson[5] and T Walley[1]

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Objectives: To assess the effectiveness and cost-effectiveness of the use of coronary artery stents in patients with coronary heart disease (CHD).
Data sources: Electronic databases.
Review methods: The review was conducted following accepted guidelines for conducting systematic reviews. Randomised controlled trials that include comparisons of percutaneous transluminal coronary angioplasty (PTCA) versus PTCA with stent, stent versus coronary artery bypass graft (CABG), and drug-eluting stents (DES) versus non-DES in patients with CAD in native or graft vessels and those with stable angina or acute coronary syndrome (ACS) and unstable angina were also included. Data on the following outcome measures were included in the review: combined event rate or event-free survival, death, acute myocardial infarction, target vessel revascularisation, repeat treatment (PTCA, stent or CABG) and binary restenosis. An economic model was developed based on extrapolation of trends in mortality and revascularisation from clinical trials data to a 5-year time horizon.
Results: The inclusion criteria were fulfilled by 50 studies comparing the use of stents with PTCA, six comparing stents with CABG and 12 comparing DES eluting stents with non-DES. No studies were identified that compared DES with PTCA or DES with CABG. Existing quality of life data suggest that revascularisation procedures reduce the patient's quality of life for a short period only. Stents were found to be more effective than PTCA in preventing adverse events and revascularisations. In multiple-vessel disease there was no evidence of a difference in mortality (at 1 year) between patients treated surgically and those receiving a stent. Patients treated surgically required fewer revascularisations. There is no evidence of a difference in mortality between patients receiving DES and those treated with bare metal stents at 1 year. A reduction in event rate at 9 and 12 months was found in patients treated with DES. This event rate is primarily made up of increased revascularisation rates in patients treated with bare metal stents. Two-year outcome data from one study indicate that this benefit of DES continues over the longer term. The economic model proved sufficient to indicate long-term trends in cost-effectiveness. CABG was found initially to be more expensive than bare metal stenting in multivessel disease and may have higher immediate risks, but over time the cost differential is reduced and long-term outcomes favour CABG over stenting. A similar situation was found for DES versus CABG in multiple-vessel disease. However, DES may not generally be considered a cost-effective alternative to bare metal stenting in single-vessel disease by policy makers as substantially higher costs are involved with a very small outcome benefit.
Conclusions: DES might be considered cost-effective if the additional cost (compared with ordinary stents) was substantially reduced, the outcome benefits from the use of DES were much improved, and/or its use were targeted on the subgroups of patients with the highest risks of requiring reintervention. Long-term clinical studies are needed that focus on significant outcomes such as mortality. Further research should consider: the differences among plain stents; head-to-head comparisons within DES,

CABG compared with DES; and the evaluation of newer non-DES against DES. Evaluation of the effects of revascularisation procedures and especially repeat revascularisation procedures on the patient's quality of life would also be useful, as would the development and testing of risk assessment tools to identify patients likely to need further revascularisations.

Contents

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, widely used during stenting procedures.

Acute coronary syndrome (ACS) Syndrome that includes coronary events previously referred to as unstable angina, non-ST-segment elevation myocardial infarction and ST elevation myocardial infarction.

Angina Pain (usually chest) resulting from lack of oxygen supply to heart muscle.

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

Atherosclerosis Disease of the arteries in which fatty plaques develop in the inner walls leading to reduced blood flow or obstruction.

Bailout stent Stent inserted as an emergency during percutaneous transluminal coronary angioplasty because of dissection of the vessel wall.

Binary restenosis Refers to the percentage of lesions with greater than 50% luminal narrowing following balloon angioplasty or stenting.

Braunwald classification Classification of unstable angina.

Cardiac catheterisation Passing of a catheter from a femoral or radial artery into coronary arteries for diagnosis and/or treatment.

Clopidogrel Drug that inhibits platelet function.

Creatinine kinase A cardiac enzyme release during myocardial infarction.

De novo **lesion** A coronary lesion not previously treated.

Direct stenting Stent implantation without predilation.

Drug-coated stent Stent with a drug or substance that adheres to the stent.

Drug-eluting stent Stent with a drug that elutes into tissue at the placement site.

Elective Non-emergency treatment.

In-stent restenosis A renarrowing or blockage of an artery within a stent.

IVUS Method using intravascular ultrasound to visualise a full 360° circumference of the vessel and provides direct measurement of the diameter of the artery.

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

Minimally invasive coronary artery bypass grafting Technique using a small thoracotomy and not necessarily involving stoppage of the heart with bypass.

Neo-intimal hyperplasia Excessive growth of smooth muscle tissue.

Ostial lesion Lesion of the ostium of a coronary artery.

Provisional angioplasty Angioplasty that satisfies predefined criteria of optimal results (based on pressure gradients, early loss of minimal lumen diameter or intravascular ultrasound measurements).

Provisional stenting Stent placement depending on suboptimal result from percutaneous transluminal coronary angioplasty

continued

Glossary *continued*

Q-wave An abnormal wave on ECG indicating previous myocardial damage.

Recoil (stent) A measure of the elastic contraction that a stent experiences when balloon is deflated.

Restenosis A renarrowing or blockage of a coronary artery.

Revascularisation Maintaining or improving coronary artery blood supply.

Stent Small prosthesis inserted into a coronary artery to maintain the lumen and blood flow.

Thrombus Blood clot.

Ticlopidine Drug that inhibits platelet function.

List of abbreviations

ACC	American College of Cardiology
ACS	acute coronary syndrome
AE	Accident and Emergency
AHA	American Heart Association
AMI	acute myocardial infarction
ARTS	Arterial Revascularisation Therapy Study
BARI	Bypass Angioplasty Revascularisation Investigation
BCIA	British Cardiovascular Industry Association
BCIS	British Cardiac Intervention Society
BCS	British Cardiac Society
BHF	British Heart Foundation
BMS	bare metal stents
BRR	binary restenosis rate
CABG	coronary artery bypass graft(ing)
CAD	coronary artery disease
CCSC	Canadian Cardiovascular Society Classification
CCTR	Cochrane Trials Register
CCU	coronary care unit
CDSR	Cochrane Database of Systematic Reviews
CEA	cost-effectiveness analysis
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CIC	commercial in confidence
CRD	Centre for Reviews and Dissemination
CTO	chronic total occlusion
CUA	cost–utility analysis
CVA	cerebrovascular accident (stroke)
DARE	Database of Abstracts of Reviews of Effectiveness
DES	drug-eluting stent
DM	diabetes mellitus
EF	ejection fraction
FDA	Food and Drug Administration, US Department of Health and Human Services

continued

List of abbreviations *continued*

FED	finished consultant episode
GI	gastrointestinal
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
ISR	in-stent restenosis
ITT	intention-to-treat
i.v.	intravenous
IVUS	intravascular ultrasound
LAD	left anterior descending
LM	left main
LRIG	Liverpool Reviews and Implementation Group
LVEF	left ventricular ejection fraction
MACCE	major adverse cardiac and cerebral events
MACE	major adverse cardiac events
MI	myocardial infarction
MIDCAB	minimally invasive direct vision coronary artery bypass
MLD	minimal lumen diameter
NHSEED	NHS Economic Evaluation Database
NICE	National Institute for Clinical Excellence
NSF	National Service Framework
OR	odds ratio
PCI	percutaneous coronary intervention (includes PTCA, stenting, atherectomy, excimer laser, rotablator)
PTCA	percutaneous transluminal coronary angioplasty
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RVD	reference vessel diameter
SA	sensitivity analysis
SCTS	Society of Cardiothoracic Surgeons
SOS	Stent or Surgery
SVG	saphenous vein graft
TIMI	thrombolysis in myocardial infarction
TLR	target lesion revascularisation
TTO	time trade-off
TVF	target vessel failure
TVR	target vessel revascularisation

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Objectives

To assess the effectiveness and cost-effectiveness of the use of coronary artery stents in patients with coronary heart disease (CHD).

Specifically, the review compares the use of:

- stent versus percutaneous transluminal coronary angioplasty (PTCA)
- stent versus coronary artery bypass graft (CABG)
- drug-eluting stents (DES) versus non-DES.

Background

CHD is a major cause of morbidity and mortality in the UK. Treatment models include medical management, percutaneous interventions (PCI) and surgery. Although PCI provides initial relief of symptoms, there is a high rate of restenosis and need for repeat treatment. There has been rapid evolution of treatment in the area of coronary artery stents, including the development of drug-eluting stents (DES).

The rapid developments in stenting in the treatment of coronary artery disease (CAD) have made it necessary to re-examine the available research evidence to inform national guidance.

Methods

The review was conducted following accepted guidelines for conducting systematic reviews, including the identification of clinical and economic studies, application of inclusion criteria, quality assessment of included studies and data extraction and analysis.

Inclusion criteria

Randomised controlled trials that include comparisons of PTCA versus PTCA with stent, stent versus CABG and non-DES versus-DES in patients with CAD in native or graft vessels and those with stable angina or acute coronary syndrome (ACS) and unstable angina were included in the review. Data on the following outcome measures were included in the review: combined event rate or event-free survival, death, acute myocardial infarction (AMI), target vessel revascularisation, repeat treatment (PTCA, stent or CABG) and binary restenosis.

Full economic evaluations that compared two or more options and considered both costs and consequences, including cost-effectiveness, cost–utility analysis or cost–benefit analysis undertaken in the context of high-quality randomised controlled trials, were included in the review.

Clinical findings

Sixty-eight studies fulfilled the inclusion criteria. These included 50 studies comparing the use of stents with PTCA, six comparing stents with CABG and 12 comparing DES eluting stents with non-DES. No studies were identified that compared DES with PTCA or DES with CABG.

Studies included a variety of stent designs and eluting drugs. In the surgical trials both standard and minimally invasive surgical techniques were reported.

Mortality is a rare event and none of the included studies was powered to assess effectiveness of the treatment in relation to this outcome. The primary outcome in all studies was either a composite end-point such as major adverse cardiac (and/or cerebrovascular) events, a composite event rate made up of death, AMI and revascularisation or revascularisation rate.

Definition of revascularisation rates varied across studies, with some including all target lesion or vessel revascularisation (whether need was clinically or angiographically identified), others reporting only clinically driven rates and others reporting a mix of both. No studies reported total revascularisation (e.g. repeat treatments carried out on target vessels or lesions and treatment to any other vessel).

Studies were not powered to assess effectiveness across groups of high-risk patients (i.e. patients with diabetes, patients with long lesions). Data on subgroups of high-risk patients have been presented within study reports but were not available for further analysis.

Existing quality of life data suggest that revascularisation procedures reduce the patient's quality of life for a short period only.

PTCA versus stent

Data analysis was carried out with studies grouped according to patient characteristics (non-specific, AMI, totally occluded vessels and small vessels).

Stents are more effective than PTCA in preventing adverse events and revascularisations. These results confirm the trends presented in the previous review that informed the national guidance.

Stent versus CABG

All studies were a comparison of bare metal stents with surgery. Studies comparing drug-eluting stents with CABG have commenced but no reports of results are currently available.

Analysis of data was carried out considering patients with single- and multiple-vessel disease. Studies in the former group were small and did not report results that could be used in the analysis past 6-month follow-up.

In multiple-vessel disease there was no evidence of a difference in mortality (at 1 year) between patients treated surgically and those receiving a stent. Longer term data from these studies are now becoming available. Patients treated surgically required fewer revascularisations.

Stent versus DES

Data are limited by the lack of reporting of longer term outcomes. There is no evidence of a difference in mortality between patients receiving DES and those treated with bare metal stents at 1 year.

There is a reduction in event rate at 9 and 12 months in patients treated with DES. This event rate is primarily made up of increased revascularisation rates in patients treated with bare metal stents. Two-year outcome data from one study indicate that this benefit of DES continues over the longer term.

Economic evaluation

The existing economic literature in this area is limited and of variable quality and relevance. The nature of CAD as a life-long condition means that outcomes and costs should be considered over extended time periods. In our view, the submitted company models were inadequate in this respect.

We developed an economic model based on extrapolation of trends in mortality and revascularisation from clinical trials data to a 5-year time horizon. This proved sufficient to indicate long-term trends in cost-effectiveness:

- Bare metal stenting versus CABG in multivessel disease
  CABG is initially more expensive and may have higher immediate risks, but over time the cost differential is reduced and long-term outcomes favour CABG over stenting.
- DES versus CABG in multiple-vessel disease
  Here the situation is not qualitatively different from bare metal stenting. Reduced costs from fewer repeat revascularisations is more than offset by the higher costs of stents and the improved efficacy of the new stents does not eliminate the long-term outcome advantage of CABG.
- DES versus bare metal stenting in single-vessel disease
  This leads to substantially higher costs with a very small outcome benefit, so that DES would not normally be considered a cost-effective alternative.

DES might be considered cost-effective if one or more of the following options apply:

- The additional cost of DES (compared with ordinary stents) was substantially reduced.
- The outcome benefits from the use of DES are much improved.
- The use of DES is targeted on the subgroups of patients with the highest risks of requiring reintervention.

Implications for the NHS

The net cost implications to the NHS, depending on which patients receive DES, range from £4.2 million to £23 million per year, at current levels of stent provision.

Recommendations for further research

This review indicates a need for research in a number of areas:

- Long-term clinical studies that focus on significant outcomes such as mortality.
- Further studies on (a) differences among plain stents (this might be possible from a systematic review, but is not addressed in the current review), (b) head-to-head comparisons within DES (new trial data required), (c) CABG compared with DES (already planned) and (d) evaluation of newer non-DES against DES.
- Evaluation of the effects of revascularisation procedures and especially repeat revascularisation procedures on the patient's quality of life.
- Development and testing of risk assessment tools to identify patients likely to need further revascularisations.
- The rapid rate of change in this area suggests that a further review should be undertaken in 12–18 months.

Chapter 1

Review aims

To assess the effectiveness and cost-effectiveness of the use of coronary artery stents in patients with coronary artery disease (CAD).

Specifically, the clinical review compares the use of:

- stent versus percutaneous transluminal coronary angioplasty (PTCA)
- stent versus coronary artery bypass and graft (CABG)
- stent versus drug-eluting stent (DES).

The economic analysis compares the cost effectiveness of:

- stent versus DES
- stent versus CABG.

Chapter 2
Background

Introduction

NHS guidance on the use of stents in coronary angioplasty was provided in 2000 by the National Institute for Clinical Excellence (NICE).[1] This was based on a systematic review which included 35 trials.[2] However, an additional 16 trials were excluded because they were in progress. The primary end-point considered in the review was revascularisation rates. The review was limited by a lack of available data related to the use of stents versus CABG. The review examined available economic evaluations but did not carry out cost-effectiveness analysis.

Research in this clinical area is expanding rapidly and a significant number of studies have been reported since the release of the original review[2] and subsequent NICE guidance.[1] These include the reporting of studies comparing stent and CABG and also the initial assessment of the evaluation of DES. Recently produced guidelines in the USA indicate that this field of care is changing so rapidly that their guidelines will be reviewed annually.[3] Of importance is that the American College of Cardiology (ACC) Expert Consensus Panel[4] also noted that: "The rapid evolution of stent design, deployment approaches, and adjunctive therapy have led to changes in clinical practice patterns that precede rigidly controlled supporting scientific data."

This rate of change and rapid adoption of change in practice make it difficult for those responsible for developing clinical guidance to ensure that their recommendations are based on both rigorous and up-to-date evidence. This review was commissioned to address this rapidly expanding area of clinical research and to inform new national guidance.

Description of health problem

Disease

CAD is a condition caused by a narrowing or occlusion of the coronary arteries that supply blood to the heart muscle. The disease may be silent or may lead to symptoms such as angina. Continued curtailment of the blood supply leads to heart muscle damage in the form of a myocardial infarction (MI) or death.

Manifestation of symptoms of CAD may be acute or chronic. Recently the term acute coronary syndrome (ACS) has been defined as an operational term that includes acute myocardial infarction (AMI) (ST segment elevation and depression, Q-wave and non-Q-wave) and unstable angina.[3] Previous research reports have not necessarily utilised this definition and have differentiated between AMI and subacute manifestations of CAD that include angina and unstable angina.

Epidemiology

Basic data are available in the UK regarding the overall importance of cardiovascular disease in the health/disease profile of UK residents. Routine data provided by the British Heart Foundation (BHF)[5] indicate that coronary heart disease (CHD) (which includes CAD) is the most common cause of mortality in the UK. It accounts for more than 125,000 deaths per year. Mortality rates vary by gender and account for one in four deaths in men and one in six deaths in women. CAD is also responsible for extensive morbidity in the UK population. Statistics indicate that approximately 1.5 million people in the UK suffer from angina, the most common form of morbidity from CHD.

Rates of CAD have been decreasing in the UK over the past three decades. However, this decrease has not been consistent across age groups, gender or socio-economic class. A more rapid reduction has been seen in younger age groups (45–54 years), in men and in higher socio-economic groups. In addition, the rate of decline in the UK has been slower than that in other developed countries (e.g. Denmark, Norway, Australia).

Characteristics of the disease

Blockage of the coronary arteries is a process that evolves over time. It is caused through the deposition of material inside the artery, eventually leading to a decrease in blood flow or a total obstruction. One reported measure of the extent of the disease includes a description of the blockage or lesion. Standardised criteria have

TABLE 1 *Lesion types*

Lesion type	Characteristics
A	Discrete Less than 10 mm Concentric readily accessible in a non-angulated segment Less than 45° with a smooth contour Little or no calcium Less than totally occlusive Not ostial in location No major side-branch involvement Absence of thrombus
B	Lesions are tubular 10–20 mm length Eccentric Moderate tortuousity of proximal segment Moderately angulated segment between 45 and 90° May have an irregular contour Moderate to heavy calcification Total occlusion less than 3 months old Can be ostial in location Can be a bifurcation lesion
C	Lesions have a combination of being diffuse Greater than 20 mm in length Excessive tortuousity of the proximal segment before lesion Extremely angulated segments with 90° May be total occlusion

Adapted from *Textbook of Interventional Cardiology*. 3rd ed.[6]

been developed to describe the various lesion types and these are presented in *Table 1*.

Other characteristics of the disease process are also important and of specific interest in this review. These include not only the lesion type but also the extent of the disease process (e.g. single- versus multiple-vessel disease; total versus partial occlusion of vessels) and the size of the diseased vessel. Patient characteristics that are important include such things as the presence of risk factors such as diabetes. Where possible these issues are addressed within this review.

Current treatments

Treatment protocols may include:

- medical management
- percutaneous treatment (PTCA with or without stent)
- surgical intervention (CABG).

Medical management

Medical management is designed to assist in the modification of risk factors, reduction of symptoms and prevention of disease progression and adverse events. The treatment may include the use of medications such as beta-blockers, nitrates, calcium channel blockers, antiplatelet agents or anticoagulants. This area has been extensively reviewed and is not considered in this report.[3,7,8]

Given current waiting times for interventional treatments such as percutaneous procedures or surgery, medical management of symptoms is seen as a crucial component of care. Medical management is reassessed and adjusted following other invasive treatments.

CABG

The development of surgical treatment such as CABG began in the late 1960s. The treatment involves bypassing the area of arterial blockage using either the internal mammary artery or a graft from another vessel [e.g. saphenous vein graft (SVG) from the leg]. Use of CABG may be elective or used in emergency circumstances (e.g. failed PTCA). In the case of elective CABG, the treatment has historically been limited to patients with multiple-vessel or diffuse disease or disease of the left anterior descending (LAD) artery. Changes in the intra- and postoperative management of patients has improved patient outcomes following CABG.[3]

In addition, in the past all patients undergoing CABG required the use of a bypass machine that maintained blood circulation during the surgical procedure. Minimally invasive surgery, that does not require the use of total bypass and has shortened surgical time, is currently being introduced and evaluated.[9,10] It is not the remit of this review to examine the effectiveness of these newer surgical techniques.

The invasive nature of the surgery with its inherent operative risk and extensive in-hospital and postdischarge recovery time prompted researchers to identify less invasive effective treatments.

PTCA

Research in the late 1970s focused on the development of less invasive treatments. The first PTCA was performed in Switzerland in 1977.[11]

A coronary angioplasty in its simplest form involves the inflation of a balloon within a

coronary artery at the site of an atherosclerotic lesion. This balloon inflation will compress the atherosclerotic matter and stretch the vessel to accommodate the compressed plaque material. On deflation, the vessel has a wider lumen to allow increased blood flow. Prior to 1987, angioplasty consisted predominantly of balloon inflations (also known as plain old balloon angioplasty). Rapid dissemination and refinement of techniques meant that by the mid-1980s the use of PTCA was common.

Adjunct techniques evolved as a part of what has come to be classified as percutaneous coronary intervention (PCI). The term PCI may be used to include balloon angioplasty, artherectomy and stenting.[4]

Initial success of elective PTCA ranges between 96 and 99%.[12] However, there are two major drawbacks to the use of PTCA. The first is acute closure of the target vessel during treatment. This is considered an emergency and in the past has required emergency CABG. Acute closure is reported in 2–10% of cases of PTCA and has been the basis for recommendations that PTCA only be carried out with the backup of emergency CABG facilities. A later advance in PTCA was the use of 'bailout stenting' (see p. 6).

The second drawback of PTCA is restenosis. The cause of restenosis is probably multifactorial and may include the development of scar tissue, vessel re-coil or vessel remodelling. Restenosis of the treated vessel requires repeat procedures in approximately 20–50% of patients.[2] Reports also indicate lower treatment success rates in patients with small arteries, long lesions, previous CABG and diabetes.[13]

These problems prompted the research into methods to decrease or eliminate restenosis. This included the development of coronary artery stents.

PTCA including stents

A coronary artery stent is a small, metal prosthesis placed within the artery at the time of angioplasty, to scaffold the vessel open (see *Figure 1*). The technology was developed to address the two key issues faced during PTCA, acute closure and restenosis.

A number of different stent types are available/licensed for use in the UK. There also exist a number of different stent platforms or devices that may be used during the insertion of the stent. An illustration of the process of PTCA and stent insertion is presented in *Figure 1*. It is

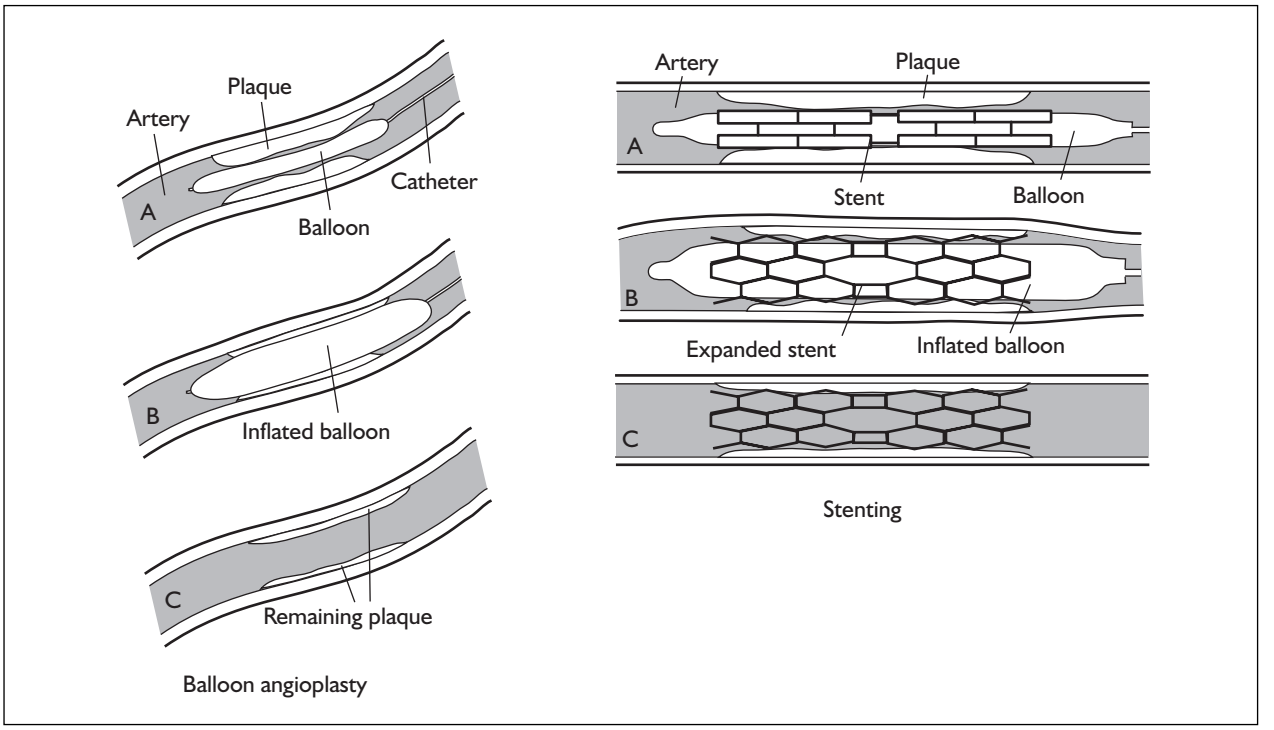


FIGURE 1 *Illustration of the process of PTCA and stent insertion. Representation of (left) PTCA (balloon angioplasty) and (right) stenting. Image reproduced by permission of the Texas Heart Institute. Copyright 1996–2002 Texas Heart Institute (www.texasheartinstitute.org)*

not within the remit of this review to compare the effectiveness of various stent designs or guidance systems.

In addition to differences in stent design and placement, there are variations in the approaches used during the insertion process.

Stent placement

Elective stenting

Elective stenting is a planned procedure and includes insertion of a stent regardless of the results of the PTCA.

Provisional stenting (suboptimal PTCA)

Provisional stenting is carried out following assessment of the success of the initial balloon angioplasty, for example 'suboptimal' results from angioplasty. Definitions of optimal response vary but generally include the visual or objective assessment of the success of the artery's response to balloon expansion together with a measurement of the thrombolysis in myocardial infarction (TIMI) flow grade.[14] The acceptance of provisional stenting within clinical practice is based on the assumption that if optimal expansion is achieved then a stent is not required. This logic was used as a rationalisation for limiting the use of stents and subsequently the cost of treatment. It is not the purpose of this review to assess the effectiveness of provisional versus elective stenting, although it is briefly discussed within the section of this review that deals with stent versus PTCA.

Bailout stenting

Acute closure or dissection of the coronary artery may occur during PTCA. This may be due to a rupture of the plaque during balloon inflation. This is considered an emergency situation and previously has required CABG. Since the development of stents, they have been used in a process called bailout stenting, in which the stent is used to support the walls of the coronary artery and maintain coronary circulation. The emergency nature of the event means that it is unlikely that randomised trial data will ever compare the effectiveness of emergency CABG versus bailout stenting in cases of acute closure during PTCA. The availability and rapid uptake of the use of stents have meant that bailout stenting has become the preferred clinical option. Given that the majority of PTCA procedures in the NHS now involve elective stenting, bailout stenting is rare.

Direct stenting

Direct stenting involves the simultaneous expansion of the artery and placement of the stent, as opposed to expansion of the artery by balloon followed by placement of the stent.

DES

The shift to the use of stents was made on the basis of evidence of effectiveness in relation to restenosis following PTCA. However, in-stent stenosis remains an important adverse event following insertion of coronary artery stents. This is usually due to intimal hyperplasia, that is, the growth of cellular matrix in and around a stent and a reaction to tissue injury. Methods for the treatment of in-stent stenosis are being extensively researched. In addition, the development of stents which have lower rates of stenosis has moved ahead rapidly.

Research has focused on a number of areas. One of these has been the evaluation of coated stents. These coatings are considered passive and are being evaluated to assess their effects on platelet function and endothelial activity and ability to decrease acute (up to 30 days) rates of thromboembolism.[15] There is to date no evidence that coated stents reduce the long-term risk of restenosis. This review does not examine the effectiveness of coated stents.

A second and extensive area of research has been DES. These stents may have a polymer coating which facilitates gradual release of drug into the local tissue. The theory base for using stents that elute substances is that cell progression can be interrupted to inhibit cell proliferation and therefore potentially reduce in-stent restenosis (ISR).[15] Specific agents have been identified that act at different sites and these are identified in *Table 2*. The agents that have been the subject of the most extensive research are Sirolimus (rapamycin) and paclitaxel.[16]

Sirolimus is a macrolide immunosuppressant used systemically to treat renal transplant rejection. It halts proliferation of smooth muscle cell cycle. It binds to a receptor protein and inhibits a regulatory enzyme that in turns shuts off the cell cycle.

Paclitaxel is a derivative of the yew plant. It also inhibits the cell cycle and has been used as an anti-proliferative drug in the treatment of breast, lung and ovarian cancer.

Adjunctive pharmacotherapy

In addition to new mechanical devices, the 1990s witnessed the use of established pharmaceuticals (e.g. aspirin) and the development and testing of

TABLE 2 *Drug-eluting stent: modes of action*

Mode of action	Injury: anti-inflammatory	Proliferation: anti-proliferative	Migration: migration inhibitor	Healing: promotes healing and re-endothelisation
Drug	Dexamethasone Methylprednisolone	Angiopeptin Actinomycin D Paclitaxel Sirolimus	Batimastat	Estradiol (VEGF)

new agents to be used as adjuncts to percutaneous coronary revascularisation. Glycoprotein IIb/IIIa inhibitors have been shown to reduce ischaemic complications in patients undergoing PCI.[17,18] Use of ticlopidine has been stopped owing to adverse reactions and the use of clopidogrel has become common, although the length of time for continued treatment continues to be debated.[19] The clinical and cost-effectiveness of these treatments are now being reported[20] and a review of the effectiveness of clopidogrel is currently being carried out in the UK.

The scope of this review does not include an assessment of the effectiveness of these agents. However, given that their use is important, the data extraction from trials includes a listing of adjunctive pharmacotherapy and is included in the study characteristic tables. The effectiveness of clopidogrel will be assessed in a forthcoming NICE review.

Patient subgroups

As noted earlier in this chapter, previous research has shown that there are subgroups of patients who are considered to be at higher risk of complication or lower rate of treatment success. These groups are discussed here.

AMI

The unstable nature of patients experiencing AMI meant that they were originally excluded from treatment until their clinical condition had been stabilised. This is no longer the case and the use of PTCA and stents is now common in this group of patients. Other treatment for this subgroup includes the use of early thrombolysis. A review of the effectiveness of PTCA with stent compared to early thrombolysis is due to be completed in early 2003.

Diabetes

Patients with diabetes mellitus have consistently had higher rates of restenosis and other adverse events following PTCA (with or without stent) and CABG.[21]

Chronic total coronary artery occlusion

Initially the treatment of this population of patients was limited by the ability to pass a catheter beyond the occlusion. Even when passage was possible and PTCA performed, this group of patients reported higher restenosis rates and other adverse events.

Small vessels and long lesions

Early trials of stents required that the vessel diameter be >3.0 mm. However, it was found that a number of patients in the early trials did indeed have vessel diameters of <3.0 mm, but that clinical and angiographic outcomes did not seem to improve in these patients with the use of stents.[22,23] Since that time, trials specifically designed to examine the effects of stents on small and long vessels have been carried out. Reports from some of these trials are included in this report.

Bifurcations

As would be expected, the treatment of disease that occurs at the bifurcation of two vessels is more difficult than treatment within a straightforward lesion. As reported in the submission from the British Cardiac Society (BCS) and British Cardiac Intervention Society (BCIS),[15] treatment of these lesions is technically challenging and associated with higher rates of complications and lower success rates. Although this is an important subgroup of patients, data are more limited and it is not dealt with directly in this review.

Gender

Research related to CAD is dominated by results related to male participants. However, researchers are examining the differences in clinical disease patterns, clinical presentation, treatment and response to treatment in females. This issue has recently been addressed through examination of PCI outcomes by gender over a 5-year period in New England, USA.[24] It is not within the remit of this review to address these comparisons. The data extraction for the review does, however, indicate the proportion of males in each study.

Estimates of subgroups

It is important to be able to estimate the number of patients receiving CABG or PCI in each of these subgroups. The submission to NICE from the British Cardiovascular Industry Association (BCIA)[25] combined data from BCIS and EUROHEART to estimate the number of patients in each of these subgroups in relation to numbers of patients undergoing treatment in the UK. These data are presented in *Table 3*.

The data are limited in their ability to present a complete picture, as they do not allow for estimates across groups, for example, the number of diabetic patients with multiple-vessel disease. They do, however, provide estimates on which to base further discussion.

Restenosis

The primary end-point for the majority of PCI studies and in the previous review[2] has been restenosis based on angiographic findings. Early studies focused on binary restenosis rates (e.g. the percentage of lesions with >50% luminal narrowing).

Restenosis is composed of three major factors: immediate postballoon vessel recoil, late negative remodelling/narrowing and tissue growth at the site of treatment due to migration of smooth muscle cells from the medial layer of the vessel wall to produce a new proliferating intimal layer. In theory, cell progression can be interrupted at any number of stages.

Stents themselves deal with recoil and negative remodelling but do not impact on the rate of intimal hyperplasia because the stent induces vessel wall injury. Specific agents are now being loaded on to stents to inhibit the growth of smooth muscle cells that lead to ISR.

Assessment of restenosis is complex. The simplest method is through the appearance of clinical symptoms (e.g. angina, AMI). Initial studies included angiographic assessment that focused on binary restenosis rates. These rates were based on the proportion of patients in which the treated vessel has >50% luminal narrowing. These rates do not necessarily correlate with clinical symptoms. It has been estimated that ~50% of patients with angiographic stenosis actually experience symptoms and present for treatment.[26]

Subsequently, more specific and complex measures have been utilised. One of these is late loss. Late loss is defined as the difference between postintervention minimal lumen diameter (MLD) and MLD at follow-up. However, simply measuring this loss can be deceptive since a loss of 0.8 mm in a vessel that is 2.5 mm is much more important than a similar loss in a vessel that is 3.5 mm. In an attempt to deal with this, the figures can be converted to index of luminal loss. At present there is no standardised use of these measures or indices.

Variations also exist in relation to the exact location of the stenosis, with some reports of

TABLE 3 *Estimate of patients undergoing PCI in the UK who fall into key CAD subgroups*

	Percentage of PCI patients[a]	Percentage of CABG patients[a]	Estimated number of PCI patients	Estimated number of CABG patients
UK PCI procedures in 2001			38,992	
UK CABG procedures 1999–2000				24,728[b]
Single-vessel disease total	48		18,716	
Normal single-vessel disease	8		3,119	
Longer lesions	21		8,188	
Single small vessel disease	22		8,578	
Diabetes	20	22	7,798	5,440
LAD lesions	61		23,785	
Multiple-vessel disease total	52	90	20,276	
Two-vessel disease	33	28	12,867	6,924
Three-vessel disease	19	62	7,408	15,331

[a] Data source: EUROHEART N&W WHO Regions
[b] Data from BCIS on surgery rates presented later are slightly higher.
Adapted from BCIA submission.[25]

stenosis within the stent, stenosis at the stent margins or both. Trial reports also focus on measures of target lesion revascularisation (TLR) and/or target vessel revascularisation (TVR) rates. Again, definition of these terms is not standard and varies across studies.

Restenosis rates served as one of the primary outcome measures in trials assessing the effectiveness of PTCA. These rates were the primary outcome measure in the previous review of PTCA and remain one of the primary outcome measures for trials of newer interventions. As indicated previously, these rates do not always correlate with the clinical presentation of the patient and the limitation of their use is discussed as a part of this review.

Current service provision

Introduction

Current care guidance was provided by NICE in 2000.[1] This guidance is presented in *Table 4*.

Within the National Service Framework (NSF) for coronary heart disease,[7] there is an estimate that to meet service targets a minimum number of procedures will need to be carried out. This is defined as 750 procedures per million population for each of two groups (stent and surgical) of interventions.

TABLE 4 *NICE guidance on coronary artery stents, May 2000*

Reference	Guidance
1.1	For patients with either stable or unstable angina or AMI and where PCI is the clinically appropriate procedure, stents should be used routinely
1.2	Where it is considered clinically appropriate to undertake either PCI or CABG, the availability of stents should push the balance of clinical decision-making towards PCI
1.3	Arteries with a diameter <2.5 mm and >3.5 mm should only normally be stented in the setting of a so called 'bailout' procedure (i.e. when acute closure of the vessel occurs following PCI), or if there has been a suboptimal result following ballooning alone or as part of properly conducted trials. These criteria do not apply to SVG. The Institute is aware that new evidence on stenting in arteries with a diameter <2.5 mm is likely to become available soon. If necessary, this guidance will be amended to take account of the fully reported results
1.4	This guidance specifically relates to the present clinical indications for PCI and excludes conditions (such as many cases of stable angina) which are currently adequately managed with standard drug therapy

Data systems

In the UK, no system currently exists to capture all PCI and CABG procedures fully. The BCIS and the Society of Cardiothoracic Surgeons of Great Britain and Ireland maintain audit datasets that collate data from centres providing information on a voluntary basis. Some semicommercial sources of data are also available which collate completed episodes from over 100 trusts and institutions in the country, together with associated overall costs. A comprehensive system of data management would be useful as a tool to monitor changes in care delivery patterns within the NHS.

Diagnostic and care provision centres

In 2001 there were 126 intervention and diagnostic centres (NHS and private) across the UK. Of these, 62 provide diagnostic services only. Details of the number of centres and their activity levels for 2001 are presented in *Table 5*.

TABLE 5 *UK intervention and diagnostic centres, 2001*

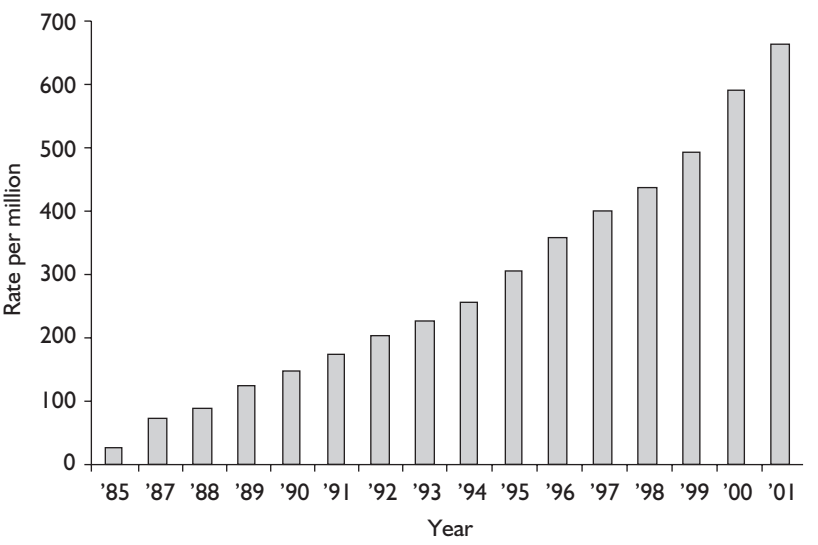
	Number of centres	Centres without catheterisation data (%)	Catheterisation (% of total)	PCIs (% of total)
NHS interventional	48	5 (10%)	100,350 (70%)	36,698 (94%)
Private interventional	16	4 (25%)	8,407 (5.8%)	2,294 (5.9%)
Diagnostic only	62	4 (6.5%)	35,086 (24%)	0
Total	126	–	143,843[a]	38,992[b]

[a] These totals may include the double counting of some patients (e.g. those who have a catheterisation and go on to have a PCI). Adapted from reference 27.

TABLE 6 *PCI rates in the UK, 1991–2001*

Year	Centres	Total procedures	Rate per million	Increase (%)
1991	52	9,933	174	
1992	52	11,575	203	16.5
1993	53	12,937	227	11.8
1994	54	14,624	256	13.0
1995	54	17,344	304	18.6
1996	53	20,511	359	18.1
1997	58	22,902	402	11.7
1998	61	24,899	437	8.7
1999	63	28,133	494	13.0
2000	66	33,652	590	20.0
2001	64	38,992	663	15.9

Adapted from reference 27.



From de Belder M. BCIS audit returns of interventional procedures 2001. Edinburgh: Council of the British Cardiovascular Intervention Society; 2002. URL: http//www.bcis.org.uk/audit/oct02.html

FIGURE 2 *PTCA: rates per million in the UK 1985–2001*

PCI rates

There has been a continual increase in the number and rate per million of PCIs carried out over time. Rates for 1991 to 2001 are shown in *Table 6*.

Although these rates are increasing, as can be seen in *Figure 2*, they lag behind rates in other European countries. Recent editorials have attempted to explain some of these differences in relation to the models of care and decision making related to treatment preferences in different countries.[28]

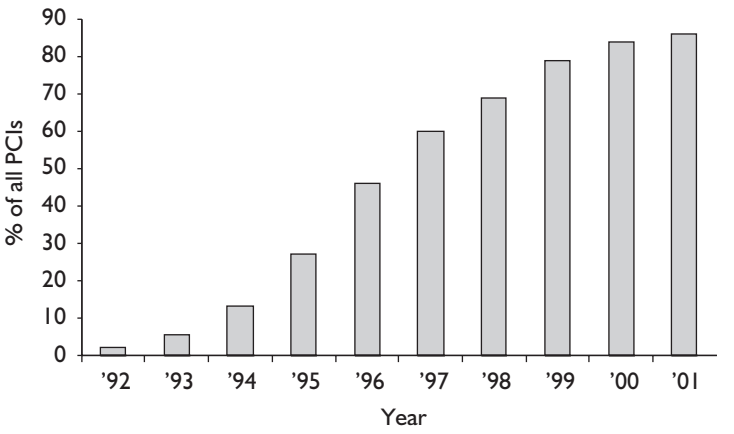
Figure 3 represents the trends in the use of stents in the UK from 1992 to 2001. It is also interesting that the increase in number of treatment events preceded the release of NICE guidance on the use of stents. This is discussed later in this report.

Use of drug-eluting stents

To date, five DES have received the CE marking: the Cordis CYPHER™, Cook ACHIEVE™ and V-Flex Plus PTX™, Boston Scientific TAXUS™ and Abbott Laboratories Dexamet™ stent systems.[29–33] Data are not readily available regarding the utilisation of DES in the UK.

CABG rates

There has been a significant increase in rates of CABG in the UK, with rates having doubled over



From de Belder M. BCIS audit returns of interventional procedures 2001. Edinburgh: Council of the British Cardiovascular Intervention Society; 2002. URL: http//www.bcis.org.uk/audit/oct02.html

FIGURE 3 *PCI with stent rates UK 1992–2001*

TABLE 7 *CABG: rates in the UK, 1989–2000*

	CABG	CABG with another procedure	Total	Rates per million[a]
1989	12,648	1,342	14,187	236
1990	14,431	1,536	16,145	269
1991	15,659	1,710	17,538	292
1992	19,241	1,963	21,398	356
1993	21,031	2,037	23,274	388
1994–95	22,056	2,282	24,513	408
1995–96	22,475	2,362	24,960	416
1996–97	22,160	2,078	24,599	409
1997–98	25,639	2,433	28,198	469
1999–2000	24,728	2,641	27,831	464

[a] Estimate: data calculated based on population base of 60 million.
Adapted from reference 34.

the past 10 years. Approximately 28,000 operations are carried out each year. *Table 7* shows the growth in surgical rates over time.

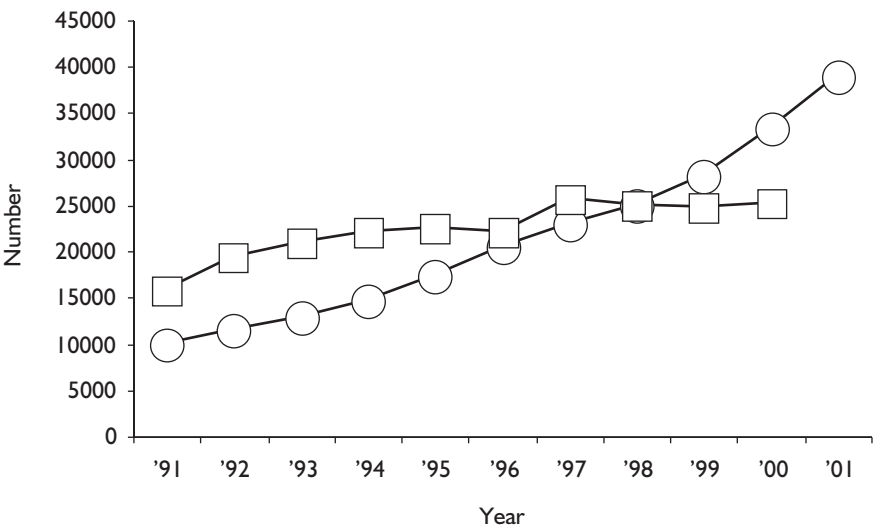
The data in *Table 7* are from the UK Cardiac Surgical Register, collected by the Society of Cardiothoracic Surgeons of Great Britain and Ireland. Twenty-nine (83%) of the 35 NHS Trusts and Units undertaking adult cardiac surgery in the UK contribute data to the register. No data are available for 1998–99.

Although the total number of CABG procedures has been rising, the rate of increase, as seen in *Figure 4* is less than that seen in the use of PCI.

As mentioned previously, the use of stents has replaced CABG following acute artery closure during PTCA. As seen in *Figure 5*, the use of stenting, either elective or bailout, has decreased the number of emergency CABG procedures recorded after PTCA.

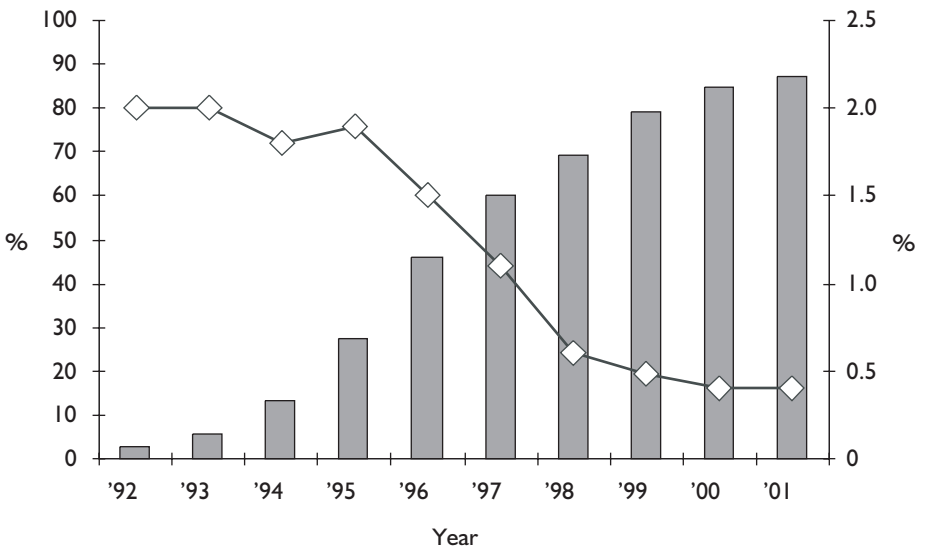
Limitations of the review

This review was commissioned to inform the appraisal process and development of national guidance regarding the use of coronary artery stenting. As such, the remit is broad. In spite of this, the review is extremely limited in its scope.



From de Belder M. BCIS audit returns of interventional procedures 2001. Edinburgh: Council of the British Cardiovascular Intervention Society; 2002. URL: http//www.bcis.org.uk/audit/oct02.html

FIGURE 4 *CABG rates (□) compared with PCI (○), 1991–2001*



From de Belder M. BCIS audit returns of interventional procedures 2001. Edinburgh: Council of the British Cardiovascular Intervention Society; 2002. URL: http//www.bcis.org.uk/audit/oct02.html

FIGURE 5 *Emergency CABG rates (◇, left ordinate) compared with PCI (boxes, right ordinate), 1991–2001*

Specifically, the review does not address:

- PTCA versus medical management
- comparison of various stent designs or delivery platforms
- comparison of various stent placement techniques (e.g. direct versus provisional stenting)
- use of multiple stents
- adjunct medical therapies (e.g. anticoagulant, antiplatelet)
- in-stent stenosis
- PTCA or stenting compared with other PCI interventions (e.g. atherectomy, rotablator, brachytherapy)
- comparisons of different surgical methods (e.g. minimally invasive or off-pump surgery).

That is not to say that these are not important issues related to the delivery of care – they were simply outside the remit provided to the review team.

Review considerations: clinical

The review team benefited from the review work previous carried out by Meads and colleagues.[2] Their work highlighted some of the challenges that could be expected in updating and expanding the review. These can be summarised in four categories: comparability of interventions, outcomes, subgroups of patients and data availability.

Comparability of interventions

Comparability of interventions is a critical issue when making decisions regarding the appropriateness of combining data. The previous review highlights a number of areas where decisions to combine interventions could influence the outcome of the review.

The first is the assumption that all non-DESs were equally effective.[35] This is an oversimplification – a number of different stents are available and current reports indicate that this technology is about to take another step forward with changes in stent design and material. There are also differences in efficacy between stents in randomised controlled trials (RCTs), generally in favour of newer designs with thinner struts. An attempt to identify a comprehensive list of all the stents currently licensed and used in the UK was not successful. It could be argued that analysis of data should be carried out according to the type of stent inserted. This review does not attempt to consider or compare the effectiveness of various stent designs.

Advances in pharmacological research have added variation of pharmaceutical agents to the comparison. These agents have been designed either to coat the stent or to elute into surrounding tissue. The agents and their actions differ and there is a question of how far the results of studies using different agents should be combined. For the purpose of this review, DES are considered as a group, although data are presented to allow for assessment of effectiveness within drug-stent types.

Along with stent design is the issue of the platform from which the stent is inserted. A variety of guidewires and devices to assist insertion of the stents exist and, although some stents are provided on set insertion systems, interventionists do have some choice. The analysis in the review does not take into consideration types of insertion devices.

The second issue is related to the insertion technique used for stent placement. These have been mentioned earlier and include such things as provisional stenting, predilation and direct stenting. All of these could be factors that affect the outcome of the procedure and the long-term success of the procedure. The analysis in the review does not differentiate between different insertion procedures.

Adjunct medical treatment during and following stent insertion is the topic of multiple research papers. Medical treatment protocols have evolved over time and there has been a recent shift in the drugs utilised (e.g. use of clopidogrel) and the length of treatment. This has undoubtedly improved the outcomes over time and in part encouraged the expansion of stenting into the types of lesions not addressed in early research. The review identifies the adjunct therapies used in the included trials but does not include this information in the data analysis.

Operator skill, as in all areas of clinical interventions, is a factor. The experience and skill of the person carrying out the procedure are critical. Over time, clinicians have gained extensive experience and expertise related to the placement of stents. It might be assumed that this will lead to improved clinical results. The review has not attempted to deal with such changes over time.

Outcomes

Event rates

The term 'event rate' is reported in almost all studies. These are reported as composites such as major adverse cardiac events (MACE) or major adverse cardiac and cerebral events (MACCE). They can include mortality, AMI or revascularisation, but the definitions vary across studies.

There is a further problem with the use of such composite end-points in that they may obscure real and important differences in outcomes. For instance, repeat revascularisations are reported as events in the same way and with the same weight as a clinical MI or death.

Mortality

Trials have been powered to measure differences in restenosis rates (which are assumed to be fairly

large), but are not powered to assess the difference in mortality – an event that is rare. This issue is addressed later in the section related to the parameters for economic evaluation (p. 15).

Revascularisation

Current guidance is based on outcomes related to the need for revascularisation following treatment. As noted above, these may also be presented within composite outcomes of MACE or MACCE.

Revascularisation rates, however, can be affected by the study protocol. That is, a revascularisation may occur because the patient presents with symptoms, is assessed and a decision to intervene is made (clinically driven revascularisation). However, the presence of restenosis detected at a planned angiographic follow-up has been used as an indicator for revascularisation procedures (angiographically driven revascularisation). Therefore, in those studies that involve a routine 6-month angiographic follow-up of patients, there may be an excess of 'events' around 6 months, and these events may not be truly clinically relevant. There is an argument that some of those classified as angiographically driven at 6 months would have progressed by 12 months or later to become symptomatic and requiring a clinically driven revascularisation, but this should be detected in long-term follow-up.

There is a lack of consistency across studies for reporting of revascularisation. Reports may report TLR, TVR or both. Definitions for these are not always provided. There are also limited data on total revascularisation, e.g. a patient may have another procedure carried out in a vessel, other than the one originally treated. This reporting is appropriate when assessment of the effectiveness of a specific stent is being carried out, but data related to any revascularisation are needed when assessing the costs of patient treatment.

More recently, definitions of clinically driven revascularisations have become standardised and this is seen more clearly in the later trials particularly of DES. The definition is mandated by the US Food and Drug Administration (FDA) and states that the procedure was considered clinically driven if the patient had "a positive functional study, ischaemic ECG changes at rest in a distribution consistent with the target vessel, or ischaemic symptoms and an in-lesion diameter stenosis greater than 50%. Revascularisation of a target lesion with an in-lesion diameter stenosis greater than 70% in the absence of the above mentioned ischaemic signs or symptoms was also considered clinically driven."

A 'functional test' refers to a positive exercise ECG or nuclear perfusion scanning. The key point here is that even by this definition, 'clinically driven events' can be defined by angiographic indices alone. It assumes that with a stenosis >70%, even if the patient is not symptomatic at the time, it is highly likely that they will soon 'tip over' into a symptomatic state and require a repeat revascularisation soon after.

Length of follow-up

Outcomes based on revascularisation events mean that length of follow-up is short. Most trials report up to 1 year. This is an issue raised again as part of the economic evaluation.

Quality of life

The previous review did not report on this outcome. They are not data that have routinely been included in trials but, as noted as part of the economic analysis, are required for the assessment of long-term outcomes.

Subgroups of patients

Differences in outcomes in specific patient populations (e.g. diabetic patients, people with ACS) have been reported inconsistently across different trials. Other subgroups relate to the actual type of lesion, vessel type or extent of disease. These subgroups have been described earlier. Meads and colleagues[2] made attempts to carry out subgroup comparisons but were limited by the availability of the data.

Data availability

Results of systematic reviews are contingent on the availability and quality of the data. Meads and colleagues[2] identified a number of studies that were not yet complete and therefore final data were not available. They also identified studies that were reported only in abstract format, limiting their ability to judge the quality of the data.

Our review process was complicated by the speed and manner of appearance of data, especially in the area of DES. Presentation of new trial data appeared monthly during the period when the review was being conducted. In addition, most data were available only from specialised websites. Frequently these data were released simultaneously in the form of electronic visual presentations (such as Microsoft PowerPoint slides) used during a conference presentation. Obviously this form of

presentation is not peer reviewed or validated, and it provided constant challenges to the review team as they endeavoured to cross-check data and assess the quality of the included studies.

Review considerations: economic

At an early stage in planning this review, we concluded that the breadth of potential comparators and the apparent paucity of clinical evidence for any specific combination of treatment alternatives precluded full evaluation of all options. Instead we determined to address the two main claims underlying the submissions received in support of increased use of stenting, especially of DES:

- That DES are cost-effective for some patients currently treated with bare metal stents (on the grounds that fewer repeat revascularisations are necessary).
- That stents and/or DES are cost-effective substitutes for CABG for some patients in whom either treatment may be thought to be of equivalent clinical value.

Establishing or refuting the validity of these claims could then be seen as offering a framework for constructing guidance of general relevance. Consideration of the second of these claims was viewed as necessary as a direct result of its inclusion in several of the industry and professional submissions, which argued on pragmatic grounds that the volume of PCIs carried out could be expanded more rapidly than the volume of CABG procedures for a defined group of patients, without any loss of benefit. If confirmed, this contention may have profound implications for national policy in the future development of cardiac care services, and therefore should be subject to careful scrutiny.

An economic evaluation requires simultaneous consideration of evidence on three factors:

- postintervention longevity
- postintervention quality of life (QoL)
- healthcare costs associated with the intervention or resulting from it.

When estimating the utility associated with measurable outcomes of a treatment, these three factors are not of equal significance. In particular, since measures of health-related QoL are merely modifiers of longevity, treatments which extend life necessarily yield benefits one or two orders of magnitude greater than those which only improve the QoL. Similarly, in a chronic condition, healthcare costs usually include a component related to the length of survival, so that longevity directly influences costs in most cases. Hence, regardless of treatment objectives or preconceptions, it is essential to consider the question of differential mortality as of primary importance before proceeding to examine QoL or other measures of efficacy and effectiveness. If mortality is not properly considered, this constitutes a very strong, implicit *a priori* assumption that is difficult to sustain without a great deal of data (in both number of cases and duration of exposure). The risks of drawing false conclusions in chronic conditions by neglecting what is potentially the most influential factor are clearly substantial and therefore we concluded that this question must be addressed first.

The nature of CAD, as a life-long progressive condition with both chronic debilitating symptoms (i.e. angina, dyspnoea) and the increased risk of life-threatening acute episodes (i.e. AMI and sudden death), obliges the economist to consider potential long-term costs and consequences of each intervention even if the primary purpose of the treatment is short-term or palliative. In this case, even though the primary therapeutic objective of a procedure may be to relieve symptoms, the associated risks of mortality and morbidity may lead to life-long disbenefits which differ between procedures. Nor, for the purpose of long-term economic evaluation, is it sufficient to state that there is no evidence that a particular outcome measure differs between treatments at a particular time. Since the economic modeller of a chronic condition must attempt to project costs and outcomes into the future, the crucial issue is one of **trend** equivalence – even if two procedures appear to be similar in outcomes after 12 months or 2 years, they may nonetheless diverge significantly after 5 or 10 years.

Therefore, we accepted that the traditional non-parametric statistical methods applied in meta-analyses to compare point estimates of outcomes, although useful for addressing some specific questions, provide only a partial assessment of the relative merits of different treatments. For trend estimation, it would be necessary to employ parametric survival models, based on certain *a priori* assumptions about the nature of disease and outcome progression over time. This difference of methodology is most apparent in cases where new technologies are involved and the

bulk of available evidence is of short duration (as with DES).

At first sight, it may appear that conclusions drawn in the chapter covering clinical trial evidence, based on conventional meta-analytic techniques, are in conflict with those described later in the context of economic modelling. However, this confusion is resolved when we recognise that different analytic approaches are required to answer different but complementary questions: 'What has happened to date?' and 'What should we expect to happen in the future?'.

Chapter 3
Methods

Methods for reviewing clinical effectiveness

Search strategy: clinical effectiveness

The search incorporated a number of strategies. Search terms for electronic databases included a combination of index terms (e.g. stent and coronary artery disease) and free text words (e.g. stent and coronary).

Electronic searches included the following databases and covered the period from 1990 to December 2002, as it was in the early 1990s that coronary artery stents were first developed:

- MEDLINE
- EMBASE
- Science Citation Index/Web of Science
- Cochrane Trials Register (CCTR) (2002, 4)
- Cochrane Database of Systematic Reviews (CDSR)
- *Health Technology Assessment* (HTA)
- Database of Abstracts of Reviews of Effectiveness (DARE)
- Science Citation Index/ISI Proceedings.

Specific search strategies and the number of references retrieved for each search are provided in *Table 75* in Appendix 1.

Searching was limited to English language reports.

Reference lists of included studies and pharmaceutical company submissions were searched to identify other relevant studies. Hand searching of recent issues of cardiology journals, including *American Heart Journal*, *American Journal of Cardiology*, *BMJ*, *Catheterization and Cardiovascular Interventions*, *Circulation*, *European Heart Journal*, *Heart*, *International Journal of Cardiology*, *Journal of the American College of Cardiology*, *JAMA*, *Journal of Thoracic and Cardiovascular Surgery*, *Lancet* and *New England Journal of Medicine*, was carried out for the period December 2001 to December 2002 to identify any newly published papers that might not yet have been indexed in electronic databases.

In addition, handsearching of cardiology conference proceedings for the following meetings was conducted:

- ACC (2000, 2001 and March 2002)
- American Heart Association (AHA) (2000, 2001 and November 2002)
- British Cardiac Society (2000, 2001 and May 2002)
- European Society of Cardiology (2000, 2001 and August 2002)
- Transcatheter Cardiovascular Therapeutics (2000, 2001 and September 2002)
- Cardiovascular Revascularization Therapy (January 2003).

The included and on-going studies identified by Meads and colleagues[2] were cross-checked to identify any further studies.

Internet resources (including industry-supported websites) that include searchable content on cardiovascular interventions were examined for information on clinical trials.

All the references were exported to the EndNote reference database (ISI ResearchSoft, Carlsbad, CA, USA.

Inclusion and exclusion criteria: clinical effectiveness

The identified citations were assessed for inclusion in two stages and disagreements were settled by discussion at each stage. Three reviewers independently scanned all the titles and abstracts and identified the potentially relevant articles to be retrieved (YD, RD, RH). Full text copies of the selected papers were obtained and assessed independently by four reviewers for inclusion (AR, RD, RH, YD).

Inclusion criteria

Studies were considered eligible for inclusion if they met the following criteria:

Study design

RCTs.

Population

- adults with CAD in native or graft vessels
- patients with stable angina or ACS, which includes AMI (ST segment elevation and depression, Q-wave and non-Q-wave) and unstable angina.

Intervention
Coronary artery stents of any type inserted as an elective procedure.

Comparators
- PTCA without stent versus PTCA with stent.
- Stent versus CABG.
- Non-DES versus DES.

Outcomes
Studies were included if they reported one or more of the following outcomes: combined event rate or event-free survival; death; AMI; TVR; repeat treatment (PTCA, stent or CABG); and binary stenosis (>50%).

Exclusion criteria
Studies were excluded based on the following criteria:

RCTs that:

- Are continuing to recruit patients.
- Provide only unplanned, interim findings (studies which reported outcomes at pre-established end or time points were eligible for inclusion in the review; information on the intended reporting of outcomes was obtained from trial protocols or early conference presentations).
- Provide data on only a subgroup of patients.

Comparisons of:

- PTCA with stents with medical management.
- Single-versus multiple-vessel stenting.
- Various stent designs.
- Anticoagulant or antiplatelet comparisons (data on their use in include trials were noted).
- PTCA or stenting with other PCI interventions (e.g. atherectomy, Rotablator, brachytherapy).

Data extraction: clinical effectiveness
Data extraction was carried out by four reviewers (YD, RH, RD, AR). Data were independently extracted by one reviewer and then checked by a second reviewer into pretested data extraction forms. Data presented from multiple reports of single trials were extracted on to a single data extraction form.

Quality assessment: clinical effectiveness
Four reviewers (YD, RH, RD, AR) independently evaluated the included primary studies for methodological quality. This involved methodological assessment for clinical effectiveness based on Centre for Reviews and Dissemination (CRD), York, Report 4 (see Appendix 2). Any discrepancies were resolved through consensus.

Methods for reviewing cost-effectiveness

Search strategy: cost-effectiveness
A comprehensive review of the literature was undertaken to identify all literature that may provide evidence with regard to the cost effectiveness of percutaneous coronary interventions.

A total of 648 papers were identified. The abstracts of these papers were obtained and assessed. Search strategies and results of the searches undertaken are provided in *Table 76* in Appendix 1. The following databases were searched for English language papers:

- MEDLINE (1987–2002)
- EMBASE (1987–2002)
- NHS Economic Evaluation Database (NHSEED) (1995–2002)
- DARE (1995–2002)
- Science Citation Index/Web of Science (1987–2002)
- Science Citation Index/ ISI Proceedings (1990–2002)
- Cochrane Trials Register (2002, 4)
- HTA (1990–2002).

Inclusion and exclusion criteria: cost-effectiveness
Using explicit, predetermined criteria, two reviewers (AH, RD) independently identified studies for inclusion in the cost-effectiveness review process. Disagreements were resolved through discussion. A total of 117 papers were selected as being of potential value to the study and their full papers were obtained and reviewed. These papers were used to inform the background of the economic analysis with a subset of 91 papers providing data to inform aspects of the independent economic model. Further subsets of papers were used to inform the budgetary impact analysis. The inclusion and exclusion criteria used in the review are presented below.

A further joint review of the 117 full papers was undertaken by three health economists (AB, AH, RMM). The aim of this review was to assess which economic evaluations had been undertaken in the context of high-quality RCTs. Papers were

excluded if the source of clinical efficacy data was from non-randomised clinical trials (or where the source was not explicitly stated) and if there had been no attempt to measure both resource use and outcomes within the randomised trial design. Unfortunately, none of the published full economic analyses evaluated cost-effectiveness within the context of the NHS. To rectify this gap, we obtained access to the unpublished economic analysis of the recently completed Stent or Surgery (SOS) trial.

Inclusion criteria

Full economic evaluations that compare two or more options and consider both costs and consequences, including:

- cost-effectiveness analysis
- cost–utility analysis
- cost–benefit analysis.

Population

Adults with CAD and patients with stable angina or ACS, which includes AMI (ST segment elevation and depression, Q-wave and non-Q-wave) and unstable angina.

Intervention

Coronary artery stents of any type inserted as an elective procedure.

Comparators

- PTCA without stent versus PTCA with stent
- stent versus CABG
- non-DES versus DES.

Economic outcomes

Utility weights related to clinical outcomes.

Exclusion criteria

- main source of clinical efficacy data from non-RCT or not explicitly stated
- no attempt to synthesise costs and benefits
- letters, editorials, reviews, commentaries or methodological papers.

All the references were exported to the EndNote reference database (ISI ResearchSoft).

Chapter 4

Stents versus percutaneous transluminal coronary angioplasty (PTCA)

PTCA: included studies

Introduction

Fifty studies fulfilled the inclusion criteria. These included 23 studies[36–58] comparing stenting with PTCA in patients with non-specific CAD, 11 comparing stents with PTCA following AMI,[59–69] eight[70–77] including patients with small coronary arteries and eight including patients whose vessels had chronic total occlusion (CTO).[78–85]

Thirty-nine studies were assessed from reports published in peer-reviewed journals. The remainder were abstracts of conference proceedings. Despite search efforts, further information on these abstracts was not available.

The study and participant characteristics are presented in Appendix 3 ordered by specified subgroups of patients with:

- Non-specific CAD. These studies may have a varied case mix of patients, for example, patients with stable or unstable angina.
- Experiencing an AMI.
- Small coronary arteries.
- CTO of a coronary artery.

This ordering is maintained in the meta-analyses.

Provisional stenting

Five of the included studies[41,43,46,48,49] defined in their methods and included a strategy of provisional stenting in which stents were implanted in patients with suboptimal results following PTCA. Crossovers from PTCA to stent implantation in these trials varied between 13.5 and 56.4% (BOSS, 36%; FROST, 48.4%; DESTINI, 56.4%; OCBAS, 13.5%; and OPUS, 37%).

PTCA: study characteristics

Numbers of participants, centres and locations

Trials ranged in size from 60 to 2399 patients, randomising more than 16,500 patients. Thirty-eight studies had fewer than 500 patients in total; two studies enrolled over 1000 patients.[45,60]

Forty-one studies were multicentred. Of these, 21 were carried out in more than one country. The remainder were conducted in a single country [Canada, Poland, Spain, Israel, The Netherlands, Italy, Japan (three studies), France (four studies), USA (two studies), Germany (five studies)]. Nine studies were single-centred and were conducted in Italy,[56,62] Germany,[67] The Netherlands,[61] Spain,[75] Switzerland,[44] Korea[74] and the UK.[47,80]

Details of study characteristics of RCTs comparing stents with PTCA are presented in *Table 77* in Appendix 3.

Adjunctive treatment

All studies used various adjunct treatments. In early studies, warfarin was used as the standard antithrombotic treatment.[38,47,51–53,56,79,80,82] Ticlopidine has been used more commonly in recent years. In some trials,[57,61] the drug regimen for the stent patients was changed from warfarin to ticlopidine owing to the increased risk of bleeding complications. In the CADILLAC trial,[60] patients were assigned to four interventions including PTCA alone, PTCA plus abciximab, stenting alone or stenting plus abciximab, but the only results included in this review are for the PTCA and stenting alone groups. Abciximab was used in a small proportion of patients in other studies.[69,73]

PTCA: participant characteristics

Thirty-nine studies included patients with both stable and unstable angina; one study[38] was limited to patients with stable angina. Eleven studies included patients within 12–24 hours of MI onset. Of these, four[60,61,68,69] excluded patients with cardiogenic shock.

Ten studies[36–38,42,44,46,50,56,57,76] included patients with single-vessel disease. Two studies[51,55] included patients who had lesions in SVGs.

The majority of participants were male [range 63.4 (74)–87.5% (56)] and the mean age in the trials ranged from 52.1 (37) to 67.3 (65) years. The proportion of patients with diabetes mellitus varied across the studies, the lowest proportion

was in BOSS study[41] and the highest was seen in CHIVAS[71] (stent group 51.4% and PTCA group 48.6%).

Participant characteristics are presented in *Table 78* in Appendix 3.

PTCA: Study outcomes

Outcomes reported

Thirty-two of the 50 included studies described similar outcomes and combined event rates (mainly mortality, AMI and repeat revascularisation). In 15 of the 32 studies, this was explicitly defined as 'major adverse cardiac events' (MACE); the remaining 17 studies did not clearly define their outcomes as MACE. Seven studies[37,38,44,60,68,73,82] included cerebrovascular events, one study[63] included recurrent ischaemia and four studies[49,56,83,84] included recurrence of angina as part of their combined event rate. The remaining seven studies did not have clearly defined combined outcomes or did not include all major adverse cardiac events.

Event rate definitions for each study are presented in *Table 8*.

Follow-up

The length of follow-up varied across the studies. Angiographic follow-up at 6 months was available from 26 of the studies. In 29 studies, clinical follow-up was available at 6 months; however, few studies reported on the longer term outcomes for each intervention arm. Thirteen studies[38,39,42,43,49,53,54,56,57,63,65,69,77] reported outcomes at 1 year, two studies[61,67] at 2 years, one study[52] at 4 years and in one study the longest period of follow-up was 5 years.[38] Three studies[45,68,86] reported on follow-up separately for those with diabetes mellitus (DM).

Outcome data for PTCA studies are presented in *Table 79* in Appendix 3.

Quality assessment of included PTCA studies

Methodological quality of studies is summarised in *Table 9* using the criteria based on CRD Report 4 (Appendix 2).

In each trial, the treatment allocation was randomised, although 18 studies (including those reported as conference abstracts) did not describe their method of randomisation or whether the allocation sequence was concealed. Where reported, baseline characteristics were generally comparable in each intervention arm.

Because of the nature of interventions in this category, it is not possible to blind investigators or patients to the treatment location and therefore the studies were not scored for quality.

Crossovers were high in some studies [from PTCA to stent these ranged from 0 (80) to 56.4% (43)], but all trials, apart from those assessed from conference abstracts where information was limited or not available, appeared to include an intention-to-treat (ITT) analysis.

Follow-up rates for clinical outcomes in all studies were excellent, (>90%). Apart from one study,[41] follow-up for angiographic outcomes was also high at >80%.

PTCA: data analysis

Analysis of data included combined event rates, mortality, any AMI and binary restenosis rates. Treatment effects are presented using odds ratios (OR) and with corresponding 95% confidence intervals (CI). All analyses use a fixed-effects method unless qualitative heterogeneity was demonstrated, in which case both fixed and random effects results are provided.

As discussed earlier, studies are divided and presented in four categories. These groups are studies in patients with:

- Non-specific CAD. These studies may have a varied case mix of patients, for example, patients with stable or unstable angina.
- Experiencing an AMI.
- Small coronary arteries.
- CTO of a coronary artery.

Studies within the non-specified patient groups may include patients with recent MI and chronic total occlusion. Some of the studies[36,38,43,46,53] in this group also include a number of patients with small coronary vessels (vessel diameter <3.0 mm).

Forest plots of the meta-analyses discussed below are presented in *Figures 6–9*.

PTCA: event rates

All studies used a combination of major adverse events and this varied across the studies. The event rate definitions used in the trials are summarised in *Table 8*. The results related to this measure predominantly represent revascularisation procedures.

TABLE 8 *Stent versus PTCA: included studies event rate definitions*

Study	Event rate composition
ADVANCE	MACE – cardiac death, MI, CABG or PTCA
AS	Death, CVA, MI, TLR (PTCA or CABG)
BENESTENT	All deaths, CVA, MI (Q- and non-Q-wave), CABG, PTCA of previously treated lesion
BENESTENT II	All deaths, MI, CABG, PTCA
BESMART	MACE – death, MI, CABG, PTCA
BESSAMI	Death, MI, reintervention, CABG
BEST	Not defined
BOSS	Not defined
CADILLAC	MACE – death (all causes), reinfarction, TVR or CVA
CHIVAS	MACE – death (all causes), CABG, PTCA
COAST	Not defined
CORSICA	MACCE – not defined
DEBATE II	MACE – all deaths, non-fatal MI, TLR (CABG or PTCA)
DESTINI	MACE – death (cardiac), MI, re-TLR
Eeckhout, *et al*.	Death, CVA, MI, CABG, PTCA
EPISTENT	Any death, MI or reinfarction, or severe ischaemia requiring CABG or PTCA
ESCOBAR	All deaths, MI, TVR by CABG or PTCA
FRESCO	Death, MI, TVR
FROST	MACE – death, MI, TLR
GISSOC	Death, MI, CABG, re-PTCA, TVR
GRAMI	Death, recurrent ischaemia, MI, CABG
Hancock *et al*.	Death, MI, CABG, PTCA
ISAR-SMART	Death (all causes), MI, stroke, TVR (CABG or PTCA)
Jacksch *et al*.	Not defined
Knight *et al*.	Treatment failure (requirement for urgent CABG/re-PTCA, restenosis) and cardiac death
OCBAS	Cardiac death, MI (Q- and non-Q-wave), angina, TVR
OPUS	Death, MI, TVR, CABG
Park *et al*.	Death, MI, TVR
PASTA	MACE – cardiac death, MI, TLR
PRISAM	Not defined
PSAAMI	Death, MI, TLR
RAP	MACE – death, MI or TVR
RSSG	Death, MI, CABG, PTCA of target vessel
SARECCO	Death, MI, CABG, PTCA
SAVED	Death, MI, CABG, TLR
SICCO	MACE – cardiac death, CVA, lesion treated MI, lesion treated CABG or PTCA
SISA	MACE – death, MI (Q, non-Q), CABG or re-PTCA
SISCA	MACE – cardiac death, AMI, TVR
SPACTO	MACE – death, MI, CABG, PTCA, recurrence of angina
START	Death (cardiac), AMI, TVR (CABG, PTCA)
STENTIM II	Death, MI, TLR (by PTCA or CABG)
STENT PAMI	Death, CVA, MI, ischaemia-driven TVR (PTCA or CABG)
STOP	MACE – death, recurrent AP, MI (Q-wave), PTCA, CABG
STRESS	All deaths, MI, CABG, PTCA
STRESS II	Same as STRESS
TOSCA	Death, MI, any revascularisation in hospital
VENESTENT	MACE – death, MI, CABG or PTCA of the target vessel
Versaci *et al*.	Death, MI, recurrence of angina
WIDEST	Death, MI, vessel occlusion, CABG, PTCA
WIN	Not defined

CVA, cerebrovascular accident.

There was no difference in event rate to 36 days for studies with non-specified participants or with patients with small vessel disease. However, there is a statistically significant reduction in event rate in those patients where the indication for PCI was AMI, in favour of stents at all time frames analysed. At 6 months the event rate is significantly reduced in favour of stents in all groups (for non-specific group, OR 1.64, 95% CI 1.44 to 1.87; for AMI group, OR 2.36, 95% CI

TABLE 9 *PTCA: quality assessment of included studies*

Study	Randomisation			Baseline comparability				Blinding				Withdrawals		
	Truly random	Allocation concealment	No. stated	Presented	Achieved	Eligibility criteria specified	Co-interventions identified	Assessors	Administration	Participants	Procedure assessed	>80% randomised in final analysis	Reasons stated	ITT
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
ADVANCE	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
AS	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
BENESTENT I	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
BENESTENT II	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
BESMART	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
BESSAMI[a]	×	×	✓	×	×	×	×	×	×	×	×	×	×	×
BEST[a]	×	×	✓	×	×	×	×	×	×	×	×	×	×	×
BOSS	NS	NS	✓	✓/×	✓/×	✓	✓	×	×	×	×	✓	✓	✓
CADILLIC	NS	NS	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
CHIVAS[a]	×	×	✓	×	×	×	×	×	×	×	×	×	×	×
COAST[a]	×	×	✓	×	×	×	×	×	×	×	×	×	×	×
CORSICA[a]	×	×	✓	×	×	×	×	×	×	×	×	×	×	×
DEBATE II	NS	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓/×	✓
DESTINI	NS	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
Eeckhout *et al.*	NS	NS	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
EPISTENT	NS	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
ESCOBAR	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
FRESCO	NS	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
FROST	NS	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
GISSOC	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
GRAMI	NS	NS	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
HINCOCK	NS	NS	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
ISIR-SMIRT	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
Knight *et al.*	NS	NS	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
Jacksch[a]	×	×	✓	×	×	×	×	×	×	×	×	×	×	×
OCBAS	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
OPUS	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
Park *et al.*	✓	NS	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
PASTA	NS	NS	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓

continued

TABLE 9 *PTCA: quality assessment of included studies (cont'd)*

Study	Randomisation			Baseline comparability				Blinding				Withdrawals		
	Truly random	Allocation concealment	No. stated	Presented	Achieved	Eligibility criteria specified	Co-interventions identified	Assessors	Administration	Participants	Procedure assessed	>80% randomised in final analysis	Reasons stated	ITT
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
PRISAM[a]	×	×	✓	×	×	×	×	×	×	×	×	×	×	×
PSAAMI	NS	NS	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
RAP[a]	✓/×	×	✓	×	×	✓/×	×	×	×	×	×	×	×	×
RSSG	✓/×	✓/×	✓	✓	✓	✓	×	×	×	×	×	✓	×	✓
SARECCO	✓/×	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
SAVED	✓/×	×	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
SICCO	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
SISA	✓/×	×	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
SISCA	✓/×	×	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
SPACTO	✓/×	×	✓	✓	✓/×	✓	✓	×	×	×	×	×	✓	✓
START	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
STENTIM II	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
STENT PAMI	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
STOP	NS	NS	✓	✓	✓	✓	✓	×	×	×	×	×	✓	✓
STRESS I	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
STRESS II[a]	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
TOSCA	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
VENESTENT[a]	×	×	✓	×	×	✓	×	×	×	×	×	✓	×	✓
Versaci *et al*.	NS	NS	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
WIDEST	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
WIN[a]	✓/×	×	✓	×	×	×	×	×	×	×	×	×	×	×

Items graded: ✓, yes (item adequately addressed); ×, no (item not adequately addressed); ✓/×, partially (item partially addressed); NS, not stated. Quality assessment checklist items are described in full in Appendix 2.

[a] Trials were reported as conference abstracts only.

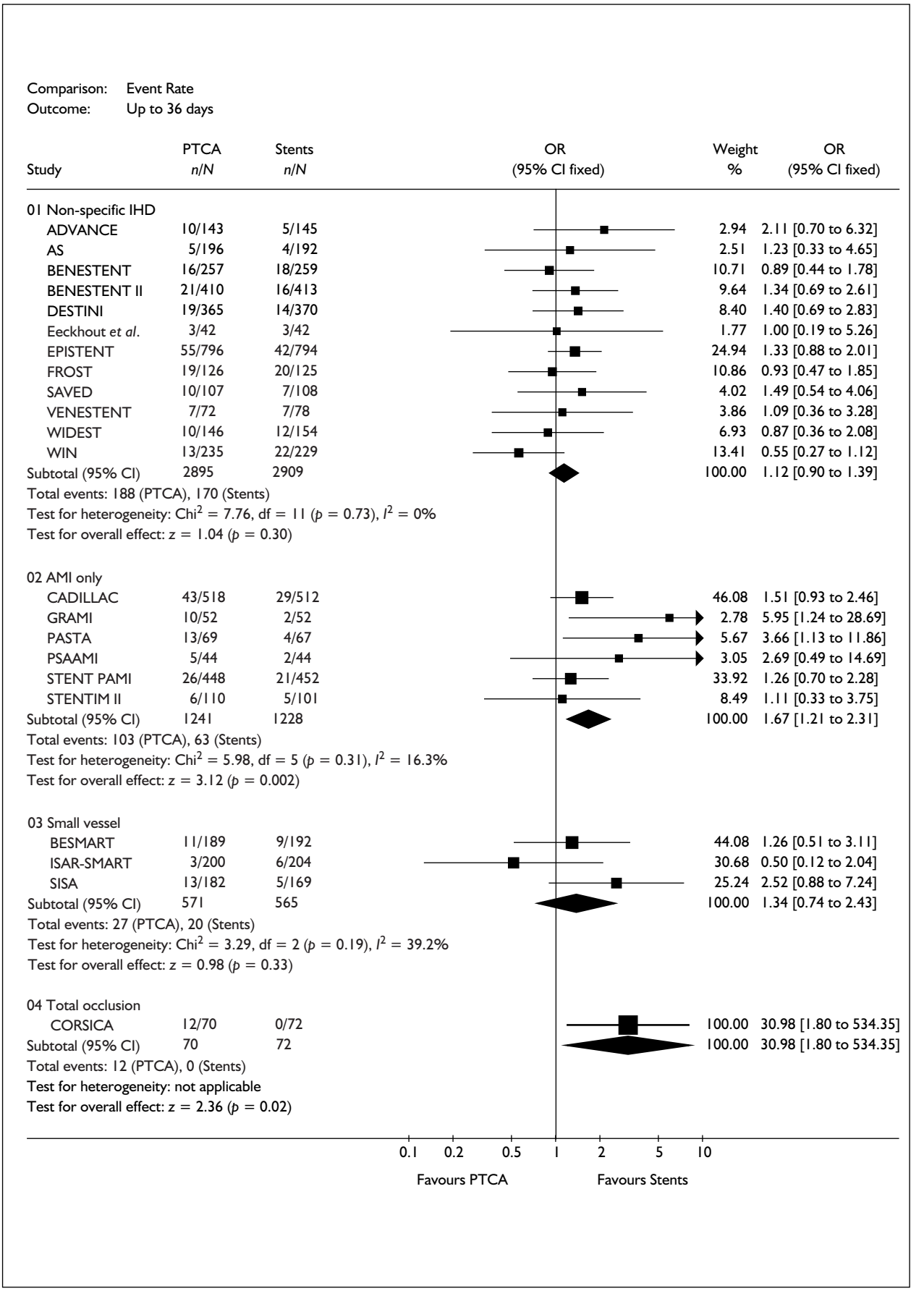


FIGURE 6 *PTCA: meta-analysis of event rate*

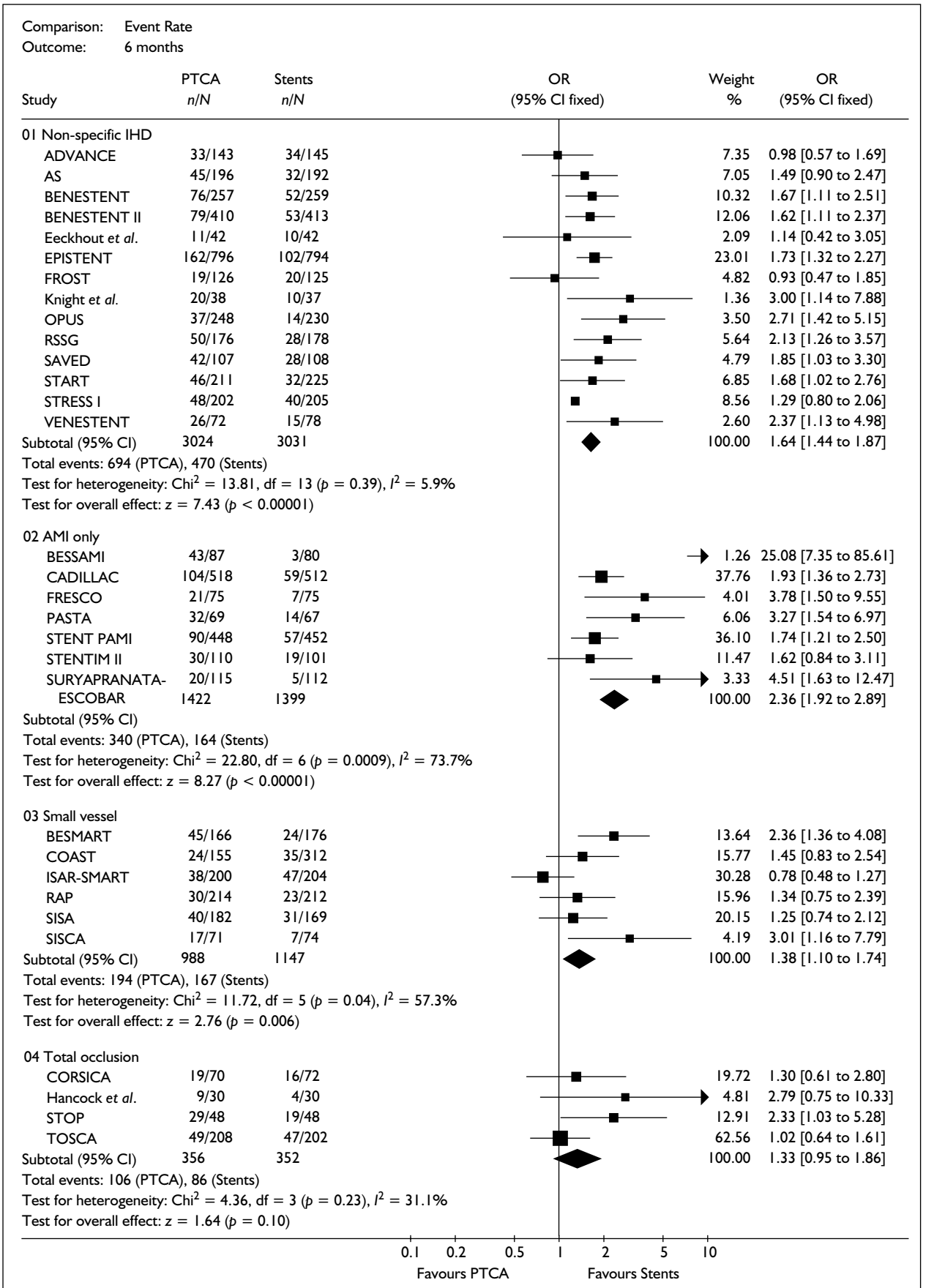


FIGURE 6 *PTCA: meta-analysis of event rate (cont'd)*

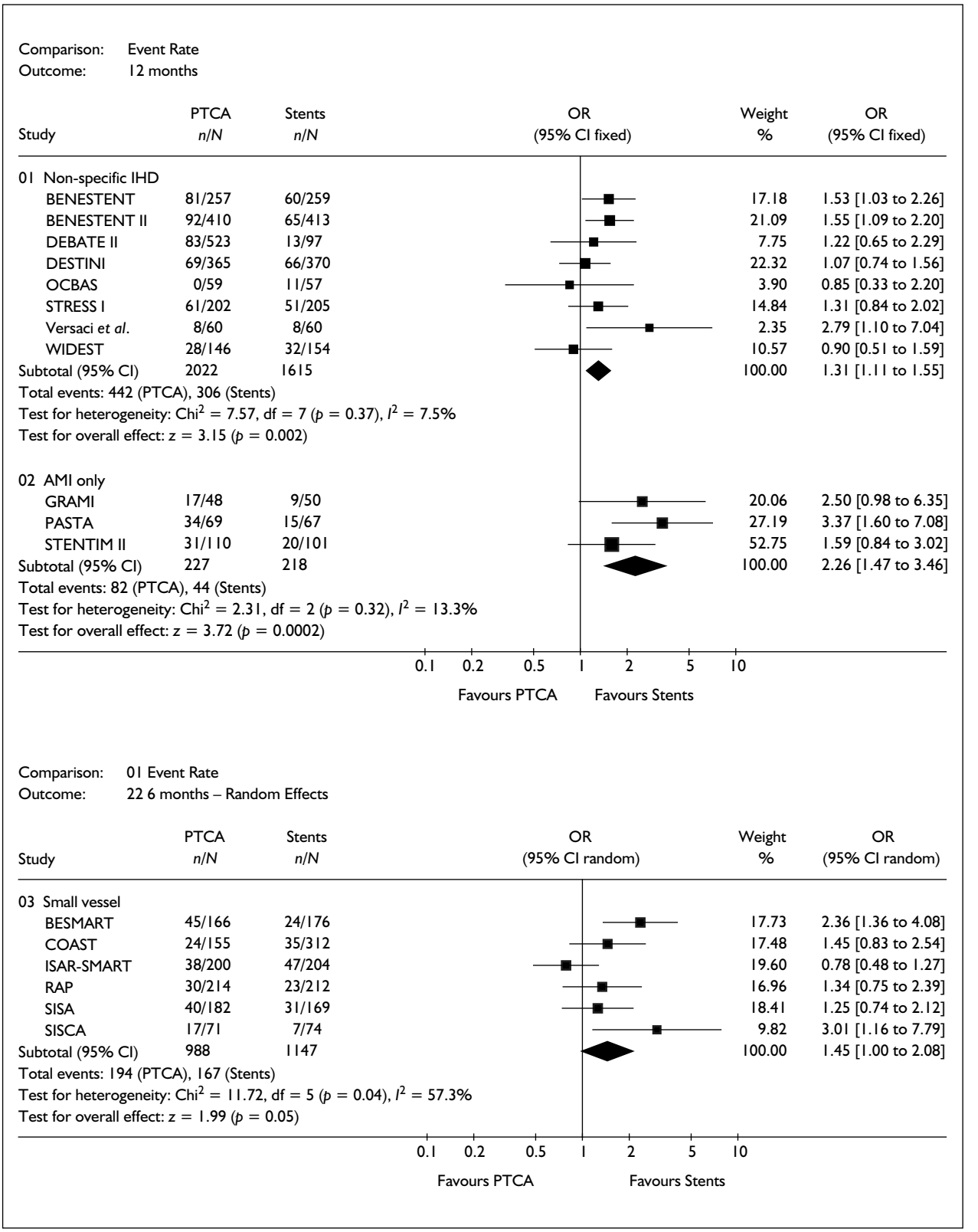


FIGURE 6 *PTCA: meta-analysis of event rate (cont'd)*

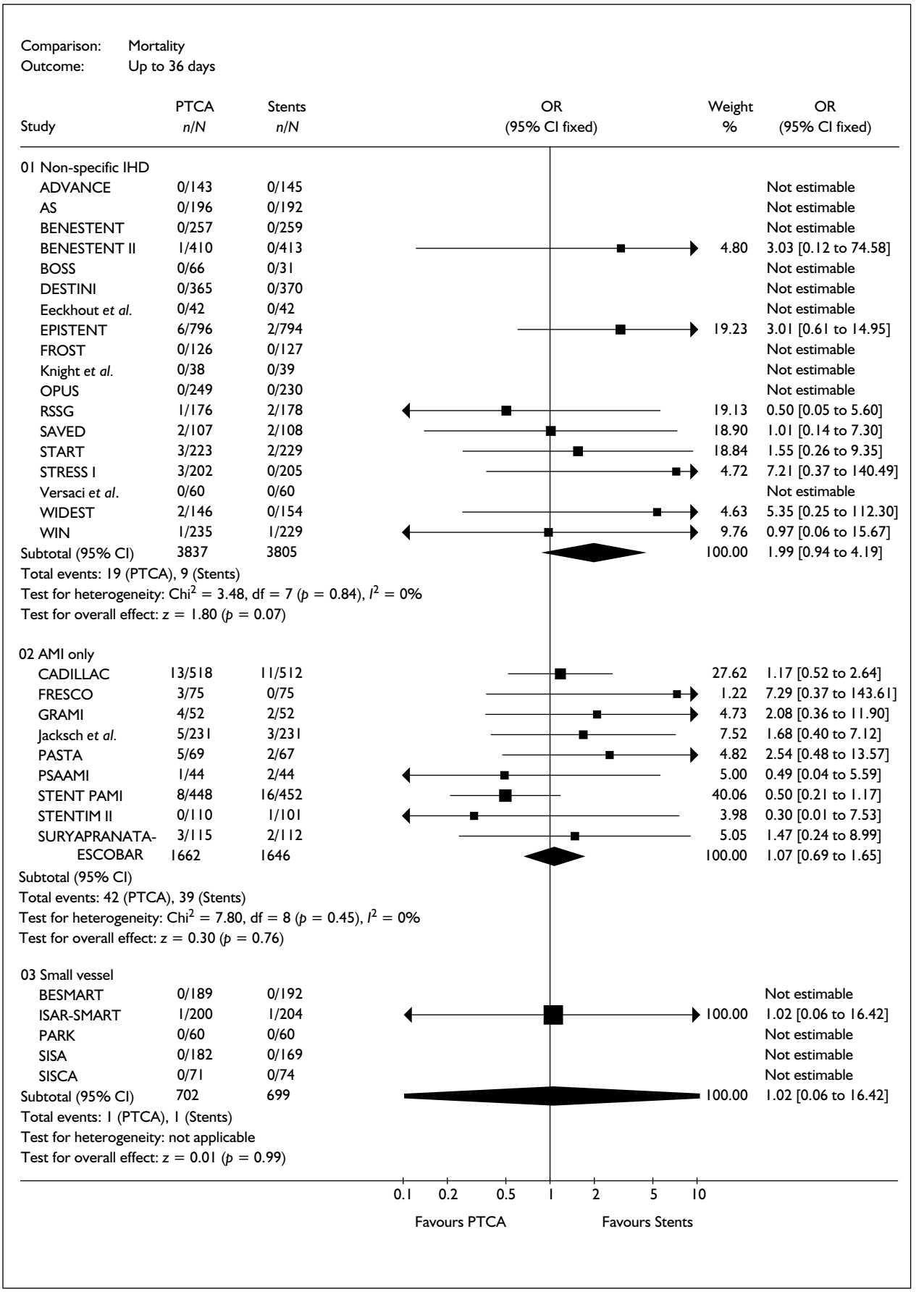


FIGURE 7 *PTCA: meta-analysis of mortality*

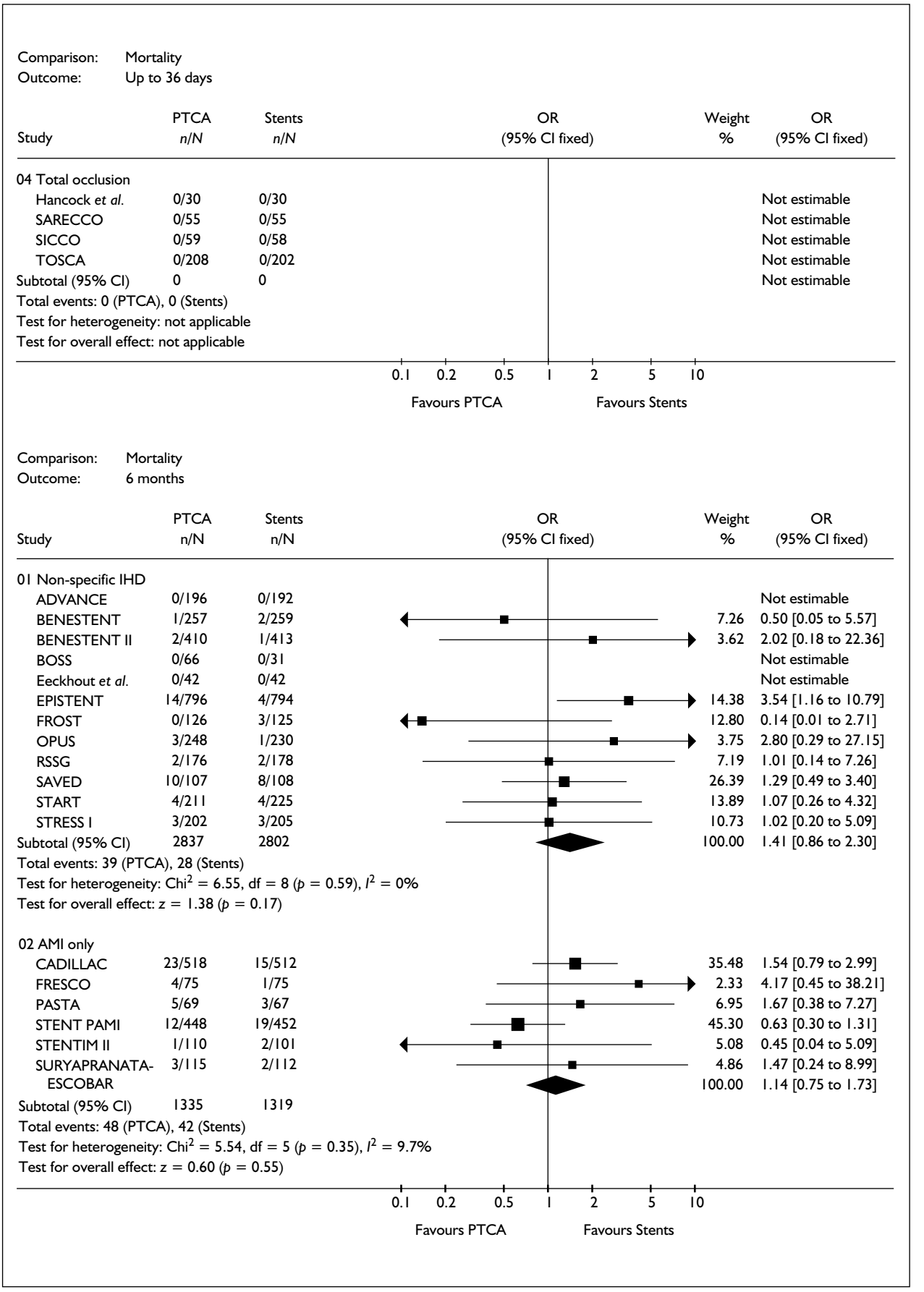


FIGURE 7 *PTCA: meta-analysis of mortality (cont'd)*

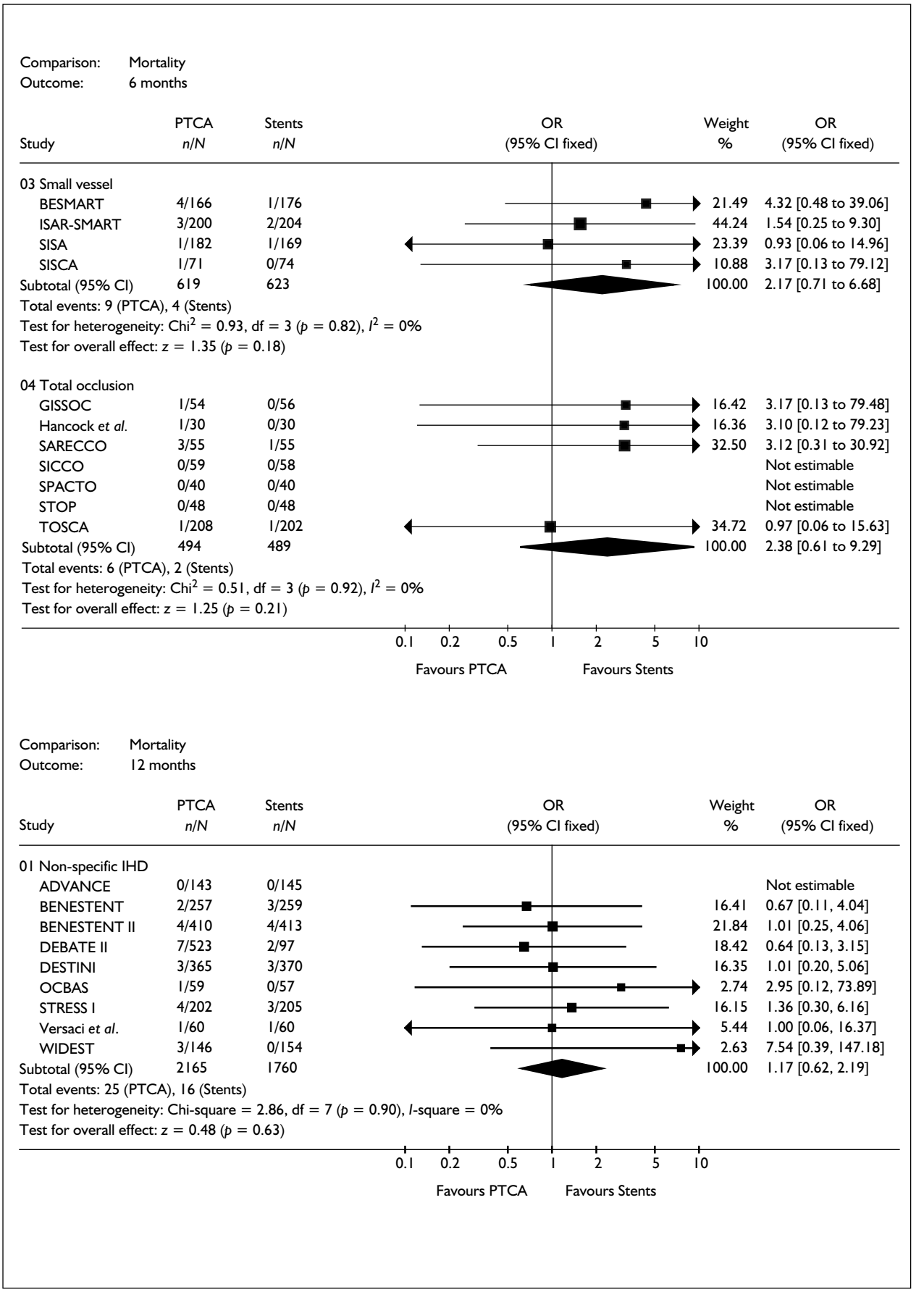


FIGURE 7 *PTCA: meta-analysis of mortality (cont'd)*

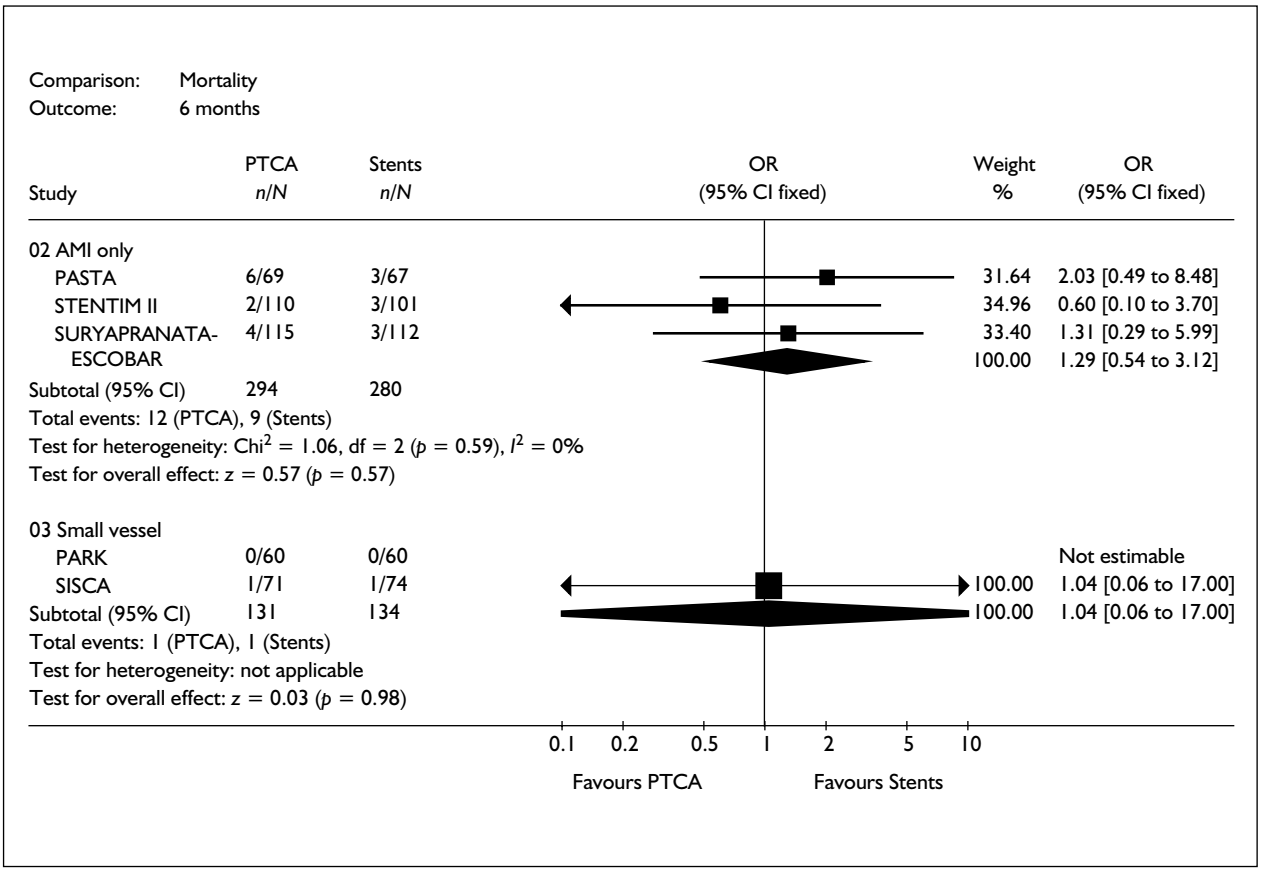


FIGURE 7 *PTCA: meta-analysis of mortality (cont'd)*

1.92 to 2.89; for small vessel group, OR 1.38, 95% CI 1.10 to 1.74) except those with total occlusion, where there is a trend in the same direction. Results of analysis of the small vessel group at 6 months indicated qualitative differences and both random and fixed effects analyses are presented.

The event rate at 12 months is reported from only a small number of studies, but is significantly reduced for the two groups (non-specific CAD and AMI) examined (OR 1.31, 95% CI 1.11 to 1.55; for AMI, OR 2.26, 95% CI 1.47 to 3.46).

As this is the main area where a benefit for stents has been shown, we must consider at some length what exactly 'events' and this reduction in event rate actually mean. This is explored in the section 'Outcomes' (p. 38).

PTCA: mortality

Mortality is a rare event. The analysis shows no evidence of effectiveness in relation to decreasing mortality in any group at any period analysed.

PTCA: myocardial infarction

In the short term, there are no differences in MI rates between stents and PTCA in studies with non-specific CAD patients, small vessels or CTO groups. Analysis of studies including only AMI patients indicates a statistically significant benefit for patients receiving stents (OR 2.21, 95% CI 1.2 to 4.09). This benefit does not continue into the 6-month and 1-year analyses. In the CTO group, the analysis indicates an advantage towards PTCA (OR 0.41, 95% CI 0.21 to 0.83) at 6 months. This result is dominated by the results of one trial (TOSCA). No 1-year data were available for analysis.

PTCA: binary stenosis

Binary restenosis is normally reported at 6 months. This was the case in all studies but one.[64] In each subgroup, a statistically significant benefit for stents was observed; this was greatest for CTO (OR 2.8, 95% CI 2.15 to 3.65) and AMI only (OR 2.44, 95% CI 1.92 to 3.12). Analysis of the non-specific group at 6 months indicated a qualitative heterogeneity and both random and fixed effects are presented.

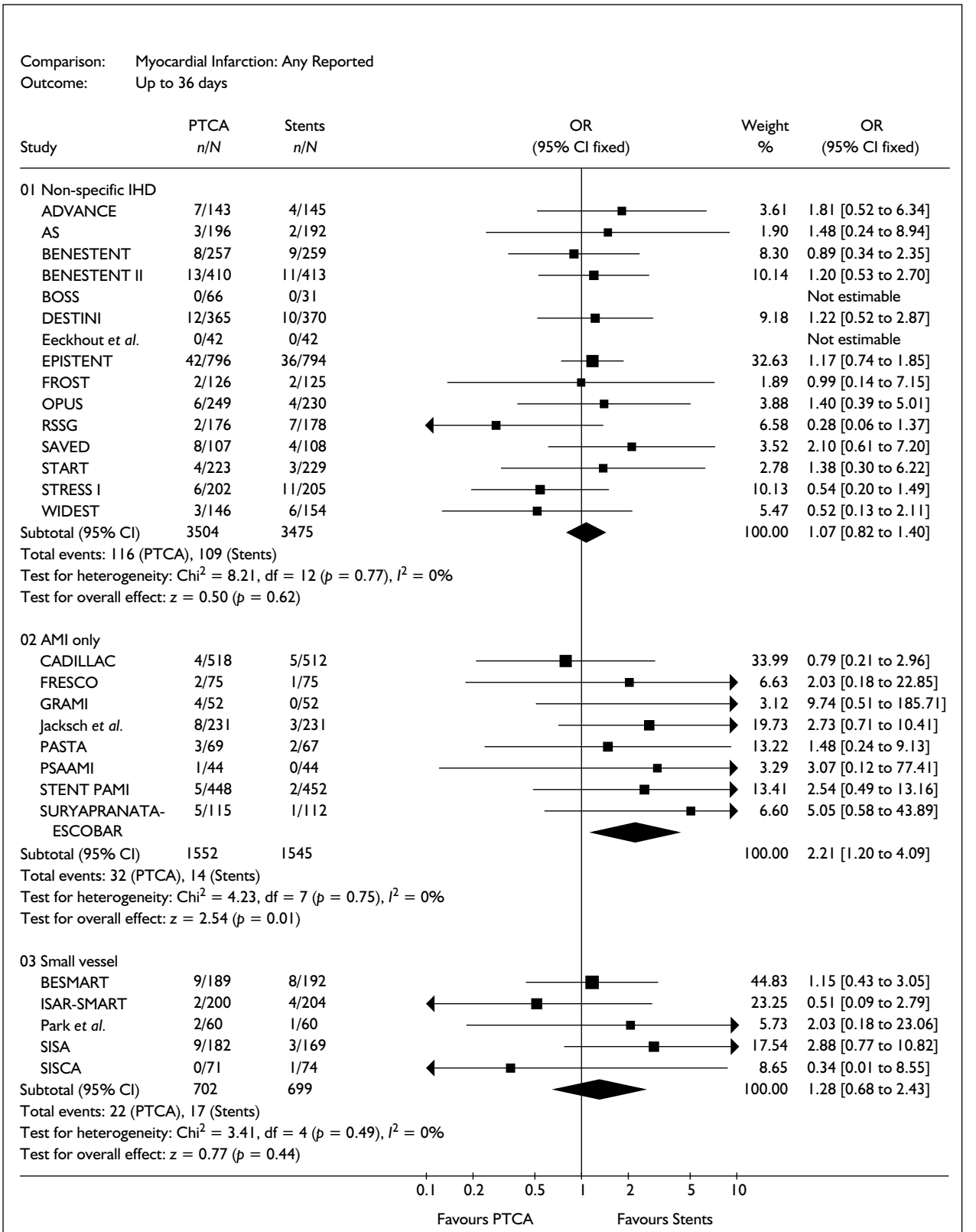


FIGURE 8 *PTCA: meta-analysis of any reported myocardial infraction*

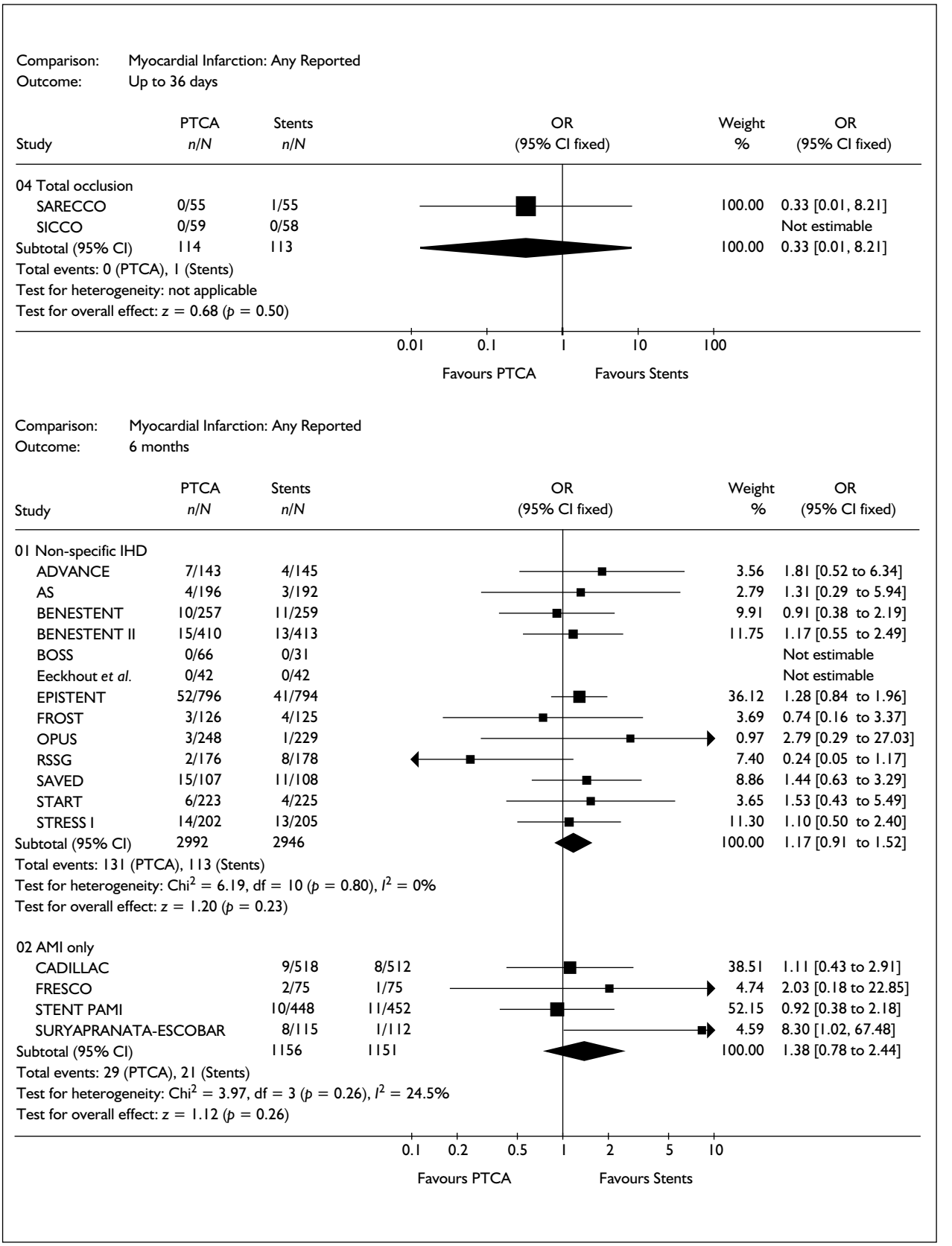


FIGURE 8 *PTCA: meta-analysis of any reported myocardial infraction (cont'd)*

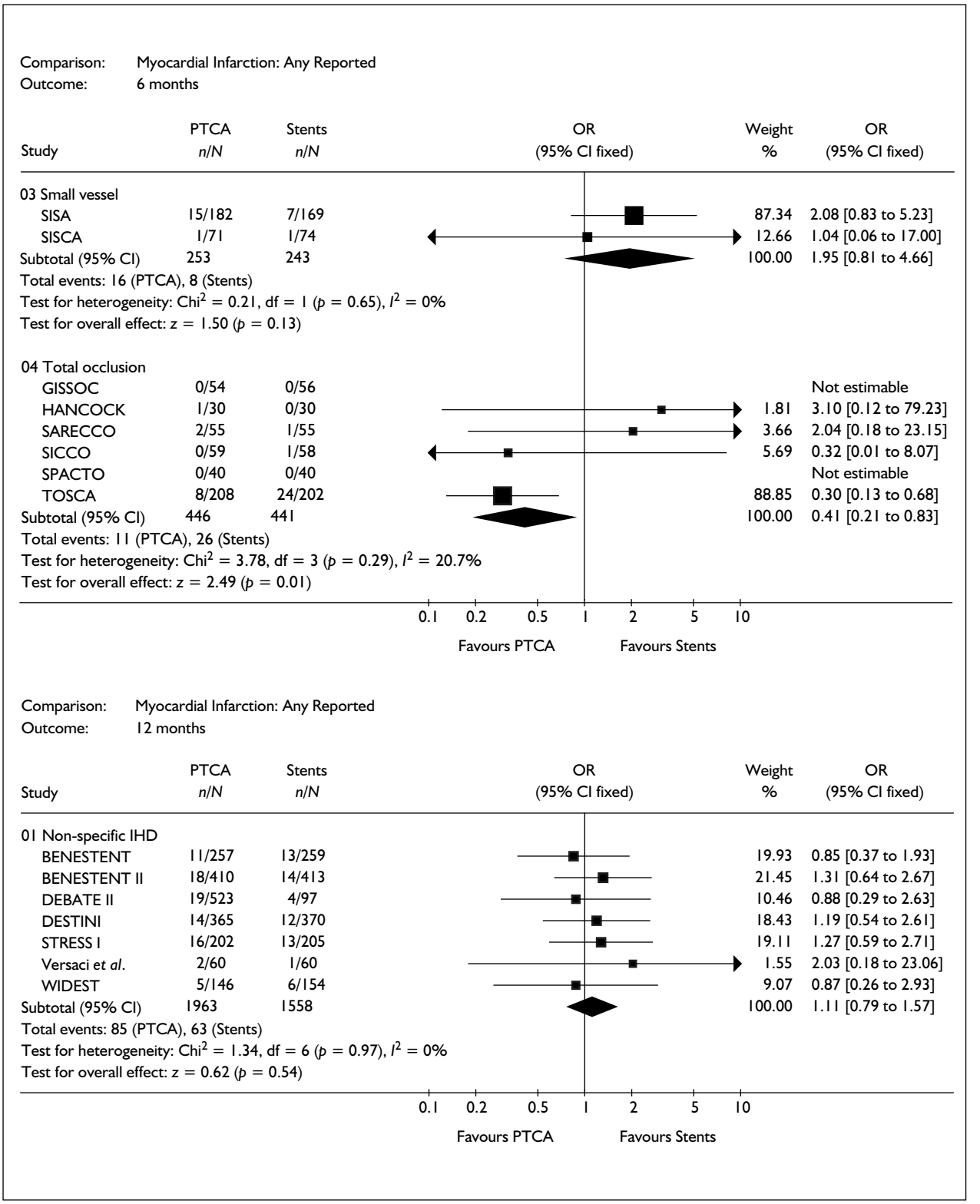


FIGURE 8 *PTCA: meta-analysis of any reported myocardial infraction (cont'd)*

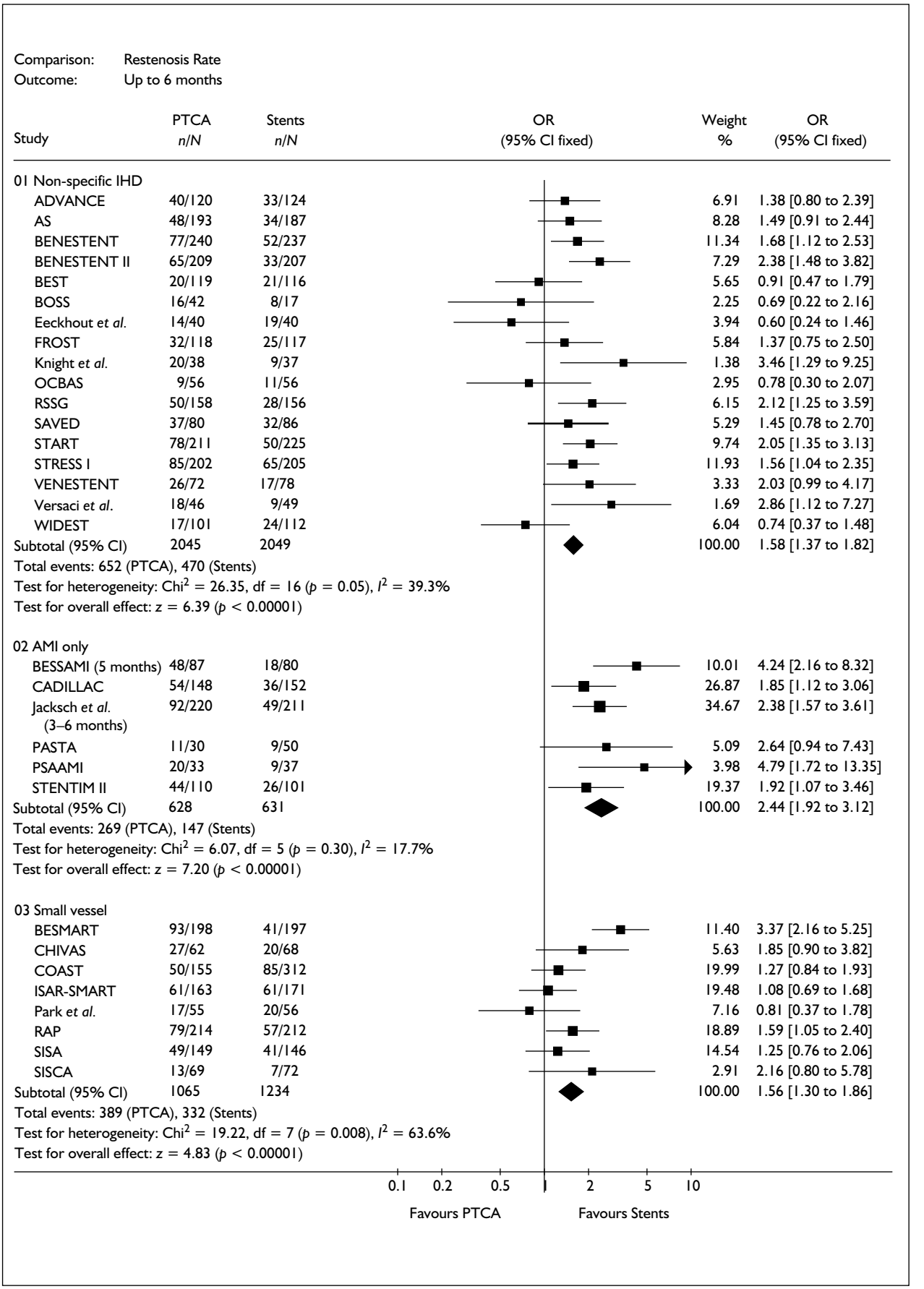


FIGURE 9 *PTCA: meta-analysis of restenosis*

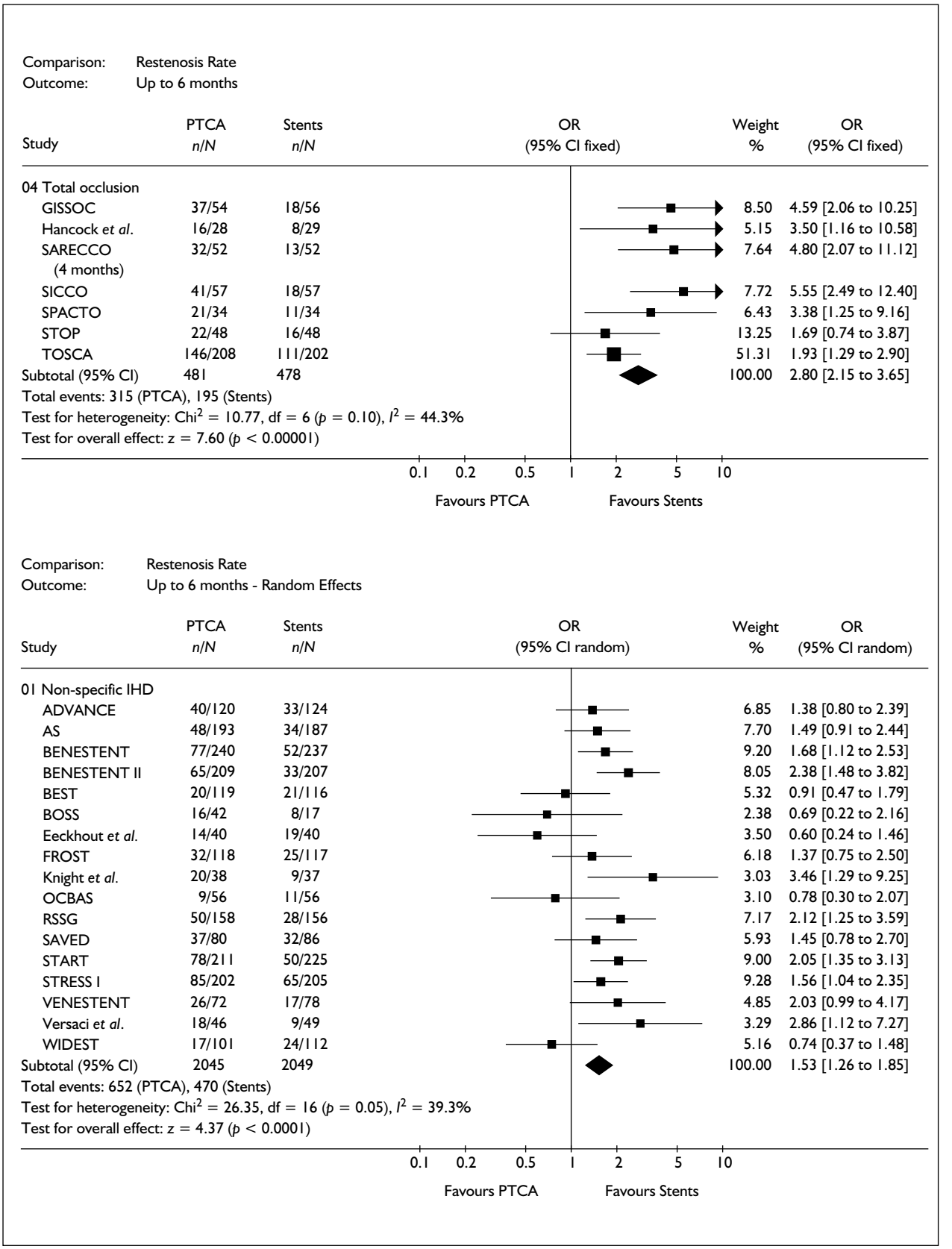


FIGURE 9 *PTCA: meta-analysis of restenosis (cont'd)*

Discussion

Mortality

There is no evidence of benefit in mortality. In relation to stenting versus simple angioplasty in AMI, this confirms the results of an earlier meta-analysis.[87]

However, it must be acknowledged that the power of the studies or meta-analysis to detect a benefit in mortality, even if it existed, is low (see later for power calculation). Mortality may not therefore be a realistic outcome to consider in terms of these small studies, albeit the most important from the patient perspective. This point emphasises what benefits can actually be expected from stenting in such studies – reduction in revascularisations, perhaps in angina, but not in mortality. Registry studies also have not shown decreased mortality so far.[24]

Event rate

The included studies show evidence of reduction in major adverse cardiac event rate with the use of stents, which appears more pronounced in highest risk patients, that is, those with AMI. This benefit in event rate seems to persist for at least up to 12 months in those studies reporting follow-up to that point.

The benefits in AMI were observable in the early stages after stenting. The issue of the role of PTCA and stenting in AMI has recently been examined in a meta-analysis[88] that compares it with thrombolysis. The review demonstrated greater immediate and long-term benefits in the stented patient group.

The reduction in event rates is in keeping with those seen in the earlier review by Meads and colleagues,[2] which considered only the 25 studies then available, rather than the 50 considered here. A number of the studies identified by Meads and colleagues[2] as not yet complete or published have now produced results and been included (see *Table 10*). There are a small number of studies yet to report but the review team anticipate that these will not significantly alter the current conclusions.

Restenosis rates

Binary restenosis rates were reduced by stenting. In part this correlates with event rates because the event rates were often driven by protocol-based angiographic findings. We cannot draw a correlation between angiographic appearances and clinically driven event rates from the studies reviewed.

Comparability of interventions

There are differences in the technologies used in the included trials. A substantial range of stents was used, and we have assumed that there is no major difference according to type of stent between studies. This may be incorrect as there is evidence that newer stent designs with thinner struts may have lower restenosis rates than older stents.[95,96] In one retrospective study, the stent design was the second most important factor in predicting restenosis after lesion type, and different stents had restenosis rates of between 20 and 50%.[97] There are also other ways in which technology differed or has changed – in particular the adjuvant drug therapies may differ substantially between those early studies that used aspirin, heparin, ticlopidine or clopidogrel, or the much more recent studies which have used the glycoprotein IIb/IIIa receptor antagonists. The latter are now recommended as standard therapy in many cases and may lead to substantially improved outcomes.[45] Very few of the studies comparing angioplasty with stenting and reported here (see *Table* 77 in Appendix 3 for co-therapies) have used such drugs.

Outcomes

The simplest clear outcome across all subjects might be mortality but, as mentioned above, the studies were not powered to detect this, nor is it

TABLE 10 *Summary of studies identified by Birmingham review failing to report further data*

Study name	Patient group	Status 1999[a]	Status 2002
GIPSI[89]	CAD, non specific	Allocation not complete	No further information available
MAJIC[90]	CTO	Allocation not complete	No further information available
Sato *et al.*[91]	CTO	No patient numbers in either arm	No further information available
SOAR[92]	CAD, non specific	Allocation not complete	No further information available
SVS[93]	Small vessels	Allocation not complete	No further information available
TASC[94]	CAD, non specific	No patient numbers in either arm	No further information available

[a] As presented in the review by Meads and colleagues.[2]

likely that even the meta-analysis would have any significant power in this area. Instead, studies report a large number of outcomes of varying importance.

Primary outcomes for the studies were revascularisation – an angiographically relevant result perhaps, but less relevant to the patient than total revascularisations, to include target or other vessels. This might be regarded as the parallel between the measurement of efficacy (angiographic outcome) and the measurement of effectiveness (clinical events). From the patient's point of view, it would matter little whether revascularisation was done to the target lesion or to some other lesion in terms of number of events, and therefore we believe that total revascularisation is the more important outcome measure.

Most trials report a composite outcome such as MACE, although with varying definitions. The use of such composite end-points is common in drug-related studies where they achieve a higher baseline event rate by merging a series of related events, in a hierarchical manner so that the same event is not counted more than once. This gives the study a statistical power which it might otherwise lack if it examined only one or two of the elements of the composite. However, the elements included in the composite end-points must be carefully considered, and should be reported in a disaggregated manner. It might be argued that since the composite end-point was a preset end-point, its use is statistically valid; however, if the end-point is unsatisfactory, the fact that it was preset for the analysis is surely irrelevant.

The means of detecting the end-point might also be important. Rates of MI may vary as many studies detect MI not as a clinical event with chest pain hospital admission, but as an ECG appearance at routine 6-monthly follow-up. Such variations influence clinical end-point rates and may impact on cost and on QoL measures.

The single largest element of event rate was repeat revascularisation procedures. Many protocols required a repeat angiography at 6 months after the original procedure, even in the absence of clinical symptoms. This led to a large increase in the detection of what might be considered angiographic poor results and increased the number of revascularisations. An example is the BENESTENT II study,[39] where a number of patients had repeat angiography and a smaller number did not. In both groups the number of revascularisations was similar in the first 5 months of the 12-month follow-up (6.1% in the no angiography patients versus 8.9% in the angiography patients) and in the last 4 months of the study (2.4% no angiography versus 2.6% angiography). In the period 6–8 months, the revascularisation rates were 3.4% in the no angiography patients, but 8.9% in the angiography group ($p < 0.05$).[98] It might be argued that the higher rate in the angiography arm results in a reduced rate later in the study, compared with the control arm. Investigations involving longer term follow-up should capture this.

In the included studies, it is unclear which events were true clinical events and which were largely protocol driven. Protocol angiography may therefore have a significant effect on the event rate between different studies and is at odds with common clinical practice where further angiography is carried out only if clinically indicated. Cardiologists[15] quote a rule of thumb that half of all angiographically driven revascularisations would have occurred on clinical grounds anyway, although this is uncertain. Given the scarcity of data, it is not possible to correct for any effect of protocol angiography in different studies. This will be discussed again in Chapter 6.

Finally, the follow-up of many studies was relatively short, usually 12 months, whereas more rigorous reporting of follow-up to at least 5 years would be desirable.

Subgroups of patients

The included studies involved a variety of patients. For the purposes of analysis we have grouped the studies, where possible, according to the patient population. However, this left us with a large group of studies with non-specific populations.

Reports often have not included details of outcomes for other major subgroups of patients, thus limiting the analysis. For instance, we have been unable to separate unstable angina from stable angina in many studies, although one would expect that outcomes might be different between these two groups. Similarly, we have had little ability to look at subgroups according to some of the desired risk factors, for example, between diabetic and non-diabetic, patients with long lesions versus short lesions, patients with complex or multivessel disease rather than single-vessel disease, small vessels (<3.0 mm) or larger vessels

where they were in anything other than specific small vessels studies, or the type of lesion classified according to its site (A, B or C; *Table 1*). We expect that there might be substantial differences according to these subgroups; however, data are not available to explore these differences.

Data availability

It is disappointing that so many studies were available only in abstract form and not in formal reports from peer-reviewed journals. Even for those that were reported in peer-reviewed journals, the reporting was often poor or incomplete. This has limited the extractable data from many reports.

Conclusions

All of these problems create difficulty in the conduct of meta-analysis. However, despite these problems, the main results seem robust as described above.

Chapter 5

Stent versus coronary artery bypass graft (CABG)

CABG: included studies

Introduction

Six studies met the inclusion criteria and their results are included in this report.[99–104] Two other trials met the inclusion criteria. One[105] aimed to randomise 280 patients and was completed. The authors were contacted and are preparing the results for publication and were not in a position to share results. In the other study,[106] it was not possible to extract data regarding patients who had received a stent. All included studies were assessed from reports published in peer-reviewed journals.

An additional three trials identified as comparing stents with CABG are planned or in progress. These include AMIST,[107] a UK study examining minimally invasive surgery versus stent, CARDia,[108] a UK and Ireland study comparing CABG with stents, and FREEDOM (Farkouh B, Mount Sinai NYU Health: personal communication, 2003), a North American study comparing CABG with DES.

The search identified all three CABG trials[100–102] noted in Meads and colleagues' review.[2]

Quality assessment of included CABG studies

Methodological quality was assessed using the checklist described in CRD Report 4[109] and summarised in Appendix 2. The results of the assessment are presented in *Table 11*.

Numbers randomised were presented for all trials and, with the exception of SIMA[102] and Drenth and colleagues,[104] evidence of adequate randomisation and allocation concealment could be identified.

Eligibility for participation, comparability and co-therapies were described in all studies. Compositions of allocated treatment arms of all studies appeared to be comparable. Withdrawals were tracked and data on >80% of participants were available in the final analyses of all reports. ITT analysis was carried out in all included studies.

Blinding of outcome assessment in trials comparing PTCA with stenting versus bypass graft surgery is not totally impossible, but is logistically very difficult. Similarly, it would not be possible to estimate the magnitude and direction of any such possible bias that this lack of blinding might introduce. None of the included trials indicate that there was any attempt to blind outcome assessors.

Summary details describing the study and participant characteristics are presented in *Tables 12* and *13*.

Study characteristics

Five of the included trials were multicentred. Three were conducted in Europe only,[100,102,104] one in Europe and Canada,[103] one in Argentina[101]and one that included 67 centres in 18 countries.[99] The study by Drenth and colleagues[104] was single-centred and was conducted in Netherlands. Trial sizes ranged from 102 to 1205 with a total of 3088 patients involved in the six studies.

Two studies[100,104] used minimally invasive surgery and one other compared stenting with internal mammary artery grafting.[102] The remainder of the trials used standard surgical techniques, although the SOS trial[103] indicates that in some institutions standard care may have included minimally invasive surgery.

Three studies included patients with multiple-vessel disease[101,103,110] and three[100,102,104] included patients with isolated single-vessel (LAD) disease. All but two studies[100,102] explicitly excluded patients who had a history of revascularisation.

Participant characteristics

Patients were primarily male (range 73–79%) and the mean age within studies ranged from 59.5 to 62 years. One trial excluded patients with ACS and the remainder included a mix of patients with stable and unstable angina. The proportion of patients with DM varied across studies. The highest proportion was seen in the study by Diegeler and colleagues[100] (stent group 34% and CABG group 25%).

TABLE 11 *CABG: quality assessment of included studies*

Study	Randomisation			Baseline comparability				Blinding				Withdrawals		
	Truly random	Allocation concealment	No. stated	Presented	Achieved	Eligibility criteria specified	Co-interventions identified	Assessors	Administration	Participants	Procedure assessed	>80% randomised in final analysis	Reasons stated	ITT
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
ARTS	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
Diegeler *et al.*	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
Drenth *et al.*[a]	✓	NS	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
ERACI II	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
SIMA	NS	NS	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓
SOS	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	✓	✓

✓, yes (item adequately addressed); ×, no (item not adequately addressed); ✓/×, partially (item partially addressed); NS, not stated.
[a] Quality assessment based on conference abstracts only.

TABLE 12 *CABG: study characteristics*

Study name	Intervention	Primary outcomes	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Follow-up	Type of stent
Multiple-vessel disease									
ARTS[99]	Stents 600 CABG 605	Absence of major MACE for 1 year	Angina status Medications Costs and cost-effectiveness QoL Combined end-point of death, MI or stroke, death, MI, stroke, revascularisation procedures at 1 year	Multicentre, international	Multiple-vessel CAD Presence of ≥ 2 *de novo* lesions located in different major epicardial coronary arteries Eligible for CABG or stenting Total occlusion present < 1 month	Previous CABG or PTCA, LEF <30%, overt CHF, previous CVA, MI in previous week, severe hepatic or renal disease, diseased saphenous veins, neutropenia or thrombocytopenia, CI to ASA or ticlopidine, aortic or LV aneurysm resection, surgery for abdominal aortic aneurysm	Abciximab	1 year 3 years	Cordis Palmaz-Schatz Crown or CrossFlex stent
ERACI II[101]	Stents 225 CABG 225	MACE		Multicentre, Argentina	Multiple-vessel disease indication for revascularisation Severely limiting stable angina (CCS III–IV) despite max. medical therapy and unstable angina No angina or min. symptoms, but large area of heart at risk Unstable angina Angiographic evidence of severe obstruction At least one of the vessels to be treated (PTCR) should appear >3.0 mm	Single-vessel disease, previous CABG, PTCA in last year; previous stenting; AMI during first 24 h, poor LVF (ejection fraction <35%); >2 CTO, severe valvular heart disease, limited life expectancy (age or illness)	Aspirin Ticlopidine Heparin (Abciximab for rest pain or post-MI)	30 days 1 year	Primary device Gianturco Roubin II (Cook) SOS

continued

TABLE 12 *CABG: study characteristics (cont'd)*

Study name	Intervention	Primary outcomes	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Follow-up	Type of stent
SOS[103]	488 (480 treated with stents) CABG 500 (487 treated by CABG)	Rate of repeat revascularisation	Death Q-wave MI All-cause mortality Symptoms angina (CCS) Cardiac medication LVF	Multicentre, international (53)	Symptomatic patients Multiple-vessel CAD Appropriate for either intervention At least one vessel had to be identified as suitable for stenting	Previous thoracotomy, previous coronary, revascularisation patients requiring invention for pathology of valves, great vessels or aorta	No protocol restriction on medication	6 months 1 year Annually until March 2001	No restriction of types used[a]
Single-vessel disease									
Diegeler *et al.*[100]	Stent 110 CABG 110	Freedom from MACE within 6 months	Cardiac death MI TVR Clinical status (CCS) Need for antianginal drugs at 6 months Adverse events	Multicentre, Germany	Isolated, high grade (≥ 75% diameter stenosis) Lesions in proximal LAD artery, lesion between origin of left circumflex and first septal branch	ACS requiring immediate intervention, previous surgery or PCI, additional clinically significant lesions or valvular heart disease requiring treatment, stenosis of the first diagonal branch or stenosis extending over major diagonal branch, TO, intramyocardial course of LAD	Nitroglycerin (2% received IIb/IIIa inhibitors)	6 months MACE on 108, 108 Restenosis analysed on 106, 98	Various: GFX (Medtonic) Pura-Vario (Devon Medical) Inflow (Inflow Dynamics) Micro II (AV Engineering) MAC (AMG) MAC Carbon (AMG) Sito (Jomed)

continued

TABLE 12 *CABG: study characteristics (cont'd)*

Study name	Intervention	Primary outcomes	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Follow-up	Type of stent
Drenth *et al.*[104]	Stent 51 CABG 51	Freedom from MACCE at 3 years Angiographic outcome at 6 months	Angina class (CCS) Antianginal medication Clinical events MACCE without RV 6 months clinical outcome	Single-centre, The Netherlands	Isolated stenosis (grade B2 or C) Angina class 2 or greater due to high-grade stenosis of proximal LAD Eligible for both PCI or CABG		Aspirin Ticlopidine (1 month, stent group)	In-hospital, 6 month angiography 6 month intervals up to 3 years	
SIMA[102]	Stent 62 treated CABG 59 treated	Event-free survival	Angina functional class Exercise tolerance Antianginal medication QoL Post procedural drug regimen	Multicentre, Europe (6)	Symptomatic or silent cardiac ischaemia with single lesion (LAD) Ejection fraction >45% Vessel >3.00 mm	Unstable angina refractory to medical treatment; previous Q-wave infarction or occurrence of new Q-wave	Aspirin Heparin Ticlopidine (1 month)	Baseline 6 months 1 year and annually	Any CE marking approved, but Palmaz-Schatz recommended
Studies satisfying inclusion criteria, but where data are unavailable for analysis									
AWESOME[106]	PCI[b] 222 (120/222 received stents) CABG 232 (Multiple-vessel disease)	Clinical effectiveness: absence of re-intervention MACE Cerebrovascular events Cardiovascular death at 1year	Angina QoL Exercise capacity Cost-effectiveness	Multicentre, USA (16)	Medically refractory MI and one of more 'high-risk' (of 30-day operative mortality with CABG) factors	Single-vessel disease; >50% left main stenosis; no graftable or dilatable vessels; co-morbidity likely to limit life in next 6 months			

continued

TABLE 12 *CABG: study characteristics (cont'd)*

Study name	Intervention	Primary outcomes	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Follow-up	Type of stent
OCTOSTENT[105]	No information identified on participant numbers (multiple-vessel disease)	Absenced MACCE for 1 year (death, stroke, TIA, reversible ischaemic neurological deficits, non-fatal MI, repeat revascularisation by PCI or surgery)	Angina status Medications Costs and cost-effectiveness QoL Combined end-point of death, MI or stroke, death, MI, stroke, revascularisation procedures at 1 year	Multicentre, Europe	Multiple-vessel CAD eligible for CABG or stenting Presence of ≥ 2 *de novo* lesions located in different major epicardial coronary arteries Total occlusion present > 1 month	Previous CABG or PTCA, LEF <30%, overt CHF, previous CVA, MI in previous week, severe hepatic or renal disease, diseased saphenous veins, neutropenia or thrombocytopenia, CI to ASA or ticlopidine, aortic or LV aneurysm resection, surgery for abdominal aortic aneurysm	Abciximab		

ASA, aspirin; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; CI, contraindication; LEF, left ventricular ejection fraction, LVF, left ventricular function; LV, left ventricular; PTCR, percutaneous transluminal coronary revascularisation; RV, revascularisation; TIA, transient ischaemic attack; TO, total occlusion.

[a] Medtronic, Guidant, Boston Scientific stents replaced free of charge.

[b] PCI which involved stenting as well as other PCI technologies. A reported 54% of participants undergoing PCI received stents.

TABLE 13 *CABG: participant characteristics*

Study name	Intervention	Age (years), mean [SD]	Gender (% male)	Lesion category (%)	ACS (%)	Previous cardiac event (%)	DM (%)
Multiple-vessel disease							
ARTS[99]	Stent 600	61 [10]	77		Unstable angina 37 Silent ischaemia 6	MI 44	
	CABG 605	61 [9]	76		Unstable angina 35 Silent Ischaemia 5	42	
ERACI II[101]	Stent 225	62.5 [11.5]	77.3		Unstable[a] 92.1	MI 28.5	17.3
	CABG 225	61.4 [10.1]	81.4		Unstable[a] 90.7	27.7	17.3
SOS[103]	Stent 488 (480 treated with stents)	61 [9.2]	80			MI 44	14
	CABG 500 (487 treated by CABG)	62 [9.5]	78			47	15
Single-disease							
Diegeler *et al.*[100]	Stent 110	62.5 [10.2]	72	Type A 16 Type B 59 Type C 25			34
	CABG 110	61.6 [10.0]	77	Type A 13 Type B 64 Type C 24			25
Drenth et al.[104]	Stent 51	61 [1.3]	75	Study population with B2 and C lesions		MI 18	18
	CABG 51	60 [1.6]	78	Study population with B2 and C lesions		24	8
SIMA[102]	Stent 62	Age (range) stent 59 (57–62); CABG: 60 (58–63)	76				11
	CABG 59		83				13

[a] Braunwald Class II, III-C.

TABLE 14 *CABG: outcomes*

Study name	Intervention	Event rate (%)		Mortality (%)		MI (%)		Revascularisation (%)		CABG (%)		PTCA (%)		BRR 6 months (*n*, %)
Multiple-vessel disease														
ARTS[99]	Stent	1 year	26.2	30 days	1.5	1 year	5.3	1 year	21.0	1 year	6.7	1 year	15.7	
		3 years	34.2	1 year	2.5	3 years	6.2	3 years	21.3	3 years	6.7	3 years	14.7	
				3 years	3.7									
	CABG	1 year	12.2	30 days	0.5	1 year	4.0	1 year	3.8	1 year	0.7	1 year	3.3	
		3 years	16.9	1 year	2.8	3 years	4.3	3 years	5.5	3 years	0.8	3 years		
				3 years	4.6									
ERACI II[101]	Stent	30 days	3.6	30 days	0.9	30 days[e]	0.9	30 days	1.8	30 days	0.0	30 days	1.8	
				18.5 months[a]	3.1									
	CABG	30 days	12.3	30 days	5.7	30 days[e]	5.7	30 days	0.0	30 days	0.0	30 days	0.0	
				18.5 months[a]	7.5									
SOS[103]	Stent	1 year	110/488	1 year	2.5	1 year[e]	4.3	1 year	18	1 year[f]	7.8	1 year[f]	11.3	
				2 years	4.5[b]	2 years[e]	5.3	2 years	22					
								3 years	24					
	CABG	1 year	62/500	1 year	0.8	1 year[e]	6.8	1 year	4	1 year[f]	1.0	1 year[f]	3.2	
				2 years	1.6[b]	2 years[e]	8.2	2 years	6					
								3 years	7					
Single-vessel disease														
Diegeler *et al*.[100]	Stent	6 months	31.5	6 months	0.0	30 days	1.9	30 days	1.9					(35/106) 33.0[a]
						6 months	2.8	6 months	28.7					
	CABG	6 months	14.8	6 months	1.9	30 days	3.7	30 days	3.7					(18/98) 18.4[a]
						6 months	4.6	6 months	8.3					
Drenth *et at*.[104]	Stent	6 months	13.7	In hospital[c]	0.0	6 months	9.8	2.9 years[d]	15.7	6 months	2.0	6 months	7.8	(14/49) 28.6[g]
		1 year	23.5	6 months	0.0	2.9 years[d]	9.8							
		3 years	24.1	2.9 years[d]	0.0									
	CABG	6 months	7.8	In hospital[c]	3.9	6 months	2.0	2.9 years[d]	3.9	6 months	0.0	6 months	3.9	(2/46) 4.3[g]
		1 year	7.8	6 months	3.9	2.9 years[d]	2.0							
		3 years	8.3	2.9 years[d]	3.9									

continued

TABLE 14 *CABG: outcomes (cont'd)*

Study name	Intervention	Event rate (%)	Mortality (%)	MI (%)	Revascularisation (%)	CABG (%)	PTCA (%)	BRR 6 months (*n*, %)
SIMA[102]	Stent	2.4 years 36.5	Postprocedure 1.6 2.4 years 1.6	Postprocedure 4.8 2.4 years 4.8	2.4 years 24.2	2.4 years 6.5	2.4 years 12.9	
	CABG	2.4 years 6.8	Postprocedure 0.0 2.4 years 1.7	Postprocedure 3.4 2.4 years 3.4	2.4 years 0.0	2.4 years 0.0	2.4 years 0.0	

BRR, binary restenosis rate; LD, luminal diameter.
[a] 18.5 ± 6.4 months, range 9–33 months.
[b] Median 2 years.
[c] In hospital and within 1 week of discharge.
[d] Range 2–4 years, mean 2.9 years.
[e] Only Q-wave MI reported.
[f] 'All repeat interventions' [hierarchical: stent 29/488, CABG 2/500]; [hierarchical: stent 44/488; CABG 15/500].
[g] In-stent restenosis detected in stent patients; CABG patients who had stenosis of >50% LD.

Outcomes

Outcomes reported and combining of events

Key outcomes as identified in the review protocol were extracted from the included studies and are presented in *Table 14*.

The six included trials described broadly comparable outcomes and combined event rates (mortality, AMI, repeat revascularisation). *Table 15* provides definitions of combined event rates used in each study. Four trials[102–104,110] included cerebrovascular events as part of their event rate.

Follow-up

Follow-up for the studies included clinical evaluation at various times in the first year. One study utilised angiographic follow-up[100] and a second recommended it but it was not mandatory.[102] Three studies utilised exercise or stress testing in their follow-up procedures.[100–102] The length of follow-up varied. One study[100] reports follow-up to 6 months. The remainder provide follow-up to at least 1 year. Two studies[103,110] state that they plan to continue follow-up to 5 and 4 years, respectively, and one study provided follow-up at 3 years[104]. The ARTS study reported 3-year data, but at the time of writing only in a conference presentation[111] and is described in the discussion only.

CABG: data analysis

Meta-analysis was performed using the key outcome variables of event rate, mortality, any AMI and revascularisation. Data are pooled using a fixed effect model with OR and 95% CIs. Where qualitative heterogeneity was apparent, application of a random effects analysis is also presented.

For the purposes of the analysis, studies were divided into two clinical categories: studies treating patients with multiple-vessel disease and those treating patients with single-vessel disease. Although some reports indicate that minimally invasive surgery was used, these data were not analysed separately. Studies examining single-vessel disease are small and conclusions from the analysis need to be treated with caution.

Forest plots of the meta-analysis are given in Figures 10–14.

TABLE 15 *CABG: event rate definitions*

Study	Event rate definition
ARTS	MACCE: all deaths, CVA, MI, repeat revascularisation (CABG, PTCA)
Diegeler *et al.*	MACE: death (cardiac), MI, TLR
Drenth *et al.*	MACCE: death, MI, stroke, TVR
ERACI II	MACE: all deaths, MI, repeat revascularisation
SIMA	All deaths, MI, CVA; repeat revascularisation (CABG, PTCA)
SOS	All deaths, CVA; MI, CABG, PTCA

CABG: event rate

Event rates in both single- and multiple-vessel studies favour CABG at 6 and 12 months (OR 0.41, 95% CI 0.22 to 0.74; OR 0.42, 95% CI 0.34 to 0.53 respectively). Given that death is an infrequent event, these data are primarily comprised of the combination of repeat revascularisation (~ 60% of total MACCE) and of any AMI.

CABG: mortality

Data from single-vessel trials are limited and were not available for analysis. Meta-analysis of data from multiple-vessel disease trials showed evidence of heterogeneity, and results from the application of analysis using both fixed and random effects models are presented. The difference is related to the lower mortality rate in the SOS trial and the higher early mortality rate in ERACI II, as discussed later. There is no evidence of a difference in the mortality rates at 1 year.

Mortality: calculation of hazard ratios for multivessel disease CABG studies

Data have been extracted that allow the calculation of the hazard ratios for death over the entire follow-up period for the ERACI II[101] and SOS[103] trials and at 1 year for ARTS.

The method used takes into account the fact that individuals have been followed up for variable lengths of time.[112,113] If the hazard ratio stays approximately constant over time, then the estimate can be interpreted as the typical relative risk at any time. However, it is worth noting, in particular in the ERACI II trial, that the relative effects of the two interventions may differ in the postoperative and longer term follow-up periods.

For ARTS (all followed for 1 year as relevant data for longer periods were not available[99,111]), the hazard ratio for death for stents compared with CABG is estimated to be 1.12 (95% CI 0.56 to 2.24). For ERACI II, the hazard ratio for death for stenting compared with CABG is estimated to be 0.38 (95% CI 0.17 to 0.84).

For SOS, the hazard ratio for death for stenting compared with CABG is estimated with be 2.91 (95% CI 1.29 to 6.53).

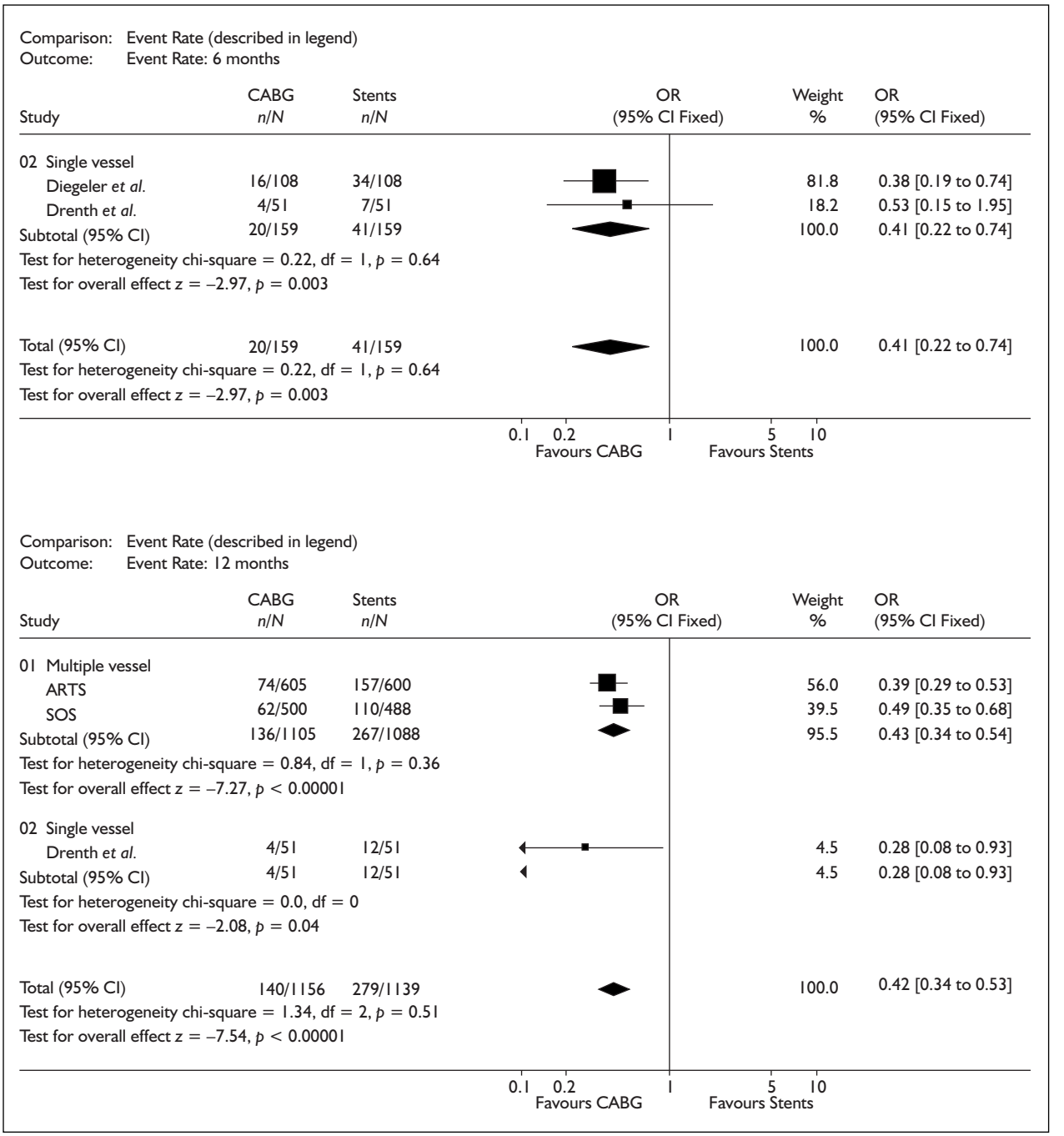


FIGURE 10 *CABG: meta-analysis of event rate*

These results have not been pooled, as they are clearly qualitatively different.

CABG: any AMI

Analysis of the data for multiple- and single-vessel studies shows no evidence of a difference between stent and CABG at any MI event point (up to 36 days, 6 months, 1 year).

CABG: revascularisation

Data for single-vessel trials are limited but in the one reporting trial show a benefit of CABG over stents. In multiple-vessel disease at 1 year, two studies (ARTS and SOS) report a statistically significant advantage of CABG over stenting (OR 0.16, 95% CI 0.12 to 0.23).

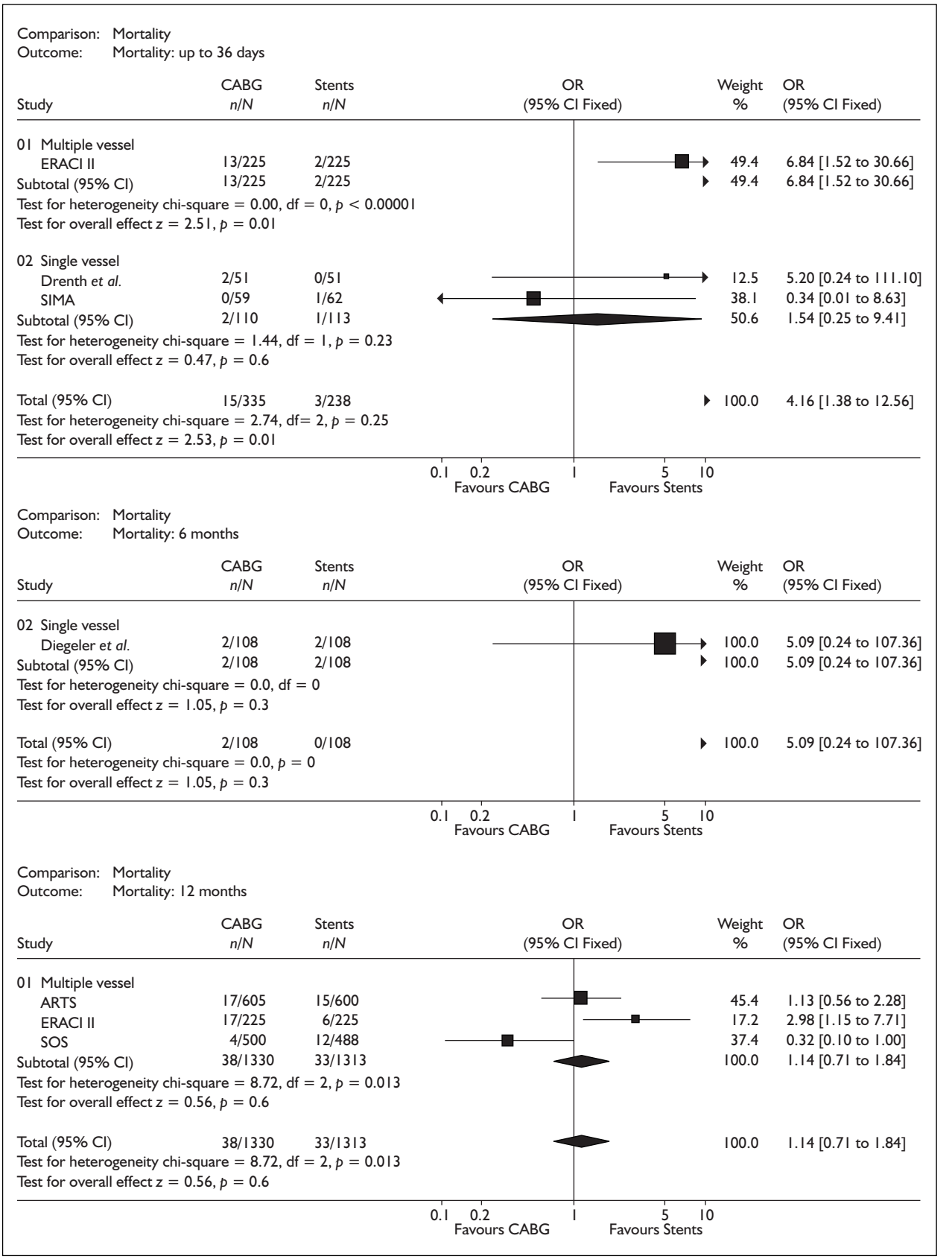


FIGURE 11 *CABG: meta-analysis of mortality. ERACI II, 12-month mortality: follow-up 9–33 months, assumed that all survived 9–12 months. Survival (and therefore death rates) have been read from Kaplan–Meier plots, Figure 4 in reference 101.*

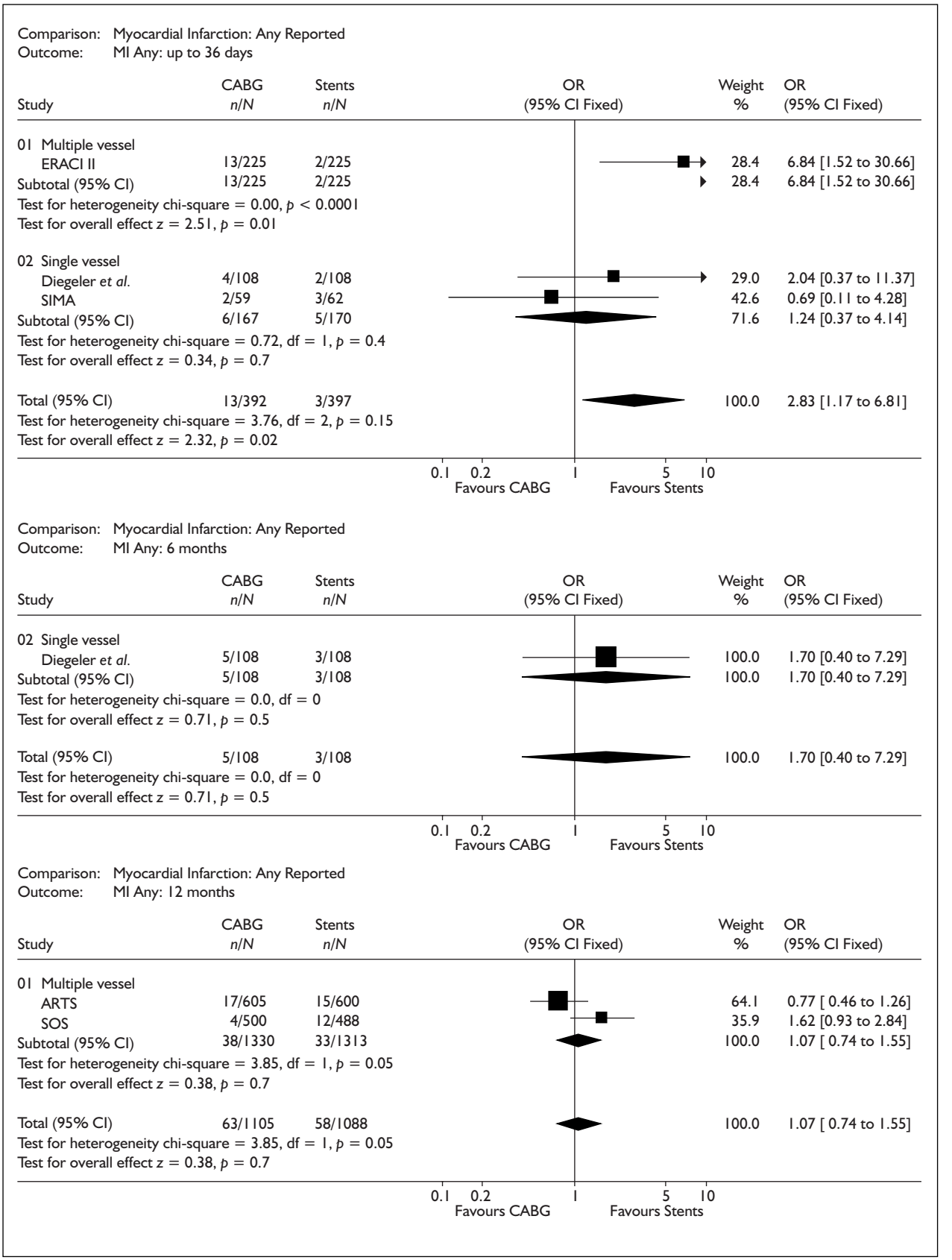


FIGURE 12 *CABG: meta-analysis of acute myocardial infarction*

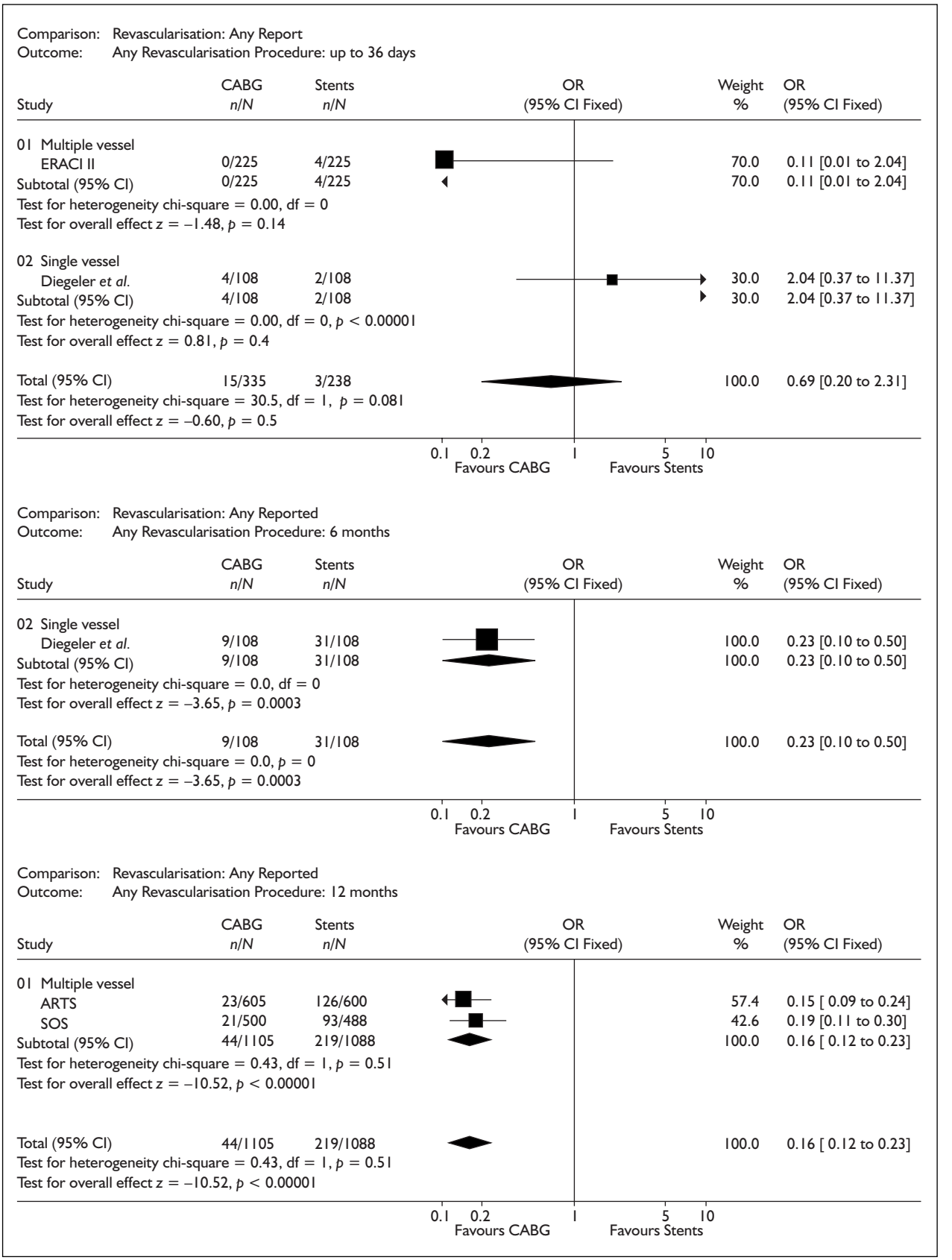


FIGURE 13 *CABG: meta-analysis of any reported revascularisation*

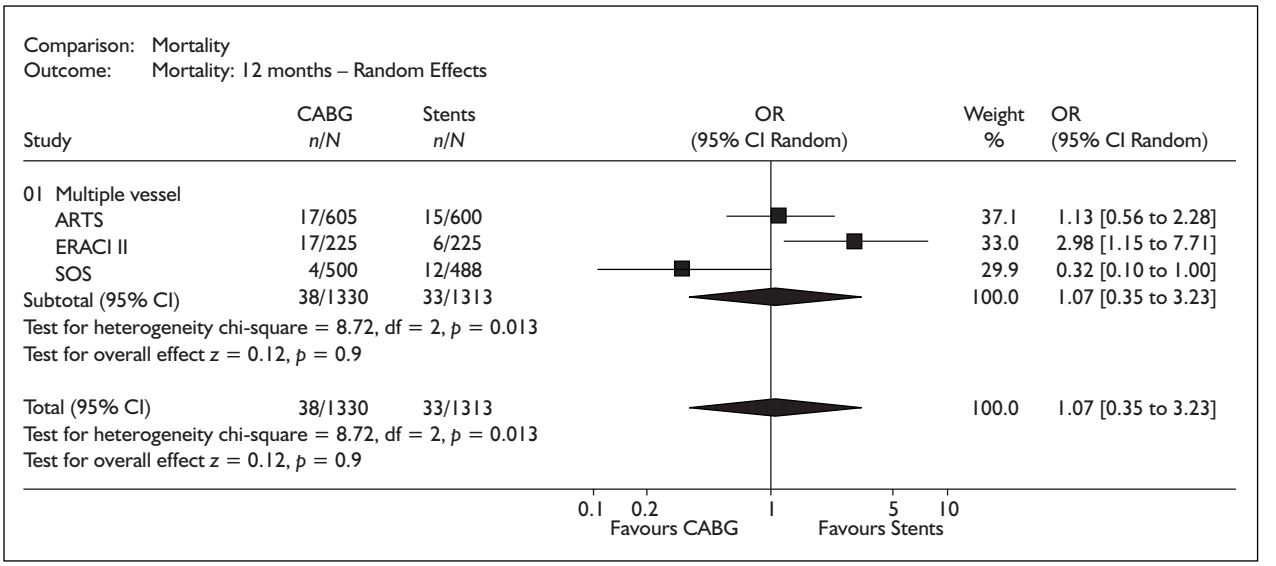


FIGURE 14 *CABG: meta-analysis of mortality – random effects. ERACI II, 12-month mortality: follow-up 9–33 months, assumed that all survived 9–12 months. Survival (and therefore death rates) have been read from Kaplan–Meier plots, Figure 4 in reference 101.*

Discussion

Mortality

Overall the meta-analysis demonstrates that there is no difference in mortality at any reported time point. Surgical mortality in SOS was exceptionally low (0.2% versus 2.4% in common practice). This may be a reflection of the low risk nature of the trial population. The SOS study showed a greater benefit in mortality in favour of CABG at 12 months, which increases proportionately with later follow-up, although the numbers of patients with 3 year follow-up reported so far is small (167 in total). At 2-year median follow-up (this is not a specific time point, so this figure is not used in the meta-analysis), this research reports that nine out of 18 deaths in the 488 stented patients and three out of seven deaths with 500 surgically treated patients were non-cardiovascular.

Eight of the non-cardiovascular deaths in the stent arm were attributed to cancer compared with only one in the CABG arm. This may represent no more than the play of chance, as the authors suggest. Only one other study (BENESTENT,[114]) comparing conventional balloon angioplasty and stents) reported details of deaths from cancer separately. Combining figures from these two RCTs confirms that the SOS result appears to be sustained ($p = 0.002$ on Fisher's exact test). There seems no biological basis for any increase in cancer mortality related to stents and we can only recommend that further research be undertaken. Case–control studies based on registries of the use of stents might be appropriate.

A conference presentation of the ARTS study has reported a point estimate of 3-year follow-up.[111] It is reported that mortality in the stented arm was 22/600 and in the CABG arm 28/604. It is unclear how many patients were followed up to this point. Because of the incomplete nature of these data, they have not been included in the meta-analysis. However, contact with the authors indicates that that more complete data will soon be made available.

In contrast to SOS and ARTS, the smaller ERACI II study showed high early mortality in the surgical group [13 deaths (5.7%) within 36 days in surgical group versus two deaths (<1%) in stented group], giving a reported survival advantage with stenting. However, later mortality did not indicate a difference between the treatment groups (four in the stented arm versus five in the CABG arm). A recent report on a subgroup from ERACI II is discussed below.

A complication in interpreting death rates is that the trials report a strict ITT analysis, that is, deaths after randomisation but in some cases before procedure. In the SOS study, patients were required to have their procedure within 6 weeks of randomisation. A similar requirement was not so strictly enforced in ARTS, and delays for surgery were greater than delays for stenting; partly as a result, there were no deaths in the ARTS patients before stenting but three while awaiting CABG.

The overall conclusion at this point is therefore that for the types of patients selected for inclusion

in the trials (largely patients with single- or two-vessel disease and normal left ventricular function), there is no difference in overall mortality between the two interventions. This result might be considered consistent with an earlier meta-analysis of medical therapy versus CABG by Yusuf and colleagues,[115] which showed an overall survival benefit for patients with CABG, but not for the low-risk patients who were similar to those in the current stent versus CABG trials.

Revascularisation

These studies showed a substantial reduction in revascularisation procedures in favour of the CABG arms in all studies reporting this outcome. This is clearly the main benefit of CABG. How this translates into patient QoL or utility will be clearer when the ARTS study reports its longer term results.

Comparability of interventions

The number of studies identified in this chapter is substantially smaller than for the studies comparing stent versus PTCA. The six studies fall broadly into two categories: those including patients with single-vessel disease and where in one case follow-up was both angiographic and clinical, and those studies where patients with multi-vessel disease were studied and where the follow-up and event rate are clinically driven. The latter studies are closer to clinical practice since, as discussed in Chapter 9, over 90% of procedures on patients with single-vessel disease involve stenting rather than CABG. Conversely, patients with three-vessel disease by and large receive CABG rather than stenting. The margin for choice therefore between stenting and CABG largely lies in patients with two-vessel disease, or possibly in some high-risk patients with single-vessel disease, such as left main stem or LAD disease.

As in all trials, there are a number of issues that may limit the generalisability of the results. First, the highly selected nature of patients entered into such studies is not typical of the patients seen by cardiologists or heart surgeons: by definition, the patients have to be suitable for either intervention. We are unclear as to the proportion of potential patients who were excluded from these trials on the basis of unsuitability for surgery or for stenting; this is important as an imbalance in this may bias the trials towards one intervention or the other. For instance, if a high proportion of patients were rejected from the trial not on the grounds of unsuitability for surgery but on the grounds of unsuitability for stenting, then a population of patients with characteristics favourable for a good outcome with stenting would have been selected and the results biased.

Second, practice has changed over the periods of the trials. For instance, only ~10% of stented patients in the two major studies, ARTS and SOS, had a glycoprotein IIb/IIIa inhibitor, in contrast to 60–70% today. Conversely, surgical practice is also evolving. Changes include the use of 'off pump' CABG,[10] especially in high-risk patients, or the improved benefits of bilateral over unilateral internal mammary artery grafting.[116] As we shall see later, in common practice today the case mix between these procedures differs with the more severely affected multiple-vessel disease patients often with impaired left ventricular dysfunction having surgery and patients with single- or two-vessel disease rarely being referred for surgery at all. The relative benefits of such developments in CABG versus developments in stenting (new stent design or DES) in patients with different profiles will need further investigation in the future.

Outcomes

Since these studies largely depend on real clinical events and not on angiographic measures, the outcomes seem clear and reliable.

Subgroups

It was not possible to consider subgroups of patients in the meta-analysis. There is potential for within- and between-study heterogeneity related to the patients entering the study (e.g. patients suffering from either stable or unstable angina, varying numbers of diabetic patients and variations in underlying risk).

Reports of subgroups are so far limited in detail. Individual patient analysis may allow this in the future and we understand that such a study is under way (SOS investigators, personal communication, 2003). It is important not to confuse statistically significant results in subgroups with definitive outcomes: these were not the main focus of the study and the studies were not powered to examine subgroups. Nevertheless, such results may provide useful pointers.

A recent subgroup analysis from ERACI II[117] looks at the half of the total patients who had proximal LAD lesions, for up to 41 months rather than the 18.5 months previously reported for the whole trial. This report identifies the high early mortality but, remarkably, by 41 months this completely disappears, with a 41-month survival of 96.4% on stents versus 95% for CABG ($p = 0.98$). Similarly, an inconclusive reduction in revascularisations

previously reported becomes highly significant in favour of CABG (27% in the stented group versus 3.4% in CABG). That this subgroup of 50% of total trial patients should show such a different pattern of outcomes may be due to the longer term follow-up, or may identify a particular subgroup warranting more attention in other studies, or may suggest serious heterogeneity or other systematic problems in this trial.

People with diabetes are an important subgroup. The main source of information on this patient population is a conference presentation from the ARTS study.[111] There is a substantial group of people with diabetes in the ARTS study (112 in the stent arm and 96 in the CABG arm, about 20% of the total trial patients), with follow-up to 3 years.[111] This confirms the higher rate of MACCE rates in diabetic compared with non-diabetic patients, although interestingly only in the stented group: 31% in stented non-diabetics versus 47% in those with diabetes, but 17% in CABG randomised non-diabetics versus 18% in those with diabetes. Repeat revascularisations as a specific part of MACCE were significantly reduced in the group of diabetic participants treated by CABG as opposed to stent (28.6% stent versus 4.3% CABG), as in the non-diabetic patients. There were no differences in deaths or MIs.

The conclusion is that diabetics are a group at particularly high risk of events after stenting, but not after CABG.

No results for diabetic patients included in the SOS trial have yet been reported. However, we understand that so far no major differences between diabetic patients treated with stents or CABG has been detected (Stables R, Cardiothoracic Centre, Liverpool, personal communication, 2003).

The ARTS results may translate into survival in long-term follow-up, and if so might predict a similar pattern to that seen in the BARI study in diabetics, where there was a 5-year survival of 80.6% in people with diabetes receiving CABG versus 65.5% in those receiving angioplasty.

Studies have also reported that some other aspects of patient characteristics, such as lesion type (mainly the single-vessel studies) and numbers of patients with previous cardiac events may be important predictors of outcome. This is not consistent across all studies, but further details may be available for specific analysis from triallists at a later date.

Availability of data and quality

There are limitations to the data. First, some of the data have not been reported in peer-reviewed literature and often only in other less satisfactory forms, for example, the ARTS 3-year data which have appeared so far only in a conference abstract. These data are incomplete and in many respects unsatisfactory. ARTS investigators have been approached for further data, which they have agreed to supply, but it was not available by the time of submission of this report. However, even 3-year data are relatively short term given what is known of the natural history of patients after CABG; the ARTS study plans follow-up to 5 years.

The previous Birmingham study[2] was unable to comment on the value of stents versus CABG as the studies identified had not yet reported results. It is disappointing that within this systematic review we were unable to obtain results for two studies despite contacting the authors. The major data expected from currently outstanding trials are the long-term data from ARTS.

There are no data comparing DES with CABG until the studies identified earlier in this chapter have reported.

Conclusions

Currently, long-term mortality data comparing stents to CABG are limited and short-term data indicate heterogeneity between trial findings and no difference in mortality.

In comparison with stenting, CABG is associated with reduced events by 55% and with reduced revascularisations by ~80% in multiple-vessel disease and in single-vessel disease. The review will examine how this affects QoL and the cost-effectiveness of each intervention strategy within the economics sections. There is no difference in mortality apparent between interventions to date.

Chapter 6

Non-drug-eluting stents versus drug-eluting stents

Part A: Analysis of clinical effectiveness completed for appraisal report

DES: included studies

Twelve studies, comparing DES with non-DES (stents), satisfied the inclusion criteria for the review.

Of these studies, seven (ASPECT, DELIVER, ELUTES, PATENTCY, TAXUS I,[118] TAXUS II, SCORE) focused on stents eluting taxane compounds (paclitaxel, 7-hexanolytaxol), four (E-SIRIUS, FUTURE, RAVEL,[119] SIRIUS) investigated sirolimus or everolimus eluting stents and one study involved actinomycin-dosed stents (ACTION). Additional RCTs were identified in our search for studies of clinical effectiveness, but are in progress or yet to report their findings. Included and ongoing studies comparing stents to DES are listed in *Table 16*.

Two of the 12 included studies were suspended. The ACTION study was suspended owing to low efficacy and SCORE was suspended owing to a high incidence of MACE in the DES group. These two studies appear to have been reported according to protocol.

In the case of the PATENTCY study, although plans to recruit participants to evaluate a paclitaxel-eluting stent were suspended, the initial feasibility study recruited its intended 50 participants and reported on these at 30 and 270 days.[120]

Development of the paclitaxel-eluting stent evaluated in the DELIVER study is reportedly[121] not to continue. However, DELIVER has reported data up to 270 days.

Given that these four studies all reported according to protocol, available data are included for analysis in the review.

Sources of evidence on effectiveness of DES compared with stents

The majority of results of trials assessing evidence on clinical effectiveness of DES (relative to stents) is not, as yet, published. Therefore, data were primarily obtained from conference abstracts, Internet-based sources of materials presented at conferences and the submission to NICE. At the time of writing, only RAVEL[119] and TAXUS I[118] have been published in peer-reviewed journals.

In this section of the review, standard referencing will be used for journal-published sources of information. As no single published reference has been identified to describe the remaining 10 studies, only the study name (displayed in capital letters, without citations) is used when describing these studies. A full list of the data sources used for DES studies is given in Appendix 5.

Non-randomised DES studies

Although not included in the review, early non-randomised studies of DES are worthy of note and are briefly described within this subsection.

DELIVER II and TAXUS III[167] are non-randomised studies evaluating paclitaxel-eluting stents. In the DELIVER II study 1533 patients at 'high risk of restenosis' have been enrolled and will be followed (unblinded) for up to 3 years. Initial safety data have been publicised. TAXUS III is a prospective non-randomised study, involving a relatively small number of participants (30 people receiving slow-release paclitaxel stents, 28 available at follow-up) focusing on in-stent restenosis, but reporting on 30-day MACE as its primary end-point and MACE up to 5 years, revascularisations and restenosis as additional end-points.

Tacrolimus-eluting devices (Jomed) are undergoing evaluation in two parallel, non-randomised studies, PRESENT and EVIDENT.[168] The EVIDENT study is investigating the use of a tacrolimus-eluting 'stent-graft' designed for use in SVG.[169]

The STRIDE study[170] investigates the efficacy of dexamethasone-loaded, phosphorylcholine polymer-coated stents (Bio*divYsio* stents, produced by Abbott Vascular Devices). This non-randomised registry involved 70 participants, utilising a historical cohort (from the DISTINCT[171] stent

TABLE 16 *Summary of drug-eluting stent RCTs identified in search*

Agent	Drug	Study name	Status	Publication types and reference
Taxane	Paclitaxel	ASPECT	Reported at 6 months	Abstracts, conference reports[122–128,129]
	Paclitaxel	DELIVER	Some 9-month data presented Jan. 2003, further data expected 2nd quarter of 2003	Abstract, Conference report[130–132]
	Paclitaxel	ELUTES	Reported at 6-months	Abstracts[133–140]
	Paclitaxel	PATENTCY	Feasibility study completed, reported at 9 months. Full trial suspended	Conference report[120]
	Paclitaxel	TAXUS I	Reported at 6 months; 6-month and 1-year data published (Jan. 2003)	30-day, 6-month, 1-year data: published report, abstracts[118, 141–147]
	Paclitaxel	TAXUS II	6-month data reported, 1-year data expected to be available to review team 1st quarter of 2003	Conference report[143,145,147,148]
	Paclitaxel	TAXUS IV	In progress – enrolment complete; reports expected in 2nd–3rd quarters 2003	Conference report[146,147]
	Paclitaxel	TAXUS V	In progress – enrolment to end 4th quarter of 2002	Conference report[147]
	Paclitaxel	TAXUS VI	In progress – enrolment to end 1st quarter of 2003	Conference report[147]
	QP2 (7-hexanollytaxol)	SCORE	Reported at 6 months, 1 year. Enrolment stopped due to early MACE	Abstracts[149–156]
Rapamycin	Sirolimus	RAVEL	1-year data published, 2-year released in confidence – Feb. 2003	1 year data: Published report, abstracts, confidential data[119]
	Sirolimus	SIRIUS	1-year data released in confidence – Feb. 2003	Conference report, abstracts, confidential data[157–162]
	Sirolimus	E-SIRIUS	In progress	
			9-month data released in confidence – Feb. 2003	Conference report, abstracts, confidential data[162]
	Everolimus	FUTURE	In progress	
			Early (FUTURE I) data reported 3rd quarter of 2002, further expected 1st quarter of 2003	Abstracts, conference report[121,163,164]
Other	Actinomycin	ACTION	Stopped – Trial stopped owing to inability to reduce restenosis as seen in animal studies	Conference report[165,166]

versus stent trial) as controls. The primary end-point of the STRIDE study was binary restenosis. A CE Marking application for this stent has recently been approved.[172] Also from Abbott, EASTER investigates estradiol-eluting Bio*divYsio* stents in a prospective pilot registry which may include up to 120 participants among multiple locations.[173] The primary end-point of this non-randomised study is binary restenosis at 6 months, and secondary investigation of MACE and intravascular ultrasound (IVUS) analysis.

Quality assessment of DES studies

The same quality assessment checklist[109] as for other stent comparisons was used to evaluate study conduct and reporting. A summary of assessed quality of drug-eluting stent studies is provided in *Table 17*.

The ability to judge the methodological quality of DES studies was limited by the available information (at the time of preparation of this report). However, using the one published paper,[119] reports included in the submission to NICE and published conference abstracts, an overview of apparent study quality is presented. Assessment of quality may be liable to revision, as further published information is made available.

Twelve DES trials were assessed for quality. The RAVEL study[119] was available as a published journal article, so this source was used to assess quality. Detailed information on TAXUS I and TAXUS II trails was provided, in confidence, within the industry submission to NICE (full publication of TAXUS I[118] occurred after the quality assessment was completed). For eight of the remaining studies (ACTION, ASPECT, E-SIRIUS, DELIVER, ELUTES, FUTURE, SCORE and SIRIUS), published abstracts were used for quality assessment. Owing to lack of information, quality assessment of the PATENTCY trial was based only on a single conference presentation.[120]

Adequate randomisation and allocation concealment methods were identified for RAVEL,[119] TAXUS I[118] and TAXUS II. Numbers randomised were presented and participant retention of 80% or more was apparent for all studies, except for FUTURE, where the number randomised was not stated explicitly, and ACTION, where only 74% of those originally randomised to receive non-eluting stents were apparently included in analyses at 6 months. Intention to treat-based analyses were included in 10 of the studies. The exceptions include the DELIVER study, where patient numbers less than those originally randomised are reported, so it is difficult to assess if analysis has maintained original treatment allocation, and the FUTURE study, where we were unable to assess this quality component. Eligibility criteria were at least partially (ASPECT, SCORE) or adequately described for all the studies. Co-therapies were described in some detail for all but FUTURE and SCORE.

Unlike the PTCA and CABG comparisons, blinding can be achieved for DES studies where the drug-loaded and bare stents were of comparable structure. The RAVEL trial[119] blinded those deploying the stents and those receiving stents to the drug-eluting properties of the devices. The TAXUS studies (TAXUS I,[118]) TAXUS II) also blinded the interventionist to the pharmaceutical properties of the stents, but TAXUS II alone indicates that recipients were also blinded. Participants in ELUTES study also appear to have been blinded to the nature of the stent they received.

ELUTES, PATENTCY, RAVEL,[119] TAXUS I[118] and TAXUS II indicate concealment of the intervention from the outcome assessors.

Quality of data available from DES studies

As previously stated, only two of the 12 studies have been published as peer-reviewed publications. In order to be comprehensive in a rapidly changing field such as coronary artery stents, the review team kept abreast of the release of new data through international cardiology meetings and contact with triallists.

The availability of visual information presented at conferences is a useful aid to individuals with a clinical interest wishing to keep informed of developments in their field. These materials also present an opportunity for data on design, participants and outcomes to be integrated into systematic reviews. These sources may not, however, be subject to rigorous reviewing for clarity and data checking and therefore data accuracy. Given that only one 'channel' of the presentation, the prepared, formal, visual part of the conference event, is available, additional detail, qualifications, dialogue or errata may be missed.

The quality (in terms of accuracy, detail and clarity) of data extracted and summative analyses based on these data are presented here. However, these data were subject to change and caution needs to be used in interpreting the outcomes. Systems were applied to support the precision of transfer of data from these sources to the review.

Incomplete or inconsistent reporting of data was apparent among the electronic and printed abstract sources used. Examples include the ACTION study, where one reference[165] lists numbers in the stent allocation arm as 121, DES 2.5 μg as 120 and DES 10 μg as 119 participants, whereas another reference[174] lists stent 119 (and 118), DES 2.5 μg as 120, 10 μg as 121 for patient allocations. In ACTION, MI at 30 days differs in reporting in two sources, with no MI in the stent group and four in the DES group[165] but one MI in the stent group and three in the DES group in another reference.[174] In an abstract regarding SCORE for ACC 2002,[150] numbers of participants reported for each intervention arm appear

TABLE 17 *DES: quality assessment of included studies*

Study	Randomisation			Baseline comparability				Blinding				Withdrawals		
	Truly random	Allocation concealment	No. stated	Presented	Achieved	Eligibility criteria specified	Co-interventions identified	Assessors	Administration	Participants	Procedure assessed	>80% randomised in final analysis	Reasons stated	ITT
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
ACTION[a]	×	×	✓	×	×	✓	✓	×	×	×	×	✓×[b]	×	✓
ASPECT[a]	×	×	✓	×	×	✓×	✓	×	×	×	×	✓	×	✓
DELIVER[a]	NS	NS	✓	✓	✓	✓	✓	NS	NS	NS	×	✓	×	×
FUTURE[a]	NS	NS	×	✓	×	✓	×	NS	NS	NS	×	✓	×	NS
ELUTES[a]	NS	NS	✓	×	NS	✓	✓	✓	NS	✓	×	✓	×	✓
E-SIRIUS	×	×	✓	✓×	✓×	✓	✓	×	×	×	×	✓	×	✓
PATENTCY	NS	NS	✓	✓	✓	✓	✓	✓	NS	NS	×	✓	✓	✓
RAVEL	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓
SCORE[a]	×	×	✓	✓×	✓×	✓×	×	×	×	×	×	✓	×	✓
SIRIUS[a]	×	×	✓	✓×	✓×	✓	✓	×	×	×	×	✓	×	✓
TAXUS I	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓
TAXUS II	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓

✓, yes (item adequately addressed); ×, no (item not adequately addressed); ✓/×, partially (item partially addressed); NS, not stated.

[a] Quality assessment based on conference abstracts only.

[b] Only 88 of 119 (74%) randomised to stent arm reported at 6 months.

TABLE 18 *Stent types and manufacturers for included DES RCTs*

Agent		Study name	Company	Drug-eluting stent
Taxane	Paclitaxel	ASPECT	Cook	Supra G
	Paclitaxel	DELIVER	Guidant	ACHIEVE: MULTI-LINK RX PENTA CSS
	Paclitaxel	ELUTES	Cook	V-Flex plus
	Paclitaxel	PATENTCY	Cook	Logic PTX
	Paclitaxel	TAXUS I	Boston Scientific	NIRx-Express
	Paclitaxel	TAXUS II	Boston Scientific	NIRx-Express
	QP2	SCORE	Quanum Medical/Boston Scientific	QUANAM
Rapamycin	Sirolimus	E-SIRIUS	Cordis	CYPHER BxVelocity
	Sirolimus	RAVEL	Cordis	CYPHER BxVelocity
	Sirolimus	SIRIUS	Cordis	CYPHER BxVelocity
	Everolimus	FUTURE	Biosensors	Challenge S-stent
Other	Actinomycin	ACTION	Guidant	MULTI-LINK TETRA

reversed (DES 134, stent 126) as in a presentation for the CRF Drug-Eluting Stent Symposium 2002[156] and other sources[149] numbers are stent 138, DES 128. Reasons for these differences remain unclear.

DES: study characteristics

Numbers of participants, centres and locations

A total of 4367 participants were studied in the included trials. Numbers of people randomised in each study ranged from 36 (FUTURE) to >1000 (DELIVER, SIRIUS). All but one study (FUTURE, a single centre based in Germany) were organised across multiple centres; seven of these involved European centres (ACTION, E-SIRIUS, ELUTES, SCORE, TAXUS I,[118] TAXUS II and RAVEL[119]), ASPECT was based in Asia and DELIVER, PATENTCY and SIRIUS were restricted to the USA.

Stent type

All the DES studies involved comparison of a drug-eluting device compared with bare stents (*Table 18* summarises DES types and manufacture), but three of the paclitaxel-eluting stent studies randomised participants to receive DES varying in dose loading and drug release profiles. ASPECT compared high- and low-dose paclitaxel stents with bare stents. ELUTES studied four doses of DES in comparison with uncoated implants, whereas TAXUS II included two DES types which were loaded with a similar quantity of drug, but were characterised by either slow or moderate release of the agent. The ACTION study evaluated actinomycin-eluting stents at two densities of drug.

Co-therapies

All but two studies (FUTURE, SCORE) reported details of concurrent medication prescribed for patients. These included aspirin (ASPECT, DELIVER, E-SIRIUS, ELUTES, RAVEL[119], SIRIUS, TAXUS I[118] and TAXUS II) and clopidogrel (ASPECT, DELIVER, E-SIRIUS, ELUTES, PATENTCY, RAVEL,[119] SIRIUS, TAXUS I[118] and TAXUS II), cilostazol (ASPECT) or ticlopine (E-SIRIUS, RAVEL,[119] SIRIUS). ACTION, E-SIRIUS and SIRIUS provided glycoprotein IIb/IIIa inhibitors for patients.

DES: primary and secondary end-points

Primary and secondary end-points varied across the studies and are presented in *Table 19*. Although the majority of studies used a MACE or MACCE composite outcome, definitions were not entirely consistent between studies. Event rate definitions for each trial are presented in *Table 20*.

Revascularisation

Consideration of revascularisation as a part of a composite event requires attention to two main issues. First, are the reported revascularisations specific to the target (treated) lesion (TLR), vessel (TVR) or non-specific (possibly including non-target vessels)? *Table 21* indicates the variety of revascularisation reporting across included trials.

Given the limited data related to definition of these terms within studies, it was not possible to compare the data from the trials directly except where the revascularisation was included in the event rate.

The second issue related to whether the revascularisation was initiated through protocol driven angiographic follow-up or presentation with symptoms. TAXUS I and II, RAVEL, SIRIUS and E-SIRIUS protocols or reports (contained within the submission to NICE) indicate that they

TABLE 19 *DES: study characteristics*

Study name	Intervention	Primary outcomes	Secondary outcomes	Location and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Follow-up
ACTION	**Actinomycin** Uncoated MULTI-LINK TETRA Actinomycin-coated MULTI-LINK TETRA-D (2.5 and 10 μg loaded stents)	MACE at 30 days Local tissue effects at 6 months Reduction in volumetric burden at 6 months Reduction in angiographic % diameter stenosis at 6 months	Acute success, TVF at 30 days, 6 months, 12 months, Angiographic BRR at 6 months	Multicentre (28), Europe, Australia, New Zealand, Brazil	Native coronary artery, vessel diameter 3–4 mm, lesion covered with 18-mm stent, target lesion coronary branch with DS >50% and <100%, acceptable for GABG	Untreated lesion of >40% proximal and distal to target lesion site, aorto-ostial location, unprotected left main CA, multiple lesions requiring staged intervention within 30 days prior or after procedure, viral infection	GP IIb/IIIa receptor antagonist	Clinical 30 days, 6 months, 1 year Angiographic: postprocedure, 6 months
ASPECT	**Paclitaxel** Bare Supra G stent Supra G paclitaxel (non-polymeric) coated stents High-dose 3.1 μg/mm^2, Low-dose 1.3 μg/mm^2	*Effectiveness:* Angiographic per cent DS at 4–6 months; Late loss at 6 months, Restenosis rate *Safety:* MACE at 1 and 6 months		Multicentre (3), Asia	Single, *de novo* or non-in-stent restenosis; lesions in native artery; 2.25–3.5 mm, <15 mm long	Graft lesion; severe calcification, severe proximal tortuousity, angulation >45°, thrombus, total occlusion, MI within 72 h, CI to antiplatelet agents; left main lesion; LVEF <40%	Aspirin Clopidogrel (137) or Cilostazol (37) for 1–6 months postprocedure	
DELIVER	**Paclitaxel** Uncoated MULTI-LINK PENTA stent ACHIEVE MULTI-LINK PENTA non-polymeric paclitaxel stent	TVF at 270 days	'MACE' ABR at 240 days Per cent diameter stenosis at 240 days	Multi-centre (≥ 16), USA	Multivessel disease with focal *de novo* lesions in native coronary arteries, 2–5 to 4.0 mm diameter	Target lesion aorto-ostial, unprotected left main CA, angiographic evidence of thrombus, heavy calcification, extreme angulation, tortuousity LVEF <30%, prior or planned intervention within 180 days	Preprocedure: Aspirin Clopidogrel During: Heparin GP IIb/IIIa inhibitors in use by 652/1043 patients Postprocedure: Aspirin £365 days Clopidogrel 90 days	Clinical, in-hospital, 30 days, 270 days Angiographic 240 days

continued

TABLE 19 *DES: study characteristics (cont'd)*

Study name	Intervention	Primary outcomes	Secondary outcomes	Location and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Follow-up
E-SIRIUS	**Sirolimus** Uncoated Bx Velocity Stent CYPHER Sirolimus-eluting stent[A]	In-stent MLD at 8 months	MACE at 1, 6, 9, 12 months and 2–5 years Angiographic BRR (≥ 50%) at 8 months TLR, TVR, TVF at 9 months Device/lesion/ procedure success (in-hospital)	Multicentre (35), Europe	Single *de novo* coronary lesion; between 2.5 and 3.0 mm diameter, 15 and 32 mm long; DS >50%; CCS angina or UA (Braunwald B&C, I–II) or documented silent ischaemia	MI £24 h; unprotected left main disease; ostial lesion; total occlusion; thrombus; calcified lesion; LVF £25%; impaired renal function; pretreatment with devices other than balloon angioplasty, prior or planned intervention within 30 days	Pre-procedure: Aspirin Clopidogrel or ticlopidine During procedure: Heparin GP IIb/IIIa inhibitors (at operator's discretion) Postprocedure: Aspirin (indefinitely) Clopidogrel or ticlopidine (2 months)	Clinical 1, 6, 9, 12 months and 2–5 years Angiographic 8 months
ELUTES	**Paclitaxel** V-flex Plus PTX DES with non-polymeric paclitaxel at four concentrations (0.2, 0.7, 1.4, 2.7 μg/mm^2)	*Effectiveness:* Per cent diameter stenosis Late loss at 6 months *Safety:* MACE at 1 and 6 months		Multicentre (10), Europe	*De novo* lesions (length <15 mm, type A/B1) in native 2.75–3.50-mm vessels	Severe calcification, left main lesion, multiple lesions in target vessel	Aspirin Clopidogrel for 3 months	
FUTURE	**Everolimus** Uncoated S-stent Challenge S-stent eluting everolimus	MACE at 30 days	*Clinical performance:* Device success, MACE, angiogram, restenosis at 6 months	Single centre, Siegburg, Germany	*De novo* coronary lesion; between 2.75 and 4 mm, less than 28 mm long, DS 50–99%, symptoms of angina/ischaemia, suitable for CABG	AMI within 4 weeks, cardiogenic shock, co-existing congenital heart disease, DM, LVEF <30%, thrombus or poor distal flow, side branch >2 mm diameter, more than one stent needed		Clinical assessment at 1, 6 months Angiogram at 6 months

continued

TABLE 19 *DES: study characteristics (cont'd)*

Study name	Intervention	Primary outcomes	Secondary outcomes	Location and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Follow-up
PATENTCY	**Paclitaxel** Uncoated Logic stent Logic PTX paclitaxel-eluting stent (2.0 μg/mm^2)		*Safety:* MACE at 30 days MACE at 9 months	Multicentre (6), USA	*De novo* lesion in native coronary artery, RVD 2.7–4.0 mm		Clopidogrel for 3 months	Clinical assessment at 1, 9, 18 months angiogram at 6 months
RAVEL[119]	**Sirolimus** Bare metal Velocity stent Bxvelocity sirolimus-eluting stent[a]	In-stent late luminal loss (immediately postprocedure and at 6 month)	Per cent in-stent restenosis, binary restenosis, composite end-point (death, MI, TVR) at 1, 6 and 12 months	Multicentre (19), international	Single primary lesion, native coronary artery 2.5–5.5 mm diameter (could be covered with 18-mm stent), 51–99% luminal diameter stenosis, ≤ TIMI 1, stable, unstable or silent ischaemia	Evolving MI; left CA stenosis; unprotected by graft, causing luminal narrowing of ≥ 50%; ostial lesion; calcified lesion (unable to be dilated before stenting); visible thrombus; LVEF <30%; intolerance to aspirin, clopidogrel, ticlopidine, stainless steel or contrast material; pregnancy	Aspirin Heparin Clopidogrel or ticlopidine	
SIRIUS	**Sirolimus** Bare metal Velocity stent Bxvelocity sirolimus-eluting stent[a]	TVF at 9 months	MACE, angiographic BRR (≥ 50%) at 8 months; TLR and TVR at 9 month; angiographic late loss and MLD at 8 months	Multicentre (53), USA	Single *de novo* native coronary lesion; ≥ 2.5 and ≤ 3.5 mm diameter, ≥ 15 mm long; DS >50 and 100%; CCS angina (I–IV) or UA (Braunwald B&C, I–II) or silent ischaemia	MI ≤ 24 h; left main disease; ostial lesion; total occlusion; thrombus; calcified lesion; LVF ≤ 25%; impaired renal function; pretreatment with devices other than balloon angioplasty	Preprocedure: Aspirin Clopidogrel Ticlopidine During procedure: Heparin GP IIb/IIIa inhibitors Postprocedure Aspirin Clopidogrel Ticlopidine	

continued

TABLE 19 *DES: study characteristics (cont'd)*

Study name	Intervention	Primary outcomes	Secondary outcomes	Location and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Follow-up
SCORE	**Taxane derivate** QP2 (7-hexanolytaxol) Bare stent (81% QueST stent) QUANAM QP-2-eluting stent ('sustained elution' from polymer sleeves – 3200, 4000, 4800 μg per stent)	*Safety:* MACE *Efficacy:* TVR at 6 months, restenosis at 6 months, late lumen loss, MLD, IVUS assessment		Multicentre (15), Europe	*De novo* coronary lesions, native vessel, RVD 3.0–3.5 mm, lesion length <20 mm	Major side branch (>2 mm), suboptimal PTCA results, severe tortuousity, severe calcification, AMI <1 week, LVEF <30%	'Long-term' Plavix recommended	
TAXUS I[118]	**Paclitaxel** Bare metal NIR[b] paclitaxel-eluting (slow-release polymer coated) NIRx Conformer coronary stent[b]	MACE at 30 days	Per cent diameter stenosis, MLD, loss in MLD, restenosis rate (>50% DS) at 6 months	Multicentre (3), Germany	Single *de novo* or restenotic lesions, ≤ 12 mm long; vessel size 3.0–3.5 mm diameter, DS 50–99%	Recent MI (<72 h), LVF >30%, stroke within 6 months, renal dysfunction, CI to aspirin, clopidogrel or ticlopidine, requirement for >1 stent	Preprocedure: Aspirin Heparin Clopidogrel Postprocedure: Aspirin 12 months Clopidogrel 6 months	1, 6, 9, 12 months postprocedure and 6 months angiogram
TAXUS II	**Paclitaxel** Bare metal NIR paclitaxel-eluting NIRx (slow release, moderate release)	6-month per cent net in-stent volume obstruction (assessed by IVUS)	MACE at 6, 12 months to 5 year TVR, TLR, per cent diameter stenosis, restenosis rate	Multicentre (61), 15 countries, Europe	Single *de novo* lesions, 3.0–3.5 mm, <12 mm, documented AP	Recent MI (<72 h), stroke within 6 months, renal dysfunction, LVF >30%	Aspirin 6 months Clopidogrel 6 months	

For definitions of event rates, see *Table 20*.
ABR, angiographic binary restenosis; BRR, binary restenosis rate; CA, coronary artery; DS, diameter stenosis; GP, glycoprotein; TVF, target vessel failure; UA, unstable angina.
[a] CYPHER sirolimus stent delivery system.
[b] Hand-mounted stent.

TABLE 20 *DES: included studies event rate definitions*

Study	Event rate: composition
ACTION	MACE: death, MI, TLR
ASPECT	MACE: death, MI, CABG, TLR and TLR for SAT
DELIVER	TVF: death, MI, TLR, TVR ['MACE' reported at 30 days, but not defined[130]
ELUTES	Death, MI, CABG, TLR, SAT
FUTURE	MACE: not defined
PATENTCY	MACE: death, MI, CABG, TLR, SAT
RAVEL	MACE: death, CABG, TL PTCA, SAT, acute thrombosis, MI
SCORE	MACE: death, MI, TVR
SIRIUS	MACE: death, MI, TVR
TAXUS I	MACE: death, MI, TVR, stent thrombosis
TAXUS II	MACE: death (cardiac), MI, TVR

SAT, Subacute thrombosis.

have used the currently accepted FDA definition of clinically driven TLR or TVR, which is:

> "A TVR/TLR will be considered as clinically driven if: (a) the patient had a positive functional study; (b) ischemic ECG changes at rest in a distribution consistent with the target vessel; or (c) ischemic symptoms and an in-lesion diameter stenosis ≥ 50% by QCA. Revascularization of the target vessel with an in-lesion (target or non-target) diameter stenosis ≥ 70% (by QCA) in the absence of the above mentioned criteria will also be considered clinically driven. In the absence of QCA data for relevant follow-up angiograms, the clinical need for revascularization will be adjudicated using the presence or absence of ischemic signs and symptoms.
>
> "Non-clinically driven repeat TVR/TLRs are those in which the patient undergoes a non-emergent revascularization of the target vessel with an in-lesion (target or non-target) diameter stenosis <50% (by QCA). Non-emergent repeat TVR/TLR for an in-lesion (target or non-target) diameter stenosis <70% (by QCA) in patients without either a positive functional study or angina is also considered non-clinically driven."
>
> Quoted from source within the submission to NICE.

However, even using these definitions, it is often difficult to distinguish the data. For instance, the 2002 journal publication of the RAVEL[119] study reports both the angiographically and clinically driven results for MACE in the table, whereas the 'clinically driven' events (i.e. due to angina or abnormal stress test) are reported in the text; it is unclear from the text whether these are all of the clinically driven events, as the description in the text would seem to exclude those who might have had a procedure based on the 'clinically driven' criterion of >70% stenosis. Company submission data seem to suggest that there were no patients who met this criterion alone. Whereas full MACE figures for RAVEL as reported in the cited paper[119] are 34 out of 118 in the non-DES arm, the figures are only 23 out of 118 for 'clinically driven' MACE. This latter figure is included in the meta-analysis. Since no patient in the DES arm had an angiographically driven revascularisation, the event rate in this arm is unchanged by this distinction.

This issue will be discussed again below and in the economic discussion, where the data needed to assess costs needs to include not only revascularisation of the target lesion, but any revascularisation experienced carried out.

TABLE 21 *DES: reported revascularisation*

Study	SAT	TLR	TLR + TVR	TVR (non-TLR)	Target-RR	Non-T-RR	Any RR
ACTION		Reported		Reported			
ASPECT	Reported	Reported					
DELIVER	Reported	(Reported)		(Reported)			
ELUTES	Reported	Reported					
FUTURE							
PATENTCY	Reported	Reported					
SCORE	Reported	Reported		Reported			
SIRIUS	Reported	Reported		Reported			
RAVEL		Reported			Reported		
TAXUS I		Reported	Reported	Reported	Reported		
TAXUS II	Reported	Reported	Reported	Reported			

SAT, subacute thrombosis; TLR, target lesion revascularisation; TVR, target vessel revascularisation; TLR + TVR, Sum of TLR and TVR; Target-RR, target revascularisation; Non-T-RR, non-target revascularisation; Any RR, any revascularisation (target-RR + non-T-RR).

Restenosis and angiographic outcomes

All studies planned angiographic investigations at a medium-term postintervention (8 months SIRIUS and E-SIRIUS, 6 months all others). Follow-up was achieved in 95–100% of TAXUS I[118] and TAXUS II trial participants, 85–91% among SIRIUS, ASPECT, RAVEL[119] and ELUTES and 81% for SCORE.

The relevance of binary restenosis and the introduction of more clinically relevant outcomes were discussed in the background. Use of this measure is being replaced. However, it was included as an outcome in the protocol for this review and is reported here.

DES: study participants

Sample size

Details of the characteristics of study participants are provided in *Table 22*.

In all, 4367 patients were involved in the included studies. Of these, 2323 were involved in trials evaluating taxane (or derivative), 1684 evaluating sirolimus and 360 in the ACTION study assessing actinomycin. Numbers randomised to treatment (DES) versus control (stent) arms are not equal owing to the nature of two trials (ACTION, ASPECT and ELUTES) that assessed various concentrations of drug elution, but used single control groups.

Little reference to crossover from allocated invention is made. The ASPECT study reported technical success for 99.4% of participants. In another example, DELIVER reports 'device success' of 99.0% for non-eluting stents from a partner registry and 98.5% for DES within the trial. Within the TAXUS I publication,[118] it is stated that 100% procedural and technical success was achieved, although non-study stents were used in 4/30 of the stent and 6/31 of the DES participants. Provision of allocated treatment in other DES studies may also have been high, but this cannot be quantified from the available information.

Trial inclusion and exclusion criteria

Populations are broadly comparable with the exception of SIRIUS, which included patients with smaller vessels and longer lesions, and RAVEL, which included patients with smaller vessels.

Age, gender and type of stent

Mean age ranged from 59 to 65 years and males predominated in all studies, comprising between 65 and 89% of participants in each study.

Acute or chronic conditions, vessel and lesions involved and lesion characteristics

Recent or current MI excluded potential participants in ASPECT, E-SIRIUS, FUTURE, RAVEL SIRIUS, SCORE, TAXUS I[118] and TAXUS II. ELUTES and ACTION do not state that MI excluded participants.

Information on past or concurrent health factors was identified for all studies. The proportion of participants with DM varied from around 14 to 29%. People with type 2 DM made up 14.5% of those included in ACTION and TAXUS II; SIRIUS included 26.4% overall and DELIVER included the highest proportion of people with DM (28.7%). The FUTURE study excluded people with diabetes.

All studies presented at least some information on lesion or target vessel characteristics (lesion category, vessel diameter or length).

DES: data analysis

Meta-analysis is presented for event rate, mortality, AMI and binary restenosis. Data are pooled using a fixed-effect model with ORs and 95% CIs. Where qualitative heterogeneity exists, a result of the application of a random effects analysis is also presented.

It is not within the remit of this review to compare stents eluting different pharmaceutical agents. However, within the presented analyses, stents loaded with related compounds are labelled and grouped for ease of reference. Three studies (ASPECT, ELUTES and SCORE) evaluated the effects of differing doses of the same agent, and TAXUS II evaluated the effects of slow and moderate drug release. For the purposes of this analysis, the results from these groups have been combined. Results of the analysis are presented in forest plots in *Figures 15–19*, and details are provided here.

DES: event rate

Analysis of event rates favours DES at 6 months (OR 0.49, 95% CI 0.38 to 0.61) and 12 months (OR 0.37, 95% CI 0.27 to 0.50). However, in the 6-month analysis there is heterogeneity, and the analysis was recalculated using a random effects model. This more conservative analysis shifts the OR to 0.59 (95% CI 0.31 to 1.11). The direction and significance of this is maintained in the 2-year RAVEL data (OR 0.46, 95% CI 0.22 to 0.97).

DES: mortality

Death in all studies was a rare event. There is no

TABLE 22 *DES: participant characteristics*

Study name	Intervention *n*	Age, mean (SD) (years)	Gender (% male)	Lesion category (%)	ACS (%)	Previous cardiac event (%)	DM (%)
ACTION	Stent[a] 121 (119)	61 (±11) (*n* = 119)	78	A 5 B1 32 B2 62 C 0 (*n* = 118))		Prior MI 41 (*n* = 119)	5 (*n* = 119)
	DES[a] 239 (241) 2.5 μg/cm^2 120 *(120)* 10 μ/cm^2 119 *(121)*	2.5 (*n* = 120),2.5 (*n* = 120) 10 (*n* = 121), 59 (±11)	2.5 (*n* = 120) 78 10 (*n* = 121) 79	2.5 (*n* = 120) A 9 B1 31 B2 59 C 1 10 (*n* = 121) A 2 B1 45 B2 53 C 1	UA 10 (*n* = 121) 2.5 (*n* = 120)	Prior MI 2.5 (*n* = 120) 38 10 (*n* = 121) 38	2.5 (*n* = 120) 15 10 (*n* = 121) 21
ASPECT	Stent 59	58 (±11)	76	Overall: (*n* = 177) A 53 B1 40 B2 5 C 1 A and B1 lesions Stent 92			17
	DES 118 1.3 μg/mm^2 60 3.1 μg/mm^2 58	3.1 58 (±9) 1.3 60 (±9)	3.1 80 1.3 72	3.1 92 1.3 97			3.1 18 1.3 24
DELIVER	Stent 519	62.7 70.7				Prior MI: 27.2	26.8
	DES 524	61.8 70.5				Prior MI: 25.7	30.7

continued

TABLE 22 *DES: participant characteristics (cont'd)*

Study name	Intervention *n*	Age, mean (SD) (years)	Gender (% male)	Lesion category (%)	ACS (%)	Previous cardiac event (%)	DM (%)
E-SIRIUS	Stent 175	62.6 (±10.3) (*n* = 177)[b]	71.2 (*n* = 177)[b]		CCS class III or IV: (*n* = 166) 42.2	Prior MI: (*n* = 175) 43.4	(*n* = 176) 27.3
	DES 175	62.0 (±11.4)	70.3		CCS class III or IV: (n=168) 43.5	Prior MI: (*n* = 174) 40.8	18.9
ELUTES	Stent 38	Overall: 60 (±11)	Overall: 82.3	Type B1 59 Type B2 10			Overall: 15.6
	DES 152			B1 64 B2 8			
	0.2 μg/mm^2 37 0.7 μg/mm^2 39 1.4 μg/mm^2 39 2.7 μg/mm^2 37			B1 0.2 59 0.7 72 1.4 64 2.7 62 B2 0.2 5 0.7 8 1.4 5 2.7 13			
FUTURE	Stent 12	65.1 (±10)		A 25.0 B1 50.0 B2 25.0		Prior MI: 16.7	0.0
	DES 24	63.5 (±9)		A 16.7 B1 66.7 B2 16.7		Prior MI: 4.2	0.0
PATENTCY	Stent 26		62	B1, B2 and C 77			23
	DES 24		67	B1, B2 and C 92			25
RAVEL	Stent 118	59.7 (±10.1)	81	A 4 B1 35 B2 61	UA: 52	Prior MI: 33.9	21.2

continued

TABLE 22 *DES: participant characteristics (cont'd)*

Study name	Intervention *n*	Age, mean (SD) (years)	Gender (% male)	Lesion category (%)	ACS (%)	Previous cardiac event (%)	DM (%)
	DES 120	61.8 (±10.7)	70	A 8 B1 38 B2 54	UA: 48	Prior MI: 37.5	15.8
SCORE	Stent 138	63.1 (35–81) 62.5 (34–80)	78	A 17 B1 49 B2 25 C 8		Prior MI: 41	21
	DES 128	61.2 (34–80) 60.6 (33–79)	81	A 20 B1 48 B2 21 C 9		Prior MI: 39	20
SIRIUS	Stent 525	62.4	69.6	A 7.8 B1 38.1 B2 33.5 C 20.6	UA: 53.9	Prior MI: 32.9 (n = 519)	28.2
	DES 533	62.1	72.6	A 7.4 B1 34.0 B2 32.6 C 26.0	UA: 53.1	Prior MI: 28.2 (n = 521)	24.6
TAXUS I[118]	Stent 30	63.8±7.8	83	Type A 13.3 Type B1 43.3 Type B2 43.3 Type C 0.0		Prior MI: 30	DM 13
	DES 31	66±6.8	94	Type A 32.3 Type B1 38.7 Type B2 29.0 Type C 0.0		Prior MI: 26	DM 23
TAXUS II	Stent 270	59.7	77.9		UA: 36	Prior MI: 42.0	15.1
	DES 266	Slow DES 61.5 Moderate DES 59.3	Slow DES 70.2 Moderate DES 76		UA: Slow DES 35.1 Moderate DES 30.0	Prior MI: Slow DES 35.1 Moderate DES 39.0	Slow DES 10.7 Moderate DES 17.0

[a] ACTION[165] lists stent 121, DES 2.5 μg 120, 10 μg 119 for patient allocations; Reference 174 lists stent 119 (and 118), DES 2.5 μg 120, 10 μg 121 for patient allocations. Patient numbers reported in data source will be provided with percentages.
[b] Patient numbers for stent arm 177 within information provided by Cordis.

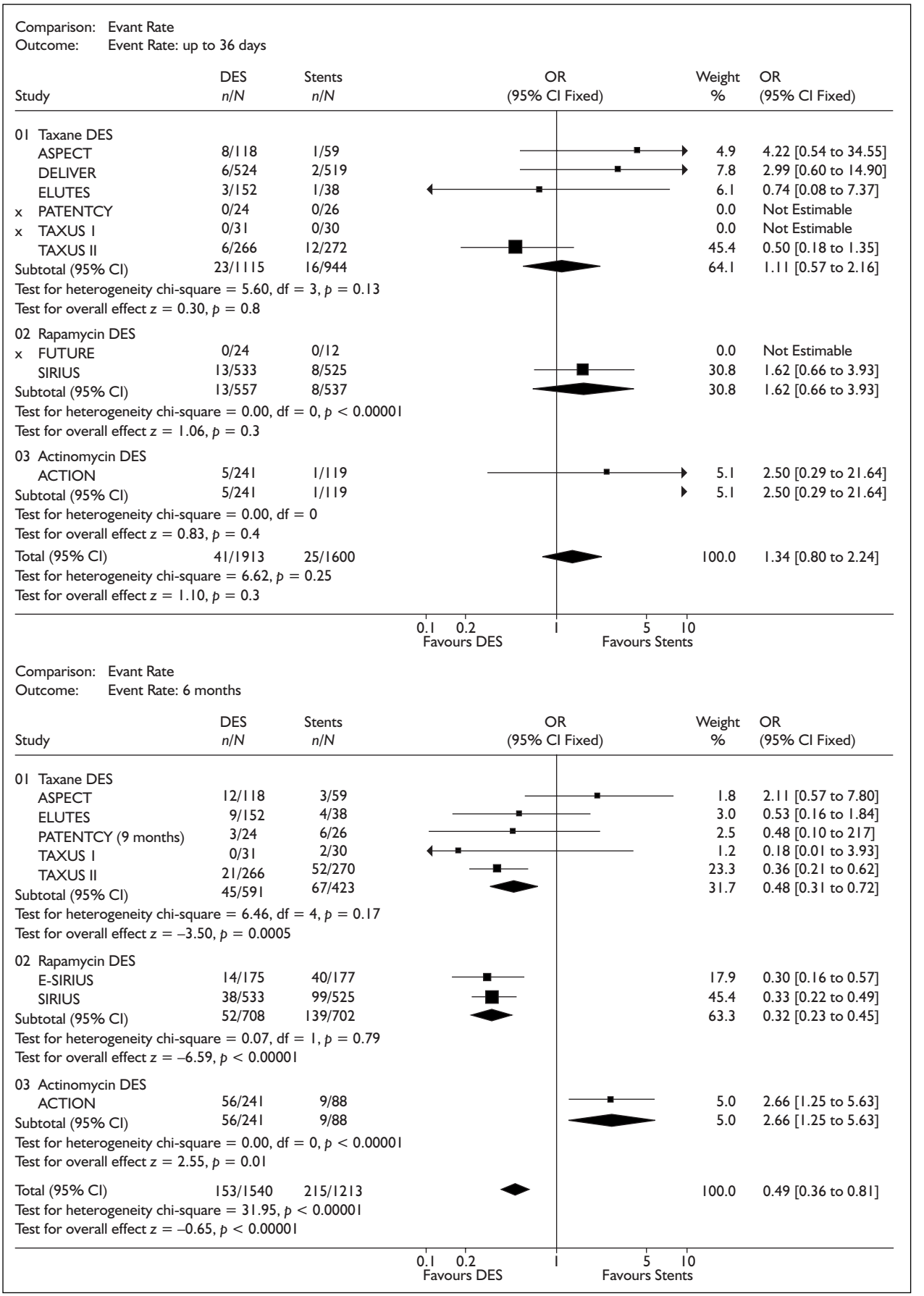


FIGURE 15 *DES: meta-analysis of event rate. RAVEL 12-month event rate data are clinically driven.*

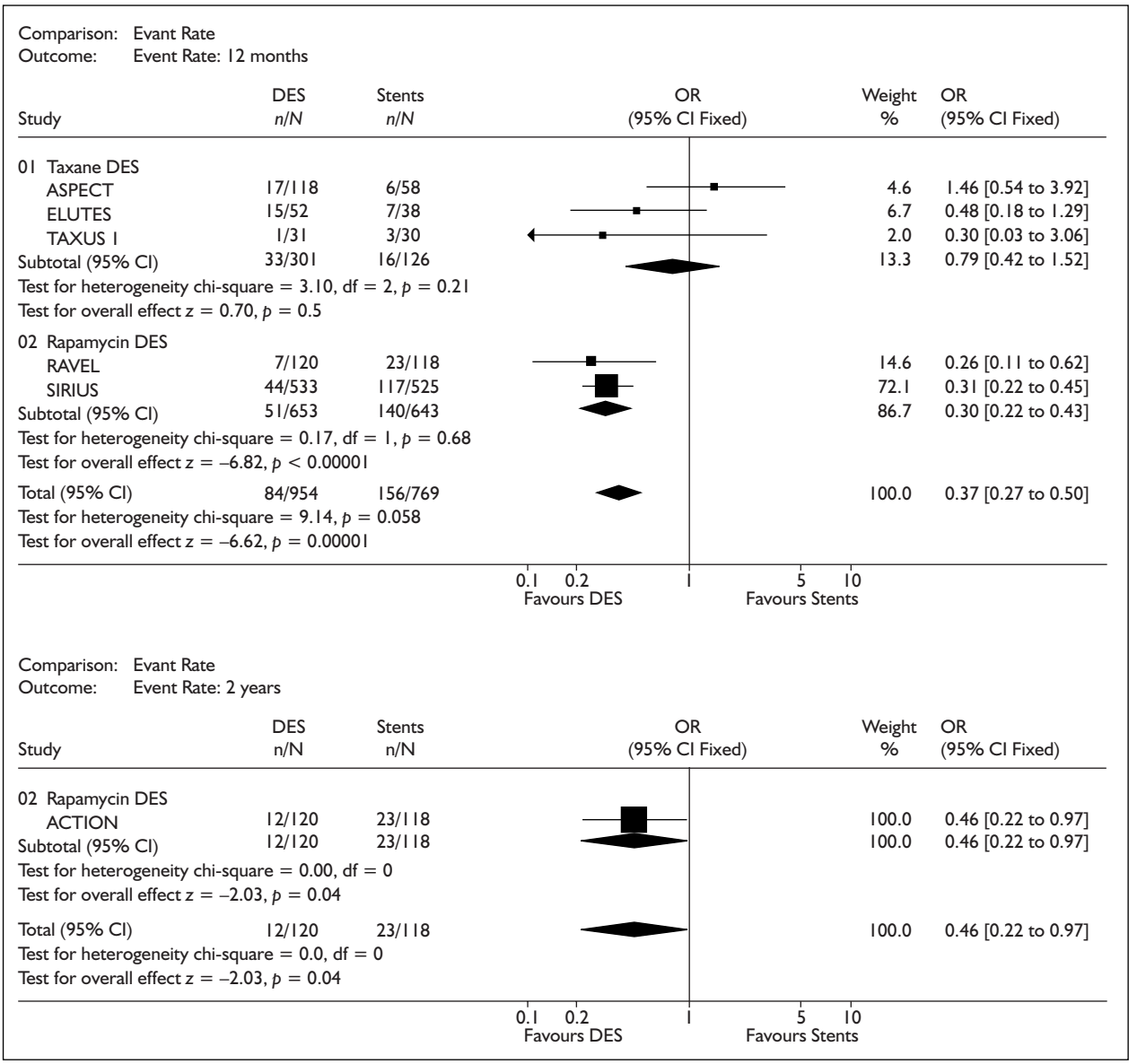


FIGURE 15 *DES: meta-analysis of event rate. RAVEL 12-month event rate data are clinically driven (cont'd).*

evidence of a difference between the groups. Event rates in the short term do not differ between the groups. This trend is maintained in the RAVEL 2-year data. There are five non-cardiac deaths in the DES arm of RAVEL to 2 years compared with one in the non-DES arm, compared with one and two cardiac deaths in each, respectively.

DES: AMI

There is no evidence of a difference in incidence of AMI between DES and stents in the short term or at 6 months. Data at 12 months indicate an increase in AMI in the DES group. This outcome is predominated by the outcome of the SCORE trial. Two-year RAVEL data show no difference between the groups in rate of AMI.

DES: binary restenosis

Binary restenosis (>50%) is reported for seven of the included studies at 6 months and at 9 months for PATENTCY, SIRIUS and E-SIRIUS. Analysing these data together suggests a benefit of DES over non-eluting stents in the taxane and sirolimus groups. This advantage is not evident in the evaluation of actinomycin in the ACTION trial.

Discussion

DES represent a simple adaptation of a currently provided technology. One of the attractions therefore is that if considered effective and subject to funding, it could be easily adopted. Most

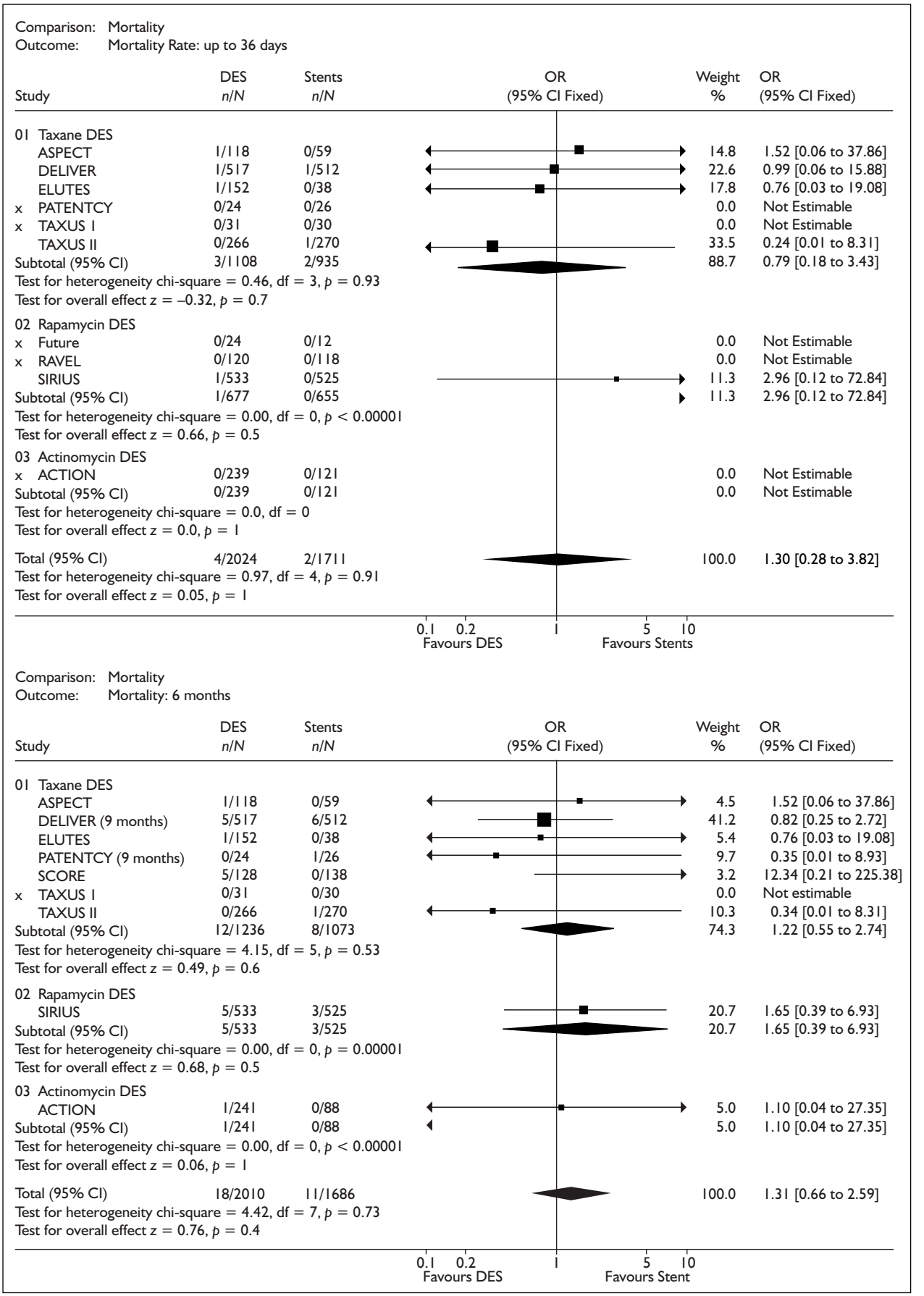


FIGURE 16 *DES: meta-analysis of mortality*

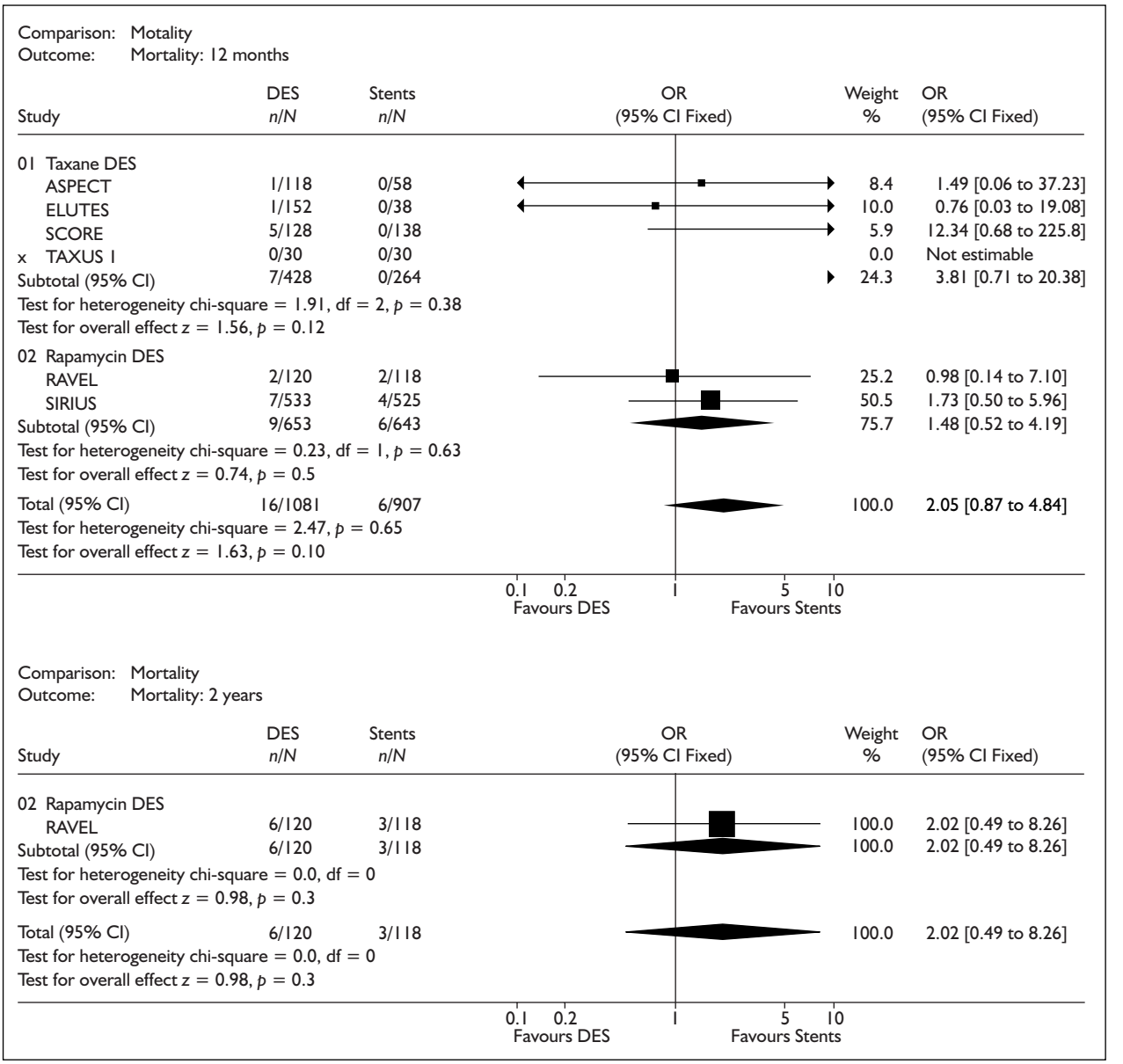


FIGURE 16 *DES: meta-analysis of mortality (cont'd)*

interventional cardiologists are enthusiastic about the use of DES. However, current available data have limited follow-up and it remains to be seen whether there will be greater frequency of late thrombosis or delayed restenosis; as with all new technology, it may be expected after the initial enthusiasm to have some drawbacks.

Not all cardiologists are enthusiasts: some point to evidence from preclinical animal studies that DES can cause significant medial necrosis and persistent local fibrin deposition, suggesting delayed healing. Animal studies have also shown a reduction in restenosis with DES at 1 month which is lost by 6 months, that is, that the effects of the DES were temporary and probably only delayed healing. By comparison with animal models, the temporal response to healing is much delayed in humans, and therefore some fear that short-term reductions in restenosis may not translate into long-term gains as late restenosis becomes more common.[175] Others point out that animal models differ depending on the species studied, and that these cannot be easily translated into human biology. We need therefore to consider the long-term human studies so far reported.

First in humans was an open non-comparative study in patients with CHD treated with a single sirolimus-eluting velocity stent in Brazil and The Netherlands. Twelve-month follow-up has been reported for the 45 patients,[176] showing no patient

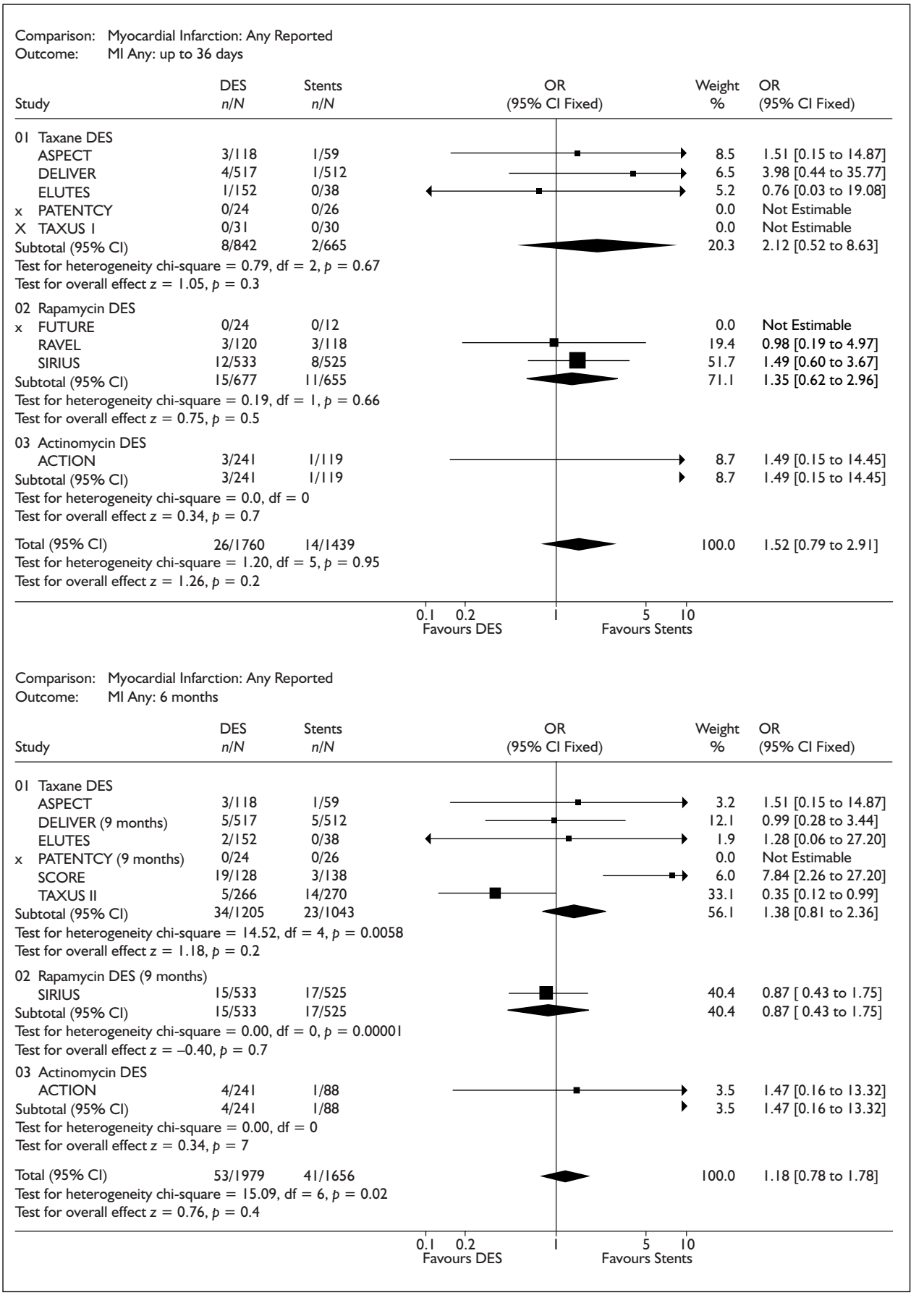


FIGURE 17 *DES: meta-analysis of any myocardial infarction*

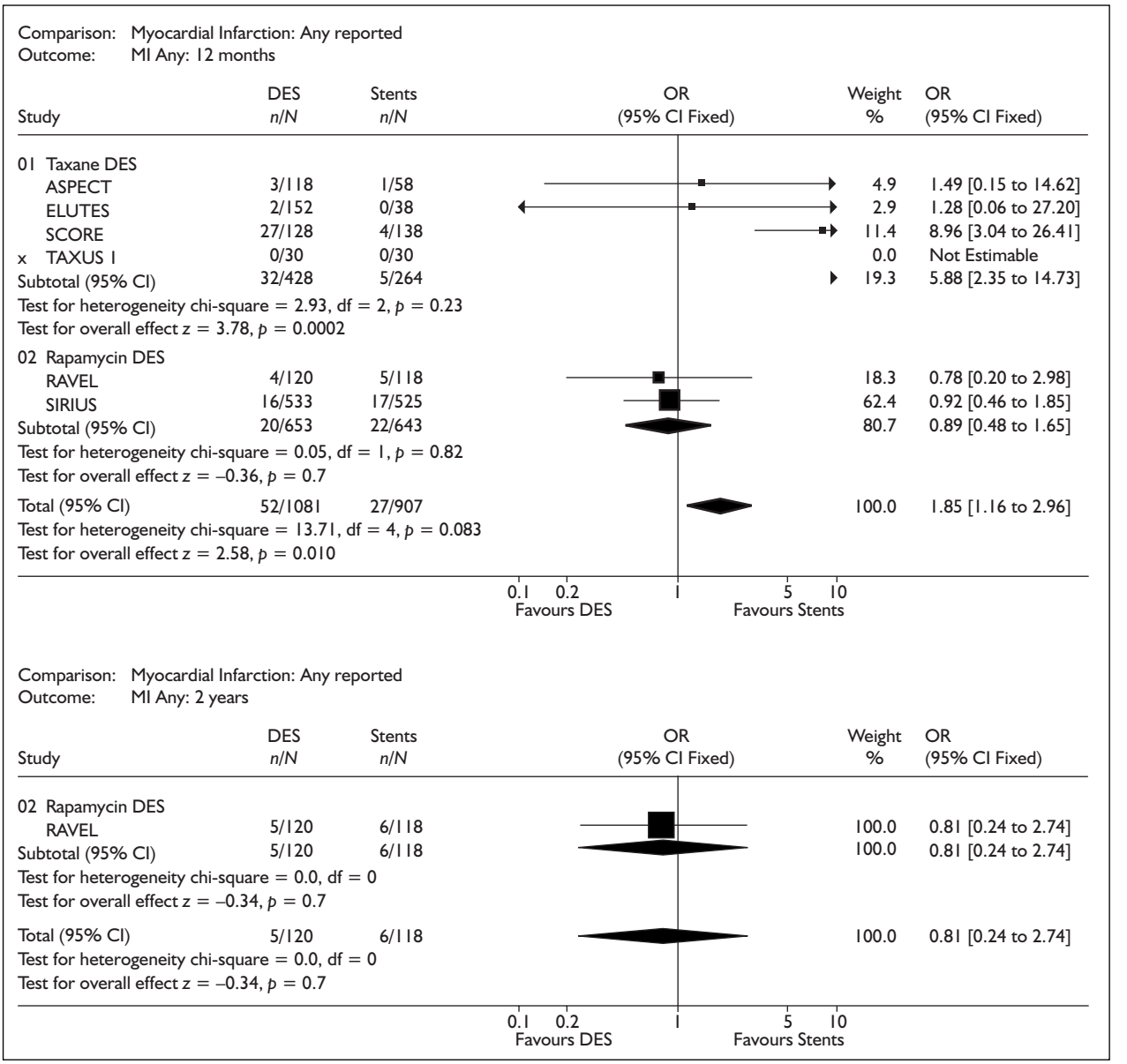


FIGURE 17 *DES: meta-analysis of any myocardial infarction (cont'd)*

reaching more than 50% diameter stenosis at 1 year based on angiography. Neo-intimal hyperplasia, as assessed by IVUS, was found to be virtually absent at both 6 and 12 months. The authors conclude that the study demonstrates a sustained suppression of neo-intimal proliferation by the DES. Two-year data have also been reported for the 15 patients from The Netherlands.[177] Within the following 2 years there were no additional events in these patients except that two had undergone significant lesion progression in a site remote from the sirolimus-eluting stent and which required further intervention. Angiography showed no significant change in the stent minimal luminal diameter or percentage diameter stenosis compared with earlier angiography. In general these studies are reassuring about the long-term safety of this DES. The 2-year data from RAVEL greatly increase the information available at 2 years, and are similarly reassuring about the long-term safety of this device. The results in revascularisations at 2 years are discussed below.

Comparability of interventions

There are many technical issues which remain to be resolved with DES, including polymer biocompatibility, the suitability of and relative effectiveness of pharmacological agents, suboptimal *in vivo* pharmacokinetic properties, local drug toxicity and manufacturing process. At present, significant differences have by and large

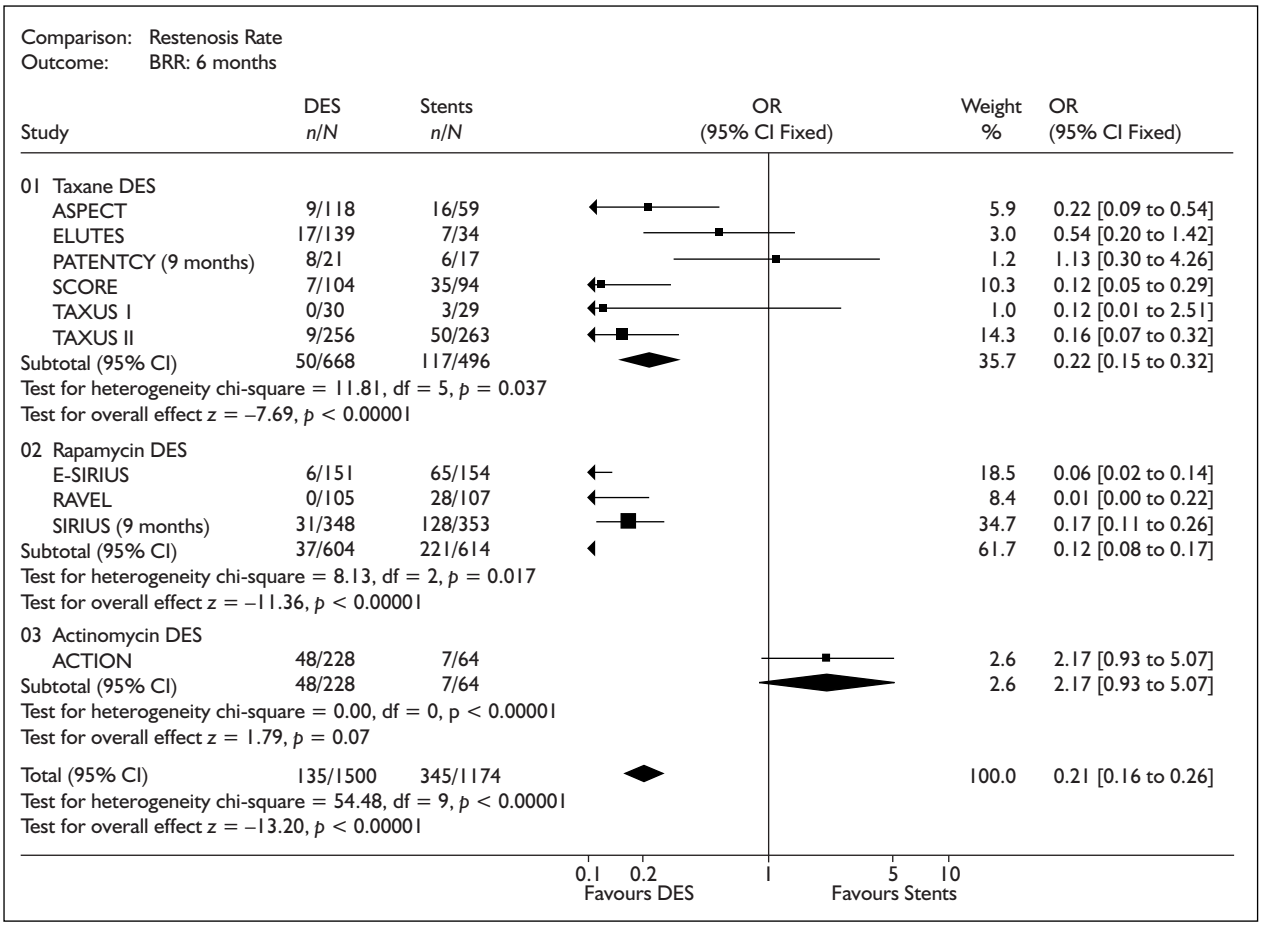


FIGURE 18 *DES: meta-analysis of binary restenosis*

not been shown between medium- and slow-release coatings. A dose–response curve has been evident in some studies (ELUTES or ASPECT, for instance).

Much of the stent coating technology is proprietary, and each stent design and drug–polymer combination is unique. The pharmacokinetics of local intracoronary drug delivery by eluting stents will obey very specific mechanisms that may be influenced not only by drug competition and concentration but also by factors such as stent design and homogeneity of stent replacement. Therefore, the interaction of each drug–polymer–stent complex with the vessel wall and plaque may differ from those of other DES.

This is particularly important when examining the data analysis because three of the studies to evaluate stents or drugs are no longer being evaluated. Actinomycin (ACTION) and the taxol derivative 7-hexanolytaxol (SCORE), have been discontinued: the former because of an inability to reduce restenosis rates and the latter owing to high rates of early major adverse cardiac events.

The third trial, DELIVER, enrolled 1043 patients and its primary end-point was target vessel failure (MI or TLR or TVR at 9 months). The study was powered to detect a 40% reduction. A secondary end-point was angiographic binary restenosis at 8 months. Although there was a 20% reduction in the rate of the primary end-point in favour of the DES, this was less than the benefit for which the study was powered and considerably less than seen in other DES studies. This was therefore a negative study, which the authors attribute to the excellent results from the control stent. The reporting of this study remains incomplete.

Two included studies reported in the taxane group were dose-ranging trials with different densities of drug per square millimetre of stent surface area. ELUTES used four dose densities and ASPECT two dose densities compared with a bare metal stent. These arms with DES have been merged for the meta-analysis, but there were differences between them. In ELUTES, the binary restenosis rate was 21% in the controls versus 3% in the highest dose DES group (2.7 $\mu g/mm^2$). In ASPECT, the rates were 27% in the control group versus 4% in the

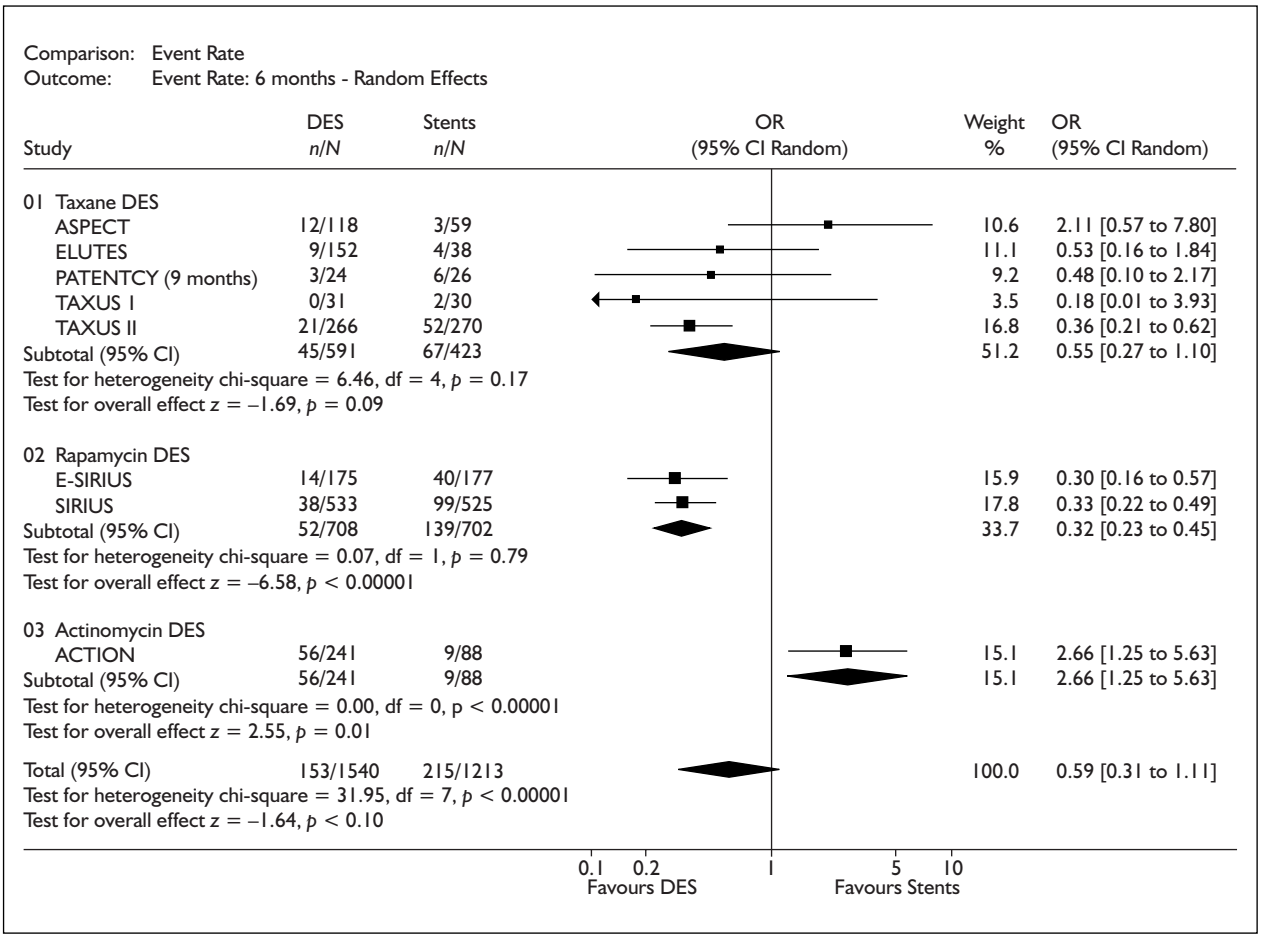


FIGURE 19 *DES: meta-analysis of event rate – random effects*

high-dose DES group (3.1 μg/mm^2). There was no statistically significant difference between DES and control at lower doses densities in either study, although a dose–response relationship was observed.

The other factor that has not been taken into consideration in this analysis is the stent used in the control groups. New non-eluting stents with lighter strut design may be less likely to trigger neointimal hyperplasia. However, this requires further study.

The key point of this is that results from one type of DES (even with the same drug) cannot be extended to another; each must be considered on its own merits. We therefore have a concern about meta-analysis which combines a variety of interventions. The decision to present the analysis was based on the fact that data are limited, and therefore those appraising the evidence should be able to view all the data in relation to the appropriate outcomes. There are no head-to-head comparisons of different DES.

There are, as yet, no comparisons of DES with CABG. The FREEDOM and CARDia studies will compare diabetic patients with multiple-vessel disease randomised to either CABG or to PTCA with sirolimus-coated stents. FREEDOM plans to randomise ~1500 patients with the primary end-point being the follow-up at 12 months without protocol-driven reangiography. There will also be longer term follow-up including mortality, up to 5 years. It remains to be seen whether similar rates of MACCE (mainly repeat revascularisations) can be achieved over a prolonged period with DES as with CABG in diabetics patients, and whether DES will span the current gap in outcomes between standard stents and CABG.

Outcomes

The trials reported to date repeat some of the problems identified in the comparison of stents with PTCA (*Table 23*). They identify a variety of definitions of MACE or MACCE. Therefore, the difficulties of interpreting composite end-points remain. There are problems identifying when

TABLE 23 *DES: outcomes*

Study name	Intervention	Event Rate (%)	Mortality (%)	Any MI (%)	Revascularisation (%)	CABG (%)	PCI (%)	BRR (%)
ACTION[174]	Stent[a] 119	30 days (n = 119) 0.8 6 months (n = 88) 10.2	30 days (n = 119) 0.0 6 months (n = 88) 0.0	30 days[d] (n = 119) 0.8 6 months (n = 88) 1.1	TLR 30 days (n = 119) 0.0 6 months (n = 88) 9.1 TVR 30 days (n = 119) 0.0 6 months (n = 88) 0.0	30 days (n = 119) 0.0 6 months (n = 88) 0.0	30 days (n = 119)	6 months (n = 64) 11
	DES[a] 241 2.5 μg/cm^2 120 10 μg/cm^2 121	30 days[d] 2.5 0.8 10 3.3 6 months 2.5 (n = 120) 18.3 10 (n = 121) 28.1	30 days 2.5 (n = 120) 0.0 10 (n = 121) 0.0 6 months 2.5 (n = 120) 0.8 10 (n = 121) 0.0	30 days[d] 2.5 (n = 120) 0.0 10 (n = 121) 2.5 6 months 2.5 (n = 120) 0.0 10 (n = 121) 3.3	TLR 30 days 2.5 (n = 120) 0.8 10 (n = 121) 0.0 TLR 6 months 2.5 (n = 120) 17.5 10 (n =121) 23.1 TVR 30 days 2.5 (n = 120) 0.0 10 (n = 121) 0.8 TVR 6 months 2.5 (n = 120) 0.0 10 (n = 121) 0.8	30 days 2.5 (n = 120) 0.0 10 (n =121) 0.0 6 months 2.5 (n = 120) 0.0 10 (n = 121) 1.7	30 days 2.5 (n = 120) 10 (n = 121)	2.5 (n = 113) 17 10 (n = 115) 25
ASPECT	Stent 59 (58)	1 month 1.7 6 months 5 1 year (n = 58) 10.3	1 month 0.0 6 months 0.0 1 year (n = 58) 0.0	1 month 1.7 6 months 1.7 1 year (n = 58) 1.7	TLR 6 months 3.4	30 days 0.0 6 months 0.0 1 year 0.0	1 year (n = 58) 8.6	6 months 27
	DES 118 1.3 μg/cm^2 58 3.1 μg/cm^2 60	1 month 3.1 8.3 1.3 5.2 6 months 3.1 11.7 1.3 8.6 1 year 3.1 16.3 1.3 12.4	1 month 0.8 3.1 0.0 1.3 1.7 6 months 0.8 3.1 0.0 1.3 1.7 1 year 0.8 3.1 0.0 1.3 1.7	1 month 3.1 3.3 1.3 1.7 6 months 3.1 3.3 1.3 1.7 1 year 2.5 3.1 3.3 1.3 1.7	6 months 3.4	30 days 0.0 6 months 0.0 1 year 0.8 3.1 0.0 1.3 1.7	1 year 8.5 3.1 10.3 1.3 6.6	6 months 3.1 4 1.3 12
DELIVER	Stent 519 (512)	MACE[c] 30 days 0.4 TVF 9 months 14.6 (n = 512)	30 days 0.2 9 months 1.2 (n = 512)	30 days 0.2 9 months 1.0 (n =5 12)	TVR 30 days – 9 months 1.4 TLR 30 days – 9 months 11.3 (n = 512)	TVR 0.4 TLR 1.2	TVR 1.0 TLR 10.2	
	DES 524 (517)	MACE[c] 30 days 1.2 TVF 9 months 12.0 (n = 517)	30 days 0.2 9 months 1.0 (n = 517)	30 days 0.8 9 months 1.0 (n = 517)	TVR 30 days – 9 months 1.6 TVR 30 days 9 months 8.1 (n = 517)	TVR 0.0 TLR 1.2	TVR 1.6 TLR 7.0	

continued

TABLE 23 *DES: outcomes (cont'd)*

Study name	Intervention	Event Rate (%)		Mortality (%)		Any MI (%)		Revascularisation (%)		CABG (%)		PCI (%)		BRR (%)	
E-SIRIUS (data from company)	Stent 177	9 months	22.6					TVR free 9 months TLR free 9 months	76.9 78.3					8 months: (*n* = 154)	42.2
	DES 175	9 months	8.0					TVR free 9 months TLR free 9 months	76.9 95.9					8 months: (*n* = 151)	4.0
ELUTES	Stent 38	Event-free survival: 1 month 6 months 1 year	97 89 82	1 month 6 months 1 year	0.0 0.0 0.0	1 month 6 months 1 year	0.0 0.0 0.0	TLR 6 months 1 year	7.9 15.8	30 days 6 months 1 year	0.0 0.0 2.6			6 months in-stent: (*n* = 34)	20.6
	DES 152	Event-free survival: 30 days		1 month 6 months	0.7 0.7	1 month 6 months	0.7 1.3	6 months Combined	3.3	30 days 6 months	0.0 0.0			6 months in-stent 0.2	20
	0.2 μg/cm^2 37	0.2	100	1 year		1 year	1.3	0.2	2.7	1 year	0.7	1 year	6.6	0.7	11.8
	0.7 μg/cm^2 39	0.7	100	0.2	0.7			0.7	2.6	0.2	0.0	0.2	5.4	1.4	13.5
	1.4 μg/cm^2 39	1.4	100	0.7	0.0			1.4	2.6	0.7	2.7	0.7	5.1	2.7	3.1
	2.7 μg/cm^2 37	2.7	92	1.4	0.0			2.7	5.4	1.4	0.0	1.4	10.6	(*n* = 139 calculated)	
		6 months		2.7	0.0			1 year		2.7	0.0	2.7	5.4		
		0.2	95					Combined	7.2						
		0.7	95					0.2	5.4						
		1.4	97					0.7	7.7						
		2.7	89					1.4	10.3						
		1 year						2.7	5.4						
		0.2	95												
		0.7	90												
		1.4	90												
		2.7	86												
FUTURE I	Stent 12	30 days	0.0	30 days	0.0	30 days	0.0			30 days	0.0	30 days	0.0		
	DES 24	30 days	0.0	30 days	0.0	30 days	0.0			30 days	0.0	30 days	0.0		
PATENTCY	Stent 26	30 days	0.0	30 days	0.0	30 days	0.0			30 days	0.0	30 days	0.0	9 months	35.3
		270 days	23.1	270 days	3.8	270 days	0.0			270 days	3.8	270 days	15.4	(*n* = 17)	
	DES	30 days	0.0	30 days	0.0	30 days	0.0			30 days	0.0	30 days	0.0	9 months	38.1
	2.0 μg/cm^2 24	270 days	12.5	270 days	0.0	270 days	0.0			270 days	0.0	270 days	8.3	(*n* = 21)	

continued

TABLE 23 *DES: outcomes (cont'd)*

Study name	Intervention	Event Rate (%)		Mortality (%)		Any MI (%)		Revascularisation (%)		CABG (%)		PCI (%)		BRR (%)	
RAVEL[e,g]	Stent	1 year	28.8	In hospital	0.0	In hospital	2.5	TVR (not TL)		In hospital	0.0	TLR		6 months	26.6
(2-year data	118	2 years	19.5	1 year	1.7	1 year	4.2	1year	1.7	1year	0.8	1 year	22.9	(in stent, n = 107)	
from company)				2 years	2.5	1 year[f]-(7/118)	5.9			2 years	0.0	2 years	13.6		
						2 years	5.1	TLR (all)							
						1year	23.7								
						TVR (not TL)									
						2 years	2.5								
						TLR (all)									
						2 years	13.6								
	DES	1 year	5.8	In hospital	0.0	In hospital	2.5	TVR (not TL)		In hospital	0.0	TLR		6 months	0.0
	120	2 years	10.0	1 year	1.7	1 year	3.3	1 year	0.8	1 year	0.8	1 year	0.0	(in stent, n = 105)	
				2 years	5.0	1 year[f]-(4/120)	3.3			2 years	0.8	2 years	1.7		
						2 years	4.2	TLR (all)							
								1year	0.8						
								TVR (not TL)							
								2 years	0.8						
								TLR (all)							
								2 years	2.5						
SCORE	Stent	1 year		6months	0.0	6 months	2.3	TLR 1 year	25.4					6 months	36.9
	138	Non-hierarchical		1 year	0.0	1 year	2.9	TVR 1 year	5.1					(In stent n = 94)	
	DES	1 year		6 months	3.9	6 months	14.5	TLR 1 year	21.1					6 months	6.4
	128	Non-hierarchical		1 year	3.9	1 year	21.1	TVR 1 year	11.7					(In stent n = 104)	
SIRIUS	Stent	In hospital	1.5	In hospital	0.0	In hospital	1.5	TVR (non-TL)		30 days		30 days		8 months in segment:	
(1-year and	525	9 months	18.9	9 months	0.6	9 months	3.2	In hospital	0.0	0% blinded data		0% blinded data			36.3
CABG/PCI		1 year	22.3	1 year	0.8	1 year	3.4	9 months	4.8	9 months CABG		9 months PTCA		8 months in stent:	
9-month data								1 year	6.7	(target lesion) 8/525		(target lesion) 8/525			35.4
from company)														(n = 353)	
								TLR		TVR + TLR					
								30 days	0.0	1 year	3.0	TVR + TLR			
								9 months	16.6			1 year	24.8		
								1 year	20.0						
	DES	In hospital	2.4	In hospital	0.2	In hospital	2.3	TVR (non-TL)		9 months CABG		9 months PTCA		8 month in segment	8.9
	533	9 months	7.1	9 months	0.9	9 months	2.8	In hospital	0.0	(target lesion) 3/533		(target lesion) 20/533		8 month in stent	3.2
		1 year	8.3	1 year	1.3	1 year	3.	9 months	3.2						
								1 year	3.6	TVR + TLR		TVR + TLR			
										1 year	1.5	1 year	7.5	(n = 348)	
								TLR							
								30 days	0.2						
								9 months	4.1						
								1 year	4.9						

continued

TABLE 23 *DES: outcomes (cont'd)*

Study name	Intervention	Event Rate (%)		Mortality (%)		Any MI (%)		Revascularisation (%)		CABG (%)		PCI (%)		BRR (%)	
TAXUS I[118b]	Stent	30 days	0.0	30 days	0.0	12 months	0.0			6 months	3.0	TLR (PCI)		6 months (n = 29)	10.3
	30	6 months	6.6	12 months	0.0			30 days	0.0	12 months	3.0	6 months	6.6		
		12 months	10.0									6 months	10		
								TLR							
								6 months	6.6			Non-TLR (PCI)			
								1 year	10.0			1 year	0.0		
												1 year	0		
								TVR, non-TLR							
								1 year	0.0						
	DES	30 days	0.0	30 days	0.0	12 months	0.0			6 months	0.0	TLR (PCI)		6 months (n = 30)	0.0
	31 (30)	6 months	0.0	12 months	0.0			30 days	0.0	12 months	0.0	6 months	0		
		12 months	3.0									1 year	0		
								TLR							
								6 months	0.0			Non-TLR (PCI)			
								1 year (n = 30)	0.0			6 months	3		
												1 year	3		
								TVR, non-TLR							
								1 year (n = 30)	3.0						
TAXUS II	Stent	30 days	4.4	6 months	0.4	6 months	5.2	TVR		6 months	0.7			Stented segment:	
	270	6 months	19.3					6 months	15.5	(n = 263)				6 months	19.0
								TLR						(n = 263)	
								6 month	13.0						
								(n = 263)							
	DES	30 days	2.3	6 months	0.0	6 months	1.9	TVR:		6 months	0.7			Stented segment:	
	266	6 months	7.9					6 months	6.8	(n = 259)				6 months	3.5
								TLR						(n =2 56)	
								6 months	3.7					Slow DES	2.3
								(n = 259)						(n = 128)	
														Moderate DES	4.7
														(n = 128)	

[a] ACTION[165] lists stent 121, DES 2.5 μg 120, 10 μg 119 for patient allocations. Reference 174 lists stent 119 (and 118), DES 2.5 μg 120, 10 μg 121 for patient allocations. Patient numbers reported in source of data will be provided with percentages.

[b] TAXUS I TLR, one person had PTCA then CABG at 198 days.

[c] Deduced (using patient numbers in unblinded report) from blinded 30-day data.

[d] ACTION AMI 30 days, two sources differ in reporting, e.g. of MI events with no MI in the stent group and four in the DES in reference165, one MI in the stent group and three in the DES group in reference 174. Reasons for these differences and unclear.

[e] Combined clinically driven and angiographically driven data, as presented in reference 119.

[f] Data for MI as reported in submission to NICE.

[g] Only clinically driven events are reported.

revascularisations in particular were clinically or angiographically driven. A standardised definition of clinically driven revascularisations is now available and was applied in many of the studies reported here. However, the definition may mislead. For instance, in the 9- and 12-month results of SIRIUS, we are told that the revascularisation rate represents 'clinically driven' events only, but the definition of 'clinically driven' includes a purely angiographic criterion – 'a target lesion with an in-lesion diameter stenosis greater than 70 percent in the absence of the above mentioned ischaemic signs or symptoms'. It is argued that this criterion only identifies patients who would go on to have a clinically driven procedure within a short space of time anyway. However, its effects on revascularisation rates are clearly seen in the RAVEL study, where a Kaplan–Meier plot (*Figure 2*, p. 1778 of the article)[119] shows a clear increase in revascularisations at the time of the planned angiography. Some of this may have been because in patients with developing angina, the clinically driven intervention was delayed slightly in the knowledge that the patient was due to have an angiography in the near future. Nevertheless, the results do suggest that the angiographic appearance had an effect on the revascularisation rate. The text describes patients either as having clinically indicated revascularisations but only in terms of angina or positive stress test, or in terms of purely angiographically driven revascularisations. It makes no clear distinction about whether any patients had revascularisation on the basis of >70% restenosis alone. Communications with the sponsor suggest that no patients in fact had revascularisations for this indication only.

A point of note is the rate of revascularisation in the control arms of this and the SIRIUS study. The SIRIUS trial, in long lesions, reports broadly similar event rates in the control arm at 12 months (22.3%) to RAVEL at 12 months (22% in the control group). The PRESTO study is quoted in the BCIS submission[178] as an example of likely revascularisation rates in clinical practice; it randomised 11,484 patients to either systemic immune suppression using tranilast or to placebo before PTCA, which involved stenting in 83% of cases. The primary end-point was death, MI or ischaemia-driven target vessel revascularisation: only a subgroup of 20% of patients had protocol driven angiograms. This combined event measure occurred in 15.8% in the placebo group and a similar number of the treated group at 12 months, and tranilast was therefore unsuccessful.

This rate of events is substantially less than reported in the control arms of RAVEL or SIRIUS. This may be an artefact, reflecting the patient selection for these trials with either relatively small (RAVEL) or small and long lesions both of which would carry a higher rate of restenosis than might have been seen in the less selected patients in PRESTO. It is claimed by the authors of the RAVEL[119] study that the higher restenosis rates in RAVEL were in keeping with a linear regression model derived from the BENESTENT[39] studies. However, part of the difference might also lie in revascularisations being in part angiographically driven in RAVEL and SIRIUS.

In a PRESTO subgroup (about 20% of the total) studied by angiography, there was an association between restenosis and major adverse coronary events. In patients with no restenosis, 5% had MACE and 95% did not; in patients with restenosis 46% had MACE and 54% did not. This and other studies show a clear link between angiographic appearance and clinical event rates, although it is difficult to quantify this directly. The BCIS submission to NICE suggests that approximately half of angiographically indicated revascularisations were also clinically indicated. However, in the 9-month data from SIRIUS, the number of clinically driven TLRs is quoted as 4.1% in the DES arm and 16.6% in the non-DES arm and a rate of angiography-driven revascularisations of 1.9% in the DES arm and 4.0% in the DES arm. Hence here we have between 70 and 80% of TLR 'clinically driven' as defined by the trial, rather than 50% typically suggested by cardiologists. Given the criteria for 'clinically driven revascularisations' in the study cited above, this high ratio of angiographic to clinically driven events seems artificial and probably no different to those in other studies.

The 2-year data from RAVEL provide further information on this aspect: there were no further angiographic follow-ups in the 12–24-month period and so any further revascularisations may be more confidently attributed to clinical need. In the control arm, there were 16/118 clinically driven revascularisations by 12 months and no further revascularisations by 24 months. In the DES arm, there was one clinically driven revascularisation by 12 months and a further two (total 3/120) by 24 months. The absolute benefit is therefore 11.1% at 2 years. This suggests neither a major loss of effect of the DES due to delayed restenosis nor any additional benefit over the second 12 months. Longer term follow-up is still desirable.

Subgroups of patients

Studies included in the review were not powered to assess effectiveness in subgroups of patients and therefore analysis of data by subgroup must be interpreted very cautiously. Key subgroups would be diabetics, patients with small vessels or long lesions and LAD lesions.

Some preliminary results from SIRIUS have been reported to the review team in confidence: of the 1058 patients randomised, 279 had diabetes. For those people with diabetes, the TLR rates at 12 months were 8.4% in the sirolimus DES group versus 26.4% in the control group. MACE rates were 11.5% in the sirolimus DES group versus 29.1% in the control group – a relative reduction by 60%, in keeping with the proportional reduction in the study as whole.

The RAVEL study also included a subgroup of diabetics but to date the only comment on outcomes in them is that the benefits seen overall were similar in diabetic and non-diabetic subjects, but whether this is in proportions of patients with restenosis or in the extent of restenosis is unclear. Some results from a diabetic subgroup in RAVEL are quoted in the BCIS submission to NICE, although a reference is not given, nor are these data found in the publication to date.

Inclusion criteria for five of the included studies (ASPECT, ELUTES, RAVEL, SIRIUS and E-SIRIUS) indicated that they would include patients with vessel diameter <3.0 mm (small vessel). Presentation of the data did not allow for assessment of outcomes related to vessel size.

Other subgroups reported in SIRIUS, so far only in conferences, are those for lesions of the LAD artery, another high-risk group. Here, the TLR on sirolimus was 5.1% versus 19.7% in the control group, and the MACE rates were 8.5% on sirolimus versus 22.5% non-DES.

Patients experiencing AMI were excluded from studies of DES and therefore results cannot be generalised to this population.

So far, therefore, data on subgroups are limited and should not be overstated. What limited data there are indicates that the relative benefits of DES are maintained in high-risk subgroups of diabetic patients and those with small vessels. Given the higher background risk of these patients, maintaining the proportionate benefits would lead to a greater absolute benefit and this may provide useful pointers in targeting DES. This is discussed in greater detail in Chapters 9 and 11.

Data availability

There are key limitations in the available data. First, of the three areas considered in this review, this is the one which is developing most rapidly. Although current data are limited in terms of the number of studies and the number of patients, a range of studies are due to report either their preliminary or longer term results within the next 12 months. The results of DELIVER, until recently embargoed as a result of legal action, have recently been presented in part at a conference;[132] we have contacted the lead author, who tells us that fuller results are to be presented at a conference in early April 2003. Initial results from E-SIRIUS and 1-year follow-up of SIRIUS were released to the review team just before completion of this section of the report. Data were held in confidence until their release at a conference in March 2003. Twelve-month results from TAXUS II are expected at the same time, while TAXUS IV has been delayed (Wenk Lang A, Boston Scientific, personal communication, 2003).

The second consideration is that most studies as yet have only reported short follow-up. The 2-year RAVEL data are a exception but have been made available in confidence until their official release at a conference in March 2003. With longer term follow-up, the risks and benefits of DES will become more apparent.

A third critical issue is that the speed of development of the technology is such that many of the reports are only available as conference presentations or abstracts rather than as full peer-reviewed papers. We have had to rely at times on conference presentations or the slides from such presentations with only partial presentation of the data, which is sometimes of uncertain quality. For instance, there are often discrepancies in the numbers of patients reported with no explanation of the missing patients. It is a familiar finding that the reports in conference presentations often differ from the reports finally published in peer-reviewed journals. The conference presentations cannot themselves be considered peer-reviewed.

Nevertheless, given the speed of development of this area, there was little option but to depend on such data, but they should be treated with the greatest caution. It is imperative that the results considered here are taken only as provisional and it must be acknowledged that they will require rapid updating and review.

Conclusions

The available data do not allow for any conclusions to be made with regard to the effect of DES on mortality or in the case of AMI.

Overall, the results indicate that the DES decrease rates of restenosis and therefore revascularisation following placement. The exact rate of lowering of revascularisations seems to be ~60–70% at 12 months, but there are difficulties in definitions of how many of these were clinically driven. Outcomes from one study (RAVEL) indicate that this benefit is largely maintained over 2 years. However, we stress that these results are interim and incomplete, and we await definitive publication of studies confirming patient numbers and outcome.

Part B: Further analysis of selected DES (completed at the request of the Appraisal Committee)

Clinical effectiveness of selected DES

Introduction

The analyses presented in this part were prepared following a first meeting of the Appraisal Committee to consider the original Liverpool Reviews and Implementation Group (LRIG) report. Part B deals with specific requests from the Appraisal Committee for further consideration of aspects of the original report, but more importantly, it deals with new information which became available only after the submission of the original report and further analysis arising from that information. Hence, some analyses may supersede elements of the original report.

Five DES have been awarded the CE Marking. Only the CYPHER™ sirolimus-eluting stent from Cordis, the TAXUS™ paclitaxel-eluting stent from Boston Scientific and the Dexamet™ dexamethasone-eluting stent from Abbott (*Table 24*) are expected to be available as commercial products in the near term. New information has been provided on two of these, the CYPHER and TAXUS stents.

Evidence on the clinical effectiveness of selected DES

There remain no direct comparisons of different DES, therefore the data are presented independently.

For this summary of selected DES, data from published journals or submitted by manufacturers were included. Data from other sources, such as conference presentations or reports, were not sufficiently detailed and therefore were not considered eligible for inclusion in the analyses. (most such presentations have been well covered by the manufacturers' reports).

Data regarding Dexamet™ are based on a single report of non-randomised registry data. No new information has been provided on this.

The CYPHER and TAXUS DES have been evaluated within RCTs. Data from these trials are presented in the form of meta-analysis Forest plots for a range of outcomes including MACE, all-cause mortality, MI and binary restenosis rate (BRR).

TAXUS

There have been two trials of the TAXUS stent, TAXUS I and II. However, TAXUS II is perhaps best considered as two separate trials, one of a moderate-release stent and the other of a slow-release stent (also used in TAXUS I). Recruitment to the moderate-release element of TAXUS II followed completion of recruitment to the slow-release element. Data up to 1 year are now available from these trials. These stents are of identical design and drug dose density (1.0 $\mu g/mm^2$ of paclitaxel), but have different polymer-to-drug ratios to mediate the rate of

TABLE 24 *Drug-eluting stents with CE Marking intended for commercialisation*

System name	Agent and stent	Manufacturer	Study name	Design	Data available up to
TAXUS	Paclitaxel	Boston	TAXUS I	RCT	1 year
	NIRx		TAXUS II	RCT	1 year
CYPHER	Sirolimus	Cordis	RAVEL	RCT	2 years
	BxVelocity		SIRIUS	RCT	1 year
			E-SIRIUS	RCT	9 months
Dexamet	Dexamethasone	Abbott	STRIDE	Registry	Short term (Abbott)
	BiodivYsio DD PC				

release of the drug. The current CE Marking applies only to the slow-release TAXUS stent.

In the earlier report, it was not possible to separate out the two elements of TAXUS II. We now present the results of each element of TAXUS II separately with their controls, and then proceed to meta-analysis with TAXUS I.

Sources of data on the evaluation of TAXUS stents (compared with non-eluting controls) are restricted to manufacturer reports, provided in the initial submission to NICE, and reports provided to the review team by Boston Scientific in March 2003. The published article on TAXUS I[118] was also used for reference.

Reporting of mortality in the TAXUS studies was limited to cardiac death, although details of all deaths were noted within patient flow tables and patient-level data. Using this additional information, the Review Team present 'all deaths' in the analyses of mortality outcomes.

The combined event rate used in the TAXUS studies was MACE. This included specifically cardiac death, MI (Q- or Non-Q-wave) or 'clinically driven' target vessel revascularisation (repeat PCI or CABG performed on the vessel previously treated by stenting), as defined by the FDA. It should be remembered that this definition includes the possibility of a solely angiographic criterion of revascularisation.

The definition is mandated by the FDA and states that the procedure was considered clinically driven if the patient had

> "a positive functional study, ischemic ECG changes at rest in a distribution consistent with the target vessel, or ischemic symptoms and an in-lesion diameter stenosis greater than 50 percent. Revascularisation of a target lesion with an in-lesion diameter stenosis greater than 70 percent in the absence of the above mentioned ischemic signs or symptoms was also considered clinically driven."

A 'functional test' refers to a positive exercise ECG or nuclear perfusion scanning. The key point here is that even by this definition, 'clinically driven events' can be defined by angiographic indices alone. It assumes that with a stenosis >70%, even if the patient is not symptomatic at the time, it is highly likely that they will soon 'tip over' into a symptomatic state and require a repeat revascularisation soon after.

Non-cardiac death or revascularisation (e.g. other than target vessels or lesion) outside the definition of 'clinically driven' would not contribute to MACE.

The binary restenosis rates used in the meta-analysis are for the in-stent region only.

CYPHER

Data on the CYPHER stent are currently available from three RCTs, with RAVEL reporting up to 2 years follow-up. Design of the CYPHER stent did not differ between trials (dose density 1.4 $\mu g/mm^2$ in all three studies), although only 18-mm stents were used in RAVEL, a combination of 18, 18- and 8-mm or two 18-mm stents could be deployed and overlapped in the SIRIUS trials. Over a quarter of participants in SIRIUS received overlapping stents.

Sources of data on the evaluation of the CYPHER stent (compared with non-eluting controls) are restricted to manufacturer reports, which were provided in the initial submission to NICE, and reports (on RAVEL, SIRIUS and E-SIRIUS) provided to the review team by Cordis in February 2003. The published paper on RAVEL[119] was used for reference.

As for TAXUS, all-cause mortality was recorded for the CYPHER trials considered here.

The definition of MACE varied slightly between the CYPHER stent trials. Both RAVEL and SIRIUS defined MACE as all-cause death, MI (Q- or non-Q-wave) and TLR (by PCI or by CABG). The E-SIRIUS trial rate includes 'emergent CABG' – where emergency surgical invention may have been necessary (in fact there were no such events in E-SIRIUS). A further variation is that only events determined to be 'clinically driven' (FDA definition) in SIRIUS, E-SIRIUS and RAVEL at 2 years were provided within items submitted by Cordis, whereas the original submission to NICE and published paper on RAVEL at 1 year appear to report a amalgamation of both clinically driven and non-clinically driven events. In order to resolve this disparity, only events determined to be 'clinically driven' at 1 year have been provided for RAVEL and are utilised in the analyses.

Another composite event rate, target vessel failure (TVF), is presented within reports of the CYPHER studies. TVF comprised cardiac death, MI which could not be clearly attributed to a vessel other than the target vessel, or TVR by PCI or CABG.

Binary restenosis rate considered is in-stent at 8 months.

Presentation of alternative event rates for CYPHER trails

Analyses here will be of TVF and MACE for the CYPHER trials. The reason for this is that the composition of MACE in the TAXUS studies seems closer to the TVF in the CYPHER studies than MACE as defined in SIRIUS or RAVEL. The composition of 'MACE' in the TAXUS studies and the 'TVF' in the CYPHER trials appear to be comparable. Both event rates specify cardiac death, MI, TVR ('clinically driven', revascularisation of the vessel by PCI or CABG).

Meta-analysis of clinical data on DES

Event rate – TAXUS MACE, CYPHER MACE and CYPHER TVF

Event rates were reduced significantly by the use of either TAXUS or CYPHER stents at 6 and 12 months. The results were broadly similar for both types of stent, with a reduction in events by approximately two-thirds compared with bare metal stents (BMS) (*Figure 20*). Most events occur within the first 6 months. There are now data up to 2 years for CYPHER in the RAVEL study; these show that the event rate remains reduced.

ORs and 95% CIs for pooled estimates appear similar for CYPHER MACE and CYPHER TVF.

Within the RAVEL trial, a reduced event rate in the CYPHER arm and increase in the control arm is observed when TVF is substituted for the CYPHER defined MACE. ORs decrease from 0.46 [95% CI 0.22 to 0.97] (MACE) to 0.23 (95% CI 0.10 to 0.56] (TVF) in RAVEL at 2 years.

Mortality

There were no significant differences in mortality rates between DES and BMS at any time point (*Figure 21*).

MI (any reported)

MI was significantly reduced in the TAXUS meta-analysis at 6 months but not at 12 months. There was no difference for CYPHER at any time point (*Figure 22*).

Restenosis (in the range of 6 or 8 months)

There was a marked reduction in binary restenosis rates at 6–8 months as detected by angiography. Since these studies do not have a further protocol-

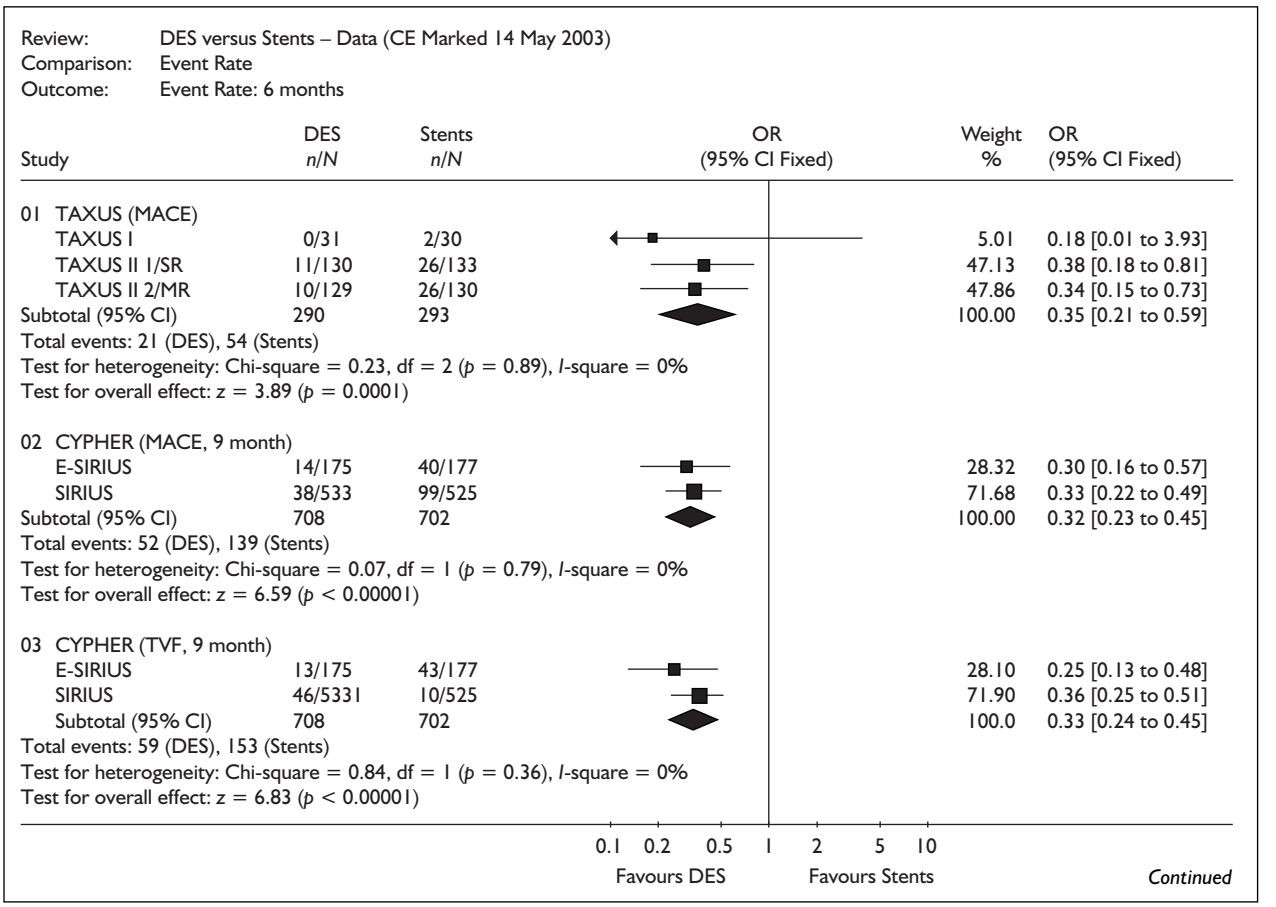


FIGURE 20 *Event rate TAXUS MACE/CYPHER MACE/CYPHER TVF. Event rate for RAVEL at 1 year represents only clinically driven events. Cordis provided these data at our request. TVF data at 1 year for SIRIUS provided by Cordis at our request.*

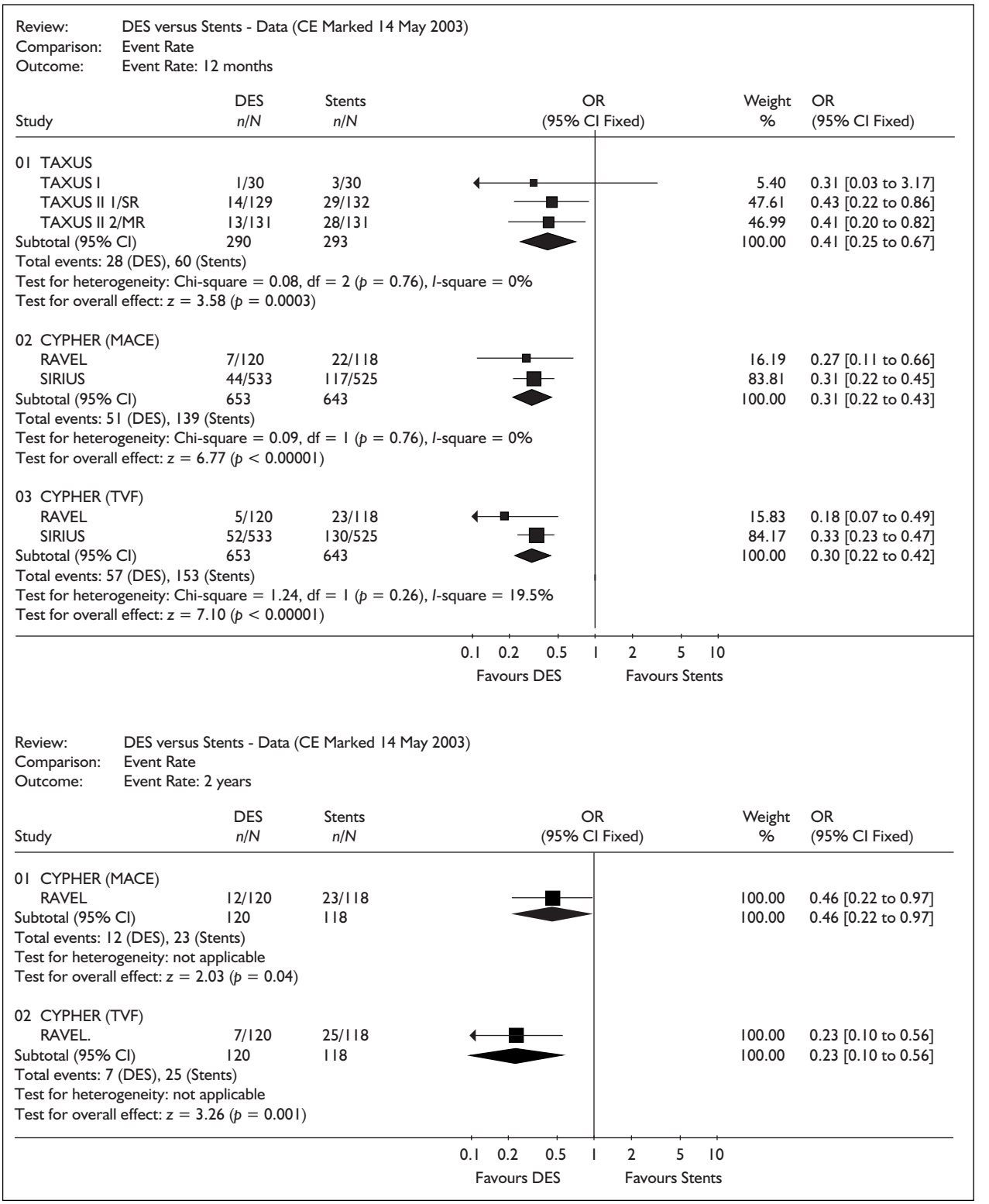


FIGURE 20 *Event rate TAXUS MACE/CYPHER MACE/CYPHER TVF. Event rate for RAVEL at 1 year represents only clinically driven events. Cordis provided these data at our request. TVF data at 1 year for SIRIUS provided by Cordis at our request (cont'd).*

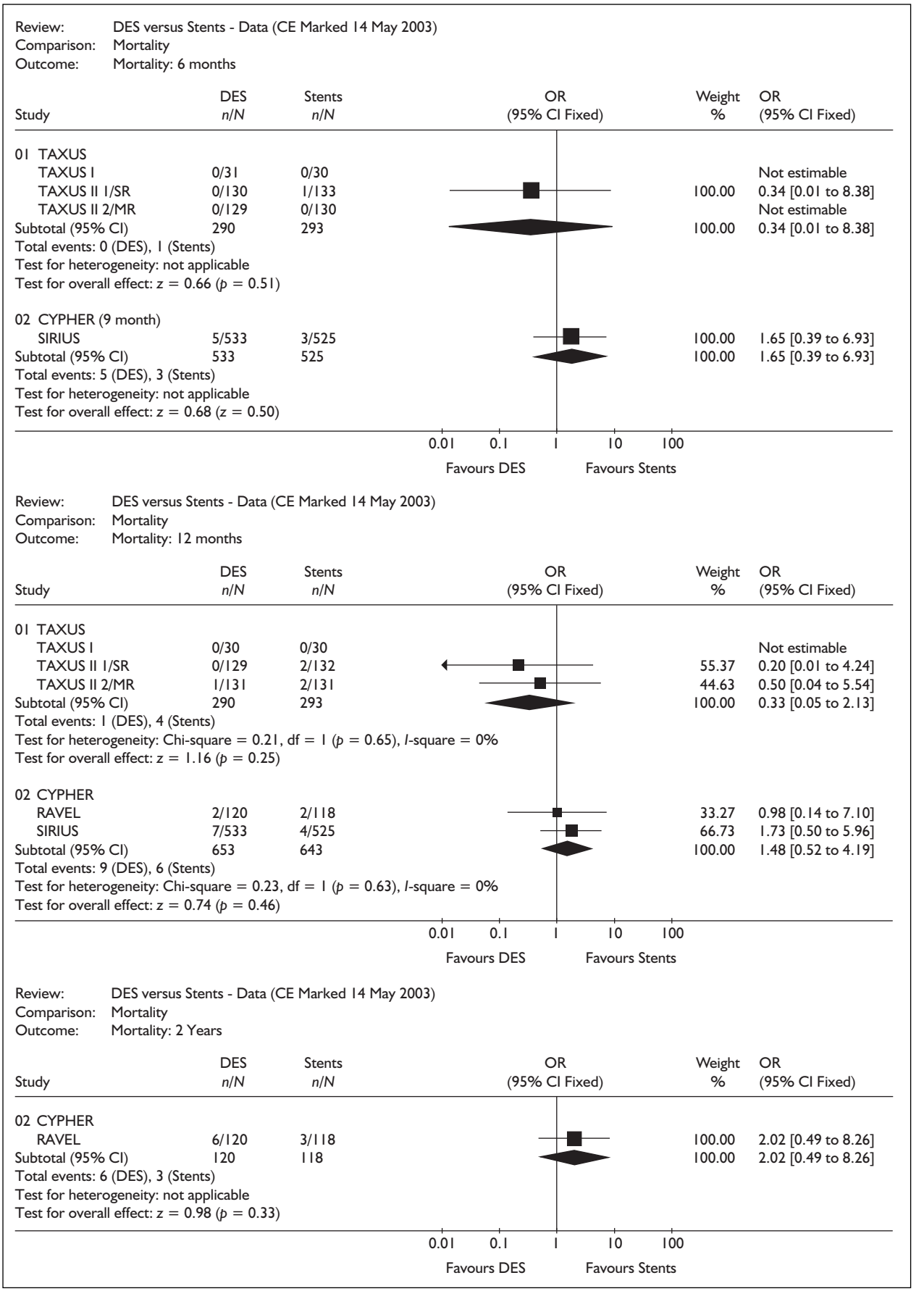


FIGURE 21 *All-cause mortality*

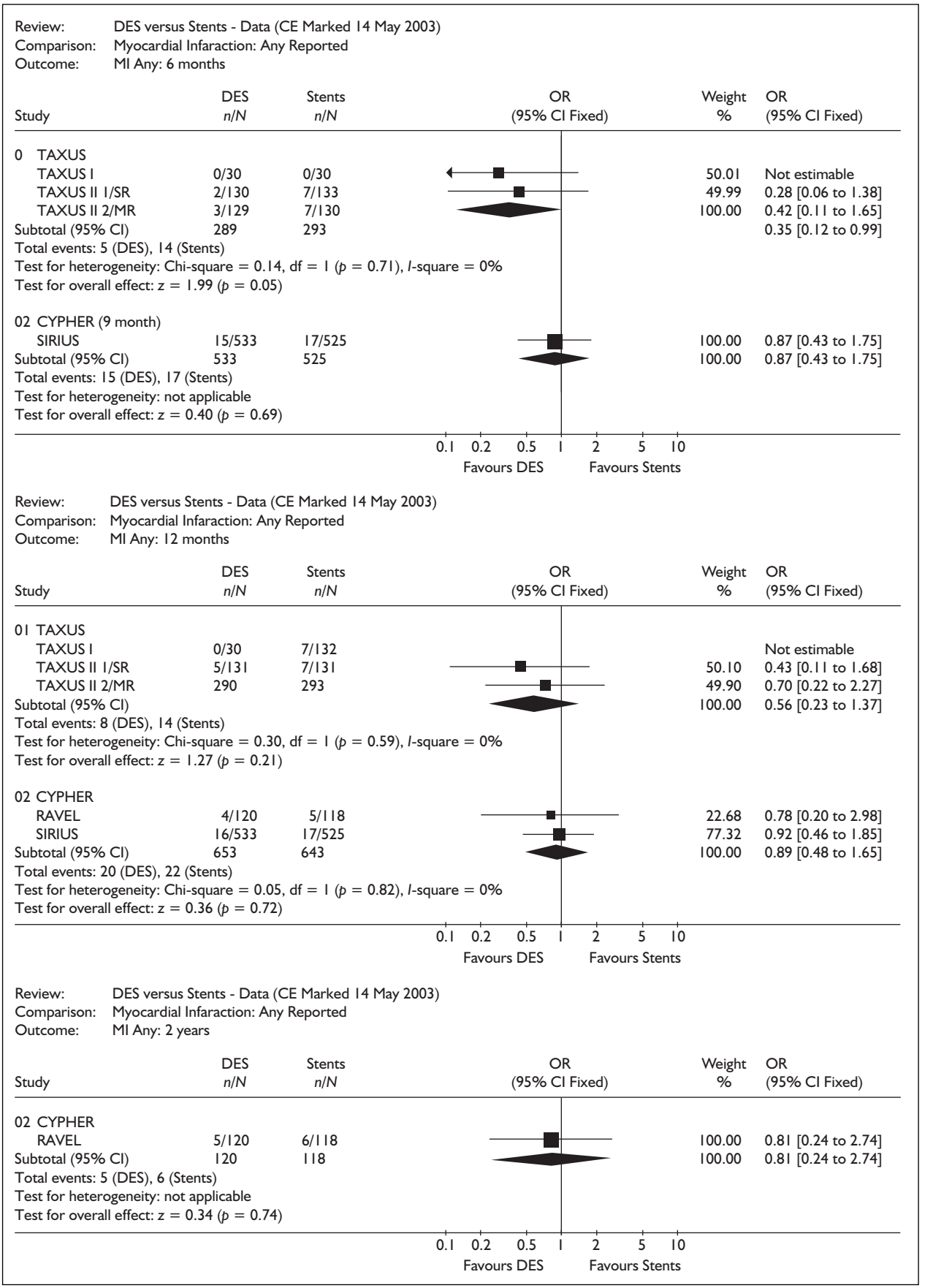


FIGURE 22 *Myocardial infarction. In the sources of information made available for RAVEL, variations in rates of MI at 1 year were noted. The values reported by Morice and colleagues[119] are used in the meta-analysis.*

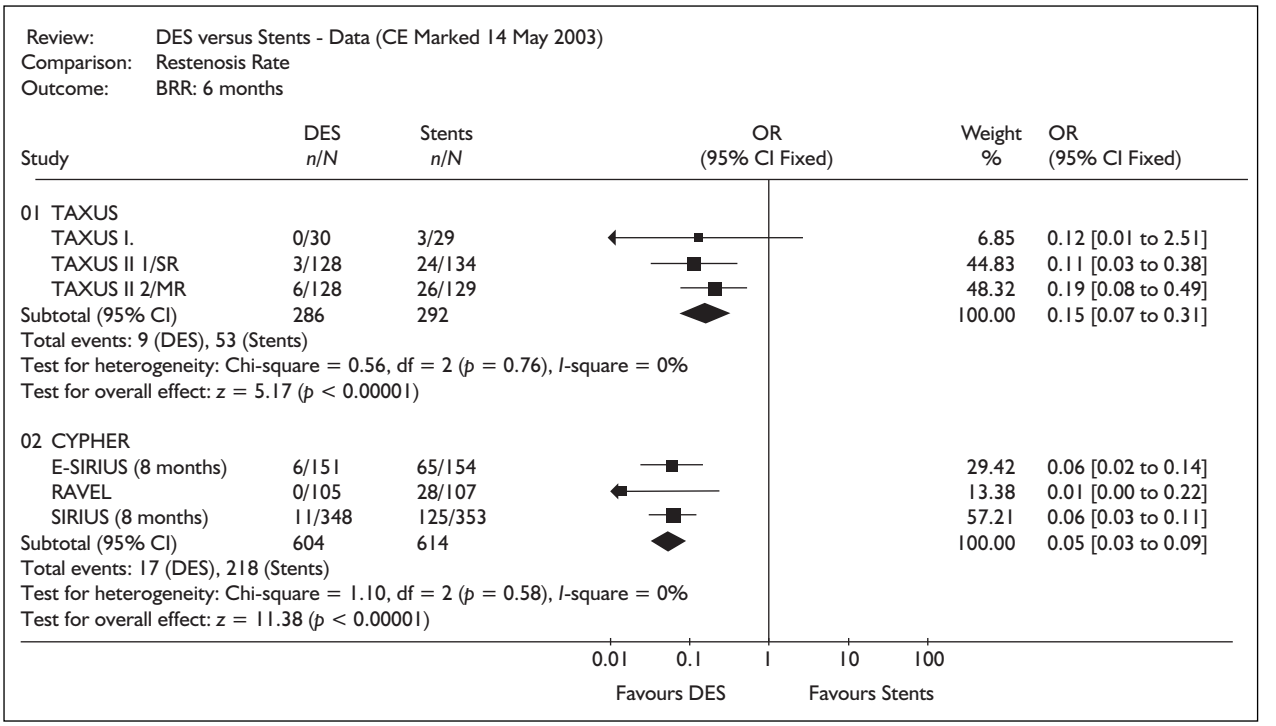


FIGURE 23 *Binary restenosis*

driven angiography, there are no later data on this (*Figure 23*).

There was no heterogeneity of results and therefore random effects models were not used.

Discussion

The data presented here are a large expansion of those previously considered for DES versus non-DES: these were limited before to the RAVEL and TAXUS I studies (total 297 patients), but now extend to SIRIUS, E-SIRIUS and TAXUS II (total 2230 patients).

The results show a marked decrease in events up to12 months and, in the case of RAVEL, up to 2 years.

Issues around the outcomes reported were discussed before in the main report and persist to some extent. Kaplan–Meier plots of each of the trials show a marked increase in number of revascularisations at the time of the protocol-driven angiogram – this continues concerns about the extent to which the events reported are based on the appearance at angiogram and would not reflect real clinical practice. Furthermore, the use of FDA definitions of clinically driven revascularisations include an angiographic component, although we are told by companies that in practice this was rarely invoked in the absence of other criteria. For instance:

> "the 9m SIRIUS report to the FDA … showed that of the 87 patients in the control group who had repeat revasc(ularisation) at 9m, 71/87 had recurrent angina, 16/87 had a positive functional study and 47/87 had stenosis ≥ 70%. … (This) shows that 70% stenosis only as a criterion could have had only minimal impact because of the proportion with angina and/or positive functional study."
>
> Fearns S, Cordis: communication to LRIG and NICE.

One reason for the sharp increase in revascularisations on the protocol-driven angiograms may be that there was an accumulation of truly clinical indications which waited until the angiogram for action. Even in the case of true clinically indicated angiograms, the decision to revascularise or not is still angiographic as it depends on the results of the angiogram: this distinction is clear in BENESTENT II, where the rate of revascularisation in the protocol-driven angiogram arm was higher than in the arm where angiograms were clinically driven. We believe that this issue is unresolved and that the extent of the favourable results here might not therefore be repeated in common clinical practice. In calculating the cost-effectiveness of stenting later, we have adopted a BENESTENT

II-type correction for rates of revascularisation, as we think this is a conservative and the most appropriate approach.

It should also be remembered that meta-analysis as conducted here will tend to hide important differences which may become apparent with more detailed study of subgroups.

The 'life expectancy' of the current data needs to be considered: the TAXUS IV trial (slow release, single stents in of vessels 2.5–3.5 mm diameter, up to 28 mm long, ~1350 patients) was due to report its 9-month data on 15 September 2003. The Canadian arm of the SIRIUS trial family, C-SIRIUS, but with only 100 patients, has already reported its 9-month data at conferences (presented at ACC, April 2003). Although not included in the analysis here, as it is only available as a conference presentation, the results are consistent with those of the studies considered here. In addition, there will of course be regular updates of the results of the other studies. The SIRIUS trial itself has been submitted for publication.

These results are therefore probably the most reliable available in the short term, but may require reconsideration depending on the results of TAXUS IV.

Subgroups

In addition to summary data, for TAXUS II we were also supplied with patient-level data which allowed us to consider subgroups. These are explored more fully in Part B of Chapter 9.

This information is used in the economic evaluation of subgroups to try to help to define where DES may be most cost-effectively deployed.

There are several caveats to this:

- None of the studies have been powered to examine subgroups and therefore the results in subgroups can only be considered tentative.
- The results in trials are usually reported in an ITT manner – entirely appropriate for clinical trials, but less useful than an on-treatment analysis for economic review. Our analysis in Chapter 9, Part B, is based on the latter.
- The data are also patient driven rather than event driven: each patient is therefore recorded as having or not having a MACE/TVF end-point. The hierarchical nature of these event rates (i.e. patients can only be recorded as having one MACE/TVF event, and are documented as having the most important event; e.g. a patient who dies will be recorded as a death, but the number of revascularisations that such a patient may have had may not be so well captured).

Despite these limitations, we believe that useful conclusions can be drawn from this and these are presented in Chapter 9, Part B [see the section 'Economic modelling: evaluation of drug-eluting stents for single-vessel disease' (p. 156)].

Chapter 7

Economic overview and literature review

Data sources

National data sources

This section provides an overview of economic aspects of percutaneous coronary revascularisation and coronary bypass grafting. The nature of the procedures and their associated costs are changing rapidly, so costs calculated historically will have limited relevance to current practice. In addition, clinical practice and unit cost variations mean that costs from other countries, particularly the USA, may also have very limited relevance to the UK. In evaluating the cost of current practice from an NHS perspective, we were greatly assisted by being granted access to the as yet unpublished economic analysis of the Stent or Surgery (SOS) trial, which assessed comparative resource use associated with CABG and PTCA from an NHS perspective.

As previously noted, there is no comprehensive system to track and identify the numbers of PTCA and CABG procedures undertaken in the UK. NHS statistics combine data from each trust but do not include the ~8% of patients treated privately. A number of other sources of data are available including the audit analyses undertaken by the BCIS and the Society of Cardiothoracic Surgeons (SCTS), which collate data on the number and nature of procedures. Despite the undoubted value of such voluntary audit analyses, a mandatory system would be useful in providing accurate information concerning revascularisation procedures in the UK.

Local data sources

High-quality data sources were essential in establishing an accurate baseline for current practice. In this respect, our analysis benefited greatly from being granted access to a large-scale audit database held on two regional registers in Liverpool covering patients undergoing cardiac surgery and those undergoing PTCA. Access to this database enabled us to:

- characterise the case mix of patients for each type of treatment
- estimate values for the main outcome variables over both the short and long term
- estimate the risk of adverse events associated with each treatment type
- estimate immediate NHS resource use associated with each intervention
- estimate long-term changes in NHS resource use and outcomes associated with each intervention.

The data extraction was undertaken by the Research and Audit Department of Liverpool Cardiothoracic Centre and anonomised to preserve patient confidentiality. An initial overview was undertaken to assess the subset of audit data that would be of value to our review. The extensive subset of the audit data used in our review is provided in Appendix 1 for the cardiac surgery database and Appendix 2 for the PTCA database. A detailed analysis was undertaken for six subgroups of adult patients:

1. elective CABG only (no valve surgery, etc.)
2. non-elective CABG only (excluding bailout following PTCA)
3. elective PTCA
4. non-elective PTCA
5. elective PTCA with stent
6. non-elective PTCA with stent.

The CABG analysis evaluated all procedures performed between January 2000 and March 2002 at the four service providers in the north-west of England (Blackpool Victoria, Liverpool CTC, Manchester Royal Infirmary and Wythenshawe Hospital). A total of 7366 CABG patients were analysed, of whom 1664 (22.6%) were non-elective. The PTCA analysis analysed all procedures performed in the period covered by the CABG data set (January 2000 to March 2002). However, on the advice of the Research and Audit Department, the scope of this analysis was restricted to patients treated at the Liverpool CTC to maximise the quality and reliability of the dataset. A total of 2519 PTCA patients were analysed, of whom 761 (30.2%) were non-elective. A summary of the patient population together with a summary of patient outcomes for both CABG and PTCA are provided in Appendices 3 and 4. Given the scale and nature of the patient population covered by the audit dataset, it can be interpreted as being closely representative of the entire CABG/PTCA treatment population in the UK.

Changes in resource use

Length of stay

Stent technology has changed, allowing a change in targeted patients from low risk (discrete single-vessel lesions) to encompass those with more complex multiple-vessel disease. Part of the reason why the UK has seen such a significant expansion in stent use is the improved pharmacotherapeutic management of such patients. A key aspect was the development of more aggressive antiplatelet therapies (aspirin and ticlopidine or aspirin and clopidogrel to reduce problems associated with stenting).

From a UK perspective, Palmer and colleagues[179] identified a reduced length of stay for PTCA between 1994 and 1998 of 4.3 and 2.6 days ($p < 0.001$) and the increasing use of groin closure devices is likely to reduce the length of stay further for transfemoral PTCA. Some UK and German centres are even undertaking day case or outpatient PTCA on low-risk patients. Despite one US–Amsterdam collaborative study identifying a 60% reduction in hospital costs for outpatient stenting,[180] currently only 2% of NHS patients are treated as day-cases. The development and utilisation of minimally invasive direct vision coronary artery bypass (MIDCAB) procedures may also facilitate a significant reduction in the length of stay associated with CABG. Lengths of stay following MIDCAB procedures[181] ranged between 1.76 and 3.3 days postprocedure.

There are likely to be significant variations in length of stay between different subgroups of patients, although this factor is less likely to influence PTCA – the variations in length of stay for CABG patients in the SCTS lie between 6 and 8 days depending on the risk profile of the patient. Lengths of stay associated with both PTCA and CABG are therefore significantly affected by the characteristics of both the patients and service providers, and a range of technological advances are likely to facilitate a significant reduction in length of stay for all patient groups.

Consumables

In the early days of PTCA, the main consumable components were contrast media, diagnostic catheters, guiding catheter, guidewires and angioplasty balloons. When stents were initially introduced, they had to be hand-crimped by the operator on to a PTCA balloon. After deployment, balloons of varying characteristics (diameter, length and compliance with pressure) were required to postdilate the stent fully, initially with normal and then with high-pressure balloons. Stents are now manufactured balloon-mounted and a greater choice now exists of stent lengths, so that whereas previously a long lesion may have required two stents, one long (32-mm) stent will now cover the lesion. Each of these technical improvements influences the number of balloons and stents used per patient, which is a key determinant of the comparative costs associated with PTCA. A summary of the number and cost of major consumable items identified in previous trials is provided in *Table 25*.

Another factor considerably affecting the cost of stenting is the number of stents used per procedure. For single-vessel lesions an average of between 1.03 and 1.4 stents may be used in each procedure. However, for multiple-vessel stenting,

TABLE 25 *Individual resource usage in stenting*

Item	Southampton[a]		RITA 2[b]	Leeds[c]			RAVEL[d]	
	Unit cost (£)	No. per stent patient	Unit cost (£)	Unit cost (£)	No. per PTCA patient	Unit cost (€)	Sirolimus[e]	Bare metal[f]
Guiding catheter	67	1.51	36	70	1.58	98	1.10	1.07
Guidewires	63	1.22	60	78	2.37	115	1.08	1.04
Balloons	339	2.67	196	257	1.42	491	1.32	1.37
Stents	793[g]	1.61	582	553	1.63	2000/672[g]	1.05	1.05

[a] $n = 200$, 1996.
[b] PTCA arm, 1999.
[c] $n = 29$, 1998.
[d] Exchange rate utilised in RAVEL study: €1 =£0.65.
[e] $n = 120$.
[f] $n = 118$.
[g] Year 2002 DES/BMS costs.

the number of stents implanted per patients can range from 2.4 to 2.7, which represents a significant cost given the comparatively high unit cost of drug-coated stents. The audit dataset indicated an average utilisation of 1.3 stents per procedure for single-vessel disease and 2.4 stents per procedures for two-vessel disease. Given the preponderance of single-vessel disease, this led in the entire patient population to an average of 1.74 stents per procedure being utilised.

PTCA with stenting will normally also require variable lengths of course of adjunctive antiplatelet therapies of aspirin and clopidogrel with a glycoprotein IIB/IIIA receptor antagonist being used in most cases. Given such variability in resource usage, it is perhaps not surprising that the cost of percutaneous coronary interventions varies significantly between individual patients and individual centres.

Outcomes measures for percutaneous coronary interventions

Outcomes used in economic analyses

The primary outcomes of interest in economic analysis have been changes in resource use (initial costs of procedures balanced by future resource savings) and the impact of procedures on mortality and QoL. In analysing the impact of revascularisation rates on cost-effectiveness, it is important to acknowledge that such rates are variably addressed within reports of clinical trials comparing different treatment strategies.

The sources of variability include:

- What types of repeat revascularisations (CABG versus repeat PTCA) follow each type of initial procedure (PTCA versus stent versus CABG versus minimally invasive CABG)?
- What is the absolute number of repeat revascularisations per patients considering that some patients may have multiple repeat procedures?
- Over what time horizon are repeat revascularisations followed up?
- What is the definition of a repeat procedure as opposed to a new procedure, that is, does a lesion being revascularised proximal to the original target vessel constitute a repeat or a new revascularisation?
- Should rates of binary restenosis be the key measure or the rates of repeat revascularisation? For example, in the large PRESTO trial, rates of revascularisation were only half the rates of binary stenosis.
- In analysing rates of revascularisation, should only revascularisation in target lesions be reported or should all revascularisations be reported?

The primary cost element that must be incorporated in any long-term analysis comparing stenting versus CABG and DES versus BMS is the impact of variations in the rates of repeat revascularisation. The RITA-1 study provides useful background data as it estimated 5-year costs of care for patients undergoing PTCA and CABG. Unfortunately, the cost estimates will have little relevance to current practice given that data collection was undertaken between 1988 and 1991. However, RITA-1 illustrates the crucial importance of the time frame underlying the evaluation in any analysis of the comparative costs of PTCA and CABG. CABG inevitably exhibits higher short-term costs, with this cost advantage becoming increasingly eroded over time. In RITA-1, the mean total 5-year cost was £426 higher in the CABG group than in the PTCA group (95% CI from £383 lower to £1235 higher), but this excess cost in the CABG group was not statistically significant ($p = 0.30$). Although the cost of the initial CABG procedure was nearly twice that of the initial PTCA procedure, the costs arising from subsequent procedures were six times higher in the PTCA group, whereas estimated medication costs in the PTCA group were more than double those in the CABG group over the 5-year period. The comparative impact on mortality and QoL is analysed below.

Mortality data

The BCIS audit dataset for 2001 recorded a mortality rate of 0.75% for PTCA. The SCTS dataset records an average CABG mortality of 2.21% with a mortality specific to elective operations of 1.77% (1999 figures). Given these mortality rates (0.75 and 1.77%), it would require an RCT containing 5022 patients with 5% alpha and 90% power to prove a significant difference in mortality between the procedures. Using the comparative mortality rates seen in ARTS (2.5 and 2.8%), a trial would require 120,464 patients to identify a statistically significant difference in mortality. In comparison, the comparative mortality rates exhibited in SOS (4.5 and 1.6%) would require 1474 patients to prove significance. No trials of multiple-vessel stent versus CABG have recruited such numbers of patients to date, nor do combined patient numbers in meta-analyses achieve such numbers. ARTS is the

largest study with 1205 patients, but with higher mortality rates in the CABG arm than seen in SOS or in the SCTS audit dataset but lower than that seen in ERACI II. In such circumstances, it is impossible to state definitively which strategy (PTCA with stenting or CABG) leads to a significant mortality benefit. In such circumstances, clinical and cost-effectiveness studies must therefore inevitably be seen as being preliminary given the limited evidence base underpinning such analyses. This result reflects the results of the clinical analysis provided in Chapter 5.

Quality of life data

Since there is no evidence that coronary restenosis affects survival after PCI, the primary benefit of treatments that reduce restenosis is an improvement in QoL. Hence, any assessment of the cost-effectiveness of a treatment that reduces restenosis must depend critically on the utility weight assigned to the restenosis health state. The major aspect of QoL reduction associated with the need for restenosis is likely to be the pain associated with the symptoms of angina and the disutility associated with revascularisation. Unfortunately, the relationship between the symptoms associated with angina and a patient's prognosis is highly complex given that patients may experience symptoms due to obstructions in small vessels with low risk of major events or may be free of symptoms yet exhibit a high risk of stenosis in one or more major vessels.

Few quality-adjusted life-year (QALY) analyses have been undertaken for patients with and without restenosis or repeat revascularisation following CABG and stenting (BMS or DES). ARTS and SOS are the only such trials comparing modern PTCA with stenting with CABG in terms of cost-effectiveness data. Although a multinational trial, SOS is particularly relevant to practice within the NHS given that 39.6% of the patient population were UK patients and the cost-effectiveness data are generated using UK unit costs. For this reason a detailed assessment of the results of this trial is provided in the section 'Previous cost-effectiveness analyses' (p. 99).

A wide range of studies have examined health-related quality of life (HRQoL) after PCI using a battery of disease-specific and generic measurements. In a prospective substudy of the Stent–Primary Angioplasty for Acute Myocardial Infarction (Stent-PAMI) trial, Rinfret and colleagues[182] reported that compared with conventional balloon angioplasty, initial stent placement was associated with significantly better HRQoL at 6-month follow-up but no differences at 1 year. These differences were primarily explained by the reduced rates of angiographic and clinical restenosis associated with stenting. Hence there appears to be fairly consistent evidence that coronary restenosis has an important, albeit limited, impact on HRQoL.

One critical aspect is that the disutility of a restenosis event is often very short-lived. Cohen and Baim[183] found that an intervention with initial stenting would save an additional 0.03 QALY (2 healthy weeks) with respect to standard angioplasty whereas angioplasty with stenting for restenosis would only save an additional 0.01 QALY in comparison with standard angioplasty. Such figures emphasise the constraints associated with using QALY analysis to assess the QoL gains associated with the avoidance of restenosis.

The impact of waiting times on comparative outcomes

The average UK waiting time for a CABG is 7 months in comparison with 3 months for PTCA, implying that patients waiting for CABG may suffer significantly greater morbidity and mortality while awaiting their procedure. If additional waiting time is an inherent characteristic of the provision of CABG (patients have to wait longer to be suitable for the procedure), then increased preprocedure morbidity and mortality are an important element of the procedure. Conversely, if the variation in waiting time merely reflects a historical imbalance in resource availability between two procedures (a reduction in allocative efficiency), then any variation in technical efficiency (reductions in outcomes, increases in costs) that results should not be incorporated into the analysis.

The aim of our analysis is to compare two adequately resourced services working efficiently. If the efficiency of one of those services (CABG) is artificially reduced as a consequence of historical under-funding of service provision leading to higher waiting times, then the economic analysis undertaken should attempt to take account of, and extrapolate away from, such distortions. The National Service Framework can be interpreted as ideally calling for a balanced expansion in CABG and PTCA which ultimately would be expected to bring waiting lists between the two procedures into equilibrium. If this aim is to be realised, it is likely to require a significant expansion in capital

investment in developing treatment facilities for CABG.

The importance of accurate cost data

The importance of accurate costs is crucial in this therapeutic area, given the limited and frequently contradictory evidence concerning outcome variations between different procedures. The importance of subgroup analysis is particularly relevant in the revascularisation field, where costs and benefits are likely to vary significantly between individual patients. For example, whereas restenosis rates in all vessels are between 15 and 20% with stenting, in small vessels the restenosis rates lie between 30 and 40%. In addition, diabetes carries with it an additional 50% risk of restenosis events compared with non-diabetic patients and long lesions and chronically obstructed vessels equally carry higher restenosis rates of 40 and 60%. These factors are particularly relevant to PTCA, as variations in restenosis rates following CABG are very much lower over a short time horizon. Therefore, the cost-effectiveness of PTCA is likely to be highly sensitive to a number of parameters relating to baseline risk, which will vary significantly between individual patients. The measured costs and benefits of procedures will therefore be closely related to the population analysed.

Previous cost-effectiveness analyses

Please note that exchange rates used in these analyses were current as of February 2003.

Coronary angioplasty (PTCA) for single-vessel disease

In general, angioplasty has been shown to be cost-effective compared with medical therapy for all patients with single-vessel disease, except those with very mild angina. For example, in patients with severe angina, normal ventricular function, and single-vessel (LAD coronary artery) disease, the quality-adjusted life expectancy with angioplasty (as initial therapy) was 18.3 QALYs compared with 17.4 QALYs with initial conservative therapy, with an estimated cost-effectiveness ratio of US$6000 per QALY gained. For patients with only mild angina, however, initial PTCA was projected to be significantly less attractive, with incremental cost-effectiveness ratios in the order of US$80,000–100,000 per QALY. A summary of the major studies comparing PTCA against medical therapy is provided in *Table 26*.

Stents versus balloon angioplasty

Since 1995, several important studies have examined the relative costs of stenting and balloon angioplasty in a variety of patient populations and clinical settings (*Table 27*). The STRESS trial randomised 410 patients undergoing elective revascularisation of a single, discrete coronary stenosis to balloon angioplasty or Palmaz–Schatz coronary stent implantation. At 6-month follow-up, patients assigned to initial stenting had less angiographic restenosis (31 versus 42%, $p < 0.05$) and required less frequent clinically driven target vessel revascularisation (10 versus 15%, $p = 0.06$) compared with patients assigned to initial PTCA.[35] The STRESS Economic Sub-study included 207 consecutive patients randomised to stenting or PTCA at eight of 13 US clinical sites.[184] Stent patients required more contrast volume and more angioplasty balloons than patients who underwent conventional PTCA. As a result, catheterisation laboratory costs were US$1200 (£746) higher for stenting than for balloon angioplasty. In addition, the use of high-dose oral anticoagulation after stenting in the STRESS trial led to significant increases in major vascular complications with stenting (10 versus 4%) and a 2-day longer hospital stay leading to initial hospital costs being $2200 (£1367) higher for stenting than for PTCA. Over the first year of follow-up, patients treated with initial stenting required fewer subsequent hospital admissions and fewer repeat revascularisation procedures. As a result, follow-up medical care costs (not including outpatient or indirect costs) were, on average, $1400 (£870) lower after stenting. Although these cost savings were insufficient to offset fully the higher initial cost of stenting, additional savings would have been likely to arise beyond this initial period of analysis.

Although advances in stent deployment techniques (routine high-pressure postdilation, aspirin plus theinopyridine antiplatelet agents) have both improved the safety of stenting significantly and reduced length of stay, these benefits appear to have been offset by increasing resource intensity of the stent procedure itself.[185] In the BENESTENT 2 trial, which used the heparin-coated Palmaz–Schatz stent and the current dual antiplatelet–antithrombotic regimen,[39] initial hospital costs remained more than $2000 (£1243) higher with stenting than with balloon angioplasty [$10,376 (£6447) versus $8198 (£5094),

TABLE 26 *Summary: costs and effects of direct PTCA against thrombolysis for patients with AMI*

Trial	No. of participants	Cost measure	Time frame	Net cost PTCA – thrombolysis (lower)		Clinical outcomes/overall	Treatment strategy	Rate (%)
				US$	£			
MAYO[a][204]	108	Charges	Initial and 6 month	(6837)	(4250)	6 weeks death/MI Same	t-PA PCI	4 2
PAMI-1[205]	358	Charges	Initial	(2574)	(1600)	In hospital death/MI Better	t-PA PCI	12.0 5.1
GUSTO IIB[206]	1138	Costs	Initial and 1 year	302	188	1-month death/MI/CVA Slightly better	t-PA PCI	13.7 9.6
MITI[a][207]	3145	Costs	Initial and 3 year	2122	1319	In-hospital death Same	Any thrombolytic PCI	5.6 5.5

Exchange rate used: £1 = $1.6087 as at February 2003.
t-PA, tissue plasminogen activator.
[a] Initial and follow-up hospitalisations.

TABLE 27 *Selected cost studies comparing coronary stenting with balloon angioplasty*

Study	Date	Method[a]	*N*	Cost measure	Time frame	Device[b]	MACE (%)[c]	Cost	
								US$	£
STRESS[184]	1991–93	RCT	207	Hospital costs, MD fees	Initial hospitalisation	PTCA		7,505	4,665
						Stent/Warf		9,738	6,053
					1-year total	PTCA	21[d]	10,865	6,754
						Stent	15[d]	11,656	7,246
BENESTENT 2[186]	1995–96	RCT	823	Hospital costs, MD fees	Initial hospitalisation	PTCA		8,198	5,096
						Stent		10,376	6,450
					1-year total	PTCA	21	10,726	6,667
						Stent	11	11,618	7,222
EPISTENT[187]	1996–97	RCT	1438	Hospital costs, MD fees	Initial hospitalisation	PTCA/abciximab		11,357	7,060
						Stent/placebo		11,923	7,412
						Stent/abciximab		13,228	8,222
					1-year total	PTCA/abciximab	25.30	17,370	10,798
						Stent/placebo	24.00	17,109	10,635
						Stent/abciximab	20.10	17,951	11,159
DUKE[188]	1995–96	OBS	496	Hospital costs, MD fees	Initial hospitalisation	PTCA		10,076	6,263
						Stent		13,294	8,264
					1-year total	PTCA	30[d]	22,571	14,031
						Stent	14[d]	22,140	13,763
Stent-PAMI[193]	1996–97	RCT	900	Hospital costs, outpatient costs, MD fees	Initial hospitalisation	PTCA		15,004	9,327
						Stent		16,959	10,542
					1-year total	PTCA	22	19,595	12,181
						Stent	13	20,571	12,787

Exchange rate used: £1 = $1.6087 as at February 2003.
[a] OBS, observational study; RCT, randomised controlled trial.
[b] Stent/Warf, stenting with oral anticoagulation; Stent; stenting with oral antiplatelet agents such as ticlopidine.
[c] MACE, major adverse cardiac events (death, MI or repeat revascularisation).
[d] Event rate indicates only repeat revascularisation.

$p < 0.001$].[186] Although 1-year cardiac event rates were substantially lower with stenting (21 versus 11%), aggregate 1-year costs remained $1200 (£746) per patient higher with stenting than PTCA. Hence the cost-effectiveness ratio for stenting in the BENESTENT 2 population was ~$12,000 (£7459) per additional 1-year event-free survivor.

An economic evaluation of coronary stenting was also performed in conjunction with the Evaluation of Platelet IIb/IIIa Inhibitor for STENTing (EPISTENT) trial that compared three strategies of percutaneous coronary revascularisation. As was seen in the previous randomised trials, stenting increased initial hospital costs by $1900 (£1181) per patient and did not fully 'pay for itself' by 1-year follow-up.[187] Aggregate 1-year costs were thus ~$600 (£373) per patient higher with stenting than PTCA alone (both on a background of abciximab therapy).

One study that suggests that stents may save money over the long term compared with conventional PTCA is a single-centre registry from Duke University Medical Center.[188] Peterson and colleagues examined in-hospital and 1-year costs for a consecutive group of stent patients ($n = 384$) and 'stent-eligible' PTCA patients ($n = 159$). Although initial hospital costs were more than $3200 (£1989) higher for the stent group, stent patients were much less likely to be rehospitalised (22 versus 34%) or undergo repeat revascularisation (9 versus 26%) during follow-up. As a result, 1-year costs were actually slightly lower in the stent group [$22,140 (£13,762) versus $22,571 (£14,030), $p = 0.26$]. Potential explanations for the differences between the Duke registry experience and the RCTs include the higher risk nature of the Duke population (as suggested by higher rates of follow-up CABG), higher single-centre treatment costs and possible unmeasured confounding.

Direct stenting compared with conventional stenting

One of the many strategies employed to reduce the costs of stenting includes the implantation of a stent without the traditional predilation of the lesion by balloon angioplasty (i.e. direct stenting). Although preliminary observations suggest that the strategy of direct stenting may be applicable with modern stents in up to about 40–60% of all coronary interventions, such a strategy is not common in the UK. Most trials have reported similar clinical outcomes in selected lesion types (avoiding calcified lesions in markedly tortuous vessels).

Several studies have examined the economic outcomes of direct stenting compared with conventional stent techniques. Briguori and colleagues performed a retrospective comparison of patients undergoing direct and conventional stenting.[189] Direct stenting was successful in 94% of cases in this single-centre analysis, with no in-hospital deaths, MIs or emergency bypass surgery. In the direct stenting group there were significant reductions in procedure time (by 30%), radiation exposure time (by 25%), contrast dye, balloon use and cost. The total cost was reduced from $2210 (£1436) for conventional stenting to $1305 (£848) for direct stenting. In a prospective randomised study of 122 patients with single, non-occluded lesions, Danzi and colleagues[190] also reported that procedural costs were significantly lower with direct stenting [$2398 (£1490) against $3176 (£1974), $p < 0.001$] with similar 6-month event-free survival rates and incidence of angiographic restenosis. Carrie and colleagues[191] reported similar findings in the multi-centre, randomised Benefit Evaluation of direct coronary sTenting (BET) study with mean procedural costs of $956 (£594) and $1164 (£723) with and without direct stenting ($p < 0.0001$).

Stenting versus PTCA for emergency procedures (acute myocardial infarction)

In the last 5 years, various improvements in antithrombotic regimes have occurred to reduce the risk of sub-acute thrombosis with intracoronary stenting in the setting of an AMI. Stenting in the context of an AMI therefore became a viable option. The Stent Primary Angioplasty in Myocardial Infarction (Stent-PAMI) trial[192] was the first randomised trial to address prospectively the economic impact of a primary angioplasty strategy for AMI with and without routine stenting. The combined primary end-point at 6 months of death, reinfarction, disabling stroke or TVR occurred in fewer patients in the stent strategy than the balloon arm, 12.6 versus 20.1% ($p < 0.01$), although the mortality end-point alone was higher in the stent arm, 4.2 versus 2.7% ($p = 0.27$). For the economic analysis, Stent-PAMI[193] examined initial hospital resource utilization and costs and also included 1-year aggregate costs for further events and readmissions, using a bottom-up costing methodology. Compared with conventional PTCA, stenting increased procedural costs by ~$2000 (£1243) per patient. However, stenting was associated with significant reductions in the need for repeat revascularisation (13 versus 22%, $p < 0.001$) and rehospitalisation (24 versus 31%, $p = 0.03$) in the 1-year follow-up period. Follow-up costs for Stent-PAMI over the year were therefore significantly

lower with stenting, but total 1-year total costs remained ~$1000/patient (£622) higher with stenting than with PTCA [$20,571 (£12,787) versus $19,595 (£12,181, $p = 0.02$]. The cost-effectiveness ratio at 1-year for stenting compared with PTCA was $10,550 (£6558) per repeat revascularisation avoided. This cost-effectiveness ratio is highly time dependent and is likely to diminish as the time frame of patient follow-up expands.

Percutaneous versus surgical revascularisation for multivessel disease

A number of studies have compared PTCA costs with those of CABG and the results of the main studies are summarised in *Table 28*. In particular, five randomised clinical trials have incorporated an economic analysis which could be utilised to compare the costs of PTCA with bypass surgery. A summary of the general strengths and weaknesses of these RCTs using a checklist of good practice is presented in *Table 29*. The first two trials in the table (RAVEL, BENESTENT II) do not directly compare stent with CABG, but they are nonetheless useful for generating evidence on this comparison.

Although each of these studies had specific inclusion and exclusion criteria and used different time frames and cost measurement techniques, several general observations can be made. First, the initial hospital cost for PTCA is ~30–50% lower than that of bypass surgery, and these cost savings persist for the first year of follow-up. Second, despite the substantial initial cost savings with multiple-vessel PTCA, over a 3–5 year follow-up period much of these initial cost savings is lost owing to the need for repeat PTCA or bypass surgery in ~50% of patients.

As an example, Weintraub and colleagues[194,195] reported 3- and 8-year economic data for the 386 patients randomised to balloon angioplasty or bypass surgery in the Emory Angioplasty versus Surgery Trial (EAST). Initial hospital costs and professional charges for the PTCA group were an average of $19,824 (£12,322) compared with $27,793 (£17,276) for the CABG group. By the end of 3 and 8 years of follow-up, however, mean PTCA costs had increased to 91 and 95% of those for bypass surgery, and the difference was no longer statistically significant. In patients with focal two-vessel disease, however, the 3-year cost of PTCA [$20,875 (£12,976)] remained significantly lower than for bypass surgery [$23,639) £14,694, $p < 0.001$)].

Results of a 5-year economic substudy of the Bypass Angioplasty Revascularisation Investigation (BARI) have been reported.[196,197] To date, this study remains the largest and most comprehensive economic evaluation of alternative revascularisation strategies for patients with multiple-vessel coronary disease. Among 934 patients randomised to PTCA or bypass surgery, initial cost of care was 35% lower with PTCA [$21,113 (£13,124) versus $32,347 (£20,107)]. Over the first 3 years of follow-up, this cost difference narrowed progressively such that by the end of 5 years of follow-up, aggregate costs with PTCA remained slightly (5%) but significantly lower than with bypass surgery [$56,225 (£34,950) versus $58,889 (£36,607, $p = 0.047$)]. Subgroup analysis demonstrated that PTCA remained ~$6000 (£3729) less expensive than CABG for patients with two-vessel disease, but that 5-year costs were no different for patients with three-vessel disease. Since bypass surgery was associated with a trend towards improved survival in BARI, formal cost-effectiveness analysis was performed to determine whether routine CABG would be economically attractive for such patients. The BARI investigators found the overall cost-effectiveness ratio for bypass surgery as compared with angioplasty to be $26,000 (£16,162) per year of life gained. Although this analysis suggests that CABG may be an economically attractive initial revascularisation strategy for patients with multiple-vessel disease, the confidence limits around this cost-effectiveness ratio were wide and included a 13% probability that the cost-effectiveness ratio was greater than $100,000 (£62,162) per life-year gained. Further analyses will be required to identify patient- and treatment-specific determinants of long-term cost and cost-effectiveness in these populations.

The studies discussed above largely compared conventional balloon angioplasty with coronary bypass surgery in the context of the US health care system. The comparative costs and outcomes associated with the modern clinical practice of stenting will be significantly different from those of balloon angioplasty. Two large, randomised clinical trials that have also been undertaken comparing stenting with bypass surgery are the Arterial Revascularisation Therapy Study (ARTS) and SOS studies, both of which included prospective evaluations of both healthcare costs and QoL. The ARTS study also analysed resource use from the perspective of the US healthcare system, whereas the SOS study used an NHS perspective. At 1-year follow-up of the ARTS there were no differences in mortality between multiple-vessel stenting (2.5%) and CABG (2.8%) groups with overall 1- and 2-year event-free survival rates of 88% and 85% with CABG versus 74 and 69% with stenting.[99,198] This

TABLE 28 *Cost studies comparing percutaneous coronary revascularisation with bypass surgery*

Study	Date	Method[a]	*N*	Diseased vessels (*n*)	Cost measure	Time period	PTCA[b]		CABG[b]	
							US$ cost	£ cost	US$ cost	£ cost
Reeder *et al.*[200]	1979–81	OBS	168	1, 2, 3	Medical charges	Initial hospitalisation 1 year	7,571 11,384	4,706 7,076	12,154 13,387	7,555 8,321
Kelly *et al.*[201]		OBS	163	1, 2, 3	Hospital and MD charges	1 year	7,689	4,780	13,559	8,425
EAST[194]	1987–90	RCT	384	2, 3	Hospital costs, MD charges	Initial hospitalisation 3-year total costs	16,223 23,734	10,085 14,754	24,005 25,310	14,922 15,733
RITA[202]	1993–94	RCT	999	2, 3	Hospital costs	Initial hospitalisation:				
						London centre		3,753		7,319
						Non-London centre		3,024		5,722
					Hospital procedural medication costs	2-year total costs:				
						London centre		6,916		8,739
						Non-London centre		5,448		6,498
BARI[196]	1988–95	RCT	952	2, 3	Hospital and outpatient costs, MD fees	Initial revascularisation 5-year total cost	21,113 56,225	13,124 34,951	32,347 58,889	20,107 36,060
ARTS[99]	1997–98	RCT	1200	2, 3	Hospital costs, MD fees	Initial revascularisation 1-year total	€7,366 €10,665	4,823 6,984	€11,295 €13,638	7,397 8,931
SOS[203]	1997–99	RCT	967	2, 3	Hospital and outpatient costs	Initial revascularisation 1-year total		4,205 6,419		7,396 8,914

[a] OBS, observational study; RCT, randomised controlled trial.
[b] Exchange rates used: £1 = $1.6087; £1 = €1.5270 as at February 2003.

TABLE 29 *Quality assessment of economic analyses attached to RCTs*

	Checklist items[a]									
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
RAVEL I[b]	✓	✓	×	✓	✓	×	N/A	✓	✓	✓
BENESTENT II[c]	✓	✓	✓	✓	✓	×	N/A	✓	✓	✓
ARTS[d]	✓	✓	×	✓	✓	✓	N/A	✓	×	×
ERACI II[d]	✓	✓	×	✓	✓	✓	×	×	×	×
SOS[d]	✓	✓	×	✓	✓	✓	N/A	✓	✓	×

Item graded: ✓, yes; ×, No; N/A, not applicable (time frame was ≤ 1 year).

[a] 1. Was a well-defined question posed in answerable form?
2. Was a comprehensive description of the competing alternatives given?
3. Was there evidence that the programmes' effectiveness has been established?
4. Were all the important and relevant costs and consequences for each alternative identified?
5. Were costs and consequences measured accurately in appropriate physical units?
6. Were costs and consequences valued credibly?
7. Were costs and consequences adjusted for differential timing?
8. Was an incremental analysis of costs and consequences of alternatives performed?
9. Was a sensitivity analysis performed?
10. Did the presentation and discussion of study results include all issues of concern to users?

[b] DES vs stent in single-vessel disease; Appendix A, Cordis submission.

[c] Stent vs PTCA in multiple-vessel disease; Serruys and colleagues, 1998.[39]

[d] CABG vs stent in multiple-vessel disease; ARTS, Serruys and colleagues, 2001;[198] ERACI II: Rodriguez and colleagues, 2001;[101] SOS, SOS Investigators, 2002.[103]

difference in event rates was mostly driven by repeat revascularisation rates of 16.8% in the stent group. Nonetheless, repeat revascularisation rates with the stenting group were approximately half those seen in earlier multiple-vessel PTCA trials and represented a considerable clinical improvement of stenting over plain balloon angioplasty. The ARTS economic analysis calculated total procedural costs of $6441 (£4004) for the stent and $10,653 (£6622) for the CABG groups and 1-year total direct medical costs of $10,665 (£6629) and $13,638 (£8477) ($p < 0.001$), respectively. Interestingly, the cost differences between PTCA and CABG were similar for both diabetic and non-diabetic patients.[199] The incremental cost-effectiveness ratio of CABG over stenting was $21,000 (£13,054) for each patient who remained event free at 1 year. Long-term follow-up is planned to determine the extent of any further erosion of the cost differences over 3–5 years. Given the importance and relevance of the SOS trial, this is discussed in greater detail in the next section.

In summary, both observational studies and recent randomised trials have consistently demonstrated that multiple-vessel stenting is considerably less resource intensive and less costly than bypass surgery during the initial hospitalisation. However, due to the need for more frequent repeat revascularisation procedures, the initial economic advantage of multiple-vessel PTCA diminishes over time. The studies undertaken to date have predominantly been short term and provide a very limited evidence base by which to assess the cost-effectiveness of modern clinical practice. The results obtained are strongly influenced by the patient set and time frame analysed within the trial. The majority of trials were also undertaken from a North American perspective. In such circumstances, the evidence base provides a very insubstantial basis for establishing the comparative cost-effectiveness of different procedures from an NHS perspective. The next section analyses whether the quality of this insubstantial evidence base is significantly improved by the recent SOS trial.

The Stent or Surgery (SOS) trial: economic evaluation

The contents of this section are academically in confidence.

DES versus bare metal stents

Much of the content of this section is academically in confidence. We are, however, able to include the introductory and concluding sections in this report.

Data sources

DES are a recent innovation and hence robust and reliable evidence concerning their cost implications and associated benefits is extremely rare. Very little was found to be available in the published literature, with the majority of analyses available still largely in the form of abstracts, slide presentations or short reports of work in progress. In this respect, extensive use was made of websites to identify the most up-to-date results of research in progress concerning the cost-effectiveness of DES. In addition, extensive networking was undertaken with HTA groups from other countries to assess whether they had developed cost-effectiveness analyses on DES. On the advice of Kirsten Garces (Research Officer, Canadian coordinating office for HTA), we contacted Dr Nicole Mittman, Assistant Professor at the Hope Research Centre located at Sunnybrook Hospital, Toronto. The Hope Group were conducting an economic analysis of DES and had developed an economic model underlying their use. Dr Mittman kindly allowed us access to their model and undertook on our behalf an analysis using the model incorporating NHS parameters and resource data.

Academic in confidence information removed, Sunnybrook Hospital, Toronto.

Conclusion

Throughout our collaboration, the Sunnybrook group emphasised that their analysis was still in the process of development, their results were preliminary and the group are currently in the process of updating and finalising their analysis. The major weakness that they readily acknowledged was that their clinical outcomes were based on the results of one possible atypical study (RAVEL). In particular, measured cost-effectiveness of DES in the Canadian model is largely driven by the apparent mortality benefit arising to DES patients in the RAVEL trial. At this stage, we feel that there is insufficient evidence to justify such an assumed mortality benefit in mainstream clinical practice.

This meta-analysis indicates that a broader overview of trial results does not, as yet, justify the assumption of a mortality gain related to the use of DES. Hence, although we gratefully acknowledge their assistance, we felt it essential that we develop our own model to estimate the costs and benefits arising from the use of DES in the context of the NHS. This model is based on a much broader review of the literature. The assumptions, methodology, and results obtained using our economic model are outlined in detail in Chapter 9.

Conclusions

As in most medical studies, economic evaluations of percutaneous coronary revascularisation techniques have generally found that newer treatments tend to increase costs compared with the established alternatives. For example, despite increasing medical care costs, balloon angioplasty has been found to be cost-effective compared with medical therapy for patients with moderate to severe angina and single- or two-vessel coronary disease. Similarly, coronary stenting increases long-term costs for most patients but has been found to be associated with improved outcomes compared with conventional PTCA, particularly for patients with single, discrete lesions.

There are currently no significant published studies evaluating the cost-effectiveness of DES. Hence there is a need for a significant expansion in the evidence base underlying their use in different patient groups before it will become possible to make definitive statements concerning the cost-effectiveness of DES.

In comparing the cost-effectiveness of CABG and stents/DES, the length of follow-up is crucial. All studies show that CABG initially costs more but that over time the extra costs in the follow-up period associated with stents tend to erode this cost advantage. Given that the majority of studies undertaken to date cover a comparatively short time period (12 months), it is perhaps not surprising that the higher long-term cost savings related to CABG have not been adequately captured in the published analyses. The economic model developed in Chapter 9 attempts to rectify this deficit by analysing costs and outcomes over a 5-year period.

Chapter 8

Critical review of submitted models

Critical appraisal of the submitted economic models

Introduction

Four economic models were submitted in support of the industry submissions from Abbott, Boston, Cordis and Guidant. A summary of the models is provided in *Tables 30* and *31*. The models varied widely in their underlying assumptions, methodology and structure of analysis and also in the depth and nature of their underlying documentation. Each model was analysed in detail and a range of strength and weaknesses were identified. In each case, a standard checklist was applied[208] to assess the extent to which each model complied with the expectations of a high-quality economic evaluation. The results of this checklist for each model are provided in *Table 32*.

A summary of the general strengths and weaknesses of the four economic models is presented below, followed by a critique on the relative merits of each individual submission.

Common methodological issues

Since all the submitted economic evaluations responded to the NICE appraisal call, by definition the question to be addressed was clearly stated, and each submission presented evidence in support of their advocated technology, although the definition of the characteristics of the comparators and their relevance to current practice was often less precise, specially in relation to CABG. All but one of the submissions (Abbott) presented subgroup analyses according to the disease characteristics of patients, and in one case DES was not evaluated. The source of effectiveness tended in all cases to be trials lasting from 6 months to 1 year for DES, whereas controlled studies lasting up to 5 years were used in three instances (Abbott, Cordis and Guidant) to populate the models for the CABG, PTCA and BMS options. Of these models, results were presented for a 5-year time frame only for Abbott and Guidant. Therefore, in all studies, the validity of the estimate of effectiveness may be questioned owing to the short-term nature of the evidence presented in support of DES, a more important issue for the DES versus CABG comparison than for the DES versus BMS comparison (although see the Abbott model section below). In general, the data sources used to populate the models referred to patient populations relevant to the subgroups in question. The exception was the estimates of impact on patient preferences for HRQoL outcomes of symptomatic restenosis and revascularisation ('utilities'), which were derived from a multiple-vessel disease population (ARTS trial) in all but one case (Abbott; the model used data from a 1980 study, adequate details of which were not provided). The validity of applying those utilities as measures of QoL outcomes of single-vessel disease patients is an open question.

Costs measured included in all cases the costs of initial procedures plus hospitalisation and routine cardiac drugs, antiplatelet therapy, emergency procedures, adverse events (non-fatal MI) and revascularisations (angiograms and procedures) either for 6 or up to 12 months. The economic studies varied in the level of detail for reporting measured costs and the length of time after first treatment for which costs were measured.

Critical appraisal of Abbott model

This submission presented two comparisons, one involving a PC polymer-coated stent versus BMS, and another comparing a PC polymer-coated stent with anti-inflammatory drug elution ('Dexamet') versus BMS. Since the economic model submitted by the manufacturer was not accompanied by a document describing the aims, methods and results of applying the model to issues relevant to the submission, the following assessment is based on the very limited technical information in the model.

Comparison with checklist

A distinctive strength of this model is its account of the effects of angina on the QoL of patients, although the values used refer to a separate study published in 1980 (precise details were not given). Given the technological advances in the field, the use of such source may not reflect the likely impact of disease of the present time.

A serious limitation of the model relates to the limited duration (6 months) of the trial on which the evidence for Dexamet was based, meaning that the effectiveness of the technology cannot be ascertained. Moreover, the structure of the model

TABLE 30 *Summary of economic submissions to NICE*

Submission	Study type	Comparators	Population and subgroups	Time frame	Model used	Cost elements and sources (other than BCIA)	Effectiveness and benefit outcome measures	Cost/price of device (£)	Assumptions repeat revascularisation (%)
Cordis	CEA CUA	DES vs BMS DES vs CABG DES vs PTCA (single vessel)	As in RAVEL and SIRIUS Patients with small vessels (<3.0 mm) and single vessel Diabetic Long lesions (>16 mm) Multiple vessel	1 year 5 years	DA plus assumptions DA model for indirect comparisons (multiple-vessel group) RCT plus assumptions (small-vessel group)	Price of DES and BS; procedures (re-PTCA, CABG); hospital (ICU, CCU, ward); medication; angiogram; vascular surgery; transfusions; AE visit; observation unit; outpatient rehabilitation; rehabilitation	MACE avoided at 1 year (small vessel), Revascularisation avoided (longer lesions), Mortality Utility weights (restenosis free, restenosis) Time to restenosis (long lesions)	CIC	*DES and BMS*[a]*:* PTCA 65–68 BMS 22 CABG 9–13 *CABG:* PTCA 6 BMS 50 CABG 44
Boston	CEA CUA	DES vs BmS DES vs CABG	As in TAXUS II Single-vessel *de novo* lesions Diabetic in single vessel Small vessel (2.5–3.0 mm) within single vessel Very small vessel (<2.5 mm) single vessel Long lesions (>16 mm)	6 months	DA	Price of DES and BS; procedures (PTCA, CABG); hospital (ICU, CCU and ward), antiplatelet therapy (DES); angiogram; IIb/IIa injection; hospitalisation (MI non-fatal, stroke); arterial surgery for severe vascular bleeding; transfusions; dialysis; procedures: E-CABG: assumption	All-cause mortality at 6 months Utility weights (restenosis free, restenosis, minor stroke, AMI, renal failure) TLR rate (long lesions)	CIC	*DES and BMS*[b]*:* PTCA 12.1 BMS 81.1 CABG 6.8 *CABG:* PTCA 10.8 BS 72.5 CABG 16.7
Guidant	CEA CUA	DES vs BS (in 'high risk') DES vs CABG	As in SIRIUS/BCIA Single-vessel *de novo* Small vessel Long lesion Diabetics Multiple vessels	1 year 5 years	DA. Results at 1 year extrapolated to 5 years assuming constant outcomes	Price of stent (DES, BMS) – company, BCIS Procedures (PTCA, elective CABG, emergency CABG), hospital (ICU, CCU and ward) MI non-fatal, CVA, antiplatelet therapy (DES), IIb, IIa injection	Event-free survival 1 year Years of life saved at 5 years Utility weights (symptomatic restenosis, CABG, healthy after CABG/PCI, CVA, MI)	CIC	*DES:* PTCA 78 BMS 2 CABG 20 *BS:* PTCA 40 DES 40 CABG 20

continued

TABLE 30 *Summary of economic submissions to NICE (cont'd)*

Submission	Study type	Comparators	Population and subgroups	Time frame	Model used	Cost elements and sources (other than BCIA)	Effectiveness and benefit outcome measures	Cost/price of device (£)	Assumptions repeat revascularisation (%)
Abbott	CUA	Anti-inflammatory eluting stent vs BMS	As in STRIDE Diabetics and non-diabetics combined	5 years	Probabilistic model. Results at 6 months for anti-inflammatory eluting stent assumed constant up to 5 years	Price of stent ('DES', BMS) Procedures (PTCA, bailout stent, E-CABG and CABG), hospital (ICU, CCU and ward), fatal and non-fatal MI, follow-up costs (outpatient visits)	Years of life saved at 5 years Utility weights (stable, unstable, severe, silent angina, from procedure)	CIC	*DES*[c]: PTCA 100 *BS*[c]: PTCA 66.6 CABG 33.3

AE, accident and emergency; CCU, coronary care unit; CEA, cost-effectiveness analysis; CIC, commercial in confidence information; CUA, cost-utility analysis; DA, decision analysis; ICU, intensive care unit

[a] Long lesions group.

[b] Taxus II total population

[c] 6-month data.

TABLE 31 *Sensitivity analyses within economic submissions to NICE*

	Sensitivity analysis					
	Univariate	**Multivariate**	**Stochastic**			
Submission	**Univariate or threshold analyses**	**Deterministic or scenario analysis**		**Parameters varied**	**Most influential parameters[a]**	**Notes**
Cordis	Yes	Yes	Yes, only for small vessel group	Mortality at 1 year Revascularisation rates Follow-up costs Utility weights	Mortality benefit – for small-vessel group	For single small vessel and diabetics the 'scenario' analysis was based on assumption of equivalent mortality outcomes Does not include CABG risk of peri-operative death
Boston	Yes	No	Yes	AMI rate TLR rate Utility weight for restenosis Utility weight for 'healthy' after revascularisation Cost CABG Cost PTCA Duration of antiplatelet therapy for DES	Efficacy in very small (<2.5 mm) group	Includes QoL effects but not costs, of renal failure after E-CABG Too limited a time frame for meaningful analysis
Guidant	Yes	No	No	Reintervention rate Reintervention mix Number of stents used Duration of antiplatelet therapy for DES	Reintervention rate Number of stents used per PCI	Costs measured for 1 year whereas health benefit measured for 5 years Models do not include vascular surgery and transfusion costs Risk of renal failure after E-CABG not accounted for DES vs CABG model does not include second episode of restenosis although DES vs BMS did Uses LOS for CABG and PTCA from UK Reference Costs 2001

continued

TABLE 31 *Sensitivity analyses within economic submissions to NICE*

	Sensitivity analysis					
	Univariate	**Multivariate**	**Stochastic**			
Submission	**Univariate or threshold analyses**	**Deterministic or scenario analysis**		**Parameters varied**	**Most influential parameters[a]**	**Notes**
Abbott	No	No	Yes	Success rate initial treatment MI rate Relative risks DM short-term and 1 year (death, MI, CABG, re-PTCA) All utilities All costs, except DES/BMS	NA	Methods were not clearly presented

LOS, length of stay; NA, not applicable.
[a] According to author's results.

TABLE 32 *Quality assessment of submitted economic models*

Model	Checklist items[a]									
	1	2	3	4	5	6	7	8	9	10
Abbott	N/S	N/S	×	✓	✓	×	✓	✓	✓	×
Boston	✓	✓	×	✓	✓	×	N/A	✓	✓	✓
Cordis	✓	✓	×	✓	✓	✓	✓	✓	✓	×
Guidant	✓	✓	×	×	✓	✓	✓	✓	✓	×

Item graded: ✓, yes; ×, no; N/S, not stated; N/A, not applicable since time frame of analysis was 1 year or shorter.
Checklist items:
[a] 1. Was a well-defined question posed in answerable form?
2. Was a comprehensive description of the competing alternatives given?
3. Was there evidence that the programmess' effectiveness has been established?
4. Were all the important and relevant costs and consequences for each alternative identified?
5. Were costs and consequences measured accurately in appropriate physical units?
6. Were costs and consequences valued credibly?
7. Were costs and consequences adjusted for differential timing?
8. Was an incremental analysis of costs and consequences of alternatives performed?
9. Was a sensitivity analysis performed?
10. Did the presentation and discussion of study results include all issues of concern to users?

was also determined by the limited follow-up data available, so that a 5-year time frame is modelled in 6-monthly cycles. Although there is some evidence supporting the claim that most of the episodes of restenosis occur within 6 months after the stenting procedure,[39] the possibility of development of late restenosis[35,209] and long-term safety issues[209] remain an open question for which further research evidence is needed. Therefore, a model such as this, based on evidence limited to the first 6 months, is likely to miss critical health outcomes.

Although the model includes the quantities of resource utilisation, unit costs and outcome data and parameter assumptions and data sources used to populate the model, the structural relationships between parameters in the model are not always clearly laid out, which makes it difficult to replicate the model. As for the presentation of results, the model was evaluated using probabilistic sensitivity analysis. The findings of this analysis clearly show that both the estimates of total costs and QALYs are heavily skewed, and that a more appropriate description of the variability in the estimates would present the results in terms of median and interquartile ranges. The original result that Dexamet was dominant over the PC uncoated stent is not robust to variability in model parameters, and the analysis is therefore inconclusive.

There is no distinction in the sensitivity analysis between the uncertainty due to lack of data, as opposed to that caused by variability in the population; the implications for the results of those two types of uncertainty are different since the former is more likely than the latter to jeopardise the validity of a study.

Impact of variations in key assumptions

Although univariate sensitivity analysis of model results was not presented, the cost of CABG (including hospital costs) for elective cases (£6856) and the absolute risk difference in emergency CABG between Dexamet and the uncoated stent at 30 days (0 versus 3.05%, respectively) are the most influential parameters in the model. An 8-day length of hospital stay for CABG was assumed in the model, based on data from the ARTS trial,[99] an RCT comparing CABG with BMS in multiple-vessel disease patients treated during 1997–99 in four countries. This assumption may not be appropriate for the UK, where shorter hospital stays after surgery are likely to apply relative to other European and North American countries, and thus unduly favour the anti-inflammatory drug-eluting option. Also, the price differential between the new and the conventional stent turned out to be the most important cost factor for most patients.

Critical appraisal of Boston model

Comparison with checklist

The critical assessment of this company's submission to NICE that follows does not consider the updated 1-year data from the SIRIUS trial comparing DES with BMS since that information was made available to the LRIG only a few days before the deadline for completion of the final version of this report.

The submission compared DES against BMS and DES against CABG for patients with single-vessel

de novo lesions, both overall and by subgroup [diabetic, small (2.5–3.0 mm), very small (<2.5 mm) vessel, long lesions (>16 mm)]. This submission measured costs and benefits up to 6 months and, as such, is the one with the shortest time frame; the quality of the evidence submitted is subject to the same objections as stated earlier (see section 'Common methodological issues', p. 107) and is unlikely to capture important differences in quantity of life between treatment options in the DES versus CABG comparison.

The comparison between DES and BMS was based on a single RCT (TAXUS II), whereas the DES versus CABG analysis is based on an indirect comparison using data from TAXUS II (for DES) and the ARTS trial in multiple-vessel subgroup (CABG). The clinical evidence presented for the latter comparison should therefore be considered with caution owing to the different prognoses in the respective populations serving as sources of data. This is most evident in the all-cause mortality rate of CABG at 6 months (2.8%) serving as the basis for this model.

The methods used to measure and value costs and consequences of angina treatment were all adequately reported. This information revealed that, in the DES versus CABG comparison, the QoL effects of renal failure occurrence after emergency CABG were measured although the corresponding costs (e.g. due to dialysis for acute cases) were not. In addition, the valuation of outcomes lacks credibility in relation to utility weights for HRQoL in restenosis and postrevascularisation, which combined evidence from two disparate sources; estimates from the ARTS trial in the multiple-vessel population referred to above were pooled with the average estimates for mild and severe angina patients from studies published in 1981 and 1985.[210–212] This area of health outcome research is where the need for further study is most evident.

Given the short time frame and low death rates (0.8% at 6 months for DES and BMS, 2.8% for CABG) for each comparator at 6 months, the sample variation in the estimates of quality weights rendered the comparative QALY estimates imprecise and the analysis of incremental cost per QALY produced statistically ambiguous results.

Impact of variations in key assumptions

The authors report that results favouring the use of DES in single-vessel patients are subject to qualifications only in the case of the group with vessel diameters of <2.5 mm, where the rate of repeat revascularisations (TLR) appears to vary dramatically between different speeds of release formulations. In general terms, a critical assumption is the differential overall mortality rate at 6 months between DES/BMS and CABG, which appears to be overly optimistic in favour of stenting and which, as stated before, is based on an indirect clinical trial comparison using data from different populations.

In conclusion, the evidence supporting DES (TAXUS) against CABG in multiple-vessel subgroups is insufficient, and longer follow-up data are needed to perform meaningful cost-effectiveness analyses of the technology for all relevant subgroups.

Critical appraisal of Cordis model

The economic evaluation of the PCI stent technologies was based both on an economic evaluation alongside the RAVEL trial, for the patient group with vessel diameters of <3.0 mm (single 'small-vessel group'), and, for all other groups, on the modelling by decision analysis of the costs and benefits using data from different sources. The validity of results from each of these methods will be discussed in turn.

Comparison with checklist

For the analysis of the small vessel patient group (<3.0 mm vessel diameter), the analysis used data from the RAVEL trial, which compared DES versus BMS. The authors recognised the bias inherent in the design of the study, where protocol restrictions (fixed angiogram examination at 6 months) meant that the pattern of detection of need for repeat revascularisation was distorted relative to what would happen in normal practice. An indirect comparison against CABG was also presented on the basis of assumptions of clinical and resource-related outcomes made in order to estimate costs and benefits. Although these assumptions appear conservative (e.g. costs of CABG included only those of the procedure and length of hospital stay), the 1-year time frame adopted is a limitation of the analysis. A PTCA arm was also included in the comparisons using conservative assumptions on costs, which used the same acute hospitalisation costs as BMS in RAVEL, plus follow-up costs of BMS in RAVEL multiplied by the relative risk of repeat revascularisation of PTCA versus BMS in BENESTENT II,[39] a comparative study in the population of suitable candidates for CABG with one or more *de novo* lesions of length <18 mm in vessels of diameter >3.0 mm. Moreover, the utility weights were derived from a multiple-vessel patient population (ARTS trial) as opposed to the single-vessel population in question.

As for the remaining subgroups, decision analysis models for the subgroup of diabetic patients and patients with long lesions were populated using a trial comparing DES (CYPHER) with BMS, SIRIUS, which was designed to include patients at relatively high risk for restenosis and disease progression. These models combined the 9-month data from SIRIUS with EuroQol-5D utility data from a multiple-vessel disease patient group (the ARTS trial), and data from single studies with 5-year follow-ups for PTCA (Benestent II) and CABG.[213] The source of data used for PTCA also provided long-term data for BMS, and this information was built into the model for the BMS, DES and PTCA arms, and also that for CABG, although the 5-year results were not presented in the economic evaluation report.

The main threats to validity in the estimated benefits relate to (i) the short time frame of analysis (1-year results were presented, although the model was built for a 5-year time frame), (ii) the assumption of equal time to 'restenosis' with CABG as with DES and (iii) the omission from analysis of the higher peri-operative risk of death with CABG. [**Commercial in confidence information removed, Cordis, Boston Scientific.**] In addition, the incidence of CABG use for repeat revascularisations was higher in Cordis than in Boston for the CABG arm (1.75 versus 0.3%) but almost the same in the DES (0.56 versus 0.4%) and BMS (1.52 versus 1.2%) arms for the long-lesion patient subgroup. This less favourable representation of CABG by the Cordis submission (which derived its estimates from a single 1999 Scandinavian study as opposed to the ARTS trial data used by Boston for repeat revascularisations) is mirrored in the single-vessel diabetic patients group.

In relation to the multiple-vessel group, the authors acknowledge the lack of evidence regarding benefit of DES by assuming the same clinical outcomes as documented for BMS in ARTS – with the exception of outcomes following revascularisation, which were assumed equal to CABG. These tentative analyses produced highly unattractive cost-effectiveness ratios (i.e. higher than £30,000 per QALY) a result consistent with the higher risk of repeat revascularisation and surgery in this subgroup than that of other patients.

The presentation of results and sensitivity analysis in the submission were focused primarily upon findings that assumed an equal mortality benefit at 12 months across therapies. As a consequence, the submission downplays the finding that, in the long-lesion group, DES is associated with an incremental cost-effectiveness ratio (ICER) of £57,000 relative to BMS when that assumption is dropped and the observed estimates in the SIRIUS trial are replaced; since the trial data source was not powered to test equivalence in mortality, the assumption of equal mortality benefit based on the absence of a statistically significant difference between trial groups at conventional levels is misleading.

Impact of variations in key assumptions

In spite of the discrepancy in the assumptions discussed above, it is the higher initial procedural cost of CABG that is the most important difference between the Cordis and Boston models (£8040 versus £7812, respectively). This difference was due to the inclusion of a higher cost of complications in Cordis than in Boston (i.e. higher cost of repeat revascularisation with CABG and dialysis following renal failure). The high costs of CABG were translated into cost-effectiveness ratios that appeared prohibitive relative to DES when the additional QALY gain by the former relative to the latter was combined with its increased costs in both the diabetics and long-lesion subgroups.

Overall, the Cordis evaluation followed a more balanced view than that of Boston on measuring costs and benefits, with a clear description of assumptions and data sources. The only qualification as to the validity of the estimated costs and benefits of DES, other than that regarding the limited time frame of analysis common to all submissions, relates to the way in which the results were presented and the analysis of uncertainty carried out, which appeared to be highly selective.

Critical appraisal of Guidant model

This submission presented two separate decision analysis models, one comparing DES versus BMS for patients at high risk of restenosis and another for the comparison of DES versus CABG for those considered suitable to the latter treatment.

Comparison with checklist

The comparison of DES versus BMS is based on data from the SIRIUS trial, the primary source used by Cordis. This trial reports outcomes for the comparator up to 9 months, and the model is used to combine these data with data on QoL benefits from the ARTS trial, utilities from a single EQ-5D study (QoL effects of minor bleed) and assumptions (effects of a MI), expert opinion on frequency of surgical and treatment with stents for repeat revascularisation and costs from the BCIA data. The evaluation of DES for patients who 'are normally' treated with CABG is based on the

simplistic assumption that the only difference in health outcomes relates to the increased peri-operative death with surgery. This assumption, although partly conservative in that it ignores any cost implications of CABG due to repeat revascularisations, fails to acknowledge any long-term benefit in survival for surgery over DES. Moreover, it is not clear from the documentation in the submission how the additional risk of peri-operative death of CABG was derived (4.0 versus 0.64 with DES).

Although this evaluation attempted to address a clear issue relevant to the NICE review, it faced both methodological problems common to all submissions and pitfalls of its own design. In relation to the former, the authors attempted to address the issue of adequately accounting for long-term effectiveness, but in doing so they resorted to the arbitrary assumption of constant mortality benefits after 1 year and up to 5 years. This assumption ignores possible long-term survival benefits of surgery over stenting. The possible bias inherent in this simplification was compounded on the cost side by the failure to account for any costs occurring in the same final 4-year period. Therefore, while additional life-expectancy and QoL benefits were taken into account by extending the time frame from 1 to 5 years, the additional costs of a longer expected life due to say, outpatient visits were entirely omitted from the analysis. This bias makes DES to appear in a more favourable light relative to BMS and CABG.

An inconsistent modelling approach was adopted between the DES versus BMS and DES versus CABG comparisons. The surgery versus DES model did not permit the occurrence of a second episode of restenosis, a possibility that was included in the DES versus BMS model. On the cost side, an element not included in the submitted models was that of vascular surgery and transfusions.

Impact of variations in key assumptions

Results supporting the use of DES, as opposed to BMS, were found sensitive to the rate of target vessel revascularisation and the number of stents required per PCI. Also, the evaluation presented a sensitivity analysis using 2001 UK Reference Costs, a methodological advantage of this relative to other submissions in that it serves as a test of how robust the results are to evidence from an independent source. The analysis failed, however, to take account of uncertainty due to sample variation in the SIRIUS trial and, for the case of DES versus CABG, to perform any sensitivity analysis whatsoever.

In conclusion, the results presented in this submission are likely to be biased in favour of DES, although some methodological advantages, such as the effects of using an alternative set of costs to those set by the BCIA submission and the likely importance of longer time frames for analysis, are provided.

Summary of critical review of submitted models

The critical review of the four submitted models and their accompanying economic evaluations leads us to conclude the following:

1. Evaluations tended to be erroneously limited to 1 year or shorter intervals, with Guidant being the sole exception that both built a model that covered outcomes beyond 1 year and that presented and discussed the results of the model in the submission. Although this limitation reflects the fact that the effectiveness of the new devices has yet to be proved, it does not necessarily mean that the modelling of costs and health outcomes needs to be restricted to such a time frame.
2. Including a 5-year time frame using data from complementary sources yields cost-effectiveness ratios that lead to qualitatively different results, although the same rigour should have been applied to the identification and measurement of long-term costs as it was to benefits in the only submission that reported and discussed its results (Guidant).
3. In addition to the qualifications in 1 and 2 above, the evidence supporting the case of DES in the Cordis and Boston submissions may be questionable on methodological bias grounds for long lesions and diabetic patients in Cordis and multiple-vessel disease in Boston. Unreliability of estimates appears to be an issue in the supporting evidence for DES for very small vessel disease in the Boston evaluation. The methods of the Abbott economic model were not clearly presented, making it difficult to replicate its results, nor was a discussion of results provided.
4. Further research is needed on long-term safety and effectiveness outcomes of DES and BMS, and the effects of reoccurrence of angina symptoms and outcomes following repeat revascularisations on the QoL of patients. The effect on the latter parameter is likely to be more significant for cost-effectiveness the longer the time frame used in analysis.

Chapter 9

Economic evaluation

Part A: Economic evaluation completed for appraisal report

Key issues for economic models

Before describing the economic models developed by LRIG to support our review, it is important to address several issues, some pragmatic and some of principle, which establish the basis for our approach to modelling, and by implication some of the reasoning underlying our assessments of the submitted industry models.

The context for this discussion is provided by the two main claims put forward jointly and severally in the industry submissions:

- That DES are cost-effective when used as alternatives to conventional bare metal stents for patients currently undergoing PTCA, especially for subgroups at higher risk of restenosis.
- That PTCA with use of DES is a cost-effective substitute for CABG in the treatment of some patients who would currently be offered CABG on clinical grounds.

No trial of DES versus plain stents has thus far shown any evidence of differences in mortality. However, none of these trials was designed with mortality as a primary end-point and therefore they have been under-powered for that purpose. The meta-analysis of mortality end-points reported in earlier sections has also failed to show any differences, and therefore we must proceed to compare DES and plain stenting on the assumption of survival equivalence. This means that economic differences will predominantly arise from the offsetting effects of the extra purchase cost of DES and the reduced costs of subsequent reinterventions avoided, as well as any expected changes in health-related utility due to reductions in restenosis and consequent repeat revascularisations. Since measures of HRQoL are merely modifiers of longevity, treatments which only improve the QoL necessarily yield benefits one or two orders of magnitude less than treatments which extend life.

By contrast, mortality cannot be so easily dismissed where PTCA with DES is considered as a substitute for CABG. There is a long history of studies comparing CABG with PTCA, some of which were RCTs and some registry analyses. Although it is not possible to arrive at conclusive results for all patients from these varied sources, some strong differences have been reported for left main (LM) vessel stenosis[214] and for patients with diabetes (BARI investigators for all treated diabetes[215] and Weintraub for insulin-requiring patients[216]). Although interventions for LM vessel disease is currently undertaken almost exclusively by CABG, suggestions have been made to extend use of DES to these patients.[217] Diabetic patients are one of the main subgroups proposed in several of the industry submissions as suitable for PTCA with DES instead of CABG.

In order to evaluate this substitution claim, it is therefore necessary to consider carefully what reliable evidence exists on mortality risks of PTCA with stenting compared with CABG, since establishing such a difference adds an additional important dimension to the economic evaluation. It is not sufficient to argue that PTCA with stenting is not undertaken with the objective of reducing mortality, since **any** difference in mortality between two treatments considered for the same patients must be taken into account whether it is viewed as a direct immediate consequence of the intervention, or is seen as a later adverse event. It is not uncommon for apparently successful therapeutic innovations to fail the test of cost-effectiveness solely on the grounds of unintended and unexpected later events.

Mortality

Inevitably, only limited evidence will have been accumulated in respect of newer technologies at the time when they are first evaluated. Nevertheless, the evaluation of any treatment for a chronic disease must focus on long-term outcomes to be at all meaningful, particularly mortality and survival.

CABG versus PTCA with conventional stent

Three recent randomised trials have been reported comparing CABG with PTCA using conventional stents for the treatment of patients

with multiple-vessel disease, which include details of follow-up of 12 months or longer. SOS[103] included 488 patients undergoing CABG and 500 undergoing PTCA with stent, followed for up to 3 years. ERACI II[101] studied 225 patients in each arm for up to 5 years and ARTS[99] randomised 600 patients to CABG and 605 to stent, reporting survival after 12 months. In each case (i.e. six separate trial arms), a bipartite survival model has been fitted to the published survival/mortality curve, after digitising plots in the trial reports (Figure 4 in SOS,[103] Figure 1A in ARTS[99] and Figure 4 in ERACI II[101]). This involved simultaneously estimating, by minimising squared deviations, the proportion of patients subject to early mortality (represented by an exponential function), and the remainder whose long-term risk is modelled by a Weibull curve. A metamodel was then obtained by combining these results, weighted for the size of each trial arm, to obtain a single modelled estimate of future expected survival projected to 5 years. More details of this analysis are included in Appendix 4. This approach to meta-analysis is preferred to simple point estimation at a single time point, since it encompasses much more of the information available from the constituent trials and provides a rational basis for limited trend projection. The results are shown in *Figure 24*, with and without the shorter ARTS trial.

This analysis suggests that although CABG patients may suffer a greater immediate post-operative risk of death than those undergoing PTCA with stent, the long-term risk profile strongly favours CABG, such that mortality risks are equal after about 18 months, and thereafter survival in the CABG arm improves relative to stented PTCA patients as the survival curves diverge. In terms of expected life-years, we project that the early advantage of PTCA is greatest after 18 months but amounts to an average of less than 3 days per patient. Thereafter, a typical CABG patient will steadily accrue additional life expectancy so that if projected to 10 years an extra 6 months of life could be expected. Ultimately over the remainder of life, a total of 2.5 additional life-years might be expected for CABG patients compared with those undergoing PTCA with BMS. This general pattern is supported from other earlier trials involving conventional PTCA without stenting (BARI[215]) and EAST[218]) and also the Duke University registry study of diabetic patients undergoing revascularisation.[219]

Further support is provided by comparing the mortality rates recorded for different time periods in the available randomised trials in meta-analyses:

- Combining mortality in-hospital/up to 30 days from ARTS and ERACI II yields a relative risk of 1.45 for CABG compared with stent.
- Combining mortality from 30 days to 12 months from ARTS, ERACI II and SOS leads to a relative risk of 0.73.
- Combining mortality risk over 12 months from ERACI II and SOS produces a relative risk of 0.39.

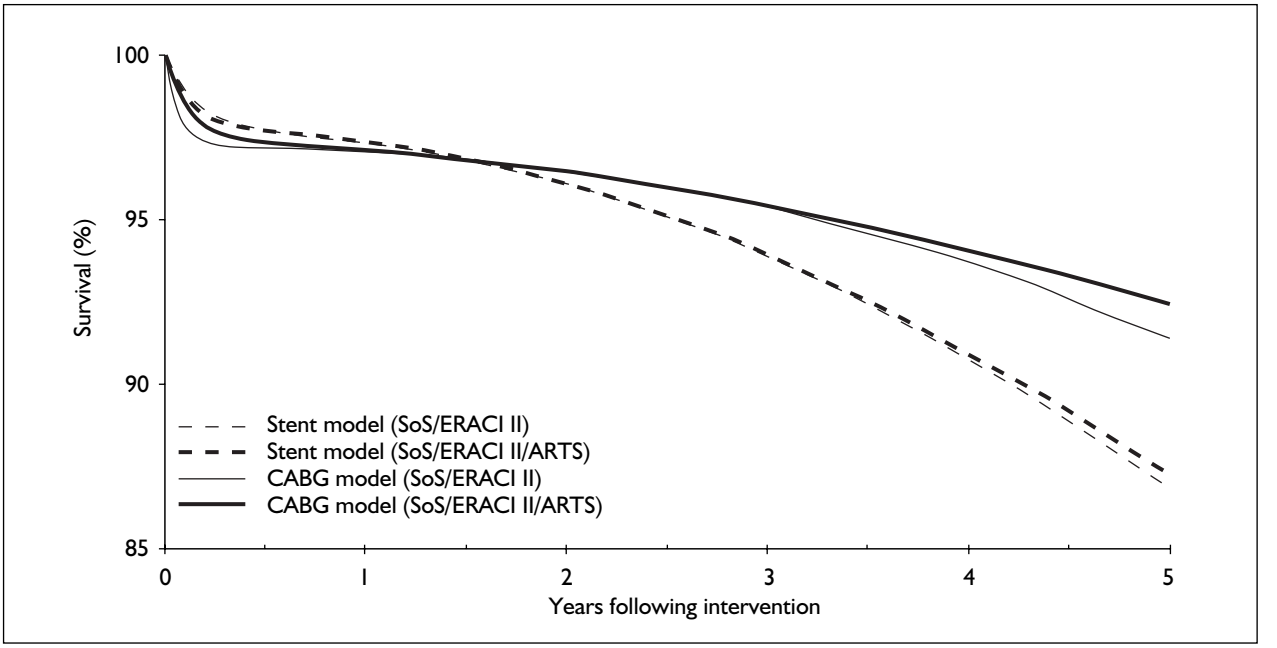


FIGURE 24 *Survival metamodels of three trials of CABG versus stent for multivessel disease*

Although none of these results is individually significant, the trend is clearly consistent with a steady shift in the balance of mortality risk in favour of CABG after an initial disadvantage.

These references generally relate to traditional surgical techniques, which are recognised to incur a markedly higher perioperative mortality risk. More recently, SOS reported very low early mortality (<1%) among CABG patients. While it has been argued that this was unusually low, Raco and colleagues[220] showed in 520 consecutive patients undergoing elective surgery with intermittent aortic cross-clamping a mortality rate of 0.57%, compared with an expected risk-adjusted mortality of 2–4%. Hence it may be argued legitimately that any evaluation of new revascularisation techniques should not be relative to historical methods of cardiac surgery, but the current state of surgical practice.

It was recently brought to our attention that a conference presentation has alluded to point estimates of mortality after 3 years follow-up of the ARTS trial, and it has been suggested that this should be included in our analysis. Unfortunately, we have as yet been unable to obtain from the triallists an equivalent survival plot for ARTS to 3 years, which would be necessary to incorporate such findings in the mortality metamodel in a reliable and consistent fashion. Without the additional information on long-term trends in hazard rates provided by a full survival plot against time (preferably from a peer-reviewed source), it is not possible to anticipate how the addition of new ARTS data might alter the results of a revised analysis. However, it is probably the case that it would be necessary for ARTS to show a near-significant trend in favour of the stent arm in order to counter fully the contrary finding in the existing metamodel.

PTCA with drug-eluting stent

When comparing DES with conventional stenting, there are few randomised trials available, and none reporting mortality rates later than 12 months after the initial procedure (2-year RAVEL data arrived too late for consideration in this section). Meta-analysis of the available trials provides no direct evidence of any difference in survival between patient groups receiving the two types of stent (see Chapter 6). Any claims of a survival advantage for DES compared with other stents will involve assuming the existence of a causal link between restenosis rates and subsequent adverse events with additional risk of mortality. However, differing rates of reintervention in similar patients were found in BENESTENT II[221] to have no measurable effect on any outcomes. The default position must therefore be that there is currently no basis upon which to assume preferential long-term survival for DES patients compared with plain stent patients.

In order to consider adopting an alternative position, it is necessary to establish a plausible mechanism by which such a difference might come about, and also to demonstrate that this is consistent with the evidence currently available from reported trials. The only clinical event for which a statistically significant difference has been established is the need for further revascularisation after recurrence of symptoms. Thus any argument for differential mortality favouring DES must be based on a causal pathway consequent on such a difference in revascularisation rates.

Clinical outcomes

The majority of trials involving DES have focused on process and intermediate measures of 'success'. In particular, much space has been devoted to detailed measures of angiographically determined stenotic lesions. Following from these investigations, many investigators have assessed successful outcomes in terms of target vessel or target lesion restenosis, and revascularisation interventions to these vessels or lesions.

This is a classic case of mistaking measures of the process for measures of true benefit. From a patient's perspective, the two issues which determine true success in the treatment of coronary artery disease are, 'Will I live longer?' (i.e. are the risks of premature death reduced?) and 'Will I feel better?' (i.e. are the painful and debilitating symptoms I am suffering removed or at least improved?). The relationship between these criteria of success and the commonly used indicators of good outcomes in the reported clinical trials are neither simple nor obvious. In particular, a substantial degree of restenosis of a previously treated vessel or lesion may not be accompanied by worsening angina. Equally, a fully patent treated vessel(s) does not necessarily prevent early re-emergence of severe angina.

It is common practice for triallists to report outcomes only for TLR/TVR. However, in TOSCA[85] (a trial of patients with occluded arteries), it is clear that there is a persistent number of patients suffering serious symptoms arising from disease in other than the initially

targeted vessels (around 10% of PTCA patients per year of follow-up requiring revascularisation) which is not altered by the trial intervention. The 12-month follow-up results from STRESS I[222] show that although TLRs are reduced by 32% as a result of stenting, all revascularisations fell by only 17%, indicating that interventions which benefit disease in specific vessels do not lead to equivalent changes in the number of patients needing repeat treatment (i.e. other problems remain to be treated in many of the same patients). This leads us to believe that large reductions in TLR/TVR rates in trials cannot be directly converted to fewer patient admissions in actual clinical practice without some means of estimating the downgrading of these figures.

The only relevant published figures that we have been able to examine on this question concern comparisons on PTCA and conventional stenting. In a comparison of DES with conventional stenting, we would expect that non-TVR reinterventions would be proportionately higher, and therefore that the reported benefits would need to be downgraded more substantially. However, without direct evidence of trial outcomes for **all** revascularisations from the DES versus stent trials, we are unable to make meaningful estimates on the size of this effect. The RAVEL study provides some pointers but most studies are not reported yet in this depth.

A further difficulty arises within many clinical trials (as discussed in Chapters 4 and 6) in that the additional procedures necessary to establish process outcomes can seriously distort other apparently objective outcome measures by providing additional information to clinicians which influences their clinical decisions. Thus there is substantial evidence that a protocol-driven angiography after 6 months is followed by a sudden increase in decisions to revascularise patients (approximately double in BENESTENT II[221]).

For the purposes of projecting the true benefit to be derived from a treatment strategy, the modeller must restrict his/her attention to genuine outcomes, which are life extension and the quality of that life. Any events or intermediate outcomes are only admissible if they can be shown to arise spontaneously (such as AMI), or they are undertaken on the basis of objective standards for intervention, and unbiased evidence exists of the relevant incidence rates and severity indices. Moreover, there must be a clear and direct causal relationship between the events/interventions and the true outcome measures (longevity and QoL).

On this basis, we have concluded that neither intracoronary dimensional measures of restenosis nor assessments/interventions restricted to target lesions or target vessels are sufficiently well related to final outcomes to be useful in modelling the expected benefits of revascularisation interventions. We focus on changes in long-term survival, and QoL principally, and consider other events only where they can be shown to impact on these measures or on the costs of treatment. Thus, we do not believe measures of restenosis are of direct relevance. We consider **all** revascularisations together since it is difficult from routine data sources to distinguish the precise location and nature of an intervention to allow separate analysis and costing. From the viewpoint of the NHS, it is the overall cost of all such treatments that matters, and from the patient's perspective, changes in symptoms cannot be allocated between two lesions which are revascularised at the same time: one undergoing a repeat intervention and the other a separate *de novo* intervention in another vessel.

Case-mix and subgroups

It is important to define the nature of appropriate groups of patients prior to undertaking any comparison between treatments. We are grateful for assistance received from the Cardio-Thoracic Centre in Liverpool in facilitating access to their registers of cardiological and surgical interventions in Liverpool and the north-west of England for this purpose. We were able to obtain details in relation to all cardiac surgical interventions undertaken at the four specialist centres in the north-west of England (Manchester Royal Infirmary, Wythenshawe, Blackpool Victoria and Liverpool CTC) during the period January 2000–March 2002. These data are described in more detail in Chapter 7 and Appendix 4. The equivalent comprehensive database for all PTCAs is at an earlier stage of development, so we were restricted to full data only from the Liverpool CTC for the same period. Both databases include a full range of nationally agreed audit information relating to patient history and condition, procedures undertaken, in-hospital adverse events and follow-up to 12 months postdischarge. This resource allowed us to obtain an overview of current NHS workload and clinical practice as a basis for establishing a realistic baseline for economic evaluation.

The majority of patients treated were classed as elective (77% of CABGs and 70% of PCIs), the remainder being emergency admissions and urgent cases requiring treatment before discharge. In view of these figures, and the larger body of

evidence for elective treatment, we follow the industry models in restricting attention in our model to elective patients only. Hence we are unable to make any comment on the cost-effectiveness of PTCA with DES in the context of non-elective treatment.

Figures 25(a, d) reveal a very clear distinction in case severity between elective patients receiving PTCA and those undergoing CABG. More than 90% of those patients with single vessel disease are treated by interventional cardiologists, whereas over 86% of patients with three or more diseased vessels are treated by cardiac surgeons.

When comparing different types of PTCA with stents, including DES or conventional stents, the comparison should normally be undertaken for single-vessel disease as the base case, with variations in severity considered as special variations.

The comparison between PTCA with stenting and CABG is most meaningful for patients with two-vessel disease, where it is possible that substitution of one treatment by the other could be considered clinically appropriate on the basis of current practice. However, it is important to ensure genuine comparability in the evidence base for modelling two-vessel disease outcomes, since there are clear trends evident in the registry data toward greater severity of disease and frequency of complicating conditions in the group currently treated by CABG. This can be seen in *Figure 25(b, e)* in respect of ejection fraction rating and in *Figure 25(c, f)* for a range of predisposing risk factors. Great care must be taken when combining outcome estimates in an economic evaluation even when derived from RCTs, as there is a substantial risk of introducing unintentional bias, generally favouring PTCA with stent over CABGs.

Time

Time horizon

The correct timescale over which to assess any chronic disease should be the whole remaining lifetime of patients from a well-defined event or treatment decision. By contrast, a self-resolving medical condition with definite outcomes may be assessed over a short period without loss of precision. However, in cases where outcomes differ between treatment options concerning the long-term QoL of patients (e.g. degrees of residual disability), some allowance for such differences over the remaining period of life may be necessary.

In view of our earlier conclusions [see the section 'Mortality' (p. 117)] concerning long-term mortality experience, it is clear that economic assessment of cardiac revascularisation interventions properly requires whole-life modelling, provided that the quality of available evidence will support projection so far into the future. For surgical mortality, there is published information with some relevance and merit out to 10 years or more, but the efficacy data on conventional stenting are of shorter duration, and for DES they are extremely limited. We therefore favour a compromise position for this exercise. In the north-west registers, the median age of patients receiving elective PTCA with stent is 60 years and for elective CABG 63 years, so that the natural limit of projection for these high-risk patients may not be much more than 20 years. Since mortality equivalence between CABG and stenting does not occur until 18 months have elapsed and expected life-years are not equal until nearly 3 years have elapsed, we believe that projection should continue sufficiently long thereafter to allow the long-term trajectory of costs and outcomes to be established, in the range 5–10 years.

Trial bias

Even RCTs may be subject to unintentional bias, owing to a failure to recognise the potential effects of the service environment of the trials. This is particularly the case with elective interventions undertaken in a seriously resource-constrained healthcare system such as the NHS. It is the case in all parts of the country that elective patients typically wait three times longer for CABG than for PTCA (i.e. as long as 18 months). If the traditional approach to RCT analysis is adopted, patients randomised to CABG are likely to suffer additional disease-related events (typically AMI and sudden death) before ever receiving the designated treatment. Under normal ITT methods, the extra adverse events are falsely ascribed as related to treatment with CABG, rather than to waiting for treatment, thus biasing results against CABG. This was the case in the ARTS trial,[99] where three patients died, one suffered a stroke and four suffered AMI while awaiting CABG compared with just one AMI in a patient awaiting PTCA with stent. In such cases ITT results must be corrected as far as is possible before results are employed in populating an economic model.

Cost-effectiveness analysis and policy

It is important to distinguish the concept of cost-effectiveness as a direct comparison of inherent features of an intervention (relative to the current normal practice), from the impact of introducing a

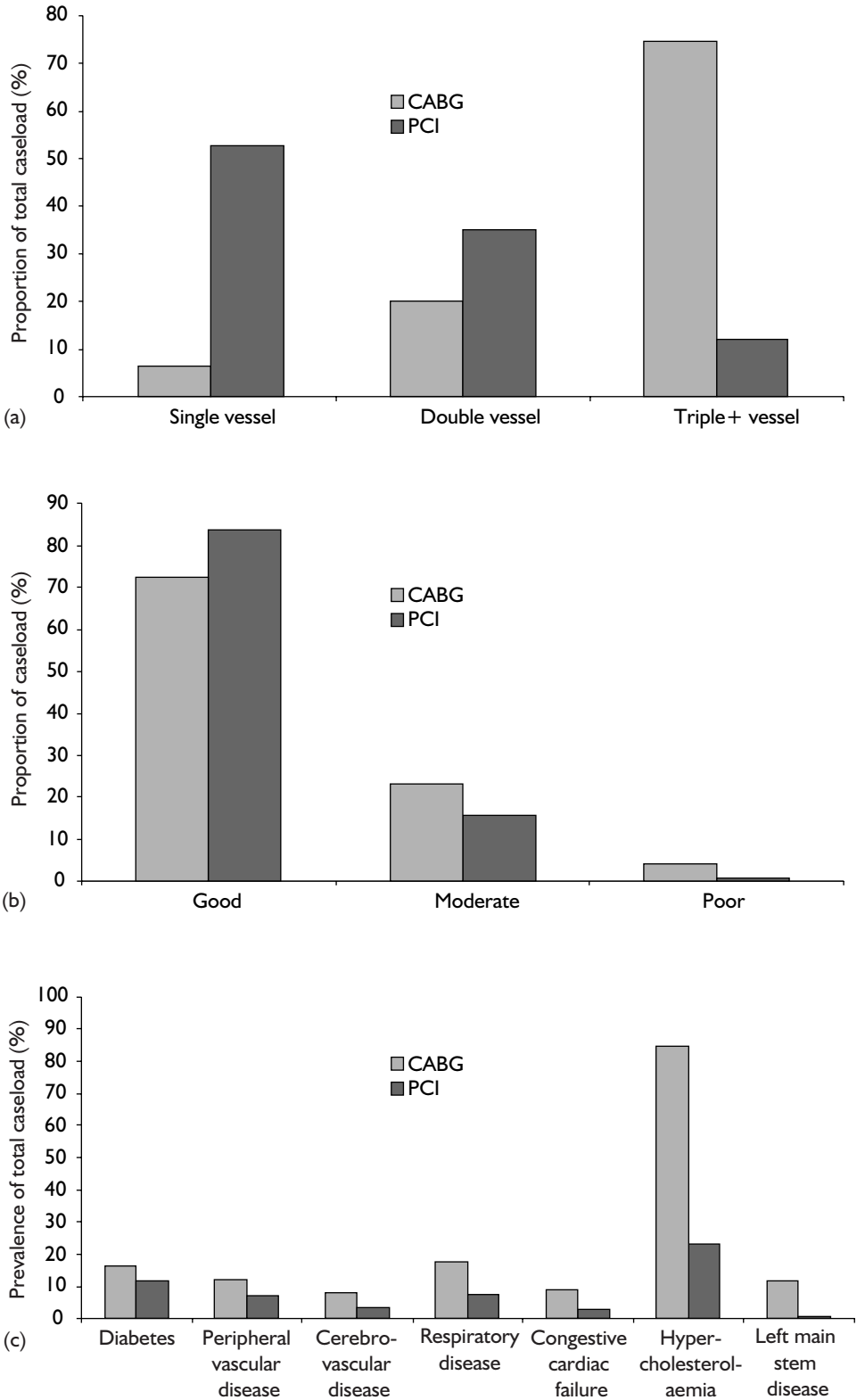
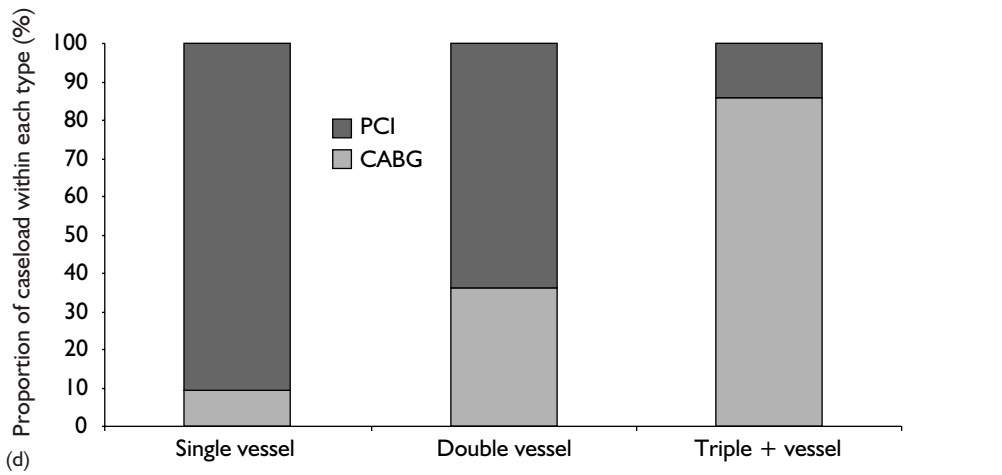
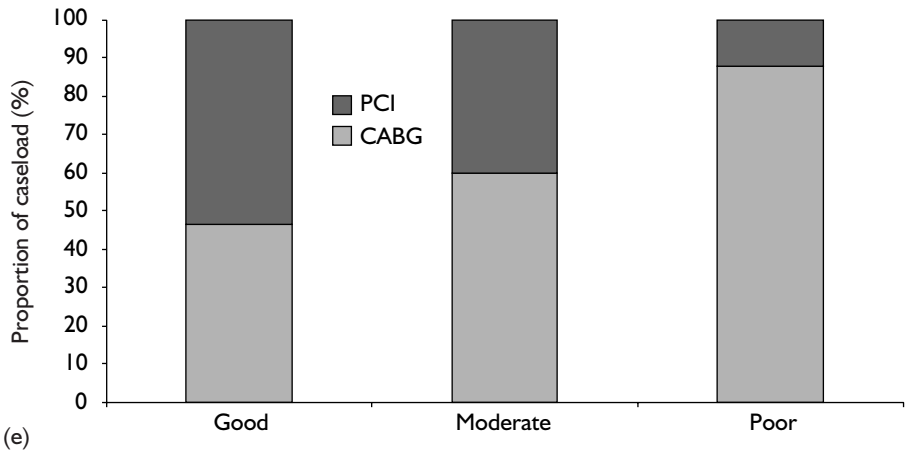


FIGURE 25 *Elective revascularisations: north-west registry data (1 January 2000– 31 March 2002). (a) proportion of the total caseload for CABG and PCI by extent of disease; (b) proportion of total caseload for CABG and PCI by ejection function; (c) prevalence of risk factors in CABG and PCI caseload; (d) proportion of caseload for each extent of disease subgroup by type of revascularisation; (e) proportion of caseload for each ejection fraction subgroup by type of revascularisation; (f) proportion of caseload for each risk factor subgroup by type of revascularisation.*





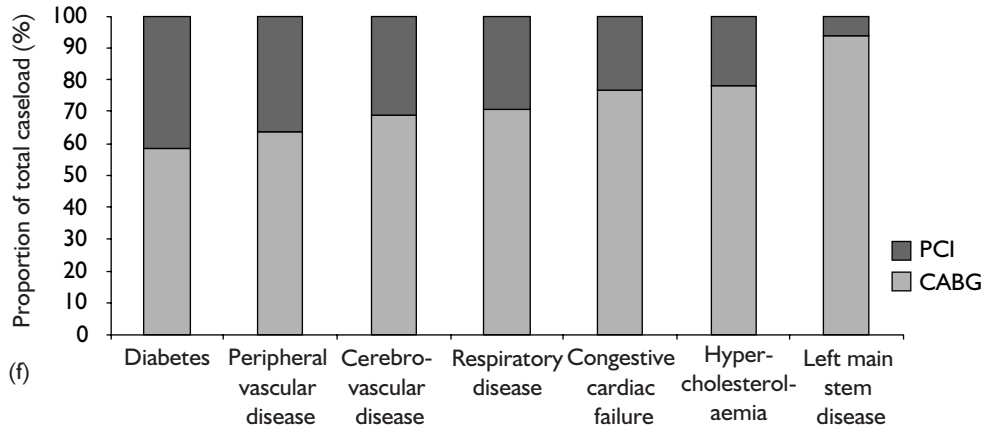


FIGURE 25 *Elective revascularisations: north-west registry data (1 January 2000– 31 March 2002). (a) proportion of the total caseload for CABG and PCI by extent of disease; (b) proportion of total caseload for CABG and PCI by ejection function; (c) prevalence of risk factors in CABG and PCI caseload; (d) proportion of caseload for each extent of disease subgroup by type of revascularisation; (e) proportion of caseload for each ejection fraction subgroup by type of revascularisation; (f) proportion of caseload for each risk factor subgroup by type of revascularisation. (cont'd)*

new therapy within a constrained environment. At present, the national volume of CABG surgery is restricted by capacity constraints related to availability of capital funds to expand surgical facilities. This leads directly to large differences in waiting times, and means that CABG patients are exposed to greater risk of deterioration or death before the procedure. However realistic this may appear in the current organisational context, it has nothing to do with cost-effectiveness, which requires that the options be compared *ceteris paribus* so that we obtain an appreciation of their relative merits independent of these extraneous influences. In particular, the pragmatic implementation of public policy in allocating resources (allocative efficiency) must not be allowed to obscure legitimate questions about the balance of costs and benefits in cardiac revascularisation (technical efficiency). For this reason, our model assumes **equal** waiting times for all elective interventions, as short as is consistent with practical management of patients. This assumption is implicit for index interventions since in practice all model comparisons begin at the time of admission for the elective procedure. It is not possible to eliminate all bias against CABG interventions in the case of *de novo* revascularisation when using UK data to populate a model. However, we can certainly do so in respect of second and subsequent revascularisations, by not allowing differential waiting times for these patients to generate apparent gains in outcomes and utility for PTCA interventions compared with CABG.

Utility

One source is referenced in three of the four industry-submitted models for utility values related to revascularisation – the ARTS trial. Cordis used just two figures from the published results to attribute utility values to patients in need of revascularisation and to patients following a successful procedure. Guidant use these plus the 1-month post-CABG disutility, augmented by a figure from a different source for the poststroke state, and an author's estimated utility for the effect of non-fatal AMI. Boston are more adventurous in attempting to combine the ARTS EuroQol results with time-trade-off (TTO) results from Cohen and colleagues.[210] In addition, the Boston model employs three independent sources for utility values for minor stroke (in type 1 diabetes), AMI (in type 2 diabetes) and renal failure requiring dialysis. Since ARTS only reported utilities for a 12-month period, the modellers resort to imputing various values to different short periods, including time spent waiting for a second revascularisation.

The Abbott model is different in avoiding use of the ARTS utility estimates. Instead, the authors employ utility values for mild and severe angina[223] combined with Cohen and colleagues' TTO figures for the effects of revascularisations and AMI. At first sight, using anginal symptom severity is attractive since it promises to link utility estimation directly to the primary therapeutic objective. However, the authors had to go back more than 20 years to find any evidence, and the changes in clinical practice and utility measurement in the intervening period raise serious doubts as to the legitimacy of combining these figures with those of Cohen and colleagues and indeed of ARTS.

Unfortunately, the ARTS trial does little to dispel the general evidence void concerning utility and QoL around cardiac revascularisation. It suggests average utility values for patients with multiple-vessel disease (excluding LM stem stenosis) and fair or good ejection fraction before their first revascularisation, and then up to 12 months following. It does not indicate how utility is affected by the return of symptoms of a severity sufficient to warrant a second intervention, or how the positive effect of a successful second (or third) procedure compares with the index intervention. Nor can ARTS provide any insight into long-term trends in utility for patients undergoing different procedures – all we know is that at 12 months both CABG and stented patients have achieved comparable improvements. Nor does ARTS allow us to infer values for patients with single-vessel disease (excluded from the trial). Also, there are no results available for specific subgroups (such as diabetic patients and those with long lesions or small diseased vessels). The authors of the submitted models have made many heroic assumptions on all these questions in difficult circumstances.

Given this weak basis for constructing meaningful QALY measures, we believe that elaborate model constructions are not warranted. We have adopted the following general approach:

- There is a short-term disutility associated with undergoing a revascularisation procedure, which can be considered as a small fixed QALY quantum. It is probably slightly larger for CABG than for stent.
- There is a short-term disutility incurred for a period before each subsequent revascularisation (corresponding to the average loss of utility from the time symptoms first recur until the next intervention occurs), the same for all patients.

- As discussed previously, there is no justification for according differential waiting periods to patients receiving CABG and PTCA with stent.
- There is no reason to assume that long-term utility values are different for any patients in whom symptoms do not recur and have not suffered any serious adverse events.
- Patients suffering additional related chronic disease or disability can be expected to suffer continuing loss of utility indefinitely.

Costs

The selection of appropriate costs for an economic model is generally driven by the availability of suitable data, rather than theoretical principles. Nonetheless, it is important to appreciate the compromises that we are obliged to make and the impact that these may have on our findings.

In this instance, the BCIA commissioned a joint costing exercise to establish a common basis for the various industry submissions, and in most cases these figures have been employed directly or with minor adjustments in the submitted models. Although this exercise drew on several disparate sources, the most important reference is to a paper reporting costs from the RITA-2 trial.[224] The trial was carried out in 20 hospitals across UK and Ireland from 1992 onwards. By contrast, unit costs were derived from a separate costing exercise carried out subsequently in five regional referral centres. The resource use data from the RCT (e.g. lengths of stay in different types of ward) were then combined with the average survey unit costs to obtain estimates for the cost of cardiac procedures, etc.

It is clear from Tables 3 and 6 in Sculpher and colleagues paper[224] that the five centres provided widely differing cost estimates of the key modelling parameters. In particular, the difference between CABG and PTCA costs varied between £1452 (a ratio of 1.7:1) and £4505 (5.8:1). Whether these differences arose from variations in local clinical practice, the organisation of services or accounting procedures, this casts doubt on the reliability of costs estimates obtained from a small and probably unrepresentative sample of hospitals. A further complication is introduced by the application of these costs to historic resource use information accumulated over a period when clinical practice was developing rapidly. Throughout the 1990s, the length of elective inpatient hospital stays was reducing generally, and particularly in the field of interventional cardiology. We must therefore question whether RITA-2-based cost calculations for CABG and PTCA interventions will reflect current NHS practice. Instead, we have based cost estimates on the mean costs shown in the Department of Health Reference Cost tables for 2001–02. In order to arrive at a total cost per CABG or stenting procedure, it is necessary to use the appropriate finished consultant episode (FCE) cost and add to it an estimate of the cost of time spent in a cardiac ICU (this would be under the care of a different consultant). We have used average lengths of ICU stay found in the Liverpool Cardiothoracic Centre register for this purpose, in the absence of national figures for specific procedures.

For the assessment of DES as a suitable alternative to CABG for two-vessel disease, we need to know the **difference** in unit cost between the two initial interventions. However, when considering the cost-effectiveness of DES compared with BMS in single-vessel disease, the **total** costs of CABG and stenting costs are important when undertaken as repeat interventions. Hence both total and incremental cost estimates are important to our evaluation.

The impact of alternative costing schemes can be gauged by examining *Table 33*. The final row shows our base estimates (assuming an excess DES cost of £520 per stent over conventional stents) derived from Reference Costs. In all cases, it appears that the submissions underestimate the excess in-hospital cost of CABG compared with PTCA with or without stents. Our estimated absolute cost for CABG is very similar to that used in two of the submitted models. The exception is the Guidant submission, which generally seems to contain idiosyncratic cost figures. For the comparison between CABG and PTCA + DES for two-vessel disease, the cost difference is strongly influenced by the disparate assumptions made in the submitted models about the prices of BMS and DES, to the extent that in one instance CABG appears to be cheaper than DES. Both the relevant trials (SOS and ARTS) suggest much longer hospital stays than the national statistics indicate, and yet generally lower hospital costs.

An important difference between the costing methodology we have employed and that presented in the industry models is that Reference Costs are inclusive of all cost elements encompassed within the relevant episode. This means that many relatively minor in-hospital adverse events which are managed as part of the original consultant episode do not need to be costed separately. As a general rule, additional costs are required only where the complication is of sufficient severity to require transfer of

TABLE 33 *Comparison of CABG and PTCA cost estimates from different sources*

Source/ submission	Cost of CABG (£)	Cost of PTCA (£)	Cost of PTCA + BMS (two vessel disease) (£)	Cost of PTCA + DES (two vessel disease) (£)	Length of stay for CABG (days)	Length of stay for PTCA + stent (days)	Excess cost: CABG vs PTCA (£)	Excess cost: CABG vs PTCA + BMS (two-vessel disease) (£)	Excess cost: CABG vs PTCA + DES (two-vessel disease) (£)
Submitted models									
Boston	7800	2500	3400	CIC	8.5	3.3	+ 5300	+ 4400	CIC
Cordis	7800	2600	4200	CIC	8.5	2.8	+ 5200	+ 3600	CIC
Guidant	6800	1700	3000	CIC	7.8	2	+ 5000	+ 3800	CIC
Trial costings									
SOS trial	7300	–	3700	–	12.3	5.5	-	+ 3700	–
ARTS trial	6900	–	3900	–	11.5	4.6	-	+ 3000	–
LRIG estimates									
Reference Costs 2001–02 and CTC data	7868	2156	3068	4316	8.3	2.9	+ 5712	+ 4800	+ 3552

responsibility for patient care to another specialist (e.g. nephrologist or vascular surgeon). This results in a simplified and more robust costing process with reduced scope for double counting.

On the basis of this analysis, we do not believe that costs based on recent trial costings (SOS and ARTS) can be considered reliable. In addition, we have concerns that use of the BCIA cost schedule (based on RITA-2) is also vulnerable to criticism, and have therefore opted to employ estimates based on Reference Costs for 2001–02 as more robust and appropriate to current UK clinical practice. It should be noted that in fact this approach suggests rather larger differences in procedure-related costs in favour of DES than is claimed in the industry submissions, and therefore if anything would favour the cost-effectiveness of DES.

Models and comparisons

In summary, we attempt to apply an economic model to address the issues raised by three direct comparisons:

1. Is PTCA using conventional stenting a cost-effective alternative treatment compared with CABG for patients requiring an elective revascularisation for confirmed two-vessel disease?
2 Is PTCA using DES a cost-effective alternative treatment compared with CABG for patients requiring an elective revascularisation for confirmed two-vessel disease?
3. Is PTCA using DES more cost-effective than PTCA using conventional BMS for patients requiring an elective revascularisation for confirmed single-vessel disease?

Questions concerning specific subgroups of patients will be considered as variations from these basic analyses, where there is sufficient reliable information of differential costs and outcomes available.

LRiG economic models

Model structure and methodology

Models to evaluate treatments for aspects of chronic progressive diseases must be established on a robust basis, particularly where they can be expected to result in long-term changes to patient experience. In chronic disease, any differences in expected longevity of patients between treatments will normally dominate the assessment of incremental outcomes, since life extension benefits are generally at least an order of magnitude greater than QoL or utility benefits.

The current widespread use of decision analysis (commonly referred to as 'decision trees') for microeconomic analysis betrays a failure among many practitioners to appreciate the limitations of this technique, which is most suitable for interventions with a clear short-term benefit and no cumulative long-term sequelae (medical or economic). Decision analytic models, Markov models and similar architectures based on projecting short-duration transition probabilities are at risk of accumulating and propagating small errors into larger deviations as the temporal scope of the model is extended. Such deviations have enhanced significance in the context of incremental CEAs, since the difference between two streams of figures each subject to accumulated errors can completely obscure true contrasts between treatment options.

One tactic used to minimise this problem is to limit the time over which the model is employed. However, this obviates the essential requirement of modelling interventions for a chronic disease – the need to anticipate the eventual costs and benefits which may continue to accrue over decades, or even the remainder of a patient's life.

All the models submitted in evidence for this review are of this kind, and none adequately addresses the issue of longevity for those suffering cardiac artery disease. Therefore, to avoid these shortcomings, we have chosen to adopt a completely different methodology, based on a hierarchical life-table structure. This places evidence and inferences about projected survival in prime position, with all other events, states and progressions as subsidiaries. This approach ensures that patient numbers for all events and patient states are reconciled throughout the model to the central survival profile, thus circumscribing the scope for accumulation of errors.

The overall structure of the model is displayed in *Figure 26*. The core of the model is the projected survival profile of a cohort of patients appropriate to the treatments being evaluated. For patients undergoing CABG, this is provided by the metamodel of survival in three clinical trials described in the section 'Mortality' (p. 117) for patients with multiple-vessel disease. For patients receiving treatment with stents, a similar metamodel was constructed based on the same trials. These base profiles are then adjusted for survival differences attributable to other patient groups derived from analysis of a range of published trial results and registry analyses. These profiles are used to generate the expected

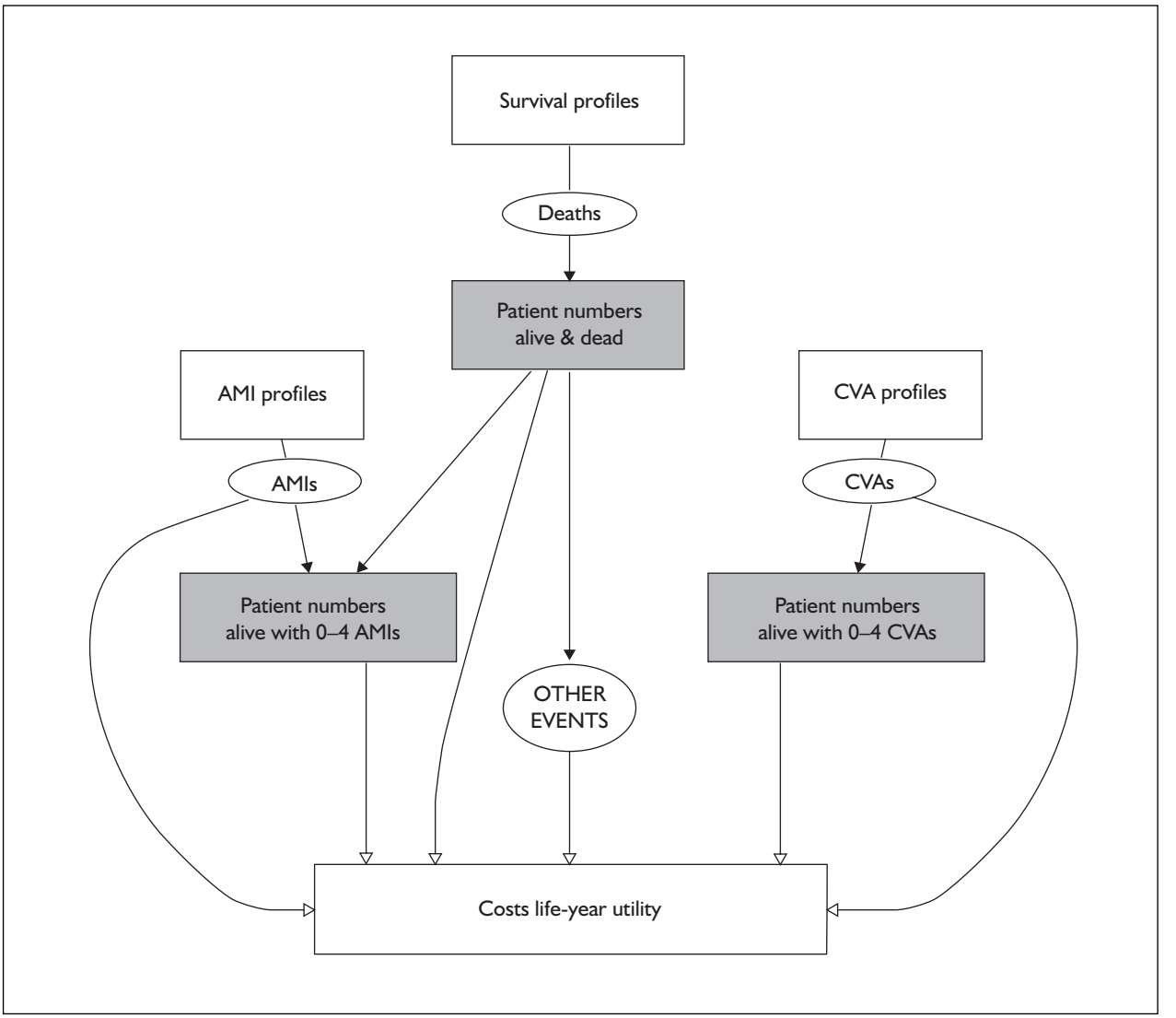


FIGURE 26 *Model structure schematic*

numbers of surviving patients for each week following the index procedure, up to the time horizon of the model.

A similar approach is taken to estimating the numbers of patients expected to suffer AMIs and strokes in each period, based on the number of surviving patients in each time period. Given the frequency of 'silent MIs' (i.e. those detected only on ECG at a routine review and not causing a clinical care episode with associated costs) and transient ischaemic episodes, we limit attention only to those events of sufficient severity to require medical intervention. These event rates are applied to estimate the number of surviving patients suffering a fatal AMI/CVA in each period, the number of non-fatal AMIs/CVAs and the resultant distribution of surviving patients according to the number of such episodes suffered following the index procedure.

A number of additional adverse events following a revascularisation procedure are also estimated on the basis of trial and registry estimates of the frequency of occurrence of acute renal failure and interventions for serious bleeding.

Costs and utility measures are estimated by applying appropriate values to both events and time spent in morbidity states. To ensure realism in costs, we base our methodology on UK Reference Costs 2001–02 as described above. This provides national mean inclusive costs for index procedures, which constitute the single largest element in the cost model (*Table 35*).

TABLE 34 *Distribution of type of subsequent revascularisation (%)*

	Subsequent procedure				
Index procedure	**PTCA**	**Stent**	**DES**	**CABG**	**Source of estimate**
CABG in two-vessel disease	20	25	25	30	Estimated from Cardiothoracic Centre registry data and clinical opinion
DES in two-vessel disease	0	80	10	10	Clinical opinion
BMS in two-vessel disease	25	55	0	20	Study of revascularisation in Medicare patients[228]
BMS in single-vessel disease	25	55	0	20	Study of revascularisation in Medicare patients
DES in single-vessel disease	0	80	10	10	Clinical opinion

TABLE 35 *Unit costs*

Resource item	**Unit of resource**	**Unit cost (£)**	**Source**
Initial revascularisation procedure			
CABG primary	Per episode	7868	2002 DOH Reference Costs (including estimate of ITU stay)
CABG redo	Per episode	8368	As index procedure + £500
Emergency CABG post-PCI failure	Per episode	7161	2002 DOH Reference Costs (including estimate of ITU stay)
PTCA	Per episode	2156	Adapted from 2002 DOH Reference Costs
PTCA (excluding stents)	Per episode	2156	Adapted from 2002 DOH Reference Costs
Single uncoated stent	Per stent	380	From industry submission
Single DES	Per stent	900	Medium estimate from industry submissions
Cardiac rehabilitation	Per course	500	Cost per course in NW England
Early complications			
Acute renal failure episode	Per episode	1680	Non-elective L49 in 2002 DOH Reference Costs
Severe bleeding episode post-PTCA	Per episode	1000	Authors' estimate
Severe bleeding episode post-CABG	Per episode	2000	Authors' estimate
Follow-up			
Cardiology outpatient review post-PTCA	Per attendance	63	E16op from 2002 DOH Reference Costs
Cardiac surgery outpatient review post-CABG	Per attendance	111	outpatient f-up attendance for specialty 170 from 2002 DOH Reference Costs
Clopidogrel	Per week	9	BNF
Recurrence of symptoms			
Cardiology outpatient review	Per attendance	63	E16op from 2002 DOH Reference Costs
Angiography	Per investigation	278	E02op from 2002 DOH Reference Costs
Repeat revascularisation procedure			
PTCA		2156	Adapted from 2002 UK Reference Costs
PTCA (excluding stents)		2156	Adapted from 2002 UK Reference Costs
CABG redo	Per episode	8368	As index procedure + £500
Acute events			
AMI episode – fatal	Per episode	814	Non-fatal AMI reduced by 20%
AMI episode – non-fatal	Per episode	1017	E11/E12 from 2002 DOH Reference Costs
Cardiology outpatient review post-AMI	Per attendance	63	E16op from 2002 DOH Reference Costs
CVA episode – fatal	Per episode	1600	Non-fatal CVA reduced by 20%
CVA episode – non-fatal	Per episode	2124	A22/A23 from 2002 DOH Reference Costs
General physician outpatient review post-CVA	Per attendance	87	outpatient f-up attendance for specialty 300 from 2002 DOH Reference Costs

Model assumptions and parameter estimates

Mortality

The metamodel described above of mortality in multiple-vessel disease for CABG and conventional stenting is used as the basis of mortality estimates. The metamodel short-term mortality rates have been adjusted to reconcile them with figures for two-vessel disease obtained from the CTC registries for CABG and stented patients. For stent and DES patients with single-vessel disease, we apply a global pro rata reduction of 26% to all mortality rates, based on a meta-analysis that we carried out of large registry studies and long-term trials reporting mortality for single- and two-vessel disease. Results employed were from the APPROACH registry,[225] BARI trial and registry,[226] supplemented by the NHLBI PTCA registry[227] and a review of seven trials by Yusuf and colleagues.[115]

Finally, a modifiable treatment effect parameter is included in the model which allows general adjustment of mortality rates for DES patients if evidence of differential mortality rates becomes available. At present, no modification is applied, as current DES versus stent trials fail to show survival differences.

Acute myocardial infarction (AMI)

This category relates only to events requiring acute medical intervention, and excludes 'silent' or minor events confirmed only by later follow-up investigation. For two-vessel disease, we assume that 50% of deaths are due to AMI and that 75% of AMIs are non-fatal. The results have been confirmed as compatible with CTC audit results. In the case of single-vessel disease, we assume that only 26% of deaths are attributable to AMI, and that 75% of AMIs are non-fatal. These assumptions are in line with the audit findings.

Cerebrovascular accident

This category relates only to events requiring acute medical intervention, and excludes transient or minor events confirmed only by later follow-up investigation. In all cases, we assume that 10% of deaths are attributable to CVA and that 20% of CVAs prove fatal. The cumulative rates have been confirmed to be compatible with 1-year outcomes reported in SOS and ARTS for CABG and stented patients.

Repeat revascularisations

A metamodel similar to that described above was developed for any revascularisation. The metamodel incidence rates have been adjusted to reconcile them with figures for two-vessel disease obtained from the CTC registries for CABG and stented patients. A modifiable treatment effect parameter is included in the model which allows general adjustment of revascularisation rates for DES patients where evidence of differential revascularisation rates is available.

The type of repeat revascularisation is determined by the proportions shown in *Table 34*. No provision is made for use of brachytherapy since there is currently restricted access to this procedure in the UK.

It is important to recognise that any additional mortality associated with repeat revascularisations is already implicit within the projected survival profiles, and additional costs (e.g. for redo CABG) are reflected in higher unit costs. Therefore no additional modelling is required to represent future patterns of revascularisation in the model cohort.

Acute renal failure

Although trials and observational studies suggest acute renal failure occurs following revascularisation at a rate of 1–2%, our clinical advisors suggested that this very rarely results in extended treatment under the care of a non-cardiac specialist. From local figures in Liverpool, we estimate a general incidence of about 0.2% of all revascularisation cases, which we apply uniformly to all patients, since we lack sufficient patient numbers to distinguish different rates resulting from different index procedures. We assume that the costs of such care are equally spread over a 3-week period following the initial revascularisation.

Severe episodes of bleeding

Based on recent experience of patients transferred for treatment of severe bleeding in Liverpool, we estimate an overall incidence rate of 0.3% of all cases, although the appropriate rate will depend upon the definition used for severe bleeding. In cases where the bleeding was treated within the original episode of care, then the cost would have been incorporated proportionately into the baseline cost for CABG and PCI. The 0.3% of patients identified as experiencing severe bleeding relates to patients whose bleeding was of sufficient severity to require an entirely separate episode of care. In such exceptional circumstances, severe bleeding of this nature would not be incorporated into baseline reference costs.

For the purpose of costing, we have assumed that bleeding post-CABG is twice as costly as that post-PCI.

Outpatient follow-up

A standard regimen is assumed for hospital follow-up of all revascularisation episodes (index and repeat) as follows, based on opinion from several clinical advisers:

For CABG:

- one outpatient consultation with cardiac surgeon 4 weeks following discharge
- four outpatient consultations with cardiologist at 4, 8, 12 and 26 weeks postdischarge
- one course of community-based cardiac rehabilitation over 4 weeks.

For stenting:

- four outpatient consultations with cardiologist at 4, 8, 12 and 26 weeks postdischarge
- one course of community-based cardiac rehabilitation over 4 weeks
- clopidogrel therapy for 4 weeks postdischarge.

Continuing drug use

In line with the findings of ARTS, we assume that a proportion of patients will no longer need antianginal drugs following a successful revascularisation, although those agents with other beneficial effects (antihypertensive and lipid-lowering) are presumed to continue. Based on ARTS findings, we assume that 6 weeks after the initial procedure 20% of PTCA patients and 40% of CABG patients have anti-anginal medication withdrawn (digitalis, beta-blockers, calcium channel blockers and nitrates) where not required for another therapeutic or preventive purpose.

In view of the likely continuing regular contacts of patients with their GPs, we make no assumption of any change in the number of GP consultations following discharge from hospital.

Recurrence of symptoms

In line with our earlier discussion, we assume that recurrence of new symptoms leading to a repeat intervention is carried out with equal despatch regardless of the intended mode of treatment. We assume each patient sees a cardiologist 1.3 times and has 1.15 angiographies 4 weeks prior to the repeat procedure. Where stents are implanted in these cases, we assume 1.3 BMS or 1.1 DES are used, based on clinical opinion (conservative in favour of DES).

Treatment for AMI and CVA

In line with our assumptions about the inclusive nature of Reference Costs, we assume that very early AMI/CVA events are included in the index episode for costing purposes (within 7 days for PTCA and 14 days for CABG). All other episodes are costed separately at an appropriate Reference Cost. Subsequently, all patients surviving AMI or CVA will have two outpatient follow-up consultations at 4 and 13 weeks with a cardiologist or general physician, respectively.

Utility values

Most of the utility values employed in the model are derived from the EQ-5D results published for the ARTS trial. Utility effects are calculated in the model as decrements relative to an assumed baseline (asymptomatic CHD) value of 0.86 (from ARTS). Effects of procedures and adverse events are assumed to be time limited, except in the case of stroke, where we anticipate that a proportion of surviving patients will suffer from continuing loss of utility (arbitrarily set at 0.3 on the EQ-5D scale) associated with serious disability. We assume that this proportion increases following each subsequent CVA episode (10% for the first stroke, 15% for the second, 25% for the third and 50% for all subsequent events).

Time-limiting the effects of the other events implies that there is a single 'lump' of disutility attached to each event, albeit spread over a short period. Hence using the ARTS results for surviving post-CABG patients (EQ-5D 68 at baseline versus 86 at 6 months), we estimate a disutility of 0.012 QALY spread over 13 weeks, compared with 0.0035 QALY for surviving stented patients (based on EQ-5D 69 at baseline versus 86 at 6 months) spread over 6 weeks. We also assume that patients developing new anginal symptoms prior to a repeat revascularisation will lose 0.02 QALY over a 6-week period. For non-fatal AMI, a more speculative value of 0.1 QALY has been assigned over 13 weeks. Although these disutility estimates are small and transient, they are entirely consistent with the ARTS findings, and suggest that claims to large QALY benefits, by avoidance of adverse events and in the absence of mortality gains, are likely to be unfounded.

Key evaluation parameters

Preliminary assessment of model behaviour clearly indicates that only a small number of variables are influential in determining the cost-effectiveness of DES relative to CABG or conventional stents. All other model parameters have very little quantitative effect, and do not affect the qualitative result in any way.

TABLE 36 *Cost-effectiveness of PTCA with BMS for two-vessel disease compared with CABG*

Time from initial procedure (years)	Cumulative incremental discounted cost (£)	Cumulative incremental discounted life-years	Cumulative incremental discounted QALYs	Incremental cost per life-year gained (£)	Incremental cost per QALY gained (£)
0	–4800	0	0	–	–
1	–4426	+0.0053	+0.011	–835,026	–421,070
2	–4298	+0.0077	+0.011	–560,638	–385,708
3	–4240	+0.0013	+0.004	–3,236,989	–1,041,971
4	–4183	– 0.0190	– 0.015	+220,467	+276,951
5	–4115	– 0.0591	– 0.051	+69,619	+80,841

These key variables are:

- the long-term rate of all revascularisations in patients undergoing PTCA with DES
- the reduction in cost of the index treatment if DES is used for patients currently receiving CABG surgery
- the additional cost of DES compared with conventional BMS for patients currently undergoing PTCA with stent
- and as the dominant element in the two previous items, the price differential between DES and conventional BMS.

Cost-effectiveness results

Comparing alternative treatments for two-vessel disease

PTCA plus bare metal stenting versus CABG

Model results for conventional stenting as an alternative to CABG in the treatment of uncomplicated two-vessel disease are the most secure, being based directly on the combined results of ARTS, SOS and ERACI II. These are shown in *Table 36* at annual intervals for 5 years follow-up and graphically in *Figure 27*.

An initial cost saving of £4800 per patient is reduced during the first year by about £400, and thereafter a further £300 is trimmed from the savings. During the first year, patients benefit from a very modest QALY improvement, but after 39 months this advantage is reversed and QALY losses then accumulate in longer-term follow-up. In this case, because of the presence of negative values for both incremental costs and benefits, ICERs cannot be interpreted intuitively. In the long term, PTCA with plain stents remains unequivocally cheaper than CABG, but clinical and utility outcomes are less satisfactory. The positive ICERs shown in *Table 36* indicate that if PTCA with stenting had been the established baseline treatment for two-vessel disease, then CABG would have been seen to offer some long-term improvements in survival and health-related utility, with a modest additional cost per patient, such that CABG may have been considered a possible cost-effective replacement treatment when considered over 5–10 years.

PTCA with DES versus CABG

The lack of reliable evidence of efficacy for DES with follow-up longer than 12 months introduces additional uncertainty into all comparisons involving DES. Here we have assumed that mortality is the same as for conventional stenting (in the absence of any evidence to the contrary). The main claim for DES is of reduced rates of repeat revascularisation, but we are not able to quantify this effect reliably from available trial evidence. The base-case evaluation has been conducted on the basis of a reduction in total repeat revascularisation rates of 30% (relative to BMS). The other principal uncertainty is the price differential between BMS and DES. We have set this at a modest £520 for the base case – considerably less than that implied by the list price of the only DES currently available in the UK.

The findings for the base case are also displayed in *Figure 27* and are reported in detail in *Table 37* at annual intervals for 5 years follow-up. They follow a very similar pattern to those obtained above for BMS. The main difference is that the net cost saving over CABG at 5 years is about £1000 less than we found for conventional stenting (mainly due to the price difference). However, the long-term loss of QALYs is very similar to that seen with BMS despite fewer repeat procedures. Hence the general conclusion is confirmed that PTCA with DES also results in reduced costs at the expense of reduced health-related utility, when compared with CABG.

To assess the effect of the two main sources of uncertainty on this finding, we carried out a two-way sensitivity analysis over a very broad range of

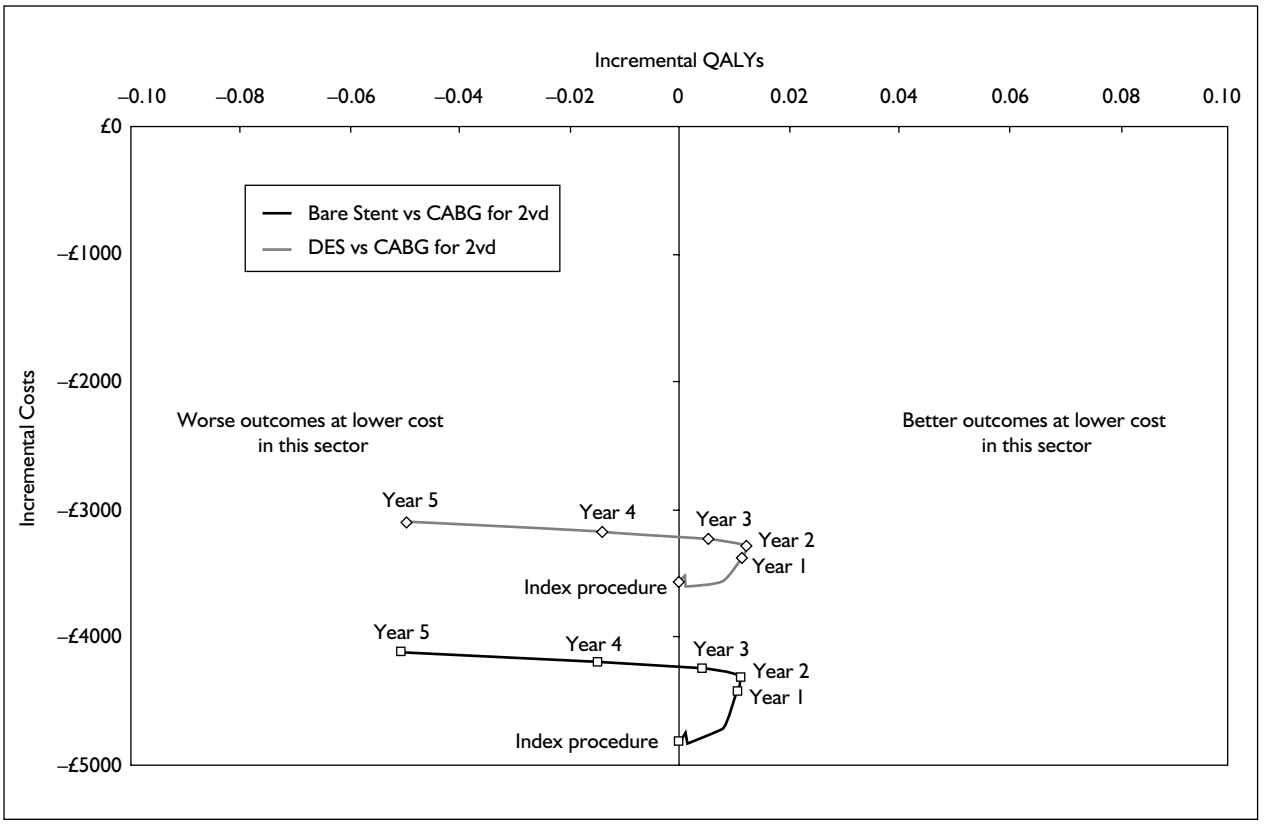


FIGURE 27 *Cost-effectiveness of PTCA plus BMS or DES compared with CABG for elective uncomplicated two-vessel disease*

TABLE 37 *Cost-effectiveness of PTCA with DES for two-vessel disease compared with CABG*

Time from initial procedure (years)	Cumulative incremental discounted cost (£)	Cumulative incremental discounted life-years	Cumulative incremental discounted QALYs	Incremental cost per life-year gained (£)	Incremental cost per QALY gained (£)
0	–3552	0	0	–	–
1	–3355	+0.0053	+0.011	–633,045	–299,288
2	–3270	+0.0077	+0.012	–426,532	–271,851
3	–3220	+0.0013	+0.005	–2,458,803	–644,783
4	–3165	– 0.0190	– 0.014	+166,843	+223,408
5	–3098	– 0.0591	– 0.050	+52,411	+61,999

feasible values, as summarised in *Table 38*. The impact of varying the efficacy of DES on repeat revascularisations is minimal for QALY values (being limited to only short periods of variation before and after the repeat procedures), but does alter costs by from +£175 to –£400 per patient. Hence although in all cases PTCA + DES remains cost-saving, it still leads to worse long-term outcomes in the absence of any survival benefit.

PTCA plus DES versus PTCA plus plain stenting

Where patient preference or clinical opinion currently leads to the use of PTCA with BMS for patients suffering uncomplicated two-vessel disease, we consider whether substitution of DES is a cost-effective alternative. In this case a very simple picture emerges as detailed in *Table 39* for up to 5 years of follow-up.

The additional cost is composed largely of the additional cost of DES, and therefore is fully realised within 2–3 years. The projected utility gain is extremely small since it arises only from reduced HRQoL in patients requiring repeat revascularisation in a short period before and after the additional intervention. Without any confirmed survival benefit, the identifiable QALY gain achievable is very limited.

Our base case assumes that any benefit continues to accumulate as repeat revascularisation rates are

TABLE 38 *Main sensitivity analysis of PTCA with DES for two-vessel disease compared with CABG*

	Relative reduction in any repeat revascularisation for DES compared with BMS					
	0%	–15%	–30% (base)	–50%	–75%	–100%
	Incremental QALYs at 5 years follow-up					
	–0.051	–0.051	–0.050	–0.049	–0.049	–0.048
DES unit price excess (£)	Incremental costs at 5 years follow-up (£)					
0	–4174	–4262	–4349	–4466	–4612	–4758
250	–3571	–3659	–3747	–3865	–4012	–4158
520 (base)	–2920	–3009	–3098	–3216	–3363	–3511
750	–2366	–2455	–2544	–2663	–2811	–2960
1000	–1763	–1852	–1942	–2062	–2211	–2361
1250	–1160	–1250	–1340	–1460	–1611	–1761

TABLE 39 *Cost-effectiveness of PTCA with DES for two-vessel disease compared with PTCA with stents*

Time from initial procedure (years)	Cumulative incremental discounted cost (£)	Cumulative incremental discounted life-years	Cumulative incremental discounted QALYs	Incremental cost per life-year gained (£)	Incremental cost per QALY gained (£)
0	+1248	0	0	–	–
1	+1071	0	+0.0007	–	+1,529,445
2	+1028	0	+0.0009	–	+1,161,430
3	+1019	0	+0.0009	–	+1,101,030
4	+1017	0	+0.0009	–	+1,088,891
5	+1017	0	+0.0009	–	+1,086,356

reduced for an indefinite period after the initial procedure. It can be argued more conservatively that the impact of a drug coating will be limited to the first few months prior to the leaching of all the active drug from the device. If this is assumed, then the full impact would be apparent after about 12 months, suggesting an even greater ICER than that shown in *Table 39*. As yet, the longer-term follow-up results are not available to allow a clear decision to be made on this issue. At present, we are inclined to favour the view that the advantage of DES is likely to attenuate only slowly over several years, largely from development of *de novo* lesions in other vessels or segments. Therefore, we feel that the base-case ICER at 5 years may prove to be somewhat optimistic.

A sensitivity analysis was performed in which the most optimistic scenario for the efficacy of DES was employed – that DES eliminated **all** repeat revascularisations indefinitely. On this basis, we estimate that if the excess cost per DES over BMS is only £98, then costs are equivalent (i.e. 'break-even') at 5 years. To achieve an ICER of £30,000 per QALY gained, the excess DES cost should be no more than £110, and for an ICER of £50,000 per QALY gained the excess should be no greater than £117 per stent. This narrow range of DES price premiums does not correspond to any of the prices suggested in industry submissions.

Summary

CABG is always more expensive than PTCA, whether using conventional stents or DES, by several thousand pounds per patient. However, an initial QALY and survival advantage to PTCA with stent soon disappears as survival benefit to CABG begins to accrue. After equivalence of outcomes is achieved at about 3–4 years, CABG continues to accrue substantial life-year and QALY advantage, without any further additional cost. Hence switching from CABG to PTCA with stent for patients with ordinary risk two-vessel disease will save the NHS money in the short term but can be expected to reduce patients' life expectancy considerably. On clinical grounds, therefore, CABG remains the 'gold standard' treatment for this large group of patients, except in cases where there are very good grounds for anticipating that a patient's expected survival after successful CABG

TABLE 40 *Cost-effectiveness of PTCA with DES for single-vessel disease compared with PTCA with BMS*

Time from initial procedure (years)	Cumulative incremental discounted cost (£)	Cumulative incremental discounted life-years	Cumulative incremental discounted QALYs	Incremental cost per life-year gained (£)	Incremental cost per QALY gained (£)
0	+676	0	0	–	–
1	+549	0	+0.0005	–	+1,099,858
2	+520	0	+0.0006	–	+825,512
3	+513	0	+0.0007	–	+780,442
4	+512	0	+0.0007	–	+771,347
5	+512	0	+0.0007	–	+769,434

would be less than about 4 years, in which case PTCA with stent is preferred. In such cases, or where patients elect for PTCA with stent, the evidence so far available suggests that use of DES cannot be justified since the substantial additional costs are unlikely to yield significant additional benefit beyond that obtained by use of currently available BMS, unless the price premium charged for DES is substantially less than is currently envisaged.

BMS versus DES for single-vessel disease

As previously observed, the great majority of uncomplicated single-vessel disease is treated in the UK by PTCA with plain stent(s). Registry data in Liverpool suggest that revascularisations at 12 months for this patient group are 28% lower than in the comparable group with two-vessel disease, and this was used to estimate reintervention rates in this case. We then modelled whether the substitution of DES for BMS could be considered a valid cost-effective alternative to current practice. The results are displayed in *Table 40* for up to 5 years of follow-up.

The additional costs incurred are lower than was the case for two-vessel disease, mainly because the mean number of stents required falls from 2.4 to 1.3 per patient. However, the very small QALY gains are also lower, in line with the lower rates of repeat interventions in single-vessel disease patients.

Again a sensitivity analysis was performed in which the most optimistic scenario for the efficacy of DES was employed – that DES eliminated **all** repeat revascularisations indefinitely. On this basis, we estimate that if the excess cost per DES over BMS is only £352, then costs are equivalent (i.e. 'break even') at 5 years. To achieve an ICER of £30,000 per QALY gained, the excess DES cost should be no more than £401, and for an ICER of £50,000 per QALY gained, the excess should be no greater than £434 per stent.

Once again we conclude that the use of DES for elective treatment of uncomplicated single-vessel disease cannot be justified, in that the claimed reduction in the need for repeat interventions has not been shown to result in more than very minor and uncertain utility gains, but certainly incur substantial additional net treatment costs for the NHS.

High-risk subgroups

The industry models seek to establish results supportive of DES on the basis of limiting use to specific high-risk patient subgroups, for example those with diabetes, long lesions or small-vessel disease. As there are only preliminary data from SIRIUS described in Chapter 6 and no reliable trial evidence of long-term efficacy and outcomes in these cases, they cannot be modelled directly. Instead, we have explored a range of trials and observational/registry studies to consider the relative risks of mortality and repeat revascularisation for such groups in comparison with uncomplicated cases. However, the evidence available is extremely limited and inconclusive on most of these issues. Long-term mortality rates are approximately doubled by diabetes, and may be trebled in patients with poor LVEF, regardless of the mode of treatment used. The presence of LM stem disease is particularly serious for patients undergoing PTCA. However, we have not been able to make similar assessments for revascularisation rates.

In order to investigate the impact of targeting DES on high-risk groups, we incorporated global risk modifiers into the model, allowing us to vary both mortality and repeat revascularisation risks in all treatments. *Table 41* summarises the results obtained for follow-up to 5 years for multiple-vessel disease scenarios, using a range of global risk modifiers from ×1.0 (base case) to ×5.0.

Figure 28 displays the results obtained for multiple-vessel disease comparisons involving PTCA with BMS or DES matched against CABG. It is clear that the case in favour of CABG is strengthened for higher risk patients, since the excess cost of CABG is progressively reduced and incremental benefits increased for patients at greater mortality and reintervention risks. Assuming a much-improved efficacy for DES does not materially alter this conclusion. Hence we are confident in concluding that CABG remains the treatment of choice for most high-risk patients.

Figure 29 displays the results obtained for multiple-vessel disease comparisons involving PTCA with DES matched against PTCA with BMS for those patients unable or unwilling to undergo CABG. In this case, the argument for use of DES is strengthened for higher risk patients, since the excess cost of DES is progressively reduced and incremental benefits increased for patients at greater mortality and reintervention risks. Assuming a much improved efficacy for DES has the effect of shifting downward the relative risk ratio at which DES would be considered a cost-effective alternative treatment to conventional stenting. Hence we conclude that DES may be suitable for some high-risk patients with multiple-vessel disease who would otherwise undergo PTCA with BMS, although the degree of elevated risk required to justify this change remains unclear until the true relative efficacy of DES in avoiding reinterventions is established. In our base-case scenario, it appears that only patients with multiple factors predisposing to higher risk would be suitable (e.g. diabetes **and** poor LVEF),

TABLE 41 *Impact of high-risk subgroup selection on cost-effectiveness in multiple-vessel disease*

BMS vs CABG for high-risk multiple-vessel disease at 5 years

Relative risk	Incremental cost (£)	Incremental QALYs	Cost per QALY gained (£)
×1.0	–4115	–0.0509	+80,841
×1.5	–3715	–0.0807	+46,044
×2.0	–3291	–0.1106	+29,765
×2.5	–2838	–0.1406	+20,189
×3.0	–2349	–0.1707	+13,764
×4.0	–1233	–0.2315	+ 5,327
×5.0	–164	–0.2935	– 559

DES vs CABG for high-risk multiple-vessel disease at 5 years

	Assuming 30% DES efficacy			Assuming 75% DES efficacy		
Relative risk	Incremental cost (£)	Incremental QALYs	Cost per QALY gained (£)	Incremental cost (£)	Incremental QALYs	Cost per QALY gained (£)
×1.0	–3098	–0.050	+61,999	–3363	–0.049	+69,149
×1.5	–2825	–0.079	+35,651	–3237	–0.077	+41,929
×2.0	–2537	–0.109	+23,364	–3105	–0.106	+29,359
×2.5	–2230	–0.138	+16,162	–2966	–0.134	+22,087
×3.0	–1901	–0.167	+11,350	–2821	–0.163	+17,318
×4.0	–1154	–0.227	+ 5,088	–2499	–0.220	+11,355
×5.0	– 227	–0.287	+ 792	–2115	–0.277	+ 7,623

DES vs BMS for high-risk multiple-vessel disease at 5 years

	Assuming 30% DES efficacy			Assuming 75% DES efficacy		
Relative risk	Incremental cost (£)	Incremental QALYs	Cost per QALY gained (£)	Incremental cost (£)	Incremental QALYs	Cost per QALY gained (£)
×1.0	+1017	+0.0009	+1,086,356	+ 751	+0.0023	+332,904
×1.5	+ 890	+0.0015	+ 613,823	+ 479	+0.0035	+136,918
×2.0	+ 755	+0.0020	+ 376,843	+ 187	+0.0048	+ 38,661
×2.5	+ 608	+0.0026	+ 234,014	– 129	+0.0063	– 20,528
×3.0	+ 449	+0.0032	+ 138,188	– 471	+0.0078	– 60,207
×4.0	+ 80	+0.0048	+ 16,751	– 1265	+0.0115	– 110,403
×5.0	– 391	+0.0067	– 58,482	– 2279	+0.0161	– 141,357

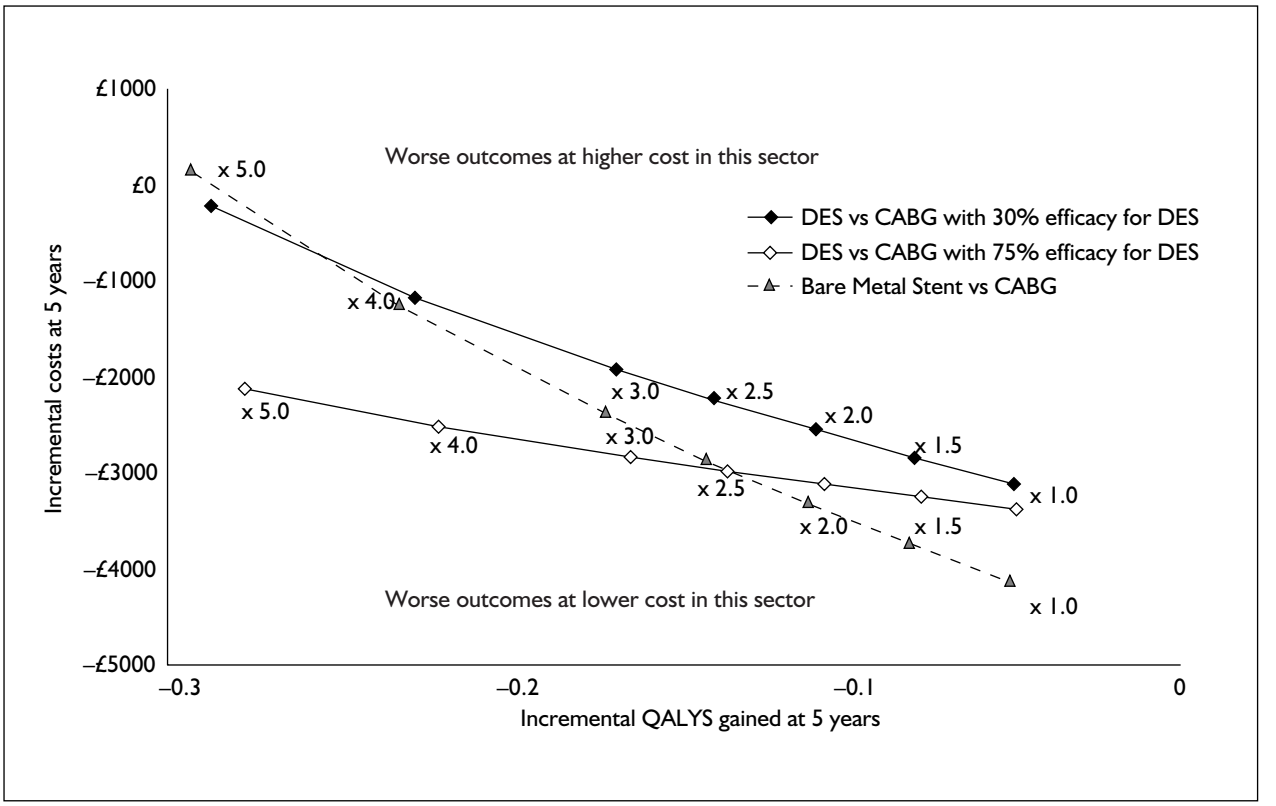


FIGURE 28 *Cost-effectiveness of PTCA with plain stent or DES compared with CABG for elective multiple-vessel disease in high-risk patients*

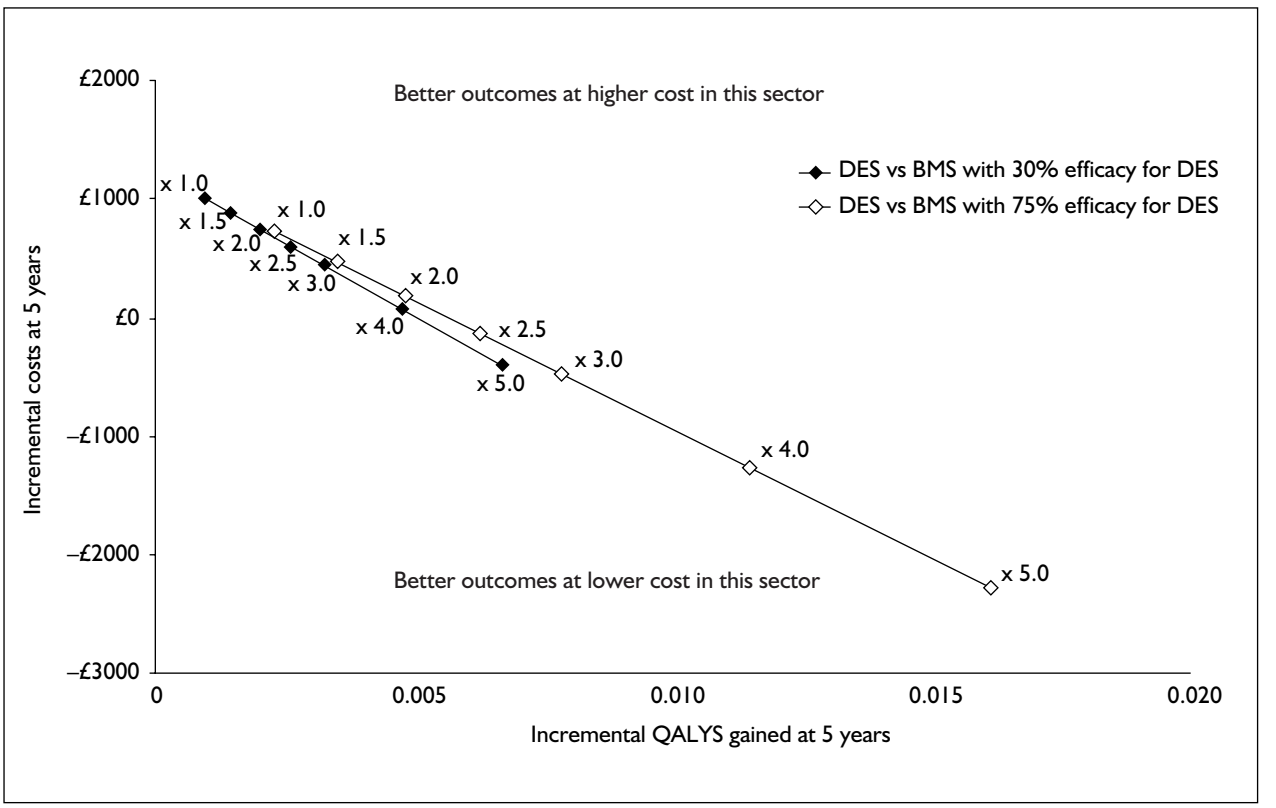


FIGURE 29 *Cost-effectiveness of PTCA with DES compared with PTCA with BMS for elective multiple-vessel disease in high-risk patients unable or unwilling to undergo CABG*

TABLE 42 *Impact of high-risk subgroup selection on cost-effectiveness in single-vessel disease: DES vs BMS for high-risk single-vessel disease at 5 years*

DES vs BMS for high-risk multiple-vessel disease at 5 years						
	Assuming 30% DES efficacy			Assuming 75% DES efficacy		
Relative risk	**Incremental cost (£)**	**Incremental QALYs**	**Cost per QALY gained (£)**	**Incremental cost (£)**	**Incremental QALYs**	**Cost per QALY gained (£)**
×1.0	+512	+0.0007	+769,434	+ 323	+0.0016	+201,364
×1.5	+424	+0.0010	+415,864	+ 135	+0.0025	+ 54,714
×2.0	+333	+0.0014	+238,848	– 63	+0.0034	– 18,685
×2.5	+236	+0.0018	+132,439	– 270	+0.0043	– 62,789
×3.0	+135	+0.0022	+ 61,319	– 488	+0.0053	– 92,249
×4.0	– 87	+0.0031	– 28,034	– 965	+0.0075	–129,215
×5.0	– 340	+0.0041	– 82,213	–1509	+0.0100	–151,568

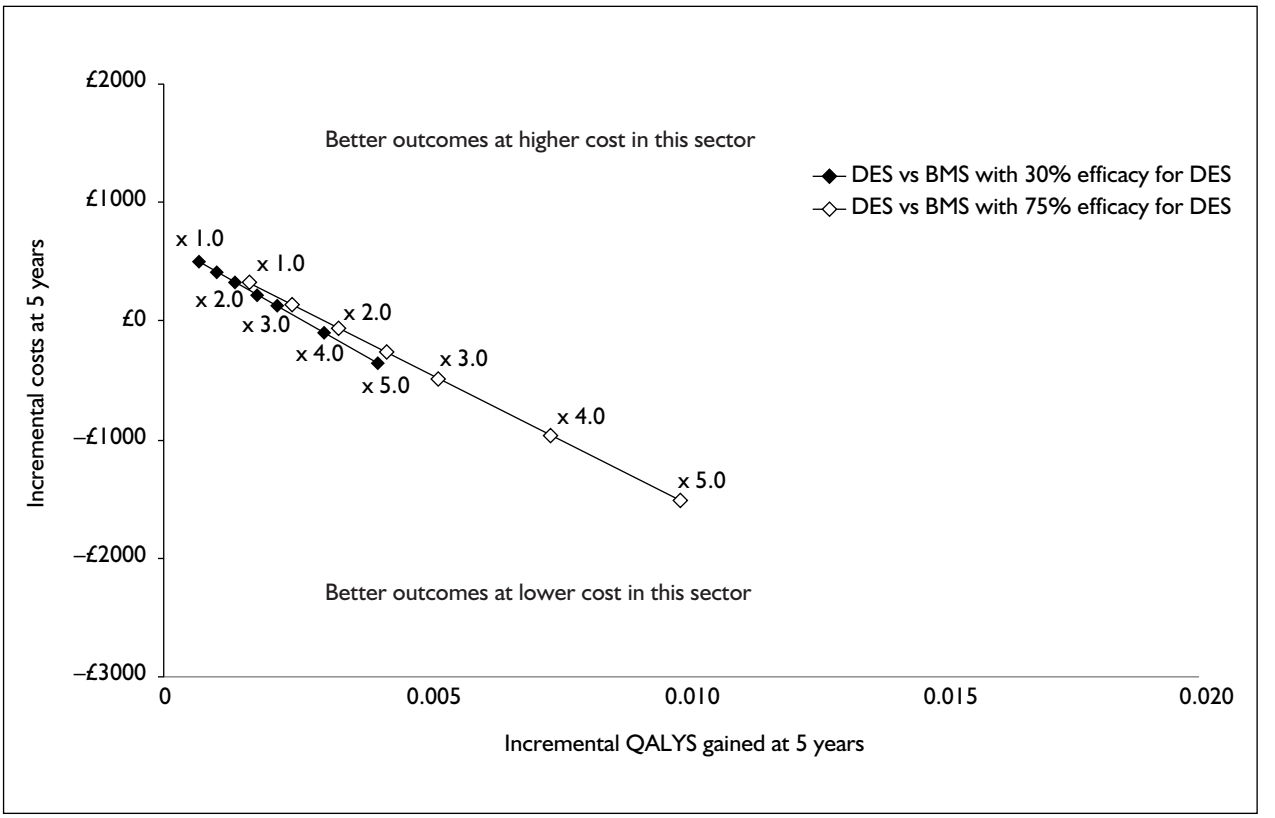


FIGURE 30 *Cost-effectiveness of PTCA with DES compared with PTCA with BMS for elective single-vessel disease in high-risk patients*

although it may be argued that some of these patients would in fact be more suitable for CABG.

Table 42 similarly summarises the results obtained for follow-up to 5 years for single-vessel disease, using a range of global risk modifiers from ×1.0 (base case) to ×5.0. *Figure 30* displays the results obtained for the single-vessel disease comparison between PTCA and BMS or PTCA with DES. The findings here are very similar to those obtained for multiple-vessel disease where BMS would otherwise be used, although here the risk threshold appropriate for switching on cost-effectiveness grounds is lower, suggesting a stronger case for single-vessel disease with other high-risk factors present.

Summary

Consideration of patient subgroups with predisposing high-risk conditions serves only to

TABLE 43 *Univariate SA of incremental cost after 5 years follow-up*

Comparison:		**DES vs CABG for 2vd**	**BMS vs CABG for 2vd**	**DES vs BMS for 2vd**	**DES vs BMS for 1vd**
Base case incremental cost:		**–£3,098**	**–£4,115**	**£1,017**	**£512**
Factor varied	**Variation**	**Effect (£)**	**Effect (£)**	**Effect (£)**	**Effect (£)**
CABG procedure cost	±10%	±782	±768	± 14	± 10
PCI procedure cost	±10%	±216	±216	± 0	± 0
All stents cost	±£100	±250	±249	± 1	± 1
Cardiac rehabilitation cost	±10%	± 54	± 56	± 2	± 1
Acute renal failure cost	±10%	± 0	± 0	± 0	± 0
Severe bleeding cost	±10%	± 0	± 0	± 0	± 0
Outpatient costs	±10%	± 8	± 6	± 2	± 1
Clopidogrel cost	±10%	± 4	± 4	± 0	± 0
Angiography cost	±10%	± 3	± 4	± 1	± 1
AMI episode cost	±10%	± 10	± 10	± 0	± 0
CVA episode cost	±10%	± 4	± 4	± 0	± 0
Antianginal drugs cost	±10%	± 3	± 3	± 0	± 0
Long-term care costs	±10%	± 2	± 2	± 0	± 0
No. of angiographies per repeat intervention	±0.15	± 5	± 7	± 2	± 1
Stents per patient in 1vd	±0.25	–	–	–	±130
Stents per patient in 2vd	±0.3	±270	±114	±156	–
BMS stents per re-procedure	±0.2	± 5	± 5	± 0	± 0
DES stents per re-procedure	±0.1	± 1	± 0	± 1	± 1

1vd, single-vessel disease; 2vd, two-vessel disease.

strengthen the conclusion that CABG is the 'gold standard' treatment of choice in multiple-vessel disease, where not contraindicated or where expected post-CABG survival is 3 years or more. In single-vessel disease, or for other patients who would normally undergo PTCA with BMS, the use of DES may be cost-effective for patients with multiple predisposing high-risk conditions (i.e. with a net relative risk of mortality/reintervention 3–4 times that of uncomplicated cases receiving PTCA with BMS).

Sensitivity analysis

A detailed sensitivity analysis (SA) has been undertaken of the various model parameter values for the base-case scenario comparisons. *Table 43* shows the results for variables related to unit costs or to resource use. These only have effects on the incremental costs of each comparison and do not alter results for life-years of QALYs. Most factors result in only trivial variations in costs, the exceptions being those items directly related to the cost of the initial intervention, which have already been explored more fully above.

Table 44 shows similar results for the utility values derived from ARTS and for the proportion of CVA survivors incurring severe disability. The variations in ARTS utilities represent 95% CIs on the 'healthy' EuroQol score and on the differences between states. Once again the effects on incremental QALYs and consequently on ICERs are very small.

Overall we conclude that the results reported above from application of our model are not vulnerable to uncertainty in particular model parameter values.

Discussion

At first sight, it may appear that conclusions in the meta-analysis (e.g. no difference in mortality between CABG and stenting) are contrary to those described here in the context of economic modelling (possible survival advantage for CABG). The key difference is that different analytic approaches are required to answer different but complementary questions – 'What has happened to date?' and 'What should we expect to happen in the future?' We therefore need to project forward using the best data to hand – the survival curves for the relevant studies rather than the point estimates used in the meta-analysis. In the absence of such survival curves in a validated source from the ARTS study, we were unable to incorporate any results beyond 12 months.

TABLE 44 *Univariate SA of incremental QALYs and ICERs after 5 years follow-up*

Comparison		DES vs CABG for 2vd		BMS vs CABG for 2vd		DES vs BMS for 2vd		DES vs BMS for 1vd	
		Incremental QALYs	ICER	Incremental QALYs	ICER	Incremental QALYs	ICER	Incremental QALYs	ICER
Base-case incremental QALYs/ICER at 5 years:		**–0.049960**	**£44,876**	**–0.050896**	**£64,033**	**0.000936**	**£1,086,356**	**0.000665**	**£769,434**
Factor varied	**Variation**	**Effect**	**Effect (£)**	**Effect**	**Effect (£)**	**Effect**	**Effect (£)**	**Effect**	**Effect (£)**
Base healthy utility	+0.01	+0.000557	+495	+0.000557	+694	0.000000	0	0.000000	0
	– 0.01	– 0.000557	– 506	– 0.000557	– 709	0.000000	0	0.000000	0
Disutility effects	+10%	+0.000203	+182	+0.000297	+372	0.000094	+98,760	– 0.000067	+69,949
	– 10%	– 0.000203	– 183	– 0.000297	– 376	+0.000094	– 120,706	+0.000067	– 85,493
Proportions disabled	+10%	+0.000061	+ 87	+0.000061	+108	0.000000	0	0.000000	0
	– 10%	– 0.000061	– 87	– 0.000061	–108	0.000000	0	0.000000	0

1vd, single-vessel disease; 2vd, two-vessel disease.

Although ideally we would want to project outcomes for the remainder of patients' lives, in practice it is necessary to compromise so as not to overreach the validity of the trial data to hand. Here, although initially intending to evaluate treatments over a 10-year time horizon, we finally settled for projecting to just 5 years (2 years beyond the published data). This seemed to be the minimum period necessary to indicate the likely trend in cost-effectiveness in the long-term.

The same parametric model formulation was used for both mortality and repeat revascularisation, although for slightly different reasons. In the case of mortality, it is generally accepted that all invasive procedures carry a peri-procedural risk, and that for some patients an elevated risk remains discernible for several weeks thereafter. In the medium and long term, a much lower mortality rate is evident. However, partly due to the effects of advancing age and partly to the continuing natural progression of CAD, hazard rates tend to increase steadily over time.

The need for repeat revascularisation (generally due to recurrence of symptoms) similarly involves two distinct stages: an early phase when restenosis or even occlusion can occur within hours or days, and a late phase involving either restenosis of the intervention vessel or progression of disease in other vessels. In this case, it is less obvious whether hazard rates would increase or decrease in the long term, and a parametric model should be able to accommodate either possibility. To encompass both outcomes, the chosen parametric model involves two subpopulations: a small group subject to early death/reintervention (subject to a high fixed hazard rate), and the larger group for whom a lower initial hazard rate may increase or decrease over time (represented by a Weibull function). We believe that this formulation is consistent with generally accepted notions of the natural history of the condition, and sufficiently flexible to represent faithfully the trend information encompassed in trial data, allowing some measure of confidence in extrapolating modestly in time beyond the available evidence.

The modelling methodology followed in this review is different from those used in any of the industry submissions, using an approach rarely taught or applied currently in health economics, although well known in other contexts. We believe that this is a result of an overemphasis on assessments of short-term/acute interventions generally and consequently of over-reliance on a limited armamentarium of techniques. There seems to be a failure in the health economics community to recognise the particular difficulties and challenges of modelling chronic diseases over extended time periods, and that these can only be faced by adopting a more eclectic and imaginative outlook in model design and formulation.

Conclusions of economic modelling

Despite a large amount of interest in the new technology developed for percutaneous cardiac interventions, and a number of recent trials under way or reporting early results, it is clear that a full and conclusive economic evaluation of DES is not yet possible. This is principally due to the chronic nature of cardiac arterial disease, so that medium/long-term follow-up of a substantial number of patients is required (5–10 years) before conclusions can be drawn on the primary outcome – survival. In the absence of such evidence for DES we have assumed the default position that there is not yet evidence that any additional survival advantage is achieved over that afforded by conventional stenting. Indeed, there are cogent arguments both for and against such a proposition so that it is by no means obvious that such a survival benefit should be expected.

In the absence of changes in mortality risk, there are two changes we can anticipate from substituting the new technology, both based on the claim of a reduced incidence of recurrent symptoms requiring reintervention: improved HRQoL and reduced net cost to the health and social services. Our model has demonstrated that the likely quality of life benefits are relatively small, principally because of their short-term nature. The issue of cost differences is largely dominated by the price premium charged or anticipated by manufacturers for DES. A two-way sensitivity and threshold analysis has demonstrated that with current prices DES may only be considered cost-effective substitutes for BMS in patients at the highest (probably multiple) risk of early mortality and incidence of repeat revascularisation. However, some of these patients may be more suitable on clinical grounds for either medical therapy or CABG.

In the case of multiple-vessel disease, the accumulated trial evidence comparing CABG with PTCA with BMS is sufficient to project over 5 years an important and substantial survival advantage for CABG over PTCA with BMS. Given that CABG is the standard therapy for most

patients with multiple-vessel disease, it is difficult to justify substitution by a less effective treatment simply on the grounds that it is cheaper. This argument remains valid also in the case of DES, since the apparent additional benefits from fewer reinterventions and consequent QoL gains are balanced by the extra costs of the new stents. Hence we find no grounds for direct substitution of CABG by DES in multiple-vessel disease. Indeed we find that higher risk individuals gain greater relative benefit from CABG, not less.

Future research

The key issue in this debate is that of mortality and survival. This can only be resolved when current and future trials have been followed up for a sufficient time (3–5 years) and in sufficient numbers to allow comparisons to be made for DES similar to those we have performed for CABG and conventional stents (ARTS, SOS and ERACI II). However, this may not be merely a question of allowing current trials to continue, since most of these are already compromised by protocol-driven angiography after 6 months, influencing clinical decisions to reintervene. There may be a case for mounting a large-scale RCT to resolve the matter, but there is a serious danger that this would be overtaken by events, owing to a combination of commercial and professional pressures long before it reported. In any event, it is important that present and future triallists should be encouraged to collect and report outcomes relevant to full evaluation, in preference to short-term interim process measures. In particular, all studies should report **all** outcomes (deaths, AMIs, CVAs and revascularisations), not just those deemed to be related to particular lesions or vessels.

At the same time as PTCA with stents has been undergoing important changes, cardiac surgery techniques have also been developing. This has not been a subject for detailed investigation or evaluation here, and without a commercial imperative it has not attracted the level of exposure or promotion seen for DES. Nonetheless, there are indications in the literature that minimally invasive and 'off-pump' surgery is likely to require reduced lengths of hospital stay and produce better outcomes than conventional bypass surgery. Hence it would be unbalanced to consider new PCI technologies without also including newer surgical strategies. We believe that there is a strong case for supporting large RCTs to assess the relative merits of these techniques in comparison with the various alternative treatments – conventional and innovative.

Part B: further economic evaluation (completed at the request of the Appraisal Committee)

Economic modelling: exploration of the sources of differences between cost-effectiveness models of coronary stenting prepared in evidence for the NICE Appraisals Committee

Introduction

This section details an investigation into the sources of apparently large differences in ICERs between the two industry models submitted in evidence to NICE, and the model prepared by the Liverpool review group (LRIG) for assessing DES in comparison with BMS.

Boston Scientific Ltd – TAXUS model

The Boston Scientific economic model is based on the results of TAXUS II using clinical results after 6 months. The model can be run with five distinct patient subgroups:

- all TAXUS II patients (single-vessel *de novo* disease)
- diabetic patients
- patients with a small diseased vessel 2.5–3 mm
- patients with a small diseased vessel <2.5 mm
- patients with long lesions.

To permit a direct comparison between the results of this model with those of the LRIG model, it is necessary to modify the input parameters of the 'patients' scenario to match the basic uncomplicated single vessel option in the LRIG model. It is also necessary to limit the model outputs to 6 months follow-up only.

Outcomes

The most important differences between the model outputs are in the health-related utility outcomes.

In the Boston model, for BMS a cohort of 1000 revascularised patients experience a total of 419.70 QALYs in the first 6 months of follow-up, that is, 0.41970 per patient.

However, in the case of TAXUS stenting, this rises to 426.57 QALYs (or 0.42657 per patient), giving a net incremental gain of 6.87 QALYs per 1000 patients (or +0.00687 per patient).

Procedural mortality
The first element of difference between the TAXUS and LRIG models involves mortality assumptions. LRIG assumes that there are no differences at all between BMS and TAXUS, but the Boston model employs the TAXUS II mortality figures directly based on a single death in the BMS trial arm, suggesting an apparent (non-significant) difference in procedural mortality of 0.4% in favour of TAXUS.

This accounts for a difference of +0.86 QALY per 1000 patients.

Procedural complications
In the TAXUS model, differences in the incidence rates of stroke and AMI recorded in the trial data are used directly, and lead to differences in the QALYs attributable to BMS and DES in the model. The difference for stroke (0.8 versus 0.4%) is non-significant. In the case of AMI, there appears to be a benefit for DES over BMS (1.5 versus 5.4%), but this effect is not sustainable in the context of the LRIG meta-analysis of taxane eluting stents. Therefore, in both instances, the LRIG model assumes that no difference exists.

These account for a difference of +0.34 QALY per 1000 patients.

Disutility of recurring symptoms
In the TAXUS model, all patients who require a repeat revascularisation within 6 months of the index procedure are assumed to suffer loss of HRQoL for an average period of 4.5 months while waiting for the second intervention, irrespective of the type of repeat revascularisation carried out (i.e. no differential in waiting times is assumed). This is unrealistic since it requires virtually all second interventions to take place in the last few weeks of the period, contrary to the evidence of virtually all studies that these events are spread fairly evenly over the first 6–9 months. By contrast, the LRIG model is based on Kaplan–Meier event-free survival plots, yielding realistic incidence rates for each week. Moreover, for those patients revascularised in the earlier part of the period, their waiting time is necessarily limited to the maximum time since the index procedure, so that a blanket application of an average waiting period to all patients is incorrect.

In the LRIG model, a typical waiting time of 6 weeks was assumed. This translates into an average time of 1.205 months for use in the TAXUS model.

This accounts for a difference of +0.04805 QALY per patient with a second procedure.

Disutility of repeat procedure
The TAXUS model makes no allowance for any disutility associated with recovery following a second intervention. However, in the LRIG model it is assumed that each CABG causes a quantum of disutility of 0.012 QALY spread over 13 weeks, and each PCI a quantum of 0.0035 over 6 weeks.

This accounts for a difference of –0.00350 QALY per patient with a second procedure.

Repeat revascularisation rates
The main source of outcome differences between the TAXUS and LRIG models is the estimated rate at which repeat revascularisations occur. This is generated by two elements: the baseline risk for patients receiving BMS in their index procedure and the proportionate reduction in this risk assumed to arise from substitution by DES.

In the TAXUS model, the 'all patients' scenario assumes that 14.1% of BMS patients undergo a second intervention within 6 months, but only 5.4% of DES patients do so (equivalent to a relative reduction of 61.7%). By contrast, the LRIG base-case scenario is based on 7.4% of uncomplicated single-vessel PCIs having another procedure in 12 months (equivalent to 5.0% at 6 months), and a relative risk reduction of 30% due to substitution with DES (30% was chosen to represent a more realistic figure of what reduction might actually be seen in clinical practice, based on the type of outcomes seen in the BENESTENT II study).

None of these values are directly comparable, owing to different definitions of both revascularisation and patient groups. The TAXUS patients include a mixture of patients with known risk factors for repeat intervention (diabetes, small vessels, long lesions, etc.), whereas the LRIG base case includes only patients without predisposing factors (diabetes, history of heart failure, low ejection fraction, etc.). Thus the LRIG baseline would be expected to be lower than that used in TAXUS. In the TAXUS model only TLRs are used (although there appears to be some ambiguity concerning TVRs), whereas the LRIG model is concerned with any revascularisation required by a patient, regardless of its origin. Since additional non-TLR, non-TVR interventions are not counted by TAXUS, the quoted risk reduction is likely to be diluted in the LRIG context, depending on the balance of new lesion type.

Within the TAXUS model, the incremental utility benefit attributable to DES due to reduced risk of repeat revascularisation can be estimated as

65.6 QALYs × (baseline rate) × (% reduction due to DES)/1000 patients

Summary for TAXUS model outcomes

Table 45 shows the outcome gains to be expected within the original TAXUS model for a range of combinations of baseline revascularisation risk and the efficacy rate of DES in reducing the need for reintervention. The bold figures indicate the scenarios preferred by Boston Scientific and LRIG (and correspondingly in subsequent table).

In *Table 46*, the changes described above have been implemented to obtain net outcome results from the TAXUS model using LRIG assumptions.

By comparing the TAXUS scenario in *Table 45* (+6.87) with the LRIG scenario in *Table 46* (+0.28), it can be seen that the Boston incremental gain is 24.5 times the size of that obtained with LRIG assumptions. Hence the ICER for DES versus BMS increases from £55,438 per QALY gained in the LRIG model to £1,359,659 per QALY gained in the Boston model, on the basis of differences in the estimation of HRQoL alone.

TABLE 45 *Unadjusted incremental QALYs gained per 1000 patients*

	Baseline revascularisation rate (6 months) (%)			
DES efficacy (%)	**5**	**10**	**14.1**	**20**
30	**+2.15**	+3.13	+3.94	+ 5.10
40	+2.48	+3.79	+4.86	+ 6.41
50	+2.80	+4.44	+5.79	+ 7.72
61.7	+3.19	+5.21	**+6.87**	+ 9.26
70	+3.46	+5.76	+7.64	+10.35

TABLE 46 *Incremental QALYs gained per 1000 patients on LRIG assumptions*

	Baseline revascularisation rate (6 months) (%)			
DES efficacy (%)	**5**	**10**	**14.1**	**20**
30	**+0.28**	+0.60	+0.85	+1.23
40	+0.39	+0.81	+1.15	+1.65
50	+0.49	+1.02	+1.45	+2.07
61.7	+0.61	+1.26	**+1.80**	+2.56
70	+0.70	+1.44	+2.04	+2.91

Costs

Differences in incremental costs are more difficult to reconcile accurately since they occur via several mechanisms within the model: the clinical assumptions (as described above for outcomes), resource use assumptions, unit costs and costing methodology differences. Indeed, it is not possible to reflect all differences by simply replacing parameter values within one model.

Table 47 shows the TAXUS model incremental costs per 1000 patients for a range of baseline revascularisation rates and DES efficacy, corresponding to the incremental outcomes shown in *Table 45*.

Some of the main sources of cost difference between the TAXUS model and the LRIG model have been identified as follows.

Procedure costs

Although both models use identical unit costs per stent, the average number of stents used per patient differs: 1.035 in TAXUS and 1.3 in LRIG. This leads to an additional net cost of £137,800 per 1000 patients in the LRIG model.

Procedural complications costs

In the same way that TAXUS model differences in outcomes all derive from non-significant trial differences, so also the TAXUS cost differences for procedural complications are all ignored in the LRIG model. In addition to stroke and AMI (discussed above), this also includes vascular bleeding where the trial incidence for BMS (3.3%) is very similar to that for DES (3.1%). All procedural complications account for a difference of £31,067 per 1000 patients.

Revascularisation costs

A complex interaction between several factors contributes to differences in repeat revascularisation costs:

TABLE 47 *Unadjusted incremental cost (£) per 1000 patients*

	Baseline revascularisation rate (6 months) (%)			
DES efficacy (%)	**5**	**10**	**14.1**	**20**
30	**653,132**	609,980	574,595	523,676
40	631,476	566,668	513,526	437,052
50	609,820	523,357	452,456	350,429
61.7	584,483	472,682	**381,005**	249,079
70	566,509	436,733	330,317	177,182

- baseline risk of repeat intervention
- reduction in risk attributable to use of DES
- distribution of patients between different types of repeat revascularisation
- number of stents used per intervention
- unit costs of procedures
- frequency of angiography
- outpatient consultations prior to reintervention.

Summary for TAXUS model costs

Aggregating all these readily identifiable differences between the TAXUS and LRIG models leads to adjusted estimates of incremental cost, based wherever possible on LRIG assumptions. These are shown in *Table 48*, allowing comparison with *Table 46*.

Incremental cost-effectiveness ratios

From *Tables 45–48* we can calculate ICERs for the original TAXUS and the adjusted model taking account of LRIG values and assumptions wherever possible. These are set out in *Tables 49* and *50*.

The ICER generated by the LRIG model directly is £1,891,326 per QALY gained, which although different from the corresponding estimate in *Table 50* (2,760,000) is of similar magnitude. In conclusion, we conclude that the major part of the apparent difference in ICER between the Boston Scientific and LRIG models is attributable to varying assumptions relating to health-related utility, especially to different baseline risks of repeat revascularisation, and the efficacy of DES in avoiding such reinterventions. Differences in costs, although important, contribute much less to the apparent difference.

Cordis – CYPHER model

The Cordis economic model is used to present results in respect of four patient subgroups:

- patients with single small-vessel disease
- patients with long lesions
- diabetic patients
- patients with multiple-vessel disease.

TABLE 48 *Incremental costs (£) per 1000 patients on LRIG assumptions*

	Baseline revascularisation rate (6 months) (%)			
DES efficacy (%)	**5**	**10**	**14.1**	**20**
30	**771,468**	713,582	653,183	583,537
40	757,770	665,538	591,008	490,515
50	724,814	618,331	527,368	397,889
61.7	694,477	561,060	**451,773**	289,597
70	678,538	524,953	396,305	213,137

TABLE 49 *Unadjusted incremental costs (£) per QALY gained*

	Baseline revascularisation rate (6 months) (%)			
DES efficacy (%)	**5**	**10**	**14.1**	**20**
30	**304,005**	194,731	145,862	102,673
40	254,995	149,579	105,571	68,157
50	217,449	117,756	78,155	45,366
61.7	183,328	90,692	**55,448**	26,900
70	163,711	75,869	43,240	17,122

TABLE 50 *Adjusted incremental costs (£) per QALY gained with LRIG assumptions*

	Baseline revascularisation rate (6 months) (%)			
DES efficacy (%)	**5**	**10**	**14.1**	**20**
30	**2,755,244**	1,189,304	768,451	474,420
40	1,943,000	821,652	513,920	297,282
50	1,479,212	606,207	363,702	192,217
61.7	1,138,487	445,286	**250,985**	113,124
70	969,340	364,551	194,267	73,243

Analysis for the first group is based on RAVEL clinical results, for the second and third groups on SIRIUS and BENESTENT II results and for the last group on ARTS results.

Since the model structure is common to the analyses presented, we carried out a comparison between the results of the multiple-vessel version of the model and the LRIG model by modifying the input parameters of the Cordis scenario to match the basic uncomplicated double-vessel option in the LRIG model. It is also necessary to limit the model outputs to 12 months follow-up only.

Outcomes

In the Cordis model, differences in health-related utility outcomes are generated solely by the delay between recurrence of angina symptoms and the timing of the repeat procedure, that is, the waiting time. In contrast to the LRIG formulation, no disutility is assigned to the repeat procedure itself. However, different assumptions are made in the Cordis models concerning the proportion of repeat revascularisations which would require a CABG, and this impacts on the incremental utility calculation.

There is an anomaly in the Cordis model in that an assumed average waiting time for CABG interventions is applied to patients identified with recurrent symptoms in the first year, truncated since most such patients are not expected to

receive the intervention within 12 months. However, it appears that the full cost of these repeat procedures is attributed to the first year of follow-up. This discrepancy has the effect of overstating the costs in the initial period.

Table 51 shows the outcome gains to be expected within the original Cordis model for a range of combinations of baseline revascularisation risk and the efficacy rate of DES in reducing the need for reintervention. The bold figures indicate the scenarios preferred by Cordis (for multiple-vessel disease) and LRIG (for uncomplicated two-vessel disease) (and correspondingly in subsequent tables).

In *Table 52*, the amendments described above for disutility of repeat procedures, type of repeat procedure and the LRIG assumptions of equal waiting times for PCI and CABG are exemplified within the Cordis model to obtain net outcome results from the Cordis model using LRIG assumptions.

By comparing the Cordis scenario in *Table 51* (+7.91) with the LRIG scenario in *Table 52* (+0.73), it can be seen that the Cordis incremental gain is 10.8 times the size of that obtained with LRIG assumptions. Thus the ICER for DES versus BMS increases from £54,237 per QALY gained (after adjusting the mean number of stents per patient for two-vessel disease) to £587,659 per QALY gained on the basis of differences in the estimation of incremental changes in HRQoL alone.

Costs

Differences in incremental costs are more difficult to reconcile accurately since they occur via several mechanisms within the model: the clinical assumptions (as described above for outcomes), resource use assumptions, unit costs and costing methodology differences. Indeed, it is not possible to reflect all differences by simply replacing parameter values within one model.

Table 53 shows the Cordis model incremental costs per 1000 patients for a range of baseline revascularisation rates and DES efficacy, corresponding to the incremental outcomes shown in *Table 51*.

An indication of the impact of differences in prices on the incremental cost can be gauged by substituting LRIG prices for the most important resources in the model. This leads to a net reduction in the incremental cost for the Cordis-preferred scenario of £70,000 per 1000 patients.

Table 54 shows adjusted estimates of incremental cost using wherever possible LRIG assumptions within the Cordis model. These may be compared with those shown in *Table 52*.

Incremental cost-effectiveness ratios

From *Tables 51–54* we can calculate ICERs for the original Cordis model and the adjusted model taking account of LRIG values and assumptions wherever possible. These are set out in *Tables 55* and *56*.

TABLE 51 *Unadjusted incremental QALYs gained per 1000 patients*

	Baseline revascularisation rate (12 months) (%)			
DES efficacy (%)	**10**	**15**	**22.3**	**30**
30	**+1.36**	+2.05	+3.04	+ 4.09
50	+2.20	+3.30	+4.91	+ 6.60
70	+3.04	+4.55	+6.77	+ 9.11
82.2	+3.55	+5.32	**+7.91**	+10.64

TABLE 52 *Incremental QALYs gained per 1000 patients on LRIG assumptions*

	Baseline revascularisation rate (12 months) (%)			
DES efficacy (%)	**10**	**15**	**22.3**	**30**
30	**+0.73**	+1.09	+1.63	+2.19
50	+1.16	+1.74	+2.59	+3.48
70	+1.59	+2.39	+3.55	+4.77
82.2	+1.85	+2.78	**+4.13**	+5.56

TABLE 53 *Unadjusted incremental cost (£) per 1000 patients (for two-vessel disease)*

	Baseline revascularisation rate (12 months) (%)			
DES efficacy (%)	**10**	**15**	**22.3**	**30**
30	**1,317,511**	1,229,607	1,101,268	965,896
50	1,201,988	1,056,323	843,653	619,328
70	1,086,466	883,040	586,037	272,761
82.2	1,015,997	777,336	**428,892**	61,354

TABLE 54 *Incremental costs (£) per 1000 patients on LRIG assumptions*

	Baseline revascularisation rate (12 months) (%)			
DES efficacy (%)	**10**	**15**	**22.3**	**30**
30	**1,110,002**	1,039,610	936,836	828,431
50	1,025,520	912,886	748,441	574,985
70	941,038	786,163	560,046	321,538
82.2	889,504	708,862	**445,124**	166,936

TABLE 55 *Unadjusted incremental costs (£) per QALY gained (for two-vessel disease)*

DES efficacy (%)	Baseline revascularisation rate (12 months) (%)			
	10	15	22.3	30
30	**965,883**	600,977	362,059	236,050
50	546,337	320,091	171,962	93,837
70	357,846	193,899	86,559	29,947
82.2	286,511	146,141	**54,237**	5,767

TABLE 56 *Adjusted incremental costs (£) per QALY gained with LRIG assumptions*

DES efficacy (%)	Baseline revascularisation rate (12 months) (%)			
	10	15	22.3	30
30	**1,520,992**	949,691	575,655	378,389
50	884,131	524,684	289,351	165,237
70	591,829	329,618	157,946	67,406
82.2	480,182	255,111	**107,754**	30,039

The ICER generated by the LRIG model directly is £1,529,445 per QALY gained, which is very similar to the corresponding figure in *Table 56*. In summary, we conclude that the major part of the apparent difference in ICER between the Cordis and LRIG models is attributable to varying assumptions relating to health-related utility, especially to different baseline risks of repeat revascularisation, and the efficacy of DES in avoiding such reinterventions. Differences in costs, although important, contribute much less to the apparent difference.

Summary

Although it is not feasible to provide a complete reconciliation between either of the submitted models and the LRIG model, owing to the contrasting model architectures, a good degree of agreement has been demonstrated if common costs and assumptions are employed, particularly relating to the baseline risk of repeat revascularisation, and the relative efficacy of DES over BMS. In general, the majority of apparent differences arise in relation to the estimation of incremental outcomes, rather than cost effects.

Economic evaluation: further consideration of differential waiting times

Introduction

Use of much longer waiting times (approximately threefold) for elective treatment by CABG compared with PCI is a major source of utility benefit in the submitted models. This is especially the case when considering PCI with DES as an alternative to CABG, but also applies to a lesser extent when comparing DES and BMS.

Clearly, this does not constitute an inherent feature of the technologies, as a scenario can be readily be envisaged in which the relative supply of service capacity was changed to favour CABG (e.g. too few trained cardiologists, inadequate radiology facilities or a shortage of specialist consumables). In such an environment, it can be anticipated that the advocates of PCI would be arguing that present constraints should not be allowed to bias a comparison, so as to inhibit the future development of the new technology.

Hence the only argument that may be advanced in favour of including an estimated disutility arising from differential waiting times in our economic evaluation is a pragmatic one. This rests on the contention that the nature of the supply constraints on CABG in the UK are sufficiently severe and likely to be of sufficient duration to render the current imbalance of supply and demand in CABG interventions irremediable, so that extended waiting is effectively inevitable for the type of patient currently assigned to elective CABG treatment.

There are two grounds on which we believe that the argument that differential waiting time should be allowed in the economic evaluation of drug-eluting stents fails: one based on recent evidence of waiting times in the NHS and the other concerning the legitimacy of implicitly endorsing an imbalance which is both contrary to government policy and probably untenable in European law.

Waiting time trends

In historical research studies and clinical trials, the time spent by elective patients on the waiting list for CABG is generally considerably longer than that for angioplasty and similar procedures. However, the impact of recent government initiatives to reduce waiting times, improve access to priority services and to expand service capacity toward typical European levels suggests that some equalisation of these disparities is to be expected. Accurate information on completed waiting time episodes is only available some time after the event, and is therefore unable to reflect recent changes in waiting time trends. However, the quarterly information on the number and

duration of wait of people currently awaiting admission is more easily obtained. *Figure 31* shows the mean waiting time for the specialties of cardiology and cardio-thoracic surgery, using the NHS quarterly statistics since 1999.

It is clear that the historical difference between the specialties is indeed present at the beginning of this period. However, there follows a steady reduction in average surgical waiting times until 2003, when the two trends converge. The patients in these specialties are not exclusively waiting for coronary artery revascularisation. Nonetheless, CABG and PCI do constitute a substantial proportion of their caseload, and it is likely that the general trend is also reflected in these specific procedures. It therefore follows that the argument for the use of differential waiting times in PCI and CABG is probably now redundant since experience has largely converged for the two groups of patients.

Patient access, public policy and European law

We believe that it can also be established on grounds of legality, public policy and economic reality that the argument for using differential waiting times is false, and that if a significant difference in waiting times still exists in favour of PCI it is completely feasible within a short period of time to expand the volume of elective CABG treatment undertaken for the benefit of NHS patients so as to reduce waiting times to comparable levels currently experienced by those undergoing PCI. If this point is conceded, then there are no legitimate grounds for considering treatment delays in the economic assessment of revascularisation procedures.

Legal position

In July 2001, the European Court of Justice ruled that patients in the UK are entitled to receive hospital care in other countries in the European Economic Area. In effect, this means that where a need for an intervention is established on clinical grounds, it is not acceptable to withhold or unreasonably delay treatment on the grounds that there are insufficient facilities or capacity locally or in the UK to provide them, if capacity to provide the service is available elsewhere in Europe. This ruling has been accepted by the UK government, which has undertaken pilot projects to explore the practical issues involved in offering overseas treatment to UK residents who would otherwise be denied treatment within a reasonable time, with a view to providing guidance to the NHS.

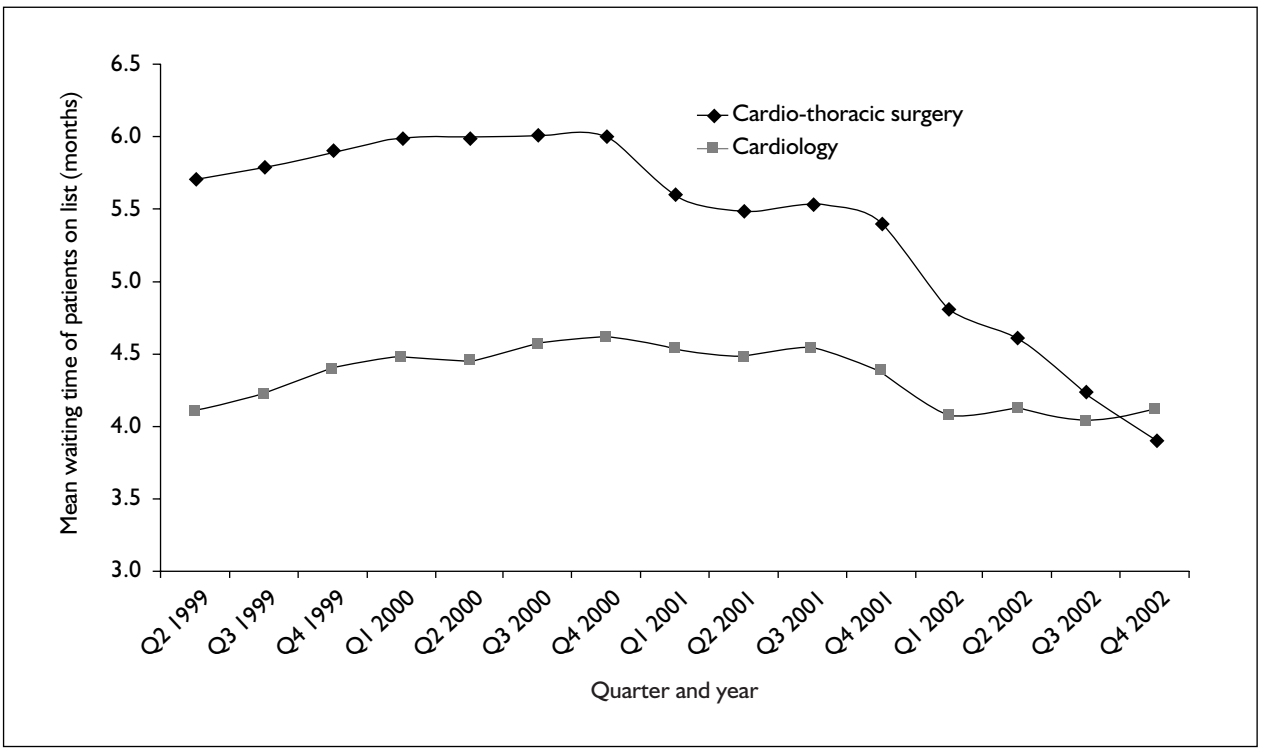


FIGURE 31 *Trends in waiting time for elective ordinary admission in England*

Public policy

Current government policy on waiting times and the development of services for treatment of CHD is clearly set out in the three-year Priorities and Planning Framework 2003–2006 (Improvement, Expansion and Reform) published in October 2002. This sets targets for "maximum waits of 3 months for revascularisation by March 2005, or sooner if possible". To achieve this it assumes there will be "increased access to diagnostic and surgical capacity to enable waiting times to be met".

A key element in meeting these targets involves "increasing the total numbers of cardiologists to 685 and cardiothoracic surgeons to 217 by 2004". In addition, the plan confirms the need to "establish additional inpatient beds and hospital capacity to meet access and clinical priority targets". Moreover, there is a general commitment to "introduce new providers from the independent sector and overseas to offer patients a greater choice over where they obtain diagnosis and treatment".

Clearly, there is every intention on the part of the UK government to bring the maximum waiting time for elective revascularisation (regardless of mode of treatment) to 13 weeks within the timescale of applicability of this NICE appraisal. That policy target maximum wait is also consistent with an average waiting time of 6–8 weeks, as used in the LRIG economic evaluation.

Economic reality

The patients currently waiting for CABG have been assigned to this mode of treatment as clinically most appropriate, notwithstanding the widespread availability of conventionally stented PTCA. Since, in the submissions made to NICE it is only suggested that a minority of these could be considered appropriate for PCI using DES, regardless of anticipated use of DES, there may remain a need to expand services in the UK for cardiac surgery. The size of any differential in waiting times would merely be a strong indicator of the urgency of the need for this expansion in capacity if public policy targets are to be achieved.

In the meantime, the only way to meet the identified need may be to seek additional service capacity from other sources, as envisaged in the policy framework. This could be from the UK private sector or from other health economies. Although the government has sanctioned arrangements with the private sector for some treatment, there are limitations on this option in that in many cases the private sector is using or sharing the same resources (i.e. skilled staff) available to the NHS, so that the net additional capacity available within the UK is probably fairly limited.

By contrast, evidence from the NHS pilot projects and also from larger schemes undertaken in Norway indicates that there is substantial spare surgical capacity available in Europe which can be purchased at prices comparable to the average cost per case incurred by the UK. Most patients who have been so treated have had good outcomes and indicated a high level of satisfaction with their treatment. The main barriers identified in the evaluation of the UK pilots was the evident reluctance and even non-cooperation of some GPs and specialists in accepting that patients could receive care from another consultant based in another unit, despite the clear benefits to patients suffering on the waiting list.

Summary

Recent evidence from NHS statistics suggests that the historical differences in waiting times for PCI and CABG may be diminishing rapidly, or may even have disappeared already. Where differences persist, it is both desirable and practical to employ available capacity elsewhere than in the NHS to remedy any existing service deficiency in the timely treatment of NHS patients requiring elective CABG. This may be appropriate in the short and medium term until investment within the UK comes to fruition, allowing all patients to receive care promptly in local facilities. Moreover, there is evidence that this can be achieved at comparable cost to conventional NHS treatment. Therefore, it appears that the pragmatic argument that differential waiting times are effectively unavoidable is untenable, and should not be allowed to distort considerations of relative cost-effectiveness between the two available technologies.

Analysis of subgroups from the clinical trials

Objective

Clinically and economically relevant subgroups of patients for whom an intervention is more effective and cost-effective is dependent on the availability of detailed information from clinical trials or patient registries, ideally at the level of the individual patient. The primary objective of

this exercise is to consider whether any evidence exists from the trials so far reported to indicate that differentiation of patients by subgroups of efficacy is both possible and desirable. For this purpose, it is necessary to estimate both the current risk of repeat revascularisation in patients receiving uncoated BMS and the reduction in risk which is attributable to use of DES.

Data sources

Some useable information exists in published trial papers, but there are currently only three trials for which such information is available:

- The RAVEL trial was restricted to patients with single lesions in small vessels [reference vessel diameter (RVD) between 2.5 and 3.5 mm], so that the trial as a whole relates to a distinct specific subgroup, although any further detail of these patients is missing.
- The SIRIUS trial enrolled patients with longer lesions in a single vessel. Outcome information after 12 months of follow-up has been made available by Cordis, and this allows consideration of patients with and without diabetes, and also results for patients receiving two overlapping stents.
- The TAXUS II trial investigated use of a DES in patients with a lesion in a small artery (RVD <3.0 mm). The recently received detailed clinical trial reports on both cohorts (slow-release and moderate-release formulations) include patient-level demographic, procedure and outcome data. These have been subjected to detailed analysis in search of insights to help in defining subgroups relevant to economic analysis.

Analytical methods and objectives

Risk measurement

It is common practice in clinical trials to measure efficacy and effectiveness in terms of relative measures: changes in relative risk or relative improvement in performance/function. This approach is mediated through the use of proportional hazards models and related statistical procedures. However, there are circumstances where relative measures are inappropriate and indeed may be misleading. All the economic models considered in our main report, including our own, have expressed benefit in terms of the relative reduction in the risk of restenosis or repeat revascularisation, following closely the pattern of published trial reports. However, as can readily be seen in the simplified model set out in pp. 150–6, for the purposes of economic assessment the critical statistic is the absolute risk reduction since this converts directly into the expected number of additional procedures avoided. For this reason, we have re-expressed all results as **absolute** risk changes, to avoid the implicit temptation to apply a relative risk change to a different group of patients without justification.

Outcome measurement

For economic analysis, the prime concern is the expected cost of repeated revascularisation. This means that the key outcome variable is the number of revascularisation events that occur, regardless of whether they occur in separate patients or involve some patients undergoing several procedures. Once again this is different from the traditional perspective of clinical researchers who generally report the number of patients affected (or equivalently the number of patients free of an event). Unfortunately, where the source of information is published papers or synopses of clinical trial reports, we are restricted to those outcome measures considered important by the authors. Hence in such cases we are obliged to rely on patient (rather than intervention) findings, using these cautiously as proxies for revascularisations.

As stated in our main report, for economic analysis we are concerned primarily with identifying **any** coronary arterial revascularisation carried out, regardless of the site of the lesion or the specific vessel involved. This focuses attention on the overall consumption of healthcare resources and avoids any subjective judgements about which interventions are to be considered 'relevant'. Unfortunately, this statistic is rarely if ever reported in the literature or in trial reports, which employ a range of anatomical/angiographically oriented definitions, such as TLR, TVR, and TVF. These different measures involve various overlaps and exclusions, which make direct comparison difficult and confusing, both within and between trials. Where no access is available to individual patient data, we are obliged to interpret these measures as best we can, recognising that any inferences drawn are necessarily tentative rather than definitive.

Correcting for protocol-driven excess interventions

In all of the trials of DES for which results are available, a key focus has been anatomical outcomes, which can only be determined accurately by angiography. This means that trial protocols include provision for a follow-up invasive investigation 6–8 months following the index

procedure. It was recognised in the early BENESTENT trials that this led to a sudden increase in repeat revascularisations occurring around the time of the follow-up angiography. This phenomenon is understood to result from the clinicians' reaction to visual evidence of significant restenosis at angiography, despite minimal or even absent patient symptoms. Clinicians feel obliged to intervene in a precautionary role when they are confronted with a restenotic lesion which appears to put their patient at risk. Although completely understandable, this pattern of response is completely atypically of service environments (such as the NHS), where follow-up does not normally involve angiography, and the decision to carry out a second intervention is judged primarily on symptoms of angina and limitations to a patient's normal activity. This phenomenon seriously undermines the reliability of estimates of the risk of revascularisation in both arms of a trial, and hence calls into question claims for the additional efficacy of DES.

Attempts have been made to avoid these problems by distinguishing between clinically driven and angiographically driven reinterventions, particularly in the FDA statement of definitions. However, even the FDA formulation includes angiographic measurements and there is sufficient scope for subjective interpretation in this exercise to bring it into serious question. Ultimately, the acid test is the time plot of survival free of revascularisation, and in all the available trials this continues to show a sharp dip in trend around the time of the protocol angiography. By contrast, some pragmatic trials of stent use (notably SOS) show no such dip, implying that where angiography is not routinely used as part of patient follow-up, the clinical need for early intervention is represented by a relatively constant 'smooth' risk function.

The first attempt to correct for this phenomenon was using information from BENESTENT II to adjust the outcomes of the RAVEL trial, which was employed by van Hout in his economic analysis (Cordis submission). This was made possible because in BENESTENT II angiographic follow-up was only carried out on a subset of patients so that a direct comparison of reinterventions was possible. An alternative approach to correcting trial outcomes involves estimating a single correction to the survival curve of each trial arm in order to bring the trend after angiography into line with that applying before. Either approach has the effect of reducing the apparent rate of repeat revascularisation in both arms of a trial, and usually also reduces the estimated additional benefit attributable to DES. In the cases considered here, we used the BENESTENT II method but confirmed that the trend adjustment approach produces broadly similar results.

Analysis of individual patient data

Our analysis of TAXUS II individual patient data was carried out on the basis of the actual treatment received, rather than ITT, since within an economic model we need to know the expected outcome conditional on a particular treatment having been undertaken, which may be partially obscured by postrandomisation variations from protocol. The main analysis was carried out using univariate analysis of variance to assess the nature and size of differences that might be related to specific factors. Subsequently, where sufficient data were present, two-way analysis was undertaken to confirm and clarify the nature of the apparent differences. We combined the two TAXUS II cohorts (slow-release and moderate-release) in order to assemble sufficient records to allow meaningful analysis to be carried out. However, we also compared results from the two substudies to assess the homogeneity of the data and any implications for our conclusions.

RAVEL

The RAVEL trial compared the use of CYPHER stents in 120 patients with single lesions in a small vessel (RVD between 2.5 and 3.5 mm) with 118 patients receiving BMS. At 12 months follow-up, three repeat revascularisations were recorded in the DES arm (2.5%) compared with 19 (16.1%) in the BMS arm, suggesting an absolute risk reduction in TLR of 13.6% and relative risk reduction of 84.5%. The corresponding figures for TVF at 12 months are 15.3% (absolute risk reduction) from 19.6% BMS to 4.2% for DES.

In RAVEL, patients were reviewed by angiography about 6 months following the index procedure so that an excess of repeat revascularisations compared with normal practice is to be expected. Applying a rate adjustment based on BENESTENT II experience reduces these estimates considerably: the revascularisation rates (TLR) are then 1.5% for DES and 9.4% for BMS, giving a revised absolute risk reduction of 7.9%. For TVR the adjusted absolute risk reduction is 8.9%.

No results for subgroups are available for RAVEL.

SIRIUS

The SIRIUS trial was carried out in the USA in a population of patients requiring stenting of a

single long lesion. In all, 533 patients were randomised to use of CYPHER and 525 to BMS. Angiographic follow-up occurred at about 8 months in this trial.

Assessment of revascularisation rates is more complex for this trial, owing to the way in which results are reported in the 12-month update report submitted. Freedom from TVR is estimated at 77.6% for BMS and 93.4% for DES. There is evidence that some patients received further treatment to more than one lesion/vessel, but it is not possible to estimate how many of these occurred on separate occasions. Hence only patient-based rates are available, and event rates cannot be determined.

Although the authors report only clinically driven repeat intervention rates, it is clear from the Kaplan–Meier survival plots that an important angiography-related effect remains in the outcomes reported. Correcting for this effect by trend displacement, we estimate the underlying 12-month risk in the BMS arm to be 16.0% and in the DES arm to be 5.0%, giving an absolute risk reduction of 11.0% (68.8% relative risk reduction).

Applying similar assumptions to the outcomes reported for the diabetic subgroup implies that patients with long lesions and diabetes gain a mean beneficial absolute risk reduction of 12.6% (61.2% relative), whereas those without diabetes achieve an absolute reduction of just 10.1% (71.6% relative).

According to an additional analysis of outcomes from SIRIUS at 9 months, approximately one-third of patients in this trial required two overlapping stents to cover the lesion. However, the reported absolute risk reduction in TLR due to use of CYPHER was very similar between the two subgroups. This suggests that the only important distinction to be made for the purposes of economic analysis is the cost of implanting an additional stent.

TAXUS II

Analysis outline

The individual patient information available offers the prospect of greater insight into the impact of the TAXUS stent, but at the same time poses some additional problems in analysis and interpretation. Initially, we carried out a simple univariate comparison of revascularisation rates within each category of each relevant risk-related variable. These results revealed important findings concerning the type of vessel stented, vessel size and the number of vessels used. In addition, a similar univariate analysis of trial cohorts indicated that the currently marketed slow-release formulation seems to deliver much less benefit than the moderate-release TAXUS stent. It is possible that these differences are the consequence of case-mix differences and statistical variation, rather than differential efficacy.

A further difficulty was identified by examining the Kaplan–Meier plots for survival free from repeat revascularisation. This showed a very strong trend deviation around the time of the protocol angiography at 6 months, indicating that estimates of baseline risk and risk reduction based on the reported data would almost certainly be overstated.

We identified problem categories as defined below (i.e. left circumflex artery target vessel, multiple stent use and RVD >3.5 mm), and decided therefore to repeat the analysis excluding these cases. In addition, we also applied an adjustment based on BENESTENT II similar to that used by van Hout, in order to approximate the results that could be expected in normal clinical practice in the UK.

The risk-related variables investigated by univariate analysis are summarised in *Tables 57* and *58*. The TAXUS II subgroup data used in the analyses have been reserved as CIC by the sponsor company (Commercial in confidence Information removed, Boston Scientific). We are therefore unable to present figures for the change of rates of revascularisation this report.

Initial univariate analysis

Data for TAXUS II and detailed results are CIC (Boston Scientific). The variables analysed are outlined in the *Table 57*.

Revised univariate analysis

The one-way comparison of subgroups was repeated following exclusion of the identified extreme categories and adjustment for angiography-associated event inflation.

Data from TAXUS II and detailed results are CIC (Boston Scientific). The variables analysed are outlined in the *Table 58*.

Multivariate analysis

A general linear model of the number of episodes of repeat revascularisation was analysed based on main effects and first-order interactions. After allowing for the contrast between the control and intervention arms of the TAXUS II trial, none of the available factors were found to be significant

TABLE 57 *Initial univariate analysis: TAXUS II revascularisation changes due to DES at 12 months*

	Patients affected:	Events occurring:
Variables analysed	**BMS risk Absolute risk change Relative risk change**	**BMS risk Absolute risk change Relative risk change**
Vessel stented	LAD, left circumflex artery, right coronary artery	CIC
RVD (mm)	<2.5, 2.5–3.5, >3.5	CIC
Lesion length (mm)	<8, 8–10, 11-12, >12	CIC
Diabetes status	Absent, present	CIC
Number of stents used	1, >1	CIC
Gender	Female, male	CIC
Age (years)	<52, 52–58, 59–62, 63–69, 70+	CIC

TABLE 58 *Revised univariate analysis: TAXUS II revascularisation changes due to DES at 12 months*

	Patients affected:	Events occurring:
Variables analysed	**BMS risk Absolute risk change Relative risk change**	**BMS risk Absolute risk change Relative risk change**
Vessel stented	LAD, RCA	CIC
RVD (mm)	<2.5, 2.5–3.5	CIC
Lesion length (mm)	<8, 8–10, 11–12, >12	CIC
Diabetes status	Absent, present	CIC
Gender	Female, male	CIC
Age (years)	<52, 52–58, 59–62, 63–69, 70+	CIC

predictors, either as main effects or as first-order interactions. This confirms that the only basis on which to distinguish between patients with single lesions in small vessels is the number of stents required to complete the procedure.

Relationship between baseline risk and absolute risk reduction

Although the primary outcome measure for economic analysis is the reduction in absolute risk of repeat revascularisation associated with the use of DES, it may also be helpful to relate this parameter to the baseline risk for any patient group when using BMS. A simple power function model was derived from the TAXUS II analyses as illustrated in *Figure 32*. In addition to the various TAXUS II subgroups, *Figure 32* also shows corresponding results for RAVEL (all patients) and SIRIUS, indicating that the power function provides a good approximation across all three studies.

Summary

The evidence available of the effectiveness of DES in specific groups of patients is severely limited at present. *Table 59* summarises the results for five types of patient where some figures can be estimated, following adjustment of rates to conform to routine clinical practice in the UK. These are used in the simplified economic model to derive estimates of relative cost-effectiveness.

Economic modelling: simplified model for non-drug eluting versus DES

Rationale for a simplified model

The model developed for our appraisal was designed to address two issues using a single model structure: whether DES may be considered a cost-effective alternative to CABG in patients with multiple-vessel disease, and whether DES is a cost-effective alternative to BMS in single-vessel disease. Since the former comparison could involve the possibility of differential survival over extended time periods, it proved necessary to employ a complex model architecture. However, the comparison of DES and BMS for single-vessel disease does not involve any question of mortality and therefore can easily be represented in a much simpler way.

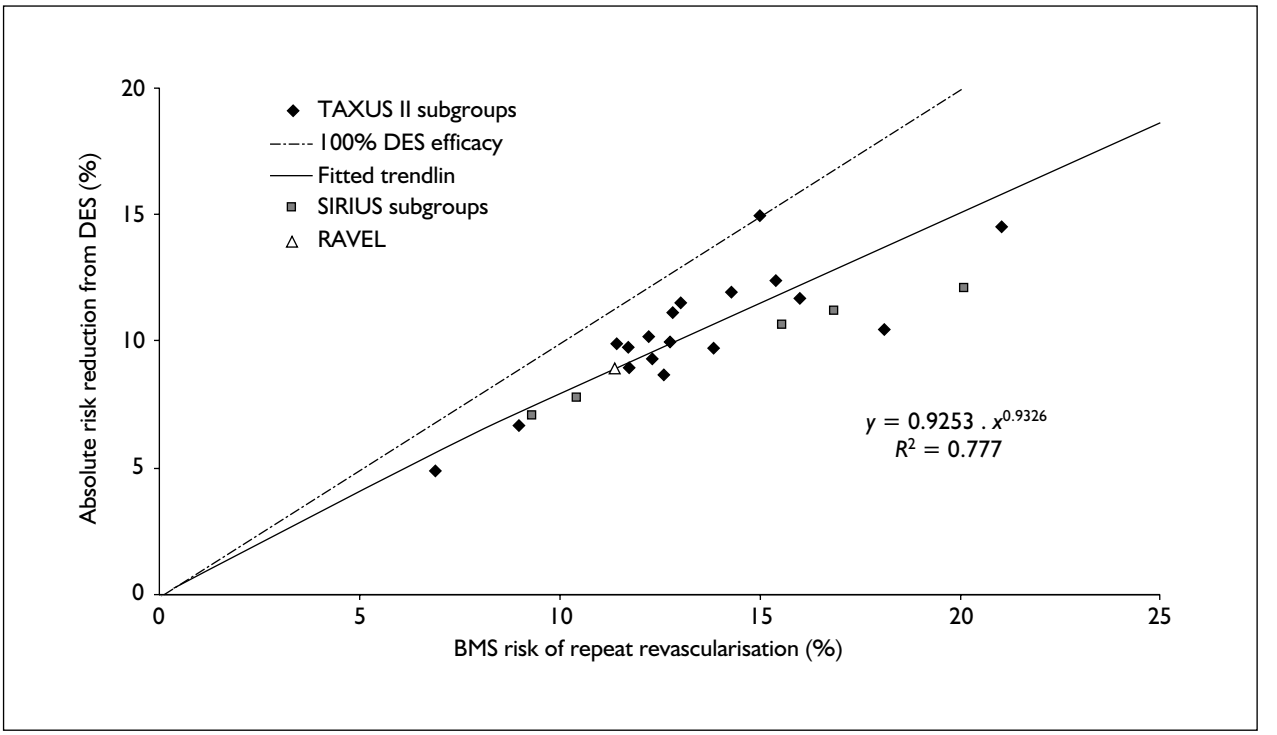


FIGURE 32 *Relating absolute risk reduction to baseline BMS risk of revascularisation*

TABLE 59 *DES effectiveness for patient groups in an NHS setting*

Patient type	Absolute risk reduction (%)	Source
Single-vessel, non-diabetic	6.0	CTC, LRIG report[a]
Single-vessel, small diameter	10.0	TAXUS II / RAVEL
Single-vessel, long lesion, non-diabetic	10.1	SIRIUS
Single-vessel, long lesion, diabetic	12.6	SIRIUS
Two-vessel, non-diabetic	7.9	CTC, LRIG report[a]

[a] Scenarios used in the evaluation in Part A.

In this section we introduce a simplified model for this purpose, which can be presented on a single Excel worksheet and encapsulates virtually all the detail of the original LRIG model for comparison of stents.

Model structure and assumptions

The principal limitation in the simplified model is that imposed by the clinical evidence available to populate it. Since none of the clinical trials provide follow-up outcomes beyond 12 months, we restricted attention to this period and therefore considered that the question of discounting costs and outcomes was redundant.

The one-page printout from the Excel spreadsheet in *Figure 33* encompasses the whole of the simplified model, which accounts for all relevant outcome elements and more than 99% of the cost elements in the original model. Model parameters are identical with those used previously, with the exception of the average waiting time prior to undergoing a repeat procedure, which has been increased from 6 to 12 weeks.

The left-hand column of the worksheet includes all incremental costs affected by the choice of stent. A simple calculation (top box) presents the additional cost per patient from substituting DES for BMS. The middle box estimates the cost of reinvestigating a patient representing with recurrent symptoms, including outpatient visits and angiography. The bottom box estimates the average cost of a repeat revascularisation procedure based on the mix of procedures used and the costs of each type of procedure, added to the cost of outpatient follow-up.

COSTS

INDEX PROCEDURE

Cost per BMS	£380 ⇐	
Cost per DES	£900 ⇐	
Number of stents used in index procedure	1 ⇐	
Extra cost per patient of using DES		£520.00

RECURRENCE OF SYMPTOMS

Average no. of Cardiology consultations	1.3 ⇐	
Average no. of angiograms	1.15 ⇐	
Cost per Cardiology OP visit	£63⇐	
Cost per angiogram	£278 ⇐	
Cost per patient reinvestigated		£401.60

REPEAT PROCEDURES

Cost of PTCA	£2,156 ⇐	
Number of stents used in repeat procedure	1.2 ⇐	
Mix of repeat procedures:		
PTCA	10% ⇐	
PTCA+BMS	70% ⇐	
PTCA+DES	0% ⇐	
CABG	20%	
Cost of repeat procedures:		
PTCA	£2,156	
PTCA+BMS	£2,612	
PTCA+DES	£3,236	
CABG	£8,368 ⇐	
OP follow-up of repeat procedures:		
No of Cardiology consultations	4 ⇐	
No of Cardiac surgeon consultations	1 ⇐	
Cost per Cardiology OP visit	£63⇐	
Cost per Cardiac Surgeon OP visit	£111 ⇐	
Cost of follow-up per patient with repeat procedure	£363.00	
Average cost per repeat procedure undertaken		£3,717.60

⇐ indicates model input

UTILITY

Disutility from repeat procedure		
PTCA	0.0035 ⇐	
PTCA+BMS	0.0035	
PTCA+DES	0.0035	
CABG	0.012 ⇐	
Average disutility per repeat procedure	0.00520	
Annual disutility of angina	0.17⇐	
Waiting time with angina (weeks)	12 ⇐	
Disutility waiting for repeat procedure	0.03923	
Total disutility per repeat procedure		0.04443

SUMMARY

Baseline revascularisation risk at 12 months	12.70% ⇐	
Absolute risk reduction from DES	10.00% ⇐	
Relative efficacy of DES vs BMS		79%
Number of DES procedures required to avoid 1 repeat procedure	10.00	
Extra cost of DES procedures to avoid 1 repeat procedure	£5,200.00	
Cost saving from 1 repeat procedure avoided	£4,119.20	
Net increase in cost per repeat procedure avoided	£1,080.80	
Disutility avoided from 1 repeat procedure avoided	0.04443	
Incremental cost per QALY from use of DES		£24,325

FIGURE 33 *Cost-effectiveness of drug-eluting stents versus non drug-eluting stents*

The central column estimates the incremental disutility associated with a repeat revascularisation, comprising a quantum related to the procedure undergone added to a time-dependent disutility from angina symptoms suffered whilst awaiting the repeat intervention.

Finally, incremental cost and utility are combined in the right-hand column. The absolute reduction in revascularisation risk associated with use of DES is used to estimate the net incremental costs incurred to avoid one repeat revascularisation. This is then combined with the corresponding disutility to arrive at the incremental cost per QALY gained.

Of the 23 input parameters, just five can be considered to influence the final result significantly:

- the unit price per BMS
- the unit price per DES
- the number of stents used per patient
- the average waiting time of patients requiring a repeat procedure
- the absolute risk reduction produced by use of DES in place of BMS in the index procedure.

Economic modelling: evaluation of drug-eluting stents for single-vessel disease

Main analysis

The simplified LRIG model was populated with the efficacy estimates for patient subgroups detailed in the section 'Analysis of subgroups from the clinical trials' (p. 149). We have diverged from previous modelling practice in presenting results separately by the number of stents employed, since this is probably the single most important parameter in the model. The previous approach used an average number of stents (between one and two), which may have been appropriate in some trial situations where information on anatomical detail may not have been available at randomisation. However, in most clinical situations this is not the case, and the interventional cardiologist will have a very good idea of how many stents will be required by any patient. This is borne out by experience in the TAXUS II trial, where only 3.5% of patients required more than one study stent.

Figure 34 and *Table 60* show the results obtained. Results for patient groups assessed using direct trial or registry evidence are indicated in the chart by circles and in the table by bold type. Other results (triangles in the chart and normal text in the table) assume the same efficacy gain, but using additional DES. The three subgroups identified from trial evidence appear to be acceptable in terms of relative cost-effectiveness. By contrast, the two broader classifications identified from the Liverpool registry do not produce sufficient benefit to justify the use of DES.

In general, it is clear that treating patients with more than a single DES is unlikely to prove cost-effective unless the likely risk reduction in the first 12 months were as high as 19% (two stents) or 29% (three stents). This is equivalent to risks of revascularisation at 12 months using BMS of 25 and 40%, respectively. On the basis of evidence currently available, it is difficult to envisage well-defined patient subgroups currently treated which would fall within this extreme range.

Sensitivity analysis

The model results were subjected to full one-way SA, with results shown in *Table 61*. As expected, the model responds most strongly to uncertainty in the extra cost of DES, the absolute risk reduction attributable to DES and factors influencing the loss of utility for patients awaiting a revascularisation procedure. In addition, the proportion of repeat procedures requiring CABG is also influential. For all other

TABLE 60 *Results of cost–utility analysis for specific patient subgroups*

		Incremental cost per QALY gained (£)		
Patient type	**Risk reduction (%)**	**1 stent**	**2 stents**	**3 stents**
Single-vessel, non-diabetic	6.0	**94,179**	289,239	484,300
Single-vessel, small diameter	10.0	**16,155**	133,191	250,227
Single-vessel, long lesion, non-diabetic	10.6	**9,531**	119,942	230,353
Single-vessel, long lesion, diabetic	12.1	**–4,157**	92,567	189,291
Two-vessel, non-diabetic	7.9	–	**195,413**	343,560

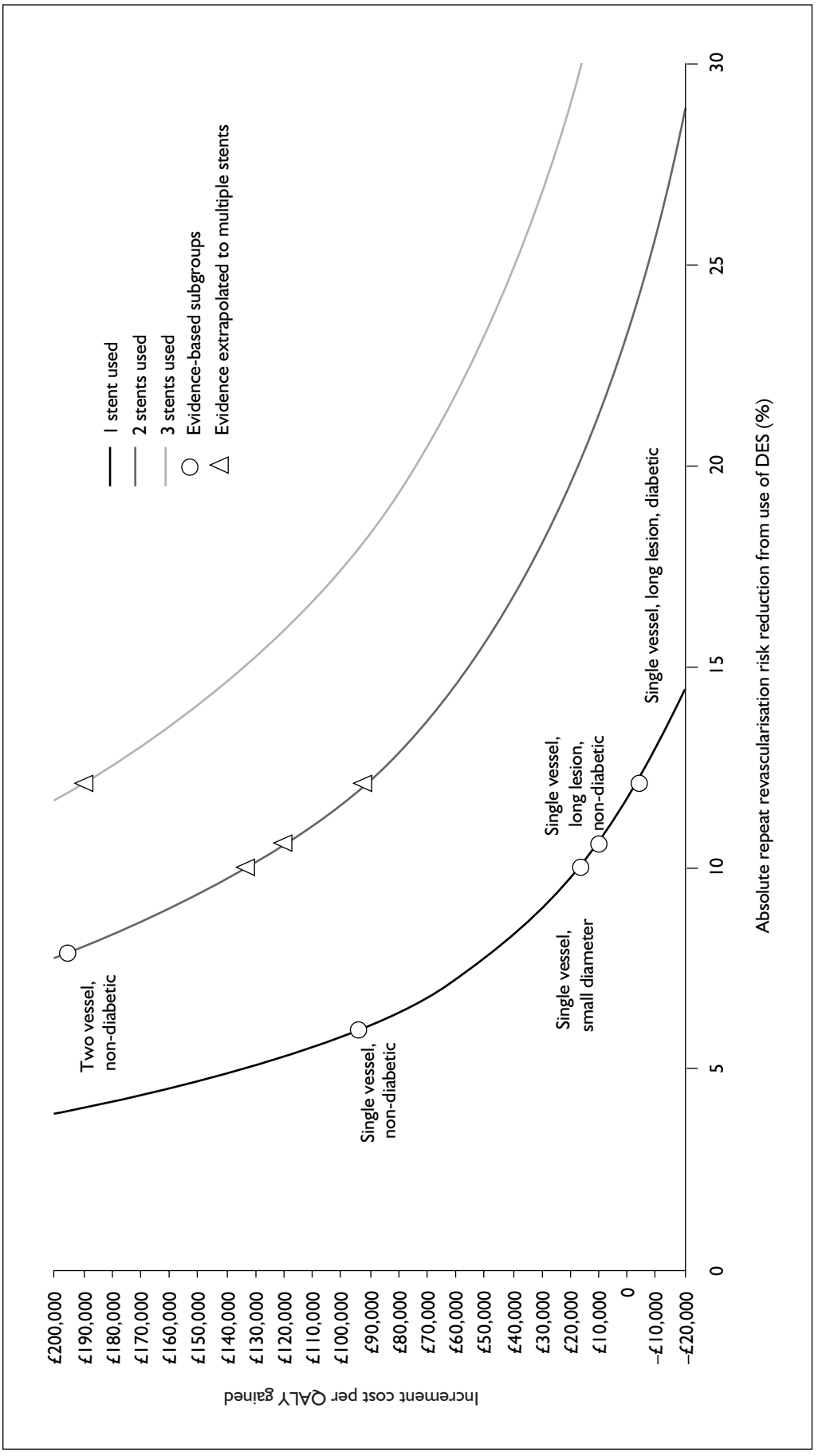


FIGURE 34 *Cost–utility ICERs for drug-eluting stents versus non-drug-eluting stents in trial subgroups*

TABLE 61 *One-way SA of simplified model results (data in £)*

Model parameter	Limits	Patient group				
		A	B	C	D	E
Excess cost per DES BMS	–20	86,299	11,276	10,162	–11,945	183,639
	+20	102,060	21,035	19,832	–4,044	207,187
Price of BMS (£)	–100	96,070	18,046	16,887	–6,104	197,304
	+100	92,289	14,265	13,106	9,885	193,523
OP reinvestigation visits	1.0	94,605	16,581	15,422	–7,569	195,839
	1.5	93,896	15,872	14,713	–8,278	195,130
Angiograms per patient	1.0	95,116	17,094	15,935	–7,056	196,352
	1.3	93,241	15,217	14,058	–8,933	194,475
Cost per cardiology OP visit (£)	55	94,886	16,862	15,703	–7,288	196,120
	70	93,097	15,073	13,914	–9,077	194,331
Cost per angiogram (£)	250	94,904	16,880	15,721	–7,270	196,138
	300	93,610	15,586	14,427	–8,564	194,844
Cost per PTCA (£)	1,940	98,069	20,045	18,886	–4,106	199,302
	2,372	90,290	12,266	11,108	–11,884	191,524
No. of stents used in repeat PCI	1.0	95,377	17,353	16,194	–6,797	196,611
	1.4	92,982	14,958	13,799	–9,192	194,216
Case-mix of repeat revascularisation (PTCA/BMS/DES/CABG)	0/75/0/25	85,854	8,570	7,422	–15,352	186,129
	20/65/0/15	102,665	23,888	22,718	–496	204,877
Cost per CABG	7,531	97,947	19,923	18,764	–4,227	199,181
	9,205	90,412	12,388	11,229	–11,762	191,645
Follow-up OP cardiology visits	3	95,597	17,573	16,415	–6,577	196,831
	5	92,762	14,738	13,579	–9,413	193,995
Follow-up OP cardiac surgery visits	0	96,678	18,654	17,495	–5,497	197,911
	2	91,681	13,657	12,498	–10,493	192,915
Cost per cardiac surgery OP visit (£)	100	94,427	16,403	15,244	–7,747	195,661
	122	93,932	15,908	14,749	–8,242	195,166
Disutility of PTCA procedure	0.003	95,035	16,302	15,133	–8,067	197,188
	0.004	93,339	16,011	14,863	–7,923	193,670
Disutility of CABG procedure	0.010	95,035	16,302	15,133	–8,067	197,188
	0.014	93,339	16,011	14,863	–7,923	193,670
Annual disutility of angina	0.15	105,097	18,028	16,735	–8,922	218,065
	0.19	85,317	14,635	13,585	–7,242	177,024
Average waiting time for reintervention (weeks)	10	110,431	18,943	17,584	–9,374	229,132
	14	82,098	14,083	13,073	–6,969	170,345
Absolute risk reduction (%)	–1	133,191	29,159	27,730	13	238,354
	+1	66,314	5,516	4,557	–14,825	162,122
Central estimate of ICER	–	94,179	16,155	14,997	–7,995	195,413

A, single-vessel, non–diabetic; B, single-vessel, small diameter; C, single-vessel, long lesion, non–diabetic; D, Single-vessel, long lesion, diabetic; E, two-vessel, non-diabetic.

model inputs the model results are very insensitive to variation. Despite these findings, it appears that uncertainty in any single variable is unlikely to alter materially the inferences made concerning cost-effectiveness for the five patient groups assessed.

The influence of price on cost-effectiveness can be judged by considering the price premium which corresponds to breakeven (i.e. zero net difference in costs at 12 months) for each patient group shown in *Table 62*.

Our base case assumed a difference in cost between BMS and DES of £520, as in the original LRIG report. NICE asked for specific comparisons of ICER using DES list prices and *Tables 63* and *64* illustrate this.

TABLE 62 *Additional price of DES versus BMS required to achieve zero net change in cost of treatment at 12 months*

	Patient subgroup	Breakeven DES price premium (£)
A	single-vessel, non-diabetic	+269
B	single-vessel, small diameter	+448
C	single-vessel, long lesion, non-diabetic	+453
D	single-vessel, long lesion, diabetic	+565
E	two-vessel, non-diabetic	+177

Likely use and budget impact of drug-eluting stents

To estimate the cost of using DES in the manner suggested in the section 'Economic modelling: simplified model for non-drug-eluting versus DES, (p. 153), we needed data on the frequency of single-vessel stenting in patients with small vessels, with long lesions and with diabetes. We understand that such data are currently being collected by BCIS but are not yet available (de Belder M, communication to NICE, March 2003). Therefore, we had to use the only other source from which we could extract some of this data rapidly, that is, the BCIA submission to NICE in November 2002 (Table 8, p. 10).

This submission quotes data from the EUROHEART study. We understand that this is only a preliminary analysis and that much more complete data will be available later. It is not clear when the data were collected, and practice may have changed since. At present, the data are crude – in particular, figures which should sum to 100% generally do not! The number of patients in this dataset is small for the UK (only 87). We have therefore viewed the wider database for the NW WHO region, allowing consideration of 1259 patients, but it should be borne in mind that the indications considered for coronary interventions may differ in different countries.

TABLE 63 *CYPHER – differences in cost (£) between BMS and DES £525*

		Incremental cost per QALY gained (£)		
Patient type	**Risk reduction (%)**	**1 stent**	**2 stents**	**3 stents**
Single-vessel, non-diabetic	6.0	**96,150**	293,085	490,021
Single-vessel, small diameter	10.0	**17,375**	135,537	253,698
Single-vessel, long lesion, non-diabetic	10.1	**16,205**	133,197	250,188
Single-vessel, long lesion, diabetic	12.6	**–7,007**	86,772	180,551
Two-vessel, non-diabetic	7.9	–	**198,357**	347,928
Bold figures are those that are plotted in *Figure 34*.				

TABLE 64 *TAXUS – differences in cost (£) between BMS and DES £500*

		Incremental cost per QALY gained (£)		
Patient type	**Risk reduction (%)**	**1 stent**	**2 stents**	**3 stents**
Single-vessel, non-diabetic	6.0	**86,299**	273,857	461,414
Single-vessel, small diameter	10.0	**11,276**	123,811	236,345
Single-vessel, long lesion, non-diabetic	10.1	**10,162**	121,582	233,003
Single-vessel, long lesion, diabetic	12.6	**–11,945**	77,368	166,681
Two-vessel, non-diabetic	7.9	–	**183,639**	326,088
Bold figures are those that are plotted in *Figure 34*.				

Despite these limitations, these data allow us to do some simple calculations as follows:

Calculations

Patient numbers

- Of 100 PCI patients, 74 are stented and 26 receive PTCA only (row 29).
- Of these, 56.24 (74 × 76%) receive 2+ stents and 17.76 receive 1 stent (row 31).
- If 52% of stented patients have multivessel disease (row 26), then we guess that there are 38.48 multiple-vessel disease stented patients (52% × 74) all having 2+ stents.
- This means that 17.76 single-vessel disease patients (56.24 – 38.48) receive 2+ stents, and 17.76 SVD patients receive one stent, that is, a 50:50 split.

Only 83% of SVD patients (100%, row 19) would be eligible for stenting according to the suggestions in Chapter 6, that is, 14.74 (83% × 17.76).

Hence about 15% of all PCI patients would receive a single DES.

Stent numbers

- Of 100 PCI patients, 74 are stented and 26 receive PTCA only (row 29).
- Mean number of stents per patient stented is 1.28 (row 30), giving a total of 94.72 stents used.
- We estimate that 14.74 patients are eligible for a single DES.
- This is equivalent to 15.56% of all stents used (14.74/94.72).

An alternative calculation using the same table is as follows:

1. Approximately 50% of single-vessel disease involves small vessels (<3.0 mm).
2. Approximately 50% of single-vessel disease involves long lesions (>16 mm).
3. Approximately 18% of single-vessel disease does not involve either small vessels or long lesions, that is, 82% of patients may be eligible for DES. This is equivalent to about 39% of all PCIs currently done (including PTCAs and multiple-vessel disease).
4. About 76% of all stented patients receive more than one stent (row 29), and 52% of patients have multiple-vessel disease (row 26). Assuming that all multiple-vessel stented patients receive two or more stents, this implies that about half of single-vessel stented patients receive more than one stent (i.e. ~25% of all PCI patients).
5. 17% of patients do not have long or small diameter lesions (row 19), so 83% do. We can therefore estimate that about 20% (25% × 83%) of all PCI patients have single-vessel disease in one of the appropriate categories and could currently receive only one stent.
6. The EUROHEART figures also show that only 74% of PCI patients receive any stent (i.e. 26% receive PTCA only), implying that the likely take-up of DES would be ~15% (20% × 75%) of patients.
7. Converting this into numbers of stents used (rather than patients): 76% receive more than one stent, 25% receive one. Total stent use in 100 patients is therefore 175 stents, so 15–25 of these would be displaced by DES, that is, 8.5%–14.5%.

Both calculations come to ~15% of all stents, but these are extremely crude figures, of uncertain relevance to NHS practice. Specific UK data should be sought from BCIS when available to allow a more accurate prediction.

The cost implications of this can be considered using the data presented previously in the main report. Use outside these categories will, of course, be more expensive and far less cost-effective.

Budget impact estimates are displayed in *Table 65*.

There will be cost offsets if DES are used in the manner suggested; these will be particularly large, for instance, for diabetic patients with long lesions, such that the use of DES in these patients may be cost saving.

Other work

Other work planned but incomplete for this report and a lower priority for the Appraisal Committee than that already described in this report included a reconsideration of differences in mortality in patients receiving stents or CABG based on long-term (3-year) data from the ARTS trial, with extensive SA.

TABLE 65 *Budget impact estimates: cost of DES*

Scenario	Total additional cost (£000,000)	
	Current service levels	NSF service levels
15% of total stenting (favoured scenario)	3.51	4.26
50%	11.72	14.92
75%	17.58	22.38
100%	23.44	29.84

Chapter 10

Budget impact analysis

Budget impact of expanding PTCA and CABG

Focus of the analysis

Over 90% of PTCAs currently involve the use of BMS, which seems to be clinically optimal. Any further extension of this practice would be unlikely and probably of little cost significance to the NHS. Therefore, this budget impact analysis does not attempt to analyse the resource implications from possible extension of the use of BMS. Equally, it is beyond the scope of this chapter to undertake a detailed analysis of the cost to the NHS of achieving the policy commitment outlined in the NSF[7] of at least 1500 procedures per million population, since this will depend on a wide range of factors which are beyond the scope of our analysis. It is, however, important to acknowledge that this target can only be achieved by diverting resources away from other valuable treatments. Although a detailed analysis of the additional investment in the training and recruitment of additional personnel and in the expansion and development of new treatment facilities to deliver the target is beyond the focus of this review, a preliminary analysis is presented. This analysis combines the necessary expansion in patient numbers in both PTCA and CABG and applies national reference costs to estimate the costs of achieving these targets.

Patient population

Estimating the need for PCIs in the NHS is complicated by international variations in the criteria for intervention. There are also significant international variations in clinical preference for PTCA and CABG, which largely reflect the level of budgetary constraints imposed on different health services and their reimbursement structures. The NSF has a policy commitment to provide at least 1500 PTCA procedures per million population per year, with at least 750 CABG per million and 750 PTCA per million. The ratio of CABG to PTCA in the UK has decreased owing to the rapid expansion of PTCA and the comparatively slow growth in CABG. In 1998, approximately the same number of procedures were undertaken through CABG and PTCA (25,000 of each), but since that time, although the rate of CABG has remained relatively constant, the rate of PTCA increased by ~50% between 1998 and 2001. The current proportion of PTCA to CABG procedures is ~4:3 with the ratio increasingly favouring PTCA.

Using national reference costs for 2000 and hospital episode statistics for 2001–02, the mean national cost for an elective in-patient PTCA was £2820 and for CABG £5673. Using these figures, the estimated total cost of the PTCA (29,434) and CABG (23,364) procedures performed by the NHS in 2001–02 are £83.0 million and £132.5 million, respectively. For these services to expand to achieve the NSF targets would require ~37,500 procedures in both CABG and PTCA (an overall level of 1500 procedures per million population). This would therefore require an additional 8066 PTCAs at an estimated additional cost of £22.7 million and an additional 14,136 CABGs at an estimated additional cost of £80.2 million (see *Table 66*). These estimated costs do not take into account the capital costs of expanding facilities to undertake more of either procedure. Such costs are likely to be substantial particularly for CABG.

Conclusion

The long-term cost of PCI will largely depend on the balance in future levels of service provision between PTCA and CABG. The recent rapid expansion in PTCA procedures has altered the PTCA:CABG ratio in favour of PTCA, largely as a consequence of the greater flexibility of PTCA as a

TABLE 66 *Cost of achieving NSF targets*

Intervention	Finished consultant episodes (2001–02)	Estimated current cost (£000,000)	Cost to achieve 750 per million population (£000,000)	Cost increase required (%)
CABG	23,364	132.5	212.7	60.5
PCI	29,434	83.0	105.8	27.4

TABLE 67 *Price of stents as provided in the industry submissions to NICE*

Company	Stent product (drug)	Price indicated for DES (£)	Price indicated for BMS (£)
Cordis	CYPHER (sirolimus)	CIC	CIC
Boston	TAXUS Express (paclitaxel)	CIC	CIC
Guidant	(sirolimus)	CIC	CIC
Abbott	BiodivYsio (dexamethasone)	CIC	CIC

source of expansion. Although this expansion enables the NHS to move more rapidly towards NSF targets, this may occur in an unbalanced manner. This would be less expensive than a balanced expansion of both PTCA and CABG, but in the long run may not coincide with the optimal structure of NHS service provision from the long-term clinical or economic perspective, as outlined in Chapter 9. In particular, a rapid expansion of PTCA should be accompanied by evidence that this is the most clinically and cost-effective way to meet patient needs.

It is also important to acknowledge that improved access to coronary interventions will extend survival (in comparison with no treatment) in patients with CHD and so ultimately increase the need for repeat coronary interventions. Again, estimating the extent of this long-term expansion in demand is outside the scope of our analysis.

Budget impact of DES

Introduction: budget impact of DES

This section analyses the potential cost implications to the NHS of the increased use of DES.

The total cost to the NHS by such increased use will depend on three factors:

1. The cost increment of the use of DES compared with normal stents
2. The target population identified for DES: do they simply replace normal stents and, if so, in which patient populations, or do they extend stenting into populations currently served by CABG?
3. The level of cost offsets resulting from reduced need for revascularisations that are associated with the use of DES.

Each of these factors is examined in greater detail below.

The cost increment attached to DES

The use of DES is also likely to require a prolongation of antiplatelet drug use (from 1 to 3–6 months) but, with the exception of this comparatively minor change, no other significant element of the initial procedure (complexity of operation, length of stay, diagnostic tests) appears to be affected by the substitution of DES for BMS. The cost increment associated with DES will determine its cost-effectiveness (see Chapter 9) and also their cost impact on the NHS.

Currently the only DES licensed for use in the UK is the CYPHER sirolimus-eluting stent, for the treatment of *de novo* coronary artery lesions of less than 30 mm in length in native (unaltered from their natural state) coronary arteries with reference diameters of between 2.25 to 5.0 mm.

However, there are a wide range of other DES under investigation with trials at various stages of development. Licensing authorisation is anticipated early in 2003 for other DES whose costs are expected to be similar to that of the CYPHER stent (see *Table 67*). Costs for both DES and BMS vary: there is at present no firm evidence to determine which BMS or DES should be used, and we need further evidence on their comparative long-term clinical and cost-effectiveness. Apart from these considerations, however, other elements will affect choice and dissemination, such as availability, operator preference and suitability for different subgroups of patients.

The target population for DES

There is as yet little evidence about the clinical and economic effectiveness of DES in specific subgroups of PTCA patients. In clinical trials to date, DES have been found to be effective in reducing rates of restenosis in relatively simple lesion types with very limited evidence being generated in patients with more complex lesions. In Chapter 9, we present an analysis which suggests that DES will be more cost-effective in

TABLE 68 *Assessment of high-risk patients suitable for DES*[a]

Patient group	Percentage of total patient population[b]
All patients with renal disease	1.9
All patients with poor ejection fraction	1.7
All patients with dyspnoea (class IV)	4.4
50% of patients with diabetes	
50% of patients with left main stem disease	
50% of patients with peripheral vascular disease	15.0
50% of patients with angina (class I or class IV)	
25% of patients with previous MI	10.0
Subtotal of above	33.0
88% of total patient population (single- or two-vessel disease)	29.0

[a] Based on prevalence of risk factors in elective PTCA patients contained in the audit data received from the Cardiothoracic Centre, Liverpool.
[b] It is likely that the patient populations for individual risk factors will overlap and therefore this analysis should be seen as being an upper estimate.

particularly high risk patients. We therefore now preset an analysis that assumes that DES will initially be targeted on patients exhibiting specific risk factors and therefore perceived as having a high-risk of restenosis. The initial target population assumed in our budget impact analysis is outlined in *Table 68*. We recognise that the risk categories analysed are not mutually exclusive, hence this preliminary analysis provides an upper estimate of the costs of initial targeted dissemination of DES.

The audit data provided by the Liverpool Cardiothoracic Centre indicates that 53% of patients presenting for elective PCI suffer from single-vessel disease, 35% suffer from two-vessel disease and 12% suffer from three- or more vessel disease. Of the 88% of patients presenting with single- or two-vessel disease, 25–30% of them are likely to be at high risk of restenosis and hence most appropriate for the initial targeted use of DES (see Chapter 9). The budget impact assessment also uses the conservative assumption of an incremental cost associated with DES of £520 (compared with BMS) and average utilisation of 1.3 stents per procedure for single-vessel disease (62% of the combined total of single- and two-vessel disease patients) and 2.4 stents per procedure for two-vessel disease (38% of the combined total). Hence an average of 1.74 stents per procedure was assumed to be required per procedure in these highest risk groups.

Cost increases associated with DES

If approved by NICE, DES will rapidly disseminate throughout the NHS to replace BMS since most of the required diagnostic and treatment procedures are common. No fundamental new structure of service or capital investment is required to change to DES at existing levels of provision. There would be some capital cost to expand PTCA with stenting to reach NSF target levels, but we have not considered these. If DES enables PTCA to expand into areas currently covered by CABG, then provision of the service may require a further limited expansion of the service to cope with any additional workload; however, at this stage, the results of the economic model do not support the substitution of CABG by DES (see Chapter 9).

A total of 29,434 finished consultant episodes in which PTCA was the main operation were provided by NHS trusts in England (2001–02). Our audit data indicate that 78% of these procedures (22,958) were elective and 88% of these elective procedures (20,203) were for either single- or two-vessel disease.

In the first case, we therefore assume that 25–30% of these elective single/two-vessel disease patients were in a risk group sufficient to justify the use of an average of 1.74 DES per procedure, then the additional cost to the NHS of substituting DES for BMS in these patients would be between £4.59 million (25% of patients) and £5.51 million (30% of patients).

If we further assume a similar proportionate usage of DES amongst emergency patients (22% of the patient population), the additional cost associated with the use of DES increases to between £5.86 million (25% of patients) and £7.03 million (30% of patients).

Finally, the additional cost of achieving the NSF target of 1500 procedures per million population (assuming that 50% of these are provided by PTCA) incorporating the targeted use of DES would be between £7.46 million (25% of patients) and £8.96 million (30% of patients).

An alternative scenario is that DES simply replace BMS in all or almost all cases.

The annual cost estimates to the NHS in *Table 69* have also been calculated based on potential market share.

TABLE 69 *Budget impact estimates: cost of DES*

Scenario	Total additional cost (£000,000)	
	Current service levels	NSF service levels
25%	5.86	7.46
50%	11.72	14.92
75%	17.58	22.38
100%	23.44	29.84

We anticipate that the time course of this uptake to at least current levels of stent use would be very short once NICE approval were given.

Cost offsets associated with DES in this target population

Although DES have a higher acquisition cost than BMS, the net cost to the NHS will depend on cost offsets associated with the reduction in reintervention costs. We use the term 'offsets' rather than savings to make it clear that, given the current under-provision of interventions, there will be no actual savings as the number of interventions in the whole population is unlikely to decrease, but rather that there are improvements in efficiency, shortening of waiting times or wider availability of the procedures.

The major cost offset from the use of DES would be a reduction in repeat revascularisations. The cost offsets therefore depend on by how much they are reduced and costs of repeat procedure. The first issue involves the nature of the second procedure. If a stent is used in the initial intervention, then do we assume a stent is used again, or may a simple balloon PTCA be used? Also, in what proportion of patients is a CABG used for restenosis? Equally, if a DES is used in the initial procedure, then if restenosis occurs, what would be the nature of this second procedure? Would a DES be used in the second stent procedure, or alternatively would CABG, BMS or even balloon angioplasty be used? For the purposes of this analysis, the structure of reinterventions utilised in the economic model was assumed (see Chapter 9).

The second issue relates to the potential savings to the NHS arising from the reduced rates of repeat procedures resulting from the use of DES. To calculate this, an SA was undertaken on the parameters of the economic model to estimate the cost offsets associated with the reduced rate of restenosis associated with DES compared with BMS. The baseline model assumes that replacing

TABLE 70 *Estimated cost offsets from reduced revascularisation*

	Relative reduction in repeat revascularisation (£)		
	Base case (30%)	Equivalence (0%)	Incremental saving
Incremental cost at 5 years' follow-up	1017	1194	177

BMS with DES leads to a 30% relative reduction in the need for repeat revascularisation. Under this assumption, the cost increase associated with the use of DES is £1017 per patient. The economic model was rerun assuming no difference in the need for repeat revascularisation between DES and BMS. Under this assumption, the cost increase associated with the use of DES was £1194 per patient. This SA therefore provides an estimated average saving of £177 for each patient resulting from the lower rates of repeat revascularisation after DES compared with BMS (see *Table 70*).

The estimated saving calculated in the economic model relates to patients with two-vessel disease at average risk of restenosis. If we assume that any limited use of DES will target patients in sequentially higher risk groups, then a number of adjustments need to be made to take account of the variable target group for DES. The initial target group assumed (25% uptake of DES) specifically targets DES on patients at high risk of restenosis, thus increasing the level of cost offsets. This target population is assumed to experience approximately double the risk of restenosis experienced in the population as a whole. This implies an average cost offset per patient arising from the reduced rate of restenosis in this initial target group of ~£350 over 5 years. As the target group for DES expands, patients at lower risk of requiring repeat procedures are incorporated with the risk being assumed to reduce linearly in individual patients until the scenario relating to universal use of DES.

The offsets in population terms are shown in *Table 71*, with an offset of £350 per patient in the highest risk group, but an average of £177 in the whole population

The impact of these cost offsets in reducing the additional costs imposed by DES are shown in *Table 72*. This table estimates the net additional

TABLE 71 *Budget impact estimates: offset due to DES*

Product	Offsets (£000,000): current service levels	Total offsets (£000,000): NSF service levels
25% (@£350 per patient)	2.58	3.28
50%	3.46	4.48
75%	4.34	5.60
100% (@£177 per patient)	5.21	6.64

TABLE 72 *Budget impact estimates: net increases in NHS cost due to DES*

Product	Total net cost (£000,000): current service levels	Total additional cost (£000,000): NSF service levels
25%	3.28	4.18
50%	8.26	10.44
75%	13.24	16.78
100%	18.23	23.20

cost to the NHS arising from different levels of utilisation of DES.

Conclusion

This major factor determining cost impact to the NHS is incremental cost of the DES over BMS and how widespread the use of DES become – do they replace all BMS, or only a proportion with DES reserved for the highest risk patients? It is important to recognise that the results of this cost analysis are not static and that a range of factors on both the cost and effectiveness sides are likely to change, which will considerably influence comparative cost-effectiveness and cost impact over time. In particular, the price of DES is likely to decrease as competition increases. More clinical evidence as outlined in earlier chapters will clarify the appropriate role of DES in time, and may demonstrate further improvements in clinical outcomes.

Chapter 11

Discussion and conclusions

Part A: Analyses completed for appraisal report

Rapidly changing technologies

This review has highlighted the speed with which clinical practice related to stenting in the treatment of ischaemic heart disease is occurring. This technology is changing so rapidly that, as one commentator put it to us, there is an information half-life of approximately 4 months. This is a substantially shorter time period than is necessary to conduct a well-designed RCT. Hence it seems that the trials are working with almost outmoded technologies, while some of the earlier pieces of evidence in the jigsaw are as yet incomplete or not fully reported.

Technological developments are happening in all aspects of interventional care for CHD, such as changes in the types of stent, placement devices and the concomitant therapies. These changes may in turn lead to changes in outcomes. One result of this has been an additional shift in case-mix, with more and more patients previously considered unsuitable for stenting now being included in clinical practice. This shift in case-mix is perhaps a marker of the clinical value of stenting that is not well captured in RCTs.

It has become almost a tradition in cardiology to lead in technological advances, and this enthusiasm has to some extent been balanced by a tradition of large clinical RCTs using firm end-points such as mortality. In the case of coronary artery stenting, in particular with DES, we see these two aspects of cardiology finely balanced: on the one hand we have the majority of cardiologists who are convinced of the benefits of stenting with DES, but on the other the evidence in relation to real clinical end-points to support their enthusiasm is as yet incomplete. A perception exists among cardiologists that the early evidence is so compelling that there should be a widespread implementation of the use of DES, and probably in lesion types not adequately studied or perhaps reported in the clinical trials to date.

The timing of this review is important. That it should be done so soon after the previous study by Meads and colleagues from Birmingham[2] reflects the rapidly changing nature of the technology. However the previous review was done largely at a time when the major changes in clinical practice had already been made. It is noteworthy that BCIS data indicate that the proportion of patients receiving stents rose from 60 to 80% between 1997 and 2000, and that this increase took place before the issuing of NICE guidance in 2000.[27] The previous guidance therefore acknowledged the changes in clinical practice that had already occurred,[107] but in reality did little to guide NHS practice in this area.

A recent survey suggests that DES are likely to have a rapid uptake in the USA. JP Morgan Securities[229] conducted a survey of 140 interventional cardiologists in the USA in anticipation of FDA approval of Johnson and Johnson's CYPHER DES. The respondents estimated that the percentage of total stenting using DES would be 77% by the fourth quarter after licensing. It was thought that this would be higher in both diabetic and small-vessel patients (88 percent each). Interestingly, the biggest obstacle to greater market penetration was seen as device cost (4.3 on a 5-point scale). Lesser barriers after this were the need for more data on complex lesions and on patient subsets (2.6/5) and data on long-term safety and efficacy (2.5/5). These data illustrate the strength of the enthusiasm of interventional cardiologists for this device despite the current lack of long-term evidence, which would not deter the cardiologists from using these devices.

In contrast to the previous appraisal, therefore, the use of DES is still at an early stage of development and of use, and the decision of the NICE Appraisal Committee will be of considerable importance in either containing or directing the spread of this technology.

The previous NICE appraisal suggested that stenting should become standard in patients having PTCA. It did this largely on the basis of the then current evidence that referred to restenosis rates, with the assumption that the restenosis would, to some degree, parallel changes in QoL or possibly in quantity of life, or in revascularisation

procedures and long-term costs to the NHS. We now have reports from a greater number of studies which can be used to address these questions. Despite these studies, and indeed sometimes because of them and the outcome markers they have chosen to report, the evidence remains incomplete.

Comparison of interventions

Extensive discussion of the differences between the various interventions has taken place with the chapters that specifically address the clinical aspects of the review. These will not be repeated here. Suffice it to say that a number of assumptions regarding the comparability of the interventions (e.g. that all non-DES are equally effective, or that early studies of an intervention can be compared with later studies of a more developed technology) have been made and these are most certainly open to challenge.

In the case of stent versus PTCA, there may be enough data to carry out some further analysis to elucidate these differences. It did not seem appropriate to do this as the technology and the policy around it have moved on, and the use of PTCA alone is now uncommon.

In the case of stent versus CABG, the number of studies and data were limited and therefore conducting any further internal comparison was not an option.

In the case of BMS versus DES, the differences between types of stent are important and unresolved. The drugs and the stent technologies were different across studies, and even on current evidence it is clear that there are substantial differences between types of DES. In the absence of direct head-to-head comparisons, and the varying entry criteria between studies, we are unable to draw any further conclusions on these differences.

It also is worth mentioning that DES are not the only new technical developments. Cardiac surgery techniques and post-operative management are changing and improving. In the area of non-DES, research continues with newer stent materials, changes in stent design, including thinner struts, and coated (but not eluting) stents in development. It was not the remit of this review to compare stent designs but there is potential that these new designs may have reduced restenosis rates compared with existing stents, and that this improvement may be made with less incremental cost over existing stents than DES.

Outcomes

As previously noted, the primary outcomes utilised in the evaluation of the effectiveness of stents is related to restenosis or revascularisation. In this there are two major considerations: the consistency with which that outcome is measured and the validity of the measure (discussed in detail in the economic discussion).

Historically, restenosis has been reported as an angiographic outcome, such as restenosis rates. Where clinical events such as revascularisation rates are used, these clinical outcomes may have reflected decisions strongly influenced by angiography rather than the clinical presentation, that is, target lesion or target vessel revascularisation driven by angiographic appearance may overstate the clinical need for procedures. The more recently accepted definition of clinically driven events, as agreed by the FDA and used in more recent DES trials, states:

"The procedure was considered clinically driven if the patient had a positive functional study, ischaemic ECG changes at rest in a distribution consistent with the target vessel, or ischaemic symptoms and an in-lesion diameter stenosis greater than 50%. Revascularisation of a target lesion with an in-lesion diameter stenosis greater than 70% in the absence of the above mentioned ischaemic signs or symptoms was also considered clinically driven."

This is clearly a compromise between truly clinically driven events and the fact that a cardiologist finding a stenosis >70%, even in an asymptomatic patient, may feel it more appropriate to proceed with revascularisation rather than await developments. This is less of a problem with longer term follow-up since the protocols usually only specify one angiographic follow-up (typically at 6 months) and therefore events following that are more likely to be truly clinically driven. It has been suggested that there may be an element of 'catch-up' procedures in the non-angiogrammed patients at a later stage of follow-up, but this is not seen clearly in studies to date.

Conversely, target lesion revascularisation may understate the total number of revascularisations experienced by the patient, such as revascularisation procedures which may involve other vessels. In many studies, there is no distinction between essentially protocol-driven revascularisations (i.e. arising after a protocol determined angiogram) clinically needed

procedures, or protocol-recorded 'events' (e.g. silent MI detected by an ECG at a set protocol determined time rather than an acute clinical MI).

Results of studies of DES are difficult to interpret for these reasons. We have presented 'clinically driven events' as defined above wherever possible, although we have reservations about the real role of the angiogram in driving these events.

There are a number of large studies still to report over the next 12–18 months. In parallel, the long-term results of existing trials will become available. This increase in data will allow firmer conclusions to be drawn from comparisons between DES and BMS.

For all of these reasons, whatever decision is reached by the NICE Appraisal Committee, we think it imperative that the area be reviewed again in the near future – probably within the next 12–18 months.

Clinical effectiveness

Comparison of stent versus PTCA

Clinical activity here has largely been supported by the previous NICE appraisal and is unlikely to change in the future. The expanded evidence confirms the results seen in the earlier review. Angiographic indices, particularly restenosis rates, are improved compared with PTCA alone. There is a substantial reduction in major adverse cardiac event rates at 6 and 12 months. Events, however, cover a multitude of definitions and the single most common event was invariably repeat revascularisation. In many trials, the revascularisation was driven by a protocol angiogram rather than by clear clinical presentation of symptoms. There is a trend towards reduction in MI but again, there needs to be a distinction between true clinical MI and protocol-detected infarction (analysis in this report combined these rates as 'any AMI'). Finally, there is no evidence of a difference in mortality rates. However, it is not realistic to expect a significant difference to be found in mortality, given the number of subjects involved in trials so far and the low incidence of this outcome.

Unfortunately, there are at present too few studies which have reported in sufficient detail over longer periods to allow us to disentangle the question of benefits in key subgroups such as patients with diabetes or patients with specific lesions, such as CTO, long lesions, or in patients with poor left ventricular function. Individual patient data analysis of trial data may allow this. In the absence of randomised clinical trials, the next level of evidence that could be accessed which might help address this question is registry data.

A limitation of the meta-analysis is that it fails to capture the developments in PTCA and stenting over the period of the studies reviewed, for instance, the development of newer antiplatelet regimens or the changing case-mix, or differences between different stent designs. It was suggested that a presentation of data by date of publication might enable us to identify some of these changes over time. A decision had been made to subgroup the patient populations and therefore this was not done.

One particular benefit of stenting has not been captured by this review, namely the decrease in the number of emergency surgical procedures required as a result of acute closure or dissection after PTCA – now routinely treated with stenting and only rarely requiring surgery. This is well illustrated by a graph in the BCIS submission.

Comparison of stent versus CABG

CABG has demonstrated effects on prognosis in certain subgroups of patient, specifically LM stem disease, three-vessel disease and those with poor left ventricular function. For these patients, it remains the current gold standard in revascularisation. For other patient groups with single-vessel (not LM) or two-vessel disease, there are possibilities for displacement of CABG by stenting and these have been considered in clinical trials. The previous review was severely limited by the available data in this area, but a number of important trials have reported since then.

Conclusions on single-vessel studies are therefore as follows: there is no evidence of differences in mortality (as mentioned above, an outcome perhaps not to be expected), and a decrease in event rates in the CABG arm has been established. By and large, stenting is now the preferred option for patients with single-vessel disease, although more study in patients with LM stem disease is needed.

Conversely, CABG is the standard for patients with three-vessel or very extensive disease. Of greater interest and reflecting where current clinical practice is not clearly in favour of either stenting or CABG, therefore, are the studies that have looked at selected patients with multiple-vessel disease. The margin for change therefore lies in two-vessel disease and this is where the SOS,

ERACI II and ARTS studies have examined outcomes.

There is no clear evidence of a difference in mortality up to 36 months in the non-parametric meta-analysis. However, parametric trend analysis suggests that an advantage in favour of CABG may be expected over longer time periods. At present, follow-up results from ARTS are only available in a compatible form up to 12 months, so that future projections rely mainly on a synthesis of SOS and ERACI II evidence. When ARTS findings to 36 months are to hand, this analysis can be updated, but it appears that it would need to show a marked difference against CABG to alter the conclusions. In addition, there is a need for more QoL data that assess the impact of the repeat revascularisation procedures required by patients who receive stents.

The more easily measured benefits were in major adverse coronary event rate and in (clinically driven) revascularisation procedures, which are substantially decreased in the CABG arm. At present, therefore, it may be said that CABG is superior in terms of reduction in revascularisations compared with stenting. Some question that the newer DES will fill this gap in outcomes between surgery and stenting.

Stents versus DES

Included studies present for the most part a short-term (12-month) picture of significantly decreased combined event rates, largely revascularisations. Here again, there is the question of whether the event rate is sometimes artificially raised by protocol-determined angiograms. Other events such as death or MI are rare and there is no evidence that DES decrease these. However, given the infrequency of these events and the limited amount of data, this is not at present a realistic outcome, although it may become so with time. Longer term results and an expansion of the number of patients reported are expected in the near future.

We were fortunate in this report to have been given access to 2-year RAVEL data. These show that the benefits seen at 1 year were largely maintained. There was no evidence of late restenosis, as was feared by some commentators, and no evidence of any new benefit over the second year. These data therefore increase our confidence in the safety and effectiveness of DES in reducing revascularisations up to 2 years There is still a need for much longer term data, but these will become available over the coming years.

It is clear that there are considerable differences between the drugs evaluated in the included trials. Three of the reviewed trials were stopped early, because of either adverse event rates or an inability to demonstrate expected effectiveness levels. The DELIVER study emphasises that new designs of non-DES may bring benefits similar to those of DES and at lower cost.

Economic analysis

Introduction

In order to translate this clinical benefit into an economic benefit, it is necessary to have a view of the extent of reduction of utility brought about by a recurrence of clinical angina and a clinically driven repeat revascularisation. Many cardiologists argue that stenting including DES will decrease patient symptoms and the need for further procedures, and thereby improve their quality if not QoL. In the economic literature, it is clear that such events reduce QoL, but generally for a short period, such that the overall diminution of QoL by the development of angina and further revascularisation procedures is small. This point is of great importance but there is a relative lack of data on changes in QoL in studies so far. This deficiency needs to be remedied.

The existing economic literature has been reviewed and, with the exception of the recent SOS and ARTS trials, is of limited relevance in that many of the costs are historical and many of the technologies examined are also no longer used. However, there is a clear broad principle emerging from these studies: CABG is more expensive in the short term, but in the long term, it is associated with fewer repeat revascularisations. Therefore, over a 1-year period, CABG will be substantially more expensive and associated with a reduction in QoL compared with stenting, but it would seem that in the long term, the benefits of CABG may exceed those of stenting.

On both clinical and economic grounds, therefore, we need to be extremely careful about being influenced by short-term point estimates and must instead model out to long-term gains. This is obviously fraught with difficulties and uncertainties. We found the company models which attempted to do this were broadly unsatisfactory, for a range of reasons, in particular their reliance on short-term benefits. The submission by the BCIS is also based broadly on short-term outcomes. We acknowledge the weakness of extrapolating outcomes beyond the

evidence base, but would argue that we cannot undertake a viable economic evaluation of these technologies without such extrapolation.

In our economic evaluation, therefore, we examined areas of importance to possible future changes in clinical practice, that is, a comparison of elective stenting versus CABG mainly in multiple-vessel disease, a comparison of DES versus BMS, a theoretical comparison of elective CABG versus DES and an SA around each of these in populations of varying risk. This last point was undertaken to try to model the effects in such populations as diabetics patients assuming that the benefits seen for each type of procedure are proportionately maintained in different subgroups. Future studies will provide firm evidence around this, for example, the FREEDOM study comparing DES with CABG in diabetics. However, the results of these studies are still some years away.

At first sight, it may appear that conclusions drawn in the chapters covering clinical trial evidence, based on conventional meta-analytic techniques, are in conflict with those described in the context of economic modelling. However, this confusion is resolved when we recognise that different analytic approaches are required to answer different but complementary questions – 'What has happened to date?' and 'What should we expect to happen in the future?'

Broad conclusions are as follows:

- CABG is more effective but at a higher cost than stenting either with BMS or DES.
- Stenting with DES may buy additional QALYs compared with standard BMS, but at a very high cost (£700,000–1,000,000 per QALY).

The most contentious aspect of our evaluation is our projection of long-term mortality differences between CABG and PTCA with BMS. It is instructive to consider briefly how our analysis and conclusions would be affected in the event that no mortality differences occurred at any future time. In the event, this would mean that the only remaining differences in QALYs would derive from the short-duration dips in utility suffered between successive revascularisations in a minority of patients. The only source of evidence that we considered reliable on the magnitude of such differences is the ARTS trial up to 12 months after the index procedure, by which time all differences had disappeared. Indeed, it might be suggested that a long-term trend for improved utility scores in favour of CABG would be compatible with the limited results so far available. In view of the very small incremental changes involved and the high degree of uncertainty in their estimation, the whole economic evaluation would collapse to simple cost minimisation in the absence of any mortality differences.

Under this scenario, the conclusions for the comparisons between DES and BMS are hardly altered at all – DES remain very expensive with limited and uncertain benefit. The comparison between stents (of either sort) and CABG for multiple-vessel disease would then suggest simply that CABG is more expensive but is efficacious for longer (i.e. requires fewer repeat procedures), but that the difference in net cost diminishes as the risk of repeat revascularisation increases. Thus, in qualitative terms, the status quo is essentially unaffected, and the issue to be addressed in guidance is the appropriate risk–cost threshold between the two alternative treatments.

The more extensive data on DES from SIRIUS (12-month), E-SIRIUS (9-month) and the 2-year data on RAVEL were received too late to be considered in the economic modelling.

Improving the cost-effectiveness of DES

The unsatisfactory cost/QALY of DES over plain metal stents could be improved in three ways:

- First, a demonstration of more effective clinical outcomes: this may come from current clinical trials but the SA emphasises how dramatic these improvements would have to be.
- Second, a fall in the cost differential between BMS and DES. Again, the SAs suggest how dramatically the price of DES would have to fall.
- Third, and perhaps most likely, by restricting the use of DES to patients at highest risk of clinically significant restenosis such that their rates of revascularisation would be increased by a factor of ≥ 3. This would substantially improve the ICERs. For instance, if we assume that DES were to reduce the rate of **all** revascularisations by 75%, then for those patients with a three-fold increased risk for a clinically necessary revascularisation, the use of a DES could be cost saving while improving QoL.

These calculations are crucially dependent on the true relative efficacy of DES in avoiding reinterventions. Until this is clarified from longer term follow-up, the degree of elevated risk required to justify the use of DES instead of non-

DES remains uncertain. We present an SA to explore this: in our base-case scenario, it appears that only patients with multiple factors predisposing to higher risk would be suitable (e.g. diabetes **and** poor LVEF), although it may be argued that some of these patients would in fact be more suitable for CABG. For instance, the lack of difference in rates of revascularisation between diabetic and non-diabetic people in ARTS in the CABG arm compared with the wide difference in the stented arm may suggest that similar diabetic patients should be offered CABG until direct comparisons between CABG and DES are available to confirm at least equivalence.

Risk stratification

If this targeting of DES is to be a realistic suggestion, then there must be some means of identifying who are the patients at highest risk of repeat revascularisations. BCIS suggest that this is not possible at present, but there are some clear indicators of lesion and patient characteristics which might suggest the high-risk groups. Our own work suggests that the patients at highest risk are, not surprisingly, those with the greatest number of risk factors for restenosis, such as diabetes, small vessel and long lesion.

Others have quantified this better. Kastrati and colleagues[230] examined correlations between risk factors and binary restenosis and risk factors and target vessel revascularisation in over 1000 patients who had angiography 6 months after stenting: the key predictors were DM [restenosis OR 1.86 (95% CI 1.56 to 2.16) and TLR OR 1.45 (95% CI 1.11 to 1.80)], use of more than one stent [restenosis OR 1.81 (95% CI 1.55 to 2.06), TLR OR 1.94 (95% CI 1.66 to 2.22)] and MLD <3 mm immediately after stenting [restenosis OR 1.81 (95% CI 1.55 to 2.06), TLR OR 2.05 (95% CI 1.77 to 2.34)] were the strongest predictors of restenosis.

Ho and colleagues[231] have described restenosis rates in clinically driven angiography in patients using these three risk factors, and have drawn up a table (*Table 73*). If the 'standard' risk of binary restenosis is for those non-diabetic patients with short (10-mm) vessels with a fairly large diameter (3.0–4.0 mm) after stenting is ~7–10%, then patients with risks of ≥ 20–30% might be considered for DES rather than BMS.

More recently, the same group[26] has revisited a number of trials and identified independent correlates describing likelihood of revascularisation rather than restenosis. Those which can be measured before procedure which were significant are given in *Table 74*.

TABLE 73 *Predicted clinical binary restenosis rate*

	Lesion length (mm)				
Vessel diameter (mm)	**10**	**15**	**20**	**25**	**30**
Diabetic patients					
2.5	23	26	29	31	34
3.0	15	17	20	22	24
3.5	10	11	13	5	16
4.0	6	7	8	9	10
Non-diabetic patients					
2.5	18	20	22	25	27
3.0	11	13	15	17	18
3.5	7	8	9	11	12
4.0	4	5	5	7	7

Adapted from Ho and colleagues.[231]

TABLE 74 *Independent correlates of target lesion revascularisation*

	OR	**95% CI**
Reference diameter of vessel (per mm)	0.48	0.40–0.59
Stent length (per 5 mm, per lesion)	1.06	1.03–1.10
Lesion length (per 5 mm, per lesion)	1.11	1.04–1.17
Diabetes	1.49	1.16–1.92
Smoking within the past year	0.64	0.47–0.88
Previous MI	0.70	0.54–0.90
Unstable angina	1.34	1.06–1.69
Hypertension	1.27	1.01–1.61

Adapted from Cutlip and colleagues.[26]

It would therefore be possible to draw up a risk table similar to their previous approach. For example, if a standard risk patient were a non-smoking diabetic person with a lesion of 3 mm diameter and 10 mm long, a diabetic person with a lesion of 2 mm diameter and 20 mm long would have an increased risk by a factor of $1.06 \times 1.06 \times (1/0.48) \times 1.49 = 3.49$.

A similar argument was made by a Sheffield group[232] recently. They report a local audit showing a restenosis rate (TLR) of ~8–10%, based on clinically driven angiograms. This is similar to that in other case series in the literature. Their review of the literature suggests that variation in angiographic restenosis rates depends on lesion length, vessel diameter and whether the patient is diabetic or non-diabetic, and ranges from 2 to 54% for each stent deployed, with clinically significant restenosis rates about half of this. They

estimate that an angiographic restenosis rate of 15% per stent in patients with 1.6 stents and 1.1 stents per lesion would equate roughly to their observed clinical restenosis rate of 10%. They then suggest threshold rates of restenosis at which a DES might be used, depending on the available levels of funding: for a rate of 15% risk of angiographic restenosis, they suggest that ~18% of all stents used would need to be DES. They also suggest diminishing returns with increased use of DES in lower risk lesions, as would be expected.

If an arbitrary cost threshold were set, or if a fixed budget were defined, it would be possible to change the parameters in the economic model such as the differential price and the evidence of benefit as these changed so as to identify the patients where benefit might be bought at a threshold price.

There may be an analogy here with our use of statins. The trials show a consistent proportional reduction of cardiovascular morality regardless of baseline risk. However, for reasons of efficiency, we target patients with higher risk of cardiovascular event such as secondary prevention patients and patients with risk of events of 3% per year or more. In considering DES, a treatment with no mortality benefit and only short-term experience, the case for targeting DES, if they are to be used at all, to the high-risk patients is surely even stronger. The positive and negative predicative abilities of any 'risk tables' to identify high-risk patients require further assessment before they can be recommended.

We stress that so far there is only limited evidence of the effectiveness of DES over non-DES in many of these highest risk groups, and no long-term evidence at all. However, the early results from the SIRIUS study suggest a proportional benefit for DES over plain stents across all subgroups, and so targeting the high-risk patients would be a good way to improve the absolute effectiveness and the cost-effectiveness of DES. Specific studies in these highest risk groups will report over the coming years and provide more data to confirm the validity of this approach.

Implications for the NHS

The impact of DES on total NHS cost must be considered. It is beyond the scope of this exercise to cost the NSF. The NSF proposes at least 750 PTCAs, the majority of which will involve stenting, per million population. DES will increase short-term costs but may decrease some of the future costs of revascularisation in these populations. There will probably be no **real** cost savings, since given the current under-provision of interventional cardiology, the total number of interventions will not drop as a result of DES; rather, there may be cost offsets and increased efficiency in the system, if repeat revascularisations are replaced by more first-time procedures. The extent of net additional costs will also depend on whether DES are used in all patients or only in the high-risk patients as might be suggested by our economic evaluation and by the Sheffield group. If given to only high-risk patients, the likely added cost to the NHS is £4.2 million per year; if given to all, £23 million per year. This does not take into account an expansion in stenting beyond current levels, although this seems likely to occur. The Sheffield group also point out that in a cash-limited health service, there may be a trade-off even within stenting whereby the increased costs of DES might be offset against increasing numbers of BMS – in our study, this is captured by the use of ICER.

We would take this point further: it might seem a short cut to achieving NSF targets to increase numbers of PTCA/stenting procedures. This is proposed by BCIS and in industry submissions. For single-vessel disease this might be appropriate, but for two-vessel disease it would not, based on the current evidence outlined in this report. In the absence of substantive clinical evidence of the superiority of stenting with DES over CABG, to encourage the widespread use of DES might undermine NSF policy objectives by pre-empting cardiac service development funds and delaying or preventing the overdue expansion of capacity for cardiac surgery. It is beyond our scope to address issues such as the capital costs of such service development.

Recommendations for future research

Despite a large amount of interest in the new technology developed for PCI, and a number of recent trials under way or reporting early results, it is clear that full and conclusive clinical or economic evaluations of DES are not yet possible. In the case of clinical evaluation, the review is limited by the small number of studies with limited follow-up and the current definition and reporting of clinical outcomes and comparators. From an economic perspective, this is principally due to the chronic nature of CAD, so that

medium/long-term follow-up of a substantial number of patients is required (5–10 years) before conclusions can be drawn on the primary outcome – survival. Ongoing trials may resolve some of these issues, but we would urge more reporting of key major adverse cardiac events in a disaggregated manner rather than only as composite end-points. We also recommend larger trials with end-points such as mortality, but as long as manufacturers can get their products to market and persuade cardiologists to use them without such evidence, it is unlikely that these trials will be funded. From a manufacturer's perspective, a commitment to such trials might not be desirable because of their expense and duration, at a time when the technology is progressing so rapidly. Commercial and professional pressures might therefore make such trials impossible. This might also be cited as a reason to avoid head-to-head comparisons of different types of DES or indeed BMS.

It is clear that there are a number of areas where further clinical research is needed:

- Differences among plain stents (this might be possible from a systematic review, but as explained above, has been avoided in the current review).
- Head-to-head comparisons within DES (new trial data required).
- CABG compared with DES (already planned).
- To evaluate newer non-DES against DES.

The major benefit of stenting is a decrease in revascularisations, which should reflect a decrease in angina and an improvement in QoL. However, at present there are only limited data on the QoL of patients with angina before and after revascularisation in single-vessel disease. Using the existing QoL evidence from patients with multiple-vessel disease may overestimate the benefits of avoiding repeat revascularisations from CABG over plain stents, or from DES relative to plain stents. More information is also required on patient QoL with repeated interventions and over longer periods of time – some of this may already exist within the ARTS study, which plans to measure quality of life repeatedly at 2, 3 and 5 years. Part of the evaluation of QoL must involve consideration of patient preferences for surgery or stenting, on which we have little information at present. This has been a serious deficiency in the data available to us in preparing this report, and we particularly recommend this as an area for further research.

Existing trial records and registries could be used to quantify the factors that put particular patients or lesions at high risk of revascularisation. Some of this early work has been identified but much more remains to be done to develop robust predictive tools to identify patients who might benefit most from CABG or from DES and at an acceptable ICER. We see this as a key area of research that the health service could fund in the near future. It may be possible to approach this by using existing patient registries within the NHS.

We have previously mentioned the possibility that there may be a risk of increased incidence of cancer associated with stenting, and believe that this should be investigated carefully by review of existing trials, although this would require cooperation from triallists to extract the additional results from their data, and by prospective registries.

Conclusions

Studies are not powered to measure the effectiveness of stenting in relation to mortality. Outcomes of trials assessing effectiveness are primarily based on their ability to decrease revascularisation rates. Although differentiation of angiographically versus clinically driven revascularisation is progressing, confusion remains and existing study reports do not easily allow for the extraction of data related to all revascularisation. We do not have adequate data on the effects of repeat vascularisations on QoL.

The rapid evolution of the various treatment modalities makes assessment at a given point in time very difficult. Stent technology is evolving in both DES and in the area of stent structure. Surgical techniques are changing, the process is becoming safer and less invasive and patients' hospital stay is decreasing. These may lead to both improved outcomes and decreased costs.

In contrast, DES, at current list prices, will increase the net cost of stenting. At present, there is no reason to allow DES to displace CABG: a 5-year model suggests that CABG is more effective, albeit at higher cost. Better clinical data from direct comparative trials will become available in the future.

In patients at low risk, DES carry a heavy extra cost compared with conventional stents for a very small benefit in terms of improvement in QoL. DES will therefore have to come down substantially in price to achieve what would be considered by decision-makers to be an acceptable

cost per QALY. On the other hand, in some populations of very high-risk patients, the reduction in revascularisation rates which might be expected from DES (if confirmed in long-term follow-up of the clinical trials) is such that the ICERs are lower.

Finally, we should bear in mind that the long-term clinical benefits and harms of these devices are not yet clear. As with a newly developed drug bearing a black triangle from the Committee on Safety of Medicines, careful patient selection and follow-up and reappraisal of the safety and effectiveness of the devices will be essential. Until these are established for DES, we consider that a process of controlled release and monitoring of outcomes would be advisable.

Part B: Discussion of the further analysis of clinical effectiveness of selected DES and economic evaluation

Further analysis: discussion and summary

Introduction

As discussed earlier in this report, further analyses of clinical effectiveness and economic evaluation of selected DES were completed at the request of the Appraisal Committee. The results of these further considerations have been presented in Part B of Chapter 6 and Part B of Chapter 9.

This part of Chapter 11 aims to summarise the findings of the additional work completed for the Appraisal Committee.

Discussion

This work updates the available clinical evidence by including the large SIRIUS, E-SIRIUS and TAXUS II studies. These results provide considerably more data than were previously available – for instance, the total number of patients has risen from 297 available in the original report where the only trials were TAXUS I and RAVEL to 2230 by pooling the results of newer trials. These results largely confirm the previous results and give greater confidence in them.

The extent of the reduction is approximately two-thirds in the RCTs, but there is some evidence that this is exaggerated by the trial protocols including angiography. A more realistic expectation might be reduction of the order of approximately half of this.

More importantly, perhaps, access to individual patient data for one of the trials, TAXUS II, has allowed us to explore subgroups. TAXUS II, however, represents a relatively small proportion of the total number of patients involved (<20%) and if individual patient data in a similar fashion were available for SIRIUS and for RAVEL, then a further subgroup analysis could be undertaken. This subgroup analysis raises some important issues. First, it was always thought that DES would be more cost-effective in certain patient subgroups that were at higher risk of restenosis. Early data suggested that the relative reduction in risk of restenosis would be similar across all groups, implying greater benefit in those groups at highest risk of restenosis, such as diabetics patients. The subgroup analysis, however, suggests that the absolute benefit is relatively constant across all subgroups and it is this figure that is most influential in determining the economic efficiency in each case.

A criticism of this work might be that we have extrapolated from subgroups in one study to the whole group; however, this is all that is possible with the data available at present. We can only assume at present that subgroup results from SIRIUS would be broadly similar to those in TAXUS II.

The next major expansion in data in this regard will be when TAXUS IV reports its first results in September 2003; this will increase the numbers of patients exposed to DES in RCTs by a further 1300.

A key change in the economic evaluation was to move away from the population average number of stents (e.g. 1.4 or 1.7) to consider the effects of putting one or two discrete stents in an individual patient – which is, of course, clinical reality. This has a substantial effect on the cost-effectiveness of the interventions and the differences between using one and two stents are graphically illustrated in Chapter 9 (*Table 34*, p. 129). This allows definition of patients in whom DES may be considered cost-effective at a conventional threshold, or even cost saving. These patients are now defined as diabetics with a long lesion in a single vessel, non-diabetics with a long lesion in a single vessel or patients with a single vessel with a small vessel diameter, that is, <3 mm. This will account for ~30% of stenting procedures and ~19% of all stents used in the UK, leading to an increased expenditure of £4–6 million depending

on the level of service provision. This cost will be offset against reduced reinterventions.

The subgroups identified as benefiting are perhaps not those that would have been predicted, for instance, from the Cutlip or Sheffield analysis considered in the earlier report. Clearly substantially more work on this area needs to be done using wider patient databases. The data for the CYPHER studies (SIRIUS, RAVEL, and E-SIRIUS) are potentially available now.

The issue around the effects of the protocol driven-angiograms and the extent to which they influence the results of these studies will only be resolved by a large pragmatic study comparing DES with BMS which does not involve such an angiogram – similar to the design of the SOS study of BMS versus CABG.

In conclusion, DES reduce the need for reintervention after PTCA to a greater extent than BMS. The use of a single DES may be cost saving with an improvement in QoL in some patients, but DES will achieve an acceptable incremental cost per QALY in some other patients. The use of more than one DES gives rise to much higher ICERs per QALY gained.

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About home unit

The Liverpool Reviews and Implementation Group (LRiG) was established within the Department of Pharmacology and Therapeutics of the University of Liverpool in April 2001. It is a multidisciplinary research group whose purpose, in the first instance, is to conduct systematic reviews commissioned by the Health Technology Assessment Programme.

Contributions of the authors

Mr Adrian Bagust (Senior Research Fellow, Health Economics) worked on the economic analysis and development of economic model. Dr Ameet Bakhai worked on the economic analysis, summary of economic data, clinical advisor. Ms Rumona Dickson (Director, Liverpool Reviews and Implementation Group) provided input into all aspects of the clinical component of the review. Dr Yenal Dündar (Research Fellow Clinical Effectiveness) developed search strategies and provided input into all aspects of clinical component of the review. Dr Alan Haycox (Senior Lecturer, Health Economics) worked on the economic analysis and summary of economic data. Dr Ruaraidh A Hill was the review coordinator and provided input into all aspects of clinical review. Mr Ruben Mujica Mota provided the evaluation and summary of submitted economic models. Ms Anne Reaney worked on the application of inclusion criteria, quality assessment and data extraction. Dr David H Roberts was the clinical advisor and provided input into background and clinical conclusions. Professor Tom Walley (Professor, Pharmacology and Therapeutics) contributed to the data assessment and interpretation of clinical and economic data. Dr Paula R Williamson was the advisor for data analysis.

All contributors took part in the editing and production of this report.

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Responsibility of report

The views expressed in this publication are those of the authors and not necessarily those of the Review Panel, peer reviewers, the HTA Programme, NICE or the Department of Health.

Furthermore, the authors acknowledge that a consensus of opinion was not achieved between the Review Team and some members of the Review Panel or peer reviewers with regard to approaches to and findings of the review.

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Appendix 1

Search strategies and search results

TABLE 75 *Search for clinical-effectiveness studies: summary*

Database	Years	Search strategy	References identified
MEDLINE	1990–2002	See below	1925
EMBASE	1990–2002	See below	1815
Science Citation Index/Web of Science	1990–2002	Coronary stent*	1361
Science Citation Index/ISI Proceedings	1990–2002	Coronary stent*	86
Cochrane Trials Register	2002 (4)	Coronary stent*	249
HTA	1990–2002	Stent$	39
DARE	1995–2002	Stent$	31
Total references identified			5506
Duplicates			2291
Total			3215

Search strategy for clinical effectiveness (MEDLINE 1990–2002)

1. randomized controlled trial.pt.
2. randomized controlled trials.sh.
3. random allocation.sh.
4. double blind method.sh.
5. single blind method.sh.
6. clinical trial.pt.
7. clinical trials.sh.
8. controlled clinical trials.sh.
9. (clin$ adj25 trial$).ti,ab.
10. ((singl$ or doubl$ or trial$) adj25 (blind$ or mask$)).ti,ab.
11. random$.ti,ab.
12. research design.sh.
13. exp Evaluation Studies/
14. follow up studies.sh.
15. prospective studies.sh.
16. (control$ or prospective$ or volunteer$).ti,ab.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. animal.sh.
19. human.sh.
20. 18 not (18 and 19)
21. 17 not 20
22. (coronary or stent$).mp
23. exp STENTS/
24. exp Coronary Disease/ or exp Myocardial Infarction/ or exp Coronary Artery Bypass/ or exp Coronary Arteriosclerosis/ or exp Coronary Vessels/ or exp Coronary Circulation/ or exp Angina Pectoris/ or exp Angioplasty, Transluminal, Percutaneous Coronary/ or exp Electrocardiography/ or exp Risk Factors/
25. 22 and 23 and 24
26. 21 and 25
27. limit 25 to (yr=1990-2002 and english language)

Search strategy for clinical effectiveness (EMBASE 1990–2002)

1. randomised controlled trial/
2. controlled study/
3. double blind procedure/
4. single blind procedure/
5. clinical trial/
6. follow up/
7. prospective study/
8. random$.ti,ab.
9. randomized controlled trial$.tw.
10. (control$ or prospective$ or volunteer$).ti,ab.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. limit 11 to human
13. (coronary or stent$).mp
14. exp stent/ or exp coronary stent/
15. exp coronary artery disease/ or exp coronary blood vessel/ or exp coronary vein/ or exp left anterior descending coronary artery/ or exp coronary reperfusion/ or exp coronary artery obstruction/ or exp left coronary artery/ or exp coronary risk/ or exp right coronary artery/ or exp coronary artery recanalization/ or exp transluminal coronary angioplasty/ or exp coronary artery spasm/ or exp coronary

artery surgery/ or exp coronary artery thrombosis/ or exp coronary vasodilating agent/ or exp coronary artery/ or exp coronary artery bypass graft/ or exp coronary artery bypass surgery/ or exp coronary artery constriction/
16. 13 and 14 and 15
17. 12 and 16
18. limit 16 to (english language and yr=1990-2002)

MEDLINE cost-effectiveness search strategy (1987–2002)

1. 1exp "costs and cost analysis"/ or exp cost-benefit analysis/ or exp quality of life/ or exp quality-adjusted life years/ or exp economics/ or model.mp.
2. 1exp stents/ or "stent".mp.
3. 1exp Coronary Disease/ or exp Myocardial Infarction/ or exp Coronary Arteriosclerosis/ or exp Coronary Artery Bypass/ or exp Coronary Vessels/ or exp Coronary Angiography/ or exp Angina Pectoris/ or exp Risk Factors/ or exp Coronary Circulation/ or exp Angioplasty, Transluminal, Percutaneous Coronary/ or exp Myocardial Revascularization/
4. 11 and 2 and 3
5. 1limit 4 to (human and english language and yr=1987-2002)

EMBASE cost-effectiveness search strategy (1987–2002)

1. 1exp cost/ or exp hospital cost/ or exp cost benefit analysis/ or exp cost control/ or exp cost effectiveness analysis/ or exp cost minimization analysis/ or exp cost of illness/ or exp cost utility analysis/ or exp drug cost/ or exp health care cost/ or exp economics/ or exp health economics/ or exp quality of life/ or model.mp.
2. 1exp stent/ or stent.mp.
3. 1exp coronary artery/ or exp coronary blood vessel/ or exp coronary artery disease/ or exp coronary artery atherosclerosis/ or exp coronary reperfusion/ or coronary artery bypass graft/ or exp coronary artery bypass surgery/ or exp coronary artery recanalization/ or exp transluminal coronary angioplasty/ or exp coronary artery spasm/ or exp coronary stent/ or exp coronary artery surgery/ or exp coronary artery thrombosis/ or exp revascularization/ or exp heart infarction/
4. 11 and 2 and 3
5. 1limit 4 to (human and english language and yr=1987-2002)

TABLE 76 *Search for cost-effectiveness studies: summary*

Database	Years	Search strategy	References identified
MEDLINE	1987–2002	See above	239
EMBASE	1987–2002	See above	371
Science Citation Index/Web of Science	1987–2002	Coronary stent* and cost*	119
Science Citation Index/ISI Proceedings	1990–2002	Coronary stent* and cost*	14
Cochrane Trials Register	2002 (4)	Coronary stent* and cost*	22
NHSEED	1995–2002	Stent$	109
HTA	1990–2002	Stent$	39
DARE	1995–2002	Stent$	31
Total references identified	944		
Duplicates	296		
New total	648		

Appendix 2

Quality assessment checklists

Quality assessment checklist for clinical studies

Studies of clinical effectiveness will be assessed using the following criteria, based on CRD Report No. 4, University of York:

- Was the method used to assign participants to the treatment groups really random? (*Computer-generated random numbers and random number tables will be accepted as adequate, whilst inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week*.)
- Was the allocation of treatment concealed? (*Concealment will be deemed adequate where randomisation is centralised or pharmacy controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque*.)
- Was the number of participants who were randomised stated?
- Were details of baseline comparability presented in terms of treatment free-interval, disease bulk, number of previous regimens, age, histology and performance status?
- Was baseline comparability achieved for treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Were the eligibility criteria for study entry specified?
- Were any co-interventions identified that may influence the outcomes for each group?
- Were the outcome assessors blinded to the treatment allocation?
- Were the individuals who were administered the intervention blinded to the treatment allocation?
- Were the participants who received the intervention blinded to the treatment allocation?
- Was the success of the blinding procedure assessed?
- Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
- Were the reasons for any withdrawals stated?
- Was an ITT analysis included?

Items graded as:

✓	yes (item adequately addressed)
No	item not adequately addressed
✓/×	partially (item partially addressed)
Unclear	or not enough information
NA	not applicable
NS	not stated

Quality assessment checklist for cost-effectiveness studies

- well-defined question
- comprehensive description of competing alternatives
- effectiveness established
- all important and relevant costs and consequences for each alternative identified
- costs and consequences measured accurately
- costs and consequences valued credibly
- costs and consequences adjusted for differential timing
- incremental analysis costs and consequences
- sensitivity analyses to allow for uncertainty in estimates of costs or consequences
- study results/discussion include all issues of concern to users.

The scores used for each dimension were as follows:

✓	dimension appropriately addressed
✓/×	dimension partially/maybe addressed
N/A	dimension not applicable

Appendix 3

PTCA versus stent clinical data

TABLE 77 *PTCA: study characteristics*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
Non-specific CAD participants										
ADVANCE[36]	145 143	MACE (cardiac death, MI, CABG or repeat PTCA, i.e. TVR) at 9 months	Angiographic success (PTCA: DS <50%, TIMI grade 3; stent diameter stenosis <30%, TIMI grade 3)	Multicentre, European	Stable or unstable angina or reversible ischaemia, single, native, primary lesion, 2.5–4.0 mm, 20–50 mm long	MI ≤ 5 days, Q-wave MI in target vessel area, EF <30%, history of stroke, GI bleeding ≤ 6 months, severe hepatic disease, unprotected LM coronary artery lesion, CTO, bifurcation (side branch >2.0 mm), aorto-ostial lesion, thrombus	Aspirin Heparin Ticlopidine or clopidogrel	NIR		31 days 6 months 9 months
AS[37]	200 (192) 200 (196)	Restenosis rate at 6 months (angiographic evidence of restenosis at angiographic follow-up); event-free survival at 2 years	Angiographic success rate (<50% residual stenosis); MLD on postprocedure and follow-up angiogram; composite end-point (death, CVA, MI or TLR by PTCA, stenting or CABG at 6, 12 and 24 months)	Multicentre (9), Poland	CAD, single new lesions, >50% in diameter and <15 mm long, reference diameter ≥ 2.5 mm	Acute or recent MI, treatment of CTO, true bifurcated lesion and LAD	Aspirin Heparin Ticlopidine	Palmaz–Schatz	3/192 not stented; 19/196 received stent	At discharge 6 months
BENESTENT I[38,114]	262 258	Clinical: death, CVA, MI, CABG, PTCA Angiographic: MLD	Angiographic success rate (<50% stenosis on visual assessment); procedural success rate (<50% stenosis on quantitative assessment); functional class–Canadian Cardiovascular Society at 6 months or intercurrent angiography; stenosis rate	Multicentre, International. Europe, Argentina	Single and multiple new lesion, native coronary artery, suitable for CABG, <15 mm long, >3 mm diameter	Ostial, bifurcation, severe vessel tortuousity, thrombus	Aspirin Heparin Warfarin	Palmaz–Schatz	PTCA 16/257 stent 24/259	In-hospital, 7 months, 1 year, 5 years

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
BENESTENT II[39]	414 413	Event-free survival at 6 months (death, MI, need for revascularisation); MLD at follow-up	Restenosis rate at 6 months, cost-effectiveness at 12 months; angiographic and procedural success rate; major bleeding complications; vascular complications	Multicentre, Europe	Stable or unstable angina, new lesions (≥ 1), <15 mm long, >3 mm diameter; >1 lesion per patient allowed to be randomised	LM lesion, bifurcation, great vessel lesion; LVEF <30%, evolving MI within 1 week	Aspirin Heparin Ticlopidine	Heparin-coated stent (Palmaz–Schatz)	PTCA 55/410 (13.4%) Stent 14/413 (3.4%)	1, 6, 12 months
BEST[40]	122 132	6-month angiographic restenosis rate	MLD; IVUS minimal lumen cross-sectional area; clinical outcome between the two strategies	Multicentre, (France)					PTCA to stent 58 (44%) ('Insufficient result in 34, dissection in 24')	6 months
BOSS[41]	31 66	TVR (8 months)	Angiographic: restenosis; 'accuracy of subjective determination of an adequate PTCA by the operator'	Multicentre (6), USA	*De novo* lesions in native vessels, ≥ 3.0 mm diameter, <15 mm long, acceptable for stenting	Angina at rest (within 24 h); MI (within 72 h), CTO; multiple, heavily calcified, restenotic, SVG lesions; multiple-vessel interventions, thrombus	Aspirin Heparin Ticlopidine	Palmaz–Shatz stent (Cordis, Johnson & Johnson Miami, FL)	PTCA to stent 24/66 (36%); stent to PTCA 2/31 (6%); Total PTCA = (66 – 24) +2 = 44 treatment received analysis available)	Angiographic follow-up 6–8 months [stent 17/31, PTCA 42/66, 61% of all patients (12 treatment ratios)]
DEBATE II[42]	97 523	Cost-effectiveness	Benefit differences; relative cost/benefit ratio; efficacy end-points MACE within 12 months; death (any cause), (non-fatal) MI, CABG, TLR (by PCI or CABG)	Multicentre, Europe	Stable or unstable angina pectoris (excluding Braunwald III), single new lesions, target lesion <25 mm long	CTO, ostial/ bifurcation lesions, bypassed vessels, tortuous or contained thrombus, previous Q-wave MI		Not specified (although Cordis acknowledged for providing stents free of change)	Bailout stenting in 129/523 PTCA patients	12 months, ECG, angina status and physical 1, 6 and 12 months

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
DESTINI[43]	370 365	Development of ≥ 1 lesion-related MACE at 12 months, defined as death, MI or repeat target lesion revascularisation		Multicentre (55), international	Suitability of lesion for stent	MI within 24 h, previous Q-wave MI with akinesia or diskinesia of territory supplied by target vessel, CTO, graft + ostial stenosis, 2nd restenosis after PTCA stent restenosis, rotablator/ atherectomy	Aspirin Heparin Ticlopidine GP IIb/IIIa (i.v. 4% of patients)	Johnson & Johnson 36.5%; NIR (Boston) 32.6%; ACS & AVE 20.5%; GR, Wiktor & 'other coils' 10.4%	PTCA to St 206/365	6 months (physical, ECG and stress testing); 1 year (patients/ families contacted for incidence of MACE or repeat of symptoms)
EECKHOUT[44]	42 42	Death, MI, stroke, CABG, crossover, repeat non-surgical revascularisation; early and subacute vessel closure, revascularisation	Vascular complications, duration of hospital stay, angina functional class (CCS)	Single centre, Switzerland	Right coronary artery stenosis – new onset, symptomatic and documented angina, vessel >3 mm	Evolving MI, previous extensive myocardial necrosis, risk for loss to follow-up, poor candidates for CABG, ostial or long lesion (>20 mm), thrombus, vessel tortuousity	Aspirin Heparin	Wiktor stent	PTCA 3/42 (7.1%), S 2/42 (4.8%)	In-hospital and 6 months
EPISTENT[45,233]	1603[c] 796[c]	Combination of death, MI or reinfarction, or severe myocardial ischaemia requiring urgent CABG or revascularisation within 30 days	Death or MI, death or large MI	Multicentre (63), USA, Canada	Ischaemic heart disease, stenosis >60%, lesions amenable to PTCA or stenting	Target vessel LM stem stenosis, bleeding diathesis, intracranial neoplasm, CVA within 2 years, uncontrolled hypertension, recent surgery, PCI within 3 months, concurrent warfarin	Aspirin Heparin Abciximab	First choice: Palmaz–Schatz (Johnson and Johnson)		30 day (St-plc 799/809, St-abc 787/794, PTCA-abc 773/796); 6 months

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
FROST[46]	126 127 (2 excluded from analysis)	Final MLD at the target site measured at 6 months follow-up	BRR, incidence of MACE at 6 months follow-up	Multicentre (17), France	Myocardial ischaemia, *de novo* lesions, native coronary arteries	AMI within 3 weeks, LVEF <50%, abnormal wall motion in area of target vessel, hypertrophic cardiomyopathy	Aspirin Heparin Ticlopidine	PS-153 (Johnson & Johnson Interventional Systems, Warren, NJ)		In-hospital and 6 months
Knight *et al.*[47,234]	39 38	Restenosis rate at 6 months		Single centre, UK	Suboptimal result of PTCA, *de novo* stenosis (>50% reduction in luminal diameter), native arteries, ≥ 2.5 mm	CTO, restenosis, SVG lesions, emergency PTCA, PTCA for AMI	Aspirin Heparin Warfarin	Palmaz–Schatz PS 153/104 (3/29 randomised to stent had an alternative stent implanted)	Stent 1, CABG 1 withdrawal	6 months symptoms and angiography (St 37/39, PTCA 38/38)
OCBAS[49,235]	57 59	Binary restenosis (by angiogram) at 6 months; TVR at 6 months	Event-free survival (cardiac death, Q- or Non-Q-wave MI, angina, repeated TVR) at 6 months	Multicentre, Argentina, Chile, Uruguay, USA	Symptomatic CAD, *de novo* lesions, native arteries, lesions <20 mm long, reference diameter >2.5 mm, successful PTCA with good angiographic result immediately before randomisation	Diffuse or severe LM disease, severe vessel tortuousity, lesions with acute complications, suboptimal PTCA result	Aspirin Heparin Ticlopidine	Gianturco Roubin II (33), Palmaz–Schatz (21), Multilink (5), Wiktor (3), Wallstent (3), AVE (2)	PTCA to stent 8/59 (2nd angiogram in PTCA group 30 minutes after procedure leading to crossover if early loss detected)	Clinical assessment at 1, 3, 6 months (except for deaths and TVR during 'early follow-up') Clinical follow-up in first year (9–23 months) available for all patients Angiography 7.6 ±0.4 months, on 112/116 patients

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
OPUS[48]	230 249	Composite of MI, TVR, cardiac surgery or death at 6 months	Costs at 6 months, angina severity or functional status	Multicentre (44), USA, Canada	Stable or unstable angina, single vessel, <20 mm long, >3 mm diameter, >70% stenosis	MI within <24 h, requirement for tx of >1 vessel, >45° angulation of the lesion, moderate to severe calcification, ostial stenosis	Aspirin Heparin Ticlopidine	Palmaz–Schatz (77%), Cooke (1%), other 20%	93 (37%) PTCA patients received provisional stents	In-hospital, 6 months
RSSG[50]	191 (178 analysed) 192 (176 patients analysed)	Angiographic evidence of restenosis (stenosis of >50% of luminal diameter) at 6 months	Event-free survival including death, MI, CABG, TVR after randomisation	Multicentre, 6 countries	Symptomatic IHD, single lesion in a coronary artery after 1st, 2nd, 3rd or subsequent PTCA with luminal narrowing >50%	Lesion ≥ 10 mm long	Aspirin Heparin	Palmaz–Schatz	PTCA: 12/176 (1.1%) stent: 12/178 (6.7%) did not have stent placed	In-hospital, 6 months

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
SAVED[51]	110 110	Restenosis (luminal diameter ≥ 50 at follow-up); composite outcome (death, MI, repeat CABG or revascularisation at target lesion)	Procedural success rate (reduction of restenosis rate <50%), duration of hospitalisation, frequency of bleeding and peripheral vascular complications	Multicentre, USA	Angina or objective evidence of myocardial ischaemia, stenosis of SVG, stenosis >60%, diameter 3.0–5.0 mm	MI <7 days, LVEF >25%, diffuse disease needing >2 stents, thrombus, outflow obstruction of graft	Aspirin Heparin Warfarin	Palmaz–Schatz	PTCA 7/107, plus two had CABG and 2 treated medically stent 2/108 plus one in stent group to CABG	In-hospital, 6 months
START[52]	229 223	Restenosis (>50% reduction in luminal diameter at 6 months)	Composite end-point (death, AMI, TVR) at 4 years	Multicentre (5), Spain	Angina, objective evidence of myocardial ischaemia, new lesion, stenosis >70%, <15 mm long, >3 mm diameter; multiple-vessel CAD, >1 lesion per patient allowed to be randomised	AMI within 1 week, ostium, side branch >2.5 mm; CTO <3 mm, heavy calcification, vessel tortuousity, stenosis of LM coronary artery >25%, cardiogenic shock	Aspirin Heparin Warfarin Ticlopidine	Palmaz–Schatz	PTCA 25/223 (11%)	In-hospital, 6 months, 4 years

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
STRESS I[53]	207 203	Angiographic evidence of restenosis, defined as at least 50% stenosis on the follow-up angiogram. Clinical evidence of procedural success without a major complication during the index hospitalisation	Angiographic evidence of procedural success and the absolute MLD after the procedure and at follow-up, composite end-point (death, MI, CABG or need for repeat PTCA within the first 6 months after the initial revascularisation)	Multicentre (20), International	Symptomatic ischaemic heart disease, new lesions, native coronary artery, >70% stenosis, <15 mm, >3 mm diameter	MI within 7 days, LVEF <40%, thrombus, presence of multiple focal lesions or diffuse disease, serious disease in LM coronary artery, ostial lesions, severe vessel tortuousity	Aspirin Heparin Warfarin	Palmaz–Schatz	8/205 (3.9%) of the stent patients did not receive stents PTCA group 14/203 (6.9%) received emergency stent	1 month, 3 months, 6 months and 1 year
STRESS II[54] 12 months data source: reference 222	100 89	Angiographic and clinical outcomes		Multicentre, International	Same as STRESS I	Same as STRESS I	Same as STRESS I			12 months
VENESTENT[55]	78 72	Angiographic BRR (restenosis >50% diameter stenosis)	MACE (death, MI, CABG, PTCA) – free survival	Multicentre (9), The Netherlands	SVG lesions			Wiktor-I stent	PTCA 23.6%	1, 6 months
Versaci *et al*.[56]	60 60	Procedural success rate (residual stenosis <50%, absence of death, MI, need for CABG in-hospital), event-free survival rate at 12 months; stenosis rate (>50%); recurrence of angina	In-hospital complications at puncture sites; in-hospital duration	Single centre, Italy	Angina, documented myocardial ischaemia or both; single vessel LAD artery <15 mm long, >3 mm diameter, LVEF >40%	MI within 1 month, ostial, major branch within target lesion, CTO, severe vessel tortuousity	Aspirin Heparin Warfarin	Palmaz–Schatz	PTCA 4/60 (6.9%) 2 to stent, 2 to CABG stent 3/60 (5.2%) crossed to CABG	In-hospital, 12 months

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
WIDEST[57]	146 154	Procedural success rate (residual stenosis <50%, absence of MI, emergency CABG), death, CABG, vessel occlusion, AMI, repeat PTCA and target vessel PTCA, angiographic restenosis		Multicentre (9), international	New, single lesion, native artery, CAD suitable for PTCA and stent	AMI within 7 days, previous PTCA or CABG, vessel occlusion (TIMI grade 0), thrombus, need for >1 stent, ostial lesion, significant LM stem CD, uncontrolled hypertension	Aspirin Warfarin Ticlopidine	Wiktor-GX	PTCA 44/146 (30.1%) to stent Stent group: 3/154 (1.9%)	30 days, 1 year
WIN[58]	229 235	Clinical and angiographic outcome in-hospital and at 6 months – only in-hospital data reported		Multicentre, Canada				Wallstent	Bailouts (25.7%)	In-hospital, 6 months
Participants with AMI										
BESSAMI[59]	80 87	Combined complication rate: (reintervention, CABG, reinfarction and death)		Multicentre, Germany	AMI (clinically and angiographically confirmed), vessel size ≥ 2.5 mm	Severe 3-vessel disease, urgent need of CABG	Ticlopidine	Wiktor-I heparin-coated stent		In-hospital, 5 months (including IVUS)
CADILLAC[60]	518 512	MACE: death from any cause, reinfarction, repeated intervention or ischaemia-driven TRV or disabling stroke during the first 6 months after index procedure		Multicentre (76), international	AMI (≥ 30 minutes <12 h of symptoms), ST elevation in 2 contiguous leads or left brachial branch block, native artery, lesion <64 mm, reference diameter 2.5–4.0 mm	Cardiogenic shock, bleeding, drug allergy, recent major surgery	Aspirin Heparin Ticlopidine or clopidogrel	MultiLink stent		30 days, 6 months

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
ESCOBAR (Suryapranata *et al.*)[61]	112 115	Cumulative first-event rate of death, non-fatal reinfarction or TVR	Restenosis at 6 months, cost-effectiveness at follow-up	Single centre, The Netherlands	AMI within 6 h symptom onset or 6–24 h ongoing ischaemia, native CA, suitable for stenting	Prolonged cardiopulmonary resuscitation or cardiogenic shock, life expectancy <1 year; LM or severe 3-vessel disease, bifurcation, diffuse disease, vessel tortuousity, no reflow, thrombus	Aspirin Heparin Warfarin Ticlopidine	Palmaz–Schatz	Stent 2/112 (2%) PTCA 15/115 (13%)	In-hospital, 6, 24 months
FRESCO[62]	75 75	A composite clinical end-point (occurrence of death, reinfarction or repeat TVR as a consequence of recurrent ischaemia within the 1st 6 months after initial revascularisation)	Angiographic evidence of restenosis or reocclusion, defined as at least 50% stenosis of the target lesion on the scheduled or unscheduled follow-up angiogram	Single centre, Italy	Chest pain >30 minutes, ST elevation within 6 h of symptom onset or 6–24 h of ongoing ischaemia, cardiogenic shock included, reference diameter >2.5 mm, stenosis >70%	Previous fibrinolytic tx, non-optimal PTCA	Aspirin Heparin Ticlopidine	Gianturco–Roubin coronary stent (Cook)		1, 6 months
GRAMI[63]	52 52	Major cardiac complications (death, recurrent ischaemia, reinfarction and emergency CABG) in hospital	Procedural success, event-free survival (death, MI, rerevascularisation, need for TVR, angiographic restenosis (not reported), at follow-up	Multicentre (8), USA, Argentina	Angiography within 24 h, MI symptom onset (chest pain >30 minutes), ST elevation or depression, cardiogenic shock, previous CABG, any length stenosis included	Bleeding risk prohibiting use of heparin/antiplatelet agents, non-cardiac illness with survival <1 year, reference diameter <2.5 mm, severe (50%) stenosis, LM, severe multiple-vessel disease, culprit vessel stenosis <50%	Aspirin Ticlopidine	Gianturco–Roubin II coronary stent		In-hospital, 1 year

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
Jacksch *et al.*[64]	231 231			Multicentre, Germany	AMI				PTCA (27%) 62/231 Stent 32/231	Intra-hospital, control angiogram after 4.6 ± 1.3 months of 431 patients
PASTA[65]	67 69	MACE (repeat MI, TLR, cardiac death) in-hospital and at 6 months	Reocclusion of target vessel; angiographic restenosis	Multicentre (6), Japan	AMI within 12 h, TIMI grade ≤ 2, estimated diameter of culprit coronary artery ≥ 2.5 mm	Excessive bending or calcification of coronary artery proximal to the culprit lesion	Aspirin Heparin Ticlopidine	Palmaz–Schatz (manually taken off Johnson & Johnson delivery system and crimped to a 'different balloon')	PTCA 7/69 (10%) Stent 1/67 (1%)	In-hospital, 6 months, up to 12 months; angiograms at 1–2 weeks and 6 months after onset of MI; clinical follow-up for more than 12 months
PRISAM[66]	110 112			Multicentre, Japan	AMI (symptom onset <24 h)			Wiktor coil stent	PTCA 1% Stent 0	6 months; angio-graphies at 1 and 6 months

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
PSAAMI[67]	44 44	Combined end-point (death, reinfarction, TLR)		Single centre, Germany	AMI <6 h or within 24 h, ongoing ischaemia, left heart failure, cardiogenic shock, clinical indication for PTCA, native artery ≥ 3 mm, stenosis >70% diameter, TIMI flow <grade III	Indication for surgical coronary revascularisation within 6 months, previous MI, secondary or iatrogenic infarction, chronic renal insufficiency requiring dialysis	Aspirin Heparin Ticlopidine	Tensum III stents (silicone carbide-coated tantalum)	PTCA 12/44, (Stent 1/44 did not have stent placed)	30 days; long-term mean 710 ± 282 days, St 723 ± 273 days, PTCA 697 ± 293 days
STENT PAMI[68]	452 448	Composite of death, non-fatal MI (enz), disabling stroke, TVR for ischaemia (including PCI or CABG) during 6 months	Percentage stenosis, MLD, TIMI, clinical events 30 days, BRR, reocclusion at 6 months	Multicentre (62), international	AMI within 12 h of onset; ST elevation, native artery suitable for PTCA or stent, reference diameter, 3–4.5 mm, (one or more lesions) coverable by 1 or 2 15-mm stents	Likelihood of CABG within 6 months, cardiogenic shock, CVA within 1 month, renal failure, prior thrombolysis, excessive tortuousity, calcification, major side branch within lesion, warfarin use	Aspirin Heparin Ticlopidine Abciximab (10.3%)	Heparin-coated, Palmaz–Schatz	PTCA 15.1% Stent 1.3%	Clinical follow-up 1, 6 months, QoL 1, 6 months, angiography at 6.5 months

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
STENTIM-2[69]	101 (91) 110 (99)	BRR at follow-up	Procedural success [residual stenosis <50%, TIMI grade 3, a composite end-point (death, recurrent MI, repeat TVR) at 6–12 months], recurrent ischaemia, reocclusion	Multicentre, France, The Netherlands	Nitrate-resistant chest pain within 12 h of onset, ST elevation, ECG and enzyme confirmation of AMI, vessel diameter <3 mm, culprit lesion stenosis >70%	Previous thrombolytic therapy, cardiogenic shock, previous CABG, PTCA within 6 months, severe renal or liver failure, multiple vessels diseased	Aspirin Heparin Ticlopidine Abciximab	Wiktor-GX (Medtronic) 16 mm long stent; additional stent may have been placed	Stent 3/101 (3%); PTCA 40/110 (36.4%)	Procedural, hosp outcome at discharge, 6 months, 1 year; 500 days Kaplan–Meier plots
Participants with small coronary arteries										
BESMART[70]	192 189	Angiographic restenosis rate at 6 months	Procedural success [angiographic success without MACE (death, MI or revascularisation, by PCI or CABG) at 6 months follow-up], reduction in stenosis to <50% by quantitative coronary angiography	Multicentre (21), France	IHD with *de novo* lesions on small native coronary arteries, >50% stenosis; lesion <3 mm diameter, <15 mm long	MI within previous 3 days, ostial/bifurcation lesion, LVEF ≤ 30%, CI to aspirin or ticlodipidine	Aspirin Heparin (before and after procedure) Ticlodipidine (after procedure)	Bestent Small (Medtronic)	Unclear	In-hospital, 6 months (MACE follow-up in 242/381 patients)
CHIVAS[71,236]	148 154	MACE (death, CABG, PTCA)		Multicentre (23), Japan	*De novo* or 1st restenotic lesions of native arteries of <3 mm and lesions <15 mm long			ACS Multilink		6 months, angiograph at 6 months, interim analysis on 241/283 patients

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
COAST[72]	312[d] 155[d]	MLD at 6 months	Procedural success, complications, restenosis, TVR, event-free survival	Multicentre (21), Europe	Stable or unstable angina, target lesions <30 mm in native vessels, 2.0–2.6 mm diameter	MI within previous 24 h (based on CPK rise)	Aspirin Heparin Ticlopidine or clopidogrel	Non-coated or heparin-coated Jostent Flex (Jomed, Beringer, Switzerland)	27% [crossover rate (interpret as PTCA to stent) but unsure of denominator]	6 months (467/588 with angiographic follow-up)
ISAR-SMART[73,86]	204 200	Angiographic restenosis at follow-up	Adverse clinical events, such as all-cause death, MI, CVA, TVR (PTCA or CABG)	Multicentre, Germany	Angina pectoris, exercise-induced ischaemia, presence of angiographically significant lesions (≤ 70% diameter stenosis), native artery	AMI within previous 72 h, lesions situated in LM coronary artery, lesions produced by in-stent restenosis and CI to antithrombotics	Aspirin Heparin Abciximab Ticlopidine	Multi-Link	PTCA 16.5%, Stent 4.4%	30 days, 6 months
Park *et al.*[74]	60 60	Angiographic stenosis at follow-up	Incidence of clinical events: death, MI, TVR (TLR mentioned)	Single centre, Korea	Focal, *de novo* lesion (DS >50%, <15 mm long, reference diameter <3.00mm), native artery	Ostial, calcified lesion, CTO, infarct-related artery, left vessel descending (EF <40%), CI to antiplatelets	Aspirin Heparin Ticlopidine		PTCA to stents 12/60 (8 suboptimal, 4 major dissection)	In-hospital, (patients requested to attend at 1, 3 and 6 months), 15.9 ± 5.7 months Angiography 6 months
RAP[75]	212 214	Angiographic stenosis at 6 months	Incidence of MACE (death, infarction or new revascularisation process)	Single centre, Spain	Small lesions 2.2–2.7 mm, 1 or 2 new lesions, native artery			BeStent	PTCA 14%, Stent 1%	6 months

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
SISA[76]	169 182	Angiographic stenosis (stenosis ≥ 50% diameter)	Angiographic success (reduction in stenosis <50%, QCA); procedural success (<50% diameter stenosis); clinical success [angiographic success without clinical events (MACE: death, MI, CABG, TVR); TVR at 6 months; absolute MLD after procedure and follow-up]	Multicentre, international	Stable or stabilised unstable AP (Braunwald IIb), silent ischaemia, required PTCA of one *de novo* lesion, reference diameter ≥ 2.3 and ≤ 2.9 mm, ≤ 12 mm long without thrombus	LVEF <40%, CI to anticoagulants	Aspirin Heparin Ticlodipidine	BeStent Artist (Medtronic Vascular)	PTCA 37/182 (20.3%), 4/169 (2.4%)	In-hospital, 6 months
SISCA[77]	74 71	MLD at follow-up	Restenosis rate, event-free survival and angina status	Multicentre (5), Scandinavia	Single- or multiple-vessel disease, stable or unstable angina, *de novo* 2.1–3.0 mm diameter, diameter stenosis >50%, multiple-vessel and multistage PTCA	Functionally occluded vessels with multiple lesions or visible thrombus, bifurcation lesions, patent grafts and ongoing MI, CI to study medication	Aspirin Heparin Ticlopidine or clopidogrel GP IIb/IIIa inhibitors	BeStent (heparin coated with Hepamed)	PTCA 10/71 (14.1%) Stent 3/74 (4.1%)	In-hospital/ 1 month, 6 months, 1 year
Participants with CTO										
CORSICA[78,237]	72 70			Multicentre, France	CTO >15 days, stable and satisfactory results of PTCA		Aspirin Ticlopidine	Palmaz–Schatz	PTCA to stent 3/70	

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
GISSOC[79]	56 54	MLD at follow-up	Restenosis, major ischaemic events (death, MI, CABG, TVR), symptomatic status at follow-up, haemorrhagic events	Multicentre (8), Italy	Absolute or functional occlusion (TIMI 0 or I), chest pain or inducible ischaemia, suitable for CABG, >3 mm diameter, <13 mm long	AMI within 30 days, acute angina at rest 7 days, CTO at site of previous PTCA, complex dissection, occlusions for <30 days, significant LM disease, torturous, side branch, CI to anticoagulation	Aspirin Heparin Warfarin	Palmaz–Schatz	PTCA 1/54 (1.9%) Stent 0/56	In-hospital, 3, 6, 9 months
Hancock *et al*.[80]	30 30	Angiographic reocclusion	MLD at 6 months, combined clinical event rate (repeat PTCA, CABG, MI) at 6 months, death	Single centre, UK	Complete obstruction, TIMI 0 or 1, > 3 days; successful initial PTCA results with TIMI grade 3 flow distal to occlusion	Stent occlusions, poor distal flow after PTCA, stent thrombosis, coronary vein grafts, AMI, thrombus. <3 mm diameter, CI to anticoagulation	Aspirin Heparin Warfarin	Palmaz–Schatz	0/60	In-hospital and 6 months
SARECCO[81]	55 55	Acute and 4-month procedural success [diameter stenosis of <50% w/out major complications (death, MI, CABG or repeat PTCA)]	MLD, % stenosis, reocclusion rate, stenosis rate; one of the following: TVR, MI or death ≤ 2 years	Multicentre, Germany	TIMI grade 0, for ≥ 1 week estimated from clinical events or angiography, vessel >2.5 mm diameter (long lesions, diffuse disease, thrombus included)	AMI, saphenous CABG, severe vessel tortuousity, bifurcation lesions, residual stenosis >50% after PTCA, CI to anticoagulation	Aspirin Heparin Ticlodipidine	Mixed-type stents (14 Wallstent, 11 Wiktor, 14 Palmaz–Schatz, 7 Sito, 6 ACS Multilink and 23 other stents)	PTCA 0/55, Stent 1/55 (1.8%) no stent implanted	In-hospital, 4 months

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
SICCO[82]	58 59	Restenosis rate (≥ 50 DS) at 6 months, MACE (cardiac death, CVA, MI, target lesion redilation or CABG)	Reocclusion rate in MLD and DS, functional AP class according to CCS classification	Multicentre (4), Scandinavia	PTCA of occluded native coronary artery (total or functional occlusion; TIMI 0 or 1), native artery, previously undilated lesion, reference diameter >2.5 mm	Occlusions <14 days, indication for bailout stenting (major dissection), complex anatomy, lesions with poor distal runoff; thrombus, intolerance to anticoagulation	Aspirin Heparin Warfarin	Palmaz–Schatz		14 days, 6, 33 months
SPACTO[83]	42 43	Restenosis and reocclusion rates	MACE (death, MI, further revascularisation, recurrence of angina)	Multicentre (2), Germany	TO (TIMI 0), event >28 days; reference diameter ≤ 2.7 mm	Renal failure, recent CVA, CI to anticoagulation	Aspirin Heparin Ticlodipidine	Wiktor-GX	PTCA 7/43	6 months
STOP[84]	48 48	Restenosis/ reocclusion at 6 month	Procedural success/ complications; MACE [death, recurrent AP, MI (Q-wave), PTCA, CABG], need for revascularisation during 6 months	Multicentre, Israel	CTO, native artery, reference diameter ≥ 2.75 mm, successful PTCA (without stents)	Failed PTCA, need for stent for suboptimal PTCA	Aspirin Heparin Ticlodipidine	AVE Microstent (18–39 mm length)	None	Clinical 1, 3, 6 months; angiography 6 months (69/96 studied)

continued

TABLE 77 *PTCA: study characteristics (cont'd)*

Study name	N[a] stents PTCA	Primary outcome	Secondary outcomes	Location(s) and centres	Inclusion criteria	Exclusion criteria	Co-therapies	Type of stent	Crossovers	Follow-up[b]
TOSCA[85]	202 208	Failure of sustained patency	TVR, composite end-point: any revascularisation, AMI, death at 1 year, cardiovascular events at 1 year, and change in global and regional left ventricular function	Multicentre, Canada, Japan, USA, New Zealand	Native artery, suitable for stenting, reference diameter >3 mm, TIMI 0 or 1	<72 h from onset of new ST elevation, thrombus, previously revascularised occlusion, uncontrolled heart failure or shock, unsuitable for 6 months angiography, inability to cross occlusion with guidewire	Aspirin Heparin Ticlopidine	Carmeda process heparin-coated 15 mm long PS-153 Palmaz–Schatz coronary stent	PTCA 20/208 (9.6%) Stent 8/202 (4.0%)	In-hospital and 6 months

EF, ejection fraction; GI, gastrointestinal; GP, glycoprotein; LVET, left ventricular ejection fraction

[a] Numbers randomised stents/PTCA.

[b] Proposed periods of follow-up as stated in source.

[c] Stent plus placebo 809; stent plus abciximab 794; PTCA plus abciximab 796.

[d] 312 (non-coated stents 157, heparin-coated stents 155) [RH:] stents 196 (follow-up angiogram on 157); heparin-coated stents 197 (follow-up angiogram on 155); 155 PTCA 195 (follow-up on 155) (196 + 197 + 195 = 588; follow-up on 467).

TABLE 78 *PTCA: participant characteristics*

Study name	Number assigned to stents/PTCA	Age, mean (SD) (years)	Gender (% male)	ACS (%)	Diabetes (%)	Previous MI (%)
Non-specific CAD participants						
ADVANCE[36]	145 143	61.1 (9.2) 62.2 (9.6)	67.6 79	UA: 30.3 30.8	17	41.7
AS[37]	200 (192) 200 (196)	51.81 (11.6) 52.37 (10.8)	74 72		3.4	45.4
BENESTENT I[38]	262 258	57(9) 58(10)	80 82		7 6	20 19
BENESTENT II[39]	414 413	50(10) 59(11)	77.2 79.8	UA: 45 40	18.5	26.5
BEST[40]	122 132					
BOSS[41]	31 66	62 ±13 years	*Overall*: 69	UA: 48	3	
DEBATE II[42]	97 523	60 (10) 59 (11)	72 73	UA: 39 34	10	6.2 9.9
DESTINI[43]	370 365	61.0 (10.4) 59.8 (10.7)	74.6 73.2	UA: 46.4 52.3	18.5	37.9 38.1
Eeckhout *et al.*[44]	42 42	59 (55 to 63) 57 (53 to 60) (95% CI)	88.1 73.8	UA: 13 1	11 3	35.7 38.1
EPISTENT[45,233]	809 Stent + placebo 794 Stent + abciximab 796 PTCA+ abciximab	59 (11) 59 (11) 60 (11)	74.6 75.4 75.1	UA: 60.4 56.4 54.8	20.5	54.6 49.4 48.5
FROST[46]	126 127 (2 excluded)	60.6 (10.3) 59.3 (11)	83.2 81	UA: 67.2 61.9	15.6	
Knight *et al.*[47,234]	39 38	61.3 (8) 56.9 (7)	76.9 84.2		11.7	
OCBAS[49,235]	57 59	56.07 ±9 yrs 58.51 ±11 yrs	86 83.1	UA: 78.9 81.4	10.3	22.3 20.3
OPUS[48]	230 249	51, 61, 69 51, 60, 67 25th, 50th, 75th percentiles	75.2 71.5	UA: 71.7 69.1	18	44.3 41
RSSG[50]	191[a] 192[a]	59 ± 10 60 ± 8,	79.8 81.8	UA: 16.9 21.6	17.5	36.5 41.5
SAVED[51]	110 110	66 ± 9 66 ± 9,	82 79	UA: 82 77	29.5	68 70
START[52]	229 223	59 (52–66) 59 (51–67) Mean (25th, 75th percentiles)	87 85	UA: 74 69	13.5	32 32
STRESS I[53]	207 203	60 (10) 60 (10)	83 73	UA: 47 48	15.5	37 36
STRESS II[54] 12-month data source: reference 222	100 89					
VENESTENT[55]	78 72					

continued

TABLE 78 *PTCA: participant characteristics (cont'd)*

Study name	Number assigned to stents/PTCA	Age, Mean (SD) (years)	Gender (% male)	ACS (%)	Diabetes (%)	Previous MI (%)
Versaci *et al*[56]	60 60	56 ± 9 57 ± 10	92 83	UA: 17 18	15	28.3 25
WIDEST[57]	146 154	59.2 ± 9.2 57.2 ± 9.3	76 76		9	
WIN[58]	229 235	62 ± 11 years	Overall: 72	Overall: 83		
Participants with AMI						
BESSAMI[59]	80 87	61 ± 1.2 61 ± 1.5	78.8 72.4			
CADILLAC[60]	518 512	Median 60 (28–95) 59 (21–90)	72.5 71.4	–	15.7	11.9 13.9
ESCOBAR[61]	112 115	59 ± 11 57 ± 11	83 85	–		13.4 13
FRESCO[62]	75 75	62 (12) 61 (12)	75 80	–	12.5	8 8
GRAMI[63]	52 52	59 (±9) 58 (±11)	88 79	–	9	15 6
Jacksch *et al.*[64]	231 231			–		
PASTA[65]	67 69	67.4 ± 10.8 67.2 ± 11.8	73 70	–	19	7.5 4.3
PRISAM[66]	110 112					
PSAAMI[67]	44 44	61±10 61±11	80 73	–	24	9.1 9.1
STENT-PAMI[68,38]	452 448	59.2 ± 12.6 60.9 ± 12.3	74.8 74.8	–	15	10.8 11.8
STENTIM-2[69]	101 (91 1 year end-point) 110 (99 1 year end-point)	57.2 ± 12.2 57.7 ± 12.8	85.1 79.1	–	13.7	
Participants with small coronary arteries						
BESMART[70]	192 189	62 (10) 61 (10)	73.4 79.3	UA: 50.0 42.8	17	15.85 21.7
CHIVAS[71,236]	148 154				50	
COAST[72]	312 155					
ISAR-SMART[73,86]	204 200	65 (11.3) 66.5 (11)	77.5 76	UA: 42.6 36.5	24.7	34.8 39
Park *et al.*[74]	60 60	60.2 ± 7.5 61.5 ± 8.4	61.7 65	UA: 18.3 20	12.5	15 10
RAP[75]	212 214					
SISA[76]	169 182	60.6 ± 10.3 59.9 ± 10.5	66.3 67	UA: 34.3 29.1	19.3	31.9 35.1
SISCA[77]	74 71	63.1 ± 11.2 62.7 ± 10.1	56.8 73.3	UA: 25.7 21.1	13.1	41.9 45.1

continued

TABLE 78 *PTCA: participant characteristics (cont'd)*

Study name	Number assigned to stents/PTCA	Age, Mean (SD) (years)	Gender (% male)	ACS (%)	Diabetes (%)	Previous MI (%)
Participants with CTO						
CORSICA[78,237]	72 70					
GISSOC[79]	56 54	58.3 ± 6.8 57.0 ± 9.3	86 83	UA: 7 11	10	54 83
Hancock *et al.*[80]	30 30	61 60	53 73			
SARECCO[81]	55 55	61 ± 9 60 ± 11	86 69	AMI excluded		47 51
SICCO[82]	58 59	58.4 ± 12.0 57.2 ± 9.4	84 80		8.8	62
SPACTO[83]	42 43	Median 62.5 (36–78) 62.0 (34–76)	57.1 81.4	UA: 11.9 7	34.1	31 39.5
STOP[84]	48 48	59.3 ± 10.1 58.9 ± 10.9	85.4 83.3		25	58.3 70.8
TOSCA[85]	202 208	57.6 ± 10.4 57.7 ± 10	84 80		16.5	67 67

UA, unstable angina.
[a] 191 randomised (178 patients analysed); 192 randomised (176 patients analysed).

TABLE 79 *PTCA: outcomes*

Study name		Event rate (%)		Mortality (%)		AMI (%)		Revascularisation (%)		CABG (%)		PTCA (%)		BRR (%)	
Non-specific CAD participants															
ADVANCE[36]	Stent	31 days	3.4	31 days[a]	0	31 days	2.8	31 days	0.7	31 days	0.0			9 months	27
	145	300 days	23.4	300 days[a]	0	300 days	2.8	300 days	17.9	300 day	2.8				
	PTCA	31 days	7.0	31 days[a]	0	31 days	4.9	31 days	1.4	31 days	0.7			9 months	42
	143	300 days	23.1	300 days[a]	0	300 days	4.9	300 days	14.7	300 days	3.5				
AS[37]	Stent	14 days	2.1	14 days	0	14 days	1.0	TLR		0–14 days	1.04	14 days	0.0	6 months	18.2
	192	6 months	16.7	180 days	0	180 days	1.6	14 days	1.0	15–180 days	0.53	6 months	13.9		
								6 months	15.1						
	PTCA	14 days	2.6	14 days	0	14 days	1.5	TLR		0–14 days	0.5	14 days	0.5	6 months	24.9
	196	6 months	22.9	180 days	0	180 days	2.0	14 days	1.0	15-180 days	1.6	16 months	9.2		
								6 months	20.9						
BENESTENT I[38]	Stent	In-hospital	6.9	In-hospital	0.0	In-hospital	3.4	*Urgent*		In-hospital	0.4			6 months	22
	259	7 months	20.1	7 months	0.8	7 months	4.2	In-hospital	1.9	7 months	10.0				
		1 year	23.4	1 year	1.2	1 year	5.0	7 months	1.9	1 year	10.0				
		5 years	34.4	5 years	5.9	5 years	8.6	1 year	1.9	5 years	9.8				
								Elective							
								In-hospital	1.2						
								7 months	3.1						
								1 year	5.0						
								5 years	9.8						
	PTCA	In-hospital	6.2	In-hospital	0.0	In-hospital	3.1	*Urgent*		In-hospital	1.2			6 months	32
	257	7 months	29.6	7 months	10.4	7 months	3.9	In-hospital	1.6	7 months	20.6				
		1 year	31.6	1 year	0.8	1 year	4.2	7 months	1.6	1 year	20.6				
		5 years	40.2	5 years	3.1	5 years	5.8	1 year	1.6	5 years	21.9				
								Elective							
								In-hospital	0.0						
								7 months	2.3						
								1 year	3.5						
								5 years	8.2						
BENESTENT II[39]	Stent	1 month	3.9	1 month	0.0	1 month	2.7			1 month	0.7	1 month:	0.5	6 months	16
	413	6 months	12.8	6 months	0.2	6 months	3.1			6 months	1.5	6 months	8.0		
		1 year	15.7	1 year	1.0	12 months	3.4			12 months	1.9	12 months	9.4		
	PTCA	1 month	5.1	1 month	0.2	1 month	3.2			1 month	0.5	1 month	1.2	6 months	31
	410	6 months	19.3	6 months	0.5	6 months	3.7			6 months	1.5	6 months	13.7		
		1 year	22.4	1 year	1.0	1 year	4.4			12 months	1.5	12 months	5.6		
BEST[40]	Stent	6 months	16											6 months	18.1
	116														
	PTCA	6 months	18											6 months	16.8
	119														

continued

TABLE 79 *PTCA: outcomes (cont'd)*

Study name		Event rate (%)		Mortality (%)		AMI (%)		Revascularisation (%)		CABG (%)		PTCA (%)		BRR (%)	
BOSS[41]	Stent 31	–		In-hospital 8 months	0.0 0.0	In-hospital 8 months	0.0 0.0	In-hospital 8 months	0 19	In-hospital	0.0			8 months	47
	PTCA 66	–				In-hospital 8 months	0.0 0.0	In-hospital 8 months	0 21					8 months	38
DEBATE II[42]	Stent 97	1 year	13.4	1 year	2.1	1 year	4.1	1 year[b]	7.2	1 year	0.0				
	PTCA 523	1 year	15.9	1 year	1.3	1 year	3.6	1 year[b]	10.9	1 year	1.1				
DESTINI[43]	Stent 370	1 month 12 months	3.8 17.8	1 month 1 year	0.0 0.8	1 month 12 months	2.7 3.2	1 month (TLR repeat PTCA) 12 months (any TLR)	0.27 14.9	1 month Any CABG	0.8 3.5	1 month 12 months	0.3 14.9		
	PTCA 265	1 month 12 months	5.2 18.9	1 month 1 year	0.0 0.8	1 month 12 months	3.3 3.8	1 month (TLR repeat PTCA) 12 months (any TLR)	1.3 15.6	1 month Any CABG	0.5 2.1	1 month 12 months	1.4 15.6		
Eeckhout *et al.*[44]	Stent 42	In-hospital 6 months	7 24	In-hospital 6 months	0.0 0	In-hospital 6 months	0 0			In-hospital 6 months	2.4 4.8	6 months	11.9	6 months	37.5
	PTCA 42	In-hospital 6 months	7 26	In-hospital 6 months	0.0 0	In-hospital 6 months	0 0			In-hospital 6 months	0.0 2.4	6 months	16.7	6 months	35.0
EPISTENT[c45]	Stent 809 794	30 days St–plc St–abc	 10.8 5.3	30 days St–plc St–abc	 0.6 0.3	30 days St–plc St–abc	 9.6 4.5	30 days St–plc St–plc	 2.1 1.3	30 days St–plc St–abc	 1.1 0.8	30 days St–plc St–abc	 1.2 0.6		
		6 months St–plc St–abc	 18.2 12.8	6 months St–plc St–abc	 1.2 0.5	6 months St–plc St–abc	 10.3 5.2	6 months St–plc St–abc	 10.4 8.6						
	PTCA 796	30 days 6 months	55/796 162/796	30 days 6 months	0.8 1.7	30 days 6 months	5.3 6.5	30 days 6 months	1.9 15	30 days	0.6	30 days	1.3		
FROST[46]	Stent 125	6 months	16.0	In-hospital 6 months	0.0 2.4	In-hospital 6 months	1.6 2.4	6 months	14.4	In-hospital	0.0	In-hospital	0.0	6 months	21.4
	PTCA 126	6 months	15.1	In-hospital 6 month	0.0 0.0	In-hospital 6 months	1.6 3.2	6 months	15.1	In-hospital	0.0	In-hospital	0.0	6 months	27.1
Knight *et al.*[47,234]	Stent 39	6 months	26 (SD 13, 43)	Peri-procedural	0.0									6 months	24 (SD 12, 24)
	PTCA 38	6 months	53 (SD 36, 69)	Peri-procedural	0.0									6 months	53 (SD 36, 69)

continued

TABLE 79 *PTCA: outcomes (cont'd)*

Study name		Event rate (%)		Mortality (%)		AMI (%)		Revascularisation (%)		CABG (%)		PTCA (%)		BRR (%)	
OCBAS[49,235]	Stent 57	1 year	19.2	1 year	0.0	1 year non-Q-wave	0.0	1 year	17.5	1 year	7.0	1 year	10.5	7.6 ± 0.4 months St 56/57	19.2
	PTCA 59	1 year	16.9	1 year	1.7	1 year non-Q-wave	1.7	1 year	13.5	PTCA	3.4	1 year	0.2	7.6 ± 0.4 months	16.1
OPUS[48]	Stent 230	6 months	6	In-hospital 6 months	0.0 0.4	In-hospital 6 months	1.7 0.4	6 months	3.0	In-hospital	0.4	In-hospital	0.4		
	PTCA 249	6 months	37	In-hospital 6 months	0.0 1.2	In-hospital 6 months	2.4 1.2	6 months	10.1	In-hospital	1.6	In-hospital	0.8		
RSSG[50]	Stent 176	250 days	16	In-hospital 6 months	1.1 1.1	In-hospital 6 months	3.9 4.5	In-hospital 6 months	2.8 10.3	In-hospital 6 months	2.2 5.6			6 months	18
	PTCA 178	250 days	28	In-hospital 6 months	0.6 1.1	In-hospital 6 months	1.1 1.1	In-hospital 6 months	0.6 26.6	In-hospital 6 months	0.6 1.7			6 months	32
SAVED[51]	Stent 108	In-hospital 240 days	6 26	In-hospital 240 days	2 7	In-hospital 240 days	3.7 10.2	240 days	16.7	In-hospital 240 days	1.9 6.5	In-hospital (repeat PTCA) 240 days	0.9 15.9	6 months: Restenosis in-patient Restenosis in-lesion	37 36
	PTCA 107	In-hospital 240 days	11 39	In-hospital 240 days	2 9	In-hospital 240 days	6.5 14.0	240 days	26.2	In-hospital 240 days	3.7 12.1	In-hospital (repeat PTCA) 240 days	0.9 12.9	6 months: Restenosis in-patient Restenosis in-lesion	46 47
START[52]	Stent 229	6 months	14	In-hospital 6 months 4 years	0.9 1.8 2.7	In-hospital 6 months 4 years	1.3 1.8 2.2			6 months 4 years	0.4 1.3	6 months 4 years	8.9 10.7	6 months	22
	PTCA 223	6 months	22	In-hospital 6 months 4 years	1.3 1.9 2.4	In-hospital 6 months 4 years	1.8 2.8 2.8			6 months 4 years	1.9 2.4	6 months 4 years	17.1 22.3	6 months	37
STRESS I[53]	Stent 205	240 days 1 year	7.3 24.9	14 days 1 year	0.0 1.5	14 days 240 days 1 year	5.4 6.3 6.3	1 year	11.7	14 days 1 year	2.4 2.4	14 days 1 year	2 19	6 months 'restenosis'	31.6
	PTCA 202	240 days 1 year	4.0 30.2	14 days 1 year	1.5 2.0	14 days 240 days 1 year	3.0 6.9 7.9	1 year	17.3	14 days 1 year	4.0 5.0	14 days 1 year	2.0 20.8	6 months 'restenosis'	42.1
STRESS II[54]	Stent 115	In-hospital 1 year	4.6 19.7	In-hospital	3			310 days (mean)	9.8						
	PTCA 112	In-hospital 1 year	4.2 28.5	In-hospital	2			310 days (mean)	18.2						
VENESTENT[55]	Stent 78	In-hospital 6 months	9.0 19.5					6 months	11.5					6 months	21.9
	PTCA 72	In-hospital 6 months	9.7 36.1					6 months	25.0					6 months	35.6

continued

TABLE 79 *PTCA: outcomes (cont'd)*

Study name		Event rate (%)		Mortality (%)		AMI (%)		Revascularisation (%)		CABG (%)		PTCA (%)		BRR (%)	
Versaci *et al.*[56]	Stent 60	1 year	13	In-hospital 1 year	0.0 1.7	1 year	2			In-hospital 1 year	1.7 1.7	1 year	6.7	12 months	19
	PTCA 60	1 year	30	In-hospital 1 year	0.0 1.7	1 year	3			In-hospital	1.7	1 year	25.0	12 months	40
WIDEST[57]	Stent 154	30 days 1 year	7.8 20.8	30 days 1 year	0.0 0.0	30 days 1 year	3.9 3.9			30 days 1 year	2.6 4.5	30 days 1 year	3.9 15.6	6 months	21.6
	PTCA 146	30 days 1 year	6.8 19.2	30 days 1 year	1.4 2.1	30 days 1 year	2.1 3.4			30 days 1 year	2.7 4.1	30 days 1 year	3.4 13.7	6 months	17.3
WIN[58]	Stent 229	In-hospital	9.6	30 days	0.4	In-hospital	6.9			In-hospital Emergency CABG	0.4	In-hospital	2.6		
	PTCA 235	In-hospital	5.5	30 days	0.4	In-hospital	5.5			In-hospital Emergency CABG	0.9	In-hospital	0.9		
Participants with AMI															
BESSAMI[59]	Stent 80	5 months	3.75	In-hospital	0.6									5 months	23
	PTCA 87	5 months	49.4											5 months	55
CADILLAC[60]	Stent 512	30 days 6 months	5.7 11.5	30 days 6 months	2.2 3.0	30 days 6 months (cumulative)	1.0 1.6	30 days 6 months	3.4 8.9					7 months	23.7
	PTCA 518	30 days 6 months	8.3 20.0	30 days 6 months	2.5 4.5	30 days 6 months (cumulative) PTCA	0.8 1.8	30 days 6 months	6.0 16.9					7 months	36.5
ESCOBAR[61]	Stent 112	6 months 2 years	5 16	In-hospital 6 months 2 years	1.8 1.8 2.7	In-hospital 6 months 2 years	0.9 0.9 0.9	6 months 2 years	4 13	2 years	6.3	2 years	7.1		
	PTCA 115	6 months 2 years	20 38	In-hospital 6 months 2 years	2.6 2.6 3.5	In-hospital 6 months 2 years	4 7 9	6 months 2 years	17 34	2 years	15.7	2 years	18.3		
FRESCO[62]	Stent 75	6 months	9	30 days (cardiac) Other cardiac cause Non-cardiac 6 months (cardiac) Other cardiac cause Non-cardiac	0 0 0 1 0 0	30 days 6 months	1.3 1.3	30 days 6 months	1.3 6.7	30 days 6 months	0.0 0.0	30 days 6 months	1.3 6.7	Angiographic restenosis or reocclusion at 1 and 6 months reported	

continued

TABLE 79 *PTCA: outcomes (cont'd)*

Study name		Event rate (%)	Mortality (%)	AMI (%)	Revascularisation (%)	CABG (%)	PTCA (%)	BRR (%)
	PTCA 75	6 months 28	30 days (cardiac) 0 Other cardiac cause 4 Non-cardiac 0 6 months (cardiac) 0 Other cardiac cause 4 Non-cardiac 1	30 days 2.6 6 months 2.6	30 days 12.0 6 months 25.3	30 days 0.0 6 months 2.7	30 days 12.0 6 months 22.7	
GRAMI[63]	Stent 52	In-hospital 3.8 1 year 16	In-hospital[d] 3.8	In-hospital 0.0	1 year 14.0	Emergency, In-hospital 0.0 Elective 0.0	In-hospital 0.0	
	PTCA 52	In-hospital 19.2 1 year 35	In-hospital[d] 7.6	In-hospital 7.6	1 year 20.8	Emergency, In-hospital 1.9 Elective 1.9	In-hospital 5.7	
Jacksch *et al.*[64]	Stent 231		In-hospital 1.3	In-hospital 1.3		Intra-hospital 3/231	In-hospital 1.7	4.6 ± 1.3 months 23 ± 6
	PTCA 231		In-hospital 2.2	In-hospital 3.5		Intra-hospital 9/231	In-hospital 6.1	4.6 ± 1.3 months 42 ± 9
PASTA[65]	Stent 67	In-hospital 4/67 6 months 14/67 1 year 15/67	In-hospital 2/67 6 months 3/67 1 year 3/67	In-hospital 3.0	In-hospital 4/67			6 months 17.0
	PTCA 69	In-hospital 13/69 6 months 32/69 1 year 34/69	In-hospital 5/69 6 months 5/69 1 year 6/69	In-hospital 4.3	In-hospital 9/69			6 months 36.7
PRISAM[66]	Stent 110	–	6 months 0.0		6 months 22.7			
	PTCA 112	–	6 months 0.9		6 months 33.9			
PSAAMI[67]	Stent 44	30 days 2/44 700 days 10/44	30 days 4.5 710 days[e] 9.1	30 days 0 Long-term 2.3	30 days 0.0 Long-term 15.9			6 months 24 (Angiography performed on 37/44 alive)
	PTCA 44	30 days 5/44 700 days 19/44	30 days 2.3 710 days[e] 18.2	30 days 2.3 Long-term 4/44	30 days 9.0 Long-term 34.1			6 months 61 (Angiography performed on 33/36 alive)
STENT-PAMI[68]	Stent 452	1 month 4.6 6 months 12.6	1month 3.5 6 months 4.2	1 month 0.4 6 months 2.4	1 month 1.3 6 months 7.7			6.5 months 20.3
	PTCA 448	1 month 5.8 6 months 20.1	1 month 1.8 6 months 2.7	1 month 1.1 6 months 2.2	1 month 3.8 6 months 17.0			6.5 months 33.5

continued

TABLE 79 *PTCA: outcomes (cont'd)*

Study name		Event rate (%)	Mortality (%)	AMI (%)	Revascularisation (%)	CABG (%)	PTCA (%)	BRR (%)
STENTIM-2[69]	Stent 101	Event-free survival In-hospital 95.0 6 months 81.2 1 year 80.2	In-hospital 1.0 6 months 2.0 1 year 3.0	In-hospital 4.0 6 months 4.0 1 year 4.0	In-hospital 5.0 6 months 16.8 1 year 17.8	In-hospital 0.0 6 months 1.0 1 year 1.0	In-hospital 5.0 6 months 15.8 1 year 16.8	6 months 25.3
	PTCA 110	Event-free survival In-hospital 94.5 6 months 72.7 1 year 71.7	In-hospital 0.0 6 months 0.9 1 year 1.8	In-hospital 3.6 6 months 5.5 1 year 5.5	In-hospital 5.4 6 months 26.4 1 year 28.2	In-hospital 0.0 6 months 0.0 1 year 0.9	In-hospital 5.5 6 months 26.4 1 year 27.3	6 months 39.6
Participants with small coronary arteries								
BESMART[70]	Stent 192	In-hospital 4.6 6 months 13.6	In-hospital 0.0 6 months 0.6	In-hospital 4.2 6 months 0.6	6 months TLR 13	In-hospital 0.0 6 months 0.6	In-hospital re-PTCA 1.5 6 months 12.5	6 months 21
	PTCA 189	In-hospital 5.8 6 months 27.1	In-hospital 0.0 6 months 2.4	In-hospital 4.8 6 months 1.2	6 months TLR 24.6	In-hospital 0.5 6 months 1.2	In-hospital re-PTCA 1.6 6 months 23.4	6 months 47
CHIVAS[71,236]	Stent 97	–			6 months 10.3			6 months 29
	PTCA 89	–			6 months 19.2			6 months 44
COAST[72]	Stent 312	6 months[f] 11.2			6 months Non-coated stent 12 Heparin-coated stent 13			6 months 27 (angiographic stenosis)
	PTCA 155	6 months[f] 15.4			6 months 16			6 months 32
ISAR-SMART[73,86]	Stent 204	30 days 2.9 7 months 23	30 days 0.5 7 months 1.0	30 days 2.0	7 months 20.1	30 days 0.5 7 months 3.4	30 days re-PTCA 0.5 7 months 16.7	6 months 35.7
	PTCA 200	30 days 1.5 7 months 19	30 days 0.5 7 months 1.5	30 days 1.0	7 months 16.5	30 days 0.5 7 months 2.5	30 days re-PTCA 0 7 months 14.0	6 months 37.4
Park *et al.*[74]	Stent 60		In-hospital 0.0 16 months[g] 0.0	In-hospital non-Q-wave 1.7 Non-fatal MI: 15.9 ± 5.7 months 0.0	In-hospital 0.0 16 months[g] 3.3	In-hospital 0.0		6 months 935.7
	PTCA 60		In-hospital 0.0 16 months[g] 0.0	In-hospital non-Q-wave 3.3 Non-fatal MI: 15.9 ± 5.7 months 0.0	In-hospital 0.0 16 months[g] 5	In-hospital 0.0		PTCA 30.9
RAP[75]	Stent 212	6 months 14						6 months 27
	PTCA 241	6 months 14						6 months 37

continued

TABLE 79 *PTCA: outcomes (cont'd)*

Study name		Event rate (%)		Mortality (%)		AMI (%)		Revascularisation (%)		CABG (%)		PTCA (%)		BRR (%)	
SISA[76]	Stent 169	In-hospital 6 months	3.0 18.3	In-hospital 6 months	0.0 0.6	In-hospital 6 months	1.8 4.1	6 months	17.8	In-hospital 6 months	0.6 3.0	In-hospital re-PTCA	0.6	6 months	28
	PTCA 182	In-hospital 6 months	7.1 22.0	In-hospital 6 months	0.0 0.5	In-hospital 6 months	4.9 8.2	6 months	20.3	In-hospital 6 months	0.5 1.6	In-hospital re-PTCA	2.7	6 months	32.9
SISCA[77]	Stent 74	6 months 1 year	9.5 9.5	1 month 6 months 1 year	0.0 0.0 1.4	1 month S 1–6 months S	PTCA 0/71 1/74 PTCA 1/71 0/74	TVR: 1 month 6 months 12 months TLR: 1 month 6 months 12 months	0.0 0.0 0.0 1.4 9.5 9.5	6 months	1.4			179 ± 35 days	9.7
	PTCA 71	6 months 1 year	23.9 23.9	1 month 6 months 1 year	0.0 1.4 1.4	1 month S 1–6 months S	PTCA 0/71 1/74; PTCA 1/71, 0/74	TVR: 1 month 6 months 12 months TLR: 1 month 6 months 12 months	0.0 5.6 7.0 1.4 18.3 18.3	6 months	2.8			179 ± 35 days	18.8
Participants with CTD															
CORSICA[78,237]	Stent 72	1 month 6 months Event-free 6 months: reported as PTCA 64.3% (does not tally with MACCE rate), St 77.8% (consistent with MACCE rate)	0 22.2					TLR 6 months	22.2						
	PTCA 70	1 month 6 months	17.1 27.1					TLR 6 months	34.3						
GISSOC[79]	Stent 56	9 months	0.0	9 months	0.0	9 months	0.0	TLR 9 months	5	Up to 9 months	4	Up to 9 months re-PTCA	5	9.1 ± 3.3 months	32
	PTCA 54	9 months	1.8	9 months	1.8	9 months	0.0	TLR 9 months	22	Up to 9 months	7	Up to 9 months re-PTCA	18	9.1 ± 3.3 months	68
Hancock *et al.*[80]	Stent 30	6 months	13	In-hospital 6 months	0.0 0.0	6 months	0.0	In-hospital 6 months	0.0 3.3			6 months re-PTCA	10	6 months overall	28
	PTCA 30	6 months	30	In-hospital 6 months	0.0 3.3	6 months	3.3	In-hospital 6 months	0.0 6.7			6 months re-PTCA	17	6 months overall	28

continued

TABLE 79 *PTCA: outcomes (cont'd)*

Study name		Event rate (%)		Mortality (%)		AMI (%)		Revascularisation (%)		CABG (%)		PTCA (%)		BRR (%)	
SARECCO[81]	Stent 55	–		14 days 4 months >8 months	0.0 0.0 1.8	14 days 8 months	1.8 1.8			14 days 4 months	0.0 0.0	4 months re-PTCA	24	4 months	26
	PTCA 55	–		14 days 4 months 8 months	0.0 0.0 5.4	14 days 8 months	0.0 3.6			14 days 4 months	0.0 0.0	4 months re-PTCA	55	4 months	62
SICCO[82]	Stent 58	–		14 days 6 months	0.0 0.0	14 days 8 months	1.7 1.7	14 days TVR <8 months TVR	3.4 20.7	14 days 4 months >8 months	1.7 8.6 8.6	<8 months >8 months	17.2 17.2	6 months	31.6
	PTCA 59	–		14 days 6 months	0.0 0.0	14 days 8 months	0.0 0.0	14 days TVR <8 months TVR	3.4 38.9	14 days 4 months >8 months	0.0 5.0 6.7	<8 months >8 months	33.8 42.3	6 months	73.2
SPACTO[83]	Stent 40	6 months[h]	30	6 months	0.0	6 months	0.0			6 months	2.5	6 months	25.0	6 months	32.4
	PTCA 40	6 months[h]	55	6 months	0.0	6 months	0.0			6 months	5.0	6 months	40.0	6 months	63.6
STOP[84]	Stent 48	6 months[i]	19/48	6 months	0.0	6 months	0.0	TLR (PTCA + CABG) 6 months	 25	6 months	4.2	6 months	20.8	6 months	42.1
	PTCA 48	6 months[i]	29/48	6 months	0.0	6 months	2.1	TLR (PTCA + CABG) 6 months	 41.7	6 months	2.1	6 months	39.6	6 months	70.9
TOSCA[85]	Stent 202	6 months Any major event	23.3 15.8	Short-term 6 months	0.0 0.5	6 months	11.9	6 months	8.4	'Surgical revascularisation' PTCA target vessel Any vessel	 1.4 1.9	'Percutaneous revascularisation' Target vessel Any vessel	 6.9 12.4	6 months	55
	PTCA 208	6 months Any major event	23.6 23.1	Short-term 6 months	0.0 0.5	6 months	3.8	6 months	15.4	'Surgical revascularisation' ST target vessel Any vessel	 17 (8.4%) 28 (13.9%)	'Percutaneous revascularisation' PTCA target vessel Any vessel	30 (14.4%) 41 (19.7%)	6 months	70

[a] Specified as cardiac death.
[b] Interpreted TVR.
[c] EPISTENT included three intervention arms: PTCA plus abciximab (abc), Stent plus abciximab and Stent plus placebo (plc.). Only the stent–abciximab arm is compared with PTCA-abciximab in the meta-analysis.
[d] In-hospital and procedural mortality.
[e] Long-term (710 ± 282 days), all deaths.
[f] Based on numbers undergoing angiographic follow-up.
[g] 15.9 ± 5.7 months (PTCA 15.7 ± 5.6, St 16.2 ± 5.8 months).
[h] Rate includes new, stable angina.
[i] Rate includes angina.

Appendix 4

Details of survival trend metamodelling

Metamodel structure

In most revascularisation studies, the highest mortality risk occurs in the immediate postoperative period (in-hospital or within about 30 days). Thereafter mortality rates fall sharply to a much lower level that changes only slowly over several years.

For modelling purposes this can be represented by dividing patients into two mutually exclusive groups:

- a small proportion of patients subject to very high risk of mortality in the days/weeks following the procedure
- the remaining large proportion with a much lower long-term mortality risk.

The former may be modelled with reasonable accuracy using a simple exponential function, $S(t) = A\exp(-bt)$, indicative of a constant daily risk (determined by b) over the initial postprocedural period.

By contrast, studies where survival/mortality was plotted over periods of several years frequently demonstrate increasing or decreasing mortality risks with time (e.g. Barsness and colleagues[219]). In particular, increasing risks are in line with expectations, since most patients are aged ≥ 60 years, and actuarial risk accelerates steeply over the age of 65 years. To replicate this pattern in mathematical form we employ a Weibull function, $S(t) = A\exp[-(t/b)^a]$. In this case, the additional parameter, a, determines whether the risk increases (>1) or decreases (<1) over time.

Fitted trend lines for separate RCT arms

A bipartite survival function was fitted to the published results from each of the three RCTs (Figure 4 of SOS, Figure 4 of ERACI II and Figure 1A of ARTS). The data were obtained by digitising the published graphs, which were either downloaded from the electronic version of the paper or scanned from the journal hardcopy. The best-fit function was obtained by minimising the OLS deviation from the datapoints. The model parameters are shown in *Table 80*, and the fits achieved can be seen in *Figures 35–37*.

Combined metamodel trendlines

The models for each type of treatment were combined into a single metamodel by calculating weighted averages of individual regularly spaced point estimates from each model weighted by the number of patients randomised to the corresponding trial arm. The resulting combined estimates were then used to generate a new single bipartite metamodel. Hence the resulting model combines data from all three trials for the first 12 months (1318 patients for PCI and 1325 patients for CABG), then uses data from SOS and

TABLE 80 *Bipartite survival model parameters*

		Short-term component			Long-term component		
RCT	**Trial arm**	**Proportion of cohort (%)**	**Exponential rate parameter, *a***	**Proportion of cohort (%)**	**Weibull rate acceleration parameter, *a***	**Weibull rate determination parameter, *b***	**Model r^2**
SOS	PCI	2.1	6.64	97.9	2.37	10.23	0.97
	CABG	0.6	7.64	99.4	2.46	13.23	0.93
ERACI II	PCI	1.6	2.13	98.4	0.19	5.89×10^{10}	0.99
	CABG	7.3	18.34	92.7	0.36	8.58×10^{6}	0.999
ARTS	PCI	1.6	23.25	98.4	0.55	4146	0.96
	CABG	2.2	4.93	97.8	1.46	29.02	0.97

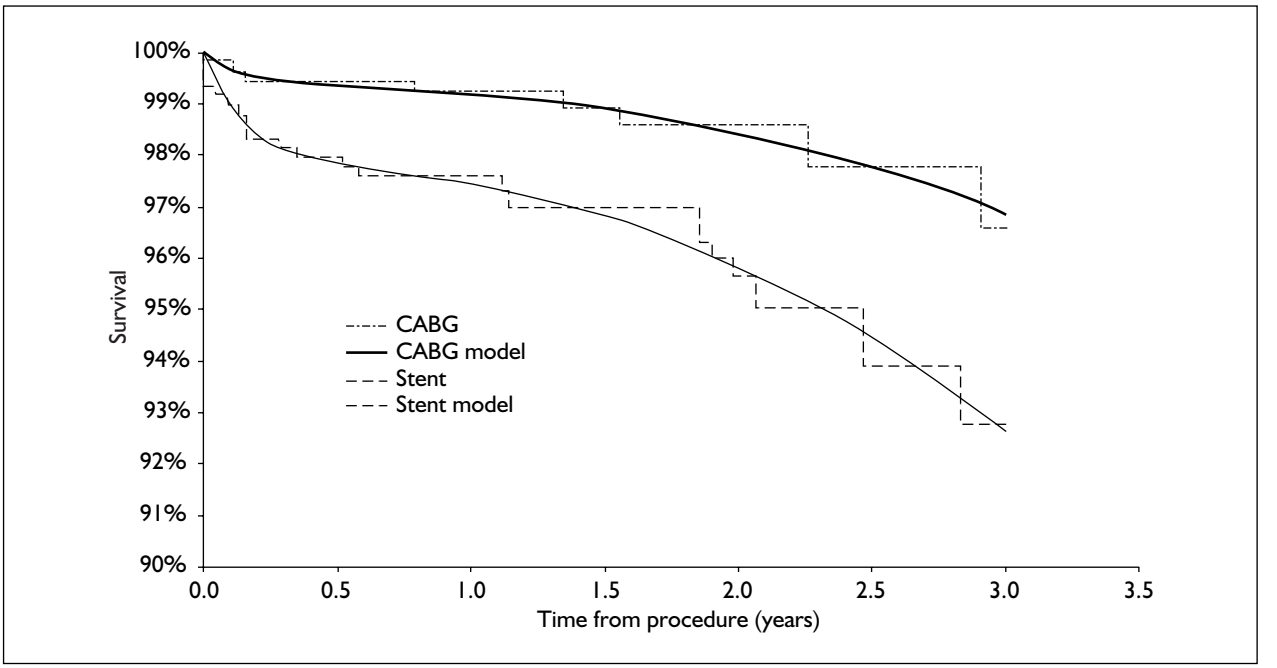

FIGURE 35 *Survival models for SOS trial*

TABLE 81 *Bi-partite survival metamodel parameters*

		Short-term component			Long-term component		
RCT	**Trial arm**	**Proportion of cohort (%)**	**Exponential rate parameter, *a***	**Proportion of cohort (%)**	**Weibull rate acceleration parameter, *a***	**Weibull rate determination parameter, *b***	**Model r^2 relative to combine date**
SOS/ ERACI II/ ARTS	PCI	2.2	8.81	97.8	2.05	14.40	0.98
	CABG	2.6	8.56	97.4	1.84	24.82	0.97

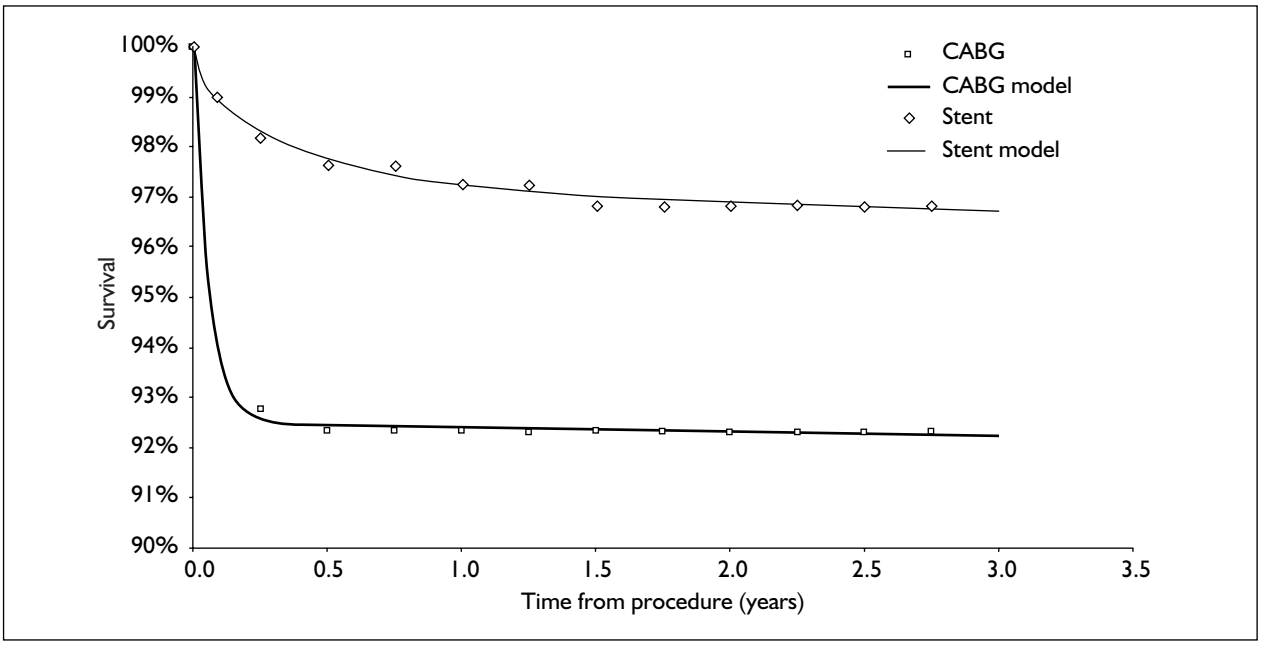

FIGURE 36 *Survival models for ERACI II trial*

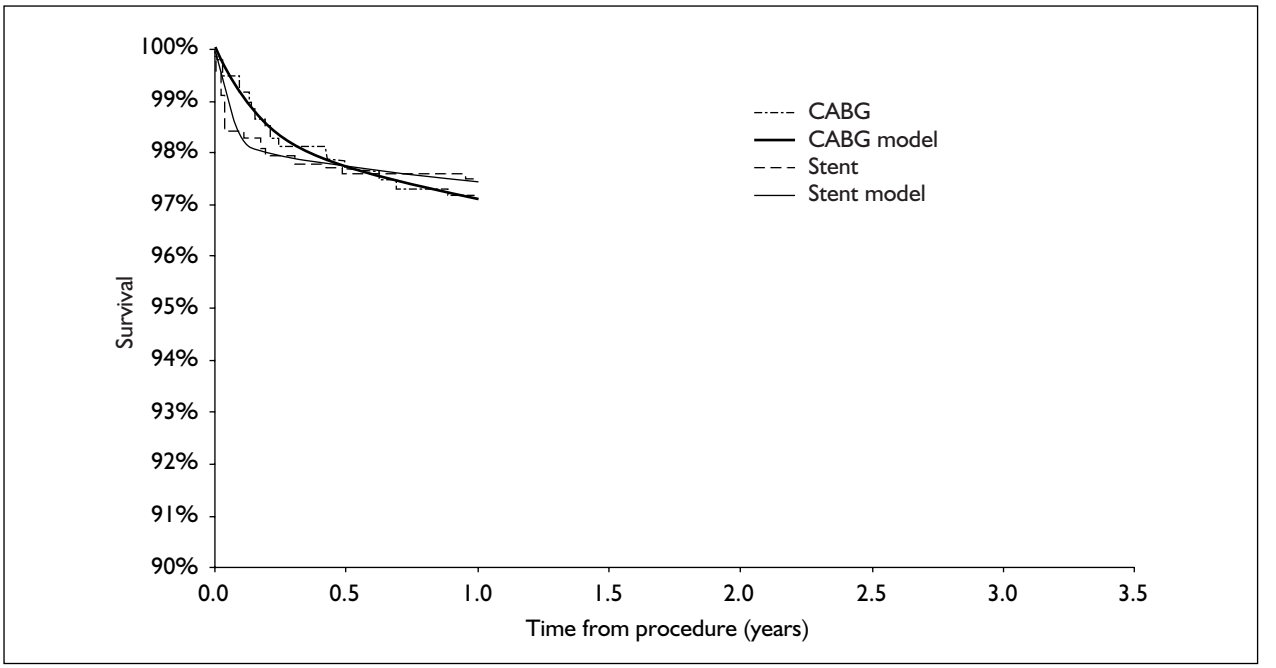

FIGURE 37 *Survival models for ARTS trial*

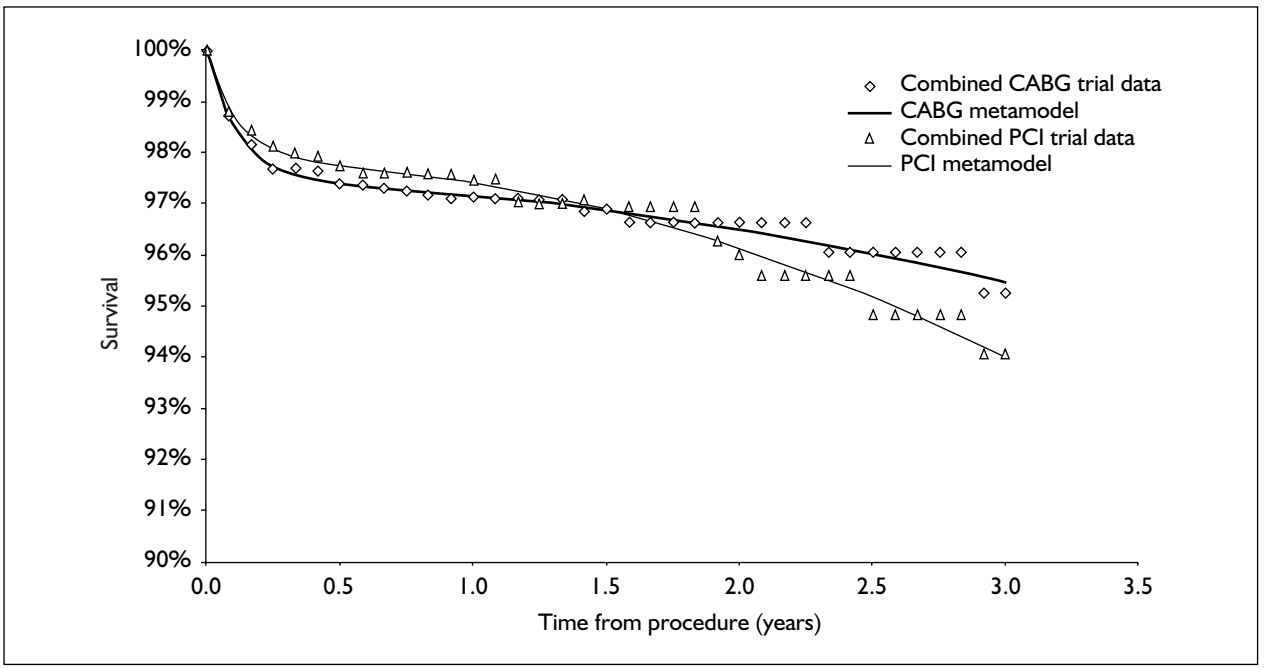

FIGURE 38 *Survival meta-models combining data from SOS, ERACI II and ARTS trials*

ERACI II for the second and third years (713 patients for PCI and 725 patients for CABG). The resulting metamodels are shown in *Figure 38* together with the combined weighted data from the three trials. The model parameters are displayed in *Table 81*.

It is not possible to calculate definitive CIs or significance levels for estimates generated by this method without access to detailed patient-level information for each of the trials, which was not available to us at the time. However, the very high r^2 values obtained suggest that confidence bands for both point estimates and trends are likely to be well behaved. However, due to this uncertainty, we have conservatively limited projection of the metamodels to a maximum of 5 years from the initial procedure.

Appendix 5
Data sources

Study	Reference(s)[a]
	Stent versus PTCA
ADVANCE	*Serruys PW, Foley DP, Suttorp MJ, Rensing B, Suryapranata H, Materne P, *et al*. A randomized comparison of the value of additional stenting after optimal balloon angioplasty for long coronary lesions: final results of the additional value of NIR stents for treatment of long coronary lesions (ADVANCE) study. *J Am Coll Cardiol* 2002;**39**:393–9. Serruys PW, Suttorp MJ, Suryapranata H, Materne P, van Den Bos A, Colombo A, *et al*. Advance: Additional value of NIR stents for treatment of long coronary lesions. A randomised study comparing long balloons versus stents: 1-month follow-up results. URL: http://aha.agora.com/abstractviewer/search.asp. 2000.
AS	Witkowski A, Ruzyllo W, Gil R, Gorecka B, Purzycki Z, KoSmider M, *et al*. A randomized comparison of elective high-pressure stenting with balloon angioplasty: six-month angiographic and two-year clinical follow-up. On behalf of AS (Angioplasty or Stent) trial investigators. Am *Heart J* 2000;**140**:264–71.
BENESTENT	*Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, *et al*. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Eng J Med* 1994;**331**:489–95. Foley DP, Serruys PW. Provisional stenting – stent-like balloon angioplasty: evidence to define the continuing role of balloon angioplasty for percutaneous coronary revascularization. *Semin Interv Cardiol* 1996;1:269-73. Keane D, Azar AJ, de Jaegere P, Rutsch W, de Bruyne B, Legrand V, *et al*. Clinical and angiographic outcome of elective stent implantation in small coronary vessels: an analysis of the BENESTENT trial. *Semin Interv Cardiol* 1996;**1**:255–62. Kiemeneij F, Serruys PW, Macaya C, Rutsch W, Heyndrickx G, Albertsson P, *et al*. Continued benefit of coronary stenting versus balloon angioplasty: five-year clinical follow-up of Benestent-I trial. *J Am Coll Cardiol* 2001;37:1598-603. Macaya C, Serruys PW, Ruygrok P, Suryapranata H, Mast G, Klugmann S, *et al*. Continued benefit of coronary stenting versus balloon angioplasty: One-year clinical follow-up of Benestent trial. *J Am Coll Cardiol* 1996;**27**:255–261. Serruys P. Continued benefit of coronary stenting versus balloon angioplasty: five-year clinical follow-up of BENESTENT-I trial. *Eur Heart J* 1999;**20**:136.
BENESTENT II	Serruys PW, Van Hout B, Bonnier H, Legrand V, Garcia E, Macaya C, *et al*. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998;**352**:673–81.
BESMART	Koning R, Eltchaninoff H, Commeau P, Khalife K, Gilard M, Lipiecki J, *et al*. Stent placement compared with balloon angioplasty for small coronary arteries: In-hospital and 6-month clinical and angiographic results. *Circulation* 2001;**104**:1604–8.
BESSAMI	Schwimmbeck PL, Spencker S, Hohmann C, Horstkotte D, Behrens S, Pauschinger M, *et al*. Results from the Berlin Stent Study in Acute Myocardial Infarction (abstract). *Circulation* 2000;**102** (Suppl II):II-813.
BEST	Schiele F, Meneveau N, Gilard M, Boschat J, Commeau P, Huret B, *et al*. Final results of the balloon equivalent to stent study (BEST): a multicenter, randomized study comparing intravascular ultrasound-guided balloon angioplasty with systematic stent implantation. *Am J Cardiol* 2002;**90**:93H.

continued

Study	Reference(s)[a]
BOSS	Dangas G, Ambrose JA, Rehmann D, Marmur JD, Sharma SK, Hemdal-Monsen C, *et al*. Balloon optimization versus stent study (BOSS): provisional stenting and early recoil after balloon angioplasty. *Am J Cardiol* 2000;**85**:957–61.
CADILLAC	*Stone GW, Grines CL, Cox DA, Garcia E, Tcheng JE, Griffin JJ, *et al*. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Eng J Med* 2002;**346**:957–66. Cox D, Grines C, Stuckey T, Garcia E, Griffin J, Tcheng J, *et al*. Do acute myocardial intervention patients without ST-segment elevation have better outcomes after primary percutaneous coronary intervention? An analysis from the CADILLAC Trial. *Am J Cardiol* 2002;**90**:184H. Cox D, Grines C, Lansky A, Stuckey T, Garcia E, Williams J, *et al*. Impact of small vessel size on long-term outcomes after primary angioplasty and stenting in acute myocardial infarction: results from the CADILLAC trial. TCT abstracts/poster. *Am J Cardiol* 2002;**90**:185H. Stone GW, Grines CL, Cox D, Stuckey T, Carroll J, Guagliumi G, *et al*. A prospective randomized trial comparing primary balloon angioplasty with or without abciximad to primary stenting with or without abciximad in acute myocardial infarction – primary endpoint analysis from the Cadillac Trial. URL: http://aha.agora.com/abstractviewer/search.asp. 2000.
CHIVAS	*Muramatsu T, Iwasaki K, Inou N, Horita Y, Tanaka T, Fujita N. Efficacy of coronary stenting versus balloon angioplasty in vessels of diameters less than 3.0 mm and less than 2.5 mm: CHIVAS Investigators. *Am J Cardiol* 2002;**90**:96H-97H. Muramatsu T, Iwasaki K, Inoue N, Horita Y, Tanaka T, Fujita N, *et al*. Coronary Heart Disease Stenting In small Vessels Versus Balloon Angioplasty Study (CHIVAS): a randomized prospective multicenter trial. *J Am Coll Cardiol* 2002;**39**:96H.
COAST	Haude M. Heparin-coated stents in small coronary arteries: results of the COAST trial. Presented at: 2002 Scientific Session of the American College of Cardiology; March 17, 2002; Atlanta, GA. *Clin Cardiol* 2002;**25**:242–4.
CORSICA	*Guerin Y, Chevalier B, Ourand P, Geslin P, Saudemont JP, Bedossa M, *et al*. The CORSICA trial, short and mid-term outcome (abstract). *Eur Heart J* 1998;**19**:471. Guerin Y, Chevalier B, Tron C, Commeau P, Commeau P, Brunel P, *et al*. Preliminary results of a randomized study between balloon versus stent in chronic coronary occlusion. *Circulation* 1997; **96**:1–268.
DEBATE II	*Serruys PW, De Bruyne B, Carlier S, Sousa JE, Piek J, Muramatsu T, *et al*. Randomized comparison of primary stenting and provisional balloon angioplasty guided by flow velocity measurement. *Circulation* 2000;**102**:2930. De Bruyne B, Groothuis W, Sousa E, Seabra-Gomes R, Vrints C, Piek JJ. DEBATE II: a randomized study to evaluate provisional stenting after guided balloon angioplasty. *Circulation* 1998;**98**:498. Serruys PW, De Bruyne B, Sousa E, Piek JJ, Muramatsu T, Vrints C, *et al*. DEBATE II – final results of the 6-month follow-up. *Eur Heart J* 1999;**20**:371. Serruys P, De Bruyne B, Gurne O, Pijls N, Belardi J, van Es GA, *et al*. DEBATE II: 'DESTINI-sation' of the DEBATE II trial data. *Eur Heart J* 1999;**20**:650.
DESTINI	*Di Mario C, Moses JW, Anderson TJ, Bonan R, Muramatsu T, Jain AC, *et al*. Randomized comparison of elective stent implantation and coronary balloon angioplasty guided by online quantitative angiography and intracoronary Doppler. DESTINI Study Group (Doppler Endpoint STenting INternational Investigation). *Circulation* 2000;**102**:2938–44. Cohen D. In-hospital and 6-month follow-up costs of universal vs. provisional stenting: results from the DESTINI trial. *Circulation* 1998;**98**:499.
Eeckhout *et al*.	Eeckhout E, Stauffer JC, Vogt P, Debbas N, Kappenberger L, Goy JJ. Comparison of elective Wiktor stent placement with conventional balloon angioplasty for new-onset lesions of the right coronary artery. *Am Heart J* 1996;**132**:263–8.

continued

Study	Reference(s)[a]
EPISTENT	*The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet* 1998;**352**:87–92. Marso SP, Lincoff AM, Ellis SG, Bhatt DL, Tanguay JF, Kleiman NS, *et al*. Optimizing the percutaneous interventional outcomes for patients with diabetes mellitus: results of the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial) diabetic substudy. *Circulation* 1999;**100**:2477–84.
ESCOBAR	*Suryapranata H, van't Hof AW, Hoorntje JC, de Boer MJ, Zijlstra F. Randomized comparison of coronary stenting with balloon angioplasty in selected patients with acute myocardial infarction. *Circulation* 1998;**97**:2502–5. Suryapranata H, Ottervanger JP, Nibbering E, van't Hof AW, Hoorntje JC, de Boer MJ, *et al*. Long-term outcome and cost-effectiveness of stenting versus balloon angioplasty for acute myocardial infarction. *Heart* 2001;**85**:667–71.
FRESCO	Antoniucci D, Santoro GM, Bolognese L, Valenti R, Trapani M, Fazzini PF. A clinical trial comparing primary stenting of the infarct-related artery with optimal primary angioplasty for acute myocardial infarction: results from the Florence Randomized Elective Stenting in Acute Coronary Occlusions (FRESCO) trial. *J Am Coll Cardiol* 1998;**31**:1234–9.
FROST	Lafont A, Dubois-Rande JL, Steg PG, Dupouy P, Carrie D, Coste P, *et al*. The French Randomized Optimal Stenting Trial: a prospective evaluation of provisional stenting guided by coronary velocity reserve and quantitative coronary angiography. F.R.O.S.T. Study Group. *J Am Coll Cardiol* 2000;**36**:404–9.
GISSOC	Rubartelli P, Niccoli L, Verna E, Giachero C, Zimarino M, Fontanelli A, *et al*. Stent implantation versus balloon angioplasty in chronic coronary occlusions: results from the GISSOC trial. *J Am Coll Cardiol* 1998;**32**:90–6.
GRAMI	Rodriguez A, Bernardi V, Fernandez M, Mauvecin C, Ayala F, Santaera O, *et al*. In-hospital and late results of coronary stents versus conventional balloon angioplasty in acute myocardial infarction (GRAMI trial). Gianturco-Roubin in Acute Myocardial Infarction. *Am J Cardiol* 1998;**81**:1286–91.
Hancock *et al*.	Hancock J, Thomas MR, Holmberg S, Wainwright RJ, Jewitt DE. Randomised trial of elective stenting after successful percutaneous transluminal coronary angioplasty of occluded coronary arteries. *Heart* 1998;**79**:18–23.
ISAR-SMART	*Kastrati A, Schomig A, Dirschinger J, Mehilli J, Dotzer F, von Welser N, *et al*. A randomized trial comparing stenting with balloon angioplasty in small vessels in patients with symptomatic coronary artery disease. ISAR-SMART Study Investigators. Intracoronary Stenting or Angioplasty for Restenosis Reduction in Small Arteries. *Circulation* 2000;**102**:2593–8. Hausleiter J, Kastrati A, Mehilli J, Dotzer F, Schuhlen H, Dirschinger J, *et al*. Comparative analysis of stent placement versus balloon angioplasty in small coronary arteries with long narrowings (The Intracoronary Stenting or Angioplasty for Restenosis Reduction in Small Arteries [ISAR-SMART] Trial). *Am J Cardiol* 2002;**89**:58–60. Mehilli J, Kastrati A, Dirschinger J, Dotzer F, Pache J, Hausleiter J, *et al*. Comparison of stenting with balloon angioplasty for lesions of small coronary vessels in patients with diabetes mellitus. *Am J Med* 2002;**112**:13–18.
Jacksch *et al*.	Jacksch R, Niehues R, Knobloch W, Schiele T. PTCA versus stenting in acute myocardial infarction (AMI) (abstract) *Circulation* 1998;**98** (Suppl I):I–307.
Knight *et al*.	Knight CJ, Curzen NP, Groves PH, Patel DJ, Goodall AH, Wright C, *et al*. Stent implantation reduces restenosis in patients with suboptimal results following coronary angioplasty. *Eur Heart J* 1999;**20**:1783–90.
OCBAS	*Rodriguez A, Ayala F, Bernardi V, Santaera O, Marchand E, Pardinas C, *et al*. Optimal coronary balloon angioplasty with provisional stenting versus primary stent (OCBAS): immediate and long-term follow-up results. *J Am Coll Cardiol* 1998;**32**:1351–7.

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Study	Reference(s)[a]
	Rodriguez AE. The role of acute wall recoil and late restenosis: results of the OCBAS trial (Optimal Coronary Balloon Angioplasty with Provisional Stenting versus Primary Stent). *Int J Cardiovasc Interv* 2001;**4**:99–106.
OPUS	*Weaver WD, Reisman MA, Griffin JJ, Buller CE, Leimgruber PP, Henry T, *et al*. Optimum percutaneous transluminal coronary angioplasty compared with routine stent strategy trial (OPUS-1): a randomised trial. *Lancet* 2000;**355**:2199–203.
	Weaver WD. Optimal angioplasty versus primary stenting (OPUS). *J Am Coll Cardiol* 1999;**34**:1.
Park *et al.*	Park SW, Lee CW, Hong MK, Kim JJ, Cho GY, Nah DY, *et al*. Randomized comparison of coronary stenting with optimal balloon angioplasty for treatment of lesions in small coronary arteries. *Eur Heart J* 2000;**21**:1785–9.
PASTA	Saito S, Hosokawa G, Tanaka S, Nakamura S. Primary stent implantation is superior to balloon angioplasty in acute myocardial infarction: final results of the primary angioplasty versus stent implantation in acute myocardial infarction (PASTA) trial. *Catheter Cardiovasc Interv* 1999;**48**:262–8.
PRISAM	Kawashima A, Ueda K, Nishida Y, Inoue N, Tanaka S, Kawamoto A, *et al*. Quantitative angiographic analysis of restenosis of primary stenting using wiktor stent for acute myocardial infarction: results from a multicentre randomized PRISAM study (abstract). *Circulation* 1999;**100** (Suppl I): I–856.
PSAAMI	Scheller B, Hennen B, Severin-Kneib S, Ozbek C, Schieffer H, Markwirth T. Long-term follow-up of a randomized study of primary stenting versus angioplasty in acute myocardial infarction. *Am J Med* 2001;**110**:1–6.
RAP	Garcia E, Gormez-Recio M, Pasalodos J, Bethancourt A, Zueco J, Iniguez A, *et al*. Stent reduces restenosis in small vessels. Results of the RAP Study. *J Am Coll Cardiol* 2001;**37**:1A–647A.
RSSG	Erbel R, Haude M, Hopp HW, Franzen D, Rupprecht HJ, Heublein B, *et al*. Coronary-artery stenting compared with balloon angioplasty for restenosis after initial balloon angioplasty. Restenosis Stent Study Group. *N Eng J Med* 1998;**339**:1672–8.
SAVED	Savage MP, Douglas JS Jr, Fischman DL, Pepine CJ, King IS, Werner JA, *et al*. Stent placement compared with balloon angioplasty for obstructed coronary bypass grafts. *N Eng J Med* 1997;**337**:740–7.
SARECCO	Sievert H, Rohde S, Utech A, Schulze R, Scherer D, Merle H, *et al*. Stent or angioplasty after recanalization of chronic coronary occlusions? (The SARECCO trial). *Am J Cardiol* 1999;**84**:386–90.
SICCO	*Sirnes PA, Golf S, Myreng Y, Molstad P, Emanuelsson H, Albertsson P, *et al*. Stenting in chronic coronary occlusion (SICCO): a randomized, controlled trial of adding stent implantation after successful angioplasty. *J Am Coll Cardiol* 1996;**28**:1444–51.
	Sirnes PA, Golf S, Myreng Y, Molstad P, Albertsson P, Mangschau A, *et al*. Sustained benefit of stenting chronic coronary occlusion: long-term follow-up of the stenting in coronary occlusion (SICCO) study. *J Am Coll Cardiol* 1998;**32**:305–10.
	Sirnes PA, Molstad P, Myreng Y, Golf S. Predictors for restenosis after angioplasty of chronic coronary occlusions. *Int J Cardiol* 1998;**67**:111–18.
SISA	*Doucet S, Schalij MJ, Vrolix MC, Hilton D, Chenu P, de Bruyne B, *et al*. Stent placement to prevent restenosis after angioplasty in small coronary arteries. *Circulation* 2001;**104**:2029–33.
	Schalij MJ, Doucet S, Hilton D, Vrolix M, De Bruyne B, Bilodeau L, *et al*. The SISA Study: a randomized comparison of balloon angioplasty and stent to prevent restenosis in small arteries: 6 month angiographic and 12 month clinical outcome. URL: http://aha.agora.com/abstractviewer/search.asp 2000.
SISCA	*Moer R, Myreng Y, Molstad P, Albertsson P, Gunnes P, Lindvall B, *et al*. Stenting in small coronary arteries (SISCA) trial. A randomized comparison between balloon angioplasty and the heparin-coated beStent. *J Am Coll Cardiol* 2001;**38**:1598–603.
	Moer R, Myreng Y, Molstad P, Albertsson P, Gunnes P, Lindvall B, *et al*. Clinical benefit of small vessel stenting: one-year follow-up of the SISCA trial. *Scand Cardiovasc J* 2002;**36**:86–90.

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Study	Reference(s)[a]
SPACTO	Hoher M, Wohrle J, Grebe OC, Kochs M, Osterhues HH, Hombach V, *et al*. A randomized trial of elective stenting after balloon recanalization of chronic total occlusions. *J Am Coll Cardiol* 1999;**34**:722–9.
START	*Betriu A, Masotti M, Serra A, Alonso J, Fernandez-Aviles F, Gimeno F, *et al*. Randomized comparison of coronary stent implantation and balloon angioplasty in the treatment of de novo coronary artery lesions (START): a four-year follow-up. *J Am Coll Cardiol* 1999;**34**:1498–506. Betriu A, Serra A, Masotti M, Delcan JL, Garcia E, Colman T, *et al*. The Spanish trial: are national randomized trials a necessary evil? *J Interv Cardiol* 1994;**7**:347–53. Masotti M. Is the initial benefit of stenting sustained over the years? Long-term results of the START trial. *Circulation* 1998;**98**:499. Masotti M, Serra A, Fernandez-Aviles F, Alonso J, Gimeno F, Colman T, *et al*. Four years follow-up of the START trial, a randomized stenting versus PTCA study. *Eur Heart J* 1999;**20**:533.
STENTIM II	Maillard L, Hamon M, Khalife K, Steg PG, Beygui F, Guermonprez JL, *et al*. A comparison of systematic stenting and conventional balloon angioplasty during primary percutaneous transluminal coronary angioplasty for acute myocardial infarction. STENTIM-2 Investigators. *J Am Coll Cardiol* 2000;**35**:1729–36.
STENT-PAMI	*Grines CL, Cox DA, Stone GW, Garcia E, Mattos LA, Giambartolomei A, *et al*. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. *N Eng J Med* 1999;**341**:1949–56. Mattos LA, Grines CL, Cox D, Sousa JE, Costantini C, Stone G, *et al*. A comparative analysis of primary stenting and optimal balloon coronary angioplasty in acute myocardial infarction. Six month results from the STENT PAMI trial. *Arq Bras Cardiol* 2000;**75**:499–514. Brodie BR, Stone GW, Morice MC, Cox DA, Garcia E, Mattos LA, *et al*. Importance of time to reperfusion on outcomes with primary coronary angioplasty for acute myocardial infarction (results from the Stent Primary Angioplasty in Myocardial Infarction Trial). *Am J Cardiol* 2001;**88**:1085–90. Mattos LA, Grines CL, Sousa JE, Sousa AG, Stone GW, Cox D, *et al*. One-year follow-up after primary coronary intervention for acute myocardial infarction in diabetic patients. A substudy of the STENT PAMI trial. *Arq Bras Cardiol* 2001;**77**:549–61.
STOP	*Lotan C, Rozenman Y, Hendler A, Turgeman Y, Ayzenberg O, Beyar R, *et al*. Stents in total occlusion for restenosis prevention. The multicentre randomized STOP study. The Israeli Working Group for Interventional Cardiology. *Eur Heart J* 2000;**21**:1960–6. Lotan C, Hendler A, Turgeman Y, Ayzenberg O, Beyar R, Disegni E. The STOP study: a randomized multicenter Israeli study for stents in total occlusion for restenosis prevention – final report. *Eur Heart J* 1999;**20**:156.
STRESS	*Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, *et al*. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Eng J Med* 1994;**331**:496–501. Cohen DJ, Krumholz HM, Sukin CA, Ho KK, Siegrist RB, Cleman M, *et al*. In-hospital and one-year economic outcomes after coronary stenting or balloon angioplasty. Results from a randomized clinical trial. Stent Restenosis Study Investigators. *Circulation* 1995;**92**:2480–7. George CJ, Baim DS, Brinker JA, Fischman DL, Goldberg S, Holubkov R, *et al*. One-year follow-up of the Stent Restenosis (STRESS I) Study. *Am J Cardiol* 1998;**81**:860–5. Savage MP, Fischman DL, Rake R, Leon MB, Schatz RA, Penn I, *et al*. Efficacy of coronary stenting versus balloon angioplasty in small coronary arteries. Stent Restenosis Study (STRESS) Investigators. *J Amn Coll Cardiol* 1998;**31**:307–11. Slota PA, Fischman DL, Savage MP, Rake R, Goldberg S. Frequency and outcome of development of coronary artery aneurysm after intracoronary stent placement and angioplasty. STRESS Trial Investigators. *Am J Cardiol* 1997;**79**:1104–6.
STRESS II	Wong SC, Zidar JP, Chuang YC, Schatz RA, S. G, Baim DS, *et al*. Stents improve late clinical outcomes: results from the combined (I+II) STent REStenosis Study. *Circulation* 1995;**92** (Suppl.1):I–281.

continued

Study	Reference(s)[a]
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