

Drug-Eluting Stents

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

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Executive summary

The procedure

Drug-eluting stents are used in the treatment of coronary heart disease. They are inserted into coronary arteries narrowed by atherosclerosis by a percutaneous procedure using a catheter loaded with the stent and an inflatable balloon. The balloon is inflated to widen the lumen of the target vessel (a procedure known as angioplasty) and then the stent is inserted and expanded to scaffold the vessel to improve lumen patency and arterial blood flow. The stent is coated with a drug that is gradually released into the local tissue to inhibit cell proliferation. The two main types of drug-eluting stents are paclitaxel-eluting stents and sirolimus-eluting stents. Paclitaxel is an antimetabolic agent that interferes with microtubule function and inhibits intracellular processes such as mitosis and cell migration. Sirolimus is an antimetabolic agent which inhibits the production of proteins necessary for cell division, and has immunosuppressive properties. The aim of treatment is to reduce the rate of restenosis associated with bare metal stent placement, thereby avoiding repeat revascularisation procedures.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Australian Government Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures and also advises under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the National Health and Medical Research Council Clinical Trials Centre was engaged to conduct a systematic review of literature on drug-eluting stents. An Advisory Panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of drug-eluting stents

This report addresses the safety, effectiveness and cost-effectiveness of drug-eluting stents for the treatment of single *de novo* lesions in coronary arteries. This review does not seek to determine whether one type of drug-eluting stent is superior to another.

Clinical need

Coronary heart disease (CHD) is the leading cause of mortality and morbidity among Australians. The health and economic burden of CHD exceeds that of any other disease.

CHD can be treated with procedures such as endoluminal metallic stent placement during percutaneous coronary intervention (PCI). In 2000, there were 21,874 PCI procedures performed in Australia, 89 per cent of which also involved stent placement compared to 30

per cent in 1995 (AIHW Davies 2003). The problem associated with bare metal stenting is the high rate of restenosis. In the literature, 14-60 per cent of patients receiving bare metal stents require revascularisation with rates varying according to patient and lesion characteristics (Hoffmann et al 2000). In 1999, 20 per cent of PCI procedures were repeat procedures (Davies & Senes 2001). Further strategies are therefore required to prevent restenosis and break the cycle of repeat coronary percutaneous intervention procedures.

Safety

The main safety concerns that have been raised regarding drug-eluting stents are stent thrombosis, the potential for toxicity arising from doubling the drug dose where stents are overlapped, and the unknown clinical sequelae associated with incomplete apposition.

Results from seven randomised controlled trials (RCT) suggest that thrombosis following drug-eluting stent placement is no worse than following bare metal stent placement at up to one year post-procedure.

There is short-term evidence from two sirolimus-eluting stent sub-studies to suggest that there are no adverse events associated with the practice of overlapping stents. However, this evidence is limited by the small patient numbers.

There is limited information addressing the issue of incomplete apposition in drug-eluting stents and this evidence is limited to studies evaluating sirolimus-eluting stents. Results from a sirolimus-eluting stent RCT sub-study found significantly greater incomplete apposition in the sirolimus-eluting stent group compared to the bare metal stent group (Serruys et al 2002). However this finding was not associated with any adverse clinical events at one year.

Effectiveness

Conclusions on the effectiveness of polymer based paclitaxel and sirolimus-eluting stents compared to bare metal stents for the treatment of *de novo* atherosclerotic lesions are based on a systematic review of seven high quality randomised controlled trials (Level I evidence). All the trials included in this review met each of the pre-specified criteria for quality.

Effectiveness in decreasing major adverse cardiac events

The pooled analysis did not demonstrate a statistically significant difference in the rates of mortality, acute myocardial infarction (AMI) or coronary artery bypass grafting (CABG) between patients using paclitaxel or sirolimus-eluting stents and bare metal stents. However, the use of paclitaxel or sirolimus-eluting stents did result in a statistically significant reduction of major adverse cardiac events (mortality, AMI and revascularisations) at 12 months compared to bare metal stents (Level I evidence). The pooled analysis of the paclitaxel-eluting stent trials favoured the paclitaxel-eluting stents at 12 months with a 48 per cent relative reduction in the risk of Major Adverse Cardiac Events (MACE) in paclitaxel-eluting stents compared to bare metal stents (n=1593; Relative Risk (RR): 0.52; 95% Confidence Interval (CI): 0.41– 0.67; p<0.00001). Likewise, the pooled analysis of the sirolimus-eluting stent trials favoured the sirolimus-eluting stents at 12 months with a 67 per cent relative reduction in the risk of MACE in sirolimus-eluting stents compared to bare metal stents (n=1296; RR: 0.33; 95%CI: 0.25-0.45; p < 0.0001). This effect appears to be largely driven by the reduction in repeat revascularisation procedures such as PCI and coronary artery bypass graft surgery (CABG).

Effectiveness in decreasing revascularisation

There is high quality trial evidence that paclitaxel and sirolimus-eluting stents are more effective at decreasing angiographic restenosis and revascularisation procedures than bare metal stents (Level I evidence). These results were consistent for both types of drug-eluting stents evaluated. The pooled analysis of Target Lesion Revascularisation (TLR) in the paclitaxel-eluting stent trials demonstrated a statistically significant difference in TLR favouring paclitaxel-eluting stents over bare metal stents at 12 months with a 71 per cent relative reduction in the risk of TLR events in the paclitaxel-eluting stents compared to bare metal stents (n=1594; RR 0.29; 95% CI: 0.20-0.49; p<0.00001). Pooled analysis of TLR favoured sirolimus-eluting stents at 12 months with an 80 per cent relative reduction in the risk of TLR events in sirolimus-eluting stents compared to bare metal stents (n=1296; RR: 0.20; 95%CI: 0.13-0.29; p<0.00001).

Effectiveness in subgroups of patients

The trial evidence is not sufficient to draw additional conclusions about differences in the effectiveness of paclitaxel or sirolimus-eluting stents compared to bare metal stents in subgroups of patients that may potentially benefit more from drug-eluting stent implantation. Information relating to the subgroups of diabetics, long lesions and small vessels was drawn from sub-studies of the larger RCTs, and interpretation of the results are limited by the low sample sizes, inadequate power, and compromised randomisation. These studies provide evidence for a statistically significant reduction in revascularisation procedures and MACE in diabetic patients and patients with long lesions or small vessels at up to 12 months. However, there is insufficient information to determine whether these sub-groups of patients are more or less likely to benefit from drug-eluting stents over patient groups where these risk factors are absent.

There is insufficient evidence available about the effectiveness of drug-eluting stents compared to bare metal stents in the treatment of in-stent restenotic lesions and bifurcation lesions of the left anterior descending coronary artery (LAD).

Research that evaluates drug-eluting stents is rapidly evolving and the conclusions outlined above represent a summary of the best available evidence to date.

Applicability of study populations to intended practice

Revascularisation definition

There are two main issues concerning the interpretation of revascularisation events in the included RCTs. The most critical issue is the limited applicability of the reported rates of target lesion revascularisation, as defined by the included trials, to rates of revascularisation in routine clinical practice. This is because it is likely that a proportion of these events will have been driven by the results of angiograms specified in the trial protocol rather than patient symptoms alone.

The second issue concerns the variation in the definition of revascularisation across the trials and in the composite endpoint MACE which limited the comparison of event rates across the trials reviewed.

Major adverse cardiac events

MACE rates may not give a true indication of clinically important adverse events if some of these procedures were protocol driven.

Limited follow-up of included trials

The short follow-up available from the drug-eluting RCTs limits conclusions about effectiveness and safety results. The angiographic follow-up was limited to 6 to 9 months and clinical follow-up to 9 to 12 months in all published trials. Current clinical expert opinion suggests that the most critical period for in-stent restenosis is likely to be within the 12 month follow-up period of included trials. Longer term trial evidence is required to exclude the possibility that restenosis is delayed rather than prevented.

Cost effectiveness

The economic evaluation conducted as part of this report is limited to short term outcome and cost data (12 months after index procedure) and does not attempt to model the efficiency of drug-eluting stents beyond the trial time horizon.

- For the clinical outcome of target lesion revascularisations avoided at 12 months, the incremental cost-effectiveness ratio ranges from approximately \$3,700 to \$6,200.
- For the clinical outcome of MACE avoided at 12 months, the ICER also ranges from approximately \$4,000 to \$6,500.
- As expected, these estimates are sensitive to the magnitude of clinical benefit associated with the DES and the number of stents used per patient.

It should be noted that given the relatively short duration of outcomes measured (clinical and resource use) for what is a chronic long-term condition, caution must be used in drawing inferences regarding the efficiency of this intervention beyond the 12 month time frame. Additional longer term data on the duration of clinical benefit and likely resource utilisation is required before definitive conclusions can be drawn regarding the long term efficiency of drug-eluting stents.

Recommendation

MSAC found that on the strength of current evidence regarding drug-eluting stents:

- The technology is as safe as bare metal stents for the treatment of *de novo* atherosclerotic lesions of the coronary arteries at up to one year post-procedure.
- The technology is more effective than bare metal stents in reducing the rates of revascularisation procedures at up to one year.
- There is insufficient evidence at this time to demonstrate a difference in the rates of myocardial infarction, coronary artery bypass grafting or mortality in patients receiving this technology compared to those receiving bare metal stents.
- There is some evidence that the technology is more effective than bare metal stents in reducing the rates of revascularisation at up to one year in patients with diabetes, long lesions greater than 18mm and small vessels less than 2.5mm. However there is insufficient evidence at this time to demonstrate any additional benefit in these and other subgroups of patients at high risk of stent restenosis.
- Cost-effectiveness is based on *de novo* single vessel lesions.
- On the basis of trial data alone, the technology is cost-effective if a cost of \$3,700-\$6,200 is considered acceptable to avoid a target lesion revascularisation. However a sensitivity analysis to estimate the cost-effectiveness in Australian clinical practice indicates that the cost per 'target lesion revascularisation avoided' may be higher than this figure. Australian clinical practice data is required to resolve this uncertainty.

- The Minister for Health and Ageing noted this recommendation on 2 March 2005.-

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of drug-eluting stents, which are therapeutic devices for the treatment of coronary heart disease. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises MSAC's assessment of current evidence for paclitaxel-eluting and sirolimus-eluting stents for the treatment of coronary heart disease. It is structured in three sections. The background section presents an overview of the technology, intended use and clinical need based on general information published in the medical literature. The second section describes the methods used to conduct the systematic review of evidence. The third section presents the results of this systematic review.

Background

Drug-eluting stents

How the technology works

Coronary stents

Coronary heart disease has been treated with balloon angioplasty (percutaneous transluminal coronary angioplasty (PTCA)) of the narrowed artery since the 1970s. The main limitation of PTCA is restenosis of the artery which depending on clinical and morphologic factors, occurs in 10-50 per cent of cases (Myler & Stertzler 1990). This has led to the development of other catheter-based techniques such as stenting. The newer term, percutaneous coronary intervention (PCI) encompasses all forms of percutaneous revascularisation, including PTCA and stenting. The practice of endoluminal metallic stent placement during PCI has become common over the last decade (Babapulle & Eisenberg 2002). Bare metal stents are cylindrical metallic devices which are inserted into coronary arteries that have been narrowed by atherosclerosis and then expanded in order to scaffold the vessel, and thus prevent re-occlusion. Stent designs vary, but may be broadly categorised as mesh, coil, ring, tubular, a composite of these, or of custom design (Popma & Bittl 2001). Bare metal stents are most commonly constructed from stainless steel; however other metals such as tantalum, platinum, and alloys based on nickel, titanium and cobalt have been employed (Goy & Eeckhout 1998).

The method of stent expansion may also vary depending on the stent design. Self-expanding stents are covered with a protective sheet, the removal of which initiates the expansion of the stent. Alternatively, the stent may be mounted on a balloon and expanded via catheter-based balloon inflation (Goy & Eeckhout 1998). A catheter loaded with the stent and inflatable balloon is inserted into the target coronary artery, usually via the femoral artery and advanced to the target site. The balloon is then inflated to a size that will sufficiently stretch the vessel wall, widening the lumen. Once the procedure is completed the balloon is deflated and the catheter removed (Baim & Grossman 1998). The procedure is conducted under local anaesthesia and requires the patient to remain in hospital for an average of one to three days.

The practice of stenting coronary arteries was first pioneered in 1986 with the aim of limiting (and ideally preventing) the occurrence of restenosis, which restricts the effectiveness of balloon angioplasty (King & Meier 2000). The phenomenon of restenosis involves a number of processes that contribute to a narrowing of the vessel due to the arterial wall damage inherent in conducting this procedure (Gershlick 2002). The act of balloon inflation during percutaneous coronary interventions (PCI) causes overstretch of the vessel, resulting in elastic recoil occurring between seconds and minutes post balloon deflation. This may result in loss of up to 40 per cent of the luminal area (Bennett 2003). PCI also causes the endothelial surface to be stripped, inducing platelet adherence and aggregation. Fibrin and platelet deposits may therefore contribute to vessel narrowing. In addition, arterial injury causes neointimal proliferation and migration of vascular smooth muscle cells. Neointimal formation results from the subsequent synthesis of extracellular matrix and collagen. Further, negative remodelling may occur where injury to the media and

adventitia results in cell proliferation and collagen synthesis, with subsequent maturation of the collagen resulting in vessel shrinkage. Finally, the occurrence of inflammation after vessel injury may also contribute to the narrowing of coronary arteries following PCI (Bennett 2003). The combination of such factors often results in the recurrence of symptoms within six months of PCI (Jenkins et al 2002).

Stenting with bare metal stents primarily addresses the effects of elastic recoil and negative remodelling (Bennett 2003). Randomised controlled trials have demonstrated that angioplasty with bare metal stent placement decreases the rate of restenosis compared with angioplasty alone (Betriu et al 1999; Fischman et al 1994; Serruys et al 1994). However, despite these reductions, in-stent restenosis (ISR) after bare metal stent implantation remains problematic. The exact rates of binary ISR (plaque covering >50 percent of the lumen diameter) vary depending on procedural details and patient and lesion characteristics. Whilst ISR rates at 6 month follow-up have been reported to be as low as 14.3 per cent (for lesions <15mm in length) (Martinez et al 2002), and up to 46 per cent for long lesions (>20mm: Oemrawsingh et al 2003) and 61 per cent for ostial lesions (Fenton et al 1994), the rate is typically reported to be between 20-30% (Fischman et al 1994; Mehilli et al 2001; Mudra et al 2001). Lesion length, vessel diameter, diabetes mellitus and previous ISR have been shown to be associated with a higher rate of ISR (Hoffman et al 2000). It should be noted that only a proportion of patients who develop restenosis on imaging (eg angiography or intravascular ultrasound) will actually develop clinical symptoms to warrant a repeat revascularisation procedure such as PCI or coronary artery bypass grafting (CABG) (Serruys et al 1994).

Drug-eluting stents

The problem of persistent ISR after PCI has led to the development of pharmacological solutions to the mechanisms of restenosis not addressed by bare metal stents. For example, intravenous administration of corticosteroids such as methylprednisolone has been studied to reduce the inflammatory response to PCI (Lee et al 1999), and hence reduce ISR. Antiplatelet therapy (intravenous abciximab, oral combined aspirin and ticlopidine) has also been trialled to reduce ISR (ERASER Investigators 1999; Kastrati et al 1997). None of these agents have been shown to result in detectable reductions in ISR after bare metal stent placement, and it has been proposed that this is primarily due to inadequate drug concentrations at the site of stent placement (Babapulle & Eisenberg 2002). Attention has thus turned to the coating of bare metal stents with biocompatible materials and drug coatings, in order to localise the effects of the relevant agent.

Stents coated with biocompatible materials such as carbon, gold, silicon carbide and phosphorylcholine are thought to reduce inflammation and thrombus, and hence reduce neointimal hyperplasia (Babapulle & Eisenberg 2002). However, it is drug-eluting stents that have generated most interest in recent times. Drug-eluting stents are those that are designed to elute the drug coating over a period ranging from a few days to many months. Such drug-eluting coatings include those that inhibit thrombus formation (heparin, hirudin), inflammation (dexamethasone), and cellular proliferation (sirolimus, paclitaxel and derivatives of these compounds). Paclitaxel and sirolimus are the agents that have generated the most research interest (Bennett 2003). Both have been approved by the Therapeutic Goods Administration for use in Australia and this current review will focus on these two stent types. General background information about these two types of drug-eluting stents from reports published in the medical literature or material provided to the public by the

manufacturers is summarised below. The methods and results of our assessment of the effectiveness of these technologies are presented in later sections of this report.

Paclitaxel-eluting stents

Paclitaxel (taxol) is an antimetabolic agent. It interferes with microtubule function and thereby inhibits intracellular processes such as mitosis and cell migration (Babapulle & Eisenberg 2002). Paclitaxel is derived from the bark of the Pacific yew tree (*Taxus brevifolia*). It has been used as a chemotherapeutic agent in the treatment of breast, ovarian and other cancers. When used as a chemotherapeutic agent, it is administered systemically at concentrations 3,000 times greater than the concentration available from local stent delivery (Silber 2003). Paclitaxel is applied directly or mixed with a polymer to the surface of a stainless steel, balloon expandable stent. The Translute™ polymer used in the TAXUS trials releases a higher concentration of paclitaxel in the first two days followed by a lower-level release sustained over 10 days (Silber 2003; Sousa 2003).

Sirolimus-eluting stents

Sirolimus (rapamycin, rapamune) is an antimetabolic agent which inhibits the production of proteins necessary for cell division, and has immunosuppressive properties (Babapulle & Eisenberg 2002). First discovered in the mid-1970s, sirolimus was used as an antifungal agent, but was not developed as an antibiotic due to its immunosuppressive effects (Oberhoff et al 2002). It is the antiproliferative effects of sirolimus, however, that provide its utility in reducing in-stent restenosis (ISR) by preventing neointimal hyperplasia. The most common drug delivery system involves coating a drug-polymer matrix onto the stent strut surface as is used on the Cypher™ stent with a non-erodable methacrylate and ethylene-based copolymer. The polymer layer over the sirolimus/polymer coating allows a controlled release of the drug over a four-week period, with approximately 80 per cent of the sirolimus eluted in this time (Vishnevetsky et al 2004).

The systematic blood levels of sirolimus peak at one hour post implantation with less than 1ng per millilitre being detected during the first two days following implantation (Vishnevetsky et al 2004). This concentration is approximately ten to twenty times lower than that achieved by oral administration of sirolimus, hence the local drug delivery achieved by sirolimus-eluting stents results in a reduced systemic exposure (Cordis (Johnson & Johnson) 2004).

Polymer and non-polymer drug delivery systems

Two types of drug-eluting stent delivery systems have been studied in clinical trials. The non-polymer-based systems have used paclitaxel adhered to the abluminal surface (outer surface) of a stent. Pre-clinical studies have estimated that up to 40 per cent of the drug is lost during stent insertion with the remaining drug released within days to weeks, leaving the bare metal stent exposed after this time (Lansky et al 2004). Non-polymer based paclitaxel-eluting stents have been evaluated in the ASPECT (Park et al 2003), DELIVER (Lansky et al 2004) and ELUTES (Gershlick et al 2004) trials, where paclitaxel has been applied to a bare-metal stent at different concentrations.

Polymer-based stents combine the drug with a polymer carrier to provide homogenous coverage of the stent platform after deployment and are designed to deliver reproducible amounts of the drug to the target area in the vessel (Silber 2003). These delivery systems have been designed to release less than 10 per cent of the total drug dose in the first 10 days, leaving the remaining drug within the polymer (Colombo et al 2003). Of the total paclitaxel

dose, approximately 90 per cent remains within the slow release (SR) polymer formulation without further measurable paclitaxel release.

Polymer-based drug delivery systems are used for the drug-eluting stents currently available in Australia and thus this review assesses trials that have evaluated polymer-based stents.

Intended purpose

In coronary artery disease, drug-eluting stents are intended for use during PCI for the treatment of atherosclerotic lesions and the prevention of restenosis. Drug-eluting stent placement is intended to replace bare metal stent placement for this purpose (MSAC Advisory Panel, May 2004). The flowchart in Appendix C outlines the potential clinical pathway for the treatment of coronary artery disease with drug-eluting stents.

This current report addresses the safety, effectiveness and cost-effectiveness of drug-eluting stents for the treatment of single *de novo* lesions in coronary arteries. The report therefore does not address the safety, effectiveness and cost-effectiveness of drug-eluting stents for vessels of other types (eg. saphenous vein grafts) or multi-vessel lesions. Expert opinion suggests that it is likely that drug-eluting stents would be used predominantly for treating *de novo* atherosclerotic lesions in native coronary arteries in the Australian setting, although they may also be used for restenotic lesions (MSAC Advisory Panel, May 2004).

Clinical need/burden of disease

Cardiovascular disease comprises all diseases and conditions involving the heart and blood vessels, including coronary heart disease (CHD), stroke, peripheral vascular disease and heart failure. The main underlying problem in cardiovascular disease is atherosclerosis. This is the deposition of fat, cholesterol and other substances in the arterial wall that can lead to restriction of the blood supply.

Incidence and prevalence

Coronary heart disease

CHD is the leading cause of mortality and morbidity among Australians despite a 60 per cent decrease in disease-related death rates over the past 30 years. In 2002, it was the most common cause of death in both sexes in Australia, claiming 26,063 lives or approximately 20 per cent of all deaths (Australian Institute of Health and Welfare 2000b). The health and economic burden of CHD exceeds that of any other disease. In 1993-94, CHD accounted for 2.8 per cent of total recurrent health expenditure, or \$894 million. The majority of costs were related to hospital inpatients, \$410 million (65%); the cost of pharmaceuticals, \$105 million (12%); medical expenditure, \$88 million (9.8%); and nursing home costs (8%) (AIHW: Mathur 2002).

Incidence of CHD is difficult to measure as new cases will often be treated in general practice and there is no system of required notification. Incidence is estimated here as the sum of the number of non-fatal hospital admissions for AMI and the number of deaths

recorded as CHD deaths; however as the non-fatal hospital admissions may be recurrent cases, this definition of incidence will provide an overestimate of the true incidence.

In 1999-00, there were an estimated 48,313 CHD events in Australia in 40-90 year-olds (29,731 in men and 18,582 in women). This translates to an incidence rate of 605 coronary events per 100,000 of population aged 40-90 years (AIHW: Mathur 2002). Over the period of 1993 to 2000, incidence rates for CHD in 40-90 year olds declined by 20 per cent or by 3 per cent per year (AIHW: Mathur 2002).

CHD incidence rates increase dramatically with age. Men aged 75-90 years had incidence rates eight times those of 40-64 years olds in 1999-00. Another consistent trend is that the age-adjusted risk of a coronary event in men is double the risk in women (AIHW: Mathur 2002). CHD mortality is higher among Aboriginal and Torres Strait Islander peoples (6-8 times that of other Australians) and among socio-economically disadvantaged groups (twice as high as those from the higher socioeconomic groups) (Department of Health and Aged Care & Australian Institute of Health and Welfare 1999).

Treatment of CHD requires medical therapy or revascularisation (PCI or CABG) as well as modification of risk factors. Patients with angina often respond to medical therapy but may eventually require revascularisation to alleviate symptoms (Selwyn & Braunwald 1998). Despite these measures CHD may lead to heart failure and premature death (Selwyn & Braunwald 1998).

Use of health services

Hospitalisation

In 2002-03, coronary heart disease accounted for 161,796 hospital separations from public and private hospitals in Australia. Of these, 83,212 were attributed to angina, 43,767 to acute myocardial infarction, 349 to subsequent myocardial infarction, 29 to complications following acute myocardial infarction, 520 to other acute ischaemic heart disease and 33,919 to chronic ischaemic heart disease (Australian Institute of Health and Welfare 2004).

Table 1 provides a summary of all the cardiovascular disease hospital separations in Australia for 2002-03.

Table 1 Cardiovascular disease hospital separations in Australia, by sex, 2002-2003^a

Ischaemic heart disease (ICD-10-AM code I20-I25)	Number
Males	105,418
Females	56,377
Total	161,795 ^b

^a Source: National Hospital Morbidity Database 1988

^b separation not classified by sex

Coronary artery revascularisation procedures

In 2000, there were 17,117 coronary artery bypass graft operations (CABG). Over the same period there were 21,874 PCI procedures performed in Australia, 89 per cent of which also involved stent placement compared to 30 per cent in 1995 (AIHW Davies 2003). Table 2

outlines the coronary interventions undertaken in Australia in 2000. A proportion of these PCI procedures would be repeat procedures due to restenosis of a previously treated lesion. In 1999, prior to the introduction of drug-eluting stents, it was estimated that 20 percent of PCI procedures performed in Australia were repeat revascularisations (Davies and Senes 2002).

Table 2 Number of coronary procedures in Australia, 2000-2001.

Procedure	ICD-9 CM codes	ICD-10-AM codes	Total number of procedures ^a	% of total
Coronary angiography	88.55 88.56 88.57	Block 668 Codes 38215-00 38218-00 38218-01 38218-02	76,339	56.7
Percutaneous transluminal coronary angioplasty (PTCA)	36.01 36.02 36.05	Block 670 Codes 35304-00 35305-00 (plus Stenting codes below)	21,874	16.2
Stenting ^b	36.06 36.07	Block 671 Codes 35310-00 35310-01 35310-02	19,333 ^c	14.4
Coronary artery bypass graft (CABG)	36.1	Block 672 Codes 38497-00 38497-01 38497-02 38497-03 Block 673 Codes 38497-04 Block 674 Codes 38500-00 38503-00	17,117	12.7

^a Number of procedures based on data from the AIHW National Cardiovascular Diseases Database (Australian Institute of Health and Welfare 2001)

^b These form a subset of the PTCA procedures and costs.

^c Patients rather than procedures.

Other existing revascularisation procedures

Procedures that are currently used to treat coronary artery disease include PTCA with or without stent placement, intravascular brachytherapy (IVB), atherectomy, excimer laser, and CABG. The choice of intervention varies according to: lesion type and location; operator skill, preference and availability; and the patient's health status. The most common interventions for myocardial revascularisation in Australia are CABG and PTCA with stenting.

PTCA

PTCA is indicated for the treatment of one or more coronary stenoses that can be reached by a catheter. The patient usually presents with moderate to severe chronic stable angina,

however PTCA is increasingly being used in the acute MI and unstable angina setting (AIHW: Mathur 2002). The procedure is conducted under local anaesthesia and requires the patient to remain in hospital for an average of one to three days. A catheter loaded with an inflatable balloon is inserted into the target coronary artery, usually via the femoral artery and advanced to the target site. Radio opaque markers are used as an aid to correct positioning of the balloon. The balloon is then inflated to a size that will sufficiently stretch the vessel wall and widen the lumen that has been narrowed by the atherosclerotic plaque, thereby improving blood flow to the heart. Repeated balloon inflation may be conducted until appropriate lumen patency is achieved. Once the procedure is completed the balloon is deflated and the catheter removed (Baim & Grossman 1998). In Australia, approximately 90 per cent of PTCA procedures also involve the addition of coronary stents (bare-metal or drug-eluting) (AIHW: Davies 2003). PTCA with or without stent placement is fully funded under the MBS (Commonwealth Department of Health and Ageing 2002).

CABG

CABG is indicated for patients with single or multi-vessel disease that are referred to surgery because stenting is not indicated due to unfavourable lesion characteristics or poor prognostic factors such as impaired global left ventricular function (left ventricular ejection fraction <45%) and significant left main coronary stenosis (Myler & Stertzer 1990). The majority of procedures are performed under cardiopulmonary bypass with grafting one or both thoracic arteries, the radial artery or a saphenous vein to form a connection with the affected coronary artery. This directs blood flow towards the heart muscle, therefore bypassing the coronary obstruction (Baim & Grossman 1998). Some of these procedures are performed without using bypass (off-pump coronary artery bypass). CABG is fully funded under the Medicare Benefits Schedule (MBS) (Commonwealth Department of Health and Ageing 2002).

Other PCI procedures

IVB, atherectomy and excimer laser are PCI procedures used to treat one or more coronary stenoses. These procedures are used infrequently in Australia. In 1999, atherectomy was performed on approximately 272 patients or 2.1 per cent of patients undergoing PCI procedures. Brachytherapy was used in only 0.7 per cent of PCI procedures and there were no excimer laser procedures performed in Australia in 1999 (Davies & Senes 2001).

Atherectomy is a catheter-based procedure used in conjunction with PCI that aims to cut and displace the plaque occupying the lumen, rather than stretching the vessel wall. Directional atherectomy (most commonly used) is indicated for the removal of non-calcified lesions; rotational atherectomy is indicated for the treatment of calcified or long lesions; and extraction atherectomy is indicated for the treatment of softer lesions located in saphenous veins. Atherectomy may also be used in conjunction with stents (Baim & Grossman 1998). A recommendation for MBS funding for rotational atherectomy was made in September 2002 (MSAC 2002a).

Intravascular brachytherapy (IVB) is a technique that utilises ionising radiation to treat atherosclerotic plaques within arteries. Used in conjunction with other PCI procedures, this technique applies radiation to the lesion from within the artery lumen via a catheter or radioactive stent. The radiation source is then left in place for a short period of time, in order to irradiate the lesion, and then retracted from the body via the catheter. A

recommendation for interim MBS funding for three years for catheter-based IVB was made in October 2002 (MSAC 2002b).

Excimer lasers also ablate coronary plaques, rather than expand the vessel wall. The patient is given local anaesthesia and a catheter containing small optical fibres is advanced toward the target site. When the catheter is pulsed with laser energy, it is able to displace the non-calcified obstruction by using a combination of photoacoustic, thermal and photochemical effects. Laser therapy in conjunction with PTCA is currently not funded under the MBS (Commonwealth Department of Health and Ageing 2002).

Comparator

In coronary artery disease, paclitaxel-eluting and/or sirolimus-eluting stents are intended to replace bare metal stents to prevent restenosis following PCI. The safety, effectiveness and cost-effectiveness of these drug-eluting stents will therefore be compared with bare metal stents for the purposes of this review. The flowchart detailed in Appendix C outlines the clinical pathway and comparator for paclitaxel-eluting and sirolimus-eluting stents.

Marketing status of the device/technology

The Cypher™ sirolimus-eluting stent and the TAXUS™ paclitaxel-eluting stent are listed on the Australian Register of Therapeutic Goods (ARTG) with the Therapeutic Goods Administration (TGA). The TGA governs the use of medicines and medical technologies to ensure they are of an acceptable standard for the protection of consumers.

When medical technologies are approved by the TGA the indications, contraindications and precautions associated with the product are documented. Manufacturer guidelines for use of both stents are summarized in Appendix D.

Current reimbursement arrangement

Coronary artery stent placement during PCI is funded under the MBS. Reimbursement for bare metal and drug-eluting stent placement during PCI can be claimed under item number 35310. Under this item, reimbursement is made at the same level regardless of the cost of the stent. Private health insurance covers the full cost of drug-eluting stents for their members (Australian Health Insurance Association 2004, <www.ahia.org.au>).

Coronary stents are now being used in most PCI procedures where drug-eluting stents are replacing the use of bare metal stents although there is marked variation in the selection of drug-eluting stents for public patients between different states and regionally between different hospitals due to the higher cost of these devices compared to bare metal stents (information provided by State Health Departments, July 2004). There is also variable practice in patient selection for drug-eluting stents in public hospitals with some attempts to target the high-risk patient groups due to the assumption of cost effectiveness in these groups (MSAC Advisory Panel, May 2004).

While there is no register to record information on the distribution of DES by insurance status or other patient characteristics, Western Australia (WA) is the only state where drug-

eluting stents are widely funded by the State Government for use in public patients (MSAC Advisory Panel, August 2004). In WA, more than 95 per cent of public and private patients receive DES including patients with diabetes and multivessel disease (personal communication, Dr Mews August 2004). Practice is less clear in other states. In unpublished data from one major coronary catheter lab in NSW, 1,184 patients were treated with coronary stents over a 12 month period. In this population, DES were used in 43 per cent of public patients compared to 96 per cent of private patients. In the public patients, the indications for using a DES included AMI, small vessels (<2.5mm), long lesions (>20mm), diabetes, ostial lesions, restenotic lesions, vein graft lesions and bifurcations (personal communication, Dr Greg Nelson August 2004). In Victoria, drug-eluting stents are only provided to public patients who have at least one of nine clinical indications which represent a perceived high risk of developing restenosis following PCI. These indications include diabetes, long lesions (>20mm in length), small diameter coronary arteries (<2.5mm diameter), chronic renal failure, ostial lesions, bifurcation lesions, chronic total occlusions, previous CABG or in-stent restenosis (personal communication, Victorian Department of Human Services, September 2004). In the period October 2003 to June 2004, 3,226 Victorian public patients required PCI for a coronary stent and 1,032 patients (32 per cent) received a drug-eluting stent. Of the 1,032 patients who received a drug-eluting stent, 495 (48 per cent) were for long lesions, 352 (34.1 per cent) were for diabetics and 315 (30.5 per cent) were for small diameter lesions (personal communication, Victorian Department of Human Services, September 2004).

Approach to assessment

The research questions

The review team worked with members of the Advisory Panel to develop specific questions addressing the use of drug-eluting stents for the treatment of coronary artery disease. These questions were formulated *a priori* based on information about the disease area, current practice and the intended purpose of the device.

A flow chart (see Appendix C) depicting the clinical pathways for treating coronary artery disease was developed with the Advisory Panel. This flow chart was used to define the potential role of drug-eluting stents in the treatment of coronary artery atherosclerotic lesions. The population, intervention, comparator and outcomes defined for the primary review question are:

- population - patients with a *de novo* atherosclerotic lesion of the coronary artery
- intervention - polymer-based paclitaxel or sirolimus-eluting stent
- comparator - bare metal stent
- outcomes - mortality, acute myocardial infarction, CABG, revascularisation of the lesion, restenosis of the lesion, adverse events, combined endpoint of major adverse cardiovascular events.

The Advisory Panel decided that this review would also focus on individual subgroups of patients that would potentially benefit from drug-eluting stent implantation. There were five patient subgroups identified:

- patients with diabetes mellitus with single vessel disease
- patients with bifurcation lesions of the LAD
- patients with in-stent restenosis (ISR)
- patients with long lesions (>18mm)
- patients with small vessels (<2.5mm).

Based on the clinical pathway flow chart, four clinical questions were developed and are addressed in this report:

- Are paclitaxel-eluting stents safer, more effective, and more cost-effective than bare metal stents?
- Are sirolimus-eluting stents safer, more effective, and more cost-effective than bare metal stents?
- For what specific groups are paclitaxel-eluting stents safer, more effective, and more cost effective than bare metal stents?
- For what specific groups are sirolimus-eluting stents safer, more effective, and more cost effective than bare metal stents?

Review of literature

The MSAC's recommendations are primarily based on the findings of a systematic literature review conducted by the National Health and Medical Research Council Clinical Trials Centre (NHMRC CTC). The medical literature was searched to identify relevant primary studies and systematic reviews for the period between 1966 and May 2004. Searches were conducted via electronic databases, as listed in Table 3.

Table 3 Electronic databases searched in this review

Database	Period covered
Medline	1966–May 2004
EMBASE	1982–May 2004
Pre-Medline	1966–May 2004
Current Contents	1993–May 2004
CINAHL	1982–May 2004
All-EBM databases	–May 2004
ACP Journal Club (ACP)	
Cochrane Database of Systematic Reviews (COCH)	
Database of Abstracts of Reviews of Effectiveness (DARE)	
Cochrane Controlled Trials Register (CCTR)	

Search strategy

The search strategy was developed using the key elements of the clinical question. It contained search terms for both paclitaxel-eluting stents and sirolimus-eluting stents and their derivatives and combined these with all the search terms for drug-eluting stents.

The search strategy shown in Table 4 was used to identify papers in Medline. A similar search strategy using the same search terms was also employed for the EMBASE, Pre-Medline, Current Contents, CINAHL and all the EBM databases.

Table 4 Search strategy

Number	Search terms
1.	(sirolimus adj5 stent\$.mp
2.	(rapamycin adj5 stent\$.mp
3.	(cypher adj5 stent\$.mp
4.	or/ 1-3
5.	Coat\$ stent\$.mp
6.	Elut\$ stent\$.mp
7.	local drug deliver\$.mp
8.	Drug\$ releas\$ stent\$.mp
9.	Drug\$ load\$ stent\$.mp
10.	(stent\$ adj1 coat\$.mp
11.	(stent\$ adj1 elut\$.mp
12.	medicat\$ stent\$.mp
13.	or/5-12
14.	rapamycin.mp. or exp Sirolimus/
15.	sirolimus.mp. or exp SIROLIMUS/
16.	cypher.mp
17.	or/ 14- 16
18.	13 and 17
19.	18 or 4
20.	(paclitaxel adj5 stent\$.mp.
21.	(taxus adj5 stent\$.mp.
22.	20 or 21
23.	Paclitaxel.mp. or exp PACLITAXEL/
24.	Taxus.mp. or exp TAXUS
25.	23 or 24
26.	25 and 13
27.	26 or 22
28.	19 or 27

Reference lists of publications were also searched for additional relevant citations that may have been inadvertently missed in searches of major databases.

In addition to the databases already listed, the websites of international health technology assessment (HTA) agencies listed in Table 5 were searched.

Table 5 HTA sites searched

Organisation	Website
International Network of Agencies for Health Technology Assessment (INAHTA)	www.inahta.org
British Columbia Office of Health Technology Assessment (Canada)	www.chspr.ubc.edu.ca/bcohta
Swedish Council on Technology Assessment in Healthcare (Sweden)	www.sbu.se
Oregon Health Resources Commission (US)	www.ohppr.state.or.us/ohrc
Minnesota Department of Health (US)	www.health.state.mn.us
Canadian Coordinating Office for Health Technology Assessment (Canada)	www.ccohta.ca
Alberta Heritage Foundation for Medical Research (Canada)	www.ahfmr.ca
Veteran's Affairs Research and Development Technology Assessment Program (US)	www.va.gov/resdev
National Library of Medicine Health Service/Technology Assessment text (US)	http://text.nlm.nih.gov
NHS Health Technology Assessment (UK)	www.hta.nhsweb.nhs.uk
Office of Health Technology Assessment Archive (US)	www.wws.princeton.edu/~ota
Institute for Clinical Evaluative Science (Canada)	www.ices.on.ca
Conseil d'Evaluation des Technologies de la Sante du Quebec (Canada)	www.cets.gouv.qc.ca
National Information Centre of Health Services Research and Health Care Technology (US)	http://www.nlm.nih.gov/nichsr/nichsr.html
Finnish Office for Health Technology Assessment (FinOHTA) (Finland)	http://www.stakes.fi/finohta/linkit/
Institute Medical Technology Assessment (Netherlands)	http://www.bmg.eur.nl/imta/
AETS (Spain)	http://www.isciii.es/unidad/aet/cdoc.htm
Agence Nationale d'Accreditation et d'Evaluation en Sante (France)	www.anaes.fr

Published literature

The search strategy retrieved a total of 378 non-duplicate citations. The numbers of non-duplicate citations retrieved from each database are presented in Table 6.

Table 6 Number of non-duplicate citations retrieved from each database

	Medline	Pre-Medline	Current Contents	Embase	All-EBM	CINAHL	HTA *	Total
Number of citations	207	0	137	24	4	1	5	378

* results of HTA sites searched

Eligibility criteria for studies

The 378 non-duplicate citations were evaluated by 2 reviewers to determine whether they met the eligibility criteria outlined in Table 7. Discrepancies in the results of this screening process were resolved by discussion.

Table 7 Study exclusion criteria

<p>1. Not a randomised controlled trial</p> <p>Reports excluded were those describing animal, laboratory or scientific studies, case reports, case series and cohort studies. Non-systematic narrative reviews and conference abstracts were also excluded in this category.</p> <p>2. Wrong patient group</p> <p>Studies were to include patients with coronary artery disease, including:</p> <ul style="list-style-type: none">• patients with diabetes mellitus with single vessel disease• patients with bifurcation lesions of the LAD• patients with in-stent restenosis• patients with long lesions• patients with small vessels. <p>3. Wrong intervention</p> <p>Studies were to use polymer-based drug-eluting stents as the intervention.</p> <p>4. Wrong comparator</p> <p>Studies were to use bare metal stents as the comparator.</p> <p>5. Wrong outcomes</p> <p>Studies had to report on at least one of the following:</p> <ul style="list-style-type: none">• mortality• acute myocardial infarction• target vessel revascularisation• in-stent restenosis• time to in-stent restenosis• Major Adverse Cardiac Events (MACE) as a composite endpoint• safety. <p>6. Not in English</p> <p>Only studies available in English were eligible for inclusion.</p>
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Based on these criteria, 332 papers (87.8%) were excluded from this review. The reasons for exclusion are listed in Table 8.

Table 8 Reasons for exclusion

Reason for exclusion	Frequency	(%) ^a
1. Not a randomised controlled trial	292	77.3
2. Wrong patient group	20	5.3
3. Wrong intervention	12	3.2
4. Wrong comparator	5	1.3
5. Wrong outcome	1	0.2
5. Not in English	2	0.5
Total	332	(87.8)

^a Percentage of frequency is calculated as a percentage of the total 378 citations identified.

Five health technology reports and two published systematic reviews were identified in the search. The health technology assessment reports were published by the National Institute for Clinical Excellence (NICE) (Hill et al 2003), Catalan Agency for Health Technology Assessment and Research (CAHHTA) (Oliva & Espallargues 2003), and Institute for Clinical Systems Improvement (ICSI), McGill University Health Centre (MUHC) and Canadian Office for Health Technology (CCOHTA). Two of these reports (Hill et al 2003; Oliva & Espallargues 2003) fulfilled the inclusion criteria for this review and provided sufficient information about the review methods and results to allow study appraisal and data extraction; the NICE report was also published as a systematic review (Hill et al 2004). The second systematic review (Babapulle et al 2004) is from researchers at the Canadian McGill University Health Centre and also fulfils inclusion criteria. One other review of drug-eluting stents (Laroia & Laroia 2004) was identified, however insufficient information about the methods were reported to determine whether it fulfilled all the criteria for a systematic review and it has not been included in this review.

The literature search identified seven randomised controlled trials (RCT) (9 citations) and eight sub-studies of these trials reported on outcomes eligible for this review. Overall, the search strategy identified three systematic reviews (four papers) and seven randomised controlled trials (17 papers) that fulfilled the selection criteria for the review. These studies are listed in Table 9. The number of papers retrieved does not represent the number of individual trials, as often a number of papers reported the results on different outcome measures from a single study such as angiographic endpoints.

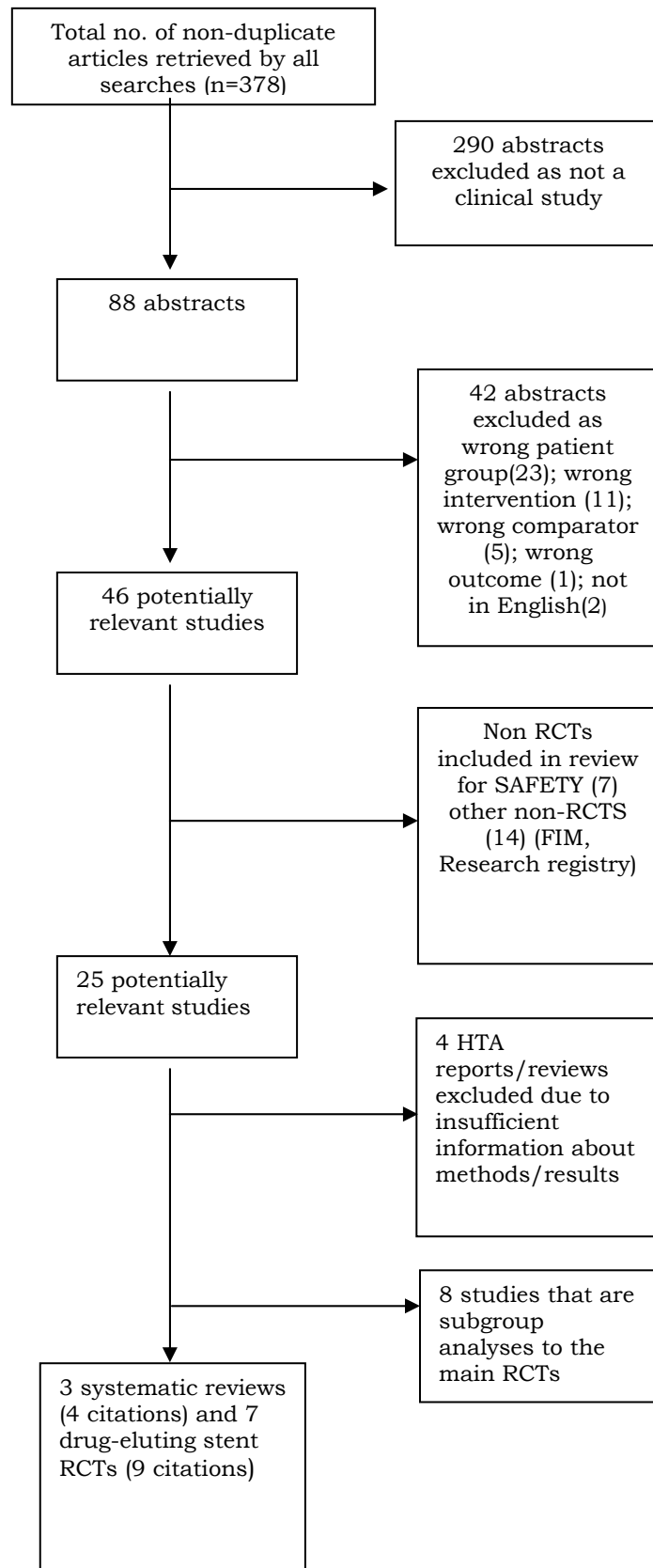
Table 9 Design characteristics of relevant studies

NHMRC Levels of evidence	Studies	No of papers
Level I	Hill et al, Oliva et al, Babapulle et al	4
Subtotal		4
Level II*	TAXUS I	2
	TAXUS II	3
	TAXUS IV	2
	RAVEL	5
	SIRIUS	3
	E-SIRIUS	1
	C-SIRIUS	1
Subtotal		17
Total		21

* Includes sub-studies

The QUORUM flowchart (Figure 1) summarises the results of the literature search and the application of the study exclusion criteria.

Figure 1 QUORUM flowchart: Studies included in the review



In addition to the studies identified as eligible for the review of clinical effectiveness, there were 14 articles reporting on non randomised trials of drug-eluting stents that were retrieved for background information about the scope of current research in this field. There were also seven studies reporting on safety issues that were retrieved to seek information for the safety section of this report. There was a lack of randomised controlled trial evidence about the relative effectiveness of drug-eluting stents versus bare metal stents in patient subgroups of interest, such as patients with diabetes. Evidence from such studies identified for the review that did not meet all the inclusion criteria, for example sub-studies of included trials and case series, are presented as a summary of the best available evidence.

Appraisal

Assessment of eligible studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000). These dimensions (Table 10) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 10 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Level	
Quality	
Statistical precision	The methods used by investigators to minimise bias within a study design.
Size of effect	The <i>p</i> -value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Relevance of evidence	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval.
	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

*See Table 11.

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 11.

Table 11 Designations of levels of evidence*

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

*Modified from NHMRC, 1999.

Quality appraisal tools

Study quality refers to the extent to which the methods used within the chosen study design are adequate to avoid potential bias. A structured appraisal to assess the quality of all included studies was performed. A standard checklist for quality appraisal of randomised control trials is given in Table 12.

Table 12 Checklist for appraising the quality of studies of interventions*

1. Method of treatment assignment

- a. Correct, blinded randomisation method described OR randomised, double-blind method stated AND group similarity documented
- b. Blinding and randomisation stated but method not described OR suspect technique (eg allocation by drawing from an envelope)
- c. Randomisation claimed but not described and investigator not blinded
- d. Randomisation not mentioned

2. Control of selection bias after treatment assignment

- a. Intention to treat analysis AND full follow-up
- b. Intention to treat analysis AND <15% loss to follow-up
- c. Analysis by treatment received only OR no mention of withdrawals
- d. Analysis by treatment received AND no mention of withdrawals OR more than 15% withdrawals/loss-to-follow-up/post-randomisation exclusions

3. Blinding

- a. Blinding of outcome assessor AND patient and care giver
- b. Blinding of outcome assessor OR patient and care giver
- c. Blinding not done

4. Outcome assessment (if blinding was not possible)

- a. All patients had standardised assessment
- b. No standardised assessment OR not mentioned

*Modified from NHMRC, 1999.

Data extraction

Data was extracted using a standardised instrument designed for this review. Data extraction was performed independently by two reviewers and any discrepancies were resolved by discussion or a third reviewer if required. The data extraction tables are provided in Appendix E.

Data Analysis

The characteristics of the study population, type of intervention and co-therapies, study quality and relevant endpoints were extracted for each trial. Where appropriate, the results of eligible studies were statistically synthesized and pooled results presented. Results are primarily reported as a relative risk (RR) which is the ratio of the risk of event in the intervention group over the risk of event in the control group. This is also expressed as the percentage reduction in risk calculated as $100(1-RR)$ per cent. Additionally, the absolute risk reduction (ARR) is reported which describes the difference in risk for an outcome between the intervention and control groups.

Assessment of heterogeneity

The clinical and epidemiological characteristics of the studies were examined to see if they were sufficiently homogenous to justify statistical pooling. Dichotomous data were summarised as relative risks and combined with the Mantel-Haenszel method (Deeks 2002). All results are given with 95 per cent confidence intervals. Heterogeneity was then assessed statistically using the Cochran Q statistic (Alderson, Green & Higgins 2004).

Meta-analysis

Results for paclitaxel and sirolimus groups were analysed separately. Meta-analysis of the event rate (dichotomous variable) in drug-eluting stents versus bare metal stents was conducted for the following study end-points at 12 months:

- mortality
- myocardial infarction (MI)
- coronary artery bypass graft (CABG)
- target lesion revascularisation (TLR)
- combined end-point (MACE).

A meta-analysis of the rate of angiographic restenosis > 50 per cent (binary restenosis) was also performed using event rates reported at 6 months.

We are aware of unpublished data reporting outcomes for up to three years in trials and four years in case series. However unpublished data has not been included in the assessment of effectiveness undertaken for this report.

Expert advice

An Advisory Panel with expertise in cardiology was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the Advisory Panel is provided at Appendix B.

Results of assessment

Is it safe?

Background

The main safety concern for stent technologies is the risk of a blood clot (thrombosis) forming within the stent and occluding blood flow. This is an unusual complication that can result in myocardial infarction and death. The incidence rate of in-stent thrombosis for bare metal stents has been reported at 0.5–3.7 per cent (Jeremias et al 2004; Mak et al 1996). Acute stent thrombosis occurs at the time of stent placement or within hours thereafter, whereas sub acute thrombosis occurs up to 30 days following stent placement (Mak et al 1996). The majority of stent thromboses are sub acute and they may be potentially fatal because patients have often been discharged from hospital by this time.

The mechanism of stent thrombosis is believed to be triggered by the thrombogenic properties of the metallic coronary stent and the mechanical injury sustained to the vessel wall during the percutaneous revascularisation procedure which activates platelets and the extrinsic coagulation cascade (Mak et al 1996). Research is ongoing to determine what other factors may contribute to this risk in patients receiving drug-eluting stents. Procedure-related factors such as over expansion of stents when used in larger diameter vessels and the suboptimal deployment of the stent within the vessel wall have been suggested as two possible contributing factors (Choi 2003; Kereiakes et al 2004). Patient-related factors such as the presence of acute coronary syndrome, small vessels, long lesions and depressed left ventricular ejection fraction, have all been associated with stent thrombosis (Kereiakes et al 2004). The correct selection and deployment of the stent and the use of antiplatelet therapy for several months following the placement of stents is recommended to reduce the risk of this complication.

Toxicity is another safety concern for drug-eluting stents (Moin & Lawson 2002). The safety and effectiveness of drug-eluting stents is dependent upon the combination of the correct drug dose and delivery profile (Grube & Bullesfeld 2002). Early studies using animal models found that high doses of paclitaxel lead to an inflammatory vessel response, medial thinning and delayed intimal healing (Farb et al 2001). The main issue of potential toxicity in the drug-eluting stents currently used relates to the practice of overlapping stents for the treatment of long lesions. Studies have shown that the non-opposition of two implanted drug-eluting stents causes substantial proliferation of neointima in the gap between the stents (Degertekin et al 2003a). Therefore, to avoid non-opposition in long lesions overlapping stents are used and the drug dose is effectively doubled in this segment. The safety of this practice is yet to be resolved, as is the effectiveness of overlapping a drug-eluting with a bare-metal stent where the dose is reduced (Moin & Lawson 2002).

Additional safety concerns raised by preclinical trials include adverse reactions such as intimal haemorrhage, incomplete healing, intimal fibrin deposition, and adventitial inflammation. Other potential concerns that have been reported in the literature include medial necrosis leading to pseudoaneurysm formation (particularly for higher drug doses), perforation, late stent-vessel wall malposition, accelerated atherosclerosis, fibrosis, and

systemic disorders (Teirstein 2001). Current evidence from the trials included in this review and other relevant literature about the safety issues of drug-eluting stents are discussed below.

Safety issues addressed by research

Toxicity

This review identified two substudies that attempted to address the question of toxicity due to overlapping drug-eluting stents. A study by Munoz et al (2004) looked at eight patients with ISR treated with overlapping sirolimus stents and performed intravascular ultrasound at 1 year. It showed no toxic effect on the vessel wall when overlapped sirolimus-eluting stent segments were compared with non-overlapped sirolimus-eluting stent segments (Munoz et al. 2004). The study design and small study numbers limit the conclusions that can be drawn from these results. In a substudy of the SIRIUS trial 344 patients with overlapping stents showed similar TLR rates to the overall study population (sirolimus group 4.5%; BMS 17.7%; $p < 0.001$) however detailed data on this subgroup has not been published (Moses et al 2003).

Studies addressing this issue in paclitaxel-eluting stents were not identified. The manufacturers of the TAXUS™ paclitaxel-eluting stent do not recommend the use of overlapping stents because the safety and effectiveness of these stents has not been evaluated for use in this manner (Appendix D). However, research looking at the amount of paclitaxel and sirolimus that are released from drug-eluting stents shows that the systemic doses of these drugs are many times less than the doses delivered at the stent site (Silber 2003; Vishnevetsky et al 2004).

Incomplete apposition

Apposition refers to the proximity of stent to the arterial wall. Good apposition is achieved when the stent is in sufficiently close contact to the vessel wall to prevent blood flow between the stent and the underlying vessel wall. Studies addressing this issue have evaluated sirolimus-eluting stents; data for paclitaxel-eluting stents are not available. Results from a RAVEL substudy found significantly greater incomplete apposition in the sirolimus-eluting stent group (21%) compared with the bare metal stent group (4%) at a follow-up of 6 months ($p < 0.001$) (Serruys et al 2002) Although there was a higher incidence of incomplete stent apposition in the sirolimus group compared to the BMS group, it was not associated with any adverse clinical events at 1 year (Serruys et al 2002). A second IVUS follow-up of 13 patients with incomplete stent apposition from the RAVEL and FIM trials was carried out at 12 months (Degertekin et al 2003b). The IVUS analysis at 6 months was compared with the IVUS findings at 12 months. This study found no significant differences between the 6 and 12 month follow-up, except in one patient who had developed an aneurysm over 3 incomplete stent apposition sites. The IVUS findings showed that the incomplete stent apposition area did not undergo positive vascular remodelling over 12 months (Degertekin, et al 2003b), however due to the small study numbers and lack of comparison group, limited conclusions can be made from this study.

Results from the SIRIUS trial have indicated that whilst post-procedure incomplete apposition rates do not differ between sirolimus and bare metal stents, new late incomplete

apposition at eight-month follow-up was only observed in the sirolimus condition (9.7%) ($p < 0.05$) (Moses et al 2003). The results regarding incomplete apposition from both studies were derived from sub-group IVUS analyses with relatively low patient numbers. Although there were reported to be no adverse clinical events associated with incomplete apposition, the long-term outcomes are still unknown.

Thrombosis

All of the trials included in this review reported on death and stent thrombosis. No statistically significant difference was identified between the drug-eluting groups compared to the bare metal stent groups in these safety outcomes in the published results from the studies included in this review up to one year post-procedure. Results of stent thrombosis from paclitaxel trials at 12 months were ($n=1593$; RR: 1.18; 95% CI=0.38–3.65; $p=0.77$) and sirolimus trials at 9 months were ($n=1748$; RR: 0.99; 95% CI=0.31–3.22; $p=0.99$). Longer follow-up of two years is available from the First in Man (FIM) case-series study. However the published results of in-stent thrombosis are limited to 1 year data (Sousa et al 2003b).

A case-series of 652 patients (776 lesions) (Jeremias et al 2004) who received sirolimus-eluting stents was carried out in one centre in the United States over a 7 month period in 2003. A median follow-up of 100 days provides information about the risk of in-stent thrombosis in a clinically varied population (35% previous AMI, 16% AMI at presentation, 25% unstable angina at presentation, 37% diabetes mellitus, 84% dyslipidaemia) that may be more representative of the type of patients that will receive drug-eluting in Australia. This study reported one death and five myocardial infarctions due to stent thrombosis. In this study, seven patients (1.1%, 95% CI=0.4–2.2%) developed stent thrombosis within 14 days of the procedure, and 1 patient had a myocardial infarction on day 39 with evidence of stent thrombus at angiography. The authors reported that a strong association existed between the discontinuation of anti platelet therapy and stent thrombus. Four (57%) of the seven patients with stent thrombus versus 1.7 per cent of patients without stent thrombus ($P < 0.001$) discontinued antiplatelet therapy after the procedure (Jeremias et al 2004). In comparison, the pooled rate of subacute stent thrombosis in bare metal stents in 598 patients in the STRESS, BENESTENT and TASC I studies was 3.7 per cent (Mak et al 1996). Lower rates ranging from 0.5–1.9 per cent have been reported elsewhere (Cutlip et al 2001).

Incidence of stent thrombosis has also been studied looking at patients from stent registries. (Regar et al 2004) analysed the incidence of stent thrombosis after sirolimus-eluting stent implantation in an unselected population of 510 consecutive patients. At 3 month follow-up, stent thrombosis was diagnosed in two patients (0.4%). These patients were diabetic women with complex lesions. The IVUS examination showed that mechanical factors (inadequate stent expansion and uncovered distal dissection) may have influenced these outcomes (Regar et al 2004). In a Swiss prospective registry, (Goy et al 2004) looked at clinical outcomes of 183 patients treated with a sirolimus-eluting stent. The rate of in-stent thrombosis in the first six months was 0.6 per cent and the MACE-free survival at 6 months was 95.6 per cent.

Hypersensitivity

The United States (US) Food and Drug Administration (FDA) has reported most cases of hypersensitivity to drug-eluting stents as minor such as skin rashes and itching; however

there have been some severe reactions including anaphylaxis. Results by type of drug eluting stent are not available.

Other evidence

The US FDA has an online register of all adverse event data associated with TAXUS™ and Cypher™ coronary stents (<www.fda.gov/cdrh/mdr-file-general.html>). This surveillance information does not allow comparison with bare metal stents and may reflect underreporting of adverse events due to the voluntary reporting by clinicians.

In 2003, the FDA issued a notification that it had received over 290 reports of subacute thrombosis (of which 60 had been fatal) and 50 reports of possible hypersensitivity reactions on the US FDA (Virmani et al 2002). In response to reports of thrombosis, J&J Cordis (2004) made the recommendation to use antiplatelet therapy for 3 months after Cypher™ stent implantation. (<www.fda.gov/cdrh/mdr-file-general.html>)

In July 2004, Boston Scientific announced a recall of specific lots of the TAXUS™ paclitaxel-eluting stent systems and Express² bare metal stent systems due to characteristics in the delivery catheters that restrict balloon deflation during the coronary angioplasty procedure. This followed 43 confirmed ‘no deflation’ complaints out of an approximate 500,000 estimated implants of the TAXUS™ paclitaxel-eluting stents and 52 confirmed ‘no deflation’ complaints out of an approximate 600,000 estimated implants of the Express² bare metal stents (<www.taxus-stent.com>, July 16 2004).

As well as the US government’s safety database, there are surveillance programs collecting coronary stent safety data that are managed by the companies that manufacture the drug-eluting stents. At the time of writing there were three surveillance programs monitoring the use of the TAXUS™ stent and two registries monitoring the use of the Cypher™ stent. These registries are described below.

TAXUS™ stent registries (<www.bostonscientific.com 2004b>):

- The WISDOM transitional registry is an international, multi-centre, prospective, observational registry that has collected data from 778 patients in 19 countries.
- The Milestone II is a registry targeting more than 100 international sites with plans to enrol at least 3,000 patients to look at the use of TAXUS stent in real-world situations.
- The ARRIVE registry is a safety surveillance program which plans to enrol 2,000 patients at up to 50 sites in the United States.

Cypher™ stent registries (<www.jnj.com 2004>):

- The Cordis Corporation has initiated a registry of Cypher™ stents to begin in 2004 called the DES cover (sm) registry. This registry plans to enrol approximately 15,000 patients at more than 200 US hospitals.
- The E-Cypher registry is an internet-based surveillance program involving 245 centres around the world with 12,180 patients being followed up to six months.

Is it effective?

Characteristics of included studies

Three systematic reviews (Level I evidence) were identified that met the inclusion criteria for this review (Hill et al 2004; Oliva & Espallargues 2003; Babapulle et al 2004). These reviews included an evaluation of paclitaxel-eluting and sirolimus-eluting stents versus bare metal stents in the context of a broader review that included drug types or delivery systems not included in this review. The Oliva & Espallargues (2003) report was printed in Spanish; however an abridged version of the methods and results of this review was available in English. A critical appraisal of the methods and the eligible evidence provided in these reviews is presented in Appendix E.

In this systematic review, an appraisal and synthesis of all eligible trial data (Level II) supersedes the Level I clinical evidence available at the time of producing the report (Hill et al 2004; Oliva & Espallargues 2003) due to the availability of additional evidence.

Seven published studies, comparing drug-eluting stents with bare metal stents, satisfied the inclusion criteria for the review. Three of these studies (TAXUS I, TAXUS II, TAXUS IV) compared paclitaxel-eluting stents with bare metal stents. The remaining four (RAVEL, SIRIUS, C-SIRIUS, E-SIRIUS) compared sirolimus-eluting stents with bare-metal stents.

The studies varied in the size of the study population, the number of study sites and the characteristics of patients (Table 15). The paclitaxel trials randomised a total of 1,911 patients ranging from 61 in the TAXUS I trial to 1,314 in the TAXUS IV trial. There were 536 patients in the TAXUS II trial; however, only the 267 patients in the slow release arm were included in the analysis. The combined number of patients randomised in the sirolimus trials was 1,748, ranging from 100 in the C-SIRIUS trial to 1,058 in the SIRIUS study. The average age in the trials varied from 60.1 to 64.9 years. Male participants predominated in all studies, comprising between 69 per cent in the C-SIRIUS trial to 88.5 per cent in the TAXUS I trial. Information on co-morbidities for patients was documented in all studies. The percentage of diabetic patients in the trials varied from 14.5 per cent in the TAXUS II trial to 26 per cent in the SIRIUS trial. Patients who smoked varied from 20 per cent in the SIRIUS trial to 50.5 per cent in the TAXUS I trial. Patients with unstable angina made up 53 per cent of the population in the SIRIUS trial compared to 33 per cent in the E-SIRIUS trial. History of a prior MI was reported in all included trials, varying from 28 per cent in TAXUS I to 45 per cent in the C-SIRIUS. The percentage of patients with multivessel disease was reported in three of the seven trials (SIRIUS 42%; E-SIRIUS 36%; and C-SIRIUS 40 % of patients with multivessel disease). The baseline characteristics for each study population are presented in Table 13.

Table 13 Baseline demographic and clinical characteristics of patients

	AGE years	SEX % men	Diabetes (% of total)	Current smoker (% of total)	Hypertension (% of total)	Hyperlipaemia (% of total)	Unstable angina (% of total)	Prior MI (% of total)
PACLITAXEL TRIALS								
TAXUS I	64.9	88.5	18	50.5	64	81	32 ^a	28
TAXUS II	60.1	75.5	14.5	24.5	61.5	NR	34.5	40
TAXUS IV	62.4	72.1	24.2	21.7	69.7	65.3	34.2	30.2
SIROLIMUS TRIALS								
RAVEL	60.7	76	19	30	61	40	50	36
SIRIUS	62.3	71	26	20	68	74	53	31
C-SIRIUS	60.5	69	24	37	52	85	51	45
E-SIRIUS	62.3	71	23	33	64	74	33	42

NR - not reported.

^aGrade III-IV angina using the Canadian Cardiovascular Society classification (inability or marked limitation of ordinary activity or rest pain).

All trials presented information on lesion characteristics. The average length of lesion varied from 9.6 mm in the RAVEL study to 15.0 mm in the E-SIRIUS trial. The E-SIRIUS trial had the smallest average reference diameter at 2.55mm compared to 2.96mm in the TAXUS I trial. Table 14 summarises the mean base line lesion characteristics of patients in each trial.

Table 14 Baseline lesion characteristics of patients in each trial

STUDY	Base-line lesion characteristics of patients		
	Average lesion length (mm) (mean± SD)	Reference vessel diameter (mm) ^a (mean± SD)	Diameter stenosis % of lumen
PACLITAXEL TRIALS			
TAXUS I	11.3 ± 4.1	2.96 ± 0.49	57.2
TAXUS II	10.5 ± 4.0	2.8 ± 0.5	64.4
TAXUS IV	13.4 ± 6.3	2.75 ± 0.48	66.0
SIROLIMUS TRIALS			
RAVEL	9.6 ± 3.3	2.62 ± 0.53	63.8
SIRIUS	14.4 ± 5.8	2.80 ± 0.47	65.1
C-SIRIUS	13.5 ± 5.8	2.63 ± 0.32	69.7
E-SIRIUS	15.0 ± 6.0	2.55 ± 0.37	65.5

^a Reference vessel is the vessel with stenosis that will undergo stenting in the study.

The type of stent varied between trials. The CYPHER™ BxVelocity (Cordis) stent was used in all four sirolimus-eluting stent trials. In the paclitaxel trials, a polymer-based TAXUS™ (Boston Scientific) stent was evaluated. The TAXUS II trial evaluated two paclitaxel-eluting release formulations: the TAXUS-SR (slow release) which was the same stent used in the TAXUS I and IV trials and the TAXUS-MR (moderate release) stent which releases paclitaxel at a concentration that is 8 times that of the SR stent over the first 10 days. As stated earlier, the TAXUS-MR stent was not included in the analysis.

Trials also varied according to the procedure used for stent insertion and the number of stents allowed per patient. The E-SIRIUS and C-SIRIUS trials were the only two studies

that permitted direct stenting in sites where this was current practice. The remaining trials required mandatory predilation before stent insertion. The number of stents used per patient varied between trials. The TAXUS I trial specified that if a second stent was required it had to be a bare metal stent. The other trials (RAVEL, TAXUS II, SIRIUS, E-SIRIUS, and C-SIRIUS) allowed the use of a second stent of the same type and TAXUS IV allowed the use of additional study stents but did not specify numbers.

All studies reported details on the use of co-therapies prescribed for patients. Clopidogrel was used in all trials but the duration of therapy varied from two months in the C-SIRIUS and E-SIRIUS trials to six months in the TAXUS trials. Ticlopidine could be used as an alternative to clopidogrel in the E-SIRIUS trial. The use of an intravenous infusion of Glycoprotein IIb/IIIa receptor blocker as additional anti-platelet therapy at the time of the procedure was operator-dependent in all of the studies, except the TAXUS I trial which did not report its use. Most studies reported the overall percentage of patients that received this co-therapy, with the E-SIRIUS, RAVEL and TAXUS II trials reporting on percentage use in each study arm. In these studies, similar numbers of patients received Glycoprotein IIb/IIIa receptor blockers in each study group. The TAXUS IV trial did not report on the percentage of patients receiving Glycoprotein IIb/IIIa receptor blockers.

This review assessed the trial evidence about the effectiveness of paclitaxel-eluting stents and sirolimus-eluting stents that are currently being used in Australian clinical practice. The analysis of the effectiveness and cost-effectiveness of drug-eluting stents excluded the moderate-release dose arm of the TAXUS II study because this stent is not available for use in Australia.

Table 15 Study characteristics

Study	Size	Dates of enrolment	Sites	Lesion characteristics	Stent type	Co-therapies	Follow-up
PACLITAXEL TRIALS							
TAXUS I	61	Oct 2000 and March 2001	3 sites in Germany	Diameter 3.0 -3.5 mm; Length ≤ 12mm	Polymer-based TAXUS NIRx paclitaxel-eluting stent (Boston Scientific™)	Clopidogrel for 6 months	Clinical outcomes at 12 months. Angiographic outcomes at 6 months
TAXUS II	536	June 2001 and January 2002	38 sites worldwide	Diameter 3.0 -3.5 mm Length ≤ 12mm	Polymer-based TAXUS-SR (slow release) and TAXUS-MR (moderate release) paclitaxel-eluting stents (Boston Scientific™)	Clopidogrel for 6 months	Clinical outcomes at 12 months. Angiographic outcomes at 6 months
TAXUS IV	1,314	March 29 2002 and July 8 2002	73 sites in US	Diameter 2.5 - 3.75 mm Length 10 to 28mm	Polymer-based TAXUS Express paclitaxel-eluting stent (Boston Scientific™)	Clopidogrel for 6 months	Clinical outcomes at 12 months. Angiographic outcomes at 9 months
SIROLIMUS TRIALS							
RAVEL	238	August 2000 to August 2001	19 sites located in Europe, Mexico and Brazil	Diameter 2.5 -3.5 mm Length <18 mm	Polymer-based sirolimus CYPHER stent (J&J Cordis™)	Clopidogrel for 2 months	Clinical outcomes at 12 months. 2 year FU only included 30 patients. Angiographic outcomes at 6 months
SIRIUS	1058	February 2001 to August 2001	53 sites in USA	Diameter 2.5 -3.0 mm; Length 15 - 32 mm	Polymer-based sirolimus CYPHER stent (J&J Cordis™)	Clopidogrel for 3 months	Clinical outcomes at 12 months. Angiographic outcomes at 8 months
C-SIRIUS	100	November 2001 and April 2002	Eight Canadian sites	Diameter 2.5 -3.0 mm; Length 15 - 32 mm	Polymer-based sirolimus CYPHER stent (J&J Cordis™)	Clopidogrel for 2 months	Clinical outcomes at 9 months. Angiographic outcomes at 8 months
E-SIRIUS	352	August 2001 and February 2002	35 European sites	Diameter 2.5 -3.0 mm; Length 15 - 32 mm	Polymer-based sirolimus CYPHER stent (J&J Cordis™)	Ticlopidine or clopidogrel for 2 months.	Clinical outcomes at 9 months. Angiographic outcomes at 8 months

The outcomes

Mortality, acute myocardial infarction (AMI), coronary artery bypass graft surgery (CABG), restenosis and revascularisation of the target vessel and in-stent thrombosis were selected as the primary outcome measures of effectiveness for the purposes of this review. Other outcomes reported in the included RCTs have not been included in this review. These were primarily angiographic measures, for example late loss, minimum luminal diameter and neointimal hyperplasia volume.

The outcomes included in this review are defined below. Data reported at 12 months for each of these outcomes is included in this review or otherwise as stated:

Mortality

In all trials, mortality was defined as death by any cause except in the TAXUS II trial where it was defined as cardiac death only. The TAXUS IV and SIRIUS trials separated mortality into cardiac and non-cardiac causes.

Myocardial infarction

Myocardial infarction included both Q-wave and non-Q wave definitions in all clinical trials, except the TAXUS I trial which included Q-wave MI only. MI was defined as either the development of pathologic Q waves lasting at least 0.4 second in at least two contiguous leads with an elevated creatine kinase MB fraction level, or in the absence of pathologic Q waves, an elevation in creatine kinase levels to more than twice the upper limit of normal with an elevated creatine kinase MB level.

Coronary artery bypass surgery

CABG was reported in all studies. Additionally, it was defined under the outcome of target vessel revascularisation in the TAXUS I, TAXUS II, TAXUS IV, SIRIUS and under target lesion revascularisation in the SIRIUS (clinically driven CABG) and TAXUS IV studies.

Restenosis

Restenosis of the stent was reported under two outcomes: revascularisation and angiographic binary restenosis.

Revascularisation

Revascularisation is defined as a percutaneous or surgical intervention performed on patients for the treatment of restenosis of the artery. Two definitions have been used in the included trials: target lesion revascularisation (TLR); and target vessel revascularisation (TVR) (See Table 16). TLR is the primary endpoint for revascularisation used in this review and is reported in all trials. It is defined as a revascularisation procedure of the stented lesion (target lesion) and 5 mm segments immediately proximal and distal to the stent. TVR is defined as a revascularisation procedure on any segment of the target vessel (including the target lesion) and has been reported in 5 of the trials.

It is not clear what proportion of these patients underwent revascularisation due to recurrent symptoms, or as a result of protocol-driven angiograms. Three trials specified that revascularisation events were clinically driven (Moses et al 2003; Stone et al 2004; Schampaert et al 2004) and two of these provided the clinical criteria used in this definition. The SIRIUS trial reported that revascularisation of the target lesion was clinically driven however the criteria on which this definition was based was not specified. Of the two trials that provide definition of the clinical criteria used to define TLR, one trial only applies the criteria for the definition of TVR, not TLR. The criteria used for the two trials are outlined below:

- TAXUS IV – TVR was defined as stenosis of at least 50 per cent of the luminal diameter of the target vessel, with either ECG changes while the patient was at rest or a functional study indicating ischaemia in the target vessel, or if there was stenosis of at least 70 per cent in combination with recurrent symptoms alone. In comparison, the published definition of TLR was repeated revascularisation for ischaemia due to stenosis of at least 50 percent of the luminal diameter anywhere within the target segment.
- C-SIRIUS – TLR was defined as procedures performed in response to recurrent angina and/or ischaemia on non-invasive tests documented prior to repeat angiography, with >50 per cent diameter stenosis by angiography, or > 70 per cent diameter stenosis by angiography in the absence of symptoms.

Angiographic binary restenosis

Binary restenosis is defined as at least 50 per cent restenosis of the target lesion by angiography. All trials performed angiography between 6 and 9 months for all/the majority of participants. This angiographic outcome was reported in all trials and the 6 month results are included in this review.

Table 16 Summary of study outcomes reported in drug-eluting stent trials at 12 months

	Mortality	AMI	CABG	Binary restenosis	Target lesion revascularisation (TLR)	Target vessel failure (TVF) ^a	Target vessel revascularisation (TVR) ^b	Stent Thrombosis ^c
PACLITAXEL TRIALS								
TAXUS I	✓	✓	✓	✓	✓	✗	✓	✓
TAXUS II	✓	✓	✓	✓	✓	✗	✓	✓
TAXUS IV	✓	✓	✓	✓	✓	✓	✓	✓
SIROLIMUS TRIALS								
RAVEL	✓	✓	✓	✓	✓	✓	✓	✓
SIRIUS	✓	✓	✓	✓	✓	✓	✓	✓
C-SIRIUS ^d	✓	✓	✓	✓	✓	✗	✗	✓
E-SIRIUS ^d	✓	✓	✓	✓	✓	✗	✗	✓

✓ - outcome reported in trial

✗ - outcome NOT reported in trial

^a TVF is defined as death from cardiac causes, AMI and any revascularisation procedure on any segment of the target vessel.

^b TVR includes TLR events. TVR is defined as a revascularisation procedure on any segment of the target vessel (including the target lesion).

^c Stent thrombosis reported at 9 months in the sirolimus trials.

^d These trials report outcomes to 9 months only.

Major adverse cardiac events

MACE is a composite measure of mortality, myocardial infarction and TVR and/or TLR (See Table 17). The definition varies slightly between studies with the paclitaxel trials (TAXUS I, TAXUS II, TAXUS IV) reporting on TVR which by definition includes TLR, whereas the sirolimus trials (RAVEL, SIRIUS, C-SIRIUS, E-SIRIUS) were reporting on TLR only. The TAXUS IV trial included outcomes for MACE and TVF; the difference between the definitions was the classification of death by cardiac causes under MACE and death by all causes under TVF. Two studies (SIRIUS and TAXUS I) included the outcome of stent thrombosis in their MACE outcome.

Table 17 Summary of MACE definitions reported in drug-eluting stent trials

Study	Definition of MACE used
PACLITAXEL TRIALS	
TAXUS I	Death, Q wave MI, TVR ^a on target vessel, CABG and stent thrombosis
TAXUS II	Cardiac death, MI, TVR ^a including target lesion and non- target lesion and CABG
TAXUS IV ^b	Cardiac death, MI and ischaemia-driven TVR ^a
SIROLIMUS TRIALS	
RAVEL	Death, AMI (Q and non-Q wave), CABG, clinically driven TLR
SIRIUS ^c	Death, AMI (Q and non-Q wave), TLR (CABG and PTCA), clinically driven TLR
C-SIRIUS	Death, MI, CABG and clinically driven TLR
E-SIRIUS	Death, MI, CABG and TLR

^a TVR includes all TLR events

^b TAXUS IV also reported target-vessel failure as death, MI and ischaemia-driven TVR.

^c SIRIUS also reported TVF as death by cardiac causes, MI and TVR (CABG or PCI).

Results

Results for paclitaxel and sirolimus groups were analysed separately. The review did not seek to determine whether one type of drug-eluting stent technology was superior to another.

Differences in the selection criteria and definition of outcomes between the existing trials limit the validity of indirect comparisons of the trial results. No statistically significant heterogeneity for either group of trials was observed for any of these outcomes. Results from the TAXUS II trial include the SR TAXUS arm only. The rates between the groups are described as relative risk (RR) and absolute risk reduction (ARR).

Mortality

Mortality was reported in less than 2 per cent of all patients in the included trials (range 0%-1.7%). A total of 36 deaths were recorded across all trials. There were no statistically significant differences in mortality rates between paclitaxel or sirolimus-eluting stents and bare metal stents at any of the time points (Pooled results for paclitaxel trials at 12 months: n=1,593; RR: 0.90; 95% CI =0.38-2.16; p=0.81. Pooled results for sirolimus trials at 12 months: n=1296; RR: 1.48; 95% CI = 0.53-4.12; p=0.46).

AMI

Acute myocardial infarction was reported in less than 4 per cent of all patients in the included trials (range 0%-3.8 %). A total of 115 AMIs were reported across all included trials. There were no statistically significant differences in AMI rates between paclitaxel or sirolimus-eluting stents and bare metal stents for the pooled analyses at any of the time points.

Paclitaxel trials: No statistically significant difference in the rates of AMI between the treatment and control groups were observed in the pooled analysis of paclitaxel trials at 12 months (n=1,593; RR: 0.70; 95% CI = 0.43-1.14; p=0.15).

Sirolimus trials: No statistically significant difference in the rates of AMI between the treatment and control groups were observed at any time point in the 4 individual trials or at 9 months in the pooled analysis of 3 trials (n= 1,510; RR: 1.04; 95% CI: 0.59-1.82; p=0.90). Two trials (RAVEL and SIRIUS) reported at data 12 months, with no statistically significant effect between sirolimus-eluting stents and bare metal stents (n=1,296; RR: 0.86; CI: 0.47-54; p=0.61).

Coronary artery bypass graft surgery

Results from the pooled analyses were suggestive of a reduced risk of coronary artery bypass grafting for patients receiving paclitaxel and sirolimus-eluting stents compared to those receiving bare metal stents. However this effect did not reach statistical significance. There were 63 CABG procedures out of a total of 3,386 patients across all the trials.

Paclitaxel trials: No statistically significant difference in the rates of CABG between the treatment and control groups were observed in the pooled analysis of all paclitaxel trials at 12 months (n=1,593; RR: 0.60; 95% CI:0.33-1.09; p=0.09).

Sirolimus trials: No statistically significant difference in the rates of CABG between the treatment and control groups were observed at any time point. There were 3 sirolimus trials (SIRIUS, C-SIRIUS, E-SIRIUS) that reported CABG as an outcome at 9 months (n=1,510; RR: 0.41; 95% CI: 0.15-1.17; p=0.10). The RAVEL and SIRIUS trials reported CABG at 12 months with no statistically difference between the groups (n= 1,296; RR: 0.59; CI: 0.22-1.62; p=0.31).

In-stent thrombosis

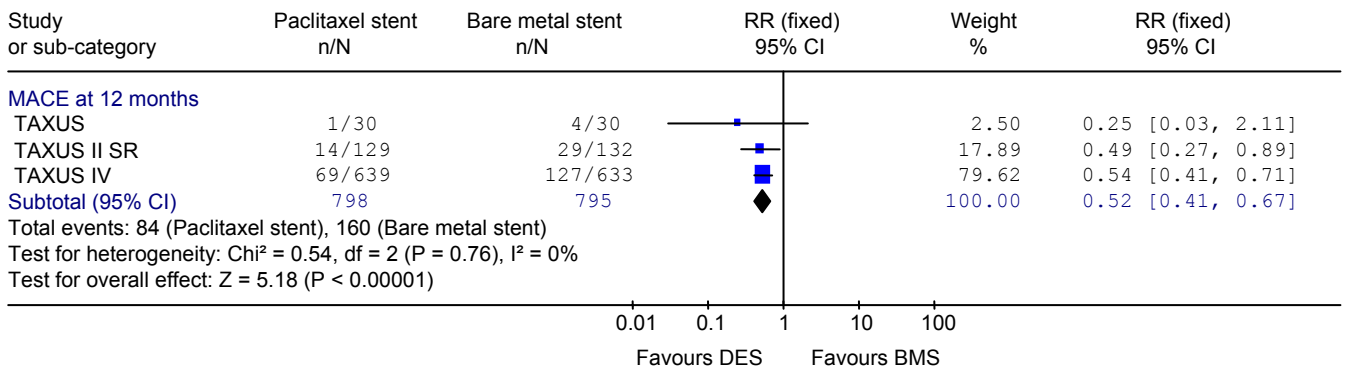
There were no statistically significant differences in the incidence of in-stent thrombosis between paclitaxel or sirolimus-eluting stents and bare metal stents for the pooled analyses or within the individual studies at any of the time points (Pooled results for paclitaxel trials at 12 months n=1,593; RR: 1.18; 95% CI = 0.38- 3.65; p=0.77. Pooled results for sirolimus trials at 9 months: n=1,748; RR: 0.99; 95% CI = 0.31-3.22; p=0.99.)

Major adverse cardiac events

Paclitaxel trials: MACE were statistically significantly reduced in the TAXUS II and TAXUS IV trials. The pooled analysis confirmed a statistically significant difference in the rates of MACE between the paclitaxel-eluting stents and BMS favouring the paclitaxel-eluting stents at 12 months with a 48 per cent relative reduction in the risk of MACE events in paclitaxel-eluting stents compared to BMS (n =1,593; RR: 0.52; 95%CI: 0.41-0.67; p<0.00001; ARR = 10% at 12 months). Figure 2 displays the MACE forest plot for paclitaxel-eluting stent trials at 12 months.

Figure 2 Forest plot of MACE at 12 months: paclitaxel-eluting stent trials

Comparison: Paclitaxel (Polymer based)
Outcome: MACE



Sirolimus trials: Each trial reported statistically significant results that demonstrated fewer MACE events associated with sirolimus-eluting stents compared to bare metal stents. Pooled analysis of MACE favoured sirolimus-eluting stents at 9 months, (n =1,510; RR: 0.36; 95%CI: 0.27-0.49; p < 0.0001) and at 12 months with a 67 per cent relative reduction in the risk of MACE events in sirolimus-eluting stents compared to bare metal stents (Figure 3, n=1296; RR: 0.33; 95%CI: 0.25-0.45; p < 0.0001; ARR= 15.7% 95%CI: 12%-20%).

Figure 3 Forest plot of MACE at 9 and 12 months: sirolimus-eluting stent trials

Comparison: Sirolimus (Polymer based)
Outcome: MACE

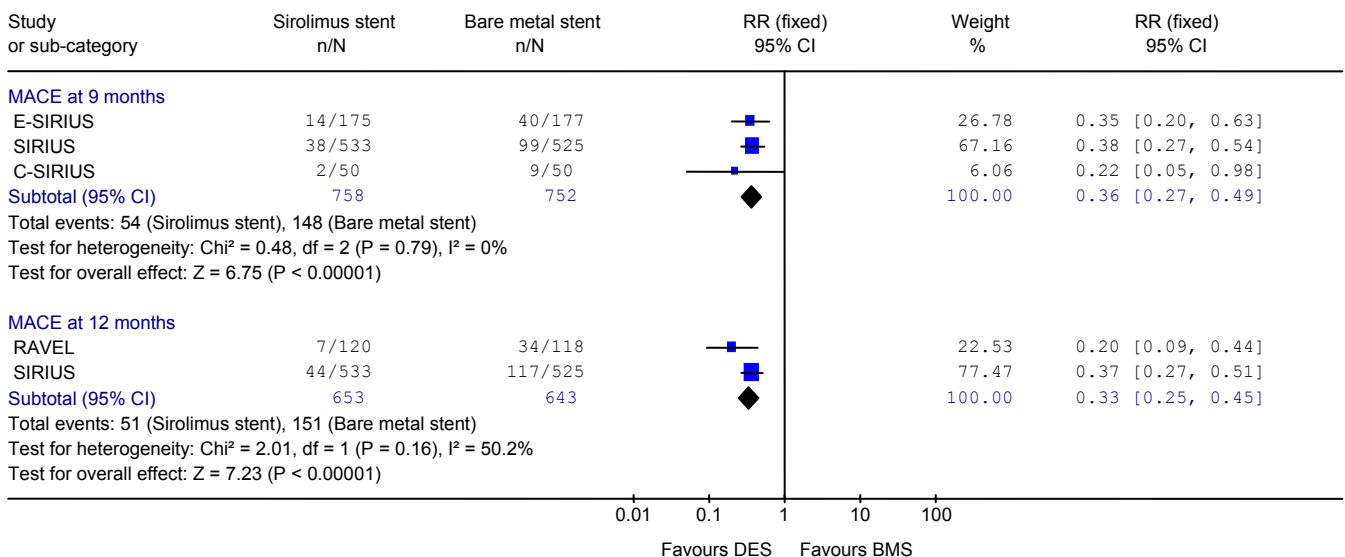


Table 18 Summary results of MACE

TRIAL	MACE					
	Rates		Absolute risk reduction ^a	CI	Risk ratio	CI
	DES	BMS				
PACLITAXEL TRIALS						
TAXUS I	1/30	4/30 ^b	10.0%	4%-24%	0.25	0.03-2.11
TAXUS II (SR)	14/129	29/132	11.2%	2%-20%	0.49	0.27-0.89
TAXUS IV	69/639	127/633	9.3 %	5%-13%	0.54	0.41-0.71
POOLED PACLITAXEL	84/798	160/795	9.6 %	6%-13%	0.52	0.41-0.67
SIROLIMUS TRIALS						
RAVEL	7/120	34/118	22.9 %	14%-32%	0.20	0.09-0.44
SIRIUS	44/533	117/525	14.0%	10%-18%	0.37	0.27-0.51
C-SIRIUS ^c	14/175	40/177	14.6 %	2%-26%	0.22	0.05-0.98
E-SIRIUS ^c	2/50	9/50	15.0%	7%-22%	0.35	0.20-0.63
POOLED SIROLIMUS	51/653	151/643	15.7 %	12%-20%	0.33	0.25-0.45

^a Absolute risk reduction = (DES rate – BMS rate) × 100%.

^b 4 MACE events reported in 3 patients.

^c These trials not included in the pooled sirolimus MACE because this outcome was reported at 9 months.

Restenosis

Paclitaxel trials

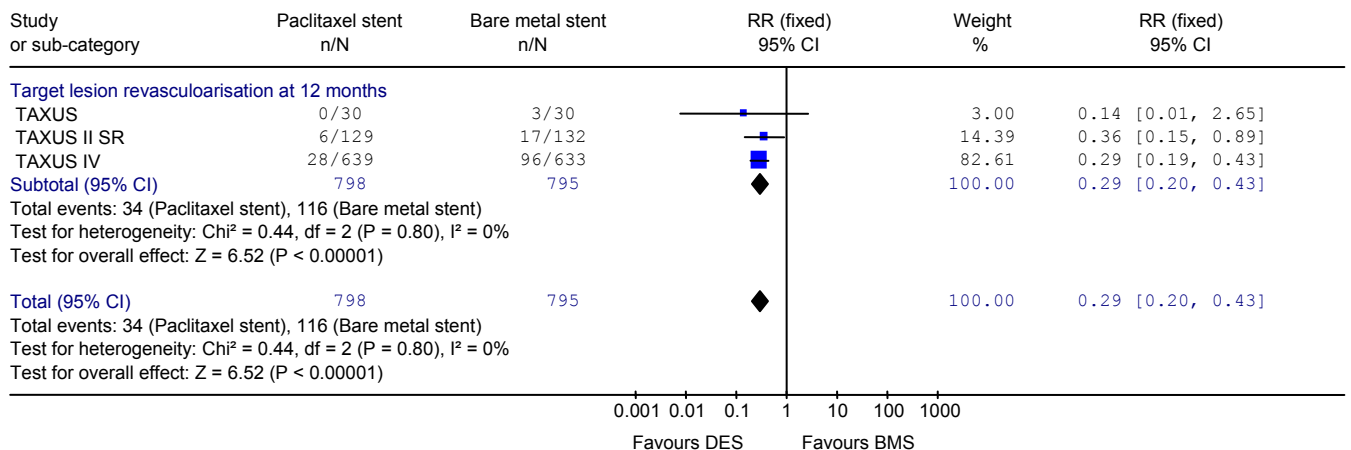
TLR

The pooled analysis demonstrated a statistically significant difference in TLR favouring paclitaxel-eluting stents over bare metal stents at 12 months with a 71 per cent relative reduction in the risk of TLR events in the paclitaxel-eluting stents compared to bare metal stents (Figure 4, n=1594; RR 0.29; 95% CI: 0.20-0.43; p<0.00001; ARR = 10.3%; 95% CI: 8%-13%).

Figure 4 Forest plot of target vessel revascularisation at 12 months: paclitaxel-eluting stent trials

Comparison: Paclitaxel (Polymer based)

Outcome: Target lesion revascularisation

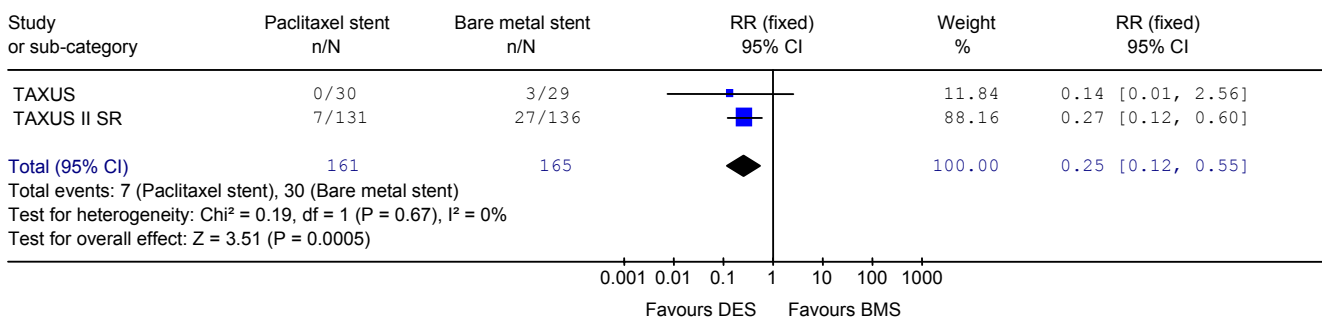


Angiographic binary restenosis

The pooled analysis for angiographic binary restenosis showed a statistically significant difference in angiographic binary restenosis favouring paclitaxel-eluting stents at 6 months with a 75 per cent relative reduction in the risk of angiographic binary restenosis in the paclitaxel-eluting stents compared to the bare metal stents (Figure 5, n= 326; RR = 0.25, 95% CI: 0.12 - 0.55;p= 0.0005). The TAXUS IV trial reported a 70 per cent relative reduction in the risk of angiographic binary stenosis at 9 months for patients receiving a paclitaxel-eluting stent compared to bare metal stents (n= 559; RR=0.30; 95% CI: 0.19 – 0.46; p<0.00001). No other paclitaxel trials reported on this outcome at 9 months.

Figure 5 Forest plot of angiographic binary restenosis at 6 months: paclitaxel-eluting stent trials

Comparison: Paclitaxel (Polymer based)
Outcome: Binary Restenosis at 6 months



Restenosis

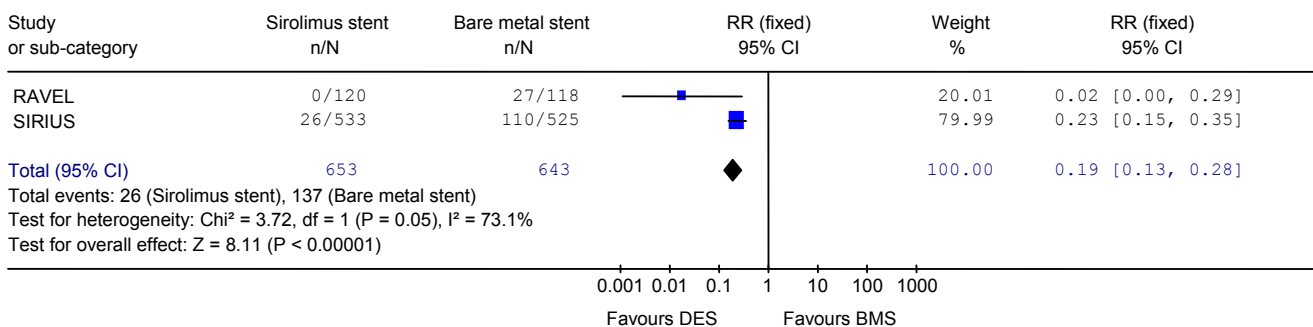
Sirolimus trials

TLR

Each trial reported statistically significantly fewer TLR associated with sirolimus-eluting stents compared to bare metal stents. Pooled analysis of TLR favoured sirolimus-eluting stents at 9 months (n=1,510; RR: 0.23; 95%CI: 0.16-0.34; p<0.00001) and at 12 months with an 80% relative reduction in the risk of TLR events in sirolimus-eluting stents compared to bare metal stents (Figure 6, n=1,296; RR: 0.20; 95%CI: 0.13-0.29; p<0.00001; ARR=16.5%; 95%CI: 14%-21%).

Figure 6 Forest plot of target lesion revascularisation at 12 months: sirolimus-eluting stent trials

Comparison: Sirolimus (Polymer based)
Outcome: Target lesion revascularisation at 12 months



Angiographic binary restenosis

Similar results were reported in the angiographic binary restenosis outcome at 8 months. Pooled data from 3 studies reporting on this outcome showed an 81 per cent relative reduction in risk in angiographic binary restenosis detected by angiography at 8 months for patients receiving sirolimus-eluting stents compared to bare metal stents (Figure 7, RR= 0.19, 95% CI: 0.14 - 0.26; n= 1099; p< 0.00001).

Figure 7 Forest plot of angiographic binary restenosis at 8 months: sirolimus-eluting stent trials

Comparison: Sirolimus (Polymer based)

Outcome: Binary Restenosis at 8 months

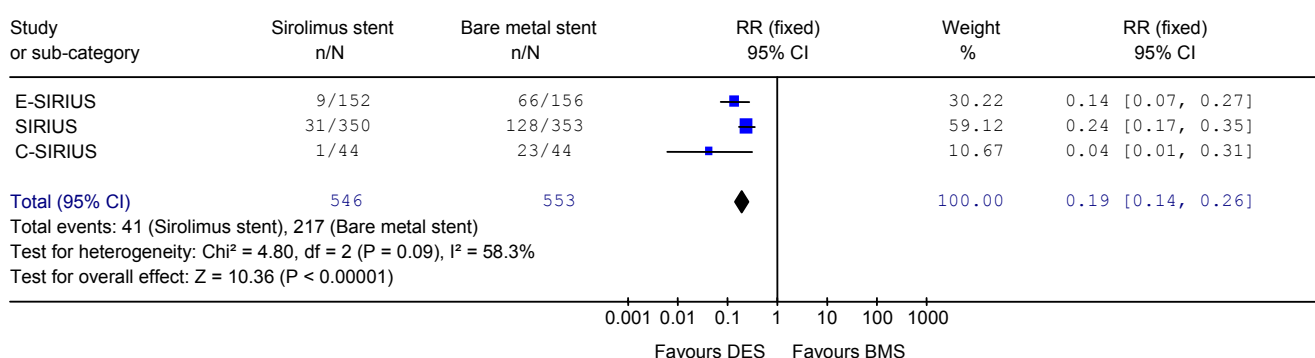


Table 19 Summary results of TLR

TRIAL	TLR at 12 months ^b					
	Rates		Absolute risk reduction ^a	CI	Risk ratio	CI
	DES	BMS				
PACLITAXEL TRIALS						
TAXUS I	0/30	3/30	10.0%	2%-22%	0.14	0.01-0.65
TAXUS II (SR)	6/129	17/132	8.2%	1%-8%	0.36	0.15- 0.09
TAXUS IV	28/639	96/633	10.8%	8%-14%	0.29	0.19- 0.43
POOLED PACLITAXEL	34/798	116/795	10.3%	8%-13%	0.29	0.20- 0.43
SIROLIMUS TRIALS						
RAVEL	0/120	27/118	22.8%	15%-31%	0.02	0.00- 0.29
SIRIUS	26/533	105/525	15.1%	12%-20%	0.24	0.16-0.37
C-SIRIUS ^b	2/50	9/50	14.0%	2%-26%	0.22	0.05-0.98
E-SIRIUS ^b	7/175	37/177	16.9%	10%-24%	0.19	0.09-0.42
POOLED SIROLIMUS	26/653	132/643	16.5%	14%-21%	0.20	0.13-0.29

^a Absolute risk reduction = (DES rate - BMS rate) × 100%.

^b These trials reported TLR at 9 months so not included in pooled sirolimus calculation.

Effectiveness in subgroups

Five subgroups of patients were identified *a priori* for this review. They were:

- patients with diabetes mellitus with single vessel disease
- patients with bifurcation lesions of the LAD
- patients with in-stent restenosis (ISR)
- patients with long lesions (>18mm)
- patients with small vessels (<2.5mm).

These subgroups were considered to have a higher risk of restenosis, or for whom stenting may prove difficult or ineffective. The diabetic subgroup is the only subgroup applicable to the current indications for use of the cypher™ and TAXUS™ stents as approved by the TGA. For long lesions, the cypher™ stent is indicated for lesions up to 30mm whereas the TAXUS™ stent is indicated for use in lesions up to 28mm (See Appendix D).

None of the included trials were designed to compare the effectiveness of drug-eluting stents in patients with these risk factors compared to patients without these risk factors. Three of the trials did report results by the subgroups of interest. The results allow an evaluation of the effectiveness of drug-eluting stents versus bare metal stents for patients with these risk factors. However, the number of patients included is not sufficient to allow a comparison of the relative risk between these patients and those without these risk factors (due to insufficient statistical power).

Two of the sirolimus-eluting stent trials (SIRIUS and RAVEL) and one of the paclitaxel-eluting stent trials (TAXUS IV) reported results on diabetic patients. All observed that target lesion revascularisation rates were lower in the drug-eluting group compared to the bare metal stent. The TAXUS IV trial also reported positive results on patients with long lesions or small vessels (Stone et al 2004). These results are presented below. Due to the limitations of this data to address the pre-specified review question about the relative value of drug-eluting stents in subgroups of patients, we also sought information from sub-studies of these trials and from the uncontrolled studies identified in our literature search but not meeting the criteria for inclusion to describe the scope of research in this area.

Diabetes

Level II evidence demonstrating the effectiveness of drug-eluting stents in diabetic patients is available in publications from the SIRIUS, RAVEL and TAXUS IV trials. An analysis of a subgroup of 279 diabetic patients in the SIRIUS trial (131 patients with sirolimus-eluting stents, 148 patients with bare metal stents) showed a significant difference in the rate of TLR at 12 months with a 70 per cent relative reduction in the risk of TLR events in the sirolimus-eluting diabetic stent arm compared to the bare metal stent diabetic arm (n=279; RR=0.30; 95%CI:0.15-0.62; ARR=15.4%, p<0.0001) (Holmes et al 2004). In this trial, MACE at 9 months were also statistically significantly reduced with a 63 per cent relative reduction in the risk of MACE in the sirolimus-eluting stent diabetic group compared to the bare metal stent diabetic group (n=279; RR=0.37; 95%CI: 0.20-0.67; ARR= 15.8%, p<0.001) (Moussa et al 2003).

The RAVEL trial had a subgroup of 44 diabetics of which 19 received sirolimus-eluting stents and 25 received bare-metal stents. There was no restenosis in the sirolimus-eluting stent groups (diabetic and non-diabetic) compared to a 36 per cent TLR rate in the diabetic patients assigned bare metal stents (ARR=36%; 95%CI: 17.2-54.8, p=0.006) (Abizaid et al 2004). MACE were statistically significantly reduced in the sirolimus-eluting stent group with a 78 per cent relative reduction in the risk of MACE in the sirolimus-eluting stent diabetic group compared to the bare metal stent diabetic group (n= 44; RR=0.22; 95%CI: 0.06-0.87; ARR=37.5%, p=0.01) (Abizaid et al 2004). Table 20 shows the summary results for diabetic patients in the SIRIUS and RAVEL trials.

In the TAXUS IV trial, the diabetic subgroup analysis demonstrated improvement in restenosis in the diabetic patients receiving the paclitaxel-eluting stent versus those in the bare metal stent group. Of the 558 patients in this trial who underwent follow-up angiography, 89 were diabetics requiring oral medication and 47 were diabetic patients requiring insulin; however the proportion of insulin dependent diabetics allocated to treatment and control groups was not reported. The 12 month TLR results favoured the TAXUS stent in insulin-dependent diabetic patients with 6.2 per cent TLR in the TAXUS group compared to 19.4 per cent TLR in control group (RR=0.32; ARR= 13.2%, p=0.07) (Stone et al 2004).

Table 20 Summary results for diabetics: sirolimus-eluting stent trials*

TRIAL		Diabetics			Non-diabetics		
		RATES		RESULTS	RATES		RESULTS
		SES	BMS		SES	BMS	
SIRIUS	TLR Reported at 12 months	9/131	33/148	RR=0.31 95%CI (0.15-0.62) ARR=15.4% p<0.001	12/402	53/376	RR=0.21 95%CI (0.11-0.38) ARR=11.1% p<0.0001
	MACE Reported at 9 months	12/131	37/148	RR=0.37 95%CI (0.20-0.67) ARR=15.8% p<0.001	26/402	62/376	RR=0.39 95%CI (0.25-0.60) ARR=10.0% p<0.0001
RAVEL	TLR Reported at 12 months	0/19	9/25	ARR=36% 95%CI (17.2%-54.8%) p=0.006	0/101	18/93	ARR=19.4% 95%CI (11.3%-27.4%) p<0.0001
	MACE Reported at 12 months	10.5	48.0	RR=0.22 95%CI(0.06-0.87) ARR=37.5% p=0.01	5/101	22/93	RR=0.21 95%CI (0.08-0.53) ARR=18.7% P=0.002

* Results are reported for the longest time period available.

Results for diabetic patients in the SIRIUS, RAVEL and TAXUS IV trials show that drug-eluting stent implantation achieved significantly lower MACE and target lesion revascularisation rates compared with bare metal stents. However, as these trials were not designed to assess the relative effectiveness in diabetics, it is difficult to formulate any additional conclusions. The diabetic subgroup analyses were conducted with small samples from larger trial populations which were not powered to detect differences in these outcomes between diabetic and non-diabetic patients. Although there is some evidence that the baseline risk of restenosis (Elezi et al 1998; Mathew et al 2003) is different in diabetics receiving PCI compared to non-diabetics,

without data to demonstrate that the relative risk reduction for those receiving drug-eluting stents is equivalent or different between these groups it is not possible to infer that diabetics will receive a greater or lesser benefit from drug-eluting stents. We did not identify any other studies addressing this question.

Bifurcation Lesions of the Left Anterior Descending artery (LAD)

No evidence on the effectiveness of drug-eluting stents compared to bare metal stents for the treatment of bifurcation lesions of the LAD was identified in our search. Two studies have reported on drug-eluting stents versus bare metal stents in bifurcation lesions (Level III evidence). A study by Lemos et al (2004c) looked at consecutive patients (n=508) with sirolimus-eluting stents enrolled in the RESEARCH registry and compared them with an historical control group containing consecutive patients (n=450) with bare metal stents. This study reported on the rates of clinically-driven TLR in bifurcation lesions and other sub-groups (including diabetes mellitus, long lesions and small vessels). Bifurcation stenting using sirolimus-eluting stents resulted in less clinically-driven revascularisations at 12 months although this effect was not statistically significant (RR=0.38; CI: 0.13-1.13; p=0.08) and not statistically different to the effect in patients with no bifurcation stenting. This finding is limited by differences in the baseline characteristics and clinical practice between the sirolimus-eluting stent group and the historical control group. In addition, it likely that this study lacked sufficient power to detect a true difference in the effectiveness of drug-eluting stents in patients with bifurcation stenting compared to those with stenting at other sites.

A sub-study of the RAVEL trial reported on the frequency of side branch occlusion and recanalisation in sirolimus-eluting stents versus bare metal stents when used in bifurcation lesions (without providing information about the site of the lesion). Patients who had one or more side branches covered by a sirolimus-eluting stent (n=63, 118 side branches) or a bare metal stent (n=65, 124 side branches) were included (Tanabe et al 2002). The groups were not significantly different in terms of baseline clinical and demographic characteristics, apart from a significantly greater proportion of males in the control group. Baseline angiographic and procedural characteristics of side branches were similar between groups, with the exception of a significantly greater duration of balloon inflation in the sirolimus group. Angiographic follow-up occurred at six months. Although the investigators observed that the recanalisation rate was favourable in the sirolimus-eluting stent group, there was no statistically significant difference in side branch occlusion or recanalisation between the study groups. The only independent predictor of side branch occlusion at follow-up was type A side branch morphology (side branch arising within the lesion, with ostial narrowing) (Tanabe et al 2002). The rate of revascularisation events between the groups was not reported.

A randomised trial by (Colombo et al 2004) that compared the safety and efficacy of using two sirolimus-eluting stents versus a sirolimus stent and PTCA for the treatment of coronary bifurcation lesions was identified in the initial search strategy but not included in the review because it did not compare sirolimus-eluting stents with bare metal stents. This small trial (n=85) was designed as a pilot study and recruitment was not based on power calculations. Therefore the observation of no significant difference in TLR at 6 months may be due to the insufficient power of the study to detect a true difference. Another major limitation of this study was the large number of patients (22/43) from the stent/PTCA group crossing into the double stenting group.

In stent restenosis

There is no evidence from the included trials or related sub-studies to estimate the safety and effectiveness of drug-eluting stents in treating in-stent restenosis.

Four non-randomised studies with small numbers of patients have evaluated the use of drug-eluting stents in in-stent restenosis. However the lack of a control group and the small study numbers in these studies prevent any conclusions about the effectiveness of drug-eluting stents versus bare metal stents in treating ISR (described below).

The TAXUS III study is a single-arm series of 28 patients with ISR treated with paclitaxel-eluting stents. 13 of the 28 patients were treated with two paclitaxel-eluting stents. There were no cases of subacute stent thrombosis. The TLR rate was 21.4 per cent (6 out of 28 patients), with two patients developing restenosis due to neointimal hyperplasia in a gap between two paclitaxel-eluting stents (Tanabe et al 2003). These results have been reported to indicate the safety of using paclitaxel-eluting stents for this indication, but conclusions are limited by the sample size and lack of comparator.

Degertekin et al (2003b) published a case series on 16 patients who received a sirolimus-eluting stent for the treatment of complex ISR. At four-months, follow-up angiography revealed one patient with a residual restenosis due to silent total reocclusion of the vessel and two patients who were asymptomatic but had greater than 50 per cent restenosis of their lesions. At nine months clinical follow-up, two of the patients had died and one had suffered an AMI but the majority of patients were MACE free (Degertekin et al 2003b). Another study published by the same author (Degertekin et al 2004), reported on the angiographic and intravascular ultrasound measurements at 4-6 months in patients enrolled in the First-In-Man registry treated with sirolimus-eluting stents comparing a sample of 41 patients with in-stent restenotic lesions with 45 patients with *de novo* coronary artery lesions. The effect of sirolimus-eluting stents in preventing neo-intimal proliferation was reported in both groups and no significant differences observed. Clinically relevant endpoints were not reported in this article.

Sousa et al (2003a) conducted a pilot study in 25 patients to determine the safety and efficacy of using a sirolimus-eluting stent for the treatment of ISR. Angiographic and intravascular ultrasounds were obtained after the procedure and at 4 and 12 months. At one year, one patient developed asymptomatic ISR as determined on follow-up angiogram and there were no MACE events (Sousa et al 2003a).

Long lesions (>18mm)

Long lesions are those where the stenosis of the vessel covers an area which is longer than 18mm. However this definition varied between trials, with the SIRIUS trial using >13.5mm to define a long lesion.

Level II evidence on the effectiveness of drug-eluting stents compared to bare metal stents in long lesions is available in two of the included trials. The TAXUS IV trial reported on a subgroup of 100 patients with long lesions but did not specify the breakdown of patient numbers into paclitaxel-eluting stents and bare metal stents. The 12 month TLR results favoured the TAXUS stent in patients with long lesions (>20mm) with 5.5 per cent TLR in the TAXUS group compared to 22.1 per cent TLR in the control group (Stone et al 2004).

Target lesion revascularisation rates for long lesions (>13.5mm) have been looked at in the SIRIUS study. The subgroup involved 519 patients although the breakdown of patient numbers into sirolimus-eluting stent group and bare metal stent group was not specified. At nine months the rate of TLR in the bare metal stent arm was increased by 17.4 per cent compared to 5.2 per cent in the sirolimus-eluting stent arm ($p<0.001$) (Moses et al 2003).

Two non-randomised studies from the RESEARCH registry using historical controls (Lemos et al 2004a; Lemos et al 2004c) have looked at effectiveness of sirolimus-eluting stents in a sub-group

of patients with long lesions. Lemos et al (2004c) reported that sirolimus-eluting stents reduced clinically-driven TLR in patients with lesions ≥ 33 mm at 12 months although this effect was not statistically significant (RR=0.41; CI:0.16-1.03; $p=0.06$). The number of patients in the long lesion group was not reported.

The results from these sub-studies favour the use of drug-eluting stents compared to bare metal stents in patients with long lesions. Interpretation of this evidence for conclusions about the effectiveness of drug-eluting stents in patients with long lesions compared to patients without long lesions is difficult given the small patient numbers and the likely inadequate power of the studies to detect an interaction between the lesion size and treatment effect. We did not identify any other studies evaluating the relative effectiveness of drug-eluting stents versus bare metal stents in long lesions.

Small vessels (<2.5mm)

Results from the RAVEL trial were analysed according to vessel size in an angiographic study (Regar et al 2002). The sample of 238 patients was stratified according to vessel diameter (baseline reference diameter in the vessel segment), with terciles defining small (<2.36mm), intermediate (2.36 –2.84) and large vessels (>2.84). The small vessel group consisted of 79 patients (42 in the sirolimus group, and 37 in the bare metal stent group). There was a significantly larger proportion of diabetic patients in this group. Angiographic findings showed that the sirolimus-eluting stents prevented neointimal proliferation and late lumen loss in small vessels. There was no binary restenosis in the sirolimus group compared to 35 per cent in the bare metal group.

The SIRIUS trial looked at a subgroup of 522 patients with small vessels defined as (<2.75 mm in diameter, which exceeds the definition used in this review) Although the number of patients per treatment arm is not recorded for this subgroup, the rate of TLR at 1 year favoured the sirolimus group (6.6%) compared to the bare metal stent group (22.3%) ($p<0.0001$) (Holmes et al 2004).

The TAXUS IV trial reported on a sub-group of 176 patients with small vessels but did not specify the breakdown of patient numbers into paclitaxel-eluting stents and bare metal stents. The 12 month TLR results favoured the TAXUS stent in patients with small lesions (≤ 2.5 mm) with 5.6 per cent TLR in the TAXUS group compared to 20.6 per cent TLR in the control group (Stone et al 2004).

In an uncontrolled study by (Lemos et al 2004b), 91 patients (112 lesions) enrolled in the RESEARCH registry were treated with 2.25mm diameter sirolimus-eluting stents (reference diameter 1.88 ± 0.34 mm) and compared with 109 patients treated with sirolimus-eluting stents ≥ 2.5 mm diameter (reference diameter 2.52 ± 0.57 mm). The 6 month angiographic restenosis rate for patients with small vessels (<2.25 mm diameter) was 10.7 per cent versus 3.9 per cent in the vessels >2.5mm diameter ($p=0.1$). The 12 month results were only reported in the small vessel group (<2.25 mm diameter) [MACE =7.7% and TLR = 5.5%]. Any true difference may have been obscured due to study size.

Results from the small vessel subgroups show beneficial results in reducing TLR and MACE in the drug-eluting stent groups compared to bare metal stent groups but as stated earlier, the small study numbers and inadequate power in these subgroup analyses prevent conclusions about any additional benefit in this subgroup. We did not identify any other studies evaluating the relative effectiveness of drug-eluting stents versus bare metal stents in small vessels.

Appraisal

Quality assessment

A standard checklist for quality appraisal of RCTs (see Table 12) was used to evaluate the seven drug-eluting stent trials. The results of the study appraisals are provided in Appendix E. All of the included studies met each of the pre-specified quality criteria for this review. All of the trials were randomised and blinded. All of the trials reported correct, blinded randomisation method described or randomised, double-blind method stated and group similarity documented. An intention to treat analysis was reported in all studies although this was restricted to evaluable patients for the angiographic endpoint. All of the studies had at least 90 per cent follow-up for the clinical outcomes and a variation of 43-97 per cent follow-up for the angiographic outcomes.

The number of patients withdrawing from the study after randomisation was reported in all studies. The number of patients excluded after randomisation was one or two patients in the E-SIRIUS and C-SIRIUS trials and 12 patients in the TAXUS IV trial. A higher number of withdrawals were reported in the SIRIUS trial. This study excluded 43 patients after the pretreatment angiogram that followed randomisation. Although the specific reasons for subject exclusion were not described by study group, baseline similarity was achieved in the patients included in the analysis.

Applicability of study population to intended practice

The applicability of the results of this review to clinical practice in Australia will be limited if the characteristics of patients in the included studies are not fully representative of the type of patients in whom this technology will be used. For example, if a larger proportion of patients in clinical practice have co-morbidities or if drug-eluting stents are used in a larger proportion of patients with multi-vessel disease. The baseline characteristics of patients varied within the included studies. The RAVEL trial had a limited study population in terms of lesion and clinical complexity compared to the E-SIRIUS trial. The baseline sample characteristics of diabetes mellitus (18.5%), previous CABG (1.7%) and previous PTCA (18.1%) and multi-vessel disease (29.4%) indicate that the trial included patients with relatively low cardiac risk factors and clinical complexity (Morice et al 2002). The E-SIRIUS trial had a higher risk profile for restenosis, such as a small mean reference diameter, longer lesions (15.0 mm versus 9.6 mm in RAVEL, $p=0.001$) and 42 per cent previous MI. This is reflected in the angiographic binary restenosis rate at 8 months in the controls which was 42.3 per cent compared with 26.6 per cent in the RAVEL trial (Schofer et al 2003). The pooled analyses provided in this review provide an estimate of treatment effect using data from this range of trial participants.

It is not possible to generalise the results from the included trials to the types of patients and lesions that were excluded from the trials, including bifurcation lesions, stenosis of the left main coronary artery, vessels smaller in diameter than 2.5 mm or greater than 32mm or lesions with in-stent restenosis. Non-randomised studies reporting on the safety and effectiveness of drug-eluting stents in routine clinical practice are underway (<www.bostonscientific.com 2004a>; <www.jnj.com 2004>).

Co-therapies

The variation in protocols for anti-platelet therapy between the studies is a factor to consider when interpreting the results of the meta-analysis as well as generalising the results to clinical practice in Australia. The use of clopidogrel was consistent across trials but the duration of use

varied from one month to six months. The TAXUS trials used clopidogrel for 6 months; patients in the E-SIRIUS trial received ticlopidine or clopidogrel for two months versus three months clopidogrel for the SIRIUS trial. The potential interaction between duration of antiplatelet therapy and the prevention of in-stent thrombosis across these trials has not been assessed.

In Australia, the duration of clopidogrel use is believed to range from 3- 12 months for drug-eluting stents (MSAC Advisory Panel May 2004). The average duration of use has been estimated to be 6 months which is more comparable to the trials evaluating paclitaxel-eluting stents than those evaluating sirolimus-eluting stents. It is unknown whether the effectiveness of drug-eluting stents compared to bare metal stents is modified by the duration of clopidogrel use, limiting further conclusions about the generalisability of the trial results to Australian practice.

The use of Glycoprotein IIb/IIIa receptor blocker was operator dependent in most studies and varied widely with 16 per cent use reported in the E-SIRIUS trial compared to 60 per cent use in the SIRUS trial. Overall, there were similar numbers of patients receiving Glycoprotein IIb/IIIa receptor blockers in the two groups except the TAXUS I and TAXUS IV trials which did not report its use. This therapy is not routinely used in Australia for drug-eluting stent PCI (only used in AMI angioplasty) and without evidence that its use modifies the effectiveness of drug-eluting stents compared to bare metal stents it is unclear if this variation in practice would alter the applicability of the trial results (MSAC Advisory Panel August 2004). If Glycoprotein IIb/IIIa receptor blockers were introduced as standard practice in Australia this would increase the cost of the drug-eluting stent procedure.

Revascularisation definition

There are two main issues concerning the interpretation of revascularisation events in the included RCTs. The most critical issue is the limited applicability of the reported rates of target lesion revascularisation, as defined by the included trials, to rates of revascularisation in routine clinical practice. This is because it is likely that a proportion of these events will have been driven by the results of angiograms specified in the trial protocol rather than patient symptoms alone. In practice, post-procedural angiography is not performed unless the patient presents with recurrent symptoms and thus only those patients who are symptomatic will be evaluated for repeat revascularisation. There is substantial evidence that the rate of revascularisation is higher in patients when the findings from routine angiography are used in addition to recurrent clinical symptoms. A pooled analysis of individual patient data from 6 clinical trials of coronary stents (n=6,186) observed that only 45 per cent of 419 lesions classified as ≥ 50 per cent restenosis on angiogram were associated with ischaemic symptoms and/or a positive functional study of ischaemia or an adjudicated clinical event (Cutlip et al 2002). The difference observed in individual studies has ranged from 33-45 per cent in trials (Fischman et al 1994; Serruys et al 1994a) to 76 per cent in a PTCA registry study reporting on the proportion of patients with restenosis ($\geq 50\%$) on follow-up angiography who had definite or probable angina (Holmes et al 1984).

In each of the trials included in this review that provided a definition of TLR, this definition included an angiographic criterion of ≥ 50 per cent restenosis. In these trials it is likely that the findings of routine angiography performed at 6-9 months influenced the decision to perform revascularisation. The one exception is the C-SIRIUS trial in which the >50 per cent restenosis criterion was only applied to symptomatic patients. In this trial, patients with no symptoms and >70 per cent restenosis on routine angiography underwent TLR which was reported as 'clinically driven' revascularisation (Schampaert et al 2004). Of the 11 patients in this trial who had TLR at 9 months, 9 (82%) patients were symptomatic, while 2 (18%) patients had TLR as a

result of routine angiography (> 70% restenosis). Exclusion of non-symptomatic patients who had TLR results in TLR rates of 4 per cent in the sirolimus-eluting stents group and 14 per cent in the BMS group. These rates are within the ranges of TLR reported by the other trials (see table 19).

In the RAVEL trial, both angiographically and clinically driven results for MACE are reported in a table and the 'clinically driven' results are described in the text, but the criteria used for this definition is not provided (Morice et al 2002). As previously discussed, the SIRIUS trial reports that TLR was clinically driven. However the criteria on which this definition was based was not specified. As with the clinical driven revascularisation in the C-SIRIUS trial, the TLR rates of 4.9 per cent in the sirolimus-eluting stents group and 20 per cent in the BMS group in the SIRIUS trial are within the ranges of TLR reported by the other trials (see table 19). If revascularisation was driven by angiography rather than clinical symptoms it is possible that the TLR rates may overestimate the true number of patients requiring revascularisation in clinical practice. While this problem is not expected to produce bias in the comparison of revascularisation rates for drug-eluting stents relative to bare metal stents (risk ratio) because the same definition applies to both arms, it will have an impact on the absolute risk reduction observed and thus the analysis of cost-effectiveness. This issue is addressed in the economic evaluation by using a sensitivity analysis that includes the trial reported revascularisation rates and the rates if we assume that 50 per cent or 75 per cent of these are events that are clinically driven.

The second issue concerns the variation in the definition of revascularisation across the trials and in the composite endpoint MACE. The TAXUS I, TAXUS II and TAXUS IV trials reported revascularisation as a broader term of target vessel revascularisation (TVR) in the composite endpoint whereas the sirolimus trials recorded it as target lesion revascularisation (TLR). This slight variation in definitions needs to be considered when comparing the MACE rates across studies.

Major adverse cardiac events

This review demonstrated statistically significant fewer MACE in patients receiving drug-eluting stents and those receiving bare metal stents. However differences in the outcomes of mortality, AMI and CABG between these two groups were not observed in the pooled analysis. (The one exception was the largest trial which did demonstrate a difference in CABG.) This finding may be due to a lack of power to detect a difference in these rarer outcomes. It may also be the case that the only effect of drug-eluting stents will be to prevent revascularisation procedures without an impact on AMI and death. MACE rates in this review are driven by revascularisation procedures and so may not give a true indication of clinically important adverse events if some of these procedures were protocol driven (as discussed above). A different composite endpoint of MACE that does not include revascularisation would provide an endpoint based on important objective clinical adverse events (ie exclude the protocol driven events).

Limited follow-up of included trials

A limitation of the evidence on effectiveness and safety is the short follow-up available from the drug-eluting RCTs. The angiographic follow-up was limited to 6-9 months and clinical follow-up to 9-12 months in all reported trials which may be insufficient to detect the true effect of treatment, for example, if restenosis is delayed rather than prevented. Two year follow-up has occurred in the SIRIUS trial but these results were not published at the time of writing. 18 month follow-up of clinical and angiographic outcomes have been published in the TAXUS I trial, however, the numbers are small with only 20 patients in the paclitaxel-eluting stent group. The evidence from this paper is limited given such a small number of patients and no follow-up of the control group to compare outcomes.

What are the economic considerations?

Economic evaluation of new health care technologies is particularly important where the new technology offers health benefits at additional cost. It is clear there will always be a limit to the additional cost that would be paid for a given health gain. Economic evaluation is generally aimed at determining whether such incremental costs represent value for money.

The usual process for an economic evaluation is first to consider the additional benefits accrued with the new device/procedure relative to the comparator (ie the incremental effectiveness), and to then proceed with determining cost differences between the new procedure and the comparator (ie incremental costs). When both of these quantities are known, then an incremental cost-effectiveness ratio (ICER) can be determined. The calculation of an incremental cost-effectiveness ratio is shown below:

$$ICER = \frac{Cost_{NEW} - Cost_{COMPARATOR}}{Effectiveness_{NEW} - Effectiveness_{COMPARATOR}}$$

In cases where a new technology offers inferior or equal health benefits at a higher cost it clearly does not provide value for money. This technology is “dominated” by the comparison technology. In cases where the new technology offers superior health benefits at a lower cost to the comparator it is said to be “dominant”.

Literature search

A literature search was conducted to identify published papers of economic evaluations of drug-eluting stents to end August 2004.

The following broad search strategy was used

#	Terms	Results
1	(Cypher\$ or sirol\$ or rapamyc\$).mp.	4,079
2	(taxus\$ or paclitax\$).mp.	10,046
3	(anti-prolif\$ or antiprolif\$).mp.	10,186
4	stent\$.mp.	25,116
5	(econ\$ or cost\$).mp.	281,371
6	1 and 4 and 5	23
7	2 and 4 and 5	14
8	3 and 4 and 5	7
9	6 or 7 or 8	29

Of the 29 non-duplicate papers identified by this search, 18 were review papers and four were letters, four were not related and two provided general information on costs only. One paper (Greenberg et al, 2002) examined the economic impact of restenosis, and provided a brief summary (two paragraphs) of potential implications for cost-effectiveness of antiproliferative stents. There was limited information on the structure and assumptions underlying the model.

They reported a range of up to \$12,500 (USD, 1998) per repeat revascularisation avoided, and as would be expected, indicated that the estimate was dependent on the patient group, cost of both stents and follow up and the long term clinical effectiveness. An additional publication (Cohen et al, 2004) was identified by the Advisory Panel as the journal volume had not been indexed in Medline at the time of the search. This paper reports on the resource utilisation and cost-effectiveness of sirolimus-eluting stents as part of the SIRIUS trial. The authors report a ‘cost per repeat revascularisation avoided’ of US\$1,650, and cost per QALY of US\$27,540. As would be expected, incremental cost effectiveness ratios were particularly sensitive to patient subgroup and the predicted target lesion revascularisation rate.

Economic evaluation

Resource utilisation data at index hospitalisation and over the 12 months following the trial procedure was collected as part of both the SIRIUS and TAXUS IV trials. We have used a trial based economic model to compare Cypher stents, TAXUS stents and bare metal stents (BMS).

The clinical outcomes (TLR and MACE at 12 months) for this evaluation are based upon a meta-analysis of the SIRIUS and RAVEL trial data (for Cypher stents) and a meta-analysis of the TAXUS, TAXUS II SR and TAXUS IV trials (for TAXUS stents).

The costs are based upon data about the healthcare resources used for the insertion of the stent and follow-up care at 12 months collected as part of the Cypher SIRIUS trial (Cypher stents) and as part of the TAXUS IV trial (Taxus stents). The resource use related to non-target lesions occurring from the time of the procedure up to 12 months was not provided by the TAXUS IV trial. As a result, it is assumed that this resource use is the same as that reported in the SIRIUS trial.

As both these trials were conducted outside Australia, it is difficult to determine the extent to which treatment practice variations may influence the likely costs in Australia. The base case analysis has assumed that resource utilization is as documented in the trial. Sensitivity analyses have been performed to estimate the possible effect of treatment practice variations on costs and benefits.

Clinical outcomes

Both clinically driven target lesion revascularisation (TLR) and the combined clinical endpoint of major adverse cardiac events (MACE) at 12 months have been used as outcomes for this evaluation.

Table 21 Target lesion revascularisation at 12 months

Trial	Drug eluting stents (DES)	BMS	Reduction in TLR with DES
TAXUS (paclitaxel)	0/30	3/30	10.0%
TAXUS II SR (paclitaxel)	6/129	17/132	8.2%
TAXUS IV (paclitaxel)	28/639	96/633	10.8%
Total for paclitaxel	34/798	116/795	10.3%
RAVEL (sirolimus)	0/120	27/118	22.8%
SIRIUS (sirolimus)	26/533	105/525	15.1%
Total for sirolimus	26/653	132/643	16.5%

Table 22 MACE at 12 months

Trial	Drug eluting stents (DES)	BMS	Reduction in MACE with DES
TAXUS (paclitaxel)	1/30	4/30	10.0%
TAXUS II SR (paclitaxel)	14/129	29/132	11.2%
TAXUS IV (paclitaxel)	69/639	127/633	9.3%
Total for paclitaxel	84/798	160/795	9.6%
RAVEL (sirolimus)	7/120	34/118	22.9%
SIRIUS (sirolimus)	44/533	117/525	14.0%
Total for sirolimus	51/653	151/643	15.7%

Cost estimates

The cost component of this analysis has been split into costs associated with the procedure itself and those costs associated with subsequent clinical follow up after the study procedure. This second category has been measured in the trials out to 12 months.

Study procedure

Staff costs

It is unlikely that there will be any additional staff costs associated with the use of a drug eluting stent over and above those associated with the use of a bare metal stent. As such, staff costs have not been included explicitly below as they are likely to be the same for both treatment groups. Staff costs are captured by DRG F15Z, which also captures other costs such as overheads, pharmacy and imaging costs during the period of hospitalisation. DRG F15Z is the DRG for percutaneous coronary angioplasty, with stenting. As DES have been costed separately (see Disposables below), the prosthetic component of DRG F15Z (ie the stents) has been subtracted from the total procedural costs.

Drug costs

Clopidogrel was almost exclusively used in the trials of both DES, and is the most commonly used therapy in Australia. It has been assumed that patients in both the DES and BMS groups are treated with clopidogrel 75 mg daily for 6 months.

Disposable costs

Resource utilization data was collected as part of the SIRIUS trial. There are few significant differences in resource use in the study procedure. The only resource difference reported was volume of contrast medium ($p=0.02$) (Cohen et al, 2004). The magnitude of difference between groups was small; therefore the likely cost difference is negligible and was not included in the analysis.

Stent costs were based on the average selling price for each type of stent (as determined by a survey of Australian states).

SIRIUS and TAXUS IV trials specifically treated a single lesion with DES. Stent usage in clinical practice in Australia has been estimated by the Advisory Panel at 1.5 stents per patient. This has been tested in a sensitivity analysis over the range of 1.0-2.0 stents per patient.

Table 23 Summary of resource utilisation for study procedures

Component	CYPHER	BMS	TAXUS	BMS	Data source
PCI procedure (including staff costs)					
Units used	1	1	1	1	
Cost per unit	\$4,571	\$4,571	\$4,571	\$4,571	DRG F15Z, NHCDC public sector estimated, AR-DRG version 4.1, 2001-2002, (total cost - cost of prostheses).
Total cost	\$4,571	\$4,571	\$4,571	\$4,571	
Drug costs					
Type	Clopidogrel	Clopidogrel	Clopidogrel	Clopidogrel	Advisory Panel Expert Opinion
Units used	75mg daily for 6 months	75mg daily for 6 months	75mg daily for 6 months	75mg daily for 6 months	Advisory Panel Expert opinion
Cost per unit	\$84.08	\$84.08	\$84.08	\$84.08	Item 8358X, PBS, 1 May 2004, per month (Indication: Prevention of recurrence of myocardial infarction or unstable angina)
Total	\$504.48	\$504.48	\$504.48	\$504.48	
Disposable costs					
Study stent					
Type	CYPHER	Bx Velocity	TAXUS	BMS	
Units used	1.5	1.5	1.5	1.5	Advisory Panel expert opinion
Cost per unit	\$2,400	\$855	\$2,400	\$855	Average selling price (state survey)
Total cost	\$3,600	\$1,283	\$3,600	\$1,283	
Total	\$8,675	\$6,358	\$8,675	\$6,358	

DRG = Diagnosis Related Group, NHCDC = National Hospital Cost Data Collection, PBS = Pharmaceutical Benefits Schedule.

All pharmacy costs associated with the procedure itself (including the use of GP IIb/IIIa inhibitors) are incorporated into the average procedure cost derived for the DRG F15Z (\$4,571). The drug costs that have been included separately are those which are not included in the index procedure costs, eg procedure related drug costs after discharge from hospital (6 months clopidogrel).

In addition to the costs relating to the trial procedure, patients may incur additional costs for other events and interventions that occur during the period of hospitalization for the study procedure, ie prior to discharge. The average additional costs incurred by patients are detailed below.

Table 24 Average additional hospitalisation costs at study procedure for SIRIUS and TAXUS IV trials

Event	DRG	Unit cost	SIRIUS					TAXUS IV				
			Cypher (%)	Cost	BMS (%)	Cost	Source of utilisation estimate	Taxus (%)	Cost	BMS (%)	Cost	Source of utilisation estimate
Death	F60C	\$3,711	0.002	\$7.42	0	\$0.00	Cohen et al, 2004	0	\$0.00	0.003	\$11.13	Applicant
MI	Sep weighted DRG F60A/F60B/F10Z/ F41A/F41B	\$5,372	0.023	\$123.56	0.015	\$80.58	Cohen et al, 2004	0.024	\$128.93	0.021	\$112.81	Applicant
CABG	Sep Weighted F05A/F05B/F06A/ F06B	\$19,550	0.002	\$39.10	0	\$0.00	Cohen et al, 2004	0	\$0.00	0.002	\$39.10	Applicant
Repeat PCI	Sep Weighted DRG F15Z/F16Z	\$5,753	0.002	\$11.51	0	\$0.00	Cohen et al, 2004	0.003	\$17.26	0.002	\$11.51	Applicant
Diagnostic catheterization	MBS item 38218, 21941	\$668	0.004	\$2.67	0.002	\$1.34	Cohen et al, 2004	0.012	\$8.02	0.003	\$2.01	Applicant
Stroke	Sep weighted DRG B70A/ B70B/ B70C	\$8,198	0.002	\$16.40	0.008	\$65.59	Applicant(rate per patient)	0	\$0.00	0.002	\$16.40	Applicant
Vascular complications req. surg. / transfusion	Sep Weighted DRG F14A / F14B / F14C	\$6,420	0.017	\$109.14	0.023	\$147.65	Cohen et al, 2004	0.016	\$102.72	0.019	\$121.97	Applicant
<i>Total costs</i>				\$309.79		\$295.16			\$256.92		\$314.93	

Follow up treatment costs (between study procedure at discharge and 12 months)

Resources included

The resource use reported as part of SIRIUS and TAXUS IV are presented on the following page.

Where peer reviewed, published data were available, these have been used to estimate resource use. This data has been supplemented with additional data from applicants. The SIRIUS trial provided information on follow up events and resource use between discharge and 12 months (Cohen et al, 2004). Other outpatient resource usage such as diagnostic and pathology tests, outpatient drug therapy (excluding clopidogrel) and inpatient and/or outpatient cardiac rehabilitation were not measured.

The TAXUS IV trial provided data for estimation of resource utilisation between discharge and 12 months for death, MI and for CABG and PCI concerning only the target vessel. As data was not provided for non-target lesion resource use for the TAXUS IV trial, we have assumed non-target lesion related resource use is the same as that reported in the SIRIUS trial. TAXUS IV also did not collect information on other cardiovascular admissions and events such as emergency and outpatient visits over this time period; we have also assumed that these are the same as reported for the SIRIUS trial.

Unit costs

Follow-up treatment costs have been calculated using:

- NHCDC public sector estimated, AR-DRG version 4.2 (round 6) costs for 2001-2002 (separation-weighted where appropriate) for hospitalisations;
- Australian Ambulatory Classification (updated) for non-admitted services (Manual of Resource Items 2001);
- MBS fees for outpatient doctor visits (May 2004) (separation-weighted where appropriate); and
- Pharmaceutical Benefits Schedule (PBS) dispensed prices for drugs

Table 25 summarises the costs and resources used between discharge and 12 months for the SIRIUS and TAXUS IV studies. The sources of resource use estimates for each trial are indicated in the table.

Table 25 Public sector costs of resources used between discharge and 12 months for SIRIUS and TAXUS IV

Event	Source	Unit cost	SIRIUS					TAXUS IV						
			Cypher (%)	Cost	BMS (%)	Cost	Δ	Source	Taxus (%)	Cost	BMS (%)	Cost	Δ	Source
Death	DRG F60C	\$3,711	0.011	\$40.82	0.008	\$29.69	\$11.13	Cohen et al 2004	0.021	\$77.93	0.014	\$51.95	\$25.98	Applicant
MI	Sep weighted DRG F60A/F60B/ F10Z/F41A/F41B	\$5,372	0.008	\$42.98	0.019	\$102.07	-\$59.09	Cohen et al 2004	0.011	\$59.09	0.025	\$134.30	-\$75.21	Applicant
PCI	Sep Weighted DRG F15Z/F16Z	\$5,249												
	6 mo clopidogrel (@\$84/mo)	\$504												
PCI (target lesion)		\$ 5,753	0.0398	\$228.96	0.205	\$1,179.29	-\$950.34	Meta-analysis	0.0426	\$245.06	0.201	\$1,156.28	-\$911.22	Meta-analysis
PCI (all other lesions)		\$ 5,753	0.1102	\$633.94	0.119	\$684.56	-\$50.62	Cohen et al 2004 meta-analysis	0.1102	\$633.94	0.119	\$684.56	-\$50.62	Assumption ¹
PCI (total)		\$ 5,753	0.15	\$862.90	0.324	\$1,863.86	-\$1,000.96	Cohen et al 2004 (rate per patient)	0.1528	\$879.00	0.32	\$1,840.85	-\$961.84	Sum (target + non-target PCI)
CABG	Sep Weighted F05A/F05B/ F06A/F06B	\$19,550	0.013	\$254.15	0.03	\$586.51	-\$332.35	Cohen et al 2004 (rate per patient)	0.017	\$332.35	0.038	\$742.91	-\$410.56	Applicant (target vessel only)
Diagnostic catheterizations	MBS 38218, 21941	\$668	0.128	\$85.56	0.185	\$123.66	-\$38.10	Cohen et al,2004 (rate per patient)	0.128	\$85.56	0.185	\$123.66	-\$38.10	Assumption ² (rate per patient)
Stroke	Sep weighted DRG B70A/ B70B/ B70C	\$8,198	0.008	\$61.53	0.013	\$109.31	-\$47.78	Applicant (rate per patient)	0.008	\$61.53	0.013	\$109.31	-\$47.78	Assumption ² (rate per patient)
Vascular surgery	Sep Weighted DRG F14A / F14B / F14C	\$6,420	0.006	\$36.13	0	\$0.00	\$36.13	Applicant (rate per patient)	0.006	\$36.13	0	\$0.00	\$36.13	Assumption ² (rate per patient)
Other cardiac admissions	Sep weighted F42A/42b/66a/ 66b/67a/67b/72a/ 72b/74z	\$1,985	0.27	\$535.90	0.411	\$815.76	-\$279.86	Cohen et al 2004	0.186	\$369.18	0.264	\$523.99	-\$154.82	Applicant
Emergency, not admitted	AAC Gp 24	\$55	0.107	\$5.88	0.116	\$6.39	-\$0.51	Applicant (rate per patient)	0.107	\$5.88	0.116	\$6.39	-\$0.51	Assumption ² (rate per patient)
Outpatient doctor visits	Sep weighted MBS 104/105	\$51	0.94	\$48.09	0.95	\$48.92	-\$0.83	Applicant (rate per patient)	0.94	\$48.09	0.95	\$48.92	-\$0.83	Assumption ² (rate per patient)
Total costs				\$1,974		\$3,686	-\$1,712			\$1,955		\$3,582	-\$1,627	

Assumption¹ The applicant has only provided target vessel revascularisation rates, we have assumed that non-target vessel revascularisation occurs at the same rates for DES and BMS as reported in the SIRIUS trial

Assumption² Data on these events were not collected as part of TAXUS IV trial. Rates for DES and BMS have been assumed to be the same as reported in the SIRIUS trial

Total costs

The overall cost difference between Cypher DES and BMS at 12 months is \$620, and between TAXUS and BMS at 12 months is \$632 (Table 26). These costs do not include other costs such as diagnostic (other than diagnostic catheterization) and pathology costs, or rehabilitation costs. Ideally we would like to see costs collected over a longer time period to gain a clearer picture of what happens over time. As these costs have been rounded to whole dollars for simplicity, so some costs do not add up.

Table 26 Cost differences at 12 months SIRIUS and TAXUS IV

Cost	Cypher			TAXUS		
	CYPHER group	BMS group	Difference	TAXUS group	BMS group	Difference
Study procedure (table 3)	\$8,675	\$6,358	\$2,318	\$8,675	\$6,358	\$2,318
Any additional hospitalization costs prior to discharge for study procedure (table 4)	\$309.79	\$295.16	\$15	\$256.92	\$315	-\$58
12 month follow-up (table 5)	\$1,974	\$3,686	-\$1,712	\$1,955	\$3,582	-\$1,628
<i>Total</i>	\$10,959	\$10,339	\$620	\$10,887	\$10,255	\$632

Results

All calculations have been conducted using appropriate number of decimal places, but data presented here has been rounded to the nearest whole dollar.

Base case analysis

$$ICER = \frac{Cost_{NEW} - Cost_{COMPARATOR}}{Effectiveness_{NEW} - Effectiveness_{COMPARATOR}}$$

Table 27 Incremental cost-effectiveness ratio for TLR and MACE

Cost	Cypher			TAXUS		
	CYPHER group	BMS group	Difference	TAXUS group	BMS group	Difference
Total costs at 12 months	\$10,959	\$10,339	\$620	\$10,887	\$10,255	\$632
Target lesion revascularisation						
TLR rates at 12 months	26/653	132/643	16.5%	34/798	116/795	10.3%
ICER: Cost per TLR avoided at 12 months	\$3746/TLR avoided			\$6117/TLR avoided		
Major Adverse Cardiac Events						
MACE rates at 12 months	51/653	151/643	15.7%	84/798	160/795	9.6%
ICER: Cost per MACE avoided at 12 months	\$3955/MACE avoided			\$6583/MACE avoided		

Sensitivity analyses

There is uncertainty regarding the applicability of trial based resource utilisation rates, particularly over the time from discharge to 12 months, to current Australian clinical practice. To provide an indication of the likely changes in the incremental cost effectiveness ratio (ICER) to the trial measured resource use, a number of scenarios were examined in sensitivity analyses designed to reflect possible Australian practice. The following sensitivity analyses have been conducted; results from these analyses are presented on the following page.

- It is possible that the rates of PCI in non-target lesions and rates of diagnostic catheterizations may not reflect the rates of these interventions in Australia. A sensitivity analysis was done where TLR and MACE rates are as reported in trials, but non-target lesion PCI rates and diagnostic catheterization rates are reduced to 50% of trial rates.
- Number of stents used
 - base case 1.5
 - lower 1 stent /pt
 - upper 2 stents /pt
- Target lesion revascularisation rates
 - all rates as per trial data
 - 50% of trial rates
 - outcome measures (TLR rates at 12 months) were adjusted to 50% of those reported in the trials
 - costs (ie resource use) of PCI (all target and non-target vessels/lesions) and CABG rates were adjusted to 50% of those reported in the trials
 - 75% trial rates
 - outcome measures (TLR rates at 12 months) were adjusted to 75% of those reported in the trials
 - costs (ie resource use) of PCI (all target and non-target vessels/lesions) and CABG rates were adjusted to 75% of those reported in the trials

Table 28 Sensitivity analyses

Cost	Cypher					TAXUS				
	CYPHER group	BMS group	Difference	\$/TLR avoided	\$/MACE avoided	TAXUS group	BMS group	Difference	\$/TLR avoided	\$/MACE avoided
Base case analysis	\$10959	\$10339	\$620	\$3746	\$3955	\$10,887	\$10,255	\$632	\$6117	\$6583
<i>1. Revascularisation rates to reflect Australian practice</i>										
Non-target lesion PCI rates and diagnostic catheterization rates are reduced to 50% of trial rates	\$10599	\$9935	\$664	\$4014	\$4238	\$10,527	\$9,851	\$676	\$6,546.82	\$7,045.41
<i>2. Number of stents used / patient</i>										
Lower bound (1/patient)	\$9,759	\$9,912	-\$153	Cost saving	Cost saving	\$9,687	\$9,828	-\$141	Cost saving	Cost saving
Upper bound (2/patient)	\$12,159	\$10,767	\$1,392	\$8415	\$8884	\$12,087	\$10,683	\$1,404	\$13,595.21	\$14,630.59
<i>3. Trial reported rates of PCI</i>										
PCI 50% of trial reported PCI rates	\$10,443	\$9,176	\$1,268	\$15320		\$10,324	\$9,025	\$1,299	\$25,150.80	
PCI 75% of trial reported PCI rates	\$10,723	\$9,789	\$934	\$7527		\$10,627	\$9,671	\$956	\$12,338.91	

As can be seen, the results are very sensitive to both the number of DES used per patient (sensitivity analysis 2), and as expected, to the magnitude of clinical benefit in terms of target lesion revascularisations avoided (sensitivity analysis 3). They are less sensitive to assumptions regarding rates of non-target lesion/vessel interventions (sensitivity analysis 1) as these rates are approximately comparable between DES and BMS arms of the trials.

Limitations of this analysis

This analysis is based on resource utilisation data from the SIRIUS and TAXUS IV trials and the clinical outcomes for Cypher and Taxus stents. The resource utilisation from the time of the procedure over the subsequent 12 months for the TAXUS trial non-target lesion related resource use is assumed to be the same as reported in the SIRIUS trial as this data was not provided for TAXUS IV. In addition, we would ideally like to base these analyses on Australian data, particularly resource utilisation estimates. As clinical practice may vary between countries, the trial estimates of resource utilisation may not reflect standard management in Australia. This has been tested in a sensitivity analysis, but the values chosen for this analysis are based upon expert opinion.

Resource utilisation and clinical effectiveness have only been measured to 12 months post-procedure. As this is a new technology, ideally we would like to know that the differences between drug-eluting stents and bare metal stents that are seen over this short time frame are actually sustained longer term.

Conclusions

Safety

The safety conclusions are:

- Results from the seven trials included in this review indicate that the risk of in-stent thrombosis following paclitaxel-eluting stent and sirolimus-eluting stent placement is no worse than following bare metal stent placement at up to one year post-procedure (Level I evidence). Longer term follow-up of this patient population is required to fully resolve the issue of late thrombosis. The generalisability of this evidence to the more clinically complex population in which drug-eluting stents may be used in Australian practice is not clear. However evidence from one large case series of the use of sirolimus-eluting stents in a broad population in the United States (Level IV evidence) has reported an incidence of 1.1 per cent (95% CI 0.4-2.2%) in-stent thrombosis up to a median of 100 days post-procedure which is comparable to rates reported in studies of bare metal stents.
- The short-term results from two sub-studies have not demonstrated any adverse events associated with overlapping sirolimus-eluting stents; however it may be that these studies were insufficiently powered to detect clinically relevant differences in these outcomes. This practice has not been addressed in trials of paclitaxel-eluting stents.
- In the short term, sirolimus-eluting stents appear to result in increased incomplete stent apposition. This was evident at 6 months for overall incomplete apposition for a clinically limited patient population in RAVEL, and at 8 months for late incomplete apposition for a less limited, more generalisable patient group in SIRIUS. This outcome has not been assessed in trials of paclitaxel-eluting stents. Incomplete apposition has not been associated with clinically significant adverse events at this time. However long-term follow up is required to determine whether increased incomplete apposition is sustained, and to clarify whether there are adverse sequelae of this phenomenon.

Effectiveness

These conclusions about the effectiveness of drug-eluting stents in treating single *de novo* coronary lesions are based on a systematic review of seven high quality randomised controlled trials (Level I evidence). The review did not seek to determine whether one type of drug-eluting stent is superior to another. This evidence supersedes the Level I clinical evidence available at the time of producing the report due to the availability of additional published evidence to address the review questions.

1. Effectiveness in decreasing myocardial infarction and death

This review did not demonstrate a statistically significant difference in the rate of myocardial infarction or death in patients receiving paclitaxel or sirolimus-eluting stents and those receiving bare metal stents. It is possible that current trial data and the pooled

analysis presented are insufficiently powered to detect clinically relevant differences in these outcomes.

2. Effectiveness in decreasing MACE

There is high quality trial evidence that both paclitaxel-eluting and sirolimus-eluting stents are more effective at decreasing the incidence of MACE compared to bare metal stents. The pooled analysis of MACE in the paclitaxel-eluting stent trials showed a statistically significant decrease in MACE in the paclitaxel-eluting stent group compared to the bare metal stent group. The relative reductions in MACE associated with the use of paclitaxel-eluting stents compared to bare metal stents were 59 per cent at 6 months and 48 per cent at 12 months. The pooled analysis of MACE in the sirolimus-eluting stent trials showed a statistically significant decrease in MACE in the sirolimus-eluting stent group compared to bare metal stents. The relative reductions in MACE associated with the use of sirolimus-eluting stents compared to bare metal stents were 64 per cent at 9 months and 67 per cent at 12 months. The size of the true treatment effect on MACE in a clinically complex population that may be more closely representative of the use of drug-eluting stents in practice is yet to be determined.

The lack of evidence that drug-eluting stents have any effect on medium-term mortality or rates of myocardial infarction indicates that the reduction of MACE in the drug-eluting stent groups is largely driven by differences in rates of TLR between drug-eluting stents and bare metal stent.

3. Effectiveness in decreasing angiographic restenosis and revascularisation procedures

There is high quality trial evidence that both paclitaxel and sirolimus-eluting stents are more effective at decreasing angiographic restenosis and revascularisation procedures than bare metal stents. The pooled analysis of TLR in the paclitaxel-eluting stent trials showed a statistically significant decrease in TLR in the paclitaxel-eluting stent compared to the bare metal stent. The relative reduction in TLR associated with the use of paclitaxel-eluting stents compared to bare metal stents was 64 per cent at 6 months and 71 per cent at 12 months. The pooled analysis of TLR in the sirolimus-eluting stent trials showed a statistically significant decrease in TLR in the sirolimus-eluting stent group compared to bare metal stents. The relative reduction in TLR associated with the use of sirolimus-eluting stents compared to bare metal stents was 77 per cent at 9 months and 80 per cent at 12 months. In some of the included trials it is unclear whether some of the revascularisations performed were driven by the results of early angiographic studies rather than the clinical presentation of the patient. If this has occurred, the number of revascularisation events for both study groups may be higher than would be expected in clinical practice where follow-up angiography is not routine. It is not known if the inclusion of angiographic (sub-clinical) outcomes would favour drug-eluting stents compared to bare metal stents for this outcome or not.

There is no evidence to conclude whether reductions in restenosis are maintained for time periods beyond those used in the included studies. Longer term results are necessary to exclude the possibility that drug-eluting stents may defer rather than prevent the onset of restenosis and the need for revascularisation. However, current clinical expert opinion suggests that the most critical period for in-stent restenosis is likely to be within the 12 month follow-up period of included trials (Advisory Panel, August 2004).

4. Effectiveness in subgroups of patients

- The trial evidence is not sufficient to draw additional conclusions about differences in the effectiveness of drug-eluting stents compared to bare metal stents in subgroups of patients that may potentially benefit more from drug-eluting stent implantation. Information relating to the subgroups of diabetics, long lesions and small vessels was drawn from sub-studies of the larger RCTs, and interpretation of the results are limited by the low sample sizes, inadequate power, and compromised randomisation. These studies provide evidence for a statistically significant reduction in revascularisation and MACE in diabetic patients, long lesions and small vessels at up to 12 months. However, there is insufficient information to determine whether these sub-groups of patients are more or less likely to benefit from drug-eluting stents over patient groups where these risk factors are absent.
- There was insufficient evidence available about the effectiveness of drug-eluting stents compared to bare metal stents in the treatment of in-stent restenotic lesions and bifurcation lesions of the LAD for the outcomes of interest.

Due to the evolving nature of the literature, the conclusions outlined above may be subject to review once more evidence becomes available.

Cost-effectiveness

The economic evaluation conducted as part of this report is limited to short term outcome and cost data (12 months after index procedure) and does not attempt to model the efficiency of DES beyond the trial time horizon.

- For the clinical outcome of target lesion revascularisations avoided at 12 months, the ICER ranges from approximately \$3,700 to \$6,200.
- For the clinical outcome of MACE avoided at 12 months, the ICER also ranges from approximately \$4,000 to \$6,500.
- As expected, these estimates are sensitive to the magnitude of clinical benefit associated with the DES and the number of stents used per patient.

It should be noted that given the relatively short duration of outcomes measured (clinical and resource use) for what is a chronic long-term condition, caution must be used in drawing inferences regarding the efficiency of this intervention beyond the 12 months time frame. Additional longer term data on the duration of clinical benefit and likely resource utilisation is required before definitive conclusions can be drawn regarding the long term efficiency of drug-eluting stents.

Recommendation

MSAC found that on the strength of current evidence regarding drug-eluting stents:

- The technology is as safe as bare metal stents for the treatment of *de novo* atherosclerotic lesions of the coronary arteries at up to one year post-procedure.
 - The technology is more effective than bare metal stents in reducing the rates of revascularisation procedures at up to one year.
 - There is insufficient evidence at this time to demonstrate a difference in the rates of myocardial infarction, coronary artery bypass grafting or mortality in patients receiving this technology compared to those receiving bare metal stents.
 - There is some evidence that the technology is more effective than bare metal stents in reducing the rates of revascularisation at up to one year in patients with diabetes, long lesions greater than 18mm and small vessels less than 2.5mm. However there is insufficient evidence at this time to demonstrate any additional benefit in these and other subgroups of patients at high risk of stent restenosis.
 - Cost-effectiveness is based on *de novo* single vessel lesions.
 - On the basis of trial data alone, the technology is cost-effective if a cost of \$3,700-\$6,200 is considered acceptable to avoid a target lesion revascularisation. However a sensitivity analysis to estimate the cost-effectiveness in Australian clinical practice indicates that the cost per target lesion revascularisation avoided may be higher than this figure. Australian clinical practice data is required to resolve this uncertainty.
- The Minister for Health and Ageing noted this recommendation on 2 March 2005.-

Appendix A MSAC terms of reference and membership

The MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of the MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or Affiliation
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Gerry Fitzgerald	Australian Health Ministers' Advisory Committee (AHMAC) representative
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Ms Rosemary Huxtable	Department representative
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Donald Perry-Keene	endocrinology
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine

Professor Alan Lopez	medical statistics and population health
Dr Ewa Piejko	general practice
Ms Sheila Rimmer	consumer health issues
Professor Jeffrey Robinson	obstetrics and gynaecology
Professor Michael Solomon	colorectal surgery, clinical epidemiology
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Advisory Panel

Advisory Panel for MSAC application 30

Drug-eluting stents

Associate Professor Richard King (Chair) MBBS FRACP Consultant Physician, Head, Program Director Medicine Southern Health, Monash Medical Centre	MSAC member
Professor Brendon Kearney MBBS FRACP FRACMA Executive Director, Clinical Systems Department of Human Services, Adelaide	MSAC member health administrator
A/Professor John Atherton MBBS PhD FRACP Director of Cardiology Royal Brisbane and Women's Hospital	MSAC member
Dr Leo Mahar MBBS FRACP Director of Cardiology Royal Adelaide Hospital	coopted member
Dr Paul McEneiry MBBS FRACP FCSANZ FSCAI FACC Senior Staff Cardiologist The Prince Charles Hospital	coopted member
Dr Marcus Ilton MBBS FRACP Cardiologist NT Cardiac Services Darwin Private Hospital	coopted member
Dr Edward G Stafford MBBS FRACS FACS Department of Cardiac Surgery The Prince Charles Hospital	coopted member
Mrs Sheila Rimmer Consumer health advocate	MSAC member
Ms Alex Lloyd MSAC Project Manager	Health Technology Section Department of Health and Ageing

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NMHC Clinical Trials
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University of Sydney

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MBBS MSc (Epi) FRACGP
Epidemiologist
Evaluator

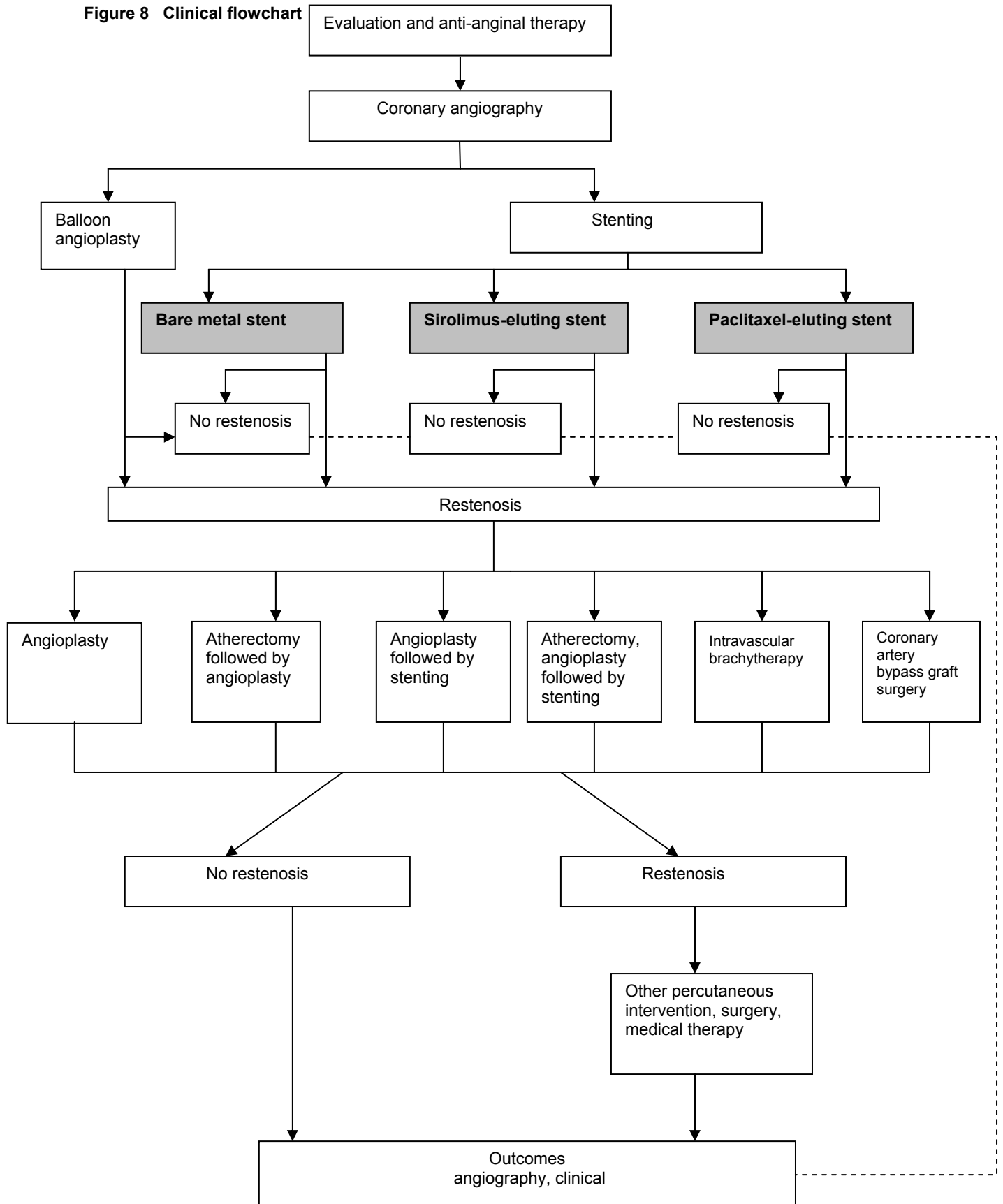
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Appendix C Clinical flowchart

Figure 8 Clinical flowchart



Appendix D Clinical indications for use of drug-eluting stents

Indications for use for Cypher sirolimus-eluting stent

Indications for Cypher
The CYPHER sirolimus-eluting stent is indicated for improving luminal diameter in patients with symptomatic ischaemic disease due to discrete de novo lesions of length ≤ 30 mm in native coronary arteries with a reference vessel diameter of ≥ 2.5 to ≤ 3.5 mm.
Contraindications for Cypher
Use of CYPHER stent is contraindicated in the following patient types: <ul style="list-style-type: none">• patients with a hypersensitivity to sirolimus or its derivatives• patients with a known hypersensitivity to polymethacrylates or polyolefin copolymers. The safety and effectiveness of the CYPHER stent have not been established in the following patient populations: <ul style="list-style-type: none">• patients with unresolved thrombus at the lesion site• patients with coronary artery vessel diameter <2.5mm or >3.5mm• patients with lesions located in left main coronary artery, ostial lesions or lesions located at a bifurcation• patients with diffuse disease or poor overflow distal to the identified lesions• patients with tortuous vessels in the region of the obstruction or proximal to the lesion• patients with a recent AMI where there is evidence of thrombus or poor flow. Use of more than 2 CYPHER stents will result in the patient receiving larger amounts of drug and polymer than the experience reflected in the clinical trials.
Use in special populations
Pregnancy - There are no adequate and well controlled studies in pregnant women. The CYPHER stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or foetus.
Use during lactation - A decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.
Paediatric use - The safety and efficacy of the CYPHER Stent on paediatric patients below the age of 18 years have not been established.
Geriatric use - Clinical studies of the CYPHER stent did not find that patients age 65 years and over differed with regard to safety and efficacy compared to younger patients.

Indications for use for TAXUS paclitaxel-eluting stent

Indications for TAXUS
The TAXUS Express paclitaxel-eluting coronary stent system is indicated for improving luminal diameter for the treatment of <i>de novo</i> lesions ≤ 28 mm in length in native coronary arteries ≥ 2.5 to ≤ 3.75 mm in diameter.
Contraindications for TAXUS Use of TAXUS Express paclitaxel-eluting coronary stent system is contraindicated for patients with: <ul style="list-style-type: none">• known hypersensitivity to paclitaxel or structurally related compounds• Known hypersensitivity to the polymer or its individual components.
The safety and effectiveness of the TAXUS Express2 paclitaxel-eluting coronary stent system have not been established in the following patient populations: <ul style="list-style-type: none">• patients with unresolved vessel thrombus at the lesion site• women who are pregnant or lactating• men intending to father children• paediatric patients• patients with unresolved vessel thrombus at the lesion site• patients with coronary artery reference vessel diameters < 2.5mm or > 3.75mm• patients with lesions located in the saphenous vein grafts, in the unprotected left main coronary artery, ostial lesions, or lesions located at a bifurcation• patients with diffuse disease or poor flow distal to the identified lesions• patients with tortuous vessels (> 60 degrees) in the region of the obstruction or proximal to the lesion• patients with a recent AMI where there is evidence of thrombus or poor flow• patients with multiple overlapping stents• patients with longer than 12 months follow-up.

Appendix E

Studies included in the review

The following tables outline the characteristics and results of the systematic reviews and randomised controlled trials included in this report.

Systematic reviews and publications of systematic reviews

STUDY	STUDY QUESTION	SEARCH STRATEGY	DATABASES SEARCHED	INCLUSION and QUALITY CRITERIA	QUALITY ASSESSMENT OF REVIEW
<p>Publication of Mc GILL systematic review (Babapulle et al 2004)</p>	<p>To conduct a meta-analysis of all randomised trials examining drug-eluting stents to quantify more accurately their effect on clinical events and restenosis rates and safety.</p> <p>Specifically the review investigated the use of drug-eluting stents with BMS in the clinical outcomes of:</p> <ul style="list-style-type: none"> • Rates of all-cause mortality • Target-lesion revascularisation • MACE • Angiographic binary restenosis <p>To assess safety, the review examined rates of thrombosis and late incomplete apposition.</p>	<p>Searched with keywords “drug*” and “restenosis” and screened titles to include antimitotic drugs currently under investigation and then limited search results to included studies in adult patients reported in English, resulting in 209 papers. The abstracts of these papers were read to identify Rats comparing DES with BMS. A second literature search was done with the identified antimitotic drugs as keywords with a second keyword “stent”.</p>	<p>Plumbed database (Dec 16 1998 to April 18 2004)</p> <p>Searched the internet including three websites dedicated to cardiovascular trials www.tctmd.com, www.theheart.org, www.clinicaltrialresults.org</p>	<p>Study design: Randomised controlled trials</p> <p>Population:</p> <ul style="list-style-type: none"> • Adults with de novo lesions in a native coronary artery. <p>Intervention: Drug-eluting stents (antimitotic drugs)</p> <p>Comparator:</p> <ul style="list-style-type: none"> • BMS • Outcomes: Combined event rate of MACE (death, MI TVR or TLR); mortality; AMI; target lesion revascularisation (TLR); angiographic binary stenosis (greater than 50%); Safety outcomes of stent thrombosis and late incomplete stent apposition. <p>Quality criteria: Meta-analysis conducted in accordance with the standard protocol recommended by the Quality of Reporting of Meta-analyses group.</p> <p>Application of methods:</p> <p>The meta-analysis was carried out in accordance with the standard protocol recommended by the Quality of Reporting of Meta-analyses group</p> <p><u>Inclusion criteria</u> – Detail of method described but unsure if identified citations were assessed for inclusion by 2 or more reviewers.</p> <p><u>Data extraction</u> – Data extraction was carried out by one reviewer and independently verified by 2 others. Disagreements were resolved by consensus.</p> <p><u>Quality assessment</u> – Reported. Not stated if duplicated by a second reviewer.</p>	<p>1) Are any inclusion/exclusion criteria reported related to the primary studies which address the review question? YES</p> <p>2) Is there evidence of a substantial effort to search for all relevant research? YES</p> <p>3) Is the validity of included studies adequately assessed? YES</p> <p>4) Is sufficient detail of the individual studies presented? YES</p> <p>5) Are the primary studies summarized appropriately? YES</p>

STUDY	STUDY QUESTION	SEARCH STRATEGY	DATABASES SEARCHED	INCLUSION and QUALITY CRITERIA	QUALITY ASSESSMENT OF REVIEW
<p>Publication of Mc GILL systematic review (Babapulle et al 2004) cont'd</p>	<p>Results Seventy-three studies fulfilled the inclusion criteria: sirolimus or rapamycin (44), paclitaxel or taxol (18), QP2 or 7-hexanoyltaxol (5), tacrolimus or FK506 (2) and mycophenolate or mycophenolic acid (1) plus 3 additional papers presenting the results of clinical trials examining DES were identified. Overall, there were 11 RCTs with usable information by outcome identified.</p> <p><u>Non drug-eluting stent versus drug-eluting stent</u></p> <p>Data are limited by the lack of reporting of longer-term outcomes. The pooled mortality rates were low for both DES and BMS with no evidence of any difference between them (OR 1.11; CI 0.61-2.06). Pooled rates of MI showed no between-group difference (OR 0.92; CI 0.65-1.25). The rate of MACE was 7.8% with DES and 16.4% with BMS (OR 0.42 CI 0.32-0.53), and the angiographic restenosis rates were lower for DES (8.9% vs 29.3%; OR 0.18; CI 0.06-0.40). Effects on rates of angiographic restenosis and revascularisation with non-polymeric paclitaxel-eluting stents were less apparent. Safety outcomes: No increase in adverse events clearly attributable to edge restenosis, stent thrombosis or late incomplete stent apposition after DES implantation were observed.</p> <p>Comments High quality systematic review although this publication does not include comprehensive details of methods. The non-drug-eluting stent vs. drug-eluting stent question can be applied to the MSAC review. The report includes all antimitotic drug-eluting stents, however data is presented to allow for assessment of effectiveness within drug-stent types. This review found that several trials that reported 'negative' results have been published in abstract form only, with incomplete follow-up and reporting of results in some cases.</p>				
<p>NICE (Hill et al 2003)</p>	<p>To assess the effectiveness and cost effectiveness of the use of coronary artery stents in patients with coronary artery disease (CAD).</p> <p>Specifically the review compared the use of:</p> <ul style="list-style-type: none"> • Stent versus Percutaneous Transluminal Coronary Angioplasty (PTCA) • Stent versus Coronary Artery Bypass and Graft (CABG) • Stent versus drug-eluting stent (DES) 	<p>Clinical effectiveness:</p> <p>1. Randomised controlled trial.pt. 2. Randomised controlled trials.sh. 3. random allocation.sh. 4. double blind method.sh. 5. single blind method.sh. 6. clinical trial.pt. 7. clinical trials.sh. 8. controlled clinical trials.sh. 9. (clin\$ adj25 trial\$).ti,ab. 10. ((singl\$ or doubl\$ or trial\$) adj25 (blind\$ or mask\$)).ti,ab. 11. random\$.ti,ab. 12. research design.sh. 13. exp Evaluation Studies/ 14. follow up studies.sh. 15. prospective studies.sh. 16. (control\$ or prospective\$ or volunteer\$).ti,ab. 17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 18. animal.sh. 19. human.sh. 20. 18 not (18 and 19) 21. 17 not 20 22. (coronary or stent\$.mp 23. exp STENTS/ 24. exp Coronary Disease/ or exp Myocardial Infarction/ or exp Coronary Artery Bypass/ or exp Coronary Arteriosclerosis/ or exp Coronary Vessels/ or exp Coronary Circulation/ or exp Angina Pectoris/ or exp Angioplasty, Transluminal, Percutaneous Coronary/ or exp Electrocardiography/ or exp Risk Factors/ 25. 22 or 23 or 24 26. 21 and 25 27. limit 25 to (yr=1990-2002 and English language)</p>	<p>Electronic searches included the following databases and covered the period from 1990 to December 2002:</p> <p>MEDLINE EMBASE Science Citation Index/Web of Science Cochrane Trials Register (CCTR) (2002, 4) Cochrane Database of Systematic Reviews (CDSR) Health Technology Assessment (HTA) Database of Abstracts of Reviews of effectiveness (DARE) Science Citation Index/ISI Proceedings References of retrieved articles and industry submissions were checked to ensure no eligible articles had been missed.</p>	<p>Study design: Randomised controlled trials</p> <p>Population:</p> <ul style="list-style-type: none"> • Adults with CAD in native or graft vessels • Patients with stable angina or Acute Coronary Syndrome, which includes AMI (ST segment elevation and depression, Q wave and non-Q wave) and unstable angina <p>Intervention: Coronary artery stents of any type inserted as an elective procedure</p> <p>Comparators:</p> <ul style="list-style-type: none"> • PTCA without stent versus PTCA with stent • Stent versus CABG • Non drug-eluting stent versus drug-eluting stent <p>Outcomes: Combined event rate or event free survival; death; AMI; target vessel revascularisation (TVR); repeat treatment (PTCA, Stent or CABG); binary stenosis (greater than 50%); utility weights related to clinical outcomes</p> <p>Quality criteria: Primary studies judged using Centre for Reviews and Dissemination, Report 4.</p>	<p>1) Are any inclusion/exclusion criteria reported related to the primary studies which address the review question? YES</p> <p>2) Is there evidence of a substantial effort to search for all relevant research? YES</p> <p>3) Is the validity of included studies adequately assessed? YES</p> <p>4) Is sufficient detail of the individual studies presented? YES</p> <p>5) Are the primary studies summarised appropriately? YES</p>

STUDY	STUDY QUESTION	SEARCH STRATEGY	DATABASES SEARCHED	INCLUSION and QUALITY CRITERIA	QUALITY ASSESSMENT OF REVIEW
<p>NICE (Hill et al 2003) cont'd</p>	<p>The economic analysis compares the cost effectiveness of:</p> <ul style="list-style-type: none"> • Stent versus DES • Stent versus CABG. <p>To assess the effectiveness and cost effectiveness of the use of coronary artery stents in Patients with coronary artery disease (CAD). Specifically the review compared the use of: Stent versus Percutaneous Transluminal Angioplasty (PTCA)</p>	<p>Cost effectiveness:</p> <p>1. exp "costs and cost analysis"/ or exp cost-benefit analysis/ or exp quality of life/ or exp quality-adjusted life years/ or exp economics/ or model.mp. 2. exp stents/ or "stent".mp. 3. exp Coronary Disease/ or exp Myocardial Infarction/ or exp Coronary Arteriosclerosis/ or exp Coronary Artery Bypass/ or exp Coronary Vessels/ or exp Coronary Angiography/ or exp Angina Pectoris/ or exp Risk Factors/ or exp Coronary Circulation/ or exp Angioplasty, Transluminal, Percutaneous Coronary/ or exp Myocardial Revascularization/ 4. 1 and 2 and 3 5. limit 4 to (human and English language and yr=1987-2002)</p>		<p>Application of methods:</p> <p><u>Inclusion criteria</u> – Identified citations were assessed for inclusion in two stages and disagreements were settled by discussion at each stage. Three reviewers independently scanned titles and abstracts and identified potentially relevant articles to be retrieved. Full text copies of the selected papers were obtained and assessed independently by four reviewers.</p> <p><u>Data extraction</u> – Data extraction was carried out by four reviewers. Data were independently extracted by one reviewer and then checked by a second reviewer into pretested data extraction forms.</p> <p><u>Quality assessment</u> – Four reviewers independently evaluated the included primary studies for methodological quality. Any discrepancies were resolved through consensus.</p>	
<p>Results</p> <p>Sixty-eight studies fulfilled the inclusion criteria. These included fifty studies comparing the use of stents with PTCA, six comparing stents with CABG and twelve comparing drug-eluting stents with non drug-eluting stents. No studies were identified that compared drug-eluting stents with PTCA or drug-eluting stents with CABG.</p> <p><u>PTCA without stent versus PTCA with stent</u></p> <p>Data analysis was carried out with studies grouped according patient characteristics (nonspecific, AMI, totally occluded vessels and small vessels). Stents were found to be more effective than PTCA in preventing events and revascularisations.</p> <p><u>Stent versus CABG</u></p> <p>All studies were a comparison of bare metal stents to surgery. Studies comparing drug-eluting stents with CABG have commenced but no reports of results are currently available. Analysis of data was carried out considering patients with single and multiple vessel disease. Studies in the former group were small and did not report results that could be used in the analysis past 6-month follow-up. In multiple vessel disease there was no evidence of a difference in mortality (at one year) between patients treated surgically and those receiving a stent. Longer-term data from these studies is now becoming available. Patients treated surgically required fewer revascularisations.</p> <p><u>Non drug-eluting stent versus drug-eluting stent</u></p> <p>Data are limited by the lack of reporting of longer-term outcomes. There is no evidence of a difference in mortality between patients receiving drug-eluting stents and those treated with bare metal stents at one year. There is a reduction in event rate at 9 and 12 months in patients treated with drug-eluting stents. This event rate is primarily made up of increased revascularisation rates in patients treated with bare metal stents. The exact rate of lowering of revascularisations seems to be by approximately 60 to 70 percent at 12 months, but there are difficulties in definitions of how many of these were clinically driven. Outcomes from one study indicate that this benefit is largely maintained over two years. None of the studies have been powered to examine subgroups.</p> <p>Comments</p> <p>High quality, systematic review. The non-drug-eluting stent vs. drug-eluting stent question can be applied to the MSAC review. The report categorises drug-eluting stents as a "group", however data is presented to allow for assessment of effectiveness within drug-stent types.</p>					

STUDY	STUDY QUESTION	SEARCH STRATEGY	DATABASES SEARCHED	INCLUSION and QUALITY CRITERIA	QUALITY ASSESSMENT OF REVIEW
<p>Publication of NICE systematic review (Hill et al 2004)</p>	<p>To conduct a systematic review and meta-analysis of available data from RCTs comparing drug eluting stents to non-drug-eluting stents to assess this health technology and inform policy in the UK.</p>	<p>Described above</p>	<p>Medline, EMBASE, Science Citation Index (Web of Science and ISI Proceedings) from Jan 1990 to Dec 2002 and Cochran Library (issue 4, 2002). Hand searched 14 cardiovascular journals (Dec 2001 – Dec 2002) and abstracts from 6 cardiovascular conferences (Jan 2000- Jan 2003).</p>	<p>Study design: Randomised controlled trials</p> <p>Population:</p> <ul style="list-style-type: none"> No limits were placed on the coronary artery disease state of the study participants (in terms of involvement of native or graft vessels, single or multiple vessels, or stable angina or acute coronary syndrome) <p>Intervention: drug eluting stents</p> <p>Comparators:</p> <ul style="list-style-type: none"> Non-drug-eluting stents <p>Outcomes: Composite event rate, mortality, AMI or binary restenosis.</p> <p>Quality criteria: Primary studies judged using Centre for Reviews and Dissemination, Report 4.</p> <p>Application of methods:</p> <p><u>Inclusion criteria</u> – Identified citations were assessed for inclusion in two stages and disagreements were settled by discussion at each stage. Two reviewers independently scanned titles and abstracts and identified potentially relevant articles to be retrieved. Full text copies of the selected papers were obtained and assessed independently by two reviewers.</p> <p><u>Data extraction</u> – Data extraction was carried out by one reviewer using pretested data extraction forms and were checked by a second.</p>	<p>1) Are any inclusion/exclusion criteria reported related to the primary studies which address the review question? YES</p> <p>2) Is there evidence of a substantial effort to search for all relevant research? YES</p> <p>3) Is the validity of included studies adequately assessed? YES</p> <p>4) Is sufficient detail of the individual studies presented? YES</p> <p>5) Are the primary studies summarised appropriately? YES</p>

STUDY	STUDY QUESTION	SEARCH STRATEGY	DATABASES SEARCHED	INCLUSION and QUALITY CRITERIA	QUALITY ASSESSMENT OF REVIEW
<p>Publication of NICE systematic review (Hill et al 2004) cont'd</p>	<p>RESULTS Fourteen studies met the inclusion criteria. Of these 8 focused on stents eluting taxane compounds and 5 investigated sirolimus or everolimus-eluting stents and one study involved actinomycin-dosed stents. Data are limited by the lack of reporting of longer-term outcomes. There is no evidence of a difference in mortality or AMI between patients receiving drug-eluting stents and those treated with bare metal stents at one year. Given the varied definitions of revascularisation, it was not possible to directly compare results across trials. The analysis indicates that drug-eluting stents can reduce event rates by 40-60% at 12 months. This event rate is primarily made up of increased revascularisation rates in patients treated with bare metal stents. The exact rate of lowering of revascularisations seems to be by approximately 60 to 70 percent at 12 months, but there are difficulties in definitions of how many of these were clinically driven. Outcomes from one study indicate that this benefit is largely maintained over two years. Binary restenosis is reported at 6 months for nine of the studies in the meta-analysis and at 8 months for SIRIUS and E-SIRIUS and at 9 months for PATENCY, DELIVER and TAXUS IV. There is a benefit of drug-eluting stents over non-drug-eluting stents in the taxanes and sirolimus groups, a marginally significant benefit in the everolimus subgroup and no advantage in the actinomycin-eluting stent group.</p> <p>Comments High quality, systematic review. The non-drug-eluting stent vs. drug-eluting stent question can be applied to the MSAC review. The report categorises drug-eluting stents as a "group", however data is presented to allow for assessment of effectiveness within drug-stent types. Event rate is heavily dependent on revascularisations and these may be inflated by protocol-dictated angiography.</p>				

STUDY	STUDY QUESTION	SEARCH STRATEGY	DATABASES SEARCHED	INCLUSION and QUALITY CRITERIA	QUALITY ASSESSMENT OF REVIEW
(Oliva & Espallargues 2003)	To review "the efficacy, effectiveness and safety of anti-proliferative drug-eluting stents for the treatment of coronary restenosis. The aim was also to ascertain how far this technology has been disseminated in Spain, its cost, legal status in terms of commercialization and impact on the health of the population and organization of the health system".	"The main biomedical databases were reviewed (until the end of October 2002) and a search was conducted in different sources of information from registers of clinical trials, and the results of the main ongoing clinical trials were also compiled. A manual search was run on the basis of bibliographic references from the articles selected and other articles revising the topic"	Only reported as the 'main biomedical data bases.	<p>Study design: "Original experimental, quasi-experimental or observational published works or revisions evaluating the benefits/risks of the technology".</p> <p>Population: Not stated.</p> <p>Intervention: Drug-eluting stent</p> <p>Comparators: Not stated.</p> <p>Outcomes: Not stated.</p> <p>Quality criteria: Selected studies assessed by Evidence Based Medicine Working Group Criteria.</p> <p>Application of methods:</p> <p><u>Inclusion criteria</u> – "Original experimental, quasi-experimental or observational published works evaluating the benefits/risks of the technology".</p> <p><u>Data extraction</u> – "Qualitative synthesis was made according to the scientific evidence classification made by CAHTA".</p> <p><u>Quality assessment</u> – Two reviewers independently evaluated the included primary studies for methodological quality.</p>	<p>1) Are any inclusion/exclusion criteria reported related to the primary studies which address the review question? YES</p> <p>2) Is there evidence of a substantial effort to search for all relevant research? YES</p> <p>3) Is the validity of included studies adequately assessed? YES</p> <p>4) Is sufficient detail of the individual studies presented? YES</p> <p>5) Are the primary studies summarised appropriately? YES</p>
<p>Results</p> <p>Five studies fulfilled the selection criteria. Two studies considered sirolimus and the remaining three considered a taxol derivative (QP2) eluting stent. One was a randomised controlled trial, and the others were case series studies. Five non-systematic reviews were also identified.</p> <p>Evidence from a high quality RCT suggests that sirolimus eluting stents are safe and effective in preventing angiographic restenosis and MACE in <i>de novo</i> lesions at 6 and 12 months respectively. Low quality evidence suggests that the slow-release formulation is more effective than the fast-release formulation in preventing restenosis. Data on QP2 eluting stents were not reported due to the discontinuation of this stent by the manufacturer. It was concluded that longer follow-up was required, but any use of sirolimus-eluting stents beyond that of the RAVEL trial should be in the framework of an RCT.</p> <p>Comments</p> <p>English summary of a HTA report originally published in Catalan. Reporting of methods is not of high quality. Longer term follow up data for the studies considered in this systematic review has subsequently become available.</p>					

Drug-eluting stent RCTs- Study characteristics and appraisal

STUDY	N	STUDY QUESTION	INTERVENTION	PATIENT CHARACTERISTICS		DESIGN	QUALITY	PROCEDURE	CO-THERAPIES
				Inclusion criteria	Exclusion criteria				
C-SIRIUS (Schampaert et al 2004)	100	Assess the safety and effectiveness of the CYPHER™ (sirolimus-eluting Bx VELOCITY™) stent in maintaining minimum lumen diameter at 8 months in de novo native coronary lesions compared with uncoated bare metal Bx VELOCITY™ stent.	Bare-metal Bx VELOCITY™ stents (control) and coated sirolimus-eluting Bx Velocity stents (CYPHER™). The sirolimus-eluting stents had a 5 µm coating consisting of a blend of 33% sirolimus and 67% non-erodable polymer containing 140 µg sirolimus per cm². 80% of sirolimus is released within 30 days, with no residual drug by 90 days.	Patients ≥18 years of age; Angina pectoris (CCS 1-4); Unstable angina (Braunwald classification B and C, I or II) or silent ischaemia. Single de novo lesion in a native vessel b/n 15 and 32 mm in length with diameter stenosis of 50% to 99%. Vessel diameter b/n 2.5 to 3.0mm (angiographic visual assessment)	Evolving MI; >50% stenosis of left main coronary artery; an ostial, calcified or thrombus containing lesion; a bifurcation lesion with a diseased side branch (≥ 2.5 mm diameter); left-ventricular ejection fraction <25%; known allergies to aspirin, clopidogrel, ticlopidine, heparin, stainless steel, contrast agent or sirolimus.	RCT, 8 centres. Sealed randomisation envelopes supplied from Harvard Clinical Research Centre in blocks of ten, 1:1 ratio	<ul style="list-style-type: none"> • Randomised, double-blind method stated and baseline similarity documented • Double blinded • ITT (2 patients deregistered) and 88% for primary outcome 	Stent implantation followed standard interventional techniques. The decision to predilate or not was at the investigator's discretion. A maximum of 2 stents could be used (same type)	<u>Pre-procedure</u> 81 to 325 mg of aspirin begun ≥ 12 hr before procedure, and 300 mg clopidogrel before or immediately post procedure <u>During procedure</u> Heparin; GP IIb/IIIa inhibitors (at operators discretion used in 53% of patients) <u>Post procedure</u> Aspirin (81 – 325 mg/day) and clopidogrel (75 mg/day) for 2 months.

STUDY	N	STUDY QUESTION	INTERVENTION	PATIENT CHARACTERISTICS		DESIGN	QUALITY	PROCEDURE	CO-THERAPIES
				Inclusion criteria	Exclusion criteria				
E-SIRIUS (Schofer et al 2003)	352	Assess the safety and effectiveness of the CYPHER™ (sirolimus-eluting Bx VELOCITY™) stent in maintaining minimum lumen diameter at 8 months in de novo native coronary lesions compared with uncoated bare metal Bx VELOCITY™ stent.	Bare-metal Bx Velocity stents (control) and coated sirolimus-eluting Bx Velocity stents (Cordis). The sirolimus-eluting stents had a 5 µm coating consisting of a blend of 33% sirolimus and 67% non-erodable polymer containing 140 µg sirolimus per cm². 80% of sirolimus is released within 30 days of implantation. Stents were 8mm and 18mm long and had diameters of 2.5mm and 3.0mm.	Single de novo coronary lesions (15-32 mm in length (visual) and 2.5 to 3.0mm in diameter (visual); DS of 50% to 99%; Vessel diameter b/n 2.5 to 3.0mm (visual); Patients ≥18 years of age; Angina pectoris (CCS 1-4); Unstable angina (Braunwald classification B and C, I or II) or silent ischaemia.	Evolving MI; >50% stenosis of left main coronary artery; an ostial, calcified or thrombus containing lesion; a bifurcation lesion with a diseased side branch (≥ 2.5 mm diameter); left-ventricular ejection fraction <25%; known allergies to aspirin, clopidogrel, ticlopidine, heparin, stainless steel, contrast agent or sirolimus.	RCT at 35 European centres.	<ul style="list-style-type: none"> • Correct, blinded randomisation method described • Baseline similar except differences in reference vessel diameter. • Double blind. • ITT conducted on all evaluable patients (87.5% available for primary endpoint) 	Stent implantation followed standard interventional techniques. The decision to predilate or not was at the investigator's discretion. A maximum of 2 stents could be used (same type)	<p><u>Pre-procedure</u></p> <p>100 mg aspirin ≥ 12 hrs before procedure, and clopidogrel 75mg 3 days pre-procedure or 300mg immediately before or after the procedure. Alternatively. Ticlopidine 250mg given twice in 24hrs post-procedure.</p> <p><u>During procedure</u></p> <p>Heparin, GP IIb/IIIa inhibitors (at operators discretion 14% SES; 18% BMS)</p> <p><u>Post-procedure</u></p> <p>Aspirin 100mg /day (indefinitely) Clopidogrel (75mg/day) or Ticlopidine (250 mg twice daily) for 2 months</p>

STUDY	N	STUDY QUESTION	INTERVENTION	PATIENT CHARACTERISTICS		DESIGN	QUALITY	PROCEDURE	CO-THERAPIES
				Inclusion criteria	Exclusion criteria				
RAVEL (Morice et al 2002)	238	To compare the safety and effectiveness of sirolimus-eluting stents with uncoated stents of the same type in patients with CHD requiring stenting of single new native lesions.	Bare-metal Bx VELOCITY™ stents (control) and coated sirolimus-eluting Bx Velocity stents (CYPHER™). The sirolimus-eluting stents had a 5 µm coating consisting of a blend of sirolimus and non-erodable polymer containing 140 µg sirolimus per cm ² . Stent designed to release 80% of sirolimus within 30 days.	18-85 years; not pregnant and protected against pregnancy during study; diagnosis of stable or unstable angina or silent ischaemia; single target lesion in a native coronary artery 2.5 -3.5 mm in diameter that could be covered with a 18 mm stent; stenosis of 51% - 99% luminal diameter (visual); TIMI flow rate of grade 1 or higher.	Evolving MI; Stenosis of LMCA, unprotected by a graft that caused a luminal narrowing of 50% or more; an ostial lesion; a calcified lesion that could not be completely dilated before stenting; An angiographically visible thrombus within target lesion; Left ventricular ejection fraction < 30%; Intolerance to aspirin, ticlopidine, heparin, stainless steel or contrast material.	RCT at 19 centres.	<ul style="list-style-type: none"> • Correct, blinded randomisation method described and baseline similarity • Double blind • ITT –clinical 100%. Primary outcome 88.7%. 	Stenting without predilation was prohibited. Dilation after implantation to ensure <20% residual stenosis.	<u>Pre-procedure</u> 100 mg aspirin ≥12 hrs before procedure and a loading dose of clopidogrel 300mg given 48 hrs before procedure. Or, ticlopidine 250mg twice /day begun 1 day pre-procedure. <u>During procedure</u> Heparin; GPIIb/IIIa inhibitors(at operators discretion used in 10.1%SES and 9.5% BMS) <u>Post-procedure</u> Aspirin 100mg daily (indefinitely) Clopidogrel (75mg/day) or Ticlopidine (250 mg twice daily) for 8 weeks.

STUDY	N	STUDY QUESTION	INTERVENTION	PATIENT CHARACTERISTICS		DESIGN	QUALITY	PROCEDURE	CO-THERAPIES
				Inclusion criteria	Exclusion criteria				
RAVEL DIABETIC SUB-STUDY (Abizaid et al 2004)	44	To compare the clinical and angiographic outcomes of diabetic patients enrolled in the RAVEL trial and compare these results with the outcomes of both the diabetic patients treated with BMS and non-diabetic patients treated with sirolimus-eluting stents.	Bare-metal Bx VELOCITY™ stents (control) and coated sirolimus-eluting Bx Velocity stents (CYPHER™). The sirolimus-eluting stents had a 5 µm coating consisting of a blend of sirolimus and non-erodable polymer containing 140 µg sirolimus per cm². Stent designed to release 80% of sirolimus within 30 days.	Patient characteristics described above in the RAVEL trial.		Study design described above in the RAVEL trial.	Patient characteristics described above in the RAVEL trial.	Patient characteristics described above in the RAVEL trial	Co-therapies described above in the RAVEL trial
SIRIUS (Moses et al 2004)	1058	Assess the safety and effectiveness of the CYPHER™ (sirolimus-eluting Bx VELOCITY™) stent in clinical restenosis in de novo native coronary lesions compared with uncoated bare metal Bx VELOCITY™ stent.	Sirolimus –eluting stents contained 140ug sirolimus per cm² within a copolymer matrix that was 5 to 10µg thick, designed to release 80% of total dose in 30 days.	Stable or unstable angina and signs of myocardial ischaemia; Single de novo lesion in a native coronary artery; Stenosis of 51-99% of luminal diameter and 15 - 30 mm in length (visual).	Recent MI (<48hrs); Ejection fraction <25%; Target lesion in an ostium, a bifurcation, or “unprotected” LMCA or in a vessel with thrombus or severe calcification; Treatment of nontarget lesions in the same of a different coronary vessel during the procedure.	RCT. Automated telephone randomisation system. Randomisation blocks were created and stratified according to the clinical centre or absence of DM.	<ul style="list-style-type: none"> •Correct, blinded randomisation method described and baseline similarity •Double-blind •ITT conducted on patients receiving stent. (After randomization but before treatment 43 patients were withdrawn) •100 % F/U for primary endpoint 	Lesions were treated standard interventional techniques, including mandated balloon dilation before stent placement. One or two stents of the assigned type were used to treat the lesion.	<u>Pre-procedure</u> Aspirin 325 mg/day and a loading dose of clopidogrel 300 to 375mg 24 hrs pre-procedure. <u>During procedure</u> Heparin;GPIIb/IIIa inhibitors (at operators discretion- 60% of patients) <u>Post-procedure</u> Aspirin 325mg daily and clopidogrel (75mg/day) for 3 months.

STUDY	N	STUDY QUESTION	INTERVENTION	PATIENT CHARACTERISTICS		DESIGN	QUALITY	PROCEDURE	CO-THERAPIES
				Inclusion criteria	Exclusion criteria				
SIRIUS DIABETIC SUB STUDY (Moussa et al 2004)	279	Assess the safety and effectiveness of the CYPHER™ (sirolimus-eluting Bx VELOCITY™) stent in a subgroup of diabetic patients and compare with the bare metal Bx VELOCITY™ stent.	Sirolimus –eluting stents contained 140ug sirolimus per cm ² within a copolymer matrix that was 5 to 10µg thick, designed to release 80% of total dose in 30 days.	As per SIRIUS trial		RCT	As per SIRIUS trial	As per SIRIUS trial	As per SIRIUS trial
TAXUS I (Grube et al 2003)	61	To compare the safety and effectiveness of paclitaxel-eluting stents with uncoated stents of the same type in patients with CHD requiring stenting of single new native lesions.	NIR™ stent (control) (Boston Scientific Corp) is an uncoated bare-metal stent. TAXUS NIRx™ stent (Boston Scientific corp) is the NIR stent coated with paclitaxel (1µg /mm ² per unit of stent surface area) in a slow-release polymer formulation.	Single de novo or restenotic lesions ≤ 12 mm long, 50 -99% diameter stenosis and vessel diameter between 3.0 and 3.5 mm.	Recent AMI; LVEF < 30%; Stroke within previous 6 months; Renal dysfunction (serum creatinine >1.7 mg/100mL); or contraindication to aspirin, clopidogrel, or ticlopidine. Target lesions requiring > 1 study stent.	RCT -3 centres	<ul style="list-style-type: none"> • Randomised, double-blind method stated and baseline similarity documented • Double blind ITT; 100% clinical F/U however, 1 pt withdrawn between 6 and 12 months but no explanation 	After predilatation, stents were deployed according to conventional techniques. Postdeployment high-pressure dilatation was at the investigator's discretion. Could use additional nonstudy stents.	<u>Pre-procedure</u> Premedicated with aspirin (>80mg), clopidogrel 300 mg, and heparin. <u>During procedure</u> Heparin <u>Post-procedure</u> Aspirin (>80 mg/day) for ≥ 12 months and clopidogrel (75mg/day) for 6 months. GPIIb/IIIa inhibitor use not reported

STUDY	N	STUDY QUESTION	INTERVENTION	PATIENT CHARACTERISTICS		DESIGN	QUALITY	PROCEDURE	CO-THERAPIES
				Inclusion criteria	Exclusion criteria				
TAXUS II (Colombo et al 2003)	536	To compare the safety and effectiveness of paclitaxel-eluting stents in two different release formulations with uncoated stents of the same type in patients with CHD requiring stenting of single new native lesions.	NIR™ stent (control) (Boston Scientific corp) is an uncoated bare-metal stent. TAXUS NIRx™ stent (Boston Scientific corp) is the NIR stent coated with paclitaxel (1µg /mm² per unit of stent surface area) in a slow-release and moderate release polymer formulations.	Patients ≥18 years of age; Stable or unstable angina or ischaemia induced by exercise; Single de novo lesion ≤ 12 mm long, 50 - 99% diameter stenosis and vessel diameter and ≤3.5 mm.	Recent coronary intervention ≤30 days; LVEF <30%; evolving MI; unprotected left main coronary disease or prespecified need to implant > 1 stent.,	RCT, 38 centres	<ul style="list-style-type: none"> •Randomised, double-blind method stated and baseline similarity documented •Double blind •ITT 91% SR group and 88% MR group 	Standard interventional techniques, Second stents if required were study stents; if a third stent was required it was a non-study stent.	<u>Pre-procedure</u> Aspirin 75mg and clopidogrel 300 mg given ≥ 4 hrs before stent placement. <u>During procedure</u> Heparin GPIIb/IIIa inhibitor use equal b/n 4 arms. <u>Post-procedure</u> Aspirin 75 mg/day indefinitely and clopidogrel 75mg/day (or ticlopidine 250mg twice daily) for at least 6 months.

STUDY	N	STUDY QUESTION	INTERVENTION	PATIENT CHARACTERISTICS		DESIGN	QUALITY	PROCEDURE	CO-THERAPIES
				Inclusion criteria	Exclusion criteria				
TAXUS IV (Stone et al 2004)	1314	To compare the safety and effectiveness of paclitaxel-eluting stents with uncoated stents of the same type in a broad population of patients with CHD requiring stenting of single new native lesions.	NIR™ stent (control) (Boston Scientific corp) is an uncoated bare-metal stent. TAXUS NIRx™ stent (Boston Scientific corp) is the NIR stent coated with paclitaxel (1µg /mm² per unit of stent surface area) in a slow-release polymer formulation.	Patients ≥18 years of age; Stable or unstable angina or ischaemia induced by exercise; Single de novo or restenotic lesions 10 -28 mm long and 2.5 to 3.75 mm diameter. Enrolment permitted after successful treatment of 1 additional nonstudy lesion in a nonstudy vessel prior to randomisation.	Previous or planned use of intravascular brachytherapy in the target vessel or of any drug-eluting stent; MI < 72 hrs before enrolment; LVEF < 25%; Haemorrhagic diatheses; Contraindication or allergy to aspirin, thienopyridines, paclitaxel or stainless steel; Previous anaphylaxis to iodinated contrast medium; Use of paclitaxel within last 12 months or current use of colchicine; Serum creatinine level > 177 µmol /L; Leucocyte count < 3500 per mm³; Positive pregnancy test, breastfeeding or the possibility of a future pregnancy; Life expectancy < 24 months. Angiographic exclusion –left main or ostial lesion, moderate or severe calcification, tortuosity or angulation, bifurcation, occlusion or thrombus in the target lesion; Use of atherectomy or cutting balloon planned before stenting.	RCT 73 centres	<ul style="list-style-type: none"> • Correct, blinded randomisation method described and baseline similarity • Double-blind • ITT 100% F/U for primary outcome 	Mandatory dilation with the use of a balloon, a stent 2 -4 mm longer than the lesion was implanted at a pressure of 12 atm. Additional study stents could be implanted if a suboptimal result (eg edge dissection type B-E).	<p><u>During procedure</u> Heparin; IIb/IIIa inhibitors (at operators discretion, % use not reported)</p> <p><u>Post-procedure</u> Aspirin (325 mg/day) indefinitely and clopidogrel (75mg/day) for 6 months.</p>

Drug-eluting stent RCTs- Study outcomes

STUDY	INTERVENTION	STUDY END POINTS	RESULTS						COMMENTS
			Mortality	AMI	CABG	Stent thrombosis	MACE	Restenosis	
C-SIRIUS (Schampaert et al 2004)	Bare-metal Bx VELOCITY™ stents (control) N=50 Coated sirolimus-eluting Bx Velocity stents (CYPHER™). N= 50	Clinical follow-up at 1 and 9 months. Angiographic follow-up at 8 months. MACE = death, AMI, CABG, clinically driven TLR at 9 months. <u>1' endpoint</u> MLD at 8 months. <u>2' endpoints</u> -in-lesion MLD - in-lesion angiographic restenosis (≥ 50% diameter) - MACE - TLR	<u>9 months</u> SES 0/50 BMS 0/50	<u>9 months</u> SES 1/50 BMS 2/50	<u>9 months</u> SES 1/50 BMS 0/50	<u>9 months</u> SES 1/50 BMS 1/50	<u>9 months</u> SES 2 /50 BMS 9 /50	<u>Clinically driven TLR</u> SES 2 /50 BMS 9 /50 <u>Binary restenosis at 8 mths (in lesion)</u> SES 1 /44 BMS 23 /44 (in stent) SES 0 /44 BMS 20 /44	<u>Limitations</u> -Only a 9 month follow-up -incomplete angiographic F/U in 88% of patients (44 in each grp), reasons why 12 withdrew not stated. <u>Other notes</u> -no 30 day data -MACE doesn't include thromboses -patients in C-SIRIUS and E-SIRIUS had more complex lesions and reported in a higher restenosis rate in the BMS group than the RAVEL and SIRIUS trials. -Glycoprotein use overall was 53% but no data given on differences between treatment and control groups. (most studies say it is up to clinician whether they use these or not so effect would be uniform across studies)

STUDY	INTERVENTION	STUDY END POINTS	9 month RESULTS						COMMENTS
			Mortality	AMI	CABG	Stent thrombosis	MACE	Restenosis	
E-SIRIUS (Schofer et al 2003)	Sirolimus (140 µg per cm ²) N=175 Bare-metal N=177	Clinical follow-up at 1 and 9 months. Angiographic follow-up at 8 months. MACE = death, AMI, CABG, clinically driven TLR at 9 months. <u>1' endpoint</u> MLD at 8 months. <u>2' endpoints</u> - angiographic binary restenosis (≥ 50% diameter) - in-lesion MLD - MACE - TLR	9 months: SES 2 /175 BMS 1/177	9 months: SES 8 /175 BMS 4 /177	9 months: SES 0 /175 BMS 3 /177	9 months SES 2 /175 BMS 0 /177	9 months SES 14/175 BMS 40/177	<u>TLR</u> SES 7 /175 BMS 37 /177 <u>Binary restenosis (8 mths) (in lesion)</u> SES 9/152 BMS 66/156 (in stent) SES 6/152 BMS 65/156	Angiographic data available for 308 patients (88%) All TLR were adjudicated by the clinical events c'tee as being clinically driven. Sirolimus group had different vessel length.

STUDY	INTERVENTION	STUDY END POINTS	RESULTS						COMMENTS
			Mortality	AMI	CABG	Stent thrombosis	MACE	Restenosis	
RAVEL (Morice et al 2002)	Sirolimus (140 µg per cm ²) N=120 Bare-metal N=118	Clinical F/U at 30 days, 6 and 12 mths. Angiographic follow-up at 6 months. MACE = death, AMI (Q or non-Q wave), CABG, clinically driven TLR at 30 days, 6 and 12 months. <u>1' endpoint</u> in-stent luminal late loss at 6 months. <u>2' endpoints</u> -% in-stent stenosis of luminal diameter - angiographic binary restenosis (≥ 50% diameter) - in-lesion MLD <u>1' clinical endpoint</u> -MACE - TLR	1 year: SES 2 /120 Control 2 /118	1 year: SES 4 /120 Control 5/118 * data extracted from number of patients reported with AMI in hospital and post-discharge.	1 year: SES 1/120 Control 1/118	No subacute or late thrombotic occlusion in either group.	1 year: SES 7/120 Control 34/118	TLR at 1 year: SES 0/120 Control 27/118 Binary stenosis ¹ SES 0/109 BMS 29/109 The denominator data for the angiographic study group at 6 months was obtained through correspondence with the study authors.	Angiographic data available for 211/ 238 patients (88.7%) Of the 27 TLR in BMS, 16 had clinical signs and 11 because of angiographic evidence. The six month angiographic study group was reported as 211 in the paper. After correspondence with the authors, the final study group was listed as 218. Study population limited by less complex demographics and lesion characteristics than found in clinical practice.

STUDY	INTERVENTION	STUDY END POINTS	RESULTS				COMMENTS		
			Clinical outcomes (MACE)	Quantitative angiographic 6 months	IVUS volumetric analysis				
RAVEL DIABETIC SUB-STUDY (Abizaid et al 2004)	Sirolimus (140 µg per cm ²) N=19 Bare-metal N=25	<u>Clinical</u> -MACE at 1 year <u>Quantitative angiographic</u> analysis at 6 months –MLD, DS (%), late loss and late loss index. <u>IVUS</u> volumetric analysis at 6 months- EEM volume, stent volume, lumen volume, PM volume, Neo-intimal volume, volume obstruction in-stent.	MACE 1 year: DES 2 /19 Control 12 /25 TLR DES 0 /19 Control 9 /25	Binary restenosis rate DES 0 vs. BMS 42%; p<0.001) Late lumen loss was significantly lower for the sirolimus group (0.07±0.20 vs. 0.82 ± 0.53 mm; p<0.001)	<u>Neointimal hyperplasia volumes</u> DES 0.9±1.2 vs. BMS 34.9±28.9 mm ³ (p=0.01) <u>Percent in-stent volume obstruction</u> DES 0.82±1.38% vs. BMS 30.2±22.9 % (p=0.008)		COMMENTS Only small study numbers Study not designed to show to compare the effectiveness of sirolimus-eluting stents in patients with diabetes compared to patients without diabetes		
STUDY	INTERVENTION	STUDY END POINTS	RESULTS						COMMENTS
			Mortality	AMI	CABG	Stent thrombosis	MACE	Restenosis	
SIRIUS (Moses et al 2004)	Sirolimus stent (140 µg per cm ²) N=533 Bare-metal stent N=525	Clinical follow-up at 30,90, 180 and 270 days. Angiographic follow-up at 8 months. MACE = death from any cause, AMI, TLR (CABG and PTCA) and stent thrombosis for 270 days. <u>1' endpoint</u> TVF within 270 days (death from cardiac causes, MI (Q or non-Q wave), TLR (CABG or PTCA). <u>2' endpoints</u> MACE	<u>9 months</u> SES 5/533 BMS 3/525 <u>12 months</u> SES 7/533 BMS 4/525	<u>9 months</u> SES 15/533 BMS 17/525 <u>12 months</u> SES 16/533 BMS 18/525	<u>9 months</u> SES 3/533 BMS 8/525 <u>12 months</u> SES 5/533 BMS 9/525	<u>9 months</u> SES 2/533 BMS 4/525 <u>12 months</u> SES 2/533 BMS 4/525	<u>9 months</u> SES 38/533 BMS 99/525 <u>12 months</u> SES 44/533 BMS 117/525	<u>TLR 9 months</u> <u>12 months</u> SES 22 /533 26/533 BMS 87/525 105/525 <u>Binary restenosis (8mths) (in stent zone)</u> SES 11/350 BMS 125/353 <u>Binary restenosis (8mths) (in-segment zone)</u> SES 31/350 BMS 128/353	Angiographic data for 703/1058 (66%) Death by all causes and by cardiac causes. 279 patients with DM SES=131;control=148)

STUDY	INTERVENTION	STUDY END POINTS	RESULTS						COMMENTS
			Mortality	AMI	CABG	Stent thrombosis	MACE	Restenosis	
SIRIUS Diabetic sub-study (Moussa et al 2004)	Sirolimus stent (140 µg per cm ²) N=131 Bare-metal stent N=148	Clinical follow-up at 30, 90, 180 and 270 days. Angiographic follow-up at 8 months. MACE = death from any cause, AMI, TLR (CABG and PTCA) and stent thrombosis for 270 days. <u>1st endpoint</u> TVF within 270 days (death from cardiac causes, MI (Q or non-Q wave), TLR (CABG or PTCA). <u>2nd endpoints</u> MACE	MACE at 9 months Diabetics SES 12/131 BMS 37/ 148	MACE at 9 months Non-diabetics SES 26/402 BMS 62/ 376	TLR at 9 months Diabetics SES 9/131 BMS 33/148	TLR at 9 months Non-diabetics SES 12/402 BMS 53/376	Eight month follow-up angiography was performed in 186 of 279 diabetic patients (67%) No statistically significant differences were observed in early and late stent thrombosis among treatment groups in diabetic and non-diabetic patients. Study not designed to show to compare the effectiveness of sirolimus-eluting stents in patients with diabetes compared to patients without diabetes		

STUDY	INTERVENTION	STUDY END POINTS	RESULTS						COMMENTS
			Mortality	AMI	CABG	Stent thrombosis	MACE	Restenosis	
TAXUS I (Grube et al 2003)	Paclitaxel (1µg /mm ² per unit of stent surface area) N=31 NIR™ stent (control) N=30 59 patients had de novo lesions, 2 had restenotic lesions 1 TAXUS patient excluded from trial reason unknown at 12 months.	Clinical follow-up at 1,6, 9 & 12 months. Angiographic follow-up at 6 months. MACE = death from any cause, MI (Q wave), TVR (CABG, TLR or PCI on non-target lesion) and stent thrombosis at 30 days. <u>1' endpoint</u> MACE at 12 months. <u>2' endpoints</u> - angiographic binary restenosis (≥ 50% diameter) - RVD; MLD; % DS; late lumen loss and late loss index.	No mortality at 12 months	No Q-wave MI at 12 months	<u>12 months</u> TAXUS 0/30 Control 1/30	No thrombosis at 12 months	<u>6 months</u> TAXUS 0 /31 Control 2/30 <u>12 months</u> TAXUS 1/ 30* Control 4 /30 * PCI of target vessel non-lesion	<u>TLR - 6 months</u> TAXUS 0/31 Control 2/30 <u>TLR - 12 months</u> TAXUS 0/30 Control 3/30 <u>In-stent binary restenosis at 6 months</u> TAXUS 0/30 Control 3/29	<u>Limitations</u> Randomisation not described. Small study numbers Exclusion of high risk patients <u>Comments</u> Lesions were short ≤ 12mm Binary stenosis 0% in study group Binary stenosis measured as in-stent lesions only. (only had small nos. of restenosis in study though)
TAXUS II (Colombo et al 2003)	Paclitaxel (1µg /mm ² per unit of stent surface area) coated with a polymer to form 2 paclitaxel-eluting release formulations TAXUS-SR (slow-release) n=131; control n=136 and TAXUS-MR (medium release) n=135; control n=134. The control stent was the uncoated NIR™ stent (control)	Clinical follow-up at 1, 6, and 12 months. Angiographic follow-up at 6 months. MACE = cardiac death, MI (Q and non-Q wave), TVR (CABG or PCI on target vessel) and stent thrombosis at 30 days. <u>1' endpoint</u> % of stent volume obstructed by neointimal proliferation at 6 mths. <u>2' endpoints</u> MACE at 1,6 & 12 months; angiographic binary restenosis (≥ 50% diameter); RVD; MLD; % DS; late lumen loss	<u>6 months</u> SR 0/130 Control 1/133 MR 0/129 Control 0/130 <u>12 months</u> SR 0/129 Control 2/132 MR 0/131 Control 0/131	<u>6 months</u> SR 2/130 Control 7/133 MR 3/129 Control 7/130 <u>12 months</u> SR 3/129 Control 7/132 MR 5/131 Control 7/131	<u>6 months</u> SR 1/130 Control 1/133 MR 1/129 Control 1/130 <u>12 months</u> SR 4/129 Control 1/132 MR 2/131 Control 2/131	<u>12 months</u> SR 2/129 Control 0/132 MR 1/131 Control 0/131 One peri procedural stent thrombosis occurred in a TAXUS SR patient	<u>6 months</u> SR 11 / 130 Control sr 26 / 133 MR 10 / 129 Control mr26 / 130 <u>12 months</u> SR 14 / 129 Control sr 29 / 132 MR 13 / 131 Control mr28 / 131 <u>TLR at 6 months</u> SR 6 / 130 Control sr 16 / 133 MR 4 / 129 Control mr19 / 130 <u>TLR at 12 months</u> SR 6 / 129 Control sr 17 / 132 MR 5 / 131 Control mr21 / 131	TLR data calculated from table percentages discrepancies noted.	

STUDY	INTERVENTION	STUDY END POINTS	RESULTS						COMMENTS
			Mortality	AMI	CABG	Stent thrombosis	MACE	Restenosis	
TAXUS IV (Stone et al) (NEJM 2004 and Circulation 2004)	Paclitaxel (1µg /mm ² per unit of stent surface area) slow-release, polymer-based stent N=662 EXPRESS™ bare metal stent (control) N=652 patients had de novo lesions, 2 had restenotic lesions	Clinical follow-up at 1, 6, 9 and yearly for 5 years. Angiographic follow-up at 6 months. MACE=death from cardiac causes, MI or ischaemia-driven TVR <u>1' endpoint</u> ischaemia-driven TVR at 9 mths <u>2' endpoints</u> TLR=stenosis ≥ 50% of diameter within stents or within 5mm proximal and distal borders TVF= death, MI or ischaemia-driven revascularisation of target vessel.	9 month results						<u>Comments</u> Restenosis defined as ischaemia- driven. TLR defined as repeated revascularisation for ischaemia owing to ≥ 50% lumen of stent ± 5 mm borders of stent. Binary stenosis measured angiographically in 559 patients. TLR differs slightly to binary stenosis at 9 months. Average no of stents inserted per PES = 1.08 ± 0.29 Per BMS= 1.09 ± 0.36 The pattern of restenosis in paclitaxel stents was more likely to be focal rather than diffuse, making it easier to manage. Stent thrombosis was low in both groups, with none occurring after 6 months.
			PES 9/662 BMS 7/652	PES 23/662 BMS 24/652	PES 7/662 BMS 22/652	PES 4/662 BMS 5/652	PES 56/662 BMS 98/652	TLR PES 20 /662 BMS 74 /652 Binary stenosis PES 23/292 BMS 71/267	
			1 year results						
			PES 9/639 BMS 8/633	PES 22/639 BMS 30/633	PES 12/639 BMS 25/633	PES 4/639 BMS 5/633	PES 69/639 BMS 127/633	TLR PES 28 /639 BMS 96 /633	

Abbreviations

ACC – American College of Cardiology

ARR – Absolute Risk Reduction

ARTG – Australian Register of Therapeutic Goods

BMS – Bare Metal Stents

CABG – Coronary Artery Bypass Graft

CAD – Coronary Artery Disease

CAHTA – Catalan Agency for Health Technology Assessment and Research

CTC – Clinical Trials Centre

DES – Drug-Eluting Stents

DRG – Diagnosis Related Group

FIM – First In Man

HTA – Health Technology Assessment

ICER – Incremental Cost Effectiveness Ratio

IHD – Ischaemic Heart Disease

ISR – In-Stent Restenosis

IVB – Intravascular Brachytherapy

IVUS – Intravascular Ultrasound

LAD – Left Anterior Descending

LCx – Left Circumflex

LVEF – Left Ventricular Ejection Fraction

MACE – Major Adverse Cardiac Event

MBS – Medicare Benefits Schedule

MI – Myocardial Infarction

MSAC – Medical Services Advisory Committee

NHCDC – National Hospital Cost Data Collection

NHMRC – National Health and Medical Research Council

NICE – National Institute of Clinical Excellence

PBS – Pharmaceutical Benefits Scheme

PCI – Percutaneous Coronary Intervention

PES -- Paclitaxel-eluting stent

PHIMDEC -- Private Health Industry Medical Devices Expert Committee

PTCA – Percutaneous Transluminal Coronary Angioplasty

QALY – Quality Adjusted Life Year

RAVEL – RCT with the Sirolimus-Eluting Stent

RCT – Randomised Controlled Trial

RR – Relative Risk

SES – Sirolimus-Eluting Stent

SIRIUS – RCT with the Sirolimus-Eluting Stent

TAXUS – Paclitaxel-eluting stent and a series of RCTs

TGA – Therapeutic Goods Administration

TIMI – Thrombolysis In Myocardial Infarction

TLR – Target Lesion Revascularisation

TVF – Target Vessel Failure

TVR – Target Vessel Revascularisation

YLD – Years Lived with Disability

YLL – Years Life Lost

Glossary

Abiciximab	A glycoprotein IIB/IIIa receptor blocker, used to inhibit blood clotting widely used during stenting procedure in the included randomised clinical trials.
Acute Coronary Syndrome	Syndrome that included coronary events previously referred to as unstable angina, non-ST-segment elevation myocardial infarction (MI) and ST elevation MI.
Angina	Pain (usually chest) resulting from lack of oxygen supply to heart muscle.
Angiography	Radiographic technique using contrast medium to show outline of the coronary artery lumens.
Atherosclerosis	Disease of the arteries in which fatty plaques develop in the inner walls leading to reduced blood flow or obstruction.
Binary restenosis	Refers to the percent of lesions with greater than 50% luminal narrowing following PCI.
Cardiac catheterization	Passing of a catheter from a femoral or radial artery into coronary arteries for diagnosis and/or treatment.
Clopidogrel	Drug that inhibits platelet function.
Creatinine kinase	A cardiac enzyme released during myocardial infarction.
<i>De novo</i> lesion	A coronary lesion not previously treated.
Direct stenting	Stent implantation without pre-dilation.
Drug-eluting stent	Stent with a drug that elutes into tissue at the placement site.
In-stent restenosis	A re-narrowing or blockage of an artery within a stent
Ischaemia	Decrease in the blood supply to the heart caused by obstruction of the coronary blood vessels.
IVUS	Method using ultrasound to visualize a full 360° circumference of the vessel and providing direct measurement of the diameter of the artery.
Late incomplete apposition	Evidence of blood flow between the stent struts and the vessel wall on IVUS that was present on follow-up but not observed immediately after the index PCI.
Late loss	A quantitative angiographic measurement of the difference between the minimal luminal diameter immediately after placement of the stent and the minimal luminal diameter at six months.

Late loss index	Late loss divided by the reference diameter.
Meta-analysis	Method of combining results from different studies to produce a summary statistic.
Neo-intimal hyperplasia	Excessive growth of smooth muscle tissue.
Ostial lesion	Lesion of the ostium of a coronary artery.
Percutaneous Coronary Intervention (PCI)	A term that describes all forms of percutaneous revascularisation, including PTCA and stenting.
Q wave	An abnormal wave on ECG indicating previous myocardial damage.
Restenosis	A re-narrowing or blockage of a coronary artery
Revascularisation	Maintaining or improving coronary artery blood supply.
Risk Ratio	Ratio of the proportions of the outcome in the research and control groups
Stent	Small prosthesis inserted into a coronary artery to maintain the lumen and blood flow.
Thrombus	Blood clot.
Ticlopidine	Drug that inhibits platelet function.

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