NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Drug-eluting stents for the treatment of coronary artery disease (part review of NICE technology appraisal guidance 71)

NOTE: This guidance replaces sections 1.2-1.4 of NICE technology appraisal guidance 71 (2003).

Sections 1.1 and 1.5 of technology appraisal guidance 71 recommend when to use a stent. This part review recommends under what circumstances a drug-eluting stent should be used.

1 Guidance

1.1 Drug-eluting stents are recommended for use in percutaneous coronary intervention for the treatment of coronary artery disease, within their instructions for use, only if:

- the target artery to be treated has less than a 3 mm calibre or the lesion is longer than 15 mm, and
- the price difference between drug-eluting stents and bare-metal stents is no more than £300.

2 Clinical need and practice

2.1 Coronary artery disease is also known as coronary heart disease (CHD) and ischaemic heart disease. It is narrowing (stenosis) of the coronary arteries as a result of deposition of atherosclerotic plaque, which results in an insufficient supply of oxygen to the heart muscle. CHD may affect one or more arteries, which may be of different diameters (calibres). The stenosis of arteries may be partial or total. Coronary artery stenosis may be asymptomatic or may lead to angina – 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 myocardial infarction (MI) or death.

2.2 Mortality rates from CHD are decreasing but CHD remains the most common cause of mortality in the UK. It 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. In the UK, annually, approximately 259,500 people experience an acute MI and approximately 341,500 new cases of angina (the most common form of CHD morbidity) are reported. In Europe, CHD has been estimated to account for 9.7% of total disability-adjusted life years lost.

2.3 Mortality and morbidity rates associated with CHD vary by socioeconomic group (rates are higher in lower socioeconomic groups), by geographical area (rates are highest in Wales, North West England, and the Northern England and Yorkshire regions, and lowest in South East England) and by 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 in men than women. The disease is more common in people with high serum cholesterol and/or high blood pressure, in people who have type 1 or type 2 diabetes mellitus, in people who smoke, and in people who are physically inactive and/or obese.

2.4 The symptoms and health risks associated with a stenosed artery may be treated medically, by modifying 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/or statins).

2.5 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 second, balloon angioplasty (or percutaneous transluminal coronary angioplasty) involves a widening from within the artery using a balloon catheter, which is inserted through a femoral artery. 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 that encompasses percutaneous transluminal coronary angioplasty with or without stenting. The comparison of CABG with PCI including coronary artery stents (bare-metal and drug-eluting) was covered by NICE technology appraisal guidance 71 and is not dealt with in this appraisal.

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

2.7 A number of problems with PCI may occur. Recoil of the artery which happens when the balloon is deflated, usually occurs immediately or within 24 hours of completing the procedure, and may be associated with acute occlusive dissection of the vessel and require emergency CABG. In the medium term restenosis of the artery after the procedure may occur and has two main causes: contraction of the outer layer of the 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 intimal hyperplasia. As a consequence of

restenosis, a repeat procedure may be required and the rate of reintervention is greater in patients who have arteries of small calibre ('small vessels' – less than 3 mm in calibre), saphenous vein grafts and long lesions (longer than 15 mm) or total occlusions. People with diabetes, who commonly have arteries affected by atherosclerosis, also have a higher rate of restenosis.

2.8 Stent technology (type and platform, including the design, alloy used and strut thickness) has developed rapidly, and recent advances aim to reduce the likelihood of restenosis. Because restenosis is correlated with the degree of inflammation present at the time of angioplasty, drug-eluting stents (DESs) were developed. These are bare-metal stents (BMSs) coated with a drug, usually an immune suppressant, to reduce inflammation or an antimitotic agent to reduce cell proliferation. 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 where the drug is held temporarily in place within a polymer 'painted' onto the metallic stent, allowing the drug to elute slowly into surrounding tissues. However, not all stents are polymer based.

2.9 According to British Cardiovascular Intervention Society (BCIS) data, approximately 70,000 PCI procedures were undertaken in the UK in 2005, equating to 1165 per million of the population. In England, the number of procedures per million of the population was 1169, and in Wales, 873.

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

2.11 According to BCIS data, in the UK, the proportion of PCI procedures using stents rose steeply between 1993 and 1999, from

below 10% to nearly 80%. It continued to increase, although more slowly, to about 94% in 2005. Data for DES use were not available before 2002. In 2003 it was reported that 17% of all stents used in the UK were DESs. In 2005 this had risen to around 62% in the UK, 60% in England and 77% in Wales. Given the increases in numbers of PCI procedures, it may be that utilisation rates are now much higher than this.

2.12 There is a risk of stent thrombosis associated with the use of both types of stent (DESs and BMSs). To prevent thrombosis occurring, patients are required to use an antiplatelet drug, such as clopidogrel, in addition to aspirin during and after the implantation of a stent. Following data published in 2006, the US Food and Drugs Administration (FDA)'s Circulatory Devices Systems Advisory Panel recommended that the duration of clopidogrel use should be extended in patients receiving a DES. The American College of Cardiologists/American Heart Association PCI guidelines (also endorsed by the Society for Cardiovascular Angiography Interventions) and the BCIS have recommended that for patients receiving DESs the duration of clopidogrel use should be increased to at least 12 months, after which time continuation of clopidogrel should be reviewed taking into account the risk for further events on an individual patient basis.

3 The technologies

3.1 This technology appraisal focuses on DESs only. The preceding appraisal of DESs (NICE technology appraisal guidance 71) considered only three devices (Taxus, Cypher and Dexamet) because at the time of publication, these were the only DESs that had been granted Conformité Européene (CE) marking for use within EU countries. Eight additional DESs have been included in this appraisal.

3.2 Each DES has an instruction for use (IFU) document that includes the indications for which the specific device can be used. The indications for use for each DES vary, although the majority specify the sizes of vessels (diameter and length) to be treated and are in accordance with their CE marking. Also included in the IFU documents are details of side effects and specific contraindications for DESs.

3.3 Different drugs elute from the stents that are included in this appraisal: paclitaxel is a broad-spectrum antimitotic agent that inhibits cell division; sirolimus (previously known as rapamycin) is an immunosuppressive agent that reduces inflammation; ABT-578 is a synthetic analogue of sirolimus; everolimus is an immunosuppressive agent 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.

3.4 The following list prices for DESs exclude VAT.

- The DES Axxion (Biosensors Limited) is a non-polymeric paclitaxel-eluting stent (PES) with a list price of £995 (BMS equivalent: Nexus).
- The DES CoStar (Biotronik Limited) is a non-polymeric PES (BMS equivalent: DepoStent). CoStar was originally included in this appraisal but is no longer available.
- The DES Taxus (Boston Scientific) is a polymeric PES with a list price of £1300 (BMS equivalent: Express).
- The second-generation DES Taxus Liberté (Boston Scientific) is a polymeric PES with a list price of £1300 (BMS equivalent: Liberté).
- The DES Cypher (Cordis Corporation) is a polymeric sirolimus-eluting stent (SES) with a list price of £1340 (BMS equivalent: Bx Velocity).
- The second-generation DES Cypher Select (Cordis Corporation) is a polymeric SES with a list price of £1340 (BMS equivalent: Sonic).
- The DES Endeavor (Medtronic AVE) is a polymeric sirolimus analogue ABT-578 (zotarolimus)-eluting stent (ZES) with a list price of £1450 (BMS equivalent: Driver).
- The DES Janus (Sorin) is a polymeric tacrolimus-eluting stent (TES) with a list price of £1500 (BMS equivalent: Janis).
- The DES Xience V (Guidant Ltd) is a polymeric everolimus-eluting stent (EES) with a list price of £1500 (BMS equivalent: Multi-Link Vision).
- The DES Dexamet (Abbott Vascular Devices Ltd) is a polymeric dexamethasone-eluting stent (BMS equivalent: BiodivYsio). Dexamet was originally included in this appraisal but is no longer available in the EU.
- The DES Yukon (Kiwimed Ltd) is a non-polymeric stent that can be coated with any drug to be eluted and has a list price of £650.

3.5 As list prices are not commonly used for procuring devices in the NHS, updated prices of DESs and BMSs were sought from the NHS Purchasing and Supply Agency. Procurement of devices is complex and it should be noted that the prices for DES and BMS are driven by a number of factors including the: market conditions at the time of contracting; contract period; renewal date for the procurement arrangements (contracts are usually updated annually and the most recent contracts show significant decreases in the prices of DESs); volume commitment; period commitment; combination of period and volume commitment; product rationalisation or standardisation; retrospective threshold discounts (for example, free set quantities of stents when agreed volumes have been exceeded); consignment stock (for instance, when a supplier provides an inventory to trust); and other added value inclusive arrangements (for example, the provision of additional training and related equipment).

3.6 From the sample 2007/08 data received from the NHS Purchasing and Supply Agency for NHS organisations in England for the stents included in this appraisal, the mean price of DES was £529 and the mean price of BMS was £131. The price difference between DESs compared with BMSs ranged from £203 to £615 across a number of Health Authorities in England, although it should be noted that the higher price differences tended to be seen in the older contracts which will be re-tendered in due course, in accordance with relevant contract renewal schedules.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

DESs versus BMSs – evidence from randomised controlled trials

4.1.1 A total of 17 randomised controlled trials (RCTs) were identified that compared DESs with BMSs, and data from all 17 were included for at least one outcome in the meta-analysis.

- 10 studies compared an SES (Cypher) with the equivalent BMS.
- Four studies compared a PES (Taxus) with the equivalent BMS.
- One study compared both an SES (Cypher) and a PES (Taxus) with a newer BMS.
- One study compared the ZES (Endeavor) with the equivalent BMS.
- One study compared the EES (Xience V) with the equivalent BMS.

No RCT evidence has yet been reported for the Axxion, CoStar, Dexamet or Janus stents. Limited RCT data were available for the Yukon stent.

4.1.2 Study outcomes used in the RCTs included rates of mortality, acute MI, target lesion revascularisation (TLR), target vessel revascularisation (TVR), composite events (major adverse coronary event [MACE] and/or target vessel failure [TVF]), angiographic binary restenosis and late luminal loss. Revascularisation was usually prompted by protocol-driven angiographic evidence of restenosis either for all participants or for a selected subgroup of participants. Only one trial (BASKET) explicitly reported that no protocol-driven angiographic follow-up was included. This trial compared both SES (Cypher) and PES (Taxus) DESs with a newer BMS in a three-arm study.

4.1.3 All but three of the 17 RCTs were multicentre trials. Study size ranged from 60 to over 1300 patients. Of the 17 trials, 11 included patients with single lesions. The studies covered a range of vessel diameters from 2.25 mm to 4.00 mm, although the lower range was not reported in some studies. Lesion length also varied, ranging

from 10 mm to 33 mm, although again the data were not always reported. All studies permitted the inclusion of people with diabetes, and all but three studies excluded acute or evolving MI. The presence of unprotected left main coronary artery excluded patients from many trials, as did severe calcification or tortuousity, total occlusion, bifurcation, the presence of thrombus in the target vessel, previous PCI within 30 days or PCI other than balloon required as part of the study intervention.

4.1.4 A total of 12 trials described the co-therapies used. Aspirin was prescribed before intervention in 11 of these studies and used after the procedure in all 12. Clopidogrel was used as an antiplatelet therapy in all of the 12 studies; ticlopidine was available for use as an alternative to clopidogrel in five studies. In one trial, tirofiban, used in combination with a DES, was compared with abciximab used with a BMS. The duration of antiplatelet therapy after intervention ranged from 2 months in three trials to 1 year in one study.

4.1.5 Meta-analysis was carried out by the Assessment Group for rates of mortality, acute MI, TLR, TVR, composite event (MACE and/or TVF), angiographic binary restenosis and late luminal loss. Analysis of mortality, acute MI and event rates used pooled results from over 7000 participants. Data in the form of an odds ratio (OR) and 95% confidence interval (95% CI) were analysed using the Mantel–Haenszel method fixed-effect model. For continuous outcomes, weighted mean differences (WMDs) were analysed. Where there was significant heterogeneity, analysis using a random-effects model was also undertaken.

4.1.6 In addition to analyses of the individual studies, pooled estimates (giving the OR and 95% CI) were provided for each ‘eluted drug’ group (for example, comparing a PES [Taxus] and all BMSs in the paclitaxel studies). Data related to the SES (Cypher) and the

sirolimus-analogue stent, ZES (Endeavor) in some instances were pooled and presented as pooled SES results. All eluted drug group results were also pooled to obtain estimates for a meta-analysis of any-type DESs compared with any-type BMSs. The meta-analysis was performed for available data at follow-ups of up to 1 month, 6–9 months, 1 year, 2 years and 3 years. The Assessment Group assumed, when making decisions about the appropriateness of combining data, that all BMSs are similar and, likewise, all DESs are similar except in the drug delivered; and that the stent design and the insertion system do not have an impact on clinical outcomes.

4.1.7 For rates of mortality and rates of acute MI, one study found a statistically significant difference in favour of the SES (Cypher) compared with the BMS for MI at 6–9 months (OR 0.19, 95% CI 0.04, 0.87). There were no statistically significant differences between the DES and the BMS in the individual studies for all other follow-up periods analysed to 3 years. There were no statistically significant differences between the DES and the BMS for the pooled eluted drug groups (PES [Taxus] and pooled SESs) and for the pooled analyses of any-type DES compared with any-type BMS for any of the follow-up periods.

4.1.8 For event rate (MACE and TVF), the individual studies of PES (Taxus), SES (Cypher) and ZES (Endeavor), and the pooled eluted drug groups analysis showed statistically significant differences in favour of DESs over BMSs. This was also the case for the overall meta-analysis, which favoured any-type DESs over any-type BMSs at all follow-up time points: 6–9 months (OR 0.46, 95% CI 0.40 to 0.53), 1 year (OR 0.39, 95% CI 0.33 to 0.47), 2 years (OR 0.43, 95% CI 0.34 to 0.54) and 3 years (OR 0.42, 95% CI 0.32 to 0.55). Statistical heterogeneity was indicated at the 6–9 months follow-up; a random-effect analysis for this time point showed only a small

effect on the OR (OR 0.44, 95% CI 0.36 to 0.54). The difference between the EES (Xience V) and the BMS was not statistically significant at the only follow-up period (6–9 months).

4.1.9 For TVR, not all individual studies of PES (Taxus) showed statistical significance compared with BMSs for all time periods up to 3 years. The individual studies for SESs (Cypher) and ZESs (Endeavor) all showed statistical significance over BMSs up to 3 years. The pooled eluted drug groups analysis showed statistically significant differences in favour of a PES (Taxus) over BMSs at follow-up time points up to 2 years: 6–9 months (OR 0.54, 95% CI 0.43 to 0.68), 1 year (OR 0.40, 95% CI 0.29 to 0.55) and 2 years (OR 0.45, 95% CI 0.34 to 0.59). At 3 years, the difference was no longer statistically significant, but the data at this time point were derived from a single, relatively small study that may have been underpowered. TVR data for a SES (Cypher) versus a BMS were available for two trials at 6–9 months and for single trials at 1 and 3 years. These showed statistically significantly differences in favour of the SES (Cypher) compared with the BMS at: 6–9 months (OR 0.33, 95% CI 0.18, 0.62), 1 year (OR 0.34, 95% CI 0.19 to 0.60) and 3 years (OR 0.35, 95% CI 0.25 to 0.49). TVR data for the ZES (Endeavor) at 6–9 months, the only time period available, was statistically significant in favour of the ZES over the BMS (OR 0.41, 95% CI 0.27 to 0.63). There were no data for EES (Xience V) for this outcome measure.

4.1.10 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 10–25% range for procedures that used a BMS. For example, in three trials of PES (Taxus), the rates were 0%, 4.7% and 4.2% for the DES compared with 10.0%, 12.9% and 14.7% for the BMS, respectively. Rates at 1 year in three trials of a SES (Cypher) were 4.6%, 0% and 4.9% for the DES compared with

24.9%, 13.6% and 20.0% for the BMS, respectively. For TLR, the pooled eluted drug groups analysis showed statistically significant differences in favour of a PES (Taxus) over BMSs at follow-up periods of up to 2 years: 6–9 months (OR 0.37, 95% CI 0.28 to 0.49), 1 year (OR 0.26, 95% CI 0.18 to 0.39) and 2 years (OR 0.28, 95% CI 0.20 to 0.40). At 3 years, the difference was no longer statistically significant, but the data at this time point were derived from a single, relatively small study that may have been underpowered. TLR data for a SES (Cypher) showed it to be statistically significantly more effective than a BMS at all time points up to 3 years: 6–9 months (OR 0.21, 95% CI 0.15 to 0.30), 1 year (OR 0.17, 95% CI 0.12 to 0.25), 2 years (OR 0.22, 95% CI 0.15 to 0.30) and 3 years (OR 0.25, 95% CI 0.17 to 0.36). The data for the ZES (Endeavor) at the follow-up period of 6-9 months showed it to be statistically significantly more effective than the BMS (OR 0.35, 95% CI 0.22, 0.56). Lower rates of TLR (3.8% versus 21.4%) were apparent for the EES (Xience V) group at 6 months (the only follow-up period) but the difference was not statistically significant. For TLR, the meta-analyses showed statistically significant differences in favour of any-type DES over any-type BMS, with improved rates of lesion revascularisation at all follow-up time points up to 3 years: 6–9 months (OR 0.30, 95% CI 0.25 to 0.37), 1 year (OR 0.21, 95% CI 0.16 to 0.27), 2 years (OR 0.24, 95% CI 0.19 to 0.31) and 3 years (OR 0.25, 95% CI 0.17 to 0.35).

DES versus BMS – DESs with non-RCT data

4.1.11 The TES (Janus) was examined in a non-controlled study as was the PES (Taxus Liberté). A range of formulations of the PES (CoStar) was evaluated in two non-randomised controlled studies, and the Yukon DES was evaluated in a dose-ranging non-randomised controlled study comparing Yukon coated with sirolimus with the same stent carrying no drug. The Dexamet DES

was studied in one non-randomised study of Dexamet compared with a BMS and four non-controlled studies (including two registries).

4.1.12 Outcome data were limited due to the short follow-up periods: 30 days for the PES (Taxus Liberté) study; 4 months for one PES (CoStar) study and 1 year for the other PES (CoStar) study; 6 months for the Dexamet studies and for the TES stent; and up to 1 year for the SES (Yukon) study. Angiographic outcomes, binary restenosis and/or late loss were reported for the PES (CoStar), Dexamet and the SES (Yukon). Because of the variety of DESs considered in these studies, the methodological limits of the available studies, and the varied and limited follow-up, the Assessment Group did not consider pooled analysis to be appropriate.

4.1.13 For the TES (Janus), limited data were reported; at 30 days no events (death, MI or TLR) had occurred. For the PES (Taxus Liberté) the data available at 30 days were marked as commercial in confidence. For the PES (CoStar), the only data available were for one of the two arms at 1 year for one trial and interim data from two of the four arms of the other ongoing study.

4.1.14 Data for the SES (Yukon) were reported at 1 month and 1 year. No deaths occurred in the first month. Rates of acute MI up to 1 month were 1.8% in the SES group and 1.3% in the BMS group. At 1 year, the composite of death or non-fatal MI was 2.7% for the Yukon SES and 3.9% for the BMS. No statistically significant differences were detected. At 1 year, TLR was reported in 12.6% of the SES group and 21.5% of the BMS group, and the difference was statistically significant in favour of the SES (OR 0.53, 95% CI 0.34 to 0.81).

4.1.15 The non-randomised trial that compared Dexamet (DES) with a BMS reported no deaths among the 100 participants receiving either stent and only one incidence of acute MI, which was in the BMS group, up to a mean of 8 months' follow-up. Revascularisations for this time period were 2% TLR in the DES group and 10% TLR (12% TVR) in the BMS group. Composite rates of MACEs, consisting entirely of revascularisations, were 2% for the DES and 12% for the BMS. Neither of these comparisons showed statistically significant differences.

DES versus DES

4.1.16 Eight RCTs comparing different DES types were identified by the Assessment Group. Six RCTs compared a SES (Cypher) with a PES (Taxus) (including one trial that was also assessed in the DES versus BMS clinical section because it had a BMS arm as well as two DES arms), one studied SES (Cypher) in comparison with the newer SES (Cypher Select) and one compared the Yukon, as a SES, with a PES (Taxus).

4.1.17 Six trials were conducted in only one or two centres in European countries, and two were multicentre and multinational. Study sizes ranged from 200 to 1350 patients. Two trials were distinct in that they did not incorporate planned angiographic assessment of trial participants. Only two trials presented randomisation details and none of the studies presented adequate information on whether the RCTs were conducted under 'blind' conditions. One study did not present an intention-to-treat analysis, and for two studies it was unclear whether events were reported according to the original randomised allocations.

4.1.18 A meta-analysis was conducted according to which pairing of DES types was compared within trials (most commonly this was the SES

[Cypher] versus the PES [Taxus]). No total pooled effect estimate was calculated across multiple groupings of DES versus DES trials.

4.1.19 There were no statistically significant differences in rates of mortality or acute MI for any of the pairings of DES types.

4.1.20 For TLR, one individual study showed a statistically significantly better rate of TLR, at 6–9 months, with the SES (Cypher) compared with the PES (Taxus) (OR 0.56, 95% CI 0.33 to 0.93). Only one RCT had data available beyond 9 months; in this study, rates of TLR at 1 year were 5.7% for the SES (Cypher) compared with 9.0% for the PES (Taxus); the difference was not statistically significant. The Assessment Group's pooled analysis of TLR up to 9 months was statistically significant in favour of the SES (Cypher) over the PES (Taxus) (OR 0.70, 95% CI 0.51 to 0.97).

4.1.21 A statistically significant reduction in TVR with the SES (Cypher) compared with the PES (Taxus) was determined from a meta-analysis of two trials at 6–9 months (OR 0.59, 95% CI 0.39 to 0.89). A reduction in the composite event rate (MACE) at 6–9 months was also statistically significant with the SES (Cypher) compared with the PES (Taxus) (OR 0.75, 95% CI 0.59 to 0.96).

Effects of DESs on the risks of thrombosis, MI and mortality

4.1.22 In December 2006, following publication of data on longer-term risks associated with DES (thrombosis, MI and mortality), the FDA convened a public meeting of its Circulatory System Devices Advisory Panel to review and analyse the available data and to provide recommendations for appropriate actions to address this issue. In January 2007, the Circulatory System Devices Advisory Panel made recommendations to the FDA. The Panel stated, 'When the DES, which are indicated for use in the USA (SES [Cypher]) and (PES [Taxus]), are used in accordance with their approved indications both are associated with a small increase in

stent thrombosis compared with BMS at 1 year after stent implantation; the increased risk of stent thrombosis was not associated with an increased risk of death or MI compared with BMS; and the concerns about thrombosis do not outweigh the benefits of DES compared with BMS when DES are implanted within the limits of their approved indications for use.' The FDA stated that a longer duration of antiplatelet therapy may be beneficial, and this has led to the recommendation in the PCI guideline of the American College of Cardiologists/American Heart Association (endorsed by the Society for Cardiovascular Angiography Interventions) that in patients receiving DESs the duration of clopidogrel use should be increased to 12 months. The BCIS has also recommended 12 months' use of clopidogrel in patients receiving a DES.

4.1.23 The Circulatory System Devices Advisory Panel also considered use of DESs in patients with more complex coronary lesions than those studied to support initial marketing approval ('off-label' use). The Panel agreed that use of DESs 'off-label' is associated with an increased risk of stent thrombosis, MI or death compared with 'on-label' use, and until more data are available DES labels (IFUs) should state that when DESs are used off-label, patient outcomes may not be the same as the results observed in the clinical trials conducted to support marketing approval. The FDA has since defined off-label use to mean the use of a medical product for treatments other than those for which the product was initially approved; or use not explicitly included in product labelling (intended use and IFU). The UK Medicines and Healthcare Products Regulatory Agency (MHRA) supports this definition of off-label use for the DESs that have been approved for use in Europe.

4.1.24 Each DES included in this appraisal has an IFU document that lists the indications for which it can be used. The sizes of vessels (diameter and length) to be treated are stated in the majority of the

IFUs, as are the specific contraindications. The FDA considers that although patients with diabetes were included in the pivotal trials, the number of patients was insufficient for either the SES (Cypher) or the PES (Taxus) to earn a specific labelled indication for people with diabetes. The UK MHRA supports the view of the FDA with regard to individuals with diabetes and only one of the DESs included in this appraisal has recently been specifically indicated for people with diabetes.

Summary

4.1.25 There were no statistically significant differences detected in death or MI between the pooled subgroups and pooled any-type DES groups. The pooled DES analysis indicated that revascularisation rates were reduced by approximately three quarters compared with BMSs, consistent across most studies of the PES (Taxus) and SESs (Cypher; Endeavor at 6–9 months). The benefits of DESs over BMSs for TLR were seen at 1 year, and this significant difference was maintained for up to 3 years. For the TVR outcome there were statistically significant differences in favour of any-type DES over BMS for most of the time points assessed.

4.2 Cost effectiveness

Published literature

4.2.1 A total of 10 full economic evaluations were included in the assessment report, all of which compared an SES with a BMS, although four evaluations also included a PES. One of the evaluations was conducted in the UK; the rest were conducted 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, nine estimated that the cost of DESs incurred a price premium/difference (the difference in cost between a given BMS and the drug-eluting

equivalent), which ranged from £233 to £1225. Four of the evaluations reported health outcomes in terms of quality-adjusted life years (QALYs). Three evaluations provided incremental costs per QALY for a general population, and these costs ranged from US$27,450 to Can$96,523 (approximately US$93,000). 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 and the other estimated it to be approximately US$7000 over 2 years. The majority of evaluations concluded that DESs are more cost effective than BMSs for patients with types of arteries that have a higher risk of restenosis, although there was great disparity between evaluations, with a variety of outcomes and a range of ICERs being reported.

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

Manufacturers' economic models

4.2.3 Three models were submitted by DES manufacturers.

4.2.4 The decision analytic model from Boston Scientific compared the PES (Taxus) with the equivalent BMS, for a general population and for subgroups. The incremental costs per QALY at 1 year were given as £29,587 for the overall population and £1020 for patients with diabetes. For patients with small vessels and long lesions, the

PES (Taxus) was dominant (both more effective and less costly than the BMS). For the PES (Taxus) at 2 years, the incremental cost per QALY for the overall population was given as £13,394, and it was dominant for patients with small vessels and those with diabetes. The model was highly sensitive to variations in the duration of clopidogrel therapy and the average number of stents used. In the manufacturer's sensitivity analyses, when the number of stents used per procedure was increased from 1.4 to 1.7, in line with the Assessment Group's model, the estimated cost per QALY at 1 year for the overall population increased to £56,731; however, the subgroup estimates were only marginally increased. If the duration of clopidogrel therapy after DES implantation was increased from 6 to 12 months, the cost per QALY at 12 months increased to £71,634 for the total population and to over £30,000 for the subgroup with diabetes.

4.2.5 The decision analytic model from Cordis compared the SES (Cypher) with the equivalent BMS for a 'no-risk-factor' population and for subgroups. The model was split into a two-way analysis of the BMS versus the SES (Cypher) and a three-way analysis of the BMS versus the PES (Taxus) versus the SES (Cypher). In extending the three-way analysis to 2 years, an indirect comparison was undertaken that made an assumption that the BMSs in both trials (Boston Scientific and Cordis BMS) are equivalent. The cost data for the technologies (the BMS and Taxus) were considered by the Assessment Group to be overestimated and when the Assessment Group re-ran the model increasing the SES (Cypher) price premium over the equivalent BMS from £433 to £695, the incremental cost per QALY increased from £29,259 to £69,613 for the 'no risk factor' subgroup; from £10,178 to £39,508 for the small-vessels subgroup; from £16,460 to £49,345 for the long-lesions subgroup; and from £9702 to £38,446 for the group with diabetes.

4.2.6 The Markov model presented by Medtronic compared the ZES (Endeavor [sirolimus analogue ABT-578]) with Medtronic's comparable BMS, for a total population. The submission measured costs and benefits at 5 years, extrapolating the 9-month trial data. In one scenario, the two arms were assumed to be equivalent in terms of risk of repeat revascularisations after 1 year. The incremental cost per QALY was estimated at £11,220. No subgroup analyses were undertaken. The Assessment Group found the model to be highly sensitive to baseline TVR rates and the number of index stents used. If baseline TVR rates were reduced below 12% (for both the BMS and the ZES), then the ICER exceeded £30,000. If the average number of stents used for the index procedure was increased to 1.4, the ICER increased to £39,174. The Assessment Group noted that the two factors to which the model was sensitive were taken from a single positive trial.

4.2.7 The submission from Kiwimed compared an SES (Yukon) with the Kiwimed BMS for a total population. The effectiveness data were taken from the SES (Cypher) trials, so an untested assumption was made that the SES (Yukon) has equivalent effectiveness to the SES (Cypher). Extrapolation from 2 to 5 years was undertaken using an assumption that patients remained in the same health state that they were in at the end of 1 year. Kiwimed's submission stated that the model results indicated that the SES (Yukon) was dominant compared with the BMS in the total population. In a sensitivity analysis varying the cost of the stent and the probability of restenosis, the ICERs for the SES (Yukon) were always under £30,000 per QALY.

Assessment Group model: methods

4.2.8 The Assessment Group's model used the framework from the original appraisal with some minor modifications as follows: the time horizon was restricted to 1 year, so no discounting was

necessary; particular risk groups were examined; in addition to the modelling of any-type DES compared with BMS, some head to head comparisons were conducted (SES (Cypher) compared with the PES (Taxus).

4.2.9 A difference between the effectiveness of DES and BMS was only seen with regard to revascularisation (TLR and TVR) and event rate (MACE and TVF). For these endpoints, the clinical trials show evidence of differences between DESs and BMSs at 1 year. The clinical trials show evidence in favour of DESs over all follow-up periods up to 3 years with a trend towards the greatest benefit occurring within the first year.

4.2.10 In the Assessment Group's model the most important factors in determining the incremental cost were the additional cost per DES implanted (price premium/difference) and the number of stents implanted per patient. The most important factors in determining benefit in the model were the absolute risk of revascularisation for patients treated with a BMS and the risk reduction attributable to the use of a DES.

4.2.11 The acquisition cost of a given stent may vary in different settings because of negotiated procurement discounts. The Assessment Group in their economic evaluation used the prices from a market survey of NHS purchasers. The survey was conducted by the NHS Purchasing and Supply Agency in May/June 2005 to identify the prices in contracts covering the period 2004/05 for both DESs and BMSs. The combined data from 12 purchasing bodies covering 20 hospital trusts provided consistent estimates of average unit prices and of the differences in price between DESs and BMSs. Results were provided for the two main suppliers of DESs: Boston Scientific (Taxus) and Cordis Corporation (Cypher). The effective sale price per Taxus PES (excluding VAT) was £815. Because there was only one recorded instance of a significant local volume discount

agreement for Cypher in the survey, the average sample price for the Cypher SES (excluding VAT) was £937. The estimated average price for a BMS in the survey (excluding VAT) was £278, so the price differences are £537 and £659 per DES for Taxus and Cypher, respectively.

4.2.12 Information received during the consultation period for the appraisal consultation document suggested that the prices for DESs had decreased since the 2005 survey. Therefore updated prices were sought from the NHS Purchasing and Supply Agency. From the sample 2007/08 data received from the NHS Purchasing and Supply Agency for NHS organisations in England for the stents included in this appraisal, the mean price of DES was £529 and the mean price of BMS was £131. The price difference between DESs compared with BMSs ranged from £203 to £615 across a number of Health Authorities in England.

4.2.13 To calculate the PCI procedure costs it was necessary to subtract the included costs of stents (DES and BMS) from the published PCI costs, and then to add back the model estimates of the number of stents, the type of stent and the cost per stent. In the final analyses, the Assessment Group assumed a wastage rate of 1%.

4.2.14 The Assessment Group base-case analysis used results from two observational studies of stented patients treated at the Liverpool Cardiothoracic Centre, 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 who underwent a second PCI required repeat treatment to previously treated lesions only. 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 DESs can be expected to produce benefit. Applying these proportions to the relative risk

reduction from the trials 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%). 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 relative risk reductions from the meta-analysis, this suggested that the reduction in the number of lesions treated in subsequent interventions was between 37% (95% CI 31 to 42%) and 53% (95% CI 47 to 59%) based on TLR (the Assessment Group counted lesions treated but excluded cases undergoing CABG rather than PCI). The Assessment Group noted that the BASKET trial, which did not include protocol-driven angiography, reported a risk reduction for DESs of 41% at 6 months. The Assessment Group therefore used 41% for the risk reduction associated with DESs in its base-case analyses.

4.2.15 The Assessment Group stated that the ICERs of any-type DESs compared with any-type BMSs are very dependent on the estimates of relative risk reduction in revascularisations and on the absolute rate of revascularisation in the types of patients in whom they are used. The absolute rates of revascularisation were derived from the Liverpool Cardiothoracic Centre audit data, and the potential of benefit was reassessed on the basis of the audit data concerning those patients in whom the repeat procedure required treatment of new lesions. This resulted in an absolute rate of revascularisation for all patients of 7.43%. The Assessment Group also carried out sensitivity analyses, varying rates of revascularisation for all patients up to 13%, based on trial data.

4.2.16 Using the Liverpool Cardiothoracic Centre audit data, the Assessment Group developed separate risk models for elective and non-elective patients using patient and lesion characteristics known at the time of the index intervention. Risk factors for the

patients were identified in the assessment report as being calcification, angulation greater than 45 degrees, restenotic lesion, triple-vessel disease, vessel diameter of less than 2 mm and prior CABG. In the final analyses, the absolute rates of repeat revascularisations for the conventional risk factors (long lesions, small vessels, diabetes and all combinations of these) were provided using the Liverpool audit data. The Assessment Group stated that, because none of these three factors in the multivariate model achieved conventional significance using the Liverpool audit data, the individual relative risks have wide confidence intervals and should be considered only as illustrative. The mean 12-month repeat revascularisation rate for all patients with small vessels was 15.25% (95% CI 9.38% to 22.24%), with a rate difference p = 0.02; for those with long lesions it was 10.23% (95% CI 8.10% to 12.57%), p = 0.09; and for those with diabetes it was 10.61% (95% CI 7.52% to 14.14%), p = 0.14.

4.2.17 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 scores between patients with severe angina and those recovered from revascularisation (0.158) was similar to the ARTS trial result (0.16), which was used in the previous appraisal. The assumptions made by the Assessment Group in the final analyses for disutilities associated with CABG versus PCI in the 6-week period following the procedure were that for a 2-week post-operative period, patients undergoing CABG experience a very low quality of life (0.0), and for the next 2 weeks the mean utility score recovers in a linear fashion achieving full benefit (0.660) by 4 weeks after the operation. Patients undergoing PCI were assumed to recover full benefit linearly over a 2-week period following the procedure. The Assessment Group concluded additionally that there was no

evidence to suggest an effect on the rate of acute MI or mortality with CABG compared with PCI plus stenting.

4.2.18 When BMSs and DESs were compared, the meta-analysis showed a trend towards increased numbers of non-fatal acute MIs with BMSs. The Assessment Group concluded in their analyses that based on the reviewed evidence, the maximum likely effect of this is equivalent to, per patient, an overall cost saving of about £13 and a utility gain of about 0.00055 when DESs are used.

4.2.19 The clinical evidence from the meta-analyses in the assessment report suggested that the SES (Cypher) reduces repeat revascularisations compared with the PES (Taxus). Because most of the clinical trials were limited to 6–9 months' duration, the Assessment Group carried out the economic evaluation assuming clinical equivalence and distinguished between stents only on the basis of price.

4.2.20 In the additional analyses requested by the Committee, the Assessment Group undertook sensitivity analyses by varying a number of the parameters in the original model. The results of the sensitivity analyses were presented as a number of tables containing the ICERs for a range of price premiums, for a range of absolute risks of revascularisation of BMSs, for the total population of stented patients and the risk-factor groups (small vessel, long lesion, diabetes and all combinations of these). Tables were presented for different numbers of stents (mean number, 1, 2 or 3) per patient. The Assessment Group also undertook new sensitivity analyses that took account of an additional 9 months' use of clopidogrel in patients receiving DESs, in accordance with the recent BCIS recommendations. These additional costs were applied only to 56% of the patient population because it was suggested by Consultees that 44% of patients would have acute coronary syndrome and therefore already be receiving 12 months'

treatment with clopidogrel in accordance with 'Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome' (NICE technology appraisal guidance 80).

4.2.21 The Assessment Group, at the request of the Committee, also provided estimates based on the analyses using a relative risk reduction with DESs of 55% as the base case and a sensitivity analysis of 65%. These relative risk reductions with DESs were used for a rate of revascularisation, using BMSs, of 11%, which was obtained from combining results for all patients (equivalent to 10% for elective and 13% for non-elective patients). The corresponding risk of revascularisation using BMSs for the risk groups and the mean number of stents were also calculated from the combined datasets for the elective and non-elective patients.

4.2.22 Following consultation, the Assessment Group provided two additional analyses. The first additional analysis updated the 2003/04 resource costs with reference costs from 2005/06. The waiting times for PCI and CABG were updated from 20 to 20.5 weeks for PCI and from 13 to 20.9 weeks for CABG. The number of patients with acute coronary syndrome was changed from 44% to 48.5%, and consequently the number of patients receiving an extra 9 months' treatment with clopidogrel was reduced from 56% to 51.5%.

4.2.23 In addition to the changes to resource costs, waiting times and number of patients with acute coronary syndrome, the second additional analysis included new parameters based on alternative suggestions from the BCIS. The Assessment Group modified BCIS's suggestion regarding the presentational case-mix. The following parameters were used in the model: the percentages of elective and non-elective patients were changed from 68% to 57% for elective patients and from 32% to 43% for non-elective patients; the absolute risk of revascularisation of BMS for all patients was

changed from 11% to 13% by combining 11.5% of elective and 15% on non-elective patients from the Liverpool Cardiothoracic Centre audit dataset; the relative risks for revascularisation in high-risk groups were set to 1.75 for small vessels, 1.35 for long lesions and 1.52 for diabetes; and the relative risk reductions from using DES were set to 60% for all patients; 69% for patients with small vessels; 70% for patients with long lesions and 61% for patients with diabetes.

Assessment Group model: results

4.2.24 Based on the Liverpool Cardiothoracic Centre audit data, the Assessment Group's original base-case scenario as described in 4.2.20 assumes the overall repeat revascularisation rate for the total population of stented patients in the UK at 12 months after PCI with BMSs is 7.43%. Using 7.43% for all patients, the absolute rates of repeat revascularisation for the risk factors become: 7.8% for long lesions; 9.0% for diabetes; and 9.9% for small vessels. Using the overall mean number of stents implanted per patient from the Liverpool Cardiothoracic Centre audit data (1.615) and assuming a price difference of £600 (approximate average of the price difference of the PES Taxus and the SES Cypher,from the survey data) the resulting incremental costs per QALY for each of the groups of elective patients are approximately: £407,000 for all patients; £380,000 for long lesions; £340,000 for diabetes; and £306,000 for small vessels. Using the overall mean number of stents implanted per patient for non-elective patients (1.467) the resulting incremental costs per QALY for each of the groups, at a price difference of £600, are: £282,000 for all patients; £250,000 for long lesions; £353,000 for diabetes; and £94,000 for small vessels.

4.2.25 Based on the Liverpool Cardiothoracic Centre audit data, the Assessment Group's re-analysis of the base-case scenario assumes an 11% overall revascularisation rate for the total

population of stented patients in the UK at 12 months after PCI with BMSs. Using 11% for all patients, the absolute rates of repeat revascularisation for the risk factors become: 11.7% for long lesions; 11.6% for diabetes; and 19% for small vessels. The relative risk reduction with DESs is assumed to be 55%. Using the overall mean number of stents implanted per patient from the Liverpool audit data, both elective and non-elective (1.571) and assuming a price difference of £600 (approximate average of the price difference of the PES [Taxus] and the SES [Cypher], from the survey data) the resulting incremental costs per QALY for each of the groups of patients are approximately: £213,000 for all patients; £183,000 for long lesions; £180,000 for diabetes; and £146,000 for small vessels. Assuming a price difference of £300 the resulting incremental costs per QALY for each of the groups of patients are approximately: £101,000 for all patients; £85,000 for long lesions; £84,000 for diabetes; and £59,000 for small vessels.

4.2.26 For the Assessment Group's sensitivity analysis for the combined elective and non-elective data, using a relative risk reduction with DESs of 65% and a price difference of £600, the resulting incremental costs per QALY for each of the groups of patients are approximately: £174,000 for all patients; £148,000 for long lesions; £146,000 for diabetes; and £116,000 for small vessels. Assuming a price difference of £300 the resulting incremental costs per QALY for each of the groups of patients are approximately: £78,000 for all patients; £65,000 for long lesions; £64,000 for diabetes; and £41,000 for small vessels.

4.2.27 The Assessment Group's additional analysis as described in 4.2.22, assuming a price difference of £600 for the base case (55% relative risk reduction of DES), results in incremental costs per QALY for each of the groups of patients of approximately: £171,000 for all patients; £158,000 for long lesions; £156,000 for diabetes; and £124,000 for small vessels. Assuming a price difference of

£300 the resulting incremental costs per QALY for each of the groups of patients are approximately: £74,000 for all patients; £66,000 for long lesions; £65,000 for diabetes; and £41,000 for small vessels. For the updated Assessment Group's sensitivity analysis (65% for the relative risk reduction of DES) the resulting incremental costs per QALY, for a price difference of £600, for each of the groups of patients are approximately: £137,000 for all patients; £126,000 for long lesions; £124,000 for diabetes; and £95,000 for small vessels. Assuming a price difference of £300 the resulting incremental costs per QALY for each of the groups of patients are approximately: £54,000 for all patients; £47,000 for long lesions; £46,000 for diabetes; and £25,000 for small vessels.

4.2.28 The Assessment Group's second additional analysis, as described in 4.2.23, resulted in incremental costs per QALY for each of the groups of patients, assuming a price difference of £600, of approximately: £111,000 for all patients; £51,000 for long lesions; £53,000 for diabetes; and £59,000 for small vessels. Assuming a price difference of £300 the resulting incremental costs per QALY for each of the groups of patients are approximately: £38,000 for all patients; £3,000 for long lesions; £4,000 for diabetes; and £4,000 for small vessels.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of DESs, having considered evidence on the nature of the condition and the value placed on the benefits of DESs by people with coronary artery disease, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.3.2 The Committee considered the evidence on the clinical effectiveness of DESs in the treatment of CHD. The Committee acknowledged that the clinical trials showed that the use of any-

type DESs reduced the rate of revascularisation in the target lesions and the target vessels, at all follow-up time points up to 3 years, compared with any-type BMSs. The Committee noted not just the trial data, but also the recent discussions on the effects of DESs on the risks of thrombosis, MI, and mortality, and accepted the findings of the FDA review that any-type DESs conferred no statistically significant benefits in mortality or acute MI rates over any-type BMSs. The Committee concluded that the key benefit of DESs is the reduction in rates of revascularisation in target lesions and target vessels compared with BMSs.

4.3.3 The Committee considered whether there was any evidence to suggest that there were differences in the clinical effectiveness of the various types of DESs. It noted that only four of the eleven DESs had been compared with each other in head-to-head RCTs. The majority of data comparing revascularisation rates were between the SES (Cypher) and the PES (Taxus). The Committee noted that the SES (Cypher) showed a statistically significant reduction in TLR, TVR and MACEs compared with the PES (Taxus), at 9 months. It was also noted that at 1 year, for the only outcome available, rates of TLR for the SES (Cypher) compared with the PES (Taxus) showed no statistically significant difference. The Committee heard testimony from the clinical specialists that different DESs are clinically comparable and that, in practice, any of the DESs would be used, although those with the greater evidence-base would be first choice.

4.3.4 The Committee considered the evidence to suggest that there were groups of patients whose vessel anatomy was more likely to be subject to restenosis. The absolute rate of revascularisation in these groups was greater than that of other patients and they therefore had the potential to gain a greater relative benefit from DESs than other patients, and this was taken into account by the sensitivity analysis in the assessment group's economic model.

The Committee considered the risk factors derived by the Assessment Group using the Liverpool Cardiothoracic Centre audit data, but it heard testimony from the clinical specialists that small vessels (less than 3 mm in calibre), long lesions (longer than 15 mm) and diabetes were the risk factors most consistently reported and that made most sense clinically. The Committee noted that, although the Assessment Group's analysis of the Liverpool Cardiothoracic Centre audit data did not prove that any of these were statistically significant risk factors, taking account of other studies, small-vessel disease and long lesions were better predictors of risk groups than diabetes, and are particularly prevalent in patients with CAD who also have diabetes. The Committee was also mindful of the regulatory concerns about the 'off-label' use of DESs. The Committee concluded that small vessels and long lesions should be considered as separate risk factors whereas diabetes should not be considered as a separate risk factor.

4.3.5 The Committee noted that the Assessment Group's model was based on the Liverpool Cardiothoracic Centre audit data that distinguished elective and non-elective (emergency) patients. The Committee heard testimony from the clinical specialists that in clinical practice the differences between these patient groups specifically related to the mode of their presentation with acute coronary syndromes, that is, non-ST-segment-elevated MI or unstable angina, and to the use of adjunctive treatments, in particular anti-platelet therapy. Due to the lack of other differences the Committee concluded that elective and non-elective patients should be considered together but that the merging of the estimates should take account of the proportions of elective and non-elective patients seen in clinical practice.

4.3.6 In considering the cost effectiveness of DESs compared with BMSs, the Committee noted that the model structure used by the

Assessment Group was appropriate. The Committee discussed the key parameters that drove the Assessment Group's economic model. It considered the absolute rate of revascularisation of BMSs in the total population of stented patients and noted that the Assessment Group used 7.43% for patients in its base case in the assessment report. The Committee heard testimony from the clinical specialists that the rate of revascularisation of BMSs was around 12% in the published literature. It noted that some of these published trials included protocol-driven angiography and revascularisation and therefore were likely to be an overestimate of actual revascularisation rates in clinical practice in the UK. The Committee noted that the Liverpool Cardiothoracic Centre audit data revascularisation rates were lower than those from other data sets including the BASKET trial (11%), which had not included protocol-driven angiography, and the Scottish Registry (11.5%). The Committee discussed the range of possible values for revascularisation and their relevance to UK practice and concluded that a rate of 11% for the absolute rate of revascularisation was a reasonable estimate for UK practice.

4.3.7 The Committee considered the relative reduction in the risk of target lesion revascularisation with DESs. The Committee noted that the trial data typically gave a relative risk reduction of 75%, but considered that this figure might over-estimate the real-life benefit of DESs because it is derived from the trials that included protocol-driven angiography and revascularisation. The Committee heard that the BASKET trial, which had not included protocol-driven angiography, had a relative risk reduction with DESs of 41% at 12 months. The Committee looked at the adjusted relative risk reduction with DESs used by the Assessment Group, and acknowledged that their approach reflected the number of patients, and not the target lesions, that would benefit from DESs. The Committee noted that the Assessment Group's figure was in line

with the BASKET trial. The Committee heard from the clinical specialists that the most plausible relative risk reduction with DESs from the clinical evidence was likely to be in the range 50–60% for the base case and 61–70% for high-risk groups. Given the variation in data the Committee considered a relative risk reduction with DESs over BMSs of 55% in the base case, and of 65% in a sensitivity analysis for the higher risk groups were the most plausible.

4.3.8 The Committee considered the mean number of stents used for each of the risk groups from the Liverpool Cardiothoracic Centre audit data and concluded that the estimate of mean number of stents per patient (1.6 for elective patients, 1.5 for non-elective patients) was likely to be a representative figure of the number used in all patients in the UK and could be used as a base case for consideration of the benefits of DESs.

4.3.9 The Committee was mindful of data in the literature on the mortality and morbidity of CABG and repeat angiography. After reviewing the utility values in the Assessment Group's model the Committee acknowledged the possibility that there could be an additional disutility associated with CABG during the initial 6 weeks following the procedure compared with PCI. The Committee accepted the Assessment Group's revisions for this parameter.

4.3.10 The Committee noted the current UK recommendation that clopidogrel should be given for an additional 9 months in patients receiving a DES and it therefore considered it appropriate that this should be taken account of in the cost-effectiveness analysis. The Committee also accepted the consultation suggestions that patients with acute coronary syndrome would already be receiving 12 months' treatment with clopidogrel and that no additional costs would be incurred in this population.

4.3.11 The Committee heard testimony from the clinical specialists and received information during the consultation period that in some areas procurement arrangements had resulted in a price difference of £300 for DESs over BMSs. The Committee also received information that although no nationally procured price currently existed for DESs, price differences that were less than £300 did exist in some regions. The Committee agreed that as this price difference existed in some regions, it was reasonable to assume that DESs could be procured in this way across all regions within the NHS and, therefore, it could be considered as an appropriate costing option in its considerations.

4.3.12 After agreeing on the parameters to use in the Assessment Group's model, the Committee discussed the resulting ICERs for the base case and risk groups, assuming:

- the absolute risk of revascularisation with BMSs for the total population is 11%, with resulting risks of revascularisation for small vessels of 19% and for long lesions of 11.7%
- the mean number of stents per patient is 1.571
- the relative risk reduction with DESs for the base case is 55% for the total population, and 65% for patients with small vessels and long lesions
- price differences of DESs over BMSs of £600 and £300.

At a relative risk reduction of 55% with DESs, the resulting ICER for the total population of patients was associated with a cost per QALY of approximately £171,000 at a price difference of £600 and £74,000 at a price difference of £300. For the higher risk groups of patients (that is, those with long lesions and those with small vessels) using a DES, with a relative risk reduction of 65%, the resulting ICERs were associated with costs per QALYs of £126,000

and £95,000, respectively, at a price difference of £600 and £47,000 and £25,000, respectively, at a price difference of £300.

4.3.13 Reflecting the testimony of the clinical specialists and the comments received during consultation, the Committee noted the small differences in the key parameters between those that the Committee had previously agreed and those suggested by BCIS. The Committee noted that the ICERs resulting from using the parameter values suggested by the BCIS into the Assessment Group's model for a price difference of £600 were associated with costs per QALYs of approximately: £111,000 for all patients; £51,000 for long lesions; £53,000 for diabetes; and £59,000 for small vessels. For a price difference of £300 the resulting ICERs were associated with costs per QALYs below £5000 for patients with small vessels and long lesions. The Committee was not persuaded that all of the parameter values suggested by BCIS were plausible, but it agreed that the percentages of elective and non-elective patients at presentation should be 57% elective to 43% non-elective. The Committee noted that taking account of this assumption would decrease the ICERs seen in the updated analysis for long lesions and small vessels (see 4.3.12), which means that, at a price difference of £300, the plausible ICERs would be much lower than cost per QALYs of £47,000 and £25,000, respectively.

4.3.14 The Committee agreed that DESs could not be considered a cost-effective use of NHS resources at a price difference of £600. After considering the alternative parameter values presented by the Assessment Group and BCIS, the Committee concluded that on balance at a price difference between DESs and BMSs of not more than £300, DESs could be considered a cost effective option in patients with small vessels and long lesions, and should be recommended for use in these patient groups. The Committee's

decision was based on the understanding that the mean absolute price of a BMS was £131 and that procurement arrangements for DESs at a price difference of £300 was already in place within many NHS regions and achievable across the NHS as a whole.

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals. NICE recognises that many NHS organisations already have contracts in place and therefore would not be able to implement the recommendations contained within the FAD immediately. However as contracts come up for renewal NHS organisations would be expected to use relevant contracting arrangements to ensure that DESs are obtained in line with the recommendations in section 1.1.

5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

NICE recognises that many NHS organisations already have contracts in place and therefore would not be able to implement the recommendations contained within the FAD immediately. However as contracts come up for renewal NHS organisations would be expected to use relevant contracting arrangements to ensure that DESs are obtained in line with the recommendations in section 1.1.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives which support this locally.
- Audit criteria to monitor local practice.

6 Recommendations for further research

6.1 The Committee noted that there are a number of trials under way comparing the clinical effectiveness of DESs with their equivalent BMS and/or with other DESs at longer follow-up periods.

7 Related NICE guidance

This technology appraisal is a part-review of technology appraisal guidance 71, and focuses on DESs only.

The use of coronary artery stents. NICE technology appraisal guidance 71 (2003). Available from: www.nice.org.uk/TA071

Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome. NICE technology appraisal guidance 80 (2005). Available from: http://www.nice.org.uk/TA080

8 Review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in April 2009.

David Barnett
Chair, Appraisal Committee
January 2008

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Darren Ashcroft

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Dr Jeffrey Aronson

Reader in Clinical Pharmacology, University Department of Clinical Pharmacology, Radcliffe Infirmary

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Mr Brian Buckley

Lay Member

Professor Stirling Bryan

Director, Health Economics Facility, University of Birmingham

Professor John Cairns

Public Health and Policy, London School of Hygiene and Tropical Medicine

Professor Mike Campbell

Statistician, University of Sheffield

Professor David Chadwick

Professor of Neurology, Walton Centre for Neurology and Neurosurgery

Dr Mark Chakravarty

Industry Member

Dr Peter I Clark

Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Merseyside

Dr Mike Davies

Consultant Physician, University Department of Medicine and Metabolism, Manchester Royal Infirmary

Professor Jack Dowie

Health Economist, London School of Hygiene

Ms Lynn Field

Nurse Director, Pan Birmingham Cancer Network

Professor Christopher Fowler

Professor of Surgical Education and Honorary Consultant Urologist

Mrs Barbara Gerggains

Lay Member

Dr Fergus Gleeson

Consultant Radiologist, The Churchill Hospital, Oxford

Ms Sally Gooch

Independent Healthcare Consultant

Mr Sanjay Gupta

Stroke Services Manager, Basildon and Thurrock University Hospitals NHS Trust

Professor Philip Home

Professor of Diabetes Medicine, University of Newcastle upon Tyne

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Professor Peter Jones

Professor of Statistics and Dean, Faculty of Natural Sciences, Keele University

Dr Mike Laker

Medical Director, Newcastle Hospitals NHS Trust

Dr George Levvy

Chief Executive, Motor Neurone Disease Association, Northampton

Ms Rachel Lewis

Nurse Advisor to the Department of Health

Mr Terence Lewis

Lay Member

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queen's University Belfast

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Neil Milner

General Practitioner, Sheffield

Dr Ruairidh Milne

Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Rosalind Ramsay

Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital

Dr Stephen Saltissi

Consultant Physician, The Royal Liverpool University Hospital

Mr Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Mr Roderick Smith

Director of Finance, Adur, Arun and Worthing PCT

Mr Cliff Snelling

Lay Member

Dr Ken Stein

Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens (Chair)

Professor of Public Health, University of Birmingham

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Joanna Richardson

Technical Lead

Dr Elisabeth George

Technical Adviser

Reetan Patel

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Liverpool Reviews and Implementation Group, University of Liverpool.

- Hill R, Boland A, Dickson R, et al. Drug-eluting stents: a systematc review and economic evaluation, November 2005

B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I and II were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

- Abbott Vascular Devices Ltd
- Biotronik UK Ltd
- Boston Scientific
- Cordis Corporation
- Guidant
- Kiwimed Ltd
- Medtronic AVE
- Sorin Biomedica UK Ltd

II Professional/specialist and patient/carer groups:

- British Association for Nursing in Cardiac Care
- British Cardiac Society
- British Cardiovascular Intervention Society
- British Heart Foundation
- Royal College of Nursing
- Royal College of Physicians
- Royal College of Physicians of Edinburgh
- Pharmaceutical Society of Great Britain
- Society for Cardiological Science and Technology
- Society of Cardiothoracic Surgeons of Great Britain and Ireland
- Action Heart
- British Cardiac Patients Association
- Coronary Prevention Group
- HEART UK

- National Heart Forum
- Heart Care Partnership (UK)

III Other consultees

- Barnet PCT
- Central Derby PCT
- Department of Health
- Welsh Assembly Government

IV Commentator organisations (without the right of appeal):

- Association of British Health-Care Industries (ABHI)
- British Cardiovascular Industry Association (BCIA)
- Board of Community Health Councils in Wales
- British National Formulary
- EUCOMED
- Medicines and Healthcare products Regulatory Agency (MHRA)
- National Collaborating Centre for Acute Care
- National Collaborating Centre for Chronic Conditions
- National Public Health Service for Wales
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland

C The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on drug-eluting stents by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Mrs Jill Bishop, Cardiac Catheter Theatre Manager, nominated by the British Association of Nursing in Cardiac Care – clinical specialist (ttended in 2006 and 2007).
- Mr Ron Box, nominated by theHeart Care Partnership – patient expert (attended in 2006 and 2007).
- Dr Martyn Thomas, Consultant Cardiologist, nominated by the British Cardiovascular Intervention Society – clinical specialist (attended in 2006 and 2007).

- Dr AH Gershlick, Consultant Cardiologist, nominated by the British Heart Foundation and the British Cardiac Society – clinical specialist (ttended in 2006 and 2007).
- Dr Keith Oldroyd, Consultant Cardiologist, nominated by NHS Quality Improvement Scotland – clinical specialist (attended in 2006 and 2007).
- Rev Dan Paterson, nominated by the Heart Care Partnership – patient expert (attended in 2006).
- Ms Liz Clarke, nominated by the Heart Care Partnership– patient expert (attended in 2007).