Drug-eluting stents:

a systematic review & economic evaluation

Final Version

NICETAR 04/42

In confidence information **not included**

This report includes information from studies relating to two drug-eluting stents that at present have not yet received CE marking. Data from these non-marked stents has not been used in the pooled estimates of effects. However, general information regarding these stents is included in the report.

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The Liverpool Reviews and Implementation Group (LR*i*G) was established within the Department of Pharmacology and Therapeutics of The University of Liverpool in April 2001. It is a multi-disciplinary research group whose purpose, in the first instance, is to conduct Health Technology Assessments (HTA) commissioned by the HTA Programme.

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Referees:

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).

Responsibility of report

The views expressed in this publication are those of the authors and not necessarily those of the Advisory Panel, the HTA Programme, NICE or the Department of Health.

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SUMMARY

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 (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 Guidance for the NHS in England and Wales.

Background

Percutaneous coronary intervention 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 (including The Cochrane Library, EMBASE and MEDLINE) as well as 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 (RCT) 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 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.

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 3 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 to BMS (for example at 1 years: TLR relative risk 0.24; 95% confidence interval 0.19 to 0.31 and TVR relative risk 0.43; 95% confidence interval 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

Data from RCTs were unavailable for 6 of the 11 DES designs eligible for assessment. Reporting of data available 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 only be cost-effective 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 is assumed that all DES are clinically equivalent. The costs and benefits of DES versus BMS are therefore identified, measured and valued.

Compared to 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 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 to £562,000) and outside the normal range of acceptability. Cost-effectiveness is only achieved for those non-elective patients who have undergone a previous CABG and have small vessels. Real world data show that patient numbers in this latter group are very small (1 in 3100 of all patients treated with PCI).

Implications for the NHS

Assessment of budgetary impact of DES on the NHS involved investigation of purchase cost as well as 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 million to £25 million.

If anecdotal evidence of 70% current DES usage is accepted, the estimated total cost of purchasing DES rises to £30 million to £36 million; if 100% DES usage is assumed the projected cost would be around £42 million to £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 to new generation BMS
- Trials of DES compared to DES

[Word count: 1192]

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
AIC	Academic in confidence
AMI	Acute myocardial infarction
ARR	Absolute risk reduction
BCIA	British Cardiovascular Industry Association
BCIS	British Cardiac Intervention Society
BHF	British Heart Foundation
BRR	Binary restenosis rate
CABG	Coronary artery bypass graft(ing)
CAD	Coronary artery disease
CCSC	Canadian Cardiovascular Society Classification
C-E	Cost-effective(ness)
CEA	Cost-effectiveness analysis
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CIC	Commercial in confidence
CK	Creatinine kinase
CK-MB	Fraction of creatinine kinase
CRD	Centre for Reviews and Dissemination
CTC Liverpool	Cardiothoracic Centre Liverpool
CTO	Chronic total occlusion
CVA	Cerebro-vascular accident (stroke)
DES	Drug-eluting stent

DM	Diabetes mellitus
ECG	Electrocardiogram
EF	Ejection fraction
EVA	Extreme values analysis
FDA	Food and Drug Administration, U.S. Department of Health and Human Services
GI	Gastrointestinal
HoDAR	Health Outcomes Data Repository
ICER	Incremental cost effectiveness ratio
ISR	In-stent restenosis
ITT	Intention to treat analysis
IV	Intravenous
IVUS	Intravascular ultrasound
LAD	Left anterior descending coronary [artery]
LCx	Left circumflex
LL	Late loss
LM	Left main coronary artery
LVEF	Left ventricular ejection fraction
MACCE	Major adverse coronary and cerebrovascular events
MACE	Major adverse coronary events
MI	Myocardial infarction
MLD	Minimal lumen diameter of coronary artery
NICE	National Institute for Health and Clinical Excellence
NSF	National Service Framework
OR	Odds ratio
PASA	NHS Purchasing and supply agency
PCI	Percutaneous coronary intervention (includes PTCA, stenting, atherectomy, excimer laser, rotablator)
PES	Paclitaxel-eluting stent
PTCA	percutaneous transluminal coronary angioplasty (the term PCI now commonly used in place of PTCA)

QALY	Quality adjusted life year
QCA	-
QCA	Quantitative coronary angiography
QoL	Quality of life
RCT	Randomised controlled trial
SA	Sensitivity analysis
SES	Sirolimus-eluting stent
STEMI	ST-segment AMI
SVG	Saphenous vein graft
TIMI flow grade	Thrombolysis In Myocardial Infarction flow grade
TLR	Target lesion revascularisation
TVF	Target vessel failure
TVR	Target vessel revascularisation

DEFINITION OF TERMS

Abciximab	a glycoprotein IIB/IIIa antagonist, used to inhibit blood clotting widely used during stenting procedure
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 percent 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	drug that inhibits platelet function
Creatinine kinase	a cardiac enzyme release during myocardial infarction
De novo lesion	a coronary lesion not previously treated
Direct stenting	stent implantation without pre-dilation
Drug-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 UK without discounts (obtained though survey of NHS purchasers conducted on behalf of the AG 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 360º circumference of the vessel and provides direct measurement of the diameter

	of the artery
Meta-analysis	method of combining results from different studies to produce a summary statistic
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)
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
QCA	three-dimensional imaging technology utilising X-rays to visualise arteries
Ticlopidine	drug that inhibits platelet function

1 ASSESSMENT AIMS

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]

2 BACKGROUND

2.1 Introduction

A previous technology assessment report (TAR) which included comparison of drug-eluting intracoronary stents (DES) to bare metal stents (BMS) was prepared for the then National Institute for Clinical Excellence through 2002 and 2003.[2] The Institute 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]

2.2 Description of health problem

2.2.1 Disease

Coronary artery 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, people with diabetes or those who smoke. Genetic and environmental factors may also contribute.

Manifestation of CAD may be acute or chronic. Acute coronary syndromes (ACS) occur 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 (with ECG changes of ST segment elevation and depression, Q wave), non ST elevation myocardial infarction 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.

2.2.2 Epidemiology

Routine data provided by the British Heart Foundation[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. Ischaemic heart disease 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).

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 to 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]

Ischaemic heart disease 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.

2.3 Current treatments

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

Treatments may include:

- Medical management;
- Interventional procedures:
    - Surgical intervention (Coronary artery bypass grafting - CABG),
    - Percutaneous intervention (PCI).

2.3.1 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.

2.3.2 CABG

This 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 PTCA, but with the only statistically significant benefit reported at five years.[7]

Changes in the intra and post-operative management of patients have improved patient outcomes following CABG.[5] New techniques including minimally invasive surgery, that 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 and will not be dealt with further in this report.[2].

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.

2.3.3 PCI

Balloon angioplasty (also called percutaneous coronary intervention, PCI) was introduced in the late 1970s.(22) 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 to 50%) patients develop restenosis within six 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 RCTs have shown that the use of a bare-metal stent during angioplasty safely reduces restenosis rates compared to 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 immonosuppressants, re-design 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 mix that allows the drug to slowly elute 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 were sirolimus and paclitaxel, used in two types of stent (Cypher, 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 drugs and stents combinations have been developed and where these DES have progressed to being awarded CE Marking they are considered in this report.

2.4 Current service provision

2.4.1 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".

2.4.2 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.

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

2.4.3 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 a 100 NHS Trusts and institutions in the country, together with associated overall costs (e.g The 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 while 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]

2.4.4 PCI rates

There has been a continual increase in the number and rate per million PCIs carried out over time, as well as an increase in the proportion of procedures that include the use of stents. Rates for 1991 to 2003 are shown in Table 2-1.

Table 2-1 PCI rates in UK 1991-2003

	Centres	Procedures Total	Procedures /Million	Change %	Stent use % (of PCI)[a]
1991	52	9933	174	-	-
1992	52	11575	203	16.5	<5
1993	53	12937	227	11.8	~5
1994	54	14624	256	13.0	~15
1995	54	17344	304	18.6	~25
1996	53	20511	359	18.1	~45
1997	58	22902	402	11.7	~60
1998	61	24899	437	8.7	~70
1999	63	28133	494	13.0	~80
2000	66	33652 (25610[b] 922[c])	590	20.0	84
2001	64	38992 (30785[b] 886[c])	664	12.5	86
2002	64	44913 (35306[b] 1131[c])	759	14.3	89.4
2003	73 (61[b] 2[c])	53261 (42234[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 (1 English centre not reporting?); c: Data reported for Wales

2.4.5 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 drug eluting stents licensed for use in the UK with more anticipated (See Table 2-2).

Table 2-2 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:	**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	✓	
Liberte™	Boston Scientific	Paclitaxel-ES	✓	Sept 2005
Xience V™	Guidant	Everolimus-ES	Pending	
Yukon™	Translumina/KiWiMed[a]	Variable, to date studied with sirolimus (non-polymeric)	✓	

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

Data for DES use were not available prior to 2002. The BCIS now reports that though 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.

2.5 Review considerations - clinical

2.5.1 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 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.

Third is related to the insertion technique used for stent placement. These include such things as provisional stenting (where stents are placed only in the case of sub-optimal expansion with angioplasty balloon alone), pre-dilation 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 six 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.

2.5.2 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-analysis 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 (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 endpoints in that they may obscure real and important differences in outcomes. For instance, repeat revascularisations are reported as events in the same way and with the same weight as a clinical myocardial infarction or death. In practice, given the rarity of coronary death or

myocardial infarction, the vast majority of MACE events are elective revascularisation procedures.

Revascularisation may be reported as TLR (target lesion revascularisation), TVR (target vessel revascularisation), revascularisation by particular technique (PCI or CABG) or it may not be specified. There are also limited data on total revascularisation, e.g. a patient may have another procedure carried out in a vessel other than the one originally treated. This reporting is appropriate 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 to 9 month angiographic follow-up of patients, there may be an excess of ‘events’ around 6 to 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 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 percent, even if the patient is not symptomatic at the time, it is highly likely that they will soon 'tip over' into a symptomatic state and require a repeat revascularisation 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 endpoint 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 one year but some have reported longer outcomes.

Quality of life

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

2.5.3 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.

2.6 Review considerations - economic

At the time the previous Technology Assessment Report 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 anticipated 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 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 patients sub-groups 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 to 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 casemix.

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 to 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 cost of all types of stent 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 alternate 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.

3 METHODS

3.1 Identification of evidence: clinical effectiveness and cost-effectiveness

3.1.1 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 were combined within the electronic searches.

The following electronic databases were searched (YD) for relevant published literature for the period from December 2002 to June 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 & 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 Aug 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 within 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. 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, Cal., USA.

3.1.2 Selection of clinical effectiveness & cost-effectiveness evidence

The records identified in the electronic searches were assessed for inclusion in two stages. Firstly 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 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 pre-tested, standardised form. Data on levels of agreement between reviewers is 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 study selection are presented in the clinical review and economics review chapters. A table summarising the selection and inclusion of studies is provided in the Appendix 1.

3.2 Methods for reviewing clinical effectiveness

3.2.1 Inclusion criteria

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

Study design

- Randomised controlled trials (RCTs); non-randomised controlled trials (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 who have their CE Marking pending. Assessment was limited to specific, named DES: Cypher™, Cordis Inc; Dexamet™, Abbott and Taxus™, Boston Scientific; CoStar™, Biotronik/Conor; Cypher Select™ Cordis; Endeavor™, Medtronic; Janis/us™, Sorin; Liberte™, Boston Scientific; Xience V™, Guidant; Yukon™, Translumina/KiWiMed).

Comparators

- Drug-eluting stent 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 (major adverse cardiac events - MACE, target vessel failure - TVF) or event free survival
- Mortality (all cause, cardiac)
- Acute Myocardial Infarction (AMI)
- Target Lesion Revascularisation (TLR)
- Target Vessel Revascularisation (TVR)
- Repeat revascularisation (PCI/stent, other PCI or CABG)
- Adverse effects (thrombosis, mal-absorption; incomplete stent apposition; device failures/defects)
- Angiographic binary restenosis
- Late loss
- Health-related quality of life.

3.2.2 Exclusion criteria: clinical effectiveness

Studies were excluded based on the following criteria:

Single case reports.

RCTs that:

- provided only unplanned, interim findings
- provided data on only a sub-group of the enrolled patients
- were continuing to recruit patients
- where patients numbers treated with specific intervention (i.e. a particular type of stent) could not be determined.

Studies of:

- treatment of in-stent restenosis
- treatment of saphenous vein grafts.

Comparison of:

- DES with other PCI interventions (e.g. Atherectomy, Rotabaltors, Brachytherapy)
- DES with surgery
- variations of drug-loading among single DES types ('brands').

3.2.3 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 pre-tested data extraction forms created within the *Access* database application, Microsoft Corporation, and then checked for accuracy by a second reviewer.

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

3.2.4 Quality assessment: clinical effectiveness

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

3.3 Methods for reviewing cost-effectiveness

3.3.1 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 the Assessment Group's own economic evaluation and budget impact assessment.

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

3.3.2 Inclusion criteria: cost-effectiveness

Study design

Full economic evaluations that compared two or more options and considered both costs and consequences including:

- Cost-effectiveness analysis
- Cost-utility analysis
- Cost-benefit analysis.

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 NHS close to the time of the assessment. As for the review of clinical effects.

Comparators

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

Health outcomes in an economic framework

- Quality adjusted life years (QALY)
- Disease specific measures, such as: MACE, repeat revascularisations avoided, MACE free survival, TLR and TVR.

3.3.3 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.

4 REVIEW OF CLINICAL EFFECTS - DES VERSUS BMS AND OVERVIEW OF NEW DES

4.1 Introduction

4.1.1 Scope of clinical review

This chapter presents the results of the systematic review of published and unpublished evidence on the clinical effects of drug-eluting stents. The review focused on identifying randomised controlled trials, but other designs (such as good quality registries of DES use) were considered were 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 Inc; *Dexamet*™, Abbott and *Taxus*™, Boston), as well as subsequent, 'new' DES designs which were expected to be available for use by 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*™, Kiwimed/Translumina). 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.

4.1.2 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 4-1.

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-randomised studies or prospective registries) 27 records were identified.

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

Handsearching and unpublished sources of evidence

As can be seen from the two right-most columns of Table 4-1, 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.

Table 4-1 Sources of evidence identified by search strategy for each DES/ included study

		Principle source types:			First identified in:	
DES	**Studies**	**Full Pubs**	**Abstract/ Conference**	**Submission**	**Electronic searches**	**Handsearch Submissions**
Cypher	BASKET	✓ (*Recent*)	-	-	-	✓
	CORPAL	-	✓	-	-	✓
	C-SIRIUS	✓	-	-	✓	-
	DIABETES	-	✓	-	✓	-
	DOMINO	-	-	✓	-	✓
	E-SIRIUS	✓	-	-	✓	-
	ISAR-DIABETES	✓ (*Recent*)	✓	-	-	✓
	Li	-	✓	-	✓	-
	Pasche	✓	-	-	✓	-
	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	✓	✓	(✓ Prev TAR)	✓	-
Costar	COSTAR I	-	-	✓	-	✓
	EUROSTAR	-	-	✓	-	✓

DES	Studies	Principle source types: Full Pubs	Abstract/ Conference	Submission	First identified in: Electronic searches	Handsearch Submissions
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); Prev TAR – study data noted from previous appraisal submission; Minimal – only minimal data provided by manufacturer, which were not used in analysis.

4.2 Drug-eluting stents versus non drug-eluting BMS – RCT-based evidence

4.2.1 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[31-79] [80-82] met the inclusion criteria for the meta-analysis. All 17 are included for at least one outcome in the meta-analysis.

4.2.2 Study characteristics

Ten of the studies compared Cypher sirolimus-eluting stents with BMS (C-SIRIUS,[53, 83] DIABETES,[54, 68] E-SIRIUS,[55, 56, 83] Li,[79] Pasche,[52] RAVEL, [57-66, 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 bare metal BMS (TAXUS I,[33-35] TAXUS II,[36-38] TAXUS IV, [39-50, 86, 87] TAXUS V[51, 88] One study, BASKET,[82] compared both Cypher and Taxus DES to a newer BMS in a three-arm study. Endeavor ABT-578 (zotarolimus)-eluting stents were compared to

BMS in ENDEAVOR II[89] and Xience V everolimus-eluting stents to BMS in SPIRIT FIRST.[31, 32]

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[31]) and 61 (TAXUS I[33]) to studies of over 1000 participants, with up to 1058 in SIRIUS, 1172 in TAXUS V, 1197 in ENDEAVOR II, and 1314 people 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 Pasche [52], 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 coronary artery disease, silent ischemia or significant stenosis (greater than 50%) of the target vessel (C-SIRIUS, DIABETES, E-SIRIUS, Pasche, 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 4.0mm were included in BASKET and TAXUS V, and were reported to be as narrow as 2.25mm 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 10mm in TAXUS II and TAXUS V to lesion of up to 33mm 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[54] study included only people with diabetes requiring pharmacological treatment.

A key exclusion for all but three studies was acute or evolving myocardial infarction. The BASKET[82] study permitted participation of people with ACS (including

STEMI) and STRATEGY[80] focused on STEMI patients. In the abstract available for Li,[79] exclusion criteria were not presented. 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, bifurcation, presence of thrombus in 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, Pasche, SES-SMART, SIRIUS, C-SIRIUS, E-SIRIUS, AiC 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, AiC 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, AiC 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, Pasche, TAXUS II, TAXUS V, TAXUS I) to 1 year (DIABETES)

Further details of study characteristics are presented within Table 1, in the appendices.

4.2.3 Participant characteristics

In Appendix 3, Table 2 presents further details of the participants included in the trials.

4.2.4 Quality assessment of included studies

Assessment of the quality of included studies, based on CRD Report 4,[22] is presented in Table 4-2. 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, Pasche, RAVEL, SES-SMART, SIRIUS, TAXUS I, TAXUS II, TAXUS IV, except for C-SIRIUS where the method of random sequence generation was not detailed (use of 'sealed randomisation envelopes' was described).[53] 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 Li. Information on allocation concealment was not available for studies without full reports. All but Pasche 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 report of Li 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, Pasche, RAVEL, SES-

SMART, SIRIUS, TAXUS I, TAXUS II, TAXUS IV) all 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.

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 not this is not stated) no withdrawals to describe.

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

Table 4-2 Quality assessment: DES versus BMS RCTs

	Randomisation:			Baseline comparability:		Eligibility criteria specified	Co-interventions identified	Blinding:				Withdrawals:		Intention to treat
	Truly Random	Allocation concealment	Number stated	Presented	Achieved			Assessors	Administration	Participants	Procedure assessed	>80% randomised in final analysis	Reasons stated	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
C-SIRIUS[53]	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[56]	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
Pasche[52]	Yes	No	Yes	Yes	Yes	Yes	Yes	NS	NS	NS	NS	Yes	Yes	Yes
RAVEL [57]	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[31]	NS	NS	Yes	Yes	Part	Yes	No	Uncl	No	Uncl	NS	Yes	Yes	No
STRATEGY[80]	Yes	Part	Yes	Yes	Yes	Yes	Yes	Noi	No	Yes	No	Yes	Yes	Yes
TAXUS I [33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
TAXUS II[36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
TAXUS IV[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
TAXUS V[51]	NS	NS	Yes	Yes	Yes	Yes	Yes	NS	NS	NS	NS	Yes	Part	Yes

Legend: NS: not stated, Uncl: Unclear; Part: Partially

4.2.5 Outcomes/Data analysis

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

Data in the form of odds ratio (OR) and 95% confidence intervals (CI) 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 difference (WMD) were analysed.

Heterogeneity was tested by the chi-squared 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 estimate incorporating available data for all DES analysed are presented in Table 4-3. 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 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 paclitaxel-eluting stent analyses and the same BMS in comparison with SES are analyses in the sirolimus-eluting stent grouping.

Meta-analysis was performed for available data reported up to 1 month, 6 to 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 (Appendix figures 1 to 6).

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 4-1, later in this chapter. Plots for analysis of other follow-up periods are located in the appendices.

AMI

No statistically significant difference in myocardial infarction was discernable 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 4-1 (ii) and for other follow-up in the appendices.

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 of 10 to 25% for BMS at 1 year (See Figure 4-1 iii 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, 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; 0.16 to 0.27, see Table 4-3) suggests a reduction of around three quarters in 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 appendices - OR for SES subgroups: 0.21, 0.15 to 0.30 at 6 months; 0.17, 0.12 to 0.25 at 1 year; 0.22, 0.15 to 0.30 at 2 years and 0.25 0.17 to 0.36 at 3 years; and for PES 0.37, 0.28 to 0.49 at 6-9 months; 0.26, 0.18 to 0.39 at 1 year; 0.28, 0.20 to 0.40 at 2 years and 0.13, 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 statically significant.

Meta-analysis plots are presented for TLR in Figure 4.1 (iii) up to 1 year and for other follow-up in the appendices.

Revascularisation – TVR

Target vessel revascularisation was analysed for PES at 6-9 months (0.51; 0.40 to 0.66), 1 year (0.40; 0.29 to 0.55), 2 years (0.45, 0.34 to 0.59) and 3 years (0.32; 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 (0.34; 0.19 to 0.60, Pasche), and 3 years (0.35; 0.25 to 0.49, SIRIUS).

Meta-analysis plots are presented for TVR in Figure 4.1 (iv) up to 1 year and for other follow-up in the appendices.

Event rate

Analysis of event rate (MACE, TVF) favoured DES at 1 month (0.74; 0.58 to 0.95), 6-9 months (0.46; 0.40 to 0.53), 1 year (0.39; 0.33 to 0.47), 2 years (0.43; 0.34 to 0.54) through to 3 years (0.42; 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 in Table 4-3), although the 1 month analysis of DES versus BMS confidence interval extended beyond statistical significance.

Direction of effect and statistical significance are maintained through to 3 years, with the value for OR for the SES subgroup (compared to BMS) and PES (compared to BMS) remaining within 0.04 (OR: 0.39, 0.42 and 0.43) during the period 1 to 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 1 year) with other trials falling within a narrower the range of 8.6 to 13.6% for DES and 19.8 to 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 4.1 (v) and for other follow-up in the appendices.

Binary restenosis

At angiographic follow-up between 6 to 9 months, rates of binary restenosis 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 confidence intervals for this analysis just breach the margin for statistically significance.

The pooled estimate for binary restenosis in the PES group was 0.27; 0.20 to 0.35; 0.08; 0.05 to 0.10 for SES and AiC 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 4-2 (i) Random-effects analyses in the appendices

Late loss

Late loss analysis at follow-up ranging 6 to 9 month favoured DES (WMD: -0.59; -0.62 to –0.56). Mean late loss was reduced by 0.45mm for PES (WMD: -0.45; -0.50 to –0.40), and by 0.79mm for SES (WMD: -0.79; -0.84 to –0.74). The single trial analysed for Xience indicated a reduction of 0.74mm (WMD: -0.74; -0.91 to –0.57). AiC removed.

High levels of statistical heterogeneity was indicated for the SES and total pooled analysis. Fixed-effect analyses are presented in Figure 4-2 (ii), random-effects in the appendices.

Time trends in outcomes

The OR presented in Table 4.3 show stability in values from 1 year through to 3 years, i.e. little or no increasing benefit of DES over BMS after the first year.

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 odds ratio 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 do not indicate that there is a trend toward higher thrombosis in either 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 and TAXUS V where the number of events were the same in DES 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.

In the course of our searching some other sources of information, including secondary research was 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.

Table 4-3 Meta-analysis: pooled estimates for comparison of DES versus BMS

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

Legend: Data presented are Odds ratio; 95% confidence intervals for the pooled effect estimate (fixed-effect model). Statistically significant effect estimates are in **bold**. RE: Where statistical heterogeneity indicated by testing Chi^2 (p=0.10 or less) or I^2 statistic (40% or more) random-effects analysis is presented underneath the fixed-effect estimate.

4.3 Drug-eluting stents without RCT evidence

4.3.1 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 AG searching activities, so information on this device is derived from the manufacturer only.
- The *CoStar* stent has been studied in the EuroSTAR and COSTAR India non-randomised controlled trials, 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 4-4 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, Liberte 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 rigor of the assessment of these DES.

Table 4-4 DES without evidence reported from RCTs

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

Consideration of the AXXION DES

During the appraisal process, the AXXION paclitaxel-eluting stent (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 or *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

CiC removed.

4.3.2 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-randomised controlled trials for another two (*CoStar, Yukon)*. The Janus tacrolimus-eluting stent was examined in the JUPITER I non-controlled study, whereas the Taxus Liberte PES was evaluated in ATLAS non-controlled study. A range of formulations of the CoStar stent eluting paclitaxel was evaluated in EuroSTAR and CoSTAR non-randomised controlled studies. The ISAR-Project was a dose-ranging non-randomised controlled study, 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 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'. CiC removed.

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

Stenosis of more than 50% was a stated entry requirement for EuroSTAR, CoSTAR I, JUPITER I. Symptoms in the 'presence of significant stenosis' were required for ISAR-Project. CiC removed.

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

Key data on design of studies of Dexamet, CoStar Janus, Liberté and Yukon DES are presented in Appendix 5, Table 7

4.3.3 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 1.

4.3.4 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 is 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 single incidence AMI in the non-DES group up to a mean 8 (+/-2) months follow-up. Revascularisations up to a mean of 8 months were 2% TLR in the DES group, 10% TLR (12% TVR) in the control group (OR: 0.18; 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; 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 month follow-up. Total MACE up to 6 months for the 'intention-to-treat' 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 month follow only one patient under went TLR (MACE 3.3%). Angiographic follow-up on 26 patient indicated BRR in 31% of patients and an average in-stent late loss 0.97 (+/- 0.63) mm. The authors of the EMPEROR Pilot state in the introduction to their paper that these findings result in the full EMPEROR RCT programme being cancelled before patient recruitment.

Two addition 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-up. 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 CEC adjudicated) analysis was 12%. Available reports of the SAFE registry indicated that in hospital analysis represented 735 patients, though 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%) as well as 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 1 of 2 arms of the EuroSTAR study are presented for information in Appendix 5, Table 8. Follow-up the second arm of EuroSTAR is ongoing. Interim data on only 2 of 4 arms of the ongoing CoSTAR I study are also presented in Table 8 of Appendix 5.

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.

CiC 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, 1.3% in the BMS group. At 1 year, composite of death or non-fatal MI was 2.7% for sirolimus-eluting formulations, 3.9% for BMS. No statistically significant difference in death, MI or composite of death or MI were 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; 0.34 to 0.81) and BRR (0.52;

0.32 to 0.83) favoured Yukon SES over non-eluting Yukon stents. Means for late loss could not be readily pooled from the available data.

Available outcome data are presented for Dexamet, CoStar Janus, Liberté and Yukon DES in the appendices, Appendix 5, Table 8.

4.4 Drug-eluting stents of different designs –evidence from registries

4.4.1 Introduction

Results from RCTs are the accepted standard for establishing clinical efficacy of a given treatment. However, the artificial setting of such studies and limitations related to participant inclusion mean 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 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.

4.4.2 Review of current DES registries

It was not the purpose of this assessment to comprehensively or systematically identify or present 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 company submission and stated it was a registry that focused on data related to DES designs included as part of this review.

4.4.3 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, 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 collection data in only one country (France, Germany, Korea, The Netherlands, Portugal, Switzerland and the USA). The number of participants registered varied with as few as 183 to more than 15,000. The majority related to only one DES and have 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 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 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.

4.5 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 neither within 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 to 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 quite 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 - is reassuring in that differences in revascularisation rates do not narrow after twelve months, i.e. the early benefit of DE 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 to 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 aspect to the benefits of CABG in most cases. Their effects are maximal by twelve months, but seem sustained thereafter. Whether they are cost effective compared to BMS will depend not just to the relative risk reduction in revascularisations, but on the absolute risk in the types of patients in whom they are used.

4.6 Summary

4.6.1 DES versus BMS

Seventeen RCTs were included in the clinical review, although at most 14 trials were analysed for any one outcome. Eleven RCTs examine 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.

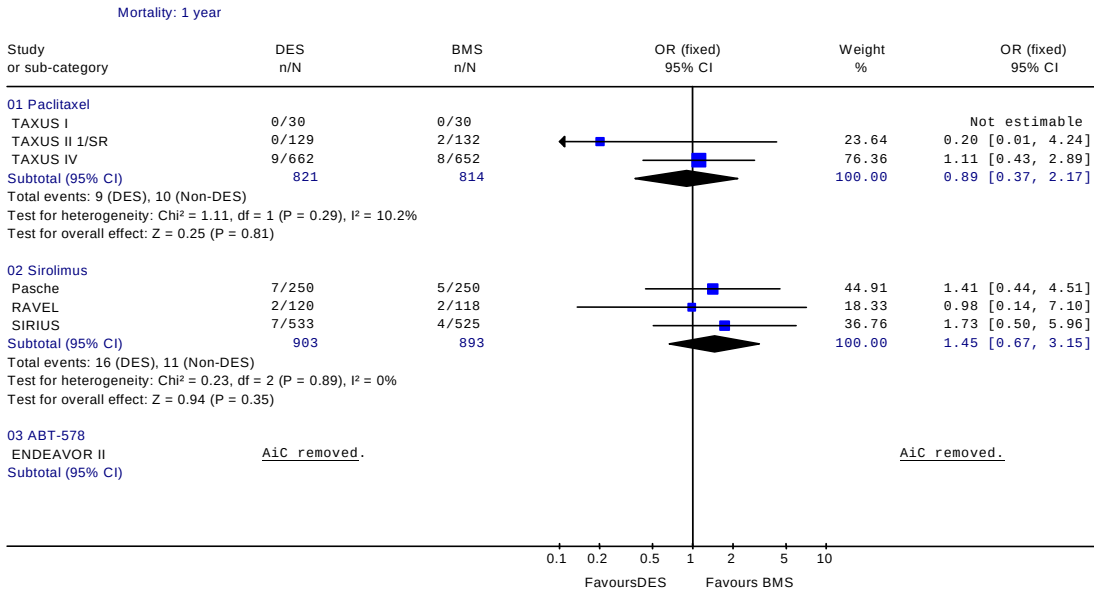
There were no benefits of DES over BMS in serious clinical events (death or AMI). Revascularisation rates were reduced by approximately three quarters, consistent across most studies. The benefits were fully seen by twelve months, and neither increased nor decreased thereafter.

4.6.2 New DES

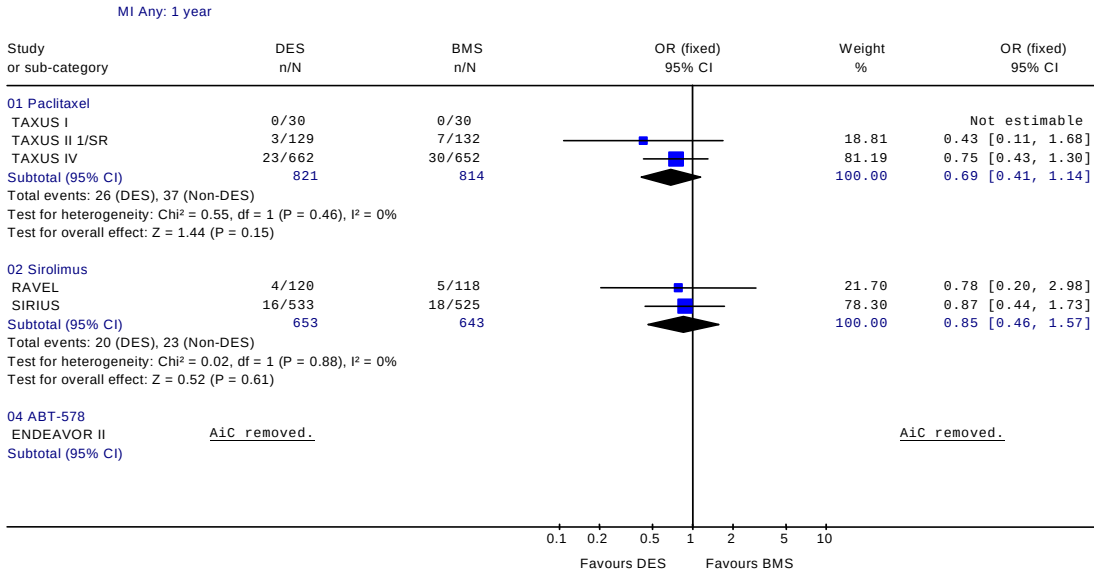
Clinical trial data on new DES – not previously considered by the Assessment Group – were still limited at the time of current assessment. Many devices only have evidence on efficacy from dose ranging trials or non-controlled studies. Meaningful comparison with BMS or other DES designs was not possible 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.

Figure 4-1 Meta-analysis DES versus BMS at 1 year

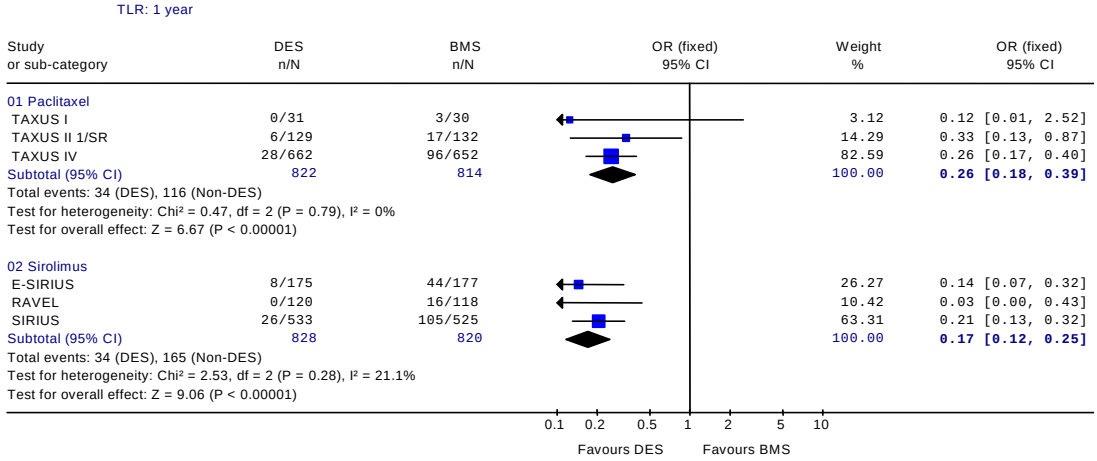
i.



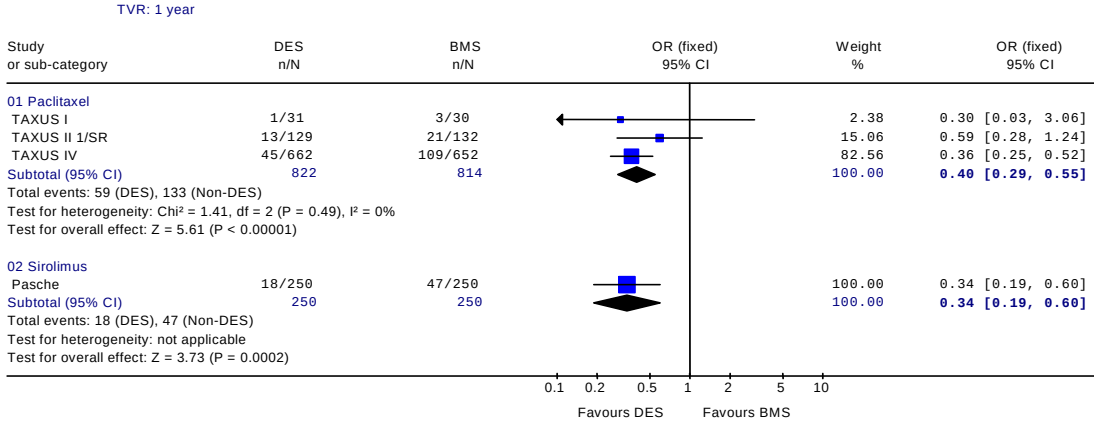
ii.



iii.


TLR: 1 year
Study or sub-category
DES n/N
BMS n/N
OR (fixed) 95% CI
Weight %
OR (fixed) 95% CI
01 Paclitaxel
TAXUS I 0/31 3/30 3.12 0.12 [0.01, 2.52]
TAXUS II 1/SR 6/129 17/132 14.29 0.33 [0.13, 0.87]
TAXUS IV 28/662 96/652 82.59 0.26 [0.17, 0.40]
Subtotal (95% CI) 822 814 100.00 0.26 [0.18, 0.39]
Total events: 34 (DES), 116 (Non-DES)
Test for heterogeneity: Chi² = 0.47, df = 2 (P = 0.79), I² = 0%
Test for overall effect: Z = 6.67 (P < 0.00001)
02 Sirolimus
E-SIRIUS 8/175 44/177 26.27 0.14 [0.07, 0.32]
RAVEL 0/120 16/118 10.42 0.03 [0.00, 0.43]
SIRIUS 26/533 105/525 63.31 0.21 [0.13, 0.32]
Subtotal (95% CI) 828 820 100.00 0.17 [0.12, 0.25]
Total events: 34 (DES), 165 (Non-DES)
Test for heterogeneity: Chi² = 2.53, df = 2 (P = 0.28), I² = 21.1%
Test for overall effect: Z = 9.06 (P < 0.00001)
0.1 0.2 0.5 1 2 5 10
Favours DES
Favours BMS

iv.


TVR: 1 year
Study or sub-category
DES n/N
BMS n/N
OR (fixed) 95% CI
Weight %
OR (fixed) 95% CI
01 Paclitaxel
TAXUS I 1/31 3/30 2.38 0.30 [0.03, 3.06]
TAXUS II 1/SR 13/129 21/132 15.06 0.59 [0.28, 1.24]
TAXUS IV 45/662 109/652 82.56 0.36 [0.25, 0.52]
Subtotal (95% CI) 822 814 100.00 0.40 [0.29, 0.55]
Total events: 59 (DES), 133 (Non-DES)
Test for heterogeneity: Chi² = 1.41, df = 2 (P = 0.49), I² = 0%
Test for overall effect: Z = 5.61 (P < 0.00001)
02 Sirolimus
Pasche 18/250 47/250 100.00 0.34 [0.19, 0.60]
Subtotal (95% CI) 250 250 100.00 0.34 [0.19, 0.60]
Total events: 18 (DES), 47 (Non-DES)
Test for heterogeneity: not applicable
Test for overall effect: Z = 3.73 (P = 0.0002)
0.1 0.2 0.5 1 2 5 10
Favours DES
Favours BMS

v.

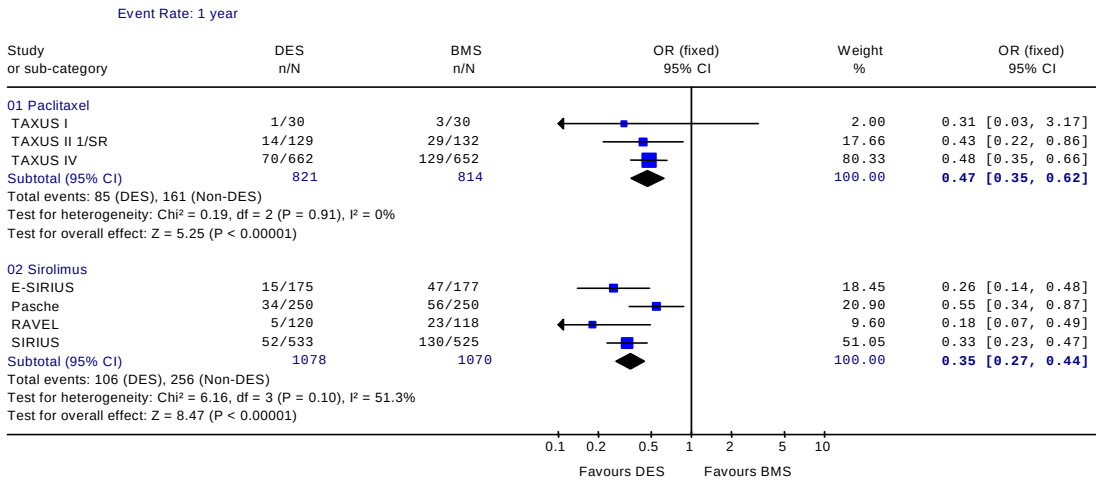
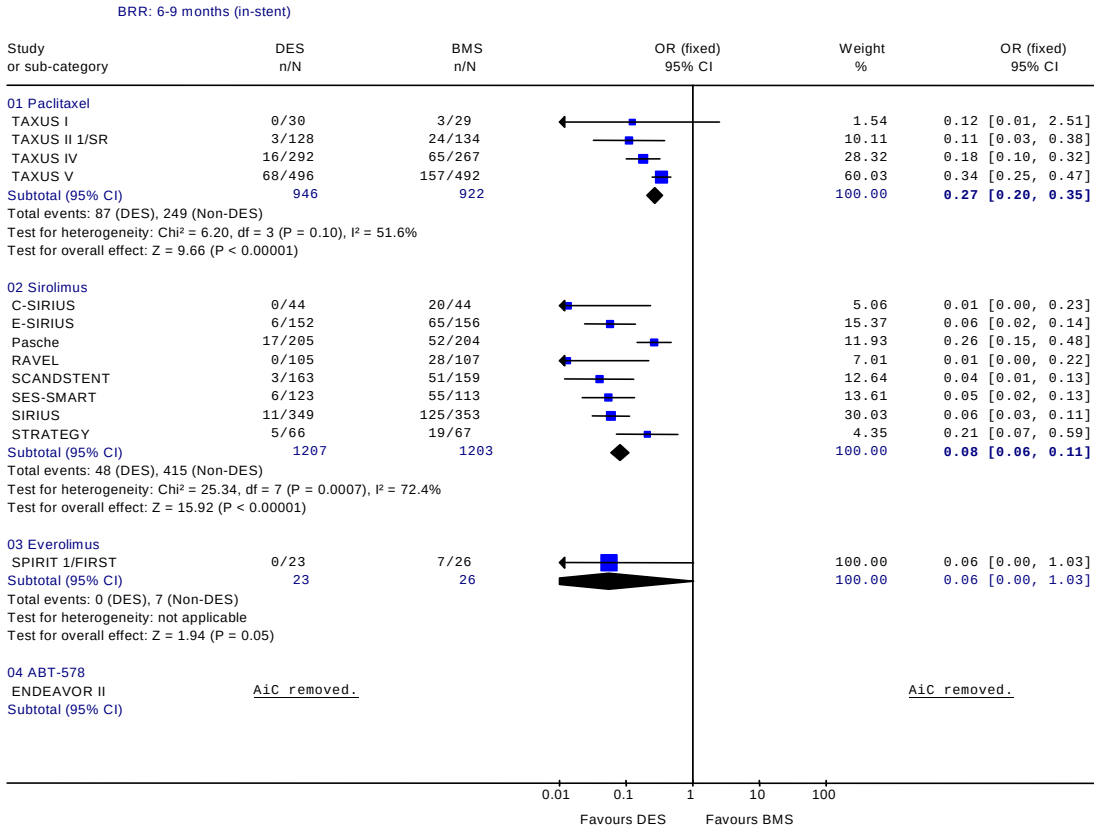
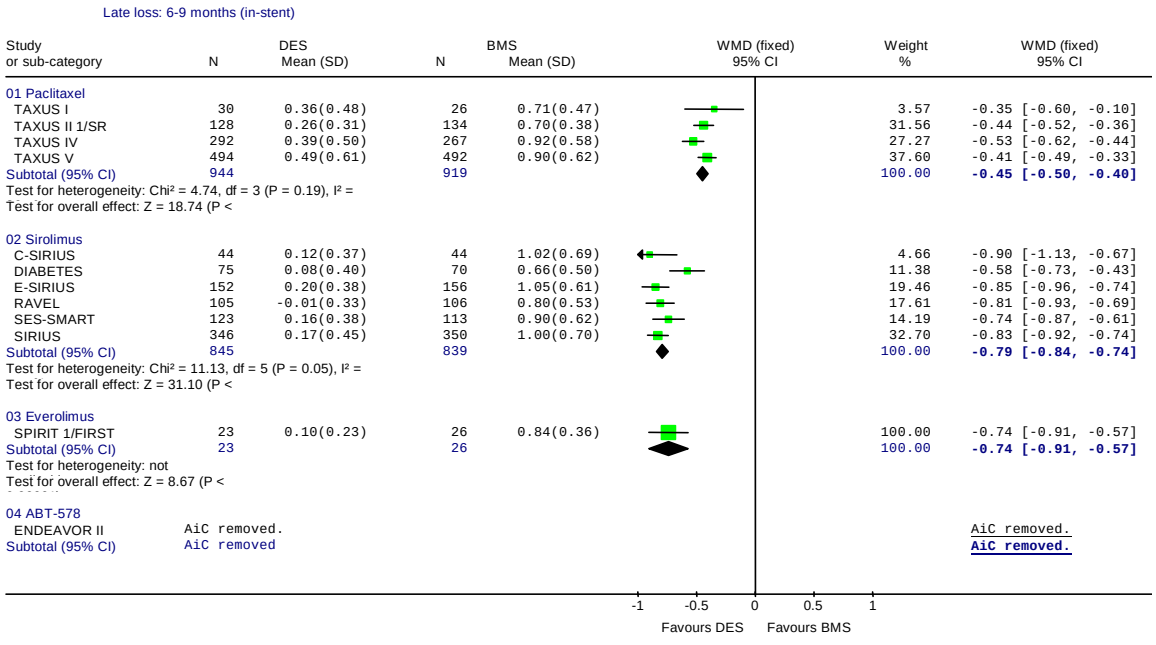

Event Rate: 1 year
Study or sub-category
DES n/N
BMS n/N
OR (fixed) 95% CI
Weight %
OR (fixed) 95% CI
01 Paclitaxel
TAXUS I 1/30 3/30 2.00 0.31 [0.03, 3.17]
TAXUS II 1/SR 14/129 29/132 17.66 0.43 [0.22, 0.86]
TAXUS IV 70/662 129/652 80.33 0.48 [0.35, 0.66]
Subtotal (95% CI) 821 814 100.00 0.47 [0.35, 0.62]
Total events: 85 (DES), 161 (Non-DES)
Test for heterogeneity: Chi² = 0.19, df = 2 (P = 0.91), I² = 0%
Test for overall effect: Z = 5.25 (P < 0.00001)
02 Sirolimus
E-SIRIUS 15/175 47/177 18.45 0.26 [0.14, 0.48]
Pasche 34/250 56/250 20.90 0.55 [0.34, 0.87]
RAVEL 5/120 23/118 9.60 0.18 [0.07, 0.49]
SIRIUS 52/533 130/525 51.05 0.33 [0.23, 0.47]
Subtotal (95% CI) 1078 1070 100.00 0.35 [0.27, 0.44]
Total events: 106 (DES), 256 (Non-DES)
Test for heterogeneity: Chi² = 6.16, df = 3 (P = 0.10), I² = 51.3%
Test for overall effect: Z = 8.47 (P < 0.00001)
0.1 0.2 0.5 1 2 5 10
Favours DES
Favours BMS

Figure 4-2 Meta-analysis DES versus BMS – angiographic outcomes at 6-9 months

i.



ii.



5 REVIEW OF CLINICAL EFFECTS – COMPARISION BETWEEN DES

5.1 RCT-based evidence

5.1.1 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 randomised controlled trials 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 through handsearching activities (SIRTAX, REALITY, ISAR-DIABETES, CORPAL, BASKET[82, 107, 108, 110-117] and two (DOMINO and ISAR-TEST[118, 119]) from manufacturer submissions to NICE.

5.1.2 Study characteristics

Six of the RCTs compared Cypher sirolimus-eluting stents with Taxus paclitaxel-eluting stents (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 a 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 in-stent restenosis (ISR). Acute myocardial infarction within 72 hours excluded patients from ISAR-DIABETES, ISAR-TEST, REALITY as did presence of unprotected left main lesions and reintervention for in-

stent restenosis 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 4, Appendix 4 presents details of study design and entry criteria.

5.1.3 Participant characteristics

Table 5, Appendix 4 presents further details of the patient groups studied in the trials.

5.1.4 Quality assessment of included studies

Assessment of included study quality is presented in Table 5-1. 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 intention-to-treat 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 intention-to-treat 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 intention-to-treat.

Table 5-1 Quality assessment: DES versus DES RCTs

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

Legend: NS: not stated, Uncl: Unclear; Part: Partially

5.1.5 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 5-1 to 5-3 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 table 6.

Mortality (Figure 5-1, i)

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

AMI (Figure 5-1, ii)

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

Revascularisation – TLR (Figure 5-2, i, ii, iii)

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 have opted to present analysis of TLR in three ways. Firstly with inclusion of TLR reported at mean 13 (+/-4) months for the CORPAL study in the same analysis of 6 to 9 months data for ISAR-DIABETES, REALITY, SIRTAX and TAXi; secondly without CORPAL at 6-9 months and thirdly with CORPAL alone at 1 year.

In the 6 to 13 month analysis of TLR (including CORPAL) a marginal, but statistically significant, advantage of SES over PES is observed (0.68; 95% CI 0.51 to 0.91). When analysing only those studies reporting at 6 to 9 months the pooled estimate favouring SES is only just within statistical significance (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 (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 (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 5-2, iv)

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

Composite event rate (Figure 5-1, iii)

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% confidence intervals only just within statistical significance (0.75; 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 5-3, i, ii)

In-stent binary restenosis, analysed on a by lesion basis, favoured Cypher SES over Taxus PES in the three trials analysed, as with other outcomes, the confidence interval for the pooled estimate is near the line of no effect (0.69; 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 broad confidence intervals, but just within statistical significance (0.33; 0.11 to 0.95). In DOMINO no statistical difference was found.

Late loss (Figure 5-3, iii, iv)

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

5.2 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 to around 7% for PES overall. It is not clear to which 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 procedures, while 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 to BMS, it may be that these differences will be maintained. While 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 to 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, though 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.

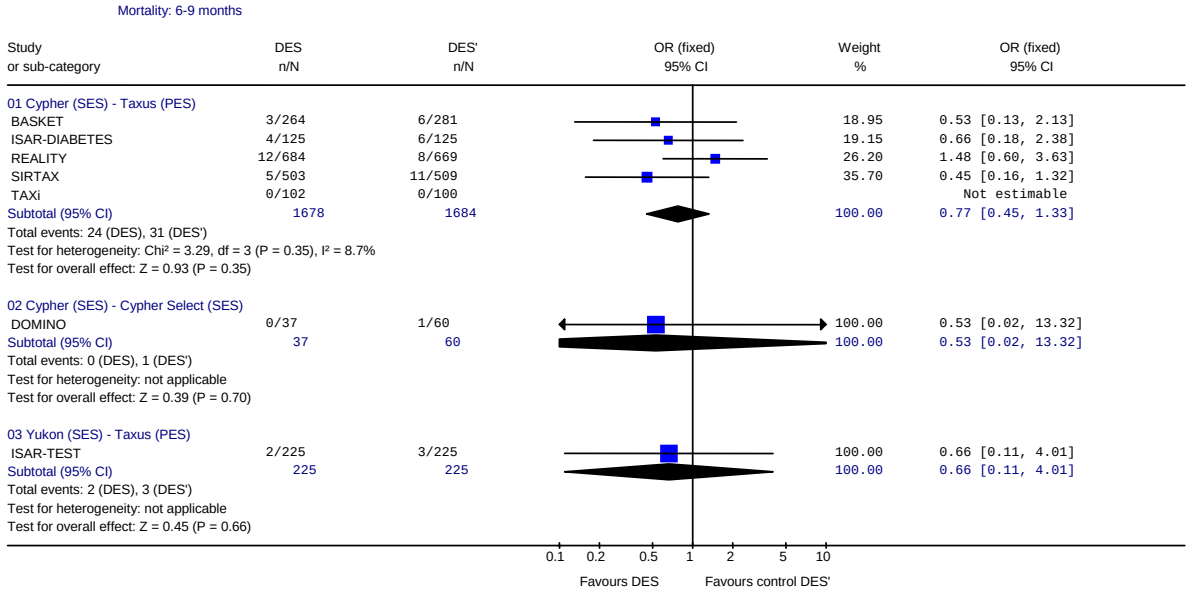
5.3 Summary

To date, eight RCTs have reported head-to-head comparisons of different DES types, but variation in study design and outcome reporting limits 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 await confirmation in peer-review publications and follow-up was limited to 9 months except for one study.[114]

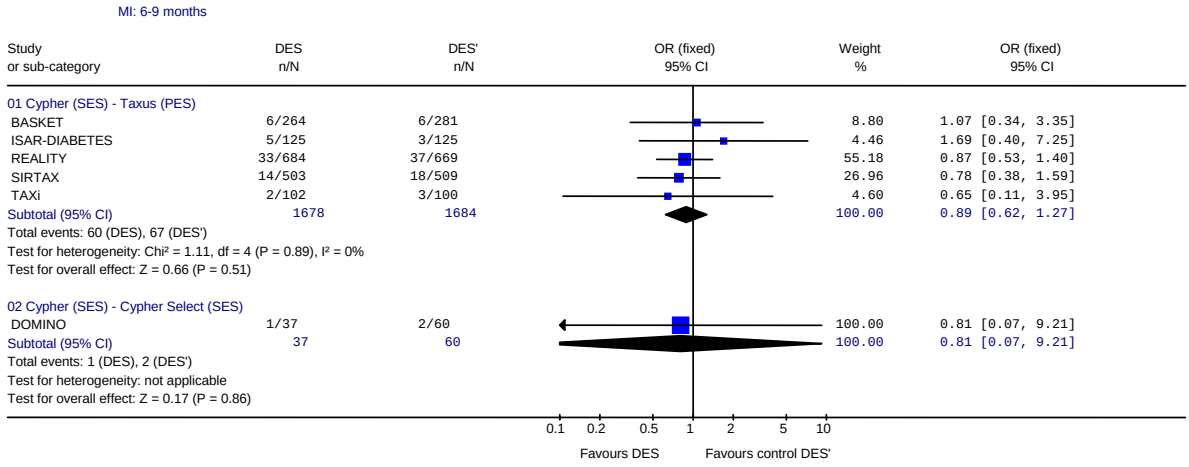
No statistically significant differences in death or AMI were detected between DES designs. Analysis of TLR up to 9 months was marginally in favour of SES over PES. A larger, although still marginal, reduction in TVR with SES was determined from meta-analysis of two trials at 9 months. Reduction in composite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

Figure 5-1 Meta-analysis DES versus DES at 6-9 months

i.



ii.



iii.

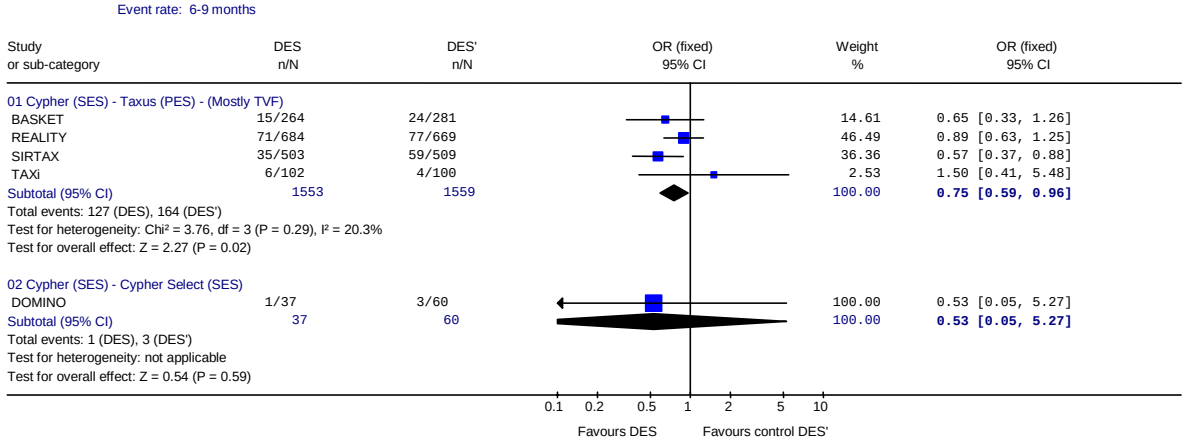
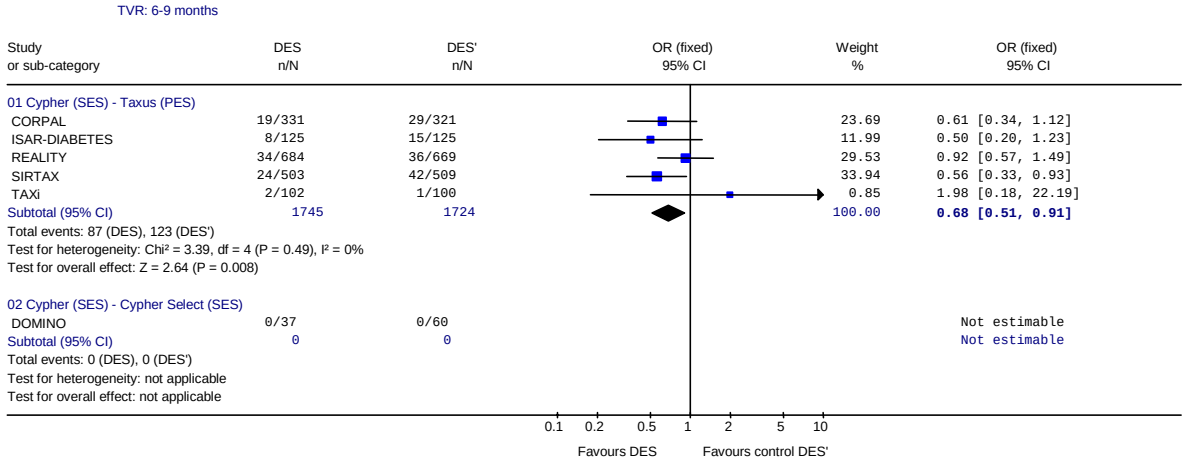
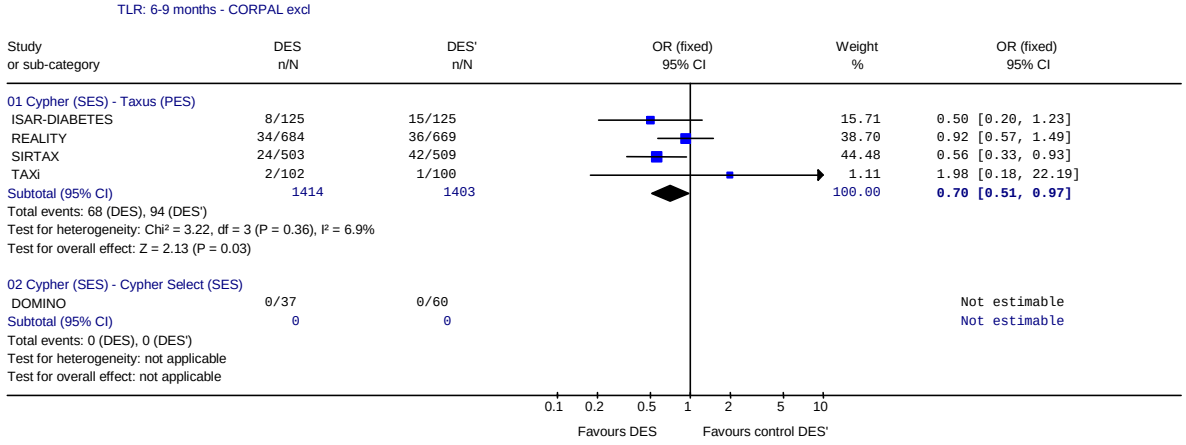


Figure 5-2 Meta-analysis DES versus DES – TLR 6-13 months, TVR at 6-9 months

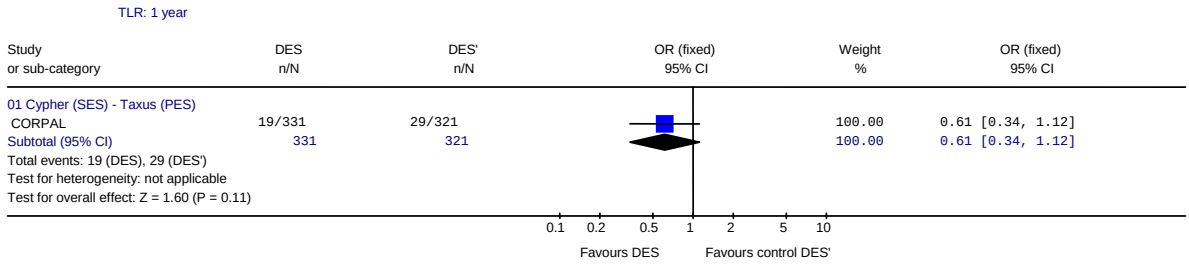
i.



ii.



iii.



iv.

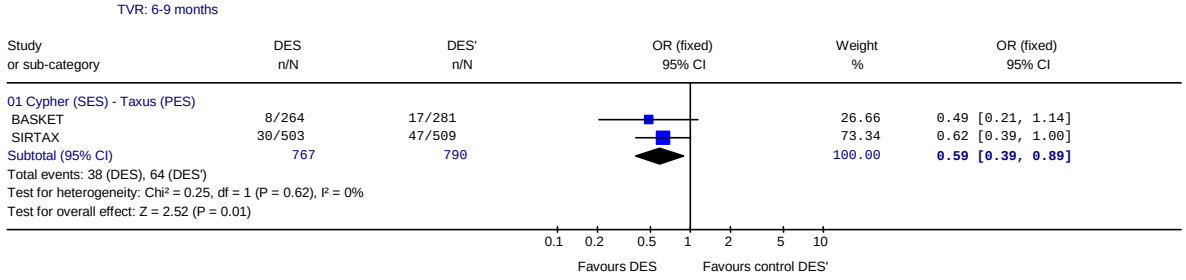
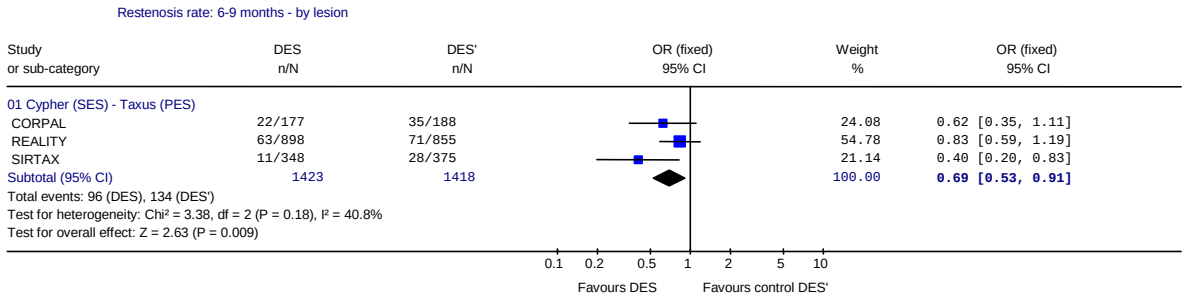
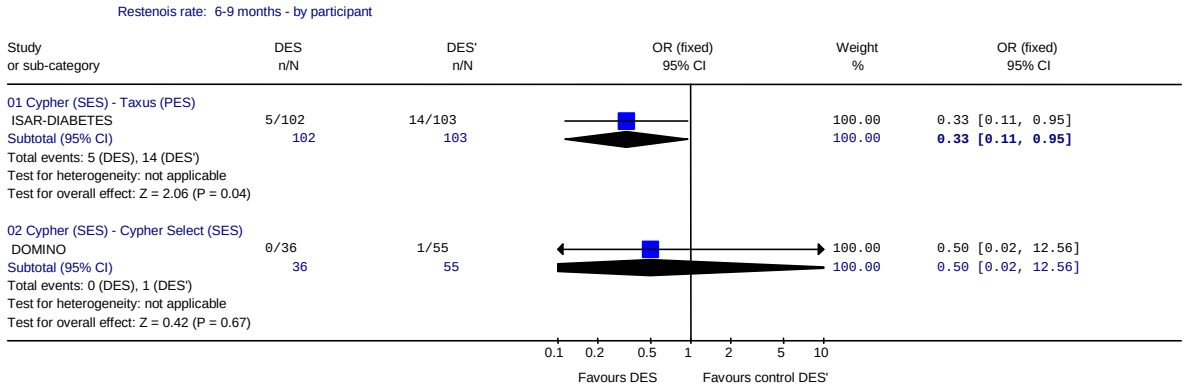


Figure 5-3 Meta-analysis DES versus DES – angiographic outcomes at 6-9 months

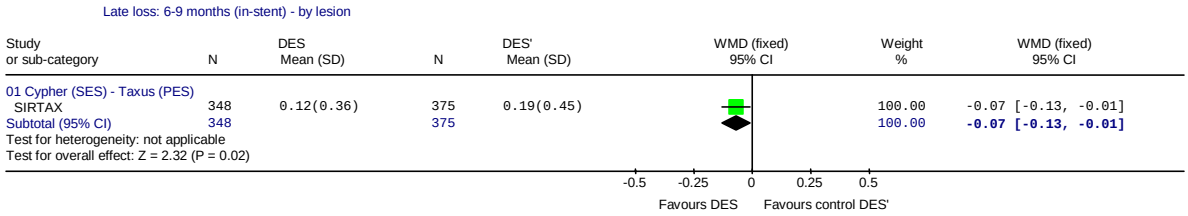
i.



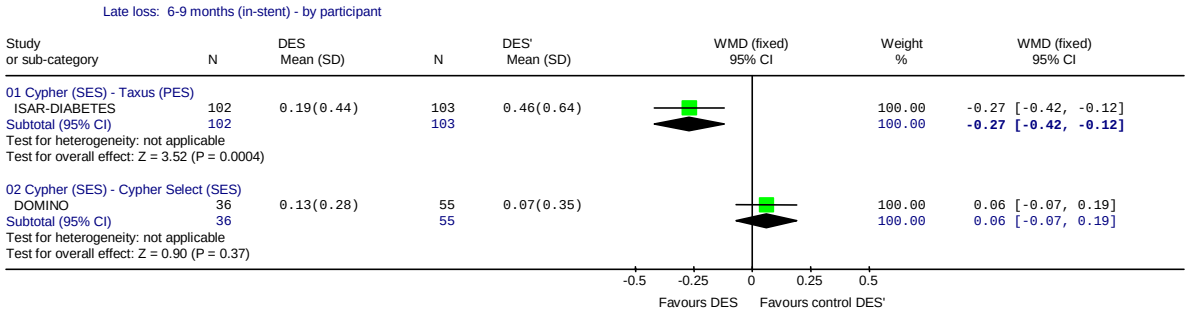
ii.



iii.



iv.



6 REVIEW OF PUBLISHED ECONOMIC EVALUATIONS

6.1 Introduction

This chapter explores the published literature on the costs and benefits of drug-eluting stents (DES) for coronary artery disease (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.

6.2 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 quality of life owing to the avoidance of repeat revascularisations. The question then is can the increased initial treatment costs of DES be offset by the reduced costs of repeat revascularisations avoided, or be justified by the small gain in quality of life? To address this question both the costs and health outcomes need to be defined.

6.2.1 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, health care personnel, and medical facilities. When comparing DES to BMS for coronary artery disease the only differences in the medical care costs will be the initial treatment costs (acquisition cost of using DES compared to BMS), and the costs of treating recurrent symptoms; including investigations, repeat revascularisations, and follow ups. Using this perspective, the high cost of DES means 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 not only include the direct health care 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.

6.2.2 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 major adverse cardiac event (MACE) free survival, target lesion revascularisation (TLR), target vessel revascularisation (TVR), and repeat revascularisation avoided (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 to BMS. Given that DES decrease the rate of restenosis compared to BMS, a small gain in health related quality of life 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 quality adjusted life year (QALY), allowing a cost-utility analysis to be undertaken.

6.3 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.

6.3.1 Identification of studies

Details of the search strategy, inclusion criteria, data extraction and quality assessment are presented in chapter three. A total of ten full economic evaluations 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] four additional papers by handsearching.[82, 126-128] One of these was in Italian,[126] and hence could only be partially reviewed.

6.3.2 Characteristics of economic studies

Four studies[120-122, 124] undertook cost-utility analysis, reporting incremental costs per QALY (see Table 6-1). The remaining studies were cost-effectiveness analyses. All of the studies compared sirolimus eluting stents with BMS, although the studies by Bagust, AETMIS, Kaiser (labelled as BASKET in the clinical review) and Mittmann also included paclitaxel eluting stents. Furthermore, the study undertaken by Kaiser included a third generation BMS comparator (Vision). Only one of the studies was set

in the UK[120]; the remaining nine were set in the US, Canada, or the rest of Europe. All of the studies were of one year in duration, except Greenberg, which was over two years, Kaiser, which was over six months, and Shrive, which was set over a patient's lifetime.

6.3.3 Economic models

All of the studies were based on some form of economic model (Table 6-2). Shrive used a Markov model with six month intervals for the duration of the patient's lifetime. The model employed by Cohen was not clearly described but involved logistic regression and prospective analysis of the SIRIUS trial results. Similarly, the model by Van Hout 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 health care provider perspective, except Mittmann, which adopted hospital and provincial perspectives. Apart from Van Hout, Kaiser and Tarricone (unable to translate Gulizia), all of the studies explored model assumptions.

6.3.4 Cost data and data sources

All of the studies apart from Tarricone estimated the cost of DES to incur a price premium (Table 6-3). In order to aid comparison, where a price year was stated, currencies where converted to UK£, 2003; the year of the only UK study (Bagust, 2005). 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 equalise the purchasing power between currencies. To inflate prices to 2003, the consumer price index (CPI) was used.[129]

Cohen, Kaiser, Mittmann and Shrive provided price years which enabled conversion to UK£, 2003. Between these studies the price premiums ranged from £233 to £1255. Switzerland (Kaiser, 2005) reported the lowest price premium, whilst 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, and Mittmann), both of whom were set in 2002 (Mittmann 2002/2003 assumed to be 2002 for CPI purposes). Shrives price premium is over Can$600 more than Mittmans, owing to the

fact that Shrive estimated DES at $2900, whilst Mittmann only estimated it at $2400, similarly BMS were estimated at $500 by Shrive, and $608 by Mittmann.

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

6.3.5 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 6-4). 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 QALY. However, repeat revascularisations avoided, TLR avoided, MACE, and MACE free survival, were also reported.

6.3.6 Cost-effectiveness results

The cost effectiveness results varied considerably across studies (Table 6-5). The IC/QALY ranged from $27,540 to Can$96,523 for a general population. Bagust did not include a general population as subgroups were found to be too dissimilar for comparison. Both Greenberg and Cohen reported ICER per repeat revascularisation avoided. Cohen estimated it to be $1650 over one year, whilst Greenberg estimated it at approximately $7000 over two years. The other studies reported various outcomes which were not comparable.

Subgroup analysis

All but 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 cost-effectiveness ratios became more acceptable for the ‘high risk’ subgroups.

In all the studies except Bagust and Kaiser, diabetes was found or assumed to be a risk factor for restenosis. Thomas[130] has recently criticized the lack of inclusion of diabetes as a subgroup by Bagust, but both Kaiser and Bagust, used ‘real world’ data which differs from the clinical trial data from which the belief of 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 was undertaken in all ten studies. Cohen, Kaiser and Van Hout employed bootstrapping and multivariate SA, whilst Bagust, Mittmann, and Shrive used univariate (one-way) SA. Mittmann also undertook probabilistic SA and expected value of perfect in formation (EVPI) analysis, which showed costs to be the most uncertain factor. Tarricone undertook a simple two-way analysis, whilst AETMIS undertook multivariate and univariate Monte Carlo SA. Greenberg 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, Van Hout was based on the early RAVEL study which was a small study undertaken using a USA-based balance of costs which do not translate to the UK NHS experience.

6.3.7 Quality of economic literature

Ten studies were quality assessed against a standard checklist.[131] Guiliza 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 (See Table 6-6), except in four key areas. Firstly, the resource use was only reported separately from costs in four of the studies, making it impossible to validate underlying assumptions. Secondly, a discount rate was not applied by Greenberg, and no explanation was given as to why not. Furthermore, the sensitivity analysis was not fully explained or justified by Greenberg. Finally and most importantly, the modelling methodology was poorly described by seven of the studies, making it difficult to access the credibility of their models.

6.4 Commentary

The balance of evidence indicates (Bagust, Cohen, AETMIS, Gulizia, Kaiser, Mittmann, and Shrive) 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 one single trial study could be said to be pragmatic and likely to reflect clinical practice outside of a trial (Kaiser). Some studies made great effort to convert efficacy in trials into clinical effectiveness, and these generally concluded with worse ICERs.

Table 6-1 Characteristics of economic studies

Study	Type of evaluation and synthesis	Interventions	Study population	Country	Time period of study
AETMIS, 2004[122]	CUA	DES (sirolimus and paclitaxel coated) versus BMS	Quebec RAMQ database, unselected patients. Repeat revascularisation risk with DES taken from Meta-analysis of published trials	Canada	6-13 months
Bagust, 2005[120]	CUA	DES (sirolimus and paclitaxel coated) versus BMS	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 nova, 15-30mm in length with a reference vessel diameter of 2.5-3.5mm. 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 cath labs	Italy	1 year
Kaiser, 2005[82]	CEA	DES (sirolimus and Paclitaxel) versus BMS (Vision, 3rd 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 1998-2000	Canada	Patient's lifetime.
Tarricone, 2004[127]	CEA	DES (sirolimus) versus BMS	Patients suffering from stable or unstable angina, with de nova lesion(s). Casemix 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 nova coronary lesions. SIRIUS trial	Netherlands	1 year

CEA: cost effectiveness analysis; CUA: cost utility analysis,

Table 6-2 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	Health care provider	No difference in survival or rates of MI	Assume 1.7 stents per PCI	Not applicable
Bagust, 2005[120]	Decision analytic model	Health care 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	Health care provider	No difference in long term survival or QoL beyond 1st yr	None stated	Not applicable
Greenberg, 2004[123]	Decision analytic model	Health care 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	Health care 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 health care 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 out-patient 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	Health care 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	Health care provider	Not applicable to model	None stated	Not applicable
Van Hout, 2005 [125]	Unclear – economic model of RAVEL results	Health care provider	Not applicable to model	None stated	Not applicable

Table 6-3 Cost data and cost data sources

Study	Price premium [a] of DES (converted to UK£, 2003 where possible)	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). Regie de l'Assurance Maladie du Qubec (RAMQ) databases	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]	$2000 (£1255)	US$, 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]	$2000	US $, no price year stated	Revascularisation procedures, complications	Several multicenter trials of contemporary PCI involving more than 3000 patients	No explicit discounting undertaken
Gulizia, 2004[126]	€ 1986	Euro, Unable to translate price year	Elective bypass, PCI, emergency room visit	Italian DRG costs	NA – only 1 year
Kaiser, 2005[82]	Cypher vs. Vision €885-1120 (£305-386) Taxus vs Vision €675 (£233)	Euro, 2003/2004	Hospital stay, intensive care, coronary angiography, CABG. Medications not included as assumed same in both arms	Swiss medical tariff (TARMED)	NA – 6months
Mittmann, 2005 [128]	Can$ 1792 (£914.42)	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 for laboratory and diagnostic tests.	Stent manufacturers, the Sunnybrrook and Womens College Health Sciences Centre (SWCHSC) drug formulary, the Ontario Drug Benefit formulary, the Ontario casing Initiative (OCCI), and personal communications	NA – 1year
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	Drug Resource Group (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

a: Price premium is the price differential between DES and BMS

Table 6-4 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	Repeat revascularisation risk reduction of drug-eluting stents 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	N/A
Bagust, 2005[120]	Meta-analysis of RAVEL TAXUS and SIRIUS trials	TVR relative risk reduction of 69.8% for sirolimus eluting stents compared with BMS. TVR risk reduction of 55% for paclitaxel eluting stents compared with BMS	TVR as a proxy for repeat revascularisations, QALY	RAVEL, SIRIUS, TAXUS	N/A
Cohen, 2004[121]	SIRIUS trial	Repeat revascularisation, 13.3% in Sirolimus group, 28.4% in BMS group. Leading to a RR reduction for repeat revascularisation of approx 53%	Repeat revascularisation avoided, QALY	SIRIUS, QoL taken from stent–PAMI trial	N/A
Greenberg, 2004[123]	Uncertain. Some data taken from a database containing one year health outcomes on 6186 patients undergoing PCI with conventional stents (database based on six clinical trials: STARS, ASCENT, SMART, NIVARNA, EXTRA, and CCS)	Relative risk (RR) reduction for TVR of 80% for sirolimus eluting stents compared with BMS	Repeat revascularisation avoided	Database and empirically derived data	No explicit discounting undertaken
Gulizia, 2004[126]	Meta-analysis of stenting (Cutlip, 2002) 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 (Cutlip, 2002) for baseline TLR BMS rates, DES TLR risk reduction taken from SIRIUS trial	N/A
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	N/A
Mittmann, 2005[128]	Meta-analysis of 11 trials	DES TLR 4.8%, BMS TLR 14.2%	TLR avoided	Meta-analysis of 11 trials	N/A
Shrive, 2005[124]	Meta-analysis of RAVEL, SIRIUS, E-SIRUS, and C-SIRIUS	Relative risk (RR) reduction for repeat revascularisation of 23% for sirolimus eluting stents 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	N/A
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 a RR reduction for TLR of approx 93%	Death, MI, TLR, MACE free survival	RAVEL	N/A

Table 6-5 Cost-effectiveness results

Study	Cost-effectiveness ratios	Subgroup analysis	Sensitivity analysis	Conclusion	Industry author affiliation
AETMIS, 2004[122]	$23,067 per repeat revascularisation avoided, 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 degrees, restenotic lesion, and triple vessel disease), and non-elective patients based on two risk factors (vessel diameter <2mm, and prior CABG). The results show DES is only cost-effective in high risk subgroups, and highly dependant on the number of stents used. Use of one sirolimus eluting stent 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 sirolimus-DES could only be justified in elective patients with three-four risk factors, and non-electives with two risk factors. The eligible population was even smaller for paclitaxel–DES. Please 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, & Z (high risk) were sensitive, though 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

Study	Cost-effectiveness ratios	Subgroup analysis	Sensitivity analysis	Conclusion	Industry author affiliation
Cohen, 2004[121]	ICER per RRA (repeat revascularisation avoided) = $1,650 ICER per QALY =$27,540	Diabetes ICER =$2,376/RRA No Diabetes ICER =$1,973/RRA TLR 10-15% ICER =$3,727/RRA TLR 15-20% ICER =$5,789/RRA TLR 20-25% ICER =$509/RRA TLR 25-30% DES DOMINANT Lesion length<15mm ICER =$4,265/RRA Lesion length15-20mm ICER=$4,459/RRA Lesion length >20mm DOMINANT Ref vessel diameter<2.5mm ICER DOMINANT Ref vessel diameter2.5-3mm ICER=$1,345	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 US	Cordis funding
Greenberg, 2004[123]	ICER of ~ $7000 per repeat revascularisation avoided	No formal subgroup analysis. However the author 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 (<3mm), and long lesions (>15mm)	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 US	Cordis, Guidant, and Medtronic funding
Gulizia, 2004[126]	11.8/100 revascularisations avoided at a net inc cost of €931 per patient	Normal SVD (vessel diameter>2.5mm, length <18mm) Long lesions >18mm Small vessels <2.5mm 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, with more than one segment treated, triple vessel disease, a stent length >20mm, or with small stent sizes, at a threshold of €7800 per MACE averted	Bootstrapping and multivariate SA, graphically depicted using CE plan	DES is not cost-effective for all patients, only those at high risk	None declared

Study	Cost-effectiveness ratios	Subgroup analysis	Sensitivity analysis	Conclusion	Industry author affiliation
Mittmann, 2005 [128]	From the hospital perspective the ICER ranged from Can$12,527 -29,048 per TLR avoided. From the provincial perspective the ICER ranged from Can $11,133 – 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 – 15,000. Given that costs were the key source of uncertainty, there 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% (to10.7%) 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
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 sensitivity analysis 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 CE plane	DES cost-effective in the treatment of single native de nova coronary lesions in the Netherlands	Cordis funding

EVPI: expected value of perfect information; PSA: probabilistic sensitivity analysis

Table 6-6 Critical appraisal of economic evaluations

Checklist item[131]	Bagust, 2005	Cohen, 2004	AETMIS, 2004	Greenberg, 2004	Gulizia, 2004	Kaiser, 2005	Mittmann, 2005	Shrive, 2005	Tarricone, 2005	Van Hout, 2005
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

Checklist item[131]	Bagust, 2005	Cohen, 2004	AETMIS, 2004	Greenberg, 2004	Gulizia, 2004	Kaiser, 2005	Mittmann, 2005	Shrive, 2005	Tarricone, 2005	Van Hout, 2005
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	✔	✔	✖	✖	✖	✖	/	✖	✖	✔
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 confidence intervals are given for stochastic data	NA	✔	✔	NA	✖	✔	✔	NA	NA	✔
27. The approach to sensitivity analysis is given	✔	✔	✔	✖	✔	✔	✔	✔	✔	✔
28. The choice of variables for sensitivity analysis is justified	✔	NA	✔	✖	/	✔	✔	✔	✖	NA
29. The ranges over which the variables are varied are stated	✖	NA	✔	✖	✔	✔	✔	✔	/	NA
30. Relevant alternatives are compared	✔	✔	✔	✔	/	✔	✔	✔	✔	✔

Checklist item[131]	Bagust, 2005	Cohen, 2004	AETMIS, 2004	Greenberg, 2004	Gulizia, 2004	Kaiser, 2005	Mittmann, 2005	Shrive, 2005	Tarricone, 2005	Van Hout, 2005
31. Incremental analysis is reported	✔	✔	✕	✔	/	✔	✔	✔	✔	✕
32. Major outcomes are presented in a disaggregated as well as aggregated form	✔	✔	✔	✕	✕	✔	✔	✕	✔	/
33. The answer to the study question is given	✔	✔	✔	✔	/	✔	✔	✔	✔	✔
34. Conclusions follow from the data reported	✔	✔	✔	✔	/	✔	✔	✔	✔	✔
35. Conclusions are accompanied by the appropriate caveats	✔	✔	✔	✔	/	✔	✔	✔	✔	✔

Legend: ✔ yes (item adequately addressed), ✕ no (item not adequately addressed), / partially (item partially addressed), **?** unclear or not enough information, NA not applicable, NS not stated.

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.

7.1 Submitted models

An overview of the economic submissions received is shown in Table 7-1. 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 7-2. The following section deals with common methodological issues, before giving a summary and critique of each of the models in turn.

Table 7-1 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 presently 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 7-2 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, N/S: not stated

7.2 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 (see Table 7-3). 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 one year and two year results using effectiveness data from individual clinical trials. Medtronic, however, presented two separate scenarios using a five year timeframe; 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 another, 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 nine months. The KiWiMed model undertook a five 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, CVA, and MI (though not supported by clinical evidence). It was not possible to conclusively determine 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 7-4 provides a summary of the key parameters in the models and their comparison with our previous publication.[120]

The main areas of discrepancy were number of stents used during repeat revascularisation procedure, 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 is substantially out of line with other submissions and publications and with current market prices (personal communication: Jonathan Burrill, NHS PASA, 12 July 2005). Cordis also used relatively high 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 over optimistic cost-effectiveness ratios. Baseline rates of TVR/TLR with BMS also appear high compared to other studies,[120] these can be expected to be lower in clinical practice.

All of the submissions undertook sensitivity analysis (Table 7-5). KiWiMed employed two-way sensitivity analysis of probability of restenosis, and cost of stent. Cordis and Medtronic employed probabilistic sensitivity analysis (PSA), whilst Boston opted for the simpler approach of univariate SA. CiC removed.

Table 7-3 Summary of economic submissions to NICE

Submission	Study type	Comparators	Population & subgroups	Time frame	Model used	Cost elements & sources (other than BCIA)	Effectiveness & benefit outcome measures	Cost/price of device (£)	Assumptions repeat revasc* (%)
Cordis	CEA CUA	2 way: Cypher vs. BMS 3 way: Cypher vs. Taxus vs. BMS	RAVEL & SIRIUS Patients subgroups: Small vessels (<3mm) Diabetic Long lesions (>15 mm) As in RAVEL, SIRIUS, REALITY, CORPAL, ISAR DESIRE, ISAR DIABETES, SIRTAX, TAXI, TAXUS trials. Patients subgroups: Small vessels (<3mm) Diabetic Long lesions (>15 mm)	1 yr 2 yrs 1yr 2yrs	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 redn 68.5% 3way: BMS 14.8% Cypher 4.4% Risk redn 70.3% Taxus 5.8% Risk reduction 60.8%
Boston	CEA CUA	DES vs. BMS	TAXUS IV Patients subgroups: Small vessels (<2.5 mm) Diabetic Long lesions (>20 mm) As in TAXUS IV Patients subgroups: Small vessels (<2.5 mm) Diabetic Long lesions (>20 mm)	1 yr 2 yrs	DA	Procedures (PTCA, CABG), material (DES, BMS, balloon, guiding catheter, guidewire) recurrence of symptoms (angiogram, cardiology visit, cardiac surgery visit); medication (clopidogrel, and IIIb/IIIa therapy). Sources of costs; material costs from Boston (CIC), procedures and recurrence of symptoms costs from Bagust et al (inflated to 2004/5); medication costs from BNF 2005	Utility weights (restenosis free, restenosis) TLR rates	CiC removed.	**TLR** BMS 15.5% DES 4.3% Risk redn 72.3%

Submission	Study type	Comparators	Population & subgroups	Time frame	Model used	Cost elements & sources (other than BCIA)	Effectiveness & benefit outcome measures	Cost/price of device (£)	Assumptions repeat revasc* (%)
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 (1 yr data)	1 yr 5 yrs	Markov model.	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 (CIC), Clopidogrel therapy BNF 2005, and cardiac rehabilitation HTA 2004 (inflated from 2003/2004)	Utility weights (restenosis free, restenosis) TVR rates	BMS £318 DES £862 PRICE PREMIUM £544	TVR BMS 12.82% DES 5.67% Risk redn 55.8%
KiWiMed [b]	CUA	DES vs. BMS	RAVEL, SIRIUS, and E-SIRIUS, from which effectiveness was taken	5 yrs	Unclear	Procedures (PTCA, CABG, Angiography), material (DES, BMS). Sources of costs; material costs Translumina & LRiG; procedure costs from NHS reference costs 2003, 2004	Utility weights	BMS £380: DES £550 PRICE PREMIUM: £170	Unclear

a: Price premium: price differential between DES and non-DES; b: KiWiMed did not provide model, parameters taken from supporting documentation where available

Table 7-4 Parameter values from industry submissions.

Parameter	Boston		Cordis		Medtronic		*Bagust et al., 2005. 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	1.87	CTC audit	Unclear	NA
Price premium	CiC removed.	NA	£433	NA	£544	NA	£500	NA	£370	NA
Cost BMS	CiC removed.	Boston average selling price	£908	List price	£318	Medtronic average selling price	£370	Market average	£380	Translumina
Cost DES	CiC removed.	Boston average selling price	£1341	List price	£862	Medtronic average selling price	£870	Market average	£550	Initial LRiG model
Cost of PTCA	£3,253	Bagust et al inflated to 2005	£2,609	NHS	£3,326	NHS spell costs 2004/5	£3,190	NHS APC spell costs 2003/4	£1,505	Personal communication
Cost of CABG	£7,904	Bagust et al inflated to 2005	£7,066	NHS	£8,080	NHS spell costs 2004/5	£7,750	NHS APC spell costs 2003/4	£7,066	NHS ref costs, 2004

	Boston		Cordis		Medtronic		*Bagust et al., 2005. For comparison.*		KiWiMed [b]	
Annual QALYs lost to angina	0.17	ARTS trial	0.15	ARTS trial	0.135	Bagust et al., 2005	0.135	ARTS and SoS trials	0.175	Serruys et al
QALY's lost per PTCA	0.0035	HTA, Hill et al., 2004	NA	NA	0.0056	Bagust et al., 2005	0.0056	ARTS and SoS trials	Unclear	NA
QALY's lost per CABG	0.012	HTA, Hill et al., 2004	NA	NA	0.03	Bagust et al., 2005	0.033	ARTS and SoS trials	0.78 (per month)	Serruys et al
Waiting time for PTCA/CABG	3 months	NS	28 weeks	Maximum NHS waiting times	15 weeks	Bagust et al., 2005	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 7-5 Sensitivity analyses within economic submissions to NICE

Submission	Sensitivity analysis Univariate: Univariate or threshold analyses	Multivariate: Deterministic or Scenario 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 (7months) Discount rate (3.5% for both) CiC removed.	Clopidogrel DES 12 months. Baseline TLR rates Cost of BMS	CiC 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 odds ratio 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.

7.3 Critical appraisal of Boston model

7.3.1 Comparison to checklist and general description

The submission compared drug-eluting stents (DES) against bare metal stents (BMS), for a general population and for subgroups (diabetic, small vessel (2.5mm), 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 quality of life. 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 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 to 'old' technology assessment procedures the discounting was appropriate.

7.3.2 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 small vessels and long lesion patients 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 long lesion patients (£5,367 cost/QALY), and is dominant, for small vessels and diabetic patients. A simple univariate sensitivity analysis was undertaken on 5 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.

CiC removed – TLR rates. An error in the calculation for this SA was found and corrected for by the assessment group.

Table 7-6 CiC removed

CiC removed	**CiC removed**	**CiC removed**	**CiC removed**
CiC removed	CiC removed	CiC removed	CiC removed
CiC removed	CiC removed	CiC removed	CiC removed

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.

7.4 Critical appraisal of Cordis model

7.4.1 Comparison to checklist and general description

The Cordis submission compared drug-eluting stents (DES) to bare metal stents (BMS), for both a 'no risk factor' population and for subgroups (diabetic, small vessel (2.5mm), 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 quality of life. 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 upon a comparison of the bare metal BX VELOCITY stent with the DES Cypher, which is a sirolimus coated BX VELOCITY stent. The three-way analysis was based on RCTs of Cypher versus Taxus. However, to extend the three-way analysis to two 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 bare metal stent 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 Ltd, NHS reference costs, and Boston Scientific list prices. The cost data for the technologies (both BMS and Taxus) appear implausible. Both the costs of Taxus and the BMS were substantially overestimated compared to 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).

7.4.2 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 (J.Burrell, NHS Purchasing and Supply Agency: personal communication: 12 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 of £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 7-7.

Table 7-7 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: PASA, personal communication, 12 July 2005); c: Midpoint range of maximum market prices by volume (source: PASA, personal communication, 12 July 2005)

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. Results are very similar when the effective list prices (i.e. maximum price charged in UK without discounts) are used instead.

7.5 Critical appraisal of Medtronic model

7.5.1 Comparison to checklist and general description

The submission compared drug-eluting stents (DES) against bare stents (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 phosphorycholine 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 quality of life.

This submission measured costs and benefits at 5 years, although trial data from ENDEAVOR II was 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 differences

remained over the 5 year period of analysis. This second scenario was not felt to be appropriate for several reasons. Firstly, 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 2nd to 5th years. Secondly the meta-analysis from which the odds ratio was taken used only evidence for Taxus, and Cypher, and not Endeavor. Finally, TVRs were approximated by TLR rates when modelling 2nd to 5th 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 odds ratios for DES (as reported in the Babapulle meta-analysis) had been used mistakenly in place of TLR odds ratios, which were in turn supposed to represent TVR rates. Therefore given the available evidence, the extrapolation of outcomes to five years as performed in the Medtronic economic model submission seems implausible.

Utility measures were taken from Bagust and colleagues, 2005 and, for the secondary analysis from Oostenbrink.[134] Waiting times for PTCA and CABG were set at 15 weeks, as estimated by Bagust and colleagues. Cost data was taken from Bagust and colleagues, 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, 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.

7.5.2 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 odds ratio from the Babapulle meta-analysis results become even more favourable for Endeavor. The subsequent probabilistic sensitivity analysis 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/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 cost-effectiveness ratio is reported in Table 7-8.

Table 7-8 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

In conclusion, the results presented in this submission are likely to be biased in favour of DES. Our main criticisms relate to the way 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 unrepresentative, and together with high revascularisation rates found in the study, may bias the results, making DES appear cost-effective compared to BMS.

7.6 Critical appraisal of KiWiMed model

This submission compared drug-eluting stents (DES) against bare stents (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 (Hill and colleagues, 2004), although its exact structure is uncertain. The model estimated the five year cost-effectiveness of Yukon versus non-DES. The effectiveness data was 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, 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 to BMS. A two way sensitivity analysis was undertaken on cost of stent (DES versus BMS) and probability of restenosis (DES versus BMS). Over a range of £250 to £500 for cost of BMS and £500 to £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.

7.7 List prices

Close to completion of this report, list prices for DES were submitted to the AG by NICE. Available list prices are presented in Table 7-9 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 Purchasing and Supply Agency (J.Burrell, PASA: personal communication: 12 July 2005).

Table 7-9 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	
Liberte™	Boston Scientific	-	(as for Taxus)
Taxus™	Boston Scientific	1300	
Xience V™	Guidant	-	CE Marking pending
Yukon™	Translumina/KiWiMed	650	

a: List prices submitted to AG (by NICE) 20 October 2005.

7.8 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:

1. The sources of data and the ways in which they are combined needs 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.

2. 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.

3. 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.

4. 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.

5. 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.

8 ECONOMIC EVALUATION: DES VERSUS BMS

8.0 Introduction

This section begins by outlining the key clinical issues of relevance to the economic assessment of drug-eluting stents versus bare metal stents (8.1). In particular, the importance of moving from efficacy-based to effectiveness-based data is highlighted (8.2). Methods of economic assessment are described, including our economic modelling and sensitivity analysis methods (8.3) and details of sources of model data (8.4). Cost-effectiveness results (8.5) and sensitivity analyses (8.6) are presented followed by a structured discussion of related issues (8.7). Key features of our economic evaluation are summarised in Figure 8-1.

Figure 8-1 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

8.1 Clinical outcomes for economic assessment

8.1.1 Survival/mortality

The meta-analysis reported in Chapter 4 shows no evidence of any mortality advantage accruing to patients treated with DES compared to those treated with BMS. The limited data available from 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.

8.1.2 Myocardial infarction

The meta-analysis of published trials in respect to 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 myocardial infarction are equivalent and will not contribute to incremental cost-effectiveness results.

8.1.3 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.

8.2 Converting efficacy to effectiveness

8.2.1 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 casemix of persons treated in a typical cardiology 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 endpoints 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; and
- 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).

8.2.2 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. Though 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. Thus 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 to BMS (TAXUS I, II & 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. Thus 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.

8.2.3 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 8-2.

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 have investigated in detail the disposition of lesions treated as part of a repeat procedure compared to 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 reduction in all repeat revascularisations (effectiveness) which could be expected in routine NHS practice.

Table 8-1 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 a 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% confidence limits 32; 44%) and 50% (44%; 57%).

A similar analysis focusing on TVR events in the CTC data is shown in Table 8-2. 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% (28%; 42%) and 46% (36%; 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 Figure 8-1 and Table 8-4. 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% (31%; 42%) and 53% (47%; 59%) (based on TLR), or between 34% (27%; 41%) and 48% (37%; 56%) (based on TVR). In patients undergoing a second PCI within 12 months only 60% of lesions treated were TLRs and 72% TVRs.

Figure 8-2 Deriving effectiveness estimates from efficacy results

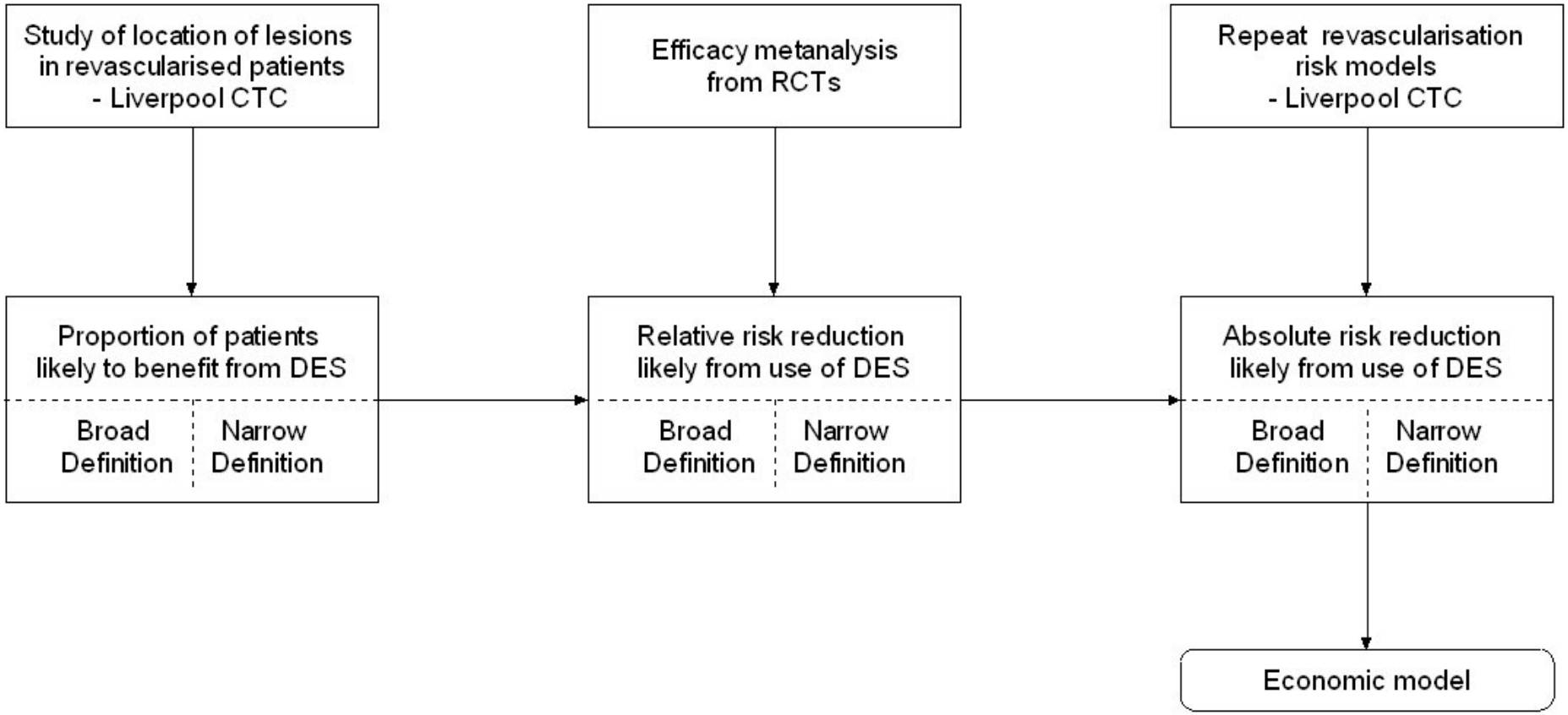


Table 8-1 Analysis of patients by site(s) of repeat revascularisation (TLR) in 12 months following index PCI in CTC database

		Patients receiving repeat intervention				Proportions					
Case type	**Index PCI**	**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%	*N/A*	*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; UCL: Upper confidence interval

Table 8-2: Analysis of patients by site(s) of repeat revascularisation (TVR) in 12 months following index PCI in CTC database

		Patients receiving repeat intervention				Proportions					
Case type	**Index PCI**	**All patients**	**TVR only cases**	**Non-TVR only cases**	**Mixed TVR / other cases**	**TVR only cases**	**95% LCL**	**95% UCL**	**TVR +/- 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 8-3: Analysis of lesions by site(s) of repeat revascularisation (TLR) in 12 months following index PCI in CTC database (excluding CABG)

		Lesions treated in repeat intervention				Proportions					
Case type	**Index PCI**	**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 8-4: Analysis of lesions by site(s) of repeat revascularisation (TVR) in 12 months following index PCI in CTC database (excluding CABG)

		Lesions treated in repeat intervention				Proportions					
Case type	**Index PCI**	**All lesions**	**TVR only cases**	**Non-TVR only cases**	**Mixed TVR / other cases**	**TVR only cases**	**95% LCL**	**95% UCL**	**TVR +/- 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%	*N/A*	*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; UCL: Upper confidence interval

8.2.4 Risk factors, subgroups and estimated benefit

We recently reported the results of an audit study of stented patients treated at CTC Liverpool over a two-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 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 <2mm). Table 8-5 and Table 8-6 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, while '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 to 3% and 3 to 5% respectively.

Table 8-5: 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 (%)
	Calcific-ation	Angulation >45 degrees	Restenotic lesion	Triple vessel disease			TLR-based		TVR-based		
							Narrow	Broad	Narrow	Broad	
A	**No risk factors**				**5.6**	**(4.3 - 6.9)**	**2.1**	**2.8**	**2.0**	**2.5**	**57.2**
B	**1 risk factor**				**8.4**	**(6.9 – 10.1)**	**3.2**	**4.2**	**3.0**	**3.8**	**31.6**
B1	*No*	*Yes*	*No*	*No*	*7.7*	*(5.4 – 10.2)*	*2.9*	*3.9*	*2.7*	*3.5*	*17.7*
B2	*No*	*No*	*No*	*Yes*	*7.7*	*(4.9 – 10.7)*	*2.9*	*3.9*	*2.7*	*3.5*	*6.3*
B3	*Yes*	*No*	*No*	*No*	*10.5*	*(7.2 – 14.1)*	*4.0*	*5.3*	*3.7*	*4.8*	*6.1*
B4	*No*	*No*	*Yes*	*No*	*11.1*	*(5.8 – 16.8)*	*4.2*	*5.6*	*3.9*	*5.1*	*1.5*
C	**2 risk factors**				**16.6**	**(14.4 – 18.8)**	**6.3**	**8.4**	**5.8**	**7.6**	**10.1**
C1	*No*	*Yes*	*No*	*Yes*	*14.8*	*(11.5 – 18.4)*	*5.6*	*7.5*	*5.2*	*6.8*	*3.6*
C2	*Yes*	*Yes*	*No*	*No*	*17.4*	*(13.8 – 21.4)*	*6.6*	*8.8*	*6.1*	*7.9*	*4.8*
C3	*Yes*	*No*	*No*	*Yes*	*17.3*	*(13.4 – 21.6)*	*6.6*	*8.7*	*6.1*	*7.9*	*0.9*
C4	*No*	*Yes*	*Yes*	*No*	*17.9*	*(12.9 – 23.7)*	*6.8*	*9.0*	*6.3*	*8.2*	*0.3*
C5	*No*	*No*	*Yes*	*Yes*	*17.9*	*(12.7 – 24.0)*	*6.8*	*9.0*	*6.3*	*8.2*	*0.4*
C6	*Yes*	*No*	*Yes*	*No*	*20.4*	*(15.0 – 26.4)*	*7.7*	*10.3*	*7.2*	*9.3*	*0.2*
D	**3 or 4 risk factors**				**24.6**	**(21.5 – 27.9)**	**9.3**	**12.4**	**8.7**	**11.2**	**1.1**
D1	*Yes*	*Yes*	*No*	*Yes*	*23.7*	*(19.6 – 28.1)*	*9.0*	*12.0*	*8.4*	*10.8*	*0.8*
D2	*No*	*Yes*	*Yes*	*Yes*	*24.2*	*(18.9 – 30.1)*	*9.2*	*12.2*	*8.5*	*11.1*	*0.1*
D3	*Yes*	*Yes*	*Yes*	*No*	*26.5*	*(21.2 – 32.4)*	*10.1*	*13.4*	*9.4*	*12.1*	*0.2*
D4	*Yes*	*No*	*Yes*	*Yes*	*26.5*	*(21.0 – 32.5)*	*10.0*	*13.4*	*9.4*	*12.1*	*0.0*
D5	*Yes*	*Yes*	*Yes*	*Yes*	*32.2*	*(26.7 – 38.0)*	*12.2*	*16.2*	*11.4*	*14.7*	*0.1*

Table 8-6: Non-elective patient subgroups derived from CTC audit study with absolute risk reduction estimated from use of DES

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

8.2.5 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, i.e. 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 2 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 to 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.

8.3 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, myocardial infarction, 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 **Incremental cost effectiveness ratio** (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 revascn. procedure **(C_3)**

- Saved costs of follow-up for patients after repeat revascn. procedure **(C_4)**

where

C_1 = DES price premium * Average number of stents per patient * Number of patients

C_2 = ARR x Number of patients * Average cost of re-referral+investigation

C_3 = ARR x Number of patients * Average cost of repeat procedure

C_4 = ARR x Number of patients * Average cost of follow-up

and

Absolute risk reduction due to DES,

ARR = (Risk of repeat procedure * Relative risk reduction due to DES)

Equation 3 **Incremental benefit** (loss of QALYs avoided due to DES)
= Angina symptoms awaiting repeat procedure **(U1)**

+ Experience of & recovery from repeat procedure **(U2)**

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

Severe angina = 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 absolute risk reduction attributable to use of DES, whereas the single important factor determining incremental outcomes is the absolute risk reduction due to DES.

8.4 Data sources and parameter values

The parameter values adopted for our Base Scenario are detailed in Table 8-7, together with data sources for each. The derivation of specific values in the table are explained more fully below.

8.4.1 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[135] 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 to BMS. We are grateful to the NHS Purchasing and Supplies Agency 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 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 quite different marketing strategies. Boston Scientific have focussed 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 two years.

It should be noted that the approach employed decreases the premium for DES compared to 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. Thus the sample prices were increased by 5% to reflect the true cost per stent deployed.

8.4.2 NHS costs

All other model costs are derived from NHS Reference Costs 2004.[135] 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.

8.4.3 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 to 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.

8.4.4 Health-related quality of life

In the previous economic assessment we relied heavily on the only published source of quality of life estimates (EuroQol, EQ-5D) for PCI and CABG patients - the ARTS trial.[136] Subsequently we were able to combine this with information from the SoS trial[137] to inform our Heart publication. Though 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 (HRGs E33/E34) after 68.0 (66.4,69.5) days;
- 456 following a PCI episode (HRG E15) after 64.0 (62.7,65.1) days;
- 421 following a CABG episode (HRGs E04) after 65.5 (59.2,71.7) days.

The HoDAR estimated EQ5-D scores for these groups are 0.502 (0.471,0.533) for angina patients, 0.660 (0.631, 0.689) for PCI patients, and 0.660 (0.597, 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 (0.640, 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 HRQoL scores between patients with severe angina and those recovered from revascularisation (0.158) is very similar to the ARTS gain (0.16), though the scores obtained in UK practice are considerably lower than those in both trials, probably reflecting the selective effect of RCT exclusion criteria.

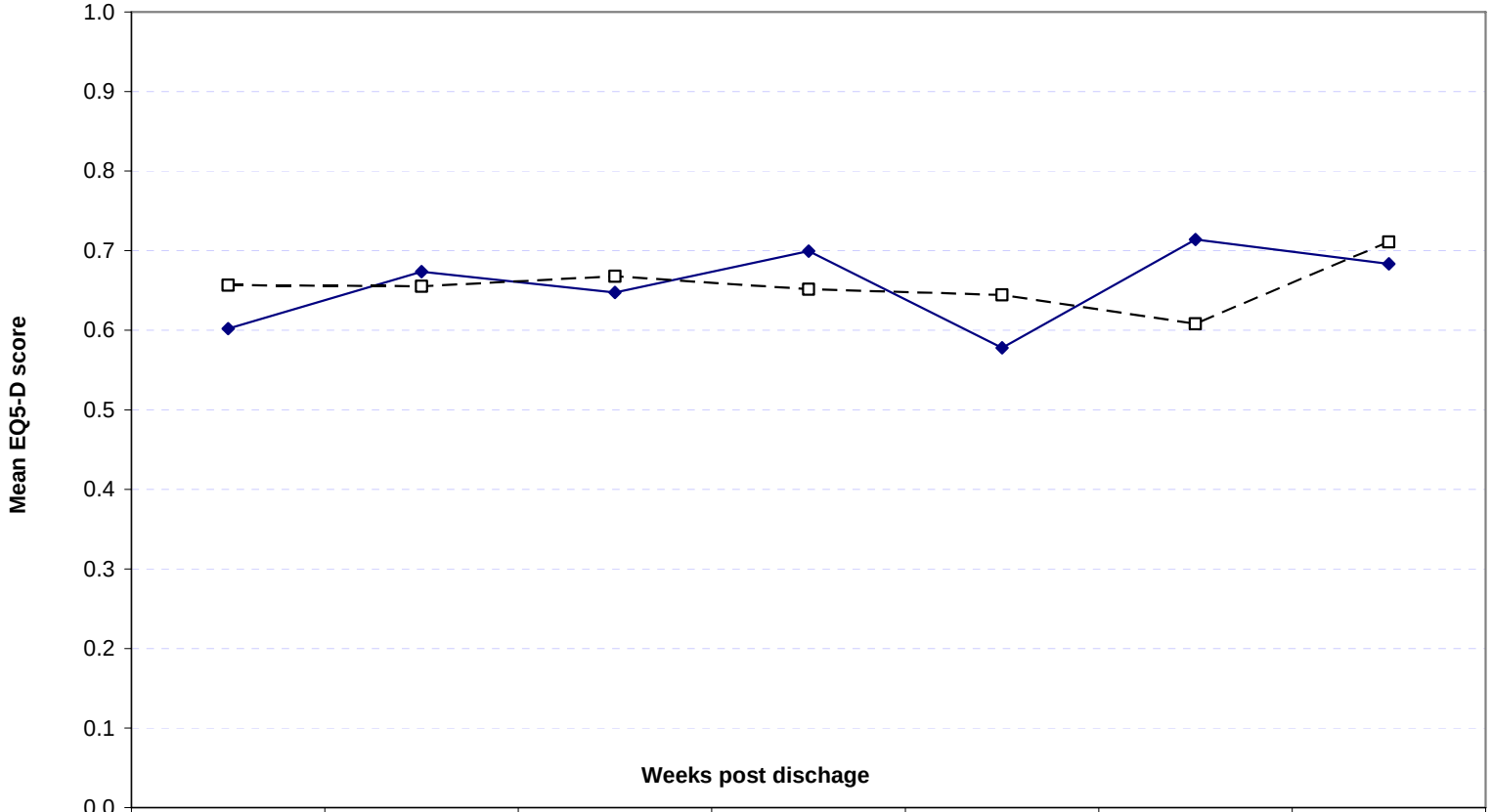
Figure 8-3 shows time trends for patients surveyed in HoDAR following CABG and PCI. It is evident that there are no meaningful differences at any time during the study period. Regression of EQ-5D scores against the time of survey post-discharge showed no evidence of time trends for either PCI or CABG patients, suggesting that any differences in HRQoL recovery experience between the two modes of treatment must be confined to no more than 6 weeks post discharge. On this basis we have 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.

8.4.5 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 two years, but the volume of CABGs undertaken remains unchanged. The consequences are that while 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 four weeks waiting time for all patients to reflect time spent with symptoms prior to listing for reintervention.

Figure 8-3 Time trends in EQ-5D mean scores for CABG and PCI patients surveyed in HoDAR



	<=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)

8.4.6 Changes since previous Technology Assessment Report

It may be helpful to summarise the changes made to the model parameter values for this TAR compared to 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 PASA (NHS Purchasing Supply Agency) survey shown in Table 8-7. 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 8-5 and 8-6, and involve reductions to the previously estimated benefits by either a third or a 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 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 HRQoL expected from PCI or CABG compared to 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]

Table 8-7: Baseline parameter values and data sources for LRiG model

Parameter	Elective	Non-elective	Source
Index stenting (C1)			
Actual Cost per DES: Taxus	£855.43		Survey of NHS purchasers for current prices May/June 2005 + 5% addition for stent wastage
Cypher	£983.51		
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 (C2-C4)			
Risk within 12 months	7.79%	10.15%	CTC Liverpool audit
Absolute RR: narrow	2.95%	3.75%	CTC Liverpool audit + clinical trial meta-analysis (TLR)
broad	3.93%	4.99%	
Investigation of recurrent symptoms (C2)			
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, Day Case E14
Cost of cardiac surgery OP visit	£208		
Cost of angiography	£724		
Repeat revascularisation (C3)			
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 Ref Costs 2004 (E15 IP less cost of stents - 1.8 per case, 50% DES use @ £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 Ref Costs 2004 (E04 IP)
Follow-up post revascularisation (C4)			
Cardiology OP follow-up visits	2.18	1.80	CTC Liverpool audit CTC Liverpool audit
Cardiac surgery OP f-up visits	0.81	0.48	
Cost of cardiology OP f-up visit	£94		NHS Reference Costs 2004: follow-up visit 320 and 170
Cost of card. surgery OP f-up visit	£156		
Health-related utility (U1 & U2)			
Average EQ5D: 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 - Quarter 4, 2004/5
for CABG	9		
Weeks prior to joining list	4		Assumption
QALY loss: awaiting PCI	0.06070		Severe angina QALY loss x weeks waiting / 52
awaiting CABG	0.03946		

8.5 Cost-effectiveness results

8.5.1 Base case results

The base case cost-effectiveness results are shown on the left of Table 8-8, 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 of Table 8-8 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/QALY gained. In non-elective patients only those with both risk factors present yield ICERs which may be favourable to DES provided the broad definition of effectiveness is used. These represent only 0.1% of non-elective patients in the CTC audit, and only 1 in 3100 of all patients.

8.5.2 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 8-9 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 proves 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 to 10%). To accommodate this risk we have included an additional 5% of stents in the calculations supporting Table 8-9.

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 8-10 shows equivalent results for patients who could reasonably be expected to require only two stents implanted.

Table 8-8: Cost effectiveness results using CTC mean number of stents per index procedure

Elective Index PCI			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
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			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
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

'Narrow' estimates are calculated from cases involving TLR/TVR only, while 'Broad' estimates are based on cases involving any TLR/TVR irrespective of any other lesions/vessels revascularised

ICER under £30,000 are in *italics.*

Table 8-9: Cost effectiveness results if only 1 index stent is expected to be required

Elective Index PCI			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
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			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
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

Assuming 1.05 stents per patient i.e. 5% of additional stents are used compared to those original anticipated

ICER below £30,000 are in *italics.*

Table 8-10: Cost effectiveness results if only 2 index stents are expected to be required

Elective Index PCI			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
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			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
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**

Delta C - Incremental cost per patient; Delta Q - Incremental QALYs per patient; ICER - Incremental cost per QALY gained; Assuming 2.1 stents per patient i.e. 5% of additional stents are used compared to those original anticipated. ICER below £30,000 are in ***italics***.

8.6 Sensitivity analysis

Univariate sensitivity analysis was carried out in respect to all model variables, varying parameter values between lower and upper 95% confidence limits 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. Table 8-11 and Table 8-12 display the sensitivity analysis results for elective and non-elective patients. 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 absolute risk reduction 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.

In addition an Extreme Values Analysis (EVA) was also 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 1 in 630 billion. The results are shown in Table 8-13, 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 absolute risk reduction (ARR) and price premium to the assessment of cost-effectiveness for DES compared to BMS. In Figure 8-4 and Figure 8-5 the relationship of ARR to cost/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 absolute risk reduction in repeat revascularisations of at least 18% (elective) or 16% (non-elective) is achievable. Clearly for the great majority of patients this is quite unrealistic.

Figure 8-6 and Figure 8-7 illustrate the strong dependence of cost-effectiveness upon the price premium of DES compared to 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 8-14 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 casemix found in the CTC audit leads to a profile of the estimated proportion of all elective (Figure 8-8) and non-elective patients (Figure 8-9) 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 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.

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 (though 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 cost-effectiveness ratios, 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 cost-effectiveness ratio then exceeds the £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.

Table 8-11: 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
Number 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
Propn. Revasc. as unstented PCI	28.9%	45.0%	£525,400	£520,800	£564,200	£559,400	£378,800	£374,200	£407,900	£403,100
Propn Revasc. as stented PCI	46.0%	62.7%	£524,900	£521,400	£563,700	£560,000	£377,600	£375,600	£406,600	£404,500
Propn Revasc. 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 f-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 f-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 f-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

Table 8-12: 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
Number 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
Propn. Revasc. as unstented PCI	19.0%	37.6%	£350,900	£345,900	£378,500	£373,200	£246,600	£241,600	£267,200	£261,900
Propn Revasc. as stented PCI	44.2%	64.9%	£353,300	£343,200	£380,900	£370,400	£247,800	£240,300	£268,400	£260,600
Propn Revasc. 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 f-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 f-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 f-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

Table 8-13: Extreme values sensitivity analysis of incremental cost per QALY gained (Base Case: effective list prices / average no. of stents used)

Elective Index PCI	Narrow				Broad			
	Taxus		Cypher		Taxus		Cypher	
	Low	High	Low	High	Low	High	Low	High
Base case ICER	£523,200		£561,900		£376,600		£405,600	
All patients	£316,700	£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	Narrow				Broad			
	Taxus		Cypher		Taxus		Cypher	
	Low	High	Low	High	Low	High	Low	High
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

ICER below £30,000 are highlighted.

Figure 8-4: Relationship between the absolute risk reduction due to DES and the incremental cost/QALY gained - elective base case

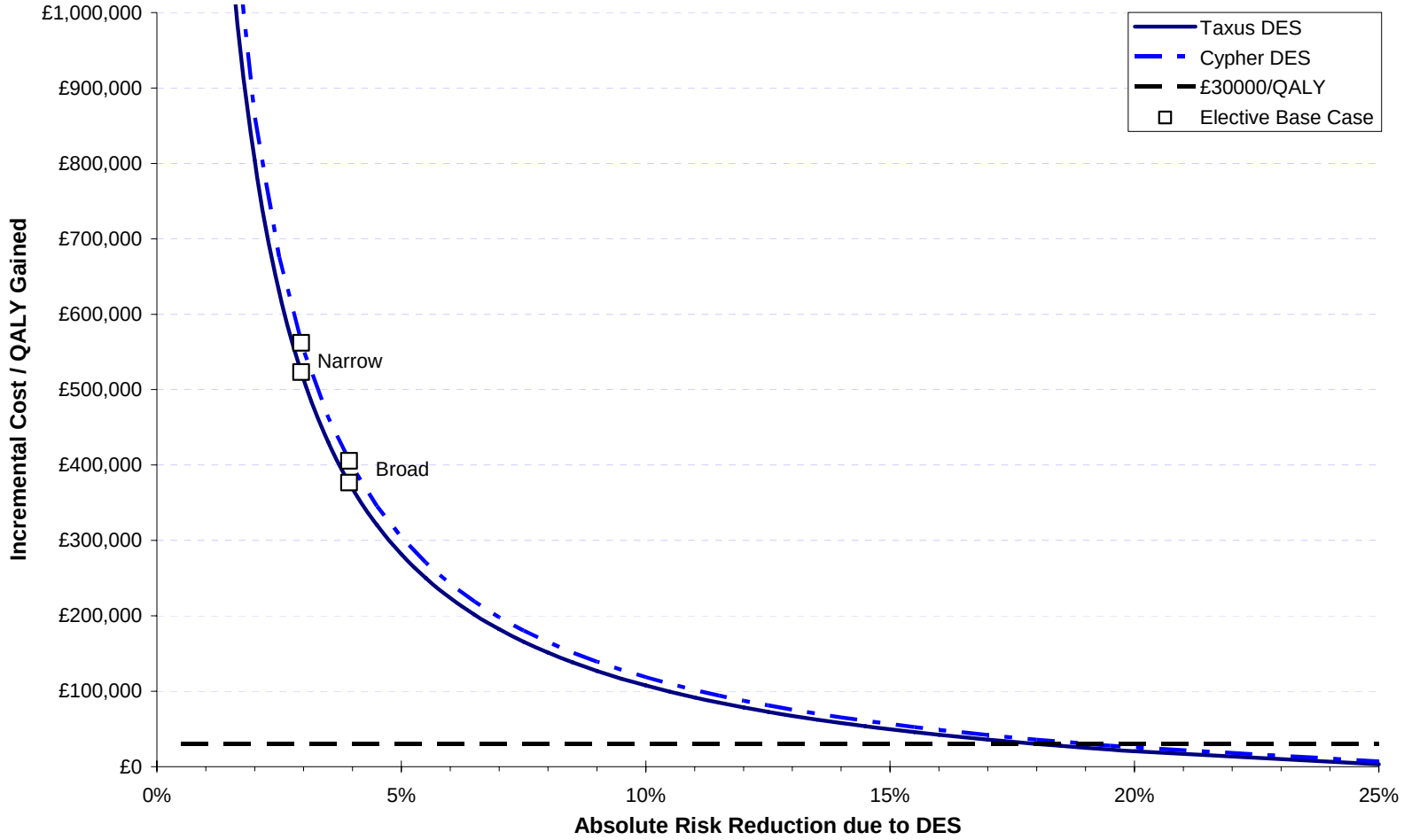


Figure 8-5: Relationship between the absolute risk reduction due to DES and the incremental cost/QALY gained - non-elective base case

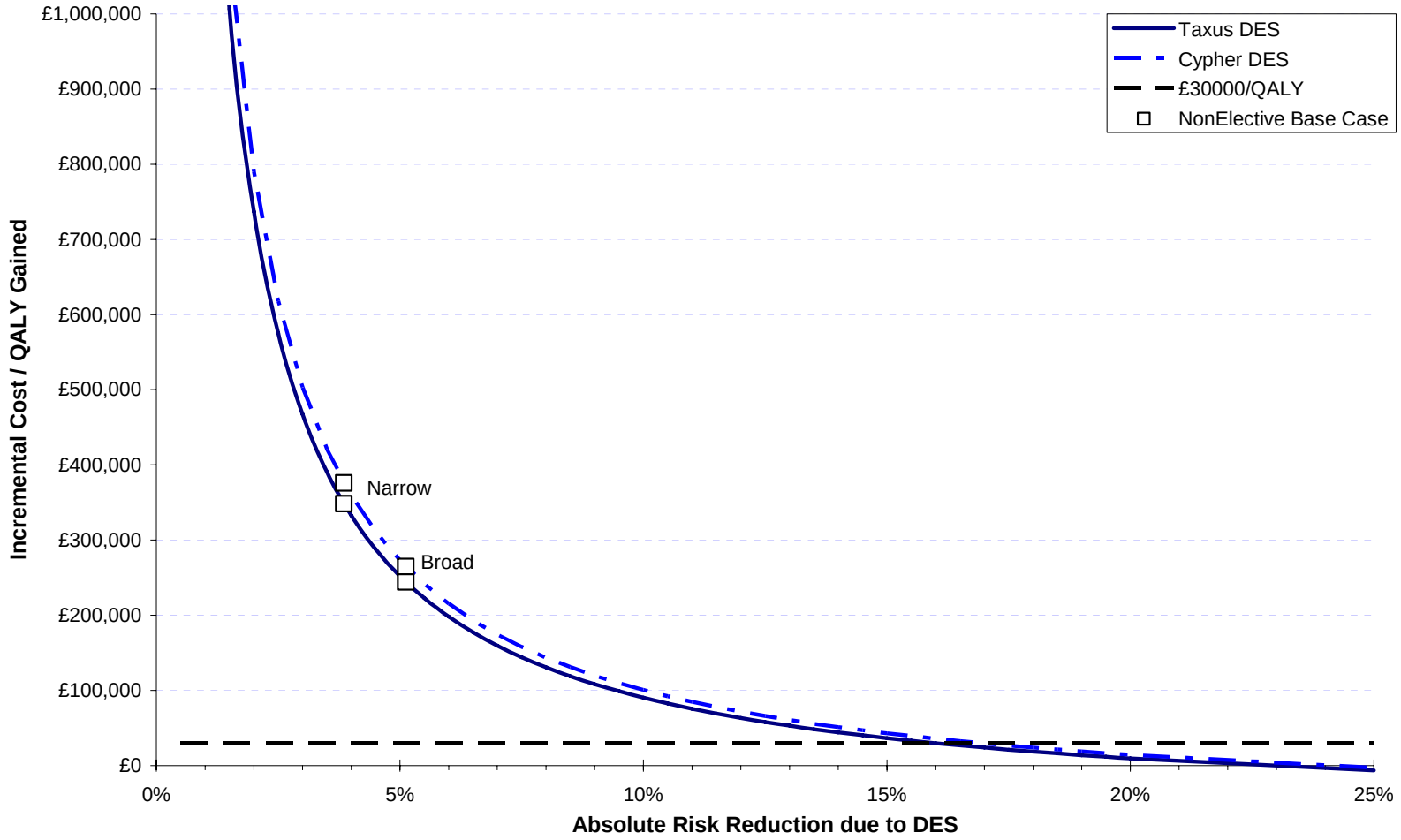


Figure 8-6: Relationship between the absolute risk reduction due to DES and price premium per DES used - elective base case

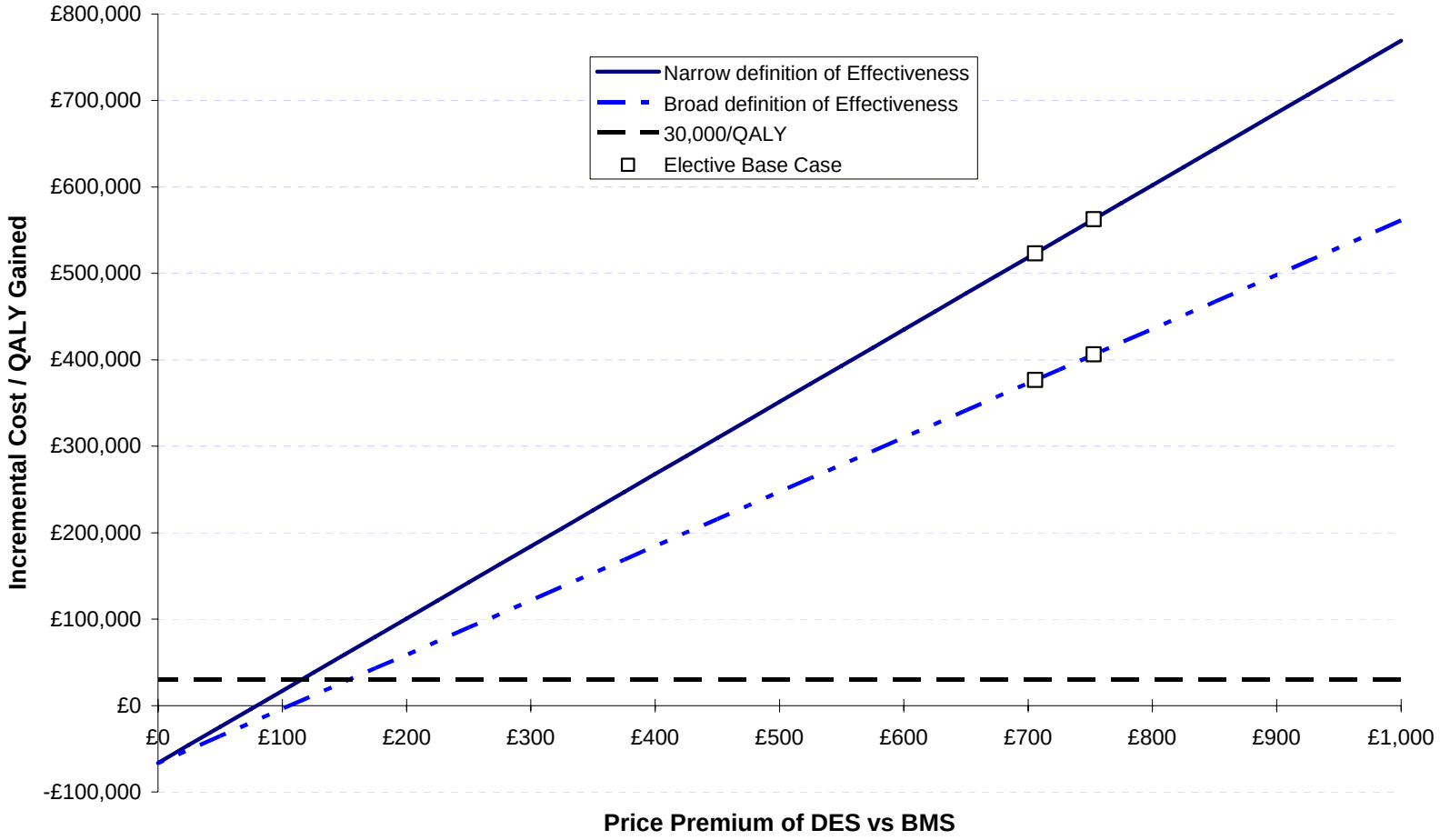


Figure 8-7: Relationship between the absolute risk reduction due to DES and price premium per DES used – non-elective base case

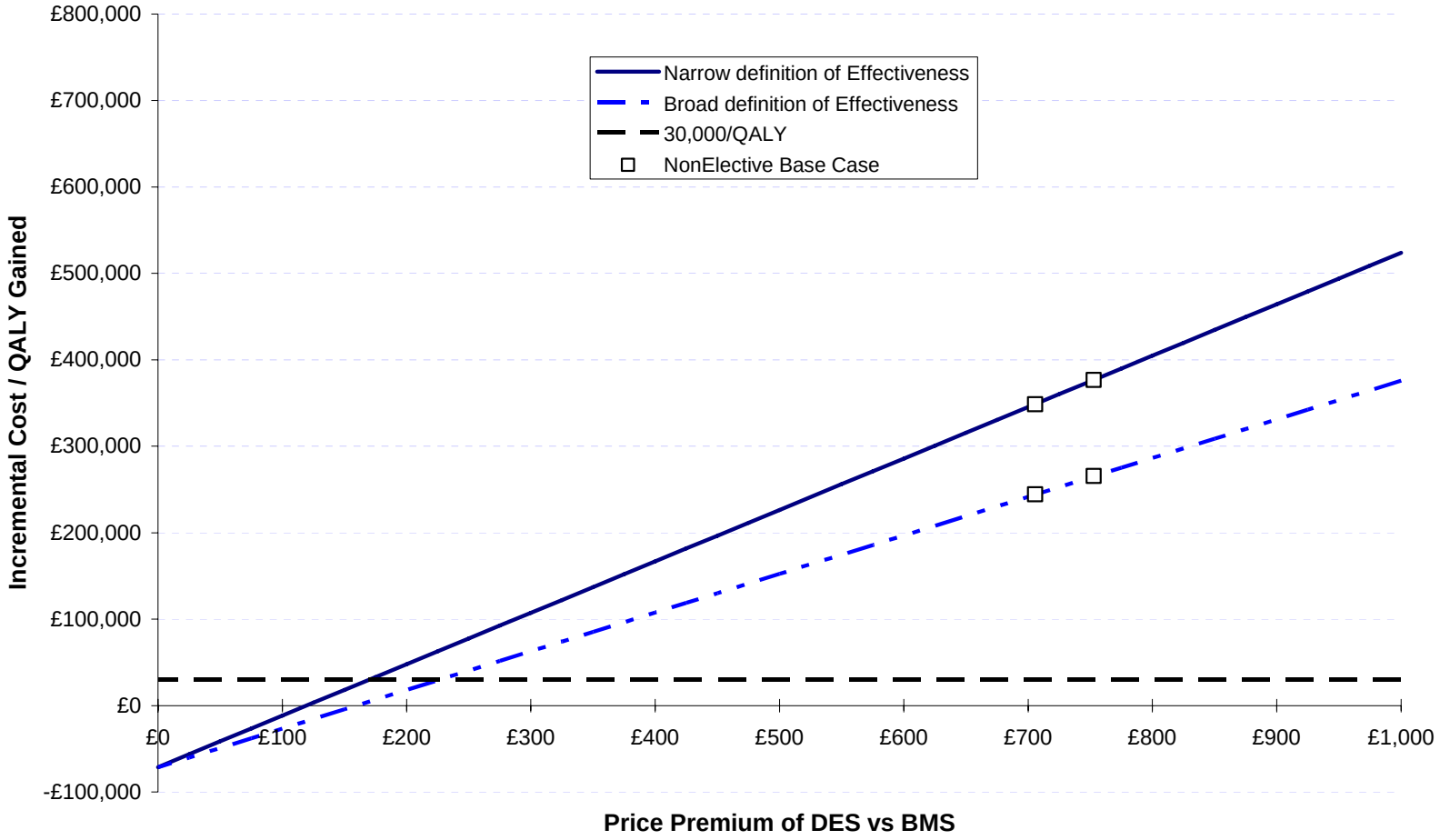


Figure 8-8: Proportion of elective stented patients for whom DES is cost-effective - variation by price premium of DES

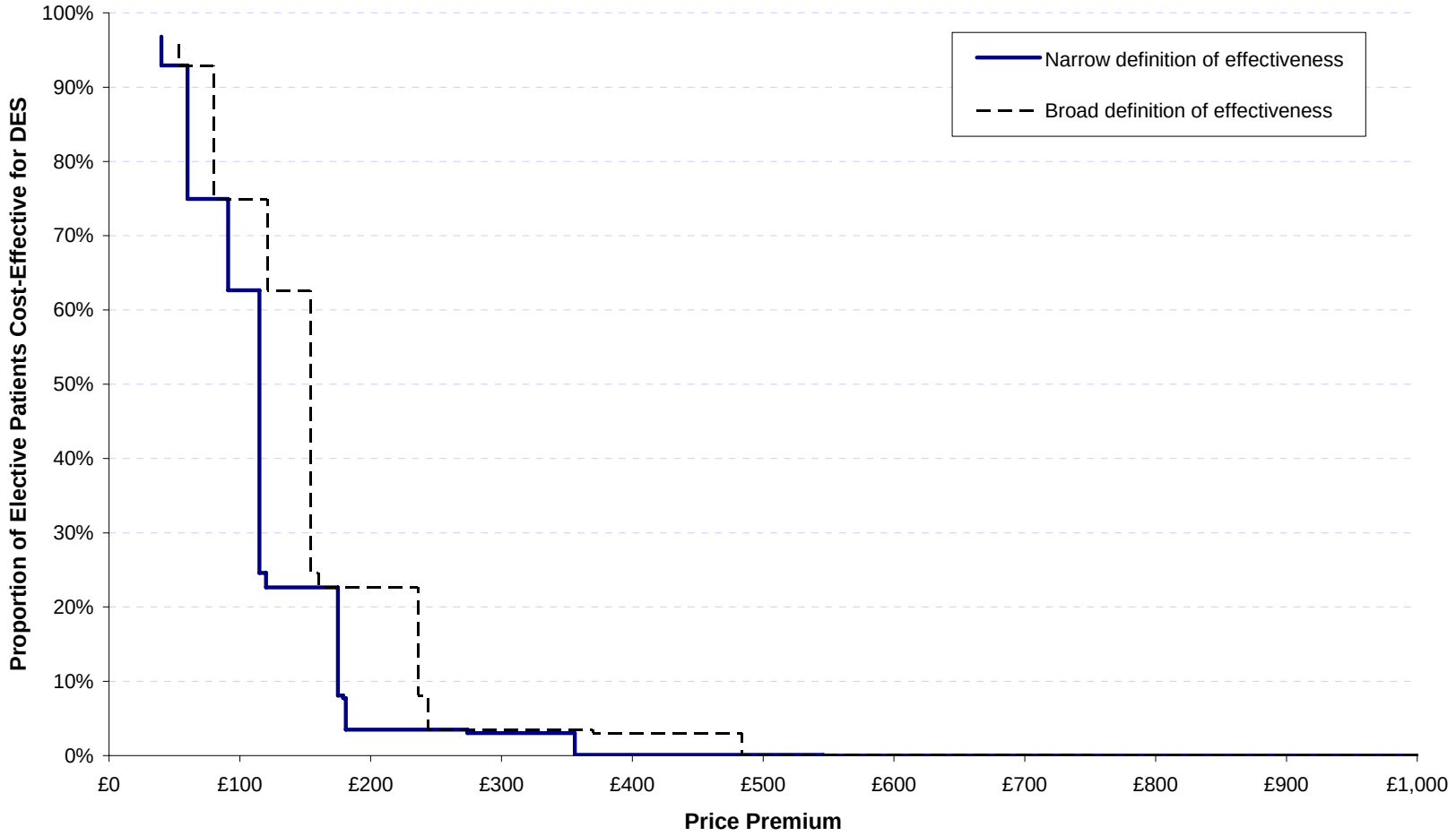


Figure 8-9: Proportion of non-elective stented patients for whom DES is cost-effective - variation by price premium of DES

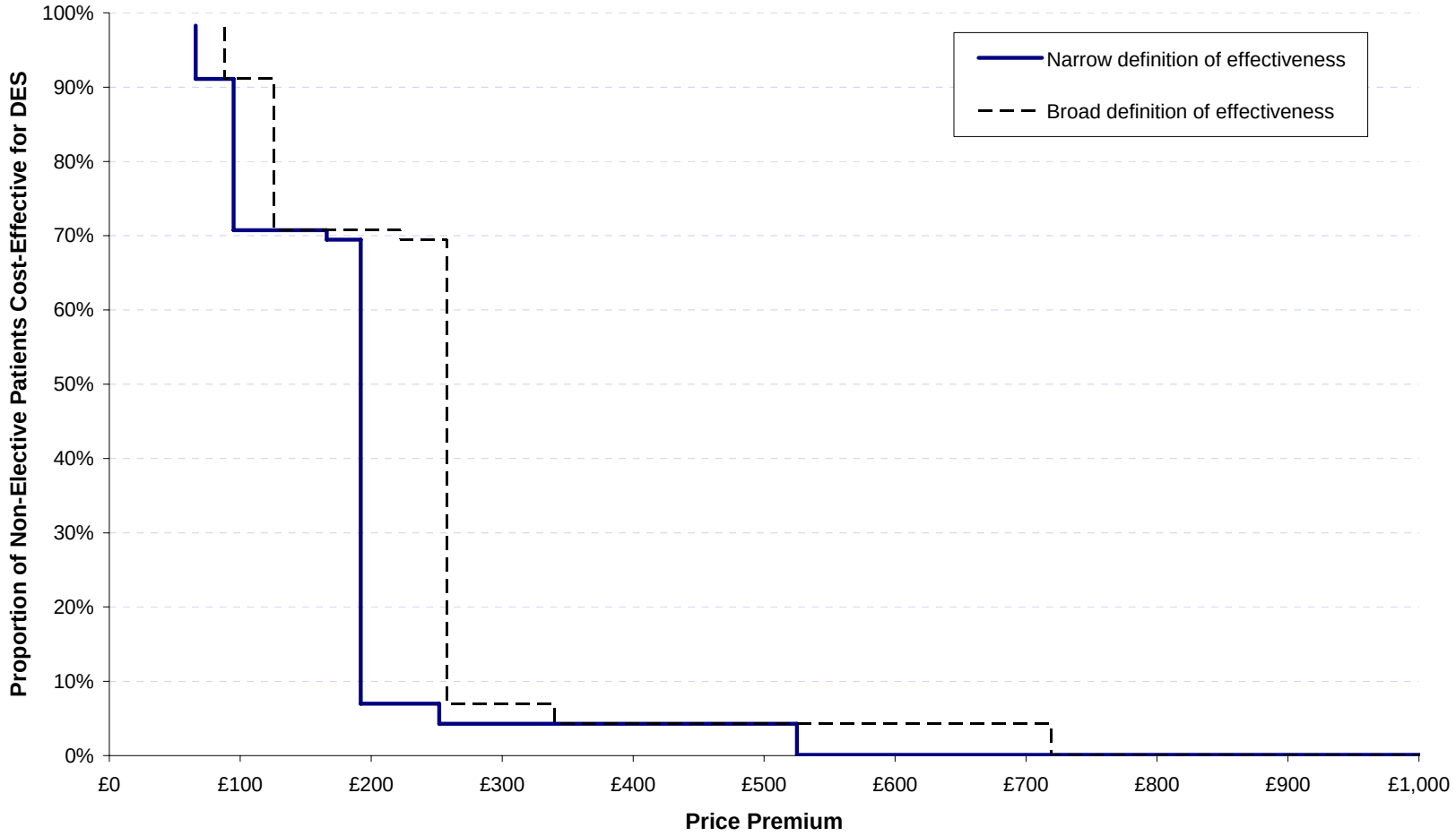


Table 8-14: Threshold values of price premium for different patient subgroups

Elective		Effectiveness criterion	
Patients	DES used	Narrow	Broad
3/4 risks	1 only	£546	£751
2 risks	1 only	£356	£484
3/4 risks	2 only	£274	£370
3/4 risks	Average	£215	£289
2 risks	2 only	£181	£244
3/4 risks	3 only	£179	£241
1 risk	1 only	£175	£236
2 risks	Average	£168	£226
All	1 only	£162	£218
2 risks	3 only	£120	£160
No risks	1 only	£115	£154
All	Average	£104	£140
1 risk	Average	£104	£139
1 risk	2 only	£91	£121
All	2 only	£84	£112
No risks	Average	£84	£112
No risks	2 only	£60	£80
1 risk	3 only	£60	£80
All	3 only	£56	£74
No risks	3 only	£40	£53

Non-elective		Effectiveness criterion	
Patients	DES used	Narrow	Broad
2 risks	1 only	£1,029	£1,450
1 risk	1 only	£525	£719
2 risks	Average	£511	£699
2 risks	2 only	£475	£649
2 risks	3 only	£309	£418
1 risk	Average	£269	£363
1 risk	2 only	£252	£340
All	1 only	£230	£310
No risks	1 only	£192	£258
1 risk	3 only	£166	£222
All	Average	£156	£210
No risks	Average	£142	£190
All	2 only	£113	£151
No risks	2 only	£95	£126
All	3 only	£75	£100
No risks	3 only	£66	£88

8.7 Discussion

Our economic model has undergone evolutionary development since the last Technology Assessment Report was prepared. These were largely driven by the lack of important information to inform the Appraisal Committees 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 two 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.

8.7.1 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 is virtually complete: all deaths are tracked, and in the past three 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 where 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 British Cardiovascular Intervention Society (BCIS) audit for 2003[140] reported that only 4.3% of PCIs were required for restenosis, though less than 20% of procedures then used were DES. This is consistent with an average risk of reintervention without DES of 5 to 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 bare metal stents (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 casemix),[82] and the Netherlands (9.6% TVR)[142] reinforcing confidence in the reliability of CTC Liverpool data, where the combined elective/non-elective rate was 8.8%. In the US, generally higher rates of repeat revascularisation are reported in registry studies: Ellis (2004)[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 (2004)[144] used a cohort treated in 1999 including unstented PCI with an overall rate of 16.2%.

8.7.2 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 multi-variate 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 found that diabetes was not included in the final multi-variate model, being correlated with many of the factors selected as significant for inclusion. Wu did not find diabetes to be significant for modelling repeat revascularizations, but only for the subgroup of repeat CABGs. Only Agema found diabetes to be required unequivocally as an independent predictor in a multi-variate analysis. Thus 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 to BMS.

8.7.3 Economic findings differ from 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 though 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.

8.7.4 Number of stents used per patient

After the price premium for DES, and the risk of repeat revascularization, 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.

8.7.5 Sensitivity analysis

In this analysis we have employed extreme values analysis (EVA) as the method for accommodating variability in multiple model parameters, rather than probabilistic sensitivity analysis (PSA). By definition, EVA involves using a much more stringent criterion than even that used conventionally in clinical trials, so that 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.

8.7.6 Choice of DES

In Chapter 5 consideration has been given of 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 to 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 equivalent ICERs can be derived if differential outcomes are accepted, by reference to the graphs shown in Figures 8-1 and 8-2. 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 & 5 are 0.78 and 1.17 respectively). Thus a simple calculation allows the reader to read from the appropriate curve in Figures 8-1 and 8-2 the ICER appropriate to each stent considered separately at the adjusted ARR value.

8.7.7 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 8-15, can be compared directly with corresponding results in Table 8-8. 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) are now confirmed instead of being equivocal. For all other patient groups the conclusions of the Base Case analysis are confirmed. Thus 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.

Table 8-15 Cost-effectiveness results re-estimated using efficacy measures

Elective Index PCI			Incremental cost per QALY gained			
Prices	Efficacy basis	Brand	No risk factors	1 risk factor	2 risk factors	3/4 risk factors
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	£231,637	£175,825	£86,078	£54,338
		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			Incremental cost per QALY gained		
Prices	Efficacy basis	Brand	No risk factors	1 risk factor	2 risk factors
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

9 BUDGET IMPACT ASSESSMENT

9.1 Data sources

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

- Hospital Episode Statistics for 2003/4
- BCIS Audit Returns 2003

9.2 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 42234 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 (personal communication: NHS PASA, 12 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 to 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 quite 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 9-1 displays the extra costs due to substitution of BMS by DES compared to two baselines: the level of DES use identified as cost-effective in the Base Case analysis of Chapter 7, 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 to 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.

9.3 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 professional aspirations, 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 9-1: 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		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

10 CONCLUSIONS AND DISCUSSION

10.1 Key conclusions

The key conclusions of this review are as follows:

- Drug-eluting stents, compared to BMS, show a reduction in composite event rate (MACE, TVF) at 12 months compared to BMS (4.2.5).
- The composite event rate is dominated by revascularisation events, and there is no difference in rates of death or myocardial infarction (4.2.5).
- The relative reduction in repeat revascularisation is similar across all studies (4.2.5).
- These benefits seem to be maximal at 6 to 12 months and there is no suggestion of a later catch-up – however the disease continues to progress in many patients (4.2.5).
- The trial data indicate a higher rate of reintervention than would be commonly seen in NHS practice (4.2.5, 8.2.3): 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 (5.1.5).
- The cost effectiveness of DES compared to 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 (8.6).
- Drug-eluting stents 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. Drug-eluting stents could be cost effective for wider groups of patients if the price premium were greatly reduced (8.6).
- It appears that DES are currently used in a far wider population than their cost-effectiveness justifies (9.2, 9.3)

10.2 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 two 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] two years ago, are addressed in the sections which follow.

10.2.1 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 to 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 a randomised controlled trial. 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 do not prolong life. The economic evaluations therefore focus on a more limited definition of clinical effectiveness.

10.2.2 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 to Taxus to a limited extent only (Section 8.7.6), 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 absolute risk reduction but the small additional benefit in absolute risk reduction 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.

10.2.3 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 to 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 to 50% compared to BMS (see Section 8.2.3). This is less than might be expected based on the trial data alone, where the reduction in events at 1 year is 60 to 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 to 5% (see Section 8.2.4), 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 this 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 to BMS. The conclusions of the current economic evaluation are therefore that that DES (at their current price premium) would not generally be considered a cost-effective alternative to bare metal stenting 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, i.e. 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 the broad definition of effectiveness is used. These represent only 0.1% of non-elective patients in the CTC audit, and only 1 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 requirement for only a single DES would only be 0.1% of elective, or 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.

10.2.4 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 six months, rather than cost per QALY as we have calculated. We acknowledge the weakness of quality of life (QoL) data here, and the uncertainty about the duration of each health state. However cost per QALY remains the expected standard for NICE assessment.

10.2.5 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: while 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 to that in other studies (e.g. ARTS), providing reassurance of the robustness of our analysis.

The survey conducted by 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 range of approximately £370 to £550.

Realistic price premiums determined from survey data (PASA) indicate that Cypher and Taxus DES cost an additional £659 and £537 per stent 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.

10.3 Robustness of results

We also believe that our results are robust. This is confirmed by the extreme values sensitivity analysis: we did not use probabilistic sensitivity analysis because it was unclear which variables were of greatest interest, and the extreme values approach 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 absolute risk reduction in repeat interventions are the most important items in influencing cost-effectiveness ratios. The £30,000 threshold is only attained if an absolute risk reduction in repeat revascularisations of at least 18% (elective) or 16% (non-elective) is achievable. Clearly for the great majority of patients this is quite 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.

10.4 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.

Areas where more research is still needed include:

- More direct comparative trials of DES to the newer non DES, (as undertaken in Pache and colleagues and the BASKET study[52, 82])
- Direct comparisons of established DES versus the newer DES since large scale studies have suggested that not all DES are clinically equal.

APPENDICES

APPENDIX 1: SEARCH STRATERGY – CLINICAL AND ECONOMICS EVIDENCE

1.1 Search strategies and search results

Database	Years	Search strategy	References identified
MEDLINE	2002-2005	See below	536
EMBASE	2002-2005	See below	542
Science Citation Index/Web of Science	2002-2005	((elut* or coat*) and (coronary or isch*emic) and stent*)	826
Science Citation Index/ ISI Proceedings	2002-2005	((elut* or coat*) and (coronary or isch*emic) and stent*)	242
The Cochrane Controlled Trials Register	2002-2005	(STENTS or stent*) and CORONARY DISEASE	414
The Cochrane Database of Systematic Reviews	2002-2005	(STENTS or stent*) and CORONARY DISEASE	28
HTA	2002-2005	(STENTS or stent*) and CORONARY DISEASE	44
DARE	2002-2005	(STENTS or stent*) and CORONARY DISEASE	10
PubMed (MEDLINE)	01Mar- 03 Aug 2005	drug$ and stent$	91
	Total references identified		**2642 (+91)**
	Duplicates		**1201**
	Total		**1441 (+91)**

1.2 Record selection

Searches of electronic databases:	**References identified**
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):	**References identified**
Clinical review	46
Economics review	4

APPENDIX 2: QUALITY ASSESSMENT – CLINICAL AND ECONOMICS EVIDENCE

2.1 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, whilst inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week)*
- Was the allocation of treatment concealed? *(Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque)*
- Was the number of participants who were randomised stated?
- Were details of baseline comparability presented in terms of treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Was baseline comparability achieved for treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Were the eligibility criteria for study entry specified?
- Were any co-interventions identified that may influence the outcomes for each group?
- Were the outcome assessors blinded to the treatment allocation?
- Were the individuals who were administered the intervention blinded to the treatment allocation?
- Were the participants who received the intervention blinded to the treatment allocation?
- Was the success of the blinding procedure assessed?
- Were at least 80% of the participants originally included in the randomisation process, followed up in the final analysis?
- Were the reasons for any withdrawals stated?
- Was an intention to treat analysis included?

Items 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 or **NS** not stated.

2.2 Quality assessment – economics studies

Studies of cost effectiveness were assessed using the following criteria, which is 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:

- 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 confidence intervals are given for stochastic data
- The approach to sensitivity analysis is given
- The choice of variables for sensitivity analysis 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 a disaggregated as well as 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

Appendix table 1 Study characteristics: DES versus BMS

	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 per day) for 6 months; 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 nove lesion; diameter 2.5 to 3.0mm; length 15 to 32mm; stenosis 50 to 99%; documented AP (CCS 1 to 4), UA (Braunwlad B, C, I or II) or SI; adult	As E-SIRIUS	Before: Aspirin (81 to 325 mg); clopidogrel (300mg loading or immediately after the procedure). During: IV of heparin (boluses, ACT inxs 250s); GPIIb/IIIa clinician discretion. After: Heparin discontinued; aspirin (81 to 325mg/day indefinitely); clopidogrel (75mg/day, 2 months)	Cordis
DIABETES	SES (Cypher, Coris) BMS	70{Sabate, 2003 #331}, 80{Sabate, 2004 #217} 76/80 70{Sabate, 2003 #331}, 80{Sabate, 2004 #217} 72/80	4 Spain	Diabetes (insulin or non insulin depandant); significant de novo stenosis in 1,2 or 3 vessles; signs or symptoms of ischemia	Diabetic without pharmacological treatment; bifurcations; SVG; LIMA; unprotected LMA; ISR; previous DES; previous Brachytherapy; renal/hepatic insufficiency; ACS (<72hrs, elevated CPKx2); malignancy	Abciximab recommended; Clopidgrel (1 yr) routinely prescribed; Aspirin (indefinitely) routinely prescribed; GP Iia/IIIb (59% of Px)	Cordis (Grant)

	Intervention	Randomised /Lost or Followed-up	Centres/ Location	Inclusion criteria	Exclusions	Co-therapy	Study support
ENDEAVOR II	ENDEAVOR, Medtronic Driver, Medtronic	598 582/598 599 585/599	72 Europe, Asia, Israel, NZ, Australia	Single de novo lesion, native vessel; stent diameter: 2.25 to 3.5mm;stent length 18 to 30 mm; lesion length 14 to 47mm.	AiC removed.	AiC removed.	Medtronic
E-SIRIUS	Cypher, Cordis Bs Velocity, Cordis	175 0 at 9 months; 177 0 at 9 months;	35 Europe	Single de novo lesion; 2.5mm to 3.0mm diameter, 15 mm to 32mm long; DS >50%; CCS angina or UA (Braunwald B & C, I-II) or documented silent ischemia	MI <24 hr; unprotected left main disease; ostial lesion; total occlusion; thrombus; calcified lesion; LVF £25%; impaired renal function; pre-treatment with devices other than balloon angioplasty, prior or planned intervention within 30 days	Pre-procedure: Aspirin, Clopidogrel or Ticlopidine During procedure: Heparin, GP IIb/IIIa inhibitors (at operators discretion) Post-procedure: Aspirin (indefinitely)Clopidogrel or Ticlopidine (2 months)	Cordis
Li	Cypher, Cordis Non-DES (not stated)	72 72/72 (Clin, 12mo); 63/72 (angio) 80 80/80 (Clin, 12mo); 65/80 (angio)	China	Small vessel; Diameter <3.0mm (by QAA)		'standard antiplatelet and anticoagualtion agents'	NS

	Intervention	Randomised /Lost or Followed-up	Centres/ Location	Inclusion criteria	Exclusions	Co-therapy	Study support
Pasche	Cypher, Cordis BeStent, Mectronic	250 205/250 (angio) 250 204/250 (angio)	2 Germany	symptomatic CAD; significant angiographic stenosis; native vessels	AMI; LMCA; ISR; contraindiactions to antiplatelet drugs, no consent	Before: clopidogrel (600mg, loaded); During IV aspirin, IV heparin; After: clopidogrel (2x75mg/day, 3days); clopidogrel (75mg, >/=6 months); Other antithrombotics at clinical discretion	NS
RAVEL	Cypher, Cordis Bx Velocity, Cordis	120 114/120, 94.2% (3years) 118 113/118, 94.1% (3years)	19 International	SA or UA or Slient ischemia; single de novo lesion; vessels 2.5 to 3.5mm	Evolving MI; uprotected LMCA; ostial traget lesion; calcified lesion (which could not be predilated); anginographically visable thrombus in target lesion	Aspirin; Heparin; Clopidogrel or Ticlopidine	Cordis
SES-SMART	Cypher, Cordis Bx sonic, Cordis	129 123/129 (angio) 128 113/128 (angio)	20 Italy	Single; de novo; 50 to 99% stenosis; native vessel; suitable for a single stent (max 33mm length); vessel dia <2.75mm; 1VD or MVD acceptable, but only non-rand lesion must be on separate vessel; adult; documented ACS; SA; silent ischemia	Recent AMI (15 days); severe calcifications; thrombus in lesion; LVEF <30%; allergies to (apsirin, clopidogrel, ticlopine, heparin, steel, contrast agents, sirolimus)	Before: Aspirin (1/day); clopidogrel (loading 300 mg at least 2 hours before) - expect if pre-treated.* During: heparin (70 U/kg, additional ACTmore than 250s); GP IIb/IIIa inhibitors clinician discretion; After: Asprin (100mg/day) indefinatly; clopidogrel (75mg/day, at least 2 months) *[Patients pretreated with ticlopidine (250 mg twice a day) or clopidogrel (75 mg once daily) for at least 72 hours did not receive a mclopidogrel loading dose].	Particpating centres/complementry funding - Cordis
SIRIUS	Cypher, Cordis Bx Velocity, Cordis	533 526/533 (1yr); 512/533 (2yr); 499/533 (3yr) 525 518/525 (1yr); 508/525 (2yr); 486/525 (3yr)	53 USA	Single de novo native coronary lesion; >/= 2.5mm and </= 3.5 mm diameter, >/=15 mm long; DS >50% and 100%; CCS angina (I-IV) or UA (Braunwald B&C, I-II) or silent ischemia	MI </= 24 hr; left main disease; ostial lesion; total occlusion; thrombus; calcified lesion; LVF </= 25%; impaired renal function; pre-treatment with devices other than balloon angioplasty	Pre-procedure: Aspirin, clopidogrel, Ticlopidine During procedure: Heparin, GP IIa/IIb clincial discresion (59.8%); Post-procedure: Aspirin, Clopidogrel, Ticlopidine	Sponsor - Cordis

	Intervention	Randomised /Lost or Followed-up	Centres/ Location	Inclusion criteria	Exclusions	Co-therapy	Study support
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 <=12mm; TIMI flow of >=1, diameter TVD >=2.8mm to <=3.2mm; SA	LVEF<=30%; Organ transplant candidate/recipient; unstable arrhyythmias; heavily calcified lesion		Guidant
STRATEGY	Cypher, Cordis & Tirofiban Sonic, Cordis (or other approved non DES) & 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 hours of symptom onset or 12-24 hours 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 months; unable to obtain informed consent	*SES group:* Tirofiban bolus 25ug/kg over 3 min, IV 0.15ug/kg/min for 18-24 hours; *Non DES group*: Abciximab: bolus 0.25ug/kg over 3 min, IV 0.125ug/kg/min for 12 hours; *ALL:* Aspirin (160-325mg loading, 125mg indefinitely), clopidogrel (300mg loading, 75mg/day for >=3 months); Heparin (before) 50u/kg and additional → ICT <=200 seconds	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 3.5mm;	History of MI; LVEF 30%; stroke within 6 months; Serum creatine >1.7 mg/100ml; contridication to aspirin, clopidogrel, ticlopine	Pre-procedure: Aspirin, Heparin and Clopidogrel Post procedure: Aspirin 12 months Clopidogrel for 6 months	Boston Sci Corp
TAXUS II	TAXUS NIRx (SR), Boston NIR Confromer (cohorts combined), Boston	266 ~1% at 1year (cohort 1) 270 ~1-2% at 1year (cohorts 1 and 2)	38 Europe	Single lesion de novo lesion, native coronary artery; stenosis between 50 to 99%; lesion length 12 mm; vessel diameter 3.0 to 3.5 mm	Recent MI (<72h), stroke within 6mo, renal dysfunction, LVF >30%, (VUS study #48, excludes Px receiving any non-study stent	Clopidogrel (300-mg loading); clopidogrel (75 mg/day) (or ticlopidine 2x250/day) for 6 months and aspirin (75 mg/day) indefinitely.	Boston Sci Corp

	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 to 28mm; diameter 2.5 to 3.75mm; (Boston Submission indicate multiple lesion and multiple vessels included in proceedure complexity)	Previous/planned vessel brachytherapy or DES; planned use of atherectomy before stenting; AMI <72 hours; LEF <25%; hemorrhagic 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 (325mg); During: heparin, GP IIb/IIIa inhibitors clinician discretion; After clopidogrel (75 mg/day) for 6 months 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 months); 79/577 (angio) 579 (586 Rand) 31/579 (9 months); 87/579 (angio)	66 USA	Single; de novo de novo; native lesions; >=10mm - <=46 mm Discrete lesions >=5mm - <=26 mm; treatable with 2 stents; RVD: >=2.25mm to <=4.0mm; stenosis >=50%	Prior or planned PCI or brachytherapy in target; Bifurcation lesions; Target vessel pre-treated with treated with unapproved device; MI <=72 72h, CK-MB >2x ULN on day of procedure	After: Clopidogrel (6 months); Aspirin (9 months)	Boston Sci Corp

SR: Slow release; [P]: protocol; Angio: angiographic; LEF: left ejection fraction; LM: left main coronary artery; CK-MB: creatine kinase; hr: hours; mo: months; ISR: in-stent restensois; CAD: coronary artery disease; SA: stable angina; UA: unstable angina; Rand: Randomised

Appendix table 2 Participant characteristics: DES versus BMS

PART I	Intervention	Number of participants	Gender % male	Age Years [SD]	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{Sabate, 2004 #217}				
	BMS	80{Sabate, 2004 #217}				
		ALL	62.5	66.5 [9]	100 (53/160 ID)	
ENDEAVOR II	ENDEAVOR, Medtronic	598	AiC removed	AiC removed	AiC removed	AiC removed
	Driver, Medtronic	599	AiC removed	AiC removed	AiC removed	AiC removed
		ALL	AiC removed	AiC removed	AiC removed	AiC removed
E-SIRIUS	Cypher, Cordis	175	70	62.0 [11.4]	19	41
	Bs 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				
Pasche	Cypher, Cordis	250	78	67.4 (59.0, 75.4) Median	29	32
	BeStent, Mectronic	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	
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

PART I	Intervention	Number of participants	Gender % male	Age Years [SD]	Diabetes %	Previous AMI %
	MULTI-LINK VISION RX, Guidant	32 (Per-P: 29) ALL	75.9	61.4	10.3	13.8
STRATEGY	Cypher, Cordis & Tirofiban	87	77	62 [54-72]	17	13
	Sonic, Cordis (or other BMS) & Abciximab	88	69	63 [55-72]	11	9
TAXUS I	TAXUS NIRx, Boston	31	94	66	23	26
	NIRx, Boston	30 ALL	83	63.8	13	30
TAXUS II	TAXUS NIRx (SR), Boston	266	70.2	35.1	10.7	61.5
	NIR Confromer (cohorts combined), Boston	270 ALL	77.9	59.7	15.1	42
TAXUS IV	TAXUS Express2 (SR), Boston	662	71.8	62.8 [11.2]	31.1	30.5
	EXPRESS, Boston	652 ALL	72.4	62.1 [10.9]	33.3	29.9
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) ALL	68.7	62.8 [10.8]	29.9	26.3

ID: insulin dependant; SR: Slow release formulation

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			AiC removed	AiC removed
	Driver, Medtronic	599			AiC removed	AiC removed
		ALL				
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				
Pasche	Cypher, Cordis	250	2.7 (2.4, 3.1)	13.0 (8.9, 18.0)	82% (MVD)	LAD 43%; RCA 28%; LCx 29%
	BeStent, Mectronic	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 to 3.5mm (inc 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%

PART II	Intervention	Number of participants	Vessel diameter mm	Lesion length mm	Vessels diseased Number: %	Complex lesions
		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%
SIRIUS	Cypher, Cordis	533		14.4	1:59; 2:25; 3: 15	
	Bx Velocity, Cordis	525		14.4	1: 58; 2: 29; 3: 14	
		ALL				
SPIRIT FIRST	XIENCE V (MULTI-LINK VISION-E® RX), Guidant	28 (*Per-Protocol: 27*)				LAD 48.1%; RCA 29.6%; LCx 22.2%
	MULTI-LINK VISION RX, Guidant	32 (*Per-Protocol: 29*)				LAD 44.8%; RCA 34.5%; LCx 20.7%
		ALL				
STRATEGY	Cypher, Cordis & Tirofiban	87			1: 46; 2: 28; 3: 13	LAD 43%
	Sonic, Cordis* & Abciximab	88			1: 57; 2: 33; 3: 19	LAD 36%
	(*or other approved non DES)	ALL				
TAXUS I	TAXUS NIRx, Boston	31				LAD 54.8%; RCA 22.6%
	NIRx, Boston	30				LAD 26.7%; RCA 36.7%
		ALL				
TAXUS II	TAXUS NIRx (SR), Boston	113				LAD 40.7%; LCx 20.4%; RCA 38.9%
	NIR Confromer (cohorts combined), Boston	240				LAD 47.9%; LCx 15.4%; RCA 36.7%
		ALL				
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	2.75 [0.49] RVD	13.4 [6.2]		LAD 41.4%; RCA 26.6%; LCx 32.0%
		ALL	2.5 to 3.75 (inc criteria)	10 to 28 (inc criteria)		
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)	RVD: 2.69 [0.56]; MLD: 0.85 [0.39]	17.2 [9.4]		
		ALL				

MVD: Multi vessel disease; RVD: Reference vessel diameter; MLD: Minimal luminal diameter

Appendix table 3 Outcomes: DES versus BMS (3 parts)

PART I		Event rate					Mortality				
Study	**Intervention**	**1 mo**	**6-9 mo**	**1 year**	**2 years**	**3 years**	**1 mo**	**6-9 mo**	**1 year**	**2 years**	**3 years**
BASKET	Cypher, Cordis	6/264	15/264				2/264 cardiac	5/264			
	Taxus, Boston	5/281	24/281				2/281 cardiac	7/281			
	Vision, Guidant	10/281	34/281				1/281 cardiac	9/281			
C-SIRIUS	Cypher, Cordis		2/50					0/50			
	Bx-VELOCITY, Cordis		9/50					0/50			
DIABETES	Cypher, Cordis	0/80	9/80				0/80	1/80			
	BMS	5/80	29/80				2/80	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	AiC removed	47/582 AiC removed.				AiC removed	7/582	AiC removed		
	Driver, Medtronic	AiC removed	90/585 AiC removed.				AiC removed	3/585	AiC removed		
Li	Cypher, Cordis							0/72			
	Non-DES (not stated)							2/80			
Pasche	Cypher, Cordis	9/250		34/250			0/250		7/250		
	BeStent, Mectronic	12/250		56/250			0/250		5/250		

PART I		Event rate					Mortality				
Study	**Intervention**	**1 mo**	**6-9 mo**	**1 year**	**2 years**	**3 years**	**1 mo**	**6-9 mo**	**1 year**	**2 years**	**3 years**
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 allTVR)	0/120		2/120	6/120**	9/114
	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 allTVR)	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 & Tirofiban	3/87	16/87				2/87	7/87			
	Sonic, Cordis (or other BMS) & 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 Confromer (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*	
TAXUS V	TAXUS Express2 (SR), Boston	29/569	84/560				0/569	3/560			
	Express2, Boston	21/576	120/567				0/576	5/567			

SR: Slow release DES formulation; Mo: months

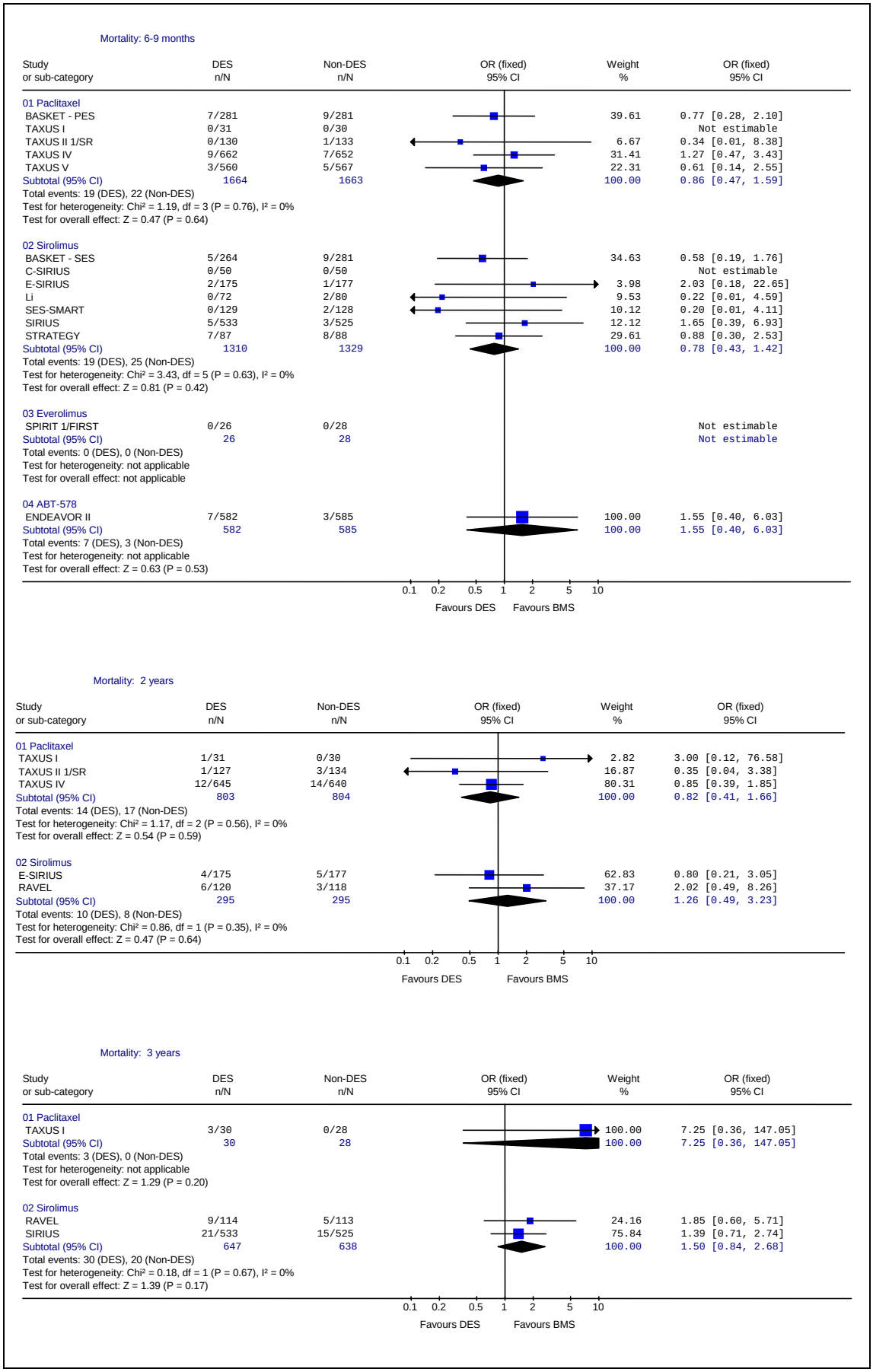
PART II Study		AMI					TLR				
		1mo	6-9mo	1 year	2 years	3 years	1mo	6-9mo	1 year	2 years	3 years
BASKET	Cypher, Cordis	3/264	6/264				3/264 TVR	8/264 TVR			
	Taxus, Boston	1/281	6/281				3/281 TVR	17/281 TVR			
	Vision, Guidant	8/281	12/281				4/281 TVR	22/281 TVR			
C-SIRIUS	Cypher, Cordis		1/50					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	AiC removed	16/582	AiC removed			AiC removed	27/582			
	Driver, Medtronic	AiC removed	23/585	AiC removed			AiC removed	71/585			
Li	Cypher, Cordis							1/72			
	Non-DES (not stated)							8/80			
Pasche	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)
	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			

PART II Study		AMI					TLR				
		1mo	6-9mo	1 year	2 years	3 years	1mo	6-9mo	1 year	2 years	3 years
STRATEGY	Cypher, Cordis & Tirofiban	1/87	6/87					5/87			
	Sonic, Cordis (or other approved non DES) & Abciximab	3/88	8/88					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 Confromer (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					89/567			

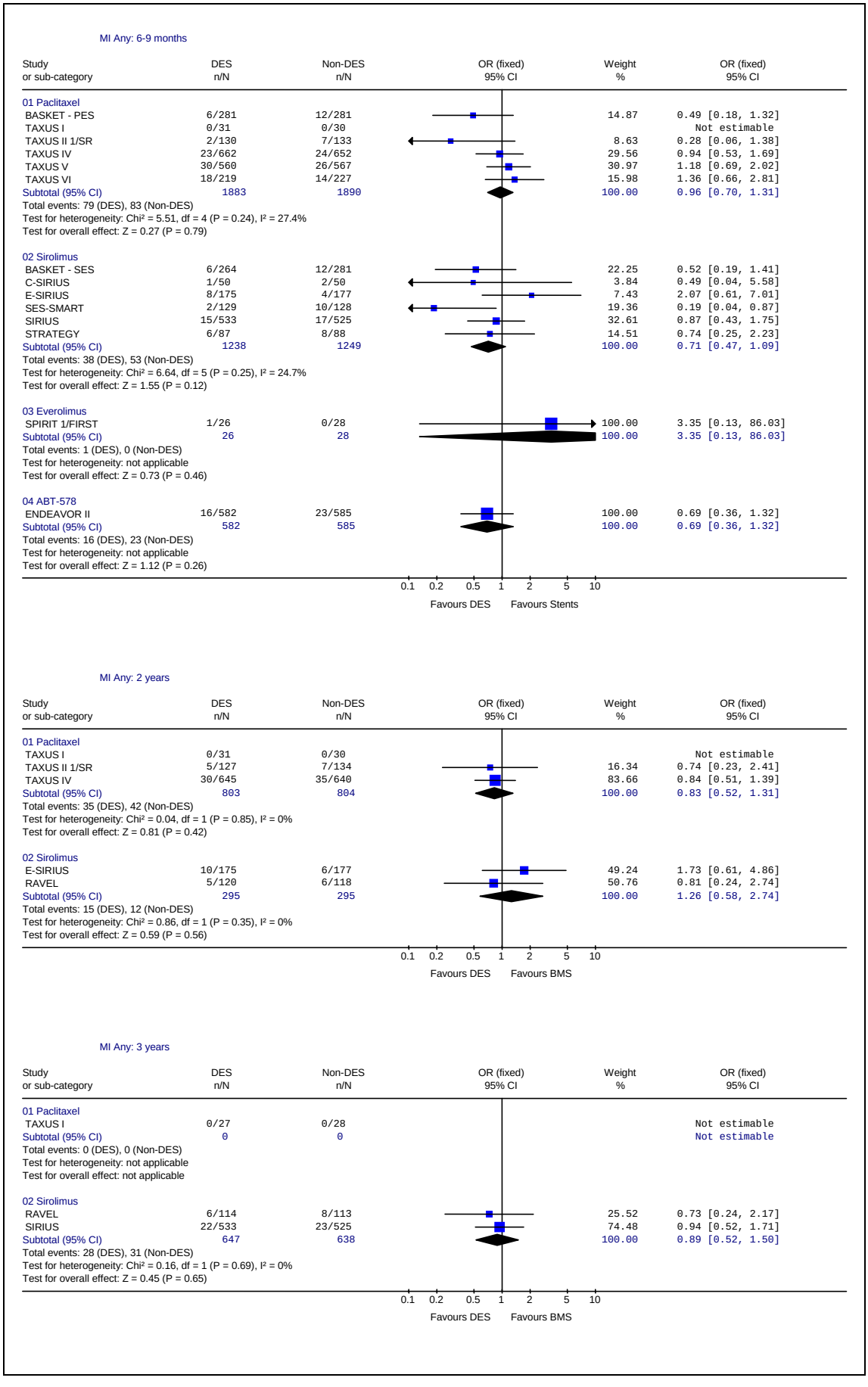
PART III Study	Intervention	BRR 6- 9 mo	Notes	Late loss 6-9 mo	Notes
C-SIRIUS	Cypher, Cordis Bx-VELOCITY, Cordis	0/44 (in-stent) 1/44 (in-lesion) 20/44 (in-stent) 23/44 (in-lesion)	8 months (all Px)	0.12 [0.37] (in-stent) 0.12 [0.35] (in-lesion) 1.02 [0.69] (in-stent) 0.79 [0.74] (in-lesion)	
DIABETES	Cypher, Cordis BMS	4.9% Lesions (in-stent) 7.7% Lesions (in-segment) 31% Lesions (in-stent) 33% 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) 0.66 [0.5] (in-stent); 0.44 (in-segment)	DES 75, BMS 70; In-seg from CRT resources
E-SIRIUS	Cypher, Cordis Bs Velocity, Cordis	6/152 (in-stent) 9/152 (in-lesion) 65/156 (in-stent) 66/156 (in-lesion)	8 months; Angio FU: DES 152/175, BMS 156/177; DES 154, BMS 151 in {Cordis, 2003 #420}	0.20 [0.38] (in-stent) 0.19 [0.38] (in-lesion) 1.05 [0.61] (in-stent) 0.80 [0.57] (in-lesion)	N=DES 152, N=BMS 156; DES 154, BMS 149{Cordis, 2003 #420}
ENDEAVOR II	ENDEAVOR, Medtronic Driver, Medtronic	AiC removed AiC removed	AiC removed	AiC removed AiC removed	AiC removed
Li	Cypher, Cordis Non-DES (not stated)	4/69 Lesions 26/72 Lesions	3/4 BRR at 'proximal site' of SES		
Pasche	Cypher, Cordis BeStent, Mectronic	17/205 52/204	6 months; rate in vessels <2.8/>2.8mm available	0.14 (–0.5, 0.43) n=205 0.94 (0.53, 1.30) n=204	6 months; Median (25th,75th) - need SD for RevMan
RAVEL	Cypher, Cordis Bx Velocity, Cordis	0/105, 0% (in-stent) 0% (in-segment) 28/107, 26.6% (in-stent) 0% (in-segment)	Angiographic data: 211/238 patients (no N for DES/BMS in Morice); DES 105, BMS 107{Cordis, 2002 #421}	-0.01 [0.33] (in-stent); 0.80 [0.53] (in-stent);	Separate proximal and distal edge data in {Morice, 2002 #419}; DES 105, BMS 106{Cordis, 2002 #421}
SCANDSTENT	CYPHER, Cordis BMS	3/163 51/159	Based on 2%, 31.9%	0.04 0.94	
SES-SMART	Cypher, Cordis Bx sonic, Cordis	6/123 (in-stent) 12/123 (in-segment) 55/113 (in-stent) 60/113 (in-segment)	Mean 8 [0.5] months; Angio FU SES: 95.3%, BMS: 88.3%;	0.16 [0.38] LLL 0.11 [0.29] LI (in-stent) 0.90 [0.62] LLL 0.68 [0.49] LI (in-stent)	In-Seqment 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 months available; cumulative frequency plots available

PART III Study	Intervention	BRR 6- 9 mo	Notes	Late loss 6-9 mo	Notes
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) 9/26 (in-segment)		0.84 [0.36] (in-stent) 0.60 (in-segment)	
STRATEGY	Cypher, Cordis & 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) & 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]	
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, 2y)	QCA/IVUS substudy QCA/IVUS substudy (Colombo, TCT 2004) - 6 month and 2 year data
	NIR Confromer (cohorts combined), Boston	24/134 (in-stent) 27/134 (Analaysis-segment)		0.70 [0.38] (in-stent) 0.54 [0.36] (in-stent, 2y)	
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] (Anlys-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] (Anlys-segment)	

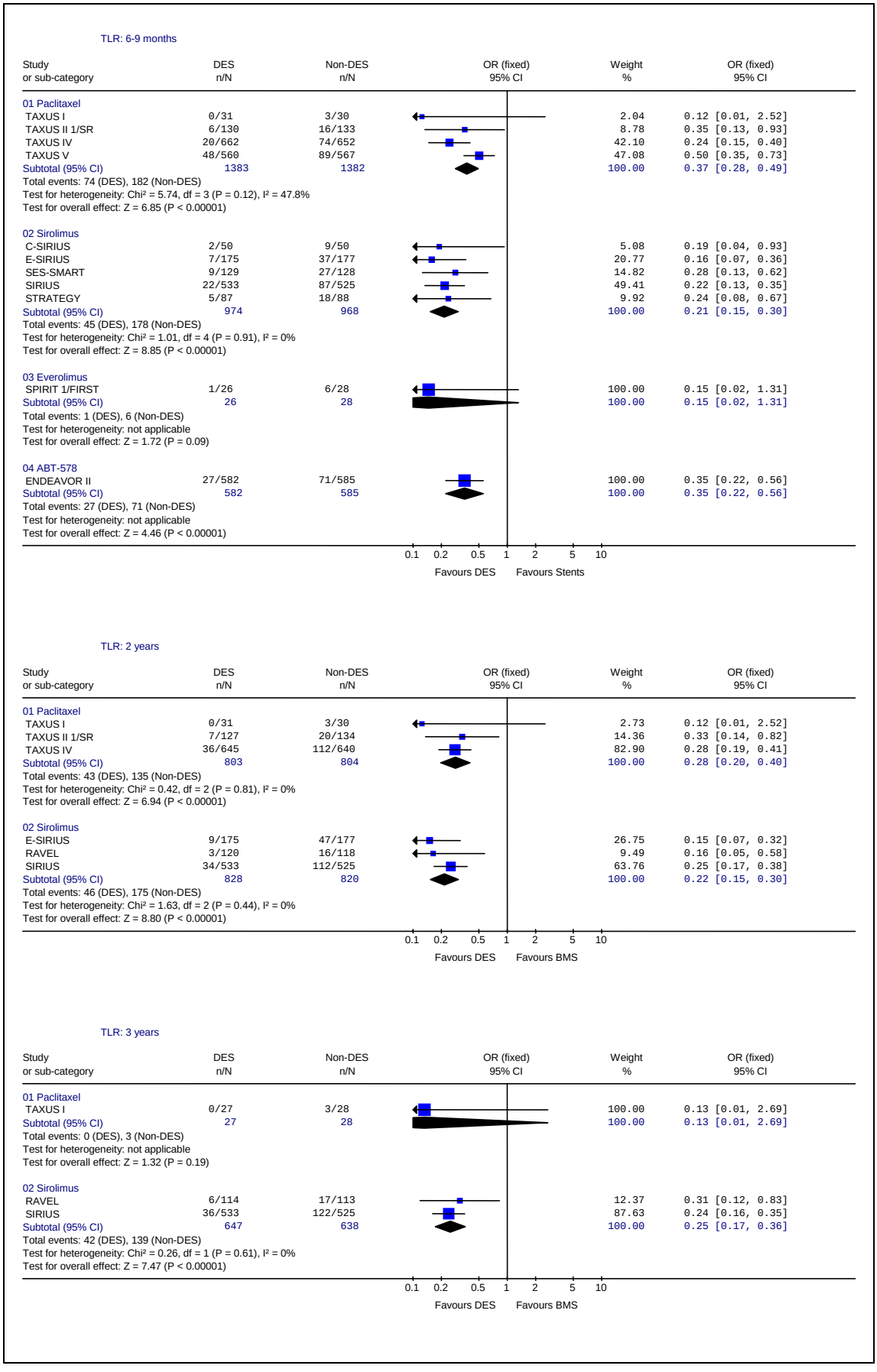
Appendix figure 1: Meta-analysis: Mortality



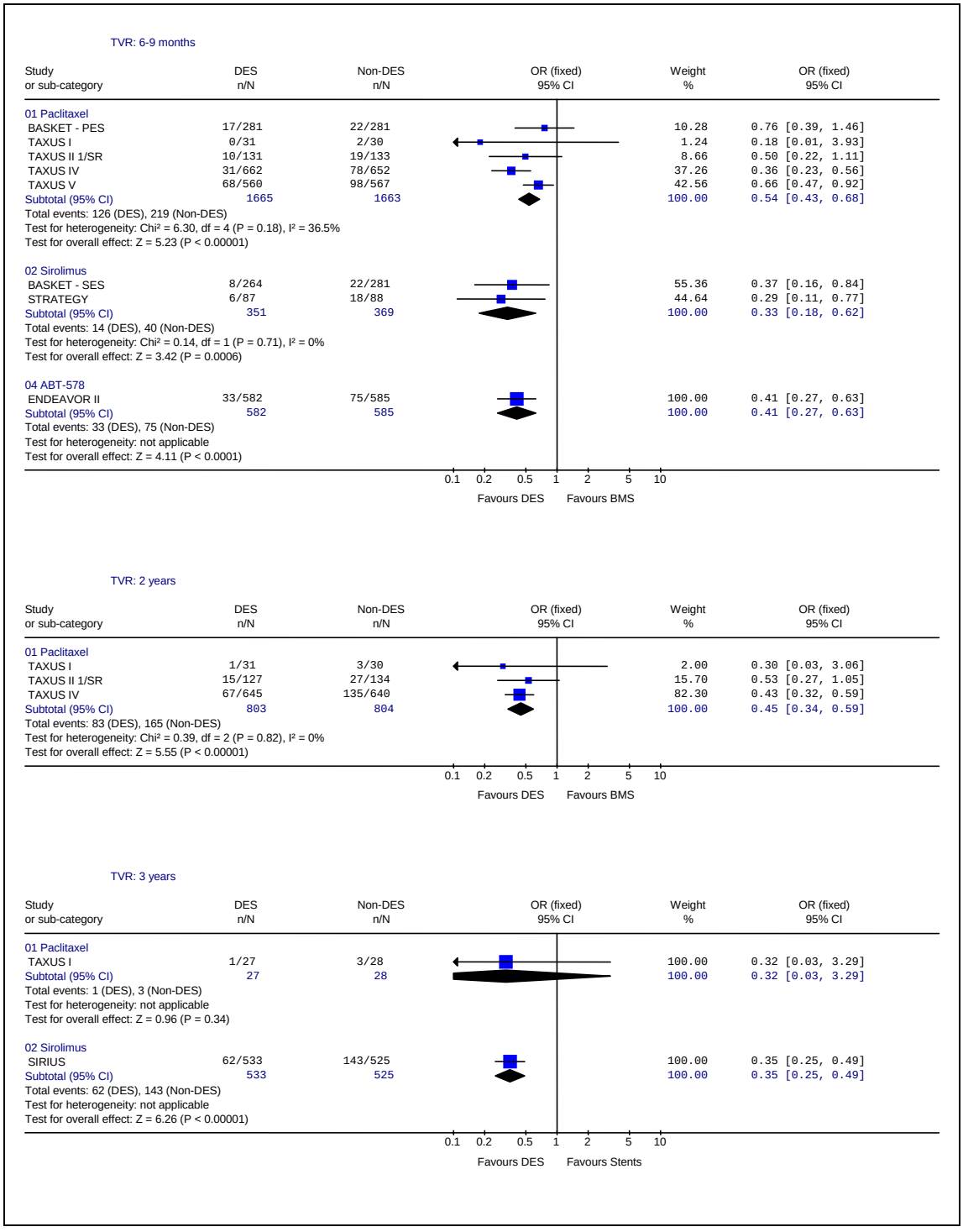
Appendix figure 2: Meta-analysis: MI



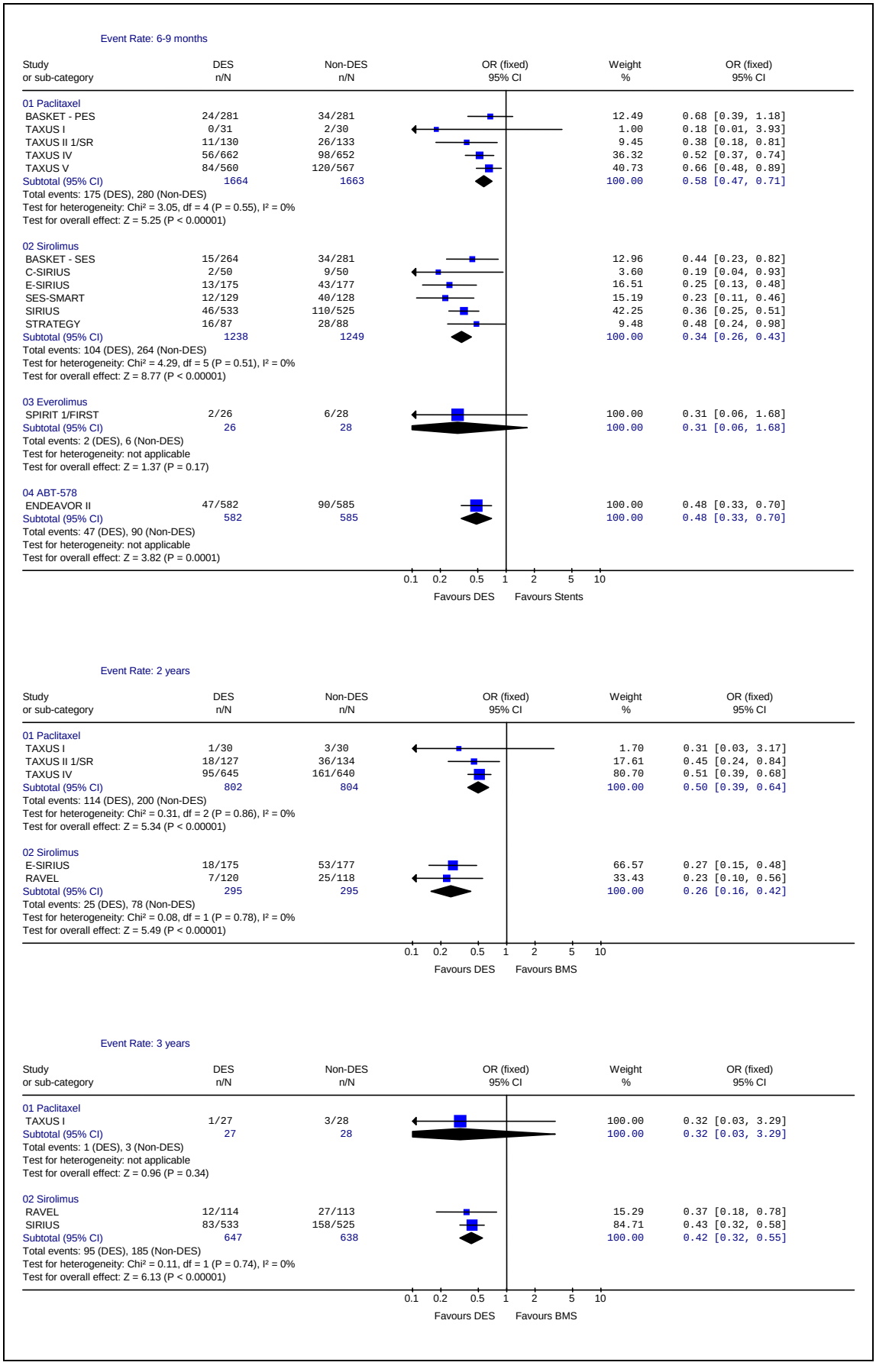
Appendix figure 3: Meta-analysis: TLR



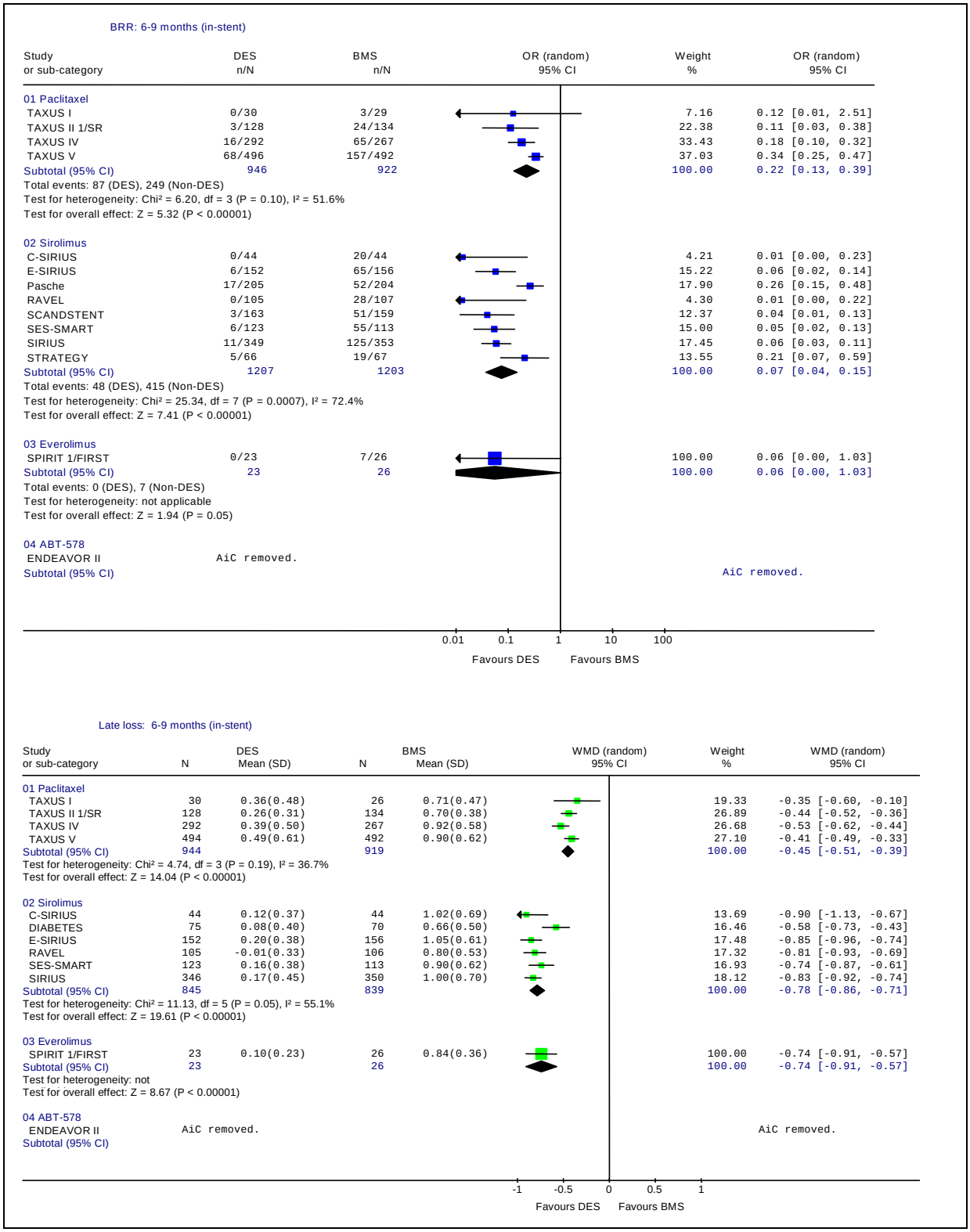
Appendix figure 4: Meta-analysis: TVR



Appendix figure 5: Meta-analysis: Event rate



Appendix figure 6: Meta-analysis: Binary restenosis, late loss (random effects analysis)



APPENDIX 4: CLINICAL REVIEW TABLES – DES VERSUS DES

Appendix table 4 Study characteristics: DES versus DES

	Intervention	Rand/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 1ry success 321; 410 lesions (after angio) 304/321 1ry 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 <23mm; vessle diameter <=3.5mm	See: {Cordis (Johnson & Johnson Medical Ltd), 2005 #409}		
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 =ve stress test; stenosis >=50%	AMI; LM; ISR; Allergy to sirolimus, paclitaxel, heparin, aspirin, clopidogrel		

	Intervention	Rand/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)	Mutiple International	AP (CCS I-IV (stable), Brunwald class B & C I-II-III (unstable), documented SI; Diameter 2.25 to 3.0mm; Length: 1st lesion >15mm, 2nd Lesion >10mm; stenosis >50%; at least TIMI I	AMI within 72 hrs; Ostial lesions; unprocted LM; LVERF <=25%; TO; ISR; PCI within 30 days	Before: Aspirin, Thienopyridin (loading dose before or immediately after); During: Heparin, GPIIb/IIIa at discretion After: Clopidogrel (75mg/days) or Ticlopidine (500mg/day), Aspirin (100mg/day) indefinitely, Thienopyridine (>=6 months Taxus >= 2months 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 to 4.0mm (RVD) length - no limit	Lesion unsuitbale for stnet implantation; participation in other study; severe co-mobidity; study stents unavailable; pregnanc; allergy to paclitaxel, sirolimus, aspirin, thienopyridines	Pre/During: Aspirin Clopidogrel (300mg) loading, Heparin (5000 IU IV or 70 IU/kg), GPIIb/IIIa operator discretion After: Aspirin (100mg/day) indefinitely, Clopidogrel (75mg/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; uncertainity of obtaining follow-up	Before: Aspirin (100mg/day) clopidogrel (75 mg/day) 5-7 days (only a minority) During: Heparin IV (70U/kg) After: clopidogrel (300mg loaded), Aspirin (100mg/day) long-term, clopidogrel (75mg/day) 12 months,GP IIb/IIIb (7/102, 4/100)	

Appendix table 5 Participant characteristics: DES versus DES (2 parts)

PART I	Intervention	Numbers included	Gender % male	Age Mean, yrs	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	Vessel length	Vessels diseased	Complex lesions
BASKET	Cypher. Cordis Taxus, Boston	264 281				
CORPAL	Cypher, Cordis Taxus, Boston	331; 434 lesions 321; 410 lesions	0.73 [0.5] MLD 2.84 [0.4] stent 0.70 [0.5] MLD 2.83 [0.4] stent	26 [14] 27 [14] stent 24 [14] 27 [14] stent		LAD 194/434; RCA 124/434; Cx 104/434; LM 12/434 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 (type-o, 225) 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% LAD %; RCA %; Cx %
REALITY	Cypher, Cordis Taxus, Boston	684 (970 lesions) 669 (941 lesions)	2.40 [0.48] RVD; 2.79 [0.28] Stent 2.40 [0.48] RVD; 2.80 [0.28] Stent	16.96 [10.04] 17.31 [10.09]		
SIRTAX	Cypher, Cordis Taxus, Boston	503 509			1: 40%; 2: 37%; 3: 23%	
TAXi	Cypher, Cordis Taxus, Boston	102 100	3.2 [0.1] RD 3.2 [0.2] RD		1v: 36/102; 2v: 35/102; 3v: 29/102 1v: 40/100; 2v: 32/100; 3v:28/100 44/202 mutivessel RV (25/ 1 session, 19/ staged)	 Most patients had complex lesions

Appendix table 6 Outcomes: DES versus DES (2 parts)

PART I Study	Intervention	Event Rate 1mo	6-9mo	1 year	Mortality 1mo	6-9mo	1 year	AMI 1mo	6-9mo	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 1ry ER 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	

PART II Study	Intervention	TLR 1mo	6-9mo	1 year	BRR 6-9mo	Late Loss 6-9mo
BASKET	Cypher, Cordis Taxus, Boston				No angiograhic follow-up	No angiograhic follow-up
CORPAL	Cypher, Cordis Taxus, Boston			19/331 29/321	22/177 Lesns 35/188 Lesns	0.36 [0.5] 0.54 [0.7]
DOMINO	Cypher, Cordis Cypher Select, Cordis		0/37 0/60		0/36 (in-stent) 1/55 (in-stent)	0.13 [0.28] 0.07 [0.35]
ISAR-DIABETES	Cypher, Cordis Taxus, Boston		8/125 15/125		5/102 (in-stent); 7/102 (in-segment) 14/103 (in-stent); 17/103 (in-segment)	0.19 [0.44] (in-stent) 0.43 [0.45] (in-segment) 0.46 [0.64] (in-stent) 0.67 [0.62] (in-segment)
ISAR-TEST	Yukon (SES), KiwiMed Taxus, Boston		8.7% 9.5%		14.1% 18.1%	0.49 [0.59] 0.47 [0.57]
REALITY	Cypher, Cordis Taxus, Boston		34/684 36/669		7.0% Lesn (in-stent); 9.6% Lesn (in-segmentment) 8.3% Lesn (in-stent); 11.1% lesn (in-segmentment)	0.09 [0.43] (in-stent) 0.04 [0.38] (in-segment) 0.31 [0.44] (in-stent); 0.16 [0.40] (in-segment)
SIRTAX	Cypher, Cordis Taxus, Boston	11/503 10/509	24/503 42/509		11/348 lesn (in-stent); 23/348 lesn (in-segment) 28/375 lesn (in-stent); 44/375 lesn (in-segment)	0.12 [0.36] (in-stent) 0.25 [0.49] (in-segment) 0.19 [0.45] (in-stent) 0.32 [0.55] (in-segment)
TAXi	Cypher, Cordis Taxus, Boston		2/102 1/100		No angiograhic follow-up	No angiograhic follow-up

APPENDIX 5: CLINICAL REVIEW TABLES – DES WITHOUT RCT EVIDENCE

Appendix table 7 New DES non-RCT study and participant characteristics

ID	Intervention	Numbers	Centres/ Location	Inclusion	Exclusion
ATLAS	Taxus Liberté, Boston	871	61 Worldwide	De novo; kength 10-28mm; diameter 2.5-4.0mm	-
EMPEROR (Pilot)	Dexamet (2.2u g/mm2), Abbott	30	1 Germany	Lesion length to be covered by one 18mm long stent;vessel diameter between 2.75-3.75mm; patients with SVD	Ejection fraction <30%; unprotected left main location; heavy calcification; excessive tortuousity of the proximal vessel; life expectancy <one year; MI within previous 72 hours; previous intracoronary brachytherapy
EuroSTAR	CoStar (10ug, 24-30d PES), Biotronik CoStar (30ug 24-30d 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 ischemia 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 hours); 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 (10ug bi 10d PES, Grp 3), Biotronik CoStar (30ug mu 30d 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, stensosis 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 hours 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 <3months; total occlusion of culprit vessel; ISR lesion; SVG lesion; vessel diameter <2.75mm; lesion length >30mm.
ISAR Project (1)	Yukon DES, KiWiMed Yukon (non-loaded), KiWiMed	602 (447 DES; 155 non-loaded)	1 Germany	Native vessel diameter 2.5 to 30mm; angina or exercise induced ischaemia in the presence of angiographically significant stenosis.	MI (within 72 hrs); LM; ISR.

ID	Intervention	Numbers	Centres/ Location	Inclusion	Exclusion
JUPITER I (Alpha)	Janus CardoStent, Sorin	58	7 Clinical investigator instituitions Italy	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; stensois 50- 100% (TIMI I); <= 2 target vessels; 1 lesion for each vessel 1 DES stent only (15-mm x 3.0-3.5 mm) for each target lesion.	
Patti	Dexamet (0.5 g/mm2), Abbott	100		Unstable coronary conditions (unstable angina or recent <1 month MI)); Single vessel disease; Stenoses >70%; vulnerable plaque deamed treatable by 1 stent.	Inflammatory diseases, malignancy, infection, <2 months surgery or trauma.
SAFE	Dexamet, Abbott	735 (pts in database)	16 countries Worldwide	Not reported	Not reported
STRIDE	Dexamet (0.5 ug/mm2), Abbott	60 (strictly met requirements); 71 (all enrolled)	8 Belguim	De novo coronary lesions; documented myocardial ischemia; vessel diameter >2.75 - <4mm; target lesion stenosis >50% - <100%; noncalcified lesions; lesion length <15mm requiring one stent of 11, 15 or 18mm in length;patients aged over 21.	Patients with ostial and bifurcation lesions; left ventricular ejection fraction <30%; MI within 72 hours; CVA or TIA <3 months; known hypersensitivity or contraindication to aspirin or stainless steel or contrast dye or heparin or ticlopidine; active peptic ulcer or upper GI bleeding; renal failure; liver disease; diabetes mellitus; life expectancy <12months.

.

Appendix table 8 New DES non RCT outcomes

Study	Interventions	Follow-up	ER	Mortality	AMI	TLR	TVR	BRR/LL[a]
ATLAS	Taxus Liberté, Boston	30 days	CiC removed.	CiC removed.	CiC removed	CiC removed		
EuroSTAR	CoStar (10ug, 24-30 day elution PES), Biotronik 145 CoStar (30ug 24-30 day elution PES), Biotronik Arm II FU not complete	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-seg) *Late Loss* 0.26 [0.39] (in-stent) 0.07 [0.38] (in-seg)
CoSTAR I (India)	CoStar (10ug bidirectional 10 day elution PES, Grp 3), Biotronik 40 (interim) 14 Lesions CoStar (30ug multi directional 30 day elution PES, Grp 1), Biotronik 10 (interim) 57 Lesions	30 days 4 months 30 days 4 months	2/40 3/40 1/10 1/10	0/40 0/40 0/10 0/10	2/40 2/40 1/10 2/10	0/40 1/40; 1/57 Lesions 0/10 0/10; 0/14 Lesions		*BRR:* 1/52 Lesions (in-stent) 2/52 lesions (in-lesion) *Late Loss* 0.43 [0.43] (in-stent) 0.24 [0.39] (in-lesion) *BRR*: 2/14 Lesions (in-stent) 2/14 lesions (in-lesion) *Late Loss* 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 (2.2u g/mm2), 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-seg)

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-seg) *Late Loss* 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/mm2), 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 ug/mm2), Abbott	30 day 6 months	2/71 4/71	1/71 1/71	1/71 1/71	0/71 2/71		

A: 'Lesions' indicate that reporting of BRR/Late loss is by lesion (rather than by patient).

APPENDIX 6: DES REGISTRIES

Appendix table 9 Data Registries

Registry name	DES	Data source	Progress	Sponsor	Available data	Primary focus
BRIDGE[146]	CYPHER or BMS n=1000	France Sites=100	Complete 2003	Cordis	unclear	Diabetic patients
E-CYPHER[147-149]	CYPHER n=>15000	International Sites >275 4 UK sites (n=424)	Target reached Aug/04	Cordis	1 year (n=10600)	Safety and reliability
GERMAN CYPHER REGISTRY[150, 151]	CYPHER n=5878	Germany Sites=102	April/02 - present	Not stated	6 month	Monitor unexpected events
PORTO I, II[146]	CYPHER N=300	Portugal Sites=13	2003- enrolment ongong	Cordis	6 month	Non-Diabetes/ Diabetic patients
LONG DES[152]	CYPHER n=294 TAXUS n=166 BMS n=177	Korea Sites=8	March/03-Feb/04	Cordis	8 month	In stent restenosis
SAFE[153]	DEXAMET n=1000	Europe, Middle East, Africa (25 countries) Sites=80	2003	Abbott	unknown	Clinical Follow-up 1 and 6 months
RESEARCH[154-156]	SES n=508 Non SES N=663	Netherlands Site=1	Non SES Oct.01-April/02 SES April/02-Oct/02	Cordis	1 year	Safety and efficacy of SES
SWISS HOSPITALS PROSPECTIVE REGISTRY [157]	SES n=183	Switzerland Sites=2	April/02 to Sept/02	Not stated	7 months	
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[158]	TAXUS n=2586	USA Sites=50	Feb/04 to May/04	Boston Scientific	1 year	12-Month site reported cardiac events
ARRIVE 2[159]	TAXUS n=5000	USA Sites=	Currently enrolling	Boston Scientific		12-Month site reported cardiac events
WISDOM[158, 160]	TAXUS n=778	International Countries=9 Sites=22	June/02 to July/03	Boston Scientific	1 year	12-Month site reported target lesion re-interventions
OLYMPIC[161]	TAXUS Liberte	International	Post CE mark of stent	Boston Scientific	Enrolling	
MILESTONE II[158]	TAXUS SR n=3688	International Countries=32	March/03 to March/04	Boston Scientific	1 year	Real world physician usage by

Registry name	DES	Data source	Progress	Sponsor	Available data	Primary focus
		Sites=164				lesion type and patient subset Safety High risk Usage patterns
DESIRE[104]	Dexamethasone	320 Italy	Completed 2004	Abbott	6 months	ACS/NSTE MI patients
	Registries where only limited information was identified					
REAL LIFE PB PACLITAXEL REGISTRY[162]	TAXUS SR					
T-SEARCH[163]	TAXUS n=576	The Netherlands Site=1	Feb/03-Sept/03	Not stated	1 year	Safety and efficacy of PES
DESCOVER[147, 164]	Consecutive PCI patients n=7500	USA	Scheduled launch Nov/04	Not stated	n/available	Also collecting QoL and economic data
DYNAMIC[147, 165]	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	[53]
	[53, 83]
DIABETES	[54]
	[54, 68]
ENDEAVOR II	[89]/[90]
	[89, 90, 166, 167]
E-SIRIUS	[56]
	[55, 56, 83]
BASKET	[82]
	[82, 168]
Li	[79]
	-
Pasche	[52]
	-
RAVEL	[61]/[57]
SCANDSTENT	[67]
	[57-66, 84, 85]
SES-SMART	[70]
	[69, 70]
SIRIUS	[71]
	[66, 71-78]
SPIRIT FIRST	[31]
	[31, 32]
STRATEGY	[80]
	[80, 81]
TAXUS I	[33]
	[33-35]
TAXUS II	[36]
	[36-38]
TAXUS IV	[42]
	[39-50, 86, 87]
TAXUS V	[88]
	[51, 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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Principle reason of exclusion	Reference
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Principle reason of exclusion	Reference
	Eluting Stent Platform: The Paclitaxel In-Stent Controlled Elution Study (PISCES). 2005. **46**(2): p. 253.
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A: Many records were excluded on the basis of information contained in title and/or abstract at first stage of source selection, so are not listed in this table.

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