NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview (October 2006)

Coronary artery stents for the treatment of ischaemic heart disease (review of *NICE technology appraisal guidance* no. 71)

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the first Appraisal Committee meeting, it is prepared before the Institute receives consultees' comments on the assessment report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

Abbreviations used in this document

95% CI: 95% confidence interval

BMS: bare-metal stent

CABG: coronary artery bypass graft

DES: drug-eluting stent

ICER: incremental cost-effectiveness ratio

MACE: major adverse coronary events

MI: myocardial infarction

OR: odds ratio

PCI: percutaneous coronary intervention

RCT: randomised controlled trial

TLR: target lesion revascularisation

TVR: target vessel revascularisation

This appraisal is a part review of the current *NICE technology appraisal guidance* no. 71.

This review focused on developments in drug-eluting stents (DES) only and compared different DES only if the evidence allowed.

Current NICE guidance

1.1 Stents should be used routinely where percutaneous coronary intervention (PCI) is the clinically appropriate procedure for patients with either stable or unstable angina or with acute myocardial infarction (MI).

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.

1 Background

1.1 The condition

Coronary heart disease (CHD) is also known as coronary artery disease and ischaemic heart disease. It is caused by an insufficient supply of oxygen to the heart muscle due to a narrowing of the coronary arteries (stenosis), as a result of deposition of atherosclerotic plaque. CHD may affect one or more arteries, which may be of different calibres; occlusion of arteries may be partial or total. Coronary artery stenosis may be asymptomatic or may lead to angina – a chest pain that may be severe enough to restrict or prevent exertion. A critical reduction of the blood supply to the heart may result in MI or death.

Mortality rates from CHD are decreasing but it remains the most common cause of mortality in the UK. CHD accounted for nearly 117,500 deaths in the UK in 2002 (about 103,000 deaths in England and Wales). CHD is also the cause of considerable morbidity and loss of ability to lead a normal life. Approximately 259,500 individuals in the UK experience an acute MI annually and approximately 341,500 new cases of angina are reported annually in the UK, the most common form of such morbidity. CHD has been estimated to be the leading cause of disability in Europe, accounting for 9.7% of total disability-adjusted life years.

Mortality and morbidity rates associated with CHD vary by socioeconomic group (higher in manual social classes), geographic area (rates are highest in Wales, the North West and Northern and Yorkshire regions and lowest in the North and South Thames regions) and ethnic group (for example, CHD rates are highest among people from the Indian subcontinent living in the UK). The prevalence of CHD also increases with age and is higher among males than females. The disease is more common in individuals with high serum cholesterol, high blood pressure, type 1 and type 2 diabetes mellitus, and in people who are physically inactive and obese.

1.2 Current management

The symptoms and health risks associated with a stenosed artery may be treated medically, by modification of risk factors (for example, smoking, hyperlipidaemia, obesity and hyperglycaemia) and/or by drug treatment (for example, beta-adrenergic blockers, nitrates, calcium channel blockers, antiplatelet agents and statins).

If these medical treatments fail or are inappropriate, two invasive therapies are available. The first, coronary artery bypass grafting (CABG), involves major cardiac surgery. The outcome of CABG versus the use of coronary artery stents was covered by the original appraisal and will not be dealt with in this review. The second, so-called balloon angioplasty, or percutaneous transluminal coronary angioplasty, involves a non-surgical widening from within the artery using a balloon catheter. When inflated, the balloon increases the calibre of the artery. Most percutaneous transluminal coronary angioplasty procedures involve the use of stents. A stent is a thin wire-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. Percutaneous coronary intervention (PCI) is a generic term to encompass percutaneous transluminal coronary angioplasty with or without adjunct techniques such as stenting.

One of the main criteria for assessing the clinical effectiveness of PCI with stents compared with standard PCI (without stents) is the incidence of subsequent attacks of angina and major adverse coronary events (MACE), which include death, MI and the need for further revascularisation procedures (CABG or repeat PCI).

The major problem with PCI is restenosis of the artery, which has three main causes. The first, recoil of the artery, happens when the balloon is deflated. It usually occurs immediately or within 24 hours of completion of the procedure, and may require emergency CABG. Stents essentially prevent recoil of the artery. The two other causes are contraction of the outer layer of an artery secondary to an injury reaction (3–6 months after the procedure), and proliferation of smooth muscle cells within the arterial wall (4–6 months after

the procedure), leading to inflammation. As a consequence, a repeat procedure is required in approximately 20% of patients. The rate of reintervention increases, up to 50%, in patients who have arteries of small calibre, saphenous vein grafts, long lesions or total occlusions and in people with diabetes.

Stent technology (stent type and stent platform) develops rapidly and recent advances have reduced some of the problems of restenosis. One such advance is introducing an emitter of radioactive particles at the stenting site (brachytherapy). In addition, the use of antiplatelet drugs and other therapeutic strategies to prevent thrombosis have improved long-term outcomes.

Because restenosis is correlated with the amount of inflammation present at the time of angioplasty, DES were developed, these are a BMS coated with a drug (usually an immune suppressant or antimitotic) to reduce inflammation. It is thought that the drug reaches therapeutic concentrations in local tissues only and may not be detectable systemically, thus avoiding systemic adverse effects. A subsequent development was the use of a drug-polymer mix the drug is held temporarily in place within a polymer ‘painted’ onto the metallic stent, allowing the drug to slowly elute into surrounding tissues. Other than one trial (the ELUTES trial), there is little evidence in favour of coating the stent directly with an active drug (without a polymer) and this issue has not been considered in the previous or current appraisal.

Patients receive antiplatelet therapy during and after the stenting procedure. The European Society of Cardiology in their 2005 publication, recommend 6 months of intensive therapy after insertion of 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).

There are no systems in the UK that record total numbers of PCI and CABG procedures. The British Cardiac Intervention Society (BCIS) collates data from centres providing information on a voluntarily basis. According to the BCIS data, approximately 53,000 PCI procedures were undertaken in the UK in

2003, equating to 894 per million of the population – a rate that had increased at an average of 15% per year over the previous 11 years. The rate for the UK remains below that of the European Union (EU) average, which exceeds 1000 per million of the population.

The National Service Framework for coronary heart disease target, set in March 2000 for revascularisations (PCIs and CABGs), is at least 1500 per million of the population (750 for each type of intervention).

In the UK, the proportion of PCI procedures using stents rose steeply between 1993 and 1999, from below 10% to nearly 80%. It has continued to increase, although more slowly, to about 92% in 2003. Data for DES use were not available before 2002. The BCIS now reports that although the use of DES varies, DES were used in 18.3% of PCI procedures in England and 28.6% in Wales in 2003. Given the increases in PCI procedures it may be that current utilisation rates are much higher.

2 The technologies

Table 1 Summary description of technologies

Product	Drug	Manufacturer	Base (BMS)	Product list price excluding VAT (£)	Type of trial evidence considered in this appraisal
Axxion	Paclitaxel (non-polymeric)	Biosensors Ltd	Nexus	995	None (RCT currently under way)
CoStar	Paclitaxel (non-polymeric)	Biotronik Ltd	CoStar	995	Non-RCT
Taxus [a]	Paclitaxel	Boston Scientific	Express/Liberte	1300	RCT (5 Taxus) Non-RCT for Liberte
Cypher [a] /Cypher Select	Sirolimus	Cordis Corporation	Cypher (Select)	1340	RCT (11 Cypher)

Endeavor	Sirolimus analogue ABT-578 (zotarolimus)	Medtronic AVE	Endeavor (II)	1700 (including VAT)	RCT (1)
Janus	Tacrolimus	Sorin	Janis	1500	Non-RCT (RCT currently under way)
Xience	Everolimus	Guidant Ltd	Xience V	1500	RCT
Dexamet [a]	Dexamethasone	Abbott Vascular Devices Ltd	BiodivYsio	1250	Non-RCT
Yukon	Physicians drug of choice (non-polymeric)	Kiwimed Ltd	Magic box system for coating Yukon stents	650	Non-RCT (RCT currently under way)

[a] Stents that were included in the previous appraisal (*NICE technology appraisal guidance* no. 71)
BMS, bare-metal stent; RCT, randomised controlled trial.

Nine DES are described in the assessment report (see table 1 for details). At the time of the previous appraisal, only three DES had been granted CE marking for use within EU countries; see table 1.

Paclitaxel is a broad-spectrum chemotherapeutic agent that inhibits cell division. Sirolimus (previously known as rapamycin) is an immunosuppressive agent that reduces inflammation, and ABT-578 is a synthetic analogue of sirolimus. Everolimus is an antiproliferative drug that is closely related to sirolimus; tacrolimus is an immunosuppressive agent; and dexamethasone is a synthetic adrenocortical steroid that reduces inflammation. These drugs may elute at different rates, depending on the presence or absence of additional polymer coatings on the stent. Because the performance of a DES depends critically on the particular drug being used, each DES should be regarded as a separate technology.

Both types of stent (BMS and DES) require the use of an antiplatelet drug in addition to aspirin. Such drugs should be used after the implantation of a stent, in accordance with the device-specific instructions for use.

List prices for both BMS and DES differ between manufacturers because of differences between BMS platforms (including design, alloy used and strut thickness), and some manufacturers produce more than one stent in each

class, at different prices. The difference in cost between a given bare-metal and the drug-eluting form is often referred to as ‘price premium’.

The cost of a given stent may vary in different settings because of negotiated procurement discounts. In order to establish the current UK position on the acquisition cost of all types of stents, the NHS Purchasing and Supply Agency carried out a market survey of NHS purchasers at the request of the Assessment Group. The survey was carried out in May/June 2005 to identify the prices in contracts covering the period 2004/5 for both DES and BMS. The combined data for 12 purchasing bodies covering 20 hospital trusts provide consistent estimates of average unit prices, and of the difference in price between DES and BMS. Results were provided for the two main suppliers of DES: Boston Scientific (Taxus) and Cordis Corporation (Cypher). The effective sale price per Taxus stent (excluding VAT) was £815. Because there was only one recorded instance of a significant local volume discount deal for Cypher in the survey, the average sample price for the Cypher stent was £937. This difference in effective price is reflected in the larger market share for the Taxus stent (about 68% of DES purchased in this sample). The estimated average price per BMS in the survey was £278, so the price premiums are £537 and £659 per stent for Taxus and Cypher, respectively.

3 The evidence

The Assessment Group made the following assumptions when making their decisions regarding the appropriateness of combining data.

- All BMS and their equivalent DES are similar, except in the drug delivered.
- Stent design or the insertion system do not have an impact, so data related to the Cypher and Endeavor stents have been pooled (sirolumus and the sirolimus analogue have been assumed by the Assessment Group to be equivalent).

Individual DES versus BMS estimates of effect have been considered by the Assessment Group and are found on pages 46–48 and pages 168–173 of the

assessment report. These results have been collated and can be found in table 4 of this overview. Stenting techniques are not considered and the use of adjunctive therapies is reported, but not considered, in the meta-analysis.

3.1 Clinical effectiveness

3.1.1 DES versus BMS – RCT evidence

A total of 17 randomised controlled trials (RCTs) were identified, and data from all 17 have been included for at least one outcome in the meta-analysis. All the RCTs compared the DES with its equivalent BMS. Table 2 lists the RCTs for each DES compared with its equivalent BMS.

Table 2 DES versus BMS RCTs

Comparison	Drug	RCTs
Cypher versus BMS	Sirolimus	BASKET, C-SIRIUS, DIABETES, E-SIRIUS[a], Li, Pasche, RAVEL[a], SCANDSTENT, SES-SMART, SIRIUS[a], STRATEGY
Endeavor versus BMS	Sirolimus analogue ABT-578	ENDEAVOR II
Taxus versus BMS	Paclitaxel	BASKET, TAXUS I[a], TAXUS II[a], TAXUS III, TAXUS IV
Xience versus BMS	Everolimus	SPIRIT FIRST

[a] Trials were included in previous appraisal.
BMS, bare-metal stent; DES, drug-eluting stent; RCT, randomised controlled trial.

A number of RCTs that were included in the previous appraisal have been excluded due to the selection criteria used in this review (see page 18 of the assessment report for a list of exclusion criteria). The BASKET trial compares both Cypher and Taxus DES with a newer BMS in a three-arm study.

Only one trial (BASKET) explicitly reported that no protocol-driven angiographic follow-up was included. Most trials included programmed protocol-driven angiography for all or for a selected subgroup of participants.

Twelve trials described the co-therapies used and prescription of aspirin before intervention was described in 11 of these studies, with all 12 trials reporting it being used after the procedure. Clopidogrel was used as an antiplatlet therapy in all of the 12 studies; ticlopidine was available for use as an alternative in five. In one trial tirofiban used in combination with a DES was compared with abciximab used with a BMS. Duration of antiplatelet therapy after intervention ranged from 2 months in three trials to 1 year in one study.

Quality assessment for five of the 17 RCTs was limited because only published peer-reviewed sources were available. For further details on quality of all the RCTs see table 4–2 on page 29 of the assessment report.

There may be some problems with generalising of the results of these trials because they covered a range of vessel diameters and lengths.

Meta-analysis is presented for mortality, acute MI, target lesion revascularisation (TLR), target vessel revascularisation (TVR), composite event rate (MACE and/or TVR), angiographic binary restenosis rates and late luminal loss. Analysis of mortality, acute MI and event rates used pooled results from over 7000 participants.

Data in the form of odds ratios (OR) and 95% confidence intervals (95% CI) were analysed using the Mantel–Haenszel method fixed-effect model. For continuous outcomes, weighted mean differences were analysed. If quantitative heterogeneity was indicated, analysis using a random-effects model was conducted for comparison with results of fixed effect-based analysis.

Pooled estimates (giving OR and 95% CI) are provided for each ‘eluted drug’ subgroup. These subgroups are pooled to obtain estimates for any-type DES compared with any-type BMS (table 3). Meta-analysis was performed for available data reported for follow-up of up to 1 month, 6–9 months, 1 year, 2 years and 3 years. The results reported in the main text of the assessment report concentrate on the 1-year results. Table 4 shows estimates for individual DES versus individual BMS.

Table 3 Meta-analysis: pooled estimates for comparison of any-type DES with any-type BMS

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

Data presented are odds ratio; 95% confidence interval 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.

BMS, bare-metal stent; DES, drug-eluting stent; MACE, major adverse coronary events; TLR, target lesion revascularisation; TVR, target vessel revascularisation.

None of the individual studies found any statistically significant differences in the rates of mortality or acute MI at all follow-up periods analysed to 3 years. This was also the case for pooled analyses of any-type DES compared with any-type BMS, pooled sirolimus-eluting stent (SES; Cypher and Endeavor), and pooled paclitaxel-eluting stent (PES; Taxus).

Rates of revascularisation (TLR) at 1 year for procedures carried out with a DES within individual trials were less than 5% and typically in the range of

10–25% for procedures that used a BMS (the BASKET study at 6–9 months had rates of TVR of 3% and 8% for DES and BMS, respectively). Only the results from the analysis of Taxus (PES) at 3 years, was not within statistical significance but this single study was relatively small and might have been underpowered. Any-type DES displayed statistically significant improved rates of lesion revascularisation within pooled analyses up to 3 years. The pooled estimate at 1 year suggests a reduction of around three quarters in rate of TLR with the use of any-type DES. Meta-analysis including all available DES data suggested that there were no further reductions in TLR rates after 1 year.

Rates of TVR were favourable for Taxus (PES) over BMS at all follow-up periods. Data for Cypher (SES) were available only for single trials at 1 and 3 years, although these also favoured Cypher (SES) over BMS.

Analysis of event rate (MACE and TVR) favoured any-type DES over any-type BMS at all time periods; moderate levels of statistical heterogeneity were indicated and random-effect analysis is presented in table 3.

Rates of binary restenosis (percentage of lesions with greater than 50% luminal narrowing following PCI) are statistically significantly lower for any-type DES, except for the everolimus-eluting stent; however, high levels of statistical heterogeneity were indicated. Late loss analysis at follow-up ranging from 6 to 9 months favoured DES (mean late loss was reduced by 0.45 mm for Taxus (PES) and by 0.79 mm for Cypher (SES); again high levels of statistical heterogeneity were indicated and random effect analysis is presented in table 3.

The Assessment Group stated that there was limited reporting of a full range of adverse events, even in the major Cypher and Taxus trials. At none of the follow-up periods in the Assessment Group’s pooled analyses were statistically significant differences identified in rates of thrombosis between any-type DES and any-type BMS.

Table 4 Meta-analysis: individual DES versus BMS

Outcome/ follow-up	6–9 months	1 year	2 years	3 years
Event rate (MACE, TVR)	**Taxus (PES): 0.58; 0.47 to 0.71** **Cypher (SES): 0.34; 0.26 to 0.43** **Endeavor (SESABT-578): 0.48; 0.33 to 0.70** Xience (Everolimus): 0.31; 0.06 to 1.68	**Taxus (PES): 0.47; 0.35 to 0.62** **Cypher (SES): 0.35; 0.27 to 0.44**	**Taxus (PES) Paclitaxel: 0.50; 0.39 to 0.64** **Cypher (SES): 0.26; 0.16 to 0.42**	Taxus (PES) Paclitaxel: 0.32; 0.03 to 3.29 **Cypher (SES): 0.42; 0.32 to 0.55**
TLR	**Taxus (PES): 0.37; 0.28 to 0.49** **Cypher (SES): 0.21; 0.15 to 0.30** CIC removed. Xience (Everolimus): 0.15; 0.02 to 1.31	**Taxus (PES): 0.26; 0.18 to 0.39** **Cypher (SES): 0.17; 0.12 to 0.39**	**Taxus (PES): 0.28; 0.20 to 0.40** **Cypher (SES): 0.22; 0.15 to 0.30**	Taxus (PES): 0.13; 0.01 to 2.69 **Cypher (SES): 0.25; 0.17 to 0.36**
TVR	**Taxus (PES): 0.54; 0.43 to 0.68** **Cypher (SES): 0.33; 0.18 to 0.62** **Endeavor (SESABT-578): 0.41; 0.27 to 0.63**	**Taxus (PES): 0.40; 0.29 to 0.55** **Cypher (SES): 0.34; 0.19 to 0.60**	**Taxus (PES): 0.45; 0.34 to 0.59**	Taxus (PES): 0.32; 0.03 to 3.29 **Cypher (SES): 0.35; 0.25 to 0.49**
Binary restenosis rates	**Taxus (PES): 0.27; 0.20 to 0.35** **Cypher (SES): 0.08; 0.06 to 0.11** CiC removed. Xience (Everolimus): 0.06; 0.00 to 1.03			

Outcome/ follow-up	6–9 months	1 year	2 years	3 years
Late luminal loss (weighted mean difference)	**Taxus (PES): –0.45; –0.50 to –0.40** **Cypher (SES): –0.79; –0.84 to –0.74** CiC removed. **Xience (Everolimus): –0.74; –0.91 to –0.57**			
Data presented are odds ratio (fixed); 95% confidence interval. Statistically significant effect estimates are in bold. Underlined text is commercial in confidence data. BMS, bare metal stent; DES, drug-eluting stent; MACE, major adverse coronary events; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; TLR, target lesion revascularisation; TVR, target vessel revascularisation.				

3.1.2 DES versus BMS – evidence from trials other than RCTs

Data from trials other than RCTs were not considered in the previous appraisal. Non-RCTs for five DES are presented in the assessment report. A summary of these are presented in table 5.

Table 5 DES versus BMS: trials other than RCTs

Product	Drug	Trial name	Design
CoStar	Paclitaxel (non-polymeric)	CoStar I EuroSTAR	Dose ranging, non-RCT Dose ranging, non-RCT
Janus	Tacrolimus	JUPITER I	Non-controlled
Dexamet	Dexamethasone	Patti Emperor Pilot STRIDE DESIRE SAFE	Non-RCT Non-controlled (pilot study) Non-controlled (with BMS historical control)/Registry Registry Registry
CiC removed	CiC removed	CiC removed	CiC removed
Yukon	Physicians own choice (non-polymeric)	ISAR-Project	Dose ranging, non-RCT
BMS, bare-metal stent; DES, drug-eluting stent; RCT, randomised controlled trial.			

Study characteristics of these non-RCTs are presented in detail in appendix 5, table 7, pages 180–181 of the assessment report. Only two studies included a non-DES control group: ISAR-Project and Patti. Because of the disparate

study designs, pooled analysis was not considered appropriate by the Assessment Group.

For outcomes for the non-RCT trials see appendix 5, table 8, pages 182–183 of the assessment report.

3.1.3 DES versus DES

The head-to-head comparison of DES designs was not considered in the previous appraisal. Eight RCTs comparing different DES designs were identified by the Assessment Group. Table 6 lists the RCTs for each DES compared with another DES.

Table 6 DES versus DES RCTs

Comparison	Drug	RCTs
Cypher versus Taxus	Sirolimus ES versus Paclitaxel ES	REALITY, SIRTAX, TAXi, CORPAL, ISAR-DIABETES, BASKET
Cypher versus Cypher Select	Sirolimus ES verus newer Sirolimus ES	DOMINO
Yukon versus Taxus	Sirolimus ES versus Paclitaxel ES	ISAR-TEST

DES, drug-eluting stent; PES, paclitaxel-eluting stent; RCT, randomised controlled trial; SES, sirolimus-eluting stent.

For further details on these studies see appendix 4, tables 4–6, pages 174–179 of the assessment report. For further details of the quality of trials see pages 50–51 of the assessment report.

No total pooled effect estimate was calculated across multiple groupings of DES versus DES trials. There were no statistically significant differences in mortality or acute MI for any of the pairings of DES designs.

Table 7 Meta-analysis effect estimates; DES versus DES

Outcome/follow-up	Event rate (MACE, TVR)	TLR	TVR	Restenosis rate – by lesion	Restenosis rate – by participant	Late luminal loss – by lesion	Late lumina loss – by participant
6–9 months	**Cypher (SES) versus Taxus (PES): 0.75; 0.59 to 0.96** **Cypher (SES) versus Cypher Select: 0.53; 0.05 to 5.27**	**Cypher (SES) versus Taxus (PES): 0.70; 0.51 to 0.97** Cypher (SES) versus Cypher Select: not estimable	**Cypher (SES) versus Taxus (PES): 0.68; 0.51 to 0.91** **(9 months) Cypher (SES) versus Taxus (PES): 0.59; 0.39 to 0.89** Cypher (SES) versus Cypher Select: not estimable	**Cypher (SES) versus Taxus (PES): 0.69; 0.53 to 0.91**	**Cypher (SES) versus Taxus (PES): 0.33; 0.11 to 0.95** Cypher (SES) versus Cypher Select (SES): 0.50; 0.02 to 12.56	**Cypher (SES) versus Taxus (PES): –0.07; –0.13 to 0.01**	**Cypher (SE versus Tax (PES): –0.2 –0.42 to –0** Cypher (SE versus Cyp Select: 0.06 –0.07 to 0.1
1 year		Cypher (SES) versus Taxus (PES): 0.61; 0.34 to 1.12					

Data presented are odds ratio (fixed); 95% confidence interval. Statistically significant effect estimates are in bold.

DES, drug-eluting stent; MACE, major adverse coronary events; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; TLR, target lesion revascularisation; TVR, target vessel revascularisation.

Table 7 shows estimates for DES versus DES.The Assessment Group's pooled analysis of rate of TLR up to 9 months was statistically significant in favour of Cypher (SES) over Taxus (PES). Only one RCT had data available beyond 9 months. When considered alone, rates of TLR for Cypher (SES) are 5.7% compared with Taxus (PES) 9.0%, but the difference is not statistically significant.

A statistically significant reduction in rate of TVR with Cypher (SES) was determined from meta-analysis of two trials at 9 months. A reduction in composite event rate (MACE) with Cypher (SES) was statistically significant. In-stent binary restenosis rates were favourable with Cypher (SES) over Taxus (PES).

3.1.4 Summary

The long-term study data that have been made available since the last appraisal have not changed many of the conclusions of the previous assessment. As with the previous assessment, no statistically significant differences were detected in the pooled and individual DES type analyses of death or acute MI. The pooled DES analysis indicated that revascularisation rates were reduced by approximately three quarters, consistent across most studies of Taxus (PES) and Cypher (Endeavor at 6–9 months) (SES). The benefits of DES over BMS were seen at 1 year and there was little or no increasing benefit after 1 year. Comparing DES types led to the comparison of Cypher (SES) with Taxus (PES). Results of the analyses were limited to 9 months but marginally favoured Cypher (SES) over Taxus (PES).

3.2 Cost effectiveness

3.2.1 Published literature

Ten full economic evaluations were included in the assessment report. All of the evaluations compared SES with BMS, although four of the evaluations also included PES. One of the evaluations was conducted in the UK, the rest were in the USA, Canada or the rest of Europe. Seven evaluations used a 1-year time horizon, one used 2 years, one used 6 months and one used a patient's lifetime. Of the 10 evaluations, 9 estimated the cost of DES to incur a

price premium, which ranged from £233 to £1225. Four of the evaluations reported health outcomes in terms of quality-adjusted life years (QALYs). Of the three evaluations that provided incremental costs per QALY for a general population these ranged from US$27,450 to Can$96,523. The fourth evaluation did not include a general population because subgroups were found to be too dissimilar for comparison. Two evaluations reported the incremental cost-effectiveness ratio (ICER) per repeat revascularisation avoided; one estimated it to be US$1650 over 1 year while the other estimated it to be approximately US$7000 over 2 years. The majority of evaluations concluded that DES are more cost effective than BMS for higher risk groups, although there was great disparity between evaluations, with a variety of outcomes and a range of ICERs being reported.

Only one economic study (Kaiser 2005; carried out alongside the BASKET RCT) could be said to reflect clinical practice (because no protocol-driven angiographic follow-up was included). This study's results suggested that DES could potentially be cost effective in the following subgroups at a threshold of €7800 per MACE avoided: patients older than 65; patients with more than one segment treated; patients with triple vessel disease; patients with a stent length of more than 20 mm; and patients with small stent diameters.

3.2.2 Manufacturers' economic models

Four models were submitted by DES manufacturers. A full list of parameter values and their sources is given in Table 7–4, pages 81–82 of the assessment report. Table 8 provides a summary of parameters used in the manufacturers and Assessment Group's models. Table 9 provides a comparison of the range of ICERS from the manufacturer's models.

Table 8 Parameters used in the manufacturers' and Assessment Group models

Parameter	Boston	Cordis	Medtronic	KiWiMed[b]	Assessment Group
TLR/TVR rate (DES for general population at 12 months)[a]	4.3%	5%*	6%	Unclear	Elective: 2.95% narrow definition 3.93% broad definition Non-elective: 3.75% narrow definition 4.99% broad definition
TLR/TVR rate (BMS for general population at 12 months)[a]	15.5%	15%*	12.8%	Unclear	7.8% elective 11.0% non-elective
Number of stents used per index procedure	1.4	1.4	1.11 BMS 1.12 DES	1.3	1.615 elective 1.454 non-elective
Number of stents used per repeat procedure	1.4	1.4	1.87	Unclear	1.868 elective 1.712 non-elective
Price premium	CiC removed	£433	£544	£170	Actual price premium: Taxus £563.48 Cypher £691.56 List price premium: Taxus £705.60 Cypher £752.85
Cost BMS	CiC removed	£908	£318	£380	£291.95
Cost DES	CiC removed	£1341	£862	£550	Survey price +5% wastage: Taxus £855.43 Cypher £983.51 List price: Taxus £997.50 Cypher £1,044.75
Cost of percutaneous transluminal coronary angioplasty	£3,253	£2,609	£3,326	£1,505	Elective: Taxus £3,316.73 Cypher £3,409.99 Non-elective Taxus £3,161.12 Cypher £3,242.01
Cost of CABG	£7,904	£7,066	£8,080	£7,066	£7,066
Annual QALYs lost to angina	0.17	0.15	0.135	0.175	0.158
QALY's lost per PCI	0.0035	NA	0.0056	Unclear	0.00658

Parameter	Boston	Cordis	Medtronic	KiWiMed[b]	Assessment Group
QALYs lost per CABG	0.012	NA	0.03	0.78 (per month)	0.00658
Waiting time for PCI/CABG	3 months	28 weeks	15 weeks	Unclear	16 weeks for PCI 9 weeks CABG Assumption of additional 4 weeks before joining waiting list with QALY loss: 0.06070 awaiting PCI 0.03946 awaiting CABG

[a] for Cordis no general population was reported, hence values are for the no-risk factor population two-way analysis.

[b] KiWiMed did not provide a model. Parameters are taken from supporting documentation where available.

BMS, bare metal stent; CABG, coronary artery bypass graft; DES, drug-eluting stent; NA: not applicable; NS: not stated; MACE, major adverse coronary events; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; QALY, quality-adjusted life year; SES, sirolimus-eluting stent; TLR, target lesion revascularisation; TVR, target vessel revascularisation.

Table 9 Comparison of range of ICERs for DES versus BMS from the manufacturer models

Product/model	ICERs for general population	ICERs for subgroups (cost/QALY)	Sensitivity analysis	Assessment Group's recalculation of models
Taxus (Boston Scientific)	£29,587 (1 year) £13,394 (2 years)	Diabetes £1,020 (1 year) Small vessels – dominant (1 year) Long lesions – dominant (1 year) Long lesions £5,367 (2 years)	When no. of stents increased to 1.7 at 1 year, for general population cost/QALY is £56,731, subgroups marginally affected. When clopidogrel therapy post DES is increased to 12 months, cost/QALY is £71,634. For diabetics cost/QALY is > £30,000	CiC removed
Cypher (Cordis) (two-way model; three-way considered inappropriate by Assessment Group)	'No-risk population' £29,259	Small vessels £10,178 Long lesions £16,460 Diabetes £9,702		By changing the price premium, ICERs for no risk, small vessels, long lesions and diabetics are £69,613, £39,508, £49,345 and £38,446, respectively.
Endeavor (Medtronic) (only 1-year scenario, 5-year not considered appropriate by Assessment Group)	£11,221	None presented		If base-case TVR rates for BMS and DES are reduced below 12% then cost/QALY > £30,000. If the no. of stents is increased from 1.11/1.12 to 1.4, the cost/QALY is £39,174.

Product/model	ICERs for general population	ICERs for subgroups (cost/QALY)	Sensitivity analysis	Assessment Group's recalculation of models
Yukon (Kiwimed) (model not presented for Assessment Group to view)	Dominant	None presented	Cost of stent DES (£500–£1750) versus BMS (£250–£500). DES cost/QALY always < £30,000 Restenosis results not clearly stated	

BMS, bare metal stent; DES, drug-eluting stent; ICER, icremental cost-effectiveness ratio; QALY, quality-adjusted life year; TLR, target lesion revascularisation; TVR, target vessel revascularisation.

Boston Scientific

The decision analytical model from Boston Scientific compared Taxus (PES) with the comparable Boston Scientific BMS, for a general population and for subgroups. The Assessment Group found an error in the model calculations CiC removed.

Cordis

The decision analytic model from Cordis compared Cypher (SES) with the comparable Cordis BMS for a 'no risk factor' population and for subgroups. The model was split into a two-way analysis of BMS versus Cypher and a three-way analysis of BMS versus Taxus versus Cypher. In extending the three-way analysis to 2 years, an indirect comparison was undertaken that made an assumption that the BMS stents in both trials (Boston Scientific and Cordis BMS) are equivalent, which the Assessment Group considered to be a controversial assumption (see page 85 of the assessment report). The cost data for the technologies (BMS and Taxus) were considered by the Assessment Group to be substantially overestimated, thus generating bias in

the results in favour of Cypher. Using market prices instead of notional list prices increased the Cordis price premium over BMS from £433 to £694.50.

Medtronic

The Markov model presented by Medtronic compared Endeavor (sirolimus analogue ABT-578) with Medtronic's comparable BMS, for a general population. The submission measured costs and benefits at 5 years, although trial data were only available up to 9 months. Although two scenarios were presented, the Assessment Group felt that only one of them was appropriate. In this scenario, the two arms were assumed to be equivalent in terms of risk of repeat revascularisations after 1 year. The Assessment Group considered that the results might be biased because the two factors that the model was sensitive to came from a single positive trial, which would make Endeavour appear cost effective compared with BMS.

Kiwimed

The model by Kiwimed was not made available, so it was not possible for the Assessment Group to critique the model. The submission compared Yukon with Kiwimed BMS for a general population. The effectiveness data were taken from the Cypher trials, so an untested assumption was made that Yukon has equivalent effectiveness to Cypher. Extrapolation from 2 to 5 years was undertaken using an assumption that patients remain in the same health state that they were in at the end of year 1. It is not clear if discounting was undertaken.

3.2.3 Assessment Group model: methods

The Assessment Group's decision analytical model used the framework from the original appraisal with some minor modifications: the time horizon was restricted to 1 year, so no discounting was necessary; and particular subgroups were examined. The previous appraisal was not product specific; in this review the Assessment Group model considered Cypher and Taxus separately against their comparable BMS. None of the other DES were considered within the economic evaluation.

The parameter values for this model are shown in table 8. The parameter sources for the base-case scenario are listed in table 8–7 on page 113 of the assessment report.

The only measures from any of the clinical trials to show evidence of differences between DES and BMS are the two measures of repeat revascularisation (TLR and TVR). These show strong evidence in favour of DES over all follow-up periods to 3 years, although it has been shown from the meta-analysis for this appraisal that the estimated benefit appears to be stable in the long term, suggesting that the greatest benefit accrues within the first year.

The Assessment Group assumed that the most important factors in determining the incremental cost are the additional cost per DES implanted (price premium), the number of stents implanted per patient and the absolute risk reduction attributable to the use of DES, whereas the single important factor of determining incremental outcomes is the absolute risk reduction due to DES.

The stent prices used in the model are not the list prices, and have come from the NHS Purchasing and Supply Agency survey, which is described in section 2. The calculation of PCI procedure costs required subtracting from the published PCI costs the included cost of stents (DES and BMS) and then adding back the model estimates of the number of stents, the type of stent and the cost per stent.

The Assessment Group used results from two observational studies of stented patients treated at the Cardiothoracic Centre (CTC) Liverpool to convert the efficacy of any-type DES to effectiveness estimates for repeat revascularisations and lesions treated in repeat revascularisations. The Assessment Group found that 51% of patients receiving a second intervention required repeat treatment only to previously treated lesions. An additional 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; these are the patients in whom DES can be expected to produce benefit. Applying these

proportions to the relative risk reduction of 74.6% for TLR obtained from the meta-analysis of any-type DES trials yielded an expected risk reduction in all revascularisations at 12 months of between 38% (95% CI, 32 to 44%) and 50% (95% CI, 44 to 57%). Using the same method, the relative risk reduction in TVR in all revascularisations at 12 months was similar; between 35% (95% CI, 28 to 42%) and 46% (95% CI, 36 to 54%).

The Assessment Group also considered the likely benefit that any-type DES may offer in reducing the number of lesions treated in repeat revascularisations. When applied to the TLR and TVR relative risk reductions from the meta-analysis, this suggests that the reduction in the number of lesions treated in subsequent interventions is between 37% (95% CI, 31 to 42%) and 53% (95% CI, 47 to 59%) based on TLR, or between 34% (95% CI, 27 to 41%) and 48% (95% CI, 37 to 56%) based on TVR (the Assessment Group counted lesions treated but excluded cases undergoing CBAG rather than PCI). The Assessment Group stated that whether any-type DES are cost effective compared with any-type BMS will depend not just on the relative risk reduction in revascularisations, but on the absolute risk in the types of patients in whom they are used.

The previous assessment report could not distinguish risk categories systematically and featured estimates for selected trial subgroups. For this assessment, the baseline risks used have been derived from the CTC Liverpool audit data and the potential to benefit has been reassessed on the basis of the audit data concerning those patients in whom the repeat procedure required treatment of new lesions. The same study of stented patients treated at CTC Liverpool over a 2-year period and followed up for 12 months allowed the Assessment Group to estimate the risk of repeat revascularisation in a typical UK population at a time when BMS were employed in regular clinical practice.

In determining which subgroups may be at greatest risk, the Assessment Group developed separate models for elective and non-elective patients using patient and lesion characteristics known at the time of the index intervention. ‘Narrow’ estimates are based on cases involving TLR/TVR only, while ‘broad’

estimates are based on cases involving any TLR/TVR irrespective of any other lesions/vessels revascularised. Risk factors for the elective patients were stated as being calcification, angulation greater than 45 degrees, restenotic lesion or triple vessel disease. Analyses of combinations of these were undertaken and labelled as one, two, three or four risk factors. Risk factors for non-elective patients were a vessel diameter of less than 2 mm and prior CABG. Most patients fell into the lowest-risk groups (57% of elective and 91% of non-elective patients), who could expect a reduction in relative risk of revascularisation from use of any-type DES of 2–3% and 3–5%, respectively. These results involve reductions to the previously estimated benefits of either a third or a half on depending on whether a ‘narrow’ or ‘broad’ definition is used.

The Assessment Group used patient survey data from the Health Outcomes Data Repository (HoDAR) database for its utility values. The difference in HoDAR health-related quality of life (HRQoL) scores between patients with severe angina and those recovered from revascularisation (0.158) is similar to the ARTS trial result (0.16), which was used in the previous appraisal.

The Assessment Group also used the CTC audit data to examine whether using a single DES in the highest-risk lesion in patients undergoing index stenting to more than one lesion would result in the patient not requiring a repeat intervention to any lesion. In elective patients initially requiring stenting to two or more lesions, the Assessment Group estimated that 37% of patients who may benefit from an ‘all DES’ policy would also be likely to benefit from a targeted single DES policy.

The clinical evidence from the meta-analyses in the assessment report suggests that Cypher (SES) reduces repeat revascularisations compared with Taxus (PES). Because the evidence is limited to 6–9 months’ duration the Assessment Group carried out the economic evaluation assuming clinical equivalence and only distinguished between stents on price. The Assessment Group calculated ICERs for both products in all scenarios. From figures 8–4 and 8–5 on pages 125–126 of the assessment report, if it is assumed that there is a relative risk reduction of 33% for Cypher over Taxus then the

absolute risk reduction for Cypher must be 0.78 times the combined absolute risk reduction, and the absolute risk reduction for Taxus must be 1.17 times the combined absolute risk reduction. The Assessment Group did not consider any of the other DES within their economic evaluation.

3.2.4 Assessment Group model: results

The base case cost-effectiveness results – including all combinations of stent pricing, effectiveness assumption, patient type and brand of DES – result in ICERs between £183,000 and £562,000 per QALY gained; see tables 10 and 11 for the range of ICERs for Taxus and Cypher (for all ICERs see page 116 of the assessment report).

Exploring the risk-related subgroups, for the elective patient subgroups the lowest ICER is £111,000 per QALY gained. In non-elective patients with both risk factors the ICERs range from £12,400 (Taxus stent, using a 'broad' definition of effectiveness and actual prices) to £73,000 per QALY gained (Cypher stent, using a 'narrow' definition of effectiveness and effective list prices). These non-elective patients with two risk factors represent only 0.1% of non-elective patients (1 in 3100 patients); see table 10 and 11 (for all ICERs see page 116 of the assessment report).

Sensitivity analysis

Evidence from RCTs suggests that more than one stent may be required only in a small number of cases (3–10%). The Assessment Group suggests that if it is judged that a single stent will suffice to treat a patient the results are only slightly more favourable for DES: the ICERs for high-risk (three or four risk factors) elective patients range from £8,700 to £62,400 per QALY. For non-elective patients, ICERs for those with two risk factors range from –£25,500 to £5,600 per QALY gained. For the single risk factor group within the non-elective patients, depending on the effectiveness assumption used some of the ICERs fall lower than £30,000 per QALY (for all ICERs see page 117 of the assessment report). However, from the CTC audit used by the Assessment Group, these results would include just 4.4% of all patients in whom use of DES could possibly be considered cost effective.

A univariate sensitivity analysis was carried out on all model variables. The variables that had the most impact on the cost-effectiveness ratios were: the additional cost of DES index stents (that is, price premium and average number of stents implanted); the absolute risk reduction in repeat interventions; and the QALY impact of undergoing/recovering from a PCI or CABG. The results of the sensitivity analysis demonstrate that the base-case results for both elective and non-elective patients are robust to uncertainty in any single variable. The impact of limiting the PCI wait to 13 weeks only modestly increased all ICERs.

The Assessment Group assumed that in the base case continuing anti-platelet therapy was the same for both DES and BMS over 12 months, and therefore omitted it from the model. When the Assessment Group modelled extending the use of clopidogrel by a further 6 months in the DES patients, the ICERs all then exceed £30,000 in all scenarios, except for non-elective patients with both risk factors in whom only one stent is required.

The use of unadjusted efficacy relative risk reductions rather than the calculated effectiveness measures resulted in ICERs ranging from £54,338 to £138,115 for elective patients with three or four risk factors and –£13,970 to £23,559 for non-elective patients with two risk factors and £31,923 to £102,969 for non-elective patients with one risk factor. See page 136 of assessment report for further information.

The Assessment Group also conducted an extreme-values analysis on all the uncertain model parameters and concluded that the resulting wider confidence range could reduce the uncertainty of a correct decision to as little as 1 in 630 billion.

Table 10 Range of ICERs from the Assessment Group model for the general population and subgroups for Taxus and Cypher in elective patients (base-case scenario and sensitivity analysis)

Product	ICERs for general population	ICERs for subgroups (cost/QALY)	Sensitivity analysis
Taxus (using list price, actual price, narrow and broad definitions of effectiveness)	£289,600 to £523,200	No risk factors: £373,200 to £662,500 One risk factor: £290,400 to £524,400 Two risk factors: £158,000 to £303,900 Three or four risk factors: £111,000 to £225,600	When 1 stent used in three or four risk factor group, cost/QALY: £8,700 to £55,000 When 2 stents used, cost/QALY: > £30,000 If post-PCI clopidogrel therapy is extended by 6 months in DES group, cost/QALY: > £30,000
Cypher (using list price, actual price, narrow and broad definitions of effectiveness)	£368,000 to £561,900	No risk factors: £368,000 to £561,900 1 risk factor: £470,000 to £710,600 2 risk factors: £206,600 to £328,000 Three or four risk factors: £148,900 to £244,500	When 1 stent used in three or four risk factor group, cost/QALY: £23,200 to £62,400 When 2 stents used, cost/QALY: > £30,000 If post-PCI clopidogrel therapy is extended by 6 months in DES group, cost/QALY: > £30,000

DES, drug-eluting stent; ICER, incremental cost-effectiveness ratio; PCI, percutaneous coronary intervention; QALY, quality-adjusted life year.

Table 11 Range of ICERs from the Assessment Group model for the general population and subgroups for Taxus and Cypher in non-elective patients (base case scenario and sensitivity analysis)

Product	ICERs for general population	ICERs for subgroups (cost/QALY)	Sensitivity analysis
Taxus (using list price, actual price, narrow and broad definitions of effectiveness)	£182,900 to £348,700	No risk factors: £208,700 to £391,600 One risk factor: £80,200 to £177,500 Two risk factors: £12,400 to £64,600	When one stent used in one risk factor group, cost/QALY: £10,300 to £61,200 When one stent used in two risk factor group, cost/QALY: –£25,500 to £1,500 When two stents used in two risk factor group, cost/QALY: £18,100 to £74,100 If post-PCI clopidogrel therapy is extended by 6 months in DES group, cost/QALY: > £30,000 except for patients with both risk factors and only one stent required.
Cypher (using list price, actual price, narrow and broad definitions of effectiveness)	£238,300 to £376,100	No risk factors £269,900 to £421,900 One risk factor £112,200 to £193,500 Two risk factors £29,000 to £73,000	When one stent used in one risk factor group, cost/QALY: £26,500 to £69,300 When one stent used in two risk factor group, cost/QALY: –£17,500 to £5,600 When two stents used, cost/QALY: > £30,000 except for patients with both risk factors and only one stent required

DES, drug-eluting stent; ICER, incremental cost-effectiveness ratio; PCI, percutaneous coronary intervention; QALY, quality-adjusted life year.

4 Issues for consideration

The Assessment Group made a number of assumptions when it combined data in the meta-analysis. Firstly, it assumed that all BMS and DES are similar, except in the drug delivered, despite the fact that stent design and material, and drug release technologies, can differ. Secondly, a variety of guidewires and devices to assist in the insertion of stents exists. Thirdly, the insertion technique used for stent placement may vary. Techniques include provisional stenting (in which stents are placed only in the case of suboptimal

expansion with angioplasty balloon alone), and pre-dilation and direct stenting (simultaneous expansion of vessel and placement of stent).

The Assessment Group pooled the data for the Cypher and Endeavor stents in the meta-analysis, thereby assuming sirolimus and the sirolimus analogue ABT-578 are equivalent.

All RCTs for DES versus BMS were considered by the Assessment Group to have exceptionally high revascularisation rates in the BMS arm: 20–25%. The Assessment Group commented that these rates may be higher than those seen in clinical practice. Two possible explanations put forward by the Assessment Group are that either only very high-risk patients entered into the trial, or the revascularisation rates were driven by the protocol-mandated angiogram in all studies except the BASKET study (which reported a rate of revascularisation of 8% in the BMS arm). The manufacturers' figures in their models range from 12.8% to 15%, while the Assessment Group's model uses 7.8% and 11% for elective and non-elective patients, respectively, for the TLR/TVR rate for BMS.

The revised version of the Assessment Group model provides information, mainly collected from the CTC Liverpool audit, 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. The British Cardiovascular Industry Association and other stakeholders have reservations about the extent to which this data is reliable and representative of current UK practice. The Assessment Group has given a response to some of these reservations on pages 132–133 of the assessment report.

Unlike the original appraisal, the review scope specified that the clinical and cost effectiveness of DES in particular subgroups would be examined. The Assessment Group's results, using the effectiveness assumptions, suggest that only 1.4% of all patients would benefit from DES compared with BMS – these were elective patients with three out of four risk factors (calcification, angulation greater than 45 degrees, restenotic lesion or triple vessel disease)

and non-elective patients with both risk factors (vessel diameter less than 2 mm and prior CABG).

The scope stated that where the evidence allows, subgroups such as those involving narrow arteries, long lesions, complicated lesions (such as bifurcation lesions), saphenous vein grafts, partial versus total occlusion, and people with diabetes or acute MI) should be investigated. The Assessment Group's reasons for excluding people with diabetes are given on p133 of the assessment report.

Follow-up data were limited for the Cypher versus Taxus trials, so for the cost-effectiveness analysis the Assessment Group assumed that Cypher DES and Taxus DES were clinically equivalent.

Three out of the nine stents considered in this appraisal are non-polymeric stents; one of the manufacturers suggests that the issue regarding polymer versus non-polymer stents should be considered. This was outside the scope of this appraisal.

The Assessment Group illustrate that DES are cost effective (if the threshold is £30,000) for the general population only if an absolute risk reduction in repeat revascularisation of at least 18% (elective) or 16% (non-elective) is achievable.

The Assessment Group also noted the strong dependence of cost effectiveness upon the price premium of DES compared with BMS. The price premium between DES and BMS would need to be between £100 and £200 (not £563 and £692 as is currently used in the model) for ICERs for DES to be below a £30,000 threshold. Threshold values of DES price premiums estimated for a range of different patient subgroups defined by risk factors and numbers of stents required are presented on page 131 of the assessment report.

The price premium between BMS and DES in the last appraisal was £520. It would appear that the price premium between BMS and DES has increased since the previous appraisal. This, combined with the outcomes from the CTC

audit that suggest that any-type DES may not be as clinically effective as thought in the previous appraisal, results in any-type DES appearing a lot less cost effective than in the previous appraisal.

The Assessment Group did not consider each of the available DES as a separate technology, and focused on only the two most currently used stents (Cypher and Taxus) in its economic evaluation.

5 Ongoing research

5.1 Randomised controlled trials

For AXXION (PES), the EAGLE RCT is currently under way. This is being conducted in three centres in Germany with a target recruitment of 125 participants, randomised 2:1 to AXXION DES or BMS. Outcomes of the study will be MACE (at 30 days and 6 months), angina and angiographic measurement for a subset of participants. CiC removed.

The Janus stent (tacrolimus) is being studied in the Jupiter II RCT, but data from the RCT appear incomplete (interim and blinded).

The Yukon DES has been evaluated in the ISAR-TEST RCT, but confirmed outcome data are limited at this time. Comments from Kiwimed include the published paper (Mehilli et al. 2006) providing results from ISAR-TEST; the results from this study have informed Kiwimed's request for the consideration of polymer versus non-polymer stents.

5.2 Other trials

The CoStar (PES) stent has been studied in two non-randomised controlled trials EuroSTAR and COSTAR, but data were incomplete at the time of assessment (CE marking pending). CiC removed.

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report: Hill RA, Bagust A, Boland A et al. (Liverpool Reviews and Implementation Group). *Drug-eluting stents: a systematic review and economic evaluation*, November 2005.

B Submissions from the following organisations:

I Manufacturers/sponsors:

- Abbott Vascular Devices Ltd
- Biosensors Europe
- Biotronik UK Ltd
- Boston Scientific Ltd
- Cordis Corporation
- Guidant Ltd
- KiwiMed Ltd
- Medtronic AVE

II Professional/specialist and patient/carer groups:

- British Cardiac Society
- British Cardiovascular Intervention Society
- The Royal College of Physicians
- Royal College of Physicians of Edinburgh
- British Cardiovascular Industry Association

III Commentator organisations (without the right of appeal):

- British Cardiovascular Industry Association

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview addendum

Coronary artery stents for the treatment of ischaemic heart disease (review of *NICE technology appraisal guidance* no. 71)

This is the second overview for this appraisal. At the request of the Committee, some additional work was commissioned following the meeting in February 2006. For full details of the additional work requested see the project specification form. Due to uncertainty over a number of the parameters that had been included in the assessment group's model some of the values were varied, taking account of some additional data that had been discussed at the meeting and examining further the issue of sub-groups. This additional work (addendum) was consulted on in April 2006, and following consultation a new series of tables has been produced (addendum supplement), which will allow the Committee to explore the impact of various scenarios of using drug-eluting stents (DES) on the cost-effectiveness estimates.

1 Addendum

The Committee requested that the base case scenario be updated to include: the risk of acute myocardial infarction (AMI); the mortality risk associated with CABG and angiography; the disutilities associated with coronary artery bypass graft (CABG) versus percutaneous coronary intervention (PCI) in the 6 week period following the procedure; the absolute risk of revascularisation of bare-metal stents (BMS) taken from the Scottish registry data; the relative risks of the independent risk factors (small vessel and long lesion) taken from the trials; and to establish whether diabetes is a risk factor. Sensitivity

analyses were also requested on the above base-case scenario around the price premium estimates, ranging from £255 (based on a cost used in Glasgow) to £1000 (list price) and stent wastage rates of 1% and 5%.

The addendum, which was sent out for consultation, sets out the parameters that the Assessment Group used in their sensitivity analysis (addendum pages 39-40). The addendum received many of the same comments from Consultees and Commentators that were submitted in response to the assessment report.

1.1 Risk of AMI

The risk of AMI is discussed in the addendum, pages 18-24. There is agreement between the Assessment Group and the Consultees and Commentators that a very compelling body of new information would be required to alter the established consensus that PCIs provide symptomatic relief but do not alter life expectancy. 'Procedural mortality' is presented as a final column in the addendum for each of the tables in the sensitivity analyses pages 40-43, this explores the magnitude of effect to be expected if this were counted as a separate additional effect (added to the Assessment Group's base case only). However the Assessment Group does not recommend this approach as procedural mortality should be included in the all cause mortality estimates.

Both the addendum and the comments received on it agree that there appears to be no statistically significant difference in the rates of AMI between DES and BMS. The Assessment Group do state however that there is a trend towards increased numbers of non-fatal AMIs when BMS are used. They conclude that, based on the reviewed evidence, the maximum likely effect of this is equivalent to an overall cost saving of about £13 per patient, and a utility gain of about 0.00055 per patient when DES are used.

1.2 Mortality risk associated with CABG and angiography

The mortality risk associated with CABG and angiography is discussed on page 20 of the addendum with the Assessment Group concluding that there is

no evidence for AMI/mortality improvements with PCI. This is an issue that is also not disputed by Consultees or Commentators.

1.3 Disutilities associate with CABG versus PCI

The assumptions made by the Assessment Group for disutilities associated with CABG versus PCI in the 6 week period following the procedure is discussed on pages 14-15 of the addendum. The Assessment Group have assumed that for a two week post-operative period, patients undergoing CABG experience a severe loss of quality of life (0.0) and for the next two weeks, the mean utility score recovers in a linear fashion achieving full benefit (0.660) by four weeks after the operation. Patients undergoing PCI are assumed to recover full benefit linearly over a two week period following the procedure. The Assessment Group have differentiated between elective and non-elective patients and have identified that among patients whose index procedure is non-elective a higher proportion of repeat interventions require CABG. They therefore concluded that it can no longer be assumed in the model that there is a common disutility effect for elective and non-elective patients. The issue has been raised by a Consultee that the Assessment Group were requested to take account of the differences for six weeks following the procedure and not four weeks.

1.4 Absolute risk of repeat revascularisation

There was controversy over which data source provides the best estimate of repeat revascularisation rates; the Liverpool (CTC) and the Leicester registry data or the randomised controlled trial data. It could be argued that the BASKET trial and the Scottish Registry data would be more representative as they had used methods that were likely to collect follow up data from all patients. The absolute risk of revascularisation of BMS is discussed on pages 25-28 of the addendum and the data sources are also outlined on pages 3-7 of the addendum. This section received heavy criticism from the Consultees and Commentators due to the addendum's emphasis on the Liverpool CTC audit data. The tables presented in the sensitivity analysis on pages 40-43 of the addendum illustrate a possible range but are centred on the Liverpool CTC audit data. There were also major concerns regarding the adjustments

made to the data sets (see pages 9-13 of Cordis's response to the addendum). The Assessment Group concluded that, based on the Liverpool CTC audit data the overall repeat revascularisation rate in the UK 12 months post PCI with BMS is within the range of 7%-9%. However, there is general agreement amongst Consultees and Commentators that the revascularisation rate should be between 12%-14%.

1.5 Risk Factors

There was uncertainty surrounding the estimate of the relative risks of repeat revascularisation associated with the independent risk factors (small vessel and long lesion) that were identified in the trials and whether diabetes is a risk factor. These issues are discussed in the addendum on pages 29-38 and the results of the additional work summarised on page 35. Consultees and Commentators felt that several risk models had been omitted from the addendum, which would demonstrate that small vessel and diabetes along with lesion length are the three main predictors of repeat revascularisation.

1.6 Stent wastage

In the original Assessment Group model, stent wastage rates were set at 5%. This was disputed therefore pages 7-13 of the Addendum explores the impact of alternative assumptions of a 1%, 5% and 10% wastage. The tables presented in the sensitivity analysis on pages 40-43 of the addendum assume a wastage rate of 1% (Consultees did not disagree with this value).

1.7 Sensitivity analyses results

For each of the scenarios (e.g. elective patients with one risk factor, elective patients with two risk factors etc) the sensitivity analyses are provided on pages 39-43 of the addendum. These tables allow a 2-way exploration of variation in the absolute risk of repeat revascularisation when BMS are used versus DES for a range of price premiums (£100 to £800). Several of the original base-case assumptions have been modified (page 39).

The range of estimates for repeat revascularisation centres on Liverpool's base-case estimates. The estimates vary slightly from the original assessment

report as the Assessment Group noted that a number of AMI patients had been inadvertently included in the non-elective group within the CTC audit data. In the addendum these patients were removed, and the risk model parameters have been re-estimated accordingly. The results are not presented for specific numbers of implanted stents, but the assumed average number of stents used in each analysis is shown (taken from CTC data).

2 Addendum supplement

Despite the criticisms of the parameters chosen by the Assessment Group, the actual model structure did not receive criticism. Therefore, to address some of the comments received, Liverpool produced an addendum supplement which expanded the tables of incremental cost-effectiveness ratios to include a wider range of absolute rates of revascularisation for one, two and three stents per patient (instead of providing only the average number of stents used). The supplement included the risk factors identified from the clinical trials (long lesion, small vessel and diabetes) with corresponding absolute risks. The average number of stents required for each combination was calculated from the CTC audit data, as this was the only dataset available to the Assessment Group. All the parameters that were used in the addendum have also been used in the addendum supplement.

Tables 1 and 2 (below) summarise the Assessment Group's estimates of the price premiums that would be required for a threshold of £30,000 per QALY. A variety of combinations of number of stents and risk factors for patients were examined, assuming the rates of repeat revascularisation for BMS are 12% for elective patients and 14% for non-elective patients. The DES rate of revascularisation is based on the Assessment Group's assumption of 41% for the effectiveness of DES, taken from the BASKET trial.

Table 1 Estimated price premiums required at a threshold of £30,000 from the Assessment Group model (addendum supplement) for the general population and subgroups of elective patients.

Parameters assumed	**Price premium at threshold £30,000 for general population**	**Price premium at threshold £30,000 for subgroups assuming one stents per patient**	**Sensitivity analysis (two or three stents per patient for different numbers of risk factors)**
Target lesion revascularisation (TLR)/Target vessel revascularisation (TVR) rate (BMS for general population at 12 months) **12%** TLR/TVR rate (DES for general population at 12 months) **4.92%**	One stent per patient £320 Two stents per patient £156 Three stents per patient £103	No risk factors: £283 One risk factor: Long lesion £336 One risk factor: Diabetes £385 One risk factor: Small vessel £424 Two risk factors: Long lesion and diabetes £465 Two risk factors: Long lesion and small vessel £510 Two risk factors: Small vessel and diabetes £590 Three risk factors: £716	When 2 stents used in patients with one risk factor, price premium ranges £162 - £205 When 2 stents used in patients with two risk factors, price premiums range £223 - £280. When 2 stents used in patients with three risk factors, price premium is £337. When 3 stents used in patients with one risk factor, price premium ranges £108 - £135. When 3 stents used in patients with two risk factors, price premium ranges £147 - £184. When 3 stents used in patients with three risk factors, price premium ranges £220.

Table 2 Estimated price premiums required at a threshold of £30,000 from the Assessment Group model (addendum supplement) for the general population and subgroups of non-elective patients.

Parameters assumed	Price premium at threshold £30,000 for general population	Price premium at threshold £30,000 for subgroups assuming one stents per patient	Sensitivity analysis (two or three stents per patient for different numbers of risk factors)
TLR/TVR rate (BMS for general population at 12 months) **14%** TLR/TVR rate (DES for general population at 12 months) **5.74%**	One stent per patient £380 Two stents per patient £185 Three stents per patient £122	No risk factors: £346 One risk factor: Long lesion £409 One risk factor: Diabetes £312 One risk factor: Small vessel £931 Two risk factors: Long lesion and diabetes £369 Two risk factors: Long lesion and small vessel £1,133 Two risk factors: Small vessel and diabetes £830 Three risk factors: £1006	When 2 stents used in patients with one risk factor, price premium ranges £153 - £434 When 2 stents used in patients with two risk factors, price premiums range £180 - £520. When 2 stents used in patients with three risk factors, price premium is £467. When 3 stents used in patients with one risk factor, price premium ranges £101 - £283. When 3 stents used in patients with two risk factors, price premium ranges £119 - £338. When 3 stents used in patients with three risk factors, price premium ranges £304.

3 Issues for consideration

Calculating the cost effectiveness of DES compared to BMS depends on the most probable estimates of a number of key parameters:

1. The absolute risk of repeat revascularisation using BMS for the general population

Two different estimates of the absolute risk of repeat revascularisation using BMS for the general population at 12 months have been identified. The Assessment Group suggest that from the CTC data the absolute risk is

between 7-9%, the Consultee and Commentators suggest that from the Scottish Registry data and BASKET trial this risk is between 12-14%.

2. The absolute risk of repeat revascularisation using BMS for patients with independent risk factors *and* the mean number of stents used.

The absolute risks of revascularisation *and* mean number of stents used, for each risk factor, have been derived from the Liverpool CTC dataset rather than the Scottish Registry data/BASKET study.

3. The absolute risk reduction of repeat revascularisation associated with DES.

Two possible options have been identified for the estimate of the absolute risk reduction of repeat revascularisation associated with DES: 41% (from the BASKET study) or 60-75% (from the RCTs at 12 months).

4. The price premium associated with DES over BMS.

There is considerable uncertainty over the price premiums associated with DES over BMS. The manufacturers stated them to be £520 (Taxus, Boston Scientific), £433 (Cypher, Cordis), £544 (Medtronic, Endeavor) and £170 (Yukon, KiwiMed). The survey by the Assessment Group resulted in actual price premiums for Taxus £563.48 and Cypher £691.56 and the list price premiums were Taxus £705.60 and Cypher £752.85. Furthermore, the Committee heard from one of the clinical experts that stated that bulk purchasing in Glasgow have resulted in DES being purchased at a price premium of £255.

4 Note on recent data about DES mortality risk

Recently emerging data have caused controversy over the comparative rates of stent thrombosis associated with DES and BMS.

- March 2006, at the American College of Cardiology Scientific Sessions in Atlanta

- Pfisterer et al followed the 746 patients who were MACE free at six months (when the main BASKET cost-effectiveness trial had concluded and clopidogrel was stopped) for an additional 12 months. For the purposes of the analysis, sirolimus- and paclitaxel-eluting stent-treated patients were combined in a single group. The BASKET-LATE data showed that the rate of Cardiac death and nonfatal myocardial infarction was higher in patients with DES than those in BMS (p=0.01). The study was seen as too small to be definitive.

- September 5th 2006, at the European Society of Cardiology conference in Barcelona two separate unpublished meta-analyses were presented which suggest DES may increase death, wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths.

  - Camenzind et al looked at death and Q-wave MI in all randomised DES trials where data were available. Results at the latest follow-up (four years) showed the incidence of death or MI was 6.3% for the sirolimus stent and 3.9% for control BMS stent (p=0.03). For the paclitaxel stent, rates were 2.6% compared to 2.3% for the BMS stent (p=0.68). He concluded that death and Q-wave MI were higher in first generation DES than BMS.

  - Nordmann et al compared cardiac to non-cardiac deaths in DES versus BMS in all randomised controlled first-generation DES trials. At four years overall mortality was higher for both cardiac and non-cardiac deaths in DES patients.

- September 14th 2006, the US Food and Drugs Administration (FDA) issued a statement, the summary of which is below.

  “FDA has been monitoring coronary drug-eluting stents closely since they came on the U.S. market in 2003 and 2004, and will continue to do so.

New data were released recently that suggest a small but significant increased risk of stent thrombosis in patients who have drug-eluting stents. The agency is keenly interested in this issue because of the potential for serious harm to patients—even though stent thrombosis occurs at low rates.

While the new data are of interest to FDA and raise important questions, we do not have enough information yet to draw conclusions. It's unclear, for example, what causes drug eluting stent thrombosis, how often it occurs, under what circumstances it occurs, or what the risk of occurrence is in a given patient.

To better understand this issue, FDA met with the two manufacturers of these products in recent months to discuss any information they might have pertaining to this issue and get their perspective. In addition, we plan to convene a public panel meeting of outside scientific experts in the near future to assist us in a thorough review of *all* the data and make recommendations about what actions may be appropriate, such as possible labelling changes or additional studies.

At this time, FDA believes that coronary drug-eluting stents remain safe and effective when used for the FDA-approved indications. These devices have significantly reduced the need for a second surgery to treat restenosis for thousands of patients each year."

- Cordis have contacted NICE explaining that they have tried to reproduce the Camenzind 3 year analysis for death + Q wave MI, using patient-level data, and they get a different (non-significant) result for their sirolimus-eluting (Cypher) stent.

- Boston Scientific have made a public statement describing a statistically significant excess of late stent thrombosis events with their paclitaxel-eluting stent (Taxus). NICE awaiting further information from the Company.

- The MHRA issued a statement stating that they were continuing to assess the safety of DES in consultation with clinicians and manufacturers.

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September 2006

Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report addendum: Hill RA, Bagust A, Boland A et al. (Liverpool Reviews and Implementation Group). *Drug-eluting stents: a systematic review and economic evaluation*, April 2006.

The assessment report addendum supplement: Hill RA, Bagust A, Boland A et al. (Liverpool Reviews and Implementation Group). *Drug-eluting stents: a systematic review and economic evaluation*, June 2006.

B Comments on the assessment report addendum from the following organisations:

I Manufacturers/sponsors:

- Boston Scientific Ltd
- Cordis Corporation
- Guidant Ltd
- Medtronic AVE

II Professional/specialist and patient/carer groups:

- British Cardiac Society
- British Cardiovascular Intervention Society
- The Royal College of Physicians
- Royal College of Physicians of Edinburgh

III Others

- South Devon PCT

IV Commentator organisations (without the right of appeal):

- British Cardiovascular Industry Association

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview addendum 2

Coronary artery stents for the treatment of ischaemic heart disease (review of NICE technology appraisal guidance 71)

A list of the sources of evidence used in the preparation of this document is given in appendix A.

This is the third overview document for this appraisal. Following the second Appraisal Committee meeting in October 2006 (where the overview and overview addendum 1 documents were included), the appraisal was suspended pending a report from the United States Food and Drug Administration's (FDA's) Circulatory System Devices Advisory (CSDA) Panel. The CSDA Panel examined specific questions posed by the FDA about adverse events related to drug-eluting stents (DESs). The FDA issued a statement in January 2007.

Following the FDA's statement:

- the issue of the use of DESs outside their approved indication has arisen
- NICE asked the Assessment Group to produce sensitivity analyses to include the cost of clopidogrel for 12 months in patients having a DES. This additional work (addendum 4'), along with the previous addendum supplement 3" were consulted in March 2007. Following this consultation NICE asked the Assessment Group to produce additional sensitivity analyses (addendum 5') to take account of the comments received that suggested 44% of patients receiving a DES are acute coronary syndrome (ACS) patients who would already be receiving 12 months of clopidogrel as recommended in 'Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome' (NICE technology appraisal guidance 80).

1 The CSDA Panel's recommendations

The CSDA Panel made the following recommendations to the FDA regarding DESs when they are used in accordance with their approved indications:

- Both DESs approved in the USA (Cypher and Taxus) are associated with a small increase in stent thrombosis compared with bare metal stents that emerges 1 year after stent implantation.
- However, based on the data available, the increased risk of stent thrombosis was not associated with an increased risk of death or myocardial infarction (MI) compared with bare metal stents. This finding may be because:
  - there was an insufficient number of patients in currently available studies, or
  - an increase in deaths or MIs was offset by a reduction in events associated with in-stent restenosis and additional revascularisation procedures.
- When compared with bare metal stents, DESs are not associated with an increased rate of all-cause mortality.
- The concerns about thrombosis do not outweigh the benefits of DES compared with bare metal stents when DESs are implanted within the limits of their approved indications for use.
- Larger and longer premarket clinical trials and longer follow-up for post-approval studies are needed, using uniform definitions of stent thrombosis and paying close attention to patient compliance with antiplatelet therapy.

The CSDA Panel was also asked to address the broader use of DES in more complex patients and coronary lesions than those studied to support initial marketing approval. The use of a drug or device outside the FDA-approved indications is known as 'off-label use'. Although the FDA regulates the manufacture, labelling, and promotion of devices, it does not regulate how they are used by individual clinicians in the practice of medicine. However, the FDA may take action if safety issues with any use of a device become a public health concern. The FDA felt that DES safety associated with off-label use

should be included in the CSDA Panel's deliberations, given observations that at least 60% of current DES use is off-label. The CSDA Panel had the following comments and recommendations:

- With more complex patients, there is an expected increased risk of adverse events. The CSDA Panel agreed that off-label use of DES is associated with an increased risk of stent thrombosis, death or MI compared with on-label use.
- The available data were insufficient to determine whether the increased risk of adverse events with off-label use was the same or different for the two currently approved DES.
- Data on off-label use are limited, and additional studies are needed to determine optimal treatments for more complex patients. Until more data are available, the DES labels should state that when DES are used off-label, patient outcomes may not be the same as the results observed in the clinical trials conducted to support marketing approval.

Regarding the duration of antiplatelet therapy:

- Data from several studies suggests that a longer duration of antiplatelet therapy than is currently included in the Cypher and Taxus labelling may be beneficial.
- The optimal duration of antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy.
- The labelling for both Cypher and Taxus should include reference to the American College of Cardiologists/American Heart Association/Society for Cardiac Angiography and Interventions percutaneous coronary intervention practice guidelines, which recommend that patients receive aspirin indefinitely, plus clopidogrel for a minimum of 3 months (for Cypher patients) or 6 months (for Taxus patients), with therapy extended to 12 months in patients at a low risk of bleeding.

2 Indications for use

The FDA considers off-label use to mean: (1) use of a medical product for treatments other than for what the product was initially approved, or (2) use not explicitly included in product labelling (intended use and instructions for use).

The FDA therefore considers DES use in longer lesions (requiring multiple or overlapping stents), non de novo lesions, bifurcation lesions and thrombus containing lesions (in acute MI) as off label. Patients with multivessel disease treated with multivessel DES were not included in the pivotal trials, so this use is also considered off-label. The FDA also considers that although diabetic patients were included in the pivotal trials for both Cypher and Taxus, the number of patients was insufficient for either DES to earn a specific labelled DES indication for individuals with diabetes, and neither study included a pre-specified endpoint for this subgroup.

For summaries of the indications for use for each of the stents included in this appraisal, see appendix B.

3 Addendum supplements 3" and 4'

The addendum-supplement 3" was seen in the Committee meeting on 3 October 2006. Following the FDA recommendation for extended use of clopidogrel use in patients having a DES and the British Cardiovascular Intervention Society's (BCIS) statement that 'a consensus in the UK exists that dual antiplatelet therapy (aspirin and clopidogrel) should be continued for 1 year following DES placement. Premature discontinuation of antiplatelet therapy is associated with an increased risk of stent thrombosis but this is currently not quantifiable. Individual high risk patients may be advised to continue dual antiplatelet therapy long term', NICE asked the Assessment Group to produce additional sensitivity analyses. The sensitivity analyses (addendum 4') included the cost of clopidogrel for an additional 9 months in patients having DES, given that patients receiving a bare metal stent would receive clopidogrel for an average of 3 months.

Addendum-supplement 3" and addendum 4' provide the reader with tables of incremental cost effectiveness ratios (ICERs) based upon different assumptions. This additional work received many of the same comments from consultees and commentators that were submitted in response to the assessment report and the original addendum. Calculating the cost effectiveness of DES compared with bare metal stents depends on the most probable estimates of a number of key parameters. Consultees and commentators have again stated figures for the key parameters that they believe should be inputted into the model.

For the absolute risk of repeat revascularisation using bare metal stents for the general population, consultees and commentators suggested that from the Scottish Registry data and BASKET trial this risk is between 12–14%. The Assessment Group suggest that from the CTC data the absolute risk is between 7–9%.

For the relative risk reduction of repeat revascularisation associated with DES, consultees and commentators suggested that the risk reduction is between 60 and 75% from the RCTs at 12 months. The Assessment Group used 41%, which is in line with the BASKET study at 6 months.

For the absolute risk of repeat revascularisation using bare metal stents for patients with independent risk factors, consultees and commentators stated that the absolute risks of revascularisation and mean number of stents used, for each risk factor, have been derived from the Liverpool CTC dataset rather than the Scottish Registry data/BASKET study.

For the relative risk reduction of repeat revascularisation associated with DES patients with independent risk factors the British Cardiac Society and BCIS suggest for the base case, small vessels, long lesions and diabetes that the relative risk reduction of repeat revascularisation associated with DES for these groups of patients are 63%, 69%, 70% and 61% respectively. The Assessment Group used 41% for each of the risk factor groups.

With regard the extended use of clopidogrel in DES patients, consultees and commentators suggested that 44% of patients receiving DES would be patients with acute coronary syndrome and therefore would already be receiving clopidogrel for 12 months in line with NICE technology appraisal guidance 80. Following this comment the Assessment Group produced an additional sensitivity analysis (addendum 5'), this analysis takes the 44% acute coronary syndrome patients into account.

4 Issues for consideration

Should the Committee consider DES only within the indications stated in their indications for use?

- Given that the risk factors long lesions and small vessels are defined in the indications for use for most stents, should these be considered as the only risk factors in this appraisal (within each DES's specific indications)?
- Despite there being a number of trials of diabetic patients, these were not part of the submissions to the MHRA when the CE markings for individual DES were approved and diabetic patients do not appear in the indications for use. Should diabetes be considered as a risk factor in this appraisal?

What are the assumptions that should be made to work out the most appropriate ICERs, with regard to the key parameters:

- the absolute risk of repeat revascularisation using bare metal stents for the general population
- the absolute risk reduction of repeat revascularisation associated with DESs
- the absolute risk of repeat revascularisation using bare metal stents and the absolute risk reduction of repeat revascularisation associated with DESs for patients with independent risk factors
- the number of stents used?

With regard the extended use of clopidogrel in patients having a DES, should acute coronary syndrome patients be viewed as a subgroup or should the

suggested proportion (44%) be applied to all the patients receiving clopidogrel for 1 year?

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June 2007

Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report addenda for this for this appraisal were prepared by the Liverpool Reviews and Implementation Group.

- Addendum supplement 3": Hill RA, Bagust A, Boland A et al. Drug-eluting stents: a systematic review and economic evaluation, sensitivity analysis tables, June 2006.
- Addendum 4': Hill RA, Bagust A, Boland A et al. Drug-eluting stents: a systematic review and economic evaluation, sensitivity analysis tables including additional use of clopidogrel, March 2007.
- Addendum 5': Hill RA, Bagust A, Boland A et al. Drug-eluting stents: a systematic review and economic evaluation, sensitivity analysis tables including additional use of clopidogrel, taking account ACS patients, May 2007.

B The following organisations accepted the invitation to comment on the addenda for this appraisal.

I Manufacturers/sponsors:

- Abbott Vascular UK
- Boston Scientific
- Cordis Corporation
- Medtronic AVE

II Professional/specialist and patient/carer groups:

- Action Heart
- British Cardiac Society and British Cardiovascular Intervention Society (joint submission)
- The Royal College of Physicians

III Others:

- Department of Health

IV Commentator organisations (without the right of appeal):

- British Cardiovascular Industry Association

Appendix B: Summary of indications for use of DES

- Axxion (paclitaxel eluting stent) is not currently used in the UK and does not have an indication for use.

- CoStar (paclitaxel eluting stent) – 'Intended for use in improving coronary luminal diameter in patients with symptomatic ischemic heart disease due to coronary artery lesions. For treatment of coronary occlusive disease in patients eligible for percutaneous transluminal angioplasty (PTCA).'

  Under 'Use in specific patient populations' in the indications for use for CoStar it states '... The safety and effectiveness of the CoStar Paclitaxel-Eluting Coronary Stent System has not been established in patients with coronary reference vessel diameter < 2.5 mm; lesion length > 30 mm, lesions in left main coronary artery, ostial lesions, lesions located at a bifurcation, lesions in saphenous vein grafts, in-stent restenosis, restenotic lesions from non-stent percutaneous coronary interventions, diffuse disease or poor distal outflow, more than two overlapping stents due to risk of thrombus and restenosis.'

- Taxus (paclitaxel eluting stent) – 'For improving luminal diameter and reducing re-stenosis within the stent and stent edges for the treatment of de novo lesions in native coronary arteries, abrupt or threatened closure in patients with failed interventional therapy. The treated lesion length should be less than the nominal stent lengths ... with reference vessel diameters from 2.25 to 5.00 mm.'

- Taxus Liberte (paclitaxel eluting stent) – 'For de novo and restenotic lesions or total occlusions in patients with coronary artery disease – angina; silent ischemia; acute MI – to improve luminal diameter and reduce restenosis within the stent and at the stent edges. Also treatment of abrupt or threatened closure in patients with failed interventional therapy. The treated lesion length should be less than the nominal stent lengths ... with reference vessel diameters from 2.25 to 4.00 mm.'

- Cypher Select (sirolimus eluting stent) – 'Improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete de novo and in-stent restenotic lesions (≤ 30 mm) in native coronary arteries with a reference vessel diameter of 2.25 mm to 4 mm'.

- Endeavour (sirolimus eluting stent) – 'Intended to improve coronary luminal diameters as an adjunct to coronary interventions and reduce restenosis in patients with symptomatic ischemic heart disease in de novo coronary artery lesions in native coronary arteries with a reference vessel diameter of 2.25 mm to 4.0 mm and a lesion length of ≤ 27 mm.'

- Janus (tacrolimus eluting stent) - 'Intended for use as an adjunct to percutaneous transluminal coronary angioplasty (PTCA) procedures performed to maintain vessel patency. Randomised clinical studies have shown that drug eluting stents can reduce significantly binary restenosis, repeated target lesion revascularisation and angiographic late loss at 6 months'. 'The Sorin stent is indicated to improve the coronary lumen diameter in patients with symptomatic ischemic cardiopathy due to de novo native coronary lesions'.

- Xience V (everolimus eluting stent) – 'Improving coronary luminal diameter in patients with symptomatic ischemic heart disease due to discrete de novo native lesions ≤ 28 mm with a reference vessel diameter of 2.5 mm–4.0 mm.'

- Dexamet (dexamethasone eluting stent) - 'Indicated for use in reference lesion diameters of ≥ 2.0 and < 4.0 mm, in patients eligible for percutaneous transluminal coronary angioplasty (PTCA) exhibited by the characteristics described' in the indications for use.' Dexamet is now no longer on sale and is being phased out by the manufacturer Abbott.

- Yukon (drug of choice eluting stent) – 'For intraluminal chronic placement in stenosed coronary artery or aortocoronary bypass grafts in order to obtain vessel patency following acute or subacute coronary artery obstruction. It is also indicated in restenosis or arterial dissection after PTCA procedures.

Patients considered for stent implantation should be acceptable candidates for coronary balloon angioplasty.'

Key contraindications

	Unprotected left main CA	In-stent restenosis	Bifurcated lesions	Chronic/total occlusion of target vessel	Heavily calcified lesions	Highly tortuous anatomy	Direct stenting	MI less than 72hrs before index procedure
CoStar	'The safety and effectiveness of the CoStar Paclitaxel-Eluting Coronary Stent System has not been established in patients with ... lesions in left main CA.	under the ''Use in specific patient populations' section of 'Warnings and precautions', 'In-stent restenosis is contraindicated'	Under 'Use in specific patient populations' in states 'The safety and effectiveness of the CoStar Paclitaxel-Eluting Coronary Stent System has not been established in patients with ... lesions located at a bifurcation.	–	–	–	–	–
Taxus	x	x	x	x	x	x	under 'Precautions', 'the target lesion must be sufficiently	x

							predilated prior to stent implantation'	
Taxus Liberte	x	Received indication extension (May 06) for in-stent restenosis	x	only 'direct stenting of total occlusions' is stated	x	x	x	–
Cypher Select	x	–	Indications for use state 'Treatment of side branch is usually a technique decision'	x	–	Indications for use state 'Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon'.	–	'The safety and effectiveness of the CYPHER SELECT+ DES has not yet been established in the following ... Patients with a recent MI where there is evidence of thrombus or poor flow'.
Endeavour	–	–	–	'Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon'	–	–	'Safety and effectiveness for direct stenting has not been established'	–
Janus	–	–	–	–	–	–	x?	–
Xience V	–	–	–		–	–	–	–

Dexamet	x	–	–	–	–	x	x	Indications for use state 'contraindication to an emergency coronary bypass surgery'
Yukon	x	–	–	Lesions that cannot be successfully pre-dilated.	Patients with proximal atherosclerosis in whom guide wire access and adequate guiding catheter support is prohibited Lesions that cannot be successfully pre-dilated.	Patients with significant vessel tortuosity in whom guide wire access and adequate guiding catheter support is prohibited.	'It is recommended to pre-dilate the lesion with a suitable PTCA balloon dilatation catheter prior to stenting. In general, dilation of the vessel is required with a balloon vessel diameter ratio of 1:1'	Patients who have experienced a myocardial infarction less than one week prior to the proposed stent implantation. Patients with imminent thrombus formation and alteration of flow after myocardial infarction.

X stated in indications for use contraindications, – absent from indications for use contraindications

Other information in indications for use

	Multi-vessel disease	Diabetes
CoStar	Indications for use state 'When multiple stents are required to treat a lesion, stents should be of a similar compositions as the risk of corrosion increases when stents of differing metals contact one another'.	Under 'Patient Selection and Treatment', 'The risks and benefits of treatment with a coronary stent should be considered before use of the CoStar Paclitaxel-Eluting Coronary Stent System. In de novo lesions that increase the risk of binary restenosis (i.e., diabetes mellitus and use of tobacco) should be assessed.'
Taxus	–	–
Taxus Liberte	–	–
Cypher Select	The indications for use state ' When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the proximal lesion. Stenting in this order obviates the need to cross the proximal stent in placement of the distal stent and reduces the chances for dislodging the proximal stent'.	The indications for use state under 'Individualization of treatment', 'The risks and benefits should be considered for each patient…. Premorbid conditions that increase the risk of a poor initial result or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed.'
Endeavour	'When multiple stents are required, stent materials should be of similar composition. Placing multiple stents in contact with each other may increase potential for corrosion'	–
Janus	Strong CYP3A4 inhibitors might provoke increased Tacrolimus exposure to levels associated with systemic effects, especially in cases of multiple stent implants.	–
Xience V	Placing multiple stents of different metals in contact with each other may increase the potential for corrosion.	Indications for use states under 'Warnings', 'Judicious selection of patients is necessary since the use of this device carries the associated risk of subacute thrombosis, vascular complications and/or bleeding events'.
Dexamet	Indications for use state 'The risk of subacute thrombosis may increase when multiple overlapping stents are used.' 'The use of adjacent stents of different metal types is not recommended'.	–

Yukon	Indications for use state 'If you have the necessity of multi stent implantation, the distal stent should be implanted first'	–

– absent from indications for use