

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Final Appraisal Determination

Coronary artery stents

1 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.

2 Clinical need and practice

- 2.1 CAD is by far the most common cause of heart disease, resulting from the narrowing of coronary arteries ('stenosis') caused by deposition of atherosclerotic plaque. 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.
- 2.2 CAD causes about 2100 deaths annually per million of the population in England and Wales (about 110,000 deaths in total), one of the highest rates in the world. CAD is also the cause of considerable morbidity and loss of ability to lead a normal life. Approximately 1.4 million people in England and Wales suffer from angina, the most common form of such morbidity.
- 2.3 Stenotic lesions are categorised as A, B1, B2 and C. A denotes a relatively short (less than 10 mm) and easily accessible lesion. C denotes lesions that: are relatively long (greater than 20 mm); may be less accessible, tortuous and/or have side branches; and may be totally occluded.
- 2.4 CAD may affect one or more arteries, which may be of different calibres. Occlusion may be partial or total.
- 2.5 The symptoms and health risks that are 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).
- 2.6 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, so-called balloon angioplasty, or percutaneous transluminal coronary angioplasty (PTCA), involves a non-

surgical widening from within the artery using a balloon catheter. When inflated, the balloon increases the calibre of the artery.

- 2.7 Recently, most PTCA procedures have involved the use of stents. Stents are thin wire-mesh structures that act as permanent prosthetic linings to keep the artery inflated and maintain its patency. PCI is a generic term to encompass PTCA with or without adjunct techniques such as stenting.
- 2.8 For disease in a single artery, PCI with a stent has been the more frequent treatment; for disease in two arteries, patient numbers for PCI with a stent and CABG have been similar; and for more than two affected arteries, CABG has been used much more frequently.
- 2.9 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 eliminate recoil of the artery. The two subsequent problems, mostly arising during the first 6 months, are contraction of the adventitia secondary to an injury reaction (3–6 months), and proliferation of smooth muscle cells within the arterial wall (4–6 months). A repeat procedure is consequently required in approximately 20% of patients with simple lesions. This rate of reintervention is much higher (up to 50%) for arteries of small calibre, saphenous vein grafts, long lesions, total occlusions and in people with diabetes.
- 2.10 Recent advances in stent technology have reduced some of the problems of restenosis, as well as lowering the cost of stents. In addition, the use of antiplatelet drugs and other therapeutic strategies to prevent thrombosis have improved long-term outcomes.
- 2.11 One of the main criteria for assessing the clinical effectiveness of PTCA with stents compared with standard PTCA (without stents) is the ability to reduce the incidence of subsequent attacks of angina as well as major adverse

coronary events (MACE), which include death, MI and the need for further revascularisation procedures (CABG or repeat PCI).

- 2.12 Patients for whom both a CABG and a PCI involving stenting are appropriate techniques would, other things being equal, choose PCI in almost all cases, even though the chances of restenosis are greater. This is because the procedure is less invasive, has a lower chance of death during the operation, and involves a much shorter and less painful recuperation time.
- 2.13 Approximately 39,000 PCI procedures were undertaken in the UK in 2001, equating to 663 per million of the population – a rate that had increased at an average of 14% per year over the previous 10 years. The rate for the UK remains below that of the European Union (EU) average, which exceeds 1000 per million of the population.
- 2.14 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 85% in 2001.
- 2.15 The number of CABG procedures performed each year in the UK has increased from 15,700 in 1991 to 24,700 in 1999/2000, or from 292 to 464 per million of the population. The rate of increase has slowed since the first half of the 1990s.
- 2.16 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). At current growth rates, the combined target will be reached by about 2005.

3 The technology

- 3.1 This appraisal is both a review of earlier NICE guidance (*NICE Technology Appraisal Guidance No. 4*; see Section 8) covering BMS, and a new appraisal of DES. BMS have already been described in Section 2 as part of

existing practice. The rest of this section is devoted to methods of reducing restenosis and, in particular, to the use of DES as a means of achieving this.

- 3.2 Methods of reducing restenosis include: coating the stent with an appropriate drug; introducing an emitter of radioactive particles at the stenting site (brachytherapy); and creating the slow release of a drug from the stent, making the stent 'drug-eluting'. For DES, the drug is held temporarily in place within a polymer 'painted' onto the metallic stent. 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); this technology, and brachytherapy, are outside the scope of this appraisal.
- 3.3 Although a number of drugs have been tested in the context of DES, only three have been granted CE (Conformite Europeene) marking for use within EU countries: paclitaxel, which inhibits cell division, elutes from the Taxus stent; sirolimus (previously known as rapamycin), an immunosuppressive agent that reduces inflammation, elutes from the Cypher stent; and dexamethasone, a synthetic adrenocortical steroid that reduces inflammation, elutes from the BiodivYsio stent. 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. However, as yet, studies directly comparing different DES have not been performed.
- 3.4 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 (IFU).
- 3.5 List prices for both BMS and DES differ between manufacturers, and some manufacturers produce more than one stent in each class, at different prices. Prices for BMS range from about £600 to £900 and for DES from about £1300 to £1500 per stent. For bare-metal and drug-eluting stents that are the same apart from their drug-eluting properties, the difference in cost

is about £500 to £600. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

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

4.1 Clinical effectiveness

4.1.1 The Assessment Report presents three sets of comparison: PCI without stents versus PCI with BMS; PCI with BMS versus CABG; and BMS versus DES.

4.1.2 Assessment of the relative clinical effectiveness of stents considers the likelihood of restenosis discovered on follow-up and the requirement for repeat intervention (revascularisation). Repeat intervention may occur: (i) because of a requirement of the trial protocol, specifying a repeat angiographic examination at a predetermined interval (so-called 'protocol-driven' reintervention); or (ii) following a recurrence of symptomatic angina in the patient (that is, 'clinically-driven' reintervention). The frequency of protocol-driven reinterventions is higher than that of clinically driven reinterventions, because angiography is usually mandatory at 6 months in the trial protocol whereas in clinical practice it is carried out only after recurrence of symptoms. Accordingly, the absolute differences observed between the treatment and control arms of clinical trials are likely to be higher than would be expected to occur in clinical practice.

PCI with BMS versus PCI (without stents)

4.1.3 Fifty randomised controlled trials (RCTs) were analysed comparing the use of PCI with BMS versus PCI without stents. Because of differences in, and completeness of, the reporting of these trials, the number of trials on which meta-analyses are based is a subset of these 50 trials. In a meta-analysis comprising 12 trials involving 5700 patients with non-specified ischaemic

heart disease, where a composite endpoint of revascularisation, MI or death (MACE) was reported, the MACE rate was statistically significantly different at 6 months' follow-up: 23.0% for the PCI without stents group versus 15.4% for the PCI with BMS group, with an odds ratio (OR) of 1.66 (95% confidence interval [CI], 1.45 to 1.90). The difference was smaller after 12 months' follow-up but still statistically significant. Of the above 12 trials, seven, involving 3500 patients, reported data for 12-months' follow-up: the MACE rate was 22.0% for the PCI without stents group versus 18.9% for the PCI with stents group (OR 1.33; 95% CI, 1.12 to 1.58).

- 4.1.4 Differences in MACE rates were due almost entirely to differences in the rate of restenosis. For the outcomes of acute MI and deaths, for which individual trials were not powered to detect statistically significant differences, meta-analyses showed that while both of these sets of events occurred less frequently in those treated with PCI using BMS than in PCI without stents, in neither case was the result statistically significant.
- 4.1.5 Overall, the results of the RCTs showed that the use of PCI with BMS has significant advantages over the use of PCI without stents, in terms of lower rates of restenosis at 6 and 12 months.
- 4.1.6 According to the joint professional submission, the likelihood of restenosis is greater in small vessels, because a given tissue regrowth will have a greater proportionate effect in a vessel of smaller calibre. In eight out of nine studies that looked at vessels of a small calibre (less than 3 mm), restenosis rates were lower in the BMS arm than in the PCI without stent arm, and in two of these studies, the difference was statistically significant. A meta-analysis showed a statistically significant advantage for PCI with BMS. However, restenosis rates were still high in this group.
- 4.1.7 According to the joint professional submission, the restenosis rate increased by an estimated 8 to 13 percentage points with every 10-mm increase in the length of BMS required.

PCI with BMS versus CABG

- 4.1.8 There were six RCTs in the meta-analysis. None of the trials involved a DES.
- 4.1.9 For single-vessel disease, the MACE rate was statistically significantly different at 6 months' follow-up in two trials involving a total of 300 patients: 12.6% for CABG versus 25.8% for PCI with BMS (OR 0.41; 95% CI, 0.22 to 0.74). The higher MACE rate for PCI with BMS reflects the higher rate of restenosis following this procedure.
- 4.1.10 For multiple-vessel disease, the MACE rate was statistically significantly different at 12 months' follow-up in two trials involving a total of 2300 patients: 12.3% for CABG versus 24.5% for PCI with BMS (OR 0.43; 95% CI, 0.34 to 0.54).
- 4.1.11 At 36 days' follow-up, the rate of acute MIs was statistically significantly lower following PCI with BMS, but the difference between the two procedures was not statistically significant at 6 and 12 months.
- 4.1.12 No statistically significant differences were reported for deaths, because the trials were not powered to detect differences in these uncommon events.

BMS versus DES

- 4.1.13 There were 12 RCTs comparing BMS with DES. Of these, seven involved paclitaxel, four sirolimus, one everolimus and one actinomycin stents. The first two sets of trials (paclitaxel and sirolimus) are considered separately below, and the last two trials have not been considered here because they involved products that have not been granted CE marking. No RCT for the third DES with a CE mark (eluting dexamethasone) has yet been reported.

4.1.14 Paclitaxel-eluting stents

- 4.1.14.1 Based on four trials with a paclitaxel DES (Taxus and non-CE-marked stents), involving almost 1000 patients, the MACE rate for PCIs using a

paclitaxel DES was not statistically significantly lower at 36 days or at 1 year, but it was statistically significantly lower at 6 months: 7.4% for DES versus 15.4% for BMS (OR 0.48; 95% CI, 0.31 to 0.73). From a random effects model (which takes account of heterogeneity of results between trials), the 6-month data for the MACE rate were not statistically significant (OR 0.58; 95% CI, 0.24 to 1.43). Most of the MACE events refer to restenosis. However, the two trials of the Taxus DES stent (which has a CE mark), involving 583 patients, yielded a statistically significantly lower MACE rate at 6 months: 7.2% for DES versus 18.4% for BMS (OR 0.35; 95% CI, 0.21 to 0.59); and at 12 months: 9.7% for DES versus 20.5% for BMS (OR 0.41; 95% CI, 0.25 to 0.67).

4.1.14.2 Paclitaxel DES have not been demonstrated to show an advantage over BMS in either mortality or prevention of MI. However, in a series of trials of the Taxus stent (the TAXUS trials), the MI rate for PCIs using a paclitaxel DES was statistically significantly lower at 6 months: 1.7% for DES versus 5.9% for BMS (OR 0.35; 95% CI, 0.12 to 0.99). The statistical significance of this result was not maintained at 12 months: 2.8% for DES versus 5.8% for BMS (OR 0.56; 95% CI, 0.23 to 1.37).

4.1.14.3 Multivariate analysis of data from the TAXUS trials shows that once the effect of small-calibre arteries and long lesions has been allowed for, the difference in performance between DES and BMS for people with diabetes is not statistically significantly different from that of people without diabetes.

4.1.15 Sirolimus-eluting stents

4.1.15.1 The MACE rate for PCIs using a sirolimus DES (Cypher and non-CE-marked stents) was not statistically significantly lower at 36 days, but it was lower at 9 months and at 1 year; at 9 months the rate was 7.4% for DES versus 18.9% for BMS (OR 0.34; 95% CI, 0.23 to 0.47), and at 1 year it was 7.8% for DES versus 21.8% for BMS (OR 0.30; 95% CI, 0.22 to 0.43). Most of the MACE events refer to restenosis. The trials of the Cypher sirolimus DES (which has a CE mark) showed a statistically significantly lower MACE

rate compared with trials of BMS at 9 months (OR 0.32; 95% CI, 0.16 to 0.45), 12 months (OR 0.31; 95% CI, 0.22 to 0.43), and 24 months (OR 0.46; 95% CI, 0.22 to 0.97).

4.1.15.2 Sirolimus-eluting stents in general have not been shown to have either a mortality or acute MI advantage over BMS in trials, and neither do the DES within the subset of Cypher stent trials.

4.1.15.3 According to the joint professional submission, in larger arteries, PCIs using a sirolimus DES have shown very low rates of restenosis, approaching zero. In small-calibre arteries, PCIs using a sirolimus DES have shown lower rates of restenosis than PCIs using a BMS (for example, 7% versus 20% restenosis at 9 months in the SIRIUS trial for vessels of mean calibre 2.3 mm).

4.1.15.4 In patients with diabetes and those with longer lesions, rates of restenosis following PCIs using a sirolimus DES have been higher than those of the 'average' patient, but still much lower than following PCIs using the BMS control. Subsequent post hoc subgroup analysis from one of the manufacturers from a trial involving patients who received a DES was considered by the Committee. The analysis compared the restenosis rate for people with diabetes with that for people without diabetes. It showed that the restenosis rate for those with diabetes as a whole was higher than for the non-diabetes group, but the difference was not statistically significant. In addition, the analysis did not control for artery calibre or length.

4.1.15.5 According to the joint professional submission, for every 10 mm increase in the length of the stent, the difference in restenosis rate between a Cypher DES and Cypher BMS increased by between 1 and 1.6 percentage points.

4.2 Cost effectiveness

4.2.1 The most recent evidence of cost effectiveness comes from models supplied by four manufacturers and one from the Assessment Group, including an addendum. The manufacturer models show that PCIs with a BMS are cost

effective compared with PCIs without stents and also compared with CABG. However, these models are relatively short-run, ranging from 6 months to 2 years. The manufacturers of the Cypher and of the Taxus stents each provided a model which examined the cost effectiveness of their own DES compared with the corresponding BMS. Each of these models showed that the DES is cost effective compared with the corresponding BMS. The Assessment Group's model showed that the Cypher and Taxus stents, as a group, are cost effective compared with BMS.

PCI with BMS versus PCI without stents

- 4.2.2 For patients with moderate or severe angina, PCI has been shown to be a cost-effective alternative to conventional medical treatment. Since the previous appraisal (by the Institute in 2000) of PCI with BMS versus PCI without stents, several further studies have demonstrated the cost effectiveness of stents in a number of patient populations and clinical settings, including elective stenting and stenting immediately following an acute MI.

PCI with BMS versus CABG

- 4.2.3 Comparative data on PCI using BMS versus CABG are available for only 3 years of follow-up. There are no data beyond 3 years and little data from years 2 to 3. The best available data are up to 2 years. Long-term models are needed to determine cost effectiveness because most patients who have stents fitted live longer than 5 years, and it is impossible to give a proper answer to the question of cost effectiveness by taking a short-term perspective.
- 4.2.4 The Assessment Group's model extrapolates the results to 5 years based on the currently available 3-year data. However, the extrapolation is very sensitive to the functional form chosen for the survival curve of patients who have undergone either stenting or CABG.

- 4.2.5 The benefits/disadvantages of PCIs using BMS compared with CABG, in terms of quality-of-life differences, derive from stents being a less invasive procedure on one hand but having higher rates of restenosis on the other. Neither of these two effects, in terms of quality-adjusted life years (QALYs), has been estimated to be very great, which means that if there was any appreciable difference in mortality between the two therapies, this factor would determine which of the therapies had the greater benefits. However, none of the meta-analyses from the trials shows any mortality benefit from PCI with either BMS or DES compared with CABG in the first 2 years. Hence, all the measurable benefits from using stents rather than CABG derive from an increase in the quality of life. Since stenting is considerably cheaper than CABG, under the 2-year models, it is therefore more cost effective, and indeed, dominates CABG.
- 4.2.6 The Assessment Group's model, however, estimated a survival benefit for CABG over PCI using BMS of the order of 0.05 QALYs per patient, after the model was extrapolated to 5 years. This benefit would be enough to make CABG the preferred technology (in terms of both clinical and cost effectiveness) for patients who were candidates for both stents and CABG. The clinician consultees to the appraisal process, however, vigorously challenged this, stating that previous studies had not reached this conclusion.

BMS versus DES

- 4.2.7 The quality-of-life component of the QALY differences between BMS and DES is small, because it relates only to the extent of the differences in restenosis rates. No differences in mortality have been demonstrated. Thus, the greatest benefits of DES over BMS will occur for categories of patients for whom the absolute differences in restenosis rates are greatest.
- 4.2.8 The addendum to the Assessment Report showed that, for single-vessel disease, PCI using a DES was estimated to be cost-saving compared with PCI using a BMS at 12 months for patients with diabetes and long lesions;

the estimated cost per QALY for patients without diabetes and long lesions was £15,000 and, for all patients with narrow vessels, it was £16,000. These estimates were derived from patient-level data derived from the TAXUS II trial. For the total population of patients with single-vessel disease, the cost per QALY was £94,000. This estimate was derived from registry data.

4.2.9 These estimates are sensitive to five factors:

- the percentage point reduction in the risk of revascularisation
- the price differential between BMS and DES
- the proportion of repeat interventions needing CABG
- the disutility caused by recurrent symptoms
- the average waiting time for repeat intervention.

4.2.10 There are no RCT data for two-vessel disease. The estimated incremental cost per QALY for two-vessel disease gained from PCI using a DES compared with PCI using a BMS for all non-diabetic patients is £195,000. This estimate is derived from registry data.

4.3 *Consideration of the evidence*

4.3.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of PCIs using a BMS and DES, having considered evidence on the nature of the condition and the value placed by users on the benefits of BMS and DES from clinical experts and those who represent patients with angina. It was also mindful of the need to ensure that its advice took account of the efficient use of NHS resources.

PCI with BMS versus PCI without stents

4.3.2 The Committee considered that no new evidence had been found since the previous appraisal to change its view that where PCI is being undertaken, the use of stents is likely to be both clinically and cost effective.

BMS versus DES

- 4.3.3 The Committee noted that there were no head-to-head trials of the sirolimus-eluting Cypher stent and the paclitaxel-eluting Taxus stent, and the clinical experts advised that there was no evidence that would allow them to favour one of these drug-eluting agents over the other.
- 4.3.4 The Committee considered that, for single-vessel disease, restenosis rates were in general low using a BMS in the majority of patients requiring PCI, and that, therefore, the routine use of a DES was not justified. However, this was not the case for patients presenting with either small-calibre arteries (< 3 mm) or long lesions (> 15 mm); in these patients, the risk of restenosis using a BMS was considerably higher, and the absolute reduction in restenosis rates would justify the use of a DES.
- 4.3.5 The Committee considered the risk factors predicting the likelihood of higher rates of restenosis after the use of a BMS. It was persuaded that the main determinants of risk were the target vessel calibre and the complexity of the arterial lesion, in particular the length of the stenosis. It recognised that the combination of small-vessel disease and long lesions was particularly prevalent in patients with CAD who also had diabetes. Whilst, in general, patients with diabetes have higher restenosis rates than those without diabetes following PCI with a BMS, the Review Group's analysis indicated that these higher rates arise predominantly from the fact that a much higher proportion of patients with diabetes needing PCI have disease of small-calibre arteries and long lesions than is true for the general population of patients requiring PCI.
- 4.3.6 The Committee discussed how the RCTs comparing BMS with DES relate to current clinical practice. In particular, in the trials, the decision to re-intervene following an initial PCI with stent procedure was often made on the basis of protocol-driven angiographic examinations at certain fixed times (for example at 6 months), rather than in response to the recurrence of clinical symptoms. It is likely that the trials would encourage reintervention that

might not be required in clinical practice, where routine re-angiography is not usual. Thus, the Committee was aware that the difference in restenosis rates between BMS and DES identified in the trials could overestimate the extent of the difference that would actually be seen in clinical practice. The addendum to the Assessment Report attempted to correct for this potential overestimate of the benefit of DES versus BMS. The Committee decided that, whether or not the correction factor was applied, the guidance in Section 1 would not be materially affected.

- 4.3.7 The Committee considered PCI with a DES for more than one target vessel in a person with symptomatic coronary disease. It was aware that the evidence from the RCTs relates to the use of DES in single-vessel disease. However, the experts indicated that treatment of more than one vessel in an individual patient during PCI might be required. This is because, despite additional investigations, it is frequently difficult to determine which of several vessels identified at angiography is the most likely cause of the patient's symptoms. The Committee considered that the risk of a need for future intervention following an initial PCI is likely to be dependent on the degree of stenosis of any of the affected vessels. The appropriateness of a DES or BMS for each diseased artery in turn would therefore depend on considering the artery's characteristics in isolation from those of other diseased arteries. It was therefore persuaded that planned treatment of more than one vessel in a single patient should be based on the requirements laid out in the guidance for a single vessel.
- 4.3.8 The Committee discussed the use of DES with regard to coronary artery vein grafts and for more complex situations such as bifurcation lesions, but noted that there was no robust evidence in this area at present.
- 4.3.9 The Committee noted statements from some manufacturers that restenosis rates using a BMS of recent design were low compared with those of other BMS, and were comparable with those of the CE-marked DES. The cost-effectiveness calculations were not based on evidence comparing these

stents with other BMS or with DES in head-to-head trials. The Committee considered that this evidence was not sufficient to affect its recommendations for guidance in Section 1. It would, however, wish to include further evidence on new developments in BMS design as part of the next review of the use of coronary stents.

PCI with BMS versus CABG

- 4.3.10 Having reviewed the Assessment Group's model and the submissions from manufacturers, together with the views of cardiologist consultees, the Committee concluded that the guidance offered in 2000 should be maintained. While it was clear that models with outcomes up to 2 years favoured stents in terms of cost effectiveness, the conclusions to be drawn from longer-term models depended critically on whether a survival advantage accrues to CABG. The Committee concluded that no convincing case had been made on this matter. Its considerations ranged over what may happen to patients requiring one or other of these procedures in different age ranges, and whether the conclusions about the most appropriate procedure would be the same for younger patients (who are more likely to need a repeat procedure) as for older ones. In none of the cases considered was there sufficient evidence of effect to be able to reach any conclusion.

5 Recommendations for further research

- 5.1 Ongoing trials for paclitaxel-eluting stents include TAXUS I (follow-up of a small initial study of slow-release formulation versus BMS in patients with either previously-untreated lesions or restenosis), TAXUS II (follow-up of a larger study of both slow- and moderate-release formulations versus BMS in patients with previously-untreated lesions), TAXUS IV (a large trial of slow-release formulation versus BMS stratified by presence or absence of diabetes and by vessel diameter), TAXUS V (focussing on small vessels, long lesions, bifurcations and in-stent restenosis) and TAXUS VI (moderate

release for long lesions). For sirolimus-eluting stents, on-going trials include RAVEL (small-diameter vessels), SIRIUS (high risk for cardiovascular disease progression and restenosis due to the lesion type, lesion length, vessel diameter, high incidence of diabetes, exposure to multiple stent implantation and use of overlapping stents) and E-SIRIUS (previously-untreated single vessels of diameter 2.5 to 3 mm and for lesions between 15 and 32 mm in length); and FUTURE (previously-untreated vessels between 2.75 and 4 mm, less than 28 mm long) for everolimus-eluting stents. REALITY, a head-to-head trial of the Cypher sirolimus DES and Taxus paclitaxel DES, is under way.

- 5.2 Until now, trials have been restricted to single-artery studies for the sake of simplicity and ease of interpretation. Extrapolation of results to more than one artery critically depends on untested assumptions. Randomised controlled trials (RCTs) of the use of DES in more than one artery concurrently are therefore required, in order to confirm or refute the appropriateness of the extrapolations used in the modelling.
- 5.3 To compare long-term outcomes, particularly with respect to stents against CABG, much longer trial follow-ups are required.
- 5.4 New BMS designs should be tested against current BMS and DES designs.
- 5.5 Head-to-head RCTs of those DES that have been CE marked and have been shown to be clinically superior to the corresponding BMS are required.
- 5.6 Studies to determine whether diabetes is a risk factor for increased rate of restenosis following PCI, independent of lesion length and artery calibre, are required. Much of this work could be performed by an analysis of patient-level data taken from trials already conducted.

6 Implications for the NHS

- 6.1 The financial impact of using DES depends on the proportion of stented arteries that are narrow or contain long lesions offset against the increased

capacity of the system resulting from a decrease in procedures to manage restenosis . Although the total number of arteries requiring a DES in the UK is unknown, it could be as high as one-third of all stents. Based on this proportion, the additional cost of DES without offsets would be between £6 and £7.2 million per year, assuming the use of about 12,000 DES stents costing an additional £500 to £600 each.

- 6.2 If the use of drug eluting stents reduced the restenosis rate by about 10 percentage points then the additional capacity generated could be used to increase the number of new stent procedures. This would have the effect of offsetting the cost of the BMS by about £4 million per year. Such cost savings, however, will often only be realised in the form of additional capacity.

7 Implementation and audit

- 7.1 Clinicians carrying out PCIs should review their current practice and policies to take account of the guidance set out in Section 1.
- 7.2 Local guidelines, protocols or care pathways that refer to PCIs and/or stents should incorporate the guidance.
- 7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.
- 7.3.1 Stents are used routinely in PCIs carried out in patients with stable or unstable angina or acute MI.
- 7.3.2 A Cypher or a Taxus stent is used in PCI for people with symptomatic CAD in whom the target artery is less than 3 mm in calibre or in which the lesion to be stented is longer than 15 mm, except if an individual has had an MI in the preceding 24 hours or has angiographic evidence of thrombus in the target artery. If more than one artery is to have a stent inserted, the same considerations apply to each artery.

- 7.4 Local clinical audits on the care of patients with CAD also could include measurement of compliance with national standards, including standards in the National Service Framework for coronary heart disease.

8 Related guidance

9 Review of guidance

- 9.1 The review date for this appraisal refers to the month and year in which the Guidance Executive will consider whether there is sufficient new evidence on the technologies to inform an update of the guidance. .

- 9.2 The guidance on this technology will be reviewed in October 2004.

Andrew Dillon

Chief Executive

August 2003

Appendix A. Appraisal Committee members and NICE project team.

A. Appraisal Committee members

NOTE 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 twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. 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.

Dr A E Ades

MRC Senior Scientist, MRC Health Services Research Collaboration, University of Bristol

Professor Ron Akehurst

Dean, School of Health Related Research, University of Sheffield

Dr Tom Aslan

General Practitioner, Stockwell, London

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Dr Sheila Bird

MRC Biostatistics Unit, Cambridge

Professor Rosamund Bryar

Professor of Community & Primary Care Nursing, St Bartholomew's School of Nursing & Midwifery, London

Dr Karl Claxton

Health Economist, University of York

Dr Richard Cookson

Senior Lecturer, Health Economics, School of Health Policy and Practice, University of East Anglia, Norwich

Professor Terry Feest

Clinical Director & Consultant Nephrologist, Richard Bright Renal Unit, & Chair of UK Renal Registry, Bristol

Professor Gary A Ford

Professor of Pharmacology of Old Age/Consultant Physician, Newcastle upon Tyne Hospitals NHS Trust

Professor John Geddes

Professor of Epidemiological Psychiatry
University of Oxford

Ms Bethan George

Interface Liaison Pharmacist, Tower Hamlets PCT and Royal London Hospital, Whitechapel

Dr Trevor Gibbs

Head, Global Clinical Safety & Pharmacovigilance, GlaxoSmithKline, Greenford

Mr John Goulston

Director of Finance, Barts and The London NHS Trust

Professor Philip Home

Professor of Diabetes Medicine, University of Newcastle upon Tyne

Dr Terry John

General Practitioner, The Firs, London

Mr Muntzer Mughal

Consultant Surgeon, Lancashire Teaching Hospitals NHS Trust, Chorley

Judith Paget

Chief Executive, Caerphilly Local Health Board, Torfaen

Mr James Partridge

Lay Representative; Chief Executive, Changing Faces, London

Mrs Kathryn Roberts

Nurse Practitioner, Hyde, Cheshire

Ms Anne Smith

Lay Representative; Trustee, Long-Term Medical Conditions Alliance

Professor Andrew Stevens (Vice-Chair)

Professor of Public Health, University of Birmingham

Dr Cathryn Thomas

General Practitioner, & Senior Lecturer, Department of Primary Care & General Practice, University of Birmingham

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Dr David Winfield

Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Dr Alastair Fischer

Technical Lead, NICE project team

Kathleen Dalby

Project Manager, NICE project team

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.

- *Coronary artery stents: rapid systematic review & economic evaluation*, February 2003
- *Assessment report – addendum A – data no longer confidential*, June 2003
- *Assessment report – addendum B - further analysis requested by the Appraisal Committee*, May 2003

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturer/sponsors:

- Abbott Vascular Devices Ltd
- Bard Ltd
- Biotronik UK Ltd
- Boston Scientific Ltd
- Cordis
- Guidant Ltd
- Jomed UK Ltd
- Kimal
- Medtronic Ltd
- Sorin Biomedica UK Ltd
- Terumo UK
- WL Gore & Associates

II Professional/specialist and patient/carer groups:

- Action Heart
- Association of British Health-Care Industries
- British Cardiac Industry Association
- British Cardiovascular Intervention Society
- British Cardiac Patients Association
- British Cardiac Society
- British Cardiovascular Industry Association
- British Heart Foundation
- Department of Health
- EUCOMED
- Heart UK
- National Collaborating Centre for Chronic Conditions
- NHS Quality Improvement Scotland
- Royal College of Nursing
- Royal College of Physicians
- Sthwark PCT & South East Public Health Network
- Welsh Assembly Government

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on coronary artery stents by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Mark de Belder, Assistant Secretary, British Cardiac Society & Consultant Cardiologist, The James Cook University Hospital, Middlesbrough

- Dr Derek Connolly, Consultant Cardiologist, Heart UK & Sandwell and West Birmingham Hospitals NHS Trust AND Honorary Clinical Senior Lecturer, University of Birmingham
- Dr. A. H. Gershlick, Consultant Cardiologist, Department of Cardiology, Glenfield Hospital NHS Trust, Leicester
- Mr S Livesey, Consultant Cardiac Surgeon, Southampton General Hospital
- Professor M Rothman, Consultant Cardiologist, London Chest Hospital

Appendix C. Detail on criteria for audit of the use of coronary artery stents

Possible objectives for an audit

An audit could be carried out to ensure that stents are being used appropriately in patients undergoing PCIs.

Local clinical audits could also confirm that PCI is the clinically appropriate procedure for patients included in the audit.

Possible patients to be included in the audit

An audit could include all patients having a PCI for stable or unstable angina, acute MI or symptomatic CAD in a suitable time period, for example, 3 months.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of stents are as follows.

Criterion	Standard	Exception	Definition of terms
1. Stents are used when a PCI is performed in an individual having any of the following: a. stable angina or b. unstable angina or c. acute MI	100% of individuals having a PCI for stable or unstable angina or acute MI	None	Clinicians will need to agree locally on any exceptions for audit purposes.
2. A Cypher or a Taxus stent is used in a PCI for an individual with symptomatic CAD when either of the following occurs: a. the target artery is < 3mm in calibre or b. the lesion to be stented is longer than 15 mm	100% of individuals having a PCI for symptomatic CAD	A. The individual has had an MI in the preceding 24 hours B. The individual has angiographic evidence of thrombus in the target artery	Clinicians will need to agree locally on any other exceptions for audit purposes.

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **criteria** plus number of patients who meet any **exception** listed}{\text{Number of patients to whom the **measure** applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.