



TITLE: **Drug-Eluding Stents as an Alternative to Traditional Stenting in the Treatment of Coronary Artery Disease**

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DRUG-ELUTING STENTS AS AN ALTERNATIVE TO TRADITIONAL STENTING FOR CORONARY ATHEROSCLEROTIC HEART DISEASE (CAD)

BACKGROUND

Coronary atherosclerotic heart disease (CAD) is the most common cause of cardiovascular disability and death in the United States. In addition, it has a major impact on quality of life including chronic pain, disability and unemployment. Men are more often affected than women with an overall ratio of 4:1, but beyond age 70 the ratio is 1:1 (Massie and Amidon, 2003). Risk factors for coronary artery disease include a positive family history, age, male gender, blood lipid abnormalities, diabetes mellitus, hypertension, physical inactivity and elevated blood levels of homocystine and C-reactive protein. Clinical trials have shown that interventions aimed at modifying some of these risk factors (e.g. smoking cessation, lipid reduction and treatment of hypertension) can both prevent CAD and delay its progression and complications.

In addition to risk modification, patients with CAD who develop angina pectoris are treated with a variety of medications (nitrates, beta-blockers, platelet inhibiting agents and calcium blocking agents) or may be offered coronary artery revascularization. The two main revascularization procedures are coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) usually with stenting. The indications for coronary artery revascularization are often debated, but the trend towards more aggressive intervention has accelerated as a result of the growing use of coronary angioplasty and stenting (Massie and Amidon, 2003).

Coronary artery stenosis can be effectively dilated by inflation of a balloon under high pressure. The mechanism of dilation involves both rupture of the plaque and remodeling of the vessel. This procedure, once reserved for proximal single vessel disease, is now widely used for patients with multiple lesions and with multi-vessel disease. Although usually initially successful, PTCA can be complicated by re-narrowing of the stenosis (restenosis) in 20-57% of procedures (Garas et al 2001).

BACKGROUND, continued

This complication has led to the widespread use of intracoronary stents with PTCA. A review of 150,000 procedures performed at 139 hospitals in the National Cardiovascular Data Registry between 1998 and 2000 found that stents were used overall in 77% of cases, with significant interhospital variability (Anderson et al, 2002). Potential indications for stenting include: 1) prevention of restenosis after PTCA, 2) following direct percutaneous coronary intervention performed for the treatment of an acute MI, 3) for the management of saphenous vein thrombosis, and 4) for the treatment of acute or threatened closure (Holmes et al, 1998). Coronary stents have significantly reduced the rate of restenosis by about half to 10%-20% in focal lesions and in vessels > 3.0 mm in diameter. However, in-stent restenosis (ISR) occurs in over 30%-60% of patients with diabetes, in diffuse lesions, in vessels less than 3 mm diameter and in bifurcation lesions (Hiatt et al 2002). About 50%-75% of patients with restenosis will experience recurrent ischemic symptoms (Leon and Wong 1994).

The major factor responsible for in-stent restenosis is thought to be neointimal hyperplasia. Neointimal hyperplasia is provoked as a result of mechanical arterial injury and foreign body response to the stent that incites acute and chronic inflammation in the vessel wall. The subsequent elaboration of cytokines and growth factors activates smooth muscle cell migration and proliferation (Hoffman et al 1996). The majority of restenosis following stenting develops within the first 3-4 months after the procedure.

Drug Eluting Stents

Stents coated with biocompatible materials (such as gold and carbon), anticoagulants (such as heparin); corticosteroids and antimetabolic agents have all been studied in humans or animals for the prevention of restenosis. For the most part, the results have been disappointing (Babapulle and Eisenberg 2002). Stents eluting antimetabolic agents, so called drug-eluting stents (DES), hold the most promise in preventing restenosis. Drug-eluting coronary stents are designed to inhibit growth of new tissue resulting from neo-intimal hyperplasia. Biocompatible polymer stent coatings can be used as a base for binding drugs and other compounds to a stent. Placement of a drug onto a stent with a special polymer coating or positioning a drug-eluting sleeve around a metal stent allows slow drug release over a period of 15-45 days. This delivery method allows minimal systemic drug release and may reduce the risk of toxicity (Sheiban et al 2002).

BACKGROUND, continued

Drug Eluting Stents (continued)

A number of stent designs coated with a variety of antiproliferative drugs are currently under active investigation to evaluate their efficacy and safety. The current lead agents include sirolimus, taxol and its derivatives paclitaxel and 7-hexanolytaxol. Sirolimus is a potent immunosuppressive agent with anti-inflammatory and anti-proliferative effects. It is a natural fermentation product produced by the fungus *Streptomyces hygroscopicus*, originally found on Easter Island (Degertekin et al 2002). The sirolimus-eluting stent (CYPHER™, Cordis, a Johnson and Johnson Co.) utilizes a nonerodable methacrylate copolymer matrix for controlled endovascular delivery of the drug to the arterial tissue. This stent-based drug delivery system provides controlled release of sirolimus over a period of 4 weeks (Hiatt et al 2002). Paclitaxel (Taxol) and its derivatives are microtubule inhibitors that prevent cell migration and proliferation, thereby interrupting the restenotic cascade at multiple levels (Grube et al 2002). The drug-eluting stent from Boston Scientific (Boston, MA) utilizes low dosages of paclitaxel in two release formulations (slow release and moderate release). Drug is released to the tissue in 2 days with the moderate release and over 15-20 days with the slow release stent.

TA Criterion 1: The technology must have the appropriate regulatory approval.

The CYPHER™ Sirolimus-Eluting Coronary Stent System (Cordis, Johnson and Johnson) received FDA PMA clearance on April 24, 2003. The FDA noted that “This device is indicated for improving coronary luminal diameter in patients with symptomatic ischemic 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. Long-term outcome (beyond 12 months) for the permanent implant is unknown at present”. There are additional post-approval requirements regarding data collection and reporting.

The TAXUS™ paclitaxel-eluting stent (Boston Scientific, Natick, MA) has received CE Mark clearance (clearance for marketing in Europe) and “expedited review” status from the FDA. TAXUS is not yet cleared for marketing in the US.

TA criterion 1 is met for CYPHER™ but not yet for TAXUS™

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The published peer reviewed literature examining the use of intracoronary drug-eluting stents to prevent restenosis in humans consists of two randomized clinical trials of the sirolimus-eluting stent (Moses et al, in press; Morice et al 2002), and two follow-up studies; (Serruys et al 2002; Regar et al 2002), three RCTs of the paclitaxel-eluting stent (Hong et al, 2003; Park et al 2003; Grube et al 2002), four papers describing results from a case series of the sirolimus-eluting stent, and three case series of drug-eluting stents in the treatment of in-stent restenosis (Tanabe et al, 2003; Sousa et al 2003; Liistro et al 2002). In addition, Kataoka et al (2002) and Honda et al (2001) report on intravascular ultrasound findings in patients who received the 7-hexanoyltaxol-eluting stent.

An RCT of this stent (the Study to Compare Restenosis rates between QueST and QuaDDS-QP2 or "SCORE") was terminated prematurely after interim analysis showed a predisposition for subacute and delayed stent thrombosis (9.4%) in the QP2-stent group compared with the uncoated stent group (Babapulle and Eisenberg 2002).

Outcomes assessed in these trials include baseline angiographic and intravascular ultrasound evaluation prior to stent placement and at one month, six months and 12 months. Quantitative coronary angiographic end-points include:

- Minimal lumen diameter of the stented segment plus the 5 mm segments proximal and distal to the stent.
- Late lumen loss -- the difference between the post-intervention minimum lumen diameter (MLD) and the MLD at follow-up.
- Restenosis -- stenosis of 50% or more of the luminal diameter.
- Late loss index -- Late lumen loss divided by gain in luminal diameter achieved by the procedure.

TA Criterion 2, continued

Clinical end-points include major adverse cardiac events (MACE) such as myocardial infarction, death and revascularization of the target lesion or vessel including coronary artery bypass grafting. Angiographic measurements are not always predictive of a patient's symptoms or prognosis. Clinical outcomes are more important in evaluating the overall clinical impact of drug-eluting stents.

To date, there is sufficient evidence to evaluate the safety and long-term efficacy of sirolimus-eluting stents but insufficient evidence to evaluate paclitaxel-eluting stents for use in routine clinical practice. The randomized studies to date of the paclitaxel-eluting stents have enrolled patients whom overall have had less complex lesions at lower risk for restenosis and the studies have not been powered to evaluate major clinical end-points. As a result, it is difficult to generalize on how paclitaxel-eluting stents will perform when used in a wide variety of patients in non-research settings. Two upcoming studies of paclitaxel-eluting stents, TAXUS IV and TAXUS V, should provide the evidence needed to evaluate the performance of these stents in more complex populations.

TA Criterion 2 is met for sirolimus-eluting stents.

Levels of Evidence: 1,5.

TA Criterion 3: The technology must improve the net health outcomes.

Patient Benefits

Sirolimus-Eluting Stents for de novo native coronary lesions

Case series

The First in Man (FIM) study was the first published nonrandomized study in humans to investigate stents coated with antimitotic agents.

TA Criterion 3, continued

Case series (continued)

It was conducted jointly in Sao Paulo, Brazil and Rotterdam, the Netherlands to assess the efficacy of a sirolimus-coated stent in inhibiting neointimal hyperplasia. Main outcomes included angiographic and intravascular ultrasound of the stented vessels at 4 months, 6 months, 12 months and up to 2 years. In the Sao Paulo registry, 30 patients were electively treated with 2 different formulations of 18 mm sirolimus-eluting Bx velocity stents (slow release n=15 and fast release n=15) (Sousa et al 2003; Sousa et al 2001). At 4 months angiographic and intravascular ultrasound (IVUS) follow-up, there was minimal neointimal hyperplasia in both groups and no in-stent or edge restenosis was observed. By one year the IVUS and angiographic findings were essentially unchanged. There was one late acute MI in the fast release group.

In the Rotterdam cohort, 15 patients were treated with the slow release formulation sirolimus-eluting stent and followed up with IVUS and quantitative angiography as well as MACE at 6 months and at 24 months in 10 of the 14 surviving patients (Rensing et al 2001; Degertekin et al 2002). There was a total of 5 MACE in 3 patients: one death from intracerebral hemorrhage, 1 MI, and 3-vessel revascularization. Minimal or no neointimal hyperplasia was found in all patients studied.

Randomized trials

The RANdomized study with the Sirolimus-coated BX VELOCITY balloon expandable stent in the treatment of patients with de-novo native coronary artery lesions (RAVEL) was a randomized, double-blind, controlled trial that evaluated a sirolimus coated stent in humans (Morice et al 2002). The sirolimus was blended with a mixture of polymers to release approximately 80% of the drug over 30 days.

TA Criterion 3, continued

Randomized trials (continued)

Two hundred thirty eight patients with low-risk lesions in native coronary arteries of 2.5 to 3.5 mm in diameter were randomized to receive either a sirolimus coated stent (n=120) or an uncoated steel stent (n=118). All patients were treated with aspirin 100 mg per day plus clopidogrel for 8 weeks post procedure. Patients were evaluated at 30 days and at 6 and 12 months. The primary angiographic end point was in-stent luminal late loss (i.e. minimal lumen diameter post procedure minus minimal lumen diameter at follow-up). Secondary end points included the rate of restenosis (luminal narrowing of 50% or more) and the minimal lumen diameter of the stented segment and of the 5 mm segments proximal and distal to the stent at 6 months. The primary clinical end point of the study was a composite of major adverse cardiac events (MACE), including death, Q-wave or non-Q-wave myocardial infarction and revascularization. Overall, 76% of the patients were men with a mean age of 60.7 years. At six months, the mean luminal diameter of the stented segment was significantly greater in the sirolimus stent group. In addition, the mean in-stent late loss and percentage of patients with 50% or more stenosis were -0.01 and 0 percent respectively in the sirolimus stent group as compared with 0.80 mm and 26.6 % in the standard stent group. In the subgroup of patients with diabetes, 19 patients received sirolimus-eluting stents and 25 received standard stents. At six months, there was a significant difference in restenosis rates of 41.7% in the standard stent group vs. 0 percent in the sirolimus stent group. The overall rate of major cardiac events was 5.8% in the sirolimus-stent group and 28.8% in the standard stent group ($p < 0.001$). The difference between the two groups was entirely due to the greater need for repeated revascularization of the target vessel in the standard stent group. Of the 27 patients in the standard stent group who underwent revascularization of the target vessel (22.9%), 16 did so because of angina or abnormal stress tests and 11 because of angiographic evidence of restenosis.

TA Criterion 3, continued

Randomized trials (continued)

Regar et al (2002) investigated the relationship between vessel diameter and angiographic outcome 6 months after sirolimus-eluting stent implantation in patients in the RAVEL trial. Subjects were stratified by vessel reference diameter at baseline. The main finding was that the sirolimus-eluting stent prevented restenosis irrespective of vessel diameter. In the standard stent group, the classic inverse relationship between restenosis rate and vessel diameter was seen.

Results from the multi-center, randomized double blind study of the SIRolimUS-eluting stent in de novo coronary lesions (SIRIUS) has been accepted for publication in the New England Journal of Medicine (Moses et al, in press). In this study, 1,058 patients from 53 centers in the US were randomized to sirolimus eluting vs. bare metal stents. All patients received aspirin (325 mg daily) and oral clopidogrel (300-375 mg loading dose 24 hours before and 75 mg daily for three months). Eligible patients had a single de novo target lesion in a native coronary artery between 51 and 99% in diameter stenosis and between 15 and 30 mm in length. Major exclusion criteria included: recent MI, ejection fraction less than 25%, target lesions in an ostial, bifurcation or left main location or in vessels with thrombus or severe calcification. The primary end-point of the trial was target vessel failure (defined as cardiac death, MI or target lesion revascularization) at 270 days. Secondary clinical end-points included all cause mortality, clinically driven CABG or repeat PTCA, and stent thrombosis. Overall, patients enrolled in this study represented a more complex cohort than previous studies including more patients with diabetes (26%), longer lesions (averaging 14.4 mm in length), and smaller coronary vessels (2.8-mm vessel diameter). Quantitative angiographic and intravascular ultrasound measurements as well as clinical outcomes were all significantly better with the sirolimus coated stent.

TA Criterion 3, continued

Randomized trials (continued)

For example, in-segment restenosis frequency was 8.9% for sirolimus stents and 35.4% for standard stents ($P < 0.001$). The primary clinical endpoint, target vessel failure at 270 days, was decreased by 59% with sirolimus stents and the out of hospital adverse events until 270-days follow-up were reduced in sirolimus stent patients including non-Q wave MI, target lesion revascularization and all major adverse events. In the patients with diabetes, the relative reductions after sirolimus stent treatments were of similar magnitude (e.g. in segment restenosis reduced from 50.5% to 17.6% and target lesion revascularization reduced from 22.3% to 6.9%). Overall, there were no adverse clinical events associated with the sirolimus-eluting stent.

Paclitaxel-Eluting Stents for de novo native coronary lesions

Case series

Honda et al (2001) used serial intravascular ultrasound to evaluate the effects of a QP2-eluting stent (QuadDS-QP2 stent) on neointimal tissue growth in 14 patients. QP2 is a taxane analogue. At follow-up, a minimal amount of neointimal proliferation was observed and no patients showed a significant in-stent or edge restenosis by 8 months.

Hong et al (2003) report on results from The ASia Paclitaxel Eluting stents Trial (ASPECT) on the use of intravascular ultrasound to evaluate the effect of a paclitaxel coating on in-stent intimal hyperplasia. Patients were randomized to placebo (bare metal stents) or 1 of 2 doses of paclitaxel. They found that with increasing doses there was a stepwise reduction in intimal hyperplasia accumulation within the stented segment. No clinical outcomes were assessed.

TA Criterion 3, continued

Randomized trials

TAXUS I (Grube et al 2002) was a prospective, double-blind, three center study of 61 patients that compared the safety and feasibility of the TAXUS NIRx stent system (n=31) compared with bare NIR stents (n=30) (Boston Scientific Corp) for the treatment of de novo or restenotic coronary lesions. All patients were treated with aspirin for 12 months and clopidogrel for 12 months. Clinical evaluation was scheduled at 1, 6, 9 and 12 months after implantation. Angiographic and IVUS imaging was performed before and after the procedure and at 6 months. The primary end-point was MACE at 30 days. Of the 61 patients enrolled, 2 had restenotic lesions. The 6 month MACE rate was 0% in the TAXUS group compared with 7% in the control group (P=NS). At 12 months the difference in the MACE rate between the control and TAXUS group was also not significant (3% vs. 10%). At six months, the in-stent binary restenosis rate was 10% (3 of 29 patients) for the control group and 0% (0 of 30) for the TAXUS stent (p=NS). Late lumen loss and IVUS assessment of neointimal hyperplasia significantly favored the TAXUS group. The authors conclude that the inability of the study to identify significant differences between the paclitaxel DES and the control stent may have been due to the excellent clinical and angiographic outcomes in the control group.

Park et al (2003) conducted a multicenter randomized controlled trial (The ASia Paclitaxel Eluting stents Trial or ASPECT trial) to evaluate the safety and efficacy of high and low dose paclitaxel-eluting stents as compared with bare metal stents in patients with de novo coronary artery lesions. Exclusion criteria were more stringent than The SIRIUS trial (e.g. EF less than 35%, lesion length greater than 15 mm). The primary end point was the percentage stenosis at angiographic follow-up. Secondary clinical end points included the incidence of death, thrombosis, MI, and revascularization. 177 patients were enrolled, 60 in the high dose group, 58 in the low dose group and 59 in the control group.

TA Criterion 3, continued

Randomized trials (continued)

While they found a dose dependent reduction in the primary end-point, the percentage of stenosis (39+/-27% in the control group, vs. 23+/-25% in the low dose group and 14+/-21% in the high dose group), they failed to demonstrate a reduction in target lesion revascularization for restenosis among treatment groups. The authors claim that this discrepancy was due to the pattern of clinical practice in the participating centers. They conclude, “conclusions regarding clinical effect are tentative in this study, whose size was based on an angiographic end point”.

Unpublished trials

The EvaLUation of PacliTaxel-Eluting Stents (ELUTES) trial was a prospective, double blind study of 180 patients with low-risk lesions who received either an uncoated stent or a paclitaxel-coated stent with no carrier polymer in 4 different concentrations. There was no difference in the 6-month MACE rates between the paclitaxel-coated and the uncoated stent (11% in both groups). A dose dependent reduction in angiographic percent-diameter stenosis was observed (Sheiban 2002). The Study to COMPare REstenosis rates between QueST and QuaDDS-QP-2 (SCORE) was a randomized multicenter trial that was terminated prematurely after interim analysis showed an increased predisposition for subacute and delayed stent thrombosis, though 6 month angiographic analysis results showed that these stents inhibit neointimal hyperplasia (Babapulle and Eisenberg 2002).

Pending Trials

There are several other ongoing or planned trials of the paclitaxel-eluting stent. TAXUS II is a randomized, double blind trial to evaluate the safety and performance of a slow and moderate release paclitaxel-coated stent on a broader population with de-novo lesions. TAXUS IV is a randomized, double blind trial of 1,600 patients to study the safety and efficacy of a moderate-release paclitaxel formulation on target vessel failure at 9 months in both de novo and in-stent restenosis lesions. TAXUS V will include a more complex population with longer lesions (up to 40mm) and allow the implantation of multiple stents. Results of these trials are expected in 2003.

TA Criterion 3, continued

Pending Trials (continued)

Other trials are planned or ongoing for other drug-eluting stents such as the ACTION trial (Actinomycin-eluting stent), the PRESENT trial (tacrolimus-eluting stent) and the TRUST trial (silicon carbide).

Patient Risks

There are a number of potential risks to patients with the use of stents in general and drug-eluting stents in particular. Stenting is now performed in the majority of percutaneous coronary interventions and increasingly in more complex and older patients (Anderson et al 2002). In spite of the growing uses of stents, the success rate has actually increased. The rate of emergent CABG has fallen to 1.9%; the rate of in-hospital Q-wave MI is 0.4%; and overall mortality is 1.4% (Anderson et al 2002).

There are a number of early complications of bare-metal stents that may also occur with the drug-eluting stents. These complications include failed delivery with potential stent embolization, stent thrombosis, myocardial infarction (typically non-Q wave), side branch occlusion, bleeding and death. Failed delivery (or failed stent deployment) is a potentially serious problem, but is infrequent. In a recent review, failed delivery occurred in 0.4-2% of cases (Bolte et al 2001). Stent thrombosis usually occurs within the first 24 hours (acute) or within 1-4 weeks (subacute) after stent placement (Leon et al 1994). With second generation stents and antithrombotic regimens the reported incidence has ranged from 0.9% to 2.5%.

In addition to the above, drug-eluting stents raise a number of different potential risks for patients. Like radioactive stents, both sirolimus and paclitaxel inhibit smooth muscle proliferation. Synthetic polymers are often used as carriers and biocompatibility is a concern as polymers often induce an exaggerated inflammatory reaction (Babapulle and Eisenberg 2002). Concerns have also been raised regarding incomplete vessel healing and re-endothelialization which may lead to an increased risk of late thrombosis (Bartorelli and Trabattoni 2002). One of the patients in the FIM study experienced a target vessel thrombosis at 14 months (Sousa et al 2001). And an excess of thrombotic events was reported in the SCORE and ASPECT trials (Liistro and Colombo 2001).

TA Criterion 3, continued

Patient Risks (continued)

No thrombotic events, however, were seen in the RAVEL study. Concern about thrombosis has prompted many clinical trials to treat enrolled patients with oral anti-thrombotics for up to 6 months after implantation (Babapulle and Eisenberg 2002).

TA criterion 3 is met for sirolimus-eluting stents but not for paclitaxel-eluting stent.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

Other strategies that have been used to prevent in-stent restenosis include radioactive stents (brachytherapy), systemic therapy and stents coated with other material such as gold and heparin. Intracoronary radiation with ribbons containing gamma or beta radioactive seeds have been found to reduce neo-intimal formation and in-stent stenosis by impairing smooth muscle cell proliferation. However, the long-term efficacy of radioactive stents is uncertain as they may delay but not prevent restenosis. In one study of 40 patients, Kay et al (2001) found that repeat catheterization and IVUS at one year demonstrated progression of neointimal hyperplasia primarily in the mid and distal part of the stent; 23% required revascularization.

A variety of systemic pharmacological therapies have been investigated to prevent thrombosis and restenosis after PTCA and after stent implantation (Garas et al 2001). Anti-platelet agents such as aspirin and ADP receptor antagonists (ticlopidine and clopidogrel) have met with the most success for the prevention of thrombosis but have had little impact on restenosis. For example, in the Stent Anticoagulation Restenosis Study, aspirin and ticlopidine were found to be better than aspirin alone or aspirin plus warfarin for the prevention of stent thrombosis (Leon et al 1998). These systemic therapies are likely to be used along with DES to prevent thrombosis. Which drugs and for how long is still being investigated.

TA Criterion 4, continued

Stents coated with other material have also been studied to prevent stent restenosis. Results thus far have been disappointing. For example, one clinical trial comparing heparin-coated stents with uncoated stents for the prevention of restenosis failed to show a significant difference between the two groups (Babapulle and Eisenberg 2002). Gold-coated stents have not been found to be associated with an improved outcome and may actually increase the amount of neointimal proliferation and restenosis (Park et al 2002).

To date, only sirolimus-eluting stents have been shown to safely and effectively improve clinical outcomes associated with decreased restenosis rates. There is insufficient data to determine if paclitaxel-eluting stents will lead to better patient outcomes, and other strategies to reduce in-stent stenosis are not satisfactory.

TA criterion 4 is met for sirolimus-eluting stents.

TA Criterion 5: The improvement must be attainable outside the investigational settings.

Drug-eluting stents are macroscopically indistinguishable from the standard stents currently being used around the world. Unlike radioactive stents, they require no special handling and no special training are needed.

TA criterion 5 is met.



RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The Blue Cross Blue Shield Association TEC Medical Advisory Panel has not reviewed this topic.

American College of Cardiology – California Chapter

The California Chapter of the American College of Cardiology has been invited to participate in the meeting.

The American College of Cardiology does not have a published position regarding drug-eluting stents. The California chapter has indicated that these stents are too new at this time for a formal position/opinion to have been developed.

Centers for Medicare and Medicaid Services (CMS)

CMS has made a decision to establish a new APC for procedures that use drug-eluting stents.

Society of Cardiac Angiography and Interventions

The Society has been invited to participate in the meeting and provide a position statement.

CONCLUSION

Coronary atherosclerotic heart disease (CAD) is the most common cause of cardiovascular disability and death in the United States. Patients with CAD are often treated with a variety of medications (nitrates, beta-blockers, platelet-inhibiting agents and calcium blocking agents) and may be offered coronary artery revascularization. The two main revascularization procedures are coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) usually with stenting. While intracoronary stents have reduced the rate of stenosis following PTCA by about half, in-stent stenosis continues to be an important problem, especially for patients with diabetes, or in smaller vessels. The search for an effective method to reduce in-stent restenosis has taken on an almost religious fervor in the cardiology community, leading one paper to describe it as: “(the) quest for the Holy Grail” (Hiatt et al 2002).

As a result, there has been an explosion of interest in drug-eluting stents for the prevention of in-stent restenosis. Stents coated with a variety of antimitotic agents have been tested in humans or are currently in clinical trials. Each of these agents has different mechanisms of action and potential adverse effects and toxicities so will have to be evaluated in separate clinical trials and approved for use individually. Currently, the two agents that have been the most rigorously studied are sirolimus and paclitaxel.

The drug-eluting stent can significantly reduce the incidence of in-stent stenosis. In the first published RCT trial of the sirolimus-eluting stent (Morice et al 2002), there was a significant reduction in MACE as well as a dramatic difference in restenosis rates between the standard stent group and the sirolimus-coated stent. In addition, there were no adverse events reported with the sirolimus stent. However, as the authors themselves cautioned, this trial did not definitively answer the question as to which patients and under what conditions the sirolimus-eluting stent should be used.

CONCLUSION, continued

The SIRIUS trial (Moses et al, in press) addressed these concerns by including more complex patients at higher risk of restenosis and found that clinical as well as angiographic outcomes were significantly improved in those patients randomized to receive the sirolimus-eluting stent.

Patient selection for drug-eluting stents will be more clearly delineated by future research. In the SIRIUS trial, the DES was very effective even in traditionally high restenosis risk subgroups such as diabetics, and vessels less than 3 mm. Further trials will be required to determine the role of DES in patients with bifurcation disease, chronic total occlusions, saphenous vein graft disease, left main lesions and multi-vessel disease.

RECOMMENDATION

It is recommended that sirolimus-eluting stents for patients with angina pectoris or silent ischemia and greater than 50 percent de novo stenosis of ≤ 30 mm in length, of one or more native coronary arteries with a diameter ≥ 2.5 mm to ≤ 3.5 mm meet California Technology Assessment Forum TA criteria.

Sirolimus-eluting stents for treatment of stenotic lesions of the left main coronary artery; for treatment of stenotic lesions of non-coronary arteries such as saphenous vein grafts, for in-stent restenosis, for treatment of non-atherosclerotic anatomies (i.e. thrombotic lesions associated with acute MI), for bifurcation lesions, or prior brachytherapy, and other drug-eluting stents do not meet California Technology Assessment Forum TA criteria.

The California Technology Assessment Forum voted to accept the recommendation as stated.

June 11, 2003

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