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Drug-eluting stents: a systematic review and economic evaluation

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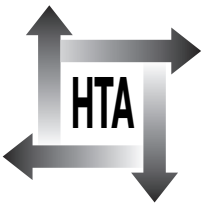

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Drug-eluting stents: a systematic review and economic evaluation

RA Hill,[1] A Boland,[1] R Dickson,[1*] Y Dündar,[1] A Haycox,[2] C McLeod,[1] R Mujica Mota,[1] T Walley[1] and A Bagust[2]

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Abstract

Drug-eluting stents: a systematic review and economic evaluation

RA Hill,[1] A Boland,[1] R Dickson,[1*] Y Dündar,[1] A Haycox,[2] C McLeod,[1] R Mujica Mota,[1] T Walley[1] and A Bagust[2]

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Objectives: To assess the effectiveness and cost-effectiveness of the use of drug-eluting coronary artery stents in percutaneous coronary intervention (PCI) in patients with coronary artery disease.

Data sources: Bibliographic databases, including MEDLINE, EMBASE and the Cochrane Library, were searched from December 2002 to August 2005. Hand-searching was also done.

Review methods: A systematic literature review of effectiveness was conducted focusing primarily on randomised controlled trials (RCTs). Full economic evaluations that compared two or more options and considered both costs and consequences were eligible for inclusion in the economics review. A critique of manufacturer submissions to the National Institute for Health and Clinical Excellence and an economic evaluation in the form of cost–utility analysis were also carried out.

Results: In the 17 RCTs of drug-eluting stents (DES) versus bare metal stents (BMS), no statistically significant differences in mortality or myocardial infarction (MI) were identified up to 3 years. Significant reductions in repeat revascularisations were determined for DES compared with BMS [for example, at 1 year: target lesion revascularisation (TLR) relative risk 0.24; 95% confidence interval (CI) 0.19 to 0.31; and target vessel revascularisation (TVR) relative risk 0.43; 95% CI 0.33 to 0.55]. This estimated benefit appears to be stable from 1 to 3 years. Binary restenosis and late luminal loss also favoured DES. In the eight RCTs of DES versus DES, no statistically significant differences in mortality or MI were detected between DES designs. In meta-analyses of TLR, TVR and composite event rate, marginal improvement in efficacy of Cypher™ over Taxus™ was observed. These results await confirmation beyond 1 year and differences in study design may have influenced reporting of outcomes. Ten full economic evaluations were included in the review and the balance of evidence indicated that DES are more cost-effective in higher risk patients. The review of submitted models confirmed the view that DES may be cost-effective only under very limited circumstances when realistic assumptions and data values were used. In the cost–utility analysis of DES versus BMS, the use of DES appears to reduce the rate of repeat revascularisations; benefit estimates used in the economic assessment are defined as 'broad' (i.e. cases involving any TLR/TVR irrespective of any other lesions/vessels undergoing revascularisation) and 'narrow' (i.e. cases involving TLR/TVR only). The incremental benefit to the patient is therefore described as the loss of quality-adjusted life-years (QALYs) avoided by not having to undergo a repeat revascularisation. Univariate sensitivity analysis and extreme values analysis indicate that the price premium, numbers of stents used in the index procedure and absolute risk reduction in repeat interventions most significantly influence the cost-effectiveness ratios. Sensitivity analyses also permit a range of values for efficacy and effectiveness to be considered for individual designs of DES. The cost-effectiveness results reveal that, all patients considered together, the calculated cost per QALY ratios are high (£183,000–562,000) and outside the normal range of acceptability. Cost-effectiveness is only achieved for those non-elective patients who have undergone a previous coronary artery bypass graft and have small vessels. 'Real-world' data show that patient numbers in this latter group are very small (one in 3100 of all patients treated with PCI).

Conclusions: The conclusions of the assessment are that the use of DES would be best targeted at the subgroups of patients with the highest risks of requiring reintervention, and could be considered cost-effective in only a small percentage of such patents. This is similar to the conclusion of our previous assessment. Trials of DES compared with new generation BMS and with DES would be useful, as would further evaluation of newer BMS in combination with drug administration.

Contents

Glossary and list of abbreviations vii
Note x

Executive summary xi

1 Assessment aims 1

2 Background 3
Introduction 3
Description of health problem 3
Current treatments 3
Current service provision 4
Review considerations – clinical 5
Review considerations – economic 8

3 Methods 11
Identification of evidence: clinical effectiveness and cost-effectiveness 11
Methods for reviewing clinical effectiveness 12
Methods for reviewing cost-effectiveness 13

4 Review of clinical effects: DES versus BMS and overview of new DES 15
Introduction 15
Drug-eluting stents versus non-drug-eluting BMS: RCT-based evidence 16
Drug-eluting stents without RCT evidence 26
Drug-eluting stents of different designs: evidence from registries 30
Discussion 30
Summary 31

5 Review of clinical effects: comparison between DES 33
RCT-based evidence 33
Discussion 38
Summary 40

6 Review of published economic evaluations 41
Introduction 41
Economic impact of DES for coronary artery disease 41
Review of the economic literature 41
Commentary 54

7 Critical review of manufacturer economic submissions 55
Submitted models 55
General methodological issues 55
Critical appraisal of Boston model 62
Critical appraisal of Cordis model 62
Critical appraisal of Medtronic model 63
Critical appraisal of KiWiMed model 65
List prices 65
Summary of critical review of submitted models 66

8 Economic evaluation: DES versus BMS 67
Introduction 67
Clinical outcomes for economic assessment 67
Converting efficacy to effectiveness 67
Economic assessment methods 72
Data sources and parameter values 74
Cost-effectiveness results 79
Sensitivity analysis 79
Discussion 89
Addendum 92

9 Budget impact assessment 129
Data sources 129
Budget impact and opportunity cost analysis 129
Discussion 129

10 Conclusions and discussion 131
Key conclusions 131
Developments in DES 131
Robustness of results 133
Research recommendations 134

Acknowledgements 135

References 137

Appendix 1 Search strategy – clinical and economic evidence 145

Appendix 2 Quality assessment – clinical and economic evidence 147

Appendix 3 Clinical review tables – DES versus BMS 149

Appendix 4 Clinical review tables – DES versus DES 179

Appendix 5 Clinical review tables – DES without RCT evidence 187

Appendix 6 DES registries 193

Appendix 7 Details of included or excluded references 197

Appendix 8 Supplement to addendum 201

Health Technology Assessment reports published to date 223

Health Technology Assessment Programme 239

Glossary and list of abbreviations

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

Glossary

Abciximab A glycoprotein IIB/IIIa antagonist, used to inhibit blood clotting, widely used during stenting procedure.

ABT-578 Sirolimus analogue, with anti-proliferate properties. Also referred to as zotarolimus.

Acute coronary syndrome 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.

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

Bare metal stent Comparator to drug-eluting stent, without drug-releasing properties. It is possible that within some DES versus BMS trials the comparator 'BMS' surface is not totally bare and 'featureless'. Some experimental BMS may be coated in drug carrier material (without drug) or have specially adapted surfaces or structures that would be used to hold drug in the active device.

Clopidogrel A drug that inhibits platelet function.

Creatinine kinase A cardiac enzyme release during myocardial infarction.

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

Direct stenting Stent implantation without predilation.

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

Elective Non-emergency treatment.

Effective list price Maximum price charged in the UK without discounts (obtained through a survey of NHS purchasers conducted by NHS PASA).

HODaR Commercial health outcomes database with data on 25,000 patients (Cardiff and Vale NHS Hospitals Trust, Wales) intended to be representative of the UK population as a whole. Routine clinical data are supplemented with quality of life, cost, drug and resource use information.

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

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

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

continued

Glossary *continued*

Neointimal hyperplasia Excessive growth of smooth muscle tissue.

Price premium Additional price for one technology over another (often the additional price for a new product compared with the established market leader).

QCA Three-dimensional imaging technology utilising X-rays to visualise arteries.

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

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/osis blood clot – SAT, LT, stent thrombosis.

Ticlopidine Drug that inhibits platelet function.

List of abbreviations

ACC	American College of Cardiology
ACCP	American College of Chest Physicians
ACS	acute coronary syndrome
AETMIS	Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé
AHA	American Heart Association
AMI	acute myocardial infarction
ARR	absolute risk reduction
ASP	average selling price
BCIA	British Cardiovascular Industry Association
BCIS	British Cardiac Intervention Society
BHF	British Heart Foundation
BMS	bare metal stent(s)
BRR	binary restenosis rate
CABG	coronary artery bypass graft(ing)
CAD	coronary artery disease
CCSC	Canadian Cardiovascular Society Classification
CEA	cost-effectiveness analysis
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CK	creatinine kinase
CK-MB	fraction of creatinine kinase
CPI	consumer price index
CRD	Centre for Reviews and Dissemination
CTC	Cardiothoracic Centre
CTO	chronic total occlusion

continued

List of abbreviations *continued*

CVA	cerebrovascular accident (stroke)
DES	drug-eluting stent(s)
DM	diabetes mellitus
ECG	electrocardiogram
EF	ejection fraction
EVA	extreme values analysis
EVPI	experted value of perfect information
FDA	Food and Drug Administration
GI	gastrointestinal
HES	Hospital Episode Statistics
HODaR	Health Outcomes Data Repository
ICER	incremental cost-effectiveness ratio
IHD	ischaemic heart disease
ISR	in-stent restenosis
ITT	intention-to-treat
IVUS	intravascular ultrasound
LCx	left circumflex
LL	late loss
LM	left main coronary artery
LRiG	Liverpool Reviews and Implementation Group
LVEF	left ventricular ejection fraction
MACCE	major adverse coronary and cerebrovascular event
MACE	major adverse coronary event
MI	myocardial infarction
MLD	minimal lumen diameter of coronary artery
NICE	National Institute for Health and Clinical Excellence
NSF	National Service Framework
OR	odds ratio
PASA	Purchasing and Supply Agency
PCI	percutaneous coronary intervention (includes PTCA, stenting, atherectomy, excimer laser, rotablator)
PES	paclitaxel-eluting stent(s)
PSA	probabilistic sensitivity analysis
PTCA	percutaneous transluminal coronary angioplasty (the term PCI now commonly used in place of PTCA)
QALY	quality-adjusted life-year
QCA	quantitative coronary angiography
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
RRA	repeat revascularisation avoided
SA	sensitivity analysis
SES	sirolimus-eluting stent(s)
STEMI	ST-segment MI
SVG	saphenous vein graft
TAR	Technology Assessment Report
TIMI	thrombolysis in myocardial infarction
TLR	target lesion revascularisation
TVF	target vessel failure
TVR	target vessel revascularisation
WMD	weighted mean difference

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

Note

This report includes information from studies relating to two drug-eluting stents that at the time of initial submission had not yet received CE Marking. Data from these stents have not been used in the pooled estimates of effects. However, general information regarding these devices is included in the report.

Following submission of the report, the NICE Appraisal Committee (for whom the report was commissioned) requested additional analyses to support its considerations. These analyses were submitted in the form of an addendum and addendum supplement and are presented at the end of Chapter 8 of this monograph. The addendum includes a point-by-point conclusion and a summary of the additional analysis completed for the Committee. The addendum supports the economic evaluation presented in Chapter 8 and conclusions presented in Chapter 10.

Executive summary

Objectives

The objectives were to assess the effectiveness and cost-effectiveness of the use of drug-eluting coronary artery stents in percutaneous coronary intervention (PCI) in patients with coronary artery disease (CAD).

Specifically, the clinical review compares the use of:

- drug-eluting stents (DES) versus non-drug-eluting bare metal stents (BMS)
- drug-eluting stents of different design (DES versus DES).

A technology assessment was completed in 2003, early in the introduction of DES. Continued, rapid development of DES suggests that it is appropriate to explore the current evidence base on DES in order to inform the development of National Institute for Health and Clinical Excellence (NICE) guidance for the NHS in England and Wales.

Background

PCI with the use of stents has become an established means for treating CAD. Although PCI is considered effective, re-narrowing (restenosis) in and around implanted stents can occur, which may require repeat treatment. Drugs released from DES aim to reduce the need for repeat intervention by limiting the processes underlying restenosis.

Methods

The assessment was conducted according to accepted procedures for conducting and reporting systematic reviews and economic evaluations.

Evidence on clinical effectiveness and cost-effectiveness of DES was identified using a comprehensive search strategy of bibliographic databases from December 2002 to August 2005 and included the Cochrane Library, EMBASE and MEDLINE and also handsearching activities. Unpublished evidence was considered for inclusion in the assessment.

Assessment of health economics evidence included review of published economic evaluations, critique of manufacturer submissions to NICE and our own economic evaluation in the form of cost–utility analysis.

Inclusion criteria

Primarily, randomised controlled trials (RCTs) comparing DES with BMS or DES with DES were considered for inclusion, but other designs of study were considered where no RCT evidence was available. Non-controlled clinical studies of DES were only considered in the absence of data from comparative studies.

The assessment was restricted to adults with CAD, undergoing treatment of native and intervention naïve vessel(s) by PCI with the use of stents. Only studies of DES awarded CE Marking [indicating European Union (EU) conformity and authorisation to market within the EU] at or around the time of this assessment were eligible for inclusion. Eleven distinct DES designs were considered: AXXION™, CoStar™, Cypher™, Cypher Select™, Dexamet™, Endeavor™, Janis™, Liberté™, Taxus™, Xience V™ and Yukon™.

Clinical outcomes included death, myocardial infarction (MI), target lesion revascularisation (TLR), target vessel revascularisation (TVR), composite event rate (major adverse cardiac event and/or target vessel revascularisation), binary restenosis rate and late luminal loss.

Full economic evaluations that compared two or more options and considered both costs and consequences were eligible for inclusion in the economics review.

Results

Clinical findings

A total of 25 RCTs were included in the review of clinical effects. These included 17 RCTs of DES versus BMS and eight RCTs of DES versus DES.

For some DES, no data from RCTs were available (in some cases, RCTs were in progress).

Handsearching and utilisation of unpublished data made an important contribution to the review.

Meta-analysis of RCTs of DES versus BMS

All 17 RCTs identified were included for at least one outcome in the meta-analysis. A range of eluting agents were studied: paclitaxel (n = 11), sirolimus (n = 5), everolimus (n = 1) and ABT-578 (n = 1). One study included three arms, comparing paclitaxel, sirolimus and non-eluting stents. Follow-up extended to 3 years for paclitaxel and sirolimus-eluting stents.

No statistically significant differences in mortality or MI were identified up to 3 years. Significant reductions in repeat revascularisations were determined for DES compared with BMS (for example, at 1 year: TLR relative risk 0.24; 95% confidence interval (CI) 0.19 to 0.31; and TVR relative risk 0.43; 95% CI 0.33 to 0.55). This estimated benefit appears to be stable from 1 to 3 years. Binary restenosis and late luminal loss also favoured DES.

DES without RCTs

For six of the 11 DES designs there were no RCTs available for assessment. Reporting of data after completion of this assessment may assist in evaluating these DES in the near future.

Meta-analysis of RCTs of DES versus DES

All eight RCTs identified were included for at least one outcome in the meta-analysis. Six of these compared Taxus (paclitaxel-eluting) and Cypher (sirolimus-eluting) directly. Follow-up was limited to 9 months, except for a single study.

No statistically significant differences in mortality or MI were detected between DES designs. In meta-analyses of TLR, TVR and composite event rate, marginal improvement in efficacy of Cypher over Taxus was observed. These results await confirmation beyond 1 year and differences in study design may have influenced reporting of outcomes.

Economic evaluation

Ten full economic evaluations were included in the review. In general, the balance of evidence indicated that DES are more cost-effective in higher risk patients.

In the review of submitted models, when more realistic assumptions and data values were used they confirmed the view that DES may be cost-effective only under very limited circumstances.

A cost–utility analysis of DES versus BMS was undertaken from the perspective of the NHS. For the purposes of our base case evaluation, it was assumed that all DES are clinically equivalent. The costs and benefits of DES versus BMS were identified, measured and valued.

Compared with BMS, the use of DES appears to reduce the rate of repeat revascularisations; benefit estimates used in the economic assessment are defined as 'broad' (i.e. cases involving **any** TLR/TVR irrespective of any other lesions/vessels undergoing revascularisation) and 'narrow' (i.e. cases involving TLR/TVR only). The incremental benefit to the patient is therefore described as the loss of quality-adjusted life-years (QALYs) avoided by not having to undergo a repeat revascularisation.

Univariate sensitivity analysis and extreme values analysis indicate that the price premium, numbers of stents used in the index procedure and absolute risk reduction in repeat interventions most significantly influence the cost-effectiveness ratios. Sensitivity analyses also permit a range of values for efficacy and effectiveness to be considered for individual designs of DES.

The cost-effectiveness results reveal that, all patients considered together, the calculated cost per QALY ratios are high (£183,000–562,000) and outside the normal range of acceptability. Cost-effectiveness is only achieved for those non-elective patients who have undergone a previous coronary artery bypass graft and have small vessels. 'Real-world' data show that patient numbers in this latter group are very small (one in 3100 of all patients treated with PCI).

Additional research and analysis were undertaken to support the NICE Appraisal Committee. Information on evidence sources considered for the report and range of *post hoc* sensitivity analyses are presented within the full monograph.

Conclusions

The conclusions of the assessment are that the use of DES would be best targeted at the subgroups of patients with the highest risks of requiring reintervention, and could be considered cost-effective in only a small percentage of such patents. This is similar to the conclusion of our previous assessment.

Implications for the NHS

Assessment of budgetary impact of DES on the NHS involved investigation of purchase cost and trends in DES usage. On the basis of assumptions in the NHS Tariff Prices and 50% use of DES, the annual volume of DES purchased by the NHS in England (assuming 5% wastage) is estimated to be between 35,000 and 42,000 units, costing an additional £21–25 million.

If anecdotal evidence of 70% current DES usage is accepted, the estimated total cost of purchasing DES rises to £30–36 million; if 100% DES usage is assumed the projected cost would be around £42–51 million.

Recommendations for further research

This assessment was able to utilise long-term follow-up from trials of DES, head-to-head studies of DES versus DES and more real-world data from registries and the NHS. However, further research would be useful in the following areas:

- trials of DES compared with new generation BMS
- trials of DES compared with DES
- further evaluation of newer BMS in combination with drug administration.

Chapter 1

Assessment aims

The aims were to assess the effectiveness and cost-effectiveness of the use of drug-eluting coronary artery stents in percutaneous coronary intervention (PCI) in patients with coronary artery disease (CAD).

Specifically, the clinical review compares the use of:

- drug-eluting stent (DES) versus non-drug-eluting 'bare metal' stent (BMS)
- drug-eluting stents of different design (DES versus DES).

The economic analysis compares the cost-effectiveness of:

- drug-eluting stent versus non-drug-eluting BMS
- drug-eluting stents of different design (DES versus DES) – as far as data permit.

Only adults with CAD, undergoing treatment of native and intervention naïve vessel(s) by PCI with the use of stent(s) were considered within this assessment.

This review has been commissioned[1] to update the previously conducted health technology assessment of coronary artery stents.[2]

Chapter 2
Background

Introduction

A previous Technology Assessment Report (TAR), which included comparison of DES with BMS, was prepared for the then National Institute for Clinical Excellence (NICE) through 2002 and 2003.[2] NICE subsequently issued guidance and, as the use of DES was seen to be a rapidly evolving technology, an early date was set to review the guidance.[3]

Description of health problem

Disease

CAD results in narrowing or occlusion of the coronary arteries that supply blood to the heart muscle. This is usually due to atherosclerosis leading to plaque formation over many years.

Risk factors related to the development of atherosclerosis are well recognised.[4] The disease is more common in individuals with higher serum cholesterol, high blood pressure, diabetes or those who smoke. Genetic and environmental factors may also contribute.

Manifestation of CAD may be acute or chronic. Acute coronary syndrome (ACS) occurs when there is either a rupture or sudden expansion of an atherosclerotic plaque leading to sudden partial or complete obstruction of the coronary vessel. The term ACS includes classical acute myocardial infarction (AMI) (with ECG changes of ST segment elevation and depression, Q-wave), non-ST elevation MI and unstable angina.[5] More sensitive markers of myocardial damage show that these features of ACS are not as distinct as previously thought and even carry similar long-term prognoses. Angina pectoris (angina) is a chronic symptom manifesting as chest pain typically related to exertion, which is usually due to stable partial obstruction (stenosis) of a coronary artery.

Epidemiology

Routine data provided by the British Heart Foundation (BHF)[4,6] indicate that even though rates of ischaemic heart disease (IHD, almost synonymous with CAD) are decreasing, it remains the most common cause of mortality in the UK. Mortality rates vary by gender and account for around one in five deaths in men and one in six for women. IHD caused around 114,000 deaths in the UK in 2003; many of these (46,000) are considered premature deaths (i.e. in people under the age of 65 years).

Mortality rates from IHD have been decreasing in the UK over the past three decades. However, this decrease has not been consistent across age groups, gender or socio-economic class. A more rapid reduction has been seen in younger age groups (45–54 years), in men and in higher socio-economic groups. The rate of decline in the UK has been slower than that in other developed countries (e.g. Denmark, Norway, Australia).[4]

IHD is also responsible for extensive morbidity in the UK population. Statistics indicate that approximately 259,500 individuals experience an AMI annually (142,000 in men and 117,500 in women) and, in addition, approximately 341,500 new cases of angina are reported annually (181,000 in men and 160,500 in women). Prevalence data indicate that approximately 1.2 million people or about 2% of the general population in the UK suffer from angina.

Current treatments

Stable angina is not in itself a life-threatening disease, so treatment focuses on controlling symptoms to improve quality of life (QoL) and reducing the long-term risks of progression to AMI or mortality.

Treatments may include:

1. medical management
2. interventional procedures:
   (a) surgical intervention [coronary artery bypass grafting (CABG)]
   (b) PCI.

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.

CABG

CABG involves surgically 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 in emergency circumstances (e.g. failed PCI). CABG has been shown to increase life expectancy in patients with multi-vessel or diffuse disease or disease of the left main stem artery. A recent meta-analysis up to 8 years indicated a trend towards improved survival for patients undergoing CABG versus percutaneous transluminal coronary angioplasty (PTCA), but with the only statistically significant benefit reported at 5 years.[7]

Changes in the intra- and postoperative management of patients have improved patient outcomes following CABG.[5] New techniques including minimally invasive surgery which does not require the use of total bypass and has shortened surgical time, is currently being introduced and evaluated.[8,9] The outcomes of CABG versus use of coronary artery stents was the topic of a previous review[2] and will not be dealt with further in this report.

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

PCI

Balloon angioplasty [also called percutaneous coronary intervention (PCI)] was introduced in the late 1970s. An uninflated balloon carried on a catheter is threaded into the coronary artery through a peripheral artery; the balloon is inflated to the site of coronary artery stenosis, thereby opening up the blocked artery. Although effective for treating coronary artery stenosis, many (20–50%) patients develop restenosis within 6 months of treatment, requiring further intervention.[2] The reasons for this have been explained through three mechanisms: elastic recoil of the vessel wall, remodelling of the vessel and proliferation of the innermost layer of the vessel wall (neointimal proliferation – growth of cellular matrix in and around a stent and a reaction to tissue injury).

Stents were developed to minimise restenosis. A stent is a mesh tube loaded over an angioplasty balloon. When the balloon inflates, the stent expands like a scaffold to hold the vessel open, and is left behind after the balloon is deflated and withdrawn. Several large randomised controlled trials (RCTs) have shown that the use of a BMS during angioplasty safely reduces restenosis rates compared with balloon angioplasty alone.[2] Although stents resolved the problems of recoil and vessel remodelling, they did not resolve the third element, that of neointimal proliferation.

A range of methods have been researched to try to reduce this reaction. These include the use of systemic immunosuppressants, redesign of stent structure and coating of stents (i.e. heparin coating). Available stent types and stent platforms (catheter and balloon) have been modified regularly.

Since restenosis was correlated with the amount of inflammation present at the time of angioplasty, a more promising approach was the development of stents coated with a drug or drug–polymer mixture that allows the drug to elute slowly into the surrounding tissues. The drugs to be eluted were either immune suppressants (e.g. sirolimus) or antimitotics (e.g. paclitaxel) that might reduce neointimal proliferation either by suppressing inflammation or by decreasing local cell division. The drug achieves therapeutic concentrations in local tissues only and may not be detectable systemically, thereby avoiding systemic adverse effects.

Among the drugs considered in the previous report[2] were sirolimus and paclitaxel, used in two types of stent (Cypher and Taxus DES, respectively). Sirolimus is a macrolide immunosuppressant used systemically to treat renal transplant rejection. It halts the cell cycle and so limits proliferation of smooth muscle. Sirolimus acts by binding to a receptor protein and inhibiting a regulatory enzyme which in turn shuts down the normal cell cycle. Paclitaxel also inhibits the cell cycle and has been used as an anti-proliferative drug in the treatment of breast, lung and ovarian cancer. A range of other drug and stent combinations have been developed and where these DES have progressed to being awarded CE Marking they are considered in this report.

Current service provision

Previous evidence

The conclusions of the previous assessment[2] were as follows:

Clinical

"There is no evidence of a difference in mortality between patients receiving DES and those treated with bare metal stents at 1 year. A reduction in event rate at 9 and 12 months was found in patients treated with DES. This event rate is primarily made up of increased revascularisation rates in patients treated with bare metal stents. Two-year outcome data from one study indicate that this benefit of DES continues over the longer term."

Cost-effectiveness

"DES may not generally be considered a cost-effective alternative to bare metal stenting in single-vessel disease by policy makers as substantially higher costs are involved with a very small outcome benefit.

"DES might be considered cost-effective if the additional cost (compared with ordinary stents) was substantially reduced, the outcome benefits from the use of DES were much improved, and/or its use were targeted on the subgroups of patients with the highest risks of requiring reintervention. Long-term clinical studies are needed that focus on significant outcomes such as mortality".

Previous guidance

NICE guidance[3] recommended:

"1.2 It is recommended that when considering the use of a bare-metal stent (BMS) or a drug eluting stent (DES) the decision should be based on the anatomy of the target vessel for stenting and the symptoms and mode of presentation of the disease.

"1.3 The use of either a Cypher (sirolimus-eluting) or Taxus (paclitaxel-eluting) stent is recommended in PCI for patients with symptomatic coronary artery disease (CAD), in whom the target artery is less than 3 mm in calibre (internal diameter) or the lesion is longer than 15 mm. This guidance for the use of DES does not apply to people who have had an MI in the preceding 24 hours, or for whom there is angiographic evidence of thrombus in the target artery.

"1.4 If more than one artery is considered clinically appropriate for stenting then the considerations in Section 1.3 apply to each artery.

"1.5 This guidance specifically relates to the present clinical indications for PCI and excludes conditions (such as many cases of stable angina) that are adequately managed with standard drug therapy."

NICE estimated that on the basis of these recommendations, approximately 30% of patients might receive DES rather than BMS.[3]

Data systems

In the UK, no system currently exists to capture total numbers of PCI and CABG procedures. The British Cardiac Intervention Society (BCIS) 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 100 NHS Trusts and institutions in the country, together with associated overall costs [e.g. Health Outcomes Data Repository (HODaR)].

Diagnostic and intervention centres

Data for BCIS audit of 2003[10] indicate an increase in the number of intervention and diagnostic centres (NHS and private) across the UK. Of these 114 centres, 68 provide diagnostic services only whereas 73 are considered to be intervention sites (of which 56 are NHS centres and 17 are privately run). The increase in facilities has been accompanied by an increase in the number of interventional cardiologists, by 16% in 2003, bringing the total number of interventional cardiologists working in UK centres to 362.[11]

PCI rates

There has been a continual increase in the number and rate per million of PCIs carried out over time, and also an increase in the proportion of procedures that include the use of stents. Rates for 1991 to 2003 are shown in *Table 1*.

Evolution and use of DES

At the time of the previous NICE guidance, there were three DES licensed for use in the UK. There are currently eight DES licensed for use in the UK with more expected (see *Table 2*).

Data for DES use were not available prior to 2002. The BCIS now reports that although the use of DES varies, DES were used in 18.3% of PCI procedures in England and 28.6% in Wales in 2003.[11] Given incremental increases in PCI procedures, it may be that utilisation rates are currently much higher then this now. Evidence on this is presented later.

Review considerations – clinical

Comparability of interventions

Assumptions about the comparability of interventions are critical issues when making decisions regarding the appropriateness of combining data. A number of these are discussed here.

The first is the assumption that all BMS are similar, and likewise that all DES are similar except

TABLE 1 *PCI rates in UK 1991–2003*

Year	Centres	Procedures total	Procedures per million	Change (%)	Stent use (%) (of PCI)[a]
1991	52	9,933	174	–	–
1992	52	11,575	203	16.5	<5
1993	53	12,937	227	11.8	~5
1994	54	14,624	256	13.0	~15
1995	54	17,344	304	18.6	~25
1996	53	20,511	359	18.1	~45
1997	58	22,902	402	11.7	~60
1998	61	24,899	437	8.7	~70
1999	63	28,133	494	13.0	~80
2000	66	33,652 (25,610[b], 922[c])	590	20.0	84
2001	64	38,992 (30,785[b], 886[c])	664	12.5	86
2002	64	44,913 (35,306[b], 1131[c])	759	14.3	89.4
2003	73 (61[b] 2[c])	53,261 (42,234[b], 1308[c])	894	17.8	92.1

Data from BCIS.[10]
[a] Abstracted from bar chart, % assumed to be calculated from numbers of PCI procedures as presented in column 3, above.
[b] Data reported for England (one English centre not reporting?)
[c] Data reported for Wales.

TABLE 2 *DES CE Marking awards*

Existing DES	Manufacturer	Drug/carrier	CE Marking
Cypher™	Cordis	Sirolimus-ES	✓
Taxus™	Boston Scientific	Paclitaxel-ES	✓
Dexamet™	Abbott/Biocompatibles	Dexamethasone-ES	✓
New DES[a]	**Manufacturer**	**Drug/carrier**	**CE Marking**
AXXION™	Biosensors	Paclitaxel-ES (non-polymeric)	✓ July 2005
CoStar™	Biotronik/Conor	Paclitaxel-ES (non-polymeric)	Pending
Cypher Select™	Cordis	Sirolimus-ES	✓
Endeavor™	Medtronic	ABT-578-ES	✓ July 2005
Janus™	Sorin	Tacrolimus-ES	✓
Liberté™	Boston Scientific	Paclitaxel-ES	✓ September 2005
Xience V™	Guidant	Everolimus-ES	Pending
Yukon™	Translumina/KiWiMed[b]	Variable, to date studied with sirolimus (non-polymeric)	✓

[a] As of 14 October 2005.
[b] Although Translumina is the manufacturer of the Yukon DES, KiWiMed is the UK distributor and named Appraisal Consultee.

in the drug delivered. This is clearly an oversimplification – a number of different stents of different designs, both BMS and DES, are available and more will be developed over time. Different materials may also be used in stents. The drug release technologies in DES may differ, affecting the rate of drug elution or biocompatibility, for instance.

Second is the issue of the stent system 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 third assumption is related to the insertion techniques used for stent placement. These include such things as provisional stenting (where stents are placed only in the case of suboptimal expansion with angioplasty balloon alone), predilation and direct stenting (simultaneous expansion of vessel and placement of the stent). All of these could be factors that affect the outcome of the procedure and the long-term success of the procedure.

Patients receive antiplatelet therapy during and after the stenting procedure. Continued evaluation of concomitant therapy has taken place since publication of the previous guidance. The European Society of Cardiology has recently published guidelines for PCI which include recommendations for the use of such therapies.[12] These recommendations are for 6 months of intense therapy after a BMS, but 12 months after a DES (based on practice within the relevant clinical trials rather than on firm comparative evidence on this point).

In this review, data related to stents with similar drugs are combined without consideration of stent design or insertion system. Stenting techniques are not considered and the use of adjunct therapies is reported, but not considered in the meta-analysis.

Outcomes

Key considerations

A key factor to measuring clinical effectiveness relates to the outcome measure considered. In the case of CHD, the key outcomes to be measured are mortality and morbidity. A number of recent meta-analyses have failed to show an effect of DES in relation to mortality.[2,13–17] Similarly, these reviews have been unable to demonstrate a difference in rates of AMI in patients treated with DES versus those treated with BMS.

The primary end-point for most PCI studies and reviews[2,13–18] has been either the major adverse coronary event (MACE) (a composite outcome including mortality, AMI or revascularisation) or simply repeat revascularisation rates. There are substantial variations in the interpretation of these. Death may be reported as all death, or only cardiac death, or may not be specified. There is a further problem with the use of such composite end-points in that they may obscure real and important differences in outcomes. For instance, repeat revascularisations are reported as events in the same way and with the same weight as a clinical MI or death. In practice, given the rarity of coronary death or MI, most MACE events are elective revascularisation procedures.

Revascularisation may be reported as target lesion revascularisation (TLR), target vessel revascularisation (TVR), revascularisation by particular technique (PCI or CABG) or it may not be specified. There are also limited data on total revascularisation; for example, a patient may have another procedure carried out in a vessel other than the one originally treated. This reporting is appropriate for assessment of the efficacy of a specific stent, but data related to any revascularisation are needed when assessing the practical effectiveness and costs of patient treatment.

Revascularisation rates, however, can be affected by the study protocol: 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 protocol planned angiographic follow-up may be an indicator for revascularisation procedures (angiographically driven revascularisation). Therefore, in those studies that involve a routine 6–9-month angiographic follow-up of patients, there may be an excess of 'events' around 6–9 months, and these events may not be truly clinically relevant.

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 has been provided by the US Food and Drug Administration (FDA) and states that;

> "The procedure was considered clinically driven if the patient had a positive functional study, ischaemic ECG changes at rest in a distribution consistent with the target vessel, or ischaemic symptoms and an in-lesion diameter stenosis greater than 50 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."

Even by this definition, 'clinically driven events' can be based on angiographic indices alone. The definition assumes that with a stenosis greater than 70%, even if the patient is not symptomatic at the time, it is highly likely that they will soon 'tip over' into a symptomatic state and require a repeat revascularisation and therefore should be treated.

Trial reports therefore demonstrate a higher rate of revascularisation than is seen in clinical practice, where it is recurrence of angina that prompts reinvestigation and reintervention. Unfortunately, few trials have documented the recurrence of angina as an end-point and hence there are problems in translating these trials into common practice; this is considered in depth later as it has a major effect on the cost effectiveness of DES.

Length of follow-up

Animal studies suggest that restenosis, if it is going to occur, will happen within the first 6 months after intervention. Most DES actively release their intended dose of drug over a period of 14–45 days. On this basis, therefore, any benefit of DES in preventing neointimal proliferation will be seen by 6 months, and hence the justification of this time-point for protocol angiography. An implication of this is that any clinical benefit of the DES will be seen up to perhaps 12 months, but after this the clinical course will be determined by the natural history of the patient's disease.Most trials have reported up to 1 year, but some have reported longer outcomes.

Quality of life

Current trial reports are very limited and include inconsistent data related to QoL. However, such data are crucial to the economic analysis. New sources of UK-specific QoL data have become available since the last review and are used in this review.[19,20]

Data availability

Results of systematic reviews are contingent on the availability and quality of the data. Our earlier review was complicated by the speed and manner of appearance of data related to DES. The issues related to this data presentation have been addressed in a recent methodological review.[21]

DES are a rapidly evolving technology, and presentation of new trial data occurs almost monthly. This is usually made available first on specialised websites, often as conference presentation slides. Obviously this form of presentation is not peer reviewed or validated, and it provides constant challenges to reviewers as they endeavour to cross-check data and assess the quality of the included studies.

Review considerations – economic

At the time the previous TAR was prepared, it was evident that there was little independent evidence available to address some important issues confronting the Appraisal Committee. Virtually all of the clinical trial results were obtained from industry-sponsored trials where the selected patient populations were not representative of the mix of conditions presenting in normal UK practice. Moreover, the measures of efficacy generally reported were often not directly translatable into terms relevant to treatment decisions in the consulting room. The previous guidance attempted to reflect an understanding of the limited body of evidence then to hand, but key questions remained unresolved which could potentially alter the balance of costs and benefits in either direction.

In this current assessment, we have attempted to supply some of this want of evidence from several sources, and undertaken a revised economic evaluation taking the new information into account. Four questions of particular importance are addressed.

How big is the healthcare problem?

Perhaps the single most important factor in determining the cost-effectiveness of DES is the magnitude of the risk patients face of needing a repeat intervention. Most published trials comparing DES with BMS have studied selected populations, with an expected high risk of early symptom recurrence. Moreover, the design of many trials, mandating early angiographic follow-up, is known to prompt higher rates of reintervention. Thus the risk of repeat revascularisation in a normal unselected population cannot be estimated from trial findings. In the previous report, we employed summary results from a local cardiac registry, which showed that the underlying risk was considerably lower than anecdotally reported. In this report, we have been able to identify several other registries or unselected case sequence studies from the UK and other countries, which broadly confirm the event rates we previously used for economic evaluation.

Which patients are most likely to benefit?

In the previous report, we were unable to address this question systematically, but did carry out an exploratory reanalysis of a limited dataset of individual patient results from one published trial. This suggested that some of the widely accepted factors (in particular diabetes) assumed to predispose patients to a high risk of restenosis following PCI may not be supported by the evidence. Subsequently, we were able to carry out a thorough analysis of a full battery of potential risk factors in order to derive new risk factor models for repeat revascularisation after PCI. We have used these as the basis for comparing cost-effectiveness between patient subgroups with different inherent levels of risk.

How effective are DES in avoiding repeat revascularisation?

A major limitation of the analysis carried out for the previous report was that the evidence base for

efficacy (the reduction in revascularisations due to DES) related almost exclusively to single lesions treated, and in some cases reported only reinterventions related to the study lesion. Since many patients have more than one lesion requiring initial treatment, and many subsequently need another revascularisation to non-index lesions/vessels, this is inadequate evidence for considering general use of DES in normal practice.

To address this problem, we conducted a further study of audit data, looking at the number and location of stented lesions in those patients having a second PCI compared with the sites of the index stented lesions. This has provided important information to suggest the proportion of restenotic lesions which may not have given rise to reintervention were DES to be used initially, and for which patients the use of DES would not have prevented the recurrence of their symptoms and their representation for further treatment. Inevitably, this new information leads to a downgrading of the single-lesion RCT estimates of DES efficacy when we consider the likely effectiveness of treating a normal UK case mix.

What influences the cost of using DES?

In our previous report, we identified two factors contributing to the large extra cost per patient of using DES: the additional cost per stent of using a DES compared with an uncoated stent (the 'price premium') and the number of stents implanted per patient. In order to establish the current UK position on the acquisition costs of all types of stent, a market survey of NHS purchasers was conducted, on our behalf, by the NHS Purchasing and Supply Agency (PASA). Purchasers anonymously shared information which enabled us to confirm the range of prices being paid, and to estimate size of the price premium for DES.

The number of DES used per patient is of central importance to the calculation of cost-effectiveness results and to the estimation of the impact of DES use on NHS budgets. Using audit data, we have explored alternative treatment strategies (including mixing DES and BMS in the same patient) aimed at containing the additional costs of DES, but concluded, as before, that costs would be best constrained (and cost-effectiveness assured) if DES use is defined in terms of the number of stents expected to be required to treat a patient.

Chapter 3
Methods

Identification of evidence: clinical effectiveness and cost-effectiveness

Search strategy

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

No limitation was included on study type and therefore identification of clinical effectiveness and cost-effectiveness data was combined within the electronic searches.

The following electronic databases were searched (YD) for relevant published literature for the period from December 2002 to August 2005. Searching dated from the limit of the searches in our previous assessment.[2]

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- DARE (Database of Abstracts of Reviews of Effectiveness)
- EMBASE
- HTA database
- ISI Web of Science – Proceedings (Index to Scientific and Technical Proceedings)
- ISI Web of Science – Science Citation Index Expanded
- MEDLINE
- NHS EED (NHS Economic Evaluation Database)

In addition, MEDLINE (using the PubMed interface) was searched again later in the assessment (spanning 1 March to 3 August 2005) in order to identify publications that might not have been indexed at the time of the main electronic searching.

Details of the search strategies and the number of references retrieved for each search are provided in Appendix 1.

Reference lists of included studies and device manufacturer submissions were searched to identify other relevant studies of clinical effectiveness, costs or cost-effectiveness.

Handsearching of cardiology conference abstracts was conducted. The latest conference proceedings for the following meetings were obtained for the purposes of handsearching:

- American College of Cardiology
- American Heart Association
- British Cardiac Society
- European Society of Cardiology
- Transcatheter Cardiovascular Therapeutics.

Internet resources were examined for information on clinical studies and cost data. These included the following:

- Cardiovascular Revascularization Therapies (www.crtonline.com)
- The heart.org (www.theheart.org)
- Transcatheter Cardiovascular Therapeutics (www.tctmd.com).

All the references were exported to an EndNote bibliographic database (Thomson ISI, ResearchSoft, Carlsbad, CA, USA).

Selection of clinical effectiveness and cost-effectiveness evidence

The records identified in the electronic searches were assessed for inclusion in two stages. First, pairs of reviewers independently scanned all the titles and abstracts and identified the potentially relevant articles to be retrieved (RD–RH, CMcL–RH). Any differences in selection choice were discussed between the pairs and consensus was reached in all cases. Full text reports of these selected papers were then obtained and assessed independently by at least two reviewers for inclusion (RD, RH, CMcL, RM). The inclusion/exclusion assessment of each reviewer was recorded on a pretested, standardised form. Data on levels of agreement between reviewers are available from the Assessment Group upon request.

Further details of the inclusion/exclusion criteria applied to clinical effectiveness and cost-effectiveness evidence are provided in the next two sections of this chapter.

Results of the study selection are presented in Chapters 4–6. A table summarising the selection and inclusion of studies is provided in Appendix 1.

Methods for reviewing clinical effectiveness

Inclusion criteria

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

Study design

- RCTs; non-RCTs (such as prospective registries); non-controlled studies (except case reports of single patient experience).

Population

- Adults with CAD, undergoing treatment of native and intervention naïve vessel(s) by PCI with the use of stent(s).

Intervention

- Drug-eluting coronary artery stents which were expected to be available for use by the NHS close to the time of the assessment.

The scope of this assessment does not consider all stent designs, but rather only those DES awarded CE Marking before 30 September 2005 or those which have their CE Marking pending. Assessment was limited to specific, named DES: Cypher™, Cordis; Dexamet™, Abbott; Taxus™, Boston Scientific; CoStar™, Biotronik/Conor; Cypher Select™, Cordis; Endeavor™, Medtronic; Janis/us™, Sorin; Liberté™, Boston Scientific; Xience V™, Guidant; Yukon™, Translumina/KiWiMed).

Comparators

- DES versus non-drug-eluting BMS
- DES of different design (i.e. DES versus DES).

Outcomes

Studies were included in the clinical review if they reported primary data on one or more of the following outcomes:

- combined event rate [MACE, target vessel failure (TVF)] or event-free survival
- mortality (all cause, cardiac)
- AMI
- TLR
- TVR
- repeat revascularisation (PCI/stent, other PCI or CABG)
- adverse effects (thrombosis, malabsorption; incomplete stent apposition; device failures/defects)
- angiographic binary restenosis
- late loss
- health-related QoL.

Exclusion criteria: clinical effectiveness

Studies were excluded based on the following criteria:

1. Single case reports.
2. RCTs:
   (a) that provided only unplanned, interim findings
   (b) that provided data on only a subgroup of the enrolled patients
   (c) that were continuing to recruit patients
   (d) where patient numbers treated with specific intervention (i.e. a particular type of stent) could not be determined.
3. Studies of:
   (a) treatment of in-stent restenosis
   (b) treatment of saphenous vein grafts.
4. Comparison of:
   (a) DES with other PCI interventions (e.g. atherectomy, rotablators, brachytherapy)
   (b) DES with surgery
   (c) variations of drug-loading among single DES types ('brands').

Data extraction: clinical effectiveness

Data extraction for the review of clinical effectiveness was carried out by two reviewers (RH, RD). Data were independently abstracted by one reviewer into pretested data extraction forms created within the Access database application (Microsoft) and then checked for accuracy by a second reviewer.

Data presented from multiple reports of single trials were extracted on to a single data extraction record.

Quality assessment: clinical effectiveness

Two of three reviewers (RH and RD, RH and YD) independently evaluated the included studies for methodological quality (utilising forms created in Access) using criteria based on Centre for Reviews and Dissemination (CRD), Report 4[22] (see Appendix 2). Any discrepancies in quality grading were resolved through discussion.

Methods for reviewing cost-effectiveness

Inclusion and exclusion criteria: cost-effectiveness

Using explicit, predetermined criteria, two reviewers (CMcL and RH) independently identified reports for inclusion in the review of published economic evaluations and as a source of cost or related data to inform development of the Assessment Group's own economic evaluation and budget impact assessment.

Any disagreements in inclusion for the cost-effectiveness assessment were resolved through discussion.

Inclusion criteria: cost-effectiveness

Study design

The study included full economic evaluations that compared two or more options and considered both costs and consequences, including:

- cost-effectiveness analysis (CEA)
- cost–utility analysis
- cost–benefit analysis.

Population

The population comprised adults with CAD, undergoing treatment of native and intervention naïve vessel(s) by PCI with the use of stent(s).

Intervention

Intervention was drug-eluting coronary artery stents which were expected to be available for use by the NHS close to the time of the assessment, as for the review of clinical effects.

Comparators

- DES versus non-drug-eluting BMS
- DES of different design.

Health outcomes in an economic framework

- quality-adjusted life-years (QALYs)
- disease-specific measures, such as MACE, repeat revascularisations avoided, MACE-free survival, TLR and TVR.

Exclusion criteria: cost-effectiveness

Reports were excluded from the review of economic evaluations if:

- The main source of clinical efficacy data was not explicitly stated.
- No attempt to synthesise costs and benefits was conducted.
- The source was a letter, editorial, review, commentary or methodological paper.

Chapter 4

Review of clinical effects: DES versus BMS and overview of new DES

Introduction

Scope of clinical review

This chapter presents the results of the systematic review of published and unpublished evidence on the clinical effects of DES. The review focused on identifying RCTs, but other designs (such as good-quality registries of DES use) were considered where it was felt necessary to supplement RCT-based evidence.

This assessment continues from a previous health technology assessment of coronary artery stents completed by our Assessment Group in 2003.[2] The current assessment considers 'existing' DES, which were reviewed previously (Cypher™, Cordis; Dexamet™, Abbott; Taxus™, Boston), and subsequent, 'new' DES designs which were expected to be available for use by the NHS close to the time of this assessment (AXXION™, Biosensors; CoStar™, Biotronik, Conor; Cypher Select™, Cordis; Endeavor™, Medtronic; Janus™, Sorin; Liberté ™, Boston Scientific; Xience V™, Guidant; Yukon™, Translumina KiWiMed). The scope of this assessment does not therefore consider all stent designs, but rather specific DES awarded CE Marking before 30 September 2005 or whose CE Marking was pending.

The clinical review considered studies of DES compared with BMS (DES versus BMS), but also compares the effects of different DES designs, where results of head-to-head (DES versus DES) studies were available.

Selection of evidence

Evidence identified from bibliographic databases

Searches of bibliographic databases yielded 1533 non-duplicate records, which were screened for inclusion in the clinical and economics reviews. Of the records screened, 395 were selected for detailed consideration of the full text.

The sources of evidence identified are detailed in *Table 3*.

For the clinical review of DES versus BMS, 17 RCTs (reported in 58 records) were identified. For the clinical review of DES versus DES, eight RCTs (reported in 11 records) were identified. For assessment of new and existing DES outside RCTs (such as non-RCTs or prospective registries), 27 records were identified.

Of the 310 records excluded from the review, 122 were background papers, six were relevant to the economics (but excluded from the clinical review), seven were systematic reviews and eight were determined to be non-systematic reviews of DES. Further details of excluded citations are presented in Appendix 7.

Of the records selected for further consideration, eight[23–30] were unable to be obtained within the timescale of this review.

Evidence from manufacturer submissions to NICE

Data on DES were also provided within manufacturer submissions to NICE. These submissions provide supportive information on the clinical effectiveness of particular manufacturers' DES. The submissions can provide the opportunity for the Assessment Group to review up-to-date data, in confidence, before they have been made publicly available.

The breadth and detail provided within these submissions varied. Some provided detailed trial reports (as appendices to their submission), or quoted publicly available data including grey literature sources such as conference abstracts and conference presentations (on their own or other manufacturers' devices) or pooled data, providing aggregated analyses. For some devices, even the datasets provided by manufacturers were incomplete, as some trials are still ongoing or in early stages.

The absence of complete datasets, suitably detailed reports and presentation of aggregate data limited the depth of assessment of the manufacturer submissions.

Much of the grey literature sources were retrieved independently by the Assessment Group and considered for data abstraction, as appropriate.

Given that both manufacturer and Assessment Group review of some studies relies on unpublished sources of data, caution is necessary when considering outcomes abstracted from non-peer-reviewed sources.

Among manufacturers, differences in study design, participant make-up and reporting of data make comparison of different DES difficult.

Handsearching and unpublished sources of evidence

As can be seen from the last two columns in *Table 3*, handsearching activities (including review of submissions to NICE) to identify non-indexed and unpublished data sources make a significant contribution to the review of such a new and evolving health technology. In all, 16 of 37 studies included in the review were initially identified through handsearching, rather than being retrieved in electronic databases such as EMBASE or MEDLINE.

Drug-eluting stents versus non-drug-eluting BMS: RCT-based evidence

Included studies

Selection of included studies

As described in the preceding section, comparative studies of selected designs of DES were considered for inclusion in the review. For the meta-analysis, only RCTs comparing DES with BMS were eligible for inclusion.

Description of included studies

Seventeen RCTs comparing DES with BMS[31–82] met the inclusion criteria for the meta-analysis. All 17 are included for at least one outcome in the meta-analysis.

Study characteristics

Ten of the studies compared Cypher sirolimus-eluting stents with BMS (C-SIRIUS,[54,83] DIABETES,[55,68] E-SIRIUS,[56,57,83] Li,[79] Pache,[53] RAVEL,[31,58–66, 84, 85] SCANDSTENT,[67] SES-SMART,[69,70] SIRIUS,[66,71–78] STRATEGY.[80,81] Four studies compared the Taxus (slow release) paclitaxel-eluting stent with BMS (TAXUS I,[34–36] TAXUS II,[37–39] TAXUS IV,[40–51,86,87] TAXUS V.[52,88] One study, BASKET,[82] compared both Cypher and Taxus DES with a newer BMS in a three-arm study. Endeavor ABT-578 (zotarolimus)-eluting stents were compared with BMS in ENDEAVOR II[89] and Xience V everolimus-eluting stents with BMS in SPIRIT FIRST.[32,33]

Of the 17 RCTs, all but three were multicentre. The BASKET[82] study was conducted in a single centre in Switzerland and STRATEGY[80] involved a single referral centre in Italy. The study by Li and colleagues,[79] which was only available as a conference abstract, did not describe the number of centres involved in the trial. Study size ranged from 60 (SPIRIT FIRST[32]) and 61 (TAXUS I[34]) to studies of over 1000 participants, with up to 1058 in SIRIUS, 1172 in TAXUS V, 1197 in ENDEAVOR II and 1314 in TAXUS IV.

Most studies were restricted to treatment of single lesions (11 of the 17 RCTs: ENDEAVOR II, C-SIRIUS, E-SIRIUS, SES-SMART, SIRIUS, SPIRIT FIRST, RAVEL, TAXUS I, TAXIS II, TAXUS IV, TAXUS V). The Pache,[53] Li[79] and STRATEGY[80] studies did not detail this feature of their sample groups. Eight of the studies specifically reported evidence of symptoms of CAD, silent ischaemia or significant stenosis (>50%) of the target vessel (C-SIRIUS, DIABETES, E-SIRIUS, Pache, RAVEL, SES-SMART, SIRIUS). The STRATEGY study exclusively enrolled patients with acute ST-segment MI (STEMI), whereas the BASKET study accepted all patients presenting for PCI, and as a result 21% of its participants had acute STEMI.

The studies covered a range of vessel diameters and lesion lengths. Vessel diameters up to 4.0 mm were included in BASKET and TAXUS V, and were reported to be as narrow as 2.25 mm for TAXUS V and ENDEAVOR II. As a number of studies describe only inclusion criteria based on maximum vessel diameter, the lower range of vessel 'calibre' is uncertain for these studies. Lesion length ranged from as short as 10 mm in TAXUS II and TAXUS V to up to 33 mm in SES-SMART, C-SIRIUS and E-SIRIUS. Again, these data are incompletely reported for a number of studies.

All the included studies permitted recruitment of people with diabetes. The DIABETES[55] study included only people with diabetes requiring pharmacological treatment.

A key exclusion for all but three studies was acute or evolving MI. The BASKET[82] study permitted the participation of people with ACS (including STEMI) and STRATEGY[80] focused on STEMI patients. In the abstract available for the Li study,[79] exclusion criteria were not presented. The presence of unprotected (no patent vessel or graft below) left main coronary artery excluded patients from many trials, as did severe calcification or tortuousity, total occlusion,

TABLE 3 *Sources of evidence identified by search strategy for each DES/included study*

DES	Studies	Principal source types			First identified in	
		Full publications	**Abstract/ conference**	**Submission**	**Electronic searches**	**Handsearch submissions**
Cypher	BASKET	✓ (recent)	–	–	–	✓
	CORPAL	–	✓	–	–	✓
	C-SIRIUS	✓	–	–	✓	–
	DIABETES	–	✓	–	✓	–
	DOMINO	–	–	✓	–	✓
	E-SIRIUS	✓	–	–	✓	–
	ISAR-DIABETES	✓ (recent)	✓	–	–	✓
	Li	–	✓	–	✓	–
	Pache	✓	–	–	✓	–
	RAVEL	✓	–	–	✓	–
	REALITY	–	✓	–	–	✓
	SCANDSTENT	–	✓	–	–	✓
	SES-SMART	✓	–	–	✓	–
	SIRIUS	✓	–	–	✓	–
	SIRTAX	✓ (recent)	✓	–	–	✓
	STRATEGY	✓ (recent)	–	–	✓	–
	TAXi	✓	–	–	✓	–
Taxus	BASKET	✓ (recent)	–	–	–	✓
	CORPAL	–	–	–	–	✓
	ISAR-DIABETES	✓ (recent)	✓	–	✓	–
	REALITY	–	✓	–	–	✓
	SIRTAX	✓ (recent)	✓	–	–	✓
	TAXi	✓	–	–	✓	–
	TAXUS I	✓	–	–	✓	–
	TAXUS II	✓	–	–	✓	–
	TAXUS IV	✓	–	–	✓	–
	TAXUS V	✓ (recent)	–	–	✓	–
	ISAR-TEST	–	–	✓	–	✓
Dexamet	DESIRE	–	✓	–	✓	–
	EMPEROR-Plt	✓	–	–	✓	–
	Patti	✓		–	✓	–
	SAFE		✓	–	–	✓
	STRIDE	✓	✓	(✓ previous TAR)	✓	–
Costar	COSTAR I	–	–	✓	–	✓
	EUROSTAR	–	–	✓	–	✓
Cypher Select	DOMINO	–	–	✓	–	✓
Endeavor	ENDEAVOR II	–	✓	✓	–	✓
Janis	JUPITER I	–	✓	–	✓	–
	JUPITER II	–	✓	(✓ minimal)	–	✓
Liberté	ATLAS	–	–	✓	–	✓
Xience V (pending)	SPIRIT FIRST	–	✓	✓	✓	–
Yukon	ISAR-Project	✓	–	–	✓	–
	ISAR-TEST	–	–	✓	–	✓

DES versus DES studies are listed twice as they consider both Cypher and Taxus stents; recent, studies first published during the time course of this assessment (and following commencement of our study selection and data abstraction); previous TAR, study data noted from previous appraisal submission; minimal, only minimal data provided by manufacturer, which were not used in analysis.

bifurcation, presence of thrombus in the target vessel, previous PCI within 30 days or PCI other than balloon required as part of the study intervention.

Angiographic follow-up and outcomes

The BASKET[82] trial was the only study that explicitly reported that no protocol-driven angiographic follow-up was included. Most other trials included programmed, protocol-driven angiography for all or a selected subgroup of participants.

Co-therapies

Prescription of aspirin prior to intervention was described (DIABETES, TAXUS IV, RAVEL, Pache, SES-SMART, SIRIUS, C-SIRIUS, E-SIRIUS, [**confidential information removed**], TAXUS I, STRATEGY) and reported to be continued after the procedure (BASKET, DIABETES, TAXUS IV, RAVEL, SES-SMART, SIRIUS, C-SIRIUS, E-SIRIUS, TAXUS V, [**confidential information removed**], TAXUS I, STRATEGY) for most studies. Other antiplatelet therapies involved the use of clopidogrel within all of the 12 studies describing co-therapy, although ticlopidine was available for use as an alternative in some studies (RAVEL, TAXUS II, SIRIUS, E-SIRIUS, [**confidential information removed**]). Tirofiban, used in combination with DES, or abciximab, used with BMS, were compared in STRATEGY. Duration of antiplatelet therapy after invention ranged from 2 months (SES-SMART, C-SIRIUS, E-SIRIUS), 3 months (SIRIUS, ENDEAVOR II), 6 months (TAXUS IV, Pache, TAXUS II, TAXUS V, TAXUS I) to 1 year (DIABETES)

Further details of study characteristics are presented in *Table 63* (Appendix 3).

Participant characteristics

In Appendix 3, *Table 64* presents further details of the participants included in the trials.

Quality assessment of included studies

Assessment of the quality of included studies, based on CRD Report 4,[22] is presented in *Table 4*. It is important to note that quality assessment of five of the studies was limited as only non-peer-reviewed sources (conference abstracts or conference presentations) were available. The ENDEAVOR II study had not been published when conducting the assessment, but the manufacturer made a comprehensive trial report available to the Assessment Group. This source was used for purposes of quality assessment.

Where full reports were available, study quality was determined to be high.

Sufficient detail on method of randomisation was provided for the studies with full reports (peer-reviewed publications or trial report), ENDEAVOR II, E-SIRIUS, Pache, RAVEL, SES-SMART, SIRIUS, TAXUS I, TAXUS II, TAXUS IV, except for C-SIRIUS where the method of random sequence generation was not detailed (the use of 'sealed randomisation envelopes' was described).[54] The method of randomisation was not stated in the limited information sources for SCANDSTENT, SPIRIT FIRST, TAXUS V, but was described for DIABETES and partially for the Li study. Information on allocation concealment was not available for studies without full reports. All but the Pache study indicated that adequate allocation concealment had been employed. The STRATEGY study stated that it was open label, but used sealed envelopes to conceal allocation. The BASKET study also described the use of sealed envelopes, but randomised by day of procedure. Both STRATEGY and BASKET were given a 'partial' scoring for allocation concealment. Only SCANDSTENT did not state the number of patients randomised in the study.

Baseline comparability, based on key patient characteristics, was described for all studies except Li. The Li report also did not comment whether study arms were comparable. There was evidence of some disparity of study arms in C-SIRIUS, DIABETES, SES-SMART, SPIRIT FIRST. These characteristics are described in Appendix 3.

All studies provided at least basic details of entry requirements for participants. Only SCANDSTENT and SPIRIT FIRST (both not full reports) omitted information on co-therapies.

Details of masking (blinding) procedures seemed particularly limited for DIABETES, Li, SCANDSTENT, SPIRIT FIRST and TAXUS V. Information on masking was not stated or unclear for these five trials, which are yet to be published in peer-reviewed form. Of the full reports, nine (ENDEAVOR II, E-SIRIUS, Pache, RAVEL, SES-SMART, SIRIUS, TAXUS I, TAXUS II, TAXUS IV) masked outcome assessors to the intervention received by the patient and seven (C-SIRIUS, E-SIRIUS, RAVEL, SIRIUS, TAXUS I, TAXUS II, TAXUS IV) appeared to mask patients and those administering the invention. The STRATEGY study was single blind, masking only the patients to which intervention combination they received.

TABLE 4 *Quality assessment: DES versus BMS RCTs*

	Randomisation			Baseline comparability		Eligibility criteria specified	Co-interventions identified	Blinding				With-drawals		ITT
	Truly random	Allocation concealment	Number stated	Presented	Achieved			Assessors	Administration	Participants	Procedure assessed	>80% randomised in final analysis	Reasons stated	
C-SIRIUS[54]	Uncl	Yes	Yes	Yes	Part	Yes	Yes	Uncl	Yes	Yes	NS	Yes	Yes	Yes
BASKET[82]	NS	Part	Yes	Yes	Part	Yes	Yes	NS	NS	NS	NS	Yes	Yes	Yes
DIABETES[68]	Yes	NS	Yes	Yes	Part	Yes	Yes	NS	NS	NS	NS	Yes	Part	Yes
ENDEAVOR II[89,90]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NS	Yes	NS	Yes	Yes	Yes
E-SIRIUS[57]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Li[79]	Part	NS	Yes	No	NS	Yes	Yes	NS	NS	NS	NS	Yes	NA	NS
Pache[53]	Yes	No	Yes	Yes	Yes	Yes	Yes	NS	NS	NS	NS	Yes	Yes	Yes
RAVEL[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
SCANDSTENT[67]	NS	NS	No	Yes	Yes	Yes	No	NS	NS	NS	NS	Yes	No	Yes
SES-SMART[70]	Yes	Yes	Yes	Yes	Part	Yes	Yes	Yes	No	Uncl	NS	Yes	Yes	Yes
SIRIUS[71]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
SPIRIT FIRST[32]	NS	NS	Yes	Yes	Part	Yes	No	Uncl	No	Uncl	NS	Yes	Yes	No
STRATEGY[80]	Yes	Part	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes
TAXUS I[34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
TAXUS II[37]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
TAXUS IV[43]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
TAXUS V[52]	NS	NS	Yes	Yes	Yes	Yes	Yes	NS	NS	NS	NS	Yes	Part	Yes

NS, not stated; Part, partially; Uncl, unclear.

All studies retained at least 80% of those who originally entered the study. Withdrawals were detailed in all studies except SCANDSTENT and Li, where there seem to have been broad entry criteria and possibly (although this is not stated) no withdrawals to describe.

Only SPIRIT FIRST provided a per-protocol analysis in preference to intention-to-treat (ITT).

Outcomes/data analysis

Outcome data from trials comparing DES with BMS are presented in *Table 65* in Appendix 3. Meta-analysis is presented for mortality, AMI, composite event rate (MACE, TVF), TLR, TVR, angiographic binary restenosis rates and late luminal loss.

Data in the form of odds ratios (ORs) and 95% confidence intervals (CIs) were analysed using the Mantel–Haenszel method, fixed-effect model provided by the RevMan Analyses 1.0 application within RevMan 4.2. Similarly, for continuous outcomes, weighted mean differences (WMDs) were analysed.

Heterogeneity was tested by the χ^2 test and the I^2 statistic was obtained to describe the proportion of the variability using RevMan Analyses 1.0. Where quantitative heterogeneity was indicated, analysis using a random-effects model was conducted for comparison with results of fixed-effect-based analysis.

For convenience, studies are grouped according to drug eluted in the meta-analysis. Pooled estimates (OR, 95% CI) are provided for each 'eluted drug' subgroup. Pooled effect estimates incorporating available data for all DES analysed are presented in *Table 5*. The meta-analyses presented in the figures are only pooled within subgroups, permitting display of study weighting and heterogeneity measures within these subgroups.

Two approaches to analysis of data for BASKET[82] [which randomised patients to either sirolimus-eluting stent (SES), paclitaxel-eluting stent (PES) or BMS] were applied. For calculation of pooled effect estimates across all included trials and 'eluted drug' subgroups, the DES arms of BASKET were combined (the two DES groups as

TABLE 5 *Meta-analysis: pooled estimates for comparison of DES versus BMS*[a]

Outcome/ follow-up	Event rate		Mortality	AMI	TLR	BRR		LL (WMD)		Thrombosis
1 month	**0.73; 0.59 to 0.91** **0.72; 0.47 to 1.12**	RE	–	–	–	–		–		0.85; 0.47 to 1.56
6–9 months	**0.46; 0.40 to 0.53** **0.44; 0.36 to 0.54**	RE	0.87; 0.58 to 1.31	0.84; 0.67 to 1.07	**0.30; 0.25 to 0.37**	**0.15; 0.13 to 0.19** **0.11; 0.07 to 0.18**	RE	**–0.59; –0.62 to –0.56** **–0.63; –0.74 to –0.52**	RE	0.59; 0.32 to 1.10
1 year	**0.39; 0.33 to 0.47**		1.31; 0.78 to 2.20	0.73; 0.52 to 1.03	**0.21; 0.16 to 0.27**	–		–		0.89; 0.35 to 2.25
2 years	**0.43; 0.34 to 0.54**		0.96; 0.55 to 1.68	0.92; 0.62 to 1.37	**0.24; 0.19 to 0.31**	–		–		1.93; 0.69 to 5.43
3 years	**0.42; 0.32 to 0.55**		1.64; 0.94 to 2.87	0.89; 0.52 to 1.50	**0.25; 0.17 to 0.35**	–		–		Not estimatable

[a] Data presented are ORs with 95% CIs for the pooled effect estimate (fixed-effect model). Statistically significant effect estimates are in bold. RE: where statistical heterogeneity indicated by testing χ^2 ($p = 0.10$ or less) or I^2 statistic (40% or more), random-effects analysis is presented underneath the fixed-effect estimate.

one 'generic' DES group) and compared with the BMS arm to avoid double counting of the non-DES control group. Alternatively, within the meta-analysis presented with only totals for each subgroup, the BASKET PES and BMS arms appear in PES analyses and the same BMS in comparison with SES are analyses in the SES grouping.

Meta-analysis was performed for available data reported up to 1 month, 6–9 months, 1 year, 2 years and 3 years. The results below concentrate on the 12-month results: analyses for other time points are summarised in the text where relevant and presented in full in Appendix 3 (*Figures 19–24*).

Mortality

Death (cardiac or all-cause mortality, depending on available data) was an uncommon event, with no significant differences identified between DES and BMS in meta-analysis of all DES treated as a group, SES or PES subgrouping or indeed within any individual study at all follow-up periods analysed to 3 years.

There was no indication of the presence of statistical heterogeneity that might 'mask' notable differences in rates between the two interventions.

Meta-analysis plots are presented for mortality at 1 year in *Figure 1*. Plots for analysis of other follow-up periods are presented in Appendix 3 (*Figure 19*).

AMI

No statistically significant difference in MI was discernible between DES and BMS for any DES grouping, study or period of follow-up.

Meta-analysis plots are presented for AMI for 1 year in *Figure 1(b)* and for other follow-ups in Appendix 3 (*Figure 20*).

Revascularisation – TLR

In general, DES displayed statistically significant (within 95% CI) improved rates of target lesion revascularisation within pooled analyses up to 3 years. Only the analysis of PES at 3 years, which included only the relatively small TAXUS I study, was not within statistical significance. In absolute terms, rates of TLR for DES within individual trials were below 5% and typically in the range 10–25% for BMS at 1 year (see *Figure 1(c)* for trials included in this example) [e.g. 4.6, 0 and 4.9% for SES, compared with 24.9, 13.6 and 20.0% for BMS in the trials reporting 1-year follow-up in E-SIRIUS, RAVEL and SIRIUS, respectively; 0, 4.7, and 4.2% for PES and 10.0, 12.9 and 14.7% for BMS in TAXUS I, II(SR) and IV respectively]. The pooled estimate at 1 year (OR 0.21; 95% CI 0.16 to 0.27; see *Table 5*) suggests a reduction of around three-quarters in the rate of TLR with the use of DES.

Meta-analysis including all available DES data suggested that there were no major further reductions in TLR after 1 year [see Appendix 3 (*Figure 21*): OR for SES subgroups 0.21, 95% CI 0.15 to 0.30 at 6 months; 0.17, 95% CI 0.12 to 0.25 at 1 year; 0.22, 95% CI 0.15 to 0.30 at 2 years; and 0.25, 95% CI 0.17 to 0.36 at 3 years; and for PES, OR 0.37, 95% CI 0.28 to 0.49 at 6–9 months; 0.26, 95% CI 0.18 to 0.39 at 1 year; 0.28, 95% CI 0.20 to 0.40 at 2 years; and 0.13, 95% CI 0.01 to 2.69 at 3 years].

At 9 months, the Endeavor stent was associated with reduction of TLR (4.6% DES versus 12.1% BMS). Although lower rates of TLR (3.8% versus 21.4%) were apparent for the everolimus-eluting stent group in the SPIRIT FIRST trial at 6 months, the difference was not statistically significant.

Meta-analysis plots are presented for TLR in *Figure 1(c)* for up to 1 year and for other follow-ups in Appendix 3 (*Figure 21*).

Revascularisation – TVR

TVR was analysed for PES at 6–9 months (OR 0.54, 95% CI 0.43 to 0.68), 1 year (0.40; 95% CI 0.29 to 0.55), 2 years (0.45, 95% CI 0.34 to 0.59) and 3 years (0.32; 95% CI 0.03 to 3.29) and favoured PES over BMS at all follow-up. Data for SES were only available for single trials at 1 year (OR 0.34, 95% CI 0.19 to 0.60, Pache) and 3 years (0.35, 95% CI 0.25 to 0.49, SIRIUS).

Meta-analysis plots are presented for TVR in *Figure 1(d)* for up to 1 year and for other follow-ups in Appendix 3 (*Figure 22*).

Event rate

Analysis of event rate (MACE, TVF) favoured DES at 1 month (OR 0.74, 95% CI 0.58 to 0.95), 6–9 months (0.46, 95% CI 0.40 to 0.53), 1 year (0.39, 95% CI 0.33 to 0.47), 2 years (0.43, 95% CI 0.34 to 0.54) through to 3 years (0.42, 95% CI 0.32 to 0.55).

In pooled analysis of all subgroups at 1 month and 6–9 months, moderate statistical heterogeneity was detected ($p = 0.04$, I^2 43.1%; $p = 0.09$, I^2 36.1%). Use of a random-effects model altered ORs by very little (see *Table 5*), although the 1-month analysis of DES versus BMS 95% CI extended beyond statistical significance.

Mortality: 1 year

Study or subcategory	DES n/N	BMS n/N	OR (fixed) 95% CI	Weight (%)	OR (fixed) (95% CI)
01 Paclitaxel					
TAXUS I	0/30	0/30			Not estimatable
TAXUS II 1/SR	0/129	2/132		23.64	0.20 (0.01 to 4.24)
TAXUS IV	9/662	8/652		76.36	1.11 (0.43 to 2.89)
Subtotal (95% CI)	821	814		100.00	0.89 (0.37 to 2.17)
Total events: 9 (DES), 10 (Non-DES)					
Test for heterogeneity: $\chi^2 = 1.11$, df = 1 ($p = 0.29$), $I^2 = 10.2\%$					
Test for overall effect: $Z = 0.25$ ($p = 0.81$)					
02 Sirolimus					
Pache	7/250	5/250		44.91	1.41 (0.44 to 4.51)
RAVEL	2/120	2/118		18.33	0.98 (0.14 to 7.10)
SIRIUS	7/533	4/525		36.76	1.73 (0.50 to 5.96)
Subtotal (95% CI)	903	893		100.00	1.45 (0.67 to 3.15)
Total events: 16 (DES), 11 (Non-DES)					
Test for heterogeneity: $\chi^2 = 0.23$, df = 2 ($p = 0.89$), $I^2 = 0\%$					
Test for overall effect: $Z = 0.94$ ($p = 0.35$)					
03 ABT-578					
ENDEAVOR II	[**Confidential information removed**]		[**Confidential information removed**]		
Subtotal (95% CI)					

0.1 0.2 0.5 1 2 5 10

(a) Favour DES Favour BMS

MI any: 1 year

Study or subcategory	DES n/N	BMS n/N	OR (fixed) 95% CI	Weight (%)	OR (fixed) (95% CI)
01 Paclitaxel					
TAXUS I	0/30	0/30			Not estimatable
TAXUS II 1/SR	3/129	7/132		18.81	0.43 (0.11 to 1.68)
TAXUS IV	23/662	30/652		81.19	0.75 (0.43 to 1.30)
Subtotal (95% CI)	821	814		100.00	0.69 (0.41 to 1.14)
Total events: 26 (DES), 37 (Non-DES)					
Test for heterogeneity: $\chi^2 = 0.55$, df = 1 ($p = 0.46$), $I^2 = 0\%$					
Test for overall effect: $Z = 1.44$ ($p = 0.15$)					
02 Sirolimus					
RAVEL	4/120	5/118		21.70	0.78 (0.20 to 2.98)
SIRIUS	16/533	18/525		78.30	0.87 (0.44 to 1.73)
Subtotal (95% CI)	653	643		100.00	0.85 (0.46 to 1.57)
Total events: 20 (DES), 23 (Non-DES)					
Test for heterogeneity: $\chi^2 = 0.02$, df = 1 ($p = 0.88$), $I^2 = 0\%$					
Test for overall effect: $Z = 0.52$ ($p = 0.61$)					
03 ABT-578					
ENDEAVOR II	[**Confidential information removed**]		[**Confidential information removed**]		
Subtotal (95% CI)					

0.1 0.2 0.5 1 2 5 10

(b) Favour DES Favour BMS

FIGURE 1 *Meta-analysis DES versus BMS at 1 year*

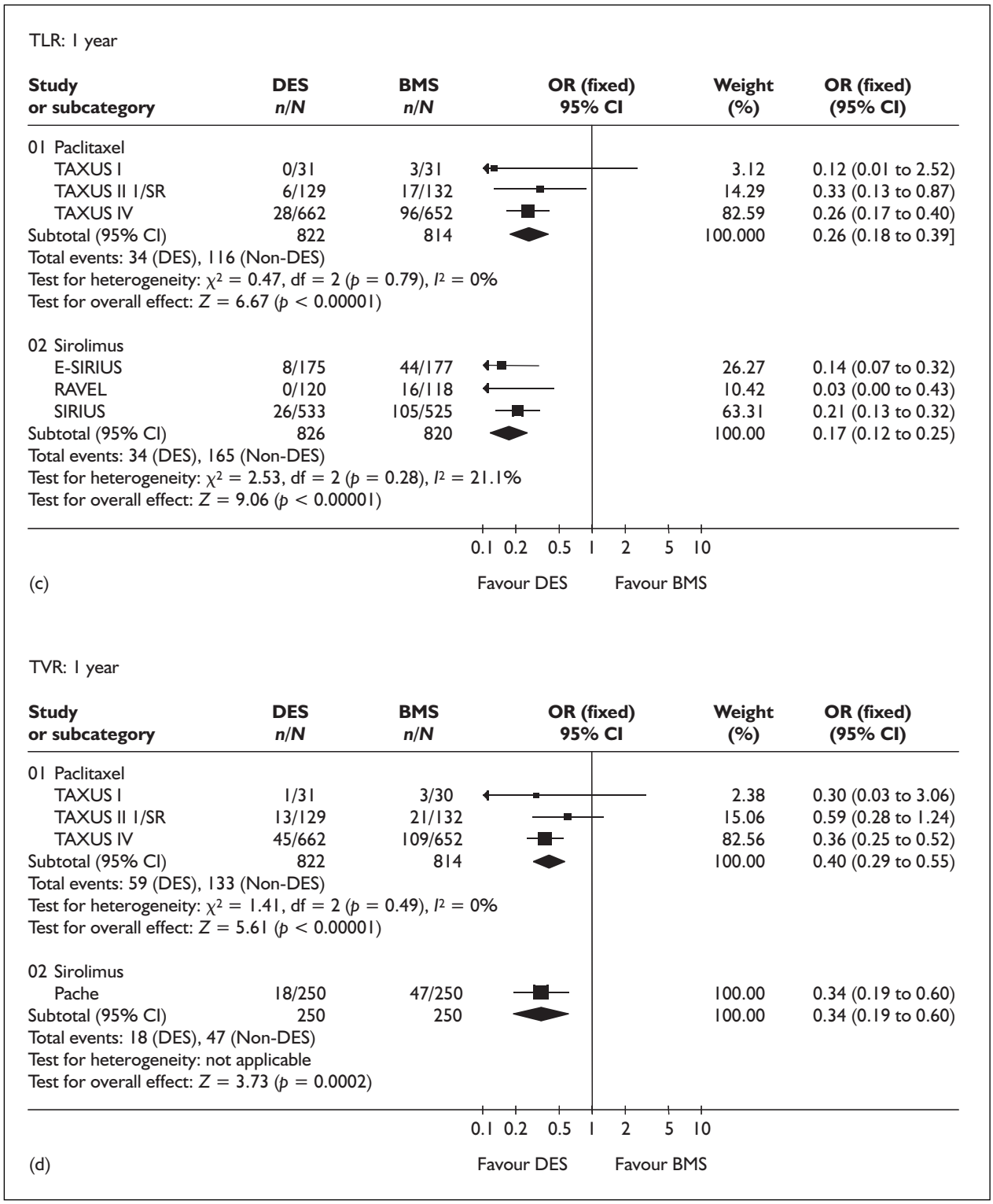


FIGURE 1 *(cont'd)*

Direction of effect and statistical significance are maintained through to 3 years, with the value for OR for the SES subgroup (compared with BMS) and PES (compared with BMS) remaining within 0.04 (OR 0.39, 95% CI 0.42 and 0.43) during the period 1–3 years. Composite events rates at 1 year were below 11% for DES and below 27% for BMS in each study analysed. The earlier DES trials, RAVEL and TAXUS I, reported the lowest event rates (4.2 versus 19.5% and 3.3 versus 10.0% at

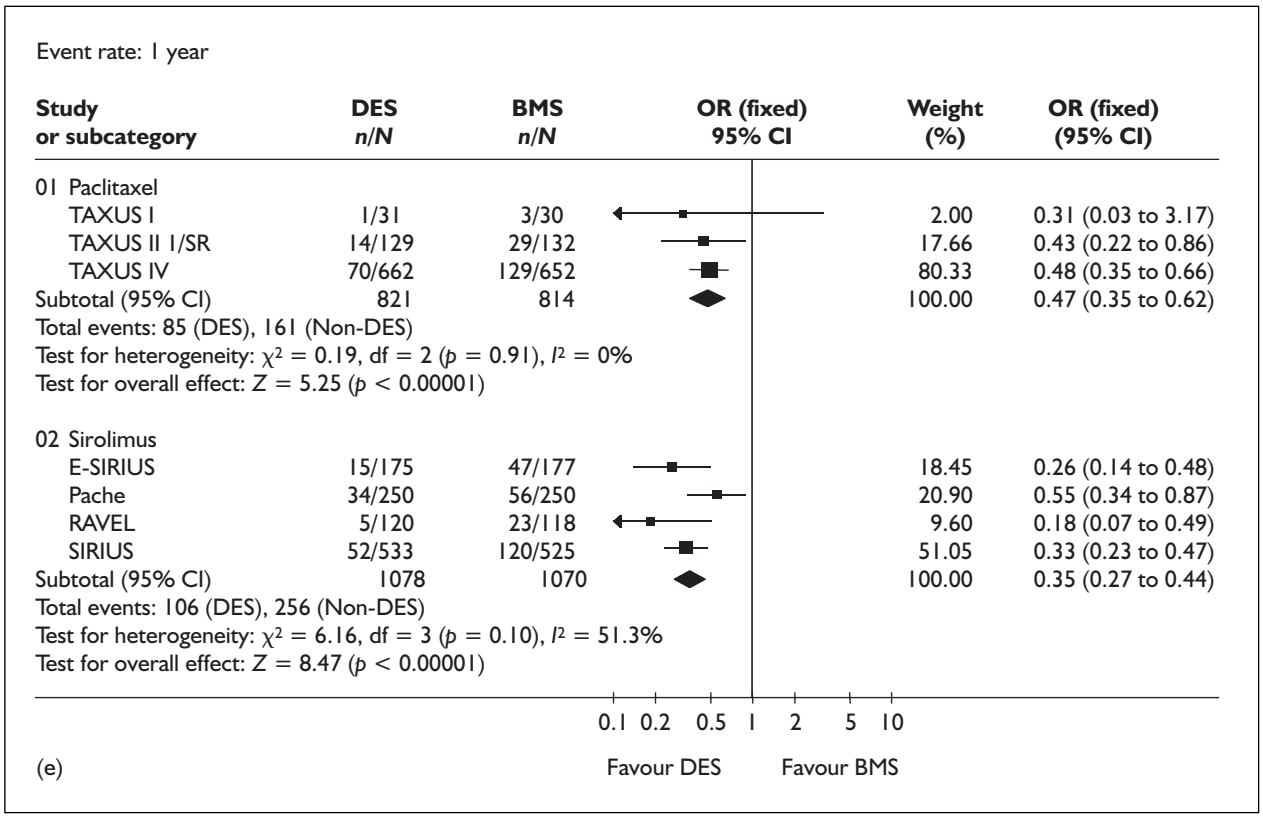


FIGURE 1 *(cont'd)*

1 year) with other trials falling within a narrower range of 8.6–13.6% for DES and 19.8–26.6% for BMS. The benefit of DES over BMS, in terms of lower composite event rates, which is driven largely by lower revascularisation rates, would appear to be maintained and remain relatively stable through the 3-year period analysed to date.

Meta-analysis plots are presented for event rate in *Figure 1(e)* and for other follow-ups in Appendix 3 (*Figure 23*).

Binary restenosis

At angiographic follow-up between 6 and 9 months, binary restenosis rates (BRRs) are statistically significantly lower for all DES, except for the everolimus-eluting stent studied in SPIRIT FIRST. Although no BR was detected in-stent in the Xience DES group and around one-quarter of those analysed in the BMS group exhibited restenosis, the broad 95% CIs for this analysis just breach the margin for statistical significance.

The pooled estimate for binary restenosis in the PES group was OR 0.27, 95% CI 0.20 to 0.35 and 0.08, 95% CI 0.06 to 0.11 for SES and [**Confidential information removed**].

High levels of heterogeneity for the pooled analysis of all trials and the SES subgroup were indicated by the I^2 statistic. Fixed-effect analyses are presented in *Figure 2(a)* and random-effects analyses in Appendix 3 (*Figure 24*).

Late loss

Late loss (LL) analysis at follow-up ranging from 6–9 months favoured DES (WMD –0.59, 95% CI –0.62 to –0.56). Mean late loss was reduced by 0.45 mm for PES (WMD –0.45, 95% CI –0.50 to –0.40) and by 0.79 mm for SES (WMD –0.79, 95% CI –0.84 to –0.74). The single trial analysed for Xience indicated a reduction of 0.74 mm (WMD –0.74, 95% CI –0.91 to –0.57). [**Confidential information removed**].

High levels of statistical heterogeneity were indicated for the SES and total pooled analysis. Fixed-effect analyses are presented in *Figure 2(b)* and random-effects in Appendix 3 (*Figure 24*).

Time trends in outcomes

The ORs presented in *Table 5* show stability in values from 1 year through to 3 years, that is, little or no increasing benefit of DES over BMS after the first year.

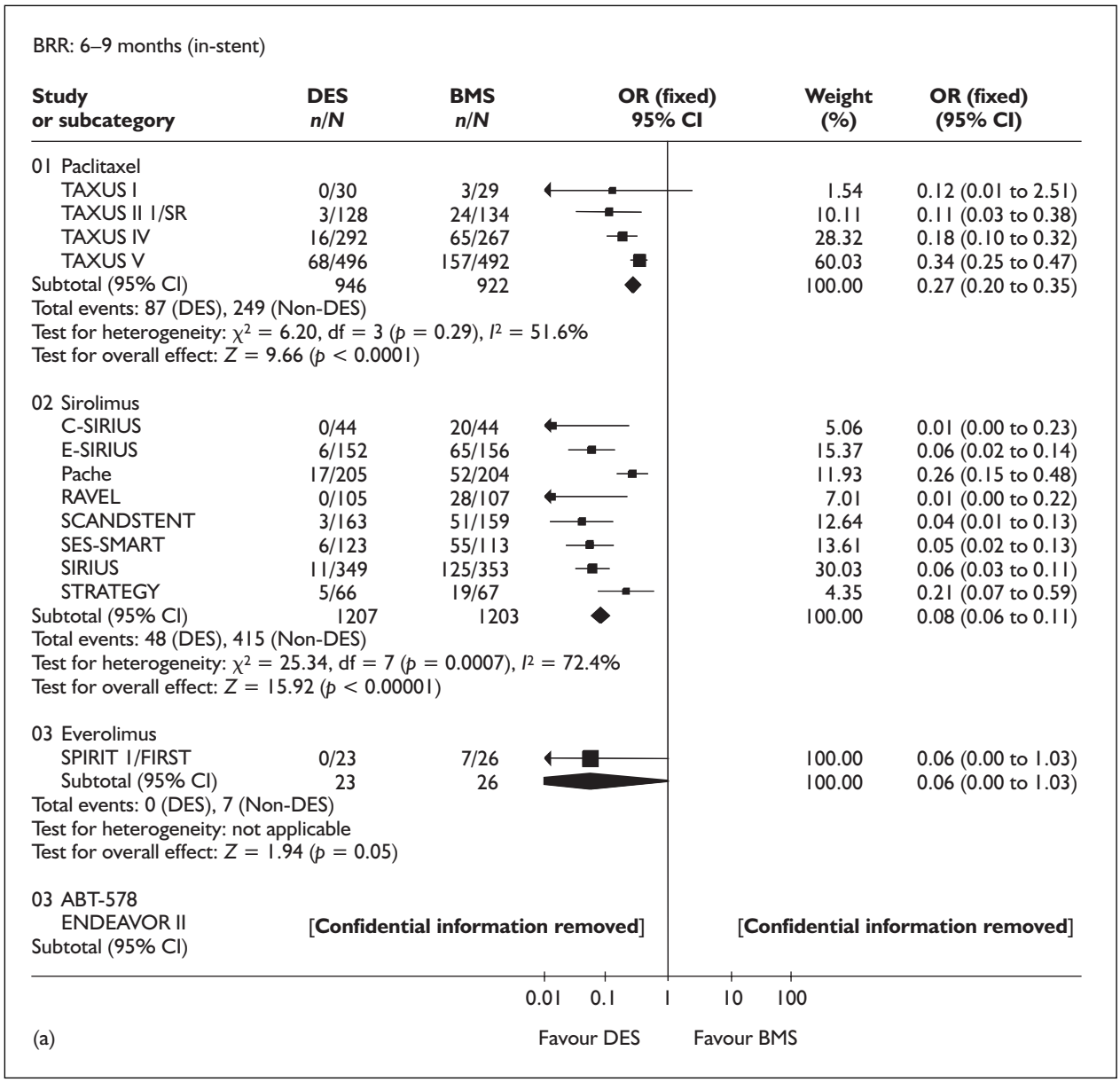


FIGURE 2 *Meta-analysis DES versus BMS – angiographic outcomes at 6–9 months*

Device associated adverse events

There was limited reporting of a full range of adverse events – even in the major Cypher and Taxus trials. Data on incidence of thrombosis were identified up to 3 years – although only the relatively small TAXUS I reported at this period of follow-up and, as zero incidence of thrombosis was apparent, calculation of ORs is not possible. At none of the follow-up periods analysed were statistically significant differences in rates of thrombosis between DES and BMS identified.

Considering that monitoring of safety-related outcomes might justify closer examination and that statistical power might be expected to be lacking, further examination of the rate of thrombosis and meta-analysis plots does not indicate that there is a trend toward higher thrombosis in either the DES or BMS groups. At 6 months greater rates of thrombosis are observed for BMS except for TAXUS II (SR), where the one event occurred in the DES group, and TAXUS V, where the number of events were the same in DES group and BMS groups. It is only at 2 years, where data are limited to TAXUS II and TAXUS V, that greater rates of thrombosis are reported for the DES group.

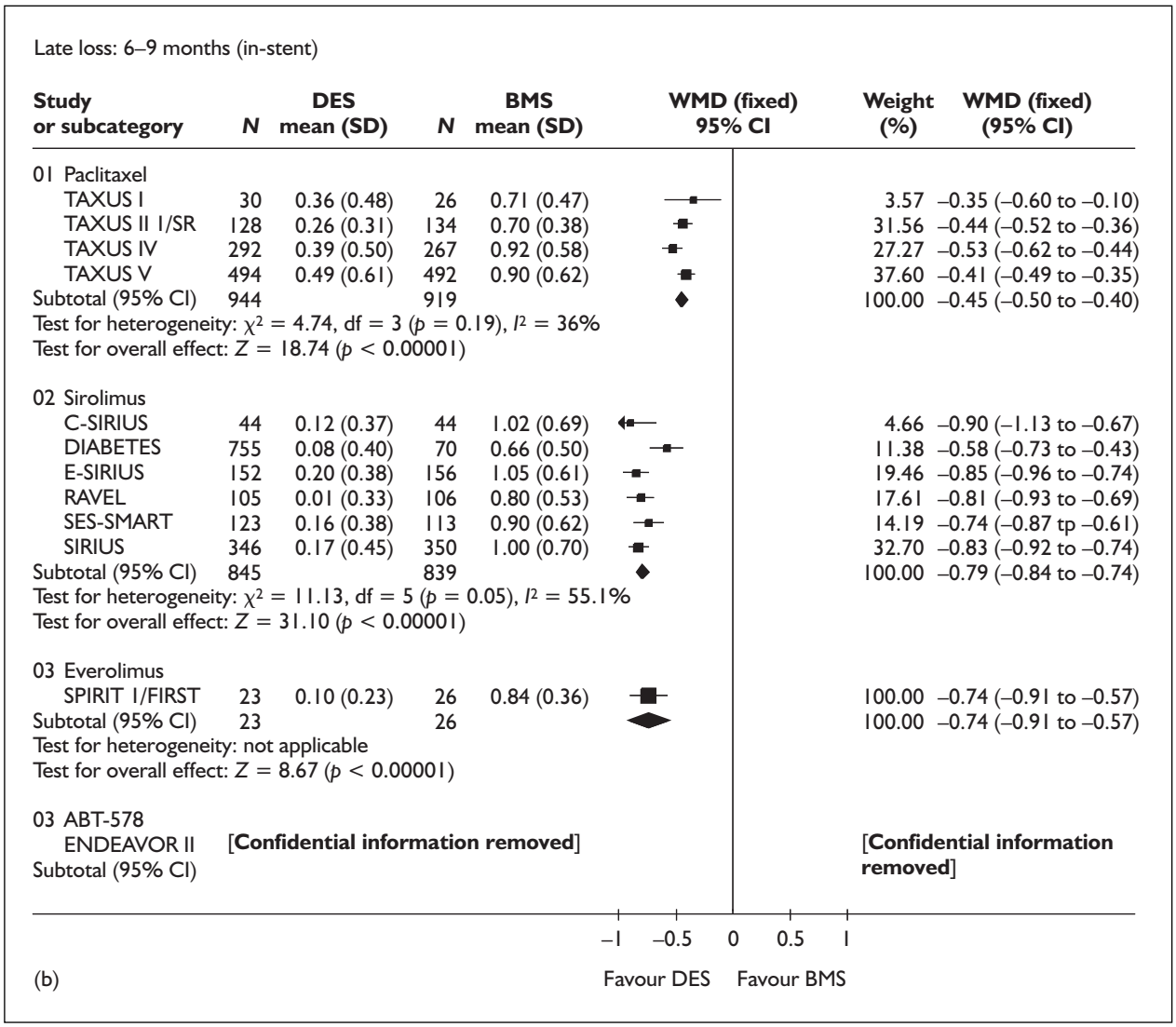


FIGURE 2 *(cont'd)*

In the course of our searching, some other sources of information, including secondary research, were identified. A recently published meta-analysis combining RCTs and data from the RESEARCH registry reported no statistically significant difference in rates of thrombosis between SES and BMS.[91] Occurrence of late thrombosis was studied for both SES and PES in an observational study involving 2229 patients in Germany and Italy.[92] At 9 months' follow-up, stent thrombosis was recorded for 29/2229 patients overall, 9/1062 (0.8%) in the SES group and 20/1167 (1.7%) in the PES group. Although apparently higher for PES, the difference between SES and PES was not statistically significant at a p-value of 0.05 (reported as $p = 0.09$). In multivariate analyses conducted by the researchers,[92] premature discontinuation of antiplatelet therapy was the strongest predictor of stent thrombosis.

Drug-eluting stents without RCT evidence

Included evidence

DES designs considered

The scope[1] of this assessment included some DES where RCT-based evidence was not available at the time of the review:

- The AXXION stent is currently being evaluated within the EAGLE RCT. At the time of the assessment, recruitment had only just been completed and no outcome data were available. The AXXION was not included in the TAR protocol, but based on its CE Marking during this assessment, the device was incorporated into the assessment. No studies of this device were identified though Assessment Group searching activities, so information on

TABLE 6 *DES without evidence reported from RCTs*

DES	Study name	Design
AXXION	EAGLE	RCT (in progress, no outcome data available)
CoStar (pending)	CoSTAR I	Dose ranging, non-RCT
	EuroSTAR	Dose ranging, non-RCT
Dexamet	Patti	Non-RCT
	EMPEROR Pilot	Non-controlled (pilot study)
	STRIDE	Non-controlled (with BMS historical control)/registry
	DESIRE	Registry
	SAFE	Registry
Janus	JUPITER I	Non-controlled
Liberté	ATLAS	Non-controlled (with DES historical control)
Yukon	ISAR-Project	Dose ranging, non-RCT

this device is derived from the manufacturer only.
- The CoStar stent has been studied in the EuroSTAR and COSTAR India non-RCTs, but data were incomplete at the time of assessment.
- The Dexamet stent has only been assessed within non-controlled studies (one of which used historical BMS control groups for comparison).
- The Janus stent is being studied in the JUPITER I non-controlled trial and the JUPITER II RCT, but data from the RCT appear incomplete (interim and blinded).
- The Taxus Liberté is the subject of a large non-controlled trial, ATLAS, which utilises selected Taxus stent recipients from the TAXUS trials as controls.
- The Yukon DES has been evaluated in the ISAR-TEST RCT, but confirmed outcome data are limited at this time. Data from the ISAR-Project dose ranging trial are available, but no BMS comparator group was studied.

Included non-RCTs

Table 6 summarises the sources of evidence identified for the assessment of DES lacking results from RCTs.

Five non-RCTs of new DES are included in this section. The CoStar DES was investigated in EuroSTAR and CoSTAR India, the Janus in JUPITER I, Liberté in ATLAS and Yukon in ISAR-Project. At the time of the assessment, only results of studies of the Dexamet stent[93–95] and ISAR-Project[96] had been published in peer-reviewed journals. Design of the JUPITER I study was overviewed within a publication in 2003,[97] but no outcome data were presented. Information on studies was obtained by a combination of manufacturer submissions to NICE and unpublished sources (such as conference abstracts and presentations). Within much of the manufacturer submissions the level of detail which would be expected within a peer-review publication of a study was not available. These factors, along with the relatively early stage of research, limit the rigour of the assessment of these DES.

Consideration of the AXXION DES

During the appraisal process, the AXXION PES (manufactured by Biosensors) was awarded CE Marking (11 July 2005). Although we obtained product information[98] by our own searching, no clinical study involving the AXXION device was identified. We contacted the manufacturer and were informed that AXXION was being studied within the EAGLE randomised study, which was conducted over three centres in Germany with a target recruitment of 125 participants, randomised 2:1 to AXXION DES and Calix (Nexus II+) non-eluting stent. Stated outcomes of the study were MACE (at 30 days and 6 months), angina and angiographic measurement for a subset of participants. At the time of the assessment, no outcome data were available to the Assessment Group, so this particular device will not be considered further in the clinical review.

Consideration of data on the Dexamet DES

[**Confidential information removed**].

Non-RCT study characteristics

Of the five DES considered within this section, data were identified exclusively from non-controlled studies for two (Janus, Liberté) and

dose-ranging non-RCTs for another two (CoStar, Yukon). The Janus tacrolimus-eluting stent was examined in the JUPITER I non-controlled study, whereas the Taxus Liberté PES was evaluated in the ATLAS non-controlled study. A range of formulations of the CoStar stent eluting paclitaxel was evaluated in EuroSTAR and CoSTAR non-RCTs. The ISAR-Project was a dose-ranging non-RCT, which compared Yukon SES with the same stent carrying no drug. The Dexamet DES was studied in a mix of one non-randomised study of Dexamet compared with non-eluting BiodivYsio stents and four non-controlled studies (including DESIRE and SAFE, which are described as registries). Only the ISAR-Project and Patti studies included a non-DES control group, so effectively most are 'DES only' studies with no direct comparison with non-DES or -BMS available.

Study size ranged from smaller studies of 30 and 50 participants included in the EMPEROR Pilot and JUPITER I studies, respectively, to larger studies of 332 (DESIRE registry), 602 (ISAR Project) and 871 (ATLAS). The available report of the Dexamet SAFE registry indicated that 1000 participants were to be recruited, but included analysis of 735. Both studies of the CoStar DES were incompletely reported at the time of the assessment. Outcome data on the planned enrolment of 120 for CoSTAR I was reported for only 50 participants and for the 273 enrolled in EuroSTAR data for only 145 participants were reported.

The ATLAS, EuroSTAR, COSTAR I, JUPITER I and STRIDE studies stated that patients with de novo lesions would be included. The ISAR-Project study detailed that lesions with in-stent restenosis (ISR) would be excluded. People with up to two lesions could be included in EuroSTAR, CoSTAR I and JUPITER I (up to two vessels, providing one lesion per vessel, each to be covered with one DES). The ISAR-Project study stated that multiple DES could be used to "cover one or more lesions". [**Confidential information removed**].

Vessel diameters included ranged from 2.5 to 4.0 mm for ATLAS, 3.0 to 4.0 mm for JUPITER I, 2.5 to 3.5 mm for EuroSTAR and CoSTAR I and 2.5 to 3.0 mm for ISAR-Project. Participants with lesions ⩽12 mm were eligible for JUPITER I, in the range 10–28 mm for ATLAS and up to 25 mm for EuroSTAR and CoSTAR I. The ISAR-Project study permitted the use of multiple stents to cover one lesion, so the scope of lesions considered is unclear (although it is stated that the shortest stent available was 8 mm and the longest 25 mm).

Stenosis of more than 50% was a stated entry requirement for EuroSTAR, CoSTAR I and JUPITER I. Symptoms in the "presence of significant stenosis" were required for ISAR-Project. [**Confidential information removed**].

Recent MI was recorded as a basis for exclusion from EuroSTAR, CoSTAR I and ISAR-Project.

Key data on the design of studies of Dexamet, CoStar Janus, Liberté and Yukon DES are presented in Appendix 5, *Table 69*.

Non-RCT participant characteristics

Data on participants in selected non-RCTs are presented for Dexamet, CoStar, Janus, Liberté and Yukon DES in Appendix 5, *Table 69*.

Outcomes

Outcome data were limited to 30-day follow-up for ATLAS, 4 months (interim data) for CoSTAR I, 6 months for three DEXAMET studies (Patti, EMPEROR Pilot, STRIDE) and JUPITER I (with only very limited reporting), but extended to 1 year for EuroSTAR and ISAR-Project. Angiographic outcomes, binary restenosis and/or late loss were reported for five studies: CoSTAR I, EMPEROR Pilot, EuroSTAR, ISAR-Project and STRIDE.

Summative analysis across devices or studies is not appropriate for a number of reasons, including the variety of DES devices considered among the studies, methodological limits of the available studies, varied and limited follow-up and absence of any common control. Furthermore, given that new DES have only been subject to early investigations focusing on feasibility, safety and basic efficacy, the likelihood of obtaining robust data on key outcomes was low.

This being said, available outcome data for different DES designs will be quoted below for information. Data for different formations of the same DES design are combined as it was not within the scope of this assessment to investigate dose-ranging or formulation variations of DES.

Dexamet – dexamethasone-eluting stent (PC-coated)

Evaluation of the Dexamet DES included a range of study designs. The non-randomised study of

Dexamet compared with non-eluting BiodivYsio stents (Patti) reported no deaths among the 100 participants receiving either stent and only a single incidence of AMI in the non-DES group up to a mean 8 (±2) months of follow-up. Revascularisations up to a mean of 8 months were 2% TLR in the DES group and 10% TLR (12% TVR) in the control group (OR 0.18, 95% CI 0.02 to 1.63). Composite rates of MACE, comprised entirely of revascularisations, were 2 and 12% for DES and non-DES respectively (OR: 0.15; 95% CI 0.02 to 1.29).

The single-arm STRIDE study reported one death (1.4%) during hospital stay and that one patient developed AMI during 30-day follow-up. No further mortality or AMI were observed up to 6 months. Symptom-driven revascularisation (determined to be ISR) was completed for two patients (2.8%) at 6 months' follow-up. Total MACE up to 6 months for the ITT dataset (based on 71 participants) was 5.6%. The EMPEROR pilot study of a high-dose variant of Dexamet reported no MACE up to 30 days, and up to 6 months' follow-up only one patient under went TLR (MACE 3.3%). Angiographic follow-up on 26 patients indicated BRR in 31% of patients and an average in-stent LL of 0.97 (±0.63) mm. The authors of the EMPEROR Pilot state in the introduction to their paper that these findings resulted in the full EMPEROR RCT programme being cancelled before patient recruitment.

Two additional studies of Dexamet (DESIRE, SAFE), both of which were described as registries, included over 1000 participants between them, but at the time of assessment data were incomplete for all available follow-ups. Interpretation of results may require some caution due to the design employed and the apparent preliminary nature of some data. Finalised data, on all participants enrolled, was available for 30-day outcomes from the DESIRE registry. Two people died and four experienced AMI, contributing to a total MACE rate of 1.8%. Up to 6 months, analysis of 274 patients (82% of those enrolled) noted two deaths, six MI and 26 clinically driven TVR (9.5%). Total MACE in this 'preliminary' [but Clinical Events Committee (CEC) adjudicated] analysis was 12%. Available reports of the SAFE registry indicated that in-hospital analysis represented 735 patients, although the registry appeared to aim to collect data on 1000 'real-world' patients. Adjudicated outcomes in-hospital amounted to one death (0.13%), three MI (0.40%), four TLR (0.54%) and one additional TVR by CABG (if independent from all TLR, then total TVR 0.68%). The rate of in-hospital MACE for 735 patients was 0.68%.

CoSTAR – PES (non-polymeric)

Only partial data on the CoSTAR paclitaxel-loaded stent were available. Studies with incomplete follow-up or reporting would not usually be considered with the clinical review.

Data up to 1 year for one of two arms of the EuroSTAR study are presented for information in Appendix 5, *Table 70*. Follow-up the second arm of EuroSTAR is ongoing. Interim data on only two of four arms of the ongoing CoSTAR I study are also presented in Appendix 5, *Table 70*.

Janus – tacrolimus-eluting stent (non-polymeric, 'film coating' and surface wells)

Limited data were identified for the Janus stent. Available data from the JUPITER I study, reported at 30 days, indicated that no events (death, MI or TLR) occurred. Data for 6 months were unclear in the publicly available source. No suitable information was provided from the manufacturer.

Liberté – PES (polymeric)

Only 30-day data were available. Data in the public domain were only presented as percentages and 'masked' with the TAXUS study historical control data; unmasked, absolute numbers were provided, commercially in confidence, to the Assessment Group.

[**Confidential information removed**].

Yukon – SES (non-polymeric)

Data for the Yukon DES were reported at 1 month and 1 year. No deaths occurred up to 1 month. Rates of AMI up to 1 month were 1.8% in the SES groups and 1.3% in the BMS group. At 1 year, composite of death or non-fatal MI was 2.7% for sirolimus-eluting formulations and 3.9% for BMS. No statistically significant difference in death, MI or composite of death or MI was detected (OR, 95% CI calculated by fixed-effect model). At 1 year, TLR was reported in 12.6% (SES) and 21.5% of lesions (BMS); BRR for 13.9% (SES) and 23.8% of lesions. Statistically significant differences in TLR (OR 0.53, 95% CI 0.34 to 0.81) and BRR (0.52, 95% CI 0.32 to 0.83) favoured Yukon SES over non-eluting Yukon stents. Means for LL could not be readily pooled from the available data.

Available outcome data are presented for Dexamet, CoStar Janus, Liberté and Yukon DES in Appendix 5, *Table 70*.

Drug-eluting stents of different designs: evidence from registries

Introduction

Results from RCTs are the accepted standard for establishing the clinical efficacy of a given treatment. However, the artificial setting of such studies and limitations related to participant inclusion means that these results frequently fail to reflect the 'real world' of care or the overall effectiveness of the treatment in clinical practice. This is clearly reflected in the area of DES, where trial participants do not reflect the make-up of real-world cardiology practice, where protocol-driven angiographic follow-up inflates the incidence of revascularisation and where the devices are frequently used in clinical situations in which they have not been tested.[99] Good-quality registries or audit data may contribute to our understanding of real-world effectiveness and adverse events.

Review of current DES registries

It was not the purpose of this assessment to identify or present comprehensively or systematically data from registries of patients receiving DES. However, the number of registries directly addressing the issue of real-world outcomes has increased dramatically since the first assessment and it was felt by the Assessment Group that it would be appropriate to provide information about the registries currently available.

Specific DES registries were identified in a number of ways. In the first instance they were identified from the initial broad literature search conducted for the review. Reviewers (RD, RH, CMcL) scanned the initial search results and identified any citations that referred to PCI or DES registries. This list of titles and abstracts was then examined by one reviewer (RD), who identified registries that had a primary focus of DES. A second stage of identification was carried out by two reviewers (RH, RD) through examination of company submissions.

Registries were selected if they were available as a published paper or part of a company submission and it was stated that the registry focused on data related to DES designs included as part of this review.

Selected registries

A total 24 registries were identified. In the case of six registries, insufficient data were available to discern if data related to patients receiving DES were included.[100–105] Information related to data sources and sponsors could be extracted for the remaining 18 registries. The data registries are described in brief in Appendix 6.

All but one of the registries collected data from multiple sites. Five collected data internationally with the remainder collecting data in only one country (France, Germany, Korea, The Netherlands, Portugal, Switzerland and the USA). The number of participants registered varied from as few as 183 to more than 15,000. The majority related to only one DES and had been sponsored by commercial interests (manufacturer, distributor) in the DES being utilised.

The nature of the registries has evolved over time. For instance, in RESEARCH the original data compared a historical cohort of BMS patients with a new cohort of SES patients when SES received CE Marking. When the Taxus PES was approved, the group reported on the use of PES and recorded this in the T-SEARCH registry.

As would be expected, a number of registries report an evolution of the patient characteristics. The severity of the disease has increased over time. In early registry data, patients frequently had single-vessel disease, whereas current patient statistics indicate treatment of patients with multiple-vessel disease.

Although such registries provide important data regarding the real world of patient experience, the lack of consistency across registries means it would not be appropriate to draw conclusions from a pooling of their data. Future developments in consistency of data collection and definition may allow for more appropriate use of such real-world findings in the future.

Discussion

Several more studies have been added to the available data since the original appraisal, and longer term follow-up is now available for many of the studies considered then. Some of the conclusions remain unchanged, however.

As for our previous assessment, no statistically significant differences in death or AMI were detected between DES and BMS, within either DES subgroups or pooled analyses.

There were major differences in revascularisation rates in favour of DES and, as a direct consequence

of this, also in favour of composite event rates which are largely driven by revascularisations. However almost all studies considered had exceptionally high revascularisation rates in the BMS arm – typically up to 20–25%, and far higher than is seen in common clinical practice. The conclusion, therefore, must be either that only very high-risk patients were entered into the trial, or that the revascularisation rates were in turn driven by the protocol-mandated angiogram in all studies except BASKET. The BASKET study reported a lower absolute event rate than the other studies, reflecting perhaps its pragmatic clinical approach.

The relative reduction in event rate is fairly consistent across most studies, and strongly favours DES over BMS. However, the economic arguments will be driven not just by the relative reduction, but very importantly by the underlying absolute clinical risk of the need for revascularisation, which seems overestimated in the current studies. This is considered in detail in Chapter 8.

Longer term data – extending to 3 years – are reassuring in that differences in revascularisation rates do not narrow after 12 months, that is, the early benefit of DES is maintained, but conversely that there is no further added value of DES after the first year. This evidence was lacking at the time of the previous appraisal. We remain unable to evaluate the influence of patient characteristics such as vessel diameter, lesion length or co-morbidities with the available data – a detailed meta-analysis using individual patient data would be required for this.

In conclusion, DES reduce revascularisation rates compared with those experienced in patients given BMS. They have no effect on serious coronary events and could not be said to be life saving, but rather are symptom reducing – a worthwhile gain in itself, and similar in this respect to the benefits of CABG in most cases. Their effects are maximal by 12 months, but seem sustained thereafter. Whether they are cost-effective compared with BMS will depend not just on the relative risk reduction in revascularisations, but on the absolute risk in the types of patients in whom they are used.

Summary

DES versus BMS

Seventeen RCTs were included in the clinical review, although at most 14 trials were analysed for any one outcome. Eleven RCTs examined SES, five studied PES and single RCTs each studied the Endeavor or Xience V DES in comparison with BMS. Analysis of mortality, AMI and composite event rates pooled results from over 7000 participants. Analysis of revascularisation outcomes (TLR, TVR) pooled around 5000 patients. Follow-up extended to 3 years, but for only three RCTs.

There were no benefits of DES over BMS in serious clinical events (death or AMI). Revascularisation rates were reduced by approximately three-quarters, consistent across most studies. The benefits were fully seen by 12 months, and neither increased nor decreased thereafter.

New DES

Clinical trial data on new DES – not previously considered by the Assessment Group – were still limited at the time of current assessment. Many devices only have evidence on efficacy from dose-ranging trials or non-controlled studies. Meaningful comparison with BMS or other DES designs was not possible at the time of assessment. Furthermore, many devices may not be evaluated within large RCTs and therefore direct comparison with BMS or – potentially – indirect comparison with other DES designs may remain problematic.

Chapter 5

Review of clinical effects: comparison between DES

RCT-based evidence

Included studies

Selection of included studies

Only head-to-head RCTs comparing selected DES of different types (in design or drug delivery) were eligible for inclusion in this meta-analysis.

A recent systematic review and meta-analysis by Kastrati and colleagues[106] was published. We examined the list of included studies and found no deficit in our included studies. We added one further study, BASKET.

Description of included studies

Eight RCTs comparing DES with other DES designs were included in the clinical review.[82,107–117] Of these eight RCTs, only one (TAXi) was identified in our initial electronic search of bibliographic databases, five (SIRTAX, REALITY, ISAR-DIABETES, CORPAL, BASKET[82,107,108,110–117]) through handsearching activities and two (DOMINO and ISAR-TEST[118,119]) from manufacturer submissions to NICE.

Study characteristics

Six of the RCTs compared Cypher SES with Taxus PES (REALITY, SIRTAX, TAXi, CORPAL, ISAR-DIABETES, BASKET), one studied Cypher in comparison with the newer Cypher Select SES (DOMINO) and the ISAR-TEST trial compared the Yukon sirolimus-loaded stents with the Taxus PES. The BASKET trial was also included in the previous chapter as it included a BMS control group. The study will be treated as an SES versus PES RCT within this chapter.

Most of the head-to-head trials were conducted in only one or two centres in European countries (Germany, ISAR-DIABETES, ISAR-TEST; Spain, CORPAL; Switzerland, BASKET, SIRTAX, TAXi); DOMINO and REALTY were multicentre and multinational.

The ISAR-DIABETES study exclusively recruited patients with diabetes, whereas BASKET, SIRTAX and TAXi imposed few limits on study eligibility – adopting an 'all comers' approach. The BASKET study recruited a significant proportion of patients with ACS or STEMI, and CORPAL included a proportion of patients with ISR. AMI within 72 hours excluded patients from ISAR-DIABETES, ISAR-TEST and REALITY, as did the presence of unprotected left main lesions, and reintervention for ISR was a stated exclusion from these three trials. Only DOMINO and REALITY were determined to be industry supported (both by Cordis). The BASKET, TAXi and SIRTAX studies stated that they were conducted independently of industry support.

The BASKET and TAXi trials were distinct in that they did not incorporate programmed angiographic assessment of trial participants.

Table 66 in Appendix 4 presents details of the study design and entry criteria.

Participant characteristics

Table 67 in Appendix 4 presents further details of the patient groups studied in the trials.

Quality assessment of included studies

Assessment of included study quality is presented in *Table 7*. Four of the studies were not available as peer-reviewed publications, so depth of quality assessment may be limited for these studies.

Randomisation details were presented for only two of the eight included DES versus DES trials (ISAR-DIABETES, SIRTAX). Only the SIRTAX study presented a description of an adequate allocation concealment system being in place. The ISAR-DIABETES study indicated that allocation information was concealed within envelopes. The BASKET adopted a system where type of intervention (PES, SES or BMS) was randomly allocated to certain days where only the allocated device would be planned to be implanted. The allocation sequence was concealed within envelopes. The use of envelopes – even if opaque – is not accepted as an adequate concealment method in CRD Report 4,[22] but a 'partial' score was awarded in our assessment. Information on allocation concealment was not available for other studies during the clinical review stages of the assessment. All studies provided data on numbers of patients randomised.

Baseline comparability was presented and at least partially achieved for all studies.

All studies reported eligibility criteria, although CORPAL, DOMINO, ISAR-TEST and REALITY failed to provide details of co-interventions.

Little information was provided on masking of those involved in the studies apart from the full report of SIRTAX, where the study was described as 'single blind' (masking patients), but also detailed that angiographic outcome assessors, the clinical event committee and statistical analysts were not aware of which device had been implanted. The ISAR-DIABETES study report stated that the quantitative coronary angiography assessors and clinical events committee were unaware of the treatment device used, but provided no information on any other masking arrangements.

At least 80% of participants were retained at follow-up in DOMINO, REALITY, SIRTAX and TAXi, but this was unclear for CORPAL and ISAR-TEST, in part because outcomes were expressed in a mix of 'by patient' and 'by lesion', making assessment of number followed up difficult. The DOMINO study did not present an ITT analysis, whereas for CORPAL and ISAR-TEST it was unclear whether events were reported according to original allocations. The REALITY, SIRTAX and TAXi studies all present ITT analyses. In ISAR-DIABETES, all patients received their allocated device and were reportedly included in 9-month clinical follow-up, so whether planned or not, the analysis is as ITT.

Outcomes/data analysis

Comparisons are grouped together in the meta-analysis according to which pairing of DES designs were compared within trials (most commonly this was Cypher SES versus Taxus PES). *Figures 3–5* present meta-analysis plots for DES versus DES RCTs. No total pooled effect estimate was calculated across multiple groupings of DES versus DES trials. Outcome data are presented in Appendix 4, *Table 68*.

Mortality (Figure 3a)

No statistically significant difference in mortality was apparent in our analysis of five Cypher SES versus Taxus PES (OR 0.77, 95% CI 0.45 to 1.33), Cypher SES versus Cypher Select SES (OR 0.53, 95% CI 0.02 to 13.22) or Yukon SES versus Taxus PES (OR 0.66, 95% CI 0.11 to 4.01) trials at 6–9 months.

AMI (Figure 3b)

No statistical difference was observed for the same five Cypher SES versus Taxus PES RCTs at 6–9 months (OR 0.89, 95% CI 0.62 to 1.27). Cypher Select and Cypher were statistically indistinguishable in our analysis.

TABLE 7 *Quality assessment: DES versus DES RCTs*

Checklist items	Randomisation			Baseline comparability		Eligibility criteria specified	Co-interventions identified	Blinding				With-drawals		ITT
	Truly random	Allocation concealment	Number stated	Presented	Achieved			Assessors	Administration	Participants	Procedure assessed	> 80% randomised in final analysis	Reasons stated	
BASKET[82]	NS	Part	Yes	Yes	Part	Yes	Yes	NS	NS	NS	NS	Yes	Yes	Yes
CORPAL[114]	NS	NS	Yes	Yes	Part	Yes	No	NS	NS	NS	NS	Uncl	No	Uncl
DOMINO[119]	NS	NS	Yes	Yes	Part	Yes	No	NS	NS	NS	NS	Yes	Yes	No
ISAR-DIABETES[113]	Yes	Part	Yes	Yes	Yes	Yes	Yes	Part	NS	NS	NS	Yes	Yes	NA/ Yes
ISAR-TEST[118]	NS	NS	Yes	Yes	Part	Yes	No	NS	NS	NS	NS	Uncl	No	Uncl
REALITY[116]	NS	NS	Yes	Yes	Yes	Yes	No	NS	NS	NS	NS	Yes	Part	Yes
SIRTAX[110]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Part	No	Yes	NS	Yes	No	Yes
TAXi[109]	NS	NS	Yes	Yes	Yes	Yes	Yes	NS	NS	NS	NS	Yes	Yes	Yes

NS, not stated; Part, partially; Uncl, unclear.

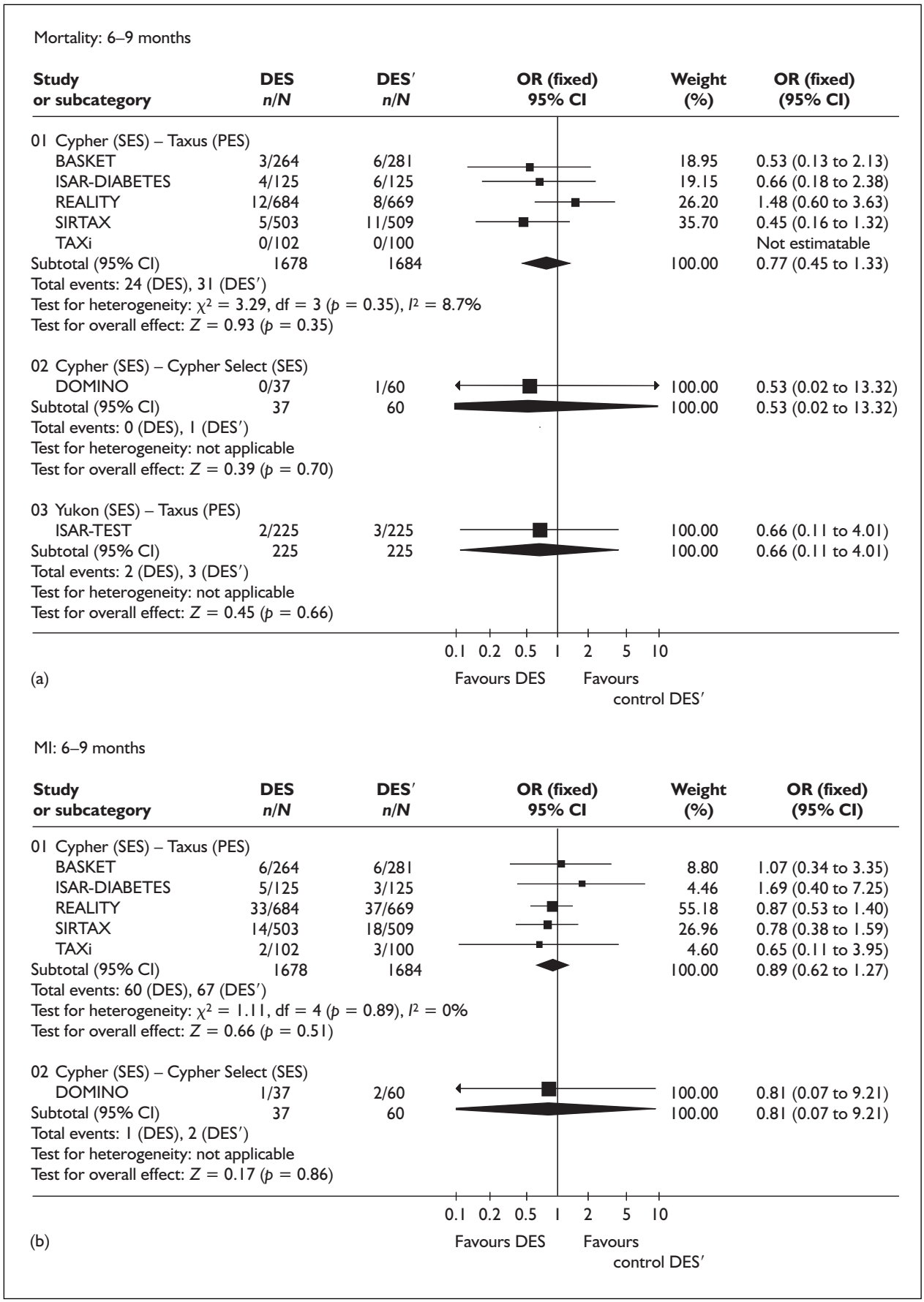


FIGURE 3 *Meta-analysis DES versus DES at 6–9 months*

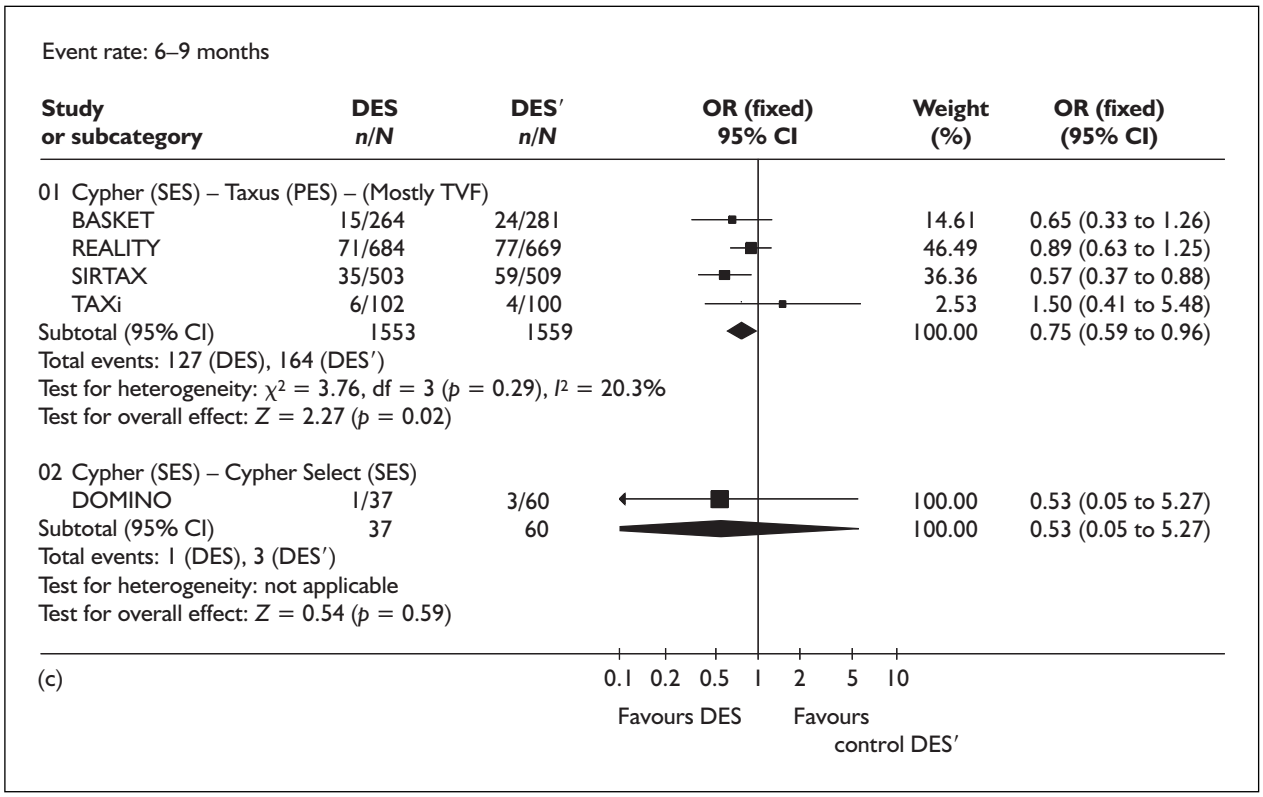


FIGURE 3 *(cont'd)*

Revascularisation – TLR (Figure 4a–c)

In our data abstraction for the CORPAL study, it was unclear whether TLR was reported 'by patient', or 'by lesion', so the outcome was not included in our review until we could determine in which manner the data had been reported. Following the use of CORPAL in the systemic review by Kastrati and colleagues,[106] we opted to present the analysis of TLR in three ways: first with inclusion of TLR reported at mean 13 (±4) months for the CORPAL study in the same analysis of 6–9 months data for ISAR-DIABETES, REALITY, SIRTAX and TAXi, second without CORPAL at 6–9 months and third with CORPAL alone at 1 year.

In the 6–9 month analysis of TLR (including CORPAL), a marginal, but statistically significant, advantage of SES over PES is observed (OR 0.68, 95% CI 0.51 to 0.91). When analysing only those studies reporting at 6–9 months, the pooled estimate favouring SES is only just within statistical significance (OR 0.70, 95% CI 0.51 to 0.97). The CORPAL study was the only RCT to date with data available beyond 9 months. When considered alone, rates of TLR for SES are 5.7% compared with PES 9.0%, but do not differ to a statistically significant degree (OR 0.61, 95% CI 0.34 to 1.12).

When considering the result of individual trials, only SIRTAX presents a marginal statistically significant improvement in rate of TLR with SES over PES (OR 0.56, 95% CI 0.33 to 0.93).

More robust analysis of this particular outcome requires further quality assured data in the form of peer-reviewed publications, data from additional trials and longer follow-up.

Revascularisation – TVR (Figure 4d)

Analysis of the BASKET and SIRTAX Cypher SES and Taxus PES trials indicate a statistically significant advantage for SES over PES (OR 0.59, 95% CI 0.39 to 0.89) in terms of TVR at 6–9 months.

Composite event rate (Figure 3c)

Event rate (such as MACE) analysed at 6–9 months for Cypher SES versus Taxus PES appeared to favour SES over PES, but with 95% CIs only just within statistical significance (OR 0.75, 95% CI 0.59 to 0.96). Differences in composite event rates in the DOMINO trial, although higher for Cypher Select, were not statistically significant.

Binary restenosis (Figure 5a, b)

In-stent binary restenosis, analysed on a by lesion basis, favoured Cypher SES over Taxus PES in the

TLR: 6–9 months

Study or subcategory	DES n/N	DES′ n/N	OR (fixed) 95% CI	Weight (%)	OR (fixed) (95% CI)
01 Cypher (SES) – Taxus (PES)					
CORPAL	19/331	29/321		23.69	0.61 (0.34 to 1.12)
ISAR-DIABETES	8/125	15/125		11.99	0.50 (0.20 to 1.23)
REALITY	34/684	36/669		29.53	0.92 (0.57 to 1.49)
SIRTAX	24/503	42/509		33.94	0.56 (0.33 to 0.93)
TAXi	2/102	1/100		0.85	1.98 (0.18 to 22.19)
Subtotal (95% CI)	1745	1724		100.00	0.68 (0.51 to 0.91)
Total events: 87 (DES), 123 (DES′)					
Test for heterogeneity: $\chi^2 = 3.39$, df = 4 ($p = 0.49$), $I^2 = 0\%$					
Test for overall effect: $Z = 2.64$ ($p = 0.008$)					
02 Cypher (SES) – Cypher Select (SES)					
DOMINO	0/37	0/60			Not estimatable
Subtotal (95% CI)	0	0			Not estimatable
Total events: 0 (DES), 0 (DES′)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

(a)

0.1 0.2 0.5 1 2 5 10

Favours DES Favours control DES′

TLR: 6–9 months – CORPAL excl.

Study or subcategory	DES n/N	DES′ n/N	OR (fixed) 95% CI	Weight (%)	OR (fixed) (95% CI)
01 Cypher (SES) – Taxus (PES)					
ISAR-DIABETES	8/125	35/125		15.71	0.50 (0.20 to 1.23)
REALITY	34/684	36/669		38.70	0.92 (0.57 to 1.49)
SIRTAX	24/503	42/509		44.48	0.56 (0.33 to 0.93)
TAXi	2/102	1/100		1.11	1.98 (0.18 to 22.19)
Subtotal (95% CI)	1414	1403		100.00	0.70 (0.51 to 0.97)
Total events: 68 (DES), 94 (DES′)					
Test for heterogeneity: $\chi^2 = 3.22$, df = 3 ($p = 0.36$), $I^2 = 6.9\%$					
Test for overall effect: $Z = 2.13$ ($p = 0.03$)					
02 Cypher (SES) – Cypher Select (SES)					
DOMINO	0/37	0/60			Not estimatable
Subtotal (95% CI)	0	0			Not estimatable
Total events: 0 (DES), 0 (DES′)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

(b)

0.1 0.2 0.5 1 2 5 10

Favours DES Favours control DES′

FIGURE 4 *Meta-analysis DES versus DES – TLR 6–13 months, TVR at 6–9 months*

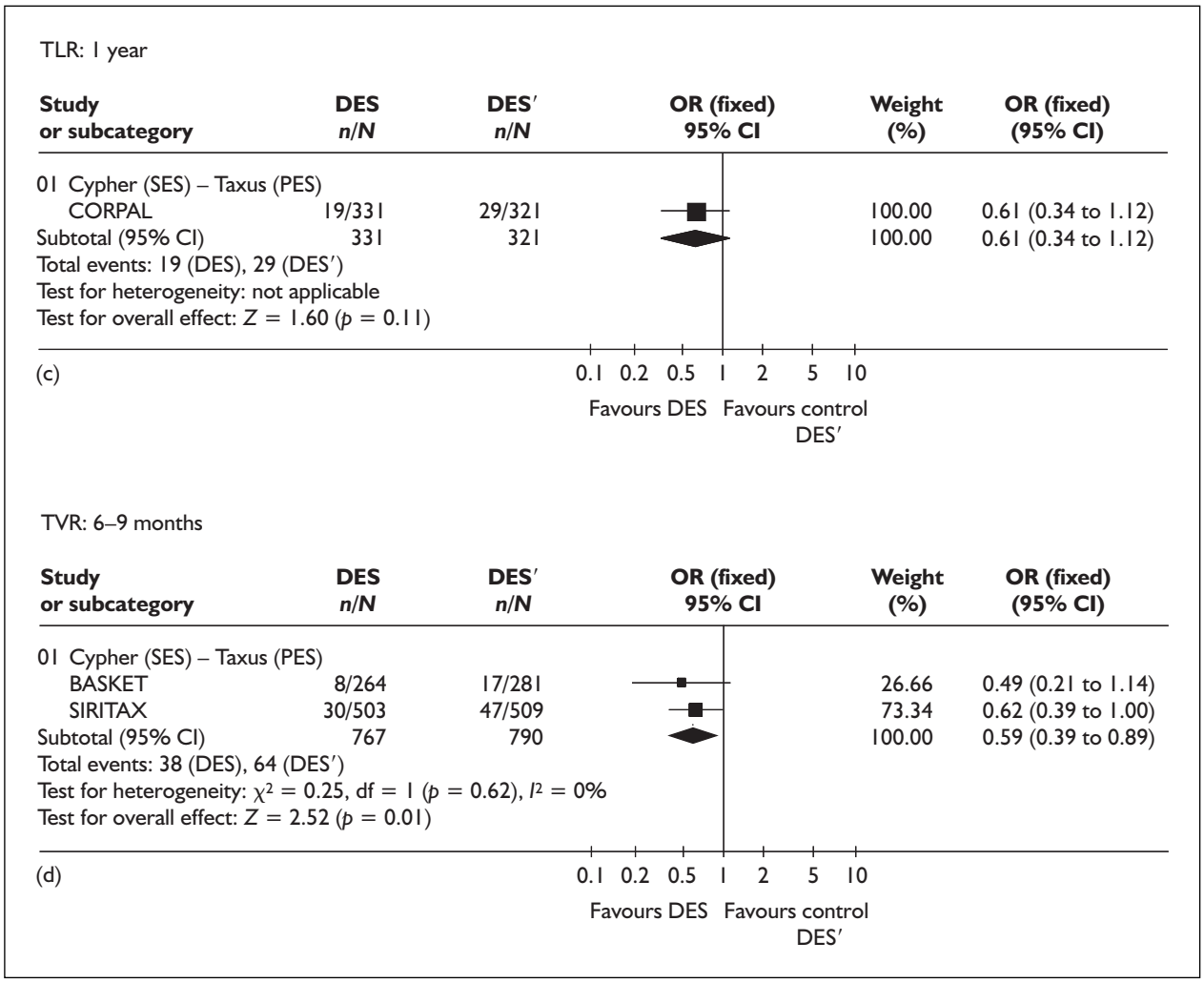


FIGURE 4 *(cont'd)*

three trials analysed; as with other outcomes, the 95% CI for the pooled estimate is near the line of no effect (OR 0.69; 95% CI 0.53 to 0.91).

The ISAR-DIABETES and DOMINO studies presented in-stent binary restenosis by patient. A large reduction in restenosis was observed in ISAR-DIABETES, with 95% CIs, but just within statistical significance (OR 0.33; 95% CI 0.11 to 0.95). In DOMINO, no statistical difference was found.

Late loss (Figure 5c, d)

LL data were analysed by lesion for SITAX and by patient in ISAR-DIABETES and DOMINO. A statistically significant, but small, reduction of 0.07 mm in mean LL was determined for Cypher SES in SIRTAX (WMD –0.07, 95% CI –0.13 to –0.01). For Cypher in ISAR-DIABETES, a reduction of 0.27 mm in mean LL (the trial's primary end-point) was indicated (WMD –0.27; 95% CI –0.42 to –0.12). In DOMINO, the Cypher Select SES exhibited less LL than the existing Cypher design, but the difference was not statistically significant (WMD 0.06, 95% CI –0.07 to 0.19).

Discussion

The available data compare Cypher SES with Taxus PES and indicate that there may be differences between these DES in revascularisations. The statistical significance of all measures analysed was marginal. The relative risk reduction was consistent at around 30%. The absolute difference in revascularisation events was small: around 5% for SES compared with around 7% for PES overall. It is not clear to what degree these rates were driven by protocol angiograms: of the two studies with no angiogram, TAXi reported only three revascularisations in total out of 200

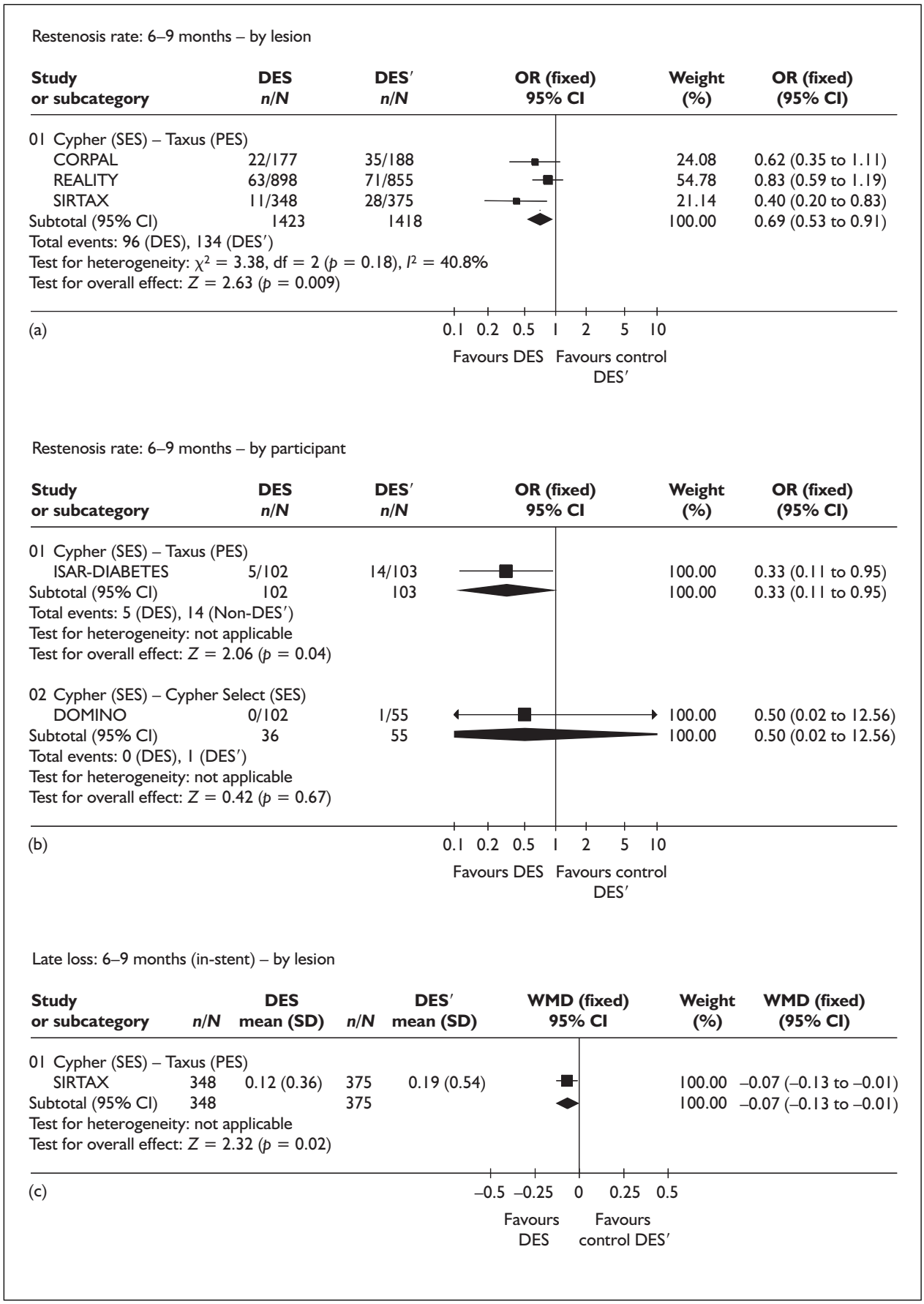


FIGURE 5 *Meta-analysis DES versus DES – angiographic outcomes at 6–9 months*

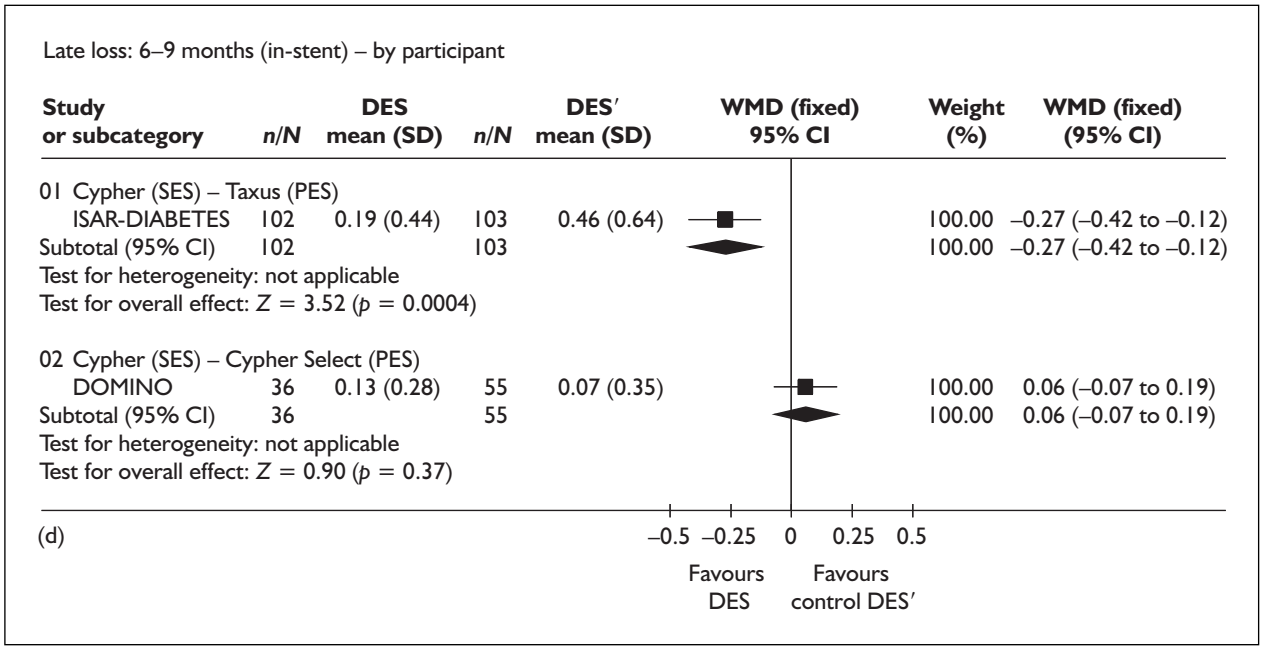


FIGURE 5 *(cont'd)*

procedures, whereas BASKET reported a revascularisation rate only slightly lower than that in the studies that included an angiogram, and a similar relative difference between PES and SES. Indeed, the event rate in TAXi was so low that the study could no longer detect a difference between the two stents and so was abandoned.

These results await confirmation at and beyond 1 year. Based on longer experience in DES compared with BMS, it may be that these differences will be maintained. Although these results might be enough to persuade cardiologists to opt for the Cypher SES, in practice there are two barriers to this: first a limited supply of Cypher, and second a price differential (in terms of a premium in price for Cypher compared with BMS). Furthermore, there are newer designs of both SES and PES as well as other DES coming to market which may have advantages over these, although clear evidence of this is needed.

It may be that one DES is more cost-effective than another. This is considered briefly in Chapter 8. Again, the key to this might be the underlying risk of the patients treated.

Summary

To date, eight RCTs have reported head-to-head comparisons of different DES types, but variations in study design and outcome reporting limit summative assessment. All of the RCTs included comparison with either Cypher SES or Taxus PES. Six RCTs compared these directly. At the time of this assessment, some data awaited confirmation in peer-review publications and follow-up was limited to 9 months except for one study.[114]

No statistically significant differences in death or AMI were detected between DES designs. Analysis of TLR up to 9 months was marginally in favour of SES over PES. A larger, although still marginal, reduction in TVR with SES was determined from meta-analysis of two trials at 9 months. Reduction in composite event rate (MACE) with SES was just within statistical significance.

Chapter 6

Review of published economic evaluations

Introduction

This chapter explores the published literature on the costs and benefits of DES for CAD. It begins by examining the economic impact of DES, and discusses the costs and health outcomes within the framework of an economic evaluation. It goes on to report the results of the economic literature search including a description and critical appraisal of the identified studies.

Economic impact of DES for coronary artery disease

As described in Chapters 4 and 5, no benefit in terms of life extension has been observed with DES, although there is expected to be some small benefit in terms of QoL owing to the avoidance of repeat revascularisations. The question then is whether the increased initial treatment costs of DES can be offset by the reduced costs of repeat revascularisations avoided (RRA), or be justified by the small gain in QoL. To address this question, both the costs and health outcomes need to be defined.

Costs of revascularisation

The costs included in an economic evaluation depend on the perspective taken. From the NHS perspective, the only costs of interest are the direct medical care costs, which include the costs of tests, drugs, supplies, healthcare personnel and medical facilities. When comparing DES with BMS for CAD, the only differences in the medical care costs will be the initial treatment costs (acquisition cost of using DES compared with BMS), and the costs of treating recurrent symptoms, including investigations, repeat revascularisations and follow-ups. Using this perspective, the high cost of DES means that initial treatment costs will be higher. However, the total costs of further treatment (investigating, treating and following up) should be lower for patients treated with DES as the lower rates of restenosis result in fewer patients needing a repeat intervention.

Extending the perspective to the publicly funded personal social services, the costs of interest include not only the direct healthcare costs (as described above), but also the costs which fall on the social service budget. There is currently no published literature on these costs for repeat revascularisation, but they can be expected to be limited in amount and duration and hence are not addressed in this report.

Health outcomes of revascularisation

As outlined in Chapter 2, a number of different health outcome measures are reported in the literature comparing DES and BMS. Most frequently, these are MACE-free survival, TLR, TVR and RRA. These measures could all be used in a cost-effectiveness analysis, although as intermediate outcomes they are not ideal. Life-years gained are not a relevant outcome since drug-eluting stents have not demonstrated an overall survival benefit in comparison with BMS. Given that DES decrease the rate of restenosis compared with BMS, a small gain in health-related QoL can be expected, in relation to short-term pain and disability prior to and associated with undergoing a repeat revascularisation. Thus, the preferred outcome in this study is the QALY, allowing a cost–utility analysis to be undertaken.

Review of the economic literature

The aim of the review of economic evaluations was to identify published cost-effectiveness studies of any DES versus any other DES or BMS for the treatment of CAD.

Identification of studies

Details of the search strategy, inclusion criteria, data extraction and quality assessment are presented in Chapter 3. A total of 10 full economic evaluation studies (Bagust, Cohen, AETMIS (Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé), Greenberg, Gulizia, Kaiser, Mittmann, Shrive, Tarricone, Van Hout) were included. Six papers were identified from the electronic search[120–125] and four additional papers by handsearching.[82,126–128] One of these was in Italian,[126] and hence could only be partially reviewed.

Characteristics of economic studies

Four studies[120–122,124] undertook cost–utility analysis, reporting incremental costs per QALY

(*Table 8*). The remaining studies were CEAs. All of the studies compared SES with BMS, although the Bagust, AETMIS, Kaiser (labelled BASKET in the clinical review) and Mittmann studies also included PES. Furthermore, the Kaiser study included a third-generation BMS comparator (Vision). Only one of the studies was set in the UK[120] and the remaining nine were set in the USA, Canada or the rest of Europe. All of the studies were of 1 year duration, except Greenberg, which was over 2 years, Kaiser, which was over 6 months, and Shrive, which was set over a patient's lifetime.

Economic models

All of the studies were based on some form of economic model (*Table 9*). The Shrive study used a Markov model with 6-month intervals for the duration of the patient's lifetime. The model employed in the Cohen study was not clearly described but involved logistic regression and prospective analysis of the SIRIUS trial results. Similarly, the Van Hout model was poorly described but appeared to include bootstrapping of RAVEL trial results. Decision analytic models were employed by the remaining studies. All of the studies adopted the healthcare provider perspective, except the Mittmann study, which adopted hospital and provincial perspectives. Apart from the Van Hout, Kaiser and Tarricone (unable to translate Gulizia) studies, all of the studies explored model assumptions.

Cost data and data sources

All of the studies apart from the Tarricone study estimated the cost of DES to incur a price premium (*Table 10*). In order to aid comparison, where a price year was stated, currencies where converted to UK£, 2003, the year of the only UK study (by Bagust and colleagues[120]). Purchasing price parities were used to convert currencies (http://www.oecd.org/dataoecd/61/56/1876133.xls) rather than exchange rates, as these not only convert to a common currency but also equalise the purchasing power between currencies. To inflate prices to 2003, the consumer price index (CPI) was used.[129]

The Cohen, Kaiser, Mittmann and Shrive studies provided price years, which allowed conversion to UK£, 2003. Between these studies, the price premiums ranged from £233 to £1255. Switzerland (Kaiser) reported the lowest price premium, whereas the US and Canadian studies (Cohen, Shrive) were over five times higher. It is worth noting the premium difference between the two Canadian studies (Shrive, Mittmann), both of which were set in 2002 (Mittmann 2002/2003, assumed to be 2002 for CPI purposes). The Shrive price premium is over Can$600 more than in the Mittman study, owing to the fact that the former estimated DES at $2900, whereas the latter estimated it at only $2400, and similarly BMS were estimated at $500 and $608, respectively.

Only the Shrive study[124] discounted costs at 3%; the Greenberg study did not mention discounting, which should have been undertaken as the study was over 2 years. The remaining six studies did not apply discounting, which was appropriate as they were only of 1 year in duration or less.

Health outcome data and data sources

The economic evaluation utilised a variety of sources of efficacy data, ranging from meta-analyses to single trial data (see *Table 11*). In terms of efficacy values reported, values ranged from 23% relative risk reduction for repeat revascularisation to a 94% reduction in TLR.

Four of the studies reported health outcomes in terms of QALYs. However, RRA, TLR avoided, MACE and MACE-free survival were also reported.

Cost-effectiveness results

The cost-effectiveness results varied considerably across studies (*Table 12*). The incremental cost per QALY ranged from Can$27,540 to Can$96,523 for a general population. The Bagust study did not include a general population as subgroups were found to be too dissimilar for comparison. Both the Greenberg and Cohen studies reported the incremental cost-effectiveness ratio (ICER) per RRA. Cohen estimated it to be $1650 over 1 year whereas Greenberg estimated it at approximately $7000 over 2 years. The other studies reported various outcomes which were not comparable.

Subgroup analysis

All except four of the studies provided subgroup analysis. A number of different subgroups were examined, including diabetes, long lesions, small vessels, triple vessel disease, calcification, prior CABG and older patients. As could be expected, the ICERs became more acceptable for the 'high-risk' subgroups.

In all the studies except the Bagust and Kaiser studies, diabetes was found or assumed to be a risk factor for restenosis. Thomas[130] has recently criticised the lack of inclusion of diabetes as a subgroup by Bagust, but both the Kaiser and Bagust studies used real-world data, which differ from the clinical trial data from which the belief of

TABLE 8 *Characteristics of economic studies*

Study	Type of evaluation and synthesis	Interventions	Study population	Country	Period of study
AETMIS, 2004[122]	CUA	DES (sirolimus and paclitaxel coated) versus BMS	Régie de l'Assurance Maladie du Québec (RAMQ) database, unselected patients. Repeat revascularisation risk with DES taken from meta-analysis of published trials	Canada	6–13 months
Bagust, 2006[120]	CUA	DES (sirolimus and paclitaxel coated) versus BMS	Cardiothoracic Centre (CTC) Liverpool population, unselected patients. Subgroup characteristics determined from a meta-analysis of published trials and CTC database	UK	1 year
Cohen, 2004[121]	CEA and CUA	DES (sirolimus) versus BMS	1058 patients with planned PCI of a single complex coronary artery stenosis (single native coronary artery). The lesion was *de novo,* 15–30 mm in length with a reference vessel diameter of 2.5–3.5 mm. SIRIUS trial	USA	1 year
Greenberg, 2004[123]	CEA	DES (sirolimus) versus BMS	Unselected patients	US	2 years
Gulizia, 2004[126]	CEA	DES (sirolimus) versus BMS	Data obtained from literature and adapted to Sicilian population, using data from a survey conducted in seven local catheterisation laboratories	Italy	1 year
Kaiser, 2005[82]	CEA	DES (sirolimus and Paclitaxel) versus BMS (Vision, third-generation BMS)	836 patients included in the BASKET study – 'real-world setting'	Switzerland	6 months
Mittmann, 2005[128]	CEA	DES (sirolimus and Paclitaxel) versus BMS	Patients treated in the trials (SIRIUS, TAXUS) and Babapulle meta-analysis	Canada	1 year
Shrive, 2005[124]	CUA	DES (sirolimus) versus BMS	Unselected patients, based on Canadian database of 7334 patients undergoing PCI between 1998 and 2000	Canada	Patient's lifetime
Tarricone, 2004[127]	CEA	DES (sirolimus) versus BMS	Patients suffering from stable or unstable angina, with *de novo* lesion(s). Case mix derived from unselected population of 1809 patients	Italy	1 year
Van Hout, 2005[125]	CEA	DES (sirolimus) versus BMS	238 patients with stable or unstable angina with planned PCI for single *de novo* coronary lesions. SIRIUS trial	The Netherlands	1 year

CEA, cost-effectiveness analysis; CUA, cost–utility analysis.

TABLE 9 *Economic model*

Study	Type of model	Perspective	Model assumptions		Life expectancy method
			Life expectancy and QoL	Revascularisations and other assumptions	
AETMIS, 2004[122]	Decision analytic model	Healthcare provider	No difference in survival or rates of MI	Assume 1.7 stents per PCI	Not applicable
Bagust, 2005[120]	Decision analytic model	Healthcare provider	No difference in long-term survival	Benefits of DES confined to reduction in angina and need for repeat revascularisations	Not applicable
Cohen, 2004[121]	Prospective analysis of SIRIUS results	Healthcare provider	No difference in long-term survival or QoL beyond first year	None stated	Not applicable
Greenberg, 2004[123]	Decision analytic model	Healthcare provider	Not applicable to model	TVR rate for BMS of 14%, 80% reduction in TVR with DES. Mean utilisation of 1.3 stents per single-vessel procedure	Not stated
Gulizia, 2004[126]	Decision analytic model	Healthcare provider – translation uncertain	Not applicable to model	Unable to translate	Not applicable
Kaiser, 2005[82]	Decision analytic model	Health care provider	Not applicable to model	None stated	Not applicable
Mittmann, 2005[128]	Decision analytic model	A hospital providing PCI, and the Ontario provincial healthcare system	Not applicable to model	1.5 stents are used for DES and BMS procedures. There are no resource allocation differences between DES and BMS. No incremental difference after the first year for outpatient resource utilisation. Cost of death same as cost of MI. Stent thrombosis always results in MI, and is same for both BMS and DES	Not applicable
Shrive, 2005[124]	Markov model with 6 month intervals for patients lifetime	Healthcare provider	After 1 year QoL assumed to be the same for all patients in all of the health states	Assumed 49.5% of repeat catheterisations (without PCI or CABG) following PCI with a BMS would have been avoided if a DES was used. Assumed 1.4 stents per PCI	Cox proportional hazards model
Tarricone, 2004[127]	Decision analytic model	Healthcare provider	Not applicable to model	None stated	Not applicable
Van Hout, 2005[125]	Unclear – economic model of RAVEL results	Healthcare provider	Not applicable to model	None stated	Not applicable

TABLE 10 *Cost data and cost data sources*

Study	Price premium[a] of DES	Currency and currency year	Other cost items	Cost data sources	Discount rate
AETMIS, 2004[122]	Can$1900	Can$, no price year stated	Direct hospital costs of PCI and CABG	McGill University Health Centre–Royal Victoria Hospital (MUHC–RVH). RAMQ database	NA – only 1 year
Bagust, 2005[120]	£500	UK£, 2003	Specialist consultations for patients with recurrent symptoms, hospital investigations, repeat interventions and specialist follow-ups	NHS reference costs for 2003 and CTC for resource usage	N/A – only 1 year
Cohen, 2004[121]	US$2000 (£1255)	US$, 2002	Medical care costs, catheterisation costs, other hospital costs and outpatient services	Medicare costs, mean hospital costs	N/A – only 1 year
Greenberg, 2004[123]	US$2000	US$, no price year stated	Revascularisation procedures, complications	Several multicentre trials of contemporary PCI involving more than 3000 patients	No explicit discounting undertaken
Gulizia, 2004[126]	€1986	Euro, unable to translate price year	Elective bypass, PCI, emergency room visit	Italian DRG costs	NA – only 1 year
Kaiser, 2005[82]	Cypher vs. Vision €885–1120 (£305–386) Taxus vs Vision €675 (£233)	Euro, 2003/2004	Hospital stay, intensive care, coronary angiography, CABG. Medications not included as assumed same in both arms	Swiss medical tariff (TARMED)	NA – 6 months
Mittmann, 2005[128]	Can$1792 (£914)	Can$, 2002/2003	From the hospital perspective, costs included stent and drug acquisition costs, hospitalisation costs (incorporating repeat procedures) and rehabilitation costs. From the provincial payer perspective, costs included those listed above plus physician fees and costs of laboratory and diagnostic tests	Stent manufacturers, the Sunnybrook and Womens College Health Sciences Centre (SWCHSC) drug formulary, the Ontario Drug Benefit formulary, the Ontario Case Costing Initiative (OCCI) and personal communications	NA – 1 year
Shrive, 2005[124]	Can$2400 (£1225)	Can$, 2002	Costs were categorised as hospital care, ambulatory care, home care, physician claims and medication costs	Alberta Health and Wellness for the 1995–1997 Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) cohort	3% per year
Tarricone, 2004[127]	Assume no difference, based on DRG costs	Euro, 2003	Coast of CABG, PCI with stent, cardiac death, angiography and medication	DRG costs	NA – only 1 year
Van Hout, 2005[125]	€1328	Euro, no price year stated	Index procedure, repeat revascularisations, medications, etc.	Erasmus Medical Centre (EMC), Rotterdam	N/A – only 1 year

DRG, Drug Resource Group; NA, not applicable.
[a] Price premium is the price differential between DES and BMS, here converted to UK£, 2003, where possible.

TABLE 11 *Health outcome data and data sources*

Study	Efficacy data sources	Efficacy data	Health outcomes	Health outcome data sources	Discount rate
AETMIS, 2004[122]	Meta-analysis of trial results (11 trials) Badapulle *et al.*, 2004, *Lancet*[14]	Repeat revascularisation risk reduction of DES of 74% compared with BMS	Repeat revascularisation rate, attempt at a rough QALY	Meta-analysis of trial results (11 trials) Badapulle *et al.*, 2004, *Lancet*[14]	NA
Bagust, 2006[120]	Meta-analysis of RAVEL TAXUS and SIRIUS trials	TVR RR reduction of 69.8% for SES compared with BMS. TVR risk reduction of 55% for PES compared with BMS	TVR as a proxy for repeat revascularisations, QALY	RAVEL, SIRIUS, TAXUS	NA
Cohen, 2004[121]	SIRIUS trial	Repeat revascularisation, 13.3% in sirolimus group, 28.4% in BMS group, leading to an RR reduction for repeat revascularisation of ~53%	Repeat revascularisation avoided, QALY	SIRIUS, QoL taken from stent–PAMI trial	NA
Greenberg, 2004[123]	Uncertain. Some data taken from a database containing 1-year health outcomes on 6186 patients undergoing PCI with conventional stents (database based on six clinical trials: STARS, ASCENT, SMART, NIVARNA, EXTRA and CCS)	RR reduction for TVR of 80% for SES compared with BMS	Repeat revascularisation avoided	Database and empirically derived data	No explicit discounting undertaken
Gulizia, 2004[126]	Meta-analysis of stenting for baseline TLR BMS rates, DES TLR risk reduction taken from SIRIUS trial	Baseline TLR non-DES of 12% for normal SVD patients. Risk reduction with DES of 75.5%	Revascularisations avoided	Meta-analysis of stenting for baseline TLR BMS rates, DES TLR risk reduction taken from SIRIUS trial	NA
Kaiser, 2005[82]	BASKET study – 'real-world' setting	Cardiac death, AMI and TVR. TVR DES 4.6%, non-DES 7.8%, giving a risk reduction of 41%	MACE, cardiac death, non-fatal MI and TVR	BASKET study	NA
Mittmann, 2005[128]	Meta-analysis of 11 trials	DES TLR 4.8%, BMS TLR 14.2%	TLR avoided	Meta-analysis of 11 trials	NA
Shrive, 2005[124]	Meta-analysis of RAVEL, SIRIUS, E-SIRIUS and C-SIRIUS	RR reduction for repeat revascularisation of 23% for SES compared with BMS	Restenosis rate, QALY	RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS	3%
Tarricone, 2004[127]	TLR and MACE rates taken from RAVEL, SIRIUS and ARTS	Clinically driven TLR of 13% for non-DES, and 0.72% for DES, for the overall population of SVD patients, giving a risk reduction of 94%. TLR rate for DES calculated by multiplying BMS TLR rate by efficacy of TLR from RAVEL trial	TLR, MACE	RAVEL, SIRIUS, ARTS, BENESTENT II	NA

continued

TABLE 11 *Health outcome data and data sources (cont'd)*

Study	Efficacy data sources	Efficacy data	Health outcomes	Health outcome data sources	Discount rate
Van Hout, 2005[125]	RAVEL trial	TLR of 0.8% for sirolimus group versus 11.8% with BMS group (without angiographic follow-up), leading to an RR reduction for TLR of ~93%	Death, MI, TLR, MACE-free survival	RAVEL	NA

NA, not applicable; RR, relative risk; SVD, single vessel disease.

TABLE 12 *Cost-effectiveness results*

Study	Cost-effectiveness ratios	Subgroup analysis	Sensitivity analysis (SA)	Conclusion	Industry author affiliation
AETMIS, 2004[122]	$23,067 per RRA, for selectively high-risk patients. Cost per QALY gained of $96,523 – rough estimate	None stated	Multivariate Monte Carlo SA and univariate SA. From the univariate SA the most sensitive parameters are the capacity to select high-risk patients for DES, the cost of DES, the number of stents per procedure, the baseline revascularisation rate with BMS and the effectiveness of DES. From the multivariate SA the most sensitive parameters are the capacity to select high-risk patients for DES, the cost of DES, the number of stents per procedure, the ratio of revascularisation rates for DES/BMS, the revascularisation rate post-index PCI and the cost of BMS	At the current stent costs, there is little justification for high rates of DES implementation. A substantial fall in price of DES or our ability to identify high-risk patients might alter conclusions substantially in Canada	None declared
Bagust, 2005[120]	Bagust did not provide an overall measure as it was felt that the subgroups were too dissimilar to combine	Detailed subgroup analysis. Elective patients were analysed based on four risk factors (calcification, angulation <45°, restenotic lesion and triple vessel disease), and non-elective patients based on two risk factors (vessel diameter <2 mm and prior CABG). The results show DES is only cost-effective in high-risk subgroups, and highly dependent on the number of stents used. Use of one SES was only cost-effective for elective patients with two or more risk factors, and in non-elective patients with one or more risk factors. This represents just 11.2% of the elective patient population and 9% of the non-elective population. Use of two SES could only be justified in elective patients with three or four risk factors, and non-electives with two risk factors. The eligible population was even smaller for PES. Refer to original article for more details	One-way and extreme values SA. With univariate SA only subgroup Y (non-electives with one risk factor) were affected by four factors, revascularisation risk, efficacy of DES, number of stents used, proportion of repeat procedures involving CABG. For extreme values SA subgroups C, D, Y and Z (high-risk) were sensitive, although for 89% of elective patients and 91% of non-electives the conclusions are robust	DES is only cost-effective for a small minority of patients who are at high risk of repeat revascularisation in the UK. For 90% usage of DES the price premium for cost-effectiveness = £114 and for cost neutrality = £82	None declared

continued

TABLE 12 *Cost-effectiveness results (cont'd)*

Study	Cost-effectiveness ratios	Subgroup analysis	Sensitivity analysis (SA)	Conclusion	Industry author affiliation
Cohen, 2004[121]	ICER per RRA = $1650 ICER per QALY = $27,540	Diabetes ICER = $2376/RRA No diabetes ICER = $1973/RRA TLR 10-15% ICER = $3727/RRA TLR 15-20% ICER = $5789/RRA TLR 20-25% ICER = $509/RRA TLR 25-30% DES dominant Lesion length <15 mm ICER = $4265/RRA Lesion length 15–20 mm ICER = $4459/RRA Lesion length >20 mm dominant Ref vessel diameter <2.5 mm ICER dominant Ref vessel diameter 2.5–3 mm ICER = $1345	Bootstrapping, graphically depicted. ICER <$10,000 per RRA for 98% of bootstrap simulations. ICER <$50,000 per QALY for 63% of bootstrap simulations	DES cost-effective for patients at high risk of restenosis in the USA	Cordis funding
Greenberg, 2004[123]	ICER of ~$7000 per RRA	No formal subgroup analysis. However, the authors felt that on the basis of logistic regression to predict clinical restenosis as a function of lesion length, reference vessel diameter and diabetes, DES should be 'economically attractive' for virtually all diabetics, and for non-diabetics with small vessels (<3 mm) and long lesions (>15 mm)	SA demonstrated that treatment with DES would be cost saving for patients with a BMS TVR rate of >20% and cost-effective for patients with a BMS TVR rate of >12%	DES should be cost-effective for the majority of patients, and cost saving for high-risk patients in the USA	Cordis, Guidant and Medtronic funding
Gulizia, 2004[126]	11.8/100 revascularisations avoided at a net inclusive cost of €931 per patient	Normal SVD (vessel diameter >2.5 mm, length <18 mm) Long lesions >18 mm Small vessels <2.5 mm MVD Diabetes	Univariate SA, of ±20% for costs and efficacy of DES (95% CI from SIRIUS trial)	DES is not cost-effective for lower risk groups, and should only be considered for higher risk populations	None declared
Kaiser, 2005[82]	€17,060 to prevent one MACE	Subgroups graphically depicted on the basis of age, stent length, number of segments treated, size of stent and length of stent. The technology was deemed potentially cost-effective in patients aged >65 years, with more than one segment treated, triple vessel disease, a stent length >20 mm, or with small stent sizes, at a threshold of €7800 per MACE averted	Bootstrapping and multivariate SA, graphically depicted using cost-effectiveness plan	DES is not cost-effective for all patients, only those at high risk	None declared

continued

TABLE 12 *Cost-effectiveness results (cont'd)*

Study	Cost-effectiveness ratios	Subgroup analysis	Sensitivity analysis (SA)	Conclusion	Industry author affiliation
Mittmann, 2005[128]	From the hospital perspective, the ICER ranged from Can$12,527 to 29,048 per TLR avoided. From the provincial perspective, the ICER ranged from Can$11,133 to 27,687	No subgroup analysis as stratified data were unavailable	Univariate SA on price of DES, PSA and EVPI, which indicated costs contributed most to uncertainty	At current DES prices, DES are more cost-effective in higher risk groups. Negotiating a lower DES price or only using DES for high-risk groups may make it more acceptable to hospitals and provinces. There is no consensus on an acceptable cost per TLR avoided, suggestions range from Can$10,000 to 15,000. Given that costs were the key source of uncertainty, there is a need for better data, to reduce the uncertainty	None declared
Shrive, 2005[124]	ICER = Can$58,721/QALY	Age <65 ICER = Can$72,464/QALY Age 65–75 ICER = Can$47,441/QALY Age >75 ICER = Can$40,129/QALY Diabetes ICER = Can$44,135/QALY No diabetes ICER = Can$63,383/QALY	One-way SA with plausible ranges. Restenosis rate with DES: Decreased 25% (to 10.7%) ICER = Can$83801/QALY Increased 50% (to 21.3%) ICER = Can$33,721/QALY Efficacy of DES: Lower 95% CI in Ravel (0.01%) ICER = Can$39,777/QALY Upper 95% CI in SIRIUS (0.55%) ICER = Can$119,280/QALY Patients with complex lesions only: ICER = Can$21,312/QALY	DES more cost-effective for patients at high risk of restenosis, or high risk of death from repeat revascularisation in Canada	None declared

continued

TABLE 12 *Cost-effectiveness results (cont'd)*

Study	Cost-effectiveness ratios	Subgroup analysis	Sensitivity analysis (SA)	Conclusion	Industry author affiliation
Tarricone, 2004[127]	Incremental TLR 13.4%; incremental cost –€968, for the overall population (large vessels, short lesions)	Long lesions Inc TLR 18.6%, incremental cost –€1227 Small vessels Inc TLR 15.1%, incremental cost –€768 MVD Inc. TLR 17.8%, incremental cost –€1757 Diabetics also undertaken as above, see original paper for details	Two-way SA of breakeven additional charge for DES according to DES efficacy, and the adoption rate of CABG in treatment of TLR	Adoption of DES specific DRG 23% higher than current BMS DRG, could support the introduction of the new technology by reimbursing 80% of its acquisition costs	Cordis funding
Van Hout, 2005[125]	Cost per MACE-free survival of €234–1495 including angiogram, and excluding follow-up angiogram, respectively	None reported	Bootstrapping and multivariate SA, graphically depicted using a cost-effectiveness plane	DES cost-effective in the treatment of single native *de novo* coronary lesions in The Netherlands	Cordis funding

DRG, Drug Resource Group; EVPI, expected value of perfect information; MVD, multivessel disease; PSA, probabilistic sensitivity analysis.

TABLE 13 *Critical appraisal of economic evaluations*

Checklist item[131]		Bagust, 2005[120]	Cohen, 2004[121]	AETMIS, 2004[12]	Greenberg, 2004[123]	Gulizia, 2004[126]	Kaiser, 2005[82]	Mittmann, 2005[128]	Shrive, 2005[124]	Tarricone, 2005[127]	Van Hout, 2005[125]
1.	The research question is stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2.	The economic importance of the research question is stated	✓	✓	✓	✓	×	✓	✓	✓	✓	✓
3.	The viewpoint(s) of the analysis are clearly stated and justified	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
4.	The rationale for choosing the alternative programmes or interventions compared is stated	✓	/	/	✓	✓	✓	✓	/	✓	/
5.	The alternatives being compared are clearly described	✓	✓	✓	✓	×	✓	✓	✓	✓	✓
6.	The form of economic evaluation used is stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
7.	The choice of form of economic evaluation is justified in relation to the questions addressed	✓	✓	✓	✓	×	✓	✓	✓	✓	✓
8.	The source(s) of effectiveness estimates used are stated	✓	✓	✓	/	✓	✓	✓	✓	✓	✓
9.	Details of the design and results of effectiveness study are given (if based on a single study)	NA	✓	NA	NA	NS	✓	NA	NA	/	/
10.	Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	NA	✓	✓	NS	NA	✓	✓	NA	NA
11.	The primary outcome measure(s) for the economic evaluation are clearly stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	/
12.	Methods to value health states and other benefits are stated	✓	✓	NA	NA	NA	NA	NA	✓	NA	NA
13.	Details of the subjects from whom valuations were obtained are given	✓	✓	NA	NA	NA	NA	NA	✓	NA	NA
14.	Productivity changes (if included) are reported separately	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
15.	The relevance of productivity changes to the study question is discussed if included	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
16.	Quantities of resources are reported separately from their unit costs	✓	✓	×	×	×	×	/	×	×	✓

continued

TABLE 13 *Critical appraisal of economic evaluations (cont'd)*

Checklist item[131]	Bagust, 2005[120]	Cohen, 2004[121]	AETMIS, 2004[12]	Greenberg, 2004[123]	Gulizia, 2004[126]	Kaiser, 2005[82]	Mittmann, 2005[128]	Shrive, 2005[124]	Tarricone, 2005[127]	Van Hout, 2005[125]
17. Methods for the estimation of quantities and unit costs are described	✓	✓	/	✓	/	✓	✓	/	✓	✓
18. Currency and price data are recorded	✓	✓	✓	✓	×	✓	✓	✓	✓	✓
19. Details of currency price adjustments for inflation or currency conversion are given	✓	NS	NS	NS	×	NS	✓	NS	NS	NS
20. Details of any model used are given	✓	/	✓	/	✓	/	✓	✓	✓	/
21. The choice of model used and the key parameters on which it is based are justified	✓	×	✓	×	✓	×	✓	✓	×	×
22. Time horizon of costs and benefits is stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
23. The discount rate(s) is stated	NA	NA	NA	×	NA	NA	NA	✓	NA	NA
24. The choice of rate(s) is justified	NA	NA	NA	NA	NA	NA	NA	×	NA	NA
25. An explanation is given if costs or benefits are not discounted	NA	NA	NA	×	NA	NA	NA	NA	NA	NA
26. Details of statistical tests and CIs are given for stochastic data	NA	✓	✓	NA	×	✓	✓	NA	NA	✓
27. The approach to SA is given	✓	✓	✓	×	✓	✓	✓	✓	✓	✓
28. The choice of variables for SA is justified	✓	NA	✓	×	/	✓	✓	✓	×	NA
29. The ranges over which the variables are varied are stated	×	NA	✓	×	✓	✓	✓	✓	/	NA
30. Relevant alternatives are compared	✓	✓	✓	✓	/	✓	✓	✓	✓	✓
31. Incremental analysis is reported	✓	✓	×	✓	/	✓	✓	✓	✓	×
32. Major outcomes are presented in both disaggregated and aggregated forms	✓	✓	✓	×	×	✓	✓	×	✓	/
33. The answer to the study question is given	✓	✓	✓	✓	/	✓	✓	✓	✓	✓
34. Conclusions follow from the data reported	✓	✓	✓	✓	/	✓	✓	✓	✓	✓
35. Conclusions are accompanied by the appropriate caveats	✓	✓	✓	✓	/	✓	✓	✓	✓	✓

✓, Yes (item adequately addressed); ×, no (item not adequately addressed); /, partially (item partially addressed); ?, unclear or not enough information; NA, not applicable, NS, not stated.

diabetes as a risk factor stems, and neither found diabetes to be a risk factor. This is explored more fully in Chapter 8.

Sensitivity analysis

Sensitivity analysis (SA) was undertaken in all 10 studies. The Cohen, Kaiser and Van Hout studies employed bootstrapping and multivariate SA, whereas the Bagust, Mittmann and Shrive studies used univariate (one-way) SA. The Mittmann study also undertook probabilistic SA and expected value of perfect information (EVPI) analysis, which showed costs to be the most uncertain factor. The Tarricone study undertook a simple two-way analysis, whereas the AETMIS study undertook multivariate and univariate Monte Carlo SA. The Greenberg study did not give any details of the SA methods employed. In general, it appears that the most sensitive parameters are the cost of DES, the number of stents per procedure, the baseline revascularisation rate with BMS and the clinical effectiveness of DES.

Author findings

The majority of studies (Bagust, Cohen, AETMIS, Gulizia, Kaiser, Mittmann and Shrive) concluded that DES are more cost-effective for higher risk patients. The remaining studies (Greenberg, Tarricone and Van Hout) were more sympathetic towards DES, although it is worth noting that all of these studies had received industry funding. Furthermore, the Van Hout study was based on the early RAVEL study which was a small study undertaken using a US-based balance of costs which do not translate to the UK NHS experience.

Quality of economic literature

Ten studies were quality assessed against a standard checklist.[131] The Guiliza study was kindly quality assessed with help from Dr Tom Jefferson [Agenzia per i Servizi Sanitari Regionali (ASSR)/Cochrane Vaccines Field, Italy] owing to difficulties in translation. In general, the quality of data was reasonably high (*Table 13*), except in four key areas. First, the resource use was only reported separately from costs in four of the studies, making it impossible to validate underlying assumptions. Second, a discount rate was not applied in the Greenberg study, and no explanation was given as to why not, and furthermore, the SA was not fully explained or justified. Finally, and most importantly, the modelling methodology was poorly described in seven of the studies, making it difficult to access the credibility of their models.

Commentary

The balance of evidence indicates (Bagust, Cohen, AETMIS, Gulizia, Kaiser, Mittmann and Shrive studies) that DES are more cost-effective for higher risk groups. However there was great disparity between studies, with a variety of outcomes and a range of ICERs being reported. Some studies were based on single efficacy studies, and some on meta-analyses of these studies. Only a single trial study could be said to be pragmatic and likely to reflect clinical practice outside of a trial (Kaiser). Some studies made great efforts to convert efficacy in trials into clinical effectiveness, and these generally concluded with worse ICERs.

Chapter 7

Critical review of manufacturer economic submissions

This chapter deals with the submissions of manufacturers of drug-eluting coronary artery stents involved in the NICE appraisal process (detailed in Final Matrix of Consultees, with the exception of Biosensors, who were invited to participate after the assessment had began). Seven of the nine companies invited to participate provided submissions. No submissions were received from Abbott or Sorin Biomedica and follow-up requests did not yield any economic data.

Submitted models

An overview of the economic submissions received is shown in *Table 14*. Boston, Cordis and Medtronic each provided a detailed economic evaluation together with a copy of their working model. KiWiMed provided a detailed economic evaluation but did not provide a copy of their model. Biosensors, Biotronik and Guidant did not provide an economic evaluation or present any other economic evidence.

Each model was analysed in detail and a range of strengths and weaknesses were identified. In each case, a standard checklist was applied[131] 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 (excluding KiWiMed who did not provide the actual model) are provided in *Table 15*. The following section deals with common methodological issues, before giving a summary and critique of each of the models in turn.

General methodological issues

The question to be addressed was clearly stated and each submission presented evidence in support of their advocated technology. Boston, Cordis and Medtronic provided copies of the model together with a detailed report of the accompanying economic evaluation (*Table 16*). KiWiMed did not provide a copy of their model but did include a detailed report of their economic evaluation. As such, it was not possible to undertake a detailed analysis of the KiWiMed model, although the report itself did have sufficient detail to determine the basic structure of the model.

Boston and Cordis models presented both 1-year and 2-year results using effectiveness data from individual clinical trials. Medtronic, however, presented two separate scenarios using a 5-year

TABLE 14 *Overview of company economic submissions*

Company	DES	Overview of economic submission
Biosensors	AXXION	No economic evaluation or model presented
Biotronik	CoStar	No economic evaluation or model presented. Statement of opinion that CoStar will be at least equivalent in terms of cost-effectiveness to other DES currently available to the NHS
Boston	Taxus	Detailed economic evaluation and Excel decision analytic model provided
Cordis	Cypher (pending)	Detailed economic evaluation and WinBug decision analytic model provided
Guidant	Xience (pending)	Clinical only, no economic evaluation and no model presented
KiWiMed[a]	Yukon	Detailed economic evaluation but a copy of the model was not provided
Medtronic	Endeavor	Detailed economic evaluation and Excel Markov model provided

[a] Although Translumina is the manufacturer of the Yukon DES, KiWiMed is the UK distributor and named consultee.

TABLE 15 *Quality assessment of submitted economic models*

Checklist items	Boston	Cordis	Medtronic
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.

time frame, one in which the reduction of the risk of repeat revascularisation with DES was assumed to last until the end of the first year, and the other in which the reduction in such risk was extended beyond the first year and for the remaining period of analysis. The data, however, only supported the first scenario, as trial data are only available up to 9 months. The KiWiMed model undertook a 5-year analysis using effectiveness data from trials of Cypher (RAVEL, SIRIUS, and E-SIRIUS), under the assumption that Yukon is equivalent to Cypher. From years two to five the patients were assumed to remain in the state they were in at the end of year one, due to a lack of long-term data to furnish the model.

Boston and Cordis presented subgroup analyses according to diabetes, lesion length and vessel diameter. No subgroup analysis was presented by Medtronic or KiWiMed. The difference in revascularisation rates between the two arms was the driving factor for costs and benefits in both the Cordis and Boston submissions. Medtronic, however, also included small differences in mortality, cerebrovascular accident (CVA) and MI (though not supported by clinical evidence). It was not possible to determine conclusively the driving factors in the KiWiMed model.

The structures of the models were similar for Cordis and Boston, who both used decision analysis. Medtronic, however, used a Markov model. It was not possible to determine the type of model used by KiWiMed. The key parameters in the models were generally akin to one another and similar to those used in work previously published by the review group. *Table 17* provides a summary of the key parameters in the models and their comparison with our previous publication.[120]

The main areas of discrepancy were the number of stents used during repeat revascularisation procedures, costs of DES and BMS and waiting time for subsequent PTCA or CABG. Medtronic used 1.87 stents per repeat procedure but only 1.12 for the index procedures. This introduces bias into the analysis, as this magnitude of difference in the number of stents used for index and repeat procedures is not supported by evidence.

Cordis assumed extremely high prices for BMS and DES, which although based on list prices are substantially out of line with other submissions and publications and with current market prices (Burrill J, NHS PASA: personal communication, 12 July 2005). Cordis also used relatively long waiting times for repeat procedure, choosing to use maximum NHS waiting times rather than average waiting times, which would be more accurate. Both of these can lead to overoptimistic cost-effectiveness ratios. Baseline rates of TVR/TLR with BMS also appear high compared with other studies;[120] these can be expected to be lower in clinical practice.

All of the submissions undertook sensitivity analysis (*Table 18*). KiWiMed employed two-way sensitivity analysis of probability of restenosis and cost of stent. Cordis and Medtronic employed probabilistic sensitivity analysis (PSA), whereas Boston opted for the simpler approach of univariate SA. [**Confidential information removed**].

TABLE 16 *Summary of economic submissions to NICE*

Submission	Study type	Comparators	Population and subgroups	Time frame (years)	Model used	Cost elements and sources (other than BCIA)	Effectiveness and benefit outcome measures	Cost/price of device (£)	Assumptions repeat revascularisation (%)
Cordis	CEA	2 way: Cypher vs BMS	RAVEL and SIRIUS Patient subgroups: Small vessels (<3 mm) Diabetic Long lesions (>15 mm)	1 2	DA	Procedures (PTCA, CABG, angiography), material (DES, BMS). Sources of costs; material costs from Boston, and Cordis list prices, procedure costs from NHS reference costs 2003, 2004	Utility weights (restenosis free, restenosis) TVR rates	BMS £908 Cypher £1341 Price premium[a] £433 Taxus £1300 Price premium £392	TVR (no risk group) 2-way: BMS 16.5 Cypher 5.2 Risk reduction 68.5 3-way: BMS 14.8 Cypher 4.4 Risk reduction 70.3 Taxus 5.8 Risk reduction 60.8
	CUA	3 way: Cypher vs Taxus vs BMS	As in RAVEL, SIRIUS, REALITY, CORPAL, ISAR DESIRE, ISAR DIABETES, SIRTAX, TAXI, TAXUS trials Patient subgroups: Small vessels (<3 mm) Diabetic Long lesions (>15 mm)	1 2					
Boston	CEA	DES vs BMS	TAXUS IV Patient subgroups: Small vessels (<2.5 mm) Diabetic Long lesions (>20 mm)	1	DA	Procedures (PTCA, CABG), material (DES, BMS, balloon, guiding catheter, guidewire), recurrence of symptoms (angiogram, cardiology visit, cardiac surgery visit); medication (clopidogrel, and IIb/IIIa therapy). Sources of costs; material costs from Boston [**confidential information removed**], procedures and recurrence of symptoms costs from Bagust *et al.*[120] (inflated to 2004–5); medication costs from BNF 2005	Utility weights (restenosis free, restenosis) TLR rates	[**Confidential information removed**]	TLR BMS 15.5 DES 4.3 Risk reduction 72.3
	CUA		As in TAXUS IV Patient subgroups: Small vessels (<2.5 mm) Diabetic Long lesions (>20 mm)	2					

continued

TABLE 16 *Summary of economic submissions to NICE (cont'd)*

Submission	Study type	Comparators	Population and subgroups	Time frame (years)	Model used	Cost elements and sources (other than BCIA)	Effectiveness and benefit outcome measures	Cost/price of device (£)	Assumptions repeat revascularisation (%)
Medtronic	CEA CUA	DES vs BMS	ENDEAVOR II trial BENESTENT II trial, with DES population risk reduction with DES taken from meta-analysis by Babapulle *et al.*, 2004[14] (1-year data)	1 5	Markov	Procedures (PTCA, CABG); material (DES, BMS); recurrence of symptoms (angiogram, cardiology visit, cardiac surgery visit, clopidogrel therapy, cardiac rehabilitation); acute events (AMI, CVA, cardiology review post-AMI, general physician visit post-CVA). Sources of costs all NHS reference, tariff and APC spell costs (2004, 2005), except stent costs Medtronic [**confidential information removed**], clopidogrel therapy, BNF 2005, and cardiac rehabilitation, HTA 2004 (inflated from 2003–4)	Utility weights (restenosis free, restenosis) TVR rates	BMS £318 DES £862 Price premium: £544	TVR BMS 12.82 DES 5.67 Risk reduction 55.8
KiWiMed[b]	CUA	DES vs BMS	RAVEL, SIRIUS and E-SIRIUS, from which effectiveness was taken	5	Unclear	Procedures (PTCA, CABG, angiography), material (DES, BMS). Sources of costs; material costs Translumina and LRiG; procedure costs from NHS reference costs 2003, 2004	Utility weights	BMS £380: DES £550 Price premium: £170	Unclear

APC, ambulatory payment classification; BCIA, British Cardiovascular Industry Association; BNF, British National Formulary; CEA, cost-effectiveness analysis; CUA, cost–utility analysis; DA, decision analytic.

[a] Price premium: price differential between DES and non-DES.

[b] KiWiMed did not provide model, parameters taken from supporting documentation where available.

TABLE 17 *Parameter values from industry submissions*

Parameter	Boston		Cordis		Medtronic		Bagust *et al.*, 2006,[120] for comparison		KiWiMed[b]	
	Value	**Reference source**	**Value**	**Reference source**	**Value**	**Reference source**	**Value**	**Reference source**	**Value**	**Reference source**
TLR/TVR rate DES for general population at 12 months[a]	4.3%	TAXUS IV trial	5%	Bayesian analysis of SIRIUS, C-SIRIUS, E-SIRIUS and RAVEL trials	6%	ENDEAVOR II trial	Elective: 2.4% Cypher, 3.5% TAXUS Non-elective: 3.4% Cypher, 4.9% TAXUS	CTC audit and TVR meta-analysis	Unclear	NA
TLR/TVR rate BMS for general population at 12 months[a]	15.5%	TAXUS IV trial	15%	Bayesian analysis of SIRIUS, C-SIRIUS, E-SIRIUS and RAVEL trials	12.8	ENDEAVOR II trial	7.8% elective, 11.0% non-elective	CTC audit	Unclear	NA
Number of stents used per index procedure	1.4	MILESTONE II	1.4	MILESTONE II	1.11 BMS 1.12 DES	ENDEAVOR II trial	1.62 elective, 1.45 non-elective	CTC audit	1.3	Initial LRiG model
Number of stents used per repeat procedure	1.4	MILESTONE II	1.4	MILESTONE II	1.87	Bagust *et al.*, 2005[120]	1.87	CTC audit	Unclear	NA
Price premium	[**Confidential information removed**]	NA	£433	NA	£544	NA	£500	NA	£370	NA
Cost BMS	[**Confidential information removed**]	Boston average selling price	£908	List price	£318	Medtronic average selling price	£370	Market average	£380	Translumina
Cost DES	[**Confidential information removed**]	Boston average selling price	£1341	List price	£862	Medtronic average selling price	£870	Market average	£550	Initial LRiG model

continued

TABLE 17 *Parameter values from industry submissions (cont'd)*

Parameter	Boston		Cordis		Medtronic		Bagust *et al.*, 2006,[120] for comparison		KiWiMed[b]	
	Value	**Reference source**	**Value**	**Reference source**	**Value**	**Reference source**	**Value**	**Reference source**	**Value**	**Reference source**
Cost of PTCA	£3253	Bagust *et al*. inflated to 2005	£2609	NHS	£3326	NHS spell costs 2004–5	£3190	NHS APC spell costs 2003–4	£1505	Personal communi-cation
Cost of CABG	£7904	Bagust *et al*. inflated to 2005	£7066	NHS	£8080	NHS spell costs 2004–5	£7750	NHS APC spell costs 2003–4	£7066	NHS reference costs, 2004
Annual QALYs lost to angina	0.17	ARTS trial[136]	0.15	ARTS trial	0.135	Bagust *et al.*, 2005[120]	0.135	ARTS and SoS trials	0.175	Serruys *et al.* 2001[135]
QALY's lost per PTCA	0.0035	HTA, Hill *et al.*, 2004[2]	NA	NA	0.0056	*Bagust et al.*, 2005[120]	0.0056	ARTS and SoS trials	Unclear	NA
QALY's lost per CABG	0.012	HTA, Hill *et al.*, 2004[2]	NA	NA	0.03	Bagust *et al.*, 2005[120]	0.033	ARTS and SoS trials	0.78 (per month)	Serruys *et al.*, 2001[135]
Waiting time for PTCA/CABG	3 months	NS	28 weeks	Maximum NHS waiting times	15 weeks	Bagust *et al.*, 2005[120]	15 weeks	CTC audit	Unclear	NA

NA, not applicable; NS, not stated.
[a] For Cordis no general population was reported, hence values are for the no risk factor population 2-way analysis.
b KiWiMed did not provide model, parameters taken from supporting documentation where available.

TABLE 18 *Sensitivity analyses within economic submissions to NICE*

Submission	Sensitivity analysis: Univariate: univariate or threshold analyses	Sensitivity analysis: Multivariate: deterministic or scenario analysis	Sensitivity analysis: Stochastic (PSA)	Parameters varied	Most influential parameters	Notes
Cordis	No	No	Yes	All parameters varied according to their accompanying distributions	Cost of DES, cost of BMS, baseline TVR rates	
Boston	Yes	No	No	Clopidogrel BMS 1 and 6 months Clopidogrel DES 12 months Average number of index stents (1.7) Waiting time for CABG (7 months) Discount rate (3.5% for both) [**Confidential information removed**]	Clopidogrel DES 12 months Baseline TLR rates Cost of BMS	[**Confidential information removed**] – TLR rates
Medtronic	No	No	Yes	All parameters varied according to their accompanying distributions	Cost of DES Baseline TVR rates	In 5-year study using OR for DES, incorrect reporting of TVR
KiWiMed[a]	No	Yes – two-way	No	Probability of restenosis. Cost of stent	Probability of restenosis	No model provided, hence values taken from supporting documentation

[a] KiWiMed did not provide model, parameters taken from supporting documentation where available.

Critical appraisal of Boston model

Comparison with checklist and general description

The submission compared DES against BMS for a general population and for subgroups [diabetic, small vessel (2.5 mm), long lesions (>20 mm)]. The BMS comparator is the EXPRESS stent, which obtained CE Marking in 2002. The DES is the TAXUS EXPRESS (herein referred to as Taxus), which uses the EXPRESS platform, and the TRANSLUTE polymer coating, which releases paclitaxel. This submission measured costs and benefits up to 2 years, using data from TAXUS IV (see Chapter 4 for clinical details). A simple decision analytic model was employed that estimated the difference in repeat revascularisations (TLR) between BMS and DES, and the accompanying small difference in QoL. No difference between MI, CVA or death was observed in the TAXUS IV trial, hence none was incorporated into the model.

Utility measures were taken from the previous assessment[2] and the waiting time with symptoms was assumed to be 3 months for both repeat stented-PCI and CABG. Cost data were taken from Bagust and colleagues[120] and Boston Scientific ASP (average selling price) values, together with BNF list prices. Resource use was derived from Boston Scientific market data, MILESTONE II and the previous NICE assessment report. The number of stents used was assumed to be 1.4 per procedure, as estimated in MILESTONE II.[132] Discounting was applied to the 2-year scenario at a rate of 6% for costs and 1.5% for effectiveness. Although these were not the current NICE-recommended discount rates of 3.5% for both costs and effectiveness, as this assessment was conducted with 'old' technology assessment procedures the discounting was appropriate.

Impact of variations in key assumptions

The authors concluded that Taxus is cost-effective at 12 months for the overall population (£29,587 cost/QALY) and for patients with diabetes (£1020 cost/QALY). Furthermore, for patients with small vessels and long lesions they state that Taxus is both more effective and less costly than BMS (dominant). Similarly at 24 months, they indicate that Taxus is cost-effective for the overall population (£13,394 cost/QALY) and for patients with long lesions (£5367 cost/QALY), and is dominant, for patients with small vessels and diabetes. A simple univariate SA was undertaken on five parameters: clopidogrel therapy post-PCI, average number of stents used, TLR rates, waiting time for CABG and discount rates. Results showed that the model was highly sensitive to variation in length of clopidogrel therapy and the average number of stents used. If the number of stents used per procedure is increased from 1.4 to 1.7, the cost/QALY at 12 months for the general population increases from the base case of £29,587 to £56,731. The subgroups are only marginally affected by this change and remain cost-effective. If the length of clopidogrel therapy post-DES is increased from 6 to 12 months, the cost/QALY at 12 months for the general population increases to £71,634. This change does not greatly alter the subgroups apart from in diabetic patients, for whom the technology is now no longer cost-effective.

[**Confidential information removed**] – TLR rates (*Table 19*). An error in the calculation for this SA was found and corrected by the Assessment Group.

In conclusion, the evidence supporting the cost-effectiveness of DES (Taxus) against BMS is questionable, as small variations in key parameters negate cost-effectiveness for the general population.

Critical appraisal of Cordis model

Comparison with checklist and general description

The Cordis submission compared DES with BMS, for both a 'no risk factor' population and for subgroups [diabetic, small vessel (2.5 mm), long lesions (>15 mm)]. This submission was split into a two-way analysis of BMS versus Cypher, and a three-way analysis of BMS versus Taxus versus Cypher. A simple decision analytic model was employed that estimated the cost implications of differences in repeat revascularisations between the comparators and the accompanying effects on QoL. The competing alternatives used in either analysis were not clearly defined in the submission. However, from an inspection of the trials upon which the models were based, it appears that the two-way analysis was based on a comparison of the bare metal BX VELOCITY stent with the DES Cypher, which is a sirolimus-coated BX VELOCITY stent. The three-way

TABLE 19 [Confidential information removed]

[Confidential information removed]

TABLE 20 *Univariate sensitivity analysis of results in Cordis submission (two-way model results)*

Subgroup	Type of stent	ICER in Cordis submission[a] (£)	ICER by setting cost of BMS at £278[b] and Cypher at £972.50[c] (£)
No risk factors	BMS		
	Cypher	29,259	69,613
Small vessels	BMS		
	Cypher	10,178	39,508
Long lesions	BMS		
	Cypher	16,460	49,345
Diabetics	BMS		
	Cypher	9,702	38,446

[a] Assumed price of £1341 for Cypher and £908 for BMS.
[b] Market average maximum prices by volume (source: Burrill J, NHS PASA: personal communication, July 2005).
[c] Midpoint range of maximum market prices by volume (source: Burrill J, NHS PASA: personal communication, July 2005).

analysis was based on RCTs of Cypher versus Taxus. However, to extend the three-way analysis to 2 years, an indirect comparison was undertaken using data from RCTs of Cypher versus BMS, where the BMS is the BX VELOCITY stent, together with data from RCTs on Taxus versus BMS, where the BMS is EXPRESS. The assumption that the BMS controls are equivalent is controversial, as recent studies have shown this not to be the case.[133] Thick-strut BMS such as BX VELOCITY are inferior to thin-strut BMS such as EXPRESS. This raises serious concerns about undertaking such indirect comparisons in relation to non-random heterogeneity between studies.

Utility measures were taken from the ARTS trial and the waiting time with symptoms was assumed to be 196 days (target maximum NHS waiting times) for both repeat stented-PCI and CABG. This clearly introduces a bias into the analysis as the average will be substantially lower than this. Resource use (1.4 stents used) was based on the MILESTONE II study.[132] Cost data were taken from Cordis, NHS reference costs, and Boston Scientific list prices. The cost data for the technologies (both BMS and Taxus) appear implausible. The costs of both Taxus and BMS were substantially overestimated compared with other studies and current prices, thus generating bias in the results in favour of Cypher. This is discussed in more detail in the following section. Discounting was applied to the 2-year scenario at a rate of 3.5% for both costs and outcomes, in line with current NICE-recommended discount rates, but differing from the standard applied for this assessment (of 6% for costs and 1.5% for outcomes).

Impact of variations in key assumptions

The robustness of the Cordis model results was tested by varying the prices of BMS and Cypher and recalculating the point estimate of cost-effectiveness. The original list prices of £908 for BMS and £1341 for Cypher were replaced with the average maximum market prices (Burrill J, NHS PASA: personal communication, July 2005) of £278 and £972.50. The rationale for this is that the quoted list prices are not equal to those actually used in the market. Data from 20 UK hospital trusts have demonstrated that the maximum predominant price paid for a single Cypher stent is in the range £950–995, and that paid for a BMS is less than £300. This change effectively increases the Cordis price premium from £433 to £694.50, with respect to BMS, which is more consistent with the real world. The results for the two-way analysis change are shown in *Table 20*.

Using market prices, instead of the notional list prices quoted in the Cordis submission, has a considerable effect on the results. In all subgroups, the ICER for Cypher versus BMS is now well above conventional thresholds for cost-effectiveness. The results are very similar when the effective list prices (i.e. maximum price charged in UK without discounts) are used instead.

Critical appraisal of Medtronic model

Comparison with checklist and general description

The submission compared DES against BMS for a general population. No subgroup analyses were

presented, rendering the results of the analysis of limited value and relevance to users. The BMS used in the analysis is the well-known DRIVER stent, which is CE Marked for use in Europe in patients with small and large vessels. The DES is based on the DRIVER platform with a phosphorylcholine polymer coating which releases the compound ABT-578 (a synthetic analogue of rapamycin). A simple Markov model was employed that estimated the difference in repeat revascularisations, MI and CVA between BMS and DES, and the accompanying small difference in QoL.

This submission measured costs and benefits at 5 years, although trial data from ENDEAVOR II were available only up to 9 months. Two separate scenarios were presented in the submission: in the first, the two arms were assumed to be equivalent in terms of the risk of repeat revascularisations after 1 year, whereas the second scenario assumed that differences remained over the 5-year period of analysis. This second scenario was not felt to be appropriate, for several reasons. First, it is based on the results of a meta-analysis of studies covering only the first year of analysis,[14] and then extrapolating such benefits from the second to fifth years. Second, the meta-analysis from which the OR was taken used only evidence for Taxus, and Cypher, and not Endeavor. Finally, TVRs were approximated by TLR rates when modelling second- to fifth-year outcomes for both BMS and DES. This is not appropriate as TLR and TVR rates are not equivalent. Furthermore, upon closer inspection it was found that MACE ORs for DES (as reported in the Babapulle meta-analysis) had been used mistakenly in place of TLR ORs, which were in turn supposed to represent TVR rates. Therefore, given the available evidence, the extrapolation of outcomes to 5 years as performed in the Medtronic economic model submission seems implausible.

Utility measures were taken from Bagust and colleagues,[120] and for the secondary analysis from Oostenbrink and colleagues.[134] Waiting times for PTCA and CABG were set at 15 weeks, as estimated by Bagust and colleagues.[120] Cost data were taken from Bagust and colleagues,[120] NHS APC spell, UK NHS reference costs and Medtronic sources. Discounting was applied to the 5-year scenario at a rate of 3.5% for costs and 3.5% for effectiveness, in line with current NICE guidelines, but differing from the standard applied for this assessment. Resource use was taken from Bagust and colleagues,[120] the ENDEAVOR II trial and our previous assessment.[2] The stent resource usage was not felt to be credible as the number of index stents used (1.12) was derived from a trial population (ENDEAVOR II), and likely to be selective, whereas the number of stents used for repeat PCI (1.87) was taken from Bagust and colleagues,[120] which used a sample of patients from general practice. This is likely to introduce bias into the analysis in favour of DES as it reduces the initial cost of DES but makes repeat procedures more costly, and thus improves the cost-effectiveness ratio.

Impact of variations in key assumptions

The base-case results presented indicate that Endeavor is cost-effective for the general population, with an incremental cost per QALY gained of less than £20,000. If the model is extrapolated to 5 years using the OR from the Babapulle meta-analysis, the results become even more favourable for Endeavor. The subsequent PSA suggested that at £30,000 per QALY Endeavor had a 57% chance of being cost-effective.

Upon further investigation, the model was found to be highly sensitive to two key parameters, baseline TVR rates and the number of index stents used. If base-case TVR rates (for both BMS and DES) are reduced below 12%, then the technology yields an ICER exceeding £30,000 per QALY gained. Similarly, if the average number of stents used for the index procedure is increased above 1.31, then Endeavor is no-longer cost-effective. A recent multi-centre global observational registry of TAXUS (MILESTONE II) estimated the stent usage to be 1.4 per procedure. Since registries have a higher degree of external validity than RCTs and resource usage of DES has not been shown to be device specific, it seems plausible to assume that in the 'real world' Endeavor usage may also be in the range of 1.4 or more. With this in mind, the number of stents (both BMS and Endeavor) used per index procedure was assumed to be 1.4, and the resulting amended ICER is reported in *Table 21*.

In conclusion, the results presented in this submission are likely to be biased in favour of DES. Our main criticisms relate to the way in which disparate sources of evidence were combined to derive estimates of benefits beyond the first year of analysis, involving strong assumptions about future accumulation of benefits, and the comparability of the measures of benefit used by the different sources. Furthermore, the number of stents used in the index procedure, derived from a single trial, may be

TABLE 21 *Two-year cost-effectiveness assuming 1.4 stents per index procedure.*

Parameter to be varied	Measure	ICER in Medtronic submission (1.11 BMS, 1.12 DES per index procedure)	ICER by assuming 1.4 stents per index procedure
Number of stents per index procedure	Cost/QALY	£11,221	£39,174

TABLE 22 *DES list prices*

DES	Manufacturer	List price (£)[a]
AXXION	Biosensors	995
CoStar	Biotronik/Conor	– (CE Marking pending)
Cypher Select	Cordis	– (as for Cypher)
Cypher	Cordis	1341
Dexamet	Abbott/Biocompatibles	1250
Endeavor	Medtronic	1700
Janus	Sorin	1500
Liberté	Boston Scientific	– (as for Taxus)
Taxus	Boston Scientific	1300
Xience V	Guidant	– (CE Marking pending)
Yukon	Translumina/KiWiMed	650

[a] List prices submitted to the Assessment Group (by NICE) on 20 October 2005.

unrepresentative, and together with high revascularisation rates found in the study, may bias the results, making DES appear cost-effective compared with BMS.

Critical appraisal of KiWiMed model

This submission compared DES against BMS for a general population. No subgroup analyses were presented, rendering the results of the analysis of limited value and relevance to users. The model was not made available, so it was not possible to undertake a quality assessment or determine the impact of variations in key parameters. From analysing the supporting documentation, a very limited understanding of the model was obtained.

The model itself was based on our initial model[2] although its exact structure is uncertain. The model estimated the 5-year cost-effectiveness of Yukon versus non-DES. The effectiveness data were taken from the RAVEL, SIRIUS and E-SIRIUS trials of Cypher, as KiWiMed assume that Yukon will be equivalent to Cypher. Extrapolation from years two to five was undertaken by assuming that patients remain in the same health state that they were in at the end of year one. Utility measures were taken from Serruys and colleagues,[135] whilst costs were derived from NHS reference costs, Translumina, our initial model and personal communications. It is unclear whether discounting was applied.

The results presented claimed that Yukon was dominant (both less costly and more effective) compared with BMS. A two-way SA was undertaken on cost of stent (DES versus BMS) and probability of restenosis (DES versus BMS). Over a range of £250–500 for cost of BMS and £500–1750 for cost of DES, DES was always cost-effective at a threshold of £30,000. In terms of probability of restenosis, results were not clearly stated.

List prices

Close to completion of this report, list prices for DES were submitted to the Assessment Group by NICE. Available list prices are presented in *Table 22* for information only.

Some of these prices may not match prices included in manufacturers' original submissions as list prices were omitted or other indicators of price were used with submissions, such as average

selling/market price. Given the timing of provision of these data, we were not in a position to incorporate changes into our economic review. Furthermore, list prices are not actually used in the market, as demonstrated by our collaboration with the NHS PSA (Burrill J, NHS PASA: personal communication, July 2005).

Summary of critical review of submitted models

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

- The sources of data and the ways in which they are combined need careful attention. In particular, assumptions in the Medtronic submission based on complementary sources and extrapolations beyond the horizons of the available clinical trial evidence seem unreasonable.
- The results of the analysis by Cordis appear to rely heavily on unwarranted price values for the comparators analysed. Moreover, evidence using indirect comparisons appears to disregard serious plausible concerns in relation to non-random heterogeneity between studies.
- By omitting the analysis of population subgroups, the Medtronic submission provides little usable information that can inform practical decision-making. The robustness of their results for the overall population is nevertheless in question as plausible deviations from the assumptions in the submitted model render the technology not cost-effective at conventional thresholds.
- Without access to the actual model, as with KiWiMed, it is not possible to identify any potential weaknesses of the analysis or determine the robustness of the model.
- When more realistic assumptions and data values are used in the submitted models, they confirm the view that DES may only be cost-effective under very limited circumstances.

Chapter 8

Economic evaluation: DES versus BMS

Introduction

This chapter begins by outlining the key clinical issues of relevance to the economic assessment of DES versus BMS. In particular, the importance of moving from efficacy-based to effectiveness-based data is highlighted. Methods of economic assessment are described, including our economic modelling and sensitivity analysis methods and details of sources of model data. Cost-effectiveness results and sensitivity analyses are presented, followed by a structured discussion of related issues. Key features of our economic evaluation are summarised in *Table 23*.

Clinical outcomes for economic assessment

Survival/mortality

The meta-analysis reported in Chapter 4 shows no evidence of any mortality advantage accruing to patients treated with DES compared with those treated with BMS. The limited data available from the 3-year follow-up are equally inconclusive. On the basis of this evidence, we assume no difference in mortality/survival between the two technologies in our economic assessment.

Myocardial infarction

The meta-analysis of published trials in respect of any MI event provides a consistent result at 1 month, 6 months, 1 year, 2 years and 3 years, with no evidence of any difference in infarct rates or timing between DES- and BMS-treated patients. This allows us to assume that costs and outcomes specifically associated with MI are equivalent and will not contribute to incremental cost-effectiveness results.

Other events

Both common measures of repeat revascularisation (TLR and TVR) show strong evidence in favour of DES over all follow-up periods from 6 months to 3 years. However, the estimated benefit in the meta-analysis appears to be stable over the long term, suggesting that all or the great majority of benefit accrues within the first 12 months. This is in accord with the weight of experience concerning the timing of most restenotic events.[2] No other outcome measure shows evidence of additional differences between stent types.

Converting efficacy to effectiveness

Importance of effectiveness

The efficacy of DES compared to BMS has been estimated in Chapter 4: reductions in TLR at 12 months of 74% and in TVR at 12 months of 57.5%. However, for the purpose of carrying out an economic assessment from the perspective of the NHS, it is necessary to relate the evidence from clinical trials to the likely performance of the technology in practice in a UK context – we need to translate **efficacy** findings into realistic measures of **effectiveness**.

There are several reasons why we should expect effectiveness to differ from reported efficacy:

- The patients selected for enrolment in RCTs are not normally representative of the case mix of persons treated in a typical cardiology

TABLE 23 *Key features of economic evaluation*

Economic method:	Cost utility analysis
Perspective:	NHS
Technology:	DES versus BMS
Population:	Patients currently revascularised for angina in NHS hospitals
Effectiveness:	Reduced rate of repeat revascularisation within 12 months
Benefit:	Avoiding QALY loss from repeat revascularisation
Sensitivity analysis:	Univariate and extreme values analyses
Key parameters:	Price premium, number of stents used, reduction in absolute risk of repeat intervention

department. Inclusion criteria frequently seek to address the needs of a particular narrow segment of potential patients, representing the patients of interest to either the clinical investigators or the trial sponsors.
- Practitioners participating in RCTs are generally 'enthusiastic volunteers' with strong motivation, and exceptional skills and experience. These factors can lead to the achievement of 'best possible' results, which are unlikely to be reproducible routinely following general implementation across the health service.
- There may be selective reporting of results (bias against publishing negative trials, or omission of equivocal end-points in published studies).
- The design of trials may not address questions of central importance to the assessment of cost-effectiveness.

In order to translate efficacy to NHS effectiveness, it is important to identify information from a recent representative source on:

- all patients treated for PCI in the NHS
- the nature and distribution of risk factors affecting DES performance
- the extent to which the use of DES in place of BMS can be expected to benefit patients (taking account of operational constraints, where necessary).

Potential to benefit

Current understanding of the mode of action of DES is that the local elution of the chemical coating acts locally on the immediately proximal arterial wall to inhibit the tendency to restenosis observed following implantation of BMS. This leads to the following conclusions concerning the potential of patients to benefit from use of DES:

- The direct benefit should be directly observable in the treated lesion by the adequacy of arterial flow in the immediate area. Although frequently measured in terms of vessel patency or extent of stenosis, a more relevant measure for economic assessment is the rate at which patients present for a repeat revascularisation procedure of the index lesion (TLR).
- A secondary measure of direct benefit is the rate of presentation for repeat revascularisation anywhere in the vessel containing the index treated lesion (TVR). Since TLR is a subset of TVR, and separate lesions in the same vessel are unable to benefit from direct contact with the implanted DES, the effectiveness measured by a reduction in TVR will always be less than that measured by TLR.
- Treatment by PCI does not have any effect on the underlying systemic pathology giving rise to new lesions throughout the coronary arterial system. Hence new lesions can be expected to develop at a steady rate independent of how the index lesion(s) is treated. These will contribute to the rate at which stented patients require further PCIs but will not be affected by the initial use of DES instead of BMS, so that the final measure of effectiveness (reducing the number of subsequent revascularisations required, irrespective of location) will be less than that attained in both TLR and TVR.
- The principal studies used to determine the efficacy of DES compared with BMS (TAXUS I, II and IV, Sirius and E-Sirius) all enrolled patients receiving treatment to a single *de novo* lesion. About 25% of patients presenting for treatment in normal practice undergo multi-vessel stenting, and more than one lesion may be treated in a single vessel. Hence care is required when extrapolating trial results to real-world practice to account for the greater complexity of treatment and possible subsequent events in patients whose needs are not as straightforward as those in trials.

Effectiveness estimates from observational data

In order to quantify the impact of these factors on the relationship between efficacy and effectiveness, we combined the results of two observational studies undertaken in Liverpool with the results on the meta-analyses reported in Chapter 4. The method is described in detail below and illustrated graphically in *Figure 6*.

Repeat revascularisations

In order to quantify the impact of these factors on the relationship between efficacy and effectiveness, we carried out a detailed examination of patient-level data for the patient sample from the Cardiothoracic Centre (CTC) Liverpool, used to inform the previous assessment.[2] Findings from these data concerning the prevalent rates of revascularisation in various risk subgroups were reported recently.[120] In addition, we investigated in detail the disposition of lesions treated as part of a repeat procedure compared with the index lesion(s), in order to estimate the proportion of repeat interventions that could be expected to benefit from use of DES rather than BMS. Using trial-reported TLR/TVR as the primary source for estimates of risk reduction due to DES (efficacy), it is possible to estimate the likely real-world risk

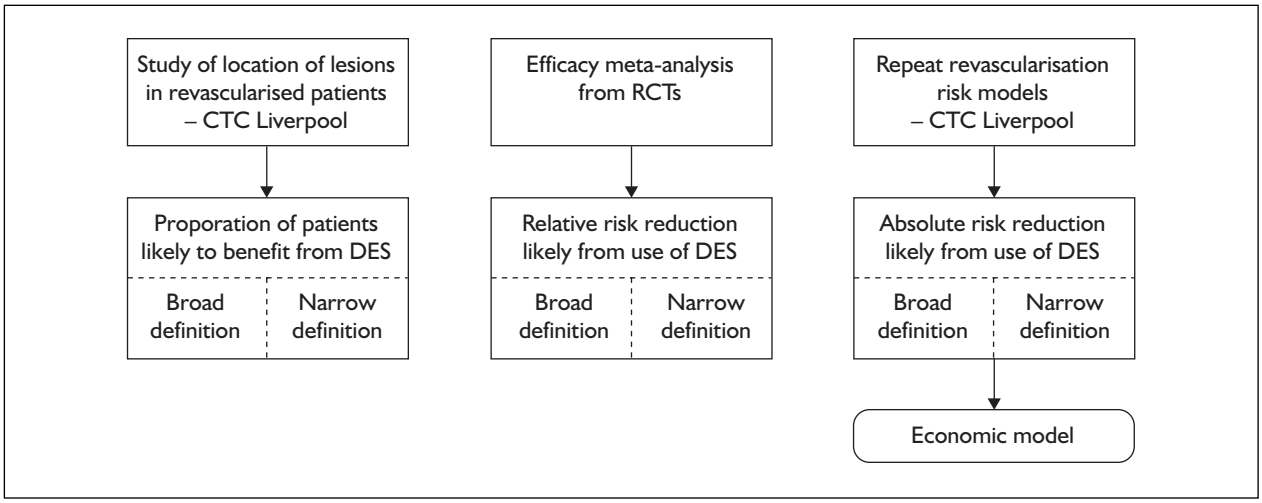


FIGURE 6 *Deriving effectiveness estimates from efficacy results*

reduction in all repeat revascularisations (effectiveness) which could be expected in routine NHS practice.

Table 24 shows the results of analysing the site of lesions involved in repeat interventions undertaken within 12 months of an index procedure. There are no statistically significant differences between patients initially treated electively and non-electively, or by the number of lesions stented. Half (51%) of patients receiving a second intervention required repeat treatment only to previously treated lesions; these are the patients in whom DES can be expected to produce benefit. A further 17% of patients received repeat treatment to a target lesion at the same time as treatment to a previously untreated lesion in the same vessel. It is not possible to determine whether or not the repeat procedures could have been avoided by use of DES in these cases, as we cannot identify which lesion(s) was the primary source of recurrent symptoms in these patients. However, it is clear that only between half and two-thirds of the reported DES benefit (in terms of reduced TLR) can be expected to result in reduced numbers of patients presenting for repeat revascularisation within 12 months.

Applying these proportions to the relative risk reduction of 74.6% for TLR obtained by meta-analysis of DES trials irrespective of type (see Chapter 4) yields an expected risk reduction in all revascularisations at 12 months of between 38% (95% CI 32 to 44%) and 50% (95% CI 44 to 57%).

A similar analysis focusing on TVR events in the CTC data is shown in *Table 25*. In this case, 61% of the repeat revascularisations required attention only to vessels previously treated, and 79% involved at least one previously treated vessel. The relative risk reduction in TVR from the meta-analysis in Chapter 4 is 57.5%; combined with the CTC results this suggests a risk reduction in all revascularisations at 12 months of between 35% (95% CI 28 to 42%) and 46% (95% CI 36 to 54%). Thus the two methods of calculation lead to similar results.

Lesions treated in repeat revascularisations

It is also useful to consider the likely benefit that DES may offer in reducing the number of lesions stented in repeat interventions. The process for calculating this estimate is similar, except that we count lesions treated but exclude cases undergoing CABG rather than PCI. Results are displayed in *Tables 26* and *27*. When applied to the TLR and TVR relative risk reductions from meta-analysis, this suggests that the reduction in the number of lesions treated in subsequent revascularisation is between 37% (95% CI 31 to 42%) and 53% (95% CI 47 to 59%) (based on TLR), or between 34% (95% CI 27 to 41%) and 48% (95% CI 37 to 56%) (based on TVR). In patients undergoing a second PCI within 12 months, only 60% of lesions treated were TLRs and 72% TVRs.

Risk factors, subgroups and estimated benefit

We recently reported the results of an audit study of stented patients treated at CTC Liverpool over a 2-year period and followed-up for 12 months.[120] This provided information on the number of patients who underwent any subsequent revascularisation episode, allowing us to estimate the risk of repeat revascularisation in a typical UK

TABLE 24 *Analysis of patients by site(s) of repeat revascularisation (TLR) in 12 months following index PCI in CTC database*

Case type	Index PCI	Patients receiving repeat intervention				Proportions (%)					
		All patients	TLR-only cases	Non-TLR only cases	Mixed TLR/ other cases	TLR-only cases	95% LCL	95% UCL	TLR ± other cases	95% LCL	95% UCL
Elective	1 lesion	60	30	25	5	50	38	63	58	46	70
	2 lesions	63	35	12	16	56	43	68	81	71	90
	3+ lesions	22	12	6	4	55	34	74	73	53	89
	All	145	77	43	25	53	45	61	70	63	78
Non-elective	1 lesion	59	24	29	6	41	29	53	51	38	63
	2 lesions	24	15	5	4	63	43	80	79	61	93
	3+ lesions	10	5	0	5	50	21	79	100	NA	100
	All	93	44	34	15	47	37	57	63	52	73
All types	All lesions	238	121	77	40	51	45	57	68	62	73

LCL, lower confidence interval; NA, not applicable; UCL, upper confidence interval.

TABLE 25 *Analysis of patients by site(s) of repeat revascularisation (TVR) in 12 months following index PCI in CTC database*

Case type	Index PCI	Patients receiving repeat intervention				Proportions (%)					
		All patients	TVR-only cases	Non-TVR only cases	Mixed TVR/ other cases	TVR-only cases	95% LCL	95% UCL	TLR ± other cases	95% LCL	95% UCL
Elective	1 lesion	60	36	14	10	60	47	72	77	65	86
	2 lesions	63	40	7	16	64	51	75	89	80	95
	3+ lesions	22	15	2	5	68	48	85	91	76	99
	All	145	91	23	31	63	55	70	84	78	90
Non-elective	1 lesion	59	30	23	6	51	38	63	61	48	73
	2 lesions	24	20	2	2	83	66	95	92	78	99
	3+ lesions	10	5	1	4	50	21	79	90	66	100
	All	93	55	26	12	59	49	69	72	63	81
All types	All lesions	238	146	49	43	61	55	67	79	74	84

LCL, lower confidence interval; UCL, upper confidence interval.

TABLE 26 *Analysis of lesions by site(s) of repeat revascularisation (TLR) in 12 months following index PCI in CTC database (excluding CABG)*

Case type	Index PCI	Patients receiving repeat intervention				Proportions (%)					
		All lesions	TLR-only cases	Non-TLR only cases	Mixed TLR/ other cases	TLR-only cases	95% LCL	95% UCL	TLR ± other cases	95% LCL	95% UCL
Elective	1 lesion	73	28	33	12	38	28	50	55	43	66
	2 lesions	98	51	14	33	52	42	62	86	78	92
	3+ lesions	41	20	10	11	49	34	64	76	62	87
	All	212	99	57	56	47	40	53	73	67	79
Non-elective	1 lesion	62	24	32	6	39	27	51	48	36	61
	2 lesions	34	25	3	6	74	58	87	91	80	98
	3+ lesions	18	13	2	3	72	50	90	89	71	99
	All	114	62	37	15	54	45	63	68	59	76
All types	All lesions	326	161	94	71	49	44	55	71	66	76

LCL: lower confidence interval; UCL: upper confidence interval

TABLE 27 *Analysis of lesions by site(s) of repeat revascularisation (TVR) in 12 months following index PCI in CTC database (excluding CABG)*

Case type	Index PCI	Patients receiving repeat intervention				Proportions (%)					
		All lesions	TVR-only cases	Non-TVR only cases	Mixed TVR/ other cases	TVR-only cases	95% LCL	95% UCL	TLR ± other cases	95% LCL	95% UCL
Elective	1 lesion	73	36	16	21	49	38	61	78	68	87
	2 lesions	98	60	9	29	61	51	71	91	84	96
	3+ lesions	41	25	4	12	61	46	75	90	80	97
	All	212	121	29	62	57	50	64	86	81	91
Non-elective	1 lesion	62	31	26	5	50	38	62	58	46	70
	2 lesions	34	30	0	4	88	76	97	100	NA	100
	3+ lesions	18	13	2	3	72	50	90	89	71	99
	All	114	74	28	12	65	56	73	75	67	83
All types	All lesions	326	195	57	74	60	54	65	83	78	86

LCL, lower confidence interval; NA, not applicable; UCL, upper confidence interval.

population at a time when only BMS were employed in regular clinical practice.

In order to determine which subgroups may be at greatest risk, we developed separate risk models for elective and non-elective patients using patient and lesion characteristics known at the time of the index intervention. Proportional hazards regression identified four significant independent factors for elective patients (calcification, angulation, restenotic lesion and triple vessel disease), and just two factors for non-elective patients (previous CABG and small vessel <2 mm). *Tables 28* and *29* reproduce these results with the addition of estimates of the expected reduction in absolute risk of repeat revascularisation for each subgroup. 'Narrow' estimates are calculated from cases involving TLR/TVR only, whereas 'broad' estimates are based on cases involving any TLR/TVR irrespective of any other lesions/vessels revascularised. The great majority of patients fall into the lowest risk groups (57% of elective patients and 91% of non-elective patients) who could expect a reduction in absolute risk of 2–3% and 3–5% respectively.

Effectiveness of selective use of DES

A further issue which can be informed from the CTC audit data concerns the extent to which a policy of selective use of DES mixed with BMS in the same patient may allow for reductions in costs greater than the likely loss of DES benefit, that is, an improvement in cost-effectiveness ratios. To explore this question, we have reviewed the experience of patients requiring a repeat revascularisation procedure who underwent index stenting to more than one lesion. Using the CTC Liverpool risk model, we identified where patients required subsequent intervention to the highest risk index lesion, a lower risk index lesion and or any previously untreated lesions. In each case we were able to ascertain whether a policy of using a single DES targeted at the highest risk lesion would have the potential for benefit in that the patient may not have required a repeat intervention to any lesion.

In elective patients initially requiring stenting to two or more lesions, we estimate that only 37% of patients who might benefit from an 'all DES' policy would also be likely to benefit from a 'targeted single DES' policy. In non-elective patients, only 26% of such patients continue to benefit. This does not necessarily mean that such a policy would not be advantageous from an economic perspective (since the high additional cost of DES compared with BMS can lead to very substantial savings when use is restricted), but it does indicate that clinical gains are likely to be seriously curtailed by a restrictive targeting policy which routinely mixes DES and BMS in the same patient. This is a direct consequence of the high rate of non-TLR lesions treated in patients undergoing second procedures, combined with the imprecision of predictive risk modelling when applied to individual cases.

Economic assessment methods

As noted in our previous assessment, the absence of clinical trial evidence of differences in long-term outcomes affecting life expectancy or disability (i.e. mortality, MI, stroke, thrombosis) greatly reduces the complexity of an economic evaluation. The latest clinical evidence has not altered the conclusions previously reached on any of the assumptions adopted, and therefore we have continued to employ the same evaluative framework with only minor modifications.

This can be readily expressed in terms of some simple equations which relate to estimates of the net additional costs incurred and additional benefits accrued at 12 months following the index procedure. The equations are set out below.

Equation 1

ICER = Incremental cost/Incremental benefit

Equation 2

Incremental cost =
- extra cost of using DES in index procedure for all patients (C_1)
- – saved costs of re-referral + investigation for patients with recurrent symptoms (C_2)
- – saved costs of treatment for patients requiring repeat revascularisation procedure (C_3)
- – saved costs of follow-up for patients after repeat revascularisation procedure (C_4)

where

C_1 = DES price premium × average number of stents per patient × number of patients
C_2 = ARR × number of patients × average cost of re-referral + investigation
C_3 = ARR × number of patients × average cost of repeat procedure
C_4 = ARR × number of patients × average cost of follow-up

and absolute risk reduction (ARR) due to DES:

TABLE 28 *Elective patient subgroups derived from CTC audit study with absolute risk reduction estimated from use of DES*

	Subgroup risk profile				Absolute risk	95% CI	Absolute risk reduction expected from DES (%)				Proportion of patients (%)
	Calcification	Angulation >45°	Restenotic lesion	Triple vessel disease			TLR-based		TVR-based		
							Narrow	Broad	Narrow	Broad	
A		**No risk factors**			**5.6**	**4.3 to 6.9**	**2.1**	**2.8**	**2.0**	**2.5**	**57.2**
B		**1 risk factor**			**8.4**	**6.9 to 10.1**	**3.2**	**4.2**	**3.0**	**3.8**	**31.6**
B1	No	Yes	No	No	7.7	5.4 to 10.2	2.9	3.9	2.7	3.5	17.7
B2	No	No	No	Yes	7.7	4.9 to 10.7	2.9	3.9	2.7	3.5	6.3
B3	Yes	No	No	No	10.5	7.2 to 14.1	4.0	5.3	3.7	4.8	6.1
B4	No	No	Yes	No	11.1	5.8 to 16.8	4.2	5.6	3.9	5.1	1.5
C		**2 risk factors**			**16.6**	**14.4 to 18.8**	**6.3**	**8.4**	**5.8**	**7.6**	**10.1**
C1	No	Yes	No	Yes	14.8	11.5 to 18.4	5.6	7.5	5.2	6.8	3.6
C2	Yes	Yes	No	No	17.4	13.8 to 21.4	6.6	8.8	6.1	7.9	4.8
C3	Yes	No	No	Yes	17.3	13.4 to 21.6	6.6	8.7	6.1	7.9	0.9
C4	No	Yes	Yes	No	17.9	12.9 to 23.7	6.8	9.0	6.3	8.2	0.3
C5	No	No	Yes	Yes	17.9	12.7 to 24.0	6.8	9.0	6.3	8.2	0.4
C6	Yes	No	Yes	No	20.4	15.0 to 26.4	7.7	10.3	7.2	9.3	0.2
D		**3 or 4 risk factors**			**24.6**	**21.5 to 27.9**	**9.3**	**12.4**	**8.7**	**11.2**	**1.1**
D1	Yes	Yes	No	Yes	23.7	19.6 to 28.1	9.0	12.0	8.4	10.8	0.8
D2	No	Yes	Yes	Yes	24.2	18.9 to 30.1	9.2	12.2	8.5	11.1	0.1
D3	Yes	Yes	Yes	No	26.5	21.2 to 32.4	10.1	13.4	9.4	12.1	0.2
D4	Yes	No	Yes	Yes	26.5	21.0 to 32.5	10.0	13.4	9.4	12.1	0.0
D5	Yes	Yes	Yes	Yes	32.2	26.7 to 38.0	12.2	16.2	11.4	14.7	0.1

TABLE 29 *Non-elective patient subgroups derived from CTC audit study with absolute risk reduction estimated from use of DES*

	Subgroup risk profile				Absolute risk reduction expected from DES (%)				Proportion of patients
	Vessel diameter <2 mm	Prior CABG	Absolute risk (%)	95% CI	TLR-based		TVR-based		(%)
					Narrow	Broad	Narrow	Broad	
X	**No risk factors**		**9.0**	**6.9 to 10.8**	**3.4**	**4.5**	**3.2**	**4.51**	**91.0**
Y	**1 risk factor**		**22.2**	**15.5 to 29.6**	**8.4**	**11.2**	**7.8**	**10.1**	**8.9**
Y1	Yes	No	25.3	13.8 to 36.8	9.6	12.8	8.9	11.6	3.4
Y2	No	Yes	20.3	11.2 to 29.4	7.7	10.2	7.2	9.3	5.5
Z	**2 risk factors**		**40.4**	**29.3 to 51.9)**	**15.3**	**20.4**	**14.3**	**18.4**	**0.1**

ARR = risk of repeat procedure × relative risk reduction due to DES

Incremental benefit (loss of QALYs avoided due to DES) = angina symptoms awaiting repeat procedure (U_1) + experience of and recovery from repeat procedure (U_2) (3)

where

U_1 = average QALY score with severe angina × average weeks with symptoms/52 × ARR × number of patients

U_2 = average QALYs lost from procedure/recovery × ARR × number of patients

where severe angina is angina 'severe' enough for it to prompt intervention.

Since the time horizon of the analysis is restricted to 12 months, no discounting of either costs or outcomes is necessary. The most important factors in determining the incremental cost are the additional cost per DES implanted, the number of stents implanted per patient and the ARR attributable to use of DES, whereas the single important factor determining incremental outcomes is the ARR due to DES.

Data sources and parameter values

The parameter values adopted for our base scenario are detailed in *Table 30*, together with data sources for each. The derivation of specific values in the table are explained more fully below.

Stent prices

This analysis focuses on the two stents which dominate the market at present, Cypher and Taxus. Other DES have not yet achieved sufficient market penetration, but the same arguments broadly apply.

Unlike prescribed medications, there is no national pricing agreement for medical appliances governing the maximum price to be charged in the NHS. In practice, each hospital through its purchasing agency negotiates local contracts with suppliers taking account of volumes of demand and the state of competition in the market. Under these circumstances, the notion of an official 'list price' is problematic: where it exists at all, it bears no relation to the prices actually being paid by purchasers and can be seriously misleading. In particular, the calculation of average costs for hospital procedures in the published NHS Reference Costs 2004[136] are based on the contracted prices rather than any notional list price. This means that any attempt to carry out an economic assessment on the basis of list prices would lead to large inconsistencies within the analysis, since the costs of stents now constitute a substantial proportion of the total cost of the Tariff Cost for PCIs.

In these circumstances, we concluded that it was necessary to identify realistic prices for stents supplied to the NHS as a basis for the economic assessment, which would be broadly consistent with NHS Reference Costs and generate a reliable estimate of the current UK price premium of DES compared with BMS. We are grateful to the NHS PASA for carrying out a survey of stent purchasers for us in May/June 2005 to identify the range of prices in contracts covering the period 2004–5 up to the present for coronary artery stents (both DES and BMS), taking account of volume discounts and other 'special deals' offered by manufacturers, which may take a variety of forms. The specific detail of contracts is confidential but the

TABLE 30 *Baseline parameter values and data sources for LRiG model*

Parameter		Elective	Non-elective	Source
Index stenting (C_1)				
Actual cost per DES:				
Taxus		£855.43		Survey of NHS purchasers for current prices
Cypher		£983.51		May/June 2005 + 5% addition for stent wastage
Effective list price:				
Taxus		£997.50		
Cypher		£1044.75		
Cost per BMS		£291.95		
Actual price premium:				
Taxus		£563.48		
Cypher		£691.56		
List price premium:				
Taxus		£705.60		
Cypher		£752.85		
Mean stents per patient		1.615	1.454	CTC Liverpool audit
Repeat revascularisation risk (C_2–C_4)				
Risk within 12 months		7.79%	10.15%	CTC Liverpool audit
ARR:	narrow	2.95%	3.75%	CTC Liverpool audit + clinical trial meta-analysis
	broad	3.93%	4.99%	(TLR)
Investigation of recurrent symptoms (C_2)				
Cardiology OP visits		2.10	1.05	CTC Liverpool audit
Cardiac surgery OP visits		0.19	0.08	CTC Liverpool audit
Angiography		1.00	1.00	Assumption
Cost of cardiology OP visit		£134		NHS Reference Costs 2004: first visit 320 and 170,
Cost of cardiac surgery OP visit		£208		Day Case E14
Cost of angiography		£724		
Repeat revascularisation (C_3)				
Proportion as unstented PCI		36.6%	27.4%	CTC Liverpool audit
Proportion as stented PCI		54.5%	54.7%	
Proportion as CABG		9.0%	17.9%	
Cost of unstented PCI		£1453.40		NHS Reference Costs 2004 (E15 IP less cost of stents – 1.8 per case, 50% DES use at £700 premium)
Stents per repeat PCI		1.868	1.712	CTC Liverpool audit
Cost of DES stented PCI:	Taxus	£3316.73	£3161.12	As above + DES used
	Cypher	£3409.99	£3242.01	
Cost of CABG		£7066		NHS Reference Costs 2004 (E04 IP)
Follow-up post revascularisation (C_4)				
Cardiology OP follow-up visits		2.18	1.80	CTC Liverpool audit
Cardiac surgery OP follow-up visits		0.81	0.48	
Cost of cardiology OP follow-up visit		£94		NHS Reference Costs 2004: follow-up visit 320 and
Cost of card. surgery OP follow-up visit		£156		170
Health-related utility (U_2 and U_2)				
Average EQ-5D:				
Severe angina		0.502		HODaR: E33/34, E04/15
Post-revascularisation		0.660		
QALY loss:				
From PCI		0.00658		Full benefit within 1 month
From CABG		0.00658		
Average weeks waiting				
For PCI		16		Derived from NHS Waiting List statistics –
For CABG		9		Quarter 4, 2004–5
Weeks prior to joining list		4		Assumption
QALY loss:				
Awaiting PCI		0.06070		Severe angina QALY loss × weeks waiting/52
Awaiting CABG		0.03946		

OP, outpatient.

aggregated data for 12 purchasing bodies covering 20 hospital trusts provides consistent estimates of average unit prices, and of the difference in price between DES and BMS (the price premium).

It is evident from the data collected that the two main suppliers of DES have adopted different marketing strategies. Boston Scientific have focused on establishing a strong market position by offering important discounts or bonus quantity deals to most trusts/purchasers. As a result, the effective sale price per TAXUS stent (excluding VAT) in our sample was about £815 (approximate confidence range ±£24), rather than the effective full price of £950. Cordis have shown a reluctance to deviate substantially from a narrow price range (£925–995), with only one recorded instance of a significant local volume discount deal. As a result, the sample average price for the Cypher stent is £937 (±£20). This difference in effective price is reflected in the larger market share for the TAXUS stent (about 68% of DES purchased in the sample).

The survey of BMS prices shows the greater variety of products available and evidence of real market competition leading to genuine choice and market differentiation. The estimated average price per BMS is £278 (approximate confidence range ±£21). From these results we can derive values for the DES price premium: for TAXUS this is £537 per stent and for Cypher £659 per stent. The former figure is similar to the premium used in the previous assessment, but the Cypher premium has increased substantially in the last 2 years.

It should be noted that the approach employed decreases the premium for DES compared with BMS and thus would tend to favour their achieving cost-effectiveness at a conventional threshold level.

Finally, we received clinical advice that in normal practice there is significant wastage of stents which cannot be successfully deployed. We have no source of numerical evidence for the size of this effect, but are advised that 5% is a realistic estimate. Therefore, the sample prices were increased by 5% to reflect the true cost per stent deployed.

NHS costs

All other model costs are derived from NHS Reference Costs 2004 [Health, 2004 #560] The calculation of PCI procedure costs required subtracting from the published PCI costs the included cost of stents (DES and BMS) as stated in Annex B to the Technical Guidance 2005/06. This led to estimation of the cost of PCI without stents, to which stent costs could then be added back using the model estimates of the number of stents, the type of stent and the cost per stent.

Continuing anti-platelet therapy

The question of follow-up medication post-PCI was explored in view of the current lack of consensus on the period of preventive anti-platelet therapy necessary to avoid later thrombosis: suggested periods range between 3 months and lifetime, and evidence that risks may be greater after DES implantation has led to suggestions that a longer treatment with clopidogrel after DES use may be needed. Our clinical guidance indicated that making this distinction in practice would be difficult, and that a common follow-up period of, for example, 12 months is more realistic. With the same treatment for DES and non-DES patients, there is no incremental cost and it has been omitted from the model. This approach tends to favour the cost-effectiveness of DES.

Health-related quality of life

In the previous economic assessment, we relied heavily on the only published source of QoL estimates (EuroQol, EQ-5D) for PCI and CABG patients – the ARTS trial.[135] Subsequently, we were able to combine this with information from the SoS trial[137] to inform our *Heart* publication.[120] Although helpful, these relate to specific selected populations, and therefore are of limited value in addressing decision-making in real-world practice. For this exercise we have made use of patient survey data from the HODaR database[19] which is a continuing unselected survey of Cardiff patients who complete EuroQol forms a few weeks post-discharge (described in more detail by Currie and colleagues.[20]

The data used from post-discharged patients are as follows:

- 490 following an angina episode [Health Related Groups (HRGs E33/E34)] after 68.0 (95% CI 66.4 to 69.5) days
- 456 following a PCI episode (HRG E15) after 64.0 (95% CI 62.7 to 65.1) days
- 421 following a CABG episode (HRG E04) after 65.5 (95% CI 59.2 to 71.7) days.

The HODaR estimated EQ5-D scores for these groups are 0.502 (95% CI 0.471 to 0.533) for angina patients, 0.660 (95% CI 0.631 to 0.689) for PCI patients and 0.660 (95% CI 0.597 to 0.723) for CABG patients. Since there is no statistical

difference between the PCI and CABG means, a pooled estimate has been used in the model of 0.660 (95% CI 0.640 to 0.680). This does not imply that CABG and PCI patients have identical experiences, merely that within the sensitivity of the EuroQol instrument, and over the measurable period, no differences are detectable.

Our previous assessment used ARTS results only, but for the published version we pooled results from the PCI arms of the ARTS and SoS trials (SoS baseline 0.625, long-term 0.727; ARTS, 0.690, 0.860) to obtain a pooled PCI-related 12-month gain of 0.135. The difference in HODaR health-related QoL scores between patients with severe angina and those recovered from revascularisation (0.158) is very similar to the ARTS gain (0.16), although the scores obtained in UK practice are considerably lower than those in both trials, probably reflecting the selective effect of RCT exclusion criteria.

Figure 7 shows time trends for patients surveyed in HODaR following CABG and PCI. It is evident that there are no meaningful differences at any time during the study period. Regression of EQ-5D scores against the time of survey post-discharge showed no evidence of time trends for either PCI or CABG patients, suggesting that any differences in health-related QoL recovery experience between the two modes of treatment must be confined to no more than 6 weeks post-discharge. On this basis, we estimated the QALY loss from post-intervention as a linear function from the angina EQ-5D value to the combined post-revascularisation EQ-5D value over a period of 4 weeks.

Waiting time to repeat intervention

Waiting time prior to repeat intervention is important in determining the outcome gains from use of DES. At the time of the previous economic assessment, there was a prevalent belief that patients waited longer on average for CABG than for PCI. However, the position now has changed dramatically: demand for PCI increased substantially in the last 2 years, but the volume of CABGs undertaken remains unchanged. The consequences are that whereas waiting times for PCI have increased considerably, those for CABG are now shorter than for PCI. Contemporary values for actual completed waits cannot be accessed directly since the data are collected retrospectively through the Hospital Activity data systems. However, quarterly cross-sectional NHS data by specialty are available for patients currently waiting. Using the NHS Waiting List statistics, Quarter 4, 2004–5, and a simple Markov model we have estimated the average elective cardiology waiting time at 16 weeks for PCI and the elective cardiothoracic waiting time at 9 weeks for CABG. We have also assumed a further waiting time of 4 weeks for all patients to reflect time spent with symptoms prior to listing for reintervention.

Changes since previous Technology Assessment Report

It may be helpful to summarise the changes made to the model parameter values for this TAR compared with those used in our previous TAR and the recent publication in *Heart*.[120]

Unit costs

All unit costs other than stent prices have been updated at each stage to reflect the most recent NHS Reference Costs. The previous TAR used a price premium of £520, which was rounded down to £500 for publication. These values have been replaced by the more detailed figures derived from the NHS PASA survey shown in *Table 30*. In all cases this involves an increase in the estimated price premium.

Resource use

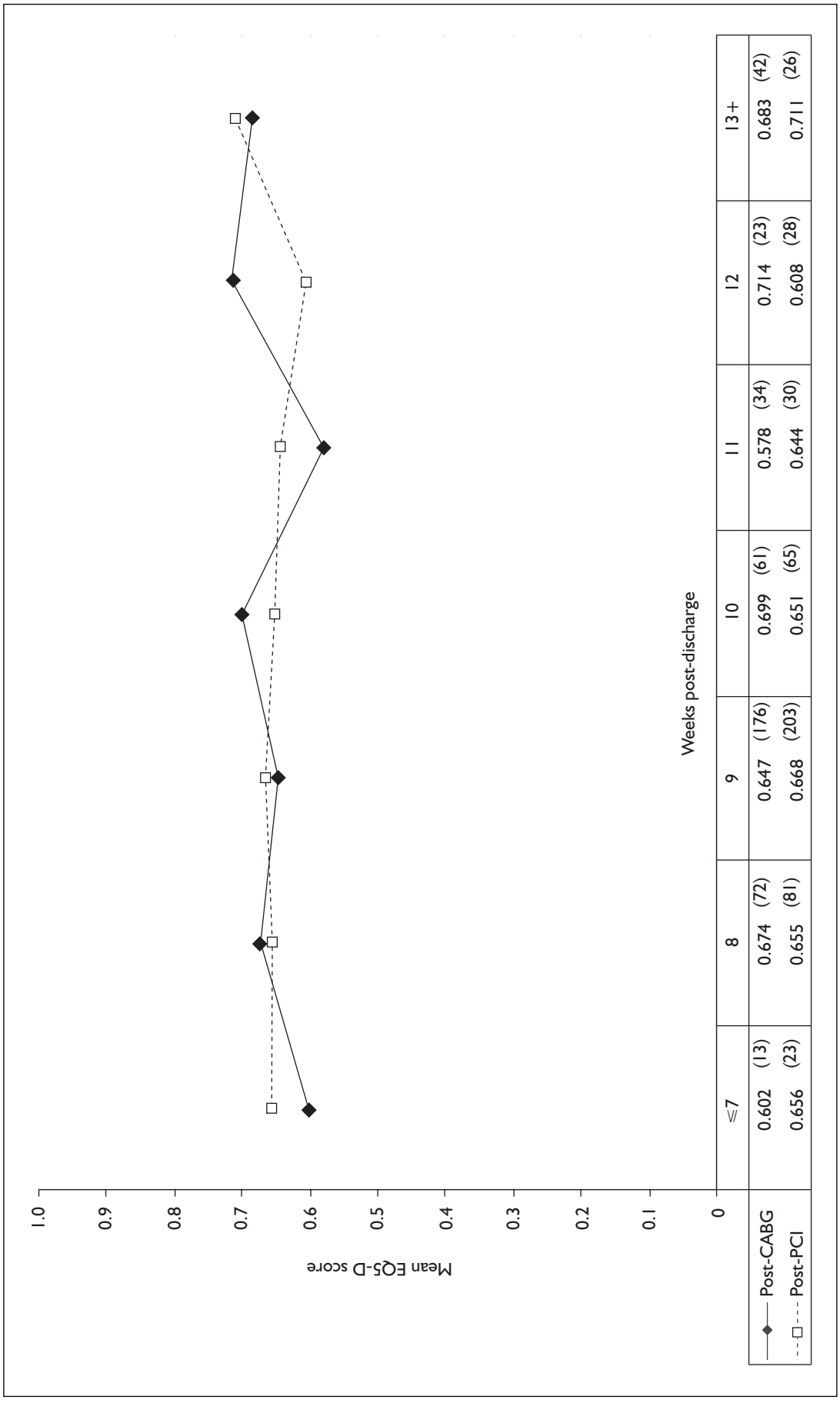
Resource use estimates in the initial TAR were based largely on informed judgement in the absence of reliable data. For the publication we obtained audit-based estimates for each item from CTC Liverpool, and these values have been carried over to the current analysis.

Absolute risk reduction from DES use

The previous TAR could not distinguish risk categories systematically and featured estimates for selected trial subgroups. In our published results, we estimated the benefit afforded by DES as a single proportionate relative risk reduction applied to the baseline absolute risk of 12-month reintervention for each risk-based subgroup derived from CTC Liverpool audit data. For the current analysis, the same baseline risks are used, but the potential to benefit has been reassessed on the basis of additional information concerning those patients in whom the repeat procedure required treatment of new lesions. The results of these calculations are shown in *Tables 28* and *29*, and involve reductions to the previously estimated benefits by either one-third or half, depending on the assumed basis of calculation ('broad' or 'narrow').

Health-related quality of life

In the previous TAR, we relied on EuroQol results obtained alongside the ARTS trial. For our



	≤7	8	9	10	11	12	13+
Post-CABG	0.602 (13)	0.674 (72)	0.647 (176)	0.699 (61)	0.578 (34)	0.714 (23)	0.683 (42)
Post-PCI	0.656 (23)	0.655 (81)	0.668 (203)	0.651 (65)	0.644 (30)	0.608 (28)	0.711 (26)

FIGURE 7 *Time trends in EQ-5D mean scores for CABG and PCI patients surveyed in HODaR*

publication, we combined the ARTS with results from the SoS trial. The selection criteria applied to trial populations generally ensure that these patients are fitter than patients seen in normal clinical practice. In this report, we have replaced these data with results obtained from the HODaR registry: 0.502 for symptomatic angina and 0.660 after revascularisation. This contrasts with previous trial-based estimates, but leads to a small reduction in the gain in health-related QoL expected from PCI or CABG compared with the previous TAR, but an increase relative to our published version (from 0.135 previously). The HODaR data also showed that there is no objective basis for a meaningful difference in recovery time by mode of treatment (PCI versus CABG) as was previously assumed. The waiting times for patients requiring a repeat procedure have been updated from the latest NHS Waiting List statistics.[138]

Cost-effectiveness results

Base case results

The base case cost-effectiveness results are shown on the left of *Table 31*, including all combinations of stent pricing, effectiveness assumption, patient type and brand of DES. In each case the cost–utility ratio is far above the normal range of acceptability: between £183,000 and £562,000 per QALY gained.

The other columns in *Table 31* allow exploration of risk-related subgroups, based on the risk models previously described. None of the elective patient subgroups appear to be cost-effective, the lowest ICER being £111,000 per QALY gained. In non-elective patients, only those with both risk factors present yield ICERs which may be favourable to DES provided that the broad definition of effectiveness is used. These represent only 0.1% of non-elective patients in the CTC audit, and only one in 3100 of all patients.

Prospective limitation of stent use

As the additional cost of DES is the dominant influence on incremental costs and ICERs, it is natural to consider whether it would be reasonable to place limits on the number of DES used per patient. Our earlier discussion of effectiveness indicated that although it is possible to mix DES and BMS to reduce initial costs, the associated loss of effectiveness may be considerable, making this an unattractive option. Instead, in *Table 32* we consider the situation where the interventional cardiologist, on the basis of angiographic evidence, judges that a single stent will suffice to treat a patient. Of course, there remains a risk that due to unforeseen circumstances this may prove not to be the case. However, the evidence from RCTs designed for single lesion/single stent patients suggests that additional stents are may only be required in a small number of cases (typically 3–10%). To accommodate this risk, we have included an additional 5% of stents in the calculations supporting *Table 32*.

The results of this exercise are only slightly more favourable to DES: the small number of highest risk elective patients could be deemed cost-effective using the broad definition of effectiveness, but those within this group who could be treated with a single stent are probably very small. Amongst non-elective patients, for those in the highest risk group DES are now clearly cost-effective, and the single-risk group now appear to yield equivocal results, depending on the effectiveness assumption made. However, the CTC Liverpool audit data indicate that under the most generous of assumptions this would include only 0.1% of elective patients and 4.3% of non-elective patients so that just 1.4% of all patients fall within groups that could possibly be considered cost-effective for use of DES.

For comparison, *Table 33* shows equivalent results for patients who could reasonably be expected to require only two stents implanted.

Sensitivity analysis

Univariate SA was carried out with respect to all model variables, varying parameter values between lower and upper 95% CIs for values derived from observational or trial sources, and a nominal ±10% for NHS Reference Costs. This is useful to indicate those model variables for which parameter uncertainty is most likely to contribute to uncertainty in decisions made on the basis of model results. *Tables 34* and *35* display the SA results for elective and non-elective patients, respectively. As expected from previous studies, the variables governing the additional cost of DES index stents (price premium and average number of stents implanted) and the ARR in repeat interventions are the most important items in influencing cost-effectiveness ratios. The only other variable with a sizeable effect is the QALY impact of undergoing/recovering from a PCI or CABG. The results demonstrate that the base case results for both elective and non-elective patients are robust to uncertainty in any single variable.

TABLE 31 *Cost-effectiveness results using CTC mean number of stents per index procedure*

			All patients			No risk factors			1 risk factor			2 risk factors			3/4 risk factors		
Prices	**Effectiveness[a]**	**Brand**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**
Elective index PCI																	
Effective list	Narrow	Taxus	1,011	0.001932	523,200	917	0.001384	662,500	1,093	0.002084	524,400	1,248	0.004108	303,900	1,375	0.006096	225,600
		Cypher	1,086	0.001932	561,900	983	0.001384	710,600	1,174	0.002084	563,300	1,347	0.004108	328,000	1,490	0.006096	244,500
	Broad	Taxus	969	0.002572	376,600	886	0.001841	481,400	1,047	0.002773	377,600	1,158	0.005466	211,900	1,241	0.008111	153,100
		Cypher	1,043	0.002572	405,600	952	0.001841	517,300	1,128	0.002773	406,600	1,256	0.005466	229,800	1,355	0.008111	167,000
Actual	Narrow	Taxus	786	0.001932	406,600	717	0.001384	517,900	850	0.002084	407,600	951	0.004108	231,500	1,030	0.006096	169,000
		Cypher	989	0.001932	511,700	897	0.001384	648,200	1,069	0.002084	512,900	1,219	0.004108	296,800	1,341	0.006096	220,000
	Broad	Taxus	745	0.002572	289,600	687	0.001841	373,200	805	0.002773	290,400	864	0.005466	158,000	901	0.008111	111,000
		Cypher	946	0.002572	368,000	867	0.001841	470,700	1,023	0.002773	369,000	1,129	0.005466	206,600	1,208	0.008111	148,900
Non-elective index PCI																	
Effective list	Narrow	Taxus	852	0.002444	348,700	844	0.002155	391,600	947	0.005332	177,500	627	0.009716	64.600			
		Cypher	919	0.002444	376,100	909	0.002155	421,900	1,032	0.005332	193,500	709	0.009716	73,000			
	Broad	Taxus	795	0.003251	244,400	793	0.002867	276,600	821	0.007095	115,700	399	0.012928	30,800			
		Cypher	861	0.003251	264,800	858	0.002867	299,200	905	0.007095	127,600	478	0.012928	37,000			
Actual	Narrow	Taxus	651	0.002444	266,200	648	0.002155	300,500	691	0.005332	129,500	382	0.009716	39,300			
		Cypher	832	0.002444	340,500	825	0.002155	382,600	921	0.005332	172,800	603	0.009716	62,100			
	Broad	Taxus	595	0.003251	182,900	598	0.002867	208,700	569	0.007095	80,200	160	0.012928	**12,400**			
		Cypher	775	0.003251	238,300	774	0.002867	269,900	796	0.007095	112,200	375	0.012928	**29,000**			

Δ_C, incremental cost per patient; Δ_Q, incremental QALYs per patient; ICER, incremental cost per QALY gained; ICERs below £30,000 are in bold type.

[a] 'Narrow' estimates are calculated from cases involving TLR/TVR only, whereas 'Broad' estimates are based on cases involving any TLR/TVR irrespective of any other lesions/vessels revascularised.

TABLE 32 *Cost-effectiveness results if only one index stent is expected to be required*

			All patients			No risk factors			1 risk factor			2 risk factors			3/4 risk factors		
Prices	**Effectiveness**	**Brand**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**
Elective index PCI																	
Effective list	Narrow	Taxus	612	0.001932	316,900	649	0.001384	468,900	602	0.002084	289,000	468	0.004108	113,800	335	0.006096	55,000
		Cypher	661	0.001932	341,800	697	0.001384	504,100	650	0.002084	312,000	514	0.004108	125,200	381	0.006096	62,400
	Broad	Taxus	570	0.002572	221,600	618	0.001841	335,900	556	0.002773	200,700	377	0.005466	69,000	201	0.008111	**24,800**
		Cypher	618	0.002572	240,200	667	0.001841	362,100	604	0.002773	217,800	423	0.005466	77,400	245	0.008111	30,200
Actual	Narrow	Taxus	467	0.001932	241,900	503	0.001384	363,300	458	0.002084	219,600	328	0.004108	79,700	200	0.006096	32,800
		Cypher	598	0.001932	309,500	634	0.001384	458,500	588	0.002084	282,100	454	0.004108	110,500	322	0.006096	52,800
	Broad	Taxus	426	0.002572	165,800	473	0.001841	257,100	413	0.002773	149,100	240	0.005466	43,900	70	0.008111	**8,700**
		Cypher	556	0.002572	216,100	604	0.001841	328,100	542	0.002773	195,600	364	0.005466	66,600	189	0.008111	**23,200**
Non-elective index PCI																	
Effective list	Narrow	Taxus	532	0.002444	217,600	588	0.002155	272,600	326	0.005332	61,200	14	0.009716	**1,500**			
		Cypher	577	0.002444	236,200	636	0.002155	294,900	370	0.005332	69,300	55	0.009716	**5,600**			
	Broad	Taxus	474	0.003251	145,800	537	0.002867	187,200	201	0.007095	**28,300**	–214	0.012928	**–16,600**			
		Cypher	519	0.003251	159,700	584	0.002867	203,800	243	0.007095	34,200	–176	0.012928	**–13,600**			
Actual	Narrow	Taxus	395	0.002444	161,500	443	0.002155	205,500	195	0.005332	36,600	–108	0.009716	**–11,100**			
		Cypher	518	0.002444	212,000	573	0.002155	266,000	313	0.005332	58,700	2	0.009716	**200**			
	Broad	Taxus	339	0.003251	104,200	394	0.002867	137,300	73	0.007095	**10,300**	–329	0.012928	**–25,500**			
		Cypher	461	0.003251	141,700	523	0.002867	182,300	188	0.007095	**26,500**	–226	0.012928	**–17,500**			

Δ_C, incremental cost per patient; Δ_Q, incremental QALYs per patient; ICER, incremental cost per QALY gained; ICERs below £30,000 are in bold type.
Assuming 1.05 stents per patient, i.e. 5% of additional stents are used compared with those originally expected.

TABLE 33 *Cost-effectiveness results if only two index stents are expected to be required*

			All patients			No risk factors			1 risk factor			2 risk factors			3/4 risk factors		
Prices	**Effectiveness**	**Brand**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**
Elective index PCI																	
Effective list	Narrow	Taxus	1,283	0.001932	663,800	1,319	0.001384	953,400	1,273	0.002084	610,600	1,138	0.004108	277,000	1,006	0.006096	165,000
		Cypher	1,376	0.001932	711,900	1,413	0.001384	1,020,900	1,366	0.002084	655,200	1,229	0.004108	299,300	1,096	0.006096	179,800
	Broad	Taxus	1,240	0.002572	482,300	1,289	0.001841	700,000	1,227	0.002773	442,400	1,048	0.005466	191,700	872	0.008111	107,500
		Cypher	1,333	0.002572	518,300	1,382	0.001841	750,600	1,319	0.002773	475,700	1,138	0.005466	208,200	960	0.008111	118,400
Actual	Narrow	Taxus	1,003	0.001932	518,900	1,038	0.001384	750,200	993	0.002084	476,400	863	0.004108	210,000	735	0.006096	120,600
		Cypher	1,255	0.001932	649,500	1,291	0.001384	933,300	1,245	0.002084	597,300	1,111	0.004108	270,400	979	0.006096	160,600
	Broad	Taxus	962	0.002572	373,900	1,009	0.001841	547,800	949	0.002773	342,100	776	0.005466	141,900	606	0.008111	74,700
		Cypher	1,213	0.002572	471,600	1,261	0.001841	685,000	1,199	0.002773	432,500	1,021	0.005466	186,800	846	0.008111	104,200
Non-elective index PCI																	
Effective list	Narrow	Taxus	1,237	0.002444	506,300	1,328	0.002155	616,400	1,032	0.005332	193,500	720	0.009716	74,100			
		Cypher	1,330	0.002444	544,300	1,426	0.002155	661,700	1,122	0.005332	210,500	807	0.009716	83,100			
	Broad	Taxus	1,180	0.003251	362,800	1,278	0.002867	445,600	906	0.007095	127,700	491	0.012928	38,000			
		Cypher	1,272	0.003251	391,200	1,375	0.002867	479,500	996	0.007095	140,400	577	0.012928	44,600			
Actual	Narrow	Taxus	958	0.002444	392,100	1,034	0.002155	480,000	759	0.005332	142,300	456	0.009716	46,900			
		Cypher	1,210	0.002444	495,000	1,299	0.002155	602,900	1,005	0.005332	188,400	694	0.009716	71,400			
	Broad	Taxus	902	0.003251	277,500	985	0.002867	343,600	637	0.007095	89,800	234	0.012928	**18,100**			
		Cypher	1,152	0.003251	354,400	1,249	0.002867	435,500	880	0.007095	124,000	466	0.012928	36,000			

Δ_C, incremental cost per patient; Δ_Q, incremental QALYs per patient; ICER, incremental cost per QALY gained; ICERs below £30,000 are in bold type.
Assuming 2.1 stents per patient, i.e. 5% of additional stents are used compared with those originally expected.

TABLE 34 *Univariate sensitivity analysis of incremental cost per QALY gained (base case: effective list prices/average no. of stents used): elective index PCI*

	Parameter range		Narrow (£)				Broad (£)			
			Taxus		Cypher		Taxus		Cypher	
Variable	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**
Base case ICER			**523,200**		**561,900**		**376,600**		**405,600**	
Price premium:										
Taxus	£683.15	£728.05	504,400	542,000	–	–	362,500	390,700	–	–
Cypher	£730.40	£775.30	–	–	543,200	580,700	–	–	391,500	419,700
ARR from DES:										
Narrow	2.41%	3.53%	654,600	427,500	702,200	459,800	–	–	–	–
Broad	3.32%	4.59%	–	–	–	–	457,800	313,000	492,200	337,700
No. of stents	1.580	1.650	510,500	535,900	548,400	575,500	367,100	386,200	395,400	415,800
Cardiology OP ref. visits	1.927	2.273	523,500	522,800	562,300	561,600	377,000	376,300	405,900	405,200
Cardiac surgery OP ref. visits	0.083	0.297	523,500	522,900	562,300	561,600	377,000	376,300	405,900	405,200
Angiography	0.749	1.251	526,000	520,400	564,700	559,200	379,400	373,800	408,300	402,800
Cost of cardiology OP ref. visit	£120.60	£147.40	523,600	522,800	562,400	561,500	377,100	376,200	406,000	405,100
Cost of cardiac surgery OP ref. visit	£187.20	£228.80	523,300	523,100	562,000	561,900	376,700	376,600	405,600	405,500
Cost of angiography	£651.60	£796.40	524,300	522,100	563,100	560,800	377,700	375,500	406,700	404,500
Proportion revascularised as unstented PCI	28.9%	45.0%	525,400	520,800	564,200	559,400	378,800	374,200	407,900	403,100
Proportion revascularised as stented PCI	46.0%	62.7%	524,900	521,400	563,700	560,000	377,600	375,600	406,600	404,500
Proportion revascularised as CABG	5.1%	15.1%	518,800	528,000	557,600	566,600	372,200	381,400	401,200	410,300
No. of stents per repeat PCI	1.623	2.151	525,200	520,800	564,100	559,500	378,700	374,300	407,700	403,100
Cost of unstented PCI	£1,308.06	£1,598.74	524,000	522,400	562,800	561,100	377,400	375,800	406,400	404,700
Cost of CABG	£6,359.40	£7,772.60	524,200	522,200	562,900	561,000	377,600	375,700	406,500	404,600
Cardiology OP follow-up visits	1.724	2.636	523,800	522,500	562,600	561,300	377,300	376,000	406,200	404,900
Cardiac surgery OP follow-up visits	0.424	1.196	524,100	522,300	562,900	561,000	377,500	375,700	406,500	404,600
Cost of cardiology OP follow-up visit	£ 84.60	£103.40	523,500	522,900	562,300	561,600	376,900	376,300	405,900	405,200
Cost of cardiac surgery OP follow-up visit	£140.40	£171.60	523,400	523,000	562,100	561,800	376,800	376,400	405,800	405,400
QALY loss from PCI	0.00511	0.00804	534,100	512,700	573,700	550,700	384,500	369,100	414,000	397,400
QALY loss from CABG	0.00511	0.00804	524,300	522,100	563,100	560,800	377,400	375,900	406,400	404,700
QALY loss awaiting PCI	0.06058	0.06079	524,100	522,500	562,900	561,200	377,300	376,100	406,200	405,000
QALY loss awaiting CABG	0.03931	0.03961	523,300	523,100	562,100	561,800	376,700	376,500	405,600	405,500

OP, outpatient.

TABLE 35 *Univariate sensitivity analysis of incremental cost per QALY gained (base case: effective list prices/average no. of stents used): non-elective index PCI*

	Parameter range		Narrow (£)				Broad (£)			
			Taxus		Cypher		Taxus		Cypher	
Variable	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**
Base case ICER			**348,700**		**376,100**		**244,400**		**264,800**	
Price premium:										
Taxus	£683.15	£728.05	335,300	362,000	–	–	234,300	254,400	–	–
Cypher	£730.40	£775.30	–	–	362,700	389,400	–	–	254,800	274,800
ARR from DES:										
Narrow	2.95%	4.82%	476,100	264,100	512,100	285,800	–	–	–	–
Broad	4.03%	6.30%	–	–	–	–	330,400	185,300	356,600	201,700
No. of stents	1.411	1.498	336,300	361,300	362,900	389,600	235,100	253,800	254,900	274,900
Cardiology OP ref. visits	0.841	1.259	349,100	348,200	376,500	375,600	244,800	243,900	265,200	264,400
Cardiac surgery OP ref. visits	0.018	0.142	348,900	348,500	376,300	375,900	244,600	244,200	265,000	264,600
Angiography	0.749	1.251	351,500	345,800	378,900	373,200	247,200	241,500	267,700	261,900
Cost of cardiology OP ref. visit	£120.60	£147.40	348,900	348,400	376,300	375,900	244,600	244,100	265,000	264,600
Cost of cardiac surgery OP ref. visit	£187.20	£228.80	348,700	348,600	376,100	376,100	244,400	244,300	264,800	264,800
Cost of angiography	£651.60	£796.40	349,800	347,500	377,200	374,900	245,500	243,200	265,900	263,700
Proportion revascularised as unstented PCI	19.0%	37.6%	350,900	345,900	378,500	373,200	246,600	241,600	267,200	261,900
Proportion revascularised as stented PCI	44.2%	64.9%	353,300	343,200	380,900	370,400	247,800	240,300	268,400	260,600
Proportion revascularised as CABG	11.1%	27.4%	343,500	355,000	371,000	382,300	239,200	250,700	259,700	271,000
No. of stents per repeat PCI	1.500	1.962	350,500	346,500	378,000	373,800	246,200	242,200	266,700	262,500
Cost of unstented PCI	£1,308.06	£1,598.74	349,300	348,000	376,700	375,500	245,000	243,700	265,400	264,200
Cost of CABG	£6,359.40	£7,772.60	350,700	346,700	378,100	374,100	246,400	242,400	266,800	262,800
Cardiology OP follow-up visits	1.448	2.152	349,200	348,100	376,600	375,600	244,900	243,800	265,300	264,300
Cardiac surgery OP follow-up visits	0.225	0.735	349,300	348,000	376,700	375,500	245,000	243,700	265,400	264,200
Cost of cardiology OP follow-up visit	£84.60	£103.40	348,900	348,400	376,400	375,800	244,600	244,100	265,100	264,500
Cost of cardiac surgery OP follow-up visit	£140.40	£171.60	348,800	348,600	376,200	376,000	244,500	244,200	264,900	264,700
QALY loss from PCI	0.00511	0.00804	355,400	342,200	383,400	369,100	249,100	239,800	269,900	259,900
QALY loss from CABG	0.00511	0.00804	350,100	347,200	377,600	374,500	245,400	243,400	265,900	263,700
QALY loss awaiting PCI	0.06058	0.06079	349,200	348,300	376,700	375,600	244,700	244,100	265,200	264,500
QALY loss awaiting CABG	0.03931	0.03961	348,800	348,500	376,200	375,900	244,500	244,300	264,900	264,700

OP, outpatient.

TABLE 36 *Extreme values sensitivity analysis of incremental cost per QALY gained (base case: effective list prices/average no. of stents used)*

	Narrow (£)				Broad (£)			
	Taxus		Cypher		Taxus		Cypher	
	Low	High	Low	High	Low	High	Low	High
Elective index PCI								
Base case ICER	523,200		561,900		376,600		405,600	
All patients	316,70	890,500	342,100	952,400	229,400	626,600	248,800	671,400
No risks	370,500	1,257,800	399,600	1,343,500	268,900	905,000	291,000	967,900
1 risk	293,100	976,700	316,800	1,044,200	210,800	694,100	228,900	743,300
2 risks	162,700	569,900	177,500	611,000	110,800	393,300	122,000	422,900
3/4 risks	89,400	496,900	99,000	533,200	55,100	342,400	62,400	368,700
Non-elective index PCI								
Base case ICER	348,700		376,100		244,400		264,800	
All patients	181,200	704,100	197,100	754,900	124,900	492,200	137,000	529,300
No risks	198,900	817,300	216,100	875,400	138,600	577,900	151,600	620,500
1 risk	62,500	497,400	70,300	534,800	32,900	341,900	38,600	369,200
2 risks	**13,800**	181,100	**18,200**	198,000	**–2,800**	107,200	**500**	119,300

ICERs below £30,000 are in bold type.

In addition, an extreme values analysis (EVA) was carried out in which all variables were set to the limits corresponding to the worst or best ICER results. This is a simple way of determining sensitivity to all variables simultaneously to a very high level of certainty. It involves simultaneously setting the values of each of uncertain model parameters to the univariate confidence level associated with the highest (or lowest) value of the model result. The results obtained yield a combined confidence range with a coverage never greater than 5% (if all variables are perfectly correlated with each other), but generally taking much smaller values (if most or all variables are mutually independent). Thus EVA for a model with only two or three types of independent uncertainty would give a confidence band corresponding to $p = 0.56\%$ or 0.069%, respectively. The current model includes at least 13 separate sources of uncertainty (excluding NHS Reference Costs), most of which are probably independently distributed. When combined by EVA, the resulting wider confidence range could reduce the uncertainty of a correct decision to as little as one in 63×10^{10}. The results are shown in *Table 36*, and confirm the conclusion that DES cannot be considered cost-effective in the UK for the generality of PCI patients, and may only be cost-effective for the subgroup of non-elective patients with both the identified risk factors.

Graphical representation best illustrates the centrality of ARR and price premium to the assessment of cost-effectiveness for DES compared with BMS. In *Figures 8* and *9*, the relationship of ARR to cost per QALY gained is shown as a continuous function of ARR, with the base case estimates marked by square symbols. An indicative £30,000/QALY threshold is only attained if an ARR in repeat revascularisations of at least 18% (elective) or 16% (non-elective) is achievable. Clearly, for the great majority of patients this is unrealistic.

Figures 10 and *11* illustrate the strong dependence of cost-effectiveness on the price premium of DES compared with BMS. The extent to which this currently exceeds the values corresponding to £30,000 per QALY gained (around £100–200) explains why so few patients can be considered appropriate for treatment with DES on economic grounds.

Table 37 details the cost-effective threshold values of DES price premium estimated for a range of different patient subgroups defined by risk factors and number of stents required. Combining these with the case mix found in the CTC audit leads to a profile of the estimated proportion of all elective (*Figure 12*) and non-elective patients (*Figure 13*) for whom DES would be cost-effective over a range of values for the DES price premium. This suggests strongly that for any values of the price premium greater than about £250 the use of DES should be restricted on economic grounds to a small group of high-risk patients in whom limited stent usage

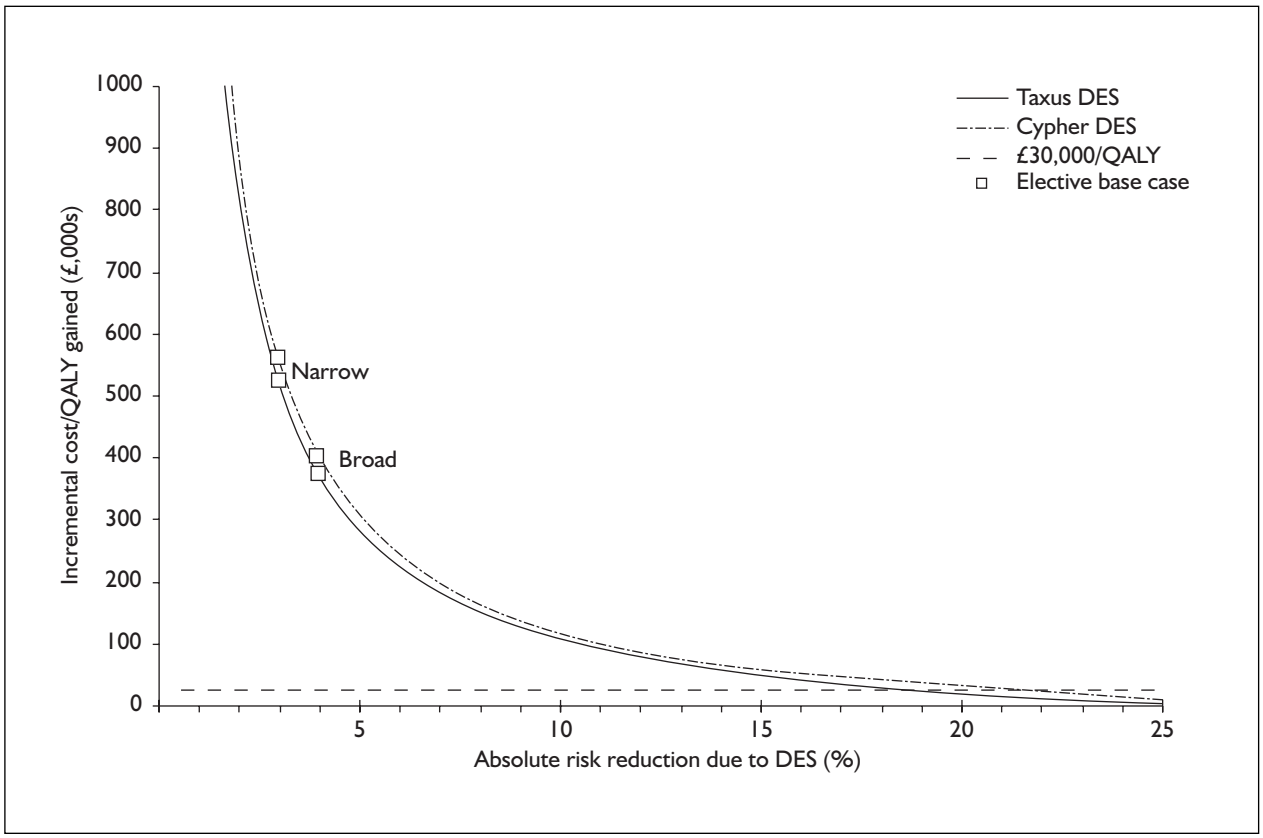


FIGURE 8 *Relationship between the absolute risk reduction due to DES and the incremental cost/QALY gained: elective base case*

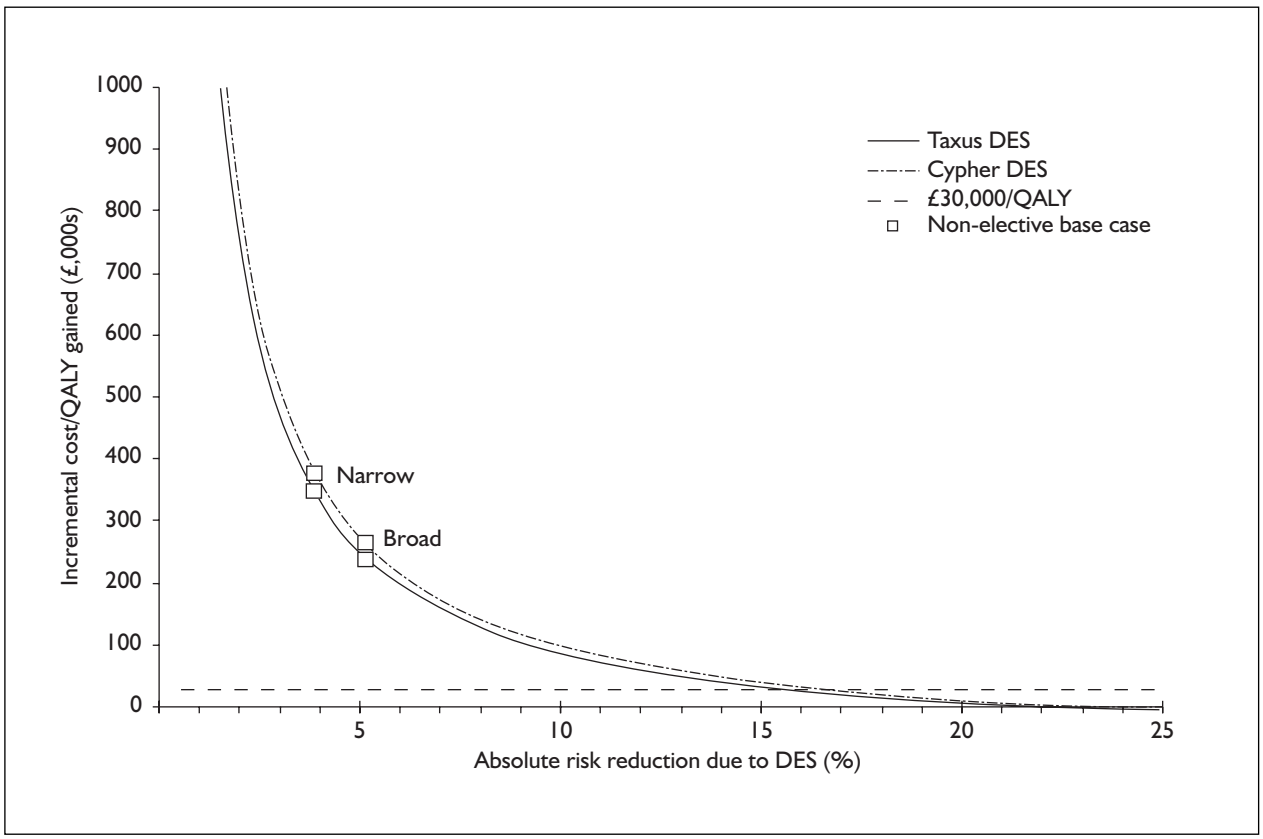


FIGURE 9 *Relationship between the absolute risk reduction due to DES and the incremental cost/QALY gained: non-elective base case*

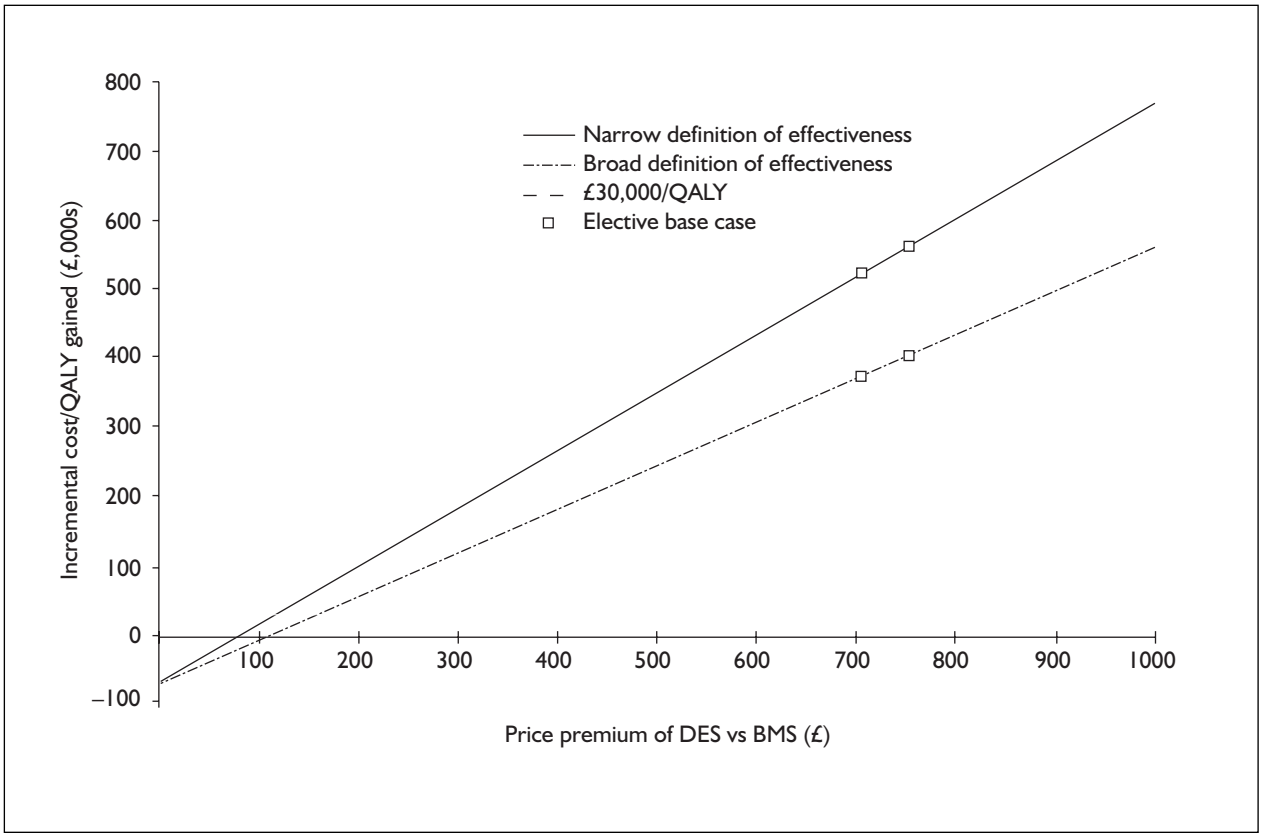


FIGURE 10 *Relationship between the absolute risk reduction due to DES and price premium per DES used: elective base case*

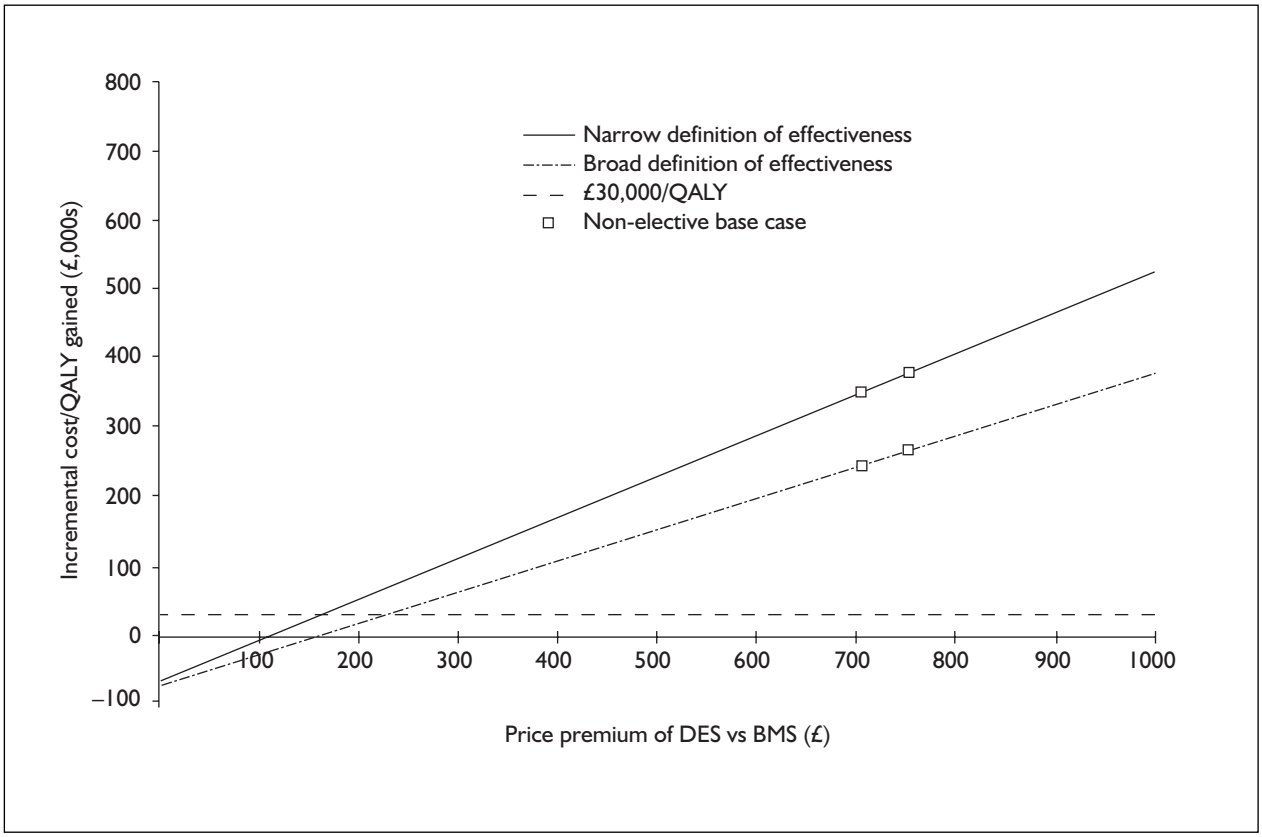


FIGURE 11 *Relationship between the absolute risk reduction due to DES and price premium per DES used: non-elective base case*

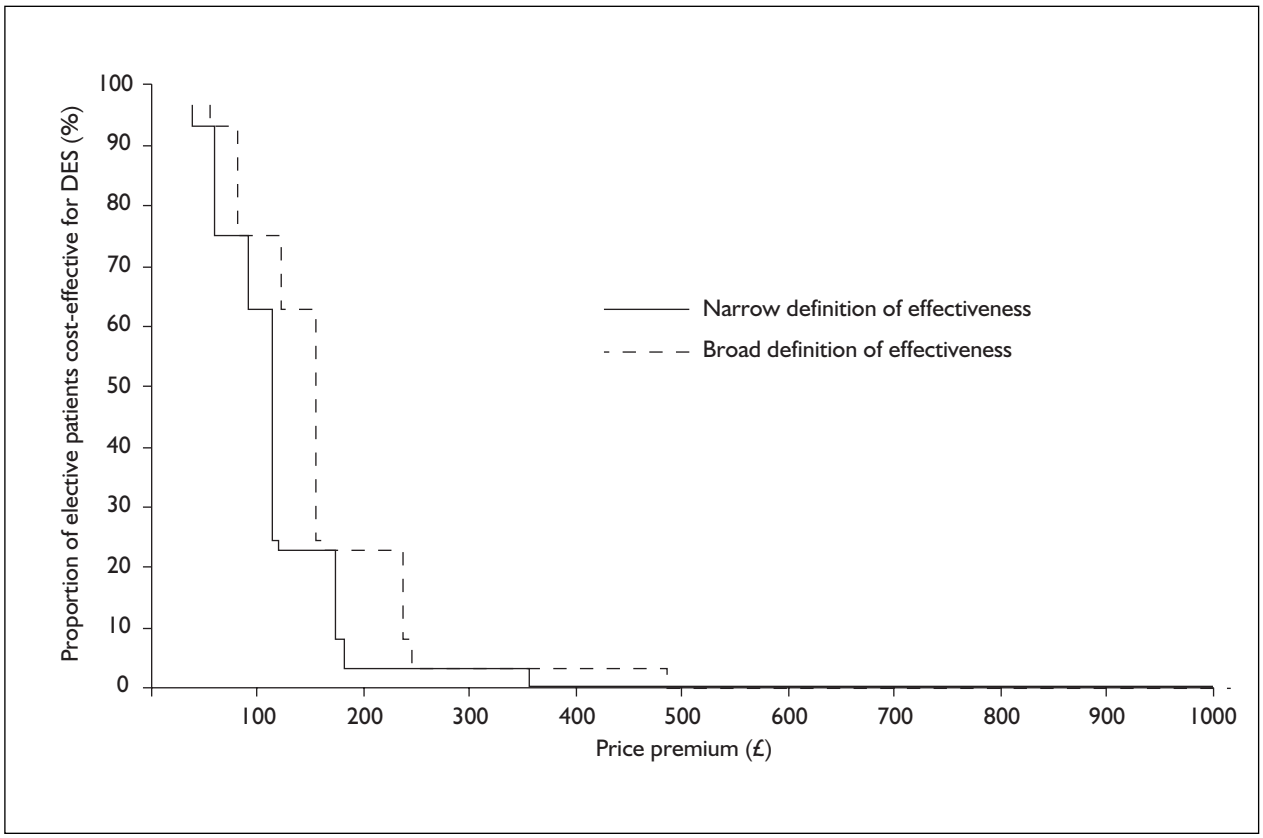


FIGURE 12 *Proportion of elective stented patients for whom DES is cost-effective: variation by price premium of DES*

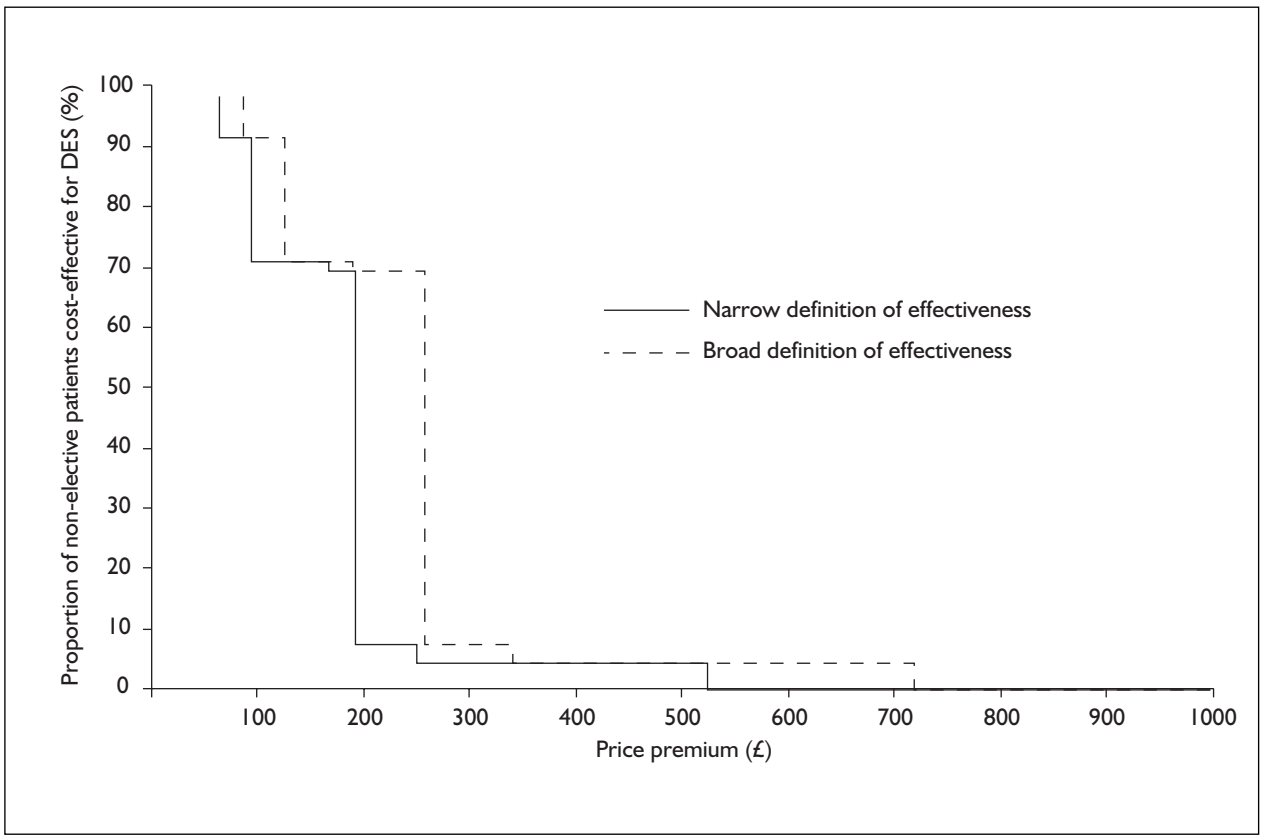


FIGURE 13 *Proportion of non-elective stented patients for whom DES is cost-effective: variation by price premium of DES*

can be reasonably predicted. If in the future the price premium falls to under £200, then more general use of DES for the majority of patients would be warranted.

The model uses average waiting times for PCI and CABG derived from published statistics. However, the waiting time target is for a maximum wait of 13 weeks from the decision to admit, which is substantially less than current average for PCIs (although CABG waits are within target). The potential impact on cost-effectiveness of limiting the PCI wait to 13 weeks has been explored. In general, it modestly increases all estimated ICERs, but is not sufficient to cause any to exceed a level of £30,000 per QALY gained.

It has been assumed that post-PCI clopidogrel therapy is of the same duration for patients treated with either BMS or DES, despite some recommendations[12] for extended treatment when DES are used. This is a conservative assumption, and we have tested the effects of extending clopidogrel use by a further 6 months only when DES are used, adding £230 to the treatment cost of all DES patients. For elective index PCIs, the ICER then exceeds £30,000 per QALY gained in all scenarios, regardless of risk profile or the number of stents used. For non-elective cases, cost-effectiveness is maintained only for patients with both risk factors present when only one stent is required.

Discussion

Our economic model has undergone evolutionary development since the last TAR was prepared. This was largely driven by the lack of important information to inform the Appraisal Committee's deliberations, specifically relating to the size and nature of risks faced by PCI patients, the benefits achievable from interventions and details of the resources employed in normal practice to deliver services. We have carried out several research and data collection exercises during the last 2 years, which have rectified some of the more important omissions, and have led to some minor modifications to the model structure to accommodate the new data. The resulting analysis now provides a more secure basis for appraising PCI technologies and considering 'value for money' in relation to specific patient subgroups.

On several issues these findings may be subject to challenge, including questions raised by Thomas in his editorial in *Heart*.[130,139] In this section we attempt to respond to the main points raised.

Are the CTC data reliable and representative?

The processes of validation of the CTC Liverpool audit data are available from the CTC Clinical Audit section. The data on which the analysis was based are virtually complete: all deaths are tracked, and in the past 3 years only two patients underwent a second revascularisation in another north-west NHS hospital, all of which participate in a common audit system.

It has been specifically suggested that the number (and therefore the calculated rates) of second interventions at 12 months' follow-up may be underestimated, due to many patients being identified for a procedure within 12 months but having to wait for admission until after 12 months. We have carried out a search on the database for such patients, and only 17 possible cases were identified. If all these were included in our analysis, then the absolute risk of a subsequent procedure would increase by a small amount (to about 8% for elective patients and under 11% for non-elective patients) – insufficient to result in a material alteration in cost-effectiveness for any subgroup.

The representative nature of CTC Liverpool reintervention rates for UK practice is confirmed from several sources. The BCIS audit for 2003[140] reported that only 4.3% of PCIs were required for restenosis, although less than 20% of procedures then used were DES. This is consistent with an average risk of reintervention without DES of 5–10%, confirming recent gains made in both technology and expertise even without the use of DES. An audit study from Leicester showed overall target lesion restenosis at 12 months of 4.9% for BMS and 2.8% for DES.[141] These UK figures are therefore consistent with the rates from Liverpool quoted in our study. Evidence from other international studies shows comparable results in unselected patients in Canada (8.2%),[124] Switzerland (12.1% TVR with a more severe case mix)[82] and The Netherlands (9.6% TVR),[142] reinforcing confidence in the reliability of the CTC Liverpool data, where the combined elective/non-elective rate was 8.8%. In the USA, generally higher rates of repeat revascularisation are reported in registry studies: Ellis and colleagues[143] obtained an overall rate of 13.4% for patients treated between 1994 and 2001, with 54% of patients in risk subgroups with rates <10% and a further 33% with a risk of 12.1%; Wu and

TABLE 37 *Threshold values of price premium for different patient subgroups*

Elective				Non-elective			
		Effectiveness criterion (£)				Effectiveness criterion (£)	
Patient	**DES used**	**Narrow**	**Broad**	**Patient**	**DES used**	**Narrow**	**Broad**
3/4 risks	1 only	546	751	2 risks	1 only	1029	1450
2 risks	1 only	356	484	1 risk	1 only	525	719
3/4 risks	2 only	274	370	2 risks	Average	511	699
3/4 risks	Average	215	289	2 risks	2 only	475	649
2 risks	2 only	181	244	2 risks	3 only	309	418
3/4 risks	3 only	179	241	1 risk	Average	269	363
1 risk	1 only	175	236	1 risk	2 only	252	340
2 risks	Average	168	226	All	1 only	230	310
All	1 only	162	218	No risks	1 only	192	258
2 risks	3 only	120	160	1 risk	3 only	166	222
No risks	1 only	115	154	All	Average	156	210
All	Average	104	140	No risks	Average	142	190
1 risk	Average	104	139	All	2 only	113	151
1 risk	2 only	91	121	No risks	2 only	95	126
All	2 only	84	112	All	3 only	75	100
No risks	Average	84	112	No risks	3 only	66	88
No risks	2 only	60	80				
1 risk	3 only	60	80				
All	3 only	56	74				
No risks	3 only	40	53				

colleagues[144] used a cohort treated in 1999 including unstented PCI with an overall rate of 16.2%.

Why do identified risk factors differ from those expected?

Doubt has also been expressed concerning the risk models derived from CTC data, and used as the basis for subgroup evaluations in this report. In particular, the absence of diabetes as a specific indicator of risk of reintervention is considered incompatible with other published studies.

In answer, it should be observed that much of the accumulated RCT evidence has been predicated on assumptions about which subgroups would be likely to have greater risk of restenosis – generally involving diabetes, small vessels and long lesions. Not surprisingly, these are then the factors included in RCT-based risk models. The rationale underlying the CTC risk models is to begin without preconceptions as to likely risk factors, but to allow all patient characteristics and lesion/vessel features to influence the model structure through a multivariate analysis. Only one of the conventional factors then featured in the final models (small vessels for non-elective patients), and diabetes was not found to be an independent predictor.

Other recent studies, based on unselected patient data, have developed independent risk

models.[142–144] Ellis and colleagues[143] found that diabetes was not included in the final multivariate model, being correlated with many of the factors selected as significant for inclusion. Wu and colleagues[144] did not find diabetes to be significant for modelling repeat revascularisations, but only for the subgroup of repeat CABGs. Only Agema and colleagues[142] found diabetes to be required unequivocally as an independent predictor in a multivariate analysis. Hence the CTC models are in no way discredited by the omission of specific variables conventionally presumed to be important.

The choice of a specific formulation for risk modelling does not in itself alter the amount of risk to be apportioned, and therefore only influences the nature and balance between subgroups. It has no effect on the general cost-effectiveness of DES compared with BMS.

Economic findings differ from those in other published papers

Early economic studies on DES were usually developed directly from specific clinical trials or were funded by industry sponsors. Recently, several independent researchers have reported on the cost-effectiveness of DES in a variety of settings (see Chapter 6),[82,122,126] and although obtaining results specific to their national context, they are unanimous in affirming that DES cannot be considered generally cost-effective except for a limited number of particularly high-risk patients.

Number of stents used per patient

After the price premium for DES, and the risk of repeat revascularisation, the most important variable in the calculation of incremental cost is the average number of stents implanted per patient. Estimates for this factor have varied considerably in trials and other studies. Shrive used 1.4 stents per patient based on APPROACH registry data,[145] but market research surveys suggest that UK usage may be approaching 1.8 stents per patient. We therefore consider that the values employed in the base case scenario are realistic or even conservative for the UK. The sensitivity analysis demonstrates that even larger variations in this parameter are extremely unlikely to alter the treatment decision for any subgroup.

Sensitivity analysis

In this analysis, we employed EVA as the method for accommodating variability in multiple model parameters, rather than PSA. By definition, EVA involves using a much more stringent criterion than even that used conventionally in clinical trials, so that the robustness of a determination of cost-effectiveness by EVA could not be bettered by other approaches (including PSA, which is best suited to situations close to the cost-acceptability decision threshold). The economic results reveal that equivocation exists only in relation to one or two categories of very high-risk patients encompassing a very small fraction of the overall population. In these cases, the principal sources of uncertainty are not associated with parameter estimation, but concern qualitative choice: the method of assessing effectiveness, the method of calculating the price premium and the decision on whether to take all DES as clinically equivalent or analyse each in its own right. In this situation, there is no realistic benefit to be gained from carrying out a computationally expensive procedure such as PSA, which would not provide additional information for decision-making.

Choice of DES

In Chapter 5, consideration was given to the evidence for and against differentiating between the two major current DES products (i.e. Cypher SES and Taxus PES) on grounds of clinical efficacy. The evidence suggests that it may be the case that sirolimus-based stents reduce repeat revascularisations compared with paclitaxel-based stents. However, the evidence available is of limited duration (6–9 months in all but one case) and barely reached significance of several outcomes, suggesting that more evidence needs to be obtained before the apparent difference can be confirmed and its magnitude estimated. Therefore, we have chosen to carry out the economic assessment on the conservative assumption of clinical equivalence, distinguishing between stents only on price.

Nonetheless, from the results we report that equivalent ICERs can be derived if differential outcomes are accepted, by reference to the graphs shown in *Figures 8* and *9*. If we assume equal weight is given to the two types of stent, and that there is a relative risk reduction of 33% for Cypher versus Taxus, then simple algebra shows that the ARR for Cypher must be 0.8 times the combined ARR in the case of Cypher, and the ARR for Taxus must be 1.2 times the combined ARR (the precise values corresponding to the meta-analyses in Chapters 4 and 5 are 0.78 and 1.17, respectively). Thus a simple calculation allows the reader to read from the appropriate curve in *Figures 8* and *9* the ICER appropriate to each stent considered separately at the adjusted ARR value.

TABLE 38 *Cost-effectiveness results re-estimated using efficacy measures*

			Incremental cost per QALY gained (£)			
Prices	**Efficacy basis**	**Brand**	**No risk factors**	**1 risk factor**	**2 risk factors**	**3/4 risk factors**
Elective index PCI						
Effective list	TLR	Taxus	304,063	234,175	121,792	82,047
		Cypher	328,143	253,575	133,666	91,260
	TVR	Taxus	413,733	323,196	177,511	125,962
		Cypher	445,157	348,557	193,116	138,115
Actual	TLR	Taxus	231,63	175,825	86,078	54,3387
		Cypher	296,911	228,412	118,265	79,311
	TVR	Taxus	319,218	246,412	130,265	89,408
		Cypher	404,399	315,663	172,875	122,352
Non-elective index PCI						
Effective list	TLR	Taxus	164,032	55,299	**–2,169**	
		Cypher	179,085	63,070	**1,755**	
	TVR	Taxus	233,908	92,693	**18,267**	
		Cypher	253,640	102,969	**23,559**	
Actual	TLR	Taxus	118,757	31,923	**–13,970**	
		Cypher	159,561	52,990	**–3,334**	
	TVR	Taxus	174,558	61,786	**2,350**	
		Cypher	228,046	89,641	**16,695**	

ICERs below £30,000 are shown in bold type.

Efficacy or effectiveness

Although on theoretical grounds there can be no dispute that economic evaluation should always be carried out on the basis of effectiveness measures rather than simple efficacy, it may be suggested that the process by which effectiveness estimates have been derived is suspect, and could be downgrading the trial-based efficacy results to an unjustifiable extent. In order to address this point, we have re-estimated the ICERs on the basis of the unadjusted efficacy relative risk reductions. The results shown in *Table 38*, can be compared directly with corresponding results in *Table 31*. Although, as expected, the ICERs generated are generally lower than those based on effectiveness estimates, the only change with respect to an indicative decision threshold (£30,000 per QALY gained) is that the cost-effectiveness for non-elective patients with two risk factors (a very small group numerically) is now confirmed instead of being equivocal. For all other patient groups, the conclusions of the base case analysis are confirmed. Hence the change to effectiveness does not materially influence the main conclusions of the analysis – that DES are only cost-effective except for a very small number of the highest risk patients.

Addendum

Overview of scope of additional evidence and analyses

The first NICE Appraisal Committee meeting for the DES appraisal was held on 1 February 2006. Clinical experts attending the meeting provided reference to additional available data on outcomes related to the use of DES. The conclusion reached by the committee was that they would appreciate additional economic analysis taking into consideration these data and also further consideration of specific outcomes. An outline of the proposed additional analysis was developed by NICE and forwarded to the Assessment Group for response. The Assessment Group replied with a list of analyses that could be carried out and reported within the available time frame (see Appendix 8).

This Addendum provides information regarding expanded data sources utilised and additional analyses, as requested.

Additional information is provided in Appendix 8 to aid in consideration of the cost-effectiveness of DES compared with conventional stents (BMS).

Results are given for specific patient groups, defined by the type of hospital admission and number of stents implanted, and the additional cost per stent (price premium) for DES compared with BMS. A table is also provided to assist in relating the three conventional risk factors most commonly explored in the clinical trials to the level of absolute risk of revascularisation with 12 months used in the addendum analyses.

Overview of data sources

Several of the issues raised by the Appraisal Committee for further consideration involve careful examination of evidence from non-RCT studies of observational or audit data. Before discussing the uses to which we put such evidence it is important to provide a brief description of each source and aspects affecting its suitability for addressing the Appraisal Committee's questions.

Scottish Coronary Revascularisation Register 2003–2004 (UK)[a1]

This is an annual review of information from all sites in Scotland carrying out interventional cardiology. Detailed data are provided of caseloads for 2003–4, particularly relating to PCIs carried out as elective/stable or non-elective/unstable procedures. The coverage is good overall, but for some of the procedural information the coverage is only partial. Long-term outcomes are provided for 30 days, 1 year and 5 years for mortality, AMI and repeat revascularisation.

There are two important caveats relating to these outcome results:

- Significant numbers of non-stented PCIs are included in the tabulations, which are likely to lead to overstating of some outcome results.
- The main long-term outcomes are calculated from patients treated over multiple years beginning at 1997, during which the take-up of stenting has increased rapidly. This inevitably means that the reported outcomes for repeat revascularisation will be overstated.

To clarify the problem of multiple years, we have consulted a peer-reviewed publication reporting findings from the Scottish Coronary Revascularisation Register (SCRR) for the years 1997–9.[a2]

BCIS Audit of Adult Interventional Procedures 2003 (UK)[a3]

This is an annual audit of virtually all PCIs undertaken in the UK, including multiple outcomes and process measures, which include procedural mortality and re-intervention rates. It is a comprehensive database of proven quality and credibility.

Cardiothoracic Treatment Centre Audit Database (UK)[a4]

All stented PCI patients treated in two calendar years (2000–1, when DES use was minimal) were followed up for 12 months. Outcomes available include in-hospital mortality and repeat revascularisation rates at 12 months. A multivariate risk model was developed and published, and is described in the main Assessment Report.

Glenfield Hospital, Leicester Audit (UK)[a5]

This is a review of clinical audit data on 1112 stented patients treated in 2003, available only in abstract form. The authors report TLR rates at 12 months.

APPROACH database (Canada)[a6]

Outcomes from the analysis of 7334 patients undergoing PCI with BMS between 1998 and 2000 are reported from the APPROACH database (which captures all patients undergoing cardiac catheterisation in Alberta, Canada). In a high proportion of cases (47%) the indication was AMI, and only 20% were for stable angina. Peri-procedural mortality, all-cause mortality at 6 months and repeat revascularisation at 12 months are reported. The APPROACH database is well known as a comprehensive and reliable source of evidence.

Agema (The Netherlands)[a7]

A multicentre study at four academic hospitals involved 3177 consecutive non-STEMI patients who underwent PCI in 1999–2001 and were followed up with outcomes reported at 9 and 12 months for clinical restenosis and TVR. Only 77% of patients were stented. Various outcomes and several multivariate models for risk indicators are reported.

BASKET (Switzerland)[a8]

This is a randomised trial of almost all stented PCI patients in one Swiss hospital treated between 2003 and 2005, including 21% STEMI cases. Outcomes are reported at 6 months for cardiac death, AMI and TVR. This is the only 'real-life' independent RCT so far reported of DES versus BMS.

Medicare 5% sample (USA)[a9]

This paper, published recently in *Circulation*, reports on a series of cross-sectional analyses of diagnostic and interventional procedures in a 5% sample of the national database for Medicare

patients (i.e. the elderly) in the USA for the period 1993–2001. This covers a period of rapid changes and describes the expansion in cardiac diagnostic services (stress testing and cardiac catheterisation) and treatments (PCI and CABG). These trends are set against the annual rate of hospital admissions for AMI in the same population, as a proxy for the underlying prevalence of CAD.

The authors detail the proportion of PCIs involving stent deployment each year, and also the proportion of patients receiving a further revascularisation within 6 months. No mention is made of mortality rates, life expectancy or subgroups relevant to the UK. The results include patients undergoing PCI as primary treatment for AMI (although probably a small proportion), and require adjustment for the large shift during the period from balloon angioplasty to stented PCI. During the reported period, the use of DES is likely to have been very limited.

Medicare in Ontario (Canada)[a10]

This paper[a10] was published in the same issue of *Circulation* as the US Medicare paper,[a9] and follows a similar methodology, but uses record linkage of multiple databases across the whole adult population of Ontario. The authors concentrate on the financial impact of the changes in service levels over time and report no outcome measures. However, they do report the annual rate of hospital admissions for AMI. The treatment rates show much lower rates of testing and intervention than in the USA, and these are broken down by age (<65 and 65+ years).

Toulouse (France)[a11]

A prospective analysis of patients treated with stented PCI in a 3-year period (1996–9) in a French hospital was designed to compare the performances of the four most commonly used types of BMS. Only patients in whom types of stents were mixed were excluded. Follow-up was for 24 months. Three types of stents were of a similar era, but one used a silicon carbide coating and represented a newer phase of development. Repeat revascularisation rates (TLR) were reported, and risk modelling was undertaken.

Cleveland (USA)[a12]

This is a retrospective analysis of any repeat revascularisation at 9 months' follow-up for 5239 consecutive BMS patients treated between 1994 and 2001 at a single US centre. Patients were excluded for coil stents use, technical failure, brachytherapy, staged procedure or stent thrombosis within 30 days.

Washington State (USA)[a13]

This is a study of 3571 non-emergent first PCIs carried out in 26 locations in Washington State during 1999. Stent placement was recorded in 87.7% of patients. Figures are reported for all revascularisations within 12 months of the index procedure.

The following sections present the results of the additional analysis carried out by the Assessment Group and the order mirrors the list of analysis presented in Appendix 1.

Wastage rates

In all base case analyses, an assumption was made on clinical advice that 5% of stents purchased are not implanted for any reason and therefore wasted. This factor was incorporated as a simple on-cost to all stent prices in the model (BMS and DES), resulting in a corresponding 5% addition to the price premium. In order to test the sensitivity to this assumption, we have recalculated all base case results with both 1% and 10% wastage rates as shown in *Tables 39–44*.

The differences from the main report results relate only to costs (not outcomes), and lead to minor variations in cost/utility ratios insufficient on their own to have any material impact on judgements of cost-effectiveness.

Procedural disutility – addendum analysis

In all base case analyses it was assumed that patients undergoing a second revascularisation procedure would incur a common disutility, independent of the type of intervention (PCI or CABG) equivalent to recovery to symptom-free QoL at a steady rate over a period of 4 weeks. It was suggested that this is unrealistic: that PCI patients feel benefit very quickly with little discomfort and few complications, but that CABG patients suffer a worse experience with severe pain and slower recovery. It is not possible to obtain observational data for the immediate period following intervention. Instead, we consider a plausible alternative scenario to reflect the suggested effects illustrated in *Figure 14*.

For CABG patients, we assume that for a 2-week post-operative period patients experience a severe loss of QoL to a level considered equivalent to the health-related utility of death (0.0). For the next 2 weeks, the mean utility score recovers in a linear fashion achieving full benefit (0.660) by 4 weeks after the operation.

TABLE 39 *Stent wastage sensitivity analysis: all elective patients*

			All patients			No risk factors			1 risk factor			2 risk factors			3/4 risk factors		
Prices	**Effectiveness**	**Brand**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**
With 1% wastage rate																	
Effective	Narrow	Taxus	969	0.001932	501,300	879	0.001384	635,300	1,047	0.002084	502,500	1,193	0.004108	290,400	1,311	0.006096	215,100
list		Cypher	1,041	0.001932	538,600	943	0.001384	681,600	1,125	0.002084	539,900	1,288	0.004108	313,500	1,422	0.006096	233,200
	Broad	Taxus	927	0.002572	360,300	849	0.001841	461,100	1,002	0.002773	361,300	1,103	0.005466	201,900	1,178	0.008111	145,300
		Cypher	998	0.002572	388,200	913	0.001841	495,700	1,079	0.002773	389,200	1,198	0.005466	219,100	1,287	0.008111	158,700
Actual	Narrow	Taxus	752	0.001932	389,200	687	0.001384	496,200	813	0.002084	390,200	907	0.004108	220,800	979	0.006096	160,600
		Cypher	947	0.001932	490,200	860	0.001384	621,600	1,024	0.002084	491,400	1,165	0.004108	283,500	1,278	0.006096	209,700
	Broad	Taxus	711	0.002572	276,600	657	0.001841	357,100	769	0.002773	277,400	820	0.005466	150,100	851	0.008111	104,900
		Cypher	905	0.002572	352,100	830	0.001841	450,800	979	0.002773	353,000	1,075	0.005466	196,800	1,146	0.008111	141,300
With 5% wastage rate																	
Effective	Narrow	Taxus	1,011	0.001932	523,200	917	0.001384	662,500	1,093	0.002084	524,400	1,248	0.004108	303,900	1,375	0.006096	225,600
list		Cypher	1,086	0.001932	561,900	983	0.001384	710,600	1,174	0.002084	563,300	1,347	0.004108	328,000	1,490	0.006096	244,500
	Broad	Taxus	969	0.002572	376,600	886	0.001841	481,400	1,047	0.002773	377,600	1,158	0.005466	211,900	1,241	0.008111	153,100
		Cypher	1,043	0.002572	405,600	952	0.001841	517,300	1,128	0.002773	406,600	1,256	0.005466	229,800	1,355	0.008111	167,000
Actual	Narrow	Taxus	786	0.001932	406,600	717	0.001384	517,900	850	0.002084	407,600	951	0.004108	231,500	1,030	0.006096	169,000
		Cypher	989	0.001932	511,700	897	0.001384	648,200	1,069	0.002084	512,900	1,219	0.004108	296,800	1,341	0.006096	220,000
	Broad	Taxus	745	0.002572	289,600	687	0.001841	373,200	805	0.002773	290,400	864	0.005466	158,000	901	0.008111	111,000
		Cypher	946	0.002572	368,000	867	0.001841	470,700	1,023	0.002773	369,000	1,129	0.005466	206,600	1,208	0.008111	148,900
With 10% wastage rate																	
Effective	Narrow	Taxus	1,064	0.001932	550,500	964	0.001384	696,500	1,150	0.002084	551,900	1,318	0.004108	320,800	1,456	0.006096	238,800
list		Cypher	1,142	0.001932	591,100	1,033	0.001384	746,900	1,235	0.002084	592,500	1,421	0.004108	346,000	1,576	0.006096	258,500
	Broad	Taxus	1,021	0.002572	397,000	933	0.001841	506,700	1,104	0.002773	398,000	1,227	0.005466	224,400	1,320	0.008111	162,800
		Cypher	1,099	0.002572	427,300	1,002	0.001841	544,400	1,188	0.002773	428,400	1,329	0.005466	243,200	1,439	0.008111	177,400
Actual	Narrow	Taxus	828	0.001932	428,400	754	0.001384	545,000	895	0.002084	429,500	1,006	0.004108	245,000	1,094	0.006096	179,500
		Cypher	1,041	0.001932	538,500	943	0.001384	681,500	1,125	0.002084	539,800	1,287	0.004108	313,300	1,420	0.006096	233,000
	Broad	Taxus	786	0.002572	305,800	724	0.001841	393,400	850	0.002773	306,600	918	0.005466	168,000	963	0.008111	118,800
		Cypher	998	0.002572	388,000	912	0.001841	495,500	1,079	0.002773	389,000	1,196	0.005466	218,800	1,285	0.008111	158,400

TABLE 40 *Stent wastage sensitivity analysis: elective patients if only one stent is required*

			All patients			No risk factors			1 risk factor			2 risk factors			3/4 risk factors		
Prices	**Effectiveness**	**Brand**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**
With 1% wastage rate																	
Effective	Narrow	Taxus	585	0.001932	302,900	621	0.001384	449,100	575	0.002084	276,000	442	0.004108	107,600	311	0.006096	51,000
list		Cypher	632	0.001932	326,900	668	0.001384	482,900	622	0.002084	298,200	487	0.004108	118,500	354	0.006096	58,100
	Broad		543	0.002572	211,200	591	0.001841	321,200	530	0.002773	191,100	352	0.005466	64,500	178	0.008111	**22,000**
			589	0.002572	229,100	638	0.001841	346,400	576	0.002773	207,600	396	0.005466	72,500	220	0.008111	**27,100**
Actual	Narrow	Taxus	446	0.001932	230,700	481	0.001384	347,500	436	0.002084	209,300	307	0.004108	74,800	180	0.006096	**29,600**
		Cypher	572	0.001932	295,700	608	0.001384	439,100	562	0.002084	269,400	429	0.004108	104,300	298	0.006096	48,900
	Broad	Taxus	405	0.002572	157,500	452	0.001841	245,300	392	0.002773	141,400	220	0.005466	40,300	52	0.008111	**6,400**
		Cypher	530	0.002572	205,900	578	0.001841	313,700	516	0.002773	186,200	339	0.005466	62,100	166	0.008111	**20,400**
With 5% wastage rate																	
Effective	Narrow	Taxus	612	0.001932	316,900	649	0.001384	468,900	602	0.002084	289,000	468	0.004108	113,800	335	0.006096	55,000
list		Cyper	661	0.001932	341,800	697	0.001384	504,100	650	0.002084	312,000	514	0.004108	125,200	381	0.006096	62,400
	Broad	Taxus	570	0.002572	221,600	618	0.001841	335,900	556	0.002773	200,700	377	0.005466	69,000	201	0.008111	**24,800**
		Cyper	618	0.002572	240,200	667	0.001841	362,100	604	0.002773	217,800	423	0.005466	77,400	245	0.008111	30,200
Actual	Narrow	Taxus	467	0.001932	241,900	503	0.001384	363,300	458	0.002084	219,600	328	0.004108	79,700	200	0.006096	32,800
		Cyper	598	0.001932	309,500	634	0.001384	458,500	588	0.002084	282,100	454	0.004108	110,500	322	0.006096	52,800
	Broad	Taxus	426	0.002572	165,800	473	0.001841	257,100	413	0.002773	149,100	240	0.005466	43,900	70	0.008111	**8,700**
		Cyper	556	0.002572	216,100	604	0.001841	328,100	542	0.002773	195,600	364	0.005466	66,600	189	0.008111	**23,200**
With 10% wastage rate																	
Effective	Narrow	Taxus	646	0.001932	334,400	683	0.001384	493,700	636	0.002084	305,200	500	0.004108	121,700	366	0.006096	60,100
lsit		Cyper	697	0.001932	360,500	734	0.001384	530,500	686	0.002084	329,300	549	0.004108	133,600	414	0.006096	67,800
	Broad	Taxus	603	0.002572	234,600	652	0.001841	354,300	590	0.002773	212,600	409	0.005466	74,800	231	0.008111	**28,500**
		Cyper	653	0.002572	254,000	703	0.001841	381,800	640	0.002773	230,600	456	0.005466	83,500	276	0.008111	34,100
Actual	Narrow	Taxus	494	0.001932	255,800	530	0.001384	383,000	485	0.002084	232,500	353	0.004108	86,000	224	0.006096	36,800
		Cyper	631	0.001932	326,600	668	0.001384	482,800	621	0.002084	298,000	485	0.004108	118,200	352	0.006096	57,800
	Broad	Taxus	453	0.002572	176,100	500	0.001841	271,700	440	0.002773	158,600	265	0.005466	48,500	93	0.008111	**11,500**
		Cyper	588	0.002572	228,800	637	0.001841	346,200	575	0.002773	207,300	394	0.005466	72,200	217	0.008111	**26,800**

TABLE 41 *Stent wastage sensitivity analysis: elective patients if only two stents are required*

			All patients			No risk factors			1 risk factor			2 risk factors			3/4 risk factors		
Prices	**Effectiveness**	**Brand**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C ()**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**
With 1% wastage rate																	
Effective	Narrow	Taxus	1,230	0.001932	636,500	1,266	0.001384	915,100	1,220	0.002084	585,400	1,087	0.004108	264,500	956	0.006096	156,800
list		Cypher	1,320	0.001932	682,900	1,356	0.001384	980,100	1,309	0.002084	628,300	1,175	0.004108	285,900	1,042	0.006096	171,000
	Broad	Taxus	1,188	0.002572	461,900	1,236	0.001841	671,400	1,175	0.002773	423,600	997	0.005466	182,400	823	0.008111	101,500
		Cypher	1,277	0.002572	496,600	1,326	0.001841	720,000	1,264	0.002773	455,600	1,084	0.005466	198,300	908	0.008111	112,000
Actual	Narrow	Taxus	961	0.001932	497,200	996	0.001384	719,700	951	0.002084	456,300	822	0.004108	200,100	695	0.006096	114,100
		Cypher	1,203	0.001932	622,800	1,240	0.001384	895,800	1,194	0.002084	572,600	1,061	0.004108	258,200	930	0.006096	152,600
	Broad	Taxus	920	0.002572	357,800	967	0.001841	525,000	907	0.002773	327,100	735	0.005466	134,500	567	0.008111	69,900
		Cypher	1,161	0.002572	451,700	1,209	0.001841	656,900	1,148	0.002773	414,100	971	0.005466	177,700	798	0.008111	98,300
With 5% wastage rate																	
Effective	Narrow	Taxus	1,283	0.001932	663,800	1,319	0.001384	953,400	1,273	0.002084	610,600	1,138	0.004108	277,000	1,006	0.006096	165,000
list		Cypher	1,376	0.001932	711,900	1,413	0.001384	1,020,900	1,366	0.002084	655,200	1,229	0.004108	299,300	1,096	0.006096	179,800
	Broad	Taxus	1,240	0.002572	482,300	1,289	0.001841	700,000	1,227	0.002773	442,400	1,048	0.005466	191,700	872	0.008111	107,500
		Cypher	1,333	0.002572	518,300	1,382	0.001841	750,600	1,319	0.002773	475,700	1,138	0.005466	208,200	960	0.008111	118,400
Actual	Narrow	Taxus	1,003	0.001932	518,900	1,038	0.001384	750,200	993	0.002084	476,400	863	0.004108	210,000	735	0.006096	120,600
		Cypher	1,255	0.001932	649,500	1,291	0.001384	933,300	1,245	0.002084	597,300	1,111	0.004108	270,400	979	0.006096	160,600
	Broad	Taxus	962	0.002572	373,900	1,009	0.001841	547,800	949	0.002773	342,100	776	0.005466	141,900	606	0.008111	74,700
		Cypher	1,213	0.002572	471,600	1,261	0.001841	685,000	1,199	0.002773	432,500	1,021	0.005466	186,800	846	0.008111	104,200
With 10% wastage rate																	
Effective	Narrow	Taxus	1,348	0.001932	697,800	1,385	0.001384	1,001,200	1,338	0.002084	642,100	1,202	0.004108	292,600	1,069	0.006096	175,300
list		Cypher	1,446	0.001932	748,300	1,483	0.001384	1,072,000	1,436	0.002084	688,800	1,298	0.004108	316,000	1,163	0.006096	190,800
	Broad	Taxus	1,305	0.002572	507,700	1,355	0.001841	735,800	1,292	0.002773	465,900	1,111	0.005466	203,200	933	0.008111	115,000
		Cypher	1,402	0.002572	545,400	1,452	0.001841	788,800	1,389	0.002773	500,800	1,206	0.005466	220,600	1,026	0.008111	126,500
Actual	Narrow	Taxus	1,055	0.001932	546,000	1,091	0.001384	788,300	1,045	0.002084	501,500	914	0.004108	222,500	785	0.006096	128,800
		Cypher	1,319	0.001932	682,800	1,356	0.001384	980,200	1,309	0.002084	628,200	1,174	0.004108	285,700	1,040	0.006096	170,700
	Broad	Taxus	1,014	0.002572	394,200	1,061	0.001841	576,300	1,001	0.002773	360,800	826	0.005466	151,100	654	0.008111	80,600
		Cypher	1,277	0.002572	496,400	1,326	0.001841	720,000	1,263	0.002773	455,500	1,083	0.005466	198,100	905	0.008111	111,600

TABLE 42 *Stent wastage sensitivity analysis: all non-elective patients*

			All patients			No risk factors			1 risk factor			2 risk factors		
Prices	**Effectiveness**	**Brand**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**
With 1% wastage rate														
Effective list	Narrow	Taxus	814	0.002444	333,200	807	0.002155	374,500	899	0.005332	168,600	583	0.009716	60,000
		Cypher	879	0.002444	359,600	870	0.002155	403,700	981	0.005332	184,000	661	0.009716	68,000
	Broad	Taxus	757	0.003251	232,900	757	0.002867	263,900	775	0.007095	109,200	356	0.012928	**27,500**
		Cypher	821	0.003251	252,600	819	0.002867	285,700	855	0.007095	120,600	432	0.012928	33,400
Actual	Narrow	Taxus	620	0.002444	253,900	618	0.002155	286,900	653	0.005332	122,500	347	0.009716	35,700
		Cypher	795	0.002444	325,400	789	0.002155	365,900	875	0.005332	164,100	559	0.009716	57,600
	Broad	Taxus	565	0.003251	173,800	569	0.002867	198,600	532	0.007095	75,000	126	0.012928	**9,800**
		Cypher	738	0.003251	227,100	738	0.002867	257,500	751	0.007095	105,800	333	0.012928	**25,800**
With 5% wastage rate														
Effective list	Narrow	Taxus	852	0.002444	348,700	844	0.002155	391,600	947	0.005332	177,500	627	0.009716	64,600
		Cypher	919	0.002444	376,100	909	0.002155	421,900	1,032	0.005332	193,500	709	0.009716	73,000
	Broad	Taxus	795	0.003251	244,400	793	0.002867	276,600	821	0.007095	115,700	399	0.012928	30,800
		Cypher	861	0.003251	264,800	858	0.002867	299,200	905	0.007095	127,600	478	0.012928	37,000
Actual	Narrow	Taxus	651	0.002444	266,200	648	0.002155	300,500	691	0.005332	129,500	382	0.009716	39,300
		Cypher	832	0.002444	340,500	825	0.002155	382,600	921	0.005332	172,800	603	0.009716	62,100
	Broad	Taxus	595	0.003251	182,900	598	0.002867	208,700	569	0.007095	80,200	160	0.012928	**12,400**
		Cypher	775	0.003251	238,300	774	0.002867	269,900	796	0.007095	112,200	375	0.012928	**29,000**
With 10% wastage rate														
Effective list	Narrow	Taxus	899	0.002444	368,000	890	0.002155	412,900	1,006	0.005332	188,700	683	0.009716	70,300
		Cypher	969	0.002444	396,700	958	0.002155	444,700	1,095	0.005332	205,400	769	0.009716	79,100
	Broad	Taxus	841	0.003251	258,700	839	0.002867	292,500	879	0.007095	123,900	452	0.012928	35,000
		Cypher	911	0.003251	280,100	907	0.002867	316,200	967	0.007095	136,300	536	0.012928	41,400
Actual	Narrow	Taxus	688	0.002444	281,600	684	0.002155	317,500	738	0.005332	138,400	426	0.009716	43,900
		Cypher	878	0.002444	359,400	870	0.002155	403,500	980	0.005332	183,700	658	0.009716	67,700
	Broad	Taxus	632	0.003251	194,300	635	0.002867	221,300	615	0.007095	86,700	203	0.012928	**15,700**
		Cypher	820	0.003251	252,300	819	0.002867	285,500	853	0.007095	120,300	428	0.012928	33,100

TABLE 43 *Stent wastage sensitivity analysis: non-elective patients if only one stent is required*

			All patients			No risk factors			1 risk factor			2 risk factors		
Prices	**Effectiveness**	**Brand**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**
With 1% wastage rate														
Effective	Narrow	Taxus	506	0.002444	207,100	560	0.002155	260,100	302	0.005332	56,700	*–7*	0.009716	**–800**
list		Cypher	550	0.002444	225,100	607	0.002155	281,600	344	0.005332	64,500	32	0.009716	**3,300**
	Broad	Taxus	449	0.003251	138,100	510	0.002867	177,900	178	0.007095	**25,100**	*–234*	0.012928	**–18,100**
		Cypher	492	0.003251	151,400	556	0.002867	193,900	218	0.007095	30,800	*–197*	0.012928	**–15,300**
Actual	Narrow	Taxus	374	0.002444	153,200	421	0.002155	195,500	176	0.005332	33,100	*–124*	0.009716	**–12,800**
		Cypher	493	0.002444	201,800	547	0.002155	253,700	290	0.005332	54,300	*–19*	0.009716	**–1,900**
	Broad	Taxus	319	0.003251	98,100	372	0.002867	129,900	55	0.007095	**7,800**	*–345*	0.012928	**–26,700**
		Cypher	436	0.003251	134,200	497	0.002867	173,200	166	0.007095	23,300	*–245*	0.012928	**–19,000**
With 5% wastage rate														
Effective	Narrow	Taxus	532	0.002444	217,600	588	0.002155	272,600	326	0.005332	61,200	14	0.009716	**1,500**
list		Cypher	577	0.002444	236,200	636	0.002155	294,900	370	0.005332	69,300	55	0.009716	**5,600**
	Broad	Taxus	474	0.003251	145,800	537	0.002867	187,200	201	0.007095	**28,300**	*–214*	0.012928	**–16,600**
		Cypher	519	0.003251	159,700	584	0.002867	203,800	243	0.007095	34,200	*–176*	0.012928	**–13,600**
Actual	Narrow	Taxus	395	0.002444	161,500	443	0.002155	205,500	195	0.005332	36,600	*–108*	0.009716	**–11,100**
		Cypher	518	0.002444	212,000	573	0.002155	266,000	313	0.005332	58,700	2	0.009716	**200**
	Broad	Taxus	339	0.003251	104,200	394	0.002867	137,300	73	0.007095	**10,300**	*–329*	0.012928	**–25,500**
		Cypher	461	0.003251	141,700	523	0.002867	182,300	188	0.007095	**26,500**	*–226*	0.012928	**–17,500**
With 10% wastage rate														
Effective	Narrow	Taxus	564	0.002444	230,600	£621	0.002155	288,300	356	0.005332	66,800	41	0.009716	**4,200**
list		Cypher	611	0.002444	250,200	672	0.002155	311,700	402	0.005332	75,300	83	0.009716	**8,600**
	Broad	Taxus	506	0.003251	155,500	570	0.002867	198,800	229	0.007095	32,300	*–190*	0.012928	**–14,700**
		Cypher	553	0.003251	170,000	620	0.002867	216,200	274	0.007095	38,600	*–150*	0.012928	**–11,600**
Actual	Narrow	Taxus	420	0.002444	171,900	470	0.002155	217,900	219	0.005332	41,000	*–87*	0.009716	**–8,900**
		Cypher	549	0.002444	224,800	606	0.002155	281,300	342	0.005332	64,200	28	0.009716	**2,900**
	Broad	Taxus	364	0.003251	111,900	420	0.002867	146,500	96	0.007095	**13,500**	*–310*	0.012928	**–24,000**
		Cypher	492	0.003251	151,200	555	0.002867	193,600	216	0.007095	30,500	*–202*	0.012928	**–15,600**

TABLE 44 *Stent wastage sensitivity analysis: non-elective patients if only two stent are required*

			All patients			No risk factors			1 risk factor			2 risk factors		
Prices	**Effectiveness**	**Brand**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**
With 1% wastage rate														
Effective list	Narrow	Taxus	1,185	0.002444	484,900	1,273	0.002155	590,800	981	0.005332	184,000	671	0.009716	69,100
		Cypher	1,274	0.002444	521,400	1,367	0.002155	634,400	1,068	0.005332	200,300	756	0.009716	77,800
	Broad	Taxus	1,128	0.003251	346,900	1,223	0.002867	426,400	856	0.007095	120,700	445	0.012928	34,400
		Cypher	1,217	0.003251	374,200	1,316	0.002867	459,100	943	0.007095	132,900	527	0.012928	40,800
Actual	Narrow	Taxus	916	0.002444	375,000	990	0.002155	459,600	718	0.005332	134,700	418	0.009716	43,000
		Cypher	1,158	0.002444	474,000	1,245	0.002155	577,800	955	0.005332	179,100	646	0.009716	66,500
	Broad	Taxus	861	0.003251	264,800	942	0.002867	328,400	597	0.007095	84,200	197	0.012928	**15,300**
		Cypher	1,102	0.003251	338,800	1,195	0.002867	416,800	831	0.007095	117,100	420	0.012928	32,500
With 5% wastage rate														
Effective list	Narrow	Taxus	1,237	0.002444	506,300	1,328	0.002155	616,400	1,032	0.005332	193,500	720	0.009716	74,100
		Cypher	1,330	0.002444	544,300	1,426	0.002155	661,700	1,122	0.005332	210,500	807	0.009716	83,100
	Broad	Taxus	1,180	0.003251	362,800	1,278	0.002867	445,600	906	0.007095	127,700	491	0.012928	38,000
		Cypher	1,272	0.003251	391,200	1,375	0.002867	479,500	996	0.007095	140,400	577	0.012928	44,600
Actual	Narrow	Taxus	958	0.002444	392,100	1,034	0.002155	480,000	759	0.005332	142,300	456	0.009716	46,900
		Cypher	1,210	0.002444	495,000	1,299	0.002155	602,900	1,005	0.005332	188,400	694	0.009716	71,400
	Broad	Taxus	902	0.003251	277,500	985	0.002867	343,600	637	0.007095	89,800	234	0.012928	**18,100**
		Cypher	1,152	0.003251	354,400	1,249	0.002867	435,500	880	0.007095	124,000	466	0.012928	36,000
With 10% wastage rate														
Effective list	Narrow	Taxus	1,303	0.002444	533,100	1,397	0.002155	648,400	1,095	0.005332	205,400	780	0.009716	80,300
		Cypher	1,400	0.002444	572,900	1,500	0.002155	695,900	1,190	0.005332	223,200	872	0.009716	89,700
	Broad	Taxus	1,245	0.003251	382,800	1,346	0.002867	469,500	968	0.007095	136,500	549	0.012928	42,500
		Cypher	1,341	0.003251	412,500	1,448	0.002867	505,000	1,062	0.007095	149,700	639	0.012928	49,400
Actual	Narrow	Taxus	1,010	0.002444	413,500	1,090	0.002155	505,600	809	0.005332	151,700	504	0.009716	51,800
		Cypher	1,274	0.002444	521,300	1,367	0.002155	634,300	1,067	0.005332	200,100	753	0.009716	77,500
	Broad	Taxus	954	0.003251	293,400	1,040	0.002867	362,600	686	0.007095	96,700	280	0.012928	**21,600**
		Cypher	1,216	0.003251	374,000	1,316	0.002867	458,900	941	0.007095	132,600	523	0.012928	40,400

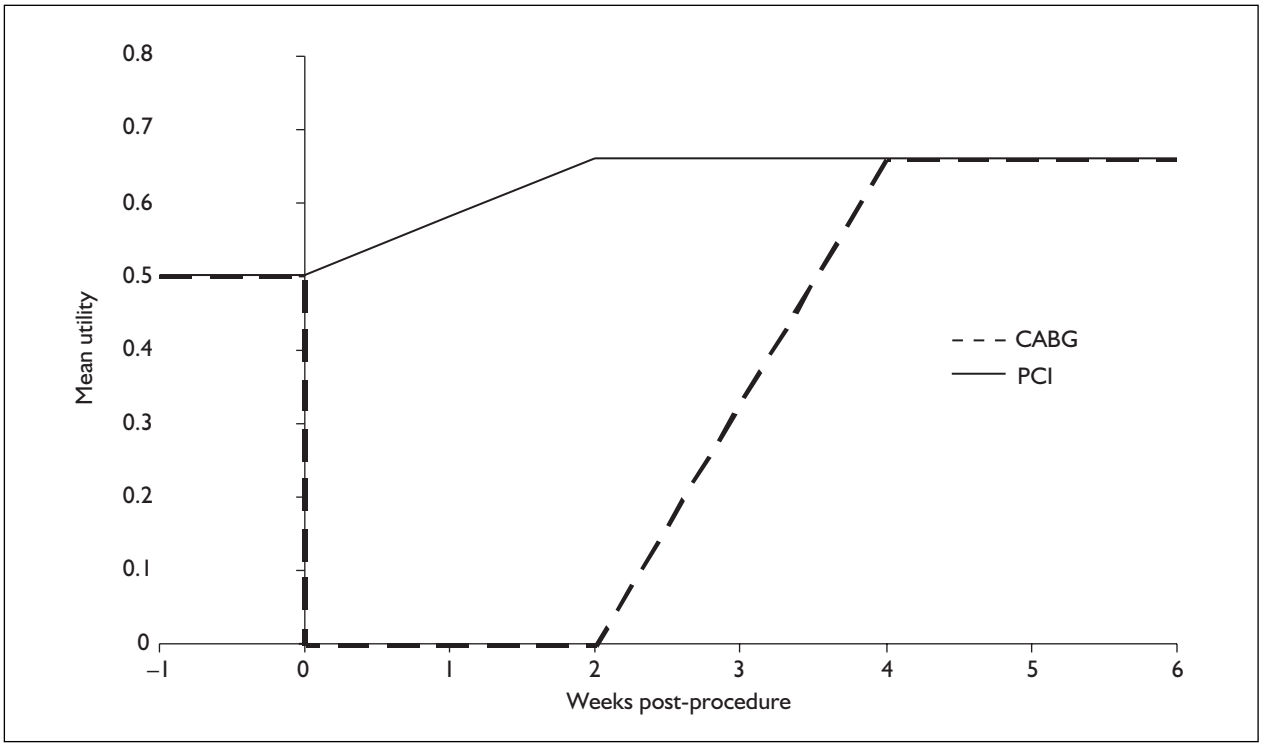


FIGURE 14 *Alternative disutility assumptions*

For PCI patients, we assume that patients recover full benefit linearly over a 2-week period following the intervention.

The effect of these assumptions is to increase substantially the disutility associated with CABG, but to decrease the procedural disutility of PCI. In addition, we can no longer assume in the model a common disutility effect for elective and non-elective patients since there is evidence that a higher proportion of repeat interventions require CABG among patients whose index procedure is non-elective (9.0% elective versus 17.9% non-elective in CTC audit data). The base case analyses have been recalculated on this new basis and are displayed in *Tables 45* and *46*.

Because of the reduced disutility for PCI and the lower proportion of CABG among elective patients, the mean disutility per patient is reduced, leading to higher ICERs for all elective patients. By contrast, for non-elective patients the ICERs generally reduce slightly, but not sufficiently to alter the determination of cost-effectiveness for any category of patients.

AMI and mortality – is there a case for a DES effect?

Understanding the issues

The extreme sensitivity of the economic analysis to any supposed survival gain has led some to question assumptions made in the Assessment Group economic model. In particular, we have assumed that there is no benefit to patients from DES arising from mortality risks associated with AMIs and peri-procedural fatalities. These assumptions were justified directly from the RCT evidence and meta-analyses presented in the main report, and which failed to find any significant differences between BMS and DES in AMIs and deaths in all follow-up periods to 3 years.

The suggestion has been made that these findings appear to be at variance with well-documented important mortality risks associated with additional interventional procedures, and with widely held clinical beliefs that avoidance of stenosis should result in reduced frequency of AMIs and AMI-related fatalities. Unless we take the radical step of discounting the combined RCT evidence as unreliable, these beliefs would need to be justified on the grounds that either the RCT evidence has no bearing on normal clinical practice, or that the combined patient numbers from the trials and/or the available follow-up time are insufficient to yield statistically significant results. In either case, it has been suggested that non-significant 'trend' benefits should nonetheless be used for economic analysis.

However, there is a conflict between the meta-analyses which renders this approach problematic.

TABLE 45 *Alternative procedural disutility assumptions: elective patients*

			All patients			No risk factors			1 risk factor			2 risk factors			3/4 risk factors		
Prices	**Effectiveness**	**Brand**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C ()**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**
Average use of stents																	
Effective	Narrow	Taxus	1,011	0.001952	517,900	917	0.001398	655,700	1,093	0.002106	519,100	1,248	0.00415	300,800	1,375	0.006158	223,300
list		Cypher	1,086	0.001952	556,200	983	0.001398	703,300	1,174	0.002106	557,500	1,347	0.00415	324,600	1,490	0.006158	242,000
	Broad	Taxus	969	0.002598	372,800	886	0.00186	476,500	1,047	0.002802	373,800	1,158	0.005522	209,700	1,241	0.008194	151,500
		Cypher	1,043	0.002598	401,400	952	0.00186	512,100	1,128	0.002802	402,500	1,256	0.005522	227,400	1,355	0.008194	165,300
Actual	Narrow	Taxus	786	0.001952	402,500	717	0.001398	512,600	850	0.002106	403,500	951	0.00415	229,200	1,030	0.006158	167,300
		Cypher	989	0.001952	506,500	897	0.001398	641,600	1,069	0.002106	507,700	1,219	0.00415	293,700	1,341	0.006158	217,800
	Broad	Taxus	745	0.002598	286,600	687	0.00186	369,400	805	0.002802	287,400	864	0.005522	156,400	901	0.008194	109,900
		Cypher	946	0.002598	364,300	867	0.00186	465,900	1,023	0.002802	365,200	1,129	0.005522	204,500	1,208	0.008194	147,400
Where only 1 stent is required																	
Effective	Narrow	Taxus	612	0.001952	313,700	649	0.001398	464,100	602	0.002106	286,000	468	0.00415	112,700	335	0.006158	54,500
list		Cypher	661	0.001952	338,300	697	0.001398	498,900	650	0.002106	308,900	514	0.00415	123,900	381	0.006158	61,800
	Broad	Taxus	570	0.002598	219,300	618	0.00186	332,500	556	0.002802	198,600	377	0.005522	68,300	201	0.008194	**24,600**
		Cypher	618	0.002598	237,700	667	0.00186	358,400	604	0.002802	215,600	423	0.005522	76,600	245	0.008194	**29,900**
Actual	Narrow	Taxus	467	0.001952	239,400	503	0.001398	359,600	458	0.002106	217,300	328	0.00415	78,900	200	0.006158	32,400
		Cypher	598	0.001952	306,300	634	0.001398	453,800	588	0.002106	279,200	454	0.00415	109,300	322	0.006158	52,300
	Broad	Taxus	426	0.002598	164,100	473	0.00186	254,400	413	0.002802	147,500	240	0.005522	43,500	70	0.008194	**8,600**
		Cypher	556	0.002598	213,900	604	0.00186	324,800	542	0.002802	193,600	364	0.005522	65,900	189	0.008194	**23,000**
Where only 2 stents are required																	
Effective	Narrow	Taxus	1,283	0.001952	657,000	1,319	0.001398	943,600	1,273	0.002106	604,400	1,138	0.00415	274,200	1,006	0.006158	163,300
list		Cypher	1,376	0.001952	704,700	1,413	0.001398	1,010,500	1,366	0.002106	648,500	1,229	0.00415	296,200	1,096	0.006158	177,900
	Broad	Taxus	1,240	0.002598	477,300	1,289	0.00186	692,800	1,227	0.002802	437,900	1,048	0.005522	189,700	872	0.008194	106,400
		Cypher	1,333	0.002598	513,000	1,382	0.00186	742,900	1,319	0.002802	470,900	1,138	0.005522	206,100	960	0.008194	117,200
Actual	Narrow	Taxus	1,003	0.001952	513,600	1,038	0.001398	742,500	993	0.002106	471,600	863	0.00415	207,900	735	0.006158	119,400
		Cypher	1,255	0.001952	642,800	1,291	0.001398	923,800	1,245	0.002106	591,300	1,111	0.00415	267,600	979	0.006158	159,000
	Broad	Taxus	962	0.002598	370,100	1,009	0.00186	542,200	949	0.002802	338,600	776	0.005522	140,400	606	0.008194	73,900
		Cypher	1,213	0.002598	466,800	1,261	0.00186	678,000	1,199	0.002802	428,100	1,021	0.005522	184,800	846	0.008194	103,200

TABLE 46 *Alternative procedural disutility assumptions: non-elective patients*

			All patients			No risk factors			1 risk factor			2 risk factors		
Prices	**Effectiveness**	**Brand**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**	**Δ_C (£)**	**Δ_Q**	**ICER (£)**
Average use of stents														
Effective	Narrow	Taxus	852	0.002549	334,300	844	0.002248	375,400	947	0.005562	170,200	627	0.010135	61,900
list		Cypher	919	0.002549	360,600	909	0.002248	404,500	1,032	0.005562	185,500	709	0.010135	69,900
	Broad	Taxus	795	0.003392	234,300	793	0.002991	265,200	821	0.007401	111,000	399	0.013485	**29,600**
		Cypher	861	0.003392	253,900	858	0.002991	286,900	905	0.007401	122,300	478	0.013485	35,400
Actual	Narrow	Taxus	651	0.002549	255,200	648	0.002248	288,100	691	0.005562	124,200	382	0.010135	37,700
		Cypher	832	0.002549	326,500	825	0.002248	366,800	921	0.005562	165,700	603	0.010135	59,500
	Broad	Taxus	595	0.003392	175,400	598	0.002991	200,100	569	0.007401	76,900	160	0.013485	**11,900**
		Cypher	775	0.003392	228,500	774	0.002991	258,800	796	0.007401	107,600	375	0.013485	**27,800**
Where only 1 stent is required														
Effective	Narrow	Taxus	532	0.002549	208,600	588	0.002248	261,400	326	0.005562	58,600	14	0.010135	**1,400**
list		Cypher	577	0.002549	226,500	636	0.002248	282,800	370	0.005562	66,500	55	0.010135	**5,400**
	Broad	Taxus	474	0.003392	139,800	537	0.002991	179,500	201	0.007401	**27,100**	**–214**	0.013485	**–15,900**
		Cypher	519	0.003392	153,100	584	0.002991	195,400	243	0.007401	32,800	**–176**	0.013485	**–13,100**
Actual	Narrow	Taxus	395	0.002549	154,800	443	0.002248	197,000	195	0.005562	35,100	**–108**	0.010135	**–10,600**
		Cypher	518	0.002549	203,300	573	0.002248	255,000	313	0.005562	56,300	2	0.010135	**200**
	Broad	Taxus	339	0.003392	99,900	394	0.002991	131,600	73	0.007401	**9,900**	**–330**	0.013485	**–24,400**
		Cypher	461	0.003392	135,900	523	0.002991	174,700	188	0.007401	**25,400**	**–226**	0.013485	**–16,700**
Where only 2 stents are required														
Effective	Narrow	Taxus	1,237	0.002549	485,400	1,328	0.002248	590,900	1,032	0.005562	185,500	720	0.010135	71,000
list		Cypher	1,330	0.002549	521,800	1,426	0.002248	634,400	1,122	0.005562	201,800	807	0.010135	79,700
	Broad	Taxus	1,180	0.003392	347,900	1,278	0.002991	427,200	906	0.007401	122,500	491	0.013485	36,400
		Cypher	1,272	0.003392	375,100	1,375	0.002991	459,700	996	0.007401	134,600	577	0.013485	42,800
Actual	Narrow	Taxus	958	0.002549	375,900	1,034	0.002248	460,200	759	0.005562	136,400	456	0.010135	45,000
		Cypher	1,210	0.002549	474,600	1,299	0.002248	578,000	1,005	0.005562	180,600	694	0.010135	68,400
	Broad	Taxus	902	0.003392	266,100	985	0.002991	329,400	637	0.007401	86,100	234	0.013485	**17,400**
		Cypher	1,152	0.003392	339,800	1,249	0.002991	417,500	880	0.007401	118,900	466	0.013485	34,500

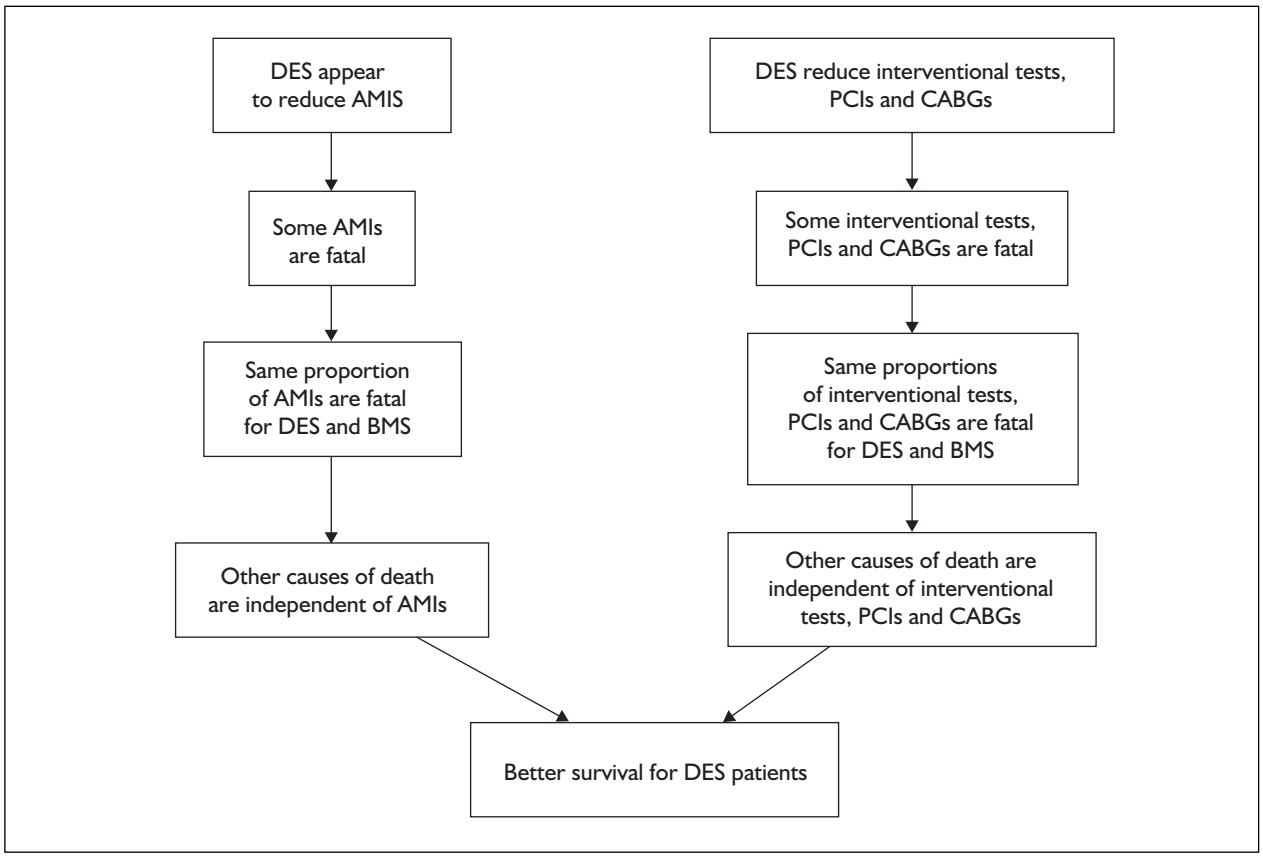


FIGURE 15 *Implicit reasoning in support of survival gain for DES versus BMS*

Although it appears that there are 'trends' in favour of DES for AMI events across all follow-up periods (6–9, 12, 24 and 36 months), this is not the case for overall mortality, where ORs of 0.87, 1.31, 0.96 and 1.64, respectively, arise from meta-analysis. Hence, even if we allow a non-significant reduction in AMI events due to DES usage, it does not follow that overall mortality reduces in line with AMIs – indeed, the balance of evidence might support the suspicion that DES could lead to loss of life expectancy.

It is instructive to analyse the train of logic on which the suggestion of survival benefits is based (*Figure 15*). All the steps shown must be established, and credible evidence-based values assigned, before any reliable estimates of survival gain (if any) can be deduced. Of particular concern are the assumptions of independence between the various process measures. To furnish realistic values for these, it would be necessary to draw on a variety of sources involving unrelated patients, and this presupposes mutual independence of effects. However, there are several known mechanisms by which important interactions can arise when values for several parameters are estimated from the same patients – not least that death acts as a censoring event for all other events. Hence in logical terms it is perfectly feasible for the initial propositions to be true, but the final assertion false.

The primary objection to the 'belief-based' line of reasoning for survival gains is that the trials have reported evidence of overall survival which encompasses both of the proposed mechanisms to deliver such gains. The failure of meta-analysis to identify a significant difference between DES and BMS, or even a consistent trend in either direction, suggests strongly that in this instance the strongly held beliefs may be founded on false perceptions.

Are AMI and mortality rates reduced by PCI/stents?

It is interesting that neither submissions nor expert evidence for the previous appraisal (which informed Guidance 71), nor for this assessment, claimed that AMI reductions were among the benefits to be expected from stented PCI. Indeed, it was clearly stated that the primary objective of PCI (with or without stenting) was to provide symptomatic relief and QoL improvement. The reason for this is that the earlier research carried

TABLE 47 *Pooled outcomes of trials comparing PTCA with medical therapy*

				AMI				Death			
	Patients		Follow-up	Rate (%)		Annual risk (%)		Rate (%)		Annual risk (%)	
Trial	PTCA	Medical	(years)	PTCA	Medical	PTCA	Medical	PTCA	Medical	PTCA	Medical
RITA-2	504	514	2.7	4.8	2.9	1.8	1.1	2.2	1.4	0.8	0.5
ACME	165	167	3.0	12.1	8.4	4.0	2.8	15.2	15.0	5.1	5.0
MASS	72	72	3.0	2.8	2.8	0.9	0.9	1.4	0.0	0.5	0.0
MASS-II	205	203	1.0	7.8	4.9	7.8	4.9	4.4	1.5	4.4	1.5
Pooled	946	956	2.4	6.6	4.3	2.7	1.8	4.9	3.7	2.0	1.5

out compared the efficacy of different modes of revascularisation (PTCA and CABG) with conservative medical therapy.[a14–17] *Table 47* shows that despite considerable differences in the patient groups studied, there was a uniformly poorer outlook for patients undergoing PTCA in respect of AMI and overall mortality across all studies. This was partly explained by early procedural adverse events for PTCA, many of which are no longer applicable, but even when these are excluded, there is no evidence for AMI/mortality improvements with PTCA.

The advent of coronary artery stenting has greatly reduced the problems of restenosis and reduced the unacceptably high rates on repeat interventions necessary following balloon angioplasty. However, the risks of AMI and death have not improved noticeably since the pre-stent era. For example, the long-term outcomes for PCI in Scotland show that AMI occurs in 3.0% of PCI patients in the first year, and 1.0% per annum thereafter. For mortality, the Scottish rates are 2.6% and 1.7%, respectively. Hence, it is far from clear that any real improvement has taken place in these outcomes, despite advances in both technology and clinical practice.

Longitudinal evidence

Further light has been cast on this issue by the recent publication in *Circulation* of the results of large population longitudinal studies of the development of cardiology services in Canada and the USA.[a9,a10] In particular, these allow direct comparison of time trends in revascularisation volumes and hospital admissions for AMI. If we believe that use of PCI leads to clinically meaningful reductions in AMI risk, then we should expect to see evidence over the last 10 years of a declining trend in AMIs corresponding to the exponential growth in PCI treatment, and particularly of stenting. However, the results are equally disappointing in both North American studies, showing no evidence of declines in AMI volumes, not even of any deflection from historic trends. *Figure 16* shows the US results; Ontario results are very similar.

These findings confirm an earlier study[a18] of all PCIs carried out in British Columbia between April 1994 and June 1997 (9594 procedures in 7880 patients), in which the authors state:

> "… there was a significant stepwise reduction in the rates of adverse cardiac events at one year (from 28.8 percent in the period from April to June 1994 to 22.8 percent in the period from January to June 1997, $p < 0.001$), due exclusively to declining rates of target-vessel revascularization (from 24.4 percent to 17.0 percent, $p < 0.001$). Overall, the one-year rates of myocardial infarction (5.4 percent, $p = 0.28$) and death from any cause (3.9 percent, $p = 0.65$) remained stable."

Evidence from DES versus BMS clinical trials

In order to understand the implications for cost-effectiveness of the non-significant trend towards additional MIs for patients undergoing BMS stenting (compared with DES), it is helpful to break down the total figures for each trial. *Table 48* shows the outcomes after 12 months in the six trials featured in the meta-analysis plus the recent BASKET trial, disaggregated to show the fatal and non-fatal AMIs. It is clear that fatality is very low among AMI patients in this period, and that the rates are identical for DES and BMS patients. This establishes that no survival difference can be imputed in favour of DES due to fewer follow-up AMIs, as no such difference exists in the RCT evidence.

It follows that any benefit in favour of DES arises from a lower incidence of non-fatal AMIs (mainly non-Q-wave MIs). These may have two important effects: to increase costs, due to extra hospital admissions, and to incur disutility from the MI event. *Table 48* also shows the proportion of non-

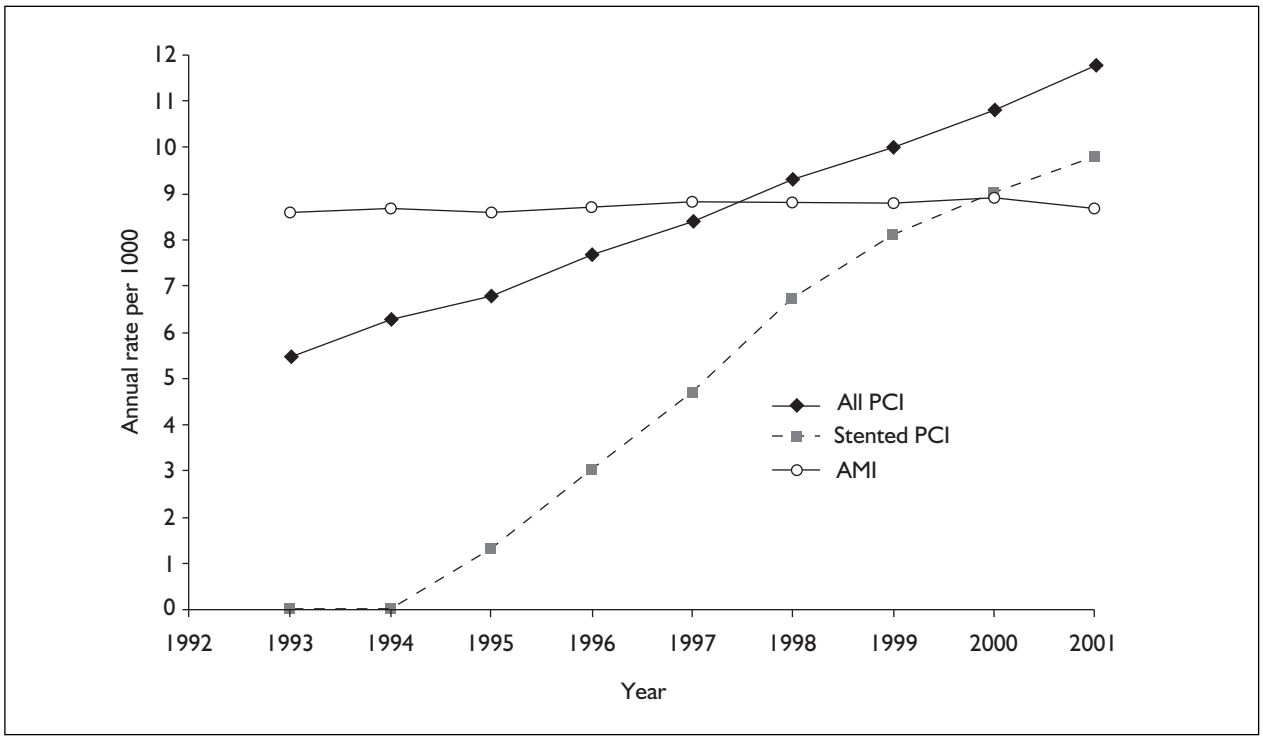


FIGURE 16 *Trends in the treatment rates for PCI and AMI in a 5% sample of US Medicare patients 1992–2001*

fatal MIs occurring while the patient is already in hospital undergoing a PCI procedure. These constitute the majority of such events, and would not incur a separate Reference Cost payment. The remainder of events, which occur in the community, will attract a hospitalisation cost if patients are admitted for treatment. It is not clear whether this will always be the case, since examination of individual patient data (IPD) from one trial suggests that many such events may have been detected retrospectively from protocol testing after 6–8 months, and not because of a specific clinical event. Nonetheless, if we assume that all community-based AMIs are hospitalised at an average cost of £1200, then the additional 1.1% of events in the BMS arm would result in a cost reduction for DES of approximately £13 per patient initially treated with DES.

Reliable information on the disutility associated with surviving an AMI is limited. The best source found is based on evidence from type 2 diabetes patients in the UKPDS trial[a19] but was nonetheless hampered by small numbers of events recorded. Based on a Tobit model, the additional loss of utility during the first year post-infarct appears to be about 0.05. Combining with the additional 1.1% non-fatal MI events in the BMS arm leads to an average utility gain per patient of 0.00055 when DES are used.

Summary

If the results of the review of clinical trial evidence for DES versus BMS were taken in isolation from all preceding and parallel studies, then there might be some justification for exploring the possibility of unaccounted survival gains through either of the routes suggested, since any unmitigated loss of life expectancy (typically estimated at about 10 years) due to procedural complications (about 2% of CABG patients and 0.5% of PCI patients), or from fatal AMIs (about 18% of all AMIs), would certainly lead to very different ICERs (although still unlikely to bring more than a small proportion of high-risk patients into the area considered acceptable on economic grounds). **However, the weight of prior evidence is sufficiently strong that a very compelling body of new information would be necessary to alter the current consensus that PCIs provide symptomatic relief but do not alter life expectancy by changing the incidence of AMI or by other means**.

This conclusion is consistent with the meta-analysis of clinical trial evidence when data are disaggregated by type of event. **However, it is clear that there is a trend towards increased numbers of non-fatal AMIs when BMS are used. The maximum likely effect of this on costs is equivalent to a cost saving of about £13 per**

TABLE 48 *Analysis of incidence of MI during 12-month follow-up after PCI*

	All MIs				Fatal MIs		Non-fatal MIs		In-hospital MIs		In-community MIs	
	DES		BMS		DES MIs	BMS MIs	DES MIs	BMS MIs	DES MIs	BMS MIs	DES MIs	BMS MIs
Trial	MIs	Cases	MIs	Cases								
TAXUS I	0	30	0	30	0	0	0	0	0	0	0	0
TAXUS II (SR)	3	129	7	132	0	0.5[a]	3	6.5	2	5	1	2
TAXUS IV	23	662	30	652	4[a]	4[a]	19	26	13	14	7	16
RAVEL	4	120	5	118	0	1	4	4	3	3	1	2
SIRIUS	16	533	18	525	0	0	16	18	12	8	4	10
ENDEAVOR II (9 months)	16	594	23	585	1	0	15	23	15	16	1	7
BASKET (6 months)	12	430	12	220	3	1	9	11	6	6	6	6
Pooled	74	2498	95	5565	8	6.5	66	88.5	54	52	20	43
Rate	**2.96%**		**4.20%**		**0.32%**	**0.29%**	**2.64%**	**3.91%**	**2.16%**	**2.30%**	**0.80%**	**1.90%**

[a] Mid-range of feasible values used where paper does not give full detail.

patient, and a utility gain of about 0.00055 per patient when DES are used.

Realistic repeat revascularisation rates

In *Table 49* we have assembled the statistics presented in the various sources relevant to estimating the repeat revascularisation rate measured 12 months post-PCI. Where possible, we have selected figures to match what would be expected in current UK practice if BMS were to be used generally. The first five entries relate to UK sources and the remaining seven to international papers.

There is no standard method of reporting outcomes, therefore it is necessary to attempt to adjust authors' chosen measures into a comparable standard, compatible with our economic model. This has involved employing additional evidence and assumptions, which in some cases are not as rigorously derived as we would have liked.

Main adjustments

The main adjustments are as follows:

1. Because of the recent rapid pace of development in interventional cardiology, the sources include widely varying use of stenting. For the purpose of this assessment, we have adjusted values (where possible) to 100% BMS use. In the case of the UK sources and The Netherlands, we have used a simple regression relationship involving BCIS historical data on stent usage and the proportion of PCIs required because of restenosis. However, this may not be appropriate in North America, so instead we calibrated a corresponding regression model from the historical Medicare sample for adjusting the US results.
2. In the case of the CTC audit data, we noted that a number of AMI patients had been inadvertently included in the non-elective group. These were removed and the revascularisation rates re-estimated – the changes from this modification are minor.
3. Where results are given in terms of TLR or TVR rates, these have been increased to estimated total revascularisations rates, based on the composition of repeat interventions observed at Liverpool and shown in *Tables 24* and *25* of the main report.
4. The BCIS report indicates that 17% of cases involved use of DES. We have increased the rate to remove the beneficial effect of DES, based on the effectiveness achieved in the BASKET trial.
5. The BCIS reported value may also be understated, due to a combination of the rapid rate of growth in PCIs in the UK and the time lag between the index procedure and any consequent repeat interventions. By applying an uplift linked to the historical growth rate, this potential effect is fully compensated (and even possibly overstated).

6. It is also necessary to make adjustments where the reporting time differs from our standard (12 months). For converting from 9 to 12 months' follow-up, we have applied a multiplier derived from the CTC revascularisation time profile. However, we found that adopting a similar approach to move from 6 to 12 months suggested unrealistically large adjusted rates. This situation arises only in respect of two international sources (USA and Switzerland), and we reasoned that differing clinical practices may not be compatible with using an adjustor based on UK experience. We have therefore adopted a more modest multiplier without specific evidence to support it.
7. In the Toulouse study, the ratio of overall revascularisation rates at 12 and 24 months was applied to estimate 12-month rates for types of stent. Also, it is not clear whether any STEMI patients are included.
8. It is clear that there are significant case-mix differences between the populations studied by each of the sources. Ideally, these should also be the subject of careful adjustment, but without a comprehensive multivariate model and data on all relevant variables from every source, this was not possible.

Discussion

The five sources from the UK show remarkable consistency after adjustment, four of them giving overall repeat revascularisation rates between 7.5 and 8.5%. The exception is the 2003–4 report from SCRR, which seems to be out of line with the published paper from the same source. A particular problem arose when attempting to adjust the 2003–4 outcomes statistics for levels of stent use, since the report only gives stent usage for the latest year, though the outcomes appear to be calculated over several years when stent use was somewhat lower. An SA shows that the 2003–4 figures match the earlier SCRR values if we assume average stent usage of 60–63% over the period for which the outcomes were estimated, and this may be a reasonable explanation for the apparent discrepancy.

The international studies yield a wider range of estimated revascularisation rates, which may reflect the differing circumstances in each country, but is also heavily dependent on some of the assumptions made in standardising the estimates, as indicated above.

On the basis of the combined evidence, it seems reasonable to assume that the overall repeat revascularisation rate in the UK 12 months post-PCI with BMS is in the range 7–9%, and the equivalent rates for elective and non-elective patients are 7–8% and 9–10%, respectively.

Risk factor models and subgroups

The choice of a suitable risk factor model is important in identifying subgroups of the population most likely to benefit from the use of DES. The factors which are included in such a model depend on the nature of the data set available (patient and procedural characteristics), clinical practice and design decisions in specifying the candidate risk factors for inclusion. The Appraisal Committee have expressed interest in understanding the range of models for the risk of the need for repeat revascularisation which have been published, with particular regard to the possible role of diabetes alongside the factors identified in the previous guidance. First, we examine these issues using the CTC audit database patient-level data. Then, we look more widely at other models found in the literature, and consider the quality and applicability to the UK situation.

LRiG/CTC, Liverpool audit data

The current NICE guidance on DES identifies two risk factors for identifying groups of patients more likely to benefit from use of DES rather than BMS: where small vessels and/or where long lesions are to be stented. These were the only two factors for which evidence was available at the time suggestive of an increased risk of repeat intervention. Only one other potential factor had been proposed by the manufacturers for which any trial evidence was available, and examination of a very limited set of individual patient data led to the conclusion that diabetes did not appear to be an independent risk factor.

In the intervening period, more peer-reviewed information has appeared, and access has been obtained to a prospective audit database of patients treated by stented PCI in Liverpool. This has facilitated derivation of new risk models using factors drawn more widely and including patient characteristics, co-morbidities and vessel/lesion characteristics.

In *Figure 17*, we display the repeat revascularisation rates (with 95% CIs), for the influence of diabetes, small vessels (<2 mm) and long lesions (>20 mm). Only in the case of small vessels in non-elective patients does there appear to be an obvious strong effect – albeit with a very wide CI. Of particular note is that diabetes has

TABLE 49 *Derivation of total revascularisation rates at 12 months post-PCI from multiple sources*

Source	Period	*n*	Reported repeat revascularisation rate	Issue	Adjustments	Corrected rate	Basis of adjustments
Pall – SCRR (Scotland)	1997–99	4,775	At 12 months: Elective (1st) 14.1% Others 18.8% Overall 17.1%	Includes unstented patients	Adjust for POBAs	Elective (1st) 7.0% Others 9.3% Overall 8.4%	BCIS: (51% → 100% BMS) × 0.493
SCRR 2003–4 (Scotland)	1997–2003	12,466	At 12 months: Elective/stable 12.9% Non-elective/unstable 16.6% Overall 14.7%	Includes unstented patients	Adjust for POBAs	Elective/stable 9.7% Non-elective/stable 13.5% Overall 11.5%	BCIS: (elective 84% → 100% BMS) × 0.752 (non-elective 89% → 100% BMS) × 0.815
CTC Audit (England)	2000–1	2,884	At 12 months: Elective 7.4% Non-elective 10.2% Overall 8.3%	Non-electives include some STEMIs	Recalculate non-elective rate excluding STEMIs	Elective 7.8% Non-elective 10.5% Overall 8.5%	
BCIS 2003 (UK)	2003	53,261	4.3% of PCIs for restenosis	Excludes non-TLR procedures. May be understated due to rapid expansion of PCI volumes. Includes 17% DES use	Adjust to total rate. Adjust for trend. Adjust for DES use	8.0%	CTC: (TLR to total) × 1.478 BASKET DES risk reduction of 41% × 1.075 BCIS: Increase 2003 vs 2002 × 1.178
Glenfield Hospital Audit (England)	2003	1,112	5.1% TLR at 12 months	Not known if STEMI included. TLR understates total revascularisations	Adjust total rate	7.5%	CTC: (TLR to total) × 1.478
Toulouse (France)	1996–9	1,340	At 12 months: TLR 9.6% At 24 months: Old stents TLR 11.4% New stents TLR 5.9% Overall TLR 10.7%	TLR understates total revascularisations	Adjust to total at 12 months	Older stents 16.9% Newer stents 7.8% Overall 14.2%	CTC: (TLR to total) × 1.478 12 month:24 month rates adjusted pro rata

continued

TABLE 49 *Derivation of total revascularisation rates at 12 months post-PCI from multiple sources (cont'd)*

Source	Period	*n*	Reported repeat revascularisation rate	Issue	Adjustments	Corrected rate	Basis of adjustment
Medicare sample (USA)	1993–2001	~180,000 revasculari-sations over 8 years	Declined from 25% in 1993 to 13% in 2001 (at 6 months)	Stents introduced during period. STEMIs included in rates but numbers not reported. Not clear if post-CABG reinterventions included in rate	Adjust for variable stent use. Adjust to 12 months	14.5%	Use 2001 rate. Regression on study data: (83% → 100% BMS) × 0.858 (6 to 12 months) × 3
Clevand (USA)	1994–2001	5,239	13.4% at 9 months	Includes 7.1% AMI and 58.8% unstable angina	Estimate elective/non-elective from multivariate model. Adjust to 12 months	Elective 13.7% Non-elective 18.7% Overall 16.6%	Stable/elective × 0.823 Unstable/non-elective × 1.124 CTC: (9 to 12 months) × 1.239
APPROACH (Canada)	1998–2000	7,334	8.2% at 12 months	Includes 47% STEMI	Adjust for STEMIs	6.1%	STEMI adjustment based on pooled analysis of 10 trials (5 papers)
Washington State (USA)	1999	3,571	16.2% at 12 months	Included 12.3% unstented patients	Adjust for POBAs	14.8%	Medicare regression (87.7% → 100% BMS) × 0.915
Agema (The Netherlands)	1999–2001	3,177	10.3% TVR minimum 9 months' follow-up	Only 74% stented. TVR understates total revascularisations	Adjust for POBAs Adjust to total rate Adjust to 12 months	10.4%	BCIS: (74% → 100% BMS) × 0.647 CTC: (TVR to total) × 1.259 CTC: (9 to 12 months) × 1.239
BASKET (Switzerland)	2003–5	264	8.2% TR at 6 months (excluding STEMIs)	Severe case mix. TVR understates total revascularisations	Adjust to total rate. Adjust to 12 months	13.4	CTC: (TVR to total) × 1.259 (6 to 12 months) × 1.3

POBA, plain old balloon angioplasty; SCRR, Scottish Coronary Revascularisation Register.

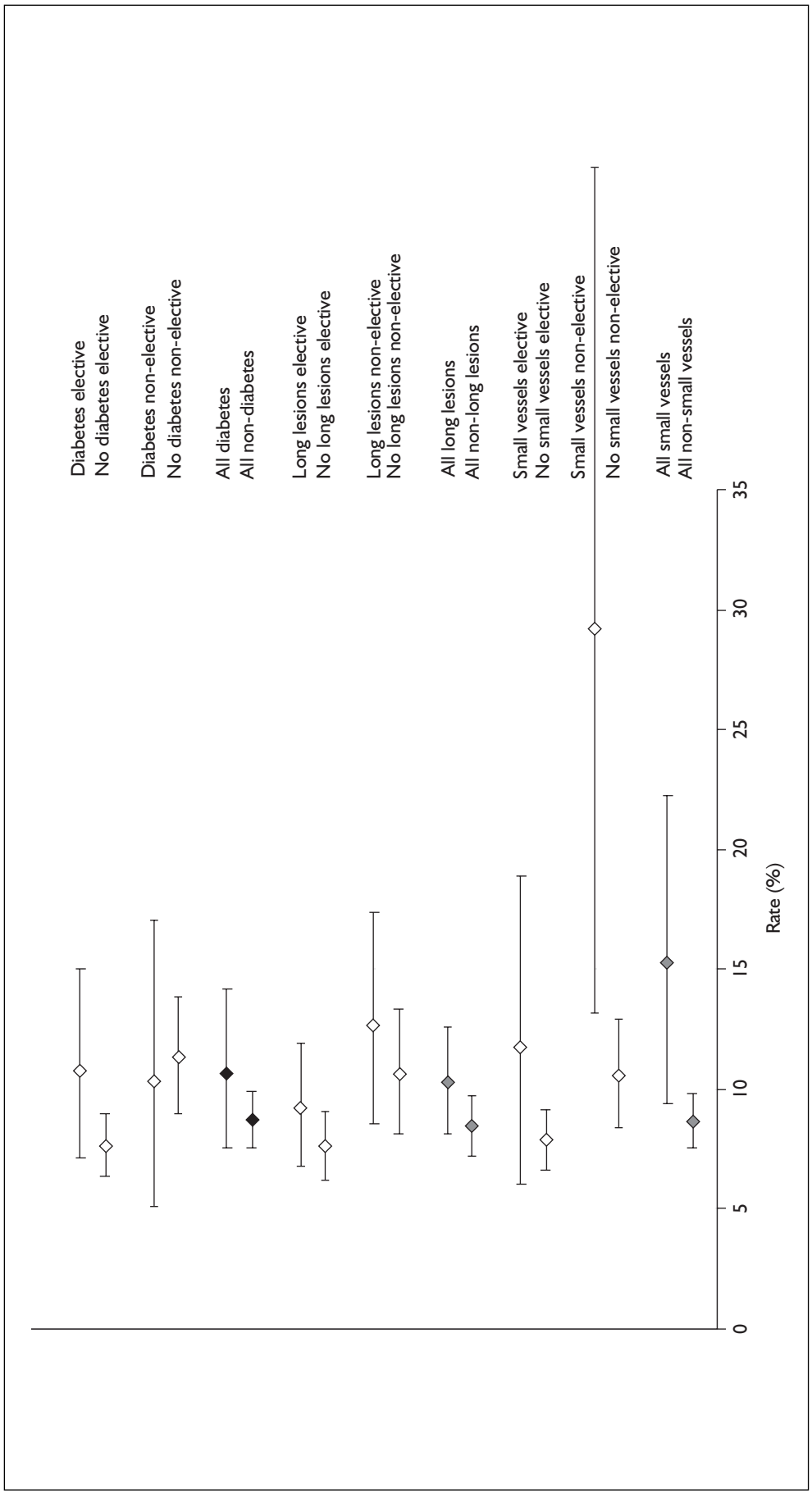


FIGURE 17 *Univariate analysis of 12-month repeat revascularisation rates in CTC audit data by conventional risk factors*

TABLE 50 *Alternative risk models derived from CTC audit data*

Patients	Risk factor	LRiG published model		Conventional factors		All factors	
		Hazard ratio	*p*	Hazard ratio	*p*	Hazard ratio	*p*
Elective patients (n = 1951)	Calculation	**1.89**	**0.002**	–	–	**1.92**	**0.001**
	Angulation >45°	**1.51**	**0.019**	–	–	**1.48**	**0.027**
	Restenotic lesion	**2.19**	**0.032**	–	–	**2.10**	**0.043**
	Triple vessel disease	**1.56**	**0.042**	–	–	1.53	0.054
	Diabetes	–	–	1.38	0.147	1.35	0.170
	Small vessel <2.0 mm	–	–	1.52	0.181	1.36	0.329
	Long lesion >20 mm	–	–	1.20	0.303	1.05	0.812
	–2log likelihood	2158.4		2179.2		2155.6	

Patients	Risk factor	LRiG published model (n = 933)		LRiG model excluding STEMI (n = 827)		Conventional factors (n = 827)		All factors (n = 827)	
		Hazard ratio	*p*	Hazard ratio	*p*	Hazard ratio	*p*	Hazard ratio	*p*
Non-elective patients	Previous CABG	**2.27**	**0.015**	**2.59**	**0.005**	–	–	**2.63**	**0.004**
	Diabetes	–	–	–	–	0.90	0.765	0.86	0.646
	Small vessel <2.0 mm	**2.91**	**0.004**	**2.78**	**0.010**	**2.62**	**0.015**	**2.81**	**0.009**
	Long lesion >20 mm	–	–	–	–	1.19	0.469	1.19	0.451
	–2log likelihood	1275.3		10.93.8		1099.4		10.93.0	

Entries in bold mark $p < 0.05$.

only a modest overall effect (about 2% greater risk overall), and this is not uniform between elective and non-elective patients.

In *Table 50*, we present results obtained by Cox proportional hazards regression analysis using several different risk model formulations.

The first elective model (LRiG) is that employed in CEA in the main report. This is compared with a model which features only the three factors in the current guidance or proposed by manufacturers. The final elective model includes all seven factors. The LRiG model was arrived at by a forward stepwise algorithm among a much wider panel of possible explanatory variables and represents the best formulation for these data. By contrast, the 'conventional factors' model not only has less explanatory power, but all three factors fail to achieve the conventional significance level required to indicate an independent predictor. The inclusion of all seven factors in the model causes only minor changes to the LRiG variable, but results in a serious worsening of the performance of the 'conventional factors'. All models were tested for interaction effects and none were found to be significant.

The published LRiG non-elective model inadvertently included data from some STEMI patients, not covered by this review. Therefore, the LRiG model has been recalibrated on the reduced data set (n = 827), and the results are presented in the lower section of *Table 50* – both factors remain significant though the balance of influence has shifted slightly. When just 'conventional factors' are used, only small vessels appears to make a significant explanatory contribution, and when all four factors are used, only the LRiG model factors are significant. In the non-elective models diabetes shows a trend to being inversely related to repeat revascularisation risk. All non-elective models were tested for interaction effects and none were found to be significant.

The success of the LRiG formulations to outperform other possibilities is not surprising, since they were developed to provide 'best fit' to these data. However, it is notable that none of the additional variables widely believed to be most influential by the clinical community (and therefore factored into trial designs) showed any indication of independent effect, or acted to modify the LRiG factors to any serious extent. This suggests that common perceptions about the genesis of restenosis may be misconceived.

Other published risk models

SCRR – Pell and Slack[a1]

This is a multivariate Cox proportional hazards model from SCRR data from elective first revascularisation procedures for the period 1997–9. It combined patients undergoing PTCA (n = 1732) with those receiving CABG (n = 1168); only about 51% of PTCA involved the use of stents.

The model for repeat revascularisation was dominated by the much lower risk associated with CABG compared with PTCA. Only **three-vessel disease** achieved statistical significance [relative risk (RR) 1.69, 95% CI 1.23 to 2.27].

The unsuccessful risk factors considered were:

- severe left ventricular impairment (RR 0.39, 95% CI 0.06 to 1.93)
- hypertension (RR 1.18, 95% CI 0.93 to 1.49)
- diabetes (RR 1.10, 95% CI 0.78 to 1.54)
- cerebrovascular disease (RR 1.25, 95% CI 0.47 to 2.62)

It is not clear to what extent restricting the model to PCI with stenting would have led to different results.

Toulouse[a11]

Risk of TLR at 24 months was subjected to Cox multivariate regression modelling, including a full range of patient, angiographic and procedural variables. When the different types of stent employed were taken into account (later types showing a 53% reduction in hazard rate compared with the earlier generation), only one variate was found to be an independent risk predictor:

- Post-procedural minimum luminal diameter <3 mm (RR 2.09, 95% CI 1.42 to 3.07).

Since this factor cannot be known when the choice of stent is made, it is of no immediate value in assessing subgroups with the highest risk of subsequent revascularisation. However, since small vessels with reference diameter <2 mm must be included within this group, it does imply that patients with small vessels stented will be at higher risk of repeat intervention. This is confirmed by the univariate analysis which showed a significant relationship of TLR with **stent diameter <3 mm** (RR 1.42, 95% CI 1.02–1.99, p = 0.04). Stent length, diabetes and other commonly cited risk factors did not show significant relationships in either analysis.

The Netherlands[a7]

A multivariate model of TVR among 2340 stented patients identified five risk factors associated with repeat revascularisation (diabetes, previous MI, total stent length, minimal stent diameter and multi-vessel disease). However, the removal criterion adopted for backwards stepwise regression was $p > 0.1$, allowing variables in the final model which would have failed the conventional standard for significance (p = 0.05). Adjusting the published results to permit direct comparison with other models suggests that only 3 variables are independently associated with risk of repeat revascularisation:

- previous MI (RR 0.68, 95% CI 0.50 to 0.92)
- total stent length (RR 1.01 per unit, CIs difficult to estimate with precision)
- larger minimal stent diameter (RR 0.50, 95% CI 0.34 to 0.73).

Cleveland, USA[a12]

Total revascularisation risk at 9 months in 5239 BMS patients was modelled by Cox multiple hazards regression. After standardisation by age, procedure date and smoking status, eight additional risk factors were identified as independently associated with repeat revascularisation:

- reference diameter <2.75 mm (RR 1.43, estimated)
- lesion length >20 mm (RR 1.50, estimated)
- ostial location (RR 1.46, 95% CI 1.24 to 1.73)
- unstable angina (RR 1.37, 95% CI 1.18 to 1.60)
- restenotic lesion (RR 1.52, 95% CI 1.16 to 1.97)
- multi-vessel disease (RR 1.20, 95% CI 1.06 to 1.39, estimated)
- saphenous vein graft (RR 1.53, 95% CI 1.10 to 1.73)
- left anterior descending (LAD) coronary location (RR 1.19, 95% CI 1.03 to 1.37).

The authors report that non-significant variables included angiotensin-converting enzyme inhibitors, diabetes, high-sensitivity CRP (Cardio CRP™), number of treated sites, renal insufficiency and statin use.

Washington State, USA[a13]

A multivariate Cox regression model of all repeat revascularisations in 2340 stented patients within 12 months identified five independent predictors:

- multivessel disease (RR 1.36, 95% CI 1.12 to 1.66)

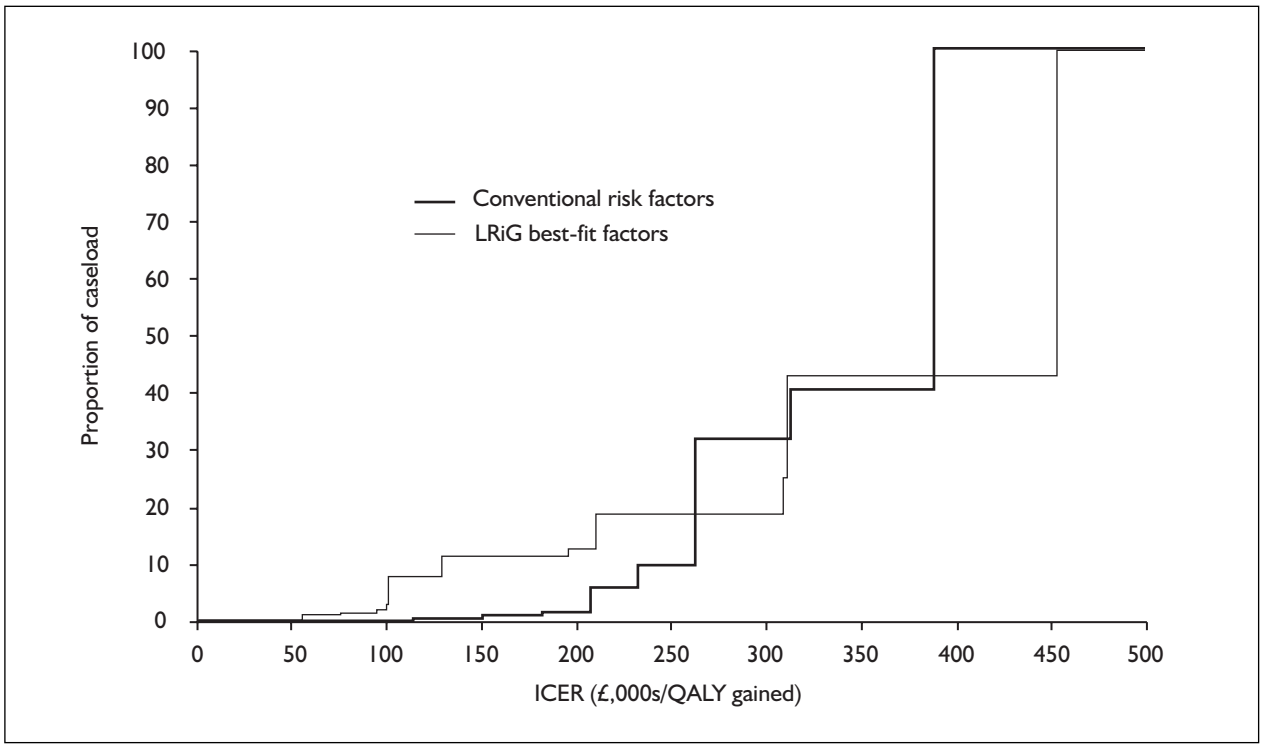


FIGURE 18 *Comparison of conventional risks and LRiG models for elective patients*

- stable angina (vs no angina) (RR 1.27, 95% CI 1.03 to 1.57)
- maximum stent length (RR 1.01 per 1 mm, 95% CI 1.002 to 1.020)
- prior MI (RR 0.77, 95% CI 0.62 to 0.96)
- creatinine >1.2 mg/dl (RR 0.74, 95% CI 0.56 to 0.98).

A sub-analysis for repeat PCIs only yielded similar results (excluding the angina variable). By contrast, three risk factors were found for CABG as a repeat intervention: diabetes, prior MI and prior CABG.

Risk factor summary

In total, seven published multivariate risk models of repeat revascularisation have been reviewed on a common basis from six sources. Although there is an inevitable variety of analytical structures leading to different collections of included variables in each model, some commonality can be identified:

- In none of the main analyses was diabetes shown to be an independent predictor.
- Very few individual factors achieved the level of significance generally considered as unequivocal evidence of a clear effect (RR of 2 or greater).
- Treating a small vessel was consistently found to be important either for all patients, or just for non-elective patients.
- Triple vessel disease and longer lesions (or total lesion length) may show less pronounced effects.
- Other factors may have more importance to particular sub-populations (e.g. elective or non-elective).
- Surviving a previous MI appears to reduce the risk of a poor long-term outcome of PCI.

Potential impact of alternative risk models on cost-effectiveness

Using the CTC audit data at the level of individual patient, it is possible to explore the implications of employing a different set of risk factors, when compared with those used in the base case. For this purpose, we compare the LRiG models (non-elective modified to exclude STEMIs) with the conventional factors models as shown in *Table 51*.

Table 52 shows how these alternative models affect the ICERs for the various risk-based subgroups. The lower explanatory power of conventional risk factors is illustrated in *Figure 18* in the case of elective patients. Greater discrimination between risk subgroups in the LRiG models is shown by the wider spread of cost-effectiveness results, with a higher proportion of caseload falling into the cost-effectiveness range. With poorer discrimination, the conventional risk models aggregate patients

TABLE 51 *Summary of risk model factors in reviewed papers*

Risk factor	SCRR	Toulouse	The Netherlands	Cleveland	Washington State	LRiG elective	LRiG non-elective	Comment
Three vessel disease	✓			✓	✓	✓		Common, but not strong
Previous MI			✓		✓			MI has lower risk
Ostial location				✓				
Unstable angina				✓			(✓)	Implied in LRiG formulation
Restenotic				✓		✓✓		
Saphenous graft				✓				
LAD				✓				
Stable angina (vs none)					✓			
Creatinine					✓			
Lesion length			✓	✓	✓			Common, but not strong
Small vessel		✓✓	✓✓	✓			✓✓	Strongest factor
Diabetes								Not included in any main analysis
Previous CABG							✓✓	
Calcification						✓✓		
Angulation						✓		

✓, $p < 0.05$ and RR < 1.6; ✓✓, RR ⩾ 1.9.

TABLE 52 *Exemplification of effects of using conventional risk factor models on cost-effectiveness by subgroups*[a]

Patients	Risk factors in subgroup			Caseload proportion (%)		Relative risk	Absolute risk by average for elective cases (%)					ICER by average for elective cases (£)				
	Long	Small	Diabetes	Subgroup	Cumulative		7%	7.79%	8%	9%	10%	7%	7.79%	8%	9%	10%
Elective	No	No	No	59.7	100.0	1.00	6.0	**6.7**	6.9	7.7	8.6	415,000	**367,500**	354,800	308,000	270,600
	No	No	Yes	8.5	40.3	1.20	7.2	**9.2**	8.2	9.3	10.3	334,800	**295,200**	284,600	245,600	214,400
	No	No	Yes	22.5	31.8	1.38	8.3	**8.0**	9.5	10.7	11.9	282,400	**248,100**	238,900	204,900	177,800
	No	Yes	No	3.8	9.4	1.52	9.1	**11.1**	10.4	11.7	13.1	250,300	**219,000**	210,700	180,000	155,300
	Yes	No	Yes	4.0	5.6	1.66	10.0	**10.2**	11.4	12.8	14.2	224,300	**195,700**	188,000	159,700	137,100
	No	Ye	Yes	0.6	1.6	1.82	11.0	**14.0**	12.5	14.1	15.7	197,600	**171,600**	164,600	138,900	118,400
	Yes	Yes	No	0.9	1.0	2.10	12.6	**12.2**	14.4	16.2	18.0	163,100	**140,500**	134,500	112,200	94,300
	Yes	Yes	Yes	0.1	0.1	2.52	15.1	**16.8**	17.3	19.5	21.6	124,900	**106,000**	101,000	82,400	67,500
	27.40	5.40	13.20													
	Risk factors in subgroup			**Caseload proportion (%)**		**Relative risk**	**Absolute risk by average for non-elective cases (%)**					**ICER by average for non-elective cases (£)**				
	Long	**Small**	**Diabetes**	**Subgroup**	**Cumulative**		**9%**	**10.00%**	**11%**	**12%**	**13%**	**9%**	**10.00%**	**11%**	**12%**	**13%**
Non-elective	No	No	Yes	8.0	100.0	0.90	7.3	**8.1**	9.0	9.8	10.6	295,100	**258,500**	228,500	203,600	182,500
	No	No	No	60.1	92.0	1.00	8.1	**9.1**	10.0	10.9	11.8	258,500	**225,600**	198,600	176,100	157,100
	Yes	No	Yes	4.5	31.9	1.07	8.7	**9.7**	10.7	11.62	12.6	236,700	**205,900**	180,700	159,800	142,000
	Yes	No	No	23.7	27.4	1.19	9.7	**10.8**	11.9	12.9	14.0	205,900	**178,200**	155,600	136,700	120,700
	No	Yes	Yes	0.2	3.7	2.36	19.2	**21.4**	23.5	25.6	27.8	68,800	**54,800**	43,400	33,800	*25,800*
	No	Yes	No	2.5	3.5	2.62	21.4	**23.7**	26.1	28.5	30.8	54,800	**42,200**	31,900	*23,300*	*16,100*
	Yes	Yes	Yes	0.2	1.0	2.81	22.9	**25.4**	27.9	30.5	33.0	46,400	**34,700**	*25,100*	*17,100*	*10,300*
	Yes	Yes	No	0.7	0.7	3.12	25.4	**28.2**	31.1	33.9	36.7	34,700	***24,100***	*15,500*	*8,300*	*2,200*
	29.1	3.7	12.9													

[a] Assumptions: average number of stents per patient, 41% relative risk reduction due to DES (BASKET), actual price premium Cypher DES, 5% wastage. Bold type indicates CTC audit point estimates of absolute risk.

closer to the average performance, losing the opportunity to distinguish very high- and low-risk sub-groups.

Sensitivity analyses

Tables 53–61 contain a set of SAs for both elective and non-elective patients. Each table allows two-way exploration of variation in the absolute risk of repeat revascularisation when BMS are used versus a range of price premium values. In addition to combined ('All patients') tables, additional tables are included for each of the risk strata employed in the main report from the LRiG risk models – these are preferred on pragmatic grounds (shortage of time) and also because they are more discriminating than models based on 'conventional' factors, as described on p. 79. The final row of each table includes the maximum (threshold) price premium value compatible with an ICER of £30,000 per QALY or below, which should be compared with the NHS PASA survey-based values (£672 or £717 for effective list price, and £537 or £659 for actual prices).

Several assumptions have been made in constructing these tables, which differ from the base case in the main report:

- Stent wastage rates have been set at 1% instead of 5%.
- The alternative procedural disutility calculations on p. 94 have been adopted.
- No assumption of additional mortality is made in respect of either procedural fatalities or as a result of AMIs (as explained on p. 104). However, each table includes a final column illustrating the magnitude of effect to be expected if procedural-related mortality were counted as a separate additional effect – this is not recommended as it should already be included in the all-cause mortality estimates.
- Modest additional utility gains and cost savings are attributed to DES as described on p. 106.
- The risk of repeat revascularisation is shown for values encompassing the range of estimates presented in *Table 49* for the UK sources, centred on the LRiG estimates (base case).
- LRiG repeat revascularisation rates have been amended to exclude all AMI indicated patients from the non-elective group, and the risk model parameters re-estimated accordingly.
- Results are not presented for specific numbers of implanted stents, but the assumed average number of stents used in each analysis is shown, so that, if required, adjusted figures can be readily calculated by the reader.

Addendum summary

The principal findings of the additional research and analysis undertaken at the request of the Appraisal Committee are as follows:

- Economic results are very insensitive to changes in stent wastage rates.
- Introducing a more sophisticated (albeit conjectural) representation of the disutility due to PCI and CABG worsens the cost-effectiveness of DES for elective patients, but improves it for non-elective patients. This is due to the different proportions of repeat revascularisations requiring CABG.
- There is a strong body of evidence from both RCTs and observational studies to indicate that survival is not affected by stenting or the type of stent used, either directly or as a consequence of subsequent AMIs or re-interventions.
- There is some evidence from RCTs that BMS may be associated with a larger risk of non-fatal AMI than are DES, resulting in a small additional cost per patient treated, and a related utility effect.
- When adjusted to a common basis, UK data sources provide remarkably consistent estimates of the risks of repeat revascularisation close to those assumed in the main report. Estimates for non-UK sources are more variable possibly reflecting different environmental influences and clinical practices.
- 'Conventional' risk factors are not efficient independent estimators for repeat revascularisation risks. In particular, diabetes does not feature in any of the published models reviewed, when assessed on a common basis. Stenting of a small vessel is the strongest predictor among the 'conventional' factors.

TABLE 53 *Sensitivity analysis: elective index PCI, all patients, average use of stents: 1.615*

		Absolute risk of repeat revascularisation at 12 months								+ Procedural mortality
Price premium (£)	**Incremental utility per patient**	**6%** **0.00215**	**7%** **0.00242**	**7.8%** **0.00263**	**8%** **0.00268**	**9%** **0.00295**	**10%** **0.00322**	**11%** **0.00348**	**12%** **0.00375**	**7.8%** **0.00397**
100	Cost per patient (£)	58	43	31	28	12	**–3**	**–18**	**–34**	31
	Cost per QALY (£)	**27,069**	**17,744**	**11,721**	**10,272**	**4,152**	**–955**	**–5,279**	**–8,988**	**7,765**
200	Cost per patient (£)	219	203	191	187	172	156	140	124	191
	Cost per QALY (£)	101,755	84,014	72,555	69,799	58,154	48,440	40,213	33,157	48,068
300	Cost per patient (£)	379	363	350	347	331	315	299	282	350
	Cost per QALY (£)	176,440	150,283	133,390	129,326	112,157	97,835	85,706	75,301	88,371
400	Cost per patient (£)	540	523	510	507	490	474	457	440	510
	Cost per QALY (£)	251,126	216,553	194,224	188,852	166,159	147,229	131,198	117,446	128,674
500	Cost per patient (£)	701	684	670	667	650	633	616	599	670
	Cost per QALY (£)	325,811	282,823	255,058	248,379	220,162	196,624	176,690	159,591	168,977
600	Cost per patient (£)	861	844	830	826	809	791	774	757	830
	Cost per QALY (£)	400,496	349,092	315,892	307,905	274,165	246,019	222,182	201,735	209,280
700	Cost per patient (£)	1,022	1,004	990	986	968	950	932	915	990
	Cost per QALY (£)	475,182	415,362	376,726	367,432	328,167	295,413	267,674	243,880	249,583
800	Cost per patient (£)	1,182	1,164	1,150	1,146	1,127	1,109	1,091	1,073	1,150
	Cost per QALY (£)	549,867	481,631	437,560	426,958	382,170	344,808	313,166	286,025	289,885
Threshold premium (£30,000) (£)		105	120	131	134	149	164	179	194	207

TABLE 54 *Sensitivity analysis: elective index PCI, no risk factors, average use of stents: 1.430*

Price premium (£)	Incremental utility per patient	Absolute risk of repeat revascularisation at 12 months								+ Procedural mortality
		4% **0.00162**	**5%** **0.00188**	**5.6%** **0.00204**	**6%** **0.00215**	**7%** **0.00242**	**8%** **0.00268**	**9%** **0.00295**	**10%** **0.00322**	**5.6%** **0.00397**
100	Cost per patient (£)	70	55	46	39	24	9	**–6**	**–22**	46
	Cost per QALY (£)	43,367	**29,093**	**22,554**	**18,360**	**9,996**	**3,294**	**–2196**	**–6,776**	**15,339**
200	Cost per patient (£)	213	197	188	181	166	150	134	118	188
	Cost per QALY (£)	131,631	104,636	92,267	84,337	68,518	55,843	45,460	36,798	62,751
300	Cost per patient (£)	356	339	330	323	307	291	275	259	330
	Cost per QALY (£)	219,895	180,178	161,981	150,313	127,039	108,392	93,115	80,372	110,163
400	Cost per patient (£)	498	482	472	465	448	432	415	399	472
	Cost per QALY (£)	308,159	255,720	231,694	216,290	185,561	160,940	140,771	123,945	157,575
500	Cost per patient (£)	641	624	614	607	590	573	556	539	614
	Cost per QALY (£)	396,423	331,262	301,408	282,266	244,083	213,489	188,426	167,519	204,987
600	Cost per patient (£)	784	766	756	749	731	714	696	679	756
	Cost per QALY (£)	484,687	406,805	371,121	348,242	302,604	266,037	236,082	211,093	252,399
700	Cost per patient (£)	926	908	898	891	873	855	837	819	898
	Cost per QALY (£)	572,951	482,347	440,835	414,219	361,126	318,586	283,737	254,666	299,811
800	Cost per patient (£)	1,069	1,051	1,040	1,032	1,014	996	978	959	1,040
	Cost per QALY (£)	661,215	557,889	510,548	480,195	419,647	371,134	331,392	298,240	347,223
Threshold premium (£30,000) (£)		86	102	112	119	136	152	169	186	176

TABLE 55 *Sensitivity analysis: elective index PCI, 1 risk factor, average use of stents: 1.746*

		Absolute risk of repeat revascularisation at 12 months								+ Procedural mortality
Price premium (£)	**Incremental utility per patient**	**7%** **0.00242**	**8%** **0.00268**	**8.4%** **0.00279**	**9%** **0.00295**	**10%** **0.00322**	**11%** **0.00348**	**12%** **0.00375**	**13%** **0.00402**	**8.4%** **0.00423**
100	Cost per patient (£)	56	41	35	25	10	**–5**	**–21**	**–36**	35
	Cost per QALY (£)	**23,200**	**15,186**	**12,403**	**8,621**	**3,144**	**–1,494**	**–5,472**	**–8,922**	**8,174**
200	Cost per patient (£)	229	214	207	198	182	166	151	135	207
	Cost per QALY (£)	94,925	79,625	74,313	67,092	56,637	47,783	40,188	33,602	48,977
300	Cost per patient (£)	403	387	380	370	354	338	322	306	380
	Cost per QALY (£)	166,649	144,065	136,223	125,564	110,130	97,060	85,848	76,125	89,779
400	Cost per patient (£)	576	560	553	543	526	510	493	477	553
	Cost per QALY (£)	238,374	208,505	198,133	184,036	163,624	146,337	131,509	118,649	130,582
500	Cost per patient (£)	749	732	726	715	698	681	664	647	726
	Cost per QALY (£)	310,099	272,945	260,043	242,507	217,117	195,614	177,169	161,173	171,385
600	Cost per patient (£)	923	905	898	888	871	853	836	818	898
	Cost per QALY (£)	381,824	337,385	321,954	300,979	270,610	244,891	222,829	203,697	212,187
700	Cost per patient (£)	1,096	1,078	1,071	1,060	1,043	1,025	1,007	989	1,071
	Cost per QALY (£)	453,549	401,824	383,864	359,451	324,103	294,168	268,490	246,221	252,990
800	Cost per patient (£)	1,270	1,251	1,244	1,233	1,215	1,196	1,178	1,160	1,244
	Cost per QALY (£)	525,274	466,264	445,774	417,923	377,596	343,445	314,150	288,745	293,792
Threshold premium (£30,000) (£)		111	124	130	138	152	166	179	193	204

TABLE 56 *Sensitivity analysis: elective index PCI, 2 risk factors, average use of stents: 2.157*

Price premium (£)	Incremental utility per patient	Absolute risk of repeat revascularisation at 12 months								+ Procedural mortality
		15% **0.00455**	**16%** **0.00482**	**16.6%** **0.00497**	**17%** **0.00508**	**18%** **0.00535**	**19%** **0.00562**	**20%** **0.00588**	**21%** **0.00615**	**16.6%** **0.00781**
100	Cost per patient (£)	**–25**	**–40**	**–49**	**–56**	**–71**	**–86**	**–102**	**–117**	–49
	Cost per QALY (£)	**–5,486**	**–8,363**	**–9,835**	**–10,937**	**–13,255**	**–15,353**	**–17,260**	**–19,003**	–6,253
200	Cost per patient (£)	187	171	162	155	139	124	108	92	162
	Cost per QALY (£)	40,991	35,454	32,619	30,498	**26,036**	**21,997**	**18,325**	**14,972**	**20,738**
300	Cost per patient (£)	398	382	373	366	350	333	317	301	373
	Cost per QALY (£)	87,468	79,270	75,074	71,933	65,327	59,348	53,911	48,946	47,728
400	Cost per patient (£)	610	593	584	576	560	543	527	510	584
	Cost per QALY (£)	133,945	123,087	117,528	113,368	104,617	96,698	89,497	82,920	74,719
500	Cost per patient (£)	821	804	794	787	770	753	736	719	794
	Cost per QALY (£)	180,422	166,903	159,983	154,802	143,908	134,048	125,082	116,894	101,709
600	Cost per patient (£)	1,032	1,015	1,005	998	980	963	945	928	1,005
	Cost per QALY (£)	226,899	210,719	202,437	196,237	183,199	171,399	160,668	150,868	128,699
700	Cost per patient (£)	1,244	1,226	1,216	1,208	1,190	1,173	1,155	1,137	1,216
	Cost per QALY (£)	273,376	254,536	244,892	237,672	222,490	208,749	196,254	184,842	155,690
800	Cost per patient (£)	1,455	1,437	1,427	1,419	1,401	1,382	1,364	1,346	1,427
	Cost per QALY (£)	319,853	298,352	287,346	279,107	261,781	246,099	231,839	218,816	182,680
Threshold premium (£30,000) (£)		178	189	196	201	212	224	235	247	308

TABLE 57 *Sensitivity analysis: elective index PCI, 3/4 risk factors, average use of stents: 2.524*

		Absolute risk of repeat revascularisation at 12 months								+ Procedural mortality
Price premium (£)	**Incremental utility per patient**	**23% 0.00668**	**24% 0.00695**	**24.6% 0.00710**	**25% 0.00722**	**26% 0.00748**	**27% 0.00775**	**28% 0.00802**	**29% 0.00828**	**24.6% 0.01132**
100	Cost per patient (£)	**–110**	–126	**–134**	**–141**	**–156**	**–172**	**–187**	**–202**	**–134**
	Cost per QALY (£)	**–16,520**	**–18,091**	**–18,933**	**–19,544**	**–20,895**	**–22,152**	**–23,326**	**–24,424**	**–11,874**
200	Cost per patient (£)	135	119	110	103	88	72	56	40	110
	Cost per QALY (£)	**20,166**	**17,127**	**15,497**	**14,314**	**11,700**	**9,267**	**6,995**	**4,870**	**9,720**
300	Cost per patient (£)	380	364	355	348	332	315	299	283	355
	Cost per QALY (£)	56,852	52,345	49,928	48,172	44,296	40,686	37,317	34,165	31,314
400	Cost per patient (£)	625	609	599	592	575	559	542	526	599
	Cost per QALY (£)	93,538	87,563	84,358	82,030	76,891	72,106	67,639	63,459	52,909
500	Cost per patient (£)	870	853	844	836	819	802	785	768	844
	Cost per QALY (£)	130,224	122,781	118,788	115,888	109,486	103,525	97,960	92,754	74,503
600	Cost per patient (£)	1,116	1,098	1,088	1,081	1,063	1,046	1,028	1,011	1,088
	Cost per QALY (£)	166,910	157,999	153,218	149,746	142,081	134,944	128,282	122,048	96,097
700	Cost per patient (£)	1,361	1,343	1,333	1,325	1,307	1,289	1,272	1,254	1,333
	Cost per QALY (£)	203,596	193,217	187,649	183,604	174,677	166,363	158,603	151,343	117,692
800	Cost per patient (£)	1,606	1,588	1,577	1,569	1,551	1,533	1,515	1,496	1,577
	Cost per QALY (£)	240,283	228,435	222,079	217,462	207,272	197,783	188,925	180,637	139,286
Threshold premium (£30,000) (£)		229	239	245	249	259	269	279	289	385

TABLE 58 *Sensitivity analysis: non-elective index PCI, all patients, average use of stents: 1.454*

Price premium (£)	Incremental utility per patient	Absolute risk of repeat revascularisation at 12 months								+ Procedural mortality
		8%	**9%**	**10.0%**	**11%**	**12%**	**13%**	**14%**	**15%**	**10.0%**
		0.00262	**0.00288**	**0.00314**	**0.00340**	**0.00365**	**0.00391**	**0.00417**	**0.00443**	**0.00522**
100	Cost per patient (£)	4	–12	**–28**	**–44**	**–61**	**–77**	**–93**	**–109**	**–28**
	Cost per QALY (£)	**1,621**	**–4,154**	**–9,028**	**–13,063**	**–16,572**	**–19,616**	**–22,283**	**–24,639**	**–5,429**
200	Cost per patient (£)	148	131	115	98	82	65	48	32	115
	Cost per QALY (£)	56,498	45,656	36,504	**28,929**	**22,342**	**16,625**	**11,618**	**7,195**	**21,950**
300	Cost per patient (£)	292	275	258	241	224	207	190	173	258
	Cost per QALY (£)	111,375	95,466	82,036	70,921	61,255	52,867	45,519	39,029	49,328
400	Cost per patient (£)	436	418	401	383	366	349	331	314	401
	Cost per QALY (£)	166,251	145,276	127,568	112,913	100,168	89,108	79,420	70,863	76,707
500	Cost per patient (£)	579	562	544	526	508	490	473	455	544
	Cost per QALY (£)	221,128	195,086	173,101	154,905	139,081	125,350	113,321	102,697	104,085
600	Cost per patient (£)	723	705	687	669	650	632	614	596	687
	Cost per QALY (£)	276,005	244,896	218,633	196,897	177,994	161,591	147,222	134,531	131,463
700	Cost per patient (£)	867	848	829	811	793	774	756	737	829
	Cost per QALY (£)	330,882	294,705	264,165	238,889	216,907	197,833	181,123	166,366	158,842
800	Cost per patient (£)	1,011	992	972	954	935	916	897	878	972
	Cost per QALY (£)	385,759	344,515	309,697	280,881	255,821	234,074	215,025	198,200	186,220
Threshold premium (£30,000) (£)		153	170	188	205	222	239	257	274	299

TABLE 59 *Sensitivity analysis: non-elective index PCI, no risk factors, average use of stents: 1.413*

		Absolute risk of repeat revascularisation at 12 months								+ Procedural mortality
Price premium (£)	**Incremental utility per patient**	**7% 0.00236**	**8% 0.00262**	**8.7% 0.00279**	**9% 0.00288**	**10% 0.00314**	**11% 0.00340**	**12% 0.00365**	**13% 0.00391**	**8.7% 0.00460**
100	Cost per patient (£)	16	0	**–11**	**–16**	**–32**	**–48**	**–65**	**–81**	**–11**
	Cost per QALY (£)	**6,925**	**57**	**–3,849**	**–5,577**	**–10,282**	**–14,270**	**–17,693**	**–20,664**	**–2,339**
200	Cost per patient (£)	156	140	129	123	107	90	73	57	129
	Cost per QALY (£)	66,244	53,369	46,048	42,809	33,990	**26,515**	**20,099**	**14,531**	**27,982**
300	Cost per patient (£)	296	279	268	262	246	229	212	195	268
	Cost per QALY (£)	125,562	106,682	95,945	91,195	78,262	67,301	57,891	49,725	58,303
400	Cost per patient (£)	436	419	407	402	384	367	350	332	407
	Cost per QALY (£)	184,881	159,994	145,842	139,581	122,535	108,086	95,682	84,919	88,625
500	Cost per patient (£)	577	559	547	541	523	506	488	470	547
	Cost per QALY (£)	244,199	213,307	195,739	187,967	166,807	148,871	133,474	120,113	118,946
600	Cost per patient (£)	717	698	686	680	662	644	626	608	686
	Cost per QALY (£)	303,518	266,619	245,636	236,353	211,079	189,656	171,266	155,308	149,267
700	Cost per patient (£)	857	838	826	820	801	782	764	745	826
	Cost per QALY (£)	362,836	319,931	295,533	284,739	255,351	230,441	209,058	190,502	179,588
800	Cost per patient (£)	997	978	965	959	940	921	902	883	965
	Cost per QALY (£)	422,155	373,244	345,430	333,125	299,624	271,226	246,850	225,696	209,910
Threshold premium (£30,000) (£)		140	158	170	175	193	211	228	246	270

TABLE 60 *Sensitivity analysis: non-elective index PCI, 1 risk factor, average use of stents: 1.880*

Price premium (£)	Incremental utility per patient	Absolute risk of repeat revascularisation at 12 months								+ Procedural mortality
		21%	**22%**	**22.8%**	**23%**	**24%**	**25%**	**26%**	**27%**	**22.8%**
		0.00598	**0.00624**	**0.00645**	**0.00650**	**0.00676**	**0.00702**	**0.00728**	**0.00753**	**0.01120**
100	Cost per patient (£)	**–163**	**–180**	**–193**	**–196**	**–212**	**–228**	**–244**	**–261**	**–193**
	Cost per QALY (£)	**–27,311**	**–28,775**	**–29,891**	**–30,122**	**–31,366**	**–32,519**	**–33,589**	**–34,586**	**–17,224**
200	Cost per patient (£)	18	2	**–12**	–15	–31	–48	–65	–81	**–12**
	Cost per QALY (£)	**3,059**	**274**	**–1,849**	**–2,289**	**–4,656**	**–6,848**	**–8,885**	**–10,781**	**–1,065**
300	Cost per patient (£)	200	183	169	166	149	132	115	98	169
	Cost per QALY (£)	33,428	**29,323**	**26,193**	**25,544**	**22,054**	**18,822**	**15,820**	**13,023**	**15,094**
400	Cost per patient (£)	382	364	350	347	330	312	295	277	350
	Cost per QALY (£)	63,798	58,372	54,235	53,377	48,765	44,492	40,524	36,828	31,253
500	Cost per patient (£)	563	546	531	528	510	492	475	457	531
	Cost per QALY (£)	94,168	87,420	82,277	81,210	75,475	70,163	65,228	60,633	47,412
600	Cost per patient (£)	745	727	712	709	691	672	654	636	712
	Cost per QALY (£)	124,538	116,469	110,319	109,043	102,185	95,833	89,933	84,438	63,571
700	Cost per patient (£)	927	908	893	890	871	853	834	816	893
	Cost per QALY (£)	154,907	145,518	138,361	136,876	128,896	121,504	114,637	108,242	79,730
800	Cost per patient (£)	1,108	1,090	1,074	1,071	1,052	1,033	1,014	995	1,074
	Cost per QALY (£)	185,277	174,567	166,403	164,709	155,606	147,174	139,342	132,047	95,889
Threshold premium (£30,000) (£)		292	305	317	319	333	347	361	375	506

TABLE 61 *Sensitivity analysis: non-elective index PCI, 2 risk factors, average use of stents: 1.869*

		Absolute risk of repeat revascularisation at 12 months								+ Procedural mortality
Price premium (£)	**Incremental utility per patient**	**39% 0.01064**	**40% 0.01090**	**40.7% 0.01107**	**41% 0.01116**	**42% 0.01142**	**43% 0.01167**	**44% 0.01193**	**45% 0.01219**	**40.7% 0.01954**
100	Cost per patient (£)	**–456**	**–472**	–483	**–488**	**–505**	**–521**	**–537**	**–553**	**–483**
	Cost per QALY (£)	**–42,867**	**–43,336**	**–43,645**	**–43,784**	**–44,211**	**–44,619**	**–45,009**	**–45,383**	**–24,742**
200	Cost per patient (£)	**–282**	**–299**	**–310**	**–316**	**–332**	**–349**	**–365**	**–382**	–310
	Cost per QALY (£)	**–26,545**	**–27,437**	**–28,023**	**–28,288**	**–29,100**	**–29,876**	**–30,619**	**–31,330**	**–15,887**
300	Cost per patient (£)	**–109**	**–126**	–137	**–143**	**–160**	**–177**	**–194**	**–211**	–137
	Cost per QALY (£)	**–10,223**	**–11,538**	**–12,402**	**–12,792**	**–13,990**	**–15,134**	**–16,229**	**–17,277**	**–7,031**
400	Cost per patient (£)	65	48	36	30	13	**–5**	**–22**	**–39**	36
	Cost per QALY (£)	**6,099**	**4,361**	**3,219**	**2,703**	**1,121**	**–392**	**–1,838**	**–3,224**	**1,825**
500	Cost per patient (£)	239	221	209	203	185	168	150	132	209
	Cost per QALY (£)	**22,421**	**20,260**	**18,840**	**18,199**	**16,231**	**14,351**	**12,552**	**10,829**	**10,680**
600	Cost per patient (£)	412	394	382	376	358	340	321	303	382
	Cost per QALY (£)	38,743	36,159	34,461	33,694	31,342	**29,093**	**26,942**	**24,883**	**19,536**
700	Cost per patient (£)	586	567	555	549	530	512	493	475	555
	Cost per QALY (£)	55,065	52,058	50,082	49,190	46,452	43,836	41,332	38,936	**28,392**
800	Cost per patient (£)	759	741	728	722	703	684	665	646	728
	Cost per QALY (£)	71,387	67,957	65,703	64,685	61,562	58,578	55,723	52,989	37,248
Threshold premium (£30,000) (£)		552	567	577	582	597	612	627	643	926

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Chapter 9

Budget impact assessment

Data sources

The latest reliable information on PCIs undertaken within the NHS comes from two sources:

- Hospital Episode Statistics (HES) for 2003–4
- BCIS Audit Returns 2003.

Budget impact and opportunity cost analysis

The HES system recorded 41,743 consultant episodes (ungrossed) coded as HRG E15 (PCI) in England. This compares well with the BCIS total of 42,234 cases in 2003 covering all but one of the English NHS interventional centres. The comparable BCIS figure for Wales is 1308.

Over a 12-year period (1991–2003), BCIS estimates suggest that there has been a reasonably consistent growth in the volume of PCIs undertaken, averaging about 15% per year. Applying this trend to the 2003 total suggests that currently (2005) about 50,000 PCI procedures are being performed in England annually. The great majority (estimated at about 93%) involve the use of stents, so that about 46,500 stented procedures are being carried out. The CTC audit data suggested that 1.45–1.6 stents were required per patient treated. However, more recently it appears that this ratio may have increased to as much as 1.8 per patient (Burrill J, NHS PASA: personal communication, July 2005). We can therefore estimate, on the basis of assumptions in the NHS Tariff Prices, and 50% use of DES, the annual volume of DES purchased by the NHS in England (assuming 5% wastage) to be between 35,000 and 42,000. Assuming a weighted average actual price premium of £606 per DES used, this equates to additional annual NHS costs of £21–25 million. If instead we accept anecdotal evidence of 70% current DES usage, the total additional cost rises to £30–36 million per annum. Finally, it is conceivable that DES could displace BMS altogether in the UK, leading to a projected total extra cost of DES purchased of £42–51 million each year.

Table 62 displays the extra costs due to substitution of BMS by DES compared with two baselines: the level of DES use identified as cost-effective in the base case analysis of Chapter 8, and the level of DES use anticipated in the previous NICE guidance (30%). Also shown in the table are the equivalent opportunity costs expressed in terms of the number of additional BMS PCIs which could be financed with the same level of additional resources. This implies that the extra costs of DES may already be equivalent to a 20% increase in annual PCI volumes when compared with the use envisaged in the previous guidance – in other words, if instead of buying more DES at high prices the extra funds were devoted to treating more patients conventionally, then an extra 10,000 patients could be treated every year.

Discussion

It is already clear that interventional cardiologists are generally operating substantially beyond the parameters of the current guidance, pursuing a more liberal practice limited mainly by the ability to secure larger budgets locally. It is not clear whether this is at the expense of limiting the expansion of cardiac services envisaged in Department of Health policy, or is drawing money away from other services.

In terms of the economics of the market, this very rapid uncontrolled expansion in demand in the UK, apparently driven mainly by the enthusiasm of professionals, ensures that the suppliers of the two products dominating the DES market have little incentive to reduce their profit margins or to compete effectively with each other. Until effective new competition enters the UK market, the NHS will continue to pay much higher prices for DES than can be justified on grounds of economic efficiency ('value for money'). There is no evidence at present that any significant reductions in DES prices are likely to materialise in the near future (1–2 years) and it should not be assumed that the budget impact for the NHS can be restricted by market mechanisms alone.

TABLE 62 *Annual budget impact and opportunity cost of DES extra costs to NHS in England (estimated for 2005)*

DES usage		Annual excess NHS cost of DES (£)				Opportunity cost: extra PCIs (BMS)			
		vs cost-effective groups		vs previous guidance		vs cost-effective groups		vs previous guidance	
Basis	**Proportion (%)**	**From**	**To**	**From**	**To**	**From**	**To**	**From**	**To**
Cost-effective groups	1.4	–	–	–	–	–	–	–	–
Previous guidance	30	+12,093,000	+14,512,000	–	–	6,394	7,673	–	–
NHS Tariff	50	+20,550,000	+24,660,000	+ 8,457,000	+10,148,000	10,865	13,038	4,471	5,366
Reported current	70	+29,006,000	+34,807,000	+16,913,000	+20,296,000	15,336	18,404	8,942	10,731
Maximum	100	+41,691,000	+50,029,000	+29,598,000	+35,518,000	22,043	26,452	15,649	18,779

Chapter 10

Conclusions and discussion

Key conclusions

The key conclusions of this review are as follows:

- DES show a reduction in composite event rate (MACE, TVF) at 12 months compared to BMS (see the section 'Outcomes/data analysis', p. 19).
- The composite event rate is dominated by revascularisation events, and there is no difference in rates of death or MI (see the section 'Outcomes/data analysis', p. 19).
- The relative reduction in repeat revascularisation is similar across all studies (see the section 'Outcomes/data analysis', p. 19).
- These benefits seem to be maximal at 6–12 months and there is no suggestion of a later catch-up – however, the disease continues to progress in many patients (see the section 'Outcomes/data analysis', p. 19).
- The trial data indicate a higher rate of reintervention than would be commonly seen in NHS practice (see the section 'Outcomes/data analysis', p. 19 and the section 'Effectiveness estimates from observational data', p. 68), implying either that reinterventions were driven by the study protocol or that the patients in the trials were selected for their high risk (or an element of both).
- There may be differences in efficacy between different DES (see the section 'Outcomes/data analysis', p. 34).
- The cost-effectiveness of DES compared with BMS depends on a number of factors: their relative effectiveness, the underlying risk of reintervention in the population in whom they are used, their price premium and the number of DES used (see the section 'Sensitivity analysis', p. 79).
- DES are not cost-effective at standard thresholds in a typical NHS population. They may be cost-effective in defined subgroups with high risks of reintervention, which can largely be predicted from clinical or angiographic features. DES could be cost-effective for wider groups of patients if the price premium were greatly reduced (see the section 'Sensitivity analysis', p. 79).
- It appears that DES are currently used in a far wider population than their cost-effectiveness justifies (see the section 'Budget impact and opportunity cost analysis', p. 129, and the section 'Discussion', p. 129).

Developments in DES

Due to the speed of development of PCI technologies and the evidence base, this review has been undertaken soon after two previous assessments.[2,18] This rapid progress has continued, with several new devices coming to market, albeit often with little supporting clinical evidence, and further evidence has accumulated about those devices for which only early evidence was previously available. These devices have achieved a remarkable degree of market penetration in the past 2 years. As this assessment shows, this has been on the basis of their clinical efficacy in selected patients, and with limited regard to their cost-effectiveness.

Changes since our previous review of this technology,[2] 2 years ago, are addressed in the sections which follow.

Efficacy and safety

The body of evidence on efficacy and safety has grown, both long-term and short-term. The superior efficacy of DES compared with BMS in reducing revascularisations in the trials is clear. This has largely confirmed the benefits previously seen, and reassured that there is no later increase in events (catch up); but nor is there any evidence that the benefits continue to increase beyond the early period. It seems, therefore, that an evaluation of the comparative effectiveness of these devices can be based on 12-month data.

One key problem remains with available evidence of efficacy. The clinical trials report their results in terms of a composite outcome, which includes serious clinical events such as MI or cardiac death, but also medical interventions, whether driven by clinical problems or study protocol. Given the rarity of serious cardiac outcomes such as death or MI, it is unrealistic to expect any benefit in these outcomes to be seen in an RCT. The use of the composite event rate which includes these events but which is dominated by medical procedures can therefore be misleading. The lack of evidence of

effect in these serious events highlights that we are looking at a technology which may have benefits in reducing symptoms and further interventions, but which does not prolong life. The economic evaluations therefore focus on a more limited definition of clinical effectiveness.

Range of devices

There are now several more stent devices available than previously, and more are coming to market in the near future. So far the clinical evidence largely relates to two products (Cypher and Taxus), although further trials of newer devices will be reported in the future. In the previous assessment, we treated the two available DES (Cypher and Taxus) as similarly effective: new evidence now suggests that the Cypher stent may be slightly more effective at reducing event rates. It will be important, therefore, to evaluate comparative evidence of efficacy and safety for any future stent, and the benefits of one cannot be extrapolated to all.

In practice, only the two DES with the most evidence (Cypher and Taxus) are currently being widely used in the NHS. For this reason, and for lack of reliable clinical evidence about other stents, we concentrated our analyses on these two devices.

We have explored the relative cost-effectiveness of Cypher compared with Taxus to a limited extent only (see the section 'Choice of DES', p. 91), since this was not initially part of our brief. It is clear that given superior efficacy, albeit at a slightly higher price, Cypher is more cost-effective than Taxus at all levels of ARR but the small additional benefit in ARR is insufficient to reduce the ICER to the conventionally accepted threshold for patient groups. Given the limited supply of Cypher stents, it is unlikely that this information can or should change clinical practice.

Translating efficacy to effectiveness

In this assessment, we have had a greater opportunity to access a patient database reflecting NHS practice. Using recent data from CTC Liverpool has allowed us to explore more fully the translation of the efficacy of the devices to their real-world effectiveness. This translation is the key to understanding the cost-effectiveness of these devices: real-world experience is not well seen in the efficacy trials because of the need to adhere to study protocol and because of the selected patent populations studied. It may also be unique to the NHS, where practice may differ from that in other systems.

The key finding from the analysis of CTC Liverpool data is the relatively low rate of reintervention in patients in whom BMS are used in NHS practice, compared with the much higher rates reported in most trials. This suggests that the protocol in the trials (or possibly local practice in a country with a high intervention rate such as the USA, where many studies were performed) drove events, or that the patients in the trials were at substantially greater risk than is seen in a typical NHS population. The selection of high risk patients for entry into efficacy studies is entirely appropriate but it is important then that efficacy from such trials be translated into effectiveness in the types of patients commonly treated in the NHS, and considered in any assessment of cost-effectiveness.

A second finding is that our effectiveness estimates suggest that DES will reduce all revascularisations by approximately 35–50% compared with BMS (see the section 'Effectiveness estimates from observational data, p. 68). This is less than might be expected based on the trial data alone, where the reduction in events at 1 year is 60–70% for largely single lesion disease and protocol-driven angiography.

Our models of risk for revascularisation indicate that the majority of patients, who fall into the lowest risk groupings, would only expect to experience a reduction in absolute incidence of revascularisation of 2–5% (see the section 'Risk factors, subgroups and estimated benefit', p. 69), consistent with the relative risk reduction in the trials but reflecting the lower baseline risk of the population for revascularisation in the real world.

Use of the CTC Liverpool database may be criticised since it relates to only a single centre; but where comparative evidence is available with other NHS centres, the use of this database is justified. Use of these NHS data has allowed much firmer conclusions to be drawn about the cost-effectiveness of DES. Economic evaluations based directly on studies with high reintervention rates and higher levels of effectiveness do not reflect the current situation in the NHS.

The underlying population risk has a marked effect on the cost-effectiveness of DES compared with BMS. The conclusions of the current economic evaluation are therefore that DES (at their current price premium) would not generally be considered a cost-effective alternative to BMS in most patients at present prices. This is consistent with the broad conclusions of our previous assessment.

We have also been able to explore patient subgroups in more detail by utilising the CTC data and have identified high-risk patients where use of DES is more cost-effective. Some of these risk factors may seem to conflict with those traditionally identified. For example, diabetes is not included as an independent risk factor, because its effects in increasing revascularisation rates is mediated through factors which are accounted for, that is, vessel/lesion architecture.

None of the elective patient subgroups appear to be cost-effective, the lowest ICER being £111,000 per QALY gained. In non-elective patients, only those with both risk factors present yield ICERs which may be favourable to DES provided that the broad definition of effectiveness is used. These represent only 0.1% of non-elective patients in the CTC audit, and only one in 3100 of all patients.

These findings raise the question of whether it would be possible, in practice, to limit DES use to particular groups of patients or to limit the number of DES used for each patient.

The latter strategy of limiting DES quantity within patients appears to have been discounted on the basis of probable reduced effectiveness and continuing uncertainties around the precision of targeted DES use. Limiting DES prospectively to only certain patient groups may be dominated by the key consideration throughout the economic analysis – DES price premium. Intervention with DES in certain patients at high risk of restenosis could be considered cost-effective, but only if a single DES was to be used in the intervention. Our analysis suggests that the proportion of high-risk patients with a requirement for only a single DES would only be 0.1% of elective and under 5% of non-elective patients.

In general, the balance of evidence from independent reviews of the cost-effectiveness of DES, as cited in Chapter 6, indicates that DES are more cost-effective in higher risk patients. In particular, the recent BASKET[82] economic assessment, which was based on a prospective pragmatic trial, supports this finding.

The conclusions here are that the use of DES would be best targeted at the subgroups of patients with the highest risks of requiring reintervention, and could be considered cost-effective in only a small percentage of such patents. Again, this is similar to the conclusion of our previous assessment.

Pragmatic studies

Efficacy trials are now being supplemented with more pragmatic effectiveness studies, notably the BASKET[82] trial, which not only compared two DES but also compared a new generation BMS. This study confirmed the enhanced effectiveness of DES but also that they were cost-ineffective except in high-risk patients.

This study reported cost per MACE prevented over 6 months, rather than cost per QALY as we have calculated. We acknowledge the weakness of QoL data here, and the uncertainty about the duration of each health state. However, the cost per QALY remains the expected standard for NICE assessment.

Quality of life databases and the PASA purchasing survey

We have been able to use other up-to-date UK NHS sources for key data such as QoL and price. We used the HODaR dataset for QoL data: although the QoL reported may seem low for both PCI and CABG by comparison with other studies, the key point is the increment in QoL between the two interventions, which is virtually identical with that in other studies (e.g. ARTS), providing reassurance for the robustness of our analysis.

The survey conducted by the NHS PASA gives new insights into the actual costs of each DES to the NHS and reflects recent clinical behaviour, which we have been able to incorporate into the economic evaluation and into the budget impact analysis. Based on data provided by manufacturers, the price premium for DES was in the approximate range £370–550. Realistic price premiums determined from survey data (PASA) indicate that Cypher and Taxus DES cost an additional £659 and £537 per stent, respectively, over and above BMS costs.

These NHS data (effectiveness, QoL and costs) have been used to inform our economic evaluation. We therefore believe the results are highly relevant to the NHS.

Robustness of results

We also believe that our results are robust. This is confirmed by the extreme values SA: we did not use probabilistic PSA because it was unclear which variables were of greatest interest, and the EVA clearly demonstrates the unlikelihood of achieving usual thresholds of cost-effectiveness. As expected from previous studies, the additional cost of DES

index stents (price premium and average number of stents implanted) and the ARR in repeat interventions are the most important items in influencing ICERs. The £30,000 threshold is only attained if an ARR in repeat revascularisations of at least 18% (elective) or 16% (non-elective) is achievable. Clearly, for the great majority of patients this is unrealistic.

This suggests strongly that for any values of the price premium greater than about £250 the use of DES should be restricted on economic grounds to a small group of high-risk patients in whom limited stent usage can be reasonably predicted. If in future the price premium falls to under £200, then more general use of DES for the majority of patients would be warranted.

NICE previously recommended the use of DES in preference to BMS in defined situations which should have allowed approximately 30% use. This is more than would have been suggested as cost-effective by our previous report, but may reflect some of the clinical uncertainties at that time. Many of these uncertainties have been resolved in this report.

In practice, DES have been much more widely used in the NHS, and there is no check on the discretion of the clinician in this regard. Any change to this position will be unpalatable to many clinicians. Nevertheless, widespread use of DES consumes NHS resources which could be deployed more efficiently (and therefore to greater patient benefit) elsewhere.

Research recommendations

Some of our recommendations in the previous report have been delivered: longer term results from the trials, head-to-head comparisons of the most widely used DES and more real-world NHS data from registries or audits are now available to inform the translation from efficacy to effectiveness.

This is a rapidly expanding area of research and the analysis of cost-effectiveness and other recent meta-analyses indicate that the first inference regarding the additional benefit of DES may have been somewhat over-optimistic.[146] Areas where more research is still needed include:

- More direct comparative trials of DES with the newer non-DES (as undertaken by Pache and colleagues[53] and the BASKET study[82]).
- Direct comparisons of established DES versus the newer DES, since large-scale studies have suggested that not all DES are clinically equal.
- Further evaluation of newer BMS in combination with drug administration.

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Advisory Panel members (who provided feedback to the team during the review process)

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Three referees (including clinical, methodological and economics expertise) considered and commented on an earlier draft of this report. The policy of NCCHTA is not to name referees; however, individuals contributing peer review of HTA Programme products are listed within the NCCHTA website (www.ncchta.org).

Contribution of authors

Adrian Bagust (Professor of Health Economics) was responsible for the economic analysis and development of economic model. Angela Boland (Research Fellow, Health Economics) had input into development of protocol, supported the economics team and was involved in writing and editing drafts of the technology assessment report. Rumona Dickson (Director of Liverpool Reviews and Implementation Group) was responsible for project management and had input into all aspects of the clinical component of the review. Yenal Dündar (Research Fellow, Clinical Effectiveness) developed the search strategies and had input into aspects of the clinical component of the review. Alan Haycox (Senior Research Fellow, Health Economics) supported the economics team. Ruaraidh Hill (Research Fellow, Clinical Effectiveness) was responsible for the review's coordination, data management and meta-analysis and had input into all aspects of clinical review. Claire McLeod (Research Fellow, Health Economics) did the economic analysis and carried out evaluation of submitted economic models and the summary of economic data. Ruben Mujica Mota (Research Fellow, Health Economics) evaluated submitted economic models. Tom Walley (Professor of Pharmacology and Therapeutics) carried out data assessment and interpretation of clinical and economic data. All authors took part in the editing and production.

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Appendix 1

Search strategy – clinical and economic evidence

Search strategies and search results

Database	Years	Search strategy	References identified
MEDLINE	2002–5	See below	536
EMBASE	2002–5	(elut* or coat*) and (coronary or isch*emic) and stent*)	542
Science Citation Index/Web of Science	2002–5	(elut* or coat*) and (coronary or isch*emic) and stent*)	826
Science Citation Index/ISI Proceedings	2002–5	(elut* or coat*) and (coronary or i sch*emic) and stent*)	242
Cochrane Controlled Trials Register	2002–5	(STENTS or stent*) and CORONARY DISEASE	414
Cochrane Database of Systematic Reviews	2002–5	(STENTS or stent*) and CORONARY DISEASE	28
HTA	2002–5	(STENTS or stent*) and CORONARY DISEASE	44
DARE	2002–5	(STENTS or stent*) and CORONARY DISEASE	10
PubMed (MEDLINE)	1 March–3 August 2005	drug$ and stent$	91
Total references identified			2642 (+91)
Duplicates			1201
Total			1441 (+91)

Record selection

Searches and selection	References identified
Searches of electronic databases	
Selected for categorisation:	395
(of which selected as background interest only)	112
Selected potentially for inclusion in review	271
Not accessible within time frame of review or determined to be duplicate during selection process	6 + 2
Categorised for inclusion in:	
Clinical review	59
Economics review	6
Handsearching (including submissions)	
Clinical review	46
Economics review	4

Appendix 2

Quality assessment – clinical and economic evidence

Quality assessment – clinical studies

RCTs of clinical effectiveness were assessed using the following criteria, based on CRD Report No. 4:[22]

- 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, while 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 will be graded in terms of: ✓, yes (item adequately addressed); ×, no (item not adequately addressed); ✓/×, partially (item partially addressed); ?, unclear or not enough information; NA, not applicable; NS, not stated.

Quality assessment – economic studies

Studies of cost effectiveness were assessed using the following criteria, which are an updated version of the checklist developed by Drummond and Jefferson.[131]

Study design

- The research question is stated.
- The economic importance of the research question is stated.
- The viewpoint(s) of the analysis are clearly stated and justified.
- The rationale for choosing the alternative programmes or interventions compared is stated.
- The alternatives being compared are clearly described.
- The form of economic evaluation used is stated.
- The choice of form of economic evaluation is justified in relation to the questions addressed.

Data collection

- The source(s) of effectiveness estimates used are stated.
- Details of the design and results of effectiveness study are given (if based on a single study).
- Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies).
- The primary outcome measure(s) for the economic evaluation are clearly stated.
- Methods to value health states and other benefits are stated.
- Details of the subjects from whom valuations were obtained are given.
- Productivity changes (if included) are reported separately.
- The relevance of productivity changes to the study question is discussed.

- Quantities of resources are reported separately from their unit costs.
- Methods for the estimation of quantities and unit costs are described.
- Currency and price data are recorded.
- Details of currency of price adjustments for inflation or currency conversion are given.
- Details of any model used are given.
- The choice of model used and the key parameters on which it is based are justified.

Analysis and interpretation of results

- The time horizon of costs and benefits is stated.
- The discount rate(s) is stated.
- The choice of rate(s) is justified.
- An explanation is given if costs or benefits are not discounted.
- Details of statistical tests and CIs are given for stochastic data.
- The approach to sensitivity analysis is given.
- The choice of variables for SA is justified.
- The ranges over which the variables are varied are stated.
- Relevant alternatives are compared.
- Incremental analysis is reported.
- Major outcomes are presented in both a disaggregated and aggregated form.
- The answer to the study question is given.
- Conclusions follow from the data reported.
- Conclusions are accompanied by the appropriate caveats.

All items will be graded as either: ✓, yes (item adequately addressed); ✗, no (item not adequately addressed); ?, unclear or not enough information; NA, not appropriate; or NS, not stated.

Appendix 3

Clinical review tables – DES versus BMS

Data are given in *Tables 63–65*, and meta-analyses are shown in *Figures 19–24*.

TABLE 63 *Criteria for allocation of patients to varicose vein categories*

Study	Intervention	Randomised/ lost or followed up	Centres/ location	Inclusion criteria	Exclusions	Co-therapy	Study support
BASKET	Cypher, Cordis or Taxus, Boston Vision, Guidant	545 (264 + 281) 281	1 Switzerland	All patients presenting for PCI (with stents) during study period	Vessel diameter of ⩾4 mm; restenotic lesion, no-consent ("mostly because of patients" or "referring physicians' preference for DES" or patients unable to give consent; involvement in other stent protocols (to avoid angiography-driven RV)	Periprocedurally: clopidogrel (300 mg); After: clopidogrel (75 mg/day) for 6 mo; aspirin (100 mg/day); statin therapy; other drugs (including GP IIb/IIIa) as clinically indicated	No industry sponsorship
C-SIRIUS	Cypher, Cordis Bx-VELOCITY, Cordis	50 50	8 Canada	Single *de novo* lesion; diameter 2.5–3.0 mm; length 15–32 mm; stenosis 50–99%; documented AP (CCS 1–4), UA (Braunwald B, C, I or II) or SI; adult	As E-SIRIUS	Before: aspirin (81–325 mg); clopidogrel (300 mg loading or immediately after the procedure). During: i.v. of heparin (boluses, ACT inxs 250s); GP IIb/IIIa clinician discretion. After: heparin discontinued; aspirin (81–325 mg/day indefinitely); clopidogrel (75 mg/day, 2 mo)	Cordis
DIABETES	SES (Cypher, Coris) BMS	70 (Sabate, 2003[68]), 80 (Sabate, 2004[55]) 76/80 70 (Sabate, 2003[68]), 80 (Sabate, 2004[55]) 72/80	4 Spain	Diabetes (insulin or non-insulin dependent); significant *de novo* stenosis in 1, 2 or 3 vessels; signs or symptoms of ischaemia	Diabetic without pharmacological treatment; bifurcations; SVG; LIMA; unprotected LMA; ISR; previous DES; previous brachytherapy; renal/hepatic insufficiency; ACS (<72 h, elevated CPK × 2); malignancy	Abciximab recommended; Clopidgrel (1 yr) routinely prescribed; aspirin (indefinitely) routinely prescribed; GP IIa/IIIb (59% of Px)	Cordis (grant)
ENDEAVOR II	ENDEAVOR, Medtronic Driver, Medtronic	598 582/598 599 585/599	72 Europe, Asia, Israel, New Zealand, Australia	Single *de novo* lesion, native vessel; stent diameter: 2.25–3.5 mm; stent length 18–30 mm; lesion length 14–47 mm	**[Confidential information removed]**	**[Confidential information removed]**	Medtronic

continued

TABLE 63 *Criteria for allocation of patients to varicose vein categories (cont'd)*

Study	Intervention	Randomised/ lost or followed up	Centres/ location	Inclusion criteria	Exclusions	Co-therapy	Study support
E-SIRIUS	Cypher, Cordis Bs Velocity, Cordis	175 0 at 9 months 177 0 at 9 months	35 Europe	Single *de novo* lesion; 2.5–3.0 mm diameter, 15–32 mm long; DS > 50%; CCS angina or UA (Braunwald B & C, I–II) or documented silent ischaemia	MI <24 h; unprotected left main disease; ostial lesion; total occlusion; thrombus; calcified lesion; LVF <25%; impaired renal function; pretreatment with devices other than balloon angioplasty, prior or planned intervention within 30 days	Pre-procedure: aspirin, clopidogrel or ticlopidine During procedure: heparin, GP IIb/IIIa inhibitors (at operator's discretion) Post-procedure: aspirin (indefinitely), clopidogrel or ticlopidine (2 mo)	Cordis
Li	Cypher, Cordis Non-DES (not stated)	72 72/72 (Clin, 12 mo); 63/72 (angio) 80 80/80 (Clin, 12 mo); 65/80 (angio)	China	Small vessel; diameter <3.0 mm (by QAA)		"Standard antiplatelet and anticoagulation agents"	NS
Pache	Cypher, Cordis BeStent, Medtronic	250 205/250 (angio) 250 204/250 (angio)	2 Germany	Symptomatic CAD; significant angiographic stenosis; native vessels	AMI; LMCA; ISR; contraindications to antiplatelet drugs, no consent	Before: clopidogrel (600 mg, loaded); During: i.v. aspirin, i.v. heparin; After: clopidogrel (2 × 75 mg/day, 3 days); clopidogrel (75 mg, ⩾6 mo); other antithrombotics at clinical discretion	NS
RAVEL	Cypher, Cordis Bx Velocity, Cordis	120 114/120, 94.2% (3 yr) 118 113/118, 94.1% (3 yr)	19 International	SA or UA or silent ischaemia; single *de novo* lesion; vessels 2.5–3.5 mm	Evolving MI; unprotected LMCA; ostial target lesion; calcified lesion (which could not be predilated); anginographically visible thrombus in target lesion	Aspirin; heparin; clopidogrel or ticlopidine	Cordis

continued

TABLE 63 *Criteria for allocation of patients to varicose vein categories (cont'd)*

Study	Intervention	Randomised/ lost or followed up	Centres/ location	Inclusion criteria	Exclusions	Co-therapy	Study support
SES-SMART	Cypher, Cordis Bx sonic, Cordis	129 123/129 (angio) 128 113/128 (angio)	20 Italy	Single; *de novo*; 50–99% stenosis; native vessel; suitable for a single stent (max. 33 mm length); vessel diameter <2.75 mm; 1VD or MVD acceptable, but only non-rand lesion must be on separate vessel; adult; documented ACS; SA; silent ischaemia	Recent AMI (15 days); severe calcifications; thrombus in lesion; LVEF <30%; allergies to (aspirin, clopidogrel, ticlopine, heparin, steel, contrast agents, sirolimus)	Before: aspirin (1/day); clopidogrel (loading 300 mg at least 2 h before) – if pre-treated.[a] During: heparin (70 U/kg, additional ACT more than 250 s); GP IIb/IIIa inhibitors clinician discretion; After: aspirin (100 mg/day) indefinitely; clopidogrel (75 mg/day, at least 2 mo)	Participating centres/ complementary funding – Cordis
SIRIUS	Cypher, Cordis Bx Velocity, Cordis	533 526/533 (1 yr); 512/533 (2 yr); 499/533 (3 yr) 525 518/525 (1 yr); 508/525 (2 yr); 486/525 (3 yr)	53 USA	Single *de novo* native coronary lesion; ⩾2.5 mm and ⩽3.5 mm diameter, ⩾15 mm long; DS >50% and 100%; CCS angina (I–IV) or UA (Braunwald B & C, I–II) or silent ischaemia	MI ⩽24 h; left main disease; ostial lesion; total occlusion; thrombus; calcified lesion; LVF ⩽25%; impaired renal function; pretreatment with devices other than balloon angioplasty	Pre-procedure: aspirin, clopidogrel, ticlopidine During procedure: heparin, GP IIa/IIb clinical discretion (59.8%) Post-procedure: aspirin, clopidogrel, ticlopidine	Sponsor – Cordis
SPIRIT FIRST	XIENCE V (MULTI-LINK VISION-E® RX), Guidant MULTI-LINK VISION RX, Guidant	28 (Per-P: 27) 1/28 (1 bailout) 32 (Per-P: 29) 3/32 (2 bailout, 1 [P] deviation)	9 Europe (Denmark/ Germany)	Single *de novo* native lesion; ⩾50%, ⩽100% stenosis; TIMI ⩾1; lesion length ⩽12 mm; TIMI flow of ⩾1, diameter TVD ⩾2.8 mm to ⩽3.2 mm; SA	LVEF ⩽30%; organ transplant candidate/recipient; unstable arrhythmias; heavily calcified lesion		Guidant

continued

TABLE 63 *Criteria for allocation of patients to varicose vein categories (cont'd)*

Study	Intervention	Randomised/ lost or followed up	Centres/ location	Inclusion criteria	Exclusions	Co-therapy	Study support
STRATEGY	Cypher, Cordis and tirofiban Sonic, Cordis (or other approved non-DES) and abciximab	87 None 88 None	1 referral centre Italy	Scheduled for primary PCI; ST-segment elevation AMI – (i) chest pain >30 min, ST-segment elevation, admission within 12 h of symptom onset or 12–24 h if continuing ischaemia	Previous fibrinolytic or GP IIb/IIIa Rx, history of bleeding diathesis or allergy to the study drugs, major surgery ⩾15 days, bleeding, previous stroke ⩽6 mo; unable to obtain informed consent	*SES group*: tirofiban bolus 25 μg/kg over 3 min, i.v. 0.15 μg/kg/min for 18–24 h *Non-DES group*: abciximab: bolus 0.25 μg/kg over 3 min, i.v. 0.125 μg/kg/min for 12 h *All*: aspirin (160–325 mg loading, 125 mg indefinitely), clopidogrel (300 mg loading, 75 mg/day for ⩾3 mo); heparin (before) 50 μ/kg and additional → ICT ⩽200 s	Fondazione Cassa dei Risparmi di Ferrara (no role in design, analysis or reporting)
TAXUS I	TAXUS NIRx, Boston NIRx, Boston	31 1/31 30 None	3 Germany	Single *de novo* focal lesions; stent diameter 3.0 and 3.5 mm	History of MI; LVEF 30%; stroke within 6 months; serum creatine >1.7 mg/100 ml; contraindication to aspirin, clopidogrel, ticlopine	Pre-procedure: aspirin, heparin and clopidogrel Post-procedure: aspirin for 12 mo, clopidogrel for 6 mo	Boston Sci. Corp.
TAXUS II	TAXUS NIRx (SR), Boston NIR Conformer (cohorts combined), Boston	266 ~1% at 1 yr (cohort 1) 270 ~1–2% at 1 yr (cohorts 1 and 2)	38 Europe	Single *de novo* lesion, native coronary artery; stenosis between 50–99%; lesion length 12 mm; vessel diameter 3.0–3.5 mm	Recent MI (<72 h), stroke within 6 mo, renal dysfunction, LVF >30%, (VUS study #48, excludes Px receiving any non-study stent	Clopidogrel (300 mg loading); clopidogrel (75 mg/day) (or ticlopidine 2 × 250/day) for 6 mo and aspirin (75 mg/day) indefinitely	Boston Sci. Corp.

continued

TABLE 63 *Criteria for allocation of patients to varicose vein categories (cont'd)*

Study	Intervention	Randomised/ lost or followed up	Centres/ location	Inclusion criteria	Exclusions	Co-therapy	Study support
TAXUS IV	TAXUS Express2 (SR), Boston EXPRESS, Boston	662 652	73 USA	Single *de novo* lesion; length 10–28 mm; diameter 2.5–3.75 mm; (Boston submission indicates multiple lesions and multiple vessels included in procedure complexity)	Previous/planned vessel brachytherapy or DES; planned use of atherectomy before stenting; AMI <72 h LEF <25%; haemorrhagic diatheses or contraindications or allergy to study medications; serum creatinine <2.0 mg/dl; LM; ostial lesion; moderate or severe calcification, tortuousity, angulation; bifurcation; occluded lesion; lesion thrombus	Before: clopidogrel (300 mg), aspirin (325 mg) During: heparin, GP IIb/IIIa inhibitors, clinician discretion After: clopidogrel (75 mg/day) for 6 mo and aspirin (325 mg/day) indefinitely	Boston Sci. Corp.
TAXUS V (*de novo*)	TAXUS Express2 (SR), Boston Express2, Boston	577 (586 rand) 37/577 (9 mo); 79/577 (angio) 579 (586 rand) 31/579 (9 mo); 87/579 (angio)	66 USA	Single *de novo* native lesions; ⩾10 mm–⩽46 mm Discrete lesions ⩾5 mm–⩽26 mm; treatable with 2 stents; RVD: ⩾2.25 mm to ⩽4.0 mm; stenosis ⩾50%	Prior or planned PCI or brachytherapy in target; bifurcation lesions; target vessel pre-treated with unapproved device; MI ⩽72 h, CK-MB >2 × ULN on day of procedure	After: clopidogrel (6 mo); aspirin (9 mo)	Boston Sci. Corp.

Angio: angiographic; CAD, coronary artery disease; CK-MB, creatine kinase; h, hours; ISR, in-stent restenosis; LEF, left ejection fraction; LM, left main coronary artery; mo, months; [P], protocol; rand, randomised; SA, stable angina; SR, slow release; UA: unstable angina.

[a] Patients pretreated with ticlopidine (250 mg twice a day) or clopidogrel (75 mg once daily) for at least 72 h did not receive a clopidogrel loading dose.

TABLE 64 *Participant characteristics: DES versus BMS (two parts)*

Study Part I	Intervention	Number of participants	Gender (% male)	Age (years)	Diabetes (%)	Previous AMI (%)
BASKET	Cypher, Cordis	264	79	64 (52–76 Range)	16	28
	Taxus, Boston	281	78	64 (53–75 Range)	19	28
	Vision, Guidant	281	79	64 (53–74 Range)	22	27
C-SIRIUS	Cypher, Cordis	50	70	60.3	24	48
	Bx-VELOCITY, Cordis	50	68	60.7	24	42
		All				
DIABETES	SES	80[55]				
	BMS	80[55]				
		All	62.5	66.5 [9]	100 (53/160 ID)	
ENDEAVOR II	ENDEAVOR, Medtronic	598	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**
	Driver, Medtronic	599	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**
		All	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**
E-SIRIUS	Cypher, Cordis	175	70	62.0 [11.4]	19	41
	Bx Velocity, Cordis	177	71	62.6 [10.3]	27	43
		All	71	62.3 [10.9]	23	42
Li	Cypher, Cordis	72				
	Non-DES (not stated)	80				
		All				
Pache	Cypher, Cordis	250	78	67.4 (59.0, 75.4) median	29	32
	BeStent, Medtronic	250	78	66.7 (59.9, 74.7) median	33	30
		All				
RAVEL	Cypher, Cordis	120	70	61.8 [10.7]	16	38
	Bx Velocity, Cordis	118	81	59.7 [10.1]	21	34
		All	76	60.7 [10.4]	19	36
SES-SMART	Cypher, Cordis	129	76.7	63.2 [11.5]	19.4	
	Bx sonic, Cordis	128	66.4	63.7 [10.9]	29.7	
		All	71.6	63.6 [11.27]	24.9	

continued

TABLE 64 *Participant characteristics: DES versus BMS (two parts) (cont'd)*

Study Part I	Intervention	Number of participants	Gender (% male)	Age (years)	Diabetes (%)	Previous AMI (%)
SIRIUS	Cypher, Cordis	533	72.6	62.1	24.6	28.2
	Bx Velocity, Cordis	525	69.6	62.4	28.2	32.9
		All				
SPIRIT FIRST	XIENCE V (MULTI-LINK VISION-E® RX), Guidant	28 (Per-P: 27)	70.4	64.2	11.1	24.0
	MULTI-LINK VISION RX, Guidant	32 (Per-P: 29)	75.9	61.4	10.3	13.8
		All				
STRATEGY	Cypher, Cordis and tirofiban	87	77	62 [54–72]	17	13
	Sonic, Cordis (or other BMS) and abciximab	88	69	63 [55–72]	11	9
TAXUS I	TAXUS NIRx, Boston	31	94	66	23	26
	NIRx, Boston	30	83	63.8	13	30
		All				
TAXUS II	TAXUS NIRx (SR), Boston	266	70.2	35.1	10.7	61.5
	NIR Conformer (cohorts combined), Boston	270	77.9	59.7	15.1	42
		All				
TAXUS IV	TAXUS Express2 (SR), Boston	662	71.8	62.8 [11.2]	31.1	30.5
	EXPRESS, Boston	652	72.4	62.1 [10.9]	33.3	29.9
		All				
TAXUS V (*de novo*)	TAXUS Express2 (SR), Boston	577 (586 rand)	70.2	62.9 [11.2]	31.7	31.4
	Express2, Boston	579 (586 rand)	68.7	62.8 [10.8]	29.9	26.3
		All				

continued

TABLE 64 *Participant characteristics: DES versus BMS (two parts) (cont'd)*

Study PART II	Intervention	Number of participants	Vessel diameter (mm)	Lesion length (mm)	Vessels diseased: (number: %)	Complex lesions
BASKET	Cypher, Cordis	264			3: 65%	LAD 53%; LCX 30%; RCA 35%; LM 0%
	Taxus, Boston	281			3: 71%	LAD 52%; LCX 32%; RCA 38%; LM 1%
	Vision, Guidant	281			3: 69%	LAD 51%; LCX 32%; RCA 33%; LM 2%
C-SIRIUS	Cypher, Cordis	50	2.62	14.5		LAD 32%; LCX 22%; RCA 46%
	Bx-VELOCITY, Cordis	50	2.65	12.6		LAD 40%; LCX 24%; RCA 36%
		All				
DIABETES	SES	80				
	BMS	80				
		All	2.9 [0.9] stent	19.2 [7] stent	37/160 multivessel stenting	
ENDEAVOR II	ENDEAVOR, Medtronic	598			**[Confidential information removed]**	**[Confidential information removed]**
	Driver, Medtronic	599			**[Confidential information removed]**	**[Confidential information removed]**
E-SIRIUS	Cypher, Cordis	175	2.60 [0.37] RVD	14.9 [5.4]	1: 64%; 2: 20%; 3: 16%	LAD 57%; RCA 22%; LCx 21%
	Bs Velocity, Cordis	177	2.60 [0.37] RVD	15.1 [6.5]	1: 65%; 2: 24%; 3: 11%	LAD 56%; RCA 19%; LCx 24%
		All	2.55 [0.37] RVD	15.0 [6.0]	1: 64%; 2: 22%; 3: 14%	LAD 56%; RCA 21%; LCx 23%
Li	Cypher, Cordis	72	2.64 [0.08] stent	19.92 [3.18] stent		
	Non-DES (not stated)	80	2.70 [0.12] stent	21.49 [2.88] stent		
		All				
Pache	Cypher, Cordis	250	2.7 (2.4, 3.1)	13.0 (8.9, 18.0)	82% (MVD)	LAD 43%; RCA 28%; LCx 29%
	BeStent, Medtronic	250	2.7 (2.4, 3.0)	12.2 (8.4, 17.0)	80% (MVD)	LAD 43%; RCA 27%; LCx 30%
		All				
RAVEL	Cypher, Cordis	120	2.60 [0.54]	9.56 [3.33]		LAD 49%; RCA 27%; LCx 24%
	Bx Velocity, Cordis	118	2.64 [0.52]	9.61 [3.18]		LAD 51%; RCA 27%; LCx 22%
		All	2.62 [0.53]; 2.5–3.5 mm (incl. criteria)	9.58 [3.25]		LAD 50%; RCA 27%; LCx 23%
SES-SMART	Cypher, Cordis	129	2.22 [0.29]	13.01 [6.53]	1: 36.4%; 2: 35.7%; 3: 27.9%	LAD 31.5%; RCA 15.7%; LCx 24.4%
	Bx sonic, Cordis	128	2.17 [0.26]	10.66 [5.51]	1: 33.9%; 2: 37.3%; 3: 29.1%	LAD 23.6%; RCA 15.8%; LCx 35.4%
		All	2.20 [0.28]	11.84 [6.15]	1: 35.2%; 2: 36.3%; 3: 28.4%	LAD 27.5%; RCA 15.7%; LCx 29.9%

continued

TABLE 64 *Participant characteristics: DES versus BMS (two parts) (cont'd)*

Study PART II	Intervention	Number of participants	Vessel diameter (mm)	Lesion length (mm)	Vessels diseased: (number: %)	Complex lesions
SIRIUS	Cypher, Cordis Bx Velocity, Cordis	533 525 All		14.4 14.4	1:59; 2:25; 3: 15 1: 58; 2: 29; 3: 14	
SPIRIT FIRST	XIENCE V (MULTI-LINK VISION-E® RX), Guidant	28 (Per-P: 27)				LAD 48.1%; RCA 29.6%; LCx 22.2%
	MULTI-LINK VISION RX, Guidant	32 (Per-P: 29) All				LAD 44.8%; RCA 34.5%; LCx 20.7%
STRATEGY	Cypher, Cordis and tirofiban Sonic, Cordis (or other approved non-DES) and abciximab	87 88 All			1: 46; 2: 28; 3: 13 1: 57; 2: 33; 3: 19	LAD 43% LAD 36%
TAXUS I	TAXUS NIRx, Boston NIRx, Boston	31 30 All				LAD 54.8%; RCA 22.6% LAD 26.7%; RCA 36.7%
TAXUS II	TAXUS NIRx (SR), Boston NIR Conformer (cohorts combined), Boston	113 240 All				LAD 40.7%; LCx 20.4%; RCA 38.9% LAD 47.9%; LCx 15.4%; RCA 36.7%
TAXUS IV	TAXUS Express2 (SR), Boston	662	2.75 [0.47] RVD	13.4 [6.3]		LAD 40.0%; RCA 31.1%; LCx 28.9%
	EXPRESS, Boston	652 All	2.75 [0.49] RVD 2.5 to 3.75 (incl. criteria)	13.4 [6.2] 10 to 28 (incl. criteria)		LAD 41.4%; RCA 26.6%; LCx 32.0%
TAXUS V (de novo)	TAXUS Express2 (SR), Boston	577 (586 rand)	RVD: 2.68 [0.58]; MLD: 0.85 [0.39]	17.3 [9.0]		
	Express2, Boston	579 (586 rand) All	RVD: 2.69 [0.56]; MLD: 0.85 [0.39]	17.2 [9.4]		

ID, insulin dependent; LAD, left anterior descending coronary; LCx, left circumflex; MLD, minimal luminal diameter; MVD, multi-vessel disease; Per-P, per protocol; rand, randomised; RCA, right coronary artery; RVD, reference vessel diameter; SR, slow-release formulation.

TABLE 65 *Outcomes: DES versus BMS (three parts)*

Study		Event rate					Mortality				
Part 1	**Intervention**	**1 month**	**6–9 months**	**1 year**	**2 years**	**3 years**	**1 month**	**6–9 months**	**1 year**	**2 years**	**3 years**
BASKET	Cypher, Cordis Taxus, Boston Vision, Guidant	6/264 5/281 10/281	15/264 24/281 34/281				2/264 cardiac 2/281 cardiac 1/281 cardiac	5/264 7/281 9/281			
C-SIRIUS	Cypher, Cordis Bx-VELOCITY, Cordis		2/50 9/50					0/50 0/50			
DIABETES	Cypher, Cordis BMS	0/80 5/80	9/80 29/80				0/80 2/80	1/80 2/80			
E-SIRIUS	CYPHER, Cordis		14/175	13/175 15/175 MACE	18/175 MACE			2/175		4/175	
	Bx-VELOCITY, Cordis		40/177	43/177 47/177 MACE	53/177 MACE			1/177		5/177	
ENDEAVOR II	ENDEAVOR, Medtronic	**[Confidential information removed]**	47/582 **[Confidential information removed]**				**[Confidential information removed]**	7/582	**[Confidential information removed]**		
	Driver, Medtronic	**[Confidential information removed]**	90/585 **[Confidential information removed]**				**[Confidential information removed]**	3/585	**[Confidential information removed]**		
Li	Cypher, Cordis Non-DES (not stated)							0/72 2/80			
Pache	Cypher, Cordis BeStent, Medtronic	9/250 12/250		34/250 56/250			0/250 0/250		7/250 5/250	6/120	9/114
RAVEL	Cypher, Cordis			5/120 4.2% 5/120; MACE 7/120	7/120 7.7%	12.1% 12/114 (TVF clin-dr); 13/114 (TVF all TVR)	0/120		2/120		

continued

TABLE 65 *Outcomes: DES versus BMS (three parts) (cont'd)*

Study		Event rate					Mortality				
Part I	**Intervention**	**1 month**	**6–9 months**	**1 year**	**2 years**	**3 years**	**1 month**	**6–9 months**	**1 year**	**2 years**	**3 years**
	Bx Velocity, Cordis			7/118 28.8% 34/118; MACE 34/118	25/118 30.6%	32.7% 27/113 (TVF clin-dr); 38/113 (TVF all TVR)	0/118		2/118	3/118	5/113
SES SMART	Cypher, Cordis	2/129	12/129				0/129	0/129			
	Bx sonic, Cordis	3/128	40/128				0/128	2/128			
SIRIUS	Cypher, Cordis	13/533	46/533	52/533		83/533	1/533	5/533	7/533		21/533
	Bx Velocity, Cordis	8/525	110/525	130/525		158/525	0/525	3/525	4/525		15/525
SPIRIT FIRST	XIENCE V (MULTI-LINK VISION-E® RX), Guidant		2/26					0/26			
	MULTI-LINK VISION RX, Guidant		6/28					0/28			
STRATEGY	Cypher, Cordis and tirofiban	3/87	16/87				2/87	7/87			
	Sonic, Cordis (or other BMS) and abciximab	7/88	28/88				3/87	8/88			
TAXUS I	TAXUS NIRx (SR), Boston		0/*31	1/31	1/30	1/27		0/31	0/31	1/31	3/30 0/27 (cardiac)
	NIRx, Boston		2/30	3/30	3/30	3/28		0/30	0/30	0/30	0/28 0/28 (cardiac)
TAXUS II	TAXUS NIRx (SR), Boston	3/131	11/130	14/129	18/127			0/130	0/129	1/127	
	NIR Conformer (cohorts combined), Boston	6/136	26/133	29/132	36/134			1/133	2/132	3/134	
TAXUS IV	TAXUS Express2 (SR), Boston	19/662	56/662	70/662	95/645			9/662	9/662	12/645	
	EXPRESS, Boston	16/652	98/652	129/652	161/640			7/652	8/652	14/640	

continued

TABLE 65 *Outcomes: DES versus BMS (three parts) (cont'd)*

Study		Event rate					Mortality				
Part I	**Intervention**	**1 month**	**6–9 months**	**1 year**	**2 years**	**3 years**	**1 month**	**6–9 months**	**1 year**	**2 years**	**3 years**
TAXUS V	TAXUS Express2 (SR), Boston	29/569	84/560				0/569	3/560			
	Express2, Boston	21/576	120/567				0/576	5/567			
Study		**AMI**					**TLR**				
Part II	**Intervention**	**1 month**	**6–9 months**	**1 year**	**2 years**	**3 years**	**1 month**	**6–9 months**	**1 year**	**2 years**	**3 years**
BASKET	Cypher, Cordis	3/264	6/264				3/264 TVR	8/264 TVR			
	Taxus, Boston	1/281	6/281				3/281 TVR	17/281 TVR			
	Vision, Guidant	8/281	12/281				4/281 TVR	22/281 TVR			
C-SIRIUS	Cypher, Cordis		1/50					2/50			
	Bx-VELOCITY, Cordis		2/50					9/50			
DIABETES	Cypher, Cordis	0/80	2/80				0/80	6/80			
	BMS	3/80	5/80				0/80	25/80			
E-SIRIUS	CYPHER, Cordis		8/175		10/175			7/175	8/175	9/175	
	Bx-VELOCITY, Cordis		4/177		6/177			37/177	44/177	47/177	
ENDEAVOR II	ENDEAVOR, Medtronic	**[Confidential information removed]**	16/582	**[Confidential information removed]**			**[Confidential information removed]**	27/582			
	Driver, Medtronic	**[Confidential information removed]**	23/585	**[Confidential information removed]**			**[Confidential information removed]**	71/585			
Li	Cypher, Cordis							1/72			
	Non-DES (not stated)							8/80			
Pache	Cypher, Cordis	9/250									
		11/250									
RAVEL	Cypher, Cordis	3/120		4/120	5/120	6/114			0/120; 1/120	3/120	6/114 (clin-dr); 7/114 (All TLR)

continued

TABLE 65 *Outcomes: DES versus BMS (three parts) (cont'd)*

Study		AMI					TLR				
Part II	**Intervention**	**1 month**	**6–9 months**	**1 year**	**2 years**	**3 years**	**1 month**	**6–9 months**	**1 year**	**2 years**	**3 years**
	Bx Velocity, Cordis	3/118		6/118	6/118	8/113			27/118; 28/118	16/118	17/113 (clin-dr); 29/113 (All TLR)
SES SMART	Cypher, Cordis	2/129	2/129				0/129	9/129			
	Bx sonic, Cordis	3/128	10/128				0/128	27/128			
SIRIUS	Cypher, Cordis	12/533	15/533	16/533		22/533	1/533	22/533	26/533	34/533	36/533
	Bx Velocity, Cordis	8/525	17/525	18/525		23/525	0/525	87/525	105/525	112/525	122/525
SPIRIT FIRST	XIENCE V (MULTI-LINK VISION-E® RX), Guidant		1/26					1/26			
	MULTI-LINK VISION RX, Guidant		0/28					6/28			
STRATEGY	Cypher, Cordis and tirofiban Sonic, Cordis (or other approved non-DES) and abciximab	1/87 3/88	6/87 8/88					5/87 18/88			
TAXUS I	TAXUS NIRx (SR), Boston		0/31	0/31	0/31	0/27		0/31	0/31	0/31	0/27
	NIRx, Boston		0/30	0/30	0/30	0/28		2/30	3/30	3/30	3/28
TAXUS II	TAXUS NIRx (SR), Boston		2/130	3/129	5/127			6/130*	6/129	7/127	
	NIR Conformer (cohorts combined), Boston		7/133	7/132	7/134			16/133	17/132	20/134	
TAXUS IV	TAXUS Express2 (SR), Boston		23/662	23/662	30/645			20/662	28/662	36/645	
	EXPRESS, Boston		24/652	30/652	35/640			74/652	96/652	112/640	
TAXUS V	TAXUS Express2 (SR), Boston	28/569	30/560					48/560			
	Express2, Boston	20/576	26/567								

continued

TABLE 65 *Outcomes: DES versus BMS (three parts) (cont'd)*

Study		BRR		Late loss	
PART III	**Intervention**	**6–9 months**	**Notes**	**6–9 months**	**Notes**
C-SIRIUS	Cypher, Cordis	0/44 (in-stent) 1/44 (in-lesion)	8 months (all Px)	0.12 [0.37] (in-stent) 0.12 [0.35] (in-lesion)	
	Bx-VELOCITY, Cordis	20/44 (in-stent) 23/44 (in-lesion)		1.02 [0.69] (in-stent) 0.79 [0.74] (in-lesion)	
DIABETES	Cypher, Cordis	4.9% lesions (in-stent) 7.7% lesions (in-segment)	FU: DES 75/80 BMS 70/80 (based on flow chart); unsure if data presented by lesion, rather than by Px; DES 102 lesions, BMS 100 lesions	0.08 [0.4] (in-stent); 0.08 (in-segment)	DES 75, BMS 70; in-segment from CRT resources
	BMS	31% lesions (in-stent) 33% lesions (in-segment)		0.66 [0.5] (in-stent); 0.44 (in-segment)	
E-SIRIUS	Cypher, Cordis	6/152 (in-stent) 9/152 (in-lesion)	8 mo; Angio FU: DES 152/175, BMS 156/177; DES 154, BMS 151 in Cordis, 2003[60]	0.20 [0.38] (in-stent) 0.19 [0.38] (in-lesion)	*N* = DES 152, *N* = BMS 156; DES 154, BMS 149[60]
	Bx Velocity, Cordis	65/156 (in-stent) 66/156 (in-lesion)		1.05 [0.61] (in-stent) 0.80 [0.57] (in-lesion)	
ENDEAVOR II	ENDEAVOR, Medtronic	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**
	Driver, Medtronic	**[Confidential information removed]**		**[Confidential information removed]**	
Li	Cypher, Cordis Non-DES (not stated)	4/69 lesions 26/72 lesions	3/4 BRR at 'proximal site' of SES		
Pache	Cypher, Cordis	17/205	6 mo; rate in vessels <2.8/>2.8 mm available	0.14 (–0.5, 0.43) *n* = 205	6 mo; median (25th, 75th) – need SD for RevMan
	BeStent, Medtronic	52/204		0.94 (0.53, 1.30) *n* = 204	
RAVEL	Cypher, Cordis	0/105, 0% (in-stent) 0% (in-segment)	Angiographic data: 211/238 patients (no *N* for DES/BMS in Morice); DES 105, BMS 107[66]	–0.01 [0.33] (in-stent);	Separate proximal and distal edge data in Morice, 2002;[58] DES 105, BMS 106[66]
	Bx Velocity, Cordis 0% (in-segment)	28/107, 26.6% (in-stent)		0.80 [0.53] (in-stent);	

continued

TABLE 65 *Outcomes: DES versus BMS (three parts) (cont'd)*

Study		BRR		Late loss	
PART III	**Intervention**	**6–9 months**	**Notes**	**6–9 months**	**Notes**
SCANDSTENT	CYPHER, Cordis BMS	3/163 51/159	Based on 2%, 31.9%	0.04 0.94	
SES-SMART	Cypher, Cordis	6/123 (in-stent) 12/123 (in-segment)	Mean 8 [0.5] mo; angio FU SES: 95.3%, BMS: 88.3%	0.16 [0.38] LLL 0.11 [0.29] LI (in-stent)	In-segment late loss available: SES: 0.16 [0.46] LLL; 0.11 [0.5] LI (in-segment); BeStent: 0.69 [0.61] LLL; 0.68 [0.68] LI (in-segment); % stenosis at 8 mo available; cumulative frequency plots available
	Bx sonic, Cordis	55/113 (in-stent) 60/113 (in-segment)		0.90 [0.62] LLL 0.68 [0.49] LI (in-stent)	
SIRIUS	Cypher, Cordis	11/349 (in-stent) 31/349 (in-segment)	CHK denominators against other sources; DES 348, BMS 353 {Cordis, 2002 #421}	0.17 [0.44] (in-stent) 0.24 [0.47] (in-segment)	DES: *N* = 350; BMS, *N* = 353 (source #323), but MLD only available for 701, so denominators may be inexact; DES 346, BMS 350) in-stent {Cordis, 2002 #421}; {Cordis, 2002 #421}
	Bx Velocity, Cordis	125/353 (in-stent) 128/353 (in-segment)		1.00 [0.70] (in-stent) 0.81 [0.67] (in-segment)	
SPIRIT FIRST	XIENCE V (MULTI-LINK VISION-E® RX), Guidant	0/23 (in-stent) 1/23 (in-segment)	QCA: DES 23/27 (Per-P); BMS 26/29 (Per-P); 180 days	0.10 [0.23] (in-stent) 0.09 (in-segment)	DES, *N* = 23; BMS *N* = 26
	MULTI-LINK VISION RX, Guidant	7/26 (in-stent) 0.84 [0.36] (in-stent)		9/26 (in-segment) 0.60 (in-segment)	
STRATEGY	Cypher, Cordis and tirofiban	5/66 (in stent) 7/66 (target vessel)		–0.22 [IQR –0.39, 0.19] (in-stent)	
	Sonic, Cordis (or other approved non-DES) and abciximab	19/67 (in stent) 24/67 (target vessel)		0.6 [IQR 0.12, 0.96] (in-stent)	
TAXUS I	TAXUS NIRx (SR), Boston	0/30 (in-stent)		0.36 [0.48]	DES, *N* = 30, BMS, *N* = 26
	NIRx, Boston	3/29 (in-stent)		0.71 [0.47]	

continued

TABLE 65 *Outcomes: DES versus BMS (three parts) (cont'd)*

Study		BRR		Late loss	
PART III	**Intervention**	**6–9 months**	**Notes**	**6–9 months**	**Notes**
TAXUS II	TAXUS NIRx (SR), Boston	3/128 (in-stent) 7/128 (analysis-segment)		0.26 [0.31] (in-stent) 0.27 [0.49] (in-stent, 2 yr)	QCA/IVUS substudy (Colombo, TCT 2004) – 6-mo and 2-yr data
	NIR Confromer (cohorts combined), Boston	24/134 (in-stent) 27/134 (analysis-segment)		0.70 [0.38] (in-stent) 0.54 [0.36] (in-stent, 2 yr)	
TAXUS IV	TAXUS Express2 (SR), Boston	16/292 (in-stent) 23/292 (in-segment)		0.39 [0.50] (in-stent) 0.23 [0.44] (in-segment)	
	EXPRESS, Boston	65/267 (in-stent) 71/267 (in-segment)		0.92 [0.58] 0.61 [0.57] (in-segment)	
TAXUS V	TAXUS Express2 (SR), Boston	68/496 (in-stent); 94/497 (analysis-segment)		0.49 [0.61] (in-stent); 0.33 [0.54] (analysis-segment)	*N* = DES 494 (in-stent), 495 (analysis-segment); *N* = BMS 492 (in-stent), 492 (analysis-segment)
	Express2, Boston	157/492 (in-stent); 167/492 (analysis-segment)		0.90 [0.62] (in-stent); 0.60 [0.59] (analysis-segment)	

FU, follow-up; LI, late loss in-stent; LLL, late loss in-lesion; mo, months; Per-P, per protocol; SR, slow-release DES formulation.

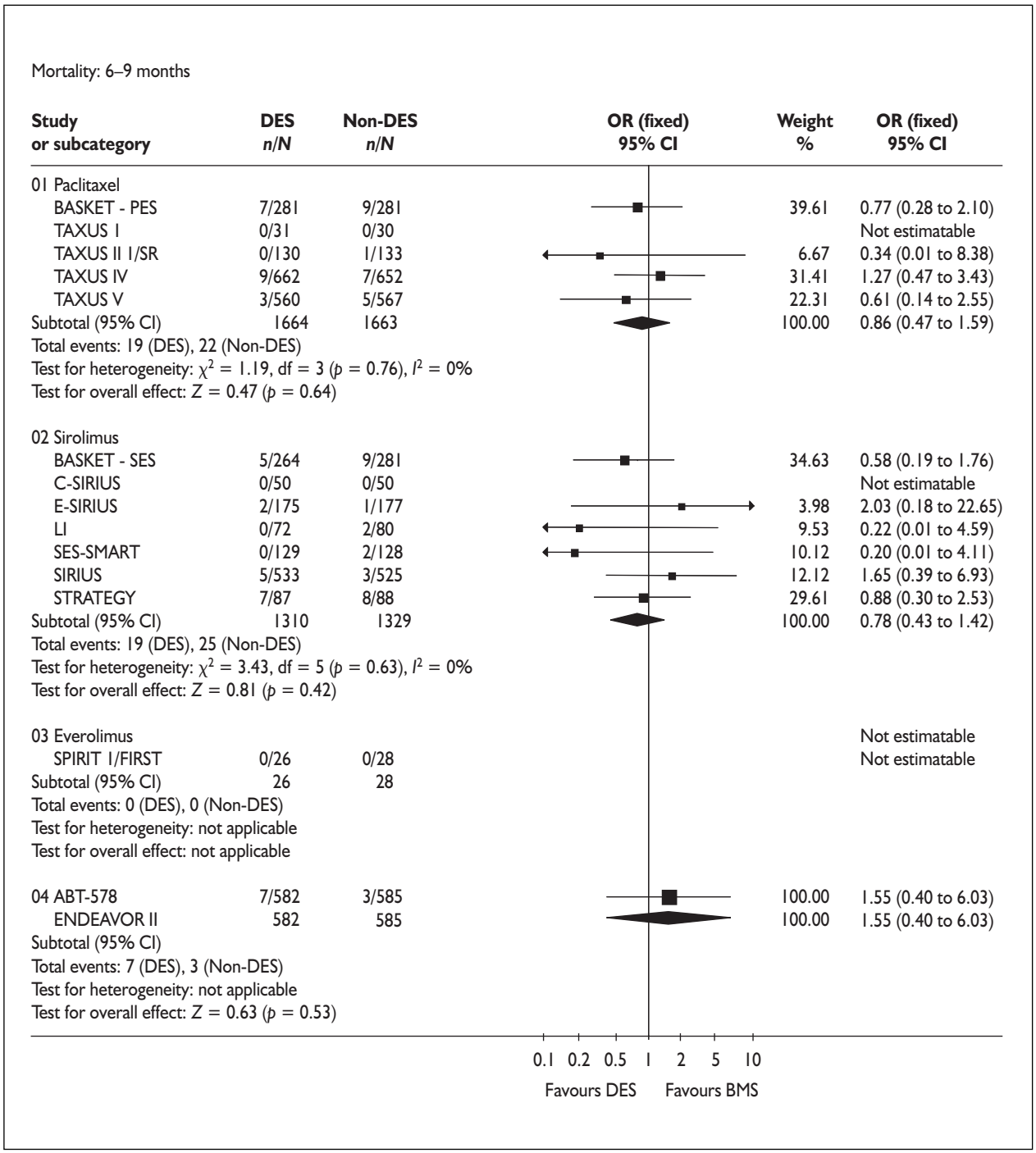

FIGURE 19 *Meta-analysis: mortality*

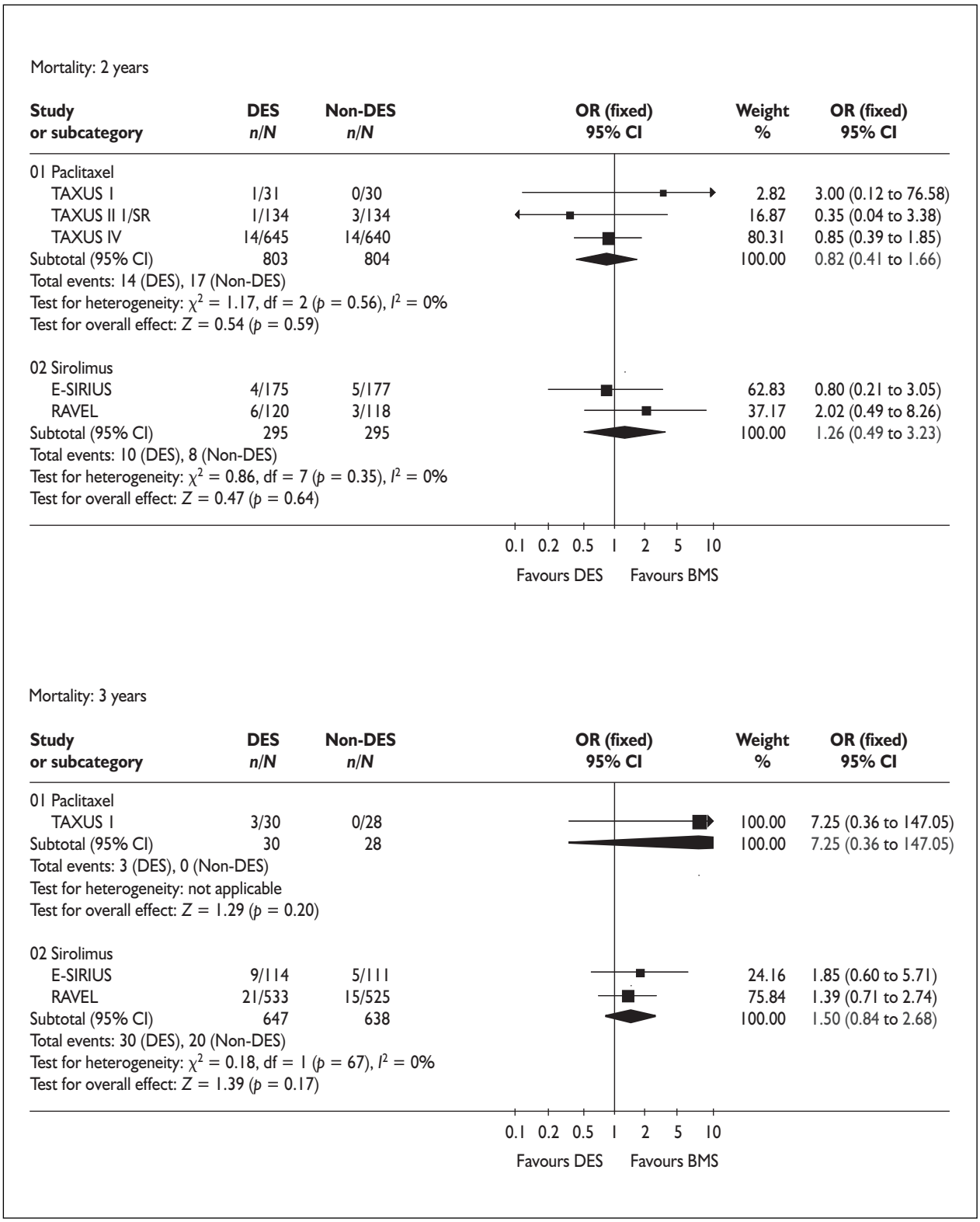

FIGURE 19 *(cont'd)*

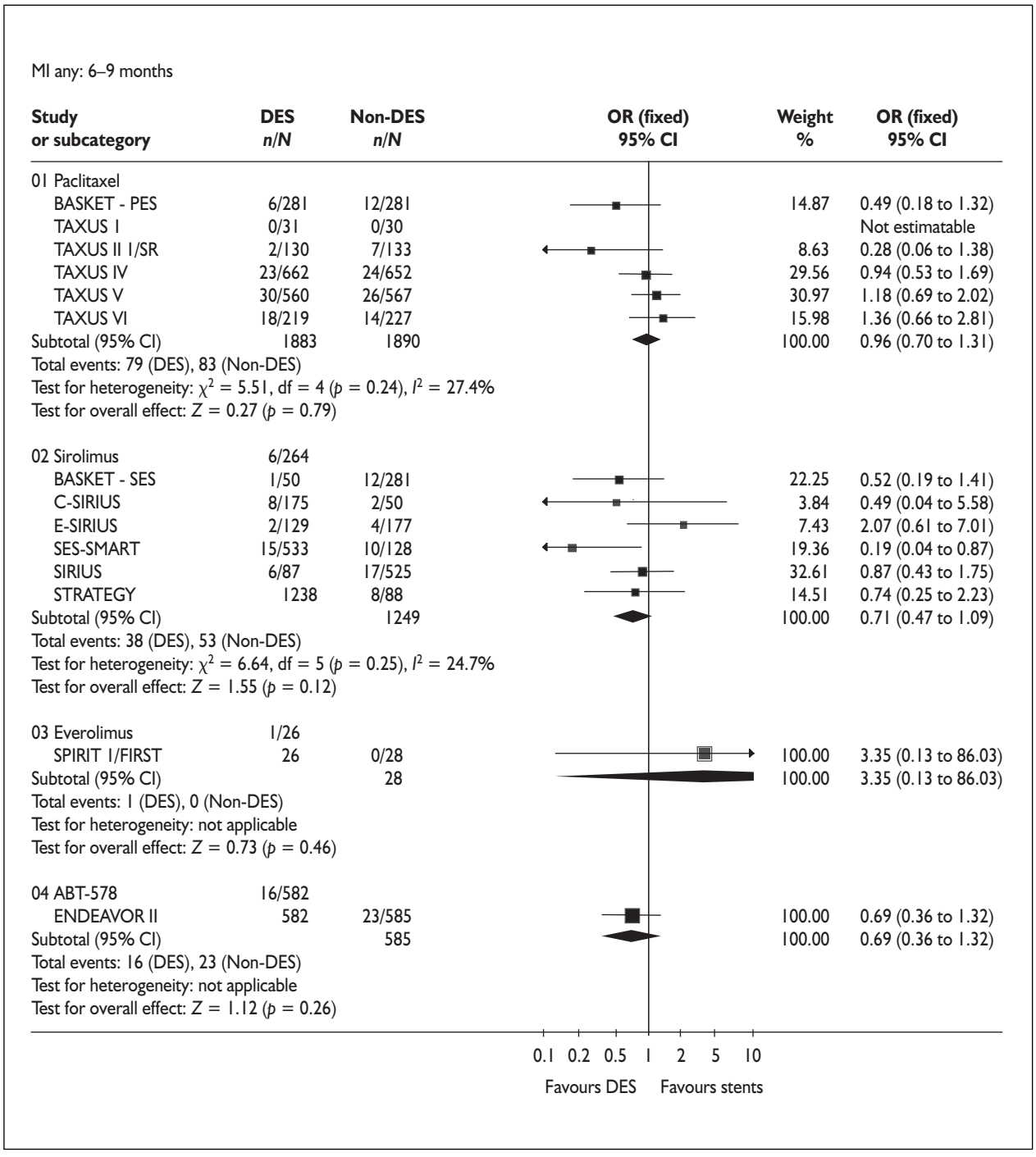

FIGURE 20 *Meta-analysis: MI*

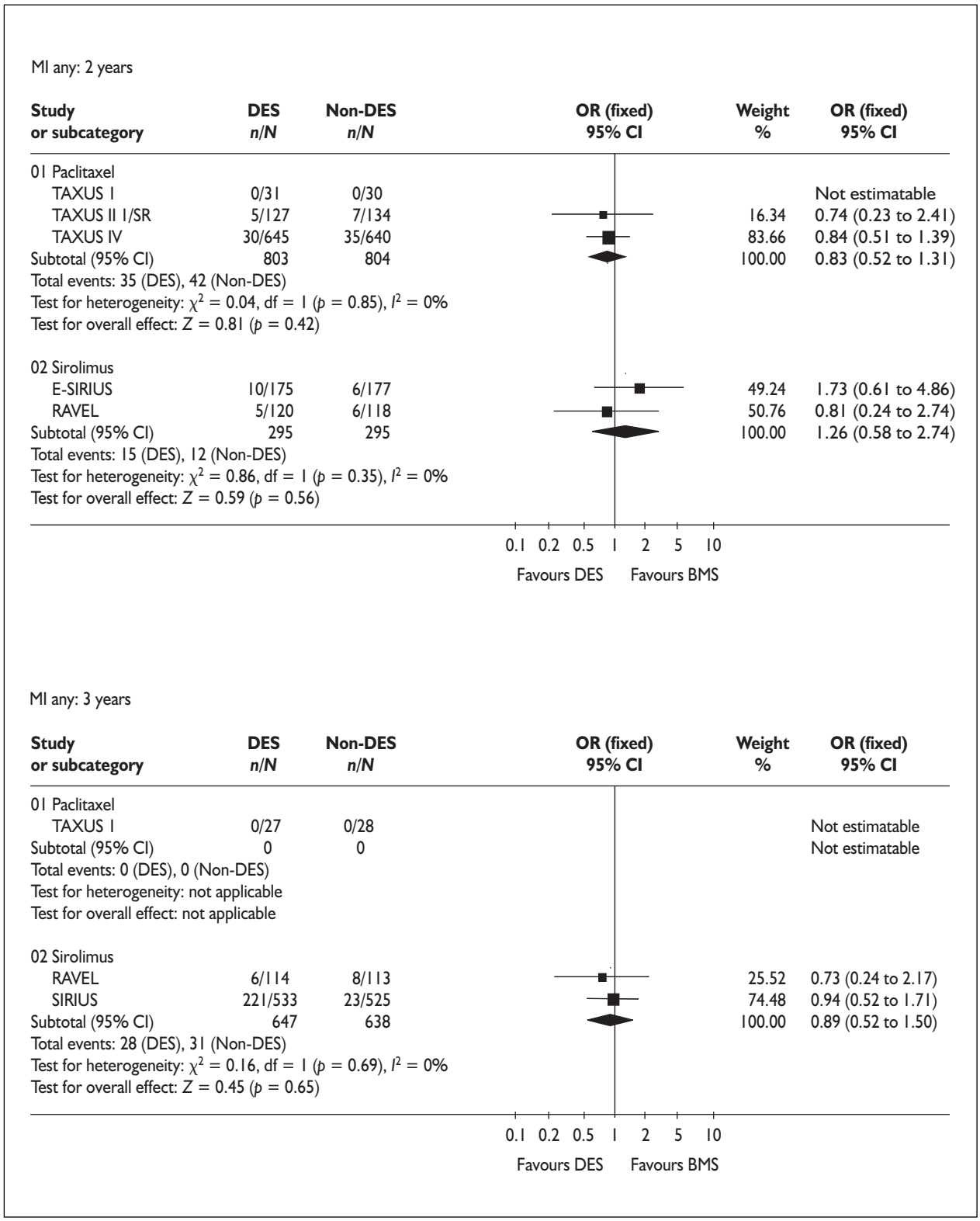

FIGURE 20 *(cont'd)*

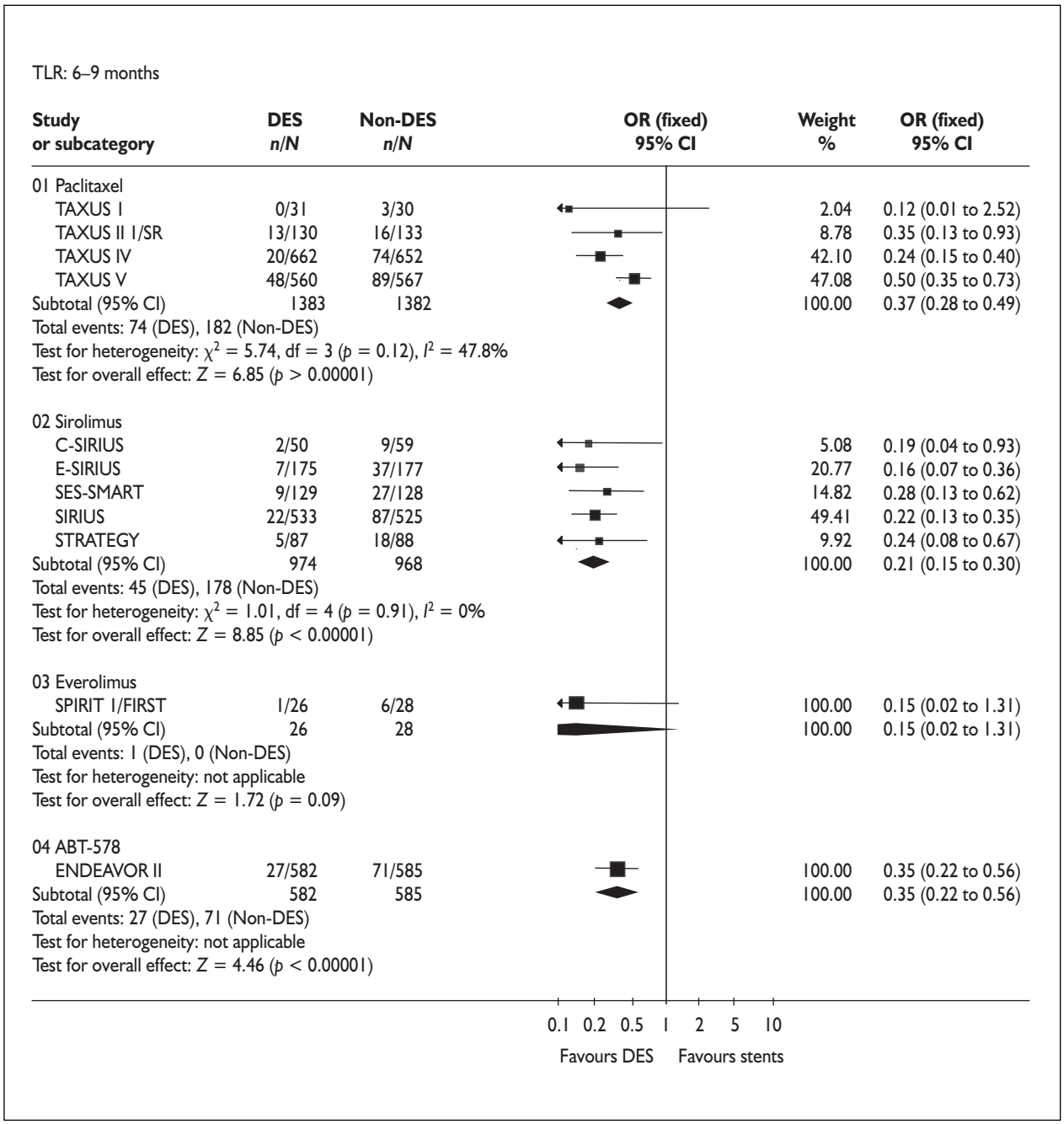

FIGURE 21 *Meta-analysis: TLR*

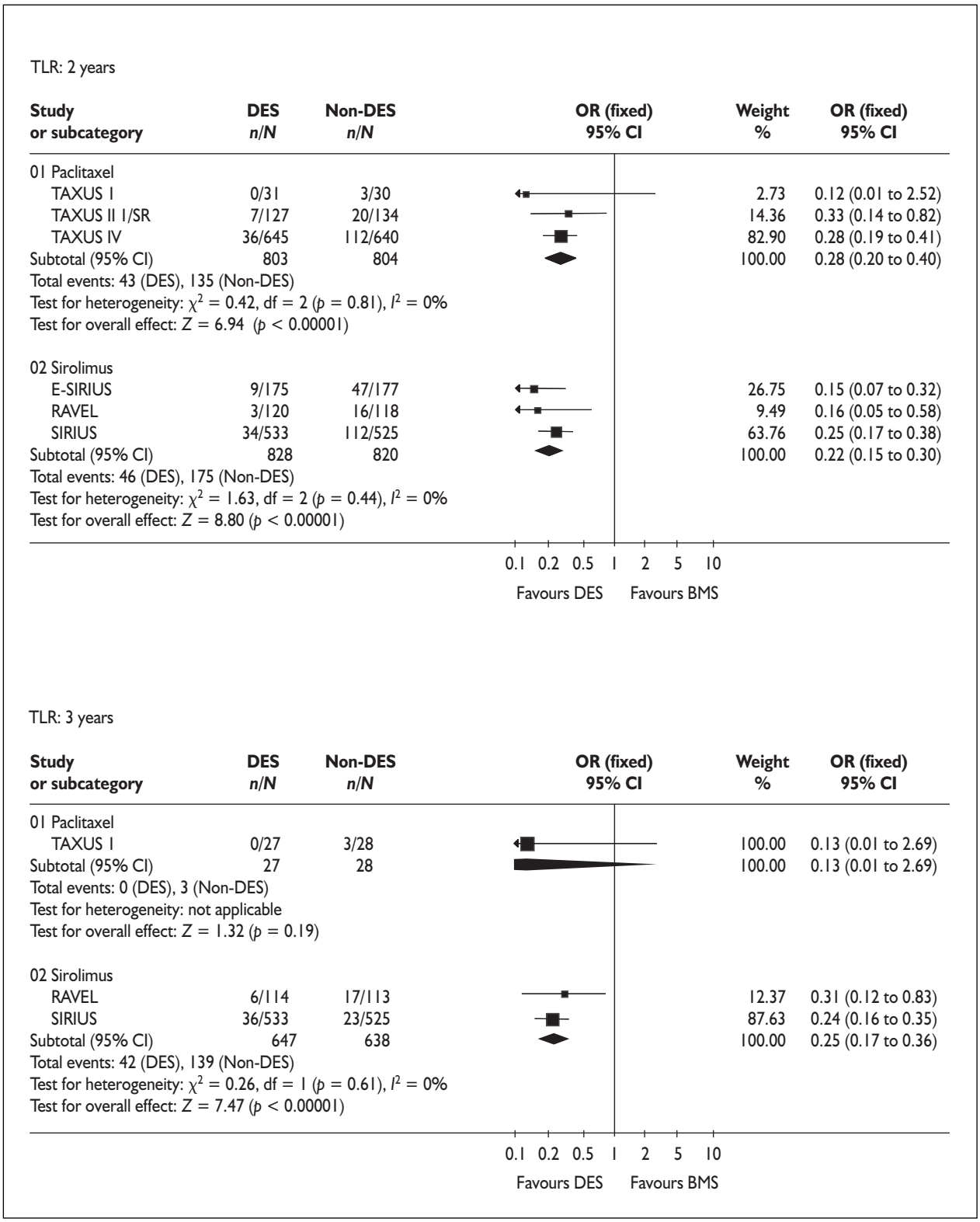

FIGURE 21 *(cont'd)*

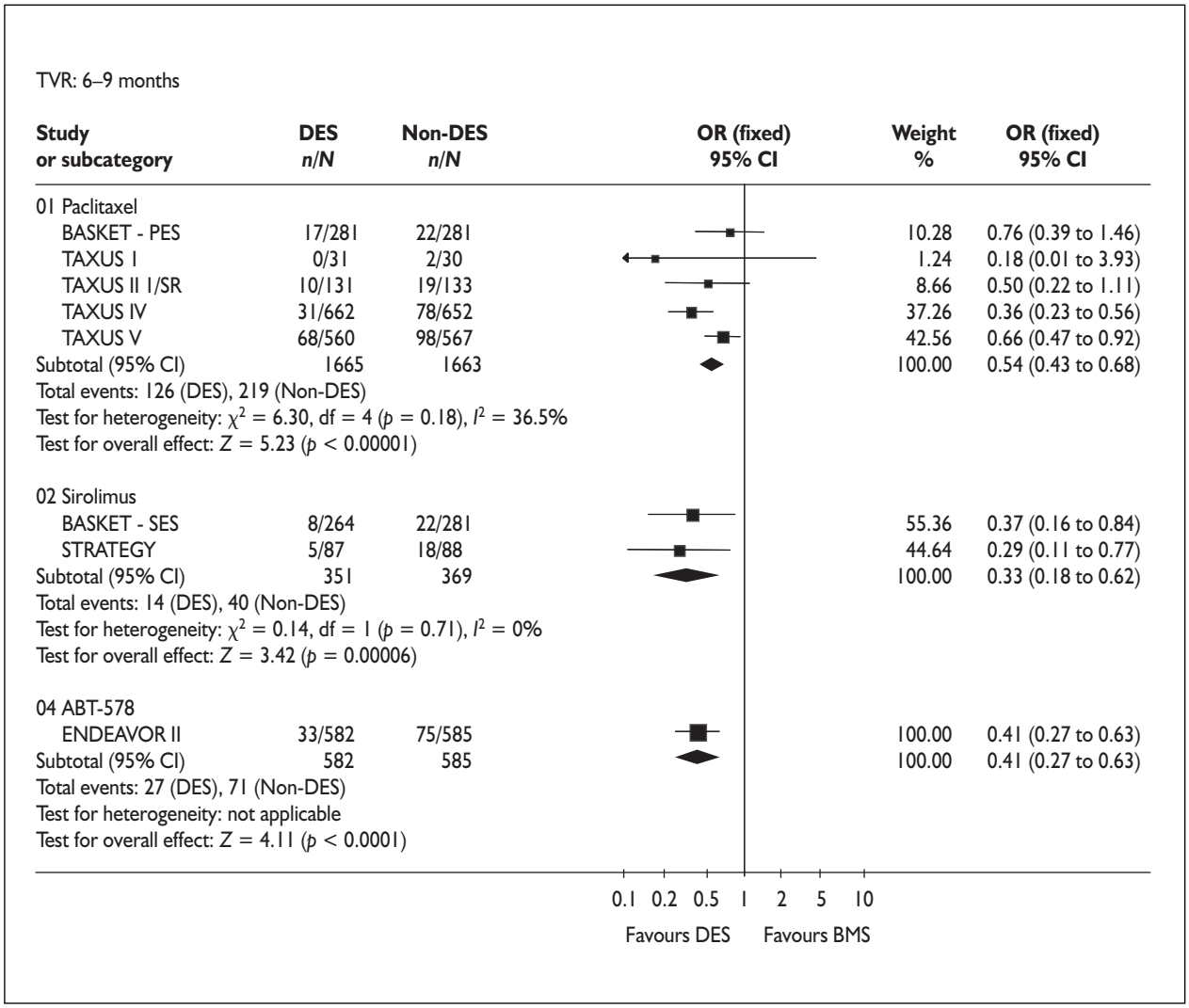

FIGURE 22 *Meta-analysis: TVR*

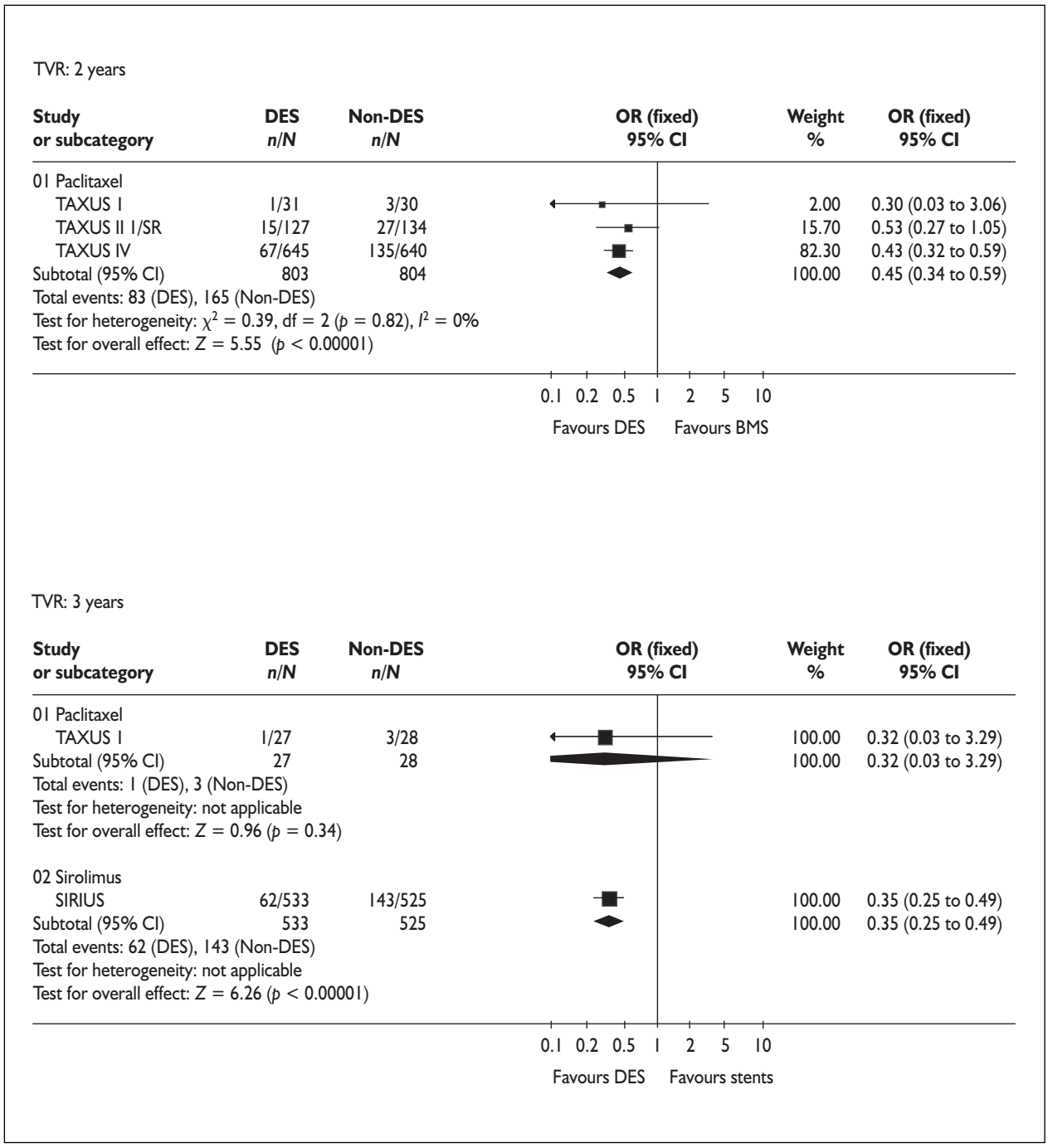

FIGURE 22 *(cont'd)*

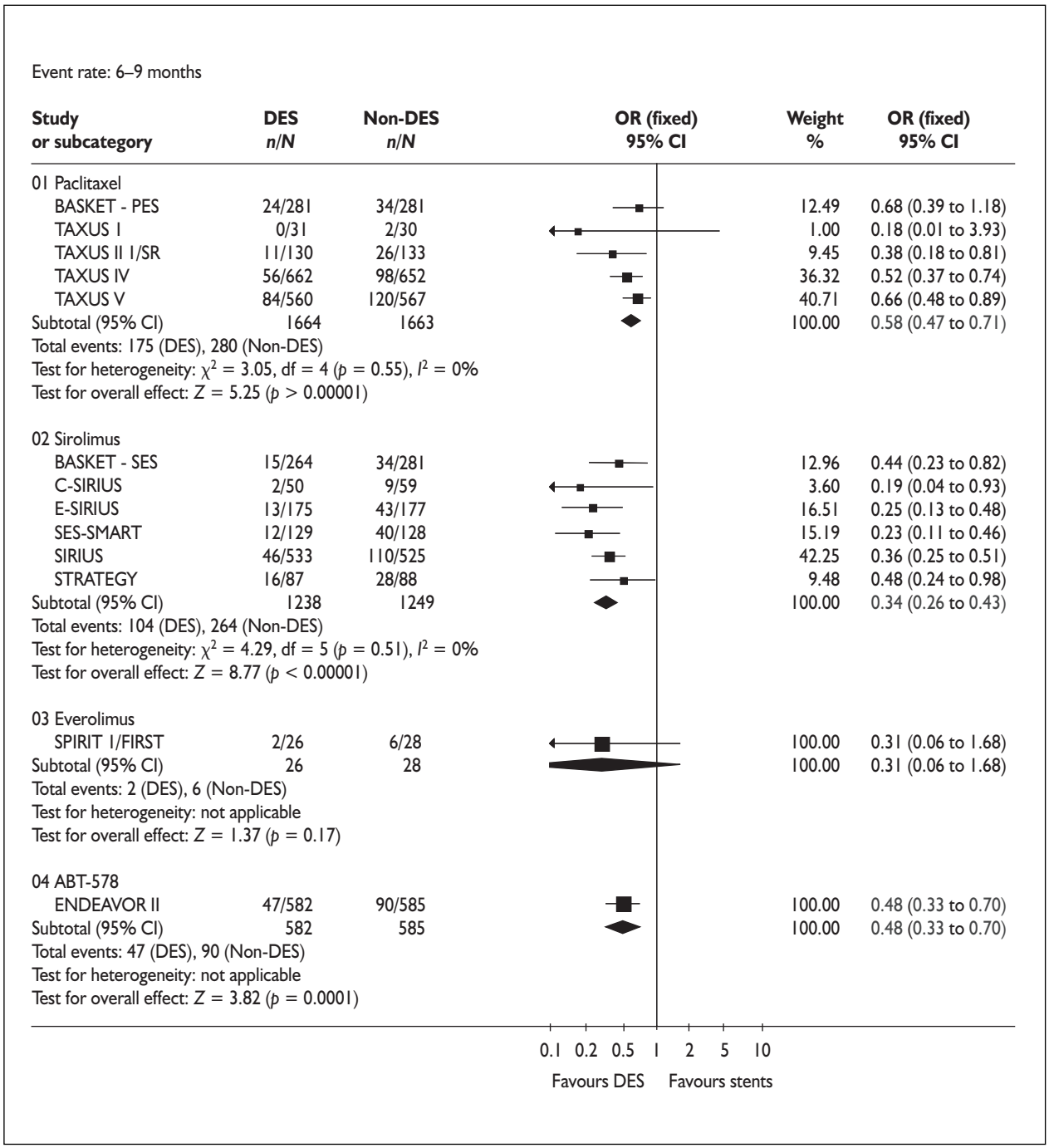

FIGURE 23 *Meta-analysis: event rate*

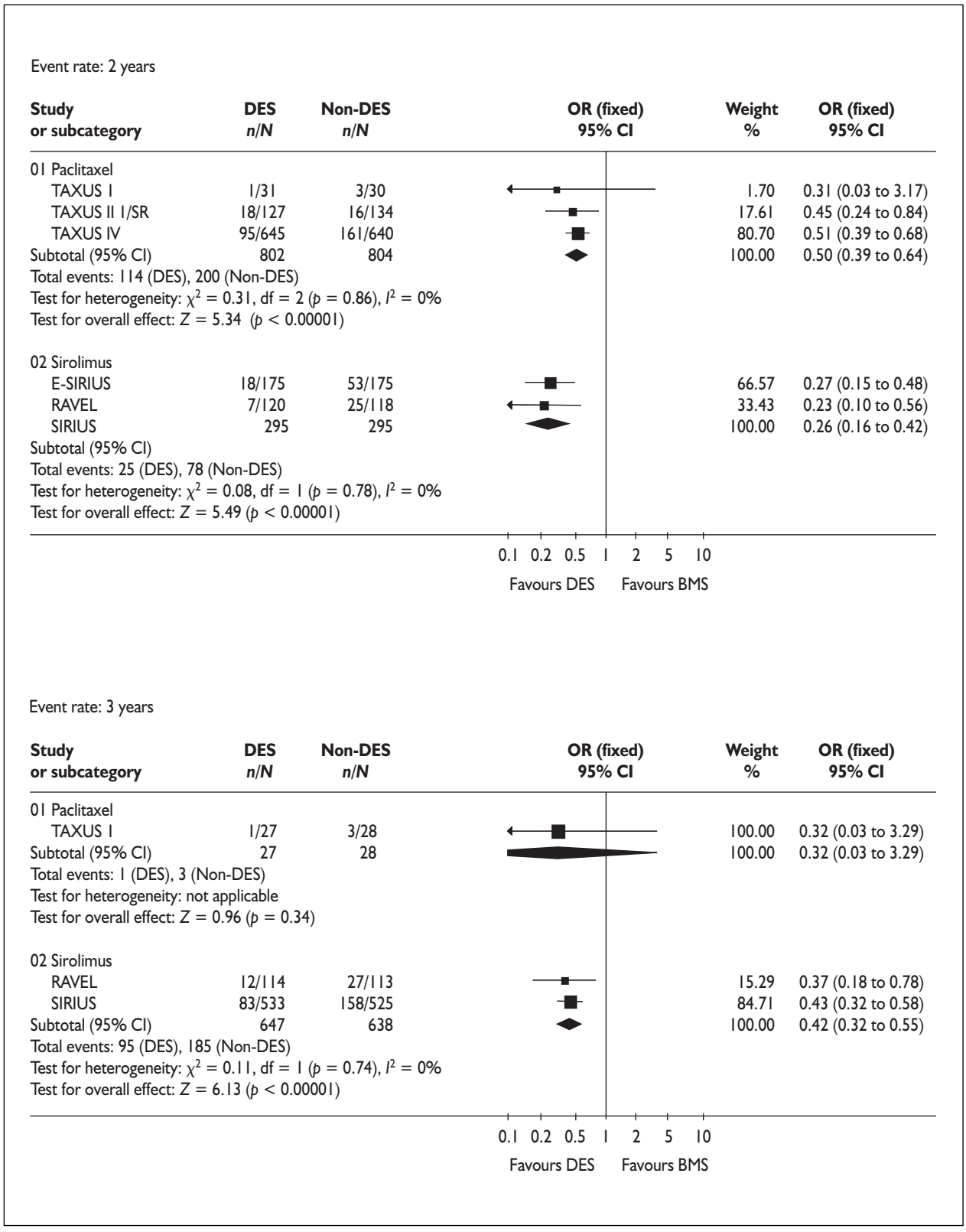

FIGURE 23 *(cont'd)*

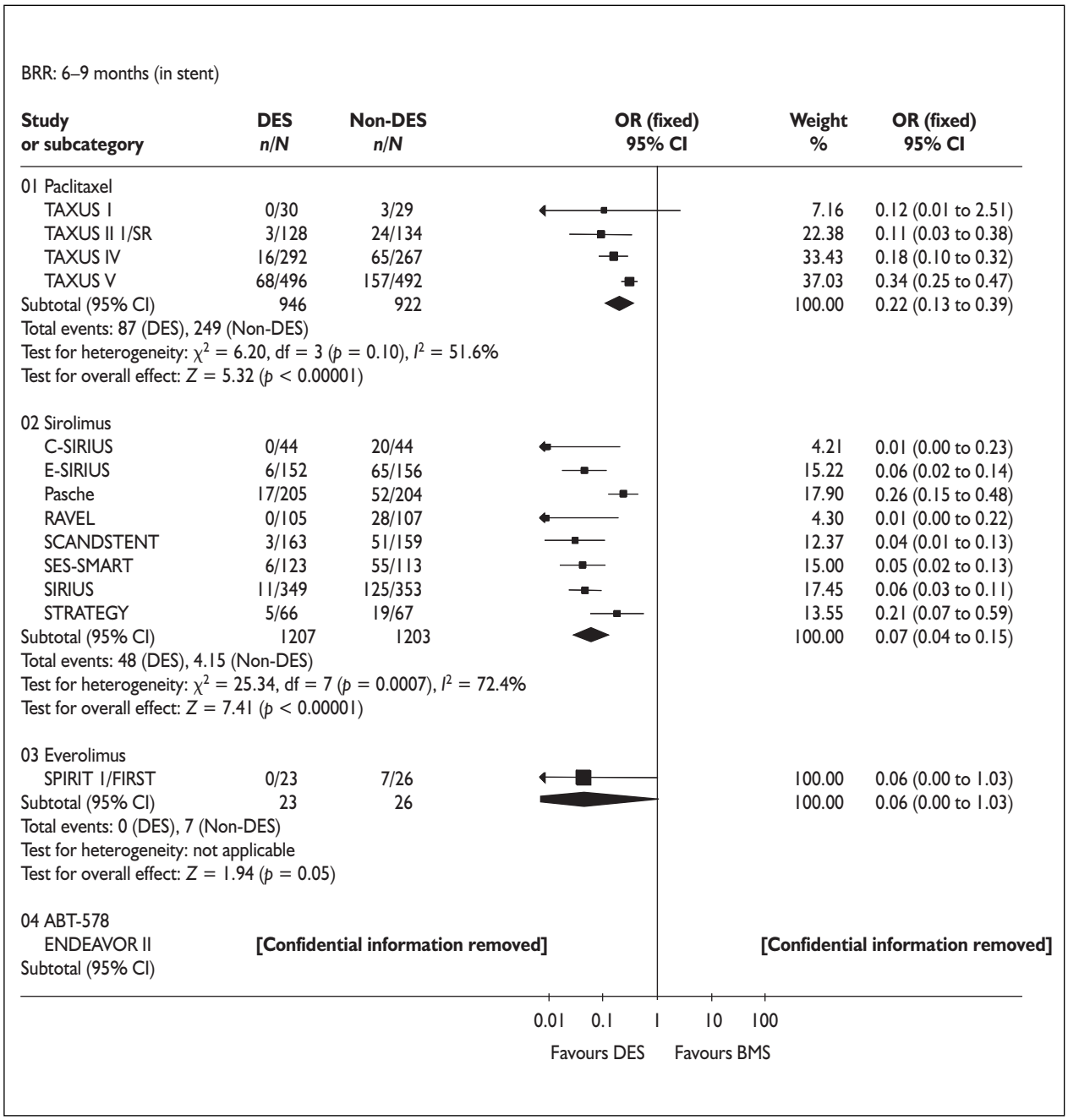

FIGURE 24 *Meta-analysis: binary restenosis, late loss (random effects analysis)*

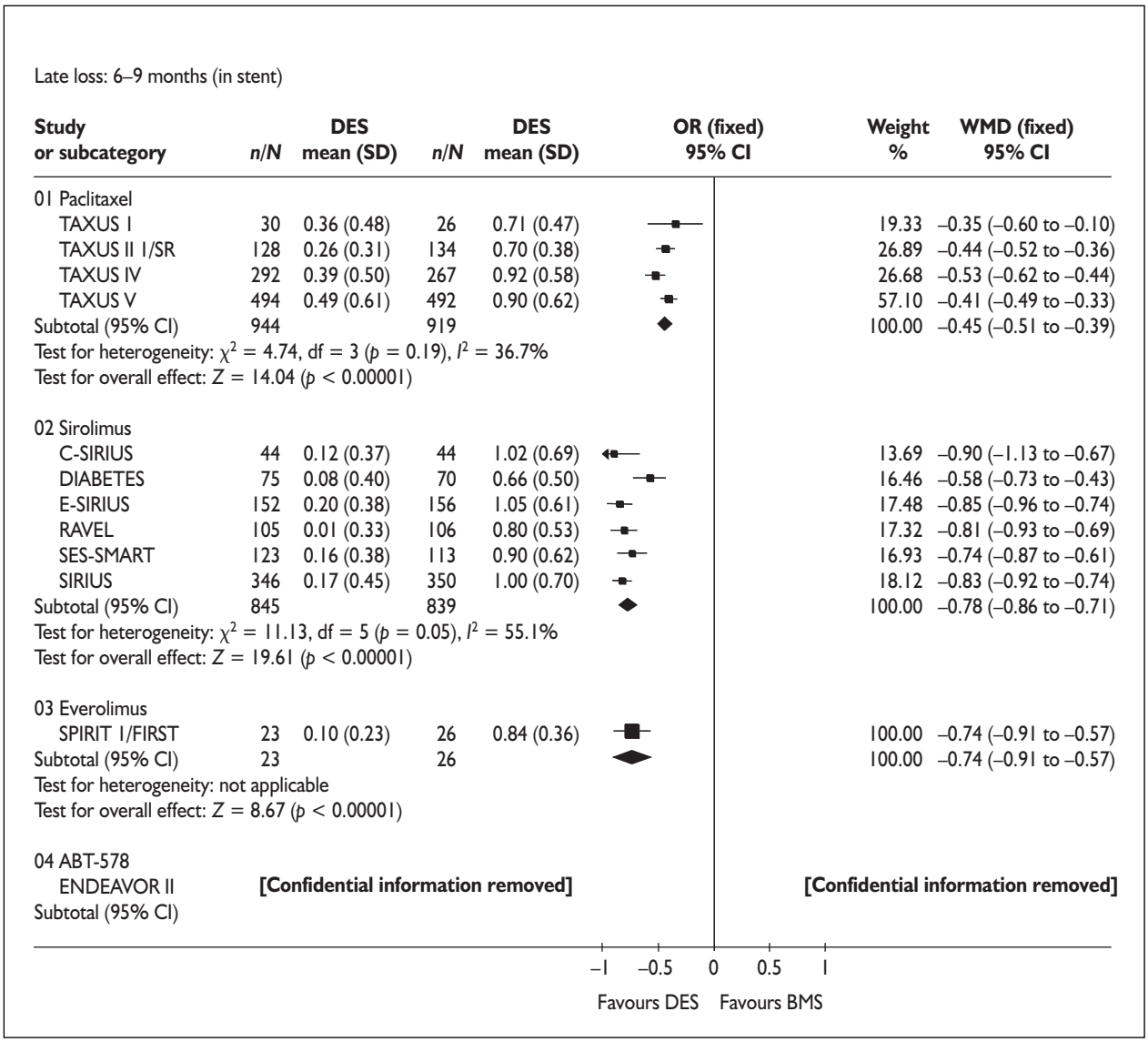

FIGURE 24 *(cont'd)*

Appendix 4

Clinical review tables – DES versus DES

TABLE 66 *Study characteristics: DES versus DES*

Study	Intervention	Randomised/lost	Centres/ location	Inclusion criteria	Exclusions	Co-therapy	Study support
BASKET	Cypher. Cordis Taxus, Boston	264 – 281 –	1 Switzerland	All patients presenting for PCI (with stents) during study period	Vessel diameter of ⩾4 mm; restenotic lesion, no consent ("mostly because of patients" or "referring physicians' preference for DES" or patients unable to give consent; involvement in other stent protocols (to avoid angiography-driven RV)	Periprocedurally: clopidogrel (300 mg); After: clopidogrel (75 mg per day) for 6 months; aspirin (100 mg/day); statin therapy; other drugs (including GP IIb/IIIa) as clinically indicated	Basel Cardiac Research Foundation/ Hospital No industry sponsorship
CORPAL	Cypher, Cordis Taxus, Boston	331; 434 lesions (after angio) 316/331 1 year success 321; 410 lesions (after angio) 304/321 1 year success	– Spain	Documented ischaemia secondary to coronary lesions prone to restenosis			
DOMINO	Cypher, Cordis Cypher SELECT, Cordis	37 (reported) – 60 (reported) –	10 Denmark	*De novo*, lesion length <23 mm; vessel diameter ⩽3.5 mm	See: Cordis, 2005[119]		
ISAR-DIABETES	Cypher, Cordis Taxus, Boston	125 – 125 –	– Germany	Diabetic patients; angina pectoris and/or positive stress test in the presence of 50% stenosis in native coronary vessels	AMI; left main disease; In-stent restenosis; allergy to sirolimus, paclitaxel, heparin, aspirin or clopidogrel		Deutsches Herzzentrum
ISAR-TEST	Yukon (SES), KiwiMed Taxus, Boston	225 – 225 –	1 Germany	Angina and/or positive stress test; stenosis ⩾50%	AMI; LM; ISR; allergy to sirolimus, paclitaxel, heparin, aspirin, clopidogrel		

continued

TABLE 66 *Study characteristics: DES versus DES (cont'd)*

Study	Intervention	Randomised/lost	Centres/ location	Inclusion criteria	Exclusions	Co-therapy	Study support
REALITY	Cypher, Cordis Taxus, Boston	684 (970 lesions) 8 months: 96% (clinical); 93% (angio) 669 (941 lesions) 8 months: 95% (clinical) 91% (angio)	Multiple International	AP (CCS I–IV (stable), Brunwald class B and C I–II–III (unstable), documented SI; diameter 2.25–3.0 mm; length: 1st lesion >15 mm, 2nd lesion >10 mm; stenosis >50%; at least TIMI I	AMI within 72 h; ostial lesions; unprotected LM; LVERF ⩽25%; TO; ISR; PCI within 30 days	Before: aspirin, thienopyridine (loading dose before or immediately after) During: heparin, GP IIb/IIIa at discretion After: clopidogrel (75 mg/day) or ticlopidine (500 mg/day), aspirin (100 mg/day) indefinitely, thienopyridine (⩾6 months taxus, ⩾2 months Cypher)	Cordis
SIRTAX	Cypher, Cordis Taxus, Boston	503 FU on 1005/1012 at 9 months 509 FU on 1005/1012 at 9 months	2 Switzerland	1 or more lesion stenosis >50% Diameter 2.25–4.0 mm (RVD) Length – no limit	Lesion unsuitable for stent implantation; participation in other study; severe co-morbidity; study stents unavailable; pregnancy; allergy to paclitaxel, sirolimus, aspirin, thienopyridines	Pre/during: aspirin, clopidogrel (300 mg) loading, heparin (5000 IU i.v. or 70 IU/kg), GP IIb/IIIa operator discretion After: aspirin (100 mg/day) indefinitely, clopidogrel (75 mg/day) for 12 months (either DES)	No industry sponsorship
TAXi	Cypher, Cordis Taxus, Boston	102 0% 100 0%	1 Switzerland	All patients selected to receive DES	Patient preference; uncertainty of obtaining follow-up	Before: aspirin (100 mg/day), clopidogrel (75 mg/day), 5–7 days (only a minority) During: heparin i.v. (70 U/kg) After: clopidogrel (300 mg loaded), aspirin (100 mg/day) long-term, clopidogrel (75 mg/day), 12 months, GP IIb/IIIb (7/102, 4/100)	

TABLE 67 *Participant characteristics: DES versus DES (two parts)*

PART I	**Intervention**	**Numbers included**	**Gender (% male)**	**Age (mean, years)**	**Diabetes (%)**	**Previous AMI (%)**
BASKET	Cypher. Cordis Taxus, Boston All	264 281				
CORPAL	Cypher, Cordis Taxus, Boston All	331; 434 lesions 321; 410 lesions	78 75	60 (12) 62 (10)	29 33	
ISAR-DIABETES	Cypher, Cordis Taxus, Boston All	125 125	 74	 68	 All	
ISAR-TEST	Yukon (SES), KiwiMed Taxus, Boston All	225 225	75 79	66.8 (10.5) 66.6 (10.2)	32 26	32 32
REALITY	Cypher, Cordis Taxus, Boston All	684 (970 lesions) 669 (941 lesions)	74.1 72.0	62.6 62.6	27.2	42.3
SIRTAX	Cypher, Cordis Taxus, Boston All	503 509	76 78	62 (11) 62 (12)	22; 6% insulin dep. 18; 7% insulin dep.	29 30
TAXi	Cypher, Cordis Taxus, Boston All	102 100	79/102 83/100	65 (10) 63 (10)	33/102 36/100	33/102, 32% 29/100, 29%
Part II	**Intervention**	**Numbers**	**Vessel diameter (mm)**	**Vessel length (mm)**	**Vessels diseased**	**Complex lesions**
BASKET	Cypher. Cordis Taxus, Boston	264 281				
CORPAL	Cypher, Cordis	331; 434 lesions	0.73 (0.5) MLD 2.84 (0.4) stent	26 (14) 27 (14) stent		LAD 194/434; RCA 124/434; Cx 104/434; LM 12/434
	Taxus, Boston	321; 410 lesions	0.70 (0.5) MLD 2.83 (0.4) stent	24 (14) 27 (14) stent		LAD188/410; RCA 101/410; Cx 114/410; LM 7/410
ISAR-DIABETES	Cypher, Cordis Taxus, Boston	125 125		13.8 12.4		LAD treated: 47% LAD treated: 51%
ISAR-TEST	Yukon (SES), KiwiMed Taxus, Boston	250 225	2.72 (0.46) 2.73 (0.49)	12.6 (5.9) 12.9 (7.0)	84% (MVD) 85% (MVD)	LAD 37%; RCA 26%; LCx 37% LAD 43%; RCA 28%; LCx 29%

continued

TABLE 67 *Participant characteristics: DES versus DES (two parts) (cont'd)*

Part II	Intervention	Numbers	Vessel diameter (mm)	Vessel length (mm)	Vessels diseased	Complex lesions
REALITY	Cypher, Cordis	684 (970 lesions)	2.40 (0.48) RVD; 2.79 (0.28) stent	16.96 (10.04)		
	Taxus, Boston	669 (941 lesions)	2.40 (0.48) RVD; 2.80 (0.28) stent	17.31 (10.09)		
SIRTAX	Cypher, Cordis Taxus, Boston	503 509			1: 40%; 2: 37%; 3: 23%	
TAXi	Cypher, Cordis	102	3.2 (0.1)		1v: 36/102; 2v: 35/102; 3v: 29/102	
	Taxus, Boston	100	3.2 (0.2)		1v: 40/100; 2v: 32/100; 3v: 28/100	
					44/202 multivessel RV (25/1 session, 19/staged)	Most patients had complex lesions

LM, left main; MLD, mid lesion diameter; RCA, right coronary artery.

TABLE 68 *Outcomes: DES versus DES (two parts)*

Study		Event rate (ER)			Mortality			AMI		
PART I	**Intervention**	**1 month**	**6–9 months**	**1 year**	**1 month**	**6–9 months**	**1 year**	**1 month**	**6–9 months**	**1 year**
BASKET	Cypher. Cordis	6/264	15/264		2/264 cardiac	5/264; 3/264 cardiac		3/264	6/264	
	Taxus, Boston	5/281	24/281		2/281 cardiac	7/281; 6/281 cardiac		1/281	6/281	
CORPAL	Cypher, Cordis				1/331		1/331	14/331		2/331
	Taxus, Boston				2/321		1/321	15/321		2/321
DOMINO	Cypher, Cordis		1/37			0/37			1/37	
	Cypher Select, Cordis		3/60			1/60			2/60	
ISAR-DIABETES	Cypher, Cordis					4/125			5/125	
	Taxus, Boston					6/125			3/125	
ISAR-TEST	Yukon (SES), KiwiMed					2/225			10/225 death or MI	
	Taxus, Boston					3/225			9/225 death or MI	
REALITY	Cypher, Cordis		71/684; 63/684 MACE			12/684; 7/684 cardiac			33/684	
	Taxus, Boston		77/669; 71/669 MACE			8/669; 6/669 cardiac			37/669	
SIRTAX	Cypher, Cordis	15/503	35/503; 31/503 1ry ER 29/503 Alt ER		0/503; 0/503 cardiac	5/503; 3/503 cardiac	12/503	14/503		
	Taxus, Boston	19/509	59/509; 55/509 1 year 49/509 Alt ER		4/509; 4/509 cardiac	11/509; 8/509 cardiac		13/509	18/509	
TAXi	Cypher, Cordis	3/102	6/102		0/102	0/102		2/102	2/102	
	Taxus, Boston	3/100	4/100		0/100	0/100		3/100	3/100	

continued

TABLE 68 *Outcomes: DES versus DES (two parts) (cont'd)*

Study		TLR			BRR	Late Loss
PART II	**Intervention**	**1 month**	**6–9 months**	**1 year**	**6–9 months**	**6–9 months**
BASKET	Cypher, Cordis				No angiographic follow-up	No angiographic follow-up
	Taxus, Boston					
CORPAL	Cypher, Cordis			19/331	22/177 lesions	0.36 [0.5]
	Taxus, Boston			29/321	35/188 lesions	0.54 [0.7]
DOMINO	Cypher, Cordis		0/37		0/36 (in-stent)	0.13 [0.28]
	Cypher Select, Cordis		0/60		1/55 (in-stent)	0.07 [0.35]
ISAR-DIABETES	Cypher, Cordis		8/125		5/102 (in-stent); 7/102 (in-segment)	0.19 [0.44] (in-stent) 0.43 [0.45] (in-segment)
	Taxus, Boston		15/125		14/103 (in-stent); 17/103 (in-segment)	0.46 [0.64] (in-stent) 0.67 [0.62] (in-segment)
ISAR-TEST	Yukon (SES), KiwiMed		8.7%		14.1%	0.49 [0.59]
	Taxus, Boston		9.5%		18.1%	0.47 [0.57]
REALITY	Cypher, Cordis		34/684		7.0% lesion (in-stent); 9.6% lesion (in-segment)	0.09 [0.43] (in-stent) 0.04 [0.38] (in-segment)
	Taxus, Boston		36/669		8.3% lesion (in-stent); 11.1% lesion (in-segment)	0.31 [0.44] (in-stent); 0.16 [0.40] (in-segment)
SIRTAX	Cypher, Cordis	11/503	24/503		11/348 lesion (in-stent); 23/348 lesion (in-segment)	0.12 [0.36] (in-stent) 0.25 [0.49] (in-segment)
	Taxus, Boston	10/509	42/509		28/375 lesion (in-stent); 44/375 lesion (in-segment)	0.19 [0.45] (in-stent) 0.32 [0.55] (in-segment)
TAXi	Cypher, Cordis		2/102		No angiographic follow-up	No angiographic follow-up
	Taxus, Boston		1/100			

Appendix 5

Clinical review tables – DES without RCT evidence

TABLE 69 *New DES non-RCT study and participant characteristics*

Study	Intervention	Numbers	Centres/location	Inclusion	Exclusion
ATLAS	Taxus Liberté, Boston	871	61 Worldwide	*De novo*; length 10–28 mm; diameter 2.5–4.0 mm	–
EMPEROR (Pilot)	Dexamet (2.2 μg/mm^2), Abbott	30	1 Germany	Lesion length to be covered by one 18 mm long stent; vessel diameter 2.75–3.75 mm; patients with SVD	Ejection fraction <30%; unprotected left main location; heavy calcification; excessive tortuosity of the proximal vessel; life expectancy <1 year; MI within previous 72 h; previous intracoronary brachytherapy
EuroSTAR	CoStar (10 μg, 24–30 days PES), Biotronik CoStar (30 μg 24–30 days PES), Biotronik	145 Arm II FU not complete	18 Europe	Up to 2 native coronary lesions, RV naïve; stable/UA (CCS Class I or greater or positive functional ischaemia test); vessel diameter 2.5–3.5 mm; 51–99% diameter stenosis; length <25 mm; at least 20 mm from other lesion; TIMI flow of Grade I or higher; acceptable PCI with no planned interventions TL(s) within 30 days of Rx	AMI (<72 h); EF <30%; recent GI bleed or renal insufficiency; recent CVA or unstable VA; known hypersensitivities or contraindication to aspirin, clopidogrel or ticlopidine, paclitaxel; angiographic: thrombus in target vessel; >2 lesions requiring treatment; bifurcation TL and adjacent vessel >2 mm requiring treatment
CoSTAR I (India)	CoStar (10 μg, 10 days PES, Grp 3), Biotronik CoStar (30 μg, 30 days PES, Grp 1), Biotronik	40 (interim); 14 lesions 10 (interim); 57 lesions	4 India	⩽2 *de novo* lesions requiring treatment in 1 or 2 native coronary arteries (no prior RV); stable or unstable angina; vessel diameter 2.5–3.5 mm, stenosis 51–99%; lesion length <25 mm (⩾10 mm from other lesions); acceptable for PCI with no intervention within 30 days prior and no planned intervention 30 days following enrolment	AMI <72 h or evolving MI; LVF <30%; significant co-morbidity with life expectancy <2 years; known hypersensitivity to cobalt, chromium, contrast medium; hypersensitivity or medical contraindication to required anticoagulants or antiplatelet therapy (aspirin, clopidogrel or ticlopidine); subject with recent GI bleed or renal insufficiency; TIMI 0 flow; presence of intraluminal thrombus in target vessel
DESIRE	Dexamet, Abbott	332	20 Italy	ACS: UA (B–C–II–III) or NSTEMI; dexamethasone implantation on target lesion (1 or more); informed consent	STE-AMI; secondary UA; LVEP <30%; serum creatine >2; PCI or CABG <3 months; total occlusion of culprit vessel; ISR lesion; SVG lesion; vessel diameter <2.75 mm; lesion length >30 mm

continued

TABLE 69 *New DES non-RCT study and participant characteristics (cont'd)*

Study	Intervention	Numbers	Centres/location	Inclusion	Exclusion
ISAR Project (1)	Yukon DES, KiWiMed Yukon (non-loaded), KiWiMed	602 (447 DES; 155 non-loaded)	1 Germany	Native vessel diameter 2.5–30 mm; angina or exercise-induced ischaemia in the presence of angiographically significant stenosis	MI (within 72 h); LM; ISR
JUPITER I (Alpha)	Janus CardoStent Sorin	58 Italy	7 Clinical investigator institutions	*De novo* coronary lesions in native vessels; vessel diameter 3 and 4 mm; lesion length 12 mm; stented vessel segment 3 mm longer than the target lesion; stenosis 50–100% (TIMI I); ≤2 target vessels; 1 lesion for each vessel 1 DES stent only (15 × 3.0–3.5 mm) for each target lesion	
Patti	Dexamet (0.5 μg/mm^2), Abbott	100		Unstable coronary conditions (unstable angina or recent <1 month MI); single vessel disease; stenoses >70%; vulnerable plaque deemed treatable by 1 stent	Inflammatory diseases, malignancy, infection, <2 months surgery or trauma
SAFE	Dexamet, Abbott	735 (patients in database)	16 countries Worldwide	Not reported	Not reported
STRIDE	Dexamet (0.5 μg/mm^2), Abbott	60 (strictly met requirements); 71 (all enrolled)	8 Belgium	*De novo* coronary lesions; documented myocardial ischaemia; vessel diameter >2.75 to <4 mm; target lesion stenosis >50 to <100%; non-calcified lesions; lesion length <15 mm requiring one stent of 11, 15 or 18 mm in length; patients aged over 21 years	Patients with ostial and bifurcation lesions; LVEF <30%; MI within 72 h; CVA or TIA <3 months; known hypersensitivity or contraindication to aspirin, stainless steel, contrast dye, heparin or ticlopidine; active peptic ulcer or upper GI bleeding; renal failure; liver disease; diabetes mellitus; life expectancy <12 months

TABLE 70 *New DES non-RCT outcomes*

Study	Interventions	Follow-up	ER	Mortality	AMI	TLR	TVR	BRR/LL[a]
ATLAS	Taxus Liberté, Boston	30 days	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	
EuroSTAR	CoStar (10 μg, 24–30 day elution PES), Biotronik 145	30 days 6 months 1 year	2/145 7/145 11/145	0/145 2/144 3/142	2/145 2/144 3/142	0/145 3/144 5/142 (assume no repeated Rx)		BRR: 5/149 lesions (in-stent) 7/149 lesions (in-segment) LL: 0.26 [0.39] (in-stent) 0.07 [0.38] (in-segment)
	CoStar (30 μg 24–30 day elution PES), Biotronik Arm II FU not complete							
CoSTAR I (India)	CoStar (10 μg bidirectional 10 day elution PES, Grp 3), Biotronik 40 (interim) 14 lesions	30 days 4 months	2/40 3/40	0/40 0/40	2/40 2/40	0/40 1/40; 1/57 lesions		BRR: 1/52 lesions (in-stent) 2/52 lesions (in-lesion) LL: 0.43 [0.43] (in-stent) 0.24 [0.39] (in-lesion)
	CoStar (30 μg multi-directional 30 day elution PES, Grp 1), Biotronik 10 (interim) 57 lesions	30 days 4 months	1/10 1/10	0/10 0/10	1/10 2/10	0/10 0/10; 0/14 lesions		BRR: 2/14 lesions (in-stent) 2/14 lesions (in-lesion) LL: 0.5 [0.74] (in-stent) 0.52 [0.66] (in-lesion)
DESIRE	Dexamet, Abbott	30 days 6 months	6/332 33/274	2/332 2/274	4/332 6/274		26/274	
EMPEROR (Pilot)	Dexamet (2.2 μg/mm^2), Abbott	30 days 6 months	0/30 0/30	0/30 0/30	0/30 0/30	0/30 1/30	0/30 1/30	
ISAR Project (1)	Yukon DES, KiWiMed	1 month 1 year	12/447	0/447	8/447	66/424 lesions		BRR: 59/424 lesions (in-stent) 72/424 (in-segment)

continued

TABLE 70 *New DES non-RCT outcomes (cont'd)*

Study	Interventions	Follow-up	ER	Mortality	AMI	TLR	TVR	BRR/LL[a]
	Yukon (non-loaded), KiWiMed	1 month 1 year	6/155	0/155	2/155	40/186 lesions		BRR: 35/147 lesions (in-stent) 38/147 lesions (in-segment) LL 0.95 [0.76] (lesions = 147)
JUPITER I (Alpha)	Janus CardoStent, Sorin 58	30 days 6 months	0/58	0/58 1/58 (non-cardiac)	0/58 0/57	0/58		
Patti	Dexamet (0.5 g/mm^2), Abbott	6 months	1/50		0/50	1/50	1/50	
	Non-eluting stent	6 months	6/50		1/50	5/50	6/50	
SAFE	Dexamet/Dexamet SV, Abbott	Not described	5/735	1/735		4/735 PCI	1/735 CABG	
STRIDE	Dexamet (0.5 μg/mm^2), Abbott	30 days 6 months	2/71 4/71	1/71 1/71	1/71 1/71	0/71 2/71		

[a] 'Lesions' indicates that reporting of BRR/LL is by lesion (rather than by patient).

Appendix 6

DES registries

DES Registries are listed in *Table 71*.

TABLE 71 *Data registries*

Registry name	DES	Data source	Progress	Sponsor	Available data	Primary focus
BRIDGE[147]	CYPHER or BMS *n* = 1000	France Sites = 100	Complete 2003	Cordis	Unclear	Diabetic patients
E-CYPHER[148–150]	CYPHER n ⩾ 15000	International Sites >275 4 UK sites (*n* = 424)	Target reached August 2004	Cordis	1 year (*n* = 10600)	Safety and reliability
GERMAN CYPHER REGISTRY[151–152]	CYPHER *n* = 5878	Germany Sites = 102	April 2002–present	Not stated	6 months	Monitor unexpected events
PORTO I, II[147]	CYPHER *n* = 300	Portugal Sites = 13	2003 – enrolment ongoing	Cordis	6 months	Non-diabetes/diabetic patients
LONG DES[153]	CYPHER *n* = 294 TAXUS *n* = 166 BMS *n* = 177	Korea Sites = 8	March 2003–February 2004	Cordis	8 months	In-stent restenosis
SAFE[154]	DEXAMET *n* = 1000	Europe, Middle East, Africa (25 countries) Sites = 80	2003	Abbott	Unknown	Clinical follow-up 1 and 6 months
RESEARCH[155–157]	SES *n* = 508 Non SES *n* = 663	The Netherlands Site = 1	Non-SES October 2001–April 2002 SES April 2002–October 2002	Cordis	1 year	Safety and efficacy of SES
SWISS HOSPITALS PROSPECTIVE REGISTRY[158]	SES *n* = 183	Switzerland Sites = 2	April 2002–September 2002	Not stated	7 months	

continued

TABLE 71 *Data registries (cont'd)*

Registry name	DES	Data source	Progress	Sponsor	Available data	Primary focus
ISAR PROJECT 1[96]	SES (Yukon DES) *n* = 602	Germany Sites = ?	Unclear	Bayerische Forschungsstiftung, Munich, Germany	1 year	Dose-ranging SES Angiographic restenosis rate
ARRIVE[159]	TAXUS *n* = 2586	USA Sites = 50	February 2004–May 2004	Boston Scientific	1 year	12-month site reported cardiac events
ARRIVE 2[160]	TAXUS *n* = 5000	USA Sites = ?	Currently enrolling	Boston Scientific		12-month site reported cardiac events
WISDOM[159,161]	TAXUS *n* = 778	International Countries = 9 Sites = 22	June 2002–July 2003	Boston Scientific	1 year	12-month site reported target lesion re-interventions
OLYMPIC[162]	TAXUS Liberté	International	Post-CE mark of stent	Boston Scientific	Enrolling	
MILESTONE II[159]	TAXUS SR *n* = 3688	International Countries = 32 Sites = 164	March 2003–March 2004	Boston Scientific	1 year	Real-world physician usage by lesion type and patient subset Safety High-risk Usage patterns
DESIRE[104]	Dexamethasone	320 Italy	Completed 2004	Abbott	6 months	ACS/NSTEMI patients
Registries where only limited information was identified						
REAL LIFE PB PACLITAXEL REGISTRY[163]	TAXUS SR					
T-SEARCH[164]	TAXUS *n* = 576	The Netherlands Site = 1	February 2003–September 2003	Not stated	1 year	Safety and efficacy of PES

continued

TABLE 71 *Data registries (cont'd)*

Registry name	DES	Data source	Progress	Sponsor	Available data	Primary focus
DESCOVER[148,165]	Consecutive PCI patients $n = 7500$	USA	Scheduled launch November 2004	Not stated	Not available	Also collecting QoL and economic data
DYNAMIC[148,166]	Consecutive PCI patients $n = 2690$	USA	4th wave DES early 2004	NHLBI	?1 year	
SHAKESPEARE REGISTRY[100]	Unclear	Europe				
SPANISH REGISTRY[101]	General	Spain				
EVASTENT[102]	SES	?France				
MULTI-CENTRE REGISTRY[103]	SES	Unknown				
MUST[105]	SES PES	Montreal				

Appendix 7

Details of included or excluded references

References for studies included in clinical review

Study	Reference for data source(s) (primary source/all sources)
C-SIRIUS	54 54, 83
DIABETES	55 55, 68
ENDEAVOR II	89/90 89, 90, 167, 168
E-SIRIUS	57 56, 57, 83
BASKET	82 82, 169
Li	79 –
Pache	53 –
RAVEL	31, 161
SCANDSTENT	67 31, 58–66, 84, 85
SES-SMART	70 69, 70
SIRIUS	71 66, 71–78
SPIRIT FIRST	32 32, 33
STRATEGY	80 80, 81

Study	Reference for data source(s) (primary source/all sources)
TAXUS I	34 34–36
TAXUS II	37 37–39
TAXUS IV	43 40–51, 86, 87
TAXUS V	88 52, 88
BASKET	82 –
CORPAL	114 –
DOMINO	119 –
ISAR-DIABETES	112 111–113
ISAR-TEST	118 –
REALITY	117 115–117
SIRTAX	110 107, 108, 110, 115, 116
TAXi	109 –

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Principal reason for exclusion	Reference
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Non-systematic review	Stanik-Hutt JA. Drug-coated stents: preventing restenosis in coronary artery disease. *J Cardiovasc Nur* 2004;**19**:404–8.
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continued

Principal reason for exclusion	Reference
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	Kettelkamp R, House J, Garg M, Stuart RS, Grantham A, Spertus J. Using the risk of restenosis as a guide to triaging patients between surgical and percutaneous coronary revascularization. *Circulation* 2004;**110**(11 Suppl):ii50–4.
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Non-TAR DES[a]	Costa RA, Lansky AJ, Mintz GS, Mehran R, Tsuchiya Y, Negoita M, *et al*. Angiographic results of the first human experience with everolimus-eluting stents for the treatment of coronary lesions (the FUTURE I trial). *Am J Cardiol* 2005;**95**:113–16.
	Serruys PW, Sianos G, Abizaid A, Aoki J, den Heijer P, Bonnier H, *et al*. The effect of variable dose and release kinetics on neointimal hyperplasia using a novel paclitaxel-eluting stent platform: the paclitaxel in-stent controlled elution study (PISCES). *J Am Coll Cardiol* 2005;**46**:253–60.
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Others: no outcome of interest, continuing to recruit, non-English language *and* unable to access	Tanabe K, Serruys PW, Degertekin M, Guagliumi G, Grube E, Chan C, *et al*. Chronic arterial responses to polymer-controlled paclitaxel-eluting stents – comparison with bare metal stents by serial intravascular ultrasound analyses: data from the randomized TAXUS-II trial. *Circulation* 2004;**109**:196–200.
	Anonymous. New study tests: ZOMAXX drug-eluting coronary stent. *Drug News Perspec* 2004;**17**:467.
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[a] Many records were excluded on the basis of information contained in title and/or abstract at the first stage of source selection, so are not listed in this table.

Appendix 8

Supplement to addendum

NICE Addendum project specification and assessment group response

Assessment group response (including statement of limitations) to original NICE project proposal

Task	Proposed work and limitations	Location of further analyses within Addendum (Page)
To consider the implications for the cost-effectiveness of DES of varying stent wastage rates.	A simple sensitivity analysis from 0% to 10% (around baseline value of 5%)	Introduction Wastage Rates (94)
To consider the implications for the cost-effectiveness of DES of uncertainty in the post-procedural disutility associated with PCI/CABG.	Best/worst case scenarios for PCI and DES, and 2-way combinations of these	Procedural disutility (94)
To consider the implications for the cost-effectiveness of DES of incorporating into the analysis the peri-procedural mortality risks associated with PCI/CABG when undertaken as repeat interventions following primary PCI.	Minor modification of model and/or analysis to allow alternate estimates to be generated. *Limitations:* availability of suitable and relevant data on mortality risks and life expectancy following repeat intervention	AMI and mortality – is there a case for a DES effect? (101)
To reassess evidence for and against differential AMI rates following DES and BMS, and consider the possible implications of such a difference for estimated costs, outcomes and the cost-effectiveness of DES.	Review of evidence that might support the use of differential AMI rates and exploration of the implications of such a difference for estimates of cost-effectiveness. *Limitations:* though efforts will be made to identify evidence, it will not be possible to carry out a systematic search for all potentially relevant sources for parameter values.	AMI and mortality – is there a case for a DES effect? (101)
To reassess evidence relevant to estimating realistic repeat revascularisation rates from unselected patient populations, and assess its suitability for estimating rates appropriate to current clinical practice in England and Wales.	Identify any additional sources of evidence, assess their quality and relevance, adjusting where possible for identifiable case-mix differences. Explore the results of using alternate estimates of repeat revascularisation rates in the model. *Limitations:* though efforts will be made to identify evidence, it will not be possible to carry out a systematic search for all potentially relevant sources. In addition, the scope for obtaining additional information from authors/custodians to ensure comparability will be severely limited. In particular, account can only be taken on Scottish Audit data if rapid access to this is obtained by NICE.	Realistic repeat revascularisation rates (107)

continued

Task	Proposed work and limitations	Location of further analyses within Addendum (Page)
To consider whether alternative published risk factor models could be employed in the analysis, and the implications of doing so for the cost-effectiveness of DES	Identify any additional sources of evidence, assess their quality and relevance, adjusting where possible for identifiable case-mix differences. Make minor modifications to the model and/or analysis to explore the implications alternate rates. *Limitations:* though efforts will be made to identify evidence, it will not be possible to carry out a systematic search for all potentially relevant sources, nor to obtain additional details from authors.	Risk factor models and sub-groups (108)
To carry out 2- or 3-way sensitivity analyses of major potential sources of uncertainty identified from the above tasks, including the influence of different values of the DES price premium.	Carry out sensitivity analyses with the current model (involving no more than minor amendments). *Limitations:* only selected sensitivity analyses can be undertaken in the time available.	Sensitivity analyses (117)

NICE project specification with location of assessment group further analyses

Specification summary	Details of specification and reference to additional analyses undertaken[a]
Synopsis of the technical issue	At the Appraisal Committee meeting to discuss the development of the Appraisal Consultation Document, a number of issues with the economic evaluation were raised. Most notably: • The Appraisal Committee was aware that no statistically significant differences for mortality or morbidity were found in the trials for DES versus BMS; however, the Committee was mindful that although the trial data showed no statistical significance, there was a difference in AMI in favour of DES and that this should be taken account of in the economic evaluation. The Committee was also mindful of data in the literature regarding mortality and morbidity of CABG and repeat angiography. See section AMI and Mortality – is there a case for a DES effect? (101) • After reviewing the utility values in the Assessment Group's model, the Committee was mindful of the possibility that there could be an additional disutility associated with CABG during the initial 6 weeks following the procedure compared with PCI. See Procedural disutility (94) • The Committee was persuaded that neither the Liverpool (CTC) and the Leicester registry data nor the RCT data were representative of repeat revascularisation rates in patients and as the BASKET trial and the Scottish Registry data had used methods that were likely to collect follow-up data from all patients, these data would therefore be more representative. See Overview (92) • The Committee heard that there was no consensus in the trials or registries regarding which risk factors would put an individual at a high risk of revascularisation. They were persuaded that the Assessment Group's risk factors used in the current assessment report, based on the CTC registry data, were one possibility; however, risk factors which had been used in the previous appraisal should also be included in the current model. The Committee also heard that diabetes should be considered as an independent risk factor for restenosis too. See Overview (92), Risk factor models (108) • The Committee discussed the significance of the price premium (difference between DES and BMS price) and were mindful of the possibility that the price premium used in the Assessment Group's model was possibly too high (£560), given the procurement deals that took place in certain areas that brought the price premium down to less than £300. See Sensitivity analysis (117) As a result of these points, further work was requested to be undertaken.

continued

Specification summary	Details of specification and reference to additional analyses undertaken[a]
Question(s) to be answered by the Assessment Group	What is the cost-effectiveness of DES in the treatment of ischaemic heart disease? The base case scenario should be updated and if data allows should include: • The risk of AMI. See AMI and mortality (101) • The mortality risk associated with CABG. See AMI and mortality (101) • The mortality risk associated with angiography. See AMI and mortality (101) • The disutilities associated with CABG versus PCI immediately (in the 6-week period) following the procedure. See Procedural disutility (94) • The absolute risk of revascularisation of BMS taken from the Scottish registry data. See Overview (92) • The relative risks of the independent risk factors (small vessel and long lesion) taken from the trials. See Overview (92), Realistic report revascularisation rates (107), Risk factor models (108) • If it is identified from the clinical evidence to be an independent risk factor, diabetes as another risk factor. See Risk factor models (108) Sensitivity analysis should be carried out on the above estimates if appropriate and around: • The price premium ranging from £255 (based on a cost used in Scotland) to £1000 (list price) for stents. See Sensitivity analysis (117) • The stent wastage rates at 1% and 5%. See Wastage rates (94)
How will these questions be addressed in an addendum?	The Assessment Group will be asked to: • Identify data in the literature regarding mortality and morbidity of CABG and repeat revascularisation. See Overview (92) • Identify additional utility values in the first 6 weeks following CABG or PCI. See Procedural disutility (94) • Identify the parameter values for the base case scenario accordingly using data from the Scottish registry for absolute risks, relative risks for the two subgroups (small vessels and long lesions) from the trial data, additional utility values and price premium. See Risk factor models (108), Sensitivity analysis (117) • Identify from the literature and review whether diabetes is an independent risk factor for restenosis. See Risk factor models (108) • Develop a model, containing these new parameters with an appropriate time horizon, for example 12 months. See Sensitivity analysis (117) • Synthesise the available information and calculate the degree of uncertainty around the cost effectiveness estimate using sensitivity analysis. See Sensitivity analysis (117)
Relevant new evidence requested	• Data in literature regarding mortality and morbidity of CABG and angiography. • Data on absolute risk of revascularisation from the Scottish registry data. • Clinical evidence regarding whether diabetes is an independent risk factor for restenosis.

[a] Specification text taken (unedited) from http://www.nice.org.uk/page.aspx?o=293164. Reference to location of further analyses as for the original Addendum.

Supplementary sensitivity analysis tables

Addendum supplement overview

This supplement provides additional information to aid in consideration of the cost-effectiveness of DES compared with conventional stents (BMS) in the context of the NHS in England and Wales. The main tables show results for specific patient groups, defined by the type of hospital admission and number of stents implanted, in each case covering a wide range of possible values for the absolute risk of repeat intervention within 12 months and the additional cost per stent (price premium) for DES compared with BMS. In each case an overview of the information in the table is also provided in graphical form.

In addition, an initial descriptive table is also included to assist in relating the three conventional risk factors most commonly explored in the clinical trials to the level of absolute risk used in the main tables. Thus, a particular combination of risk factors can be selected, and the corresponding absolute risk and average number of stents read from this table, before locating cost-effectiveness results for this combination of values in the main tables.

Explanatory notes

Initial descriptive Addendum Appendix Table 72

1. The descriptive table has been prepared using CTC Liverpool audit patient-level data and the multivariate model using conventional factors described in the Addendum in Chapter 8. This is necessary as no equivalent individual patient data unselected dataset is currently available to LRiG on which the required analysis could be performed. Readers should bear in mind that none of the three factors in this multivariate model achieved conventional significance so that the individual relative risks have wide CIs and should be considered as only illustrative.
2. Results for absolute risks and average numbers of stents are simple unadjusted means for all relevant patients. Minor differences from figures previously published are due to the exclusion of some non-elective patients not considered eligible for this review (those for whom PCI was primary treatment for AMI), and to bias adjustments required to previous estimates which made use of non-linear regression techniques.
3. Subgroups are ordered by increasing size of the relative and absolute risks. The average risks obtained in CTC data set are shown as an additional bold column (marked **Base case** underneath) for information.

Addendum appendix Tables 73–80 *and* Figures 25–32

4. The tables have been prepared on the basis of the adjustments identified in the Addendum:
   (a) stent wastage rates of 1%
   (b) alternate disutility estimates for PCI (0.00304 per patient) and CABG (0.03808)
   (c) adjustments, for reduced numbers of non-fatal AMIs, to costs (saving of £13 per patient) and utility (gain of 0.00055 per patient) when DES are used.
5. For *Tables 73* and *77*, the mean number of stents used and the mean repeat intervention rate for the whole patient group are used. However, in *Tables 74–76* and *78–80*, the emboldened absolute risks are calculated specifically for the subgroups of CTC patients in whom one, two and three or more index stents were deployed.
6. The threshold premium in the final column of the tables is the maximum value of the price premium which would yield an ICER of £30,000 per QALY gained or less.
7. The final row shows the effect on estimated cost-effectiveness for the base case of including a direct benefit from reduced mortality associated with performing repeat interventions. These calculations are made on the following assumptions:
   (a) average CTC proportions of reinterventions by CABG apply (9.0% elective, 17.9% non-elective)
   (b) additional mean life expectancy for patients surviving without reintervention of 10 years
   (c) mean utility value of patients in such additional life-years of 0.66.

   It should be borne in mind that this adjustment depends upon a strong presumption of effect for which there is no direct evidence. It is the Assessment Group's view that such an adjustment is unwarranted and probably involves 'double counting' of deaths already included in aggregate trial results.
8. *Figures 25–32* are displayed for the full range of values for absolute risk shown in *Table 72*. Points on each line which correspond to the base case risk value are picked out with grey shading.

TABLE 72 *Parameter values for risk-based subgroups, derived from CTC Liverpool audit data*

Conventional risk factors							Reintervention rate at 12 months (%)								
							Absolute risk								
Long lesion	Small vessel	Diabetes	Share of elective case load (%)	Mean stents used	LCL	UCL	Relative risk	6%	7%	7.43%	8%	9%	10%	11%	12%	13%
Elective patients																
No	No	No	59.7	1.54	1.49	1.58	1.00	5.3	6.1	**6.5**	7.0	7.9	8.8	9.7	10.5	11.4
Yes	No	No	22.5	1.63	1.55	1.72	1.20	6.3	7.4	**7.8**	8.4	9.5	10.5	11.6	12.6	13.7
No	No	Yes	8.5	1.56	1.43	1.69	1.38	7.3	8.5	**9.0**	9.7	10.9	12.1	13.3	14.5	15.8
No	Yes	No	3.8	2.3	2.11	2.48	1.52	8.0	9.3	**9.9**	10.7	12.0	13.3	14.7	16.0	17.4
Yes	No	Yes	4.0	1.72	1.52	1.91	1.66	8.7	10.2	**10.8**	11.6	13.1	14.5	16.0	17.5	18.9
Yes	Yes	No	0.9	2.53	2.19	2.87	1.82	9.6	11.2	**11.9**	12.8	14.4	16.0	17.6	19.2	20.8
No	Yes	Yes	0.6	2.67	2.23	3.11	2.10	11.1	12.9	**13.7**	14.7	16.6	18.4	20.3	22.1	23.9
Yes	Yes	Yes	0.1	3.00	NE	NE	2.52	13.3	15.5	**16.4**	17.7	19.9	22.1	24.3	26.5	28.7
Overall			100.0	1.615	1.580	1.650				**Base case**						
Patients affected by factor																
27.4	5.4	13.2														
								8%	**9%**	**10.04%**	**11%**	**12%**	**13%**	**14%**	**15%**	**16%**
Non-elective patients																
No	No	Yes	8.0	1.52	1.34	1.69	0.90	6.5	7.3	**8.2**	9.0	9.8	10.6	11.4	12.2	13.0
No	No	No	60.1	1.43	1.37	1.50	1.00	7.2	8.1	**9.1**	10.0	10.9	11.8	12.7	13.6	14.5
Yes	No	Yes	4.5	1.54	1.29	1.79	1.07	7.8	8.7	**9.7**	10.7	11.6	12.6	13.6	14.5	15.5
Yes	No	No	23.7	1.42	1.33	1.52	1.19	8.6	9.7	**10.8**	11.9	12.9	14.0	15.1	16.2	17.2
No	Yes	Yes	0.2	2.00	NE	NE	2.36	17.1	19.2	**21.4**	23.5	25.6	27.8	29.9	32.0	34.2
No	Yes	No	2.5	2.00	1.51	2.49	2.62	19.0	21.4	**23.8**	26.1	28.5	30.8	33.2	35.6	38.0
Yes	Yes	Yes	0.2	2.00	NE	NE	2.81	20.3	22.9	**25.5**	27.9	30.5	33.0	35.6	38.1	40.7
Yes	Yes	No	0.7	2.50	1.40	3.60	3.12	22.6	25.4	**28.3**	31.1	33.9	36.7	39.5	42.3	45.2
Overall			100.0	1.467	1.415	1.518				**Base case**						
Patients affected by factor																
29.1	3.7	12.9														

NE, not estimatable, LCL, lower confidence limit; UCL, upper confidence limit.

TABLE 73 *All elective patients, using mean number of stents implanted (1.615 stent per patient)*

Absolute risk (%)	Incremental utility	Incremental cost by levels of price premium (£)								Incremental cost per QALY by levels of price premium (£)								Threshold premium (£30,000) (£)
		£100	£200	£300	£400	£500	£600	£700	£800	£100	£200	£300	£400	£500	£600	£700	£800	
4	0.00162	89	250	412	573	735	896	1,057	1,219	55,000	154,800	254,700	354,500	454,400	554,200	654,100	753,900	76
5	0.00188	74	235	396	557	718	879	1,040	1,201	39,000	124,500	210,000	295,500	381,000	466,500	552,000	637,500	90
6	0.00215	58	219	379	540	701	861	1,022	1,182	**27,100**	101,800	176,400	251,100	325,800	400,500	475,200	549,900	105
7	0.00242	43	203	363	523	684	844	1,004	1,164	**17,700**	84,000	150,300	216,600	282,800	349,100	415,400	481,700	120
7.43	0.00253	36	196	356	516	676	836	996	1,156	**14,300**	77,500	140,700	203,900	267,100	330,200	393,400	456,600	149
8	0.00268	28	187	347	507	667	826	986	1,146	**10,300**	69,800	129,300	188,900	248,400	307,900	367,500	427,000	126
9	0.00295	12	172	331	490	650	809	968	1,128	**4,200**	58,200	112,200	166,200	220,200	274,200	328,200	382,200	134
10	0.00322	–3	156	315	474	633	791	950	1,109	**–1,000**	48,400	97,800	147,200	196,600	246,000	295,400	344,800	164
11	0.00348	–18	140	299	457	616	774	933	1,091	**–5,300**	40,200	85,700	131,200	176,700	222,200	267,700	313,200	179
12	0.00375	–34	124	282	440	599	757	915	1,073	**–9,000**	33,200	75,300	117,500	159,600	201,700	243,900	286,000	194
13	0.00402	–49	109	266	424	582	739	897	1,054	**–12,200**	**27,000**	66,300	105,500	144,800	184,000	223,300	262,500	210
14	0.00428	–64	93	250	407	565	722	879	1,036	**–15,000**	**21,700**	58,400	95,100	131,800	168,500	205,200	241,900	225
15	0.00455	–80	77	234	391	548	704	861	1,018	**–17,500**	**17,000**	51,400	85,900	120,300	154,800	189,200	223,700	240
16	0.00482	–95	61	218	374	531	687	843	1,000	**–19,700**	**12,700**	45,200	77,700	110,100	142,600	175,100	207,500	256
17	0.00508	–110	46	202	358	514	669	825	981	**–21,700**	**9,000**	39,700	70,300	101,000	131,700	162,400	193,000	271
18	0.00535	–126	30	185	341	497	652	808	963	**–23,500**	**5,600**	34,700	63,700	92,800	121,900	150,900	180,000	287
19	0.00562	–141	14	169	324	480	635	790	945	**–25,100**	**2,500**	30,100	57,800	85,400	113,000	140,600	168,200	302
20	0.00588	–156	–2	153	308	463	617	772	927	**–26,600**	**–300**	**26,000**	52,300	78,600	104,900	131,200	157,500	318
21	0.00615	–172	–17	137	291	446	600	754	908	**–27,900**	**–2,800**	**22,300**	47,400	72,400	97,500	122,600	147,700	334
22	0.00642	–187	–33	121	275	429	582	736	890	**–29,100**	**–5,100**	**18,800**	42,800	66,800	90,700	114,700	138,700	350
23	0.00668	–202	–49	105	258	411	565	718	872	**–30,300**	**–7,300**	**15,700**	38,600	61,600	84,500	107,500	130,400	366
24	0.00695	–218	–65	88	241	394	547	701	854	**–31,300**	**–9,300**	**12,700**	34,700	56,800	78,800	100,800	122,800	382
25	0.00722	–233	–80	72	225	377	530	683	835	**–32,300**	**–11,100**	**10,000**	31,200	52,300	73,400	94,600	115,700	398
26	0.00748	–248	–96	56	208	360	513	665	817	**–33,200**	**–12,800**	**7,500**	**27,800**	48,200	68,500	88,800	109,200	415
27	0.00775	–263	–112	40	192	343	495	647	799	**–34,000**	**–14,400**	**5,200**	**24,700**	44,300	63,900	83,500	103,000	431
28	0.00802	–279	–127	24	175	326	478	629	780	**–34,800**	**–15,900**	**3,000**	**21,800**	40,700	59,600	78,500	97,300	448
29	0.00828	–294	–143	8	159	309	460	611	762	**–35,500**	**–17,300**	**900**	**19,100**	37,400	55,600	73,800	92,000	464
With procedural mortality estimate																		
7.43	0.00381	36	196	356	516	676	836	996	1,156	**9,500**	51,500	93,500	135,500	177,500	219,500	261,500	303,500	174

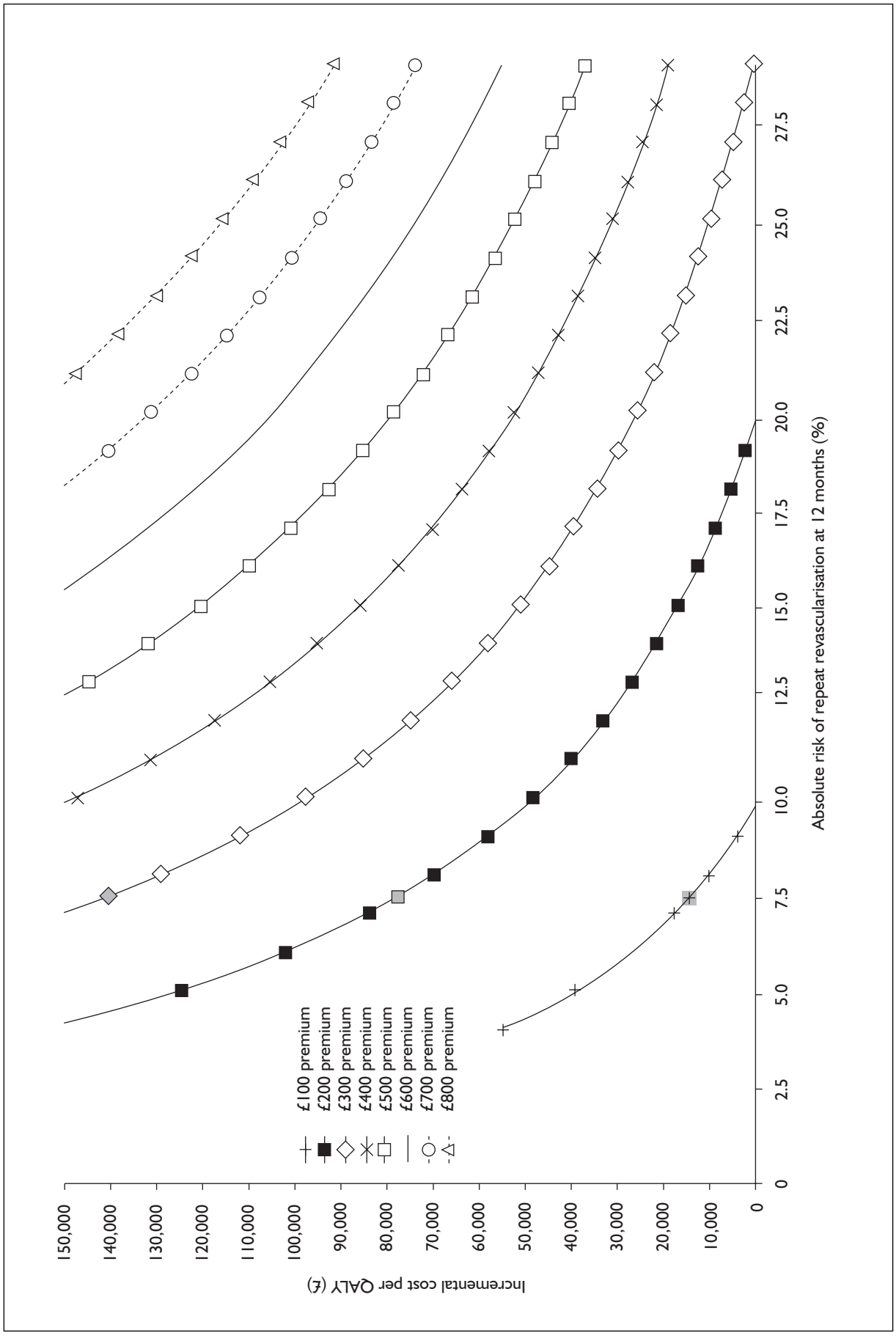

FIGURE 25 *All elective patients, using mean number of stents implanted*

TABLE 74 *Elective patients receiving a single stent*

Absolute risk (%)	Incremental utility	Incremental cost by levels of price premium (£)								Incremental cost per QALY by levels of price premium (£)								Threshold premium (£30,000) (£)
		£100	£200	£300	£400	£500	£600	£700	£800	£100	£200	£300	£400	£500	£600	£700	£800	
4	0.00162	27	126	225	325	424	523	623	722	**16,500**	78,000	139,400	200,800	262,200	323,700	385,100	446,500	123
5	0.00188	11	110	209	308	407	506	605	704	**6,100**	58,600	111,100	163,600	216,100	268,600	321,100	373,600	147
5.53	0.00202	3	102	201	299	398	497	595	694	**1,600**	50,400	99,100	147,800	196,500	245,300	294,000	342,700	160
6	0.00215	–4	95	193	292	390	488	587	685	**–1,800**	44,000	89,800	135,600	181,400	227,200	273,000	318,800	171
7	0.00242	–19	79	177	275	373	471	569	667	**–8,000**	32,600	73,200	113,700	154,300	194,900	235,500	276,000	195
8	0.00268	–35	63	161	258	356	454	551	649	**–12,900**	**23,500**	59,900	96,300	132,600	169,000	205,400	241,800	220
9	0.00295	–50	47	145	242	339	436	533	631	**–16,900**	**16,000**	49,000	81,900	114,900	147,800	180,800	213,700	245
10	0.00322	–65	32	128	225	322	419	516	612	**–20,300**	**9,800**	39,900	70,000	100,100	130,200	160,300	190,300	270
11	0.00348	–81	16	112	209	305	401	498	594	**–23,100**	**4,600**	32,200	59,900	87,500	115,200	142,900	170,500	295
12	0.00375	–96	0	96	192	288	384	480	576	**–25,600**	**0**	**25,600**	51,200	76,800	102,400	127,900	153,500	320
13	0.00402	–111	–16	80	175	271	366	462	557	**–27,700**	**–3,900**	**19,900**	43,700	67,400	91,200	115,000	138,800	346
14	0.00428	–126	–31	64	159	254	349	444	539	**–29,500**	**–7,300**	**14,900**	37,100	59,300	81,500	103,700	125,900	372
15	0.00455	–142	–47	48	142	237	332	426	521	**–31,200**	**–10,400**	**10,500**	31,300	52,100	72,900	93,700	114,500	398
16	0.00482	–157	–63	31	126	220	314	408	503	**–32,600**	**–13,000**	**6,500**	**26,100**	45,700	65,200	84,800	104,400	424
17	0.00508	–172	–79	15	109	203	297	391	484	**–33,900**	**–15,500**	**3,000**	**21,500**	39,900	58,400	76,800	95,300	451
18	0.00535	–188	–94	–1	93	186	279	373	466	**–35,100**	**–17,600**	**–200**	**17,300**	34,700	52,200	69,700	87,100	478
19	0.00562	–203	–110	–17	76	169	262	355	448	**–36,100**	**–19,600**	**–3,000**	**13,500**	30,100	46,600	63,200	79,700	505
20	0.00588	–218	–126	–33	59	152	244	337	430	**–37,100**	**–21,400**	**–5,600**	**10,100**	**25,800**	41,500	57,300	73,000	532
21	0.00615	–234	–142	–49	43	135	227	319	411	**–38,000**	**–23,000**	**–8,000**	**7,000**	**21,900**	36,900	51,900	66,900	559
22	0.00642	–249	–157	–66	26	118	210	301	393	**–38,800**	**–24,500**	**–10,200**	**4,100**	**18,400**	32,700	47,000	61,300	587
23	0.00668	–264	–173	–82	10	101	192	283	375	**–39,500**	**–25,900**	**–12,200**	**1,400**	**15,100**	**28,800**	42,400	56,100	615
24	0.00695	–280	–189	–98	–7	84	175	266	357	**–40,200**	**–27,200**	**–14,100**	**–1,000**	**12,100**	**25,100**	38,200	51,300	644
25	0.00722	–295	–205	–114	–24	67	157	248	338	**–40,900**	**–28,300**	**–15,800**	**–3,300**	**9,300**	**21,800**	34,300	46,900	672
26	0.00748	–310	–220	–130	–40	50	140	230	320	**–41,500**	**–29,400**	**–17,400**	**–5,400**	**6,700**	**18,700**	30,700	42,800	701
27	0.00775	–326	–236	–146	–57	33	122	212	302	**–42,000**	**–30,400**	**–18,900**	**–7,300**	**4,200**	**15,800**	**27,400**	38,900	730
28	0.00802	–341	–252	–163	–73	16	105	194	283	**–42,500**	**–31,400**	**–20,300**	**–9,100**	**2,000**	**13,100**	**24,200**	35,400	759
29	0.00828	–356	–267	–179	–90	–1	88	176	265	**–43,000**	–32,300	**–21,600**	**–10,900**	**–100**	**10,600**	**21,300**	32,000	789
With procedural mortality estimate																		
5.53	0.00298	3	102	201	299	398	497	595	694	**1,100**	34,300	67,400	100,600	133,800	166,900	200,100	233,300	189

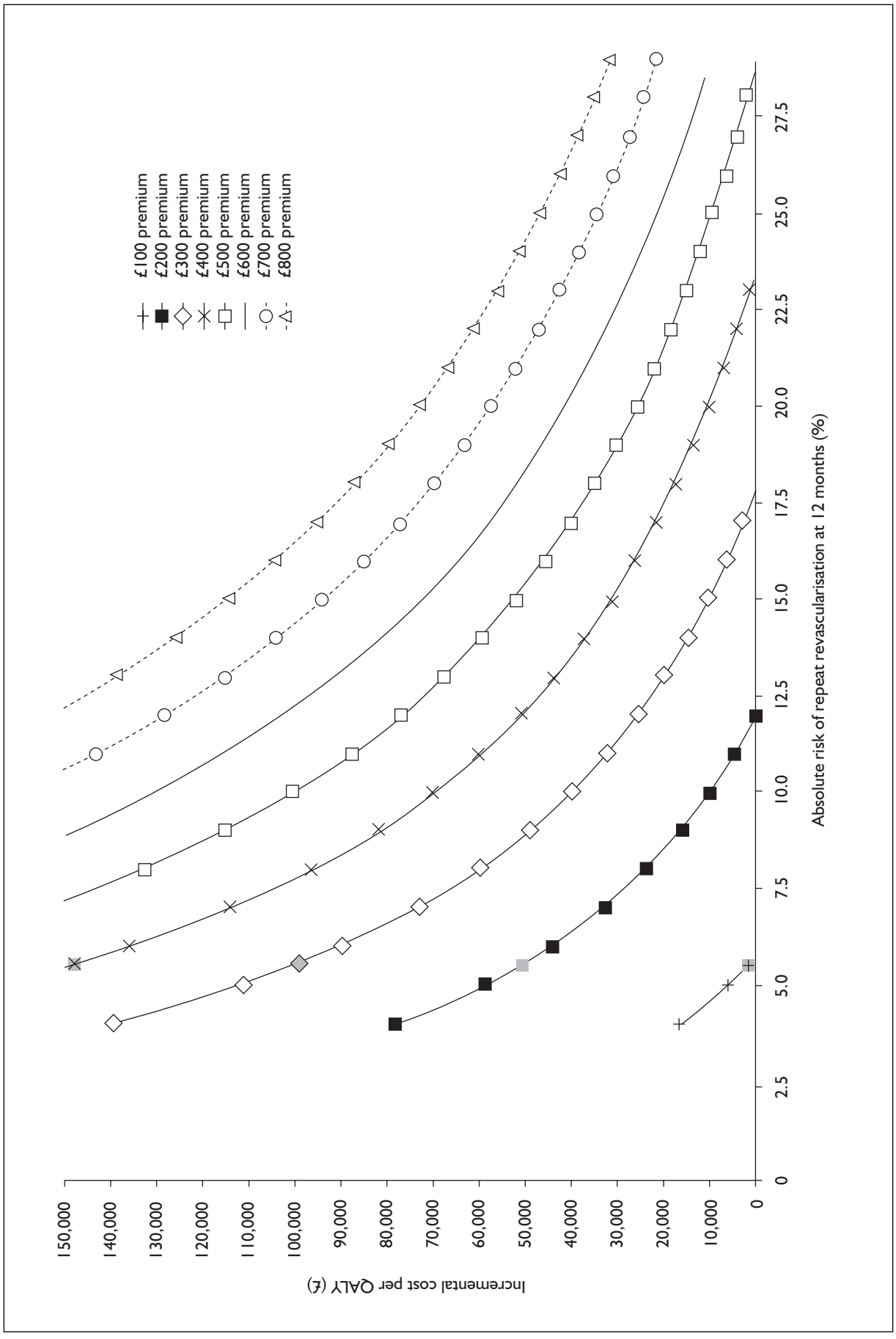

FIGURE 26 *Elective patients receiving a single stent*

TABLE 75 *Elective patients receiving two stents*

Absolute risk (%)	Incremental utility	Incremental cost by levels of price premium (£)								Incremental cost per QALY by levels of price premium (£)								Threshold premium (£30,000) (£)
		£100	£200	£300	£400	£500	£600	£700	£800	£100	£200	£300	£400	£500	£600	£700	£800	
4	0.00162	128	328	528	729	929	1,129	1,330	1,530	79,000	202,900	326,800	450,700	574,600	698,500	822,400	946,300	61
5	0.00188	112	312	512	712	912	1,112	1,312	1,512	59,700	165,800	271,900	378,100	484,200	590,300	696,500	802,600	73
6	0.00215	97	297	496	696	895	1,094	1,294	1,493	45,200	137,900	230,700	323,500	416,200	509,000	601,800	694,500	85
7	0.00242	82	281	480	679	878	1,077	1,276	1,475	33,800	116,200	198,600	280,900	363,300	445,600	528,000	610,300	96
8	0.00268	66	265	464	662	861	1,060	1,258	1,457	**24,800**	98,800	172,800	246,800	320,800	394,800	468,900	542,900	108
9	0.00295	51	249	448	646	844	1,042	1,240	1,439	**17,300**	84,500	151,700	218,900	286,100	353,200	420,400	487,600	120
10	0.00322	36	234	431	629	827	1,025	1,223	1,420	**11,100**	72,600	134,100	195,600	257,100	318,500	380,000	441,500	132
10.06	0.00323	35	233	430	628	826	1,024	1,221	1,419	**10,800**	71,900	133,100	194,200	255,300	316,500	377,600	438,800	133
11	0.00348	20	218	415	613	810	1,007	1,205	1,402	**5,900**	62,500	119,200	175,800	232,500	289,200	345,800	402,500	144
12	0.00375	5	202	399	596	793	990	1,187	1,384	**1,400**	53,900	106,400	158,900	211,400	263,900	316,500	369,000	156
13	0.00402	–10	186	383	579	776	972	1,169	1,365	**–2,500**	46,400	95,300	144,200	193,200	242,100	291,000	339,900	168
14	0.00428	–25	171	367	563	759	955	1,151	1,347	**–5,900**	39,800	85,600	131,400	177,200	222,900	268,700	314,500	180
15	0.00455	–41	155	351	546	742	938	1,133	1,329	**–9,000**	34,000	77,000	120,000	163,000	206,000	249,100	292,100	193
16	0.00482	–56	139	334	530	725	920	1,115	1,311	**–11,600**	**28,900**	69,400	110,000	150,500	191,000	231,600	272,100	205
17	0.00508	–71	123	318	513	708	903	1,098	1,292	**–14,000**	**24,300**	62,600	100,900	139,200	177,600	215,900	254,200	217
18	0.00535	–87	108	302	497	691	885	1,080	1,274	**–16,200**	**20,100**	56,500	92,800	129,100	165,500	201,800	238,100	229
19	0.00562	–102	92	286	480	674	868	1,062	1,256	**–18,200**	**16,400**	50,900	85,400	120,000	154,500	189,000	223,600	242
20	0.00588	–117	76	270	463	657	850	1,044	1,238	**–19,900**	**13,000**	45,800	78,700	111,600	144,500	177,400	210,300	254
21	0.00615	–133	60	254	447	640	833	1,026	1,219	**–21,600**	**9,800**	41,200	72,600	104,000	135,400	166,800	198,200	267
22	0.00642	–148	45	237	430	623	816	1,008	1,201	**–23,100**	**7,000**	37,000	67,000	97,100	127,100	157,100	187,200	279
23	0.00668	–163	29	221	414	606	798	990	1,183	**–24,400**	**4,300**	33,100	61,900	90,600	119,400	148,200	177,000	292
24	0.00695	–179	13	205	397	589	781	973	1,165	**–25,700**	**1,900**	**29,500**	57,100	84,700	112,300	139,900	167,500	305
25	0.00722	–194	–3	189	380	572	763	955	1,146	**–26,900**	**–300**	**26,200**	52,700	79,200	105,800	132,300	158,800	318
26	0.00748	–209	–18	173	364	555	746	937	1,128	**–28,000**	**–2,400**	**23,100**	48,600	74,100	99,700	125,200	150,700	330
27	0.00775	–225	–34	157	347	538	728	919	1,110	**–29,000**	**–4,400**	**20,200**	44,800	69,400	94,000	118,600	143,200	343
28	0.00802	–240	–50	140	331	521	711	901	1,091	**–29,900**	**–6,200**	**17,500**	41,200	65,000	88,700	112,400	136,100	356
29	0.00828	–255	–65	124	314	504	694	883	1,073	**–30,800**	**–7,900**	**15,000**	37,900	60,800	83,700	106,600	129,500	369
With procedural mortality estimate																		
10.06	0.00496	35	233	430	628	826	1,024	1,221	1,419	**7,000**	46,900	86,700	126,500	166,400	206,200	246,100	285,900	159

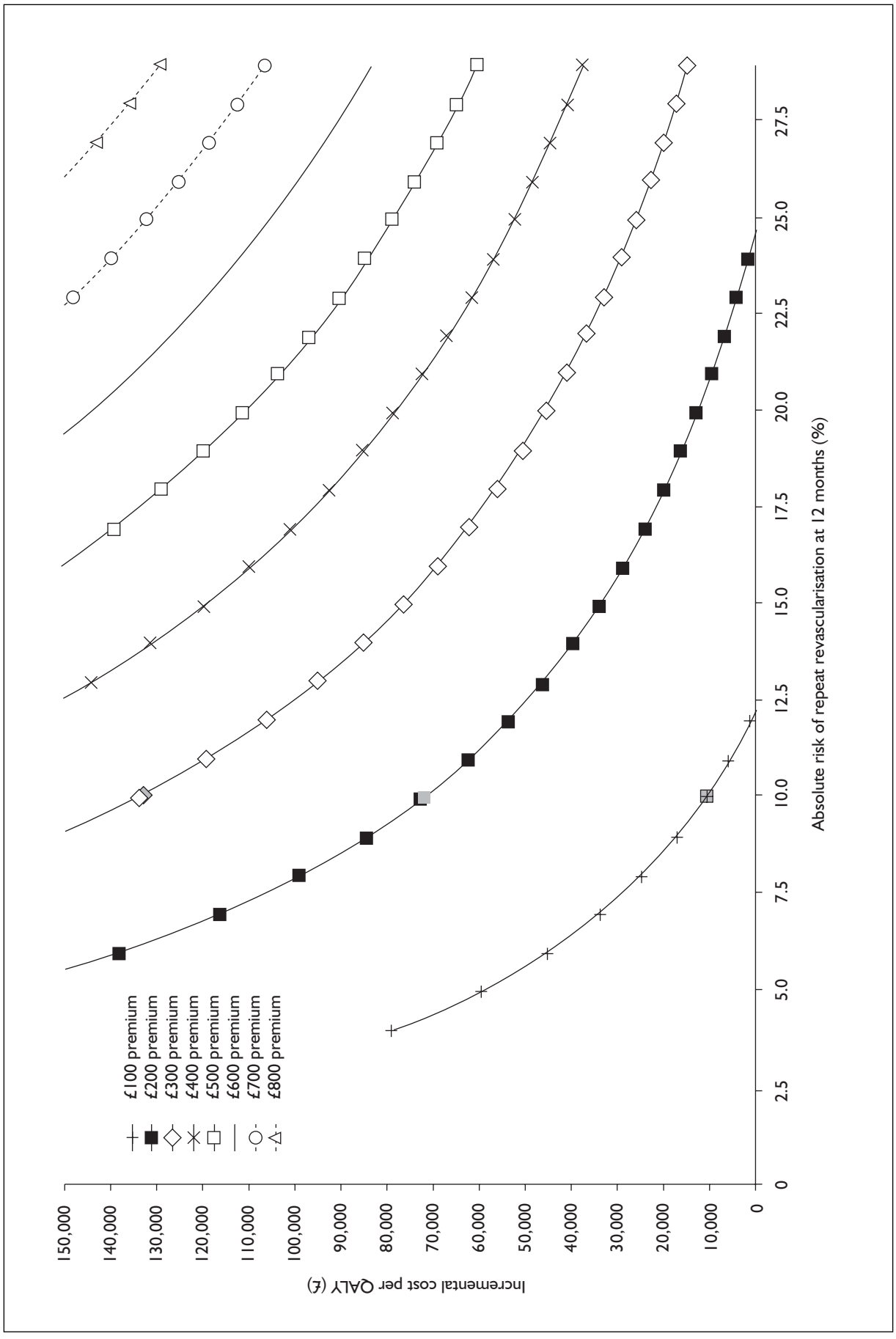

FIGURE 27 *Elective patients receiving two stents*

TABLE 76 *Elective patients receiving three stents*

Absolute risk (%)	Incremental utility	Incremental cost by levels of price premium (£)								Incremental cost per QALY by levels of price premium (£)								Threshold premium (£30,000) (£)
		£100	£200	£300	£400	£500	£600	£700	£800	£100	£200	£300	£400	£500	£600	£700	£800	
4	0.00162	229	530	831	1,133	1,434	1,735	2,037	2,338	141,500	327,800	514,200	700,600	886,900	1,073,300	1,259,700	1,446,000	41
5	0.00188	213	514	815	1,116	1,417	1,718	2,019	2,320	113,300	273,100	432,800	592,600	752,300	912,100	1,071,800	1,231,600	48
6	0.00215	198	499	799	1,100	1,400	1,700	2,001	2,301	92,100	231,900	371,600	511,400	651,100	790,800	930,600	1,070,300	56
7	0.00242	183	483	783	1,083	1,383	1,683	1,983	2,283	75,600	199,800	323,900	448,100	572,200	696,400	820,500	944,700	64
8	0.00268	167	467	767	1,066	1,366	1,666	1,965	2,265	62,400	174,100	285,700	397,400	509,000	620,700	732,300	844,000	72
9	0.00295	152	451	751	1,050	1,349	1,648	1,947	2,247	51,600	153,000	254,400	355,800	457,200	558,700	660,100	761,500	80
9.20	0.00300	149	448	747	1,046	1,346	1,645	1,944	2,243	49,600	149,200	248,800	348,400	448,000	547,600	647,200	746,700	81
10	0.00322	137	436	734	1,033	1,332	1,631	1,930	2,228	42,500	135,400	228,300	321,200	414,000	506,900	599,800	692,700	87
11	0.00348	121	420	718	1,017	1,315	1,613	1,912	2,210	34,900	120,500	206,200	291,800	377,500	463,100	548,800	634,400	95
12	0.00375	106	404	702	1,000	1,298	1,596	1,894	2,192	**28,300**	107,800	187,200	266,600	346,100	425,500	505,000	584,400	103
13	0.00402	91	388	686	983	1,281	1,578	1,876	2,173	**22,600**	96,700	170,700	244,800	318,900	392,900	467,000	541,100	111
14	0.00428	76	373	670	967	1,264	1,561	1,858	2,155	**17,600**	87,000	156,300	225,700	295,100	364,400	433,800	503,100	119
15	0.00455	60	357	654	950	1,247	1,544	1,840	2,137	**13,200**	78,400	143,600	208,800	274,000	339,200	404,400	469,600	127
16	0.00482	45	341	637	934	1,230	1,526	1,822	2,119	**9,300**	70,800	132,300	193,800	255,300	316,800	378,300	439,800	135
17	0.00508	30	325	621	917	1,213	1,509	1,805	2,100	**5,800**	64,000	122,200	180,400	238,600	296,800	355,000	413,200	143
18	0.00535	14	310	605	901	1,196	1,491	1,787	2,082	**2,700**	57,900	113,100	168,300	223,500	278,700	333,900	389,200	151
19	0.00562	−1	294	589	884	1,179	1,474	1,769	2,064	**−200**	52,300	104,800	157,400	209,900	262,400	314,900	367,400	159
20	0.00588	−16	278	573	867	1,162	1,456	1,751	2,046	**−2,800**	47,300	97,300	147,400	197,500	247,500	297,600	347,700	167
21	0.00615	−32	262	557	851	1,145	1,439	1,733	2,027	**−5,200**	42,700	90,500	138,300	186,100	234,000	281,800	329,600	175
22	0.00642	−47	247	540	834	1,128	1,422	1,715	2,009	**−7,300**	38,400	84,200	130,000	175,800	221,500	267,300	313,100	183
23	0.00668	−62	231	524	818	1,111	1,404	1,697	1,991	**−9,300**	34,600	78,400	122,300	166,200	210,100	254,000	297,800	192
24	0.00695	−78	215	508	801	1,094	1,387	1,680	1,973	**−11,200**	31,000	73,100	115,200	157,400	199,500	241,700	283,800	200
25	0.00722	−93	199	492	784	1,077	1,369	1,662	1,954	**−12,900**	**27,600**	68,200	108,700	149,200	189,700	230,300	270,800	208
26	0.00748	−108	184	476	768	1,060	1,352	1,644	1,936	**−14,500**	**24,600**	63,600	102,600	141,600	180,600	219,700	258,700	216
27	0.00775	−124	168	460	751	1,043	1,334	1,626	1,918	**−15,900**	**21,700**	59,300	96,900	134,600	172,200	209,800	247,400	224
28	0.00802	−139	152	443	735	1,026	1,317	1,608	1,899	**−17,300**	**19,000**	55,300	91,600	128,000	164,300	200,600	236,900	233
29	0.00828	−154	137	427	718	1,009	1,300	1,590	1,881	**−18,600**	**16,500**	51,600	86,700	121,800	156,900	192,000	227,100	241
With procedural mortality estimate																		
9.2	0.00458	149	448	747	1,046	1,346	1,645	1,944	2,243	32,500	97,800	163,000	228,300	293,500	358,800	424,000	489,200	97

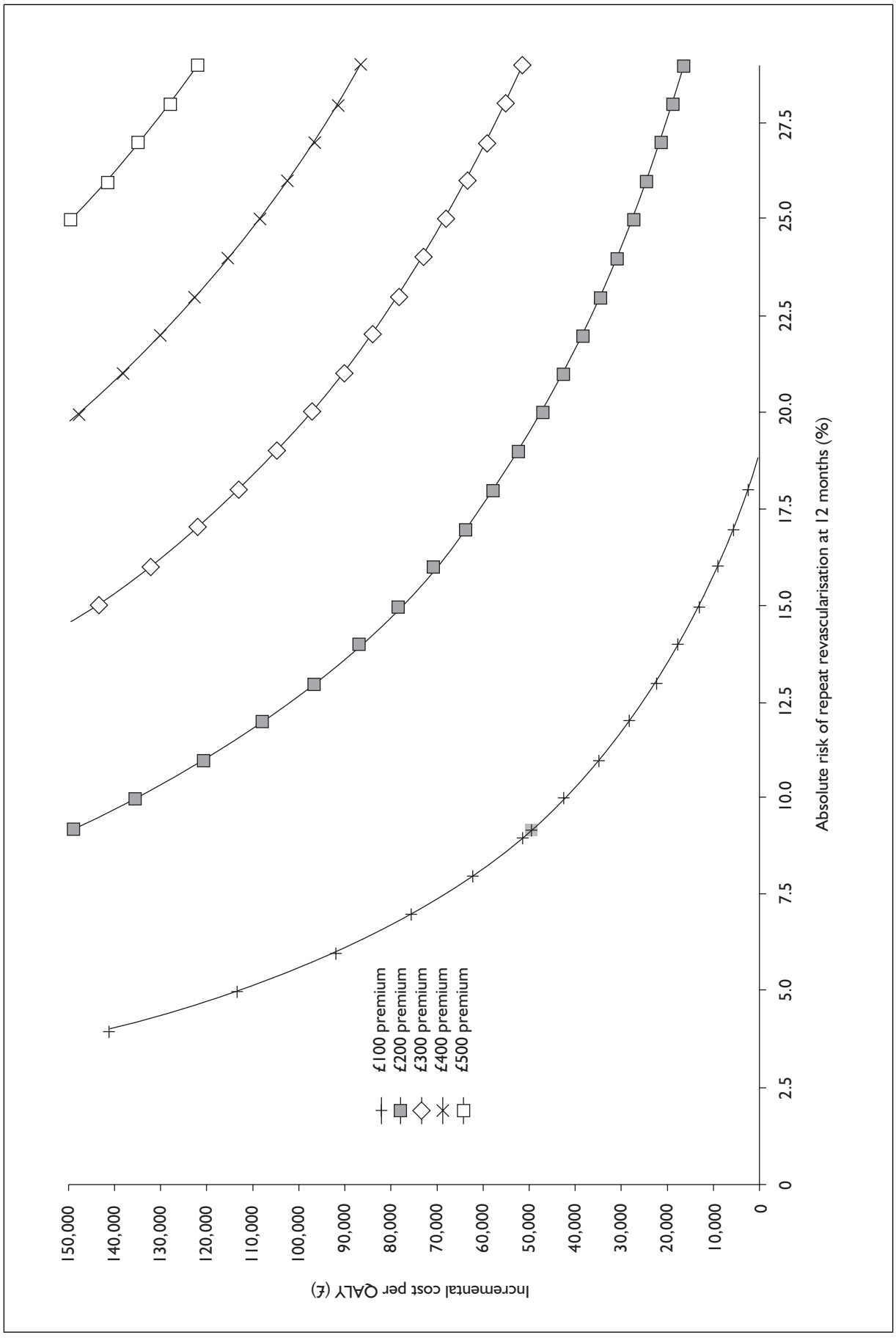

FIGURE 28 *Elective patients receiving three stents*

TABLE 77 *All non-elective patients, using mean number of stents implanted (1.46 stent per patient)*

Absolute risk (%)	Incremental utility	Incremental cost by levels of price premium (£)								Incremental cost per QALY by levels of price premium (£)								Threshold premium (£30,000) (£)
		£100	£200	£300	£400	£500	£600	£700	£800	£100	£200	£300	£400	£500	£600	£700	£800	
6	0.00210	38	184	330	475	621	767	913	1,059	**18,000**	87,400	156,800	226,100	295,500	364,900	434,200	503,600	118
8	0.00262	6	151	296	441	586	731	876	1,021	**2,100**	57,500	112,800	168,200	223,600	279,000	334,300	389,700	152
10	0.00314	–27	117	262	406	550	694	839	983	**–8,600**	37,400	83,400	129,400	175,400	221,400	267,400	313,400	186
10.04	0.00315	–27	117	261	405	550	694	838	982	**–8,700**	37,100	83,000	128,800	174,700	220,500	266,400	312,200	186
12	0.00365	–59	84	228	371	515	658	802	945	**–16,200**	**23,000**	62,300	101,600	140,800	180,100	219,400	258,600	220
14	0.00417	–92	51	194	336	479	622	765	907	**–22,000**	**12,200**	46,400	80,700	114,900	149,100	183,300	217,500	254
16	0.00469	–124	18	160	302	444	586	728	869	**–26,500**	**3,800**	34,100	64,300	94,600	124,900	155,200	185,400	289
18	0.00521	–156	–15	126	267	408	549	690	832	**–30,100**	**–2,900**	**24,200**	51,300	78,400	105,500	132,600	159,700	325
20	0.00572	–189	–48	92	232	373	513	653	794	**–33,000**	**–8,500**	**16,100**	40,600	65,100	89,600	114,200	138,700	360
22	0.00624	–221	–82	58	198	337	477	616	756	**–35,500**	**–13,100**	**9,300**	31,700	54,000	76,400	98,800	121,100	397
24	0.00676	–254	–115	24	163	302	440	579	718	**–37,500**	**–17,000**	**3,500**	**24,100**	44,600	65,200	85,700	106,300	433
26	0.00728	–286	–148	–10	128	266	404	542	680	**–39,300**	**–20,300**	**–1,400**	**17,600**	36,600	55,600	74,500	93,500	470
28	0.00779	–318	–181	–44	93	231	368	505	642	**–40,900**	**–23,300**	**–5,600**	**12,000**	**29,600**	47,200	64,800	82,400	507
30	0.00831	–351	–214	–78	59	195	332	468	605	**–42,200**	**–25,800**	**–9,400**	**7,100**	**23,500**	39,900	56,300	72,800	545
32	0.00883	–383	–248	–112	24	160	295	431	567	**–43,400**	**–28,000**	**–12,700**	**2,700**	**18,100**	33,500	48,800	64,200	583
34	0.00935	–416	–281	–146	–11	124	259	394	529	**–44,500**	**–30,000**	**–15,600**	**–1,200**	**13,300**	**27,700**	42,200	56,600	622
36	0.00986	–448	–314	–180	–46	89	223	357	491	**–45,400**	**–31,800**	**–18,200**	**–4,600**	**9,000**	**22,600**	36,200	49,800	661
38	0.01038	–480	–347	–214	–80	53	187	320	453	**–46,300**	**–33,400**	**–20,600**	**–7,700**	**5,100**	**18,000**	30,800	43,700	701
40	0.01090	–513	–380	–248	–115	18	150	283	416	**–47,100**	**–34,900**	**–22,700**	**–10,600**	**1,600**	**13,800**	**26,000**	38,100	741
42	0.01142	–545	–413	–282	–150	–18	114	246	378	**–47,800**	**–36,200**	**–24,700**	**–13,100**	**–1,600**	**10,000**	**21,500**	33,100	781
44	0.01193	–578	–447	–316	–184	–53	78	209	340	**–48,400**	**–37,400**	**–26,400**	**–15,500**	**–4,500**	**6,500**	**17,500**	**28,500**	822
46	0.01245	–610	–480	–349	–219	–89	41	172	302	**–49,000**	**–38,500**	**–28,100**	**–17,600**	**–7,100**	**3,300**	**13,800**	**24,300**	863
With procedural mortality estimate																		
10.04	0.00523	–27	117	261	405	550	694	838	982	**–5,200**	**22,300**	49,900	77,400	105,000	132,600	160,100	187,700	230

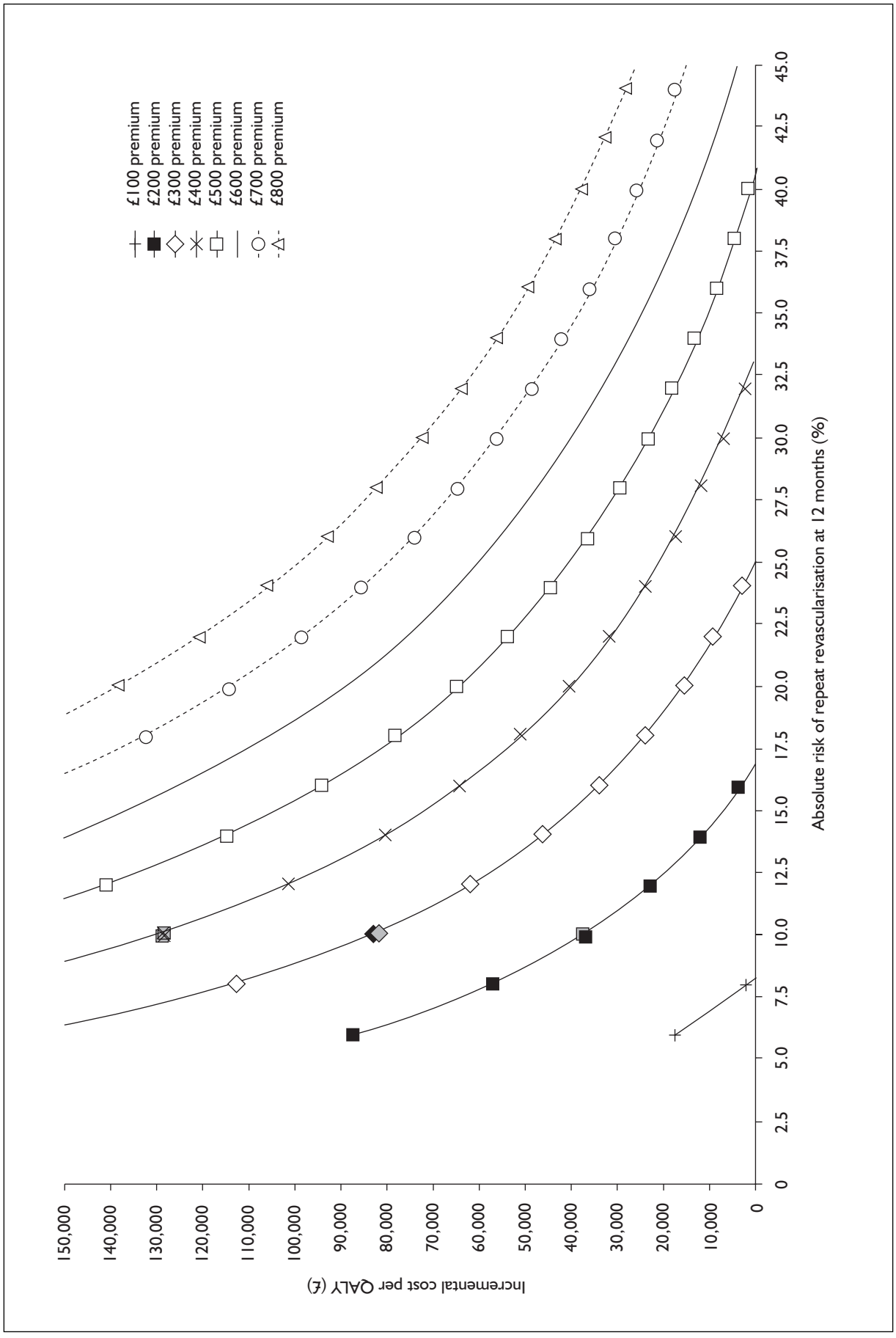

FIGURE 29 *All non-elective patients, using mean number of stents implanted*

TABLE 78 *Non-elective patients receiving a single stent*

Absolute risk (%)	Incremental utility	Incremental cost by levels of price premium (£)								Incremental cost per QALY by levels of price premium (£)								Threshold premium (£30,000) (£)
		£100	£200	£300	£400	£500	£600	£700	£800	£100	£200	£300	£400	£500	£600	£700	£800	
6	0.00210	–9	89	188	287	385	484	583	682	**–4,400**	42,600	89,500	136,400	183,400	230,300	277,300	324,200	175
8	0.00262	–42	56	154	252	350	448	546	644	**–15,900**	**21,500**	58,900	96,200	133,600	171,000	208,300	245,700	225
8.73	0.00281	–53	44	142	239	337	435	532	630	**–19,000**	**15,800**	50,500	85,300	120,100	154,800	189,600	224,400	243
10	0.00314	–74	23	120	217	314	412	509	606	**–23,600**	**7,400**	38,300	69,300	100,300	131,200	162,200	193,100	276
12	0.00365	–106	–10	86	183	279	375	472	568	**–29,100**	**–2,800**	**23,600**	50,000	76,300	102,700	129,100	155,400	327
14	0.00417	–139	–43	52	148	243	339	435	530	**–33,300**	**–10,400**	**12,500**	35,500	58,400	81,300	104,200	127,100	380
16	0.00469	–171	–76	18	113	208	303	398	492	**–36,500**	**–16,300**	**3,900**	**24,100**	44,400	64,600	84,800	105,000	433
18	0.00521	–204	–110	–16	78	172	266	361	455	**–39,100**	**–21,100**	**–3,000**	**15,100**	33,100	51,200	69,200	87,300	488
20	0.00572	–236	–143	–50	44	137	230	323	417	**–41,200**	**–24,900**	**–8,700**	**7,600**	**23,900**	40,200	56,500	72,800	543
22	0.00624	–268	–176	–83	9	101	194	286	379	**–43,000**	**–28,200**	**–13,400**	**1,400**	**16,300**	31,100	45,900	60,700	599
24	0.00676	–301	–209	–117	–26	66	158	249	341	**–44,500**	**–30,900**	**–17,400**	**–3,800**	**9,800**	**23,300**	36,900	50,500	656
26	0.00728	–333	–242	–151	–60	30	121	212	303	**–45,800**	**–33,300**	**–20,800**	**–8,300**	**4,200**	**16,700**	**29,200**	41,700	714
28	0.00779	–366	–275	–185	–95	–5	85	175	265	**–46,900**	**–35,300**	**–23,800**	**–12,200**	**–600**	**10,900**	**22,500**	34,100	773
30	0.00831	–398	–309	–219	–130	–41	49	138	228	**–47,900**	**–37,100**	**–26,400**	**–15,600**	**–4,900**	**5,900**	**16,600**	**27,400**	833
32	0.00883	–430	–342	–253	–165	–76	13	101	190	**–48,800**	**–38,700**	**–28,700**	**–18,700**	**–8,600**	**1,400**	**11,500**	**21,500**	894
34	0.00935	–463	–375	–287	–199	–112	–24	64	152	**–49,500**	**–40,100**	**–30,700**	**–21,300**	**–11,900**	**–2,500**	**6,900**	**16,300**	956
36	0.00986	–495	–408	–321	–234	–147	–60	27	114	**–50,200**	**–41,400**	**–32,600**	**–23,700**	**–14,900**	**–6,100**	**2,700**	**11,600**	1,019
38	0.01038	–528	–441	–355	–269	–183	–96	–10	76	**–50,800**	**–42,500**	**–34,200**	**–25,900**	**–17,600**	**–9,300**	**–1,000**	**7,300**	1,083
40	0.01090	–560	–475	–389	–304	–218	–133	–47	38	**–51,400**	**–43,500**	**–35,700**	**–27,900**	**–20,000**	**–12,200**	**–4,300**	**3,500**	1,149
42	0.01142	–592	–508	–423	–338	–254	–169	–84	1	**–51,900**	**–44,500**	**–37,100**	**–29,600**	**–22,200**	**–14,800**	**–7,400**	**0**	1,216
44	0.01193	–625	–541	–457	–373	–289	–205	–121	–37	**–52,400**	**–45,300**	**–38,300**	**–31,300**	**–24,200**	**–17,200**	**–10,200**	**–3,100**	1,284
46	0.01245	–657	–574	–491	–408	–325	–241	–158	–75	**–52,800**	**–46,100**	**–39,400**	**–32,800**	**–26,100**	**–19,400**	**–12,700**	**–6,000**	1,353
With procedural mortality estimate																		
8.73	0.00462	–53	44	142	239	337	435	532	630	**–11,500**	**9,600**	30,700	51,800	72,900	94,000	115,200	136,300	300

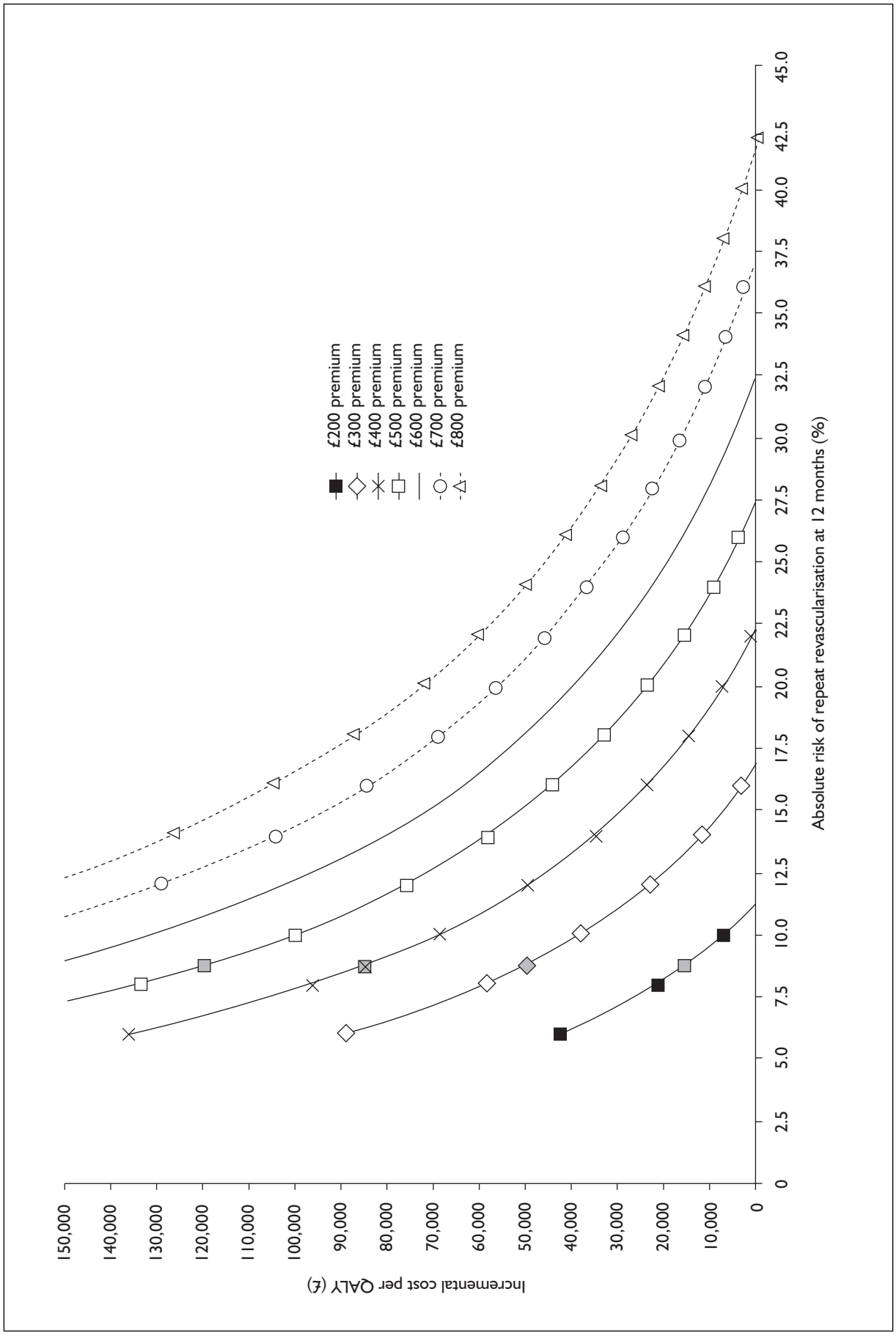

FIGURE 30 *Non-elective patients receiving a single stent*

TABLE 79 *Non-elective patients receiving two stents*

Absolute risk (%)	Incremental utility	Incremental cost by levels of price premium (£)								Incremental cost per QALY by levels of price premium (£)								Threshold premium (£30,000) (£)
		£100	£200	£300	£400	£500	£600	£700	£800	£100	£200	£300	£400	£500	£600	£700	£800	
6	0.0021	92	291	491	691	890	1,090	1,290	1,490	43,700	138,700	233,600	328,600	423,600	518,600	613,600	708,600	86
8	0.00262	59	258	457	656	855	1,054	1,253	1,452	**22,700**	98,600	174,500	250,500	326,400	402,300	478,200	554,200	111
10	0.00314	27	225	423	621	819	1,018	1,216	1,414	**8,600**	71,800	134,900	198,100	261,200	324,400	387,600	450,700	135
12	0.00365	–5	192	389	587	784	981	1,179	1,376	**–1,500**	52,500	106,500	160,500	214,500	268,500	322,500	376,500	160
12.83	0.00387	–19	178	375	572	769	966	1,163	1,360	**–4,900**	46,000	96,900	147,800	198,700	249,700	300,600	351,500	170
14	0.00417	–38	159	355	552	748	945	1,142	1,338	**–9,100**	38,100	85,200	132,300	179,400	226,500	273,700	320,800	185
16	0.00469	–70	126	321	517	713	909	1,105	1,300	**–15,000**	**26,800**	68,500	110,300	152,000	193,800	235,600	277,300	210
18	0.00521	–103	92	287	482	677	872	1,068	1,263	**–19,700**	**17,700**	55,200	92,700	130,100	167,600	205,000	242,500	235
20	0.00572	–135	59	253	448	642	836	1,030	1,225	**–23,600**	**10,300**	44,300	78,200	112,200	146,100	180,000	214,000	260
22	0.00624	–167	26	220	413	606	800	993	1,187	**–26,800**	**4,200**	35,200	66,200	97,200	128,200	159,200	190,200	286
24	0.00676	–200	–7	186	378	571	764	956	1,149	**–29,600**	**–1,100**	**27,500**	56,000	84,500	113,000	141,500	170,000	312
26	0.00728	–232	–40	152	344	535	727	919	1,111	**–31,900**	**–5,500**	**20,800**	47,200	73,600	100,000	126,300	152,700	338
28	0.00779	–265	–73	118	309	500	691	882	1,073	**–34,000**	**–9,400**	**15,100**	39,600	64,100	88,700	113,200	137,700	364
30	0.00831	–297	–107	84	274	464	655	845	1,036	**–35,700**	**–12,800**	**10,100**	33,000	55,900	78,800	101,700	124,600	391
32	0.00883	–329	–140	50	239	429	619	808	998	**–37,300**	**–15,800**	**5,600**	**27,100**	48,600	70,100	91,500	113,000	418
34	0.00935	–362	–173	16	205	393	582	771	960	**–38,700**	**–18,500**	**1,700**	**21,900**	42,100	62,300	82,500	102,700	445
36	0.00986	–394	–206	–18	170	358	546	734	922	**–40,000**	**–20,900**	**–1,800**	**17,200**	36,300	55,400	74,400	93,500	472
38	0.01038	–427	–239	–52	135	322	510	697	884	**–41,100**	**–23,100**	**–5,000**	**13,000**	31,100	49,100	67,100	85,200	499
40	0.0109	–459	–273	–86	100	287	473	660	846	**–42,100**	**–25,000**	**–7,900**	**9,200**	**26,300**	43,400	60,600	77,700	527
42	0.01142	–491	–306	–120	66	251	437	623	809	**–43,100**	**–26,800**	**–10,500**	**5,800**	**22,000**	38,300	54,600	70,800	555
44	0.01193	–524	–339	–154	31	216	401	586	771	**–43,900**	**–28,400**	**–12,900**	**2,600**	**18,100**	33,600	49,100	64,600	583
46	0.01245	–556	–372	–188	–4	180	365	549	733	**–44,700**	**–29,900**	**–15,100**	**–300**	**14,500**	**29,300**	44,100	58,900	611
With procedural mortality estimate																		
12.83	0.00654	–19	178	375	572	769	966	1,163	1,360	**–2,900**	**27,200**	57,400	87,500	117,600	147,800	177,900	208,000	212

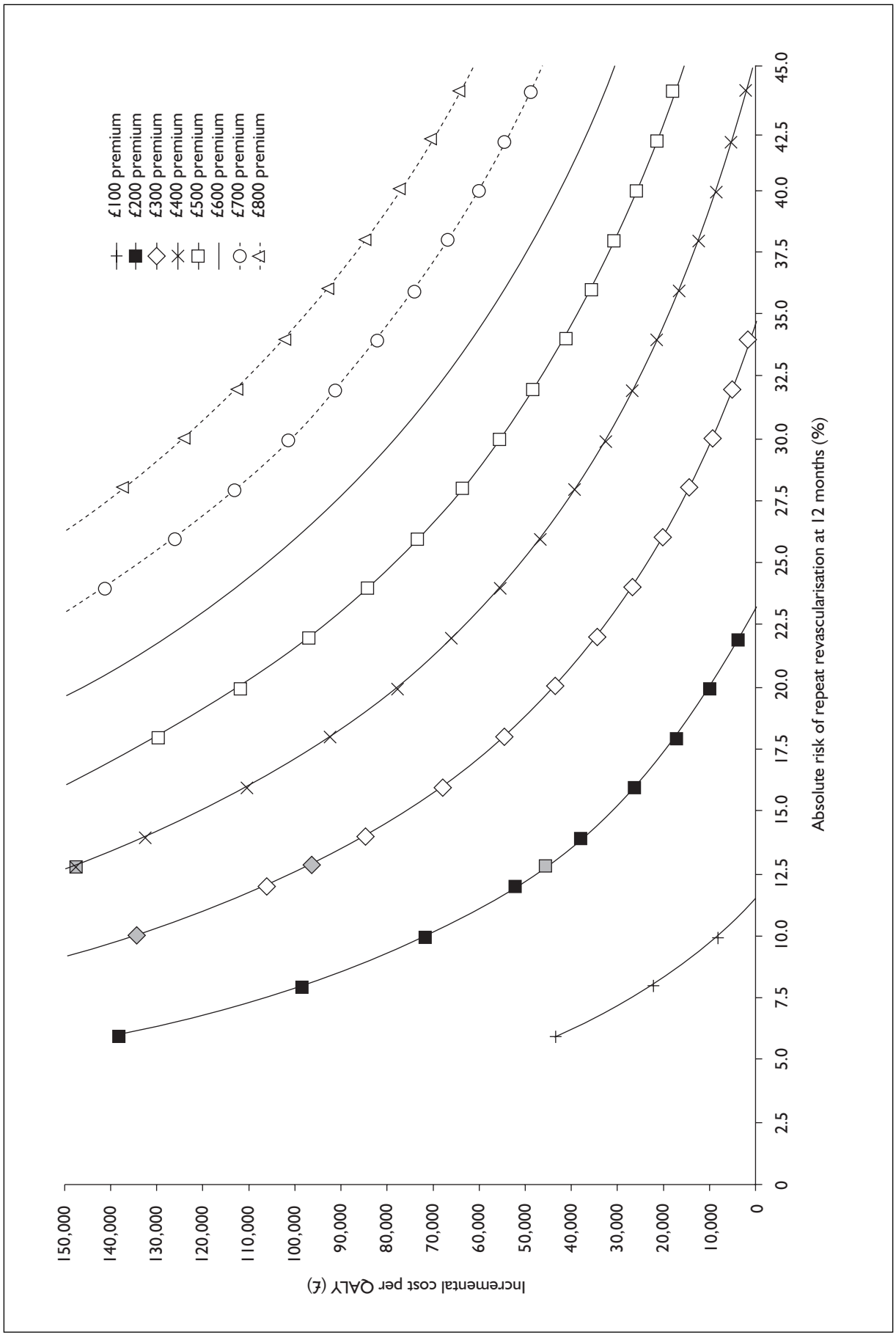

FIGURE 31 *Non-elective patients receiving two stents*

TABLE 80 *Non-elective patients receiving three stents*

Absolute risk (%)	Incremental utility	Incremental cost by levels of price premium (£)								Incremental cost per QALY by levels of price premium (£)								Threshold premium (£30,000) (£)
		£100	£200	£300	£400	£500	£600	£700	£800	£100	£200	£300	£400	£500	£600	£700	£800	
6	0.0021	193	493	794	1,095	1,395	1,696	1,997	2,298	91,700	234,700	377,800	520,800	663,800	806,900	949,900	1,092,900	57
8	0.00262	160	460	760	1,060	1,360	1,660	1,960	2,260	61,200	175,700	290,200	404,700	519,200	633,700	748,100	862,600	73
10	0.00314	128	427	726	1,025	1,324	1,624	1,923	2,222	40,800	136,200	231,500	326,900	422,200	517,600	612,900	708,300	90
12	0.00365	96	394	692	991	1,289	1,587	1,886	2,184	**26,200**	107,800	189,400	271,100	352,700	434,400	516,000	597,700	106
12.22	0.00371	92	390	689	987	1,285	1,583	1,882	2,180	**24,800**	105,100	185,500	265,800	346,200	426,600	506,900	587,300	108
14	0.00417	63	361	658	956	1,253	1,551	1,849	2,146	**15,100**	86,500	157,800	229,100	300,500	371,800	443,100	514,500	122
16	0.00469	31	328	624	921	1,218	1,515	1,812	2,108	**6,600**	69,900	133,200	196,500	259,700	323,000	386,300	449,600	138
18	0.00521	–2	294	590	886	1,182	1,478	1,775	2,071	**–300**	56,500	113,400	170,300	227,100	284,000	340,800	397,700	155
20	0.00572	–34	261	556	852	1,147	1,442	1,737	2,033	**–5,900**	45,600	97,200	148,800	200,400	252,000	303,500	355,100	171
22	0.00624	–66	228	523	817	1,111	1,406	1,700	1,995	**–10,600**	36,500	83,700	130,900	178,100	225,300	272,400	319,600	188
24	0.00676	–99	195	489	782	1,076	1,370	1,663	1,957	**–14,600**	**28,800**	72,300	115,700	159,200	202,700	246,100	289,600	205
26	0.00728	–131	162	455	748	1,040	1,333	1,626	1,919	**–18,000**	**22,200**	62,500	102,700	143,000	183,300	223,500	263,800	222
28	0.00779	–164	129	421	713	1,005	1,297	1,589	1,881	**–21,000**	**16,500**	54,000	91,500	128,900	166,400	203,900	241,400	238
30	0.00831	–196	95	387	678	969	1,261	1,552	1,844	**–23,600**	**11,500**	46,500	81,600	116,600	151,700	186,800	221,800	255
32	0.00883	–228	62	353	643	934	1,225	1,515	1,806	**–25,900**	**7,000**	40,000	72,900	105,800	138,700	171,600	204,500	272
34	0.00935	–261	29	319	609	898	1,188	1,478	1,768	**–27,900**	**3,100**	34,100	65,100	96,100	127,100	158,200	189,200	290
36	0.00986	–293	–4	285	574	863	1,152	1,441	1,730	**–29,700**	**–400**	**28,900**	58,200	87,500	116,800	146,100	175,400	307
38	0.01038	–326	–37	251	539	827	1,116	1,404	1,692	**–31,400**	**–3,600**	**24,200**	51,900	79,700	107,500	135,300	163,000	324
40	0.0109	–358	–71	217	504	792	1,079	1,367	1,654	**–32,900**	**–6,500**	**19,900**	46,300	72,700	99,000	125,400	151,800	342
42	0.01142	–390	–104	183	470	756	1,043	1,330	1,617	**–34,200**	**–9,100**	**16,000**	41,100	66,300	91,400	116,500	141,600	359
44	0.01193	–423	–137	149	435	721	1,007	1,293	1,579	**–35,400**	**–11,500**	**12,500**	36,500	60,400	84,400	108,300	132,300	377
46	0.01245	–455	–170	115	400	685	971	1,256	1,541	**–36,600**	**–13,700**	**9,200**	32,100	55,100	78,000	100,900	123,800	395
With procedural mortality estimate																		
12.22	0.00625	923	90	689	987	1,285	1,583	1,882	2,180	**14,700**	62,400	110,100	157,800	205,500	253,200	300,900	348,600	133

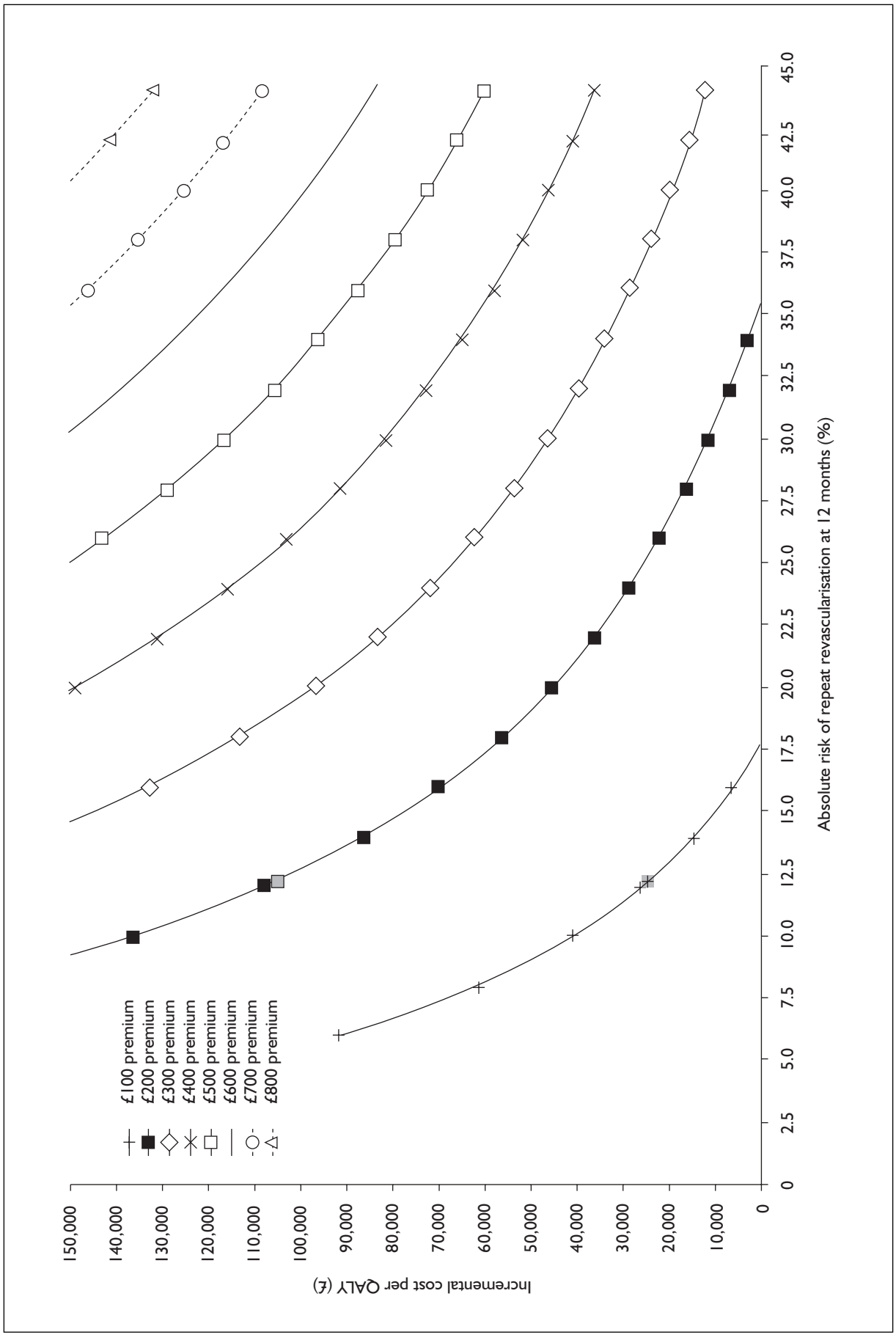

FIGURE 32 *Non-elective patients receiving three stents*

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Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.
A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, *et al*.

No. 13
'Early warning systems' for identifying new healthcare technologies.
By Robert G, Stevens A, Gabbay J.

No. 14
A systematic review of the role of human papillomavirus testing within a cervical screening programme.
By Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, *et al*.

No. 15
Near patient testing in diabetes clinics: appraising the costs and outcomes.
By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

No. 16
Positron emission tomography: establishing priorities for health technology assessment.
A review by Robert G, Milne R.

No. 17 (Pt 1)
The debridement of chronic wounds: a systematic review.
By Bradley M, Cullum N, Sheldon T.

No. 17 (Pt 2)
Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.
By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

No. 18
A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.
By Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, *et al*.

No. 19
What role for statins? A review and economic model.
By Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, *et al*.

No. 20
Factors that limit the quality, number and progress of randomised controlled trials.
A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, *et al*.

No. 21
Antimicrobial prophylaxis in total hip replacement: a systematic review.
By Glenny AM, Song F.

No. 22
Health promoting schools and health promotion in schools: two systematic reviews.
By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

No. 23
Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.
A review by Lord J, Victor C, Littlejohns P, Ross FM, Axford JS.

Volume 4, 2000

No. 1
The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.
A review by Cairns JA, van der Pol MM.

No. 2
Geriatric rehabilitation following fractures in older people: a systematic review.
By Cameron I, Crotty M, Currie C, Finnegan T, Gillespie L, Gillespie W, *et al*.

No. 3
Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.
By Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.

No. 4
Community provision of hearing aids and related audiology services.
A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

No. 5
False-negative results in screening programmes: systematic review of impact and implications.
By Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K.

No. 6
Costs and benefits of community postnatal support workers: a randomised controlled trial.
By Morrell CJ, Spiby H, Stewart P, Walters S, Morgan A.

No. 7
Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.
By French RS, Cowan FM, Mansour DJA, Morris S, Procter T, Hughes D, *et al*.

No. 8
An introduction to statistical methods for health technology assessment.
A review by White SJ, Ashby D, Brown PJ.

No. 9
Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.
By Clegg A, Bryant J, Milne R.

No. 10
Publication and related biases.
A review by Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ.

No. 11
Cost and outcome implications of the organisation of vascular services.
By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

No. 12
Monitoring blood glucose control in diabetes mellitus: a systematic review.
By Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R.

No. 13
The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.
By Elkan R, Kendrick D, Hewitt M, Robinson JJA, Tolley K, Blair M, *et al*.

No. 14
The determinants of screening uptake and interventions for increasing uptake: a systematic review.
By Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J.

No. 15
The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.
A rapid review by Song F, O'Meara S, Wilson P, Golder S, Kleijnen J.

No. 16
Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views.
By Bricker L, Garcia J, Henderson J, Mugford M, Neilson J, Roberts T, *et al*.

No. 17
A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.
By Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J.

No. 18
Liquid-based cytology in cervical screening: a rapid and systematic review.
By Payne N, Chilcott J, McGoogan E.

No. 19
Randomised controlled trial of non-directive counselling, cognitive–behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care.
By King M, Sibbald B, Ward E, Bower P, Lloyd M, Gabbay M, *et al*.

No. 20
Routine referral for radiography of patients presenting with low back pain: is patients' outcome influenced by GPs' referral for plain radiography?
By Kerry S, Hilton S, Patel S, Dundas D, Rink E, Lord J.

No. 21
Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration.
By O'Meara S, Cullum N, Majid M, Sheldon T.

No. 22
Using routine data to complement and enhance the results of randomised controlled trials.
By Lewsey JD, Leyland AH, Murray GD, Boddy FA.

No. 23
Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review.
By Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C.

No. 24
Outcome measures for adult critical care: a systematic review.
By Hayes JA, Black NA, Jenkinson C, Young JD, Rowan KM, Daly K, *et al*.

No. 25
A systematic review to evaluate the effectiveness of interventions to promote the initiation of breastfeeding.
By Fairbank L, O'Meara S, Renfrew MJ, Woolridge M, Sowden AJ, Lister-Sharp D.

No. 26
Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review.
By Parkes J, Bryant J, Milne R.

No. 27
Treatments for fatigue in multiple sclerosis: a rapid and systematic review.
By Brañas P, Jordan R, Fry-Smith A, Burls A, Hyde C.

No. 28
Early asthma prophylaxis, natural history, skeletal development and economy (EASE): a pilot randomised controlled trial.
By Baxter-Jones ADG, Helms PJ, Russell G, Grant A, Ross S, Cairns JA, *et al*.

No. 29
Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis.
By Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW.

No. 30
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina.
By McDonagh MS, Bachmann LM, Golder S, Kleijnen J, ter Riet G.

No. 31
A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma.
By Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D.

No. 32
Intrathecal pumps for giving opioids in chronic pain: a systematic review.
By Williams JE, Louw G, Towlerton G.

No. 33
Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.
By Shepherd J, Waugh N, Hewitson P.

No. 34
A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.
By MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.

No. 35
Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness.
By Berry E, Kelly S, Hutton J, Lindsay HSJ, Blaxill JM, Evans JA, *et al*.

No. 36
A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.
By Simpson S, Corney R, Fitzgerald P, Beecham J.

No. 37
Systematic review of treatments for atopic eczema.
By Hoare C, Li Wan Po A, Williams H.

No. 38
Bayesian methods in health technology assessment: a review.
By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.

No. 39
The management of dyspepsia: a systematic review.
By Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al*.

No. 40
A systematic review of treatments for severe psoriasis.
By Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC.

Volume 5, 2001

No. 1
Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review.
By Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al*.

No. 2
The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.
By Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, *et al*.

No. 3
Equity and the economic evaluation of healthcare.
By Sassi F, Archard L, Le Grand J.

No. 4
Quality-of-life measures in chronic diseases of childhood.
By Eiser C, Morse R.

No. 5
Eliciting public preferences for healthcare: a systematic review of techniques.
By Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, *et al*.

No. 6
General health status measures for people with cognitive impairment: learning disability and acquired brain injury.
By Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J.

No. 7
An assessment of screening strategies for fragile X syndrome in the UK.
By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

No. 8
Issues in methodological research: perspectives from researchers and commissioners.
By Lilford RJ, Richardson A, Stevens A, Fitzpatrick R, Edwards S, Rock F, *et al*.

No. 9
Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.
By Cullum N, Nelson EA, Flemming K, Sheldon T.

No. 10
Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.
By Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft D, *et al*.

No. 11
Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.
By Jobanputra P, Parry D, Fry-Smith A, Burls A.

No. 12
Statistical assessment of the learning curves of health technologies.
By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

No. 13
The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.
By Dinnes J, Cave C, Huang S, Major K, Milne R.

No. 14
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.
By Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J.

No. 15
Home treatment for mental health problems: a systematic review.
By Burns T, Knapp M, Catty J, Healey A, Henderson J, Watt H, *et al*.

No. 16
How to develop cost-conscious guidelines.
By Eccles M, Mason J.

No. 17
The role of specialist nurses in multiple sclerosis: a rapid and systematic review.
By De Broe S, Christopher F, Waugh N.

No. 18
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 19
The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.
By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

No. 20
Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in pre-operative assessment in elective general surgery.
By Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, *et al*.

No. 21
Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.
By Marshall M, Crowther R, Almaraz-Serrano A, Creed F, Sledge W, Kluiter H, *et al*.

No. 22
The measurement and monitoring of surgical adverse events.
By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23
Action research: a systematic review and guidance for assessment.
By Waterman H, Tillen D, Dickson R, de Koning K.

No. 24
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.
By Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, *et al*.

No. 25
A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

No. 26
Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.
By Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, *et al*.

No. 27
The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.
By Bryan S, Weatherburn G, Bungay H, Hatrick C, Salas C, Parry D, *et al*.

No. 28
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

No. 29
Superseded by a report published in a later volume.

No. 30
The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.
By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

No. 31
Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.
By McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, *et al*.

No. 32
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

No. 33
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34
Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
By David AS, Adams C.

No. 35
A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.
By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, *et al*.

No. 36
Cost analysis of child health surveillance.
By Sanderson D, Wright D, Acton C, Duree D.

Volume 6, 2002

No. 1
A study of the methods used to select review criteria for clinical audit.
By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2
Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.
By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al*.

No. 3
Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.
By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al*.

No. 4
A systematic review of discharge arrangements for older people.
By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, *et al*.

No. 5
The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6
The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7
The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.
By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al*.

No. 8
Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.
By Carroll B, Ali N, Azam N.

No. 9
Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.
By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al*.

No. 10
A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.
By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11
Screening for gestational diabetes: a systematic review and economic evaluation.
By Scott DA, Loveman E, McIntyre L, Waugh N.

No. 12
The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.
By Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A.

No. 13
The clinical effectiveness of trastuzumab for breast cancer: a systematic review.
By Lewis R, Bagnall A-M, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al*.

No. 14
The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.
By Lewis R, Bagnall A-M, King S, Woolacott N, Forbes C, Shirran L, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.
By Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC.

No. 16
The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.
By Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al*.

No. 17
A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.
By Cummins C, Connock M, Fry-Smith A, Burls A.

No. 18
Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.
By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al*.

No. 19
Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.
By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al*.

No. 20
Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.
By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freementle N, Vail A.

No. 21
The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.
By Jobanputra P, Barton P, Bryan S, Burls A.

No. 22
A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.
By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23
A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.
By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R.

No. 24
A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.
By Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, *et al*.

No. 25
A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.
By Robinson M, Ginnelly L, Sculpher M, Jones L, Riemsma R, Palmer S, *et al*.

No. 26
A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.
By Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al*.

No. 27
A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.
By Caine N, Sharples LD, Hollingworth W, French J, Keogan M, Exley A, *et al*.

No. 28
Clinical effectiveness and cost – consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.
By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29
Treatment of established osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30
Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.
By Elliott RA Payne K, Moore JK, Davies LM, Harper NJN, St Leger AS, *et al*.

No. 31
Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.
By Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al*.

No. 32
The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, *et al*.

No. 33
The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.
By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34
A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.
By Suri R, Wallis C, Bush A, Thompson S, Normand C, Flather M, *et al*.

No. 35
A systematic review of the costs and effectiveness of different models of paediatric home care.
By Parker G, Bhakta P, Lovett CA, Paisley S, Olsen R, Turner D, *et al*.

Volume 7, 2003

No. 1
How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.
By Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J.

No. 2
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.
By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, *et al*.

No. 3
Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.
By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

No. 4
A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.
By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al*.

No. 5
Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.
By Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, *et al*.

No. 6
The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.
By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.
By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, *et al*.

No. 8
A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.
By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, *et al*.

No. 9
Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.
By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10
Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.
By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, *et al*.

No. 11
First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).
By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12
The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.
By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13
A systematic review of atypical antipsychotics in schizophrenia.
By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, *et al*.

No. 14
Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.
By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, *et al*.

No. 15
Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.
By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, *et al*.

No. 16
Screening for fragile X syndrome: a literature review and modelling.
By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

No. 17
Systematic review of endoscopic sinus surgery for nasal polyps.
By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18
Towards efficient guidelines: how to monitor guideline use in primary care.
By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19
Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.
By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20
Prioritisation of health technology assessment. The PATHS model: methods and case studies.
By Townsend J, Buxton M, Harper G.

No. 21
Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.
By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, *et al*.

No. 22
The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.
By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23
The role of modelling in prioritising and planning clinical trials.
By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

No. 24
Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age.
By Allsup S, Gosney M, Haycox A, Regan M.

No. 25
The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.
By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26
Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.
By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27
Evaluating non-randomised intervention studies.
By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, *et al*.

No. 28
A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.
By Kennedy A, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, *et al*.

No. 29
The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.
By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30
The value of digital imaging in diabetic retinopathy.
By Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, *et al*.

No. 31
Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.
By Law M, Wald N, Morris J.

No. 32
Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.
By Ward S, Kaltenthaler E, Cowan J, Brewer N.

No. 33
Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review.
By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34
Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.
By Royle P, Waugh N.

No. 35
Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.
By Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K.

No. 36
A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.
By Boland A, Haycox A, Bagust A, Fitzsimmons L.

No. 37
Redesigning postnatal care: a randomised controlled trial of protocol-based midwifery-led care focused on individual women's physical and psychological health needs.
By MacArthur C, Winter HR, Bick DE, Lilford RJ, Lancashire RJ, Knowles H, *et al*.

No. 38
Estimating implied rates of discount in healthcare decision-making.
By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

No. 39
Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling.
By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, *et al*.

No. 40
Treatments for spasticity and pain in multiple sclerosis: a systematic review.
By Beard S, Hunn A, Wight J.

No. 41
The inclusion of reports of randomised trials published in languages other than English in systematic reviews.
By Moher D, Pham B, Lawson ML, Klassen TP.

No. 42
The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.
By Bankhead CR, Brett J, Bukach C, Webster P, Stewart-Brown S, Munafo M, *et al*.

Volume 8, 2004

No. 1
What is the best imaging strategy for acute stroke?
By Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, *et al*.

No. 2
Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.
By Mant J, McManus RJ, Oakes RAL, Delaney BC, Barton PM, Deeks JJ, *et al*.

No. 3
The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.
By Garside R, Stein K, Wyatt K, Round A, Price A.

No. 4
A systematic review of the role of bisphosphonates in metastatic disease.
By Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, *et al*.

No. 5
Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.
By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R.

No. 6
Effectiveness and efficiency of guideline dissemination and implementation strategies.
By Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, *et al*.

No. 7
Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.
By Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P.

No. 8
Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.
By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

No. 9
Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.
By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

No. 10
A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.
By Kaltenthaler E, Bravo Vergel Y, Chilcott J, Thomas S, Blakeborough T, Walters SJ, *et al*.

No. 11
The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.
By Barton P, Jobanputra P, Wilson J, Bryan S, Burls A.

No. 12
Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review.
By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

No. 13
Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation.
By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J.

No. 14
Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.
By Townsend J, Wolke D, Hayes J, Davé S, Rogers C, Bloomfield L, *et al*.

No. 15
Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.
By Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, Gabbay J, *et al*.

No. 16
A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.
By Reeves BC, Angelini GD, Bryan AJ, Taylor FC, Cripps T, Spyt TJ, *et al*.

No. 17
Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial.
By Gilbert FJ, Grant AM, Gillan MGC, Vale L, Scott NW, Campbell MK, *et al*.

No. 18
The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.
By Clark W, Jobanputra P, Barton P, Burls A.

No. 19
A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.
By Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, *et al*.

No. 20
Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.
By Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N.

No. 21
Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.
By Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, *et al*.

No. 22
Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.
By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23
Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.
By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24
Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.
By Dündar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, *et al*.

No. 25
Development and validation of methods for assessing the quality of diagnostic accuracy studies.
By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26
EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.
By Garry R, Fountain J, Brown J, Manca A, Mason S, Sculpher M, *et al*.

No. 27
Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon-β and glatiramer acetate for multiple sclerosis.
By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28
Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
By Dalziel K, Round A, Stein K, Garside R, Price A.

No. 29
VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.
By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ on behalf of the VenUS Team.

No. 30
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.
By Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, *et al*.

No. 31
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.
By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32
The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.
By Wiggins M, Oakley A, Roberts I, Turner H, Rajan L, Austerberry H, *et al*.

No. 33
Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.
By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34
Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.
By Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B.

No. 35
Coronary artery stents: a rapid systematic review and economic evaluation.
By Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, *et al*.

No. 36
Review of guidelines for good practice in decision-analytic modelling in health technology assessment.
By Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*.

No. 37
Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation.
By Knight C, Hind D, Brewer N, Abbott V.

No. 38
Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.
By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al.*

No. 39
Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40
Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.
By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, *et al.*

No. 41
Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.
By Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, *et al.*

No. 42
Involving South Asian patients in clinical trials.
By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.
By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44
Identification and assessment of ongoing trials in health technology assessment reviews.
By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, *et al*.

No. 45
Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine
By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

No. 46
Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.
By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al*.

No. 47
Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.
By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48
Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.
By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, *et al*.

No. 49
Generalisability in economic evaluation studies in healthcare: a review and case studies.
By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al*.

No. 50
Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.
By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, *et al*.

Volume 9, 2005

No. 1
Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.
By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, *et al*.

No. 2
Do the findings of case series studies vary significantly according to methodological characteristics?
By Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.

No. 3
Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.
By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Haites NE, *et al*.

No. 4
Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.
By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5
A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.
By Shenfine J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6
Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.
By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

No. 7
Issues in data monitoring and interim analysis of trials.
By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, *et al*.

No. 8
Lay public's understanding of equipoise and randomisation in randomised controlled trials.
By Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, *et al*.

No. 9
Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.
By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10
Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.
By Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, *et al*.

No. 11
Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.
By Green C, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, *et al*.

No. 12
A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.
By Dinnes J, Deeks J, Kirby J, Roderick P.

No. 13
Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.
By Willis BH, Barton P, Pearmain P, Bryan S, Hyde C.

No. 14
Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.
By McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E, *et al*.

No. 15
Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.
By Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, *et al*.

No. 16
A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.
By Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, *et al*.

No. 17
Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.
By Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, *et al*.

No. 18
A randomised controlled comparison of alternative strategies in stroke care.
By Kalra L, Evans A, Perez I, Knapp M, Swift C, Donaldson N.

No. 19
The investigation and analysis of critical incidents and adverse events in healthcare.
By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

No. 20
Potential use of routine databases in health technology assessment.
By Raftery J, Roderick P, Stevens A.

No. 21
Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.
By Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al*.

No. 22
A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.
By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.

No. 23
A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.
By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, *et al*.

No. 24
An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.
By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, *et al*.

No. 25
Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.
By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al*.

No. 26
Indirect comparisons of competing interventions.
By Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, *et al*.

No. 27
Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.
By Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, *et al*.

No. 28
Outcomes of electrically stimulated gracilis neosphincter surgery.
By Tillin T, Chambers M, Feldman R.

No. 29
The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.
By Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, *et al*.

No. 30
Systematic review on urine albumin testing for early detection of diabetic complications.
By Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, *et al*.

No. 31
Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.
By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32
Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.
By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, *et al*.

No. 33
Cost-effectiveness and safety of epidural steroids in the management of sciatica.
By Price C, Arden N, Coglan L, Rogers P.

No. 34
The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.
By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35
Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.
By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al*.

No. 36
The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.
By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37
A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.
By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, *et al*.

No. 38
The causes and effects of socio-demographic exclusions from clinical trials.
By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al*.

No. 39
Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.
By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, *et al*.

No. 40
A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.
By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, *et al*.

No. 41
Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.
By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42
Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.
By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, *et al*.

No. 43
The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44
Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.
By Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C.

No. 45
The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.
By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al*.

No. 46
The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.
By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47
Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.
By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al*.

No. 48
Systematic review of effectiveness of different treatments for childhood retinoblastoma.
By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

No. 49
Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.
By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, *et al*.

No. 50
The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.
By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, *et al*.

Volume 10, 2006

No. 1
The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.
By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al*.

No. 2
FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.
By Dennis M, Lewis S, Cranswick G, Forbes J.

No. 3
The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.
By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, *et al*.

No. 4
A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.
By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al*.

No. 5
Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.
By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6
Systematic review and evaluation of methods of assessing urinary incontinence.
By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.
By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al*.

No. 8
Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.
By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9
Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.
By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al*.

No. 10
Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.
By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11
Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.
By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, *et al*.

No. 12
A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.
By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, *et al*.

No. 13
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).
By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, *et al*.

No. 14
The cost-effectiveness of screening for oral cancer in primary care.
By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M *et al*.

No. 15
Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.
By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al*.

No. 16
Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.
By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, *et al*.

No. 17
Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.
By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, *et al*.

No. 18
Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.
By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, *et al*.

No. 19
Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.
By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, *et al*.

No. 20
A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.
By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al*.

No. 21
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.
By Wright M, Grieve R, Roberts J, Main J, Thomas HC on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22
Pressure relieving support surfaces: a randomised evaluation.
By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, *et al*.

No. 23
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.
By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al*.

No. 24
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.
By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al*.

No. 25
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.
By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, *et al*.

No. 26
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.
By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, *et al*.

No. 27
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context.
By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al*.

No. 28
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.
By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29
An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.
By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, *et al*.

No. 30
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.
By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, *et al*.

No. 31
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.
By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al*.

No. 32
The cost-effectiveness of testing for hepatitis C in former injecting drug users.
By Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al*.

No. 33
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.
By Kaltenthaler E, Brazier J, De Nigris E, Tumur I, Ferriter M, Beverley C, *et al*.

No. 34
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.
By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al*.

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Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.
By Brazier J, Tumur I, Holmes M, Ferriter M, Parry G, Dent-Brown K, *et al*.

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Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.
By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, *et al*.

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Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.
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A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.
By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, *et al*.

No. 39
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.
By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

No. 40
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).
By Williams J, Russell I, Durai D, Cheung W-Y, Farrin A, Bloor K, *et al*.

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The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.
By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

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A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.
By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al*.

No. 43
Telemedicine in dermatology: a randomised controlled trial.
By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

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Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.
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No. 46
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.
By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al*.

No. 47
Systematic reviews of clinical decision tools for acute abdominal pain.
By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, *et al*.

No. 48
Evaluation of the ventricular assist device programme in the UK.
By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*.

No. 49
A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.
By Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al*.

No. 50
Amniocentesis results: investigation of anxiety. The ARIA trial.
By Hewison J, Nixon J, Fountain J, Cocks K, Jones C, Mason G, *et al*.

Volume 11, 2007

No. 1
Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.
By Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, *et al*.

No. 2
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.
By Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, *et al*.

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A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.
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The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.
By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5
A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.
By Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, *et al*.

No. 6
Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.
By Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, *et al*.

No. 7
Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8
Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.
By Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, *et al*.

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Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.
By Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, *et al*.

No. 10
Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.
By Isaacs AJ, Critchley JA, See Tai S, Buckingham K, Westley D, Harridge SDR, *et al*.

No. 11
Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

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Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.
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A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.
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A systematic review and economic evaluation of statins for the prevention of coronary events.
By Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, *et al*.

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A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.
By Mason A, Weatherly H, Spilsbury K, Arksey H, Golder S, Adamson J, *et al*.

No. 16
Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.
By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17
Screening for type 2 diabetes: literature review and economic modelling.
By Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, *et al*.

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The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, *et al*.

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The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.
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A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.
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The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.
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A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.
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Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections.
By McCormack K, Rabindranath K, Kilonzo M, Vale L, Fraser C, McIntyre L, *et al*.

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The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.
By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, *et al*.

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A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.
By Boyle J, McCartney E, Forbes J, O'Hare A.

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Hormonal therapies for early breast cancer: systematic review and economic evaluation.
By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

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Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.
By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.
By McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, *et al*.

No. 29
Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.
By Colbourn T, Asseburg C, Bojke L, Philips Z, Claxton K, Ades AE, *et al*.

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Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.
By Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, *et al*.

No. 31
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.
By Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, *et al*.

No. 32
Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.
By Bamford J, Fortnum H, Bristow K, Smith J, Vamvakas G, Davies L, *et al*.

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The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.
By Black C, Cummins E, Royle P, Philip S, Waugh N.

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Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.
By Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, *et al*.

No. 35
The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Home-based compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.
By Jolly K, Taylor R, Lip GYH, Greenfield S, Raftery J, Mant J, *et al*.

No. 36
A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.
By Abubakar I, Irvine L, Aldus CF, Wyatt GM, Fordham R, Schelenz S, *et al*.

No. 37
A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.
By Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, *et al*.

No. 38
Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling.
By Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, *et al*.

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A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.
By Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, *et al*.

No. 40
Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.
By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

No. 41
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.
By Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, *et al*.

No. 42
Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.
By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

No. 43
Contamination in trials of educational interventions.
By Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, *et al*.

No. 44
Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.
By Facey K, Bradbury I, Laking G, Payne E.

No. 45
The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Rogers G, Dyer M, Mealing S, *et al*.

No. 46
Drug-eluting stents: a systematic review and economic evaluation.
By Hill RA, Boland A, Dickson R, Dündar Y, Haycox A, McLeod C, *et al*.

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