Coronary artery stents:

rapid systematic review & economic evaluation

in confidence information removed

Note:

Two Addenda to this report have been prepared and should be consulted by readers of this document.

Addendum A includes data used in the evaluation of the clinical effectiveness of drug-eluting stents (Chapter 6) which were considered commercial in confidence when the report was submitted. The report was prepared with all data for consideration by Appraisal Committee, but commercial in confidence information was removed from versions available outside the committee. These data have since been made public and therefore the relevant text in the results, discussion and conclusion sections (6.1, 6.2, 6.3) as well as outcome tables (Table 6H) and Figures 6A-E are presented with these data reinstated.

Addendum B was prepared following the first meeting of the Appraisal Committee. The Addendum 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. This new information has allowed us to consider such aspects as subgroup analysis, not previously possible.

As such Addendum B is not intended as a standalone document, though does supersede elements of the original report.

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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 multi-disciplinary research group whose purpose, in the first instance is to conduct systematic reviews commissioned by the Health Technology Assessment Programme.

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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, the HTA Programme, NICE or the Department of Health.

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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.

Specifically the review compares the use of:

- Stent versus Percutaneous Transluminal Coronary Angioplasty
- Stent versus Coronary Artery Bypass and Graft
- Stent versus drug-eluting stent

Background

Coronary heart disease 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 are of coronary artery stents including the development of drug-eluting stents (DES).

The rapid developments in stenting in the treatment of CAD (coronary artery disease) 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 stent versus drug-eluting stent 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, AMI, target vessel revascularisation (TVR), repeat treatment (PTCA, Stent or CABG) and binary restenosis.

Full economic evaluations that compared two or more options and consider 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 fifty studies comparing the use of stents with PTCA, six comparing stents with CABG and twelve comparing drug-eluting stents with non drug-eluting stents. No studies were identified that compared drug-eluting stents with PTCA or drug-eluting stents 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, acute myocardial infarction 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 reported only clinically driven rates, while others reported 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. diabetic patients, patients with long lesions). Data on subgroups of high-risk patients has been presented within study reports but was 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.

1. PTCA versus stent

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

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

2. Stent versus CABG

All studies were a comparison of bare metal stents to 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 one year) between patients treated surgically and those receiving a stent. Longer-term data from these studies is now becoming available. Patients treated surgically required fewer revascularisations.

3. Stent versus drug eluting stent

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

There is a reduction in event rate at 9 and 12 months in patients treated with drug-eluting stents. This event rate is primarily made up of increased revascularisation rates in patients treated with bare metal stents.

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 multi-vessel 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.
- *Drug-eluting stenting versus CABG in multi-vessel disease*
  Here the situation is not qualitatively different from bare metal stenting. Reduced costs from fewer from 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.
- *Drug-eluting stenting versus bare metal stenting in single vessel disease*
  This leads to substantially higher costs with a very small outcome benefit, so that drug-eluting stents would not normally be considered a cost-effective alternative.

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

- The extra cost of drug-eluting stents (compared to non drug-eluting stents) was substantially reduced.
- The outcome benefits from the use of drug-eluting-stents are much improved
- The use of drug-eluting stents is targeted on the sub-groups 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 drug eluting stents, 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 number of areas:

- Long-term clinical studies that focus on significant outcomes such as mortality
- Further studies on:
  Differences among plain stents (this might be possible from a systematic review, but is not addressed in the current review)
  Head to head comparisons within drug eluting stents (new trial data required)
  CABG compared to DES (already planned)
  To evaluate newer non drug-eluting stents 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 at particular likelihood of needing further revascularisations

- The rapid rate of change in this area suggests that a further review should be undertaken in 12 to 18 months

Abbreviations

ACC	American College of Cardiology
ACCP	American College of Chest Physicians
ACS	Acute Coronary Syndrome
AHA	American Heart Association
AMI	Acute myocardial infarction
BCIA	British Cardiovascular Industry Association
BCIS	British Cardiac Intervention Society
BHF	British Heart Foundation
CABG	Coronary artery bypass graft(ing)
CAD	Coronary artery disease
CCSC	Canadian Cardiovascular Society Classification
CCU	Coronary Care Unit
C-E	Cost-effective(ness)
CEA	Cost-effectiveness analysis
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval (95%)
CIC	Commercial in confidence
CK	Creatinine kinase
CK-MB	Fraction of creatinine kinase
CRD	The NHS Centre for Reviews and Dissemination
CTO	Chronic total occlusion
CVA	Cerebro-vascular accident (stroke)
DES	Drug-eluting stent
DM	Diabetes mellitus
ECG	Electrocardiogram
EF	Ejection fraction
FDA	Food and Drug Administration, U.S. Department of Health and Human Services
GI	Gastrointestinal

ICER	Incremental cost effectiveness ratio
ISR	In-stent restenosis
ITT	Intention to treat analysis
IV	Intravenous
IVUS	Intravascular ultrasound
LAD artery	Left anterior descending coronary artery
LM	Left main coronary artery
LVEF	Left ventricular ejection fraction
MACCE	Major adverse coronary and cerebrovascular events
MACE	Major adverse coronary events
MI	Myocardial infarction
MLD	Minimal lumen diameter of coronary artery
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
RCT	Randomised controlled trial
SA	Sensitivity analysis
SVG	Saphenous vein graft
TIMI flow grade	Thrombolysis In Myocardial Infarction flow grade
TLR	Target lesion revascularisation
TVF	Target vessel failure
TVR	Target vessel revascularisation

Definition of terms

Abciximab	a glycoprotein IIB/IIIa antagonist, used to inhibit blood clotting widely used during stenting procedure
Acute Coronary Syndrome (ACS)	syndrome that includes coronary events previously referred to as unstable angina, non-ST-segment elevation myocardial infarction (MI) and ST elevation MI.
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 PTCA because of dissection of the vessel wall
Binary restenosis	refers to the percent 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 pre-dilation
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 re-narrowing or blockage of an artery within a stent
IVUS	method using ultrasound to visualise a full 360º 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 CABG	CABG 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 PTCA
Q-wave	an abnormal wave on ECG indicating previous myocardial damage

Recoil (stent)	a measure of the elastic contraction a stent experiences when balloon is deflated
Restenosis	a re-narrowing 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

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.

2 Background

2.1 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 endpoint considered in the review was revascularisation rates. The review was limited by a lack of available data related to the use of stents versus coronary artery bypass grafting (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 as well as the initial assessment of the evaluation of drug-eluting stents (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 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 makes 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.

2.2 Description of health problem

2.2.1 Disease

Coronary artery 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 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 (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 acute myocardial infarction (AMI) and sub-acute manifestations of CAD that include angina and unstable angina.

2.2.2 Epidemiology

Basic data is available in the UK regarding the overall importance of cardio-vascular disease in the health/disease profile of UK residents. Routine data provided by the British Heart Foundation(5) indicates that coronary heart disease (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 coronary heart disease.

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 to 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 been developed to describe the various lesion types and these are presented in Table 2A.

Table 2A Lesion types

Lesion Type	Characteristics
A	Discrete Less than 10 mm Concentric readily accessible in a non-angulated segment Less than 45 degrees 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 to 20 mm length Eccentric Moderate tortuosity of proximal segment Moderately angulated segment between 45 and 90 degrees 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 tortuosity of the proximal segment before lesion Extremely angulated segments with 90 degrees May be total occlusion

Adapted from Textbook of Interventional Cardiology 3rd edition(6)

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) as well as 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.

2.2.3 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, anti-platelet 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 re-assessed and adjusted following other invasive treatments.

CABG

The development of surgical treatment such as coronary artery bypass grafting 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 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 multi-vessel or diffuse disease or disease of the left anterior descending (LAD) artery. Changes in the intra and post-operative 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 post-discharge 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 Percutaneous Transluminal Coronary Angioplasty (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 use of PTCA was common.

Adjunct techniques evolved as a part of what has come to be classified as Percutaneous Coronary Interventions (PCI). The term PCI may be used to include balloon angioplasty, artherectomy, stenting, etc.(4)

Initial success of elective PTCA ranges between 96 to 99 percent.(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 to 10 percent 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 'bail-out stenting' (see below).

The second drawback of PTCA is restenosis. The cause of restenosis is likely multi-factorial 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 percent to 50 percent of patients.(2) Reports also indicate lower treatment success rates in patients with small arteries, long lesions, previous CABG and in patients with diabetes.(13)

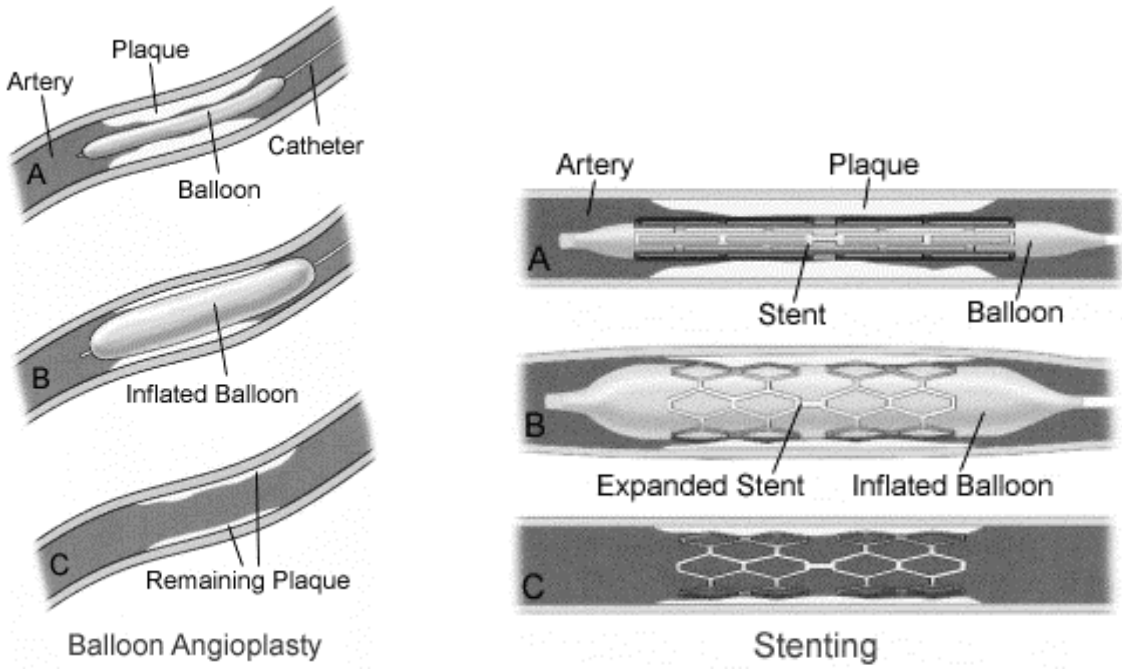
These problems prompted the research into methods to decrease or eliminate restenosis. This included the development of coronary artery stents.

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. The technology was developed to address the two key issues faced during PTCA – e.g. 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 the illustration. It is not within the remit of this review to compare the effectiveness of various stent designs or guidance systems.

Figure 2A Illustration of the process of PTCA and stenting



Representation of I: PTCA (Balloon Angioplasty); II: Stenting. Image reproduced by kind permission of the Texas Heart Institute. Copyright 1996-2002 Texas Heart Institute (www.texasheartinstitute.org).

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 (sub-optimal PTCA)

Provisional stenting is carried out following assessment of the success of the initial balloon angioplasty – e.g. 'sub-optimal' 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 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 bail-out 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 bail-out stenting in cases of acute closure during PTCA. The availability and rapid uptake of the use of stents has meant that bail-out stenting has become the preferred clinical option. Given that the majority of PTCA procedures in the NHS now involve elective stenting, bail-out 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.

2.2.4 Drug-eluting stents

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, i.e. 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 drug-eluting stents. 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.(15) Specific agents have been identified that act at different sites and these are identified in Table 2B. 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.

Table 2B Drug-eluting stent: modes of action

Mode of action	**Injury** *Anti-inflammatory*	**Proliferation** *Anti-proliferative*	**Migration** *Migration inhibitor*	**Healing** *Promote healing and re- endothelization*
Drug	Dexamethasone Methylprednisolone	Angiopeptin Actinomycin D Paclitaxel Sirolimus	Batimastat	Estradiol (VEGF)

Adjunctive Pharmacotherapy

In addition to new mechanical devices, the 1990s have witnessed the use of established pharmaceuticals (e.g. aspirin) and development and testing of new agents to be used as adjuncts to percutaneous coronary revascularisation. Glycoprotein IIb/IIIa inhibitors have been shown to reduce ischemic complications in patients undergoing percutaneous coronary interventions.(17, 18) Use of ticlopidine has been stopped due 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 is 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 their use is important the data extraction from trials includes a listing of adjuctive pharmacotherapy and is included in the study characteristic tables. The effectiveness of clopidogrel will be assessed in a NICE review later this year.

Patient subgroups

As noted earlier in this chapter, previous research has shown that there are sub-groups of patients that 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 sub-group 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 as well as other adverse events.

Small vessels and long lesions

Early trials of stents required that vessel diameter be more than 3.0 mm. However, it was found that a number of patients in the early trials did indeed have vessel diameters of less than 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 this 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(15) treatment of these lesions is technically challenging and associated with higher rates of

complications and lower success rates. Although this is an important sub-group of patients, data is 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 percutaneous coronary intervention (PCI) outcomes by gender over a 5 year period in New England.(24) It is not within the remit of this review to address these comparisons. The data extraction for the review however does 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(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. This data is presented in Table 2C.

Table 2C Estimate of patients undergoing PCI in the UK who fall into key CAD subgroups

	Percentage of PCI Patients	**Percentage of CABG Patients**	**Estimated Number of PCI Patients**	**Estimated Number of CABG Patients**
UK PCI procedures in 2001			38,992	
UK CABG procedures 1999-2000				24,728*
Single vessel disease total	48		18,716	
Normal SVD	8		3,119	
Longer lesions	21		8,188	
Single small vessel disease	22		8,578	
Diabetes	20	22	7,798	5440
LAD lesions	61		23,785	
Multivessel disease total	52	90	20,276	
2 vessel disease	33	28	12,867	6,924
3 vessel disease	19	62	7,408	15,331
	Data source: EUROHEART N&W WHO Regions	Data source: EUROHEART N&W WHO Regions		

Adapted from BCIA submission (25)

*Data from BCIS on surgery rates presented later is slightly higher.

The data is limited in its ability to present a complete picture, as it does not allow for estimates across groups – e.g. the number of diabetic patients with multiple vessel disease. It does however provide estimates from 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 percent of lesions with greater than 50 percent luminal narrowing).

Restenosis is composed of three major factors: immediate post balloon 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 onto stents to inhibit the growth of smooth muscle cells that lead to in-stent restenosis.

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 a more than 50 percent luminal narrowing. These rates do not necessarily correlate with clinical symptoms. It has been estimated that approximately 50 percent 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 post-intervention minimal luminal 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 the present time 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 stenosis within the stent, stenosis at the stent margins or both. Trial reports also focus on measures of target lesion and/or target vessel revascularisation rates (TLR/TVR). 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 previously indicated, these rates do not always correlate with the clinical presentation of the patient and the limitations of their use is discussed as a part of this review.

2.3 Current service provision

2.3.1 Introduction

Current care guidance was provided by NICE in 2000.(1) This guidance is presented in Table 2D.

Table 2D NICE Guidance on coronary artery stents, May 2000

Reference	Guidance *NICE Guidance on coronary artery stents in the treatment of ischaemic heart disease May 2000*
1.1	For patients with either stable or unstable angina, or acute myocardial infarction (MI) and where percutaneous coronary intervention (PCI) is the clinically appropriate procedure, stents should be used routinely.
1.2	Where it is considered clinically appropriate to undertake either PCI or coronary artery bypass grafting (CABG), the availability of stents should push the balance of clinical decision-making towards PCI.
1.3	Arteries with a diameter less than 2.5 mm and greater than 3.5 mm should only normally be stented in the setting of a so called 'bail-out' procedure (i.e. when acute closure of the vessel occurs following PCI), or if there has been a sub-optimal result following ballooning alone or as part of properly conducted trials. These criteria do not apply to saphenous vein grafts (SVG). The Institute is aware that new evidence on stenting in arteries with a diameter less than 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.

Within the National Service Framework 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/million population for each of two groups (stent and surgical) of interventions.

2.3.2 Data systems

In the UK, no system currently exists to capture all PCI and CABG procedures fully. The British Cardiac Intervention Society and the Society of Cardiothoracic Surgeons of Great Britain and Ireland maintain audit datasets that collate data from centres providing information on a voluntarily basis. Some semi-commercial sources of data are also available which collate completed episodes from over a 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.

2.3.3 Diagnostic and care provision centres

In 2001 there were a total of 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 2E.

Table 2E 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***	**38,992***

*This table may include the double counting of some patients (e.g. those who have a catheterisation and go on to have a PCI)
Table adapted from (27)

2.3.4 PCI rates

There has been a continual increase in the number and rate per million PCIs carried out over time. Rates for 1991 to 2001 are shown in Table 2F.

Table 2F PCI rates in 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

Table adapted from (27)

Figure 2B PTCA: rates per million in the UK 1985-2001

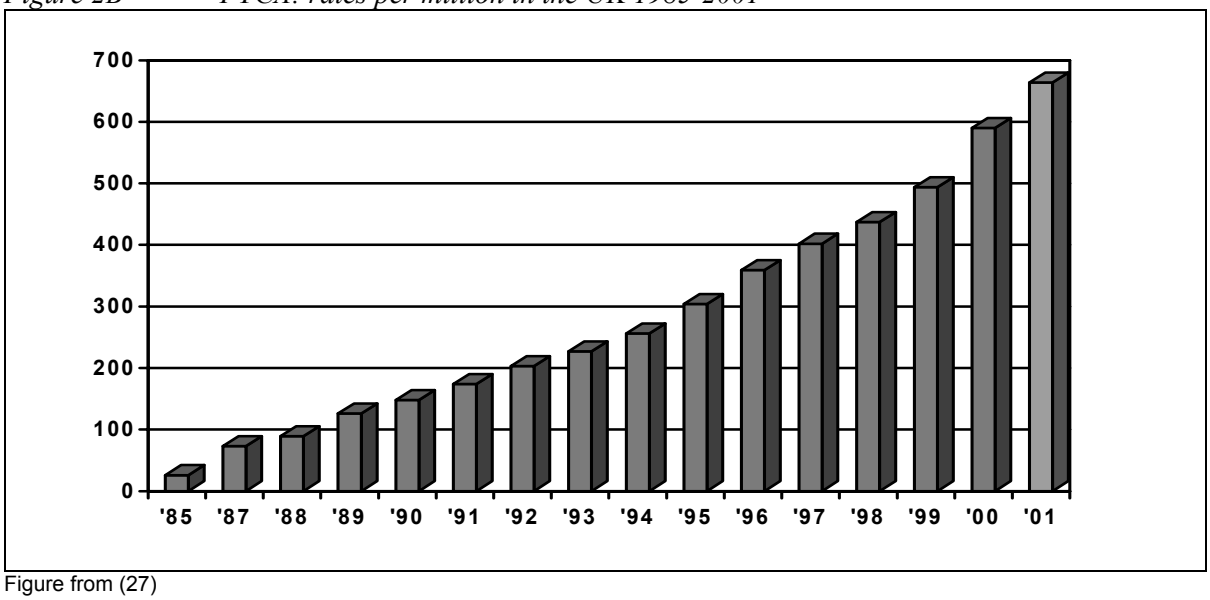


Figure from (27)

Although these rates are increasing, as can be seen in Figure 2B, these rates 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 2C represents the trends in the use of stents in the UK from 1992-2001. It is also interesting to note 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.

Figure 2C PCI with stent rates UK 1992-2001

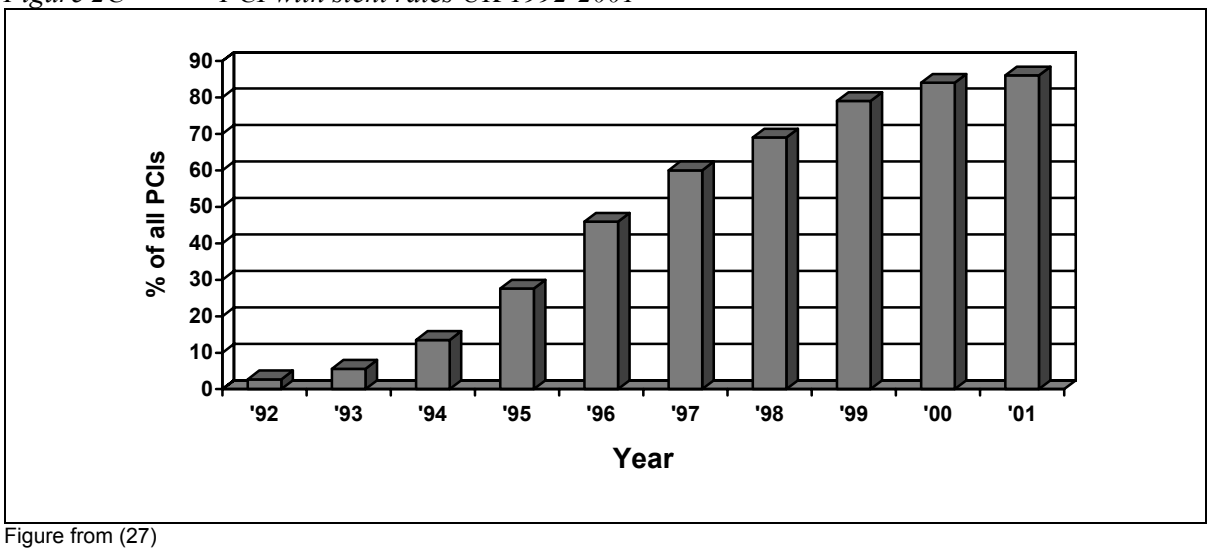


Figure from (27)

Use of drug-eluting stents

To date five drug-eluting stents 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 2002, 30 2003, 31 2002, 32 2002, 33 2003) Data are not readily available regarding the utilisation of drug-eluting stents in the UK.

2.3.5 CABG Rates

There has been a significant increase in rates of CABG in the UK with rates having doubled over the past 10 years. Approximately 28,000 operations are carried out each year. Table 2G shows the growth in surgical rates over time.

Table 2G CABG: rates in the UK 1989-2000

	CABG	CABG with another procedure	Total	Rates per million*
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
1994/5	22,056	2,282	24,513	408
1995/6	22,475	2,362	24,960	416
1996/7	22,160	2,078	24,599	409
1997/98	25,639	2,433	28,198	469
1999/00	24,728	2,641	27,831	464

*Estimate - data calculated based on population base of 60 million. Table adapted from (34)

Data in Table 2G are from the UK Cardiac Surgical Register, collected by the Society of Cardiothoracic Surgeons of Great Britain and Ireland. Twenty nine (83 percent) of the 35 NHS Trusts and Units undertaking adult cardiac surgery in the United Kingdom 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 2C is less than that seen in the use of PCI.

Figure 2C CABG rates compared to PCI 1991-2001

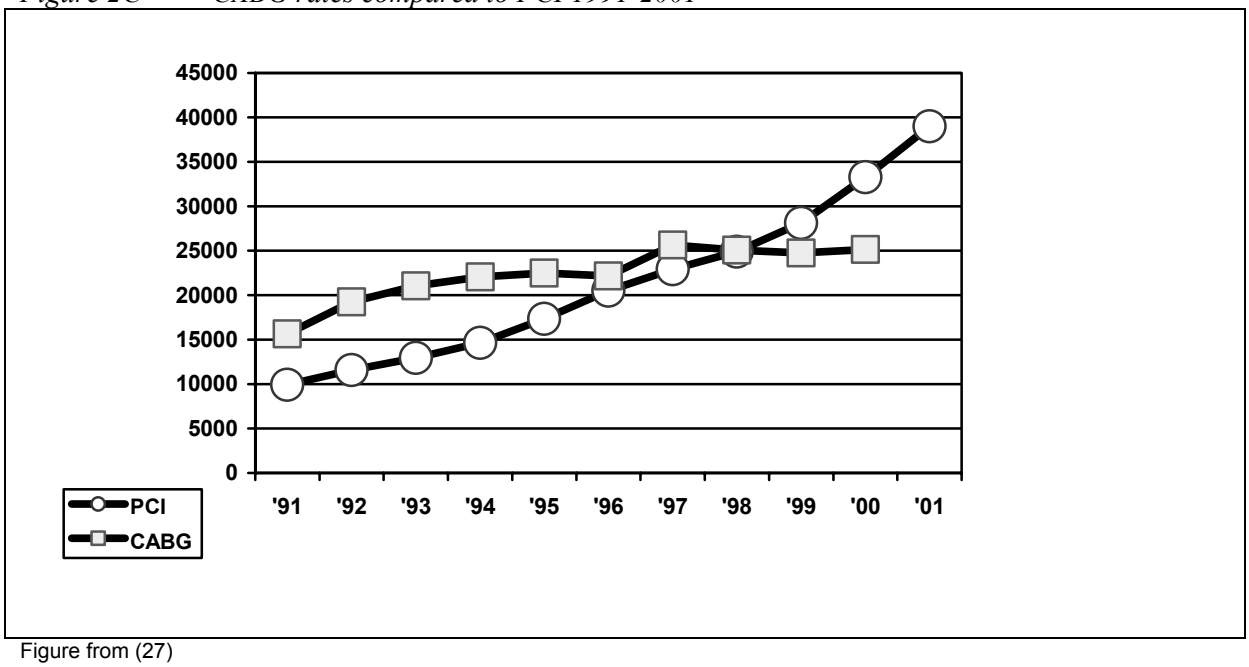


Figure from (27)

As mentioned previously, the use of stents has replaced CABG following acute artery closure during PTCA. As seen in Figure 2D the use of stenting, either elective or bail out, has decreased the number of emergency CABG procedures recorded after PTCA.

Figure 2D Emergency CABG rates compared to PCI 1991-2001

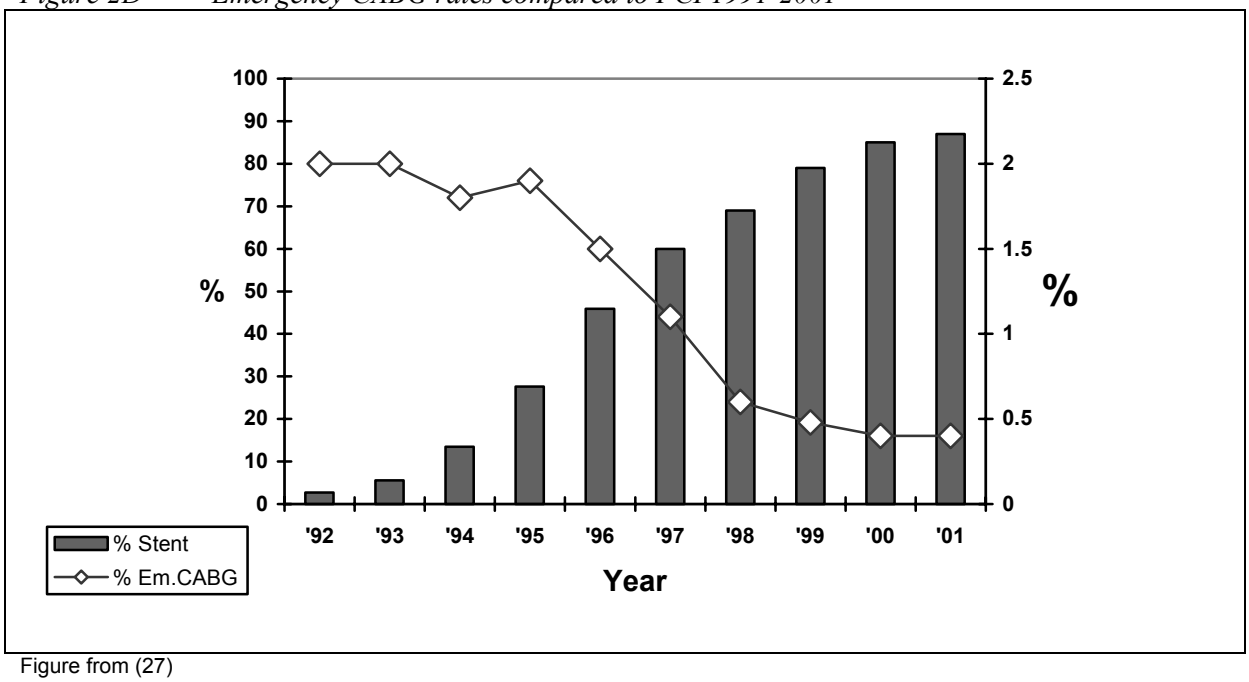


Figure from (27)

2.4 Limitations of the review

This review has been 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.

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, anti-platelet
- In-stent stenosis
- PTCA or stenting compared to 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.

2.5 Review considerations - clinical

The review team benefited from the review work previous carried out by Meads et al.(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, sub-groups of patients and data availability.

2.5.1 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-drug eluting stents 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, 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 to either 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, drug-eluting stents are considered as a group, although data is 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, pre-dilation 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 is 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.

2.5.2 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 MACCE (major adverse cardiovascular and cerebral vascular events). They can include mortality, AMI or revascularisation, but the definitions vary across studies.

There is a further problem with the use of such composite endpoints 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 myocardial infarction or death.

Mortality

Trials have been powered to measure differences in restenosis rates (which are assumed to be quite large), they 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.

Revascularisation

Current guidance is based on outcomes related to the need for revascularisation following treatment. As noted above these may also be presented within a 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 six month angiographic follow-up of patients, there may be an excess of "events" around six months, and these events may not be truly clinically relevant. There is an argument that some of those classified as angiographically driven at six months would have progressed by twelve months or later to become symptomatic & 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 target lesion revascularisation (TLR), target vessel revascularisation (TVR) or both. Definitions for these are not always provided. There is 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, but data related to any revascularisation is 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 drug eluting stents. The definition is mandated by the US 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 percent. Revascularisation of a target lesion with an in-

lesion diameter stenosis greater than 70 percent 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 greater than 70 percent, 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 one 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. It is not data that has routinely been included in trials but as noted as part of the economic analysis is required for the assessment of long-term outcomes.

2.5.3 Sub-groups 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 sub-groups have been described earlier. Meads and colleagues(2) made attempts to carry out sub-group comparisons but were limited by the availability of the data.

2.5.4 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 was 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 drug-eluting stents. Presentation of new trial data appeared monthly during the time the review was being conducted. In addition, the vast majority of data were available only from specialised websites. Frequently this data was released simultaneously in the form of electronic visual presentations (such as Microsoft PowerPoint slides) used during the 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.

2.6 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 drug-eluting stents:

- that drug-eluting stents 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 drug-eluting stents 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:

- post-intervention longevity
- post-intervention quality of life
- health care 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 quality of life 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 quality of life. Similarly, in a chronic condition, health care costs usually include a component related to the length of survival, so that longevity directly influences costs in most cases. Thus, regardless of treatment objectives or preconceptions, it is essential to consider the question of differential mortality is of primary importance before proceeding to examine quality of life 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 coronary artery disease, 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. acute myocardial infarction 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, though 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 drug-eluting stents).

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?'.

3 Methods

3.1 Methods for reviewing clinical effectiveness

3.1.1 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 1 within 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, British Medical Journal, Catheterization and Cardiovascular Interventions, Circulation, European Heart Journal, Heart, International Journal of Cardiology, Journal of the American College of Cardiology, Journal of the American Medical Association, Journal of Thoracic and Cardiovascular Surgery, Lancet and New England Journal of Medicine was carried out for the period of 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:

- American College of Cardiology (2000, 2001 and March 2002)
- American Heart Association (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)
- CRT (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), which include searchable content on cardiovascular interventions, were examined for information on clinical trials.

All the references were exported to *Endnote* reference database, ISI Research Soft, Cal., USA.

3.1.2 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).

3.1.3 Inclusion criteria

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

Study design

Randomised controlled trials (RCTs)

Population

- Adults with CAD in native or graft vessels
- Patients with stable angina or Acute Coronary Syndrome, 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 drug-eluting stent versus drug-eluting stent

Outcomes

Studies were included if they reported one or more of the following outcomes: combined event rate or event free survival; death; AMI; target vessel revascularisation (TVR); repeat treatment (PTCA, Stent or CABG) and binary stenosis (greater than 50%)

3.1.4 Exclusion criteria

Studies were excluded based on the following criteria:

RCTs that:

- Are continuing to recruit patients
- Provide only unplanned, interim findings
- Provide data on only a sub-group of patients

Comparisons of:

- PTCA with stents to medical management
- Single versus multiple vessel stenting
- Various stent designs
- Anticoagulant or anti-platelet comparisons (data on their use in include trials were noted)
- PTCA or stenting to other PCI interventions (e.g. Atherectomy, Rotabaltor, Brachytherapy)

3.1.5 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 pre-tested data extraction forms. Data presented from multiple reports of single trials were extracted onto a single data extraction form.

3.1.6 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, York, Report 4 (see Appendix 2). Any discrepancies were resolved through consensus.

3.2 Methods for reviewing cost-effectiveness

3.2.1 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 these papers were obtained and assessed. Search strategies and results of the searches undertaken are provided in Table 2, Appendix 1. The following databases were searched for English language papers.

MEDLINE (1987-2002)
EMBASE (1987-2002)
NHS Economic Evaluation Database (NHSEED) (1995-2002)
Database of Abstracts of Reviews of Effectiveness (DARE) (1995-2002)
Science Citation Index/Web of Science (1987-2002)
Science Citation Index/ ISI Proceedings (1990-2002)
Cochrane Trials Register (2002, 4)
Health Technology Assessment (HTA) (1990-2002)

3.2.2 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. One hundred and seventeen 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 and RMM). The aim of this review was to assess which economic evaluations had been undertaken in the context of high quality randomised controlled trials. Papers were excluded if the source of clinical efficacy data was from non-randomised clinical trials (or were 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.

3.2.3 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 acute coronary syndrome, 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 drug-eluting stent versus drug-eluting stent

Economic outcomes

Utility weights related to clinical outcomes

3.2.4 Exclusion criteria

- Main source of clinical efficacy data from non-randomised clinical trial or not explicitly stated
- No attempt to synthesise costs and benefits
- Letters, editorials, reviews, commentaries or methodological papers

All the references were exported to *Endnote* reference database, ISI Research Soft, Cal., USA.

4 Stents versus percutaneous transluminal coronary angioplasty (PTCA)

4.1 PTCA: Included studies

Introduction

Fifty studies fulfilled the inclusion criteria. These included twenty-three studies(36-58) comparing stenting with PTCA in patients with non-specific CAD, eleven 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.(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; e.g. patients with stable or unstable angina
- Experiencing an AMI
- Small coronary arteries
- Chronic total occlusion 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 sub-optimal results following PTCA. Crossovers from PTCA to stent implantation in these trials varied between 13.5 to 56.4% (BOSS: 36%, FROST: 48.4%, DESTINI: 56.4%, OCBAS: 13.5% and OPUS: 37%).

4.1.1 PTCA: Study characteristics

Numbers of participants, centres & locations

Trials ranged in size from 67 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 4D within 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 due 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 small proportion of patients in other studies.(69, 73)

4.1.2 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 to 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 saphenous vein grafts.

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 4E within Appendix 3.

4.1.3 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 cerebro-vascular 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 4A

Table 4A 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), 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 cause), re-infarction, TRV or CVA
CHIVAS	MACE: Death (all cause), CABG, PTCA
COAST	Not defined
CORSICA	MACCE- not defined
DEBATE II	MACE- all deaths, nonfatal MI, TLR (CABG or PTCA)
DESTINI	MACE- Death (cardiac), MI, re-TLR
Eechout, *et al.*	Death, CVA, MI, CABG, PTCA
EPISTENT	Any death, MI or re-infarction, 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 ischemia, MI, CABG
Hancock, *et al.*	Death, MI, CABG, PTCA
ISAR-SMART	Death (all cause), 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, non-Q), 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

Study	Event rate composition
RSSG	Death, MI, CABG, PTCA of target vessel
SAVED	Death, MI, CABG, TLR
SARECCO	Death, MI, CABG, PTCA
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, ischemia 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	Death, MI, recurrence of angina
WIDEST	Death, MI, vessel occlusion, CABG, PTCA
WIN	Not defined

Follow-up

Length of follow-up varied across the studies. Angiographic follow-up at six months was available from 26 of the studies. In 29 studies clinical follow-up was available at six 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 one year, two studies(61, 67) reported at two years, one study(52) at four years and in one study the longest period of follow-up was five years(38). Three studies(45, 68, 86) reported on follow-up separately for those with diabetes mellitus.

Outcome data for PTCA studies are presented in Table 4F within Appendix 3.

4.1.4 Quality assessment of included PTCA studies

Methodological quality of studies is summarised in Table 4B using the criteria based on Centre for Reviews and Dissemination (CRD) Report 4 (Appendix 2).

In each trial, the treatment allocation was randomised although eighteen 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 zero(80) to 56.4 percent(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 analysis.

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

Table 4B PTCA: Quality assessment of included studies

Checklist items:	Randomisation:			Baseline comparability:				Blinding:				Withdrawals:		
	Truly Random	Allocation concealment	Number stated	Presented	Achieved	Eligibility criteria specified	Co-interventions identified	Assessors	Administration	Participants	Procedure assessed	>80% randomised in final analysis	Reasons stated	Intention to treat
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
ADVANCE	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
AS	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
BENESTENT I	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
BENESTENT II	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
BESMART	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
BESSAMI*	✘	✘	✔	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘
BEST *	✘	✘	✔	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘
BOSS	NS	NS	✔	✔/✘	✔/✘	✔	✔	✘	✘	✘	✘	✔	✔	✔
CADILLAC	NS	NS	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
CHIVAS*	✘	✘	✔	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘
COAST*	✘	✘	✔	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘
CORSICA*	✘	✘	✔	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘
DEBATE II	NS	✔	✔	✔	✔	✔	✘	✘	✘	✘	✘	✔	✔/✘	✔
DESTINI	NS	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
EECKHOUT	NS	NS	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
EPISTENT	NS	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
FRESCO	NS	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
ESCOBAR	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
FROST	NS	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔

Checklist items:	Randomisation:			Baseline comparability:				Blinding:				Withdrawals:		
	Truly Random	Allocation concealment	Number stated	Presented	Achieved	Eligibility criteria specified	Co-interventions identified	Assessors	Administration	Participants	Procedure assessed	>80% randomised in final analysis	Reasons stated	Intention to treat
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
GISSOC	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
GRAMI	NS	NS	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
HANCOCK	NS	NS	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
ISAR-SMART	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
KNIGHT	NS	NS	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
JACKSCH*	✘	✘	✔	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘
OCBAS	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
OPUS	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
PARK	✔	NS	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
PASTA	NS	NS	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
PRISAM*	✘	✘	✔	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘
PSAAMI	NS	NS	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
RAP*	✔/✘	✘	✔	✘	✘	✔/✘	✘	✘	✘	✘	✘	✘	✘	✘
RSSG	✔/✘	✔/✘	✔	✔	✔	✔	✘	✘	✘	✘	✘	✔	✘	✔
SARECCO	✔/✘	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
SAVED	✔/✘	✘	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
SICCO	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
SISA	✔/✘	✘	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
SISCA	✔/✘	✘	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
SPACTO	✔/✘	✘	✔	✔	✔/✘	✔	✔	✘	✘	✘	✘	✘	✔	✔

Checklist items:	Randomisation:			Baseline comparability:				Blinding:				Withdrawals:		
	Truly Random	Allocation concealment	Number stated	Presented	Achieved	Eligibility criteria specified	Co-interventions identified	Assessors	Administration	Participants	Procedure assessed	>80% randomised in final analysis	Reasons stated	Intention to treat
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
START	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
STENTIM II	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
STENT-PAMI	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
STOP	NS	NS	✔	✔	✔	✔	✔	✘	✘	✘	✘	✘	✔	✔
STRESS I	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
STRESS II*	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
TOSCA	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
VENESTENT*	✘	✘	✔	✘	✘	✔	✘	✘	✘	✘	✘	✔	✘	✔
VERSACI	NS	NS	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
WIDEST	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
WIN*	✔/✘	✘	✔	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘

Items graded: ✔ **yes** (item adequately addressed), ✘ **no** (item not adequately addressed), ✔/✘ **partially** (item partially addressed), **na not applicable** or NS **not stated**. Quality assessment checklist items in are described in full in **[Appendix 1].** * Trials were reported as conference abstracts only

4.1.5 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 and then 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; e.g. patients with stable or unstable angina
- Experiencing an AMI
- Small coronary arteries
- Chronic total occlusion 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 less than 3.0 mm).

Forest plots of the meta-analyses discussed below are presented in Figures 4A to 4D, at the end of this Chapter.

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 4A. The results related to this measure predominantly represent revascularisation procedures.

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 acute myocardial infarction, 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: 1.66, 95% CI 1.45 to 1.90; for AMI group OR: 2.36, 95% CI 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 six months indicated qualitative differences and both random and fixed effects analysis 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: 1.33, 95% CI 1.12 to 1.58; 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 Section 4.2.2.

PTCA: Mortality

Mortality is a rare event. The analysis shows no evidence of effectiveness in relation to decreasing mortality in any group at any time 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 total occlusion 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 six month and one year analysis. In the total occlusion group the analysis indicates an advantage towards PTCA (OR: 0.41, 95% CI 0.21 to 0.83) at six 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 six months. This was the case in all studies but one.(64) In each sub-group, a statistically significant benefit for stents was observed; this was greatest for total occlusion (OR: 2.8, 95% CI 2.15 to 3.65) and AMI only (OR: 2.93, 95% CI 2.13 to 4.02). Analysis of the non-specific group at six months indicated a qualitative heterogeneity and both random and fixed effects are presented.

4.2 Discussion

Mortality

There is no evidence of benefit in mortality. In relation to stenting versus simple angioplasty in acute myocardial infarction, 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, i.e. those with acute myocardial infarction. 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 acute myocardial infarction were observable in the early stages after stenting. The issue of the role of PTCA and stenting in acute myocardial infarction has recently been examined in a meta-analysis(88) that compares it to 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 Meads and colleagues review(2) which considered only the 25 studies then available, rather than the 50 considered here. A number of the studies identified by the Meads and colleagues(2) study as not yet complete or published have now produced results and been included (see Table 4C). There are a small number of studies yet to report but the review team anticipate that these will not significantly alter the current conclusions.

Table 4C Summary of studies identified by Birmingham review failing to report further data

Study name	Patient Group	Status 1999*	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 pt 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 pt numbers in either arm***	***No further information available***

*As presented in Meads *et al* 2000(2)

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.

4.2.1 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 to 50 percent.(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 to stenting and reported here (see Table 4D for co-therapies) have used such drugs.

4.2.2 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 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 endpoints 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 endpoints must be carefully considered, and should be reported in a disaggregated manner. It might be argued that since the composite endpoint was a preset endpoint, its use is statistically valid, however, if the endpoint is unsatisfactory, the fact that it was preset for the analysis is surely irrelevant.

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

The single largest element of event rate was repeat revascularisation procedures. Many protocols required a repeat angiography at six 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 four 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 non-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 to 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 five years would be desirable.

4.2.3 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 sub-groups 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 anticipate that outcomes might be

different between these two groups. Similarly we have had little ability to look at sub-groups according to some of the desired risk factors, e.g. between diabetic and non-diabetic, patients with long lesions versus short lesions, patients with complex or multi-vessel disease rather than single vessel disease, small vessels (less than 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 2A). We would anticipate that there might be substantial differences according to these subgroups, however, data are not available to explore these differences.

4.2.4 Data availability

It is disappointing that so many studies were only available in abstract 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.

4.3 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..

Figure 4A PTCA: Meta-analysis of event rate

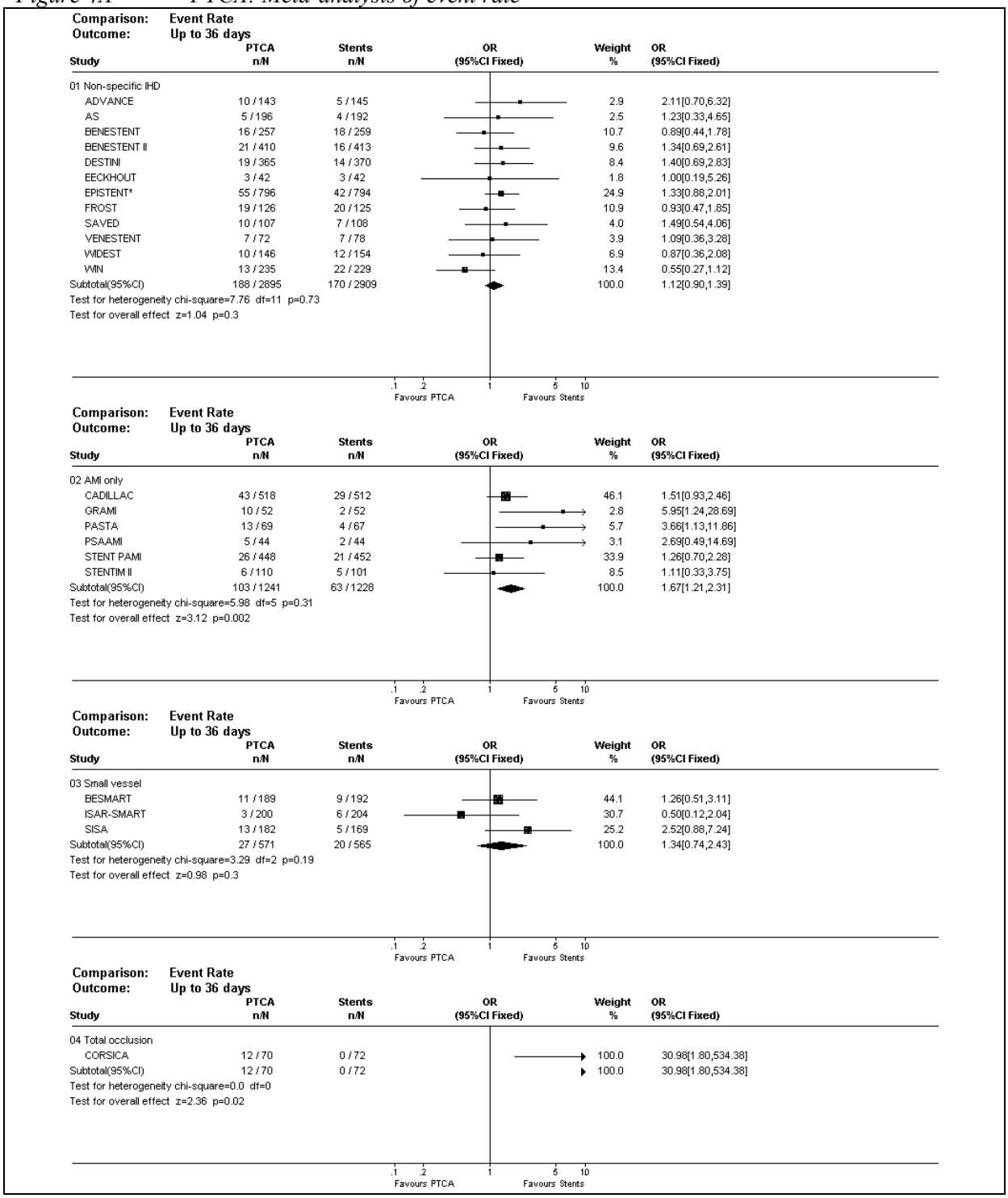


Figure 4A (continued)

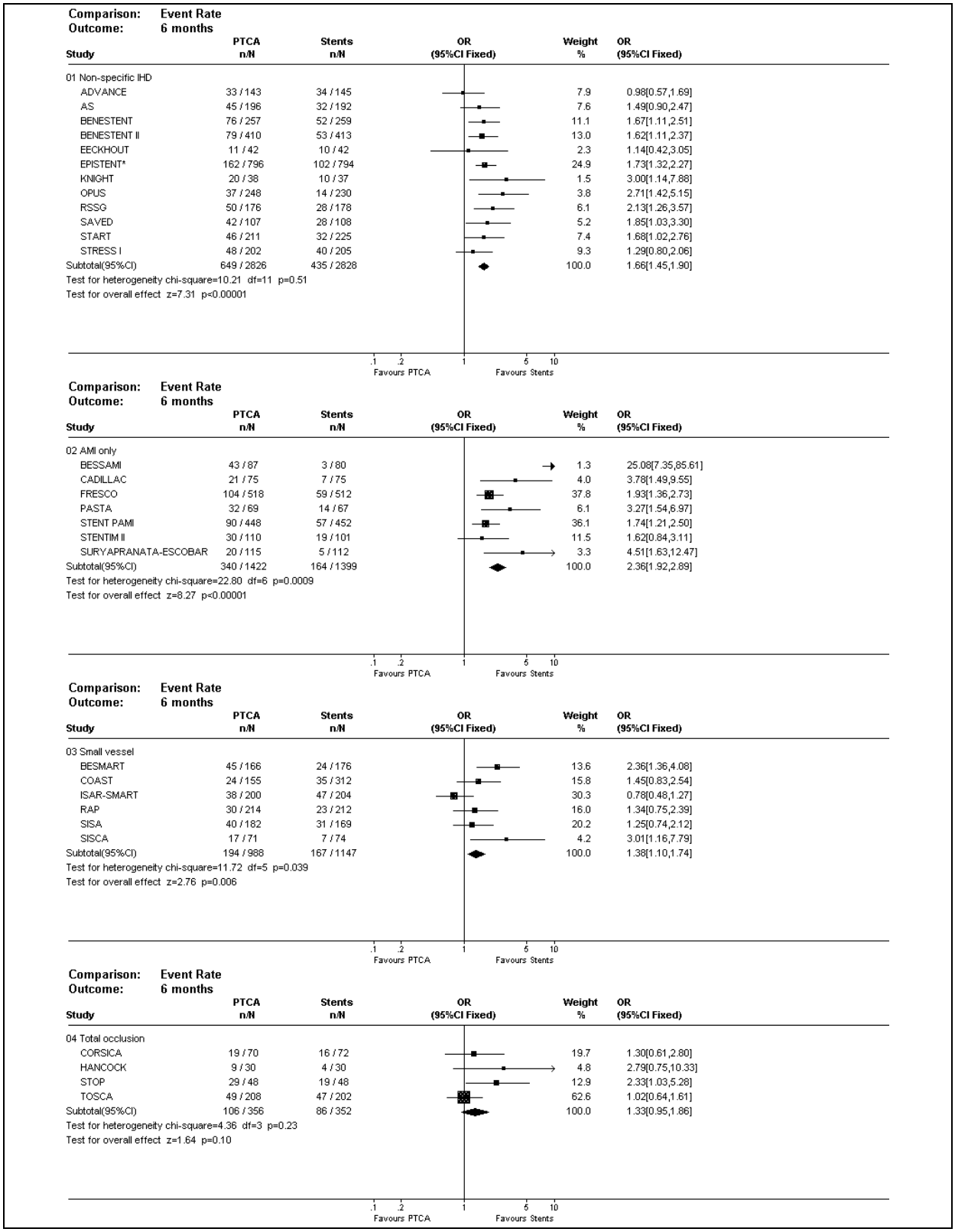


Figure 4A (continued)

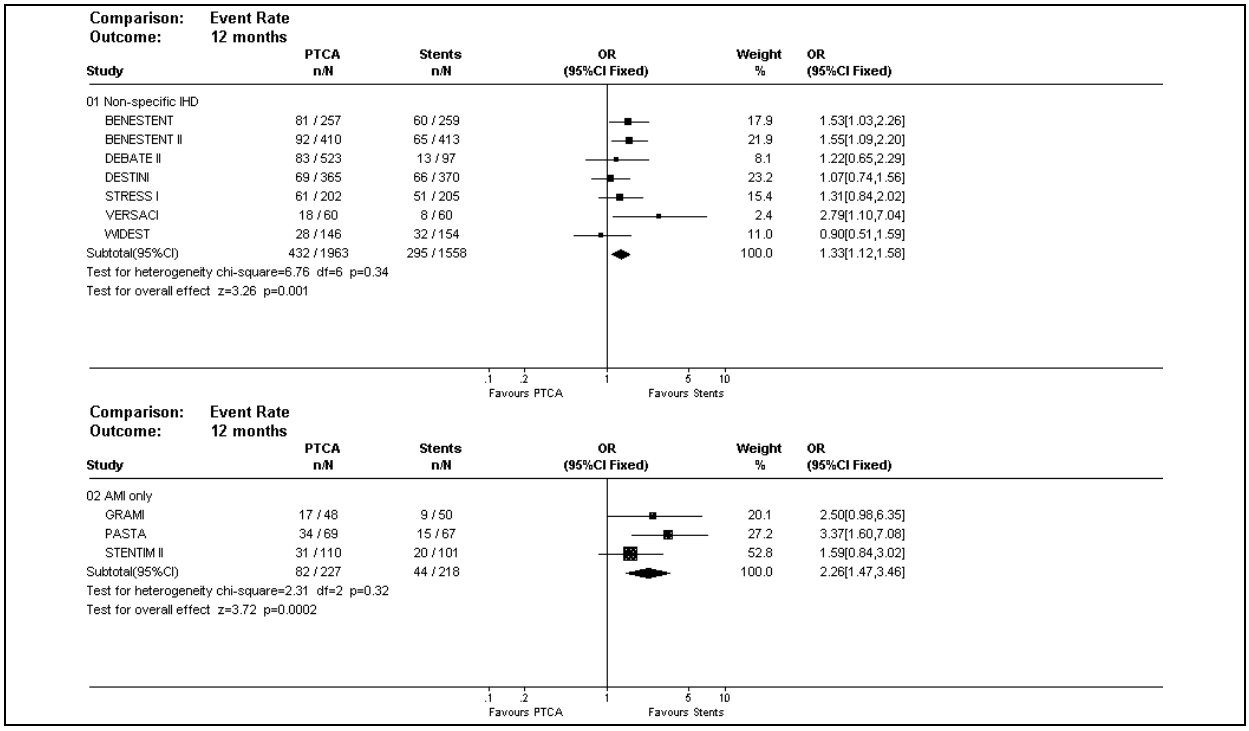


Figure 4A (continued)

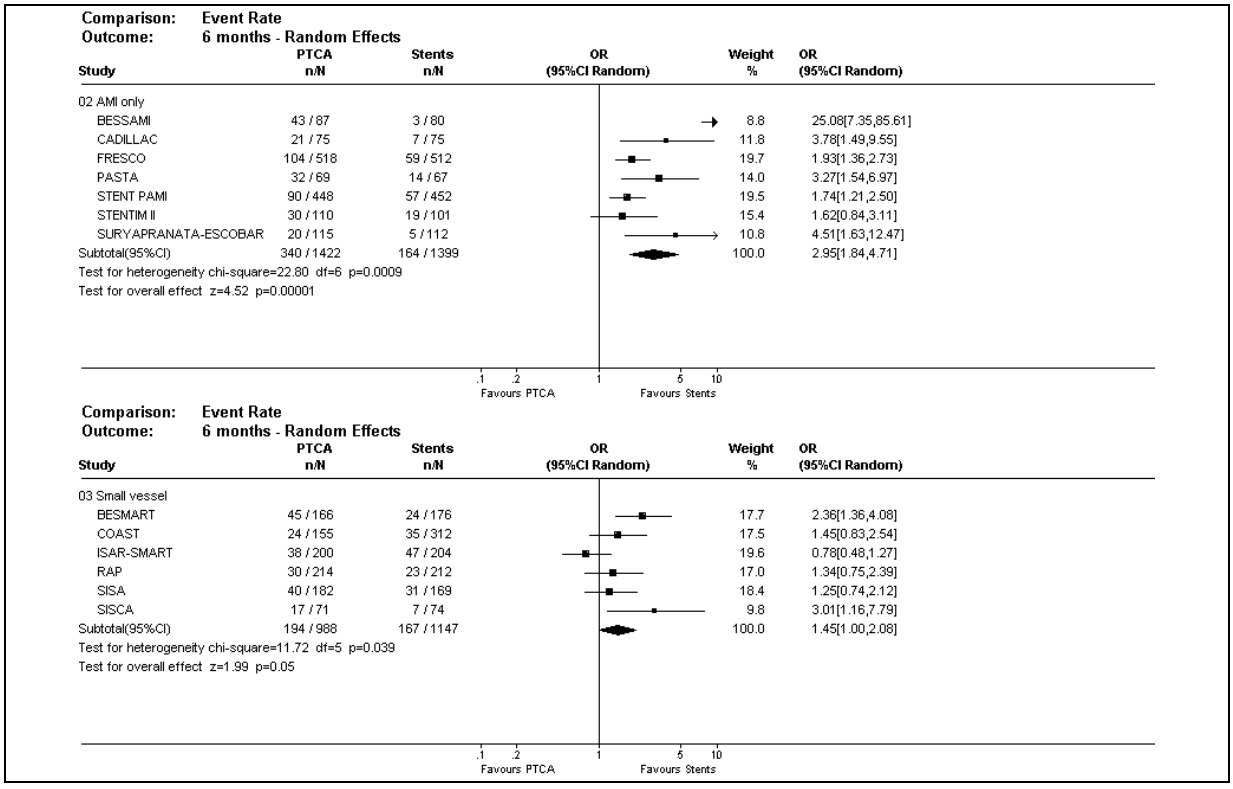
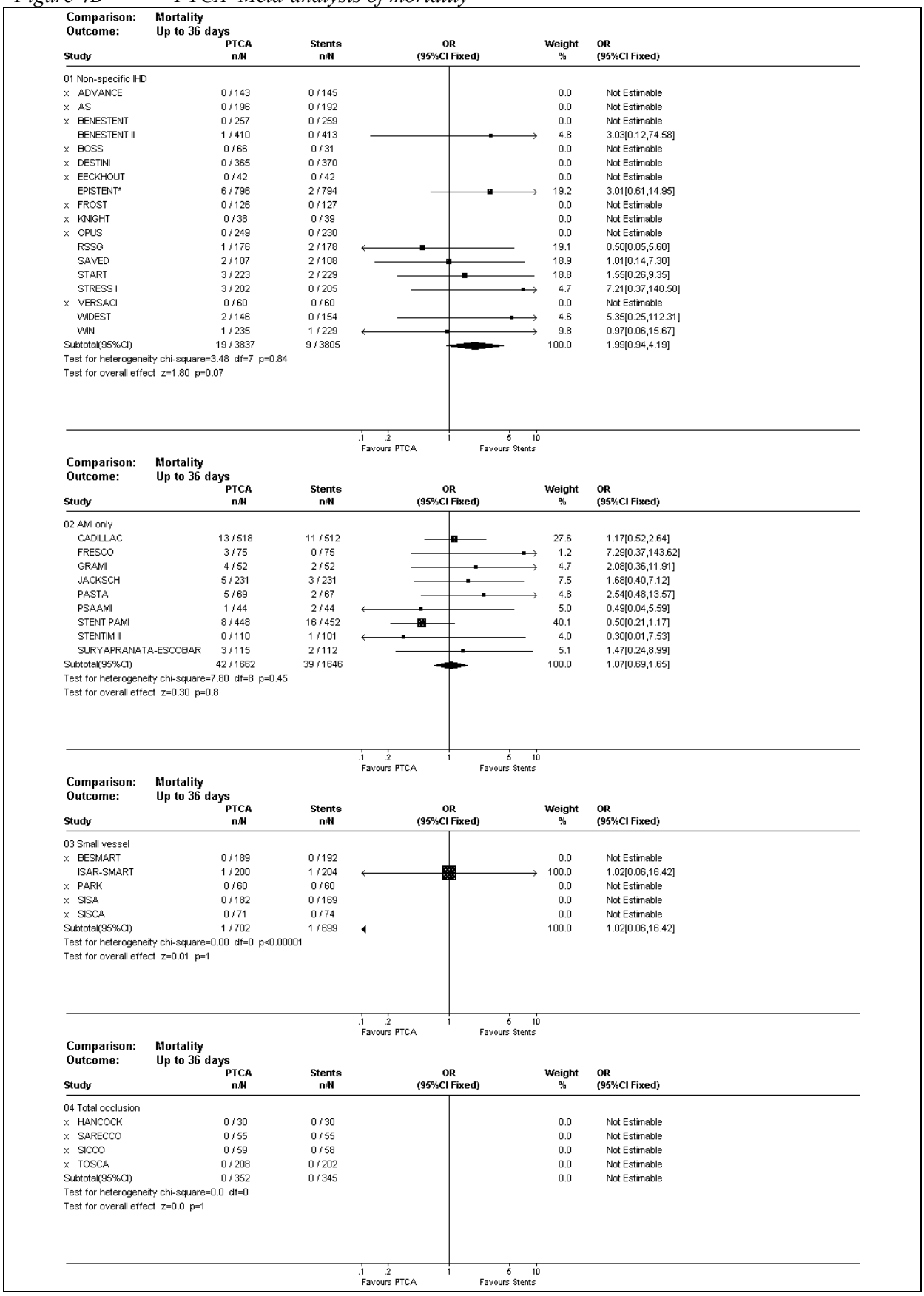


Figure 4B PTCA Meta-analysis of mortality



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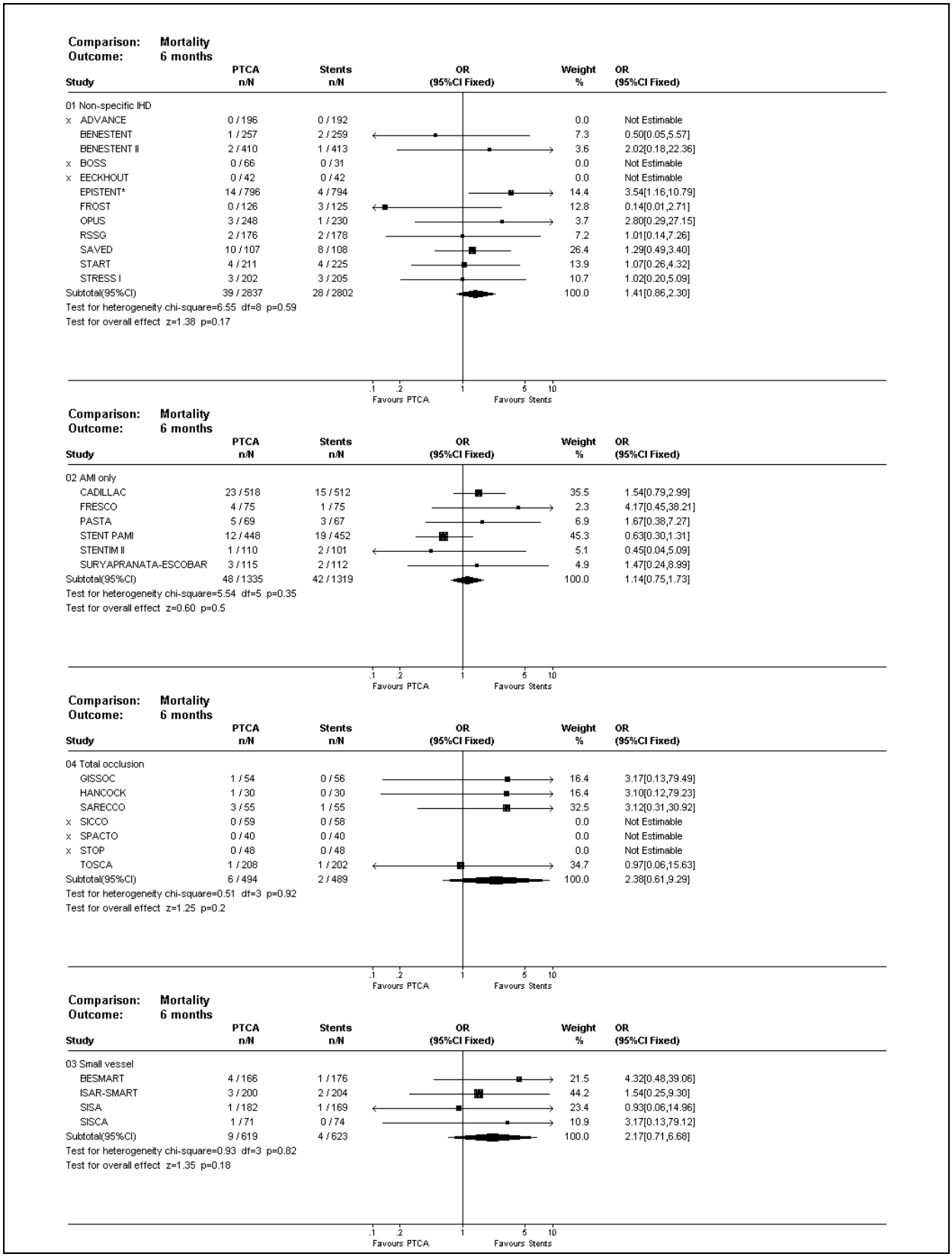


Figure 4B (continued)

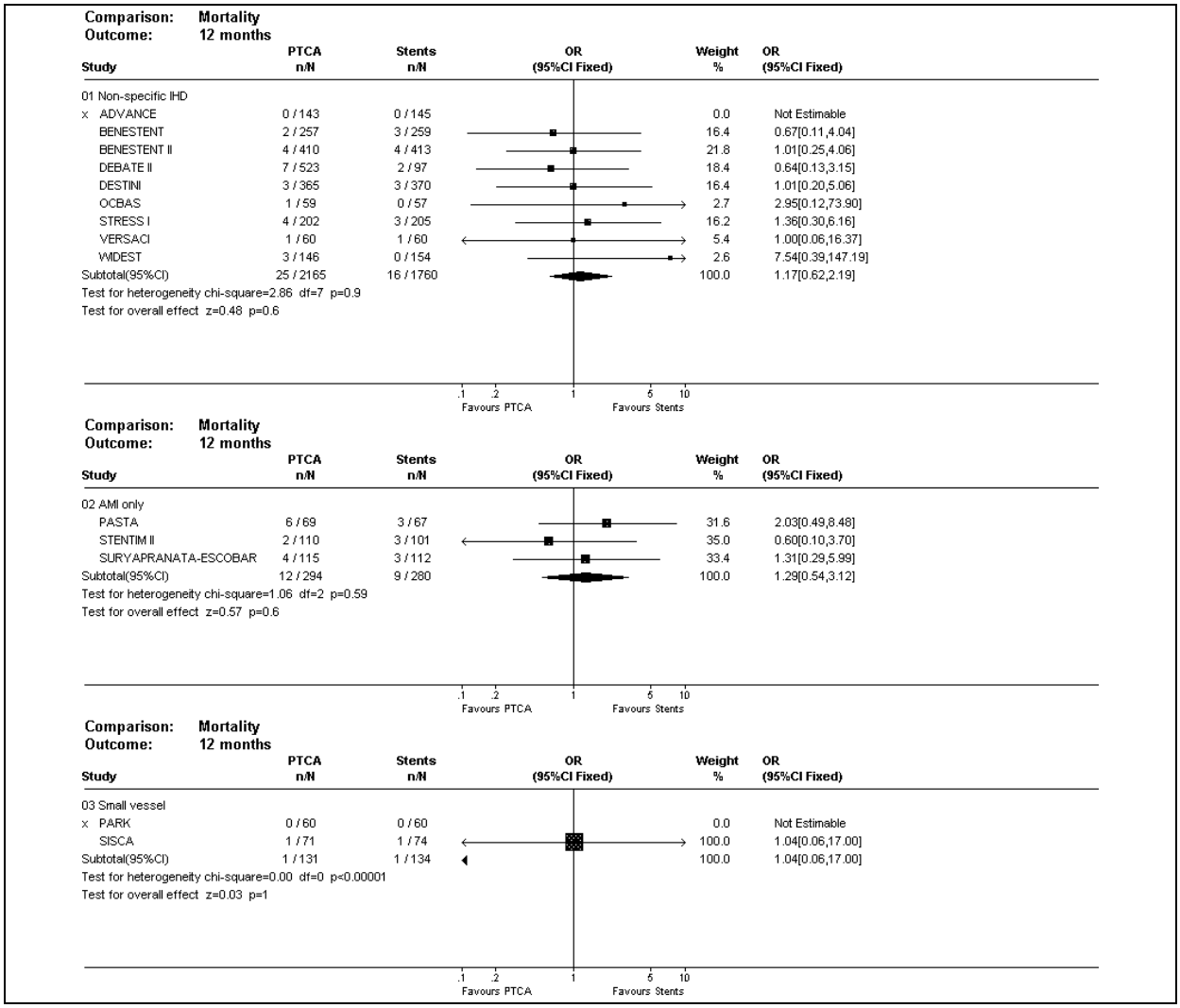


Figure 4C PTCA: Meta-analysis of any reported myocardial infraction

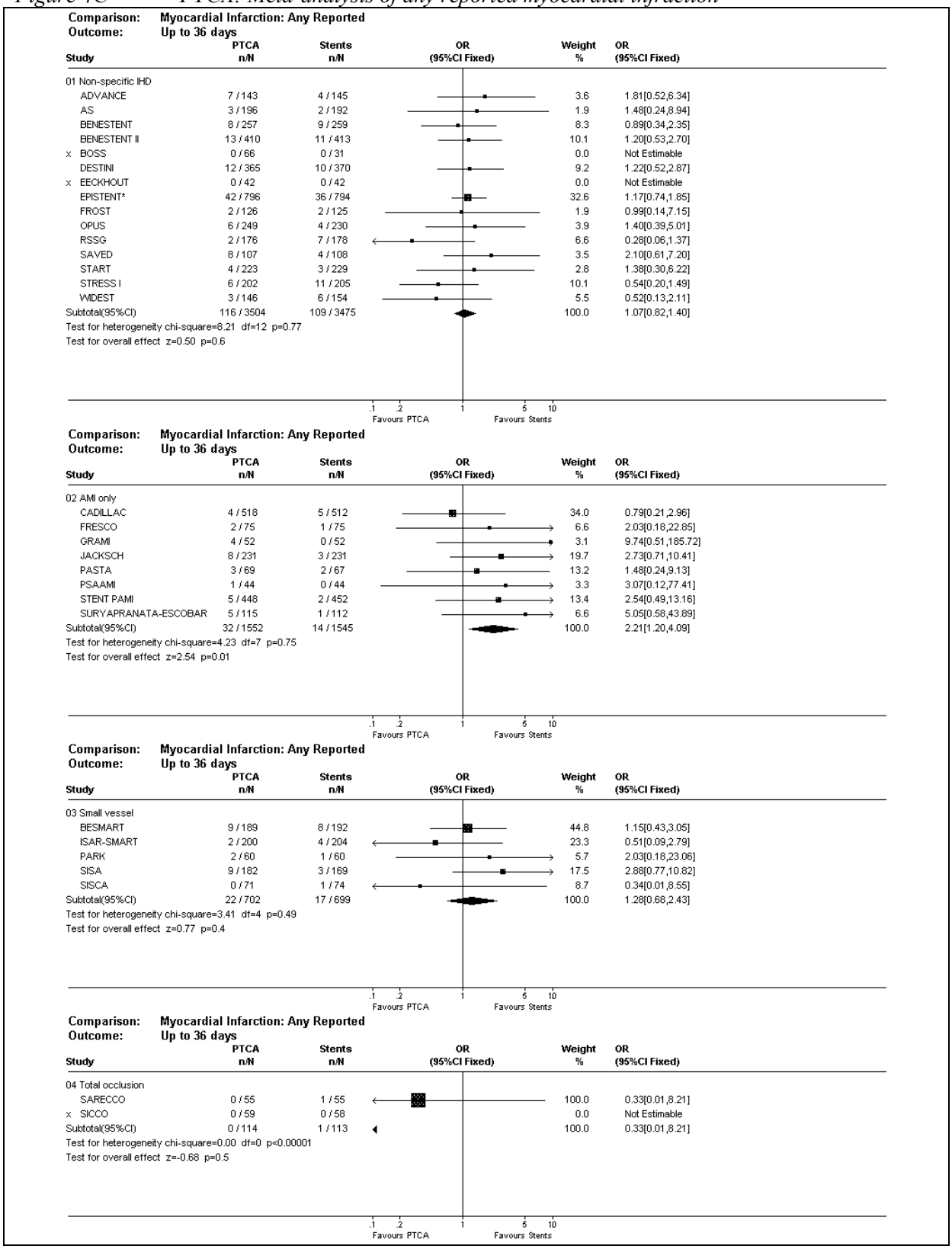


Figure 4C (continued)

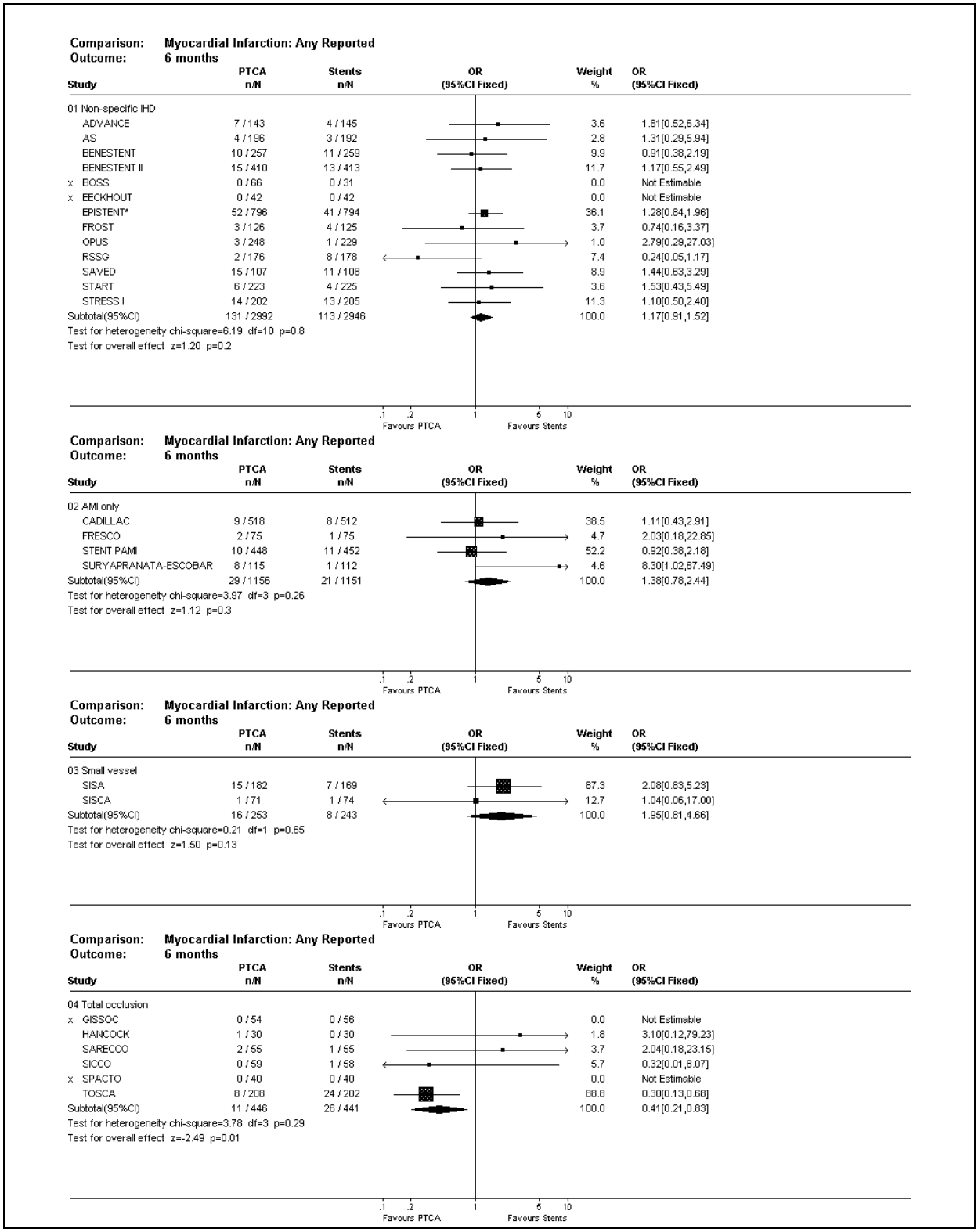


Figure 4C (continued)

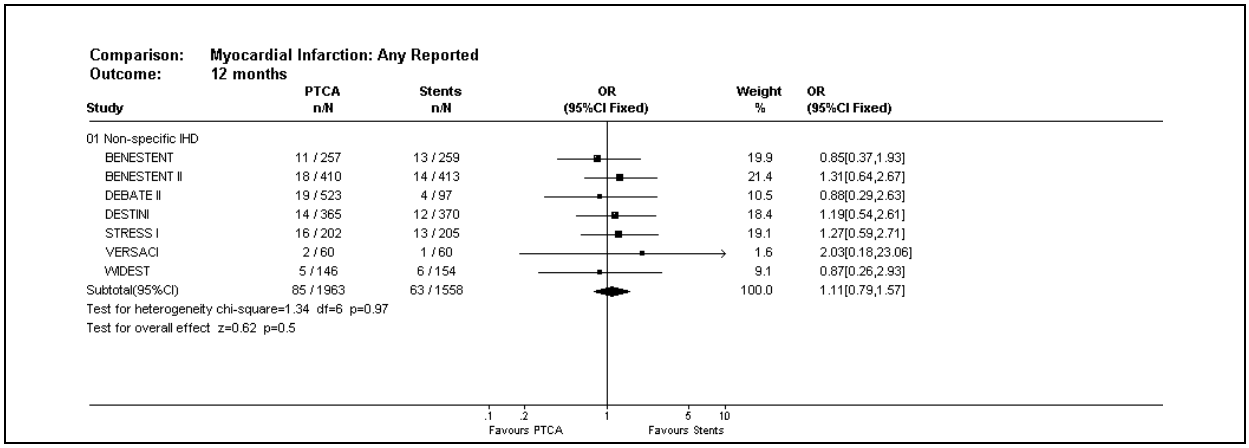


Figure 4D PTCA: Meta-analysis of restenosis

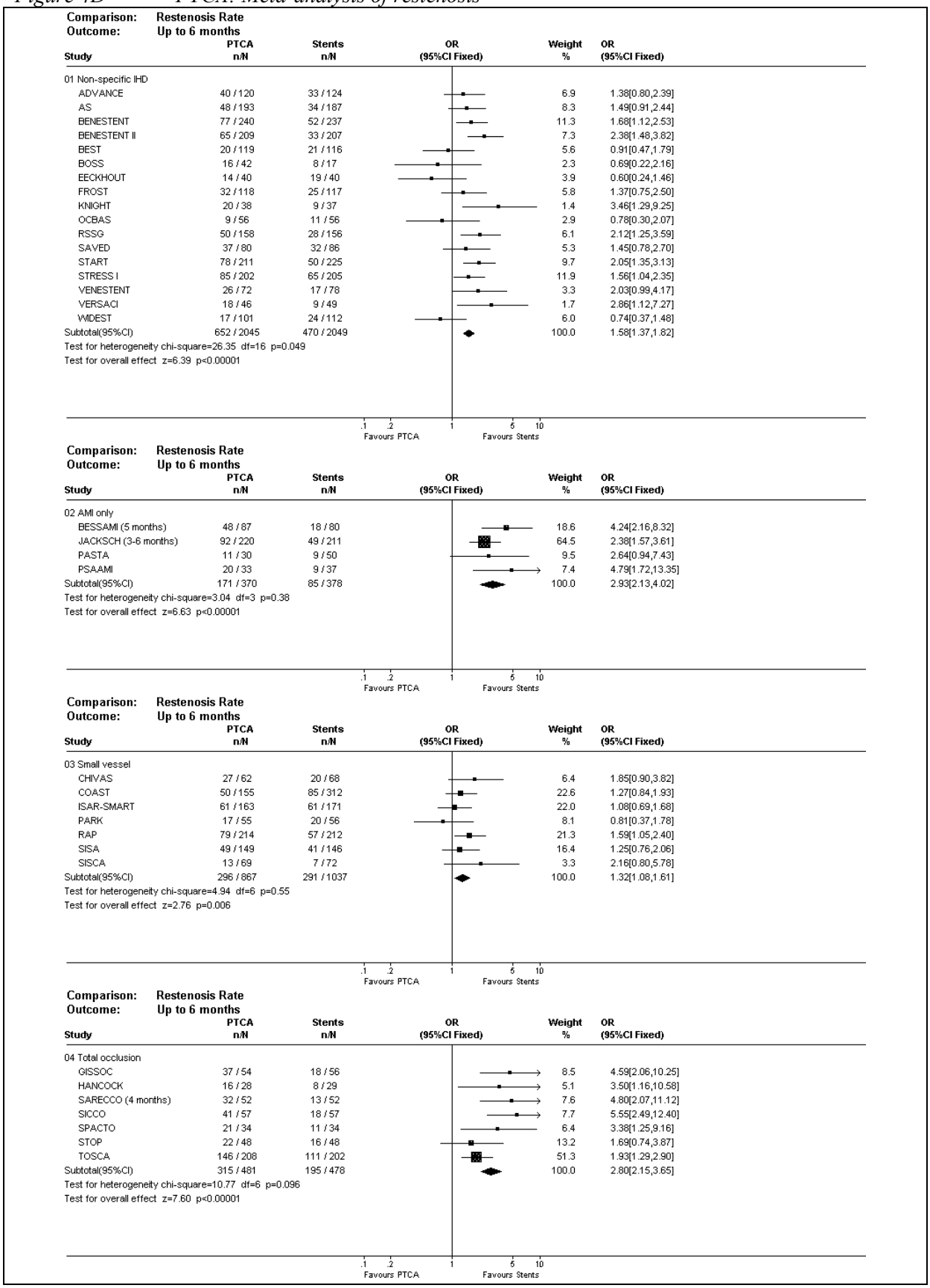
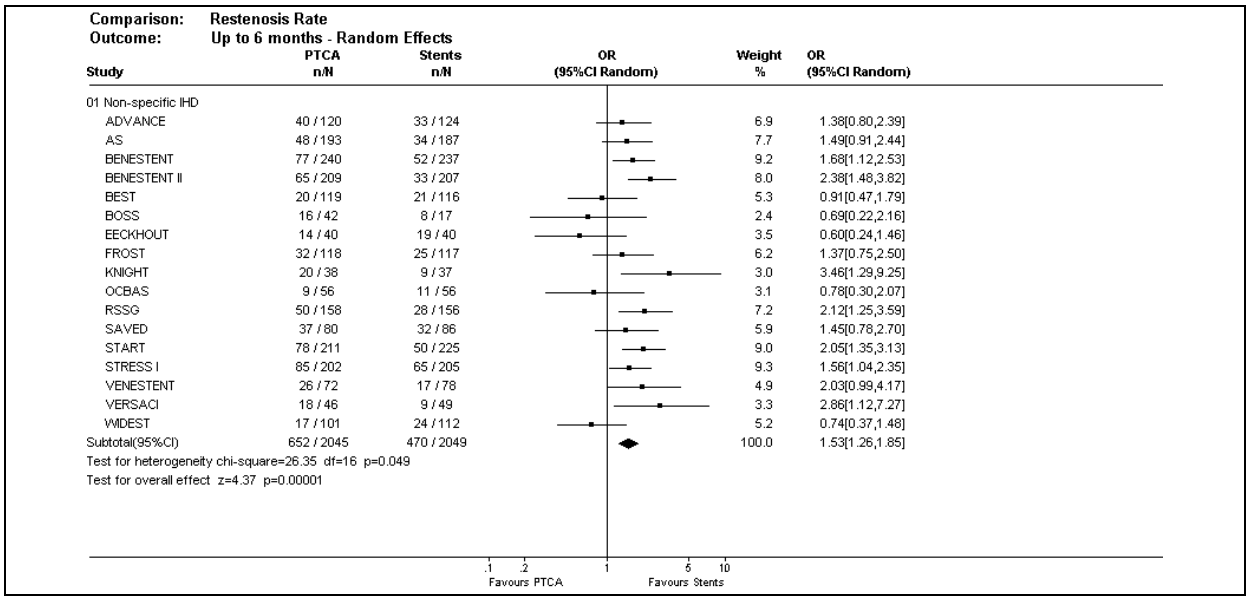


Figure 4D (continued)



5 Stent versus coronary artery bypass graft (CABG)

5.1 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 to stents and FREEDOM, (B. Farkouh ME, Mount Sinai NYU Health: personal communication, 13 January 2003 personal communication) a North American study comparing CABG to DES.

The search identified all three CABG trials(100-102) noted in the Meads and colleagues review.(2)

5.1.1 Quality assessment of included CABG studies

Methodological quality was assessed using the checklist described in the NHS Centre for Reviews and Dissemination Report 4(109) and summarised in Appendix 2. The results of the assessment are presented in Table 5A.

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

Eligibility for participation, comparability and co-therapies were described in all studies. Composition of allocated treatment arms of all studies appeared to be comparable. Withdrawals were tracked and data on more than 80 percent of participants were available in the final analyses of all reports. Intention to treat 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. None of the included trials indicate that there was any attempt to blind outcome assessors.

Table 5A CABG: Quality Assessment of included studies

	Randomisation:			Baseline comparability				Blinding:				Withdrawals		
Checklist items	Truly Random	Allocation concealment	Number stated	Presented	Achieved	Eligibility criteria specified	Co-interventions identified	Assessors	Administration	Participants	Procedure assessed	>80% in final analysis	Reasons stated	Intention to treat
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
ARTS	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
DIEGELER	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
DRENTH*	✔	**NS**	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
ERACI II	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
SIMA	**NS**	**NS**	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔
SOS	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	✘	✔	✔	✔

✔ **yes** (item adequately addressed), ✘ **no** (item not adequately addressed), ✔/✘ **partially** (item partially addressed), **na** not applicable or **ns** not stated * Quality assessment based on conference abstracts only

Summary details describing the study and participant characteristics are presented in Table 5C and Table 5D.

5.1.2 Study characteristics

Five of the included trials were multi-centred. 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 different countries. (99) The study by Drenth and colleagues(104) was single-centred and was conducted in Holland. Trial size ranged from 102 to 1205 with a total of 3088 patients involved in the five studies.

Two studies(100, 104) used minimally invasive surgery, while one other compared stenting to 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 multi-vessel disease(101, 103, 110) while three(100, 102, 104) included patients with isolated single vessel (LAD) disease. All but two studies(100, 102) explicitly excluded patients who had history of revascularisation.

5.1.3 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 while the remainder included a mix of patients with stable and unstable angina. The proportion of patients with diabetes mellitus varied across studies. The highest proportion was seen in the study by Diegeler and colleagues (100)(Stent group 34% and CABG group 25%).

5.1.4 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 5E.

The six included trials described broadly comparable outcomes and combined event rates (mortality, AMI, repeat revascularisation). Table 5B provides definitions of combined event rates used in each study. Four trials(102-104, 110) included cerebrovascular events as part of their event rate.

Table 5B 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

Follow-up

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

5.1.5 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 odds ratio and 95% confidence intervals. 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, this data has not been analysed separately. Studies examining single vessel disease are small and conclusions from the analysis need to be viewed with caution.

Forest plots of the meta-analysis are included in Figures 5A-5E

CABG: Event rate

Event rates in both single and multiple vessel studies favour CABG at six and twelve 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 primary comprised of the combination of repeat revascularisation (approximately 60% of total MACCE) and of any AMI.

CABG: Mortality

Data from single vessel trials is 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 one 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 one 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 post-operative and longer-term follow-up periods.

For ARTS (all followed for one year as relevant data for longer were not available (99, 111)), the hazard ratio for death for stents compared to CABG is estimated to be 1.12 (95% CI 0.56, 2.24).

For ERACI II, the hazard ratio for death for stenting compared to CABG is estimated to be 0.38 (95% CI 0.17, 0.84).

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

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 difference between stent and CABG at any myocardial infarction event point (up to 36 days, 6 months, one year).

CABG: Revascularisation

Data for single vessel trials is limited but in the one reporting trial shows a benefit of CABG over stents. In multiple vessel disease at one 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).

5.2 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 three year follow up reported so far is small (167 in total). At two year median follow-up (this is not a specific

time point, and so this figure is not used in the meta-analysis), this researchers report that 9 out of 18 deaths in the 488 stented patients and 3 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 to 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 three 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 this data, it has 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 or 5.7 percent within 36 days in surgical group versus 2 deaths or less than 1 percent in stented group) giving a reported survival advantage with stenting. However later mortality did not indicate a difference between the treatment groups (four in stented arm versus five in 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 intention to treat analysis, i.e. 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 double 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 quality of life or utility will be clearer when the ARTS study reports its longer-term results.

5.2.1 Comparability of interventions

The number of studies identified in this chapter are 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 angiographic as well as 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 percent of procedures on patients with single vessel disease involve stenting rather than CABG. Conversely, patients with triple 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 that 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 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 approximately 10 percent of stented patients in the two major studies, ARTS and SOS, had a glycoprotein IIb/IIIa inhibitor, in contrast to the 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 will see later, in common practice today the case mix between these procedures differs with the more severely affected multivessel 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 development in stenting (new stent design or drug eluting stents) in patients with different profiles will need further investigation in the future.

5.2.2 Outcomes

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

5.2.3 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 currently underway (SOS Investigators, Personal communication, January 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 41 month survival of 96.4 percent on stents versus 95 percent for CABG (p=0.98). Similarly, an inconclusive reduction in revascularisations previously reported becomes highly significant in favour of CABG (27 percent in the stented group versus 3.4 percent in CABG). That this subgroup of 50 percent 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 percent of the total trial patients), with follow-up to three years (111). This confirms the higher rate of MACCE rates in diabetic compared to non-diabetic patients, though interestingly only in the stented group: 31 percent in stented non-diabetics versus 47 percent in those with diabetes, but 17 percent 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 percent stent versus 4.3 percent 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, 3rd February 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 percent in people with diabetes receiving CABG versus 65.5 percent 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.

5.2.4 Availability of data and quality

There are limitations to the data:
First, some of the data has not been reported in peer reviewed literature and often only in other less satisfactory forms, e.g. the ARTS three year data which has appeared so far only in a conference abstract. This data is 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 is

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 authors. The major data anticipated from currently outstanding trials is the long-term data from ARTS.

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

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

Table 5C CABG: Study characteristics

Study name	Intervention	Primary outcomes	Secondary outcomes	Location(s) & 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	Multi-vessel CAD Presence of 2 or more de novo lesions located in different major epicardial coronary arteries Eligible for CABG or stenting; Total occlusion present less than 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	Multi-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 vessel to be treated (PTCR) should appear larger than 3.0mm	Single-vessel disease; Previous CABG; PCTA in last year; Previous stenting; AMI during first 24hr; Poor LVF (ejection fraction less than 35%); more than two CTO' severe valvular heart disease; limited life expectancy (age or illness)	Aspirin Ticlopidine Heparin (Abciximab for rest pain or post-MI)	30day 1 year	Primary device Gianturco Roubin II (Cook)
SOS [103]	488 (480 treated with St) 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 multi-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]

Study name	Intervention	Primary outcomes	Secondary outcomes	Location(s) & centres	Inclusion criteria	Exclusion criteria	Co-therapies	Follow-up	Type of stent
Single vessel disease									
DIEGELER (100)	Stent 110 CABG 110	Freedom form MACE within 6mo	Cardiac death; MI TVR Clinical status (CCS) Need for antianginal drugs at 6 mo adverse events	Multicentre Germany	Isolated, high grade (greater of equal to 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, intramycocardial course of left anterior descending artery	Nitroglycerin (2% received IIb/IIIa inhibitors)	6 months *MACE on 108, 108,* *Rest enosis 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)
DRENTH (104)	Stent 51 CABG 51	Freedom from MACCE at 3 years Angiographic outcome at 6mo	Angina class (CCS), antianginal medication, Clinical events MACCE without RV 6 mo clinical outcome	Single centre, 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 (1month, Stent group)	In-hospital, 6month 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 ischemia 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 mo)	Baseline 6mo 1 year and annually	Any CE approved, but Palmaz-Schatz recommended
Studies satisfying inclusion criteria, but where data unavailable for analysis									
AWESOME (106)	**PCI**[B] 222 (120/222 received stents) CABG 232 (Multivessel disease)	*Clinical effectiveness*: Absence of Reintervention MACE cerebrovascular events cardiovascular death at 1yr	Angina QoL Exercise capacity Cost effectiveness	Multicentre (16) USA	Medically refractory MI and one of more 'high-risk' (of 30 day operative mortality with CABG) factors	Single vessel disease; greater than 50% left main stenosis; no graftable or dilatable vessels; co-morbidity likely to limit life in next 6 months.			

Study name	Intervention	Primary outcomes	Secondary outcomes	Location(s) & centres	Inclusion criteria	Exclusion criteria	Co-therapies	Follow-up	Type of stent
OCTOSTENT [105]	No information identified on participant numbers (Multivessel Disease)	Absence MACCE for 1 year (Death, stroke, TIA, reversible ischaemic neurological deficits, nonfatal 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	Multivessel CAD eligible for CABG or stenting; Presence of 2 or more de novo lesions located in different major epicardial coronary arteries; Total occlusion present less than 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		

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 participant undergoing PCI received stents.

Table 5D CABG: Participant characteristics

Study name	Intervention	Age (years) Mean [SD]	Sex (% male)	Lesion category (%)	ACS (%)	Previous cardiac event (%)	Diabetes mellitus (%)
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 St)	61 [9.2]	80			MI: 44	14
	CABG 500 (487 treated by CABG)	62 [9.5]	78			47	15
Single disease							
DIEGELER (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 (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) St: 59 (57-62); CABG: 60 (58-63)	76				11
	CABG 59		83				13

A Braunwald Class II, III-C

Table 5E CABG: Outcomes

Study name	Intervention	Event rate (%)	Mortality (%)	MI (%)	Revascularisation (%)	CABG (%)	PTCA (%)	BBR 6 months (*n*, %)
Multiple vessel disease								
ARTS	**Stent**	1 year 26.2 3 year 34.2	30 days 1.5 1 year 2.5 3 year 3.7	1 year 5.3 3 year 6.2	1 year 21.0 3 year 21.3	1 year 6.7 3 year 6.7	1 year 15.7 3 year 14.7	
	CABG	1 year 12.2 3 year 16.9	30 days 0.5 1 year 2.8 3 year 4.6	1 year 4.0 3 year 4.3	1 year 3.8 3 year 5.5	1 year 0.7 3 year 0.8	1 year 3.3 3 year	
ERACI II	**Stent**	30days 3.6	30 days 0.9 18.5 months [A] 3.1	30 day [E] 0.9	30 days 1.8	30 days 0.0	30 days 1.8	
	CABG	30 days 12.3	30 days 5.7 18.5 months [A] 7.5	30 day [E] 5.7	30 days 0.0	30 days 0.0	30 days 0.0	
SOS	**Stent**	1 year 110/488	1year 2.5 2 years 4.5	1 year [E] 4.3 2 year [E] 5.3	1 year 18 2 year 22 3 year 24	1 year [F] 7.8	1 year [F] 11.3	
	CABG	1 year 62/500	1 year 0.8 2 year 1.6	1 year [E] 6.8 2 year [E] 8.2	1 year 4 2 year 6 3 year 7	1 year [F] 1.0	1 year [F] 3.2	

Study name	Intervention	Event rate (%)	Mortality (%)	MI (%)	Revascularisation (%)	CABG (%)	PTCA (%)	BBR 6 months (*n*, %)
Single vessel disease								
DIEGELER	**Stent**	6 month 31.5	6 months 0.0	30 days 1.9 6 months 2.8	30 days 1.9 6 months 28.7			[G](35/106) 33.0%
	CABG	6 month 14.8	6 months 1.9	30 days 3.7 6 months 4.6	30 days 3.7 6 months 8.3			[G](18/98) 18.4%
DRENTH (104)	**Stent**	6 months 13.7 1 year 23.5 3 years 24.1	In hospital [C] 0.0 6 months 0.0 2.9 years [D] 0.0	6 months 9.8 2.9 years [D] 9.8	2.9 years [D] 15.7	6 months 2.0	6 months 7.8	(14/49) 28.6%
	CABG	6 months 7.8 1 year 7.8 3 years 8.3	In hospital [C] 3.9 6 months 3.9 2.9 years [D] 3.9	6 months 2.0 2.9 years [D] 2.0	2.9 years [D] 3.9	6 months 0.0	6 months 3.9	(2/46) 4.3%
SIMA	**Stent**	2.4 years 36.5	Post Procedure 1.6 2.4 years 1.6	Post Procedure 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	Post Procedure 0.0 2.4 years 1.7	Post Procedure 3.4 2.4 years 3.4	2.4 years 0.0	2.4 years 0.0	2.4 years 0.0	

A 18.5 +/- 6.4mo, Range 9 to 33 mo; B Median 2 year; C In hospital and with 1 week of discharge; D Range 2 to 4 yrs, mean 2.9 yrs; E Only Q wave MI reported; F 'All repeat interventions' [Hierarchical: St 29/488, CABG 2/500]; [Hierarchical: St 44/488; CABG 15/500]; G In-stent restenosis detected in stent patients; CABG patients who had stenosis of more than 50% LD

Figure 5A CABG: Meta-analysis of event rate

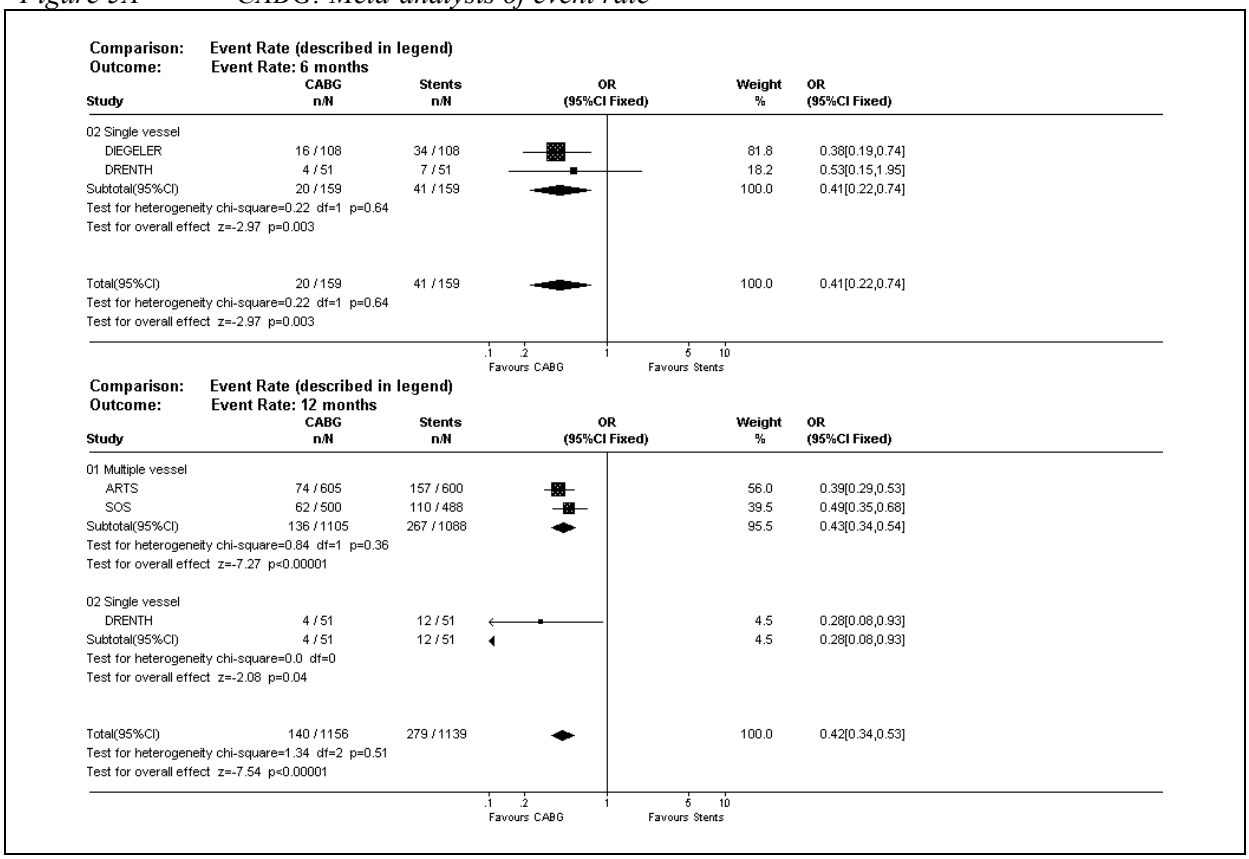
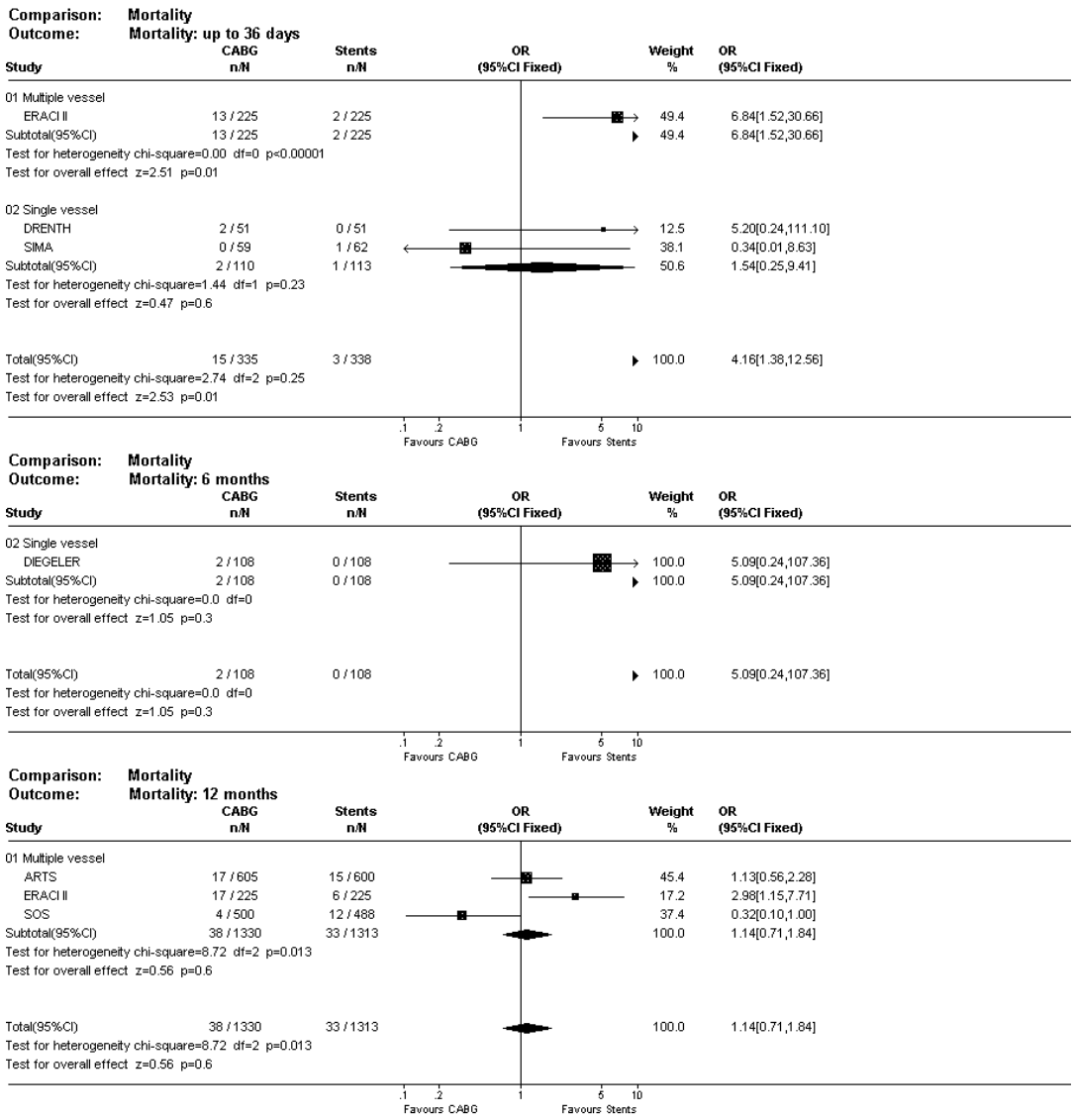


Figure 5B CABG: Meta-analysis of mortality



ERACI II, 12 month mortality: Follow-up 9 to 33 months, assumed that all survived 9-12 months. Survival (and therefore death rates) have been read from Kaplan Meier plots, Figure 4 (101)

Figure 5C CABG: Meta-analysis of acute myocardial infarction

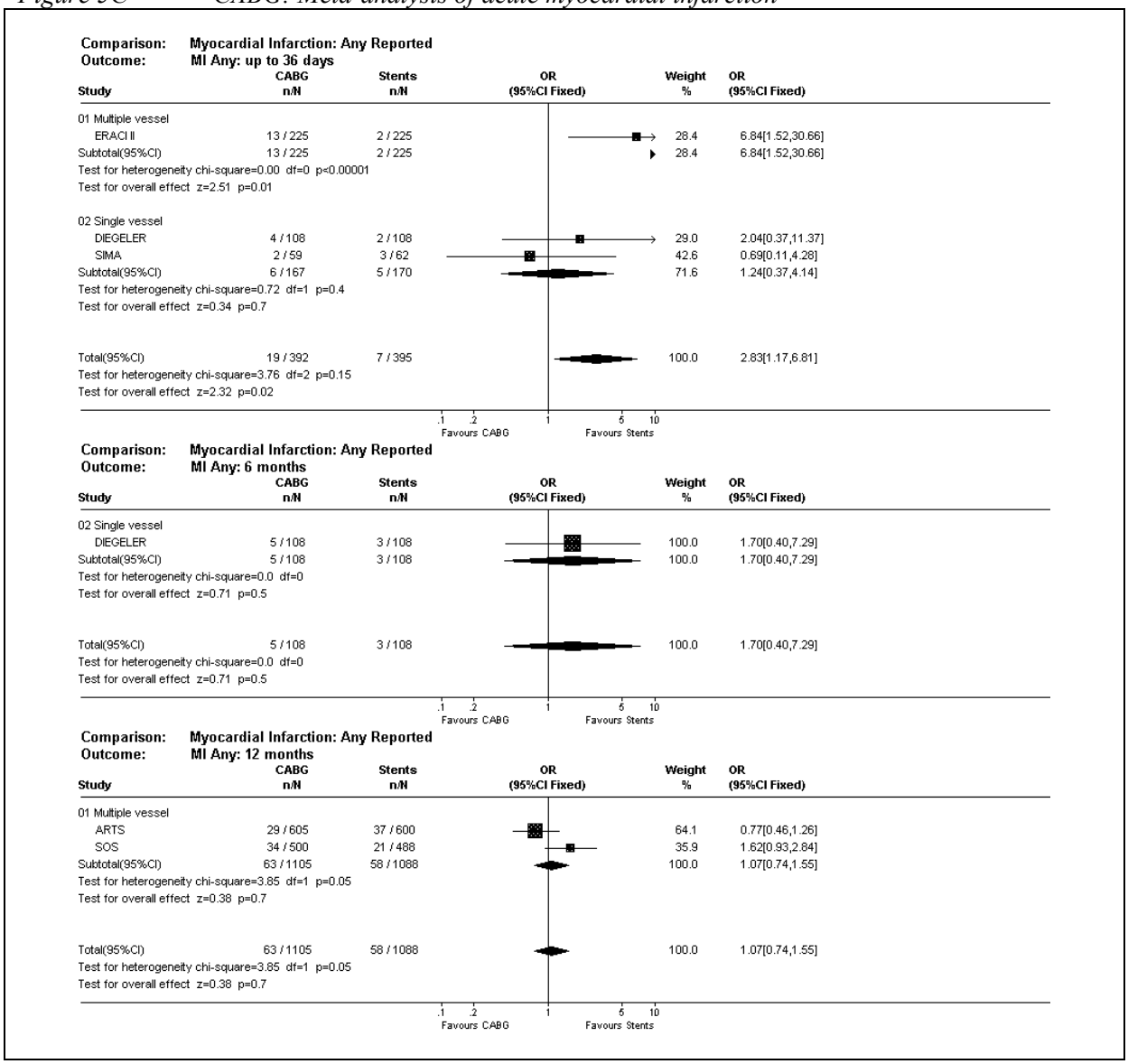


Figure 5D CABG: Meta-analysis of any reported revascularisation

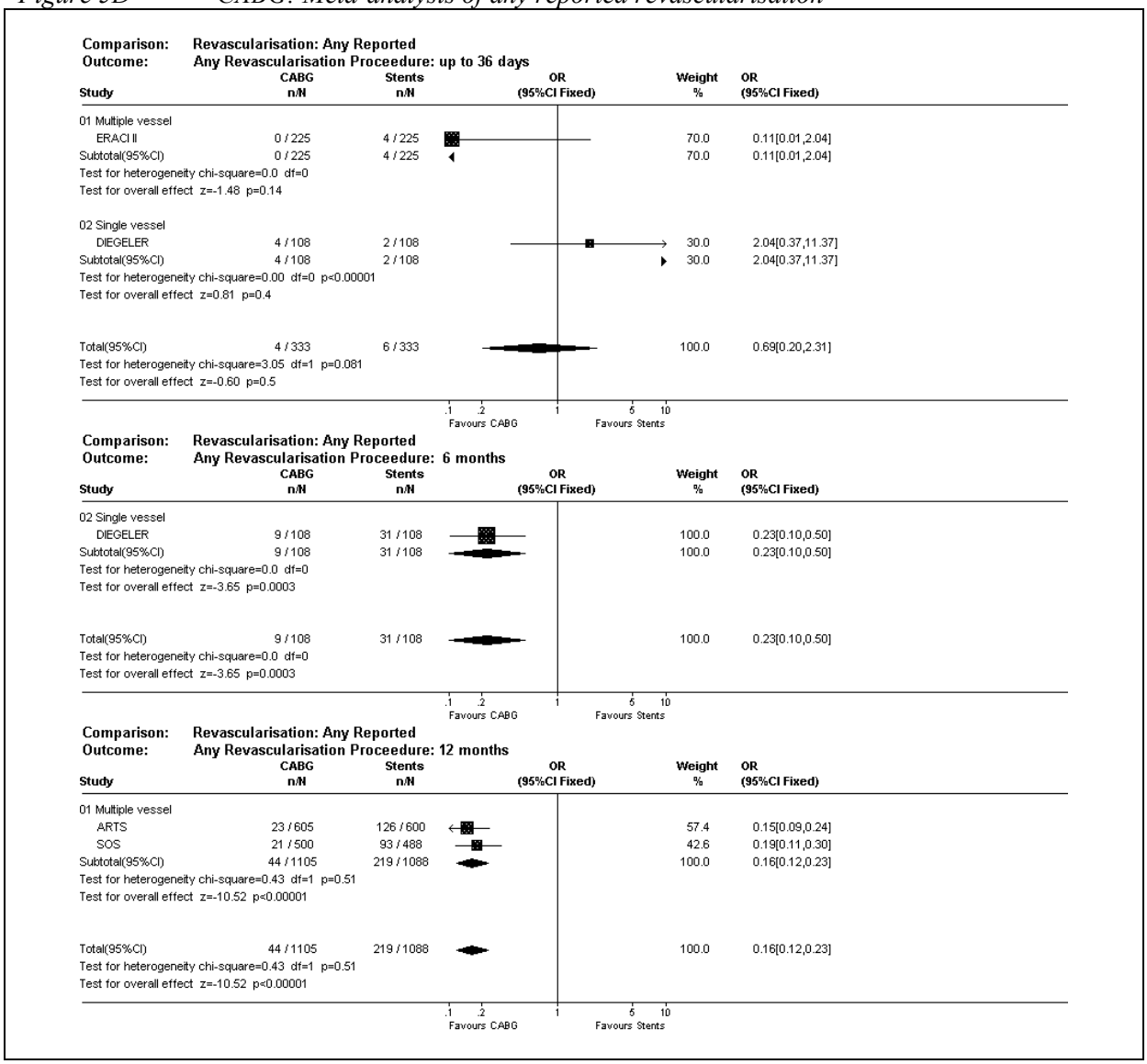
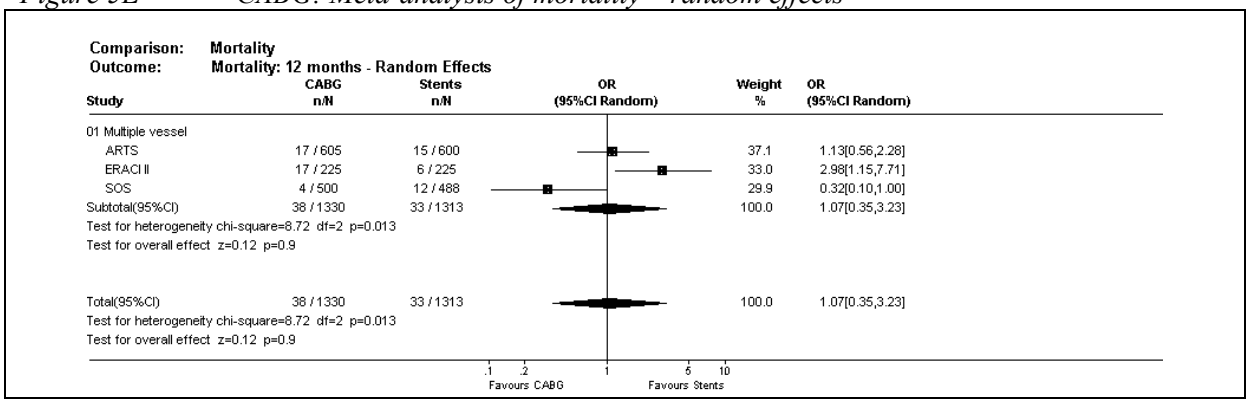


Figure 5E CABG: Meta-analysis of mortality – random effects



ERACI II, 12 month mortality: Follow-up 9 to 33 months, assumed that all survived 9-12 months. Survival (and therefore death rates) have been read from Kaplan Meier plots, Figure 4 (101)

6 Non drug-eluting stents versus drug-eluting stents

6.1 DES: Included studies

Twelve studies, comparing drug-eluting stents (DES) with non drug-eluting stents (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 drug-eluting stents are listed in Table 6A.

Two of the twelve included studies were suspended. The ACTION study was suspended due to low-efficacy, while SCORE was suspended due to a high incidence of MACE in the drug-eluting stent 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, with more detailed information expected in 2003.

Given that these four studies have all reported according to protocol, available data is 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 drug-eluting stents (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 ten 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 the References section**.**

Table 6A Summary of drug-eluting stent RCTs identified in search

Agent		Study name	Status	Publication types & references
Taxane	**Paclitaxel**	**ASPECT**	*Reported at 6 months*	*Abstracts, conference reports* (122-128) (129)
	Paclitaxel	**DELIVER**	*Some 9-month data presented January 2003, further data expected 2nd Quarter 2003.*	*Abstract, Conference report* (130, 131) (132)
	Paclitaxel	**ELUTES**	*Reported at 6 months*	*Abstracts* (133-139) (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 anticipated in 2nd-3rd quarter 2003*	*Conference report* (146, 147)
	Paclitaxel	**TAXUS V**	*In progress - enrolment to end 4th quarter 2002*	*Conference report* (147)
	Paclitaxel	**TAXUS VI**	*In progress – enrolment to end 1st quarter 2003*	*Conference report* (147)
	QP2 (7-hexanolytaxol)	**SCORE**	*Reported at 6 months, 1 year. Enrolment stopped due to inc early MACE.*	*Abstracts* (149-156)
	Sirolimus	**RAVEL**	*1 year data published, 2 year released in confidence - February 2003*	*1 year data: Published report, abstracts Confidential data* (119)
	Sirolimus	**SIRIUS**	*1 year data released in confidence to Review Team February 2003*	*Conference report, abstracts* (157-162)
	Sirolimus	**E-SIRIUS**	*In progress 9 month data released in confidence – February 2003*	*Conference report, abstracts Confidential data* (162)
	Everolimus	**FUTURE**	*In progress Early (FUTURE I) data reported 3rd Quarter 2002, further expected 1st quarter 2003*	*Abstracts, conference report* (163) (121, 164)
Other	**Actinomycin**	**ACTION**	*Stopped - Trial stopped due to inability to reduce restenosis as seen in animal studies*	*Conference report* (165, 166)

Non-randomised drug-eluting stent studies

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

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 endpoint and MACE up to 5 years, revascularisations and restenosis as additional endpoints.

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 a 'stent-graft' designed for use in saphenous vein bypass grafts.(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 versus stent trial) as controls. The primary endpoint 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 endpoint of this non-randomised study is binary restenosis at 6 months, and secondary investigation of MACE and IVUS analysis.

6.1.1 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 6B.

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. Due 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 eighty percent or more was apparent for all studies, except for FUTURE where number randomised was not stated explicitly and ACTION where only 74 percent 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 ten 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 where at least partially (ASPECT, SCORE) or adequately described for all the studies. Co-therapies where 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 where also blinded. Participants in ELUTES study also appear 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.

Table 6B DES: Quality Assessment of included studies

	Randomisation:			Baseline comparability				Blinding:				Withdrawals		
Checklist items	Truly Random	Allocation concealment	Number stated	Presented	Achieved	Eligibility criteria specified	Co-interventions identified	Assessors	Administration	Participants	Procedure assessed	>80% in final analysis	Reasons stated	Intention to treat
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
ACTION*	×	×	✓	×	×	✓	✓	×	×	×	×	✓ ×[A]	×	✓
ASPECT*	×	×	✓	×	×	✓ ×	✓	×	×	×	×	✓	×	✓
DELIVER*	NS	NS	✓	✓	✓	✓	✓	NS	NS	NS	×	✓	×	×
FUTURE*	NS	NS	×	✓	×	✓	×	NS	NS	NS	×	✓	×	NS
ELUTES*	×	×	✓	×	×	✓	✓	✓	NS	✓	×	✓	×	✓
E-SIRIUS	×	×	✓	✓ ×	✓ ×	✓	✓	×	×	×	×	✓	×	✓
PATENTCY	NS	NS	✓	✓	✓	✓	✓	✓	NS	NS	×	✓	✓	✓
RAVEL	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓
SCORE*	×	×	✓	✓ ×	✓ ×	✓ ×	×	×	×	×	×	✓	×	✓
SIRIUS*	×	×	✓	✓ ×	✓ ×	✓	✓	×	×	×	×	✓	×	✓
TAXUS I	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓
TAXUS II	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓

✓ **yes** (item adequately addressed), × **no** (item not adequately addressed), ✓/× **partially** (item partially addressed), **NA** not applicable or **NS** not stated. * Quality assessment based on conference abstracts only A Only 88 of 119 (74%) randomised to stent arm reported at 6 months.

6.1.2 Quality of data available from DES studies

As previously stated, only two of the twelve 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 were apparent among the electronic and printed abstract sources used. Examples include the ACTION study were 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, myocardial infarction at 30 days differ 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 reversed (DES 134, Stent 126) as in a presentation for CRF Drug-Eluting Stent Symposium 2002(156)and other sources(149) numbers are Stent 138, DES 128. Reasons for these differences remain unclear.

6.1.3 DES: Study characteristics

Numbers of participants, centres & locations

Over four thousand (4367) participants are studied in the included trials. Numbers of people randomised in each study ranged from 36 (FUTURE) to more than 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 6C 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 to uncoated implants, where as 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.

Table 6C Stent types and manufactures for included DES RCTs

Agent			Study name	Company	Drug eluting stent
Taxane	**1.**	**Paclitaxel**	**ASPECT**	Cook	Supra G
	2.	**Paclitaxel**	**DELIVER**	Guidant	ACHIEVE: Multi-Link RX PENTA CSS
	3.	**Paclitaxel**	**ELUTES**	Cook	V-Flex plus
	4.	**Paclitaxel**	**PATENTCY**	Cook	Logic PTX
	5.	**Paclitaxel**	**TAXUS I**	Boston Scientific	NIRx-Express
	6.	**Paclitaxel**	**TAXUS II**	Boston Scientific	NIRx-Express
	7.	**QP2**	**SCORE**	Quanum Medical/ Boston Scientific	QUANAM
	8.	**Sirolimus**	**E-SIRIUS**	Cordis	CYPHER BxVelocity
	9.	**Sirolimus**	**RAVEL**	Cordis	CYPHER BxVelocity
	10.	**Sirolimus**	**SIRIUS**	Cordis	CYPHER BxVelocity
	11.	**Everolimus**	**FUTURE**	Biosensors	Challenge S-stent
Other	**12.**	**Actinomycin**	**ACTION**	Guidant	Multi-Link Tetra

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 GP IIb/IIIa inhibitors for patients.

DES: primary and secondary endpoints

Primary and secondary endpoints varied across the studies and are presented in Table 6F. 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 6D.

Table 6D DES: included studies event rate definitions

Study	Event rate: composition
ACTION	MACE: Death, MI, TLR
ASPECT	MACE: Death, MI, CABG, TLR and TLR for sub acute thrombosis (TLR 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

Revascularisation

Consideration of revascularisation as a part of a composite event requires attention to two main issues. Firstly, are the reported revascularisations specific to the target (treated) lesion (TLR), vessel (TVR) or non-specific (possibly including non-target vessels)? Table 6E 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 directly compare the data from the trials 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 have used the currently accepted Food and Drug Administration 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, while 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 seems to suggest that there were no patients who met this criterion alone. While therefore full MACE figures for RAVEL as reported in the NEJM paper are 34 out of 118 in the non-DES arm, but the figures are only 23/118 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 6E DES: Reported Revascularisation

Study name	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: Sub Acute thrombosis; TLR: Target lesion Revascularisation; TLR+TVR: Sum of TLR and TVR; TVR: Target vessel Revascularisation (*non-TLR); Target-RR: Target Revascularisation; Non-T-RR: Non-target Revascularisation; Any RR: Any Revascularisation (t-RR+non-T-RR)

Restenosis and Angiographic outcomes

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

The relevance of binary restenosis and the introduction of more clinically relevant outcomes was 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.

6.1.4 DES: Study participants

Sample size

Details of the characteristics of study participants are provided in Table 6G, at the end of this chapter.

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 due 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 percent of participants. In another example, DELIVER reports 'Device success' of 99.0 percent for non-eluting stents from a partner registry and 98.5 percent 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 DES participants. Provision of allocated treatment in other DES studies may also have been high, but this cannot be quantified in the available information.

Trial Inclusion and exclusion criteria

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

Age, gender, type of stent

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

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

Recent or current myocardial infarction excluded potential participants in ASPECT, E-SIRIUS, FUTURE, RAVEL SIRIUS, SCORE, TAXUS I(118) and TAXUS II. ELUTES and ACTION do not state that myocardial infarction excluded participants.

Information on past or concurrent health factors was identified for all studies. The proportion of participants with diabetes mellitus varied from around 14 to 29 percent. People with Type-II diabetes made up 14.5 percent of those included in ACTION and TAXUS II; SIRIUS included 26.4 percent overall and DELIVER included the highest proportion of people with diabetes (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).

6.1.5 DES: Data analysis

Meta-analysis is presented for event rate, mortality, AMI, and binary restenosis. Data are pooled using a fixed effect model with odds ratio and 95 percent confidence intervals. 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, while 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 Figures 6A to 6E, while details are provided here.

DES: Event rate

Analysis of event rates favours DES at six (OR: 0.49, 95% CI 0.38 to 0.61) and 12 months (OR: 0.42, 95% CI 0.32 to 0.56). However, in the 6 month analysis there is heterogeneity, and the analysis was re-calculated using a random effects model. This more conservative analysis shifts the OR to 0.59 (95% CI 0.31 to 1.11).

(CIC information removed)

DES: Mortality

Death in all studies was a rare event. There is no evidence of a difference between the groups. Event rates in the short-term do not differ between the groups.

(CIC information removed)

DES: AMI

There is no evidence of a difference in incidence of AMI between DES and stents in the short-term or at six months. Data at 12 months indicates an increase in AMI in the DES group. This outcome is predominated by the outcome of the SCORE trial.

(CIC information removed)

DES: Binary restenosis

Binary restenosis (greater than 50 percent) 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.

6.2 Discussion

Drug-eluting stents 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. The vast majority of interventional cardiologists are enthusiastic about the use of drug-eluting stents. However, current available data has 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, i.e. 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 man, 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 Man was an open non-comparative study in patients with coronary heart disease 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 reaching more than 50 percent diameter stenosis at one year based on angiography. Neo-intimal hyperplasia, as assessed by intravascular ultrasound was found to be virtually absent both at 6 and 12 months. The authors conclude that the study demonstrates a sustained suppression of neo-intimal proliferation by the DES. Two year data has 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 2 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 percent diameter stenosis compared to earlier angiography. In general these studies are reassuring about the long-term safety of this DES. (CIC information removed)

6.2.1 Comparability of interventions

There are many technical issues which remain to be resolved with DES: these include polymer bio-compatibility, the suitability of and relative effectiveness of pharmacological agents, sub-optimal in vivo pharmacokinetic properties, local drug toxicity and manufacturing process. At present, significant differences have by and large 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 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 re-stenosis rates, and the latter due to high rates of early major adverse cardiac events.

The third trial, DELIVER, enrolled 1043 patients and its primary endpoint was target vessel failure (MI or TLR or TVR at 9 months). The study was powered to detect a 40 percent reduction. A secondary endpoint was angiographic binary restenosis at eight months. Although there was a 20 percent 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 to 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 percent in the controls versus 3 percent in the highest dose DES group (2.7 micrograms per square millimetre). In ASPECT, the rates were 27 percent in the control group versus 4 percent in the high dose DES group (3.1 micrograms per square millimetre). 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 drug eluting stent (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 is limited, and therefore those appraising the evidence should be able to view the 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 drug eluting stents with CABG. The FREEDOM and CARDia studies will compare diabetic patients with multivessel disease randomised to either CABG or to PTCA with Sirolimus coated stents. FREEDOM plans to randomise approximately 1500 patients with the primary end point being the follow up at 12 months without protocol driven re-angiography. 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, and whether DES will span the current gap in outcomes between standard stents and CABG.

6.2.2 Outcomes

The trials reported to date repeat some of the problems identified in the comparison of stents to PTCA. They identify a variety of definitions of MACE or MACCE. Therefore, the difficulties of interpreting composite endpoints remain. There are problems identifying when 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 nine and twelve 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 (fig 2, p 1778 of the article) 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 sponsors suggests that no patients in fact had revascularisations for this indication only. hand to which group they belong.

A point of note is the rate of revascularisation in the control arms of this and the SIRIUS study. (CIC information removed).

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 percent of cases. The primary endpoint was death, myocardial infarction or ischemia-driven target vessel revascularisation: only a subgroup of 20 percent of patients had protocol driven angiograms. This combined event measure occurred in 15.8 percent 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 maybe 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 was in keeping with a linear regression model derived from the BENESTENT(39) studies. But part of the difference might also lie in revascularisations being in part angiographically driven in RAVEL and SIRIUS.

In a PRESTO subgroup (about 20 percent of the total) studied by angiography, there was an association between restenosis and major adverse coronary events. In patients with no restenosis, 5 percent had MACE and 95 percent did not; in patients with restenosis 46 percent had MACE, 54 percent 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 approximately half of angiographically indicated revascularisations also being clinically indicated. However, in the nine month data from SIRIUS, the number of clinically driven TLRs is quoted as 4.1 percent in the DES arm and 16.6 percent in the non-DES arm and a rate of angiography driven revascularisations of 1.9 percent in the DES arm and 4.0 percent in the DES arm. So here we have between 70 percent and 80 percent of TLR “clinically driven” as defined by the trial, rather than 50 percent typically suggested by cardiologists. Given the criteria for ‘clinically driven revascularisations’ in this study cited above, this high ratio of angiographic to clinically driven events seems artificial and probably no different to those in other studies.

(CIC information removed)

Longer-term follow-up is still desirable.

6.2.3 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. (CIC information removed)

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 diabetics and non-diabetics but whether this is in proportions of patients with restenosis or in the extent of restenosis is unclear. Some results from a diabetic sub-group 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 less than 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 left anterior descending artery, (LAD) another high-risk group. Here, the TLR on Sirolimus was 5.1 percent versus 19.7 percent in the control group, and the MACE rates were 8.5 percent on Sirolimus versus 22.5 percent on percent.

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

So far therefore, data on subgroups is limited and should not be overstated. What limited data there is indicates that the relative benefits of drug eluting stents are maintained in high-risk subgroups of diabetics 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 of this report.

6.2.4 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–1, 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 will be presented at a conference in early April. Initial results from E-SIRIUS and one year follow-up of SIRIUS have only just been released to the review team and are being 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, BSCI, Personal communication, 21 January 2003)

The second consideration is that most studies as yet have only reported short follow-up. The 2 year RAVEL data is a exception but has been made available in confidence until its official

release at a conference in March 2003. With longer-term follow-up, the risks and benefits of DES will be come 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 for 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 it 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.

6.3 Conclusions

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

Overall, the results indicate that the drug-eluting stents decrease rates of restenosis and therefore revascularisation following placement. The exact rate of lowering of revascularisations seems to be by approximately 60 to 70 percent at 12 months, but there are difficulties in definitions of how many of these were clinically driven.

(CIC information removed)

The review team stress that these results are interim and incomplete and we await definitive publication of studies confirming patient numbers and outcome.

Table 6F DES: Study characteristics

Study name	Intervention	Primary outcome	Secondary outcomes	Location & centres	Inclusion criteria	Exclusion criteria	Co-Therapies	Follow-up
ACTION	**Actinomycin** Uncoated MULTI-LINK TETRA Actinomycin coated MULTI-LINK TETRA-D (2.5 µg 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, 6mo, 12 mo, Angiographic BRR at 6 mo	Multicentre (28) Europe, Australia, New Zealand, Brazil	Native coronary artery, vessel diameter 3 to 4 mm, lesion covered with 18 mm stent, target lesion coronary branch with DS greater than 50% and less than 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: Post-procedure, 6 months
ASPECT	**Paclitaxel** Bare Supra G stent Supra G paclitaxel (non-polymeric) coated stents High-dose 3.1mcg/mm^2, Low-dose 1.3mcg/mm^2	*Effectiveness:* Angiographic percent DS at 4 to 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 to 3.5 mm, <15 mm long	Graft lesion; severe calcification, severe proximal tortuousity, angulation >45 degrees, thrombus, total occlusion, MI within 72 hrs, CI to antiplatelet agents; left main lesion; LVEF <40%	Aspirin Clopidogrel (137) or Cilostazol (37) for 1 to 6mo post procedure	
DELIVER	**Paclitaxel** Uncoated MULTI-LINK stent PENTA ACHIEVE MULTI-LINK PENTA non-polymeric paclitaxel stent (3	Target Vessel Failure (TVF) at 270 days	'MACE' Angiographic binary restenosis (ABR) at 240 days Percent 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, anginographic evidence of thrombus, heavy calcification, extreme angulation, tortuosity LVEF <30%, Prior or planned intervention within 180 days	Pre procedure: Aspirin Clopidogrel During Heparin GP IIb/IIIa inhibitors in use by 652/1043 patients Post procedure: Aspirin ≤365 days Clopidogrel 90 days	Clinical, In Hospital, 30 days, 270 days Angiographic 240 days

Study name	Intervention	Primary outcome	Secondary outcomes	Location & 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 and 2-5 years Angiographic BRR (≥50%) at 8 months TLR, TVR, Target Vessel Failure at 9 months Device/lesion/procedure success (in-hospital)	Multicentre (35) Europe	Single *de novo* coronary lesion; between 2.5mm and 3.0mm diameter, 15 mm and 32mm long; DS >50%; CCS angina or UA (Braunwald B&C, I-II) or documented silent ischemia	MI ≤24 hr; unprotected left main disease; ostial lesion; total occlusion; thrombus; calcified lesion; LVF ≤25%; impaired renal function; pre-treatment 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 operators discretion) Post-procedure: 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 mcg/mm^2)	*Effectiveness:* Percent diameter stenosis Late loss at 6 month; *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 to 99%, symptoms of angina/ischemia, suitable for CABG	AMI within 4 weeks, cardiogenic shock, co-existing congenital heart disease, Diabetes Mellitus, LVEF <30%, Thrombus or poor distal flow, side branch >2mmm diameter, more than one stent needed		Clinical 1, 6 months Angiogram at 6 months
PATENTCY	**Paclitaxel** Uncoated Logic stent Logic PTX paclitaxel-eluting stent (2.0 ug/mm^2)		Safety: MACE at 30 days MACE at 9 months	Multicentre (6) USA	De novo lesion is native coronary artery, RVD 2.7 to 4.0 mm		Clopidogrel for 3 months	Clinical assessment at 1, 9, 18 months Angiogram at 6 months

Study name	Intervention	Primary outcome	Secondary outcomes	Location & centres	Inclusion criteria	Exclusion criteria	Co-Therapies	Follow-up
RAVEL(119)	**Sirolimus** Bare metal Velocity Stent Bx Velocity Sirolimus-eluting Stent [A]	In-stent late luminal loss (immediately post procedure and at 6 month)	Percent 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 ischemia,	Evolving MI; left CA y 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 Bx Velocity Sirolimus-eluting Stent [A]	Target Vessel Failure at 9 months	MACE, Angiographic BRR (>/= 50%) at 8 mo; TLR and TVR at 9 mo; Angiographic late loss and MLD at 8 mo	Multicentre (53) USA	Single de novo native coronary lesion; >/= 2.5mm 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 ischemia	MI </= 24 hr; left main disease; ostial lesion; total occlusion; thrombus; calcified lesion; LVF </= 25%; impaired renal function; pre-treatment with devices other than balloon angioplasty	Pre-procedure: Aspirin, clopidogrel, Ticlopidine During procedure: Heparin, GP IIb/IIIa inhibitors Post-procedure: Aspirin, Clopidogrel, Ticlopidine	
SCORE	**Taxane derivate** QP2(7-hexanolytaxol) Bare stent (81% QueST stent) QUANAM QP-2-eluting stent ('sustained elution' from polymer sleeves - 3200, 4000, 4800 mcg per stent)	*Safety:* MACE *Efficacy:* TVR at 6 month, restenosis at 6 month, late lumen loss, MLD, IVUS assessment		Multicentre (15) Europe	De novo coronary lesions, native vessel, RVD 3.0 to 3.5 mm, lesion length <20mm	Major side branch (>2 mm), sub optimal 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	Percent diameter stenosis, MLD, loss in MLD, restenosis rate (>50% DS) at 6 mo	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 (<72h), LVF >30%, stroke within 6mo, renal dysfunction, CI to aspirin, clopidogrel or Ticlopidine, requirement for greater than one stent	Pre-procedure: Aspirin, Heparin and Clopidogrel Post procedure: Aspirin 12 months Clopidogrel for 6 months	1, 6, 9, 12 months Post-procedure and 6 month Anginogram

Study name	Intervention	Primary outcome	Secondary outcomes	Location & centres	Inclusion criteria	Exclusion criteria	Co-Therapies	Follow-up
TAXUS II	**Paclitaxel** Bare metal NIR paclitaxel-eluting NIRx (slow release, moderate release)	6 month percent net in-stent volume obstruction (assessed by IVUS)	MACE at 6, 12 mo to 5yr TVR, TLR, Percent diameter stenosis, restenosis rate	Multicentre (61) 15 countries, Europe	Single De novo lesions, 3.0-3.5 mm, <12 mm, documented AP	Recent MI (<72h), stroke within 6mo, renal dysfunction, LVF >30%,	Aspirin 6months Clopidogrel 6 months	

A CYPHER Sirolimus stent delivery system. B Hand mounted stent For abbreviations, please see table of abbreviations in preface. For definitions of event rates, please see Table 6D within this Chapter.

Table 6G DES: Participant Characteristics

Study name	Intervention n	Age, mean (SD) years	Sex (male %)	Lesion category (%)	ACS (%)	Previous Cardiac Event (%)	Diabetes Mellitus (%)
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**[ug/cm2] **120 *(120)*** **10**[ug/cm2] **119 *(121)***	*2.5 (n=120)*61(±10) *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* *2.5 (n=120)* *10 (n=121)*	*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**[mcg/mm2] **60** **3.1**[mcg/mm2] **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

Study name	Intervention n	Age, mean (SD) years	Sex (male %)	Lesion category (%)	ACS (%)	Previous Cardiac Event (%)	Diabetes Mellitus (%)
E-SIRIUS	**Stent** **175**						
	DES **175**						
ELUTES	**Stent** **38**	*Overall:* 60 (±11)	*Overall*: 82.3	Type B1 59 Type B2 10			*Overall:* 15.6
	DES 152 **0.2$^{mcg/mm2}$ 37** **0.7$^{mcg/mm2}$ 39** **1.4$^{mcg/mm2}$ 39** **2.7$^{mcg/mm2}$ 37**			B1 64 B2 8 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
	DES **120**	61.8 (±10.7)	70	A 8 B1 38 B2 54	UA: 48	Prior MI: 37.5	15.8

Study name	Intervention n	Age, mean (SD) years	Sex (male %)	Lesion category (%)	ACS (%)	Previous Cardiac Event (%)	Diabetes Mellitus (%)
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 Mod-DES 59.3	Slow-DES 70.2 Mod-DES 76		UA: Slow-DES: 35.1 Mod-DES 30.0	Prior MI: Slow-DES: 35.1 Mod-DES 39.0	Slow-DES 10.7 Mod-DES: 17.0

A:ACTION (165) lists Stent 121, DES 2.5 ug 120, 10 ug 119 for patient allocations (174) lists Stent 119 (and 118), DES 2.5 ug 120, 10 ug 121 for patient allocations. Patient numbers reported in source of data will be provided with percentages

Table 6H DES: Outcomes

Study name	Intervention	Event Rate (%)	Mortality (%)	Any MI (%)	Revascularisation (%)	CABG (%)	PCI (%)	BBR (%)
ACTION	**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**[ug/cm2] **120** **10**[ug/cm2] **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 month 5 1 year *(n=58)* 10.3	1 month 0.0 6 month 0.0 1 year *(n=58)* 0.0	1 month 1.7 6 month 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**[mcg/mm2] **60** **3.1**[mcg/mm2] **58**	1 month *3.1* 8.3 *1.3* 5.2 6 months *3.1* 11.7 *1.3* 8.6 1 year 25.4 *3.1* 16.7 *1.3* 12.1	1 month 0.8 6 months 0.8 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

Study name	Intervention	Event Rate (%)	Mortality (%)	Any MI (%)	Revascularisation (%)	CABG (%)	PCI (%)	BBR (%)
DELIVER	**Stent** **519 (512)**	MACE[C] 30 days 0.4 TVF 9 months -	30 days 0.2 9 months 1.2 *(n=512)*	30 days 0.2 9 months 1.0 *(n=512)*	TVR 30 days - 9 months - TLR: 30 day - 9 months -	-	-	
	DES **524 (517)**	MACE[C] 30 days 1.2 TVF 9 months -	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 - TLR: 30 days - 9 months -	-	-	
ELUTES	Stent 38	*Event free survival* 1 months 97 6 months 89 1 year 82	1 months 0.0 6 months 0.0 1 year 0.0	1 months 0.0 6 months 0.0 ~~2.6~~ 1 year 0.0	TLR 6 months 7.9 1 year 15.8	30 days 0.0 6 months 0.0 1 year 2.6		*6 months In-stent:* 20.6 (n=34)
	DES 152 **0.2[mcg/mm2] 37** **0.7[mcg/mm2] 39** **1.4[mcg/mm2] 39** **2.7[mcg/mm2] 37**	*Event free survival* 30 days *0.2* 100 *0.7* 100 *1.4* 100 *2.7* 92 6 months *0.2* 95 *0.7* 95 *1.4* 97 *2.7* 89 1 year *0.2* 95 *0.7* 90 *1.4* 90 *2.7* 86	1 months 0.7 6 months 0.7 1 year *0.2* 0.7 *0.7* 0.0 *1.4* 0.0 *2.7* 0.0	1 months 0.7 6 months 1.3 1 year 1.3	6 months *Combined* *3.3* *0.2* 2.7 *0.7* 2.6 *1.4* 2.6 2.7 5.4 1 year *Combined* 7.2 *0.2* 5.4 *0.7* 7.7 *1.4* 10.3 *2.7* 5.4	30 days 0.0 6 months 0.0 1 year 0.7 *0.2* 0.0 *0.7* 2.7 *1.4* 0.0 *2.7* 0.0	1 year 6.6 *0.2* 5.4 *0.7* 5.1 *1.4* 10.6 *2.7* 5.4	*6 months In-stent* *0.2* 20 *0.7* 11.8 *1.4* 13.5 *2.7* 3.1 *(n=139 calculated)*

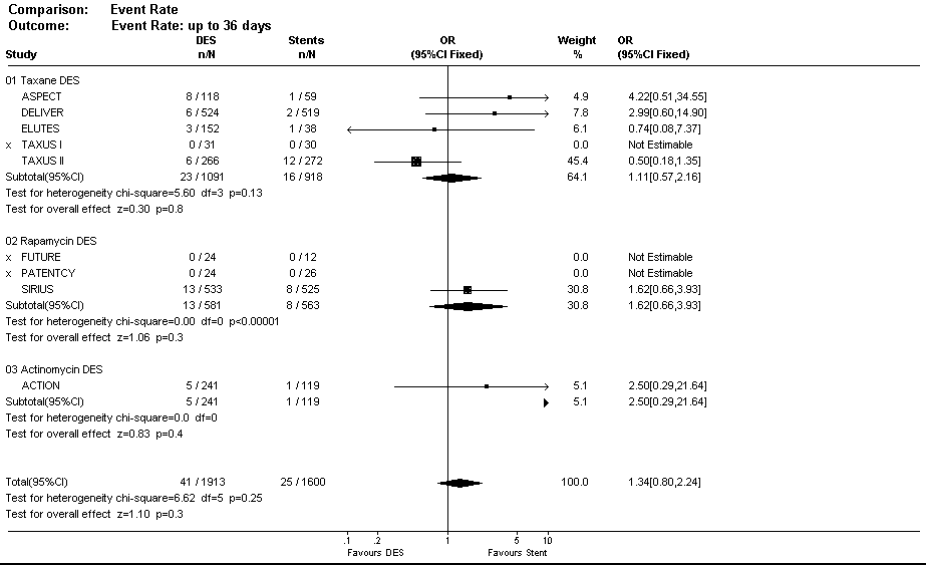
Study name	Intervention	Event Rate (%)	Mortality (%)	Any MI (%)	Revascularisation (%)	CABG (%)	PCI (%)	BBR (%)
FUTURE 1	**Stent** **12**	30 days 0.0	30 days 0.0	30 days 0.0		30 days 0.0	30 days 0.0	
	DES **24**	30 days 0.0	30 days 0.0	30 days 0.0		30 days 0.0	30 days 0.0	
PATENTCY	**Stent** **26**	30 days 0.0 270 days 23.1	30 days 0.0 270 days 3.8	30 days 0.0 270 days 0.0		30 days 0.0 270 days 3.8	30 days 0.0 270 days 15.4	9 month 35.3 (n=17)
	DES **2.0$^{mcg/mm2}$ 24**	30 days 0.0 270 days 12.5	30 days 0.0 270 days 0.0	30 days 0.0 270 days 0.0		30 days 0.0 270 days 0.0	30 days 0.0 270 days 8.3	9 month 38.1 (n=21)
RAVEL^{E}	**Stent** **118**	1 year 28.8	In Hosp 0.0 1 year 1.7	In Hospital 2.5 1 year 4.2	*TVR (not TL)* 1year: 1.7 2 years cic TLR (all) 1year 23.7 2 years cic	In Hosp 0.0 1year 0.8	TLR 1 year 22.9	6 months 26.6 (In stent, n unclear)
	DES **120**	1 year 5.8	In Hosp 0.0 1 year 1.7	In Hospital 2.5 1 year 3.3	*TVR (not TL)* 1year 0.8 2 years cic TLR (all) 1year 0.8 2 years cic	In Hosp 0.0 1 year 0.8	TLR 1 year 0.0	6 months 0.0 (In stent, n unclear)
SCORE	**Stent** **138**	1 year Non-hierarchical	6months 0.0 1 year 0.0	6 months 2.3 1 year 2.9	TLR 1 year 25.4 TVR 1 year 5.1			6 months 36.9 (In stent n=94)
	DES **128**	1 year Non-hierarchical	6 months 3.9 1 year 3.9	6 months 14.5 1 year 21.1	TLR 1 year 21.1 TVR 1 year 11.7			6 months 6.4 (In stent n=104)

Study name	Intervention	Event Rate (%)	Mortality (%)	Any MI (%)	Revascularisation (%)	CABG (%)	PCI (%)	BBR (%)
SIRIUS	**Stent** **525**	In hospital 1.5 9 months 18.9	In hospital 0.0 9 months 0.6	In hospital 1.5 9 months 3.2	*TVR (non-TL)* In-hospital 0.0 9 month 4.8 TLR: 30 day 0.0 9 month 16.6	30 days 0% blinded data	30 days 0% blinded data	*8 month In-segment:* 36.3 *8 month In-stent:* 35.4 *(n=353)*
	DES **533**	In hospital 2.4 9 months 7.1	In hospital 0.2 9 months 0.9	In hospital 2.3 9 months 2.8	*TVR (non-TL)* In-hospital 0.0 9 month 3.2 TLR: 30 day 0.2 9 months 4.1			*8 month In-segment*: 8.9 *8 month In-stent:* 3.2 *(n=348)*
TAXUS I(118) [B]	**Stent** **30**	30 days 0.0 6 months 6.6 12 month 10.0	30 days 0.0 12 months 0.0	12 months 0.0	 30 day 0.0 TLR 6 month 6.6 TVR-non TLR 1 year 0.0	6 months 3.0 12 months 3.0	TLR (PCI) 6 months 6.6 6 months 10 Non-TLR (PCI) 1 year 0.0 1 year 0	6 months (n=29)10.3
	DES **31 (30)**	30 days 0.0 6 months 0.0 12 months 3	30 days 0.0 12 months 0.0	12 months 0.0	 30 day 0.0 6 month TLR 0.0 TVR-non TLR 1 year 3.2	6 months 0 12 months 0	TLR (PCI) 6 months 0 1 year 0 Non-TLR (PCI) 6 months 3 1 year 3	6 months (n=30) 0.0

Study name	Intervention	Event Rate (%)	Mortality (%)	Any MI (%)	Revascularisation (%)	CABG (%)	PCI (%)	BBR (%)
TAXUS II	**Stent 270**	30 day (n=272) 4.4 6 month 19.3	6 month 0.4	6 month 5.2	TVR 6 month 13.0 TLR: 6 month 15.5	6 month 0.7		*Stented segment:* 6 months 19.0 (n=263)
	DES 266	30 day 2.3 6 month 7.9	6 month 0.0	6 month 1.9	TVR: 6 month 6.8 TLR 6 month 3.7	6 month 0.7		*Stented segment:* 6 months 3.5 (n=256) Slow-DES: 2.3 (n=128) Mod-DES 4.7 (n=128)

A:ACTION (165) lists Stent 121, DES 2.5 ug 120, 10 ug 119 for patient allocations (174) lists Stent 119 (and 118), DES 2.5 ug 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 (165), One MI in the stent group and three in the DES group in (174). Reasons for these differences unclear, E: combined clinically driven and angiographically driven data, as presented in (119); F: (CIC information removed), G F: (CIC information removed),

Figure 6A DES: Meta-analysis of event rate



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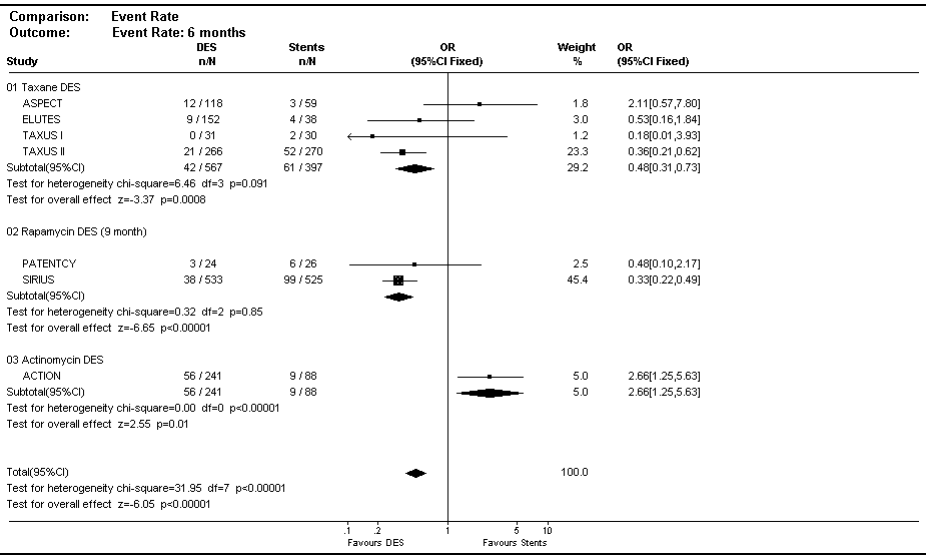

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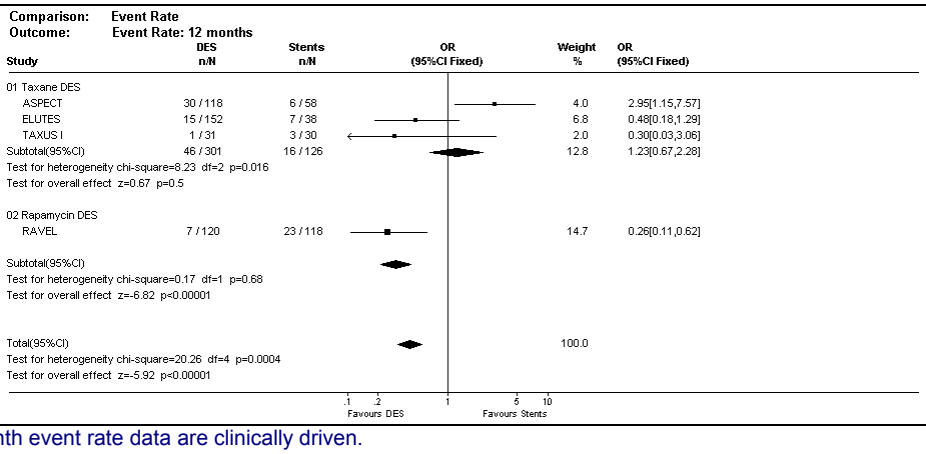
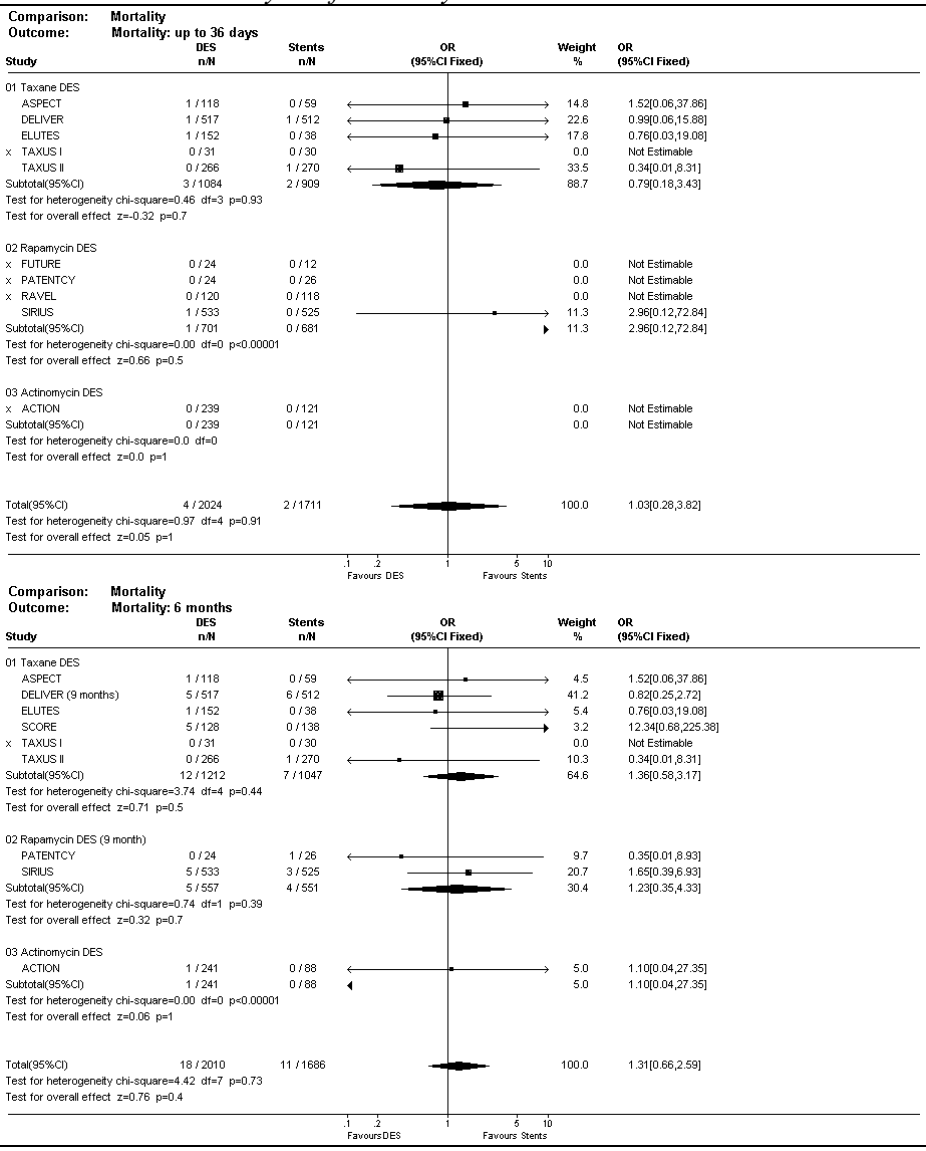


RAVEL 12 month event rate data are clinically driven.

CIC information removed

-

Figure 6B DES: Meta-analysis of mortality



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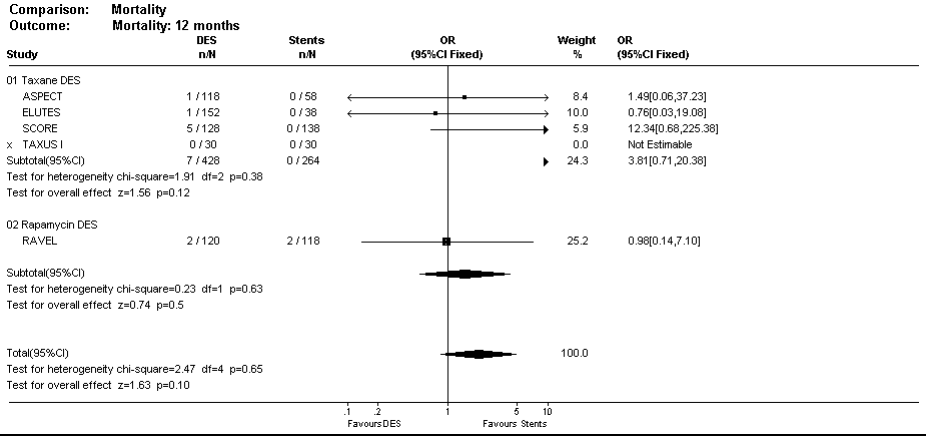

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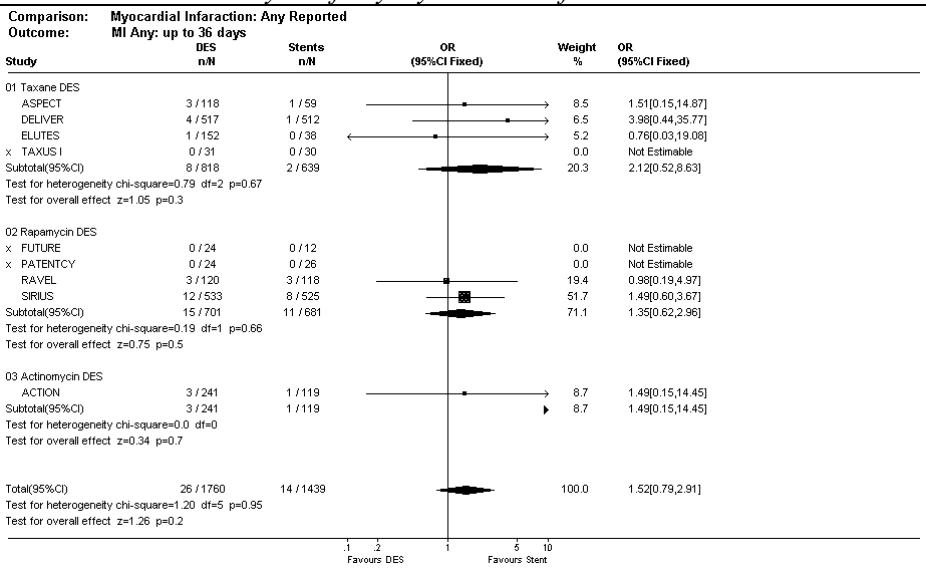
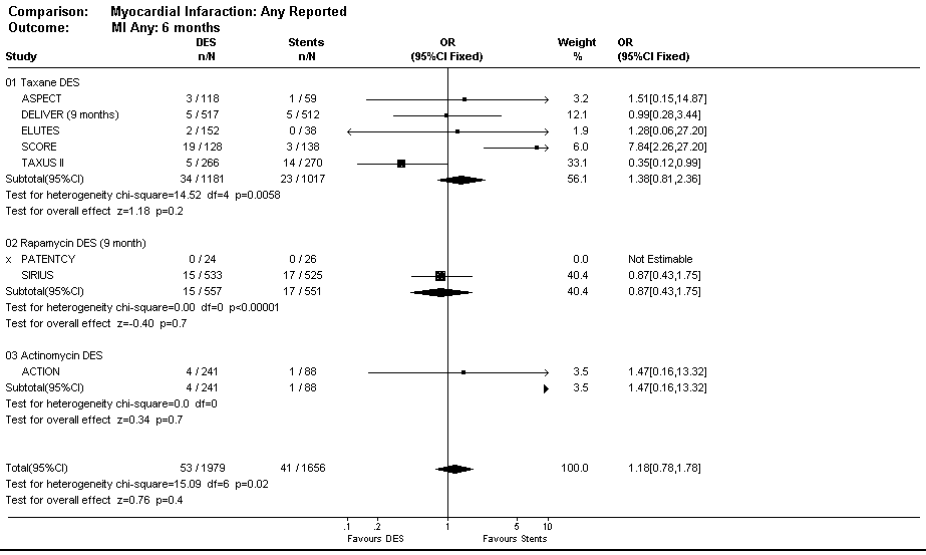
Figure 6C DES: Meta-analysis of any myocardial infarction





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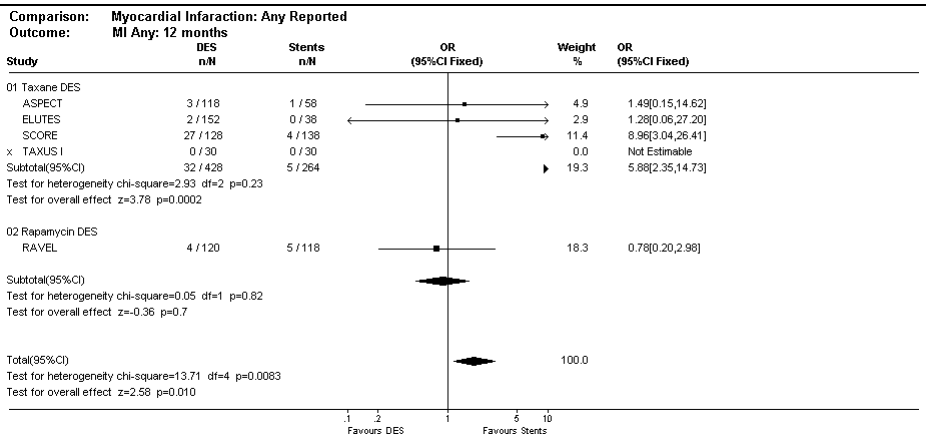

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Figure 6D DES: Meta-analysis of binary restenosis
CIC information removed

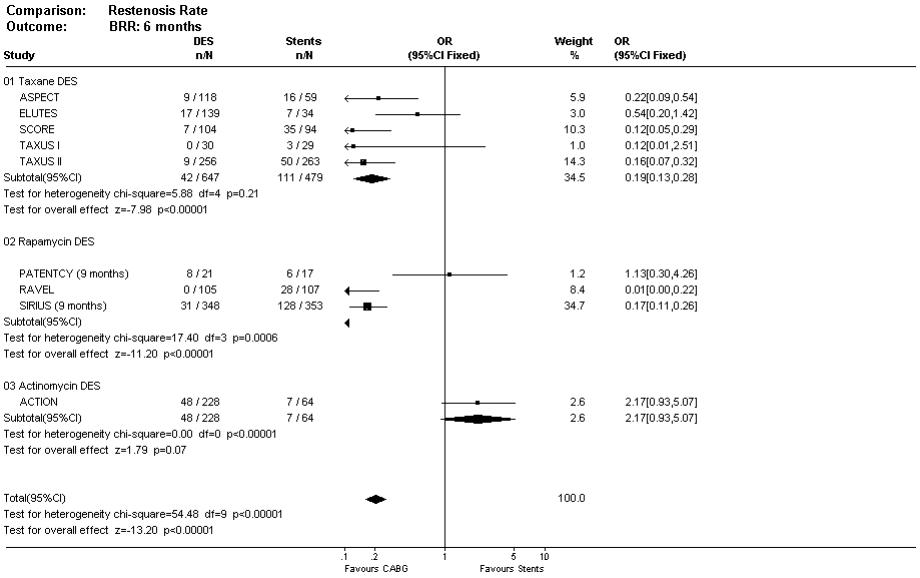
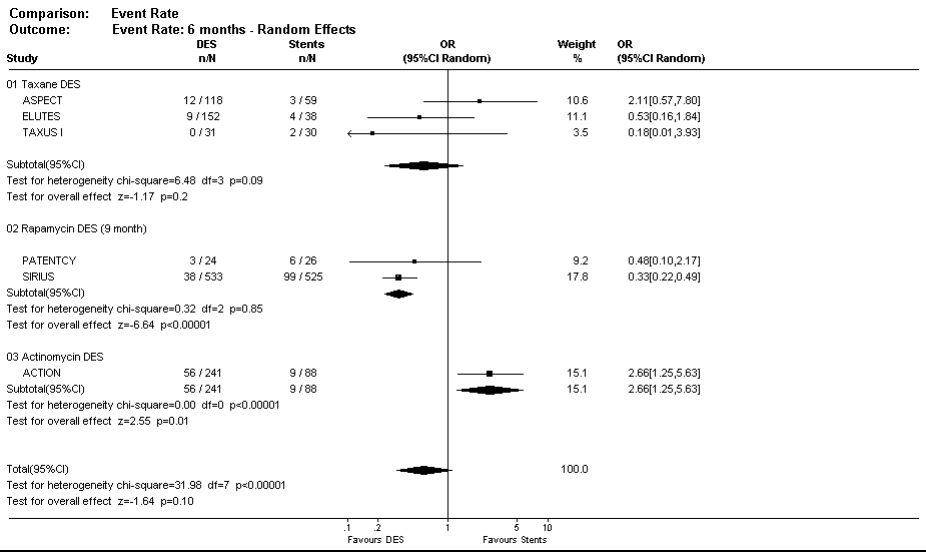


Figure 6E DES: Meta-analysis of event rate – random effects
CIC information removed



7 Economic overview and literature review

7.1.1 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 this is no comprehensive system to track identify the numbers of PTCA and CABG procedures undertaken in the UK. NHS statistics combine data from each trust but does not include the approximately 8% of patients treated privately. A number of other sources of data are available including the audit analyses undertaken by the British Cardiac Intervention Society 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 sub-groups 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 7,366 CABG patients were analysed, of which 1,664 (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 2,519 PTCA patients were analysed, of which 761 (30.2%) were non-elective. A summary of the patient population together with a summary of patient outcomes are provided 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.

7.1.2 Changes in resource use

Length of stay

Stent technology has changed, enabling a change in targeted patients from low risk (discrete single-vessel lesions) to encompass those with more complex multi-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 anti-platelet 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 further reduce length of stay 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 post-procedure.

There are likely to be significant variations in length of stay between different subgroups of patients. While this factor is less likely to influence PTCA – the variations in length of stay for CABG patients in the SCTS lies 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 onto a PTCA balloon. After deployment, balloons of varying characteristics (diameter, length and compliance with pressure) were required to post-dilate the stent fully, initially with normal and then with high-pressure balloons. Stents are now manufactured balloon-mounted and a greater choice now

exists in stent lengths so that whereas previously a long lesion may have required two stents, one long (32mm) 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 7A.

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. Meanwhile for multivessel stenting, 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 2 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 anti-platelet therapies of aspirin and clopidogrel with a GP 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.

Table 7A *Individual resource usage in stenting*

	Southampton [A]		RITA 2 [B]	Leeds [C]		RAVEL*		
Item	**Unit Costs (£)**	**Number per Stent patient**	**Unit Cost (£)**	**Unit Cost Leeds (£)**	**Number per PTCA patient**	**Unit Cost RAVEL (€)**	**RAVEL [D] Sirolimus**	**RAVEL [E] Bare Metal**
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***	1.61	*582*	*553*	1.63	*2000 / 672***	1.05	1.05

[A] n=200, 1996
[B] PTCA arm, 1999
[C] n=29, 1998
[D] n=120
[E] n=118

*Exchange rate utilised in RAVEL study i.e. € =£0.65
**Year 2002 DES/BMS costs

7.1.3 Outcomes measures for percutaneous coronary interventions

Outcomes used in economic analyses

The primary outcome 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 quality of life. 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 vs. Stent vs. CABG vs. 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? i.e. 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 drug-eluting stents versus bare metal stents, 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 timeframe 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 getting 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, while 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 is analysed in 7.1.3 impact on quality of life is analysed in 7.1.3.

Mortality data

The BCIS audit dataset for the year 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 a randomised trial 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 multivessel 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 quality of life. Thus, 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 quality of life 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 the patients 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 QALY analyses have been undertaken for patients with and without restenosis or repeat revascularisation following CABG and stenting (bare metal or drug eluting). ARTS and SOS are the only such trials comparing modern day PTCA with stenting to CABG in terms of cost-effectiveness data. Although a multi-national 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 is generated using UK unit costs. For this reason a detailed assessment of the results of this trial is provided in 7.1.6.

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) recently 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. Thus, there appears to be fairly consistent evidence that coronary restenosis has an important, albeit limited, impact on health-related quality of life.

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 quality-adjusted life years (2 healthy weeks) with respect to standard angioplasty, while angioplasty with stenting for restenosis would only save an additional 0.01 quality-adjusted life years in comparison to standard angioplasty. Such figures emphasise the constraints associated with using QALY analysis to assess the quality of life gains associated with the avoidance of restenosis.

7.1.4 The impact of waiting times on comparative outcomes

The average UK waiting time for a CABG is seven months in comparison to three 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 pre-procedure morbidity and mortality is an important element of the procedure. Conversely, if the variation in waiting time merely reflects an 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.

7.1.5 The importance of accurate cost data

The importance of accurate costs is crucial in this therapeutic area given that the limited and frequently contradictory evidence concerning outcome variations between different procedures. The importance of sub-group analysis is particularly relevant in the revascularisation field where costs and benefits are likely to vary so significantly between individual patients. For example while 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 to non-diabetics and long lesions and chronically obstructed vessels equally carry higher restenosis rates with them by magnitudes 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.

7.1.6 Previous cost-effectiveness analyses

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 (left anterior descending coronary artery) disease, the quality adjusted life expectancy with angioplasty (as initial therapy) was 18.3 quality-adjusted life years compared with 17.4 quality-adjusted life years with initial conservative therapy, with an estimated cost-effectiveness ratio of $6,000 per quality-adjusted life year gained. For patients with only mild angina, however, initial PTCA was projected to be significantly less attractive, with incremental cost-effectiveness ratios on the order of $80,000 - $100,000/QALY. A summary of the major studies comparing PTCA against medical therapy is provided in Table 7H.

Stents versus balloon angioplasty

Over the past 8 years, several important studies have examined the relative costs of stenting and balloon angioplasty in a variety of patient populations and clinical settings [Table 7G 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% vs. 42%, $p<0.05$) and required less frequent clinically-driven target vessel revascularisation (10% vs. 15%, $p=0.06$) compared with patients assigned to initial PTCA (53). The STRESS Economic Sub-study included 207 consecutive patients randomised to stenting or PTCA at 8 of 13 U.S. 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 $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% vs. 4%) and a 2-day longer hospital stay leading to initial hospital costs being $2200 (£1,367) 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. While these cost savings were insufficient to fully offset 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 post-dilation, aspirin plus theinopyridine anti-platelet 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 anti-platelet / anti-thrombotic regimen (39), initial hospital costs remained more than $2000 (£1,243) higher with stenting than with balloon angioplasty ($10,376 (£6447) vs. $8198 (£5094), $p<0.001$) (186). Although 1-year cardiac event rates were substantially lower with stenting (21% vs. 11%), aggregate 1-year costs remained $1200 (£746) per patient higher with stenting compared with PTCA. Thus the cost-effectiveness ratio for stenting in the BENESTENT 2 population was ~$12,000 (£7,459) 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 3 strategies of percutaneous coronary revascularisation. As was seen in the previous randomised trials, stenting increased initial hospital costs by $1900 (£1,181) per patient and did not fully "pay for itself" by 1-year follow-up (187). Aggregate 1-year costs were thus approximately $600 (£373) per patient higher with stenting compared with 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 Centre (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 higher for the stent group, stent patients were much less likely to be re-hospitalised (22% vs. 34%) or undergo repeat revascularisation (9% vs. 26%) during follow-up. As a result, 1-year costs were actually slightly lower in the stent group ($22,140

vs. $22,571, p=0.26). Potential explanations for the differences between the Duke registry experience and the randomised trials 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 to conventional stenting

One of the many strategies employed to reduce the costs of stenting includes the implantation of a stent without the traditional pre-dilation of the lesion by balloon angioplasty (i.e. direct stenting). While 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, myocardial infarctions 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 £2,210 (£1,436) for conventional stenting to $1,305 (£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 ($2,398/£1,490 against $3,176/£1,974, p< 0.001) with similar 6-month event-free survival rates and incidence of angiographic restenosis (190). 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 $1,164 (£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 anti-thrombotic regimes have occurred to reduce the risk of sub-acute thrombosis with intracoronary stenting in the setting of an acute myocardial infarction (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 prospectively address the economic impact of a primary angioplasty strategy for AMI with and without routine stenting. The combined primary endpoint at 6 months of death, re-infarction, disabling stroke, or target vessel revascularisation occurred in fewer patients in the stent strategy than the balloon arm; 12.6% versus 20.1% (p<0.01), although the mortality endpoint 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 approximately $2000 (£1,243) per patient. However, stenting was associated with significant reductions in the need for repeat revascularisation (13% vs. 22%, p<0.001) and re-hospitalisation (24% vs. 31%, p=0.03) in the year one 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 approximately $1000/patient (£622) higher with stenting than with PTCA ($20,571/£12,787 vs. $19,595/£12,181, p=0.02). The cost effectiveness ratio at one year for stenting compared with PTCA was $10,550 (£6,558) per repeat revascularisation avoided. This cost effectiveness

ratio is highly time dependent and is likely to diminish as the timeframe 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 summarized in Table 7F. In particular 5 randomised clinical trials have incorporated an economic analysis 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 7B.

Table 7B Quality assessment of economic analyses attached to RCTs

	Checklist items									
Article	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
RAVEL[1]	✔	✔	✖	✔	✔	✖	N/A	✔	✔	✔
Benestent II[2]	✔	✔	✔	✔	✔	✖	N/A	✔	✔	✔
ARTS[3]	✔	✔	✖	✔	✔	✔	N/A	✔	✖	✖
ERACI II[3]	✔	✔	✖	✔	✔	✔	✖	✖	✖	✖
SOS[3]	✔	✔	✖	✔	✔	✔	N/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?

✔ Yes, ✖ No, N/C: not clear, N/S: not stated; N/A: Not applicable -time frame was equal or less than 1 year

1 DES vs Stent in single vessel disease; Appendix A, Cordis Submission
2 Stent vs PTCA in multiple vessel disease; Serruys et al. 1998
3 CABG vs. Stent in multiple vessel disease; ARTS: Serruys et al. 2001. ERACI II: Rodriguez et al. 2001. SOS: The Stent or Surgery Investigators 2002.

Although each of these studies have specific inclusion and exclusion criteria and have used different time frames and cost measurement techniques, several general observations can be made. First, the initial hospital cost for PTCA is approximately 30 to 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 multivessel PTCA, over a 3 to 5 year follow-up period much of these initial cost savings are lost due the need for repeat PTCA or bypass surgery in approximately 50% of patients.

As a example, Weintraub and colleagues (194, 195). have reported 3 and 8-year economic data for the 386 patients randomised to balloon angioplasty or bypass surgery in the Emory Angioplasty vs. 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 2-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 sub-study of the Bypass Angioplasty Revascularisation Investigation (BARI) have recently been reported as well (196, 197). To date, this study remains the largest and most comprehensive economic evaluation of alternative revascularisation strategies for patients with multivessel coronary disease. Among 934 patients randomised to PTCA or bypass surgery, initial cost of care was 35% lower with PTCA ($21,113/£13,124 vs. $32,347/£20,107). Over the first three 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 vs. $58,889/£36,607, p=0.047). Subgroup analysis demonstrated that PTCA remained approximately $6000 (£3,729) less expensive than CABG for patients with 2-vessel disease, but that 5-year costs were no different for patients with 3-vessel disease. Since bypass surgery was associated with a trend toward 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 multivessel disease, the confidence limits around this cost-effectiveness ratio were wide and included a 13% probability that the cost-effectiveness ratio was > $100,000(£62,162)/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 have largely compared conventional balloon angioplasty to 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 have also been undertaken comparing stenting with bypass surgery are the ARTS and SOS studies, both of which included prospective evaluations of both health care costs and quality of life. The ARTS study also analysed resource use from the perspective of the US health care system, while the SOS study used an NHS perspective. At 1-year follow-up of the Arterial Revascularisation Therapy Study (ARTS) there were no differences in mortality between multivessel stenting (2.5%) and CABG (2.8%) groups with overall 1 and 2 year event-free survival rates of 88% and 85% with CABG vs. 74% and 69% with stenting (99, 198). This 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 multi-vessel PTCA trials and represented a considerable clinical improvement of stenting with over plain balloon angioplasty. The ARTS economic analysis calculated total procedural costs of $6,441 (£4,004) for the stent and $10,653 (£6,622) for the CABG groups and 1-year total direct medical costs of $10,665 (£6,629) and $13,638 (£8,477) (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 that 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 to 5 years. Given the importance and relevance of the SOS trial, this is discussed in greater detail in 7.1.7.6.

In summary, both observational studies and recent randomised trials have consistently demonstrated that multivessel 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 multivessel 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 are 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. Section 7.1.6.6 analyses whether the quality of this insubstantial evidence base is significantly improved by the recent SOS trial.

The Stent or Surgery (SOS) Trial

(Academically in confidence information removed)

7.1.7 Drug-eluting stents versus bare metal stents

(Academically in confidence information removed)

7.1.8 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 one 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 patients with single, discrete lesions.

There are currently no significant published studies evaluating the cost effectiveness of DES. As such there is a need for a significant expansion in the evidence base underlying their use in different patient groups before it becomes 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 tends 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.

Table 7F Cost studies comparing percutaneous coronary revascularisation with bypass surgery

Study	Date	Method*	N	Diseased vessels *(n)*	Cost measure	Time period	PTCA** $cost	PTCA** £ cost	CABG** $ cost	CABG** £ cost
REEDER(201)	1979-1981	OBS	168	1,2,3	Medical charges	Initial hospitalisation One year	7571 11,384	4,706 7,076	12,154 13,387	7,555 8,321
KELLY(202)		OBS	163	1,2,3	Hospital and MD charges	One year	7689	4,780	13,559	8,425
EAST(194)	1987-90	RCT	384	2,3	Hospital costs and MD charges	Initial hospitalisation	16,223	10,085	24,005	14,922
						3-year total costs	23,734	14,754	25,310	15,733
RITA(203)	1993-94	RCT	999	2,3	Hospital costs	Initial hospitalisation London centre Non-London centre		3,753 3,024		7,319 5,722
					Hospital procedural medication costs	2-year total costs London centre Non-London centre		6,916 5,448		8,739 6,498
BARI(196)	1988-95	RCT	952	2,3	Hospital and outpatient costs	Initial Revascularisation	21,113	13,124	32,347	20,107
					MD fees	5-year total cost	56,225	34,951	58,889	36,606
ARTS(99)	1997-8	RCT	1200	2,3	Hospital costs and MD fees	Initial Revascularisation	7366 EU	4,823	11,295 EU	7,397
						1-year total	10,665 EU	6,984	13,638 EU	8,931
SOS(204)	1997-9	RCT	967	2,3	Hospital and outpatient costs,	Initial Revascularisation		4,205		7,396
						1-year total		6,419		8,914

*OBS: observational study. RCT: randomised controlled trial.
**Exchange rates used £1=$1.6087
£1=€1.5270

Table 7G Selected cost studies comparing coronary stenting with balloon angioplasty

Study	Date	Method	*N*	Cost measure	Time frame	Device	MACE	Cost $	Cost £
STRESS (184)	1991-93	RCT	207	Hospital costs,	Initial hospitalisation	PTCA		7,505	4,665
				MD fees		Stent/Warf		9,738	6,053
					1-year total	PTCA	21% *	10,865	6,754
						Stent	15% *	11,656	7,246
BENESTENT 2 (186)	1995-96	RCT	823	Hospital costs and 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 and 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,	Initial hospitalisation	PTCA		10,076	6,263
				MD fees		Stent		13,294	8,264
					1-year total	PTCA	30% *	22,571	14,031
						Stent	14% *	22,140	13,763
STENT-PAMI (193)	1996-97	RCT	900	Hospital costs, outpatient costs,	Initial hospitalisation	PTCA		15,004	9,327
						Stent		16,959	10,542
				MD fees	1-year total	PTCA	22%	19,595	12,181
						Stent	13%	20,571	12,787

*OBS: observational study. RCT: randomised controlled trial. Stent/Warf = stenting with oral anticoagulation. Stent/Ticlid: stenting with combined anti-platelet therapy. MACE=major adverse cardiac events (death, myocardial infarction, or repeat revascularisation); RCC method: hospital charges converted to costs based on hospital-specific cost to charge ratios; * Event rate indicates only repeat revascularisation **Exchange rate used £1=$1.6087

Table 7H Summary: Costs and effects of direct PTCA against thrombolysis for patients with AMI

Trial	Number of Participants	Cost measure	Time frame	Net cost PTCA – thrombolysis (lower)**		Clinical outcomes / overall	Treatment strategy	Rates
MAYO * (205)	108	Charges	Initial and 6 month	($6837)	(£4250)	6 weeks Death/MI Same	t-PA PCI	4% 2%
PAMI-1 (206)	358	Charges	Initial	($2574)	(£1600)	In hospital Death/MI Better	t-PA PCI	12.0% 5.1%
GUSTO IIB (207)	1138	Costs	Initial and 1 year	$302	£188	1-month Death/MI/CVA Slightly better	t-PA PCI	13.7% 9.6
MITI * (208)	3145	Costs	Initial and 3 year	$2122	£1319	In hospital Death Same	Any Thrombolytic PCI	5.6% 5.5%

* Initial and follow-up hospitalisations
** Exchange rate used £1=$1.6087

8 Critical review of submitted models

8.1 Critical Appraisal of the submitted economic models

8.1.1 Introduction

A total of four economic models were submitted in support of the industry submissions from Abbot, Boston, Cordis and Guidant. A summary of the models is provided in Tables 8B and C. The models varied widely in their underlying assumptions, methodology and structure of analysis as well as 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 (209) 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 1N.

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.

Table 8A Quality Assessment of submitted economic models

	Checklist items									
Model	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Abbot	N/S	N/S	✗	✓	✓	✗	✓	✓	✓	✗
Boston	✓	✓	✗	✓	✓	✗	N/A	✓	✓	✓
Cordis	✓	✓	✗	✓	✓	✓	✓	✓	✓	✗
Guidant	✓	✓	✗	✗	✓	✓	✓	✓	✓	✗

✓: *Yes,* ✗*: No, N/S: not stated, N/A: not applicable since time frame of analysis was 1 year or shorter*

Checklist items:

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?

8.1.2 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 and the same 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, while 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 BS options. Of these models, results were presented for a 5-year time frame only for Abbot and Guidant. Therefore, in all studies, the validity of the estimate of effectiveness may be questioned due to the short-term nature of the evidence presented in support of DES, a more important issue for the DES vs. CABG comparison than the DES vs. BS one (although see Abbott section 7.2.3.1 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 health-related quality of life outcomes of symptomatic restenosis and revascularisation ('utilities'), which were derived from a multi-vessel disease population (ARTS trial) in all but one case (Abbot; the model used data from a 1980 study the adequate details of which were not provided). The validity of applying those utilities to quality of life outcomes of single-vessel disease patients is open to 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 myocardial infarction) 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.

8.1.3 Critical appraisal of Abbott model

This submission presented two comparisons, one involving a PC polymer coated stent versus bare stent, and another comparing a PC polymer coated stent with anti-inflammatory drug elution ('Dexamet') versus bare stent. 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 information provided in the submission.

Comparison to checklist

A distinctive strength of this model is its account of the effects of angina on the quality of life 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 in present times.

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 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(210) (35) and long-term safety issues(210) 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 months (0% vs. 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) a randomised controlled trial comparing CABG to BS in multi-vessel disease patients treated during 1997 to 1999 in four different countries. This assumption may not be appropriate for the UK, where shorter hospital stays after surgery are likely apply relative to other European and North American countries, and thus unduly favour the anti-inflammatory drug eluting option.

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8.1.4 Critical appraisal of Boston model

Comparison to checklist

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

The submission compared drug eluting stents (DES) against bare stents (BS) and DES against CABG for patients with single vessel de novo lesions, both overall and by subgroup (Diabetic, small (2.5 to 3.0 mm), very small (less than 2.5 mm) vessel, long lesions (greater than16 mm). This submission measured costs and benefits up to 6 months and, as such, is the one with the shortest time frame of all; the quality of the evidence submitted is subject to the same objections as those stated in the second paragraph of section 7.2.3, and is unlikely to capture important differences in quantity of life between treatment options in the DES vs. CABG comparison.

The comparison between DES and BS was based on a single randomised controlled trial (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 multi-vessel subgroup (CABG). The clinical evidence presented for the latter comparison should therefore be considered with caution due to the different prognosis in the respective populations serving as source of data. This is most evident in the all cause-mortality rate of CABG at 6 months (2.8 percent) 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 vs. CABG comparison, the

quality of life 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 health related quality of life in restenosis and post revascularisation, which combined evidence from two disparate sources; estimates from the ARTS trial in the multi-vessel population referred to above were pooled with the average estimates for mild and severe angina patients from studies published in 1981 and 1985.(211), (212), (213) 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 percent at 6 months for DES and BS, 2.8 percent 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 diameter of less than 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/BS 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 multi-vessel subgroups is insufficient, and longer follow-up data is needed to perform meaningful cost-effectiveness analyses of the technology for all relevant subgroups.

8.1.5 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 to checklist

For the analysis of the small vessel patient group (less than 3.0 mm of vessel diameter), the analysis used data from the RAVEL trial, which compared DES versus BS. The authors recognised the bias inherent in the design of the study, where protocol restrictions (fixed angiogram examination at 6 month) 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 BS in RAVEL, plus follow-up costs of BS in RAVEL multiplied by the relative risk of repeat revascularisation of PTCA versus BS in BENESTENT II,(39) a comparative study in the population of suitable candidates for CABG with one or more de novo lesions of length less than 18 mm in vessels of diameter greater

than 3.0 mm. Moreover, the utility weights were derived from a multi-vessel patient population (ARTS trial) as opposed to the single vessel one 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 BS, 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 multi-vessel disease patient group (the ARTS trial), and data from single studies with 5 year follow-ups for PTCA (Benestent II) and CABG.(214) The source of data used for PTCA also provided long-term data for BS, and this information was built into the model for the BS, DES, and PTCA arms, as well as 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.

(CIC information removed)

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%) while being almost the same in the DES (0.56% versus 0.4%) and BS (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 diabetics group.

In relation to the multi-vessel group, the authors acknowledge the lack of evidence regarding benefit of DES by assuming the same clinical outcomes as documented for BS 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 ICER of £57,000 relative to BS 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 the results were presented and the analysis of uncertainty carried out, which appeared to be highly selective.

8.1.6 Critical appraisal of Guidant model

This submission presented two separate decision analysis models, one comparing DES versus. BS 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 to checklist

The comparison of DES versus. BS 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 quality of life benefits from the ARTS trial, utilities from a single EQ-5D study (quality of life 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 four-year period. Therefore, while additional quantity and quality of life benefits were taken into account by extending the time frame from 1 year 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 BS and CABG.

An inconsistent modelling approach was adopted between the DES versus BS 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 BS 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 BS, 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 vs. 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, like 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.

8.1.7 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 multi-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, thus 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 BS, and the effects of reoccurrence of angina symptoms and outcomes following repeat revascularisations on the quality of life 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.

Table 8B Summary of economic submissions to NICE

Submission	Study type	Comparators	Population & Subgroups	Time frame	Model used	Cost elements & sources (other than BCIA)	Effectiveness & benefit outcome measures	Cost/price of device (£)	Assumptions Repeat Revasc* (%)
Cordis	CEA CUA	DES vs. BS DES vs. CABG DES vs. PTCA (Single vessel)	As in RAVEL & SIRIUS Patients with small vessels (<3.0 mm) & single vessel Diabetic Long lesions (>16 mm) Multi-vessel	1 yr 5 yrs	DA plus assumptions DA model for indirect comparisons (Multi-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), Revasc avoided (longer lesions), Mortality Utility weights (restenosis free, restenosis) Time to restenosis (long lesions)	(CIC information removed)	***DES & BS:*** PTCA 65-68 BS 22 CABG 9-13 ***CABG:*** PTCA 6 BS 50 CABG 44
Boston	CEA CUA	DES vs. BS DES vs. CABG	As in TAXUSII 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 gp Long lesions (>16mm)	6 months	DA	Price of DES and BS Procedures (PTCA, CABG); hospital (ICU, CCU & 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 mo. Utility weights (restenosis free, restenosis, minor stroke, AMI, renal failure) TLR rate (long lesions)		***DES & BS[c]:*** PTCA 12.1 BS 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 yr 5 yrs	DA. Results at 1 yr extrapolated to 5 yrs assuming constant outcomes	Price of stent (DES, BS) –company, BCIS Procedures (PTCA, Elective CABG, emergency CABG), Hospital (ICU, CCU & ward) MI Non-fatal, CVA, Antiplatelet therapy (DES), IIb, IIa Injection.	Event-free survival 1 year Years of life saved at 5 yrs Utility weights (Symptomatic restenosis, CABG, Healthy after CABG/PCI, CVA, MI)		***DES:*** PTCA 78 BS 2 CABG 20 ***BS:*** PTCA 40 DES 40 CABG 20

Submission	Study type	Comparators	Population & Subgroups	Time frame	Model used	Cost elements & sources (other than BCIA)	Effectiveness & benefit outcome measures	Cost/price of device (£)	Assumptions Repeat Revasc* (%)
Abbot	CUA	Anti-inflammatory eluting stent vs. BS	As in STRIDE Diabetics & Non-diabetics combined	5 yrs	Probabilistic model. Results at 6 months for anti-inflammatory eluting stent assumed constant up to 5 years	Price of stent ('DES', BS) Procedures (PTCA, Bail out stent, E-CABG and CABG) Hospital (ICU, CCU & ward), Fatal & non-fatal MI, Follow-up costs (outpatient visits)	Years of life saved at 5 yrs Utility weights (Stable, unstable, severe, silent angina, from procedure)		***DES***[D:] PTCA 100 ***BS***[D:] PTCA 66.6 CABG 33.3

DA: Decision Analysis; DES: Drug eluting stent; BS: Bare stent; CIC: Commercial in Confidence information; TLR: Target lesion revascularisation; * Repeat Revascularisations; *A According to author's results; **B Long lesions group; C Taxus II Total population; D 6 month data;

Table 8C Sensitivity analyses within economic submissions to NICE

Submission	*Sensitivity analysis*			Parameters varied	Most influential parameters*	Notes
	Univariate:	**Multivariate:**				
	Univariate or threshold analyses	Deterministic or Scenario Analysis	Stochastic			
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 & diabetics the 'scenario' analysis (Table26) 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 yrs 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 2nd episode of restenosis although DES vs BS did Uses LOS for CABG & PTCA from UK Ref Costs 2001
Abbot	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/BS	NA	Methods were not clearly presented

CE: Cost-effective; DES: Drug eluting stent; BS: Bare stent

9 Economic Evaluation

9.1 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 sub-groups at higher risk of restenosis; and
- 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 vs. 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 endpoints 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 health-related quality of life are merely modifiers of longevity, treatments those which only improve the quality of life 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 vessel stenosis (215) and for patients with diabetes (BARI investigators for all treated diabetes, (216) and Weintraub for insulin-requiring patients(217)). Although interventions for left main vessel disease is currently undertaken almost exclusively by CABG, suggestions have been made to extend use of DES to these patients (218). Diabetics are one of the main sub-groups 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 to 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.

9.1.1 Mortality

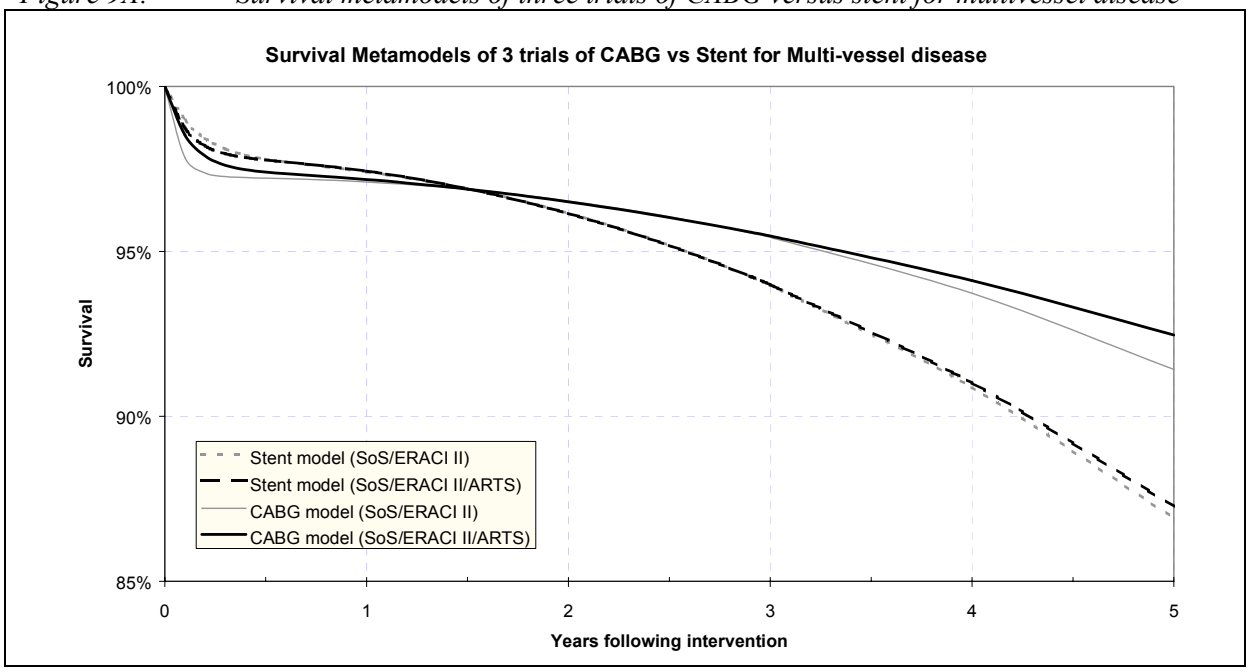
Inevitably, only limited evidence will have been accumulated in respect of newer technologies at the time when they are first evaluated. Nevertheless, the evaluation of any treatment for a chronic disease must focus on long-term outcomes to be at all meaningful, particularly mortality and survival.

CABG versus PTCA with conventional stent

Three recent randomised trials have been reported comparing CABG to PTCA using conventional stents for the treatment of patients with multi-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. 6 separate trial arms) a bi-partite survival model has been fitted to the published survival/mortality curve, after digitising plots in the trial reports (*Figure 4* in SOS, F*igure 1A* in ARTS and *Figure 4* in ERACI II(99, 101, 103)). This involved simultaneously estimating, by minimizing 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 9A, 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 less than an average of 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 anticipated for CABG patients compared to those undergoing PTCA with bare stent. This general pattern is supported from other earlier trials involving conventional PTCA without stenting (BARI (216) and EAST (219)) and also the Duke University registry study of diabetics undergoing revascularisation (220).

Figure 9A: Survival metamodels of three trials of CABG versus stent for multivessel disease



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 to stent;
- combining mortality from 30 days to 12 months from ARTS, ERACI II and SOS leads to a relative risk of 0.73, whereas
- combining mortality risk over 12 months from ERACI II and SOS produces a relative risk of 0.39.

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(221) showed in 520 consecutive patients undergoing elective surgery with intermittent aortic cross-clamping a mortality rate of 0.57%, compared to an expected risk-adjusted mortality of 2-4%. Thus, it may be argued legitimately that any evaluation of new revascularisation techniques should not be relative to historic 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 meta-model 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 fully counter the contrary finding in the existing meta-model.

PTCA with drug-eluting stent

When comparing DES to 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 to 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 (222) 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 to 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.

9.1.2 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 Target Lesion/Vessel revascularisations. 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 (223) show that although TLRs are reduced by 32% as a result of stenting, all revascularisations only fell by 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 down-gearing of these figures.

The only relevant published figures 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 rather higher, and therefore that the reported benefits would need to be down-graded more substantially. However, without direct evidence of trial outcomes for *all* revascularisations from the DES vs. 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 previously 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 (222).

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 acute MI), 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 quality of life).

On this basis, we have concluded that neither intra-coronary 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 quality of life 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.

9.1.3 Case-mix and sub-groups

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 post-discharge. 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. Thus we are unable to make any comment on the cost-effectiveness of PTCA with DES in the context of non-elective treatment.

Figures 9B.a and 9B.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 Figures 9B.B & E in respect of ejection fraction rating, and in Figures 9B.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.

9.1.4 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 time period without loss of precision. However, in cases where outcomes differ between treatment options concerning the long-term quality of life 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 (Section 9.1.1 above) 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 is of shorter duration, and for DES it is 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 elective CABG is 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 projection should continue sufficiently long thereafter to allow the long-term trajectory of costs and outcomes to be established, in the range 5 to 10 years.

Trial bias

Even RCTs may be subject to unintentional bias, due 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 UK NHS. It is the case in all parts of the country that elective patients typically wait 3 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 'intention to treat' 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 3 patients died, 1 suffered a stroke and 4 suffered AMI whilst awaiting CABG compared to just one AMI awaiting PTCA with stent. In such cases, 'intention to treat' 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 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 to CABG.

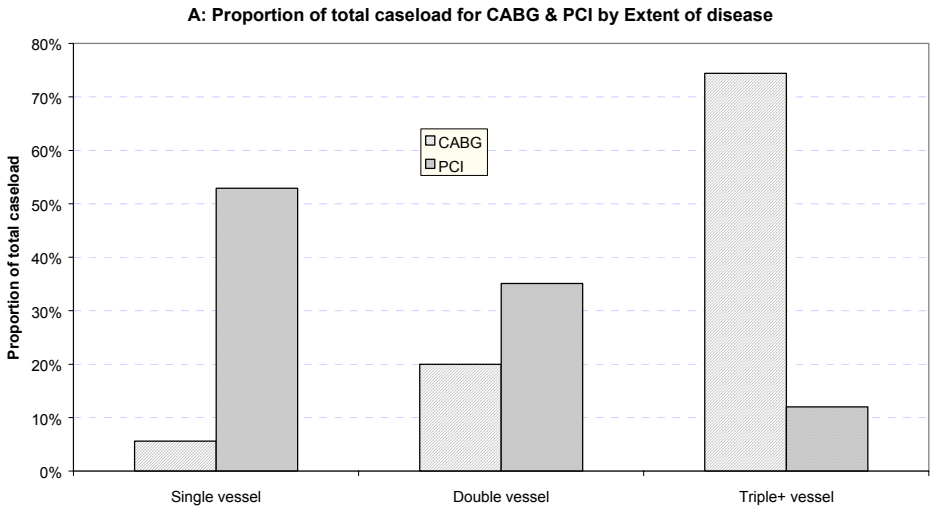
9.1.5 Utility

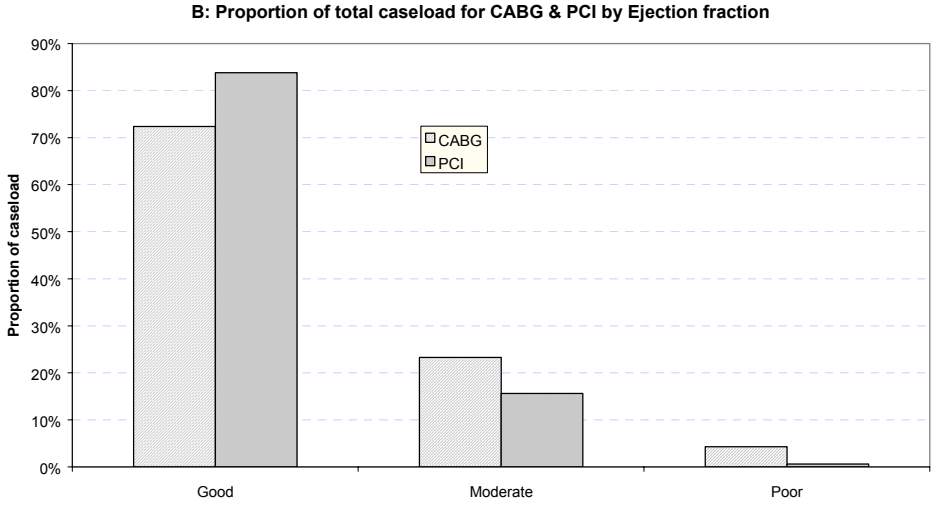
One source is referenced in 3 of the 4 industry submitted models for utility values related to revascularisation - the ARTS trial. Cordis used just two figures from the published results to attribute utility values to patients in need of revascularisation and to patients following a successful procedure. Guidant use these plus the 1-month post-CABG disutility, augmented by a figure from a different source for the post-stroke 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 (211). 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 time periods, including time spent waiting for a second revascularisation.

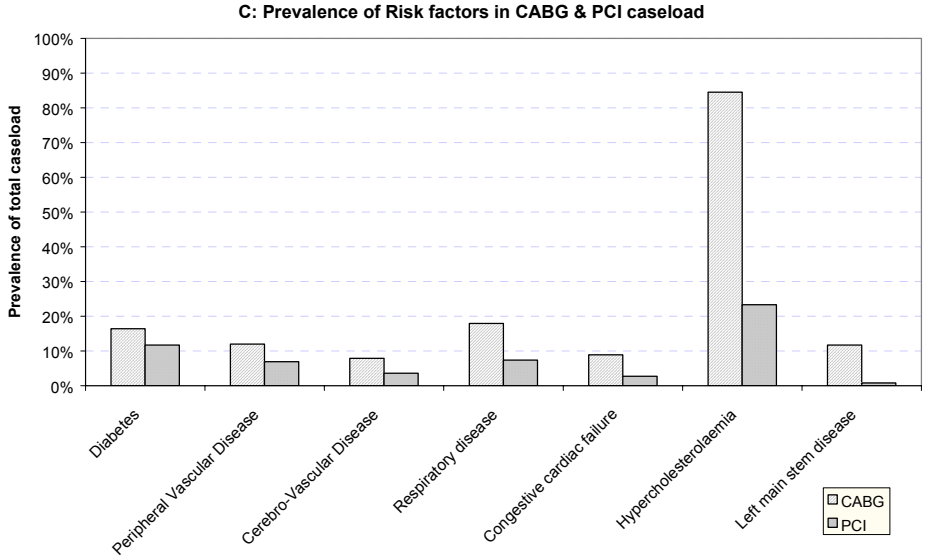
The Abbott model is different in avoiding use of the ARTS utility estimates. Instead the authors employ utility values for mild and severe angina (224) combined with Cohen's TTO figures for the effects of revascularisations and AMI. At first sight, using anginal symptom severity is attractive since it 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 indeed of ARTS.

Sadly, the ARTS trial does little to dispel the general evidence void concerning utility and quality of life around cardiac revascularisation. It suggests average utility values for patients with multi-vessel disease (excluding Left Main 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, nor how the positive effect of a successful second (or third) procedure compares to 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 sub-groups (such as diabetics, those with long lesions, or small diseased vessels, etc.). The authors of the submitted models have made many heroic assumptions on all these questions in difficult circumstances.

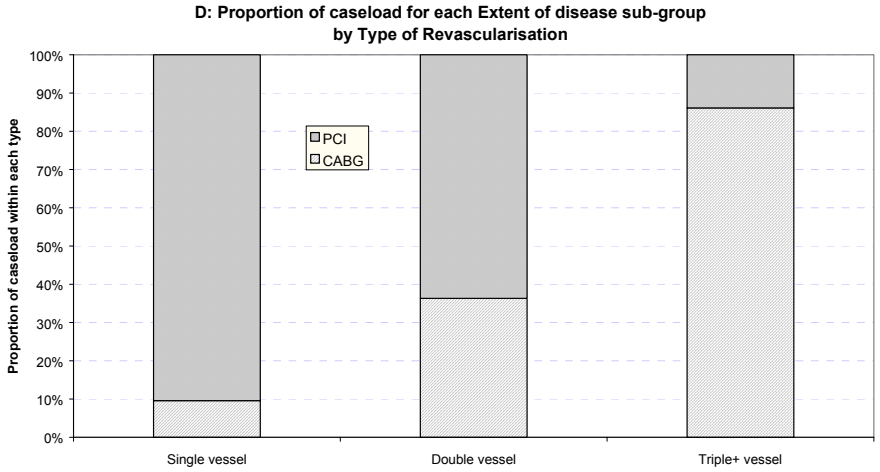
Figure 9B Elective revascularisations: North West registry data (1/1/2000 - 31/3/2002)

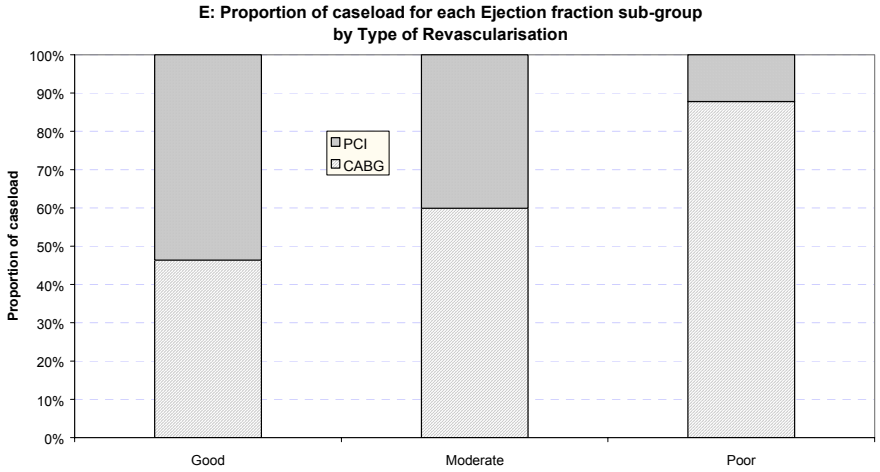


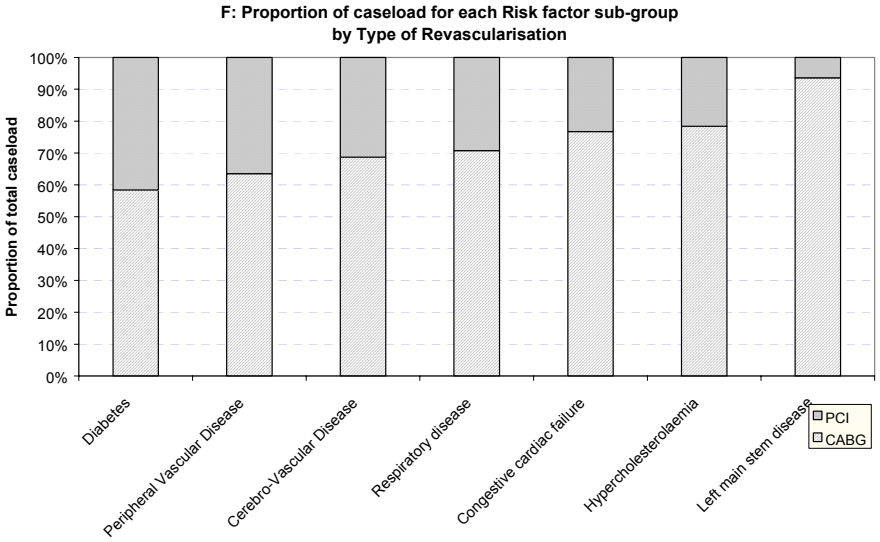




9B (continued) Elective revascularisations: North West registry data (1/1/2000 - 31/3/2002)







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 a little 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.

9.1.6 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 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 (225). 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 5 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's paper(225) 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 1990's, the length of elective in-patient 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 2001/2. In order to arrive at a total cost per CABG or stenting procedure, it is necessary to use the appropriate FCE cost and add to it an estimate of the cost of time spent in a Cardiac Intensive Care unit (this would be under the care of a different consultant). We have used average lengths of ITU stay found in the Liverpool CTC 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 2-vessel disease, we need to know the *difference* in unit cost between the 2 initial interventions. However, when considering the cost-effectiveness of DES compared to bare stenting in single vessel disease, the *total* costs of CABG and stenting costs are important when undertaken as repeat interventions. Thus both total and incremental cost estimates are important to our evaluation.

The impact of alternate costing schemes can be gauged by examining Table 9A. 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 to 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 2-vessel disease, the cost difference is strongly influenced by the disparate assumptions made in the submitted models about the prices of bare and drug-eluting stents, 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 only required where the complication is of sufficient severity to require transfer of 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 2001/2 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 Drug-Eluting Stents than is claimed in the industry submissions, and therefore if anything would favour the cost effectiveness of DES.

9.1.7 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 to CABG for patients requiring an elective revascularisation for confirmed 2-vessel disease?
2. Is PTCA using DES a cost-effective alternative treatment compared to CABG for patients requiring an elective revascularisation for confirmed 2-vessel disease?
3. Is PTCA using DES more cost-effective than PTCA using conventional bare metal stenting for patients requiring an elective revascularisation for confirmed single vessel disease?

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

Table 9A Comparison of CABG and PTCA cost estimates from different sources

Source / Submission	Cost of CABG	Cost of PTCA	Cost of PTCA + bare stent (2 vessel disease)	Cost of PTCA + DES (2 vessel disease)	Length of stay for CABG	Length of stay for PTCA + stent	Excess cost: CABG vs PTCA	Excess cost: CABG vs PTCA + bare stent (2 vessel disease)	Excess cost: CABG vs PTCA + DES stent (2 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	2.0	+ £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 2001/2 & CTC data	£7868	£2156	£3068	£4316	8.3	2.9	+ £5712	+ £4800	+ £3552

9.2 LRiG economic models

9.2.1 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 quality of life or utility benefits.

The current widespread use of decision analysis (commonly referred to as 'decision trees') for micro-economic 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 cost-effectiveness analyses, 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 address 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 subsidiary. 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 9C. 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 above in section 9.1.1 for patients with multi-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 numbers of surviving patients for each week following the index procedure, up to the time horizon of the model.

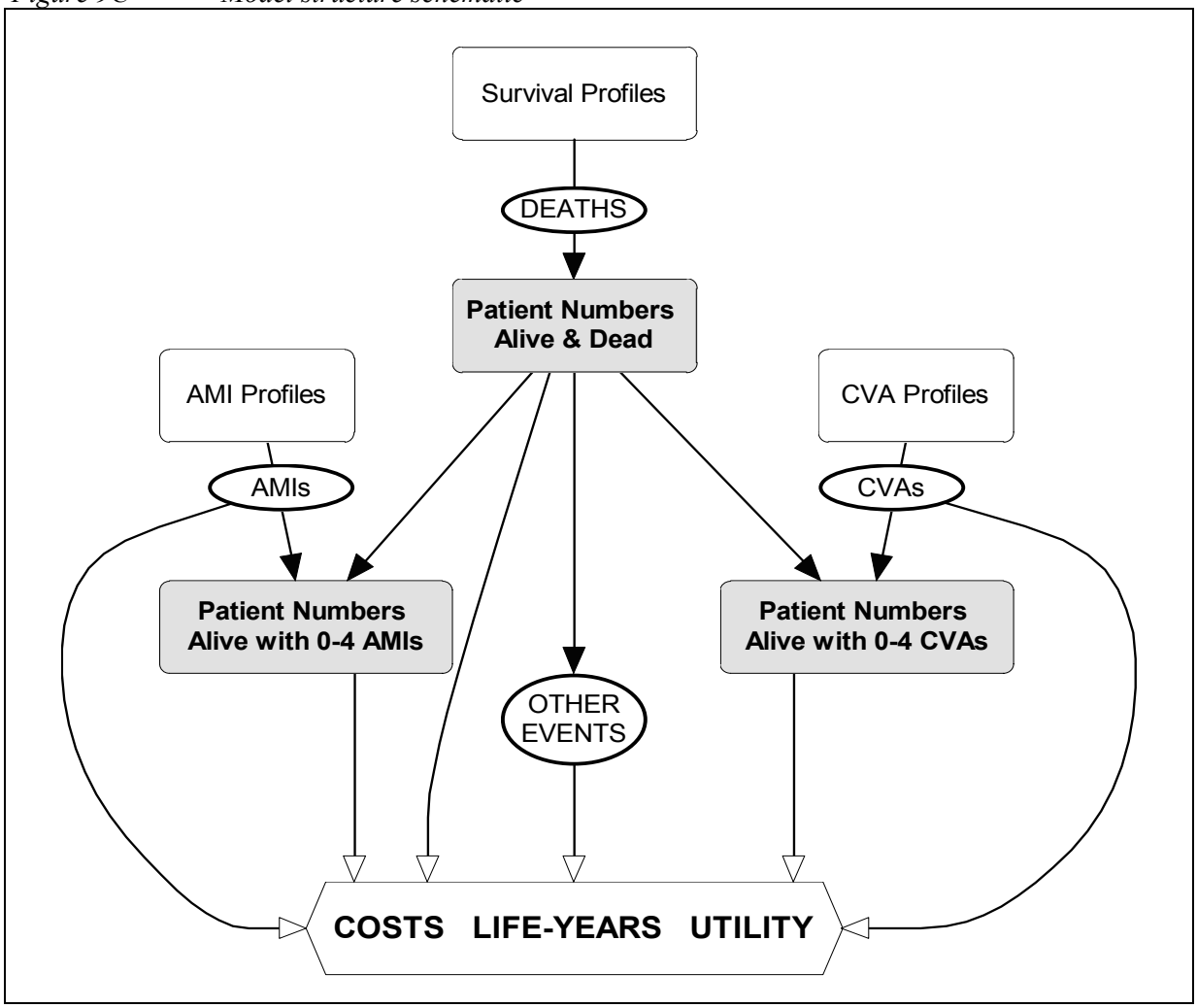
A similar approach is taken to estimating the numbers of patients expected to suffer acute myocardial infarcts and strokes in each period, based on the number of surviving patients in each time period. Given the frequency of 'silent MIs' (i.e. those detected only on ECG at a routine review and not causing 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 2001/2 as described above. This provides national mean inclusive costs for index procedures, which constitute the single largest element in the cost model.

Figure 9C Model structure schematic



9.2.2 Model assumptions and parameter estimates

Mortality

The metamodel described above of mortality in multi-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 2 vessel disease obtained

from the CTC registries for CABG and stented patients. For stent and DES patients with 1 vessel disease, we apply a global pro-rata reduction of 26% to all mortality rates, based on a meta-analysis we carried out of large registry studies and long-term trials reporting mortality for 1 and 2 vessel disease. Results employed were from the APPROACH registry (226), BARI trial and registry (227), supplemented by the NHLBI PTCA registry (228) and a review of 7 trials by Yusuf (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 vs. 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 2 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 1 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.

Cerebro-vascular accident (CVA)

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 the following table (9B). 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.

Table 9B Distribution of type of subsequent revascularisation

	Subsequent procedure:				
Index procedure	**PTCA**	**Stent**	**DES**	**CABG**	**Source of estimate**
CABG in 2 vessel disease	20%	25%	25%	30%	Estimated from CTC registry data and clinical opinion
DES in 2 vessel disease	0%	80%	10%	10%	Clinical opinion
Bare Metal Stent in 2 vessel disease	25%	55%	0%	20%	Study of revascularisation in Medicare patients(229)
Bare Metal Stent in 1 vessel disease	25%	55%	0%	20%	Study of revascularisation in Medicare patients
DES in 1 vessel disease	0%	80%	10%	10%	Clinical opinion

Note on Table 9B

(CIC information removed)

Acute renal failure

Although trials and observational studies suggest acute renal failure occurs following revascularisation at a rate of 1 to 2 percent our clinical advisors suggested 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 percent 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 percent of all cases. For the purpose of costing, we have assumed that bleeding post-CABG is twice as costly as that post-PCI.

Out-patient follow-up

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

- One out-patient consultation with cardiac surgeon 4 weeks following discharge
- Four out-patient consultations with cardiologist at 4, 8, 12 and 26 weeks post-discharge
- One course of community-based cardiac rehabilitation over 4 weeks

For stenting:

- Four out-patient consultations with cardiologist at 4, 8, 12 and 26 weeks post-discharge
- One course of community-based cardiac rehabilitation over 4 weeks
- Clopidogrel therapy for 4 weeks post discharge

Continuing drug use

In line with the findings of ARTS we assume that a proportion of patients will no longer need anti-anginal drugs following a successful revascularisation, though those agents with other beneficial effects (anti-hypertensive and lipid-lowering) are presumed to continue. Based on ARTS findings, we assume that 6 weeks after the initial procedure 20 percent of PTCA patients and 40 percent 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 on 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 bare stents or 1.1 DES are used, based on clinical opinion (conservative in favour of DES).

Treatment for AMI & 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 out-patient 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 percent for the second, 25 percent for the third, and 50 percent 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. Thus using the ARTS results for surviving post-CABG patients (EQ-5D 68 at baseline vs. 86 at 6 months) we estimate a disutility of 0.012 QALYs spread over 13 weeks, compared to 0.0035 QALYs 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 QALYs 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.

Table 9C Unit costs

Resource item	Unit of resource	Unit cost	Source
Initial Revascularisation Procedure:			
CABG primary	*per episode*	£7,868	2002 DOH Reference Costs (including estimate of ITU stay)
CABG redo	*per episode*	£8,368	As index procedure + £500
Emergency CABG post-PCI failure	*per episode*	£7,161	2002 DOH Reference Costs (including estimate of ITU stay)
PTCA	*per episode*	£2,156	Adapted from 2002 DOH Reference Costs
PTCA (excluding stents)	*per episode*	£2,156	Adapted from 2002 DOH Reference Costs
Single uncoated stent	*per stent*	£380	From industry submission
Single drug-eluting stent	*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*	£1,680	Non-elective L49 in 2002 DOH Reference Costs
Severe bleeding episode post PTCA	*per episode*	£1,000	Authors' estimate
Severe bleeding episode post CABG	*per episode*	£2,000	Authors' estimate
Follow-up			
Cardiology O/P review post-PTCA	*per attendance*	£63	E16op from 2002 DOH Reference Costs
Cardiac Surgery O/P review post-CABG	*per attendance*	£111	OP f-up attendance for specialty 170 from 2002 DOH Reference Costs
Clopidogrel	*per week*	£9	BNF
Recurrence of Symptoms			
Cardiology O/P review	*per attendance*	£63	E16op from 2002 DOH Reference Costs
Angiography	*per investigation*	£278	E02op from 2002 DOH Reference Costs
Repeat Revascularisation Procedure:			
PTCA		£2,156	Adapted from 2002 UK Reference Costs
PTCA (excluding stents)		£2,156	Adapted from 2002 UK Reference Costs
CABG redo	*per episode*	£8,368	As index procedure + £500
Acute Events			
AMI episode - fatal	*per episode*	£814	Non-fatal AMI reduced by 20%
AMI episode - non-fatal	*per episode*	£1,017	E11/E12 from 2002 DOH Reference Costs
Cardiology O/P review post-AMI	*per attendance*	£63	E16op from 2002 DOH Reference Costs
CVA episode - fatal	*per episode*	£1,600	Non-fatal CVA reduced by 20%
CVA episode - non-fatal	*per episode*	£2,124	A22/A23 from 2002 DOH Reference Costs
Gen Physician O-P review post-CVA	*per attendance*	£87	OP f-up attendance for specialty 300 from 2002 DOH Reference Costs

9.2.3 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 drug-eluting stents 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.

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 to conventional stents for patients currently undergoing PTCA with stent;
- *And as the dominant element in the two previous items,* the price differential between DES and conventional bare-metal stents.

9.3 Cost-Effectiveness Results

9.3.1 Comparing alternative treatments for 2 vessel disease

PTCA plus bare metal stenting versus CABG

Model results for conventional stenting as an alternative to CABG in the treatment of uncomplicated 2-vessel disease are the most secure, being based directly on the combined results of ARTS, SOS and ERACI II. These are shown in Table 9D at annual intervals for 5 years follow-up, and graphically in Figure 9D.

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, incremental cost-effectiveness ratios (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 9D indicate that if PTCA with stenting had been the established baseline treatment for 2-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 to 10 years.

Table 9D Cost-effectiveness of PTCA with bare metal Stents for 2 vessel disease compared to CABG

Time from initial procedure	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	-£4,800	0	0	-	-
1 year	-£4,426	+0.0053	+0.011	-£835,026	-£421,070
2 years	-£4,298	+0.0077	+0.011	-£560,638	-£385,708
3 years	-£4,240	+0.0013	+0.004	-£3,236,989	-£1,041,971
4 years	-£4,183	-0.0190	-0.015	+£220,467	+£276,951
5 years	-£4,115	-0.0591	-0.051	+£69,619	+£80,841

PTCA with DES versus CABG

The lack of reliable evidence of efficacy for drug-eluting stents 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 percent (relative to bare metal stenting). The other principal uncertainty is the price differential between bare metal stents 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 availably in UK.

The findings for the base case are also displayed in Figure 9D and are reported in detail in Table 9E at annual intervals for 5 years follow-up. They follow a very similar pattern to those obtained above for Bare Metal Stenting. The main difference is that the net cost saving over CABG at 5 years is about £1,000 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 bare metal stents despite fewer repeat procedures. Thus the general conclusion is confirmed that PTCA with DES also results in reduced costs at the expense of reduced health-related utility, when compared to CABG.

Table 9E Cost-effectiveness of PTCA with DES for 2 vessel disease compared to CABG

Time from initial procedure	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	-£3,552	0	0	-	-
1 year	-£3,355	+0.0053	+0.011	-£633,045	-£299,288
2 years	-£3,270	+0.0077	+0.012	-£426,532	-£271,851
3 years	-£3,220	+0.0013	+0.005	-£2,458,803	-£644,783
4 years	-£3,165	-0.0190	-0.014	+£166,843	+£223,408
5 years	-£3,098	-0.0591	-0.050	+£52,411	+£61,999

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 feasible values, as summarised in Table 9F. 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. Thus although in all cases PTCA with DES remains cost saving, it still leads to worse long-term outcomes in the absence of any survival benefit.

Table 9F Main sensitivity analysis of PTCA with DES for 2 vessel disease compared to CABG

	Relative reduction in any repeat revascularisation for DES compared to bare metal stents					
	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	-£4,174	-£4,262	-£4,349	-£4,466	-£4,612	-£4,758
£250	-£3,571	-£3,659	-£3,747	-£3,865	-£4,012	-£4,158
£520 (base)	-£2,920	-£3,009	**-£3,098**	-£3,216	-£3,363	-£3,511
£750	-£2,366	-£2,455	-£2,544	-£2,663	-£2,811	-£2,960
£1000	-£1,763	-£1,852	-£1,942	-£2,062	-£2,211	-£2,361
£1250	-£1,160	-£1,250	-£1,340	-£1,460	-£1,611	-£1,761

PTCA plus DES versus PTCA plus plain stenting

Where patient preference or clinical opinion currently leads to use of PTCA with plain stent for patients suffering uncomplicated 2-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 9G for up to 5 years of follow-up

Table 9G Cost-effectiveness of PTCA with DES for 2 vessel disease compared to PTCA with stents

Time from initial procedure	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	+£1,248	0	0	-	-
1 year	+£1,071	0	+0.0007	-	+£1,529,445
2 years	+£1,028	0	+0.0009	-	+£1,161,430
3 years	+£1,019	0	+0.0009	-	+£1,101,030
4 years	+£1,017	0	+0.0009	-	+£1,088,891
5 years	+£1,017	0	+0.0009	-	+£1,086,356

The additional cost is composed largely of the extra cost of DES, and therefore is fully realised within 2 to 3 years. The projected utility gain is extremely small since it arises only from reduced health-related quality of life 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 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 9.3.1. 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.

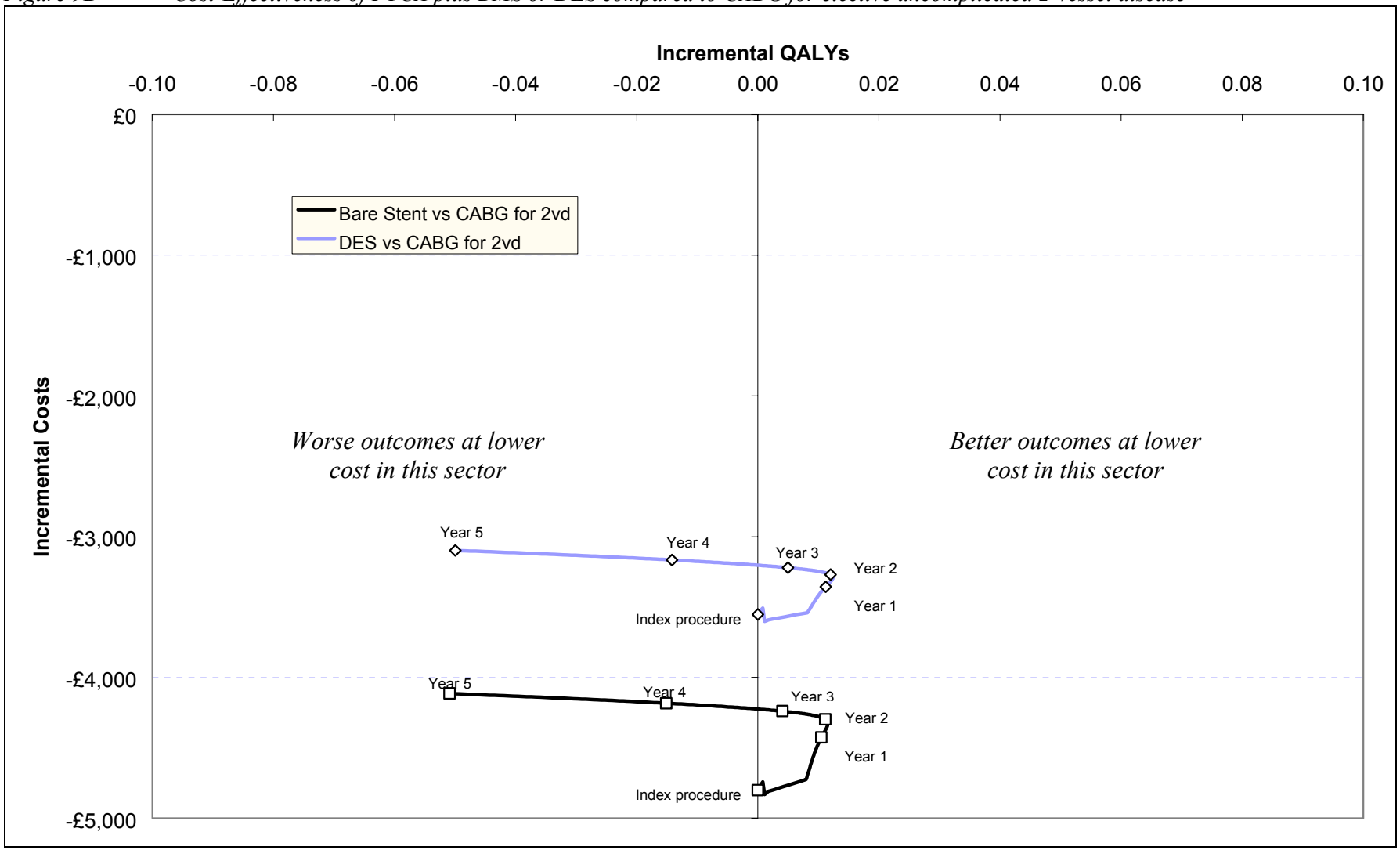
A sensitivity analysis was performed in which the most optimistic scenario for the efficacy of DES was employed - that DES eliminated *all* repeat revascularisations indefinitely. On this basis, we estimate that if the excess cost per DES over bare metal stents is only £98 then costs are equivalent (i.e. '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 to 4 years, CABG continues to accrue substantial life-year and QALY advantage, without any further additional cost. Thus switching from CABG to PTCA with stent for patients with ordinary risk 2 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 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 bare metal stents, unless the price premium charged for DES is substantially less than is currently envisaged.

Figure 9D *Cost-Effectiveness of PTCA plus BMS or DES compared to CABG for elective uncomplicated 2-vessel disease*



9.3.2 Bare stent versus DES for 1 vessel disease

As previously observed, the great majority of uncomplicated 1-vessel disease is treated in the UK by PTCA with plain stent(s). Registry data in Liverpool suggests revascularisations at 12 months for this patient group are 28 percent lower than in the comparable group with 2-vessel disease, and this was used to estimate reintervention rates in this case. We then modelled whether the substitution of DES for bare metal stents could be considered a valid cost-effective alternative to current practice. The results are displayed in Table 9H for up to 5 years of follow-up.

Table 9H Cost-effectiveness of PTCA with DES for 1 vessel disease compared to PTCA with bare metal stents

Time from initial procedure	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 year	+£549	0	+0.0005	-	+£1,099,858
2 years	+£520	0	+0.0006	-	+£825,512
3 years	+£513	0	+0.0007	-	+£780,442
4 years	+£512	0	+0.0007	-	+£771,347
5 years	+£512	0	+0.0007	-	+£769,434

The additional costs incurred are lower than was the case for 2 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 bare metal stents 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.

9.3.3 High-risk subgroups

The industry models seek to establish results supportive of DES on the basis of limiting use to specific high-risk patient sub-groups, for example those with diabetes, long lesions, or small vessel disease. As there is 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 left main 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 9I summarises the results obtained for follow-up to 5 years for multi-vessel disease scenarios, using a range of global risk modifiers from x 1.0 (base case) to x 5.0.

Figure 9E displays the results obtained for multi-vessel disease comparisons involving PTCA with plain stent 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. Thus we are confident in concluding that CABG remains the treatment of choice for most high-risk patients.

Table 9I Impact of high-risk sub-group selection on cost-effectiveness in multi-vessel disease

Bare Metal Stent vs. CABG for high-risk multi-vessel disease at 5 years			
Relative Risk	**Incremental Cost**	**Incremental QALYs**	**Cost / QALY gained**
x 1.0	-£4,115	-0.0509	+£80,841
x 1.5	-£3,715	-0.0807	+£46,044
x 2.0	-£3,291	-0.1106	+£29,765
x 2.5	-£2,838	-0.1406	+£20,189
x 3.0	-£2,349	-0.1707	+£13,764
x 4.0	-£1,233	-0.2315	+£5,327
x 5.0	+£164	-0.2935	-£559

DES vs. CABG for high-risk multi-vessel disease at 5 years						
	Assuming 30% DES efficacy			**Assuming 75% DES efficacy**		
Relative Risk	**Incremental Cost**	**Incremental QALYs**	**Cost / QALY gained**	**Incremental Cost**	**Incremental QALYs**	**Cost / QALY gained**
x 1.0	-£3,098	-0.050	+£61,999	-£3,363	-0.049	+£69,149
x 1.5	-£2,825	-0.079	+£35,651	-£3,237	-0.077	+£41,929
x 2.0	-£2,537	-0.109	+£23,364	-£3,105	-0.106	+£29,359
x 2.5	-£2,230	-0.138	+£16,162	-£2,966	-0.134	+£22,087
x 3.0	-£1,901	-0.167	+£11,350	-£2,821	-0.163	+£17,318
x 4.0	-£1,154	-0.227	+£5,088	-£2,499	-0.220	+£11,355
x 5.0	-£227	-0.287	+£792	-£2,115	-0.277	+£7,623

DES vs Bare Metal Stent for high-risk multi-vessel disease at 5 years						
	Assuming 30% DES efficacy			**Assuming 75% DES efficacy**		
Relative Risk	**Incremental Cost**	**Incremental QALYs**	**Cost / QALY gained**	**Incremental Cost**	**Incremental QALYs**	**Cost / QALY gained**
x 1.0	+£1,017	+0.0009	+£1,086,356	+£751	+0.0023	+£332,904
x 1.5	+£890	+0.0015	+£613,823	+£479	+0.0035	+£136,918
x 2.0	+£755	+0.0020	+£376,843	+£187	+0.0048	+£38,661
x 2.5	+£608	+0.0026	+£234,014	-£129	+0.0063	-£20,528
x 3.0	+£449	+0.0032	+£138,188	-£471	+0.0078	-£60,207
x 4.0	+£80	+0.0048	+£16,751	-£1,265	+0.0115	-£110,403
x 5.0	-£391	+0.0067	-£58,482	-£2,279	+0.0161	-£141,357

Figure 9F displays the results obtained for multi-vessel disease comparisons involving PTCA with DES matched against PTCA with plain stent, 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. Thus we conclude that DES may be suitable for some high-risk patients with multi vessel disease who would otherwise undergo PTCA with plain stent, 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, etc.), though it may be argued that some of these patients would in fact be more suitable for CABG.

Table 9J similarly summarises the results obtained for follow-up to 5 years for single vessel disease, using a range of global risk modifiers from x 1.0 (base case) to x 5.0. Figure 9G displays the results obtained for the single-vessel disease comparison between PTCA with plain stent or PTCA with DES. The findings here are very similar to those obtained for multi-vessel disease where BMS would otherwise be used, though 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.

Table 9J Impact of high-risk subgroup selection on cost-effectiveness in single vessel disease

DES vs Bare Metal Stent for high-risk single-vessel disease at 5 years						
	Assuming 30% DES efficacy			***Assuming 75% DES efficacy***		
Relative Risk	**Incremental Cost**	**Incremental QALYs**	**Cost/QALY gained**	**Incremental Cost**	**Incremental QALYs**	**Cost/QALY gained**
x 1.0	+£512	+0.0007	+£769,434	+£323	+0.0016	+£201,364
x 1.5	+£424	+0.0010	+£415,864	+£135	+0.0025	+£54,714
x 2.0	+£333	+0.0014	+£238,848	-£63	+0.0034	-£18,685
x 2.5	+£236	+0.0018	+£132,439	-£270	+0.0043	-£62,789
x 3.0	+£135	+0.0022	+£61,319	-£488	+0.0053	-£92,249
x 4.0	-£87	+0.0031	-£28,034	-£965	+0.0075	-£129,215
x 5.0	-£340	+0.0041	-£82,213	-£1,509	+0.0100	-£151,568

Summary

Consideration of patient sub-groups with pre-disposing high-risk conditions serves only to strengthen the conclusion that CABG is the 'gold standard' treatment of choice in multi-vessel disease, where not contraindicated, or where expected post-CABG survival is 3 years or more. In single vessel disease, or other patients who would normally undergo PTCA with plain stent, use of DES may be cost-effective for patients with multiple pre-disposing high-risk conditions (i.e. with a net relative risk of mortality/reintervention 3 or 4 times that of uncomplicated cases receiving PTCA with plain stent).

Figure 9E Cost-Effectiveness of PTCA with plain stent or DES compared to CABG for elective multi-vessel disease in high-risk patients

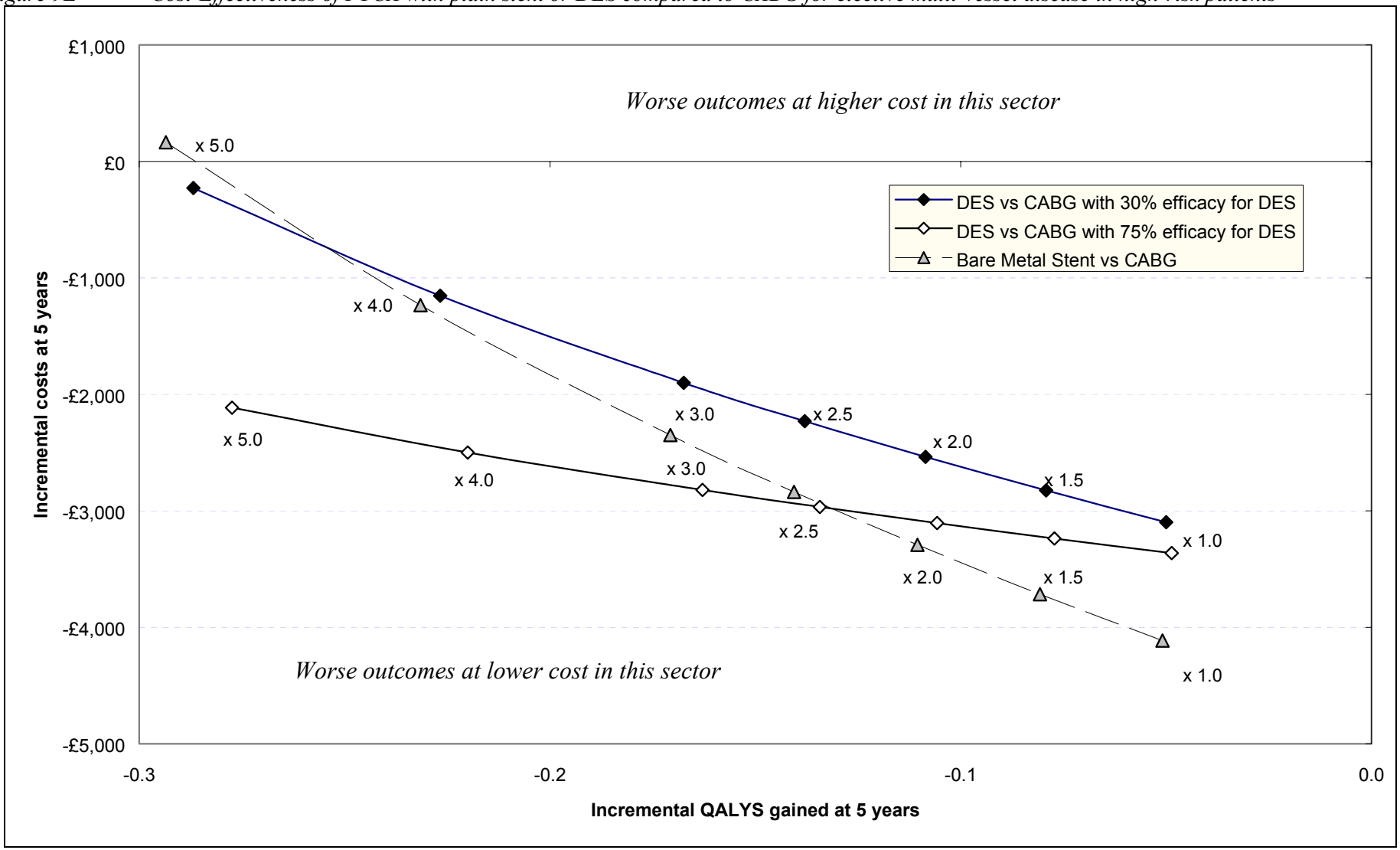


Figure 9F Cost-Effectiveness of PTCA with DES compared to PTCA with plain stent for elective multi-vessel disease in high-risk patients unable or unwilling to undergo CABG

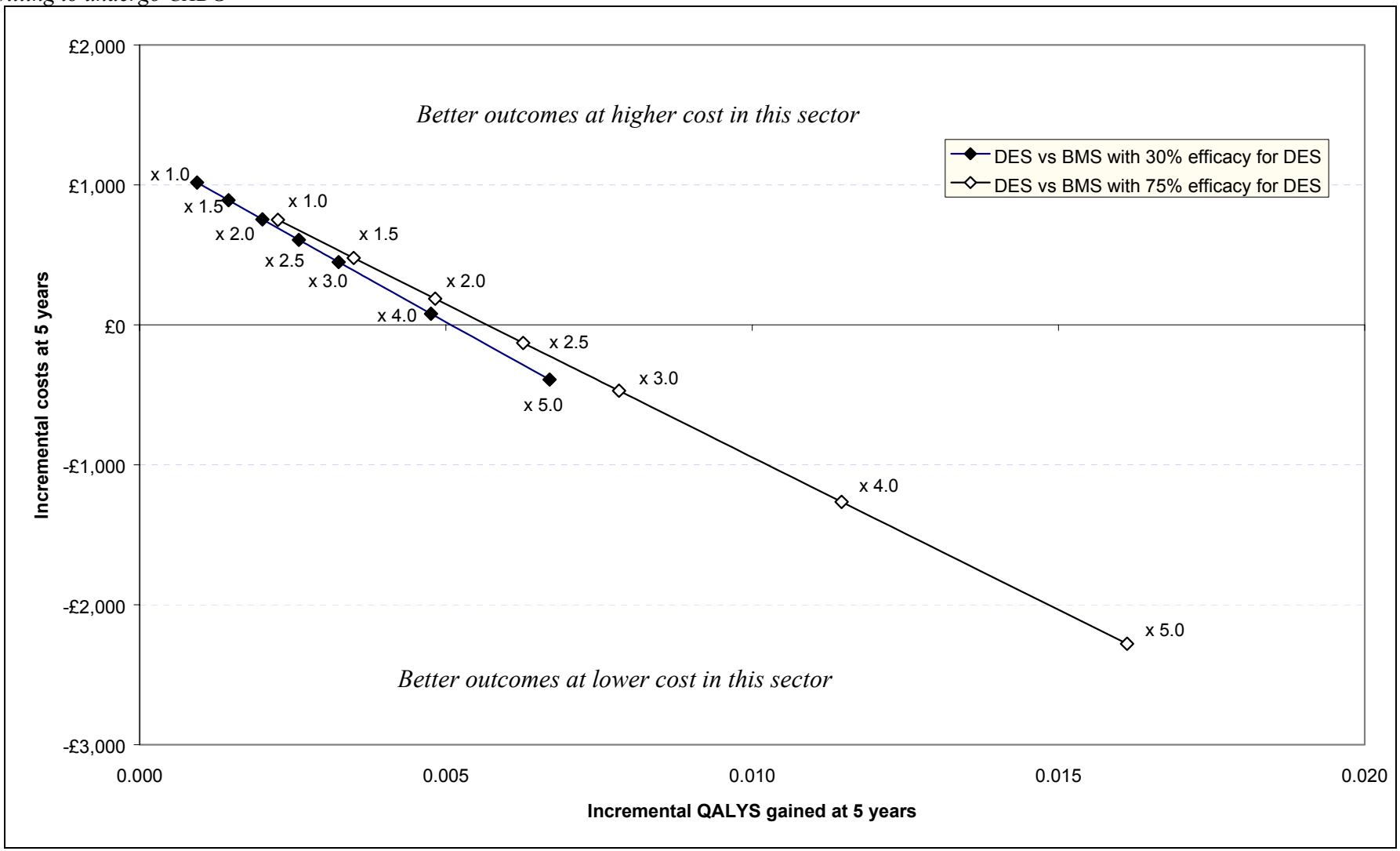
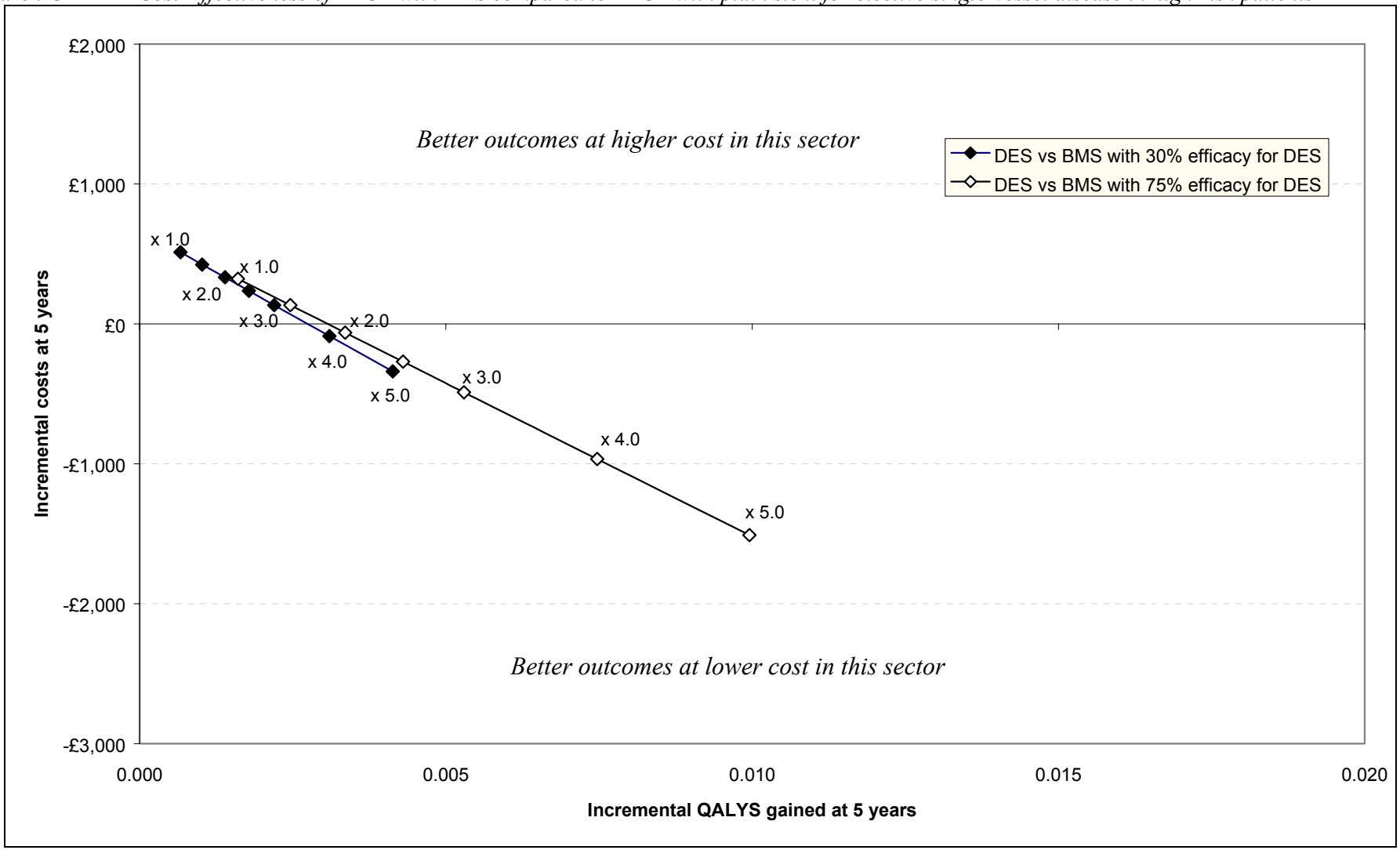


Figure 9G Cost-Effectiveness of PTCA with DES compared to PTCA with plain stent for elective single-vessel disease in high-risk patients



9.3.4 Sensitivity analysis

A detailed sensitivity analysis has been undertaken of the various model parameter values for the base case scenario comparisons. Table 9K 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 9L 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% confidence intervals 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 twelve months.

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, though 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, though 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 coronary artery disease, 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 re-stenosis 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 sub-populations: 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 this formulation is consistent with generally accepted notions of the natural history of the condition, and sufficiently flexible to faithfully represent 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 quite different from those used in any of the industry submissions, using an approach rarely taught or applied currently in health economics, though well known in other contexts. We believe this is a result of an over-emphasis 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.

9.3.5 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 underway or reporting early results, it is clear that a full and conclusive economic evaluation of drug-eluting stents 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 to 10 years) before conclusions can be drawn on the primary outcome - survival. In the absence of such evidence for drug-eluting stents 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 health-related quality of life, 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 drug-eluting stents. A two-way sensitivity and threshold analysis has demonstrated that with current prices drug-eluting stents may only be considered cost-effect substitutes for bare metal stents in patients at the highest (probably multiple) risk of early mortality and incidence of repeat revascularisation. However, some of these patients there may be more suitable on clinical grounds for either medical therapy or CABG.

In the case of multi-vessel disease, the accumulated trial evidence comparing CABG to PTCA with plain stent is sufficient to project over 5 years an important and substantial survival advantage for CABG over PTCA with plain stent Given that CABG is the standard therapy for most patients with multi-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 drug-eluting stents, since the apparent additional benefits from fewer reinterventions and consequent quality of life gains are balanced by the extra costs of the new stents. Thus we find no grounds for direct substitution of CABG by DES in multi-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 drug-eluting stents similar to those we have performed for CABG and conventional stents (ARTS, SOS an ERACI II). However, this may not be merely a question of allowing current trials to continue, since the great majority of these are already compromised by protocol driven angiography after 6 months influencing clinical decisions to re-intervene. 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, due 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 drug-eluting stents. 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 by-pass surgery. Thus, it would be unbalanced to consider new PCI technologies, without also including newer surgical strategies. We believe there is a strong case for supporting large RCTs to assess the relative merits of these techniques in comparison to the various alternative treatments - conventional and innovative.

Table 9K Univariate sensitivity analysis 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
Out-patient 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
Anti-anginal 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 1 vd	+/- 0.25	-	-	-	+/- £130
Stents per patient in 2 vd	+/- 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

BMS:Bare metal stents; 1vd One vessel disease; 2vd Two-vessel disease

Table 9L Univariate sensitivity analysis of incremental QALYs and incremental cost-effectiveness ratios (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

BMS:Bare metal stents; 2vd Two-vessel disease; ICER Incremental Cost-Effectiveness Ratios

10 Budget impact analysis

10.1 Budget Impact of expanding PTCA and CABG

10.1.1 Focus of the analysis

Over 90 percent of PTCAs currently involve the use of Bare Metal Stents, and this would seem 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 Bare Metal Stents. Equally, it is beyond the scope of this section to undertake a detailed analysis of the cost to the NHS of achieving the policy commitment outlined in the National Service Framework (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. While 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 percutaneous coronary interventions 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 1,500 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 due 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 this time, although the rate of CABG has remained relatively constant, the rate of PTCA has increased by approximately 50 percent between 1998 and 2001. The current proportion of PTCA to CABG procedures is approximately 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 was £5673. Using these figures, the estimated total cost of the PTCA (29,434) and CABG (23,364) procedures performed by the NHS in 2001/2 are £83.0 million and £132.5 million respectively. For these services to expand to achieve the NSF targets would require approximately 37,500 procedures in both CABG and PTCA (an overall level of 1,500 procedures per million population). This would thus require an additional 8,066 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 10A). 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.

Table 10A Cost of achieving NSF targets

Intervention	Finished consultant episodes (2001/2002)	Estimated current cost (£ 000,000)	Cost to achieve 750/million (£ 000,000)	% Cost Increase Required
CABG	23364	132.5	212.7	60.5
PCI	29434	83.0	105.8	27.4

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 source of expansion. While 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 to no treatment) in patients with coronary heart disease 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.

10.2 Budget Impact of drug-eluting stents

10.2.1 Introduction: budget impact of DES

This section analyses the potential cost implications to the NHS of the increased use of drug-eluting stents.

The total cost to the NHS by such increased use will depend on three factors:

1 The cost increment of the use of drug-eluting stents compared to normal stents
2 The target population identified for drug-eluting stents: (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.

10.2.2 The cost increment attached to drug-eluting stents

The use of DES is also likely to require a prolongation of anti-platelet 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 Bare Metal Stents. 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 30mm in length in native (unaltered from their natural state) coronary arteries with reference diameters of between 2.25 to 5.0mm.

Table 10B Commercial in Confidence: Price of stents as provided in the industry submissions to NICE

(CIC information removed)

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 10B). Costs for both DES and bare metal stents vary: there is at present no firm evidence to determine which bare stent 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 sub-groups of patients.

10.2.3 The target population for DES

There is as yet little evidence about the clinical and economic effectiveness of DES in specific sub-groups 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 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 10C. We recognise that the risk categories analysed are not mutually exclusive, and hence this preliminary analysis provides an upper estimate of the costs of initial targeted dissemination of DES.

Table 10C Assessment of high-risk patients suitable for DES

Patient group	Percentage of total patient population**
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 50% of patients with angina (class I or class IV)	15.0
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**

* Based on prevalence of risk factors in elective PTCA patients contained in the audit data received from the Cardiothoracic Centre, Liverpool.
** 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.

The audit data provided by the Liverpool Cardiothoracic Centre indicates that 53 percent of patients presenting for elective PCI suffer from single vessel disease, 35 percent of patients suffer from two-vessel disease, and 12 percent of patients suffer from three or more vessel disease. Of the 88 percent of patients presenting with single or two-vessel disease 25 to 30 percent 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 Bare Metal Stents) and average utilisation of 1.3 stents per procedure for single-vessel disease (62% percent of the combined total of single and two vessel disease patients) and 2.4 stents per procedure for two-vessel disease (38 percent of the combined total). Thus, an average of 1.74 stents per procedure were assumed to be required per procedure in these highest risk groups.

10.2.4 Cost increases associated with DES

If approved by NICE, DES will rapidly disseminate throughout the NHS to replace bare stents 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 (2001-2002). Our audit data indicates that 78 percent of these procedures (22,958) were elective and 88 percent of these elective procedures (20,203) were either single or two-vessel disease.

In the first case, we therefore assume that 25 to 30 percent 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 Bare Metal Stents in these patients would be between £4.59 million (25 percent of patients) and £5.51 million (30 percent of patients).

If we further assume a similar proportionate usage of DES amongst emergency patients (22 percent of the patient population), the additional cost associated with the use of DES increases to between £5.86 million (25 percent of patients), and £7.03 million (30 percent of patients).

Finally, the additional cost of achieving the NSF target of 1500 procedures per million population (assuming 50 percent of these are provided by PTCA) incorporating the targeted use of DES would be between £7.46 million (25 percent of patients) and £8.96 million (30 percent of patients).

An alternative scenario is that DES simply replace bare metal stents in all or almost all cases.

The following annual cost estimates to the NHS have also been calculated based on potential market share (Table 10B).

Table 10D Budget impact estimates: cost of DES

Scenario	Total additional cost (£ 000,000) Current Service Levels	Total additional cost (£ 000,000) 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.

10.2.5 Cost off sets associated with DES in this target population

Although DES have a higher acquisition cost than bare metal stents, the net cost to the NHS will depend on cost off sets associated with the reduction in reintervention costs. We use the term "off sets" rather than savings to make clear that, given the current under provision of interventions, there will be no actual savings as the number of interventions in the whole population are 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 re-stenosis? Equally, if a DES is used in the initial procedure, then if re-stenosis occurs, what would be the nature of this second procedure? Would a DES be used in the second stent procedure, or alternatively would CABG, bare stent 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 reduce rates of repeat procedures resulting from the use of DES. To calculate this a sensitivity analysis 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 Bare Metal Stents. The baseline model assumes that replacing Bare Metal Stents 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 £1,017 per patient. The economic model was rerun assuming no difference in the need for repeat revascularisation between DES and Bare Metal Stents. Under this assumption, the cost increase associated with the use of DES was £1,194 per patient. This sensitivity analysis therefore provides an estimated average saving of £177 for each patient resulting from the lower rates of repeat revascularisation after DES compared to bare metal stents (See Table 10E)

Table 10E 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

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 percent 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 approximately £350 over five 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 10F, with an offset of £350 per patient in the highest risk group, but an average of £177 in the whole population

Table 10F 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

The impact of these cost offsets in reducing the additional costs imposed by DES are shown in table 10G. This table estimates the net additional cost to the NHS arising from different levels of utilisation of DES.

Table 10G 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

10.2.6 Conclusion

This major factor determining cost impact to the NHS is incremental cost of the DES over bare metal stents and how widespread the use of DES become – do they replace all bare mental stents, 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 side are likely to change which will considerably influence comparative cost-effectiveness and cost impact over time. In particular, the price of drug-eluting stents 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.

11 Discussion and conclusions

11.1 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 randomised control trial. 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 coronary heart disease: e.g. 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 randomised controlled trials.

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 randomised controlled clinical trials using firm endpoints such as mortality. In the case of coronary artery stenting, in particular with drug eluting stents, 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 drug eluting stents, but on the other, the evidence in relation to real clinical endpoints 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 drug-eluting stents, 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 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 indicates that the proportion of patients receiving stents rose from 60 to 80 percent 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 Inc.(230) conducted a survey of 140 interventional cardiologists in the US in anticipation of FDA approval of Johnson and Johnson' CYPHER DES. The respondents estimated that the percentage of total stenting using DES would be 77 percent by the fourth quarter after licensing. It was thought that this would be higher in both diabetics and in small vessels (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). This data illustrates 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 drug-eluting stents 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 quality of life 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.

11.1.1 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 drug eluting stents are equally effective, or that early studies of an intervention can be compared to 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 plain stent versus drug-eluting stent, the differences between types f 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 drug-eluting stents are not the only new technical developments. Cardiac surgery techniques and post-operative management are changing and improving. In the area of non-drug eluting stents, 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 to existing stents, and that this improvement may be made with less incremental cost over existing stents than drug-eluting stents.

11.1.2 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 first is the consistency with which that outcome is measured and the second is 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; i.e. 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 drug-eluting stent 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 greater than 70 percent, 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 six 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) as opposed to 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 drug eluting stents 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 to 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 plain stents.

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 to 18 months.

11.2 Clinical effectiveness

11.2.1 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 to 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 myocardial infarction but again, there needs to be a distinction between true clinical myocardial infarction 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 sub-groups such as patients with diabetes or patients with specific lesions, e.g. chronic total occlusion, 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 – 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.

11.2.2 Comparison of stent versus CABG

CABG has demonstrated effects on prognosis in certain subgroups of patient, specifically left main 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 left main) 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 therefore are 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. These studies are small. By and large, stenting is now the preferred option for patients with single vessel disease, although more study in patients with left main stem disease is needed.

Conversely, coronary artery bypass grafting is the standard for patients with triple 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 multi-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 quality of life data that assesses 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 to stenting. Some question that the newer drug eluting stents will fill this gap in outcomes between surgery and stenting.

11.2.3 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 myocardial infarction are rare and there is no evidence that drug-eluting stents 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 is expected in the near future.

(CIC information removed)

There is still a need for much longer-term data but this wile 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, either because of adverse event rates or an inability to demonstrate expected effectiveness levels. The DELIVER study emphasises that new designs of non-drug eluting stent may bring benefits similar to those of DES and at lower cost.

11.3 Economic analysis

11.3.1 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 need for further procedures, and thereby improve their quality if not quantity of life. In the economic literature, it is clear that such events reduce quality of life, but generally for a short period, such that the overall diminution of quality of life 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 quality of life 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 quality of life compared to 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 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, i.e. a comparison of elective stenting versus CABG mainly in multi-vessel disease, a comparison of drug eluting stents versus bare metal stents, a theoretical comparison of elective CABG versus drug eluting stents, and a sensitivity analysis around each of these in populations of varying risk. This last point is undertaken to try to model the effects in such population as diabetics etc. assuming that the benefits seen for each type of procedure are proportionately maintained in different subgroups. Future studies will provide firm evidence around this, e.g. the FREEDOM study comparing drug-eluting stents to 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 plain or drug eluting stents.
- Stenting with DES may buy additional QALYs compared to standard bare metal stents, but at a very high cost (£700,000-£1,000,000/QALY).

The most contentious aspect of our evaluation is our projection of long-term mortality differences between CABG and PTCA with plain metal stents. 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 drug-eluting stents and bare metal stents are hardly altered at all – drug-eluting stents remain very expensive with limited and uncertain benefit. The comparison between stents (of either sort) and CABG for multi-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.

11.3.2 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 sensitivity analysis emphasises how dramatic these improvements would have to be.

- Second, a fall in the cost differential between bare metal and drug eluting stents. Again the sensitivity analyses suggest how dramatically the price of drug-eluting stents 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 or more. This would substantially improve the incremental cost effectiveness ratios. For instance, if we assume that DES were to reduce the rate of *all* revascularisations by 75 percent, then for those patients with a 3 fold increased risk for a clinically necessary revascularisation, the use of a DES could be cost saving while improving quality of life.

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-drug eluting stents remains uncertain. We present a sensitivity analysis 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, etc.), though 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 people with diabetes and non-diabetic people in ARTS in the CABG arm compared to the wide difference in the stented arm may suggest that similar diabetics should be offered CABG until direct comparison between CABG and DES are available to confirm at least equivalence.

11.3.3 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 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, e.g. diabetes, small vessel, long lesion etc.

Others have quantified this better. Kastrati and colleagues(231)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 diabetes mellitus (restenosis of 1.86 [1.56 to 2.16] and TLR OR 1.45 [1.11 to 1.80]), use of more than one stent (restenosis OR 1.81 [1.55 to 2.06], TLR OR 1.94 [1.66 to 2.22]) and minimal lumen diameter less than 3 mm (MLD) immediately after stenting (restenosis OR 1.81 [1.55 to 2.06], TLR OR 2.05 [1.77 to 2.34]) were the strongest predictors of restenosis.

Ho and colleagues(232)have described restenosis rates in clinically driven angiography in patients using these three risk factors, and have drawn up a table (Table 11A). If the 'standard' risk of binary restenosis is for those non-diabetic patients with short (10 mm) in vessels with a fairly large diameter (3.0 to 4.0 mm) after stenting is around 7 to 10 percent, then patients with risks of 20 to 30 percent or more might be considered for DES rather than bare metal stents.

Table 11A Predicted clinical binary restenosis rate

	Lesion length				
Vessel Diameter	**10mm**	**15mm**	**20mm**	**25mm**	**30mm**
	Diabetic patients				
2.5mm	23	26	29	31	34
3.0mm	15	17	20	22	24
3.5mm	10	11	13	5	16
4.0mm	6	7	8	9	10
	Non Diabetic patients				
2.5mm	18	20	22	25	27
3.0mm	11	13	15	17	18
3.5mm	7	8	9	11	12
4.0mm	4	5	5	7	7

Adapted from Ho and colleagues 1998(232)

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 were:

Table 11B Independent correlates of target lesion revascularisation

	Odds ratio	95 % CI
Reference diameter of vessel (per mm)	0.48	0.40-0.59
Stent length (per 5mm, per lesion)	1.06	1.03-1.10
Lesion length (per 5mm, 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 with a lesion of 3mm diameter and 10 mm long, a diabetic with a lesion of 2 mm diameter and 20 mm long would have an increased risk by a factor of (1.06 x 1.06 x 1/0.48 x 1.49 =) 3.49.

A similar argument is made by a Sheffield group (233) recently. They report a local audit showing a restenosis rate (TLR) of approximately 8 to 10 percent, 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 percent for each stent deployed, with clinically significant restenosis rates about half of this. They estimate that an angiographic restenosis rate of 15 percent 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 percent. 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 percent risk of angiographic restenosis, they suggest that approximately 18 percent 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 cardio-vascular event e.g. secondary prevention patients and patients with risk of events of 3 percent per year or more. In considering drug-eluting stents, 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 drug-eluting stents over non drug-eluting stents in many of these highest risk groups, and no long-term evidence at all. However the early results from the SIRIUS study suggests 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.

11.4 Implications for the NHS

The impact of drug eluting stents on total NHS cost must be considered. It is beyond the scope of this exercise to cost the National Service Framework. The NSF proposes at least 750 PTCAs, the majority of which will involve stenting, per million population. Drug eluting stents 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 drug eluting stents: 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 drug eluting stents 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 bare metal stenting – 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, this 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.

11.5 Recommendations for future research

Despite a large amount of interest in the new technology developed for percutaneous cardiac interventions, and a number of recent trials underway or reporting early results, it is clear that full and conclusive clinical or economic evaluations of drug-eluting stents 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 coronary 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. 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 endpoints. We also recommend larger trials with endpoints 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 bare metal stents.

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 drug eluting stents (new trial data required)
- CABG compared to DES (already planned)
- To evaluate newer non-drug eluting stents against DES.

The major benefit of stenting is a decrease in revascularisations, which should reflect a decrease in angina and an improvement in quality of life. But at present there is only limited data on the quality of life of patients with angina before and after revascularisation in single vessel disease. Using the existing quality of life evidence from the patient with multi-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 quality of life 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 quality of life 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 this should be investigated carefully by review of existing trials, though this would require co-operation from triallists to extract the additional results from their data, and by prospective registries.

11.6 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 quality of life.

The rapid evolution of the various treatment modalities makes assessment at a given point in time very difficult. Stent technology is evolving in both drug-eluting stents and in the area of stent structure. Surgical techniques are changing and the process is becoming safer, less invasive and patients' hospital stay is decreasing. These may lead to both improved outcomes and decreased costs.

In contrast, drug-eluting stents, at current list prices, will increase the net cost of stenting. At present, there is no reason to allow drug-eluting stents to displace CABG: a five 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, drug-eluting stents carry a heavy extra cost compared to conventional stents for a very small benefit in terms of improvement in quality of life. Drug eluting stents will therefore have to come down substantially in price to achieve what would seem 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 drug eluting stents (if confirmed in long term follow up of the clinical trials) is such that the ICERs are more acceptable.

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 re-appraisal of the safety and effectiveness of the devices will be essential. Until these are established for drug-eluting stents, a process of controlled release and monitoring of outcomes would be advisable.

Appendices and References

1 Appendix: Search strategies and search results

Table 1 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 or 23 or 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 or 14 or 15
17. 12 and 16
18. limit 16 to (english language and yr=1990-2002)

Table 2 Search for cost-effectiveness studies: summary

Database	Years	Search strategy	References Identified
MEDLINE	1987-2002	See below	239
EMBASE	1987-2002	See below	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**

Medline Cost-effectiveness Search Strategy (1987-2002)

1. exp "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. exp stents/ or "stent".mp.
3. exp 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. 1 and 2 and 3
5. limit 4 to (human and english language and yr=1987-2002)

Embase Cost-effectiveness Search Strategy (1987-2002))

1. exp 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. exp stent/ or stent.mp.
3. exp 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. 1 and 2 and 3
5. limit 4 to (human and english language and yr=1987-2002)

2 Appendix: 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 intention to treat 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** or **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

3 Appendix: PTCA versus stent clinical data

Table 4D PTCA: Study Characteristics

Study name	N * Stents PTCA	Primary outcome	Secondary outcomes	Location(s) & centres	Inclusion criteria	Exclusion criteria	Co-Therapies	Type of stent	Crossovers	Follow-up**
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 DS <30% TIMI grade 3)	Multicentre European	Stable or unstable angina or reversible ischemia, 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 L main coronary artery lesion, TO, 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 6mo (Angiographic evidence of restenosis at angiographic follow-up); Event free survival at 2 year	Angiographic success rate (<50% residual stenosis) MLD on post-procedure 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 <15mm long, reference diameter ≥2.5 mm	Acute or recent MI, tx 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-CCS @ 6 mo or intercurrent angiography; stenosis rate	Multicentre, International. Europe, Argentina	Single and multiple new lesion, native coronary artery, suitable for CABG, <15mm long, >3mm diameter	Ostial, bifurcation, severe vessel tortuousity, thrombus	Aspirin Heparin Warfarin	Palmaz- Schatz	PTCA 16/257 S 24/259	In hosp, 7 months, 1 year & 5 years

Study name	N * Stents PTCA	Primary outcome	Secondary outcomes	Location(s) & centres	Inclusion criteria	Exclusion criteria	Co-Therapies	Type of stent	Crossovers	Follow-up**
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 mo; 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	L main 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 %) St: 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 St 58 (44%) ('Insufficient result in 34, dissection in 24)	6 mo
BOSS (41)	31 66	TVR (8 mo)	Angiographic Restenosis; 'accuracy of subjective determination of an adequate PTCA by the operator'	Multicentre (6) USA	De novo lesions in native vessels, ≥3.0mm diameter, <15mm long, acceptable for stenting	Angina at rest (within 24hr); MI (within 72hrs), TO; multiple, heavily calcified, restenotic, SVG lesions; multivessel interventions, thrombus	Aspirin Heparin, Ticlopidine	Palmaz-Shatz stent (cordis, J&J, Miami, Flo)	PTCA to St 24/66 (36%); St tp PTCA 2/31 (6%); Total PTCA=(66-24)+2=44 (Rx-RCVD analysis available)	Angiographic follow-up 6 to 8 mo (St 17/31, PTCA 42/66, 61% of all patients [I2Rx ratios])
DEBATE II (42)	97 523	Cost-effectiveness	Benefit differences; relative cost/benefit ratio; Efficacy end points MACE within 12 mo: death (any cause), (non fatal) MI, CABG, TLR (by PCI OR CABG)	Multicentre Europe	Stable of unstable AP (excluding Braunwald III), single new lesions, target lesion <25mm long	TCO, ostial/ bifurcation lesions, bypassed vessels, tortuous or contained thrombus, prev Q-wave MI		Not specified (although Cordis acknowledged for providing stents free of change)	Bail out stenting in 129/523 PTCA patients	12 months, ECG, angina status and physical 1, 6 and 12
DESTINI (43)	370 365	Development of>/=1 lesion-related MACE @ 12 mths, defined as death, MI, or repeat target lesion revascularisation.		Multicentre (55 International	Suitability of lesion for stent	MI within 24 hrs, prev Q wave MI with akinesia or diskinesia of territory supplied by target vessel, CTO, graft+ostial stenosis, 2nd restenosis after PTCA stent restenosis, Rotabaltor/ atherectomy	Aspirin Heparin, Ticlopidine IV IIb/IIIa GP (4% pts).	Johnson & Johnson 36.5%, NIR 32.6%, ACS, AVE 20.5%, GR, Wiktor + other coils 10.4	[PTCA to St 206/365]	6 mo (physical, ECG and stress testing); 1 year (patients/families contracted for incidence of 'MACE' or repeat of symptoms)

Study name	N * Stents PTCA	Primary outcome	Secondary outcomes	Location(s) & centres	Inclusion criteria	Exclusion criteria	Co-Therapies	Type of stent	Crossovers	Follow-up**
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	R coronary artery stenosis - new onset, symptomatic and documented angina, vessel >3mm	Evolving MI, previous extensive myocardial necrosis, risk for loss of follow-up, poor candidates for CABG, ostial or long lesion (>20mm), thrombus, vessel tortuosity	Aspirin Heparin	Wiktor stent	PTCA: 3/42 (7.1%), S 2/42 (4.8%)	In hospital and 6 months
EPISTENT (45), (234)	1603 [c] 796 [c]	Combination of death, MI, or reinfarction, or severe myocardial ischaemia requiring urgent CABG or revascularisation within 30 d	Death or MI, death or large MI	Multicentre (63) USA, Canada	IHD, stenosis > 60%, lesions amenable to PTCA or stenting	Target vessel L main stem stenosis, bleeding diathesis, intracranial neoplasm, CVA within 2yrs, uncontrolled hypertension, recent surgery, PCI within 3mo, 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
FROST (46)	126 127 (2 excluded from analysis)	The final MLD at the target site measured at 6 mnth follow up.	BRR, incidence of MACE at 6 mth follow up,	Multicentre (17) France	Myocardial ischaemia, de novo lesions, native coronary arteries.	AMI within 3 wks, LVEF <50%, abnormal wall motion in area of target vessel, hypertrophic cardiomyopathy	Aspirin Heparin Ticlopidine	PS- 153 (Johnson & Johnson Interventional systems, Warren, New Jersey)		In hospital & 6 months
KNIGHT (47, 235)	39 38	Restenosis rate at 6mo		Single centre UK	Sub optimal result of PTCA, de novo stenosis (>50% reduction in luminal diameter), native arteries, ≥2.5mm	TO, restenosis, VG lesions, emergency PTCA, PTCA for AMI	Aspirin Heparin Warfarin	Palmaz-Schatz PS153/104 (3/29 randomised to St had an alternative stent implanted)	[St: 1 CABG, 1 withdrawal]	6mo symptoms and angiography (St 37/39, PTCA 38/38)
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 hrs, requirement for tx of >1 vessel, >45 0 angulation of the lesion, moderate to severe calcification, Ostial stenosis	Aspirin, Heparin Ticlopidine	Palmaz-Schatz (77%), Cooke (1%), other: 20%	93 (37%) PTCA pts received provisional stents	In-hospital, 6 months

Study name	N * Stents PTCA	Primary outcome	Secondary outcomes	Location(s) & centres	Inclusion criteria	Exclusion criteria	Co-Therapies	Type of stent	Crossovers	Follow-up**
OCBAS (49, 236)	57 59	Binary restenosis (by angiogram) at 6mo; TVR at 6mo	Event free survival (cardiac death, Q or Non-Q MI, angina, repeated TVR) at 6mo	Multicentre Argentina, Chile, Uruguay, USA	Symptomatic CAD, de novo lesions, native arteries, lesions <20mm long, reference diameter >2.5mm, successful PTCA with good angiographic result immediately before randomisation	Diffuse or severe L main disease, severe vessel tortuousity, lesions with acute complications, sub optimal PTCA result,	Aspirin, Heparin Ticlopidine	Gianturco Roubin II (33), Palmaz-Schatz (21), Multilink (5), Wiktor (3), Wallstent (3), AVE (2)	PTCA to St 8/59 (2nd angiogram in PTCA grp 30min after procedure leading to crossover if early loss detected)	Clinical assessment at 1, 3, 6 mo (except for deaths and TVR during 'early follow-up') Clinical follow-up in first year (9 to 23 mo) available for all patients; Angiography 7.6 +/- 0.4mo, on 112/116 pat
RSSG (50)	191 (178 analyzed) 192 (176 pts analyzed)	Angiographic evidence of restenosis (stenosis of >50% of luminal diameter) at 6 months	Event-free survival including death, MI, CABG, TVR after randomization	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%) S:12/178(6.7 %) did not have S placed	In-hospital, 6 months
SAVED (51)	110 110	Restenosis (luminal diameter >=50 at follow-up); composite outcome (death, MI, repeat CABG, or revascularization at target lesion	Procedural success rate (reduction of restenosis rate <50%), duration of hospitalization, frequency of bleeding and peripheral vascular complications	Multicentre USA	Angina or objective evidence of myocardial ischemia, stenosis of SVG, stenosis >60%, diameter 3.0-5.0 mm.	MI <7days, 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, S 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 mo)	Composite endpoint (death, AMI, TVR) at 4 yrs	Multicentre (5) Spain	Angina, objective evidence of myocardial ischemia, new lesion, stenosis >70%, <15 mm long, >3 mm diameter; multivessel CAD, >1 lesion per pt allowed to be randomised	AMI within 1 wk, ostium, side branch >2.5mm; TO <3mm, heavy calcification, vessel tortuousity, stenosis of L main coronary artery >25%, cardiogenic shock	Aspirin Heparin Warfarin, Ticlopidine	Palmaz-Schatz	PTCA 25/223(11%)	In-hospital, 6 months, 4yr

Study name	N * Stents PTCA	Primary outcome	Secondary outcomes	Location(s) & centres	Inclusion criteria	Exclusion criteria	Co-Therapies	Type of stent	Crossovers	Follow-up**
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 hospitalization.	Angiographic evidence of procedural success & the absolute MLD after the procedure & at follow up, composite end point (death, mi, CABG or need for repeat PTCA within the first 6 mo after the initial revascularisation).	Multicentre (20) International	Symptomatic IHD, new lesions, native coronary artery, >70% stenosis, <15mm, >3mm diameter	MI within 7 days, LVEF <40%, thrombus, the presence of multiple focal lesions or diffuse disease, serious disease in L main coronary artery, ostial lesions, severe vessel tortuousity.	Aspirin Heparin Warfarin	Palmaz-Schatz	8/205 (3.9%) of the St pts did not receive stents. PTCA group 14/203 (6.9%) received emergency stent.	1 month, 3 months, 6 months and 1year.
STRESS II (54) 12mo data source: (223)	100 89	Angiographic & clinical outcomes		Multicentre International	Same as STRESS I	Same as STRESS I	Same as STRESS I			12mo
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 (56)	60 60	Procedural success rate (residual stenosis <50%, absence of death, MI, need for CABG in-hospital), event-free survival rate at 12 mo; stenosis rate (>50%); recurrence of angina	In-hospital complications at puncture sites; in-hospital duration;	Single centre Italy,	Angina, documented myocardial ischemia or both; single vessel LAD artery <15mm long, >3mm diameter, LVEF >40%	MI within 1 mo, ostial, major branch within target lesion, TO, severe vessel tortuousity	Aspirin, Heparin Warfarin	Palmaz-Schatz	PTCA 4/60(6.9%) 2 to stent, 2 to CABG, S 3/60(5.2%) crossed to CABG	In-hospital, 12 mo
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 L main stem CD, uncontrolled HT	Aspirin, Warfarin, Ticlopidine	Wiktor-GX	PTCA 44/146(30.1 %) to stent Stent grp: 3//154(1.9%)	30 days, 1 year

Study name	N * Stents PTCA	Primary outcome	Secondary outcomes	Location(s) & centres	Inclusion criteria	Exclusion criteria	Co-Therapies	Type of stent	Crossovers	Follow-up**
WIN (58)	229 235	Clinical and Angiographic outcome in-hospital and at 6mo - only in hospital data reported		Multicentre Canada				Wallstent	Bail outs (25.7%)'	In-hospital, 6 mo
Participants with AMI										
BESSAMI(59)	80 87	Combined complication rate: (re intervention, CABG, reinfarction and death)		Multicentre Germany	AMI (clinically and angiographically confirmed), vessel size ≥2.5mm	Severe 3 vessel disease, urgent need of CABG	Ticlopidine	Wiktor-i Heparin-coated stent		In-hospital, 5mo (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 min <12 hrs of symptoms), ST elevation in 2 contiguous leads or LBBB, native artery, lesion <64mm, 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
ESCOBAR (SURYAPRANATA)(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 hrs symptom onset or 6-24 hrs ongoing ischemia); native CA, suitable for stenting	Prolonged CPR or cardiogenic shock, life expectancy <1 year; L main or severe 3-vessel disease, bifurcation, diffuse disease, vessel tortuousity, no re-flow, thrombus	Aspirin Heparin Warfarin, Ticlopidine	Palmaz-Schatz	S: 2/112 (2%), PTCA 15/115(13%)	In-hospital, 6, 24 months
FRESCO(62)	75 75	A composite clinical end point (occurrence 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 min, ST elevation within 6 hr symptom onset or 6-24 hr of ongoing ischaemia, cardiogenic shock included, reference diameter >2.5mm, stenosis >70%	Previous fibrinolytic tx, non optimal PTCA	Aspirin Heparin Ticlopidine	Gianturco-Roubin coronary stent. (Cook)		1 month & 6 months

Study name	N * Stents PTCA	Primary outcome	Secondary outcomes	Location(s) & centres	Inclusion criteria	Exclusion criteria	Co-Therapies	Type of stent	Crossovers	Follow-up**
GRAMI(63)	52 52	Major cardiac complications (death, recurrent ischemia, reinfarction and emergency CABG) in hospital	Procedural success, event-free survival (death, MI, re-revascularization, need for TVR, angiographic restenosis (not reported), at follow-up	Multicentre (8) USA, Argentina	Angiography within 24h MI symptom onset (chest pain >30 min), ST elevation or depression; cardiogenic shock, previuos CABG, any length stenosis included	Bleeding risk prohibiting use of heparin/ antiplatelet agents, non cardiac illness with survival <1yr, reference diameter <2.5mm, severe (50%) stenosis, L main, severe multivessel disease, culprit vessel stenosis <50%	Aspirin Ticlopidine	Gianturco-Roubin II coronary stent.		In hospital & 1year
JACKSCH(64)	231 231			Multicentre Germany	AMI				PTCA (27%) 62/231, St 32/231	Intra-hospital, control angiogram after 4.6+/1.3mo of 431pts
PASTA(65)	67 69	MACE (repeat MI, TLR, cardiac death) in hospital and at 6mo	Reocclusion of target vessel; angiographic restenosis	Multicentre (6) Japan	AMI within 12hrs, TIMI grade ≤ 2; estimated diameter of culprit coronary artery ≥ 2.5mm	Excessive bending or calcification of coronary artery proximal to the culprit lesion	Aspirin Heparin, Ticlopidine	Palmaz-Schatz (manually taken off J&J delivery system and crimped to a 'different balloon')	PTCA 7/69(10%) St: 1/67(1%),	In hospital, 6mo, up to 12; Angiograms at 1 to 2wks and 6mo after onset of MI; Clinical follow-up for more than 12mo
PRISAM(66)	110 112			Multicentre Japan	AMI (symptom onset <24h)			Wiktor coil stent	PTCA 1%, St 0	6mo; Angiographies at 1 and 6mo
PSAAMI(67)	44 44	Combined end point (death, reinfarction, TLR)		Single centre Germany	AMI <6 hrs or within 24hrs, ongoing ischemia, left heart failure, cardiogenic shock, clinical indication for PTCA, native artery ≥ 3mm, stenosis >70% diameter, TIMI flow < grade III	Indication for surgical coronary revascularisation within 6 mo, previous MI, secondary or iatrogenic infarction, chronic renal insufficiency requiring dialysis	Aspirin Heparin Ticlopidine	Tensum III stents (silicone carbide-coated tantalum)	PTCA: 12/44, (St 1/44 did not have St placed)	30d; Long-term Mean 710+/-282 days, St 723+/-273d, PTCA 697+/-293d

Study name	N * Stents PTCA	Primary outcome	Secondary outcomes	Location(s) & centres	Inclusion criteria	Exclusion criteria	Co-Therapies	Type of stent	Crossovers	Follow-up**
STENT PAMI(68)	452 448	Composite of death, nonfatal MI (enz), disabling stroke, TVR for ischemia (incl PCI or CABG) during 6mo	Percentage stenosis, MLD, TIMI, Clinical events 30d, BRR, reocclusion at 6mo	Multicentre (62) International	AMI within 12 h onset; ST elevation, native artery suitable for PTCA or stent, reference diameter: 3- 4.5mm, (one or more lesions) coverable by 1 or 2 15mm stents	Likelihood of CABG within 6mo, cardiogenic shock, CVA within 1mo, renal failure, prior thrombolysis, excessive tortuosity, calcification, major side branch within lesion, warfarin use	Aspirin, Heparin Ticlopidine Abciximab (10.3%)	Heparin coated, Palmaz-Schatz	PTCA 15.1% S 1.3%,	Clinical follow up: 1mo, 6mo, QoL: 1mo, 6mo, Angiography at 6.5 mo
STENTIM-2(69)	101 (91) 110 (99)	BRR @ follow-up	Procedural success (residual stenosis <50%, TIMI grade 3, a composite end point (death, recurrent MI, repeat TVR) at 6-12 mo), recurrent ischemia, reocclusion	Multicentre France, Netherlands	Nitrate-resistant chest pain within 12 hr of onset; ST elevation; ECG and enzyme confirmation of AMI, vessel diameter <3mm, culprit lesion stenosis >70%	Prev thrombolytic therapy, cardiogenic shock, prev CABG, PTCA within 6mo, severe renal or liver failure, multiple vessel diseased	Aspirin Heparin Ticlopidine Abciximab	Wiktor-GX (Medttronic) 16mm long stent; additonal stent may have been placed	St 3/101(3%); PTCA 40/110(36.4 %)	Procedural; Hosp outcome at discharge; 6mo, 1yr; 500d K-M 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 month follow-up; reduction in stenosis to <50% by QCA	Multicentre (21) France	IHD with de novo lesions on small native coronary arteries, >50% stenosis; lesion <3 mm diameter, <15 mm long	MI within prev 3 days, ostial/ bifurcation lesion, LVEF ≤30%, CI to aspirin or ticlodipidine	Aspirin Heparin (before and after procedure) ticlodipidine (after procedure)	Bestent Small (Medtronic Inc)	Unclear	In-hospital, 6 months (MACE follow-up in 242/381 pts)
CHIVAS(71, 237)	148 154	MACE (death, CABG, PTCA)		Multicentre (23) Japan	De novo or 1st restenotic lesions of native arteries of <3 mm and lesions <15mm long			ACS Multilink		6 months, Angiograph at 6 mo; Interim analysis on 241/283 patients)

Study name	N * Stents PTCA	Primary outcome	Secondary outcomes	Location(s) & centres	Inclusion criteria	Exclusion criteria	Co-Therapies	Type of stent	Crossovers	Follow-up**
COAST(72)	312 [A] 155 [A]	MLD at 6 months	Procedural success, complications, restenosis, TVR, event-free survival	Multicentre (21) Europe	Stable or unstable angina, target lesions <30mm in native vessels, 2.0-2.6mm diameter	MI within prev 24 hrs (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 ischemia, presence of angiographically significant lesions (≤70% diameter stenosis), native artery	AMI within prev 72 hrs, lesions situated in L main coronary artery, lesions produced by in-stent restenosis, and CI to antithrombotics	Aspirin Heparin Abciximab Ticlopidine	MULTI-LINK	PTCA 16.5%, S 4.4%	30 days & 6 months
PARK(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%, <15mm long, reference diameter <3.00mm), native artery	Ostial, calcified lesion, TO, infarct-related artery, LVD (EF <40%), CI to antiplatelets	Aspirin Heparin Ticlopidine		PTCA to Stents: 12/60 (8 sub-optimal, 4 major dissection)	In-hospital, (pats requested to attend at 1, 3 and 6 mo), 15.9+/-5.7mo; Angiography: 6mo
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%, S 1%	6 months
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 mo; absolute MLD after procedure and follow-up	Multicentre International	Stable or stabilised unstable AP (Braunwald IIb), silent ischemia, required PTCA of one de novo lesion, reference diameter ≥2.3 mm and ≤2.9 mm, ≤12mm 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 mo

Study name	N * Stents PTCA	Primary outcome	Secondary outcomes	Location(s) & centres	Inclusion criteria	Exclusion criteria	Co-Therapies	Type of stent	Crossovers	Follow-up**
SISCA(77)	74 71	Minimal lumen diameter (MLD) at follow-up	Restenosis rate, event-free survival and angina status	Multicentre (5) Scandinavia	Single or multivessel disease, stable or unstable angina, de novo 2.1-3.0 mm diameter, diameter stenosis >50%, multivessel 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 Glycoprotein IIb/IIIa inhibitors	BeStent (heparin coated with Hepamed)	PTCA 10/71(14.1%) St 3/74(4.1%)	In-hospital/1 mo, 6 months, 1 year
Participants with chronic total occlusion										
CORSICA(78, 238)	72 70			Multicentre France	CTO >15 days, stable and satisfactory results of PTCA		Aspirin Ticlopidine	Palmaz-Schatz	PTCA to St 3/70	
GISSOC(79)	56 54	MLD at follow-up	Restenosis, major ischemic events (death, MI, CABG, TVR; symptomatic status at follow-up; hemorrhagic events events	Multicentre (8) Italy	Absolute or functional occlusion (TIMI 0 or I), chest pain or inducible ischemia, suitable for CABG, >3mm diameter, <13mm long	AMI within 30 days, acute angina at rest 7 days, TO at site of prev PTCA, complex dissection, occlusions for <30 d, significant L main disease, torturous, side branch, CI to anticoagulation	Aspirin Heparin Warfarin	Palmaz-Schatz	PTCA1/54 (1.9%), S 0/56	In-hospital, 3,6, 9 months
HANCOCK(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; 1 of the following: TVR, MI or death <=2 years	Multicentre Germany	TIMI grade 0, for ≥1 wk estimated from clinical events or angiography, vessel >2.5 mm diameter (long lesions, diffuse disease, thrombus included)	AMI, saphenous CABG, severe vessel tortuosity, 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, S 1/55(1.8%) no stent implanted	In-hospital, 4 months

Study name	N * Stents PTCA	Primary outcome	Secondary outcomes	Location(s) & centres	Inclusion criteria	Exclusion criteria	Co-Therapies	Type of stent	Crossovers	Follow-up**
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 I), native artery, previously undilated lesion, reference diameter >2.5mm	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 months, 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 ≤2.7mm	Renal failure, recent CVA, CI to anticoagulation	Aspirin Heparin Ticlodipidine	Wiktor-GX	PTCA 7/43	6 months
STOP(84)	48 48	Restenosis/reocclusion at 6mo	Procedural success/complications; MACE (Death, recurrent AP, MI (Q-wave), PTCA, CABG); need for revascularisation during 6mo	Multicentre Israel	TO, native artery, reference diameter ≥2.75mm, successful PTCA (without stents)	Failed PTCA, need for stent for suboptimal PTCA	Aspirin Heparin Ticlodipidine	AVE Microstent (18-39mm length)	Zero	Clinical: 1mo; 3mo; 6mo; Angiography: 6mo (69/96 studied)
TOSCA(85)	202 208	Failure of sustained patency	TVR, Composite end point: any revascularisation, AMI, death at 1 yr, cardiovascular events at 1 yr, and change in global and regional left ventricular function.	Multicentre Canada, Japan, USA, New Zealand	Native artery, suitable for stenting, reference diameter >3mm, TIMI 0 or 1	<72 hrs from onset of new ST elevation, thrombus, previously revascularised occlusion, uncontrolled heart failure or shock, unsuitable for 6mo angiography, inability to cross occlusion with guidewire.	Aspirin Heparin Ticlopidine	Carmeda process heparin coated 15mm long PS-153 Palmaz-Schatz coronary stent.	PTCA-20/208 (9.6%). Stent group-8/202 (4.0%)	In hospital & 6 months.

* Numbers randomised Stents/PTCA; ** Proposed periods of follow-up as stated in source

A 312 (Non coated St: 157, Heparin-coated St: 155) [RH:] St 196 (follow-up angiogram on 157); Heparin St 197 (follow-up angiogram on 155); 155 PTCA 195 (follow-up on 155) [196+197+195=588; follow up on 467]

B 191 randomised (178 pts analysed); 192 randomised (176 pts analysed)

C St plus placebo 809; St plus Abciximab: 794; PTCA plus Abciximab: 796

Table 4E PTCA: Participant Characteristics

Study name	N umber assigned to Stents/PTCA	Age Mean (SD) years	Sex (% male)	ACS (%)	Diabetes (%)	Previous MI (%)
Non-specific CAD participants						
ADVANCE (36)	145 143	61.1 (9.2) 62.2 (9.6)	67.6 79.0	UA: 30.3 30.8	17.0	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 yrs	*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 (44)	42 42	59 (55-63) 57 (53-60) 95% CI	88.1 73.8	UA: 13 13	11	35.7 38.1
EPISTENT (45), (234)	809 St+ placebo 794 St+ 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 (47, 235)	39 38	61.3 (8) 56.9 (7)	76.9 84.2		11.7	
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 41.0
OCBAS(49, 236)	57 59	56.07+/-9 yrs 58.51 +/-11 yrs	86.0 83.1	UA: 78.9 81.4	10.3	22.3 20.3

Study name	N umber assigned to Stents/PTCA	Age Mean (SD) years	Sex (% male)	ACS (%)	Diabetes (%)	Previous MI (%)
RSSG (50)	191 [B] 192 [B]	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	207 203	60 (10) 60 (10)	83 73	UA: 47 48	15.5	37 36
STRESS II (54) 12mo data source: (223)	100 89					
VENESTENT (55)	78 72					
VERSACI (56)	60 60	56 +/-9 57+/-10	92 83	UA: 17 18	15.0	28.3 25.0
WIDEST (57)	146 154	59.2 +/-9.2 57.2+/-9.3,	76 76		9.0	
WIN (58)	229 235	62+/-11yr	*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 13.0
FRESCO(62)	75 75	62(12) 61(12)	75 80	-	12.5	8.0 8.0
GRAMI(63)	52 52	59 (+/-9) 58 (+/-11)	88 79	-	9	15 6
JACKSCH(64)	231 231			-		

Study name	N umber assigned to Stents/PTCA	Age Mean (SD) years	Sex (% male)	ACS (%)	Diabetes (%)	Previous MI (%)
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);(239)	452 448	59.2+/-12.6 60.9+/-12.3	74.8 74.8	-	15.0	10.8 11.8
STENTIM-2(69)	101 (91 1yr endpoint) 110 (99 1yr endpoint)	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, 237)	148 154				50.0	
COAST(72)	312 [A] 155 [A]					
ISAR-SMART(73, 86)	204 200	65(11.3) 66.5(11)	77.5 76	UA: 42.6 36.5	24.7	34.8 39.0
PARK(74)	60 60	60.2+/-7.5 61.5+/-8.4	61.7 65	UA: 18.3 20.0	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

Study name	N umber assigned to Stents/PTCA	Age Mean (SD) years	Sex (% male)	ACS (%)	Diabetes (%)	Previous MI (%)
Participants with chronic total occlusion						
CORSICA(78, 238)	72 70					
GISSOC(79)	56 54	58.3+/-6.8 57.0+/-9.3	86 83	UA: 7 11	10	54 83
HANCOCK(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 7.0	34.1	31.0 39.5
STOP(84)	48 48	59.3+/-10.1 58.9+/-10.9	85.4 83.3		25.0	58.3 70.8
TOSCA(85)	202 208	57.6 +/-10.4 57.7 +/-10	84 80		16.5	67 67

Table 4F PTCA: Outcomes

Study name		Event rate (%)	Mortality (%)	AMI (%)	Revasc. (%)	CABG (%)	PTCA (%)	BRR, 6 months* (%)
Non-specific CAD participants								
ADVANCE(36)	**Stent 145**	31 days 3.4 300 days: 23.4	31 days[A] 0 300 days[A] 0	31 days 2.8 300 days 2.8	31 days 0.7 300 days 17.9	31 days 0.0 300 day 2.8		9 months 27
	PTCA 143	31 days 7.0 300 days 23.1	31 days[A] 0 300 days[A] 0	31 days 4.9 300 days 4.9	31 days 1.4 300 days 14.7	31 days 0.7 300 days 3.5		9 months 42
AS(37)	**Stent 192**	14 days 2.1 6 months 16.7	14 days 0 180 days 0	14 days 1.0 180 days 1.6	TLR 14 days 1.0 6 months 15.1	0-14 days 1.04 15-180 days 0.53	14 days: 0.0 6 months 13.9	6 months 18.2
	PTCA 196	14 days 2.6 6 months 22.9	14 days 0 180 days 0	14 days 1.5 180 days 2.0	LR 4 days 1.0 months 20.9	0-14 days 0.5 15-180 days 1.6	14 days 0.5 16 months 9.2	6 months 24.9
BENESTENT I(38)	**Stent 259**	In hospital 6.9 7 months 20.1 1 year 23.4 5 years 34.4	In hospital 0.0 7 months 0.8 1 year 1.2 5 years 5.9	In hospital 3.4 7 months 4.2 1 year 5.0 5 years 8.6		*Urgent* In-hospital 1.9 7mo: 1.9 1 yr: 1.9 *Elective* In-hospital: 1.2 7 mo 3.1 1 yr 5.0 5 yr 9.8	In-hospital 0.4 7 month 10.0 1 year 10.0 5 year 9.8	6 months 22
	PTCA 257	In hospital 6.2 7 months 29.6 1 year 31.6 5 years 40.2	In hospital 0.0 7 months 10.4 1 year 0.8 5 years 3.1	In hospital 3.1 7 months 3.9 1 year 4.2 5 years 5.8		*Urgent* In-hospital 1.6 7 month 1.6 1 year 1.6 *Elective* In-hospital 0.0 7 month 2.3 1 year 3.5 5 year 8.2	In-hospital 1.2 7 months 20.6 1 year 20.6 5 year 21.9	6 months 32
BENESTENT II(39)	**Stent 413**	1 month 3.9 6 months 12.8 1 year 15.7	1 month 0.0 6 months 0.2 1 year 1.0	1 month 2.7 6 months 3.1 12 months 3.4		1 month 0.7 6 months 1.5 12 months 1.9	1 month: 0.5 6 months 8.0 12 months 9.4	6 months 16
	PTCA 410	1 month 5.1 6 months 19.3 1 year 22.4	1 month 0.2 6 months 0.5 1 year 1.0	1 month 3.2 6 months 3.7 1 year 4.4		1 month: 0.5 6 months 1.5 12 months 1.5	1 month 1.2 6 months 13.7 12 months 5.6	6 months 31

Study name		Event rate (%)	Mortality (%)	AMI (%)	Revasc. (%)	CABG (%)	PTCA (%)	BRR, 6 months* (%)
BEST(40)	**Stent 116**	6 months 16						6 months 18.1
	PTCA 119	6 months 18						6 months 16.8
BOSS(41)	**Stent 31**	-	In-hospital: 0.0	In hospital 0.0 8 months 0.0	In hospital 0 8 months 19	In-hospital 0.0		8 months 47
	PTCA 66	-		In hospital 0.0 8 months 0.0	In hospital 0 8 months 21			8 months 38
DEBATE II(42)	**Stent 97**	1 year 13.4	1 year 2.1	1 year 4.1	1 year [H] 7.2	1 year 0.0		
	PTCA 523	1 year 15.9	1 year 1.3	1 year 3.6	1 year [H] 10.9	1 year 1.1		
DESTINI(43)	**Stent 370**	1 month 3.8 12 months 17.8	1 month: 0.0 1 year 0.8	1 month 2.7 12 months 3.2	1 month 0.27 (TLR rpt PTCA) 12 months 14.9 (Any TLR)	1 month 0.8 Any CABG 3.5	1 month 0.3 12 months 14.9	
	PTCA 265	1 month 5.2 12 months 18.9	1 month 0.0 1 year 0.8	1 month 3.3 12 months 3.8	1 month 1.3 (TLR rpt PTCA) 12 months 15.6 (Any TLR)	1 month 0.5 Any CABG 2.1	1 month 1.4 12 months 15.6	
EECKHOUT(44)	**Stent 42**	In hospital 7 6 months 24	In hospital 0.0 6 months 0	In hospital 0 6 months 0		In hospital 2.4 6 months 4.8	6 months 11.9	6 months 37.5
	PTCA 42	In hospital 7 6 months 26	In hospital 0.0 6 months 0	In hospital 0 6 months 0		In hospital 0.0 6 months 2.4	6 months 16.7	6 months 35.0
EPISTENT(45)	**Stent 809 794**	30 days St-plc 10.8 St-abc 5.3 6 months St-plc 18.2 St-abc 12.8	30 days St-plc 0.6 St-abc 0.3 6 months St-plc 1.2 St-abc 0.5	30 days St-plc 9.6 St-abc 4.5 6 months St-plc 10.3 St-abc 5.2	30 days St-plc 2.1 St-plc 1.3 6 months St-plc 10.4 St-abc 8.6	30 days St-plc 1.1 St-abc 0.8	30 days St-plc 1.2 St-abc 0.6	
	PTCA 796	30 days 55/796 6 months 162/796	30 days 0.8 6 months 1.7	30 days 5.3 6 months 6.5	30 days 1.9 6 months 15	30 days 0.6	30 days 1.3	
FROST(46)	**Stent 125**	6 months 16.0	In hospital 0.0 6 month 2.4	In hospital 1.6 6 months 2.4	6 months 14.4	In-hospital 0.0	In-hospital 0.0	6 months 21.4

Study name		Event rate (%)		Mortality (%)		AMI (%)		Revasc. (%)		CABG (%)		PTCA (%)		BRR, 6 months* (%)	
	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(47, 235)	**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)
OCBAS(49, 236)	**Stent 57**	1 year	19.2	1 year	0.0	1 year Non-Q	0.0	1 year	17.5	1year	7.0	1 year	10.5	7.6+/-0.4mo St 56/57	19.2
	PTCA 59	1 year	16.9	1 year	1.7	1 year Non-Q	1.7	1 year	13.5	PTCA	3.4	1 year	0.2	7.6+/-0.4mo	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 month 4 years	0.4 1.3	6 month 4 year	8.9 10.7	6months	22
	PTCA 223	6 months	22	In hospital 6 months 4 years	1.3 1.9 2.4	In-hospital 6 month 4 year	1.8 2.8 2.8			6 month 4 years	1.9 2.4	6 month 4 year	17.1 22.3	6 months	37

Study name		Event rate (%)		Mortality (%)		AMI (%)		Revasc. (%)		CABG (%)		PTCA (%)		BRR, 6 months* (%)	
STRESS I(53)	**Stent 205**	240 days 1 year	7.3 24.9	14 days 1 years	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 years	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			310d (mean)	9.8						
	PTCA 112	In hospital 1 year	4.2 28.5	In hospital	2			310d (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
VERSACI(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 yr:	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

Study name		Event rate (%)	Mortality (%)	AMI (%)	Revasc. (%)	CABG (%)	PTCA (%)	BRR, 6 months* (%)
	PTCA 87	5 months 49.4						5 months 55
CADILLAC(60)	**Stent 512**	30 days 5.7 6 months 11.5	30 days 2.2 6 months 3.0	30d: 1.0 6mo (cumulative) 1.6	30 days 3.4 6 months 8.9			7months 23.7
	PTCA 518	30 days 8.3 6 months 20.0	30 days 2.5 6 months 4.5	30d: 0.8 6mo (cumulative) PTCA 1.8	30 days 6.0 6 months 16.9			7 months 36.5
ESCOBAR(61)	**Stent 112**	6 months 5 2 years 16	In hospital 1.8 6 months 1.8 2 years 2.7	In-hospital 0.9 6 months 0.9 2 years 0.9	6 months 4 2 years 13	2 year 6.3	2 years 7.1	
	PTCA 115	6 months 20 2 years 38	In hospital 2.6 6 months 2.6 2 years 3.5	In-hospital 4 6 months 7 2 years 9	6 months 17 2 year 34	2 years 15.7	2 years 18.3	
FRESCO(62)	**Stent 75**	6 months 9	30d (cardiac): 0 Other cardiac cause: 0 Non-cardiac 0 6mo (cardiac): 1 Other cardiac cause: 0 Non-cardiac 0	30d: 1.3 6 months 1.3	30 days 1.3 6months 6.7	30 day 0.0 6 month 0.0	30 days 1.3 6 months 6.7	Angiographic restenosis or reocclusion at 1 and 6 mo reported
	PTCA 75	6 months 28	30d (cardiac): 0 Other cardiac cause: 4 Non-cardiac 0 6mo (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 day 0.0 6 month 2.7	30 days 12.0 6 months 22.7	
GRAMI(63)	**Stent 52**	In hospital 3.8 1 year 16	In hospital [E] 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 [E] 7.6	In hospital 7.6	1 year 20.8	*Emergency* In-hospital: 1.9 *Elective* 1.9	In hospital 5.7	
JACKSCH(64)	**Stent 231**		In hospital 1.3	In-hospital: 1.3		Intra-hospital 3/231	In-hospital 1.7	4.6+/-1.3mo: 23+/-6
	PTCA 231		In hospital 2.2	In hospital 3.5		Intra-hospital 9/231	In-hospital 6.1	4.6+/-1.3mo: 42+/-9

Study name		Event rate (%)	Mortality (%)	AMI (%)	Revasc. (%)	CABG (%)	PTCA (%)	BRR, 6 months* (%)
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			6months 9/50 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 11/30 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 [F] 9.1	30d: 0 Long-term: 2.3	30d: 0.0 Long-term: 15.9			9/44 24 (Angiography performed on St 37/44 alive)
	PTCA 44	30 days 5/44 700 days 19/44	30 days 2.3 710 days [F] 18.2	30d: 2.3 Long-term: 4/44	30d: 9.0 Long-term: 34.1			20/44 61 (Angiography performed on PTCA 33/36 alive)
STENT PAMI(68)	**Stent 452**	1 month 4.6 6 months 12.6	1month 3.5 6 months 4.2	1month 0.4 6 months 2.4	1mo: 1.3 6mo: 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	1mo: 3.8 6mo: 17.0			6.5 months 33.5
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 month 2.0 1 years 3.0	In Hospital 4.0 6 month 4.0 1 years 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	6mo: 25.3
	PTCA 110	*Event-free survival* In hospital 94.5 6 months 72.7 1 year 71.7	In Hospital 0.0 6 month 0.9 1 year 1.8	In Hospital 3.6 6 month 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 mo 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-mo TLR: 13	In-hospital: 0.0 6mo 0.6	In-hospital re-PTCA: 1.5 6 mo: 12.5	6 mo 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-mo TLR 24.6	In-hospital 0.5 6mo 1.2	In-hospital re-PTCA: 1.6 6mo: 23.4	6 mo 47

Study name		Event rate (%)	Mortality (%)	AMI (%)	Revasc. (%)	CABG (%)	PTCA (%)	BRR, 6 months* (%)
CHIVAS(71, 237)	**Stent 97**	-			6 months 10.3			6 months 29
	PTCA 89	-			6 months 19.2			6 months 44
COAST(72)	**Stent 312**	6 months [D] 11.2			6 mo: Noncoated St: 12 Heparin-coated St: 13			6 months 27 (Angiographic stenosis)
	PTCA 155	6 months [D] 15.4			6 mo 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 month 20.1	30 days 0.5 7 months 3.4	30 days re-PTCA 0.5 7 months 16.7	6mo: 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	6mo: 37.4
PARK(74)	**Stent 60**		In hospital 0.0 16 months [G] 0.0	In-hospital Non-Q: 1.7 *Nonfatal MI:* 15.9+/-5.7mo: 0.0	In hospital 0.0 16 months [G] 3.3	In hospital: 0.0		6mo: 35.7
	PTCA 60		In hospital 0.0 16 months [G] 0.0	In-hospital Non-Q: 3.3 *Nonfatal MI:* 15.9+/-5.7mo: 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
SISA(76)	**Stent 169**	In hospital: 3.0 6 months 18.3	In hospital 0.0 6 months 0.6	In-hospital: 1.8 6 mo: 4.1	6 month 17.8	In-hospital 0.6 6 mo: 3.0	In-hospital re-PTCA: 0.6	6 months: 28
	PTCA 182	In hospital 7.1 6 months 22.0	In hospital 0.0 6 months 0.5	In-hospital: 4.9 6 mo: 8.2	6 months 20.3	In-hospital 0.5 6 mo: 1.6	In-hospital re-PTCA: 2.7	6 months 32.9

Study name		Event rate (%)	Mortality (%)	AMI (%)	Revasc. (%)	CABG (%)	PTCA (%)	BRR, 6 months* (%)
SISCA(77)	**Stent 74**	6 months: 9.5 1 year 9.5	1 month 0.0 6 months 0.0 1 year 1.4	1 mo: PTCA 0/71, S 1/74; 1 -6 months: PTCA 1/71, S 0/74	TVR 1 month: 0.0 6 months: 0.0 12 months 0.0 TLR 1 month: 1.4 6 months: 9.5 12 months 9.5	6 months 1.4		179+-35 days: 9.7
	PTCA 71	6 months 23.9 1 year 23.9	1 month 0.0 6 months 1.4 1 year 1.4	1 mo: PTCA 0/71, S 1/74; 1 -6 months: PTCA 1/71, S 0/74	TVR 1 month: 0.0 6 months: 5.6 12 months 7.0 TLR 1 month: 1.4 6 months: 18.3 12 months 18.3	6 months 2.8		179+-35 days: 18.8
Participants with chronic total occlusion								
CORSICA(78, 238)	**Stent 72**	1 month 0 6 months 22.2 EVENT FREE 6mo: reported as PTCA 64.3% (does not tally with MACCE rate), St 77.8% (consistent with MACCE rate)			TLR 6mo: 22.2			
	PTCA 70	1 month 17.1 6 months 27.1			TLR 6mo: 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(80)	**Stent 30**	6 months: 13	In-hospital 0.0 6 months 0.0	6 months: 0.0		In-hospital: 0.0 6 months: 3.3	6 months: Re-PTCA: 10	6 months overall: 28
	PTCA 30	6 months 30	In-hospital 0.0 6 months 3.3	6 months: 3.3		In-hospital: 0.0 6 months: 6.7	6 months: Re-PTCA: 17	6 months overall: 28
SARECCO(81)	**Stent 55**	-	14 days: 0.0 4 months Over 8 months 1.8	14 days 1.8 8 months 1.8		14 days 0.0 4 months 0.0	4 months re-PTCA 24	4 months 26

Study name		Event rate (%)	Mortality (%)	AMI (%)	Revasc. (%)	CABG (%)	PTCA (%)	BRR, 6 months* (%)
	PTCA 55	-	14 days 0.0 4 months 0.0 8 months 5.4	14 days 0.0 8 months 3.6		14 days 0.0 4 months 0.0	4 months re-PTCA: 55	4 months 62
SICCO(82)	**Stent 58**	-	14 days 0.0 6 months 0.0	14 days 1.7 8 months 1.7	14 days TVR: 3.4 <8 months TVR: 20.7	14 days 1.7 4 months 8.6 > 8 months 8.6	<8 months 17.2 > 8 months 17.2	6 months: 31.6
	PTCA 59	-	14 days 0.0 6 months 0.0	14 days 0.0 8 months 0.0	14 days TVR: 3.4 <8 months TVR: 38.9	14 days 0.0 4 months 5.0 > 8 months 6.7	<8 months 33.8 > 8 months 42.3	6 months: 73.2
SPACTO(83)	**Stent 40**	6 months[B] 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[B] 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[C] 19/48	6months 0.0	6mo: 0.0	TLR (PTCA+CABG): 6 mo: 25	6 months 4.2	6 months 20.8	6mo: 42.1
	PTCA 48	6 months[C] 29/48	6 months 0.0	6 months 2.1	TLR (PTCA+CABG): 6 mo: 41.7	6 months 2.1	6 months 39.6	6mo: 70.9
TOSCA(85)	**Stent 202**	6 months 23.3 Any major event 15.8	Short-term 0.0 6 months 0.5	6 months 11.9	6 months 8.4	"Surgical revascularisation" PTCA target vessel- 1.4 Any vessel- 1.9	"Percutaneous revascularisation" Target vessel 6.9 Any vessel 12.4	6 months 55
	PTCA 208	6 months 23.6 Any major event 23.1	Short-term 0.0 6 months 0.5	6 months 3.8	6 months 15.4	"Surgical revascularisation" ST target vessel- 17 (8.4%) , any vessel- 28 (13.9%).	"Percutaneous revascularisation" PTCA- target vessel 30 (14.4%), any vessel 41 (19.7%).	6 months 70

A Specified as cardiac death
B rate includes new, stable angina
C rate includes angina
D Based on numbers undergoing angiographic follow-up
E In hospital & procedural mortality
F Long-term (710+/-282 days), all deaths
G 15.9+/-5.7mo (PTCA 15.7+/-5.6, St 16.2+/-5.8 mo)
H Interpreted TVR
G EPISTENT included three intervention arms. PTCA plus Abciximab (Abc), Stent plus Abciximab and Stent plus placebo. Only the Stent- Abciximab arm is compared with PTCA- Abciximab in the meta-analysis.

4 Appendix: Details of survival trend meta-modelling

Meta-model structure

In most revascularisation studies, the highest mortality risk occurs in the immediate post-operative 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; and
- 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 post-procedural 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 1997). In particular increasing risks are in line with expectations, since most patients are aged 60 or over, and actuarial risk accelerates steeply over the age of 65. 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 bi-partite survival function was fitted to the published results from each of the 3 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 1, and the achieved fits can be examined in Figures 1 and 2 (both Tables and Figures are positioned at the end of this Appendix)

Combined Meta-model Trendlines

The models for each type of treatment were combined into a single meta-model 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 bi-partite metamodel. Thus the resulting model combines data from all three trials for the first 12 months (1318 patients for PCI and 1325 patientsfor CABG), then uses data from SoS and ERACI II for the second and third years (713 patients for PCI and 725 patientsfor CABG). The resulting metamodels are shown in Figure 3 together with the combined weighted data from the three trials. The model parameters are displayed in Table 2.

It is not possible to calculate definitive confidence intervals 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 this 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. But, due to this uncertainty we have conservatively limited projection of the meta-models to a maximum of 5 years from the initial procedure.

Table 1 *Bi-partite 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

Table 2 *Bi-partite survival meta-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 relative to combined data**
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 1 *Survival models for SOS trial*

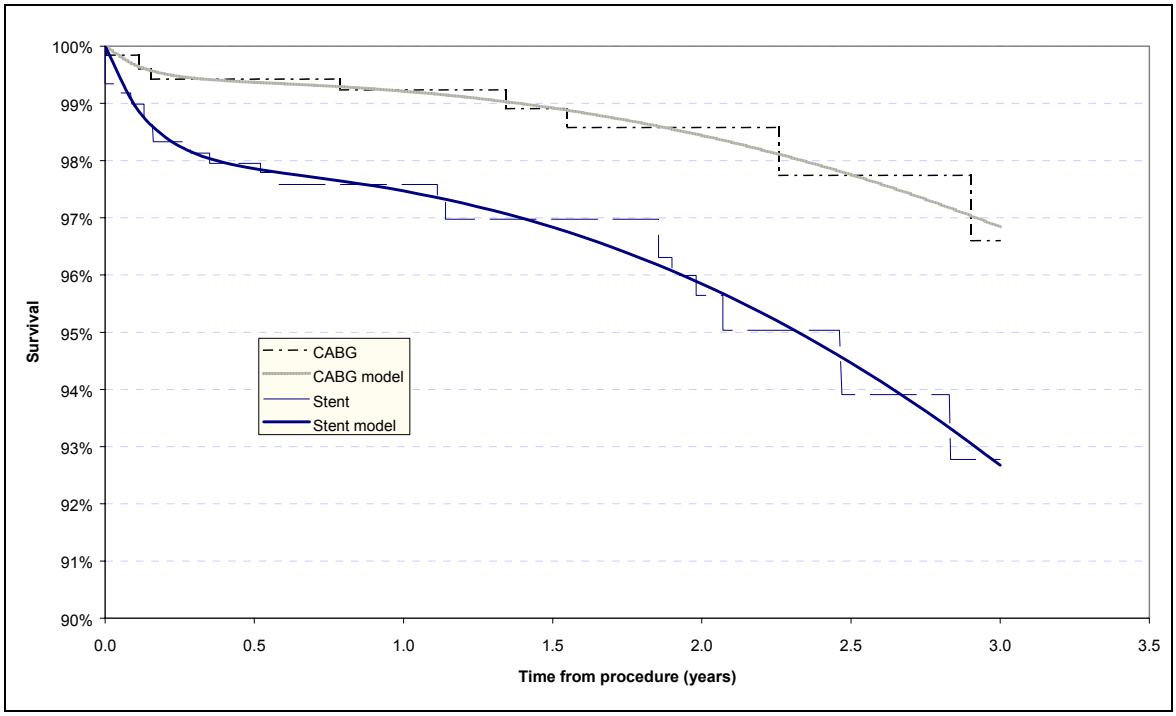


Figure 2 *Survival models for ERACI II trial*

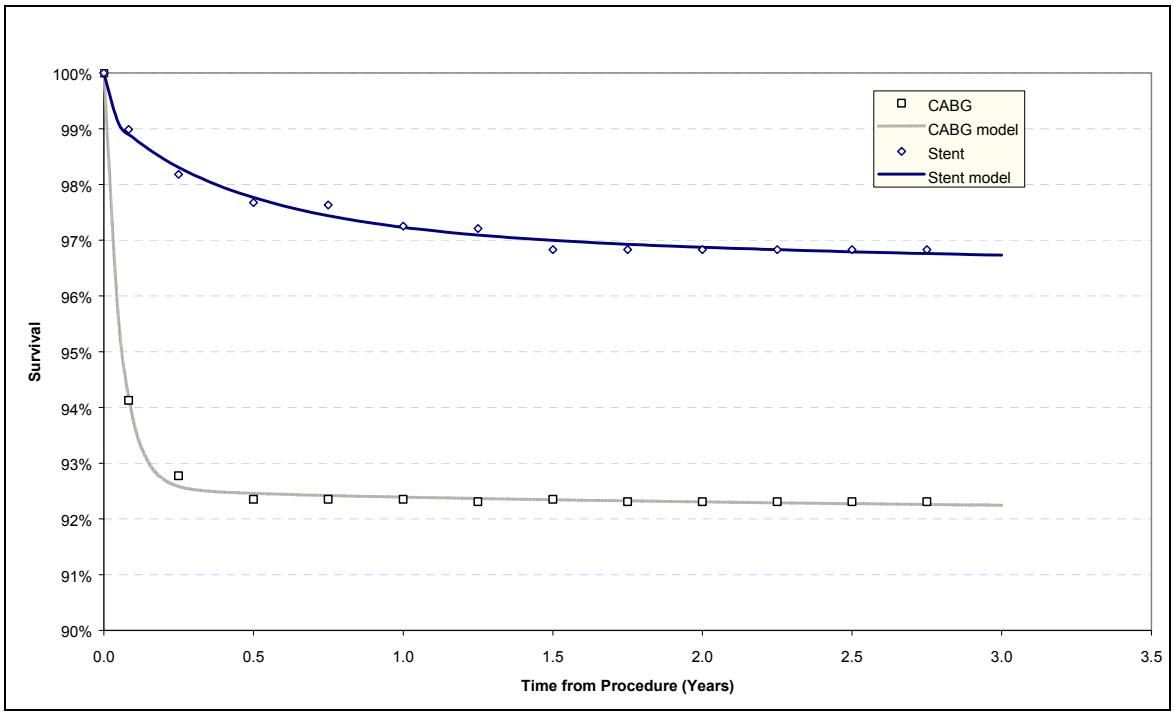


Figure 3 Survival models for ARTS trial

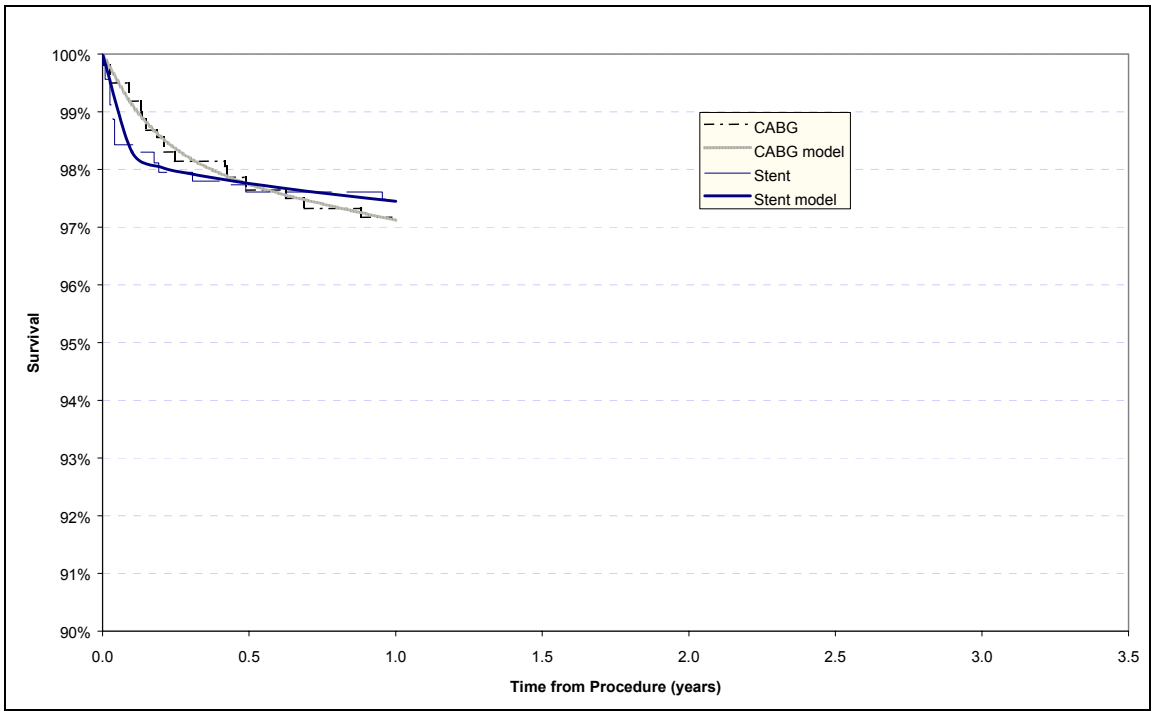
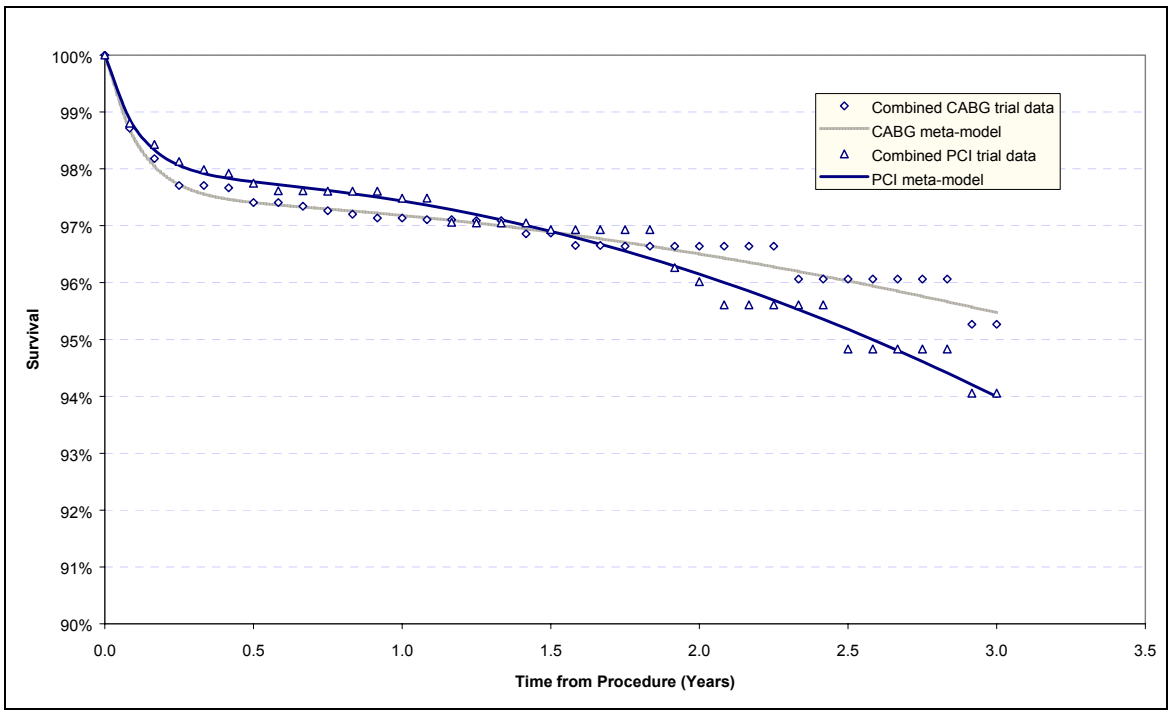


Figure.4 Survival meta-models combining data from SOS, ERACI II & ARTS trials



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Outcomes: Reports involving outcomes, which were not considered in this review.
SvS: Stent versus Stent
ISR: In-stent Restenosis
DS: Direct stenting

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