



DRUG ELUTING STENTS: AN UPDATE WITH A FOCUS ON SAFETY

INTRODUCTION

The California Technology Assessment Forum has been asked to update the prior assessments of drug-eluting stents in light of emerging evidence regarding adverse events, morbidity and mortality.

BACKGROUND

Coronary atherosclerotic heart disease (CAD) is the most common cause of cardiovascular disability and death in the United States. In addition, it significantly impacts on quality of life including chronic pain, disability and unemployment. Men are affected more often than women with an overall ratio of 4:1, but beyond age 70 the ratio is 1:1¹. Risk factors for coronary artery disease include a positive family history, age, male gender, blood lipid abnormalities, diabetes mellitus, hypertension, physical inactivity and various serum markers. 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 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 coronary intervention (PCI) usually with stenting. The indications for coronary artery revascularization are often debated, but the trend toward using more aggressive interventions has increased as a result of the growing use of coronary angioplasty and stenting¹. It was estimated that there would be approximately 2.5 million coronary interventions performed worldwide in 2005².

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.



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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, PCI can be complicated by re-narrowing of the stenosis (restenosis) in 33% of patients^{3,4}, often necessitating a repeat procedure. Patients often present with symptoms of recurrent angina, but may be asymptomatic.²

This complication has led to the widespread use of intracoronary stents. A review of 150,000 procedures performed at 139 hospitals in the National Cardiovascular Data Registry between 1998 and 2000 found that, overall, stents were used in 77% of cases, with significant inter-hospital variability⁵. Currently, virtually all PCIs involve a stent. Potential indications for stenting include: 1) prevention of restenosis after PTCA, 2) following direct percutaneous coronary intervention performed for the treatment of an acute myocardial infarction (MI), 3) for the management of saphenous vein thrombosis, and 4) for the treatment of acute or threatened closure⁶. Bare metal coronary stents significantly reduced the rate of restenosis by about half, down to 10%-20% in focal lesions and in vessels less than 3.0 mm in diameter. However, with bare metal stents, in-stent restenosis (ISR) occurs in 30%-60% of patients with diabetes, in diffuse lesions, in vessels less than 3 mm diameter and in bifurcation lesions⁷. About 50%-75% of patients with restenosis will experience recurrent ischemic symptoms⁸. The major factor responsible for in-stent restenosis is thought to be neo-intimal hyperplasia. Neo-intimal 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 proliferation⁹. The majority of restenosis following stenting with bare metal stents develops within the first three to four months after the procedure.

DRUG ELUTING STENTS

Drug eluting stents (DES) were developed to address the problem of in-stent restenosis. Unlike with bare metal stents (BMS), where neo-intimal hyperplasia may develop in response to damage to the arterial wall during implantation of the stent leading to early coronary artery restenosis, DES block intimal cell division and inhibit inflammation, thereby preventing early



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restenosis of the vessel. Stents coated with biocompatible materials (such as gold and carbon), anticoagulants (such as heparin), corticosteroids and anti-mitotic agents have all been studied in humans or animals for the prevention of restenosis. For the most part, the results have been disappointing¹⁰.

Drug-eluting coronary stents are designed to inhibit growth of new tissue resulting from neointimal 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 to 45 days. This delivery method allows for minimal systemic drug release and may reduce the risk of toxicity¹¹.

Two DES currently are FDA approved and widely used in clinical practice in the United States: a sirolimus-eluting stent (CYPHERTM, Cordis, a Johnson and Johnson Co.) and a paclitaxel-eluting stent (TAXUSTM, Boston Scientific). 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 Island¹². The sirolimus-eluting stent utilizes a non-erodable 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 four weeks⁷. The sirolimus-eluting stent (CYPHERTM) was reviewed at the CTAF meeting on June 11, 2003 and found to meet CTAF technology assessment criteria.

Paclitaxel (Taxol) is a trace compound derived from the Pacific Yew tree (*TAXUS brevifolia*) found in the Pacific Northwest and Canada¹³. Paclitaxel and its derivatives are microtubule inhibitors that prevent cell migration and proliferation, thereby interrupting the restenotic cascade at multiple levels¹⁴. As a chemotherapeutic agent, paclitaxel is administered at doses more than 3,000 times greater than that used for stent delivery. The TAXUSTM stent was reviewed by CTAF in June 2004 and found to meet CTAF technology assessment criteria. There are several different paclitaxel-eluting stents in current or past clinical trials or in development¹⁵⁻¹⁷, but only the TAXUSTM paclitaxel-eluting stent (Boston Scientific, Natick, MA) is currently FDA approved. This stent utilizes a copolymer carrier system developed to provide homogeneous coverage of the stent platform after deployment¹⁸. The polymer provides controlled biphasic release with an initial burst of paclitaxel, followed by lower level release



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through ten days. Two release formulations have been studied (slow release and moderate release); both carry the same total dose of $1.0 \mu\text{g}/\text{mm}^2$, but the moderate release stent has an eight-fold higher release over the first ten days than does the slow release¹⁸.

The CYPHERTM 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.” In 2006, the FDA approved new labeling for the use of overlapping CYPHER stents stating that they did not increase the risk of AMI compared with BMS. The TAXUSTM Express²TM Paclitaxel-Eluting Stent System (Boston Scientific, Natick, MA) received FDA premarket approval on March 4, 2004. The device is indicated for improving luminal diameter for the treatment of de novo lesions < 28 mm in length in native coronary arteries ≥ 2.5 to ≤ 3.75 mm in diameter. Post market reporting was required on an annual basis for both devices.

Other stents used in Europe include the Achieve and V-Flex Plus TTX paclitaxel eluting stents manufactured by the Cook Group, the Endeavor ABT-578-eluting stent by Medtronic and the Axxion paclitaxel stent made by Biosensors International. It estimated that DES are used in up to 90% of procedures in the United States and about 50% of PCIs in Europe, though these estimates pre-date the recent controversy regarding late thrombosis with the DES.

EFFICACY AND SAFETY OF DRUG ELUTING STENTS

Efficacy of DES: Brief Review

A number of pivotal trials have demonstrated that DES are more effective than BMS in reducing early stent restenosis and the need for target vessel revascularization (see prior CTAF systematic reviews: Feldman, 2004 and Feldman, 2003)^{19, 20}. The California Technology Assessment Forum reviewed the evidence for safety and efficacy of sirolimus eluting stents in June 2003 and paclitaxel eluting stents in June 2004 and concluded that both DES met CTAF criteria for safety and effectiveness. Specifically, the recommendation approved by the CTAF panel regarding the sirolimus-eluting stent was as follows:



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- 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.

Likewise, the panel voted that the paclitaxel stent met CTAF criteria:

- It is recommended that TAXUSTM paclitaxel-eluting stents for de novo native coronary lesions for patients with angina pectoris or silent ischemia and greater than 50 percent de novo stenosis of 10 mm – 28 mm in length, of one or more native coronary arteries with a diameter ≥ 2.5 mm and ≤ 3.75 mm meet California Technology Assessment Forum TA criteria.
- TAXUSTM paclitaxel-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 for prior brachytherapy; and other paclitaxel drug-eluting stents do not meet California Technology Assessment Forum TA criteria.

Recently, a number of meta-analyses and systematic reviews have examined the efficacy and safety of DES vs. BMS. For example, Roiron (2006) report on a meta-analysis of sirolimus and derivatives and paclitaxel and derivatives eluting stents vs. BMS²¹. They selected 19 randomized control trials (RCTs) with 8987 patients (this included some studies of stents not yet approved in the US) with endpoints of major adverse cardiac events (MACE) and restenosis rates. They found that overall occurrence of MACE was significantly reduced from 19.9% to 10.1% ($p < 0.001$), with a larger reduction of MACE in the sirolimus subgroup. Likewise, the overall adjusted rate for angiographic restenosis was 10.5% in the DES group vs. 31.7% in the control group (OR 0.25, 95% CI 0.22 to 0.29, $p < 0.001$). Overall mortality was not significantly



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different between treatment groups. Likewise, Babapulle (2004) reported on a meta analysis of 11 randomized trials involving 5103 patients with six to 12 months of clinical follow-up²². They concluded that DES are effective at decreasing rates of angiographic restenosis and MACE compared with BMS. A recent systematic review reported on a total of 11 randomized clinical trials comparing DES (CYPHER and TAXUS) to BMS, with 5287 patients that reported relevant clinical outcomes with at least six months of follow-up²³. They found that the patients enrolled in these trials were generally young and predominantly male, and that the inclusion criteria for most specified that patients had a single de novo lesion in a native artery, and that the lesions were mainly intermediate in length in medium caliber vessels. Follow-up in most trials was for no more than six to nine months. Prevalence of diabetes ranged from 14% to 31%. As with the other analyses, they found that the restenosis rate was substantially lower with DES than with BMS, with lower rates of target vessel revascularization and MACE.

STENT THROMBOSIS

Background

At the time of the initial CTAF review of DES in 2003 and 2004 there was some indication that stent thrombosis might be an issue with DES. In the CTAF review of paclitaxel eluting stents, the following caveat was raised with regards to patient safety: “Concerns have also been raised regarding incomplete vessel healing and re-endothelialization, which may lead to an increased risk of late thrombosis²⁴. However, the rate of thrombosis seen in the TAXUS and sirolimus trials has not been significantly greater than that seen with the control stents (less than one percent in all RCT’s).” Over the past few years, concerns about safety of DES, particularly in relation to late thrombosis, have continued to be raised. In 2005, the FDA released patient safety news report #43 on its’ website that was titled, “Importance of Antiplatelet Therapy with Drug Eluting Stents,” in which they stated that: “the FDA has received a number of reports of adverse events that occurred in patients who received drug-eluting coronary stents and then stopped taking their antiplatelet medication prematurely. These events included stent thrombosis, MI and death, and they occurred in patients who received both of the currently marketed drug-eluting stents: the CYPHER stent system made by Cordis Corp., and the TAXUS stent system, made by Boston Scientific Corp. Sometimes these events occurred when patients stopped antiplatelet therapy early because of non-compliance. In other cases, practitioners asked the patient to stop the medication because they were going to have elective surgical or



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

dental procedures, or because the patient experienced minor bleeding. As a result, both Cordis and Boston Scientific have now changed the labeling for their drug-eluting stents to emphasize the importance of patient compliance with the antiplatelet recommendations and the risks of prematurely discontinuing antiplatelet therapy.”

More recently, concerns about the safety of DES and late stent thrombosis escalated as a result of presentations at the European Society of Cardiology 2006 World Congress (WCC) in Barcelona, Spain followed by data presented at the Transcatheter Cardiovascular Therapeutics (TCT) 2006 meeting in Washington, DC. At the WCC, Dr. Camenzind and Dr. Nordmann presented findings from their meta-analyses²⁵ that found that patients treated with DES had higher rates of MI compared with BMS and that patients treated with the sirolimus eluting stent had significantly higher rates of MI and death compared with the BMS²⁶. Results presented at the TCT confirmed the increase in late stent thrombosis with DES compared with BMS, but did not find an excess of deaths or MI²⁶. Dr. Martin Leon presented findings from his meta-analysis of 3506 patients enrolled in five RCTs with the TAXUS stent. He reported late stent thrombosis in nine patients vs. two in the BMS group, an increase of 0.5% between one and four years after stent implantation, a rate of about 0.15% per year. Dr. Gregg Stone presented results from 1748 patients enrolled in the four pivotal trials of the CYPHER DES. He reported stent thrombosis in five DES patients vs. none in the BMS group, a rate of 0.6% between one and four years, or about 0.2% per year²⁷.

Following these meetings, the FDA issued a statement about DES on its' website in September 2006 (<http://www.fda.gov/cdrh/news/091406.html>). It stated in part that:

“At this time, FDA believes that coronary DES remain safe and effective **when used in patients having clinical and coronary anatomic features similar to those treated in the pivotal trials conducted by the manufacturers for FDA approval** (emphasis added). The approved indications are:

The CYPHER Sirolimus-eluting Coronary Stent 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 reference vessel diameter of ≥ 2.5 mm to ≤ 3.5 mm.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

The TAXUS Express Paclitaxel-Eluting Coronary Stent System is indicated for improving luminal diameter for the treatment of de novo lesions ≤ 28 mm in length in native coronary arteries ≥ 2.5 to ≤ 3.75 mm in diameter.”

On December 7 and 8, 2006 the FDA convened the Circulatory System Devices Advisory Panel to review the data emerging regarding risk of thrombosis and DES^{28, 29}. The panel concluded that both of the currently approved DES (CYPHER and TAXUS) are associated with a small increase in stent thrombosis, but not with increased MI or death, compared to BMS, that emerges one year post implantation. They concluded that there was not sufficient evidence to conclude that there were different safety concerns with the sirolimus or paclitaxel eluting stents. They also concluded that: “The concerns about thrombosis do not outweigh the benefits of DES compared to BMS bare metal stents *when DES are implanted within the limits of their approved indications for use.*” (italics added) The panel observed that at least 60% of current DES use is off label, but emphasized that the FDA does not regulate how devices are used by individual clinicians in the practice of medicine. The panel recommended, however, that while more studies are needed to determine optimal treatment for complex patients, they concluded that off label use of DES is associated with an increased risk of stent thrombosis and possibly death and MI compared to on label use, and that DES labels should state that when DES are used off-label, patient outcomes may not be the same as the results observed in the pivotal clinical trials.

Stent thrombosis generally occurs in the first month following stent implantation, so-called “subacute stent thrombosis”. When it does occur, it often leads to significant adverse outcomes such as MI or death³⁰. While DES decreased the incidence of subacute stent thrombosis, presumably by limiting intimal hyperplasia, it seems to have been at the risk of increased late stent thrombosis. Late thrombosis, occurring more than one month and up to a year or more after implantation, has emerged as an issue with DES. Speculation has centered on delayed endothelialization, incomplete neo-intimal healing and hypersensitivity reactions as the mechanisms behind late stent thrombosis leading to possible MI and death with DES³¹ (Attachment 3).. A recent autopsy study³² shed light on the patho-physiology of late thrombosis with DES. They found evidence of delayed arterial healing (persistence of fibrin and incomplete endothelialization) with both the sirolimus and paclitaxel eluting stents. As with other studies^{33, 34}, risk of late stent thrombosis increased with stent length. Other predictors of late stent thrombosis include metabolic factors (diabetes mellitus, renal failure), anatomic factors (multiple lesions, overlapping stents, bifurcation lesions), cardiac factors (low ejection fraction, acute



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

coronary syndrome) and premature discontinuation of anti-platelet therapy^{31, 35-37} (Attachment 4).

“Late” stent thrombosis is generally defined as occurring one month after stent implantation, while “very late” stent thrombosis is defined as thrombosis that occurs 12 months or more from the time of implantation. A problem in interpretation of late thrombosis events is that at the time of the pivotal trials a uniform definition was not in place. To address this issue the Academic Research Consortium developed a new, uniform standard definition for late stent thrombosis³⁸ (Attachment 5):.

Definite/confirmed – Acute coronary syndrome AND either angiographic confirmation of stent thrombosis or occlusion OR pathologic confirmation of acute stent thrombosis

Probable – Unexplained death within 30 days; target vessel infarction without angiographic confirmation of stent thrombosis or other identified culprit lesion

Possible – Unexplained death after 30 days

WHAT IS THE EVIDENCE THAT DES INCREASES THE RISK OF LATE STENT THROMBOSIS

Peer Reviewed

Pfisterer (2006) reported increased cardiac events including fatal and non-fatal AMI in patients treated with DES compared with BMS³¹. They analyzed a series of 746 patients with 1,133 stented lesions who survived the first six months after stenting without major clinical events and who then discontinued clopidogrel. Patients were randomly assigned in a two to one manner to DES vs. BMS, with the DES cohort close to evenly divided between the CYPHER and TAXUS stents. At 18 month follow-up, there was no difference in cardiac death or MI between the DES and BMS patients. However, late stent thrombosis (defined as all sudden cardiac deaths, MI's and target vessel revascularizations attributable to the target vessel between seven and 18 months after stenting) was twice as frequent after DES vs. BMS (2.6% vs. 1.3%).

Nordmann (2006) report on the results of a meta-analysis of mortality in randomized controlled trials comparing DES and BMS³⁹. They identified 17 trials with 8221 patients that reported mortality data after one year. Nine of the trials used a paclitaxel eluting stent (n=826), seven trials used a sirolimus eluting stent (n=2487) and one trial used both (n=826). They failed to



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

demonstrate a mortality benefit for DES vs. BMS, and in fact they report a trend towards an increased risk for overall mortality in patients treated with DES compared with BMS in 2-4 years of follow-up. They did not find a difference in the incidence of early or late stent thrombosis in patients treated with DES vs. BMS. They note that confidence intervals were wide. In addition, non-cardiac mortality seemed to be higher among patients treated with DES than BMS, a finding limited to trials using sirolimus eluting stents in sensitivity analysis.

Bavry (2006) report on a meta-analysis of 14 clinical trials that randomized 6675 patients to DES compared with BMS. Eight trials had more than one year of clinical follow-up⁴⁰. They found that the incidence of very late thrombosis (angiographic proven thrombosis > one year after implantation) was 5.0 events per 1,000 in DES with no events reported in BMS (risk ratio = 5.02, 95% CI, 1.29-19.52, p=0.02). Ong (2005) reported on the incidence of late angiographic stent thrombosis, defined as angiographically proven stent thrombosis associated with acute symptoms more than 30 days after DES implantation⁴¹. They followed 2,006 patients with sirolimus (n=1,017) and paclitaxel (n=989) eluting stents for a mean duration of 1.5 years. They found eight angiographically confirmed late stent thromboses (0.39%); three cases were associated with complete cessation of antiplatelet therapy, but in five cases patients were still on aspirin monotherapy. No cases occurred in patients on dual antiplatelet therapy.

Case reports

There are a number of case reports in the literature describing late thrombosis complicated by MI and sometimes death in patients who had a DES implanted⁴²⁻⁴⁹.

Unpublished abstracts and conference proceedings

As discussed above, results were presented at the Transcatheter Cardiovascular Therapeutics (TCT) 2006 conference from independent meta-analyses derived from unpublished data gathered directly from the manufacturers of the two FDA approved stents, CYPHER and TAXUS. There were 3506 patients enrolled in the five pivotal randomized controlled trials with the TAXUS stent and 1748 patients enrolled in four pivotal trials of the CYPHER stent. These analyses found a 0.4% to 0.6% increased risk of late stent thrombosis between one and four years with both the sirolimus and paclitaxel eluting stents, but with no significantly increased risk of death or MI.

Pending Clinical Trials (Hodgson, 2007)

Horizons'-AMI trial is randomizing 3,400 patients with acute myocardial infarction (AMI) to DES vs. BMS. The E-Select Registry and INSIGHT trial will examine optimal duration of clopidogrel therapy. PROTECT will examine stent thrombosis in 8,000 patients randomized to Endeavor vs. CYPHER stents. STENT Thrombosis trial will examine 10,000 patients over five years and measure aspirin and clopidogrel responsiveness.

Summary

In sum, the preponderance of evidence to date indicates that DES are associated with an increased risk of late stent thrombosis of about 0.2% per year at least through four years after stent implantation. It is important to note that this is the risk associated with "on-label" use of the stents. However, it is known that DES have largely replaced BMS in many institutions and have become the predominant stent used in most percutaneous cardiac interventions⁵⁰. It is estimated that up to 90% of coronary stents deployed in the US are DES³⁹ and that 40% to 60% of DES implantation is in lesions and/or clinical situations that were excluded from the pivotal trials³⁸. There have been reports that the risk of late stent thrombosis is increased further with off-label use^{28, 29, 40}, so it is likely that these figures underestimate the true risk of late stent thrombosis when DES are implanted in usual clinical practice.

ANTIPLATELET THERAPY AND DRUG ELUTING STENTS

Brief Review of Evidence

There are currently three classes of anti-platelet drugs that have been shown to improve outcomes in patients undergoing percutaneous coronary intervention: aspirin, thienopyridines and glycoprotein IIb/IIIa antagonists⁵¹. Aspirin prevents the synthesis of thromboxane A₂ by activated platelets and is the mainstay of therapy for primary and secondary prevention and acute treatment of ischemic coronary disease. The thienopyridines (clopidogrel and ticlopidine) inhibit adenosine diphosphate receptor mediated platelet activation and work synergistically with aspirin to inhibit platelet activation. Clopidogrel has been found to be better tolerated by patients and is generally considered to be the thienopyridine of choice with aspirin⁵¹. Studies have



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

demonstrated that dual antiplatelet therapy (clopidogrel or ticlopidine in combination with aspirin) for one month reduced the incidence of subacute stent thrombosis and early cardiac events following placement of a bare metal stent^{52, 53}. With the advent of DES, labeling instructions specified treatment with clopidogrel for at least three months after implantation of a sirolimus eluting stent and for six months following implantation of a paclitaxel-coated stent. Early discontinuation of this regimen was associated with stent thrombosis, often leading to MI and death³⁵. While stent thrombosis generally occurs in the first month following implantation (referred to as “subacute stent thrombosis”), there has been growing concern that DES increase the risk of late stent thrombosis, and, therefore, that patients should be kept on dual antiplatelet therapy longer than three to six months.

Discontinuation of anti-platelet therapy has been consistently associated with late stent thrombosis, and late stent thrombosis frequently leads to acute MI and death³⁰. Eisenstein (2006) reported on an observational study of 4666 patients undergoing percutaneous coronary intervention with a BMS (n=3165) or DES (n=1501) and who were event free at six and 12 month follow-up³⁶. They found that long term risk for death and major cardiac events was significantly increased among patients in the DES group who had discontinued clopidogrel at six or 12 months. They propose a three group randomized clinical trial to address the question of the optimal duration of clopidogrel therapy following implantation of a DES; two groups of patients would continue with therapy for 12 and 24 months, while a third group would continue through three years of follow-up. They estimate that a sample size of 10,000 patients would be required to detect a 25% reduction in death or MI at three years.

Iakovou (2005) found that the cumulative incidence of stent thrombosis nine months after successful DES implantation in “real world patients” was substantially higher than the rate reported in clinical trials³⁵. They report on a prospective observational cohort study of 2229 consecutive patients who underwent implantation of sirolimus eluting (n=1062) or paclitaxel eluting (n=1167) stents. Patients were advised to stay on aspirin indefinitely post stent implantation and to take clopidogrel or ticlopidine for at least three months (after sirolimus) or six months (post-paclitaxel). The main outcome measure was subacute (up to 30 days) and late (>30 days) cumulative stent thrombosis. At nine months, 29 patients (1.3%) had stent thrombosis (14 subacute and 15 late), and of these, 13 died (45%). Independent predictors of stent thrombosis were premature discontinuation of antiplatelet therapy, renal failure, diabetes and a lower ejection fraction.

Spertus (2006) report on a 19 center study of 500 MI patients that examined the prevalence and predictors of thienopyridine discontinuation 30 days after DES treatment³⁷. They found that 68 (13.6%) patients stopped dual antiplatelet therapy within 30 days. These patients were significantly more likely to die during the next 11 months (7.5% vs. 0.7%. hazard ration=9.0, $p<0.0001$), presumably mainly due to late thrombosis. Factors associated with early discontinuation of therapy included older age, less educational attainment and lack of receipt of discharge instructions about medications or cardiac rehabilitation.

Expert Opinion

Grines (2007) report on the recommendations of a science advisory panel consisting of representatives from the American Heart Association, the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, the American College of Physicians, the American College of Surgeons and the American Dental Association³⁰. The report endorses the use of 12 months of dual anti-platelet therapy after implantation of a DES and emphasizes the importance of educating patients and health care providers about the risks of premature discontinuation of this treatment. The panel also underscores the importance of appropriate patient selection for DES vs. BMS, and suggests that consideration should be given to avoid DES in patients not expected to comply with 12 months of thienopyridine therapy.

Hodgson (2007) offer “practical” advice to practicing physicians as assessed by the Society for Cardiovascular Angiography and Interventions Drug Eluting Stent Task Force³⁸. They “strongly recommend” that dual anti-platelet therapy be continued for at least 12 months, and that consideration be given to extending treatment longer than 12 months in some (unspecified) patients. They also underscore the importance of careful patient selection and education, and emphasize the importance of thorough documentation of medical decision-making in the medical record.

CONCLUSION

Use of DES, when compared with BMS, is associated with a significantly higher rate of late stent thrombosis. While the absolute risk of stent thrombosis with DES is small, the potential complications are high. One study found that almost two-thirds of patients with angiographically documented stent thrombosis presented with MI and/or death⁵³. Overall mortality rates



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

secondary to known or presumed stent thrombosis are reportedly 20% to 45%³⁰. Premature discontinuation of anti-platelet therapy appears to be the major risk factor for development of late stent thrombosis following implantation of a DES. This is especially true for patients with more complex lesions or with more medical co-morbidities.

A conundrum now faced by clinicians and patients is that patients more likely to benefit from DES (e.g. patients with diabetes, small vessels and chronic kidney disease) are also at higher risk for developing late stent thrombosis. It is estimated that up to 40% of DES are now implanted “off label” in patients who would have been excluded from the pivotal trials. Evidence is emerging, however, that the risk of MACE (death and MI) is significantly increased when DES is used in these more complex lesions and/or patients³⁸.

Therefore, until further evidence emerges that will help guide appropriate patient selection for DES vs. BMS vs. medical therapy alone, it is prudent for clinicians to reserve DES for patients who meet the inclusion criteria of the pivotal randomized trials. Since the FDA does not regulate clinical behavior, it is incumbent upon the major professional societies to educate clinicians and the public about the risks and benefits of PCI and coronary stenting, and the appropriate selection of DES vs. BMS. Of course, the practice of medicine requires clinical judgment, flexibility, and the ability of doctor and patient to engage in collaborative decisions that will best address the patient’s unique clinical circumstances. This will from time to time lead to rational “off label” use of DES. However, it is clear that current practice has moved too far in the other direction, where DES have become the only option at some institutions and the most common option at many. While the reasons for this rapid dominance by DES are complex and undoubtedly multi-factorial, some experts in the medical community have concluded that DES have been overused and have called for a re-evaluation of the role of DES specifically and, more generally, of the overall role of stenting in the treatment of coronary disease⁵⁴.

It is tempting to put most of the blame for late stent thrombosis on premature discontinuation of anti-platelet therapy. In this scenario, the problem is ‘bad’ patients who are non-adherent to their medications, or ‘bad’ doctors who provide inadequate patient education or who needlessly advise some patients to stop anti-platelet therapy when undergoing minor procedures etc. While it is true that discontinuation of anti-platelet therapy is a significant risk factor for the development of stent thrombosis, the proximal cause of this problem is the overuse of DES in “off label” patients at increased risk of developing late stent thrombosis. While it is important to



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

expand the use of anti-platelet therapy and to improve patient adherence with this therapy, it is equally important to better define the population of patients likely to benefit from DES. While improving patient adherence is a laudable goal, it is not one that is easily accomplished, as we know from the literature that only about 50% of patients are adherent with chronic medication⁵⁵. As the recommendations for extending anti-platelet therapy go to 12 months and beyond, assuring patient adherence will become an increasing challenge, one that must be balanced with promoting more appropriate patient selection.

RECOMMENDATIONS:

It is recommended that:

1. Drug-eluting stents be implanted only in patients who meet current FDA labeling criteria.
2. Drug-eluting stents may be implanted for "off label" indications in unusual circumstances where the clinician and the patient determine that the clinical benefits outweigh the potential risks.
3. Patients who receive one of the two currently FDA approved drug eluting stents (CYPHER or TAXUS) should be advised to take dual antiplatelet therapy, usually consisting of aspirin and clopidogrel, for 12 months after implantation. Continuation of therapy beyond 12 months may be indicated in selected patients.

The CTAF panel voted five in favor and four opposed to the first recommendation, with three abstentions.

The CTAF Panel voted unanimously to drop recommendations 2 and 3.

February 28, 2007

RECOMMENDATIONS OF OTHERS

Blue Cross and Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center has not reviewed this technology

Centers for Medicare and Medicaid Services (CMS)

CMS provides coverage for FDA approved drug-eluting stents as reasonable and necessary.

California Chapter of the American College of Cardiology (CAACC)

A CAACC representative participated in the discussion at the meeting. A joint statement has been issued by the AHA, ACC, SCAI, ACS, and ADA.

Society for Cardiovascular Angioplasty and Interventions (SCAI)

A SCAI representative participated in the discussion at the meeting.

ABBREVIATIONS

CAD: Coronary atherosclerotic heart disease

CABG: Coronary artery bypass grafting

PCI: Percutaneous coronary intervention

MI: Myocardial infarction

ISR: In-stent restenosis

DES: Drug-eluting stents

BMS: Bare metal stents

RCT: Randomized control trial

MACE: Major adverse cardiac events

WCC: European Society of Cardiology 2006 World Congress

TCT: Transcatheter Cardiovascular Therapeutics

AMI: Acute Myocardial Infarction

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CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

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APPENDIX 1

For TAXUS, the current labeling reads as follows:

Indications:

The TAXUSTMExpress^{2TM}Paclitaxel-Eluting Coronary Stent System is indicated for improving luminal diameter for the treatment of *de novo* lesions ≤ 28 mm in length in native coronary arteries ≥ 2.5 to ≤ 3.75 mm in diameter.

The following is noted on the Boston Scientific Web site under TAXUS[®] Express^{2TM} Paclitaxel-Eluting Coronary Stent System: Prescriptive Information:

The safety and effectiveness of the TAXUS Express Paclitaxel-Eluting Coronary Stent System have not been established in the following patient populations:

- Women who are pregnant or lactating
- Men intending to father children
- Pediatric patients
- Patients with unresolved vessel thrombus at the lesion site
- Patients with coronary artery reference vessel diameters < 2.5 mm or > 3.75 mm
- 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 acute myocardial infarction where there is evidence of thrombus or poor flow
- Patients with multiple overlapping stents
- Patients with longer than 12 month follow-up

Contraindications:

Use of the TAXIS Express Paclitaxel-Eluting Coronary Stent System is contraindicated in patients with:

- Known hypersensitivity to paclitaxel or structurally related compounds.
- Known hypersensitivity to the polymer or its individual components.

Coronary Artery Stenting is contraindicated for use in:

- Patients in whom anti-platelet and/or anticoagulant therapy is contraindicated.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery device.

Full labeling information can be found at: <http://www.fda.gov/cdrh/pdf3/P030025c.pdf>

Indications for CYPHER:

The CYPHER Sirolimus-eluting Coronary Stent 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 reference vessel diameter of ≥ 2.5 to ≤ 3.5 mm.

For CYPHER, the current labeling regarding contraindications and precautions is as follows:

Contraindications (as noted in the labeling information) are:

Use of the CYPHER Sirolimus-eluting Coronary Stent is contraindicated in the following patient types:

- Patients with a hypersensitivity to sirolimus or its derivatives
- Patients with a known hypersensitivity to polymethacrylates or polyolefin copolymers.

Coronary artery stenting is contraindicated for use in:

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated



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- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon

There are several Precautions noted. Some are as follows:

Use in Special Populations:

- Pregnancy – There are no adequate and well controlled studies in pregnant women.
- Use during lactation – See Drug Information. 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.
- Pediatric use: The safety and efficacy of the CYPHER stent in pediatric 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.

Lesion/Vessel Characteristics

The safety and effectiveness of the CYPHER Stent have not been established in the following patient populations

- Patients with unresolved vessel thrombus at the lesion site
- Patients with coronary artery reference vessel diameter <2.5 mm or >3.5 mm
- Patients with lesions located in the 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 acute myocardial infarction where there is evidence of thrombus or poor flow.

Full labeling information for CYPHER can be found at:

<http://www.fda.gov/cdrh/PDF2/p020026c.pdf>